STUDIES IN THE CHEMISTRY OF

α,β-ACETYLENIC OXIMES AND AMIDES

Mollin Benjamin Rampersad

A THESIS

in

The Department

of

Chemistry

Presented in Partial Fulfillment of the Requirements for

the Degree of Doctor of Philosophy at

Sir George Williams University

Montreal, Canada

September, 1972

ABSTRACT

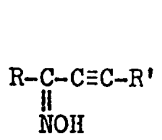
STUDIES IN THE CHEMISTRY OF α,β-ACETYLENIC OXIMES AND AMIDES.

Mollin Benjamin RAMPERSAD, Ph.D.

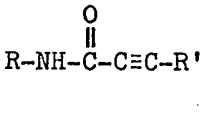
Sir George Williams University, 1972.

Supervisor: Dr. Z. Hamlet.

Several α,β-acetylenic ketoximes 1 were prepared in good yields from the reaction of various acetylenic Grignard reagents and hydroxamoyl chlorides. The syn oxime configuration (OH and C≡C syn) was established by the Beckmann rearrangement reaction using PCl_5, PBr_5 and $POBr_3$. Rearrangement and/or fragmentation reactions occurred depending on the substituent R. Acetylenic amides 30, the expected rearrangement products, were obtained in low yields with PBr_5 and $POBr_3$.



1



30

The main rearrangement products were the corresponding cis- and trans-β-chloro olefinic amides from PCl_5 and α,β-dibromo olefinic amides from PBr_5. Some aspects of the mechanism of the Beckmann rearrangement with these reagents are discussed. The ir spectra of the OH stretching region of these oximes have revealed that there is

considerable intramolecular π-hydrogen bonding between the hydroxyl hydrogen and the acetylenic function. An average frequency separation of 228 cm^{-1} between the "free" and "bonded" OH bands has been measured. Also, the narrow range of chemical shifts of the hydroxyl proton in DMSO has been used as a criterion for the syn oxime configuration.

Several α,β-acetylenic amides were synthesized in good yields from the reaction of various acetylenic Grignard reagents with isocyanates. The von Braun reaction of these acetylenic amides with PCl_5, PBr_5 and $POBr_3$ gave products similar to those obtained in the Beckmann rearrangement study. Optically active acetylenic amides fragmented to produce optically active chlorides with retention of configuration. The mechanistic implications of these results are discussed. The ir spectra of the NH stretching region of these amides all show a "shoulder" on the low frequency side of the "free" NH band with an average separation of 27 cm^{-1}. The possibility of intramolecular π-hydrogen bonding is considered.

ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation to Dr. Z. Hamlet for his guidance, encouragement and expert advice throughout the course of this work. Special thanks are due to Mr. J. Lenoir for his many helpful suggestions and assistance especially in the art of chromatography.

Assistance from various other members of the faculty as well as fellow students is also gratefully acknowledged.

Thanks are also due to Dr. T. H. Chan at McGill University for the use of the Perkin Elmer 141 Automatic Polarimeter.

The author is indebted to the Chemistry Department for the generous financial support of this work.

Finally, the author wishes to thank his wife, Sharron, for her understanding, encouragement and assistance in the preparation of this thesis.

TABLE OF CONTENTS

	Page
ABSTRACT	iii
ACKNOWLEDGEMENTS	v
LIST OF TABLES	ix
LIST OF FIGURES	xi
LIST OF SCHEMES	xii
INTRODUCTION	1
STATEMENT OF THE PROBLEM	13
DISCUSSION	14
I. Syntheses	14
A. α,β-Acetylenic Aldoximes	14
B. α,β-Acetylenic Ketoximes	19
1. Method Used in Present Study	19
2. Alternate Method of Preparation	33
3. O-Deuterated Acetylenic Oximes	36
C. α,β-Acetylenic Amides	37
D. Authentic Samples: Acrylic Acid Derivatives	44
1. Haloacrylic Acids	44
2. Haloacrylonitriles and Aldehydes	49
3. Haloacrylic Amides	53
E. Miscellaneous Compounds	66
II. Reactions of α,β-Acetylenic Oximes	74

A. The Beckmann Rearrangement and its Variations 74

B. Reaction of α,β-Acetylenic Ketoximes with Phosphorus Pentachloride 90

C. Aspects of the Mechanism of the reaction of Phosphorus Pentachloride with Acetylenic Oximes 99

D. Reaction of α,β-Acetylenic Ketoximes with Phosphorus Pentabromide 111

E. Aspects of the Mechanism of the reaction of Phosphorus Pentabromide with Acetylenic Oximes 114

F. Reaction of α,β-Acetylenic Ketoximes with Phosphoryl Bromide 119

G. Action of Other Reagents on α,β-Acetylenic Ketoximes 120

H. Reaction of α,β-Acetylenic Aldoximes with Phosphorus Pentachloride 122

III. Reaction of α,β-Acetylenic Amides with Phosphorus Pentahalides 124

A. The von Braun Reaction 124

B. Reactions of α,β-Acetylenic Amides with Phosphorus Pentachloride 128

C. Aspects of the Mechanism of the Reaction of Phosphorus Pentachloride with α,β-Acetylenic Amides 134

1. Reaction by Path A 136

2. Reaction by Path B 141

a. Stereochemical Identities of the Commercial "(+)" and "(-)"-α-Phenylethylisocyanates 143

b. The Mechanism of the N-alkyl Fission: Reaction of Phosphorus Pentachloride with Optically Active N-(α-phenylethyl) propiolamides 149

D. Reaction of α,β-Acetylenic Amides with Phosphorus Pentabromide 152

IV. Intramolecular π-hydrogen bonding in α,β-Acetylenic oximes 156

V. Infrared Spectra of α,β-Acetylenic Amides in the N-H stretching region 167

EXPERIMENTAL 172

SUMMARY 224

BIBLIOGRAPHY 226

APPENDIX 238

Ir Spectra 239

Nmr Spectra 250

Uv Spectra 268

VITA xiii

LIST OF TABLES

Table		Page
I	Ir Spectra of α,β-Acetylenic Aldoximes	18
II	Nmr Spectra of α,β-Acetylenic Aldoximes	18
III	α,β-Acetylenic Ketoximes	30
IV	O-Deuterated Acetylenic Ketoximes	36
V	Acetylenic Amides	41
VI	Uv Spectra of Acetylenic Amides	43
VII	Nmr Spectra of β-Chlorocinnamonitriles	50
VIII	Nmr Data for β-Chloroacrylic Aldehydes, Nitriles and Esters	53
IX	β-Haloacrylic Amides	57
X	α-Haloacrylic Amides	59
XI	α,β-Dibromoacrylic Amides	60
XII	Nmr Spectra of β-Haloacrylic Amides	61
XIII	Nmr Spectra of α-Haloacrylic Amides	64
XIV	Nmr Spectra of α,β-Dibromoacrylic Amides	64
XV	Uv Spectra of α,β-Dibromoacrylic Amides	65
XVI	α,β-Acetylenic Nitriles	67
XVII	Beckmann Rearrangement Reaction (Path A)	94
XVIII	Beckmann Fragmentation Reaction (Path B)	96
XIX	Beckmann Rearrangement Reaction (Path A)	113
XX	Von Braun Reaction (Path A)	130
XXI	Von Braun Reaction (Path B)	132
XXII	Molecular Rotations of (-)-α-Phenylethyl-isocyanate	144

XXIII	Molecular Rotations of "(-)"-1-Phenylaethyl Isocyanat Purum (Fluka)	147
XXIV	Molecular Rotations of "(+)"-1-Phenylaethyl Isocyanat Purum (Fluka)	147
XXV	Molecular Rotations of Amides	148
XXVI	Reaction of α,β-Acetylenic Amides with PBr_5	153
XXVII	Ir Spectra ("OH region") of α,β-Acetylenic Oximes ..	164
XXVIII	Ir Spectra ("O-D region") of α,β-Acetylenic Ketoximes	166
XXIX	N-H and C=O Frequencies of α,β-Acetylenic Amides ...	170
XXX	Aldoximes	177

LIST OF FIGURES

Figures		Page
1	Ir Spectrum of "free" and "bonded" OH region	157
2	Ir Spectra of the OH region of Oxime 1 (R = i-Pr, R' = Ph)	161

LIST OF SCHEMES

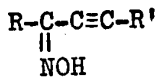
Scheme		Page
1	Postulated Mechanisms for the Reaction of Grignard Reagents with Hydroxamoyl Chlorides	28
2	Mechanism of the Beckmann Rearrangement	76
3	Modified Beckmann Rearrangement Mechanism	82
4	Reactions of α,β-Acetylenic Ketoximes with Phosphorus Pentachloride	93
5	Reactions of α,β-Acetylenic Ketoximes with Phosphorus Pentabromide	112
6	Probable Mechanism of the Reaction of Phosphorus Pentabromide with Acetylenic Oximes	116
7	Mechanism of the von Braun Reaction	125
8	Reactions of α,β-Acetylenic Amides with Phosphorus Pentachloride	129

VITA

The author was born in Trinidad, West Indies. He attended Naparima College and upon graduation in 1955 was employed with Texaco Trinidad Incorporated until 1964. He entered Sir George Williams University in 1964 and obtained his B.Sc. in 1968. He started his graduate studies in Chemistry at Sir George Williams University in 1968 and expects to obtain his Ph.D. in 1973.

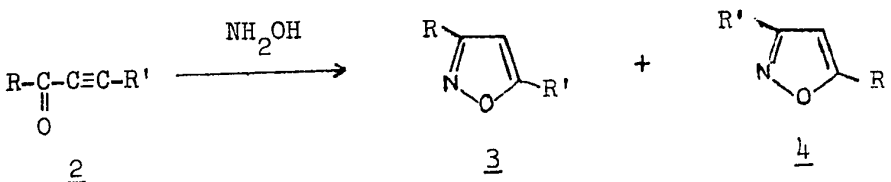
INTRODUCTION

As a class of organic compounds, α,β-acetylenic ketoximes 1 have long remained elusive. Due to their unavailability by synthesis virtually nothing is known regarding their chemistry. The notable lack of any coverage of these compounds in the recently published treatises on acetylenic compounds[1-3] is a reflection of the lack of reliable data in the literature regarding them.



1

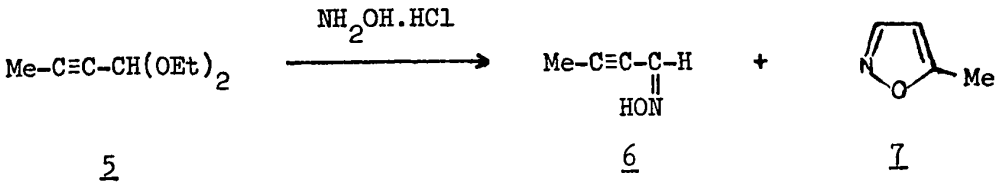
Since the turn of the century the role of α,β-acetylenic ketoximes as possible intermediates in several isoxazole syntheses has been postulated.[4,5] One of the general methods of synthesis of isoxazoles makes use of the reaction of α-acetylenic carbonyl compounds 2 with hydroxylamine.[6,7] In contrast to the other carbonyl compounds (e.g. aldehydes and ketones having no triple bond in conjugation with the carbonyl) no oxime derivatives of 2 have ever been isolated from this reaction. Instead, the products obtained are the isomeric isoxazoles 3 and 4, the ratio



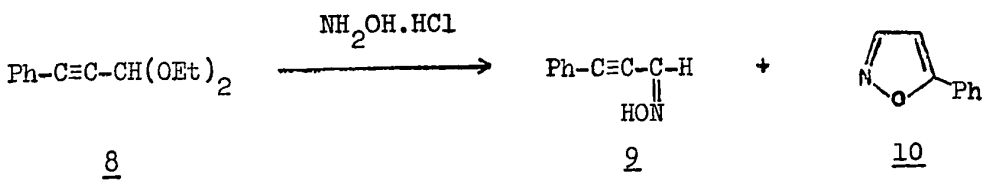
2 3 4

of the two depending on reaction conditions. Isoxazole 3 is regarded as the product obtained *via* the "1,2-addition" of hydroxylamine to the acetylenic ketone and 4 as that formed *via* the "1,4-addition". The "1,2-addition" mechanism assumes the formation of the acetylenic oxime 1, whose configuration, it has been suggested,[8-11] is such that the hydroxyl group is *syn* with respect to the acetylenic function, thus having the most favourable geometry for cyclization to the isoxazole 3.

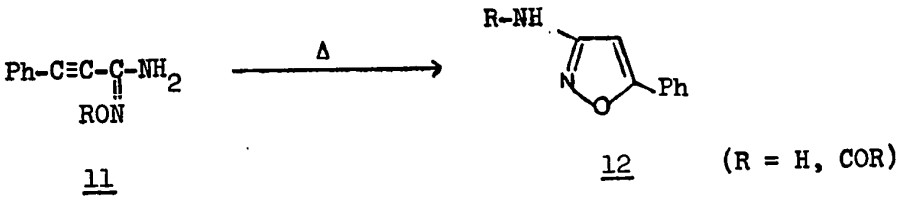
When the present study was initiated only two α,β-acetylenic aldoximes were characterized in the literature. These were tetrolaldoxime 6 and phenylpropiolaldoxime 9.[4,5] Both these oximes were synthesized from the corresponding diethyl acetals by treatment with hydroxylamine hydrochloride under acid catalysis. These oximes were shown to readily cyclize under the influence of heat or alkali to 5-methyl(7) and 5-phenyl(10) isoxazoles respectively.[10] Phenylpropynamidoximes 11 or their acyl derivatives have recently been synthesized[12] and were shown to cyclize thermally



5 6 7



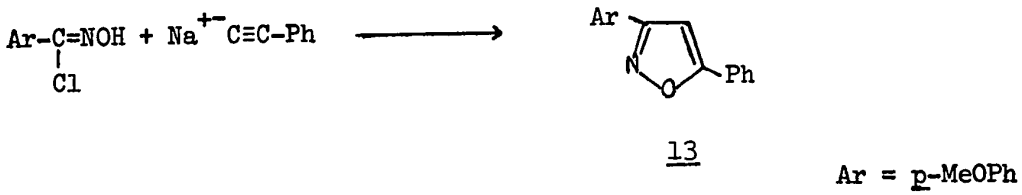
8 9 10



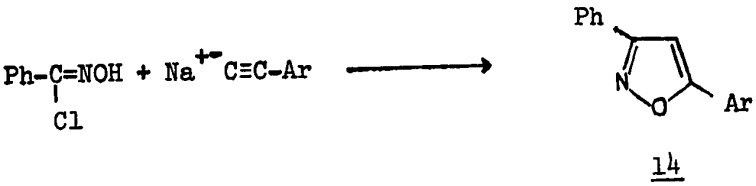
11 12 (R = H, COR)

to the isoxazoles 12.

Another method of isoxazole formation involves the reaction of the sodium salt of an acetylene with a suitable hydroxamoyl chloride.* In an attempt to establish unequivocally the structures of a pair of isomeric 3,5 disubstituted isoxazoles Weygand and Bauer[14] prepared the isoxazoles 13 and 14 by this method. However, it was later demonstrated that this reaction proceeds via the formation of the



13 Ar = p-MeOPh

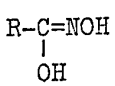


14

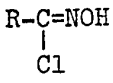
nitrile oxide 15 followed by the addition to the acetylene[15]:

---

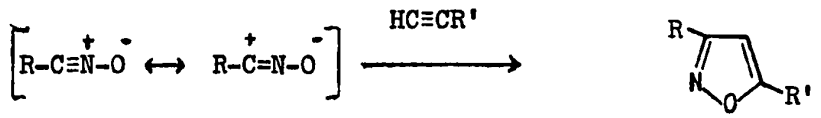
*In the literature this class of compounds has been referred to by various names, such as hydroxamic acid chlorides, hydroxamic chlorides, hydroximic chlorides, chloroximes, acyl and aroyl chloride oximes. The name "hydroxamoyl chloride" (which reflects its relationship to hydroxamic acid) will be used hereafter, as recommended by H. Ulrich[13]:



(Hydroxamic acid)

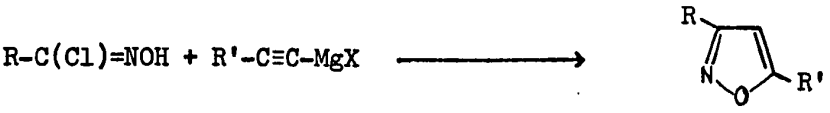


(Hydroxamoyl chloride)



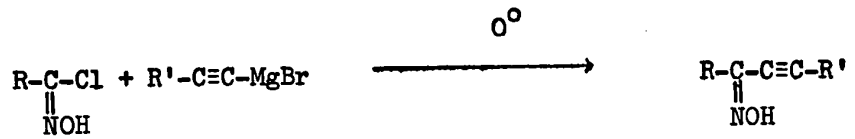
15

In a variation of this reaction it was demonstrated that sodium acetylides could be replaced by acetylenic Grignard reagents.[16-18] In the reaction of hydroxamoyl chlorides with

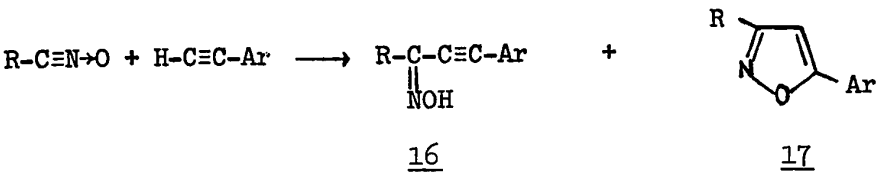


sodium acetylides or acetylenic Grignard reagents or in the reaction of nitrile oxides with acetylenes, an α,β-acetylenic oxime of the type 1 seems to be a logical precursor to the isoxazole. Although there have been allusions to the existence of such acetylenic oximes as intermediates in these reactions,[16-19] there seems to have been no efforts directed towards the isolation and characterization of these intermediates from such reactions.

α,β-Acetylenic ketoximes have been isolated and characterized for the first time in these laboratories during the course of a study directed towards the elucidation of the mechanisms of the reaction of α,β-acetylenic ketones with hydroxylamine.[20] The procedure used was a variation of that used earlier by Palazzo[16], and more recently, in a slightly modified form by Feuer and Markofsky.[18] This involved the reaction of hydroxamoyl chlorides with acetylenic Grignard reagents at 0° and subsequent decomposition of the Grignard product with 10% sulfuric acid or saturated ammonium chloride solution. The method seems to be of fairly good applicability and good yields of the oximes are obtained, uncontaminated with any isoxazoles.



While the present study was in progress, a communication appeared[21] announcing the isolation of some α,β-acetylenic ketoximes as by-products in the reaction of nitrile oxides with terminal acetylenes. The major product of the reaction was the expected single isomer of the isoxazole 17. The study included the reaction of several aliphatic and aromatic nitrile oxides with aryl acetylenes as indicated below:



16 17

a: R = Me; Ar = Ph

b: R = Et; Ar = Ph

c: R = Ar = Ph

d: R = Mesityl; Ar = Ph

e: R = Ph; Ar = α-Naphthyl

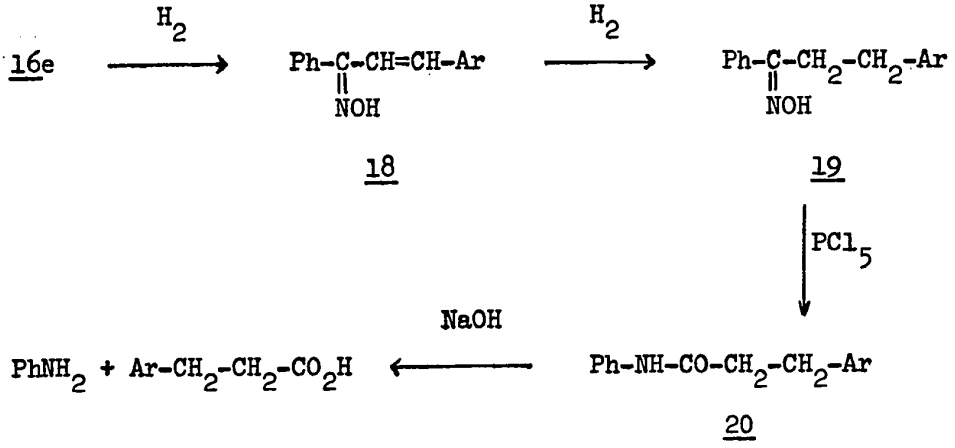
f: R = pBrC_6H_4; Ar = α-Naphthyl

g: R = Ph; Ar = Mesityl

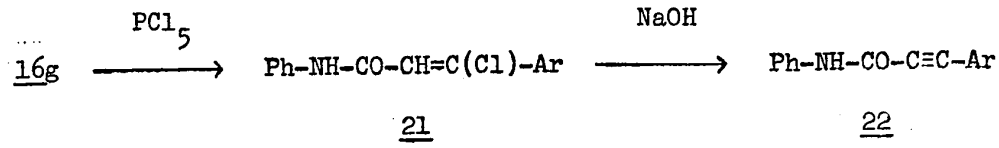
In this work only three oximes (16e, f and g) were isolated and characterized, their yields ranging from 8-24%. According to the authors[21] the other oximes were too unstable to be purified and hence were identified only by spectral and indirect chemical evidence.

In an attempt to establish the configuration of oxime 16 e the authors subjected it to the conditions of the Beckmann rearrangement using phosphorus pentachloride (PCl_5) in ether and obtained unsatisfactory results. The evidence for the configuration was therefore provided indirectly by catalytically hydrogenating the

acetylenic oxime to the corresponding saturated one and then subjecting it to the Beckmann rearrangement. The structure of the amide 20 isolated from this reaction suggested that in 16e the hydroxyl group and the triple bond were in a syn (cis) relationship.

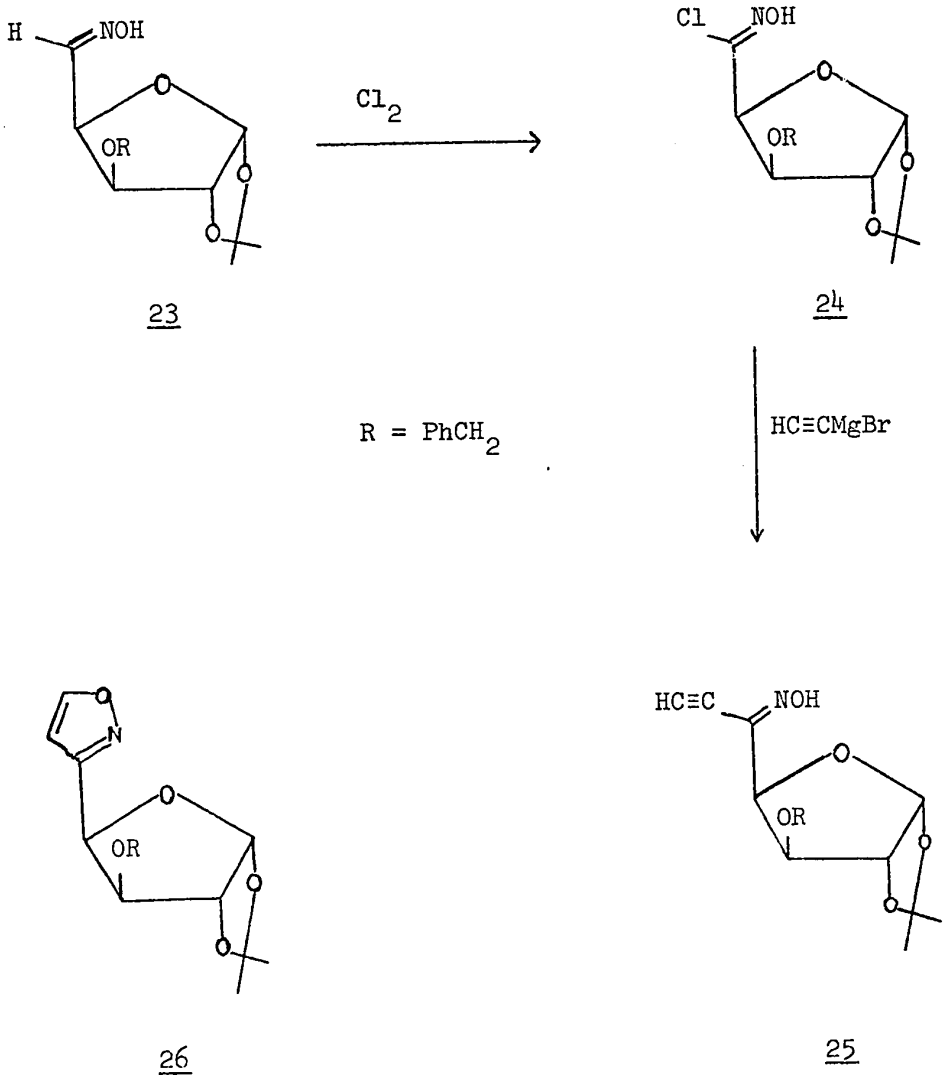


Treatment of oxime 16g with PCl_5 was reported to give the olefinic amide 21 which on subsequent treatment with 10% sodium hydroxide yielded the acetylenic amide 22. This acetylenic amide is the product one would expect from the Beckmann rearrangement of 16g if the hydroxyl group were syn with respect to the triple bond, and assuming that the triple bond remains intact during the rearrangement. No comments regarding the stereochemistry of the olefinic amide 21 were made by the authors.[21]



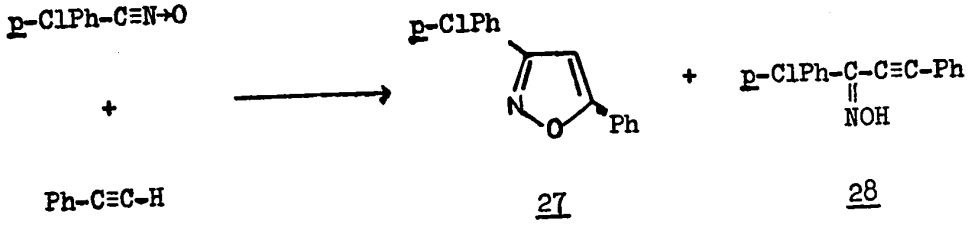
With regard to the structure of the acetylenic oximes, the authors[21] demonstrated that the ir spectra of the compounds exhibited the characteristic hydroxyl and acetylenic stretching frequencies. Some of the oximes were converted to their O-acetyl derivatives by treatment with acetic anhydride and were characterized by ir and nmr spectroscopy. In addition, 16a and 16b were converted to the corresponding 2,4-dinitrophenylhydrazones by treatment with 2,4-dinitrophenylhydrazine in the presence of sulfuric acid. Because of the fact that the oximes appeared homogeneous by tlc and by nmr spectroscopy, and because of their propensity for cyclization to the isoxazoles, these workers concluded that they were dealing with a single isomer of the oxime in each case, and that the configuration of this isomer was such that the triple bond and the hydroxyl group were in a syn arrangement.

Another report of the isolation of an α-acetylenic ketoxime in the carbohydrate field appeared, also while the present investigation was in progress.[22] The hydroxamoyl chloride 24 resulting from the chlorination of 3-O-benzyl-1,2-O-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose oxime 23, upon treatment with ethynyl magnesium bromide yielded a mixture of the acetylenic oxime 25 and the isoxazole derivative 26. The acetylenic oxime 25 was isolated by tlc on silica gel and was characterized by its ir and nmr spectra. In addition, its high susceptibility for cyclization to the isoxazole 26 was demonstrated. However, no comments were made regarding the possible configuration of the oximino group.



23 24 26 25

Soon after the appearance of the two previous communications[21,22] Battaglia and Dondoni reported the results of a study of the reaction between p-chlorobenzonitrile oxide and phenylacetylene.[23] The major product of the reaction (80%) was shown to be 3-(p-chlorophenyl)-5-phenyl-isoxazole 27 and the minor product (14%) was characterized as the corresponding α,β-acetylenic oxime 28. From the kinetics of this reaction the authors concluded that the isoxazole 27 and the acetylenic oxime 28 were produced in



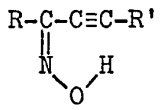
27 28

two parallel and competing processes and that the oxime was not an intermediate for the isoxazole.

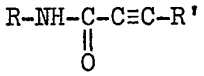
The active interest shown in the chemistry of these α,β-acetylenic ketoximes by the various groups of investigators during the course of the present work necessitated the publication of some preliminary accounts of the progress of the current investigation. The first of these concerned the method of synthesis of these oximes from hydroxamoyl chlorides and acetylenic Grignard reagents in fair to good yields.[24] This method is superior to the nitrile oxide method[21,23] in that considerably better yields of the oximes are obtained and they are uncontaminated with the corresponding isoxazoles. All of the oximes prepared by this method seem to be a single isomer in each case, as evidenced by their physical and spectral characteristics. The second report from the present work dealt with some preliminary data from the Beckmann rearrangement studies on some of the oximes.[25] These results demonstrated that the oximes do undergo Beckmann rearrangements and/or fragmentations with PCl_5 in ether, and that, contrary to a previous report,[21] the products of the reaction are readily isolated and characterized.

Physical and chemical evidence available so far seems to

indicate that all of the α,β-acetylenic oximes made available either by the procedure used in the present study or by the method used by the other investigators[21,23], have a configuration in which the hydroxyl group is syn with respect to the acetylenic bond as represented in 29.

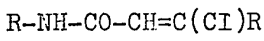


29

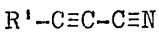


30

The Beckmann rearrangement is the classical chemical method of establishing the configuration of a ketoxime*. The generally accepted mechanism of the Beckmann rearrangement involves migration of the group anti to the hydroxyl group of the oxime. A priori, then, one would expect the acetylenic amide 30 as the product in the reaction of the acetylenic oxime 29 with PCl_5. Preliminary results[21,25] indicated that reaction of the oximes with PCl_5 did not give acetylenic amides of the type 30, but instead gave products 31 resulting from the addition of the elements of HCl to the triple bond in 30. It was also established that with oximes in which R'= Ph only trans 31 (Cl and H trans) was obtained whereas oximes



31



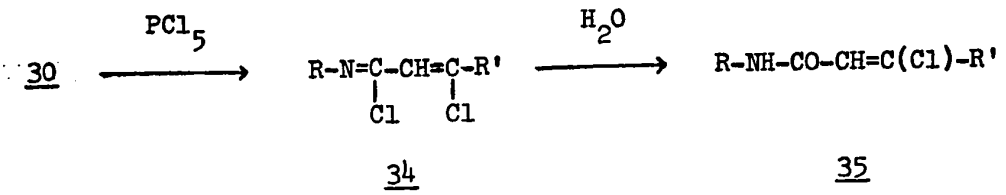
32

33

*For recent reviews on the subject see references 26-29.

with R' = CH_3 gave both cis and trans 31. Oximes in which R = t-Bu or Me(Ph)CH underwent the Beckmann fragmentation reaction[25] giving rise to the nitrile 32 and the chloride 33.

The chemistry of α,β-acetylenic amides of the type 30 is also very meager. Reaction of only two such amides, phenylpropiolanilide (30, R = R' = Ph) and phenylpropiolethylamide (30, R' = Ph, R = Et) with PCl_5 have been reported in the literature.[30] It was shown that these amides underwent HCl addition to the triple bond concomitant with the formation of the imidoyl chlorides 34 which subsequently underwent rapid hydrolysis to the β-chlorocinnamamide derivatives 35.



34 35

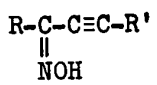
In contrast, it has been shown that under the same conditions no such addition of hydrogen chloride to the double bond occurs when the corresponding α,β-olefinic amides are treated with phosphorus pentachloride.[31-33]

Now that the long-elusive α,β-acetylenic oximes have become available by synthesis it is of interest to investigate the chemistry of this new class of compounds. Of special interest is the configuration of the oximes synthesized in the present study. If the oximes indeed have the configuration as shown in 29 (which preliminary evidence seems to indicate[24,25]), the possibility of investigating the existence of intramolecular π-hydrogen bonding between the triple bond and the hydroxyl group by using ir spectroscopy presents itself.

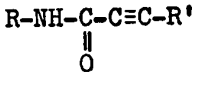
The mechanism of the unusual reactions of the oximes under Beckmann rearrangement conditions needs to be investigated. Equally interesting will be investigation of the chemistry of the acetylenic amides, particularly the mechanism of their reaction under the conditions of the Beckmann rearrangement of the related oximes, in view of the lack of data in the literature pertaining to these.

STATEMENT OF THE PROBLEM

The present study had as its objective the synthesis of a variety of α,β-acetylenic ketoximes of the type 1 and a study of their chemistry. Establishment of the stereostructure of the oximes, that is, whether the hydroxyl and acetylenic functions are in a *syn* or *anti* relationship, was highly important. In the *syn* configuration one would expect to find intramolecular π-hydrogen bonding in these molecules and the nature of this interaction could be investigated by near ir spectroscopy.



1



30

With regard to the chemical reactions of the oximes, it was interesting to investigate their behavior under Beckmann rearrangement conditions. The mechanism of the rearrangement was of special importance particularly in view of the interesting observation that the products of the rearrangement did not contain the acetylenic function.

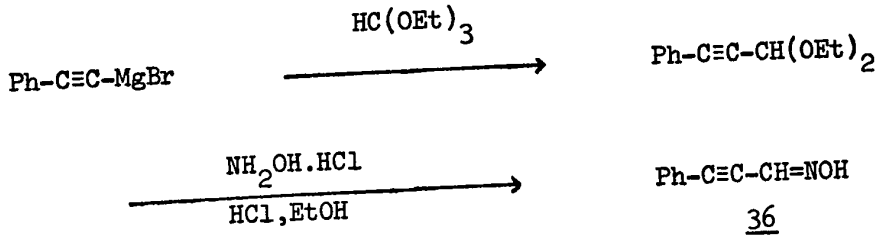
Intimately related to the problem is also the chemistry of α,β-acetylenic amides of the type 30. One of the objects of the present study was also the synthesis of some of these amides and the investigation of the mechanisms of their reactions under the Beckmann rearrangement conditions used for the corresponding oximes.

DISCUSSION

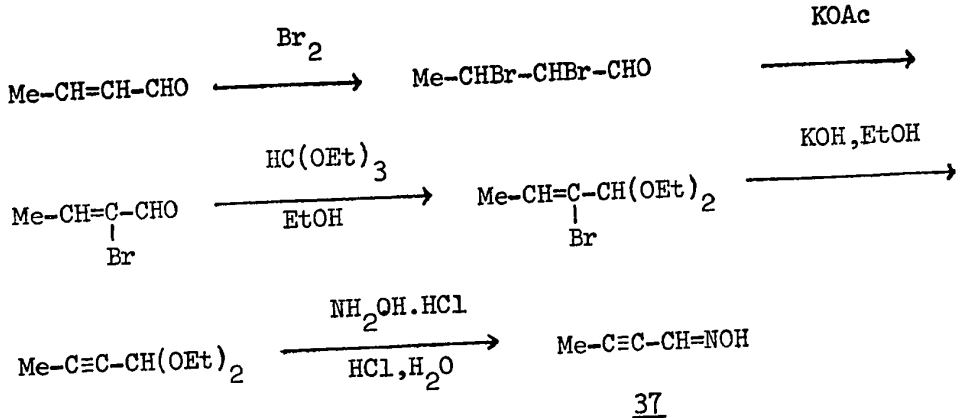
I. Syntheses

A. α,β-Acetylenic Aldoximes

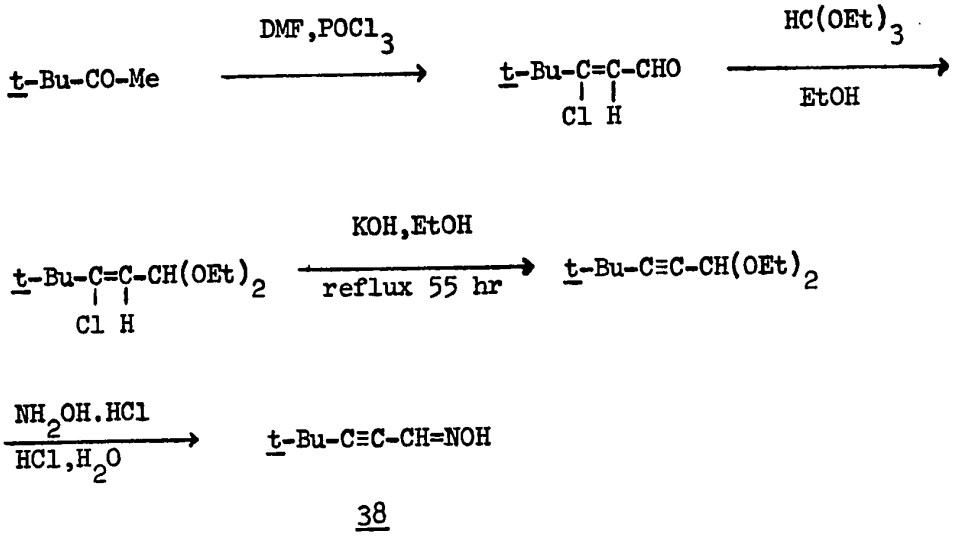
The α,β-acetylenic aldoximes used in the present study were synthesized using methods reported in the literature.[4,5,34,35] The diethyl acetals of phenyl, methyl and tert-butylpropiolaldehydes were treated with hydroxylamine hydrochloride and a trace of concentrated hydrochloric acid at room temperature to give the corresponding aldoximes (36,37,38) in good yields. The low reaction temperature was necessary to avoid cyclization of the acetylenic oxime product to the corresponding isoxazoles.



36



37



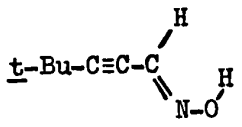
38

The ir spectra of the acetylenic aldoximes are summarized in Table I. The solution spectra are characterized by their intense OH and C≡C absorptions. The "free" OH and "bonded" OH (inter- and intramolecular) bands appear at approximately 3580 cm^{-1} and 3280 cm^{-1} respectively. Further discussion of the intramolecular hydrogen bonding in these α,β-acetylenic aldoximes will be left for a later section. The C≡C stretching vibrations occur at approximately 2230 cm^{-1} and the very weak C=N stretching band occurs at approximately 1610 cm^{-1}.

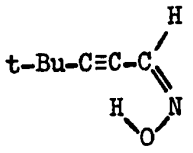
The nmr spectra of the α,β-acetylenic aldoximes are summarized in Table II. These spectra were taken in CCl_4 and DMSO-d_6 (5% w/w) solutions. Long range coupling (J ≈ 2 Hz) was observed for tetrolaldoxime 37.[36] These examples indicate that the chemical shift of the OH proton of acetylenic oximes in DMSO is characteristic of the oxime configuration 37 and this observation will be used in the proof of the structure of 38.

tert-Butylpropiolaldoxime 38, not previously reported in the

literature, is the first acetylenic oxime obtained as a mixture of syn and anti isomers (31% syn and 69% anti as determined by nmr spectroscopy).

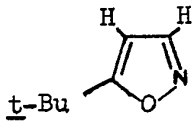


38 a syn



38 b anti

Proof of the structures of these isomers is obtained from nmr evidence. The proton on the oxime trigonal carbon is expected to be more deshielded in the syn isomer[37] (syn δ7.32, anti δ6.75), whereas the OH proton should be more deshielded in the anti isomer[37] (syn δ11.47, anti δ11.75). The value of δ11.75 is in good agreement with the value of δ11.70 observed in the case of the single isomer obtained of tetrolaldoxime 37, which is postulated to be of the anti configuration on account of its ready cyclization to the corresponding isoxazole[4] and from intramolecular π-hydrogen bonding data discussed in a later section. The two isomers 38 a and 38 b were not separable by chromatographic techniques. The syn isomer (38 a) was therefore isolated by removing the anti isomer (38 b) as the known 5-tert-butylisoxazole by selective cyclization using sodium hydride.



39

An ethereal solution of the mixture of the oxime isomers was treated with sodium hydride and the reaction mixture was poured on crushed ice. Extraction with ether removed only the isoxazole, which was identified by its boiling point and by its ir and nmr spectra. Acidification of the aqueous layer with hydrochloric acid followed by extraction with ether gave an oil which was shown to be a mixture of two products by tlc on alumina. The two products were separated by column chromatography. The product which eluted first was a colorless crystalline solid (mp 67-68°), which was identified as α-cyanopinacolone by comparison with an authentic sample synthesized independently. The second product was an oil which exhibited bands at 3580 cm^{-1} and 3270 cm^{-1} (OH), 2240 cm^{-1} (C≡C,shoulder also at 2220 cm^{-1}), and 1605 cm^{-1} (C=N). It is interesting to note that this product failed to reveal the characteristic intramolecularly π-hydrogen bonded OH absorption at 3356 cm^{-1} which was clearly visible in the mixture of the two isomers 38 a and 38 b at comparable dilution. The nmr spectrum (δ1.23,t-Bu; δ7.33,-CH=N-; δ11.53,OH) also points to its structure as the syn isomer 38 a.

TABLE I

IR SPECTRA OF α,β-ACETYLENIC ALDOXIMES (R-C≡C-CH=NOH)

COMPOUND R	νmax(cm^{-1}) OH	C≡C	C=N
Ph	3580,3300	2210	1605
Me	3580,3280	2230	1607
t-Bu	3575,3280	2230	1610

TABLE II

NMR SPECTRA* OF α,β-ACETYLENIC ALDOXIMES (R-C≡C-CH=NOH)

COMPOUND R	^{1}H NMR (δppm) R	CH	OH
Ph	7.50(m)	7.20(s)	12.10(s)
Me	2.10(d)	6.90(q)	11.70(s)
t-Bu	1.30(s)	6.75(s,anti)	11.75(s,anti)
		7.32(s,syn)	11.47(s,syn)

* solvent DMSO 5% w/w solution.

B. α,β-Acetylenic Ketoximes

1. Method Used in Present Study

The α,β-acetylenic ketoximes were prepared and isolated by the method developed in this laboratory.[20,24,25] This consisted in reacting acetylenic Grignard reagents with hydroxamoyl chlorides as indicated in the following sequence:

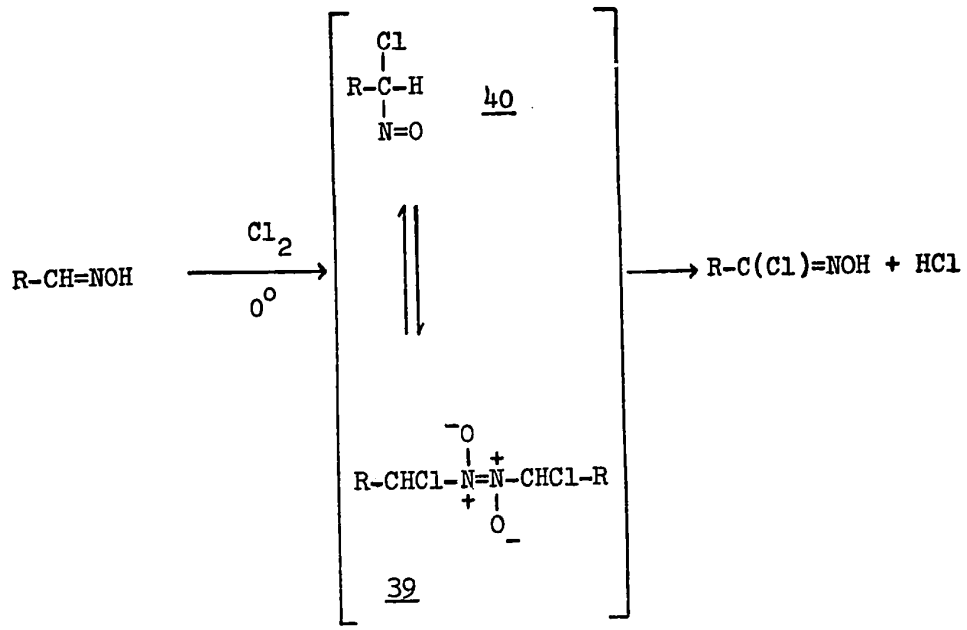
$$R\text{-}\underset{\underset{NOH}{\|}}{C}\text{-}Cl + 2\ R'\text{-}C{\equiv}C\text{-}MgBr \xrightarrow[Et_2O]{0^\circ} R\text{-}\underset{\underset{NOH}{\|}}{C}\text{-}C{\equiv}C\text{-}R' + R'C{\equiv}C\text{-}H$$

The reaction has been used earlier for the synthesis of 3,5-disubstituted isoxazoles by Palazzo[16] and more recently, with minor modifications, by Feuer and Markofsky.[18] However, in these reports no attempts were made to isolate the intermediate oximes. In the present study a dry ethereal solution of the hydroxamoyl chloride (prepared from the corresponding aldoxime) was allowed to react with the acetylenic Grignard reagent at 0°, following which the reaction mixture was worked up by treatment with 10% sulfuric acid or saturated ammonium chloride solution. The solvent was then removed under reduced pressure at room temperature to yield the acetylenic ketoxime. The oxime obtained in this manner was uncontaminated with any of the isomeric isoxazole and was shown to be only the syn isomer (OH and C≡C cis). The only contaminant, the terminal acetylene,being a gas or a low boiling liquid in most cases, was easily removed under reduced pressure at room temperature. The method seems to be of general applicability as evidenced by the

reasonably good yields obtained (cf. Table III).

The hydroxamoyl chlorides were prepared by one of two methods for use in the preparation of α,β-acetylenic ketoximes. Aliphatic aldoximes and other partially water soluble aldoximes were treated in an 8.6N HCl solution at 0^0 with chlorine gas for approximately 15 minutes.[41] Water insoluble aromatic aldoximes were dissolved in chloroform and treated with chlorine gas at 0^o for 30 minutes.[42] In some cases hydroxamoyl chlorides were obtained as crystalline solids but no attempts were made to investigate them further. They were used immediately as ether solutions in the preparation of α,β-acetylenic ketoximes.

The chlorination of aldoximes has been postulated to proceed through the chloronitroso intermediate 40.[43] However, it was later shown that the chloronitroso dimer 39 is first formed[44] and in solution is in equilibrium with its monomer 40,[44,45] which slowly



isomerizes to the hydroxamoyl chloride.

There has been disagreement as to whether there is retention of configuration in the product hydroxamoyl chloride, that is, whether a syn aldoxime gives a syn hydroxamoyl chloride (H and Cl cis) and an anti aldoxime the anti hydroxamoyl chloride. Casnati and Ricca[44] have shown by nmr spectroscopy that for acetaldoxime (R = Me), the two isomeric hydroxamoyl chlorides were obtained. However, Kinney and co-workers[46] demonstrated that starting with either syn or anti p-methoxybenzaldoxime (R = p-MeOPh), only one hydroxamoyl chloride is obtained and that it is the syn isomer.

It has been observed in the present study that although phenylacetaldoxime (R = $PhCH_2$) exists predominantly as the anti isomer in solution, chlorination and subsequent reaction with the Grignard reagent from phenylacetylene produced the α,β-acetylenic ketoxime in which the OH group had a syn disposition with respect to the triple bond. Configuration clearly is not maintained in this example and it seems to indicate that in this case syn hydroxamoyl chloride was formed from anti phenylacetaldoxime.

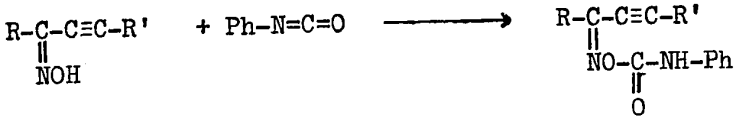
The aldoximes required for the preparation of hydroxamoyl chlorides were prepared by one of the two standard methods from commercially available aldehydes. 1-Methylcyclopentane carboxaldehyde, not commercially available, was synthesized according to the method of Rickborn and Gerkin.[38] Most aliphatic aldoximes were synthesized by the method of Wieland[39] from the respective aldehydes and hydroxylamine hydrochloride in aqueous sodium hydroxide at 0°. Trimethylacetaldoxime and all aromatic aldoximes were prepared by the method of Vogel[40] by refluxing the respective aldehydes, hydroxylamine

hydrochloride and sodium acetate in aqueous methanol. The configuration of the aldoximes as well as the equilibrium amounts of *syn* and *anti* isomers were determined by nmr spectroscopy.

A by-product in the preparation of the acetylenic Grignard reagent is the coupling product, the symmetrical diacetylene, R'-C≡C-C≡C-R' (R' = t-Bu, Ph). This was completely eliminated by resorting to higher dilution of the reaction mixture such that the concentration of the acetylene in the reaction mixture was 10% or less.

The acetylenic oximes are quite stable at low temperatures. Solid oximes have been stored unchanged in a freezer for over three years. Liquid oximes tend to cyclize more readily than the solid ones, the cyclization probably being catalyzed by the small amounts of impurities present. Purification of the crude solid oximes is possible by chromatography on silica gel and careful recrystallization. However, purification of liquid oximes by column chromatography has been unsuccessful. Small amounts of colored impurities always persisted. Distillation, sublimation or chromatography on alumina resulted in cyclization to the isomeric isoxazoles.

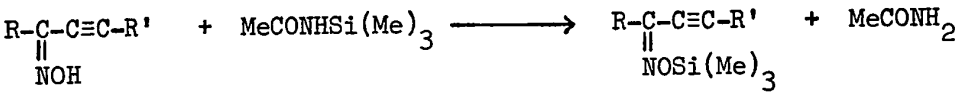
Derivatives of the oximes were prepared in an effort to characterize them or to purify the crude products. Tedious separation procedures involving column chromatography limited the usefulness of these preparations. Oxime carbamates 41 were prepared by treating the oximes with phenylisocyanate.



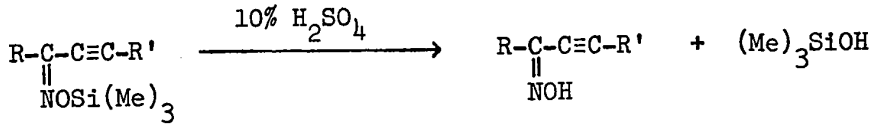
41

Oximes gave solid carbamates quite readily but in some cases the diphenyl urea impurity inevitably present could not be readily separated by column chromatography.

The O-trimethylsilyl ethers of the oximes 43 were obtained from N-trimethylsilyl acetamide 42;[48] however separation of the free oximes from trimethylsilanol 44 rendered the scheme impractical.

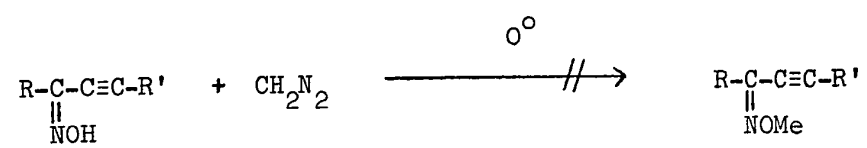


42 43



43 44

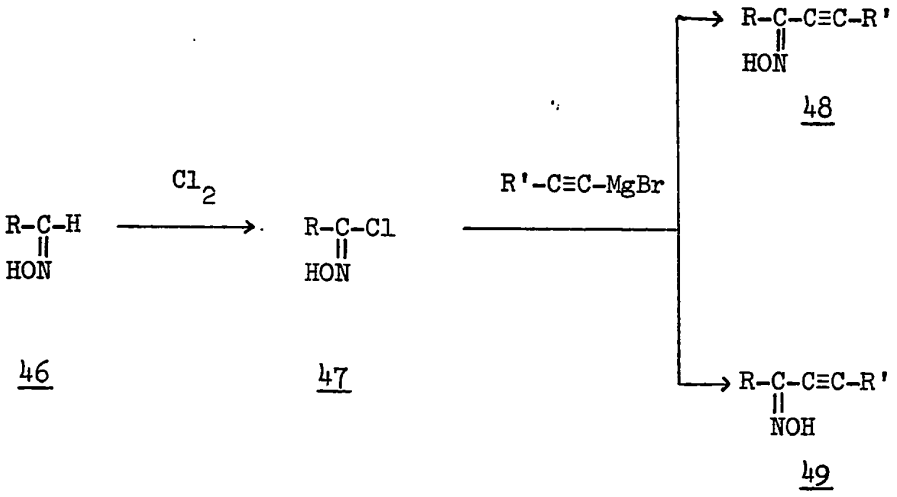
The preparation of the O-methyl ethers 45 of the oximes was attempted by reacting the oximes with diazomethane. However, only the corresponding isoxazoles were obtained.



45

Isoxazole formation was probably catalyzed by traces of base used in the preparation of diazomethane from Diazald.

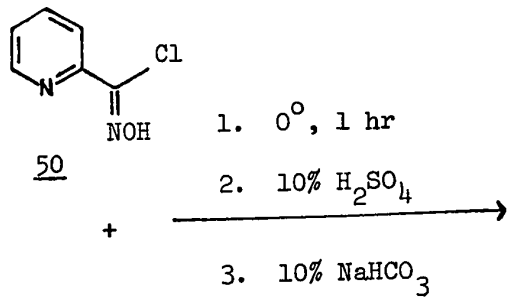
Since all α,β-acetylenic ketoximes prepared thus far were of the syn configuration 49, it was interesting to see whether an anti ketoxime 48 could be prepared starting from an anti-aldoxime 46. When 46 (R = $PhCH_2$) was used, the oxime obtained was shown to have the syn configuration 49 (R = $PhCH_2$, R' = Ph) by Beckmann rearrangement studies.



However, when 46 (R = Ph) was used, a crude yellow solid was obtained and its ir spectrum was identical to the ir spectrum of the previously prepared oxime 49 (R = Ph, R' = Me). Surprisingly, before other data could be gathered the material decomposed violently. No reason could be advanced for this strange behavior and the reaction was not attempted again.

In order to provide some diversity in the R group of acetylenic ketoximes it was decided to synthesize the oxime using

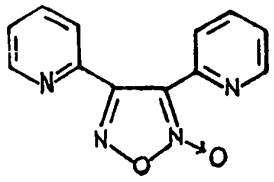
the hydroxamoyl chloride of 2-pyridine aldoxime and the Grignard reagent from phenylacetylene. When the normal workup procedure (10% H_2SO_4) was used the products isolated were the furoxan 51 and 2-pyridine-carboxamide 52 in addition to phenylacetylene. The furoxan 51 obviously is the product of dimerization of the nitrile oxide derived from the hydroxamoyl chloride 50. However, the origin of the amide 52 is not immediately obvious. When saturated



50

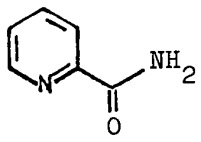
+

2 Ph-C≡C-MgBr



51

+

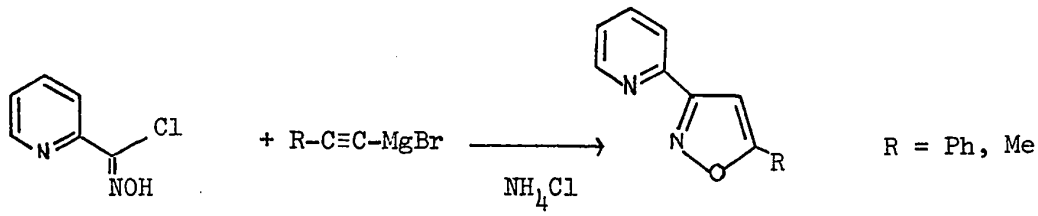


52

+

Ph-C≡C-H

NH_4Cl solution was used for the workup, only the corresponding isoxazole (R = Ph, Me) could be obtained.



50 53

Further work using hydroxamoyl chlorides of other heterocyclic systems is necessary before any generalization can be made on the failure to obtain the expected acetylenic ketoxime by this procedure.

The ir spectra of α,β-acetylenic ketoximes show the characteristic OH and C≡C stretching frequencies (cf. Table III). Detailed discussion of the inter- and intramolecularly hydrogen bonded OH frequencies at 3580 cm^{-1} and 3280 cm^{-1} is provided in a later section.

All oximes gave nmr spectra consistent with the structures proposed. Of special note is the chemical shift of the OH proton in 5% w/w DMSO solution. Most simple oximes and many containing an additional functional group exhibit a hydroxyl proton resonance signal for which the chemical shift value is essentially concentration independent and thus characteristic of the particular oxime.[33] Also, syn and anti isomers show well resolved OH proton singlets in DMSO.[33] Since all ketoximes prepared show only a single OH proton signal, only one isomer of the oxime is produced. This is also substantiated by low temperature nmr spectra ($CHCl_3$, -42°) which showed a gradual sharpening up of the OH proton resonance with lowering of the

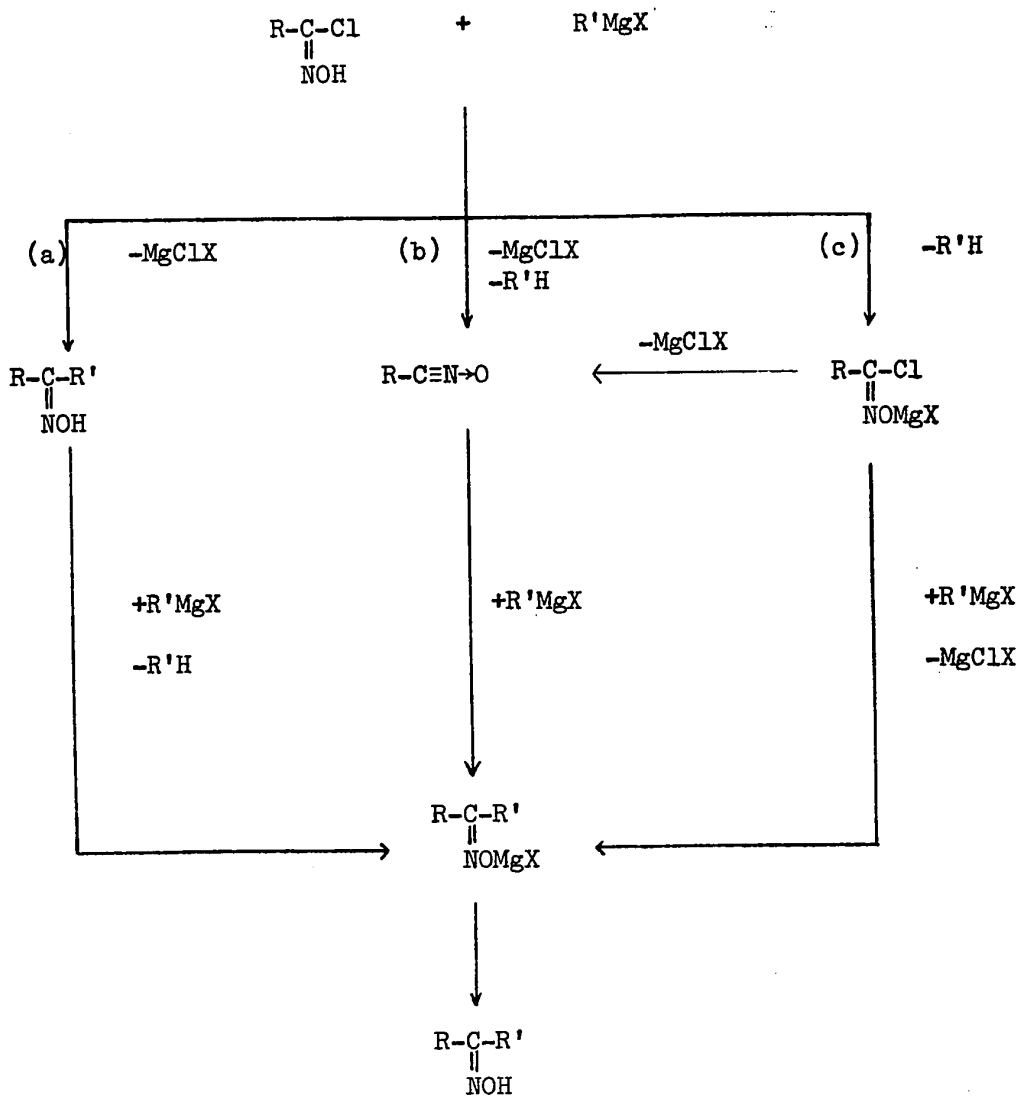
temperature. The opposite behavior would be expected if two isomers were present and proton exchange were occurring.

Table III shows the chemical shifts of the OH proton in DMSO. The notable feature is that for R = alkyl the chemical shift is smaller than when R = aromatic or substituted aromatic. Also for R' = alkyl the chemical shift is smaller than when R' = Ph. For solid oximes the chemical shifts of the OH protons lie within a narrow range 0.06 ppm (e.g. R = alkyl, R' = Ph). There is also fair agreement for liquid oximes. The small range (0.16 ppm) could be attributable to the fact that sharp OH proton resonances were not always obtained for the crude liquid oximes.

The reaction of Grignard reagents with hydroxamoyl chlorides has been postulated to proceed by one of the following pathways:[16] a) nucleophilic substitution of the Cl atom followed by the ketoxime salt formation, b) an elimination-addition sequence involving an intermediate nitrile oxide, and c) primary formation of the chloro-oxime salt, which could either dehydrochlorinate to the nitrile oxide or undergo a nucleophilic attack (Scheme I). However, it was reported that no definite evidence was available to favor any of these possible routes mentioned.[16,50] The present work on acetylenic oximes allows for a more definite appraisal of the reaction mechanism postulated above.

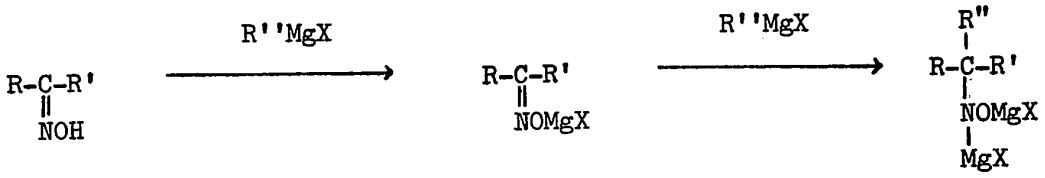
Reactions involving nitrile oxide intermediates inevitably produce furoxans, the nitrile oxide dimers.[21] Since no trace of any nitrile oxides or furoxans has ever been detected in the present work, pathway b) could probably be eliminated. Pathways a) and c) differ only in the preference of the Grignard reagent to undergo

Scheme 1. Postulated Mechanisms for the reaction of Grignard reagents with Hydroxamoyl Chlorides.



nucleophilic attack or salt formation. Grignard reagents react rapidly with the acidic hydroxyl proton of ketoximes to form oxime

salts, which slowly undergo nucleophilic addition.[51]



Hydroxamoyl chlorides, on the other hand, undergo nucleophilic substitution. Although the Cl atom is expected to activate the imino carbon to nucleophilic attack, nucleophilic substitution at unsaturated carbon is known to proceed at slow to moderate rates.[52] The relative rates of reaction should therefore allow for preferential chloro-oxime salt formation either followed by or with simultaneous nucleophilic substitution as postulated in path (c).

TABLE III

α,β-ACETYLENIC KETOXIMES (R-C(=NOH)-C≡C-R', R' = Ph)

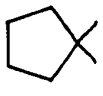
R	%Yield	mp°	IR($CHCl_3$) cm^{-1} νOH	IR($CHCl_3$) cm^{-1} νC≡C	NMR* δOH (ppm)
Me	35	liquid	3600, 3295	2230	11.71
Et	36	liquid	3580, 3280	2220	11.55
n-Pr	45	liquid	3580, 3280	2220	11.70
i-Pr	61	89-90	3580, 3295	2220	11.60
sec-Bu	51	82-3	3595, 3290	2220	11.58
t-Bu	69	102-3	3600, 3300	2220	11.62
MeCH(Ph)	39	81-2	3590, 3300	2210	11.64
$PhCH_2$	35	103-4	3570, 3280	2220, 2180	11.62
Ph	70	100-1	3580, 3300	2220	12.28
p-MePh	45	95-6	3560, 3280	2220, 2185	12.33
p-MeOPh	60	111-2	3560, 3270	2225, 2195	12.30
p-i-PrPh	34	99-100	3565, 3280	2220	12.32
 Me	70	liquid	3570, 3300	2220	11.65

TABLE III(cont'd.)

α,β-ACETYLENIC KETOXIMES ($R-\underset{\underset{NOH}{\|}}{C}-C\equiv C-R'$, R' = Me)

R	%Yield	mp°	IR($CHCl_3$) cm^{-1} νOH	IR($CHCl_3$) cm^{-1} νC≡C	NMR* δOH (ppm)
Et	55	liquid	3580, 3290	2220	-
n-Pr	83	liquid	3570, 3280	2220	11.18
i-Pr	47	liquid	3600, 3300	2220	11.23
sec-Bu	69	liquid	3570, 3280	2230	11.20
t-Bu	68	81-2	3600, 3300	2235	11.23
MeCH(Ph)	56	87-8	3590, 3300	2230	11.25
Ph	40	88-9	3560, 3280	2260, 2225	11.82
p-ClPh	68	96-8	3560, 3260	2260, 2225	11.85
p-MePh	75	liquid	3570, 3280	2260, 2225	11.70
p-i-PrPh	74	liquid	3565, 3260	2260, 2225	11.75

α,β-ACETYLENIC KETOXIMES ($R-\underset{\underset{NOH}{\|}}{C}-C\equiv C-R'$, R' = t-Bu)

i-Pr	65	liquid	3580, 3290	2210	11.33
sec-Bu	69	liquid	3590, 3300	2230	11.65
t-Bu	67	liquid	3585, 3310	2230	11.70
Ph	85	liquid	3560, 3280	2220	--

α,β-ACETYLENIC KETOXIMES (R-C(=NOH)-C≡C-R', R' = Et)

R	%Yield	mp°	IR($CHCl_3$) cm^{-1} νOH	IR($CHCl_3$) cm^{-1} νC≡C	NMR* δOH (ppm)
i-Pr	78	liquid	3570, 3300	2230	11.20
Ph	71	liquid	3570, 3300	2260, 2230	11.75
MeCH(Ph)	70	liquid	3585, 3300	2240, 2225	11.30

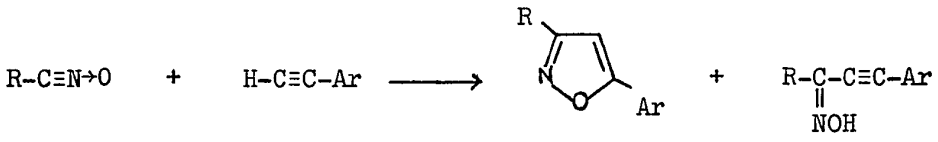
α,β-ACETYLENIC KETOXIMES (R-C(=NOH)-C≡C-R', R' = p-MeOPh)

R	%Yield	mp°	IR($CHCl_3$) cm^{-1} νOH	IR($CHCl_3$) cm^{-1} νC≡C	NMR* δOH (ppm)
i-Pr	68	liquid	3570, 3300	2210	--

* solvent DMSO

2. Alternate Method of Preparation.

While the present investigation was in progress the isolation of the following ketoximes as by-products in the reaction of nitrile oxides with terminal acetylenes was reported.[21]



54 a-g 55 a-g

a; R = Me; Ar = Ph

b; R = Et; Ar = Ph

c; R = Ar = Ph

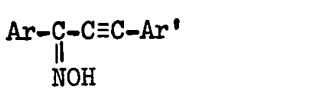
d; R = Mesityl; Ar = Ph

e; R = Ph; Ar = α-Naphthyl (18% yield)

f; R = p-BrPh; Ar = α-Naphthyl (15% yield)

g; R = Ph; Ar = Mesityl (24% yield)

It was reported that oximes 55 a-b were too unstable to be purified and characterized and hence their yields could not be calculated. Following this report other workers have utilized this method for obtaining other α,β-acetylenic ketoximes. Dondoni et al. obtained oximes 56 a-b in 45% and 16% yields respectively.[23,53]

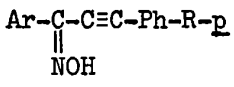


Ar' = p-ClPh

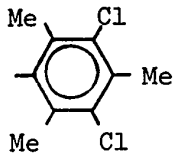
a; Ar = Mesityl (45%)
b; Ar = Ph (16%)

56 a-b

Beltrame et al.[54] obtained oximes 57 a-g. Yields were not reported. However, it was commented that 57a was the main reaction product and that oximes 57 f-g could not be isolated.



57 a-g

Ar = 

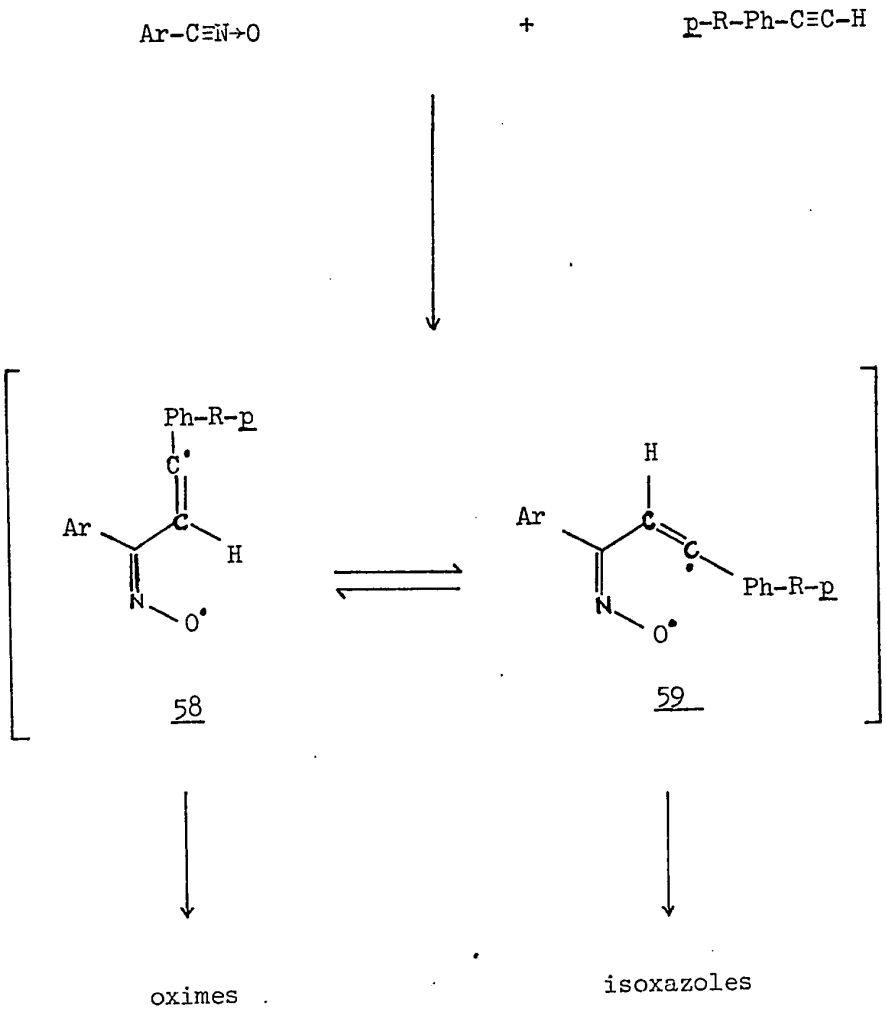
57 a-g

a; R = NMe_2
b; R = OMe
c; R = Me
d; R = H
e; R = Cl
f; R = Br
g; R = NO_2

There are obvious limitations to this method. The acetylenic oximes are produced only as minor products in the reaction, the major products being the isoxazoles, except for 56a and 57a. Isolation of products is only possible by column chromatography (55e-g, 56a-b), and by preparative tlc (55a-d, 57a-g). The low yields and the cumbersome isolation procedure severely limits the usefulness of this procedure.

These acetylenic oximes have been postulated to arise from a reaction concurrent with the one that yields isoxazoles.[21,23,53,54]

The biradical intermediates 58 and 59 were proposed to explain the products.



3. O-Deuterated Acetylenic Oximes

Some O-deuterated oximes were prepared for use in mechanistic studies of the Beckmann rearrangement reaction and for studies of the intramolecular π-hydrogen bonding of acetylenic oximes. The exchange of protium in the hydroxyl group of the oxime by deuterium was readily accomplished by stirring a solution of the oxime in anhydrous ether with deuterium oxide (99.8% D). The process was generally repeated two more times. The deuterated oximes were dried overnight in a vacuum desiccator over P_2O_5 before ir and nmr spectra were recorded. The ir spectra showed the characteristic O-D stretching vibrations. The percentage deuterium incorporation was calculated using nmr spectroscopy. These data are summarized in Table IV.

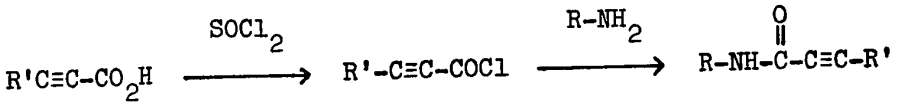
TABLE IV

(O-DEUTERATED ACETYLENIC KETOXIMES (R-C(=NOH)-C≡C-R'))

			IR(CCl_4) cm^{-1}	
R	R'	%D	νC≡C	νO-D
i-Pr	Ph	98	2210	2650, 2420
Ph	Ph	80	2220	2650, 2430
MeCH(Ph)	Ph	94	2220	2650, 2430
p-i-PrPh	Ph	83	2220	2650, 2425
Ph	Me	98	2230	2650, 2430

C. α,β-Acetylenic Amides

The synthesis of some authentic α,β-acetylenic secondary amides of the type 30 was predicated by the fact that these were required for comparison with the products obtained in the Beckmann rearrangement studies of the α,β-acetylenic ketoximes, and also because they are relatively unknown in the chemical literature. There seem to be only ten α,β-acetylenic secondary amides reported in the literature,[30,55] and these were all prepared by the reaction of the acetylenic acid chloride 61 with the appropriate primary amine.



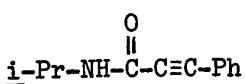
60 61 30

Although fairly good yields (60-70%) were reported[55] it was pointed out that the acid chloride 61 (R = Ph) was very unstable and was used without purification.[56] In the present investigation the acid

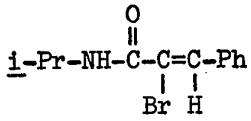
R = i-Pr, R' = Me

62 63

chlorides 61 (R = Ph, Me) were obtained in only less than 10% yields by this method. Furthermore, reaction of the crude acid chloride with isopropylamine afforded, in addition to the acetylenic amide 30, the two isomeric olefinic amides 62 and 63. When commercially available phenylpropiolyl chloride 61 (R = Ph; Pfaltz and Bauer, Inc., Flushing, New York) was reacted with isopropylamine, a mixture of two amides (ca. 1:1 ratio) resulted and these were separated by chromatography. One of the products was the expected acetylenic amide 64; the other was shown to be N-isopropyl-cis-α-bromocinnamide 65 by comparison with an authentic sample prepared



64

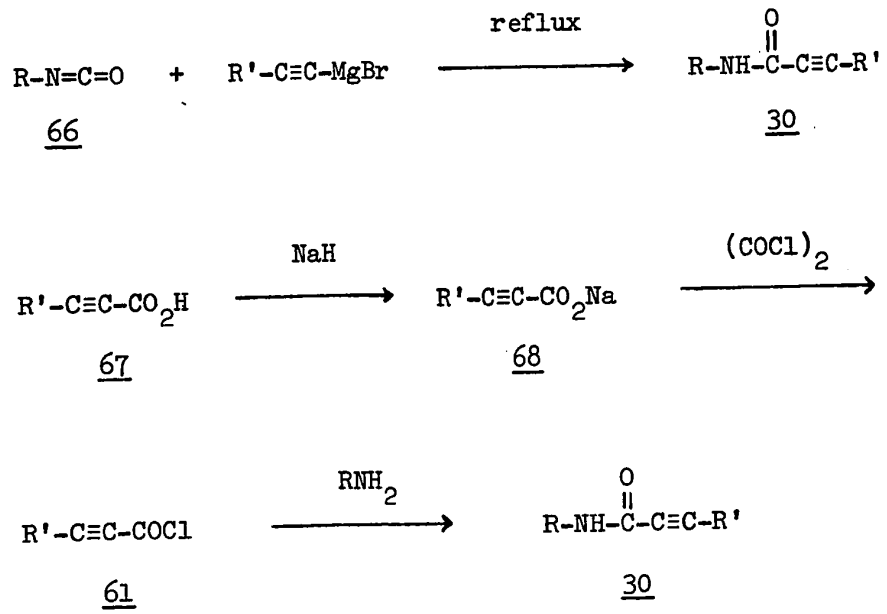


65

independently from cis-α-bromocinnamoyl chloride and isopropylamine. Evidently the commercial sample of phenylpropiolyl chloride must have contained a considerable amount of cis-α-bromocinnamoyl chloride. Because of this complication, and also because of the high cost of the material, the acid chloride route was not explored further.

Alternative procedures were therefore sought for the preparation of the acetylenic amides. The reaction of acetylenic Grignard reagents with the appropriate isocyanates 66, and the

reaction of the sodium salt[58,59] of the acetylenic carboxylic acids 68 with oxalyl chloride followed by reaction with the primary amines, were found to yield the required acetylenic amides without complication.



All the isocyanates 66 used were commercially available and were used unpurified, except for phenyl- (66, R = Ph) and p-tolyl- (66, R = p-MePh) isocyanates. The yields of the acetylenic amides ranged from poor to excellent. The main by-products of the reaction were the disubstituted ureas, the hydrolysis products of the isocyanates. The limitations of this method are the availability of the isocyanates, the terminal acetylenes, and the presence in the product of the urea impurities, which have to be removed by chromatography.

In the second method, the sodium salts 68 were easily

prepared from the acetylenic acids 67 by treatment with sodium hydride. Acid chlorides 61 were then prepared from these sodium salts at room temperature by reaction with oxalyl chloride.[58,59] The acid chlorides thus obtained were used without further purification and were found to react readily with the amine. In the two cases studied (30, R = MeCH(Ph), R' = Me, Et), the yields of acetylenic amides obtained were rather low.

The characteristic absorptions in the ir spectra of the acetylenic amides are given in Table V. The possibility of intramolecular π-hydrogen bonding involving the NH and the C≡C groups is discussed in a later section.

The uv spectra of the acetylenic amides are summarized in Table VI. For amides in which R = R' = alkyl, only one intense absorption at approximately 210 nm is observed. However, for R = alkyl and R' = Ph and R = R' = Ph, an additional equally intense absorption is observed at approximately 260-280 nm. The molar extinction coefficient (ε) is greater than 10,000 in all cases and these values are in good agreement with the α,β-unsaturation present in these amides.[60]

The nmr spectra of the acetylenic amides are consistent with their structures and are summarized in Table V. Only the NH proton resonance is shown in Table V and the values agree with reported data in that the NH protons of N-alkyl substituted amides resonate at higher field than those of N-phenyl substituted amides.[61]

TABLE V

ACETYLENIC AMIDES ($R-NH-\overset{O}{\overset{\|}{C}}-C\equiv C-R'$, R' = Ph)

R	% Yield	mp°/ bp°(mm)	IR($CHCl_3$)cm^{-1} νNH	νC≡C	νC=O	NMR§ δ NH (ppm)
Me	45	97-8	3445, 3290	2225	1640	7.1
Et	60	62-3	3440, 3300	2220	1640	6.9
i-Pr	72	85-6	3430, 3260	2220	1650	6.4
n-Bu	71	165-175 (1.0)	3440, 3300	2220	1640	7.1
t-Bu	44	69-70	3430, 3300	2225	1655	6.2
(S)MeCH(Ph)	53	110-1	3430, 3280	2220	1645	6.9
(R)MeCH(Ph)	70	110-1	3430, 3280	2220	1645	7.0
Ph	92	127-8	3425, 3280	2220 2250(sh)	1660	8.7
p-MePh	39	141-2	3420, 3280	2220 2240(sh)	1660	10.83*
p-ClPh	38	186-7	3420, 3280	2220 2240(sh)	1660	11.05*

ACETYLENIC AMIDES (R' = Me)

Me	17	58-9	3450, 3310	2260 2220	1650	6.7
Et	50	80-95 (0.6)	3440, 3300	2250	1650	7.6
i-Pr	83	84-8 (0.5)	3430, 3300	2250	1640	7.2
t-Bu	61	101-2	3430, 3300	2250	1650	5.9

TABLE V(cont'd)

ACETYLENIC AMIDES (R' = Me)

R	% Yield	mp°/ bp°(mm)	IR($CHCl_3$)cm^{-1} νNH	νC≡C	νC=O	NMR§ δ NH (ppm)
(±)MeCH(Ph)	12	79-80	3435, 3290	2255	1640	6.7
(R)MeCH(Ph)	58	-	3430, 3290	2255	1640	6.7
(S)MeCH(Ph)	53	-	3430, 3285	2255	1640	6.8
Ph	71	102-3	3420, 3280	2240	1660	8.7
p-MePh	47	130-1	3425, 3280	2240	1660	10.53*
p-ClPh	58	139-40	3420, 3280	2240	1665	10.77

ACETYLENIC AMIDES (R' = Et)

i-Pr	82	94-8 (0.5)	3430, 3300	2235 2200(sh)	1630	7.0
(±)MeCH(Ph)	31	79-80	3430, 3300	2245	1640	7.1
Ph	75	78-9	3420, 3290	2240	1655	8.6
(R)-MeCH(Ph)	78	-	3430, 3290	2245	1640	7.1

ACETYLENIC AMIDES (R' = t-Bu)

(S)MeCH(Ph)	43	87-8	3430, 3290	2225	1640	6.3
(R)-MeCH(Ph)	57	87-8	3430, 3290	2220	1640	6.3

§solvent $CDCl_3$

*measured in DMSO-d_6

TABLE VI

UV SPECTRA OF ACETYLENIC AMIDES (R-NH-C(=O)-C≡C-R')

R	R	UV (95% EtOH) nm λmax (ε)	
Me	Ph	260 (29,700)	207 (31,400)
Et	Ph	261 (21,450)	207 (21,450)
i-Pr	Ph	261 (26,100)	207 (27,350)
n-Bu	Ph	260 (20,500)	207 (22,000)
t-Bu	Ph	259 (22,850)	207 (23,750)
MeCH(Ph)	Ph	262 (18,320)	208 (23,250)
Ph	Ph	283 (26,050)	206 (25,300)
p-MePh	Ph	288 (29,600)	207 (31,450)
p-ClPh	Ph	287 (34,700)	207 (29,300)
Me	Me	-	212 (10,720)
Et	Me	-	213 (13,950)
t-Bu	Me	-	214 (11,420)
MeCH(Ph)	Me	-	210 (17,900)
Ph	Me	263 (21,450)	208 (21,950)
p-MePh	Me	268 (14,620)	209 (13,830)
p-ClPh	Me	267 (21,700)	208 (18,400)
i-Pr	Et	-	215 (12,920)
MeCH(Ph)	Et	-	210 (23,250)
Ph	Et	264 (23,700)	208 (23,700)
MeCH(Ph)	t-Bu	-	210 (13,220)

D. Authentic Samples: Acrylic Acid Derivatives.

During the course of the Beckmann rearrangement studies of the α,β-acetylenic ketoximes it became apparent that the product amides isolated were those in which the triple bond had suffered addition of the elements of HCl or Br_2 (depending on the reagent used) during the reaction. It was therefore imperative to synthesize independently authentic samples of the halogen-substituted amides for establishing the identities of the reaction products by comparison. The various amides were synthesized from the corresponding halogen-substituted acids by reaction of their acid chlorides with appropriate amines.

1. Haloacrylic Acids.

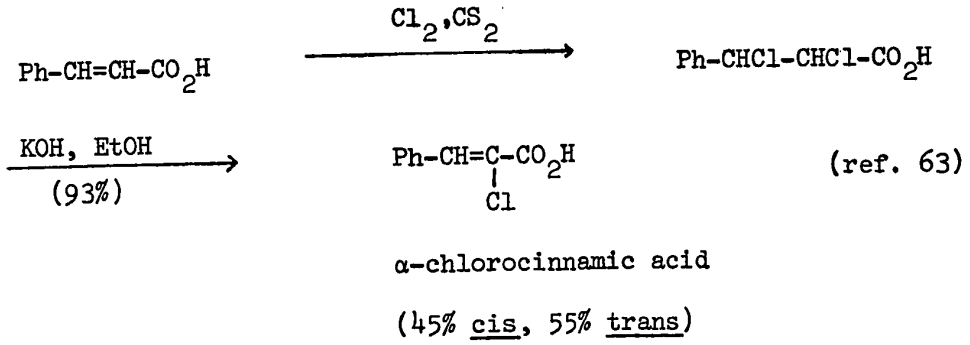
The α-chloro-, the β-chloro-, the α-bromo-, and the β-bromocinnamic acids (each as a mixture of cis and trans isomers*) were prepared, and the isomers in each case separated by the barium salt method as described in the literature.[62-65] The reaction sequences with the yields and the isomer distribution in each case are indicated in the following equations.

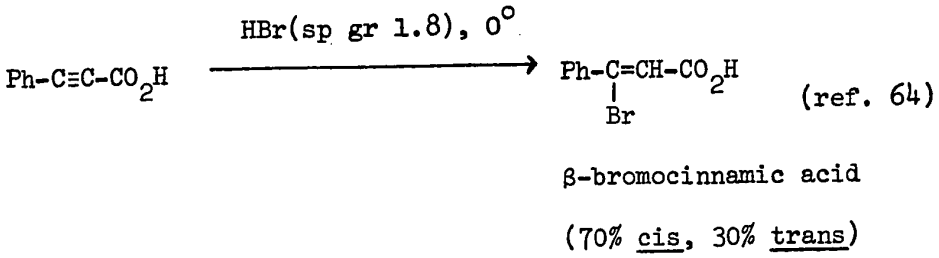
$$Ph\text{-}CO\text{-}CH_2\text{-}CO_2Et \xrightarrow[(66\%)]{PCl_5,\ PCl_3} Ph\text{-}\underset{\displaystyle Cl}{\overset{|}{C}}=CH\text{-}CO_2H \quad \text{(ref. 62)}$$

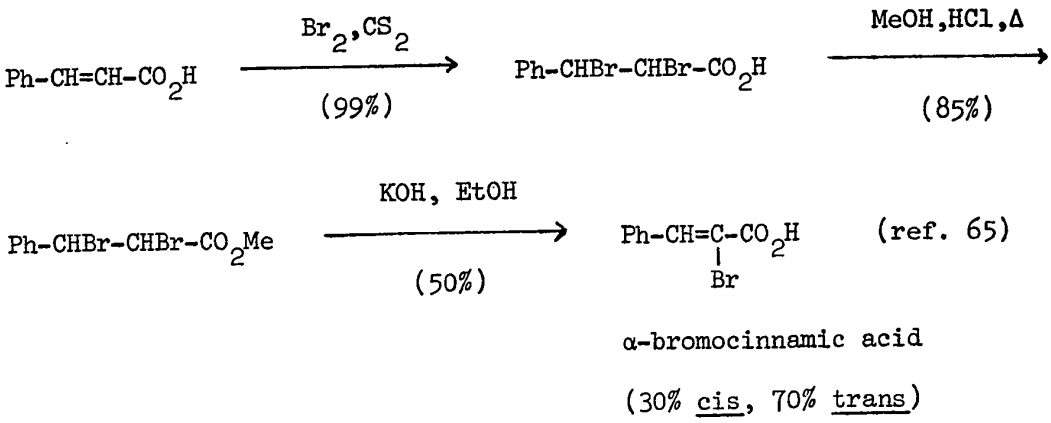
β-chlorocinnamic acid
(20% cis, 80% trans)

---

*Throughout this dissertation the cis nomenclature in the case of the α-, and β-halo-and α,β-dibromoacids refers to the structure in which the hydrogen atom and the halogen atom, or the two bromine atoms, occupy the same side of the double bond; the trans notation refers to the opposite geometry.







It must be pointed out that the addition of HBr to phenylpropiolic acid proceeded only if the specific gravity of the hydrobromic acid solution used was 1.8; the reaction was ineffective with solutions

of lower specific gravity.[64] In the synthesis of the α-bromocinnamic acids the esterification step before dehydrobromination was necessary to obtain increased yields of the trans isomer. If the dehydrobromination was carried out directly on the dibromoacid the cis and trans isomers were obtained in a 87:13 ratio.[65]

The α,β-dibromocinnamic acids were prepared by the addition of bromine to phenylpropiolic acid and the cis and trans isomers were separated by way of their sodium salts according to the method of Stoermer and Heymann.[66] Separation of the isomers was also attempted via the barium salts but the method was found to be ineffective. The

$$Ph\text{-}C{\equiv}C\text{-}CO_2H \xrightarrow[(94\%)]{Br_2, CS_2} Ph\text{-}\underset{\displaystyle Br}{\underset{|}{C}}{=}CBr\text{-}CO_2H$$

α,β-dibromocinnamic

(63% cis, 37% trans)

uv spectra of these acids were studied by Mangini and Montanari,[67] and the cis isomer was reported to absorb at slightly longer wavelengths and to have higher extinction coefficients.

The β-chlorocrotonic acids were prepared by the procedure of Jones and co-workers.[68] The cis and trans acids were separated by steam distillation. It was found however, that sublimation of the cis isomer, as suggested for its purification,[68] yielded not the pure cis isomer but rather a mixture of cis and trans acids in a 60:40 ratio as determined by nmr spectroscopy. This therefore proved to be a convenient procedure for obtaining additional amounts of the trans

isomer.

$$CH_3\text{-}CO\text{-}CH_2\text{-}CO_2Et \xrightarrow[41\%]{PCl_5, C_6H_6} CH_3\text{-}\underset{Cl}{C}\text{=}CH\text{-}CO_2H$$

β-chlorocrotonic acid

(63% cis, 37% trans)

The synthesis of the hitherto unknown 3-chloro-2-pentenoic acids from ethyl propionyl acetate was attempted using the methods of James [62] and Jones and co-workers[68] but the desired acids were not obtained.

$$Et\text{-}CO\text{-}CH_2\text{-}CO_2Et \xrightarrow[\text{or } PCl_5, C_6H_6]{PCl_5, PCl_3} Et\text{-}\underset{Cl}{C}\text{=}\underset{H}{C}\text{-}CO_2H$$

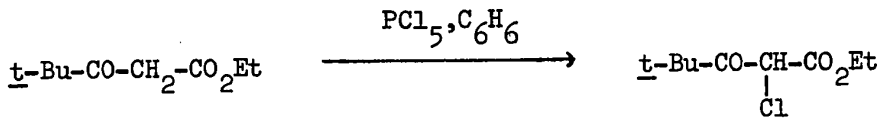
3-chloro-2-pentenoic acid

Cis-3-chloro-4,4-dimethyl-2-pentenoic acid 70 was synthesized in 88% yield by the silver oxide oxidation of the corresponding aldehyde 69.[69-71]

$$t\text{-}Bu\text{-}\underset{Cl}{C}\text{=}\underset{H}{C}\text{-}CHO \xrightarrow[(88\%)]{Ag_2O,\ NaOH,\ RT} t\text{-}Bu\text{-}\underset{Cl}{C}\text{=}\underset{H}{C}\text{-}CO_2H$$

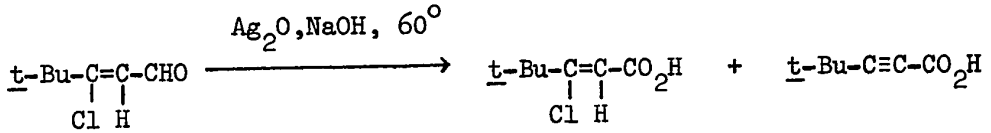
69 70

It was reported[72] that treatment of the β-ketoester 71 with PCl_5 yielded only the chloroester 72. Silver oxide oxidation of 69



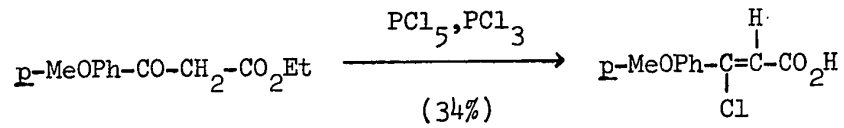
71 72

was found to be sensitive to the reaction temperature. If the oxidation was performed in the normal manner[69,70] at 60°, 10% of the corresponding acetylenic acid 73 was also obtained. However, at room temperature only trace amounts of this acid were detected.



69 70 (90%) 73 (10%)

Trans-β-chloro-p-methoxycinnamic acid 75 was prepared in 34% yield from the β-ketoester[73] 74 by the procedure of James.[62]

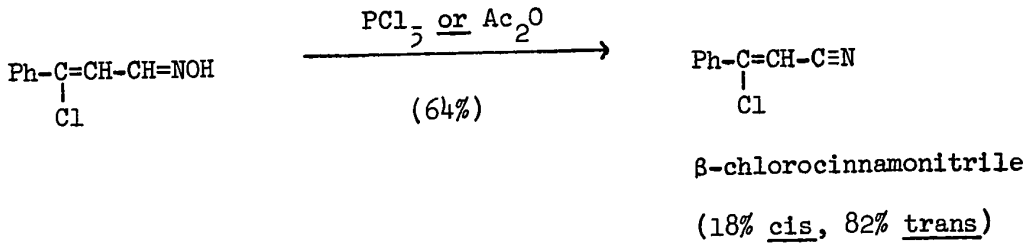


74 75

In this reaction only the trans isomer was obtained. This acid has been reported in the literature[71] but its stereochemistry has not been determined. The trans stereochemistry is assigned in this work by analogy with products obtained from the Beckmann rearrangement work. Further discussion of this point will be left to a later section.

2. Haloacrylonitriles and Aldehydes.

The β-chlorocinnamonitriles were prepared in 64% yield by the procedure of von Auwers and Hugel.[74] Separation of the cis and trans



β-chlorocinnamonitrile

(18% cis, 82% trans)

isomeric nitriles was achieved by column chromatography on acidic alumina. It was found that chromatography on basic alumina resulted in a partial dehydrochlorination yielding some of the corresponding acetylenic nitrile.

The nmr spectral data for the isomeric nitriles are summarized in Table VII.

TABLE VII

NMR SPECTRA OF β-CHLOROCINNAMONITRILES (Ph-C(Cl)=CH-C≡N)

Stereochemistry	δ ($CDCl_3$) Ph	-C=CH-
cis	7.7(m) 7.8(m)	6.0(S)
trans	7.8(m)	6.2(S)

The β-chlorocinnamaldehydes were prepared by the chloroformylation of acetophenone as reported in the literature.[75,76]

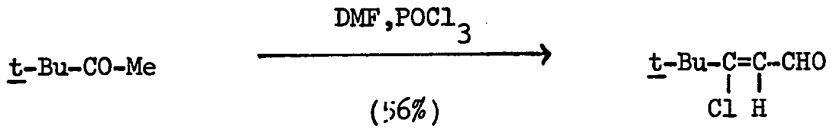
$$\text{Ph-CO-Me} \xrightarrow[(66\%)]{DMF, POCl_3} \text{Ph-C(Cl)=CH-CHO}$$

β-chlorocinnamaldehyde

(17% cis, 83% trans)

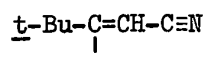
However, in both reports,[75,76] the aldehyde was assumed to be entirely the trans isomer because dehydrochlorination readily occurred under basic conditions.[75] In the present study it was found that both cis and trans aldehydes were formed in a 17:83 ratio as estimated by nmr spectroscopy. The nmr spectral data are shown in Table VIII.

β-Chloro-β-tert-butylacrylaldehyde 76 was similarly[75] prepared in 56% yield. However, only the cis isomer was isolated.

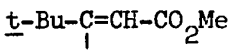


76

This result is in agreement with that of Gardner and Greer,[72] who assigned the cis stereochemistry on the basis of nmr spectroscopy. No details were given of the nmr data. The nmr spectra of cis and trans β-chloro-β-tert-butylacrylonitriles 77 were reported [72] and are included in Table VIII. The signal due to the t-butyl group appears at δ 1.23 and δ 1.42 for the cis and trans nitriles respectively. The measured value for the t-butyl group of the aldehyde is δ1.28. On this basis one is



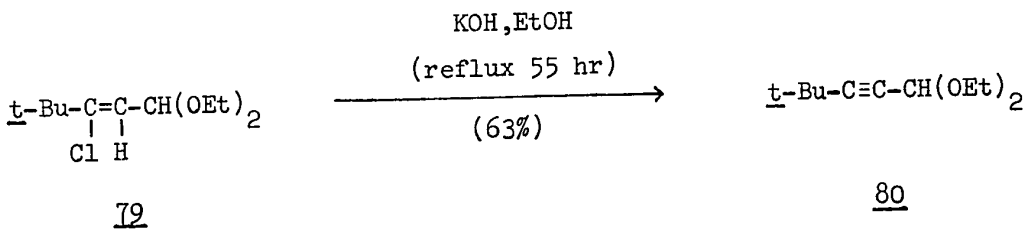
77



78

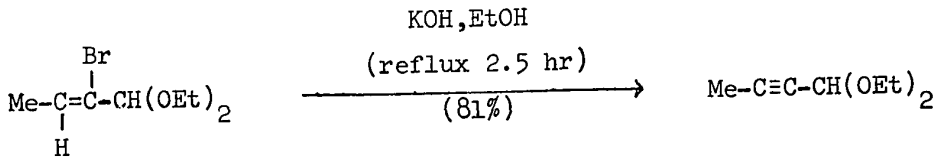
inclined to assign the cis configuration for the nitrile. However, in the nmr spectra of the corresponding methylacrylates[72] 78 (Table VIII), the t-butyl group appears at δ1.24 and δ1.29 for the cis and trans compounds respectively. Thus a definite assignment of stereochemistry cannot be made from the chemical shift values of the t-butyl group alone. A cis configuration is postulated on the basis of indirect chemical evidence. The diethylacetal of

t-butylpropiolaldehyde 80 was required in another connection and was synthesized by the dehydrochlorination of the diethylacetal 79. The considerable length of time (55 hr) required for the



79 80

dehydrochlorination reaction suggests that the hydrogen and chlorine atoms are in a cis relationship in the aldehyde. This result is in sharp contrast to the relatively short period of time (2.5 hr) required for the dehydrobromination of trans α-bromocrotonaldehyde diethyl acetal 81.[4] Elimination reactions of haloolefins to



81

acetylenes are known to proceed best when the elements to be eliminated are located trans.[77]

TABLE VIII

NMR DATA FOR β-CHLOROACRYLIC ALDEHYDES, NITRILES AND ESTERS

(R-C(Cl)=CH-X)

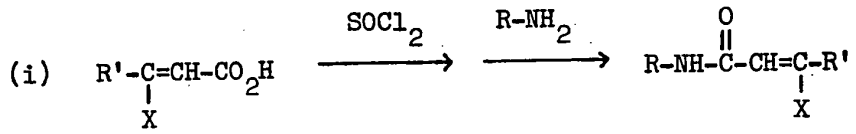
X	Stereochemistry	R	δ (ppm) R	-C=C-H	CHO
CHO	cis	Ph	7.80(m)	6.75(d)	9.80(d)
	trans	Ph	7.80(m)	6.90(d)	10.58(d)
CHO	cis	t-Bu	1.28(s)	6.17(d)	10.17(d)
C≡N	cis	t-Bu	1.23(s)	5.52(s)	
	trans	t-Bu	1.42(s)	5.58(s)	
CO_2Me	cis	t-Bu	1.24(s)	5.96(s)	
	trans	t-Bu	1.29(s)	5.98(s)	

s = singlet, d = doublet, m = multiplet.

3. Haloacrylic Amides

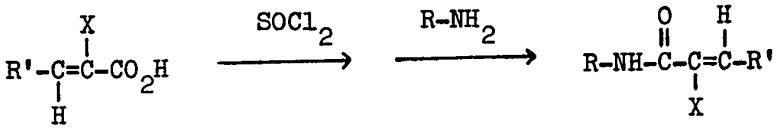
Cis-and trans-haloacrylic amides were prepared by the general methods outlined in the following equations. The reaction conditions followed were those of Yokoyama et al.[55] who used this general method for the synthesis of some α,β-acetylenic amides from the corresponding carboxylic acids.

It was found that cis-α-chloro- and bromo-cinnamic acids partly isomerized when refluxed with thionyl chloride and yielded

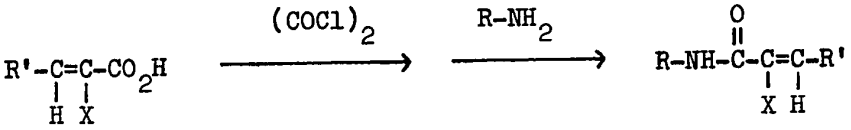
(i) 

R' = Me, t-Bu, Ph, p-MeOPh

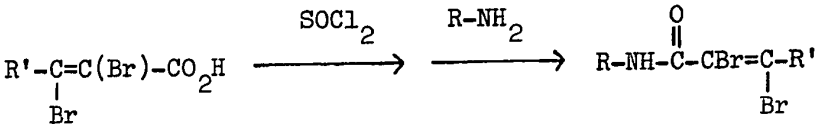
X = Cl, Br

(ii) 

R' = Ph; X = Cl, Br

(iii) 

R' = Ph; X = Cl, Br

(iv) 

R' = Ph

a mixture of the cis-and trans-acid chlorides in each case as determined by nmr spectroscopy. In the case of the cis-α-

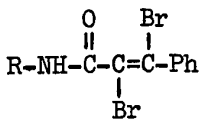
chlorocinnamic acid, a 2-hour reflux with thionyl chloride in benzene gave the corresponding cis- and trans- acid chlorides in a 35:65 ratio. However, the same acid, when refluxed in benzene in the absence of thionyl chloride for 2 hours, did not undergo any detectable isomerization to the trans- acid, indicating that heating alone did not cause the isomerization. The problem of isomerization was eliminated by using oxalyl chloride in place of thionyl chloride. Rearrangements have been previously reported when thionyl chloride is used for acid chloride preparation.[78,79]

The data for the β-halo-, α-halo- and α,β-dibromoacrylic amides that were synthesized are summarized in Tables IX-XV. The yields reported are by no means the optimum ones for these amides because these compounds were synthesized on very small scales only to serve as authentic samples for comparison with reaction products.

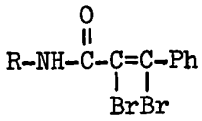
The nmr spectra of these haloacrylic amides are consistent with their proposed structures. In the β-haloacrylic amide series (R' = Ph, X = Cl), the vinyl proton of the cis-isomer is slightly more deshielded than in the trans-isomer ($\Delta\delta$ = 0.2 ppm). Also, the aromatic protons (R' = Ph) appear as a "singlet" in the cis-isomer and as a complex multiplet in the trans-isomer. For the case where R' = Ph, X = Br, the chemical shift for the vinylic proton is unchanged in both isomers; however, when R = i-Pr, the gem-dimethyl groups appear at higher fields in the cis-isomer than in the trans isomer ($\Delta\delta$ = 0.3 ppm), and for R' = Me, X = Cl, the chemical shifts of the vinylic protons differ by only 0.05 ppm in both isomers. The methyl group (R' = Me) is more deshielded in the cis-isomer by approximately 0.3 ppm. In the α-haloacrylic amide series (R' = Ph,

X = Cl,Br), the vinylic proton is strongly deshielded in the trans-isomer by 1.1 ppm. Also, the aromatic protons (R' = Ph) appear as a "singlet" in the cis-isomers and as a complex multiplet in the trans-isomers. In the α,β-dibromoacrylic amide series, the aromatic protons (R' = Ph) in both isomers appear as partly resolved doublets centered around δ7.4. However, when R = i-Pr, there is greater shielding of this group in the cis-isomer by 0.5 ppm.

The uv data for the α,β-dibromoacrylic amides are summarized in Table XV. Normally one would expect the trans-isomer to absorb at slightly longer wavelengths and to exhibit higher molar extinction coefficients than the corresponding cis-isomers.[80] The amides 82 and 83 were thus expected to show this behavior. In this case,



82 (trans)



83 (cis)

however, the cis- amide 83 absorbed at a slightly longer wavelength and showed a higher extinction coefficient (cf. Table XV). This same trend was manifested in the corresponding dibromocarboxylic acids.[67]

TABLE IX

β-HALOACRYLIC AMIDES (R-NH-C(=O)-CH=C(X)-R')

R' = Ph; X = Cl

R	Stereochemistry	% Yield	mp°	IR($CHCl_3$) cm^{-1} νNH	νC=O	νC=C
i-Pr	trans	79	96-7	3435, 3300	1650	1620(sh)
i-Pr	cis	65	118-9	3430, 3300	1650	1615(sh)
Ph	trans	81	130-1	3410, 3300	1665	1635(sh)
sec-Bu	trans	72	85-6	3430, 3300	1640	1620(sh)
Et	trans	82	106-7	3440, 3300	1640	1620(sh)
n-Pr	trans	60	57-8	3460, 3320	1650	1625(sh)
Me	trans	75	113-4	3450, 3300	1650	1615(sh)
p-MeOPh	trans	80	144-5	3420, 3300	1655	1635(sh)
p-MePh	trans	85	134-5	3420, 3300	1660	1635(sh)
p-i-PrPh	trans	90	116-7	3420, 3300	1660	1635(sh)
$PhCH_2$	trans	93	88-9	3440, 3300	1650	1610(sh)
MeCH(Ph)	trans	90	101-2	3430, 3300	1650	1620(sh)

R' = Ph; X = Br

i-Pr	trans	85	98-9	3430, 3310	1640	1615(sh)
i-Pr	cis	72	130-1	3430, 3300	1645	1615(sh)
sec-Bu	cis	64	123-4	3425, 3300	1645	1615(sh)
sec-Bu	trans	40	77-8	3430, 3310	1645	1615(sh)

TABLE IX(cont'd)

β-HALOACRYLIC AMIDES (R-NH-C(=O)-CH=C(X)-R')

R' = Me; X = Cl

R	Stereochemistry	% Yield	mp°	IR($CHCl_3$) cm^{-1} νNH	νC=O	νC=C
i-Pr	trans	32	74-5	3430, 3300	1655	1625(sh)
i-Pr	cis	50	85-6	3435, 3300	1660	1625
t-Bu	trans	60	83-4	3435, 3300	1655	1625
t-Bu	cis	27	94-5	3435, 3300	1665	1625
MeCH(Ph)	trans	53	115-6	3430, 3300	1640	
MeCH(Ph)	cis	47	93-4	3430, 3300	1660	1625
sec-Bu	trans	52	62-3	3430, 3300	1655	1620(sh)
sec-Bu	cis	48	68-9	3430, 3320	1660	1625
Et	trans	14	54-5	3440, 3310	1660	1625(sh)
Et	cis	42	57-8	3450, 3320	1660	1625
Me	cis	25	81-2	3460, 3320	1660	1625
Ph	trans	54	122-3	3420, 3300	1670	1625
Ph	cis	24	106-7	3430, 3300	1670	1625
p-i-PrPh	trans	28	76-7	3420, 3310	1660	1635(sh)
p-i-PrPh	cis	30	113-4	3430, 3310	1670	1630
p-ClPh	trans	39	130-1	3420, 3300	1670	1635
p-ClPh	cis	18	135-6	3430, 3310	1675	1630
p-MePh	trans	47	107-8	3425, 3300	1665	1635(sh)
p-MePh	cis	28	101-2	3435, 3320	1670	1630

TABLE IX(cont'd)

β-HALOACRYLIC AMIDES (R-NH-C(=O)-CH=C(X)-R')

R' = t-Bu; X = Cl

R	Stereochemistry	% Yield	mp°	IR($CHCl_3$) cm^{-1} νNH	νC=O	νC=C
i-Pr	cis	51	123-4	3435, 3300	1650	1620(sh)
sec-Bu	cis	87	119-20	3425, 3300	1645	1610(sh)
t-Bu	cis	90	151-2	3430, 3300	1650	1615(sh)
Ph	cis	60	155-6	3425, 3300	1660	1620
MeCH(Ph)	cis	63	140-1	3430, 3300	1650	1615(sh)

R' = p-MeOPh; X = Cl

i-Pr	trans	69	117-8	3430, 3300	1640	

sh = shoulder

TABLE X

α-HALOACRYLIC AMIDES (R-NH-C(=O)-C(X)=CH-R')

R' = Ph; X = Cl

R	Stereochemistry	% Yield	mp°	IR($CHCl_3$) cm^{-1} νNH	νC=O	νC=C
i-Pr	trans	71	84-5	3430, 3300	1655	1615

TABLE X(cont'd)

α-HALOACRYLIC AMIDES (R-NH-C(=O)-C(X)=CH-R')

R' = Ph; X = Cl

R	Stereochemistry	% Yield	mp°	IR($CHCl_3$) cm^{-1} νNH	νC=O	νC=C
i-Pr	cis	62	56-7	3425, 3300	1665	1615

R' = Ph; X = Br

i-Pr	trans	83	110-1	3420, 3300	1650	1610
i-Pr	cis	70	69-70	3430, 3290	1655	--

TABLE XI

α,β-DIBROMOACRYLIC AMIDES (R-NH-C(=O)-C(Br)=C(Br)Ph)

R	Stereochemistry	% Yield	mp°	IR($CHCl_3$) cm^{-1} νNH	νC=O	νC=C
i-Pr	trans	72	143-4	3430, 3300	1665	--
i-Pr	cis	95	117-8	3430, 3300	1665	--
sec-Bu	trans	81	143-4	3430, 3300	1665	--
sec-Bu	cis	92	131-2	3425, 3300	1665	--

TABLE XI(cont'd)

α,β-DIBROMOACRYLIC AMIDES (R-NH-C(=O)-C(Br)=C(Br)Ph)

R	Stereochemistry	% Yield	mp°	IR($CHCl_3$) cm^{-1} νNH	νC=O	νC=C
Ph	trans	84	169-70	3420, 3300	1685	--
Ph	cis	66	129-30	3420, 3300	1680	--

TABLE XII

NMR SPECTRA OF β-HALOACRYLIC AMIDES (R-NH-C(=O)-CH=C(X)-R')

R' = Ph; X = Cl

R	Stereochemistry	δ ($CDCl_3$) ppm R	-C=CH-	NH	R'
i-Pr	trans	i-Pr,1.2(d)	6.6	6.7	7.5(m)
i-Pr	cis	i-Pr,0.9(d)	6.4	5.5	7.5(s)
Ph	trans		6.7	8.6	7.5(m)
sec-Bu	trans		6.6	6.3	7.5(m)
Et	trans		6.6	6.5	7.5(m)
n-Pr	trans		6.6	6.7	7.5(m)
Me	trans	Me,2.95(d)	6.6	6.7	7.5(m)
p-MeOPh	trans		6.7	8.6	7.5(m)
p-MePh	trans		6.7	8.7	7.4(m)

TABLE XII(cont'd)

NMR SPECTRA OF β-HALOACRYLIC AMIDES (R-NH-C(=O)-CH=C(X)-R')

R' = Ph; X = Cl

R	Stereochemistry	δ ($CDCl_3$) ppm R	-C=CH-	NH	R'
p-i-PrPh	trans		6.7	8.8	7.4(m)
$PhCH_2$	trans	CH_2,4.45(d)	6.5	7.0	7.3(m)
MeCH(Ph)	trans		6.7	7.2	7.5(m)
R' = Ph; X = Br					
i-Pr	trans	i-Pr,1.2(d)	6.7	6.3	7.4(m)
i-Pr	cis	i-Pr,0.9(d)	6.6	5.2	7.5(s)
sec-Bu	cis		6.6	5.3	7.4(s)
sec-Bu	trans		6.7	6.1	7.4(m)
R' = Me; X = Cl					
i-Pr	trans	i-Pr,1.2	6.05(q)	6.4	2.25(d)
i-Pr	cis	i-Pr,1.1	6.00(q)	6.2	2.55(d)
t-Bu	trans	t-Bu,1.4	6.00(q)	6.1	2.25(d)
t-Bu	cis	t-Bu,1.4	6.00(q)	5.6	2.55(d)
MeCH(Ph)	trans		6.05(q)	6.8	2.20(d)
MeCH(Ph)	cis		6.10(q)	6.8	2.55(d)
sec-Bu	trans		6.00(q)	6.3	2.20(d)
sec-Bu	cis		6.10(q)	6.5	2.55(d)
Et	trans		6.05(q)	6.7	2.55(d)

TABLE XII(cont'd)

NMR SPECTRA OF β-HALOACRYLIC AMIDES (R-NH-C(=O)-CH=C(X)-R')

R' = Ph; X = Cl

R	Stereochemistry	δ ($CDCl_3$) ppm R	-C=CH-	NH	R'
Et	cis		6.05(q)	6.8	2.55(q)
Me	cis	Me,2.85(d)	6.12(q)	6.7	2.60(d)
Ph	trans	Ph,7.5(m)	6.20(q)	8.3	2.25(d)
Ph	cis	Ph,7.4(m)	6.20(q)	7.9	2.60(d)
p-i-PrPh	trans		6.10(q)	8.4	2.18(d)
p-i-PrPh	cis		6.10(q)	7.9	2.60(d)
p-ClPh	trans		6.10(q)	8.2	2.25(d)
p-ClPh	cis		6.12(q)	8.0	2.60(d)
p-MePh	trans		6.15(q)	8.3	2.25(d)
p-MePh	cis		6.20(q)	8.2	2.60(d)
i-Pr	cis	i-Pr,1.2	6.10(s)	6.3	1.2
sec-Bu	cis		6.10(s)	6.3	1.2
t-Bu	cis	t-Bu,1.4	6.05(s)	6.1	1.2
Ph	cis		6.22	8.3	1.2
MeCH(Ph)	cis		6.07(s)	6.7	1.2
R' = p-MeOPh; X = Cl					
i-Pr	trans	i-Pr,1.2	6.47	6.5	

s = singlet; d = doublet; m = multiplet; q = quartet.

TABLE XIII

NMR SPECTRA OF α-HALOACRYLIC AMIDES (R-NH-C(=O)-C(X)=CH-R')

R' = Ph; X = Cl

R	Stereochemistry	δ ($CDCl_3$) ppm R	-C=CH-	NH	R'
i-Pr	trans	i-Pr,1.25	8.1	6.7	7.4, 7.8(m)
i-Pr	cis	i-Pr,1.10	7.0	5.8	7.4(s)

R' = Ph; X = Br

i-Pr	trans	i-Pr,1.25	8.3	6.7	7.4, 7.8(m)
i-Pr	cis	i-Pr,1.0	7.2	5.6	7.4(s)

s = singlet; m = multiplet.

TABLE XIV

NMR SPECTRA OF α,β-DIBROMOACRYLIC AMIDES (R-NH-C(=O)-C(Br)=C(Br)Ph)

R	Stereochemistry	δ*($CDCl_3$) ppm R	NH	Ph
i-Pr	trans	i-Pr,1.3(d)	6.2	7.4(d)
i-Pr	cis	i-Pr,0.8(d)	5.4	7.4(d)
sec-Bu	trans		6.2	7.4(d)

TABLE XIV(cont'd)

NMR SPECTRA OF α,β-DIBROMOACRYLIC AMIDES (R-NH-C(=O)-C(Br)=C(Br)Ph)

R	Stereochemistry	δ*($CDCl_3$) ppm R	NH	Ph
sec-Bu	cis		5.5	7.4(d)
Ph	trans		11.0*	7.6(m)
Ph	cis		10.6*	7.5(m)

*solvent DMSO

d = doublet; m = multiplet.

TABLE XV

UV SPECTRA OF α,β- DIBROMOACRYLIC AMIDES (R-NH-C(=O)-C(Br)=C(Br)Ph)

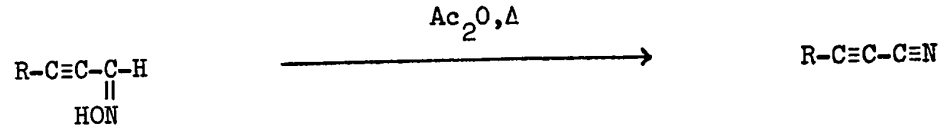
R	Stereochemistry	λ*max (ε)		
i-Pr	trans	207(16,300)	238(10,800)	275(3,075)
i-Pr	cis	211(19,220)	235(sh)	282(5,175)
sec-Bu	trans	208(15,150)	238(9,800)	275(2,702)
sec-Bu	cis	211(17,920)	235(sh)	282(4,190)
Ph	trans	207(29,000)	248(20,600)	
Ph	cis	208(22,300)	228(sh)(18,380)	274(10,520)

*in 95% ethanol

E. Miscellaneous Compounds.

The compounds discussed in this section were synthesized because they were needed as authentic samples for comparison with some reaction products, or to serve as starting materials for the synthesis of other compounds required in the study.

The α,β-acetylenic nitriles 84 (R = Me, t-Bu, Ph) were prepared in good yields by the dehydration of the corresponding acetylenic aldoximes with acetic anhydride according to the



84

procedure of Plaut and Ritter.[81] The nmr spectra of these acetylenic nitriles show only the absorptions of the R group and are therefore less informative than the ir spectra which exhibit the characteristic C≡C and C≡N absorptions. There are few[82] ir spectral data available on this class of compounds and hence unequivocal assignments of the bands are not easy. The ir spectrum of propiolonitrile 84 (R = H) has been reported[82] and the two bands at 2271 cm^{-1} and 2077 cm^{-1} were assigned to the C≡N and C≡C stretching vibrations, respectively. It was further mentioned that each band was mixed to some extent with that due to the vibrations of the other.[82] The characteristic absorptions in the "triple bond" region

for these acetylenic nitriles are indicated in Table XVI. The alkyl acetylenic nitriles (R = Me,t-Bu) exhibit two bands; the weaker band at higher wavenumbers has a relatively lower intensity in the t-butyl compound than in the methyl compound. For the aromatic acetylenic nitrile (R = Ph) two medium to weak bands appear at lower wavenumbers. In all three cases the most intense band is at approximately 2275 $cm.^{-1}$

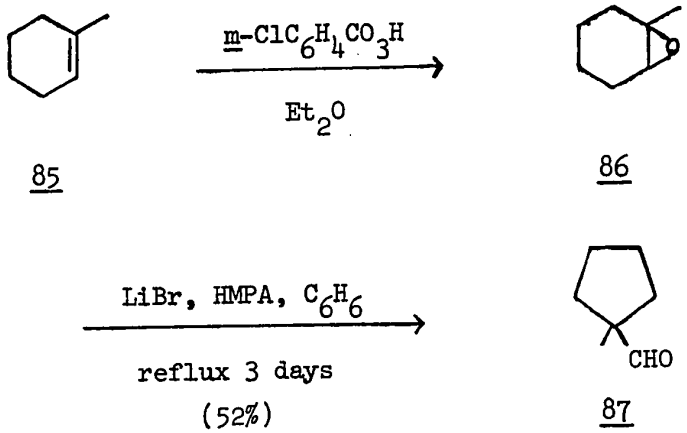
TABLE XVI

α,β-ACETYLENIC NITRILES (R-C≡C-C≡N)

R	%Yield	*Ir ($CHCl_3$) cm^{-1}
Me	87	2335(m), 2270(s)
t-Bu	66	2340(sh), 2285(s)
Ph	51	2275(s), 2210(w), 2150(m)

*Ir band intensities are indicated as medium(m), strong(s) and weak(w).

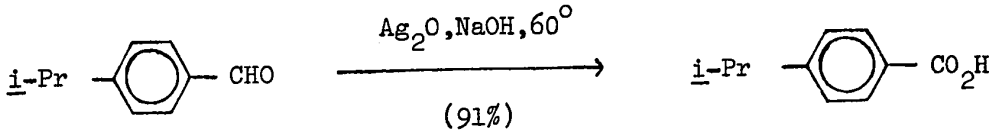
1-Methylcyclopentanecarboxaldehyde 87 was prepared in 52% yield using the procedure of Rickborn and Gerkin.[38] 1-Methylcyclohexene oxide 86, prepared from 1-methylcyclohexene 85,[83,84] was rearranged with lithium bromide in the presence of hexamethylphosphoramide (HMPA) in benzene by this newly developed procedure, and marks the application of this method to laboratory synthesis of the aldehyde.



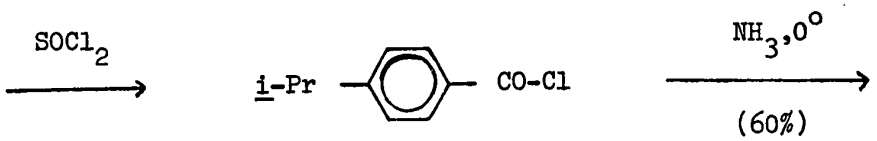
85 86 87

The rearrangement is slow and requires 3 days for completion of reaction. Progress of the reaction was monitored by ir spectroscopy by observing the appearance of the aldehydic carbonyl group. The yield could possibly be improved by further optimization of reaction conditions.

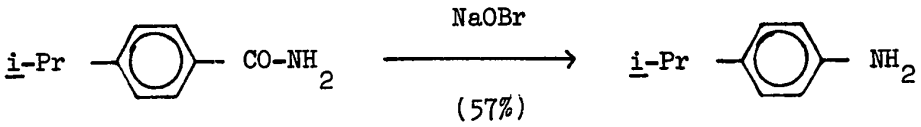
p-Isopropylaniline 92 was synthesized by the Hofmann rearrangement[85] of p-isopropylbenzamide 91 in 57% yield.



88 89



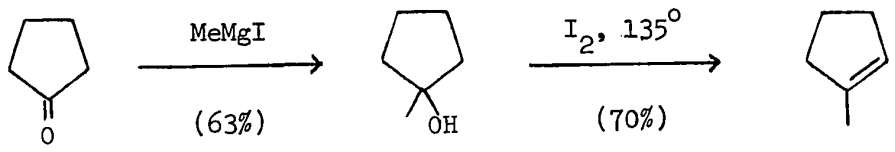
90



91 92

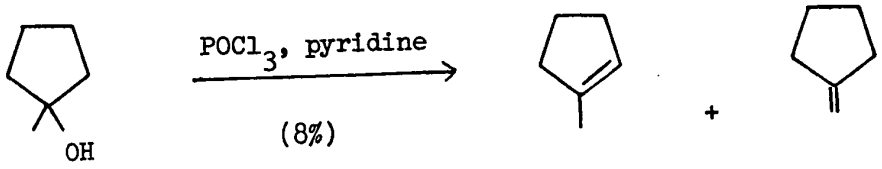
p-Isopropylbenzamide 91 was prepared from p-isopropylbenzaldehyde 88 by silver oxide oxidation[69,70] to the acid 89 in 91% yield. Conversion to the acid chloride 90 with thionyl chloride and reaction with ammonia[86] yielded p-isopropylbenzamide 91 in 60% yield.

1-Methylcyclopentanol 93, prepared from cyclopentanone and methyl magnesium iodide,[87] was dehydrated with iodine by the procedure



93 94

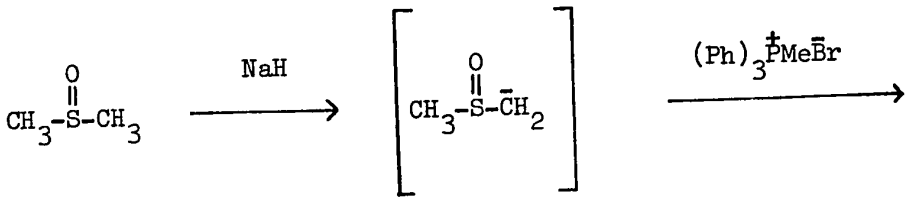
of Huckel and Magle[88] to yield isomerically pure 1-methylcyclopentene 94 in 70% yield. When the alternative procedure of Cross and Whitham[89] was used, the product was obtained in lower yield, and the olefin 94 was contaminated with its exo isomer 95 to the extent of



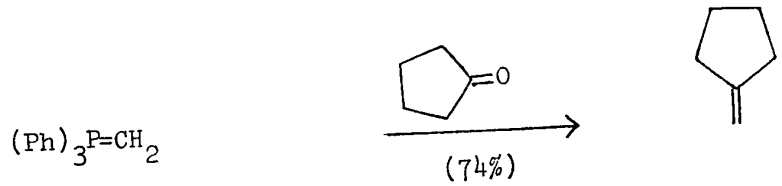
93 94 95

10% as determined by nmr spectroscopy. Separation of 94 and 95 by distillation was impossible because both isomers have similar boiling points (endo- 72°; exo- 75°).

Methylenecyclopentane 95 was synthesized by the Wittig reaction according to the procedure of Corey and co-workers[90] as shown in the following sequence.



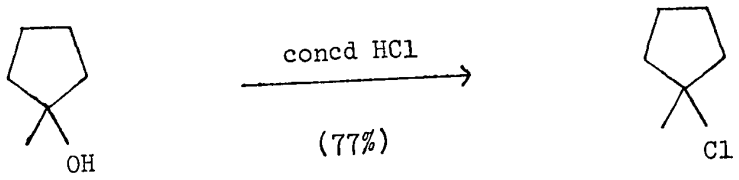
96 97



98 95

Methylsulfinylcarbanion 97, prepared from dimethylsulfoxide 96, was reacted with methyltriphenylphosphonium bromide[91] to produce the ylid 98, which was reacted immediately with cyclopentanone to produce the isomerically pure olefin 95 in the 74% yield.

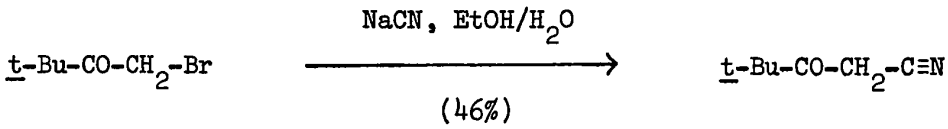
The preparation of 1-chloro-1-methylcyclopentane 99 from 1-methylcyclopentanol 93 was achieved in 77% yield by the procedure of Brown and Fletcher.[92]



93 99

α-Cyanopinacolone 101, not previously reported in the literature, was synthesized in 40% yield from α-bromopinacolone

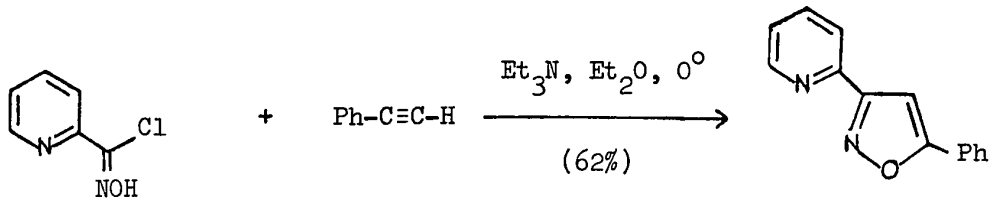
100[93] and sodium cyanide by a procedure analogous to that used by Fuson and Rabjohn.[94] It was interesting to note that



100 101

α-cyanopinacolone was the only product isolated from this reaction and that no cyanohydrin or epoxide, which could conceivably arise from competing reactions, was detected by ir and nmr spectroscopy. The absence of attack at the carbonyl carbon of the bromopinacolone is evidently due to the steric hindrance caused by the t-butyl group.

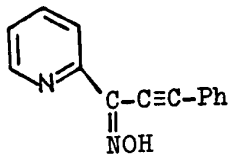
5-Phenyl-3-(2-pyridinyl)-isoxazole 53, also previously unknown in the literature, was prepared in 62% yield from the hydroxamoyl chloride 50 and phenylacetylene. In this general procedure of



50 53

isoxazole synthesis described by Morrocchi et al.,[21] acetylenic

ketoximes similar to 102 have recently been isolated; however, in this reaction no oxime was detected by ir and nmr spectroscopy.



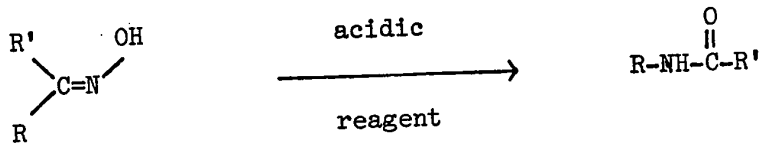
102

II. Reactions of α,β-Acetylenic Oximes.

Having synthesized a variety of this new class of acetylenic oximes, attention was directed towards the determination of the configuration of these compounds and a study of their chemical behaviour *vis-a-vis* those of typical oximes. To this end, the applicability of the Beckmann rearrangement reaction to these oximes was explored. Before venturing into the discussion of the results of the Beckmann rearrangement studies of these oximes it is appropriate to point out briefly the salient features of the current status of knowledge about this reaction.

A. The Beckmann Rearrangement and Its Variations.

The conversion of a ketoxime 103 to a secondary amide 104 by an acidic reagent, a reaction first reported by Beckmann in 1886,[95] is known as the Beckmann rearrangement. The reaction has been



103 104

extensively investigated and several reviews on the topic are available.[11,26-29,96,97] The usefulness of the reaction as a diagnostic tool for the configuration of geometrically isomeric ketoximes lies in the fact that the group *anti* to the hydroxyl function migrates preferentially.[98] However, there are numerous instances in which oximes, under the conditions used for this

reaction, give products other than the expected secondary amides 104. The products in such cases are generally nitriles, olefins and/or chlorides which result from fragmentation of the oximes. The reaction has been variously referred to as "abnormal Beckmann rearrangement", "second-order Beckmann rearrangement" and "Beckmann fragmentation reaction."* For the purpose of the present discussion the terminology "Beckmann fragmentation reaction" will be used in cases where the reactions of oximes result in products other than amides.

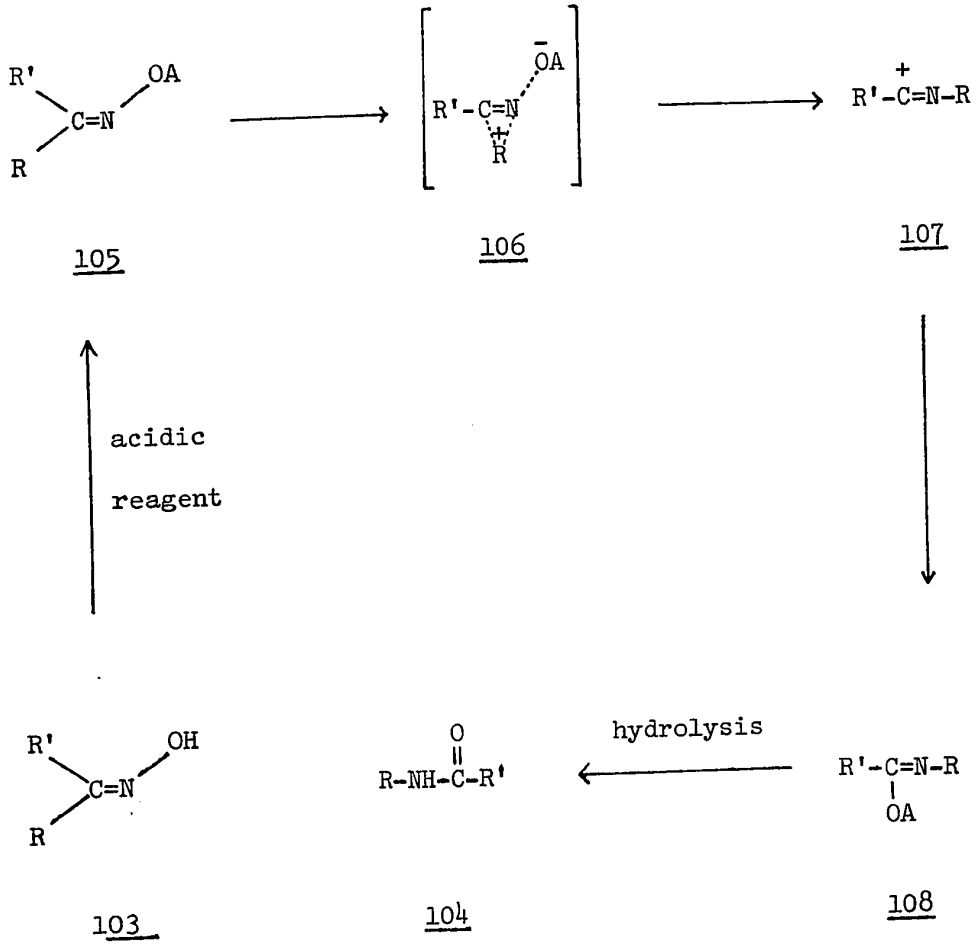
The mechanism of the Beckmann rearrangement has been the subject of numerous studies, and while a single unifying mechanism has not emerged, the basic elements of the mechanism have been identified. These are: 1) conversion of the oxime by acidic reagents to a derivative capable of rearrangement, 2) rearrangement, and 3) conversion of the initially rearranged products to the isolated forms. These concepts are summarized in Scheme 2. Oxime 103 is converted by an acidic reagent to the derivative 105 which rearranges to the imidoyl derivative 108. This arrangement is postulated to proceed intramolecularly in a concerted fashion via the pseudo-three-membered ring transition state 106. Hydrolysis of 108 would then give the expected amide 104. Some details of the critical steps involved in the mechanism are now given below.

The function of the acidic reagents is to convert the oxime hydroxyl group into a good leaving group. The more commonly used reagents are sulfuric acid, hydrochloric acid, polyphosphoric acid,

---

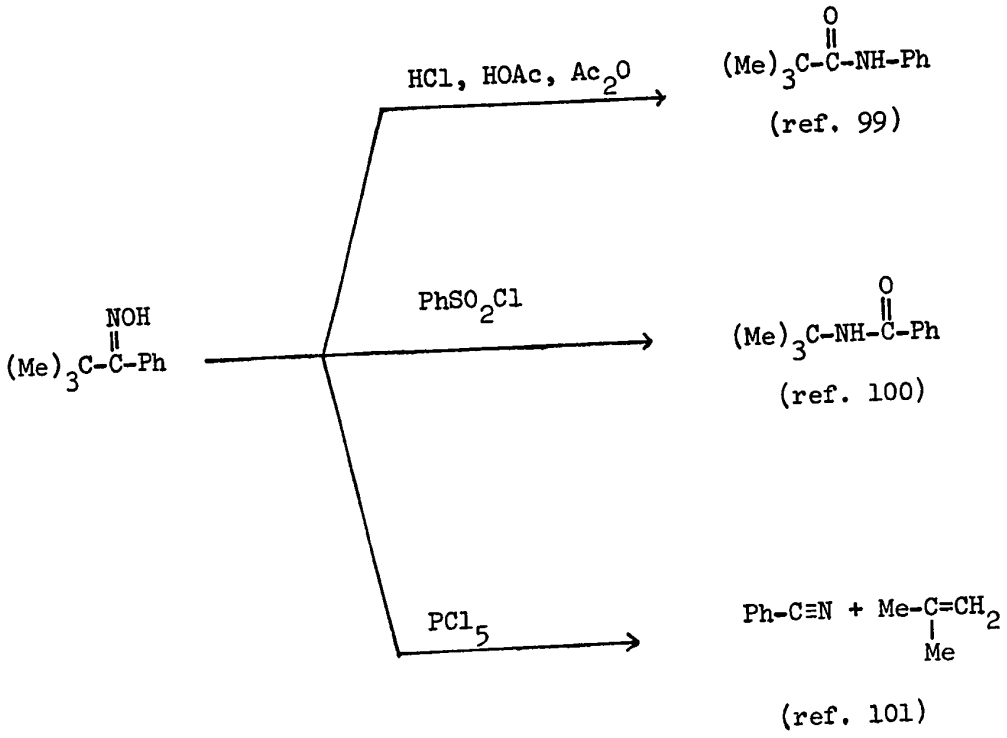
*For an excellent review of the topic see reference 97.

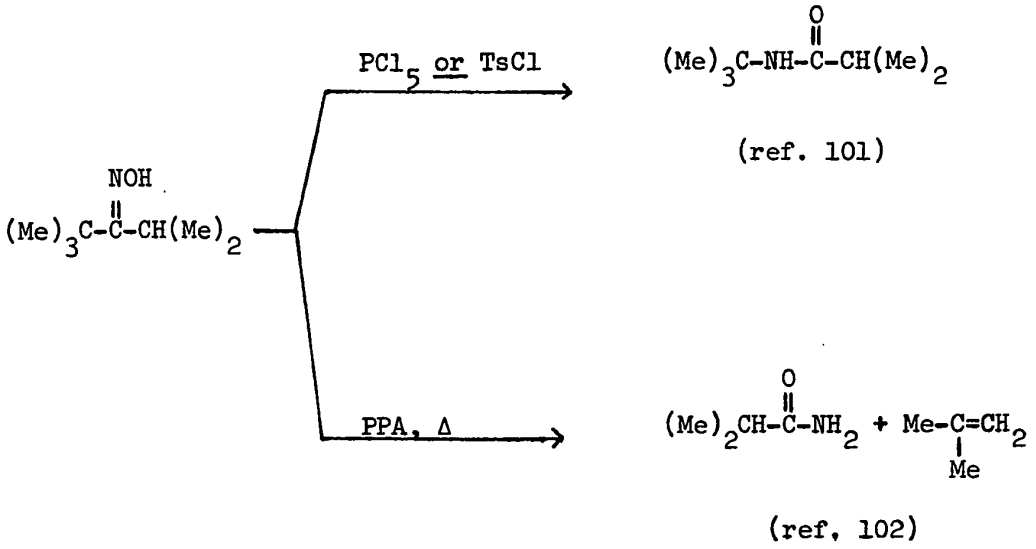
Scheme 2. Mechanism of the Beckmann Rearrangement.



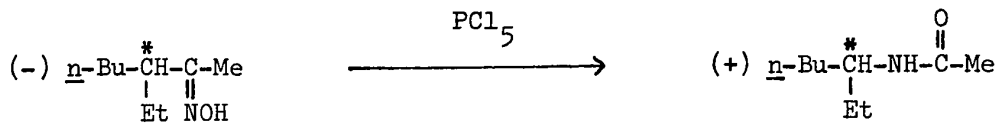
phosphorus pentachloride, thionyl chloride and aromatic sulfonyl chlorides. The choice of reagent is very critical and depends not only on the structure of the oxime, but also on the nature of the reaction medium.[97] Strong protic acids (H_2SO_4, HCl, etc.) are capable of isomerizing the oxime prior to rearrangement, thereby yielding amides not derived from the original oxime. Phosphorus

pentachloride, on the other hand, is the reagent least prone to catalyze prior isomerization.[27] Generalizations on the use of these reagents cannot be readily made as can be seen in the following examples.

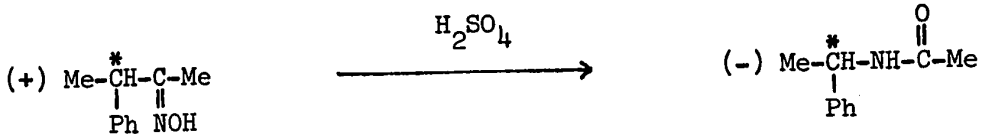




The concerted mechanism postulated requires that the stereospecific anti migration be intramolecular and should show retention of configuration in the migrating group if the point of attachment to the C=N bond is a chiral center. This has been verified by Kenyon and co-workers.[103,104] Optically active oximes 109 and 110 rearranged to the amides 111 and 112 respectively, with retention of configuration of the migrating group. Indirect evidence for the

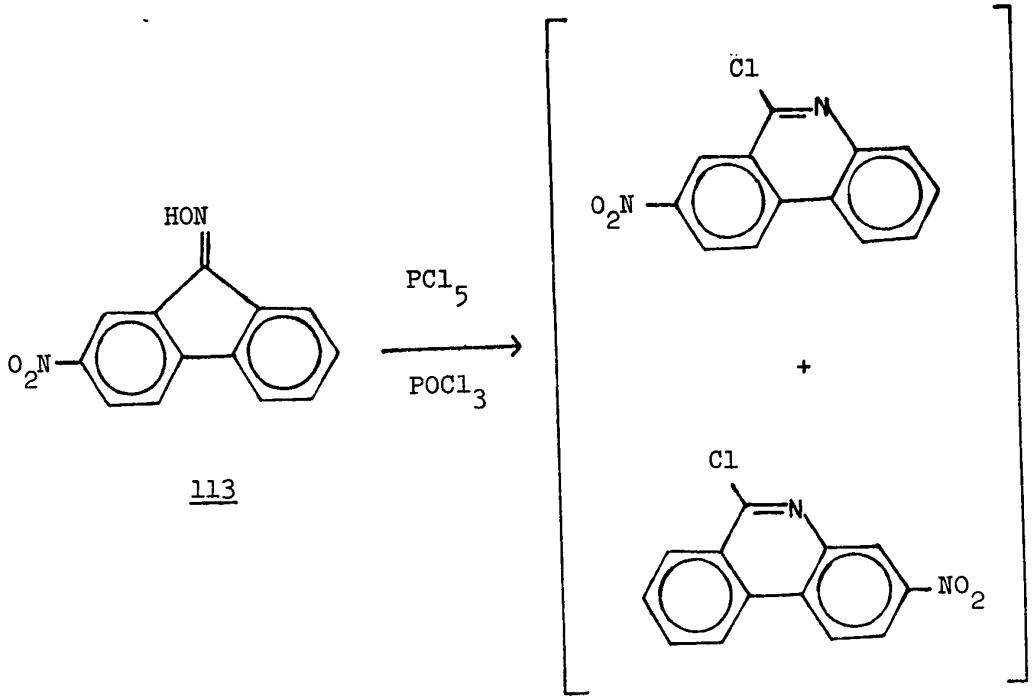


109 111



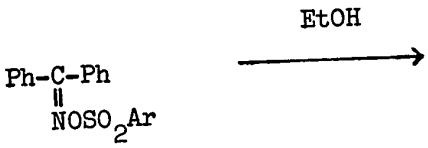
110 112

intermediacy of the imino cation 107 has been the isolation of the imidoyl chloride 116, the imidoyl ester 117, and the tetrazole 118 when the rearrangements of 113, 114 and 115 were conducted in the presence of $PCl_5/POCl_3$, ethanol, and hydrogen azide respectively.



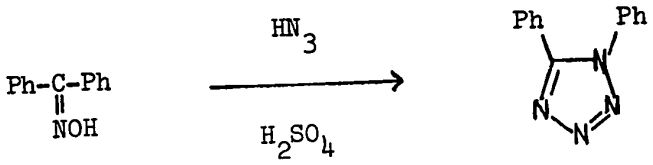
113 116

(ref. 105)



(ref. 106)

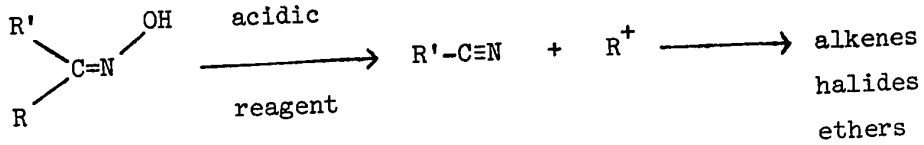
114 117



(ref. 107)

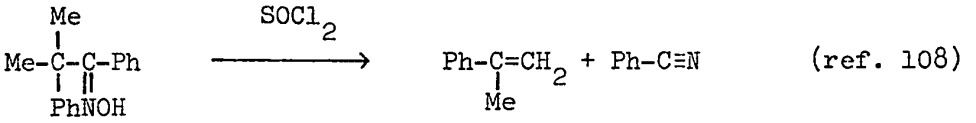
115 118

Certain ketoximes, under the conditions of the Beckmann rearrangement, have been found to give "abnormal" products resulting from the fragmentation of the oximes during the reaction.[97]

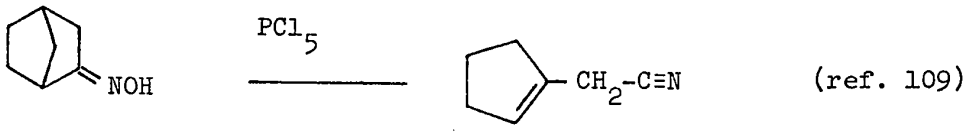


103 119 120

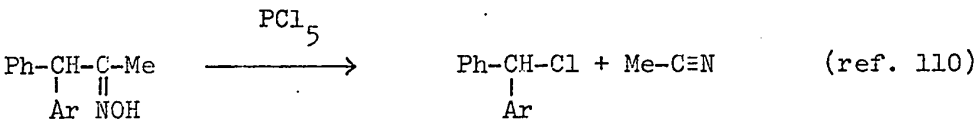
The fragmentation reaction can occur exclusively or simultaneously with the normal rearrangement reaction.



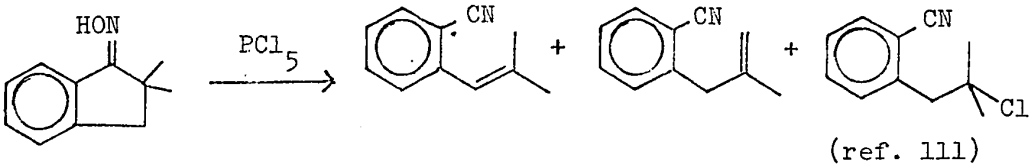
(ref. 108)



(ref. 109)



(ref. 110)



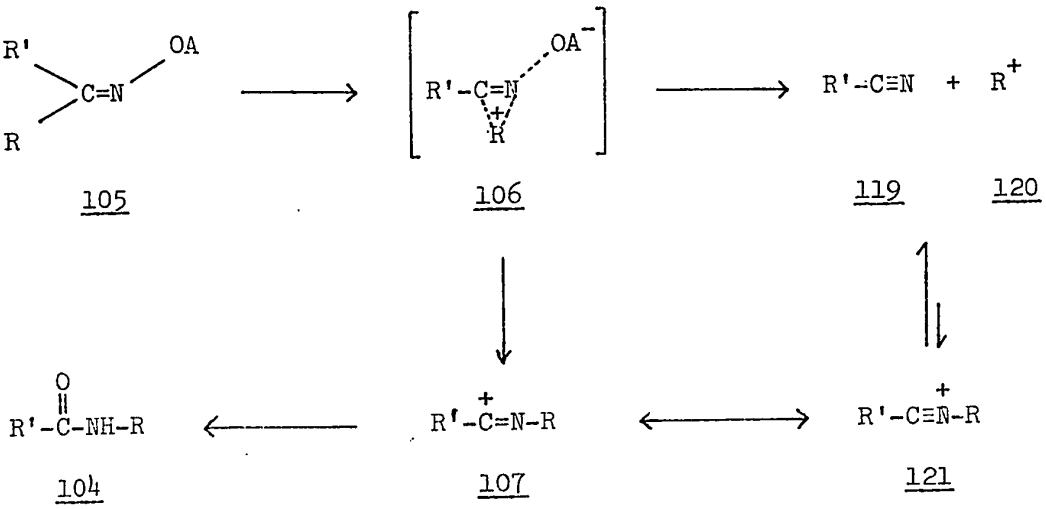
(ref. 111)

All oximes capable of this behavior have substituents on the α-carbon (β-with respect to the oximino-nitrogen) of the fragmenting group which is capable of imparting stability to the

incipient cation 120, produced during the cleavage of the $C_{\alpha-\beta}$ bond. α-Di- and tri-substituted and certain α-functionalized (keto, imino, hydroxy, etc.) ketoximes are known to undergo the fragmentation reaction.[97] Phosphorus pentachloride has generally been considered the reagent of choice for the fragmentation reaction.

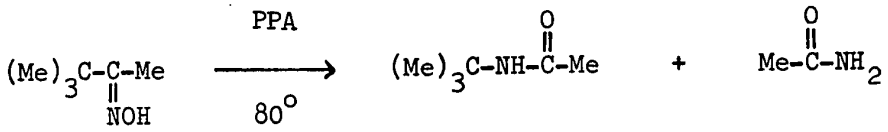
A modified mechanism for the Beckmann rearrangement has been postulated to explain the results and is summarized in Scheme 3.[97] Fragmentation could occur either from the intermediate 106 or from the nitrilium ion intermediate 121. Evidence has been presented to support both theories. If intermediate 106 ionized to the free

Scheme 3. Modified Beckmann Rearrangement Mechanism.

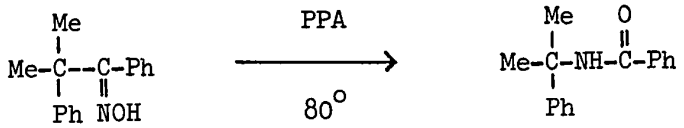


carbonium ion 120, then any subsequent nucleophilic reaction of 120 would result in a racemic product if the α-carbon in R were chiral. No work seems to have been done on any optically active substrates

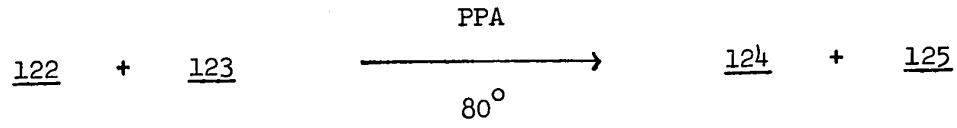
but indirect evidence has been obtained by crossover and stereochemical studies.[102] In the crossover study, the crossed products 126 and 127 were obtained in addition to the expected amides 124 and 125. The crossed products were accounted for by a "fragmentation-recombination" mechanism in which the initial

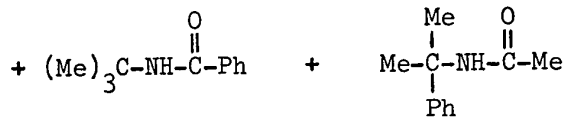


122 124



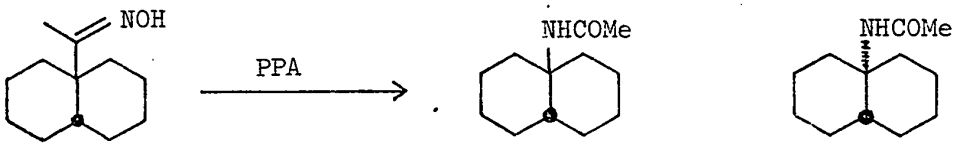
123 125





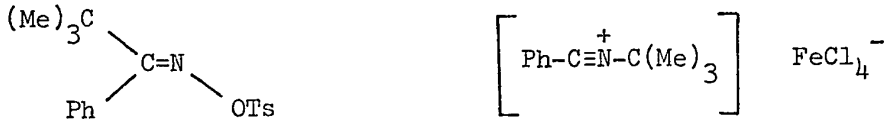
126 127

products of the fragmentation, the nitrile and the cation, combine in a Ritter-type reaction.[102] Additional evidence for the mechanism is provided by the case of the oxime 128, which gave amides 129 and 130, a result which also illustrates the fact that the steric integrity of the migrating group is not maintained.



128 129 130

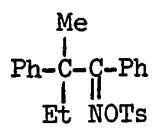
The hypothesis of fragmentation through the nitrilium ion intermediate 121 has been successfully used to explain the product obtained from the reaction of 131.[112] The same ratio of amide and



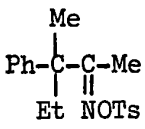
131 132

nitrile was obtained when either the oxime tosylate 131 or the nitrilium derivative 132 was subjected to the conditions of the Beckmann rearrangement.[112] Further support of this hypothesis comes from the solvolysis of the optically active oxime tosylates 133 and 134

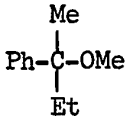
in methanol[113]. Small amounts (5%) of the expected amides were



133



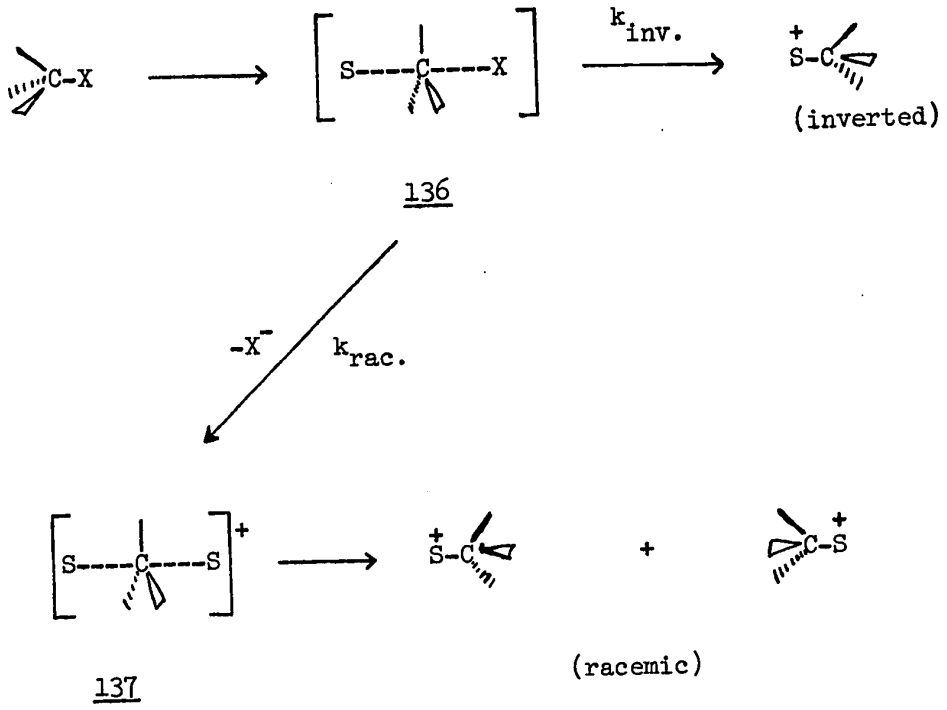
134



135

obtained with retained chirality of the migrating group. In addition to small amounts of olefin, the optically active ether 135 was also obtained as the major product with 60% inversion of configuration.

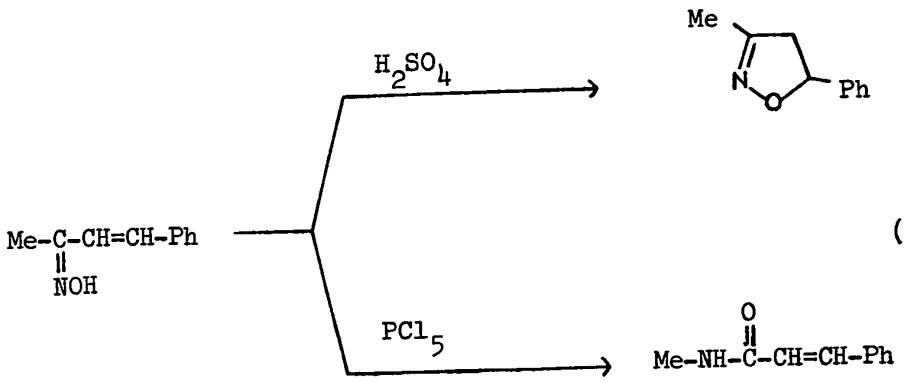
To rationalize the stereochemical results such as the one described above, where a reaction that is unmistakably S_N1 in character produces a product with predominant inversion of configuration, one of two hypotheses is frequently invoked. One hypothesis is due to Hughes[114] which states that if the life-time of the cation produced in the solvolysis " is comparable to the period of molecular oscillation of the solute within the enclosing solvent, the recession of the anion ejected from its former partner will produce a dissymmetric shielding of the latter during the period in which the course of substitution is being determined, and the result will be that substitutions with inversions will outnumber those which retain configuration." The other hypothesis proposed by Doering,[115] pictures the substitution reaction as proceeding through an intermediate 136 which has much of the character of an ion pair.[116,117] The intermediate may then react in one of two ways. The bonds about the carbon atom in 136 may "rehybridize",



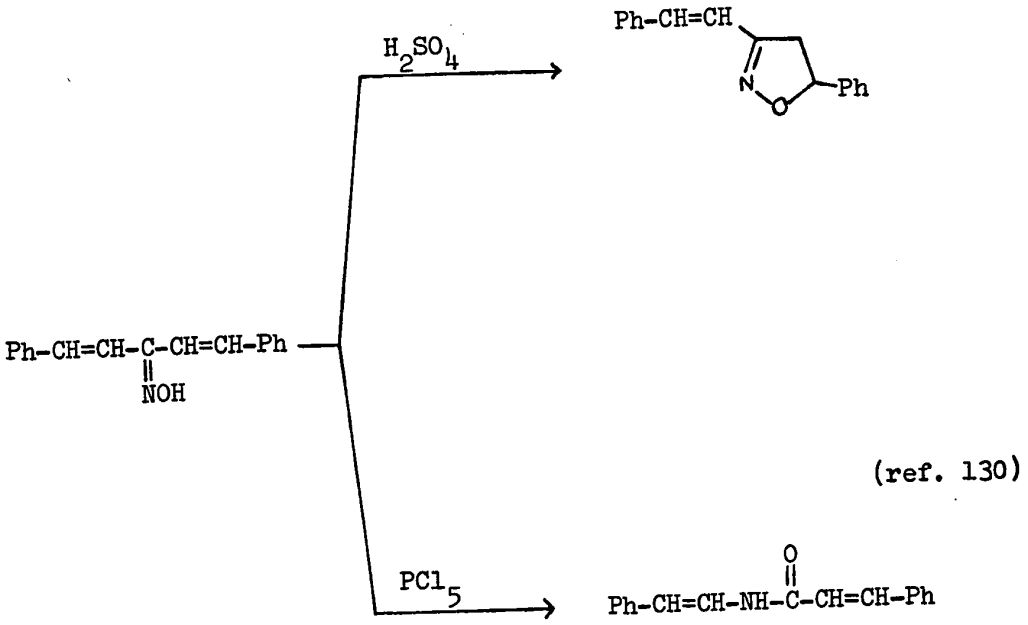
expelling the leaving group thereby producing the inverted product; or an additional molecule of solvent can replace the leaving group X, converting 136 into 137, the solvated "free" carbonium ion, from which racemic products can be produced. It is difficult to say whether this hypothesis has any overwhelming merit over the other, because it still leaves unanswered the question, "What is the nature of the process by which 136 is converted to 137?"[116] However, in the work on the methanolysis of the oxime tosylates mentioned previously[113] the author has chosen to explain the optical activity of the methyl

ether 135 by resorting to the Doering Hypothesis. Later reviewers of the topic seem to prefer the Hughes hypothesis to explain the same results.[97]

In the vast literature on the Beckmann rearrangement only a few references are available concerning the rearrangement studies on α,β-unsaturated ketoximes.[118-129] Acyclic unsaturated ketoximes yield products which are dependent on the type of reagent used.[130]

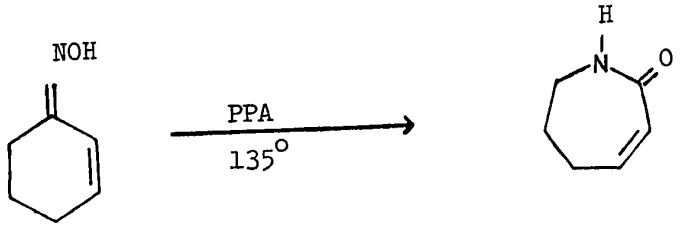


(ref. 130)

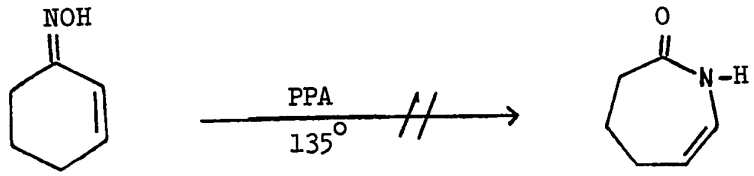


(ref. 130)

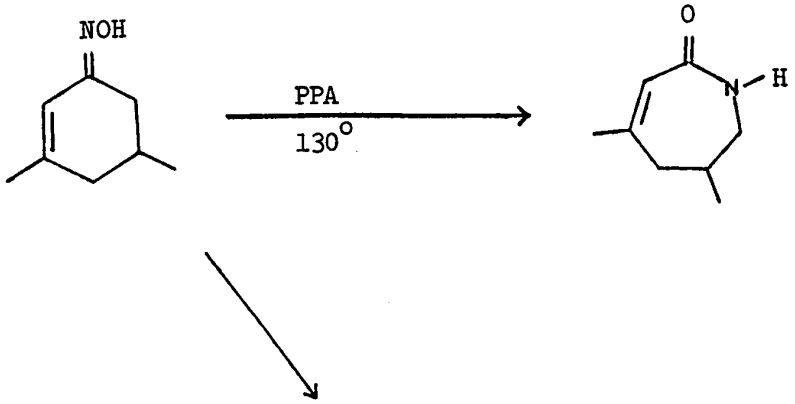
Alicyclic unsaturated ketoximes seem to be less sensitive to the type of reagent used; however, in addition to the expected lactams, aromatic amines are often isolated.



(ref. 124)

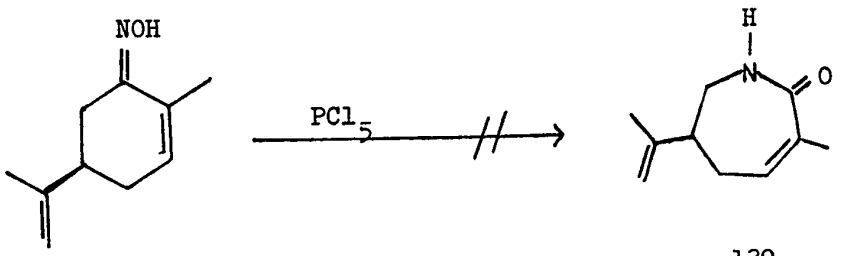


(ref. 124)



(ref. 120)

The expected lactam 139 was not obtained in the Beckmann rearrangement of d-carvone oxime 138.[121] Instead, the lactam isolated has been reported to be the one in which the elements of HCl had added across the double bond α,β to the original oxime function. No further comments as to the exact structure of the lactam were made.



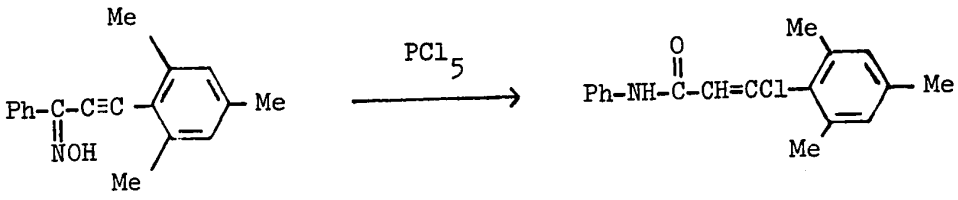
138 139

B. Reaction of α,β-Acetylenic Ketoximes with Phosphorous Pentachloride.

All of the α,β-acetylenic ketoximes synthesized in the present study seemed to be a single stereoisomer in each case, as indicated by their nmr spectra (single sharp signals for the hydroxyl protons in DMSO solution) and by the sharp melting points of those that were solids. It was of interest to obtain chemical evidence for their configuration by the traditional Beckmann rearrangement procedure, particularly because the chemistry of this class of compounds was unknown in the literature. The bahavior of these oximes towards phosphorus pentachloride in ether was therefore investigated, and it soon became apparent that they did indeed undergo the Beckmann rearrangement or a variation thereof. Examination of these amides (in cases where the reaction with phosphorus pentachloride afforded these)

indicated that they were not acetylenic amides, but instead were α,β-olefinic amides. These could formally be considered as the products of addition of HCl across the triple bond of the α,β-acetylenic amides expected *a priori* from the Beckmann rearrangement of acetylenic oximes having the hydroxyl group in a *syn* relationship with respect to the triple bond.

While the present study was underway, a communication announcing the isolation of a few α,β-acetylenic ketoximes appeared[21] in which it was stated that direct treatment of the oximes with phosphorus pentachloride in ether gave unsatisfactory results except in one case. In the case of the oxime 16 g the authors reported the isolation of the olefinic amide whose structure was written as 21,



16 g 21

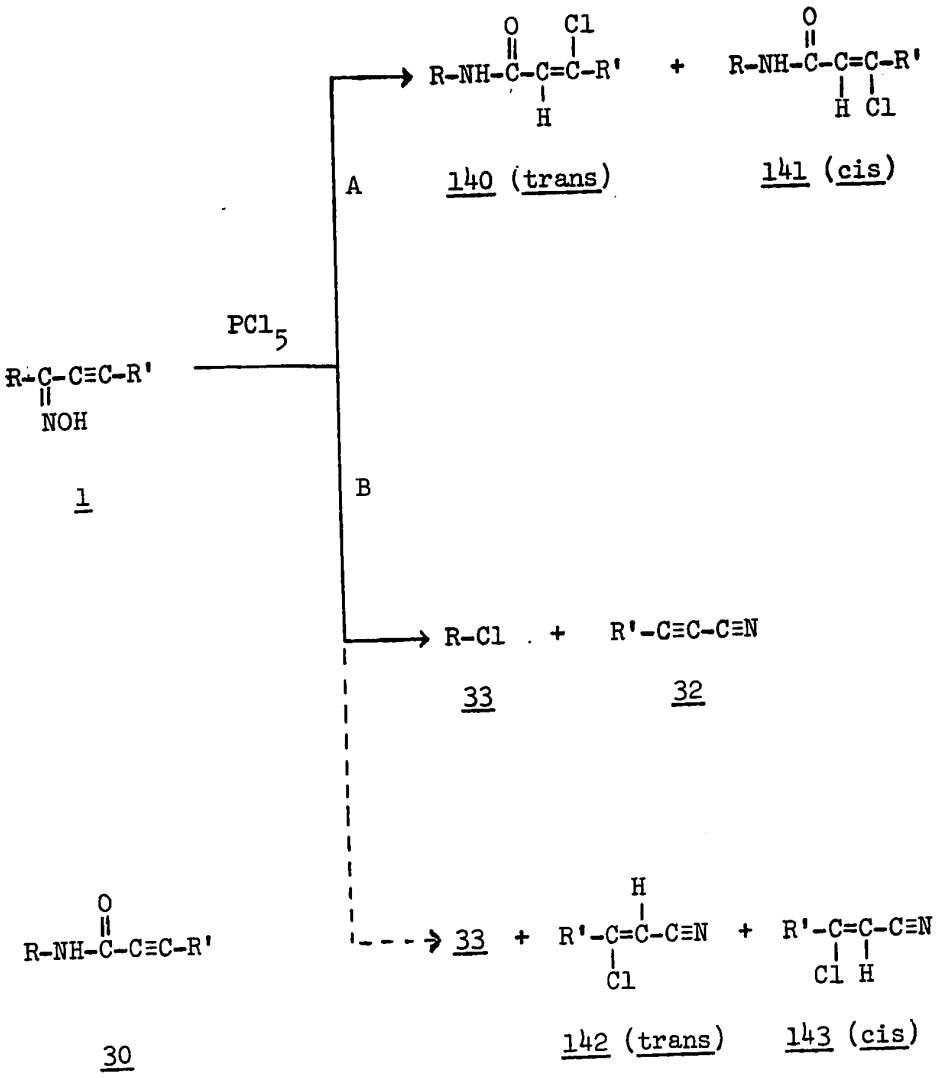
with undisclosed stereochemical dispositions of the substituents about the olefinic bond. Judging from the trend indicated in the

present study of the behavior of acetylenic ketoximes having aryl groups attached to the triple bond (vide infra), the amide 21 must have the configuration in which the H and Cl atoms are trans.

In the present study phosphorus pentachloride was found to be the best reagent for the rearrangement reaction. Other reagents usually employed for the Beckmann rearrangement such as sulfuric aicd, polyphosphoric acid, and thionyl chloride were found to be unsatisfactory, as they gave either no reaction or caused extensive isoxazole formation. Phosphorus pentabromide was also found to react with acetylenic oximes under conditions similar to those used for phosphorus pentachloride, but the course of the reaction took a slightly different turn. The results obtained from the phosphorus pentabromide reaction are discussed in a separate section.

The results of the Beckmann rearrangement of α,β-acetylenic ketoximes with phosphorus pentachloride in ether indicate that they undergo reactions by two pathways as shown in Scheme 4. Path A may be considered the normal Beckmann rearrangement pathway which, however, does not give the expected acetylenic amide 30, but instead, the olefinic amides 140 and 141 which could formally be regarded as the product of addition of HCl across the triple bond in 30. Path B, which is the so-called Beckmann fragmentation reaction, produces chlorides 33 or alkenes derived from the R group in the oxime 1, and acetylenic nitriles 32 or olefinic nitriles 142 and 143 derived from the acetylenic substituent attached to the oximino carbon. These products undoubtedly arose from the fragmentations of the oximes upon reaction with phosphorus pentachloride. The olefinic nitriles 142

Scheme 4. Reactions of α,β-acetylenic ketoximes with phosphorus pentachloride.

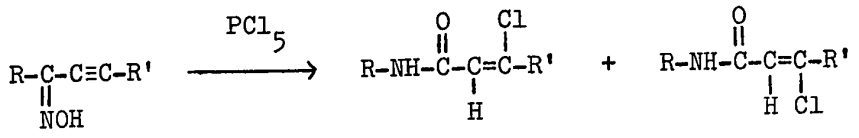


and 143 are formally the addition products of HCl across the triple bond in the acetylenic nitrile 32. The type of fragmentation products produced by a given acetylenic oxime was found to depend on the nature of the substituents R and R'.

In all cases the reaction products were identified by comparison with authentic samples synthesized by independent methods. The product ratios were estimated generally from the nmr spectra of the crude products, or, in the case of solid products, from the actual amounts of these isolated by chromatography. The results of the reaction of phosphorus pentachloride with acetylenic oximes are presented in Tables XVII and XVIII; for the sake of convenience the results of the rearrangement process (path A) are collected in Table XVII, and those of the fragmentation process (path B) are given in Table XVIII. Oximes which gave products by both pathways are found in both tables.

TABLE XVII

BECKMANN REARRANGEMENT REACTION (PATH A)



1 140 (trans) 141 (cis)

TABLE XVII(cont'd)

BECKMANN REARRANGEMENT REACTION (PATH A)

Oximes(1)		Amides		
R'	R	Total Yield (%)	%trans(mp°)	%cis(mp°)
Ph	Me	38	100 (112-3)	--
Ph	Et	14	100 (107-8)	--
Ph	n-Pr	4	100 (57-8)	--
Ph	i-Pr	40	100 (96-7)	--
Ph	sec-Bu	38	100 (85-6)	--
Ph	Ph	20	100 (130-1)	--
Ph	$PhCH_2$	11	100 (88-9)	--
Ph	p-MePh	27	100 (134-5)	--
Ph	p-MeOPh	27	100 (144-5)	--
Ph	p-i-PrPh	31	100 (116-7)	--
p-MeOPh	i-Pr	21	100 (115-6)	--
Me	Et	7	56 (54-5)	44 (57-8)
Me	i-Pr	22	53 (74-5)	47 (85-6)
Me	sec-Bu	14	50 (62-3)	50 (68-9)
Me	t-Bu	3*	55 (83-4)	45 (94-5)
Me	MeCH(Ph)	4*	60 (115-6)	40 (93-4)
Me	Ph	39	35 (122-3)	65 (106-7)
Me	p-ClPh	37	36 (130-1)	64 (135-6)
Me	p-MePh	8	55 (107-8)	45 (101-2)
Me	p-i-PrPh	17	51 (76-7)	49 (113-4)
t-Bu	i-Pr	11	--	100 (123-4)

TABLE XVII(cont'd)

BECKMANN REARRANGEMENT REACTION (PATH A)

Oximes(1)		Amides		
R'	R	Total Yield (%)	%trans(mp°)	%cis(mp°)
t-Bu	sec-Bu	27	--	100 (119-20)
t-Bu	t-Bu	4*	--	100 (151-2)
t-Bu	Ph	30	--	100 (155-6)
Et	i-Pr	22	82 (71-2)	18 (50-1)

*Products corresponding to path B have also been identified.

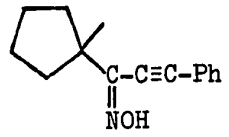
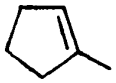
TABLE XVIII

BECKMANN FRAGMENTATION REACTION (PATH B)

Oximes	Total Yield(%)	Product Distribution
1. t-Bu-C(=NOH)-C≡C-Ph	32	t-BuCl (50%) + Ph-C≡C-C≡N (50%)
2. Me-CH(Ph)-C(=NOH)-C≡C-Ph	30	Me-CH(Ph)-Cl (50%) + Ph-C≡C-C≡N (50%)

TABLE XVIII(cont'd)

BECKMANN FRAGMENTATION REACTION (PATH B)

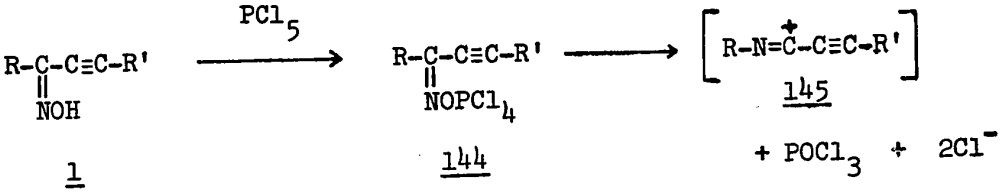
Oximes	Total Yield(%)	Product Distribution
3. 	50	 + Ph-C(Cl)=CH-C≡N (50%) (50%) (88% trans, 12% cis)
4. t-Bu-C(=NOH)-C≡C-Me	41*	t-Bu-Cl + Me-C(Cl)=CH-C≡N (50%) (50%) (61% trans, 39% cis)
5. Me-CH(Ph)-C(=NOH)-C≡C-Me	50*	Me-CH(Ph)-Cl + Me-C(Cl)=CH-C≡N (50%) (50%)
6. t-Bu-C(=NOH)-C≡C-t-Bu	23*	t-Bu-Cl + t-Bu-C≡C-C≡N (50%) (50%)

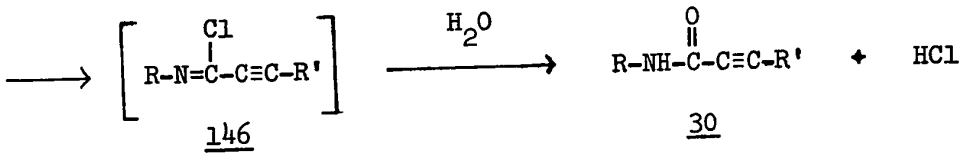
*Products arising from path A were also identified (cf. Table XVII).

It is evident from the data in Tables XVII and XVIII that the yields of product are rather low. One notable feature of the rearrangement (path A) is that all oximes (1) with R' = phenyl or p-anisyl give the β-chloroolefinic amides which are exclusively of the trans type, 140. In cases where R' is methyl and ethyl both cis and trans β-chloroolefinic amides 141 and 140 are obtained. However, when R' is the t-butyl, only the cis β-chloroolefinic amides 141 are obtained. No such general trends are obvious from the data in Table XVIII. Oximes which undergo fragmentation (path B) are those in which the groups (R) anti to the oximino group are t-butyl, α-phenylethyl, or 1-methylcyclopentyl, the first two produce the corresponding chlorides and the last one gives rise to the olefin, 1-methylcyclopentene. In each case 50 percent of the products are derived from this R group. The nature of the other 50 percent of the products derived from the acetylenic substituent in the oxime 1 seems to be determined not only by the R' group in this substituent, but also by the R group in the oxime. For example, oximes 1,2, and 6 (cf. Table XVIII)(where R' = Ph or t-Bu and R = t-Bu or α-phenylethyl) give the acetylenic nitrile 32, whereas when R' = Ph or Me and R = 1-methylcyclopentyl, t-Bu, or α-phenylethyl (oximes 3, 4, and 5, cf. Table XVIII), a mixture of the cis and trans β-chloroolefinic nitriles 143 and 142 are produced. It is noteworthy that when R' = Ph and R = sec-Bu, the oxime gave no fragmentation products (cf. Table XVII), but reacted exclusively by the rearrangement pathway. Any mechanism that is postulated for the rearrangement or the fragmentation pathways must be able to accommodate these observations.

C. Aspects of the Mechanism of the Reaction of Phosphorus Pentachloride with Acetylenic Oximes.

In analogy with the currently widely accepted mechanism for the Beckmann rearrangement,[27] one could, a priori, write the following scheme for the reaction of phosphorus pentachloride with acetylenic oximes:

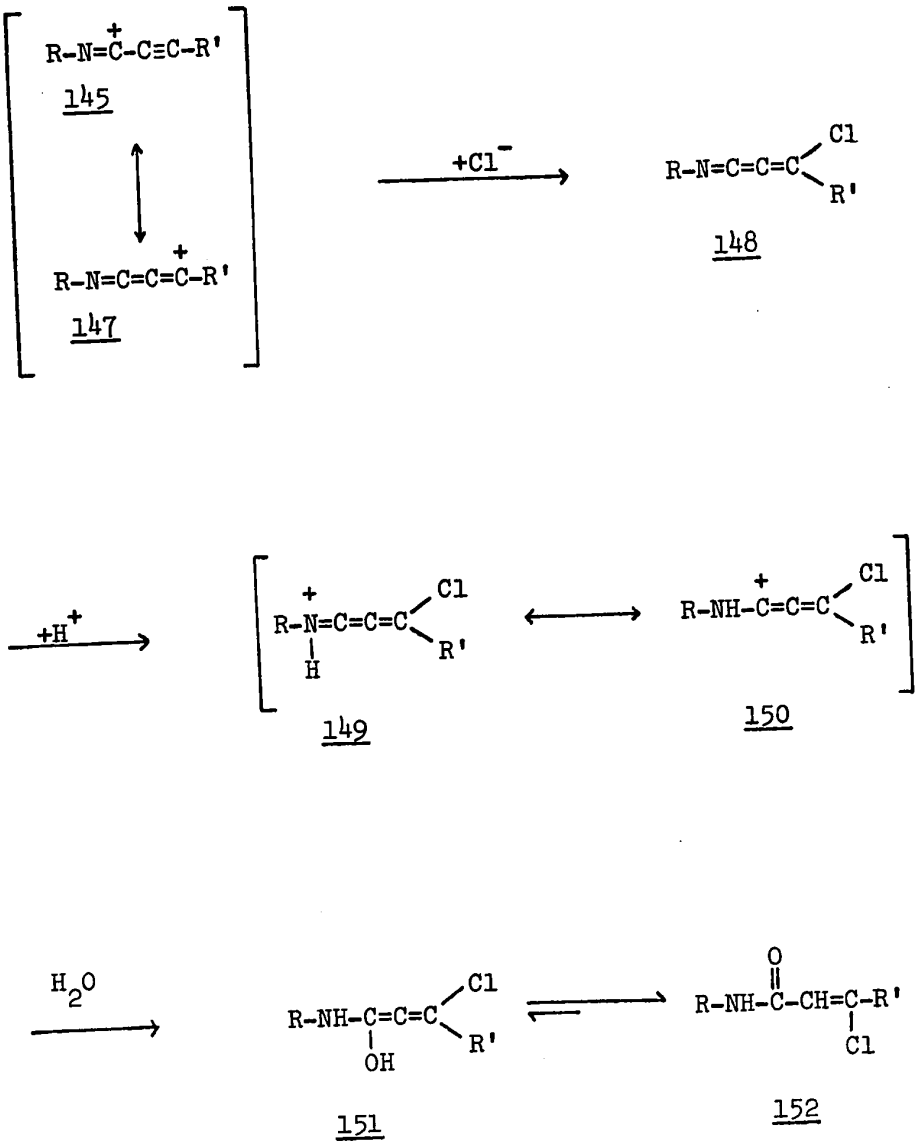




In the present study a molar excess of phosphorus pentachloride was used[26] and no acetylenic amide 30 was observed in the reaction products. It has been demonstrated that equivalent amounts or less of phosphorus pentachloride could bring about the Beckmann rearrangement as could phosphoryl chloride and imidoyl chlorides (similar to 146).[131] In the present case also, in one instance, an equivalent amount of phosphorus pentachloride was used in the reaction and no change in results was observed. In the final hydrolysis step an excess of HCl is expected to be produced, due to

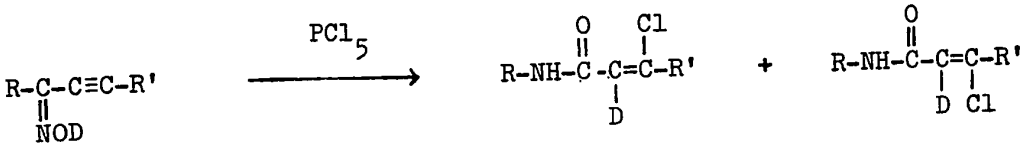
the hydrolysis of excess phosphorus pentachloride, phosphoryl chloride and imidoyl chloride, which could add to the acetylenic bond. It was at first suspected that this could explain the formation of the chloroolefinic amides 140 and 141 instead of the acetylenic amides 30. However, even when the hydrolysis was carried out using aqueous base,[132] there was no change in the nature of the products isolated. Also, in control experiments in which HCl gas was bubbled through ether solutions of the acetylenic amides 30, no addition of HCl to the acetylenic bond occurred, the amides being recovered unchanged. The addition of the elements of HCl must have taken place in one of the earlier steps. α,β-Acetylenic amides do react with phosphorus pentachloride with the net result of addition of HCl to the triple bond (vide infra) giving results very similar to those in the reaction of phosphorus pentachloride with the corresponding oximes. However, according to the mechanism of the Beckmann rearrangement using phosphorus pentachloride, the amide is produced only after the hydrolysis step at which stage the phosphorus pentachloride is not expected to survive.

If one assumes that the addition of HCl takes place at the stage of the iminium ion intermediate 145 of the previous scheme one can postulate a sequence of reactions as indicated below. This involves the postulation of a cumuleneimine of the type 148 which upon hydrolysis gives rise to the chloroolefinic amide 152. This intermediate 148 is not expected to be very stable, being susceptible to undesirable side reactions, which could explain the rather low yields of products. However, upon quenching the reaction mixtures



with D_2O instead of H_2O, the amides isolated were without detectable amounts of deuterium either on the nitrogen atom or at the vinylic position. This result makes the above postulate untenable.

Since the hydrogen atom at the vinylic position in the amide 152 was not arising from the solvent, it was suspected that this might arise from the hydroxyl group of the oxime itself. In order to check this, several O-deuterated acetylenic oximes were prepared and upon treating these with phosphorus pentachloride it was observed that the resulting amides contained deuterium in the vinylic position (on what was the α-carbon in the acetylenic oxime). The results were the same whether the reaction mixture was hydrolyzed using H_2O or D_2O. These observations also support the hypothesis that the elements of HCl add to the triple bond before the hydrolysis step.



153			154	155
R	R'	%D	%D	%D
i-Pr	Ph	98	80-6	--*
p-i-PrPh	Ph	83	14-21	--*
Ph	Me	98	68	67

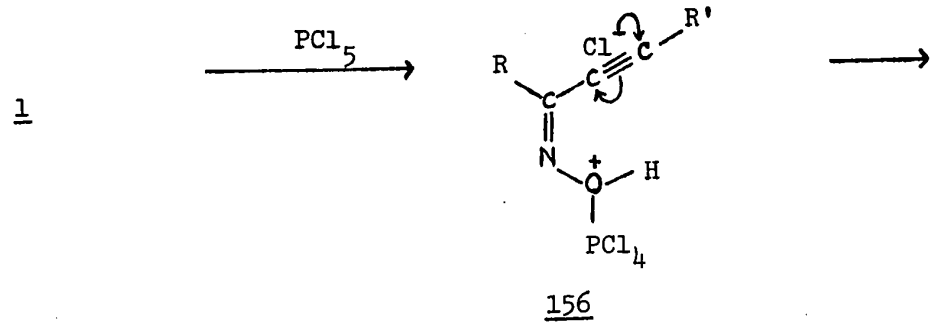
(*No cis product formed)

Having established that the vinylic hydrogen atom in the chloroolefinic amide 152 originates from the hydroxyl group of the starting acetylenic oxime, the next question to be answered was

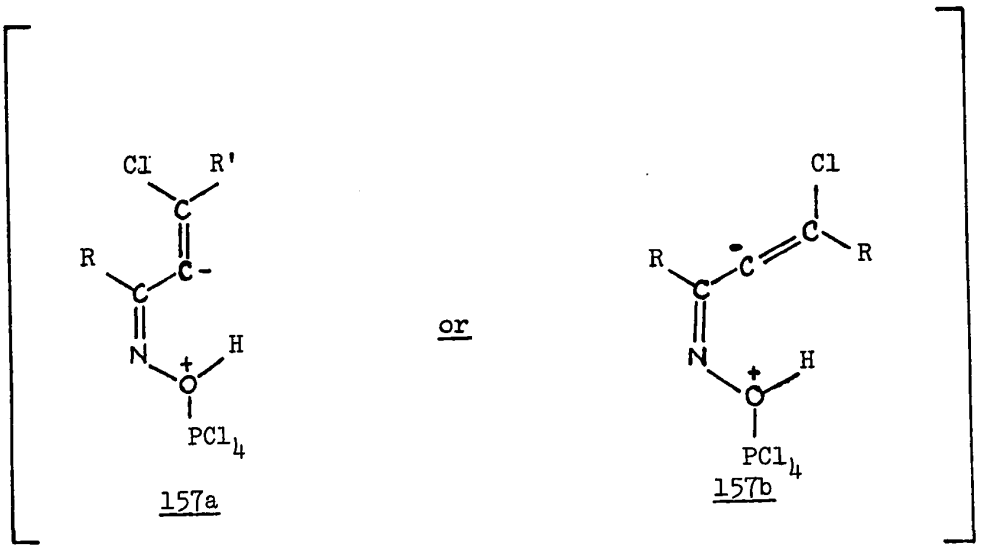
whether this hydrogen transfer during the reaction was intermolecular or intramolecular. Therefore, several crossover experiments were performed where pairs of oximes, one of which was O-deuterated, were allowed to react with phosphorus pentachloride. Analyses of the products indicated that the amides with deuterium in the vinylic position arose only from the O-deuterated oxime. No deuterium could be detected in the amides which were produced from the non-deuterated oximes. These results clearly indicate that during the reaction with phosphorus pentachloride the transfer of the hydroxyl hydrogen to the acetylenic α-carbon of the oxime is intramolecular. The intramolecularity of this transfer might arise from the strong hydrogen bonding that exists between the OH group and the triple bond in the oxime.

The questions still to be answered concern the timing of the addition of the elements of HCl and the manner and sequence of their addition as well as the reasons for the stereochemistry of the addition. The addition to the triple bond could take place either by an electrophilic mechanism (addition of H^+ first) or by a nucleophilic mechanism (addition of Cl^- first), or, less likely, by a concerted mechanism. The answers to these questions are far from being clear-cut as the results available in the present study indicate.

Simple acetylenes are known to undergo facile nucleophilic addition reactions.[133] Thus, in the reaction of phosphorus pentachloride with the oxime one could consider attack by the chloride ion at the triple bond as indicated below:

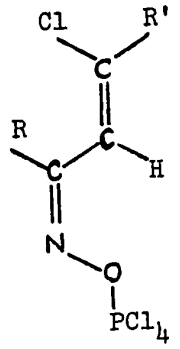


156



157a 157b

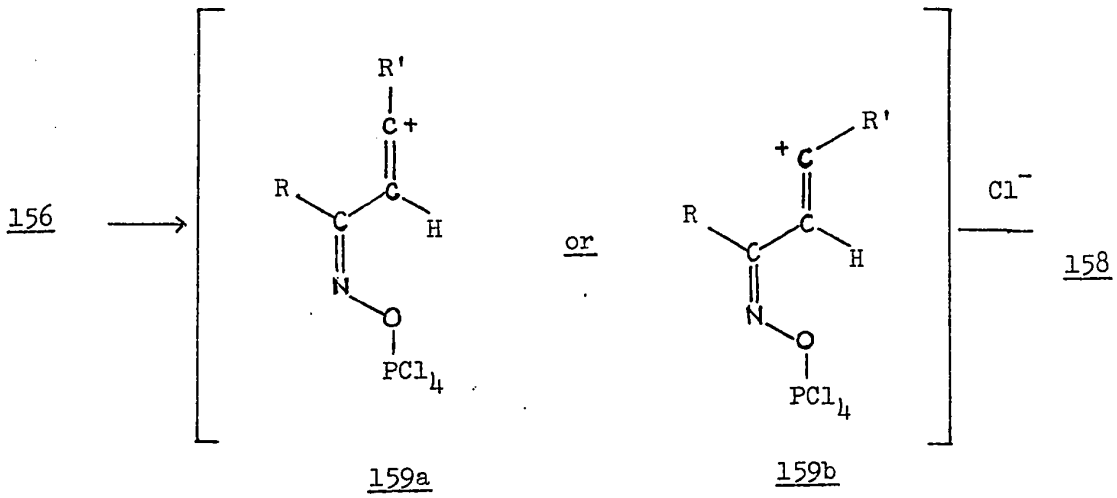
The resulting vinyl anion may have either a bent geometry 157 a or a linear one, 157 b. Vinyl anions are considered to be more stable in a non-linear geometry[134] and hence 157 a can be considered to be the more stable anion. Intramolecular proton transfer to the anion will produce the intermediate 158, which upon rearrangement is capable of producing the observed chloroolefinic amides. However, the



158

reasons for the observed stereochemistry of the addition (all trans, where R' = Ph, all cis, where R' = t-Bu, and cis and trans, where R' = Me or Et) are not immediately obvious from this scheme.

Electrophilic additions to acetylenes have also been widely investigated in recent years.[135] In the electrophilic mechanism of the reaction of phosphorus pentachloride with the acetylenic oximes one can envisage a sequence involving the intramolecular proton transfer from 156 to produce a vinyl cation. As in the case of the vinyl anion, the vinyl cation can either have a linear structure 159 a (with sp hybridization at the cationic center) or a bent structure 159 b (with sp^2 hybridization at the cationic center). Addition of chloride ion to the vinyl cation would produce the intermediate 158 that is capable of rearranging to the observed products. A linear vinyl cation is expected to be more stable;[134,136] however, this does not readily explain the stereochemistry of the additions observed in the present study.



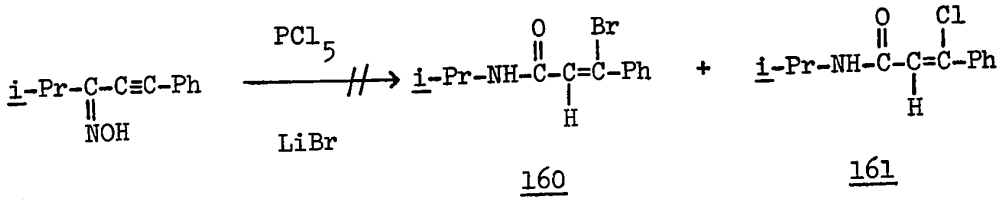
159a 159b

In a recent study of the mechanism of the electrophilic addition of bromine to acetylenes Pincock and Yates[136] postulate the intermediacy of a linear vinyl cation. These authors also postulate that when a phenyl group is attached to the cationic center this is directly conjugated with the positive charge on the sp-hybridized carbon and not with the double bond including the positive carbon (that is, the plane of the ring is oriented parallel to the π-orbitals of the double bond). Their observation of the formation of cis- and trans-dibromoamides in the case of phenylacetylenes is rationalized on the basis of this picture. In the case of alkylacetylenes the observation of only the trans-dibromoamides is rationalized by these same authors[136] as due to the formation of a cyclic bromonium ion intermediate.

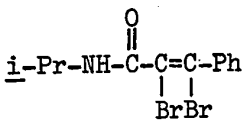
If the postulate of the linear vinyl cationic intermediate

similar to that proposed by Pincock and Yates[136] is accepted, it is difficult to see why in the present work only the trans addition products were obtained when R' = Ph. Also, where R' = Me or Et a mixture of cis and trans products are obtained. Another result also difficult to interpret in this study is the exclusive formation of the cis addition products when R' = t-Bu.

In an effort to test whether a vinyl cationic intermediate was involved in the reaction of phosphorus pentachloride with the acetylenic oximes, the reaction was carried out, in one case, in the presence of an excess of lithium bromide. It was thought that if the vinyl cation is produced in the presence of bromide and chloride ions product resulting from the capture of the bromide ion 160 in addition to that resulting from chloride ion addition 161 would be obtained.

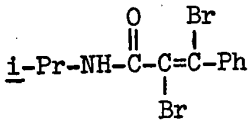


However, the only products isolated from the reaction were the dibromides 162 and 163, along with very small amounts of the acetylenic amide 64. The amide 64 is the expected product of the Beckmann rearrangement of the oxime, never before detected in reactions with phosphorus pentachloride.



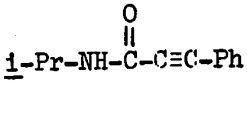
i-Pr-NH-C(=O)-C(Br)=C(Br)-Ph

162



i-Pr-NH-C(=O)-C(Br)=C(Br)-Ph

163

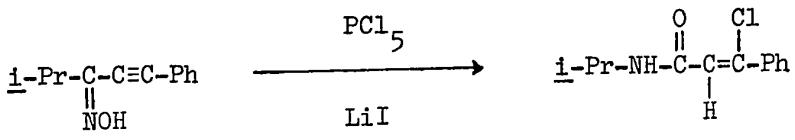


i-Pr-NH-C(=O)-C≡C-Ph

64

When the rearrangement of the same oxime was conducted with phosphorus pentabromide instead of phosphorus pentachloride, the results were identical to those obtained with phosphorus pentachloride in the presence of lithium bromide suggesting that, in the latter case, phosphorus pentabromide was the reagent responsible for the rearrangement.[137,138] A discussion of the results of the reactions of phosphorus pentabromide with acetylenic amides is presented in the next section.

In an analogous experiment the same acetylenic oxime was treated with phosphorus pentachloride in the presence of lithium iodide. The only product isolated was 161, which was also the



i-Pr-C(=NOH)-C≡C-Ph —(PCl_5, LiI)→ i-Pr-NH-C(=O)-C(Cl)=C(H)-Ph

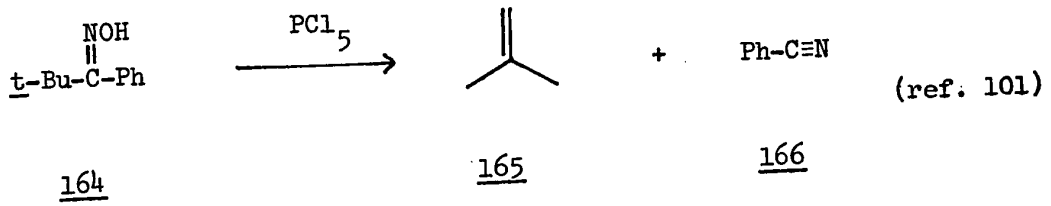
161

product obtained in the absence of lithium iodide. It is noteworthy

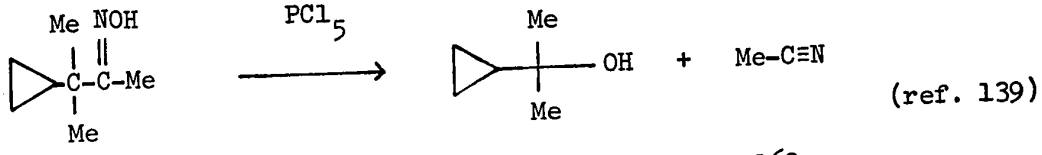
that phosphorus pentaiodide (PI_5) is as yet an uncharacterized species.[137] The results of this experiment also cast doubt on the existence of a vinyl cationic intermediate of any appreciable stability in the reaction of phosphorus pentachloride with acetylenic oximes.

All acetylenic oximes which reacted by the fragmentation pathway (see Tables XVII and XVIII) possess the structural features necessary for the stabilization of an incipient cation. The α-carbon atom in the R group (which is the potential cation in the fragmentation) is di- or tri-substituted so that the developing positive charge on the α-carbon is stabilized by the substituents on this carbon.[97] The products isolated in this present study are nitriles originating from the acetylenic substituent (with or without the addition of the elements of HCl to the triple bond), chlorides, and in one case, an olefin originating from the R group anti to the hydroxyl group in the oxime. Nitriles and olefins are the common products in the regular Beckmann fragmentations, but the chlorides are relatively unknown in such reactions; only two reports are available in the literature [110,111] where chlorides have been identified in Beckmann fragmentations. The chlorides are the products of recombination of the R^+ cations and the Cl^- anions. The alkene is also derived from R^+ by loss of a proton. In the case when R = 1-methylcyclopentyl, the corresponding chloride was not observed in the reaction products, but only the alkene derived from it by loss of a proton from the α-position with respect to the cationic center. It is noteworthy that the alkene formed is entirely the more stable endocyclic one. In contrast to the behavior of the t-Bu group

in the fragmenting acetylenic oximes in the present study, the same group in the oxime 164, upon cleavage has been reported to yield the alkene 165.[101] In another instance the oxime 167 gave the alcohol 168 under similar conditions.[139] The alcohol is derived from the hydrolysis of the corresponding chloride.



164 165 166



167 168 169

Some Beckmann fragmentations have been reported to be complete in less than 5 minutes[110] under conditions similar to those used in the present study, whereas the rearrangements took several hours.[26] The results of the fragmentation reactions of the acetylenic oximes (cf. Tables XVII and XVIII) show two types of behavior: one in which the fragmentation produces the nitrile with the triple bond intact, and the other in which the fragmentation to the nitrile is accompanied by the addition of the elements of HCl to the triple bond. As in the case of the rearrangement reactions it is not possible at present

to state the manner and sequence of addition of the elements of HCl across the triple bond. Whatever is the exact mechanism, it is evident that the addition takes place before or during fragmentation. Acetylenic nitriles do not seem to add HCl if present in the reaction in the presence of an excess of phosphorus pentachloride as indicated by entries 1 and 2 of Table XVIII. It is also reasonable to conclude that in cases where the fragmentation produces the acetylenic nitriles, this process is much faster than the addition of HCl.

From the results available, there is no compelling reason for the postulation of either a vinyl cationic or a vinyl anionic intermediate in the Beckmann rearrangement or in the fragmentation reactions of the α,β-acetylenic ketoximes. With regard to the fragmentation reactions the present results support those of Conley's[97] for saturated oximes in that "the substituents, both the migrating and the stationary group, attached to the oximino carbon atom play an important role in the fragmentation process, presumably by influencing the dissociation of the intermediate imino cationic species through either electronic or steric interactions."

D. Reaction of α,β-Acetylenic Ketoximes with Phosphorus Pentabromide.

Since the reaction of phosphorus pentachloride with α,β-acetylenic ketoximes gave rearrangement and/or fragmentation products, it was of interest to investigate the behavior of phosphorus pentabromide towards these oximes. It seems that phosphorus pentabromide has not been used before as a reagent for the Beckmann rearrangement.[26]

Scheme 5. Reactions of α,β-acetylenic ketoximes with phosphorus pentabromide.

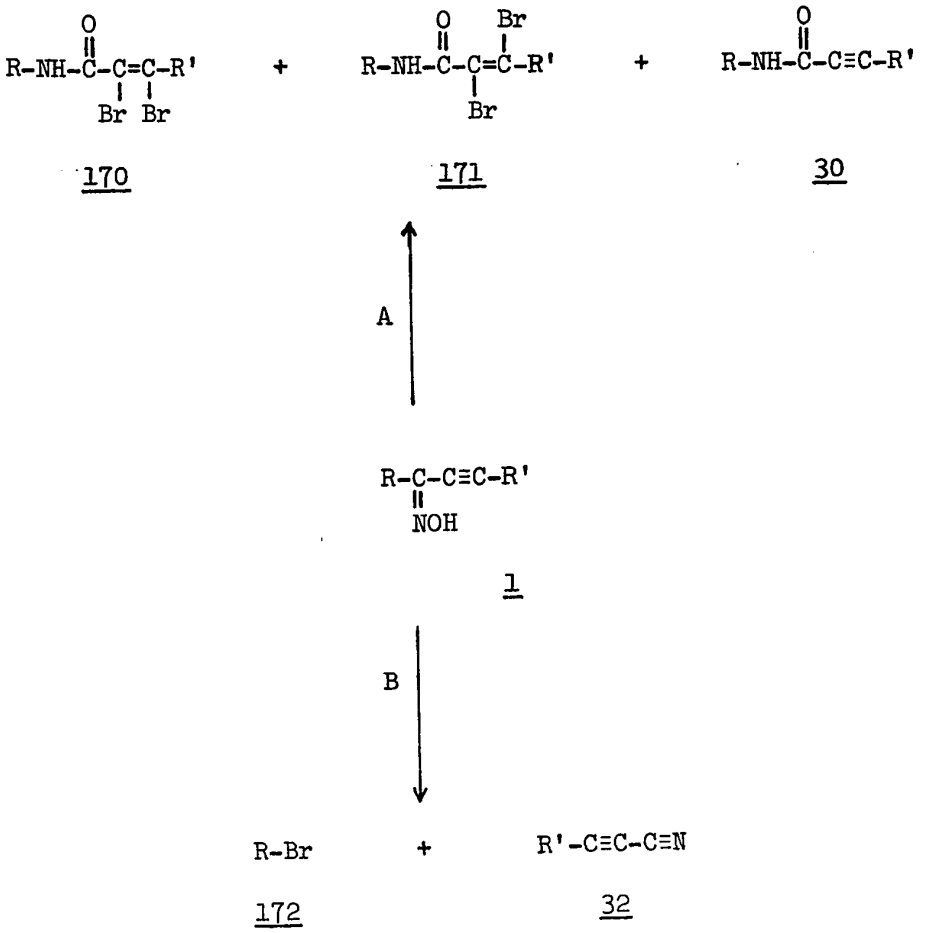
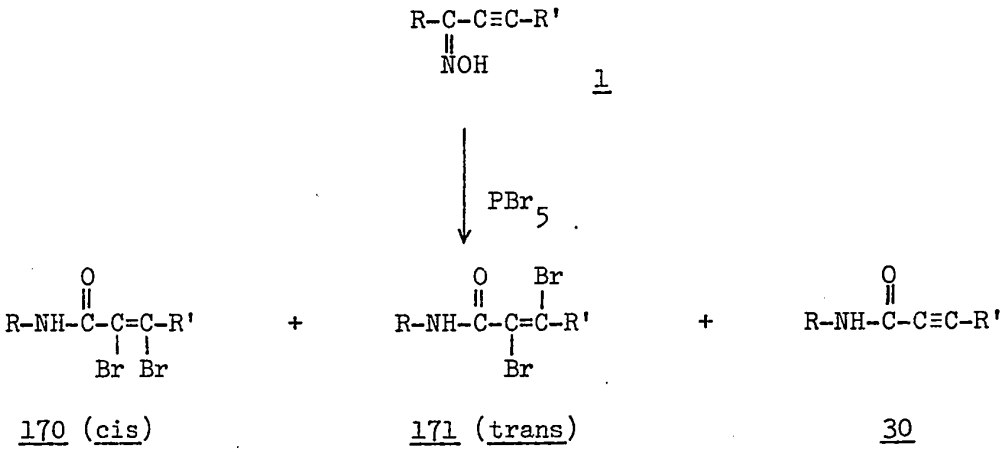


TABLE XIX

BECKMANN REARRANGEMENT REACTION (PATH A)



Oximes			Amides		
R	R'	% Yield (170 + 171)	% 170(mp°)	% 171(mp°)	% 30(mp°)
i-Pr	Ph	46	59 (117-8)	41 (143-4)	15 (85-6)
sec-Bu	Ph	49	60 (131-2)	40 (143-4)	2 (90-1)
Ph	Ph	70	64 (126-8)	36 (166-7)	5 (127-8)
i-Pr	Me	23	--*	100 (124-5)	--*

*no products detected

The results of the reaction of five α,β-acetylenic ketoximes with phosphorus pentabromide indicate that these oximes do undergo rearrangement or fragmentation as indicated in Scheme 5. However, in cases where addition to the triple bond had occurred, it was not the elements of HBr (as might be expected from the analogous reaction with phosphorus pentachloride), but instead two bromine atoms had added. Even more interesting was the isolation of the expected acetylenic amides as a minor product in each case. The results obtained are summarized in Table XIX.

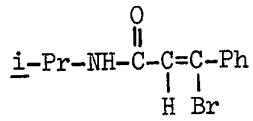
In all cases where R' = Ph(1), and where rearrangement had occurred (cf. Table XIX), the cis-, dibromo amides 170 predominated. The proportion of cis- and trans- amides was calculated from the actual amounts of these isolated by column chromatography. For the oxime with R = i-Pr and R' = Me, only one isomer was obtained. The stereochemistry of this product was not determined but could possibly be trans from arguments to be presented later (see section E). Acetylenic amides 30 were isolated albeit in small amounts. No acetylenic amide was detected for the oxime with R = i-Pr and R' = Me. Oxime 1 (R = $CH_3CH(Ph)$, R' = Ph) fragmented completely to the bromide 172 and acetylenic nitrile 32 (R' = Ph). This result is analogous to that obtained with phosphorus pentachloride.

E. Aspects of the Mechanism of the Reaction of Phosphorus Pentabromide with Acetylenic Oximes.

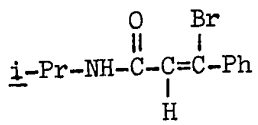
The results of the Beckmann rearrangement of acetylenic ketoximes with phosphorus pentabromide indicate that a different

mechanism to the one applicable to phosphorus pentachloride is operative.

Since the analogous HBr addition product was never detected and only the products of Br_2 addition were isolated, the possibility of the addition of molecular bromine to the acetylenic bond of the oximes was considered possible. This assumption was based on the fact that phosphorus pentabromide dissociates to some extent in solution to phosphorus tribromide and bromine.[137] In control experiments the direct addition of one equivalent of bromine to an acetylenic oxime (1, R = R' = Ph) was examined using anhydrous ether as well as chloroform as the solvent. In both solvents bromine seemed to add readily, but the products were too unstable to be characterized fully. The material balance and spectral data (ir and nmr) on the crude products seemed to indicate that they were dibromooximes of undetermined stereochemistry. However, the isolation of small amounts of the acetylenic amides from the reaction of acetylenic oximes with phosphorus pentabromide indicated that the starting oxime was probably not completely brominated. The possibility of the formation of the HBr addition product with subsequent dehydrobromination in the course of the reaction to give the acetylenic amide was considered. When either the cis- or trans-β-bromo-olefinic amide (173 and 174) was treated with phosphorus pentabromide under the same conditions, no acetylenic amide was detected in the products,

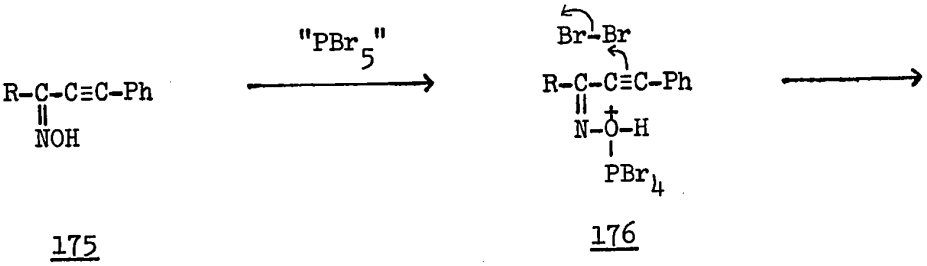


173

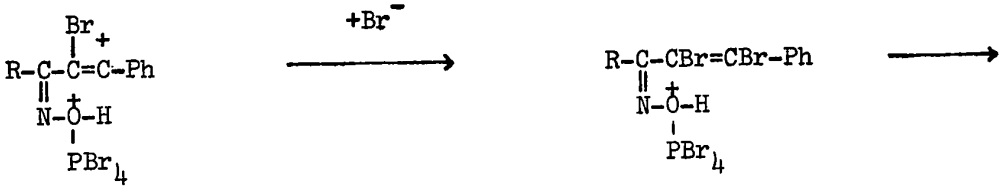


174

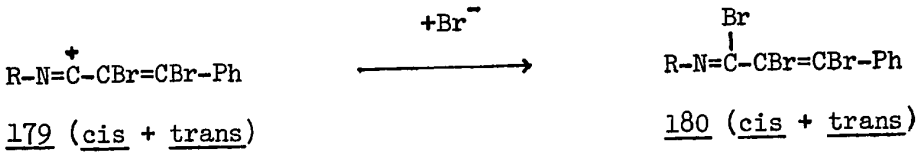
Scheme 6. Probable mechanism of the reaction of phosphorus pentabromide with acetylenic oximes.



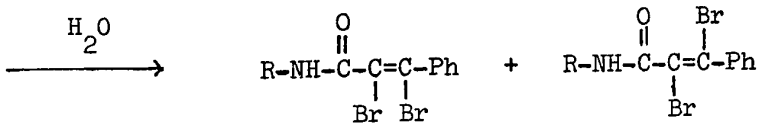
175 176



177 178 (cis + trans)



179 (cis + trans) 180 (cis + trans)



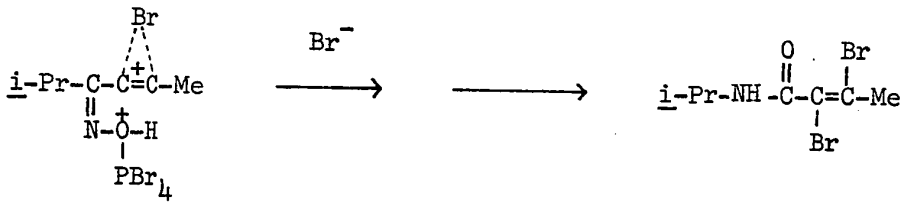
170 (cis) 171 (trans)

but each isomer underwent some isomerization yielding a mixture of the cis and trans products.

Since proton addition to the acetylenic bond had not occurred, which was the case in the reaction with phosphorus pentachloride, one has to consider the possibility of the addition of a bromine atom to the α-carbon atom of the triple bond in the acetylenic oxime. It has been shown recently by Pincock and Yates[136] that electrophilic bromine addition to aromatic acetylenes proceed via a linear vinyl cationic intermediate to give both cis- and trans- dibromo products, the latter predominating. For dialkyl acetylenes the addition of bromine was exclusively trans and it was proposed that this proceeded via a cyclic bromonium ion intermediate.[136] In the present work, cis- and trans- dibromo amides were obtained with aromatic acetylenic oximes (1, R' = Ph), the former product predominating. A mechanistic sequence as shown in scheme 6 seems plausible.

In the case of oxime 1 (R = i-Pr, R' = Me), only one dibromoamide was obtained, which, by analogy with the work of Pincock and Yates,[136] is assumed to be the trans isomer. In the present case one could therefore postulate the reaction as proceeding via a cyclic bromonium ion intermediate 181, eventually producing the trans-dibromo amide 182.

The results of the fragmentation reaction of the one acetylenic oxime reported here are very similar to those obtained in the reaction of the same oxime with phosphorus pentachloride. However, further studies of the action of phosphorus pentabromide on other



181 182

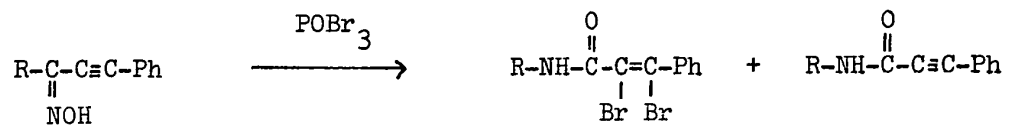
acetylenic oximes are required before a meaningful comparison of the behavior of phosphorus pentachloride and phosphorus pentabromide can be made in the fragmentation reaction. For example, it would be interesting to see, in cases where the reaction of phosphorus pentachloride gave nitriles in which the elements of HCl had added to the original acetylenic function, whether phosphorus pentabromide would give nitriles with addition of HBr or Br_2. The limited data presented here do nevertheless show striking differences in the behavior of phosphorus pentachloride and phosphorus pentabromide towards α,β-acetylenic oximes. Where rearrangement is accompanied by addition in one case it is hydrogen halide that adds and halogen in the other. Acetylenic amides resulting from the direct rearrangement of the acetylenic oximes are observable only in the reactions with phosphorus pentabromide. These products probably are produced by a pathway different from the one which gives the dibromo amides. Further study in this area is necessary before a mechanism can be suggested. In comparing the reactions of phosphorus pentachloride and phosphorus pentabromide one can concur with Payne[137] in that "many of

the reactions of phosphorus(V) bromide clearly parallel those of the chloride. Such differences as occur arise from a difference in reactivity of molecular bromine as compared with molecular chlorine, as well as from the difference of the PBr bond as compared with the PCl bond."

F. Reaction of α,β-Acetylenic Ketoximes with Phosphoryl Bromide.

Since phosphoryl chloride ($POCl_3$) is known to bring about the Beckmann rearrangement,[27] although less readily than PCl_5, it was of interest to examine the action of the analogous reagent $POBr_3$ on acetylenic oximes. As it was known that phosphoryl bromide, unlike phosphorus pentabromide, does not dissociate in solution to produce molecular bromine,[137] it was thought that the problem of the bromine addition to the acetylenic bond could be obviated by the use of this reagent, and that perhaps better yields of the acetylenic amides could be obtained.

Only two acetylenic oximes were examined in this connection and both of them were found to undergo rearrangement with results as indicated below:



	175	170	183
a:	R = i-Pr	15%	2%
b:	R = Ph	24%	--*

(*not observed)

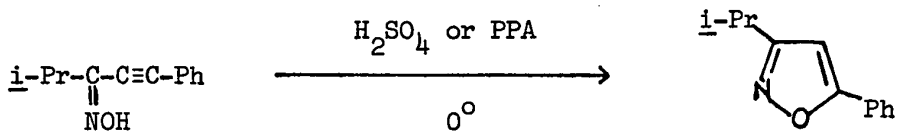
The interesting feature here, vis-a-vis the results for the same two oximes with phosphorus pentabromide, is that only the cis-dibromo derivative 170 was produced as the "addition-rearrangement" product in each case. As data are available only for two oximes this feature of the reaction cannot be considered as indicating a trend. As far as the product of the "normal" rearrangement (the acetylenic amide 183) is concerned, this was detected only in the case of one of the oximes, although both oximes gave this product with phosphorus pentabromide. In the reactions of both phosphoryl bromide and phosphorus pentabromide the acetylenic amide 183 is only a minor product. Before any generalization concerning the mechanism of the reaction of phosphoryl bromide with acetylenic oximes can be made, further study of the reaction using a wider range of oximes is essential.

G. Action of Other Reagents on α,β-Acetylenic Ketoximes.

Since acetylenic oximes cyclize readily to isoxazoles on heating, the reactions involving them have to be carried out at low temperatures (20° or lower). This requirement limited the choice of reagents that could be used to effect the Beckmann rearrangement of these oximes. In an effort to find a reagent that would bring about the rearrangement and yet leave the acetylenic function intact, several other reagents commonly used for the Beckmann rearrangement of ketoximes were investigated.

The acetylenic oxime 184 was chosen for testing the other reagents because this oxime was found to be more stable and it was

more easily obtained in the pure state. Generally the reactions with sulfuric acid and polyphosphoric acid (PPA) are conducted at optimum temperatures of over 100°;[26] lower temperatures have been used occasionally but the yields of products were low.[102]

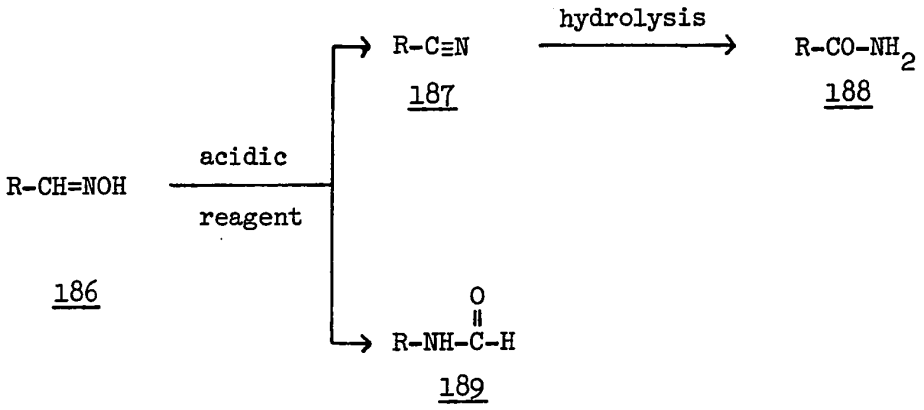


184 185

Treatment of the oxime 184 with either concentrated H_2SO_4 or PPA gave mostly the corresponding isoxazole 185 along with some unreacted starting material. Thionyl chloride, a reagent known to bring about the Beckmann rearrangement, at low temperatures,[140] was found to be unreactive towards the oxime at 0°. The tosylates of certain oximes have been reported to give Beckmann rearrangement products upon passage through a column of acidic alumina;[141] however, the tosylate of the oxime 184 was recovered unchanged under these conditions. Phosphorus pentafluoride (PF_5) does not effect the Beckmann rearrangement, but is known to form complexes with ketoximes.[142] When oxime 184 was treated with phosphorus pentafluoride in anhydrous ether only unchanged starting material could be recovered. In a recent study a dioxane-sulfur trioxide complex was used successfully with some ketoximes for the Beckmann rearrangement.[143] This reagent was also used with oxime 184 but it was not possible to characterize the reaction products.

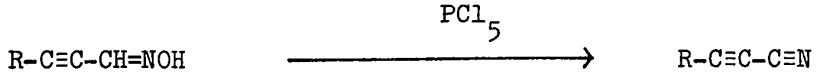
H. Reaction of α,β-Acetylenic Aldoximes with Phosphorus Pentachloride.

It seemed of interest to investigate the action of phosphorus pentachloride on α,β-acetylenic aldoximes. Saturated aldoximes 186 under the conditions of the Beckmann rearrangement usually undergo dehydration to the nitriles 187.[26] This reaction can formally be regarded as a Beckmann fragmentation reaction.



Normal rearrangement to formamides 189 is quite rare.[26] In some instances unsubstituted amides 188 are isolated, but these are considered to be hydrolysis products of the nitriles 187.[26]

Two acetylenic aldoximes 190 were treated with phosphorus pentachloride in anhydrous ether under conditions similar to those used in the same reaction of the ketoximes. The corresponding acetylenic nitriles were the only products isolated as indicated below:



190	84
R = Me	9%
R = Ph	45%

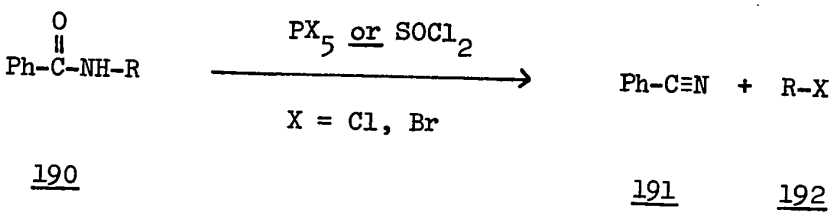
It is interesting to note that no products resulting from the addition of HCl to the acetylenic bond were detected in the reaction mixture. Thus, in at least the two cases examined, the α,β-acetylenic aldoximes show behavior analogous to the saturated aldoximes under similar conditions.

III. Reaction of α,β-Acetylenic Amides with Phosphorus Pentahalides.

It was hoped that study of the action of phosphorus pentachloride and phosphorus pentabromide on α,β-acetylenic amides might help to gain insight into the mechanism of the reactions of phosphorus pentahalides with α,β-acetylenic oximes.

A. The von Braun Reaction.

The reaction between N-alkyl benzamides and phosphorus pentahalides or thionyl chloride to produce benzonitriles 191 and alkyl halides 192 is called the von Braun degradation[144] or von Braun reaction.[145] The reaction was discovered in 1900 by von Pechmann,[146] using phosphorus pentachloride but was later

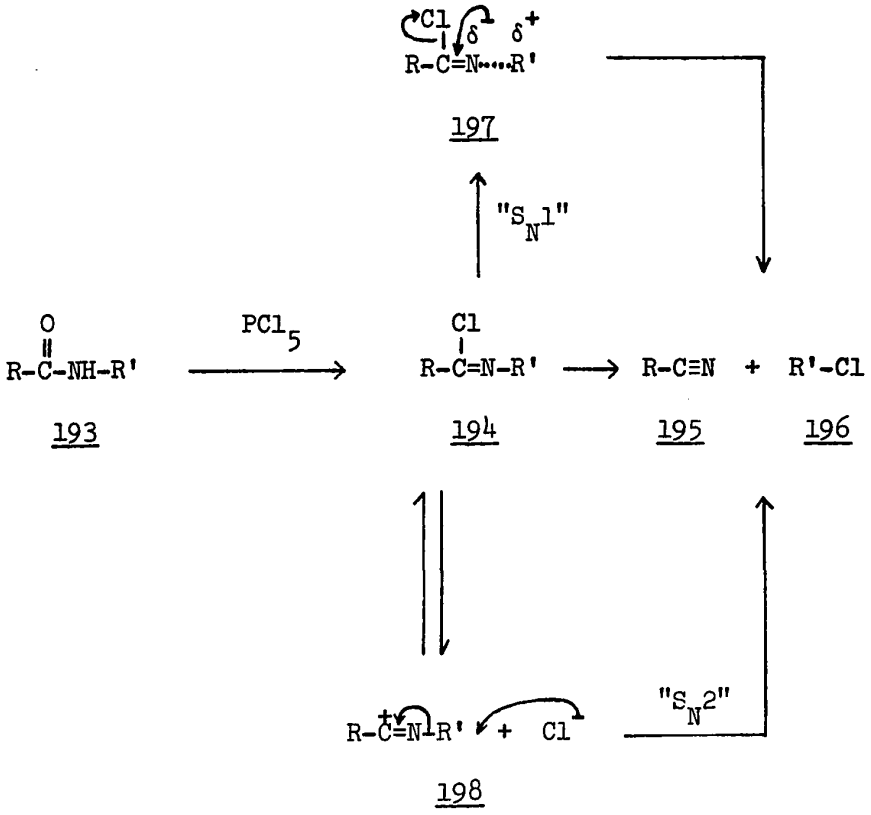


190 191 192

extensively investigated by von Braun[147] and is now referred to as the von Braun reaction. It has found limited use in the synthesis of alkyl halides, in the dealkylation of secondary and tertiary amides, and in effecting ring cleavages in cyclic tertiary amides.[144] A closely related reaction which involves the cleavage of a tertiary amine by cyanogen bromide to give an alkyl bromide and N-cyanoamine is also sometimes referred to as the von Braun reaction.[148]

Although the von Braun reaction of amides has attracted some attention in the past from a mechanistic viewpoint,[149,150] the exact details of the mechanism are as yet not unequivocally established. The mechanism indicated in Scheme 7 has been accepted as a working hypothesis for the reaction.[144,145] The evidence pointing to the

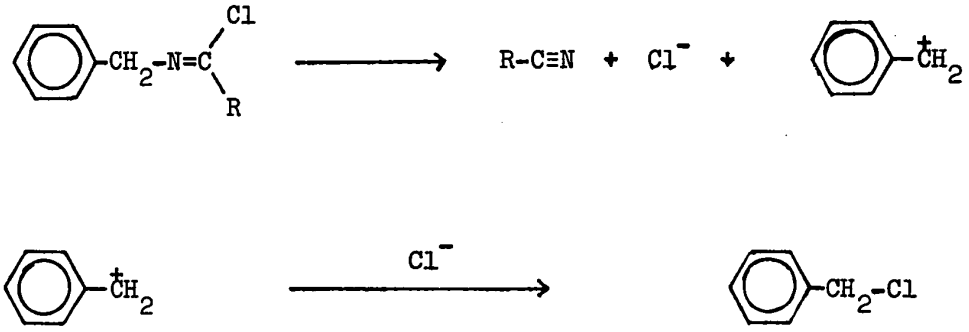
Scheme 7. Mechanism of the von Braun reaction.



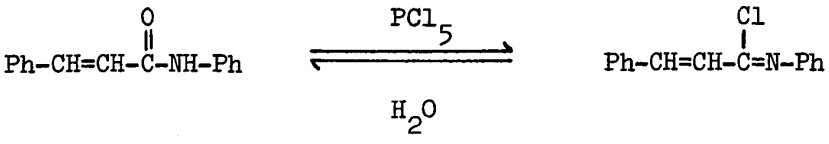
intermediacy of the imidoyl halide 194 comes from the fact that it has been isolated in some cases and has been shown to give the alkyl halide

196 and the nitrile 195 under the conditions of the von Braun reaction.[149] The decomposition of the imidoyl halide 194 to the nitrile 195 and the halide 196 has been suggested to occur via two limiting pathways.[149] The first is a "S_N1-like" mechanism which involves the heterolytic N-alkyl fission followed by rapid expulsion of the halide ion. In the second case there is loss of the halide ion which brings about a "S_N2-like" displacement on a saturated carbon atom (in the R' group).

Evidence for the two concurrent pathways comes from stereochemical studies with optically active substrates and from structural effects of both R and R' groups in 193. The S_N2 process is expected to be favored in cases where R is aromatic, as this will stabilize the intermediate cation 198, and the inversion of optical rotation reported for benzamides where the nitrogen atom is bonded to a chiral carbon atom in the R' group, is consistent with this argument.[150] On the other hand the S_N1 process should predominate with amides in which the displaced N-alkyl group (R') forms a stable cation. The plausibility of the S_N1-like process is supported by the results of N-alkylacetamides; reaction of PCl_5 with (-)-N-(α-methylbenzyl) acetamide yielded α-phenylethyl chloride which had lost most of its optical activity.[149] Furthermore, in the series where the N-alkyl group (R') was benzyl, p-methoxybenzyl, α-methylbenzyl, and benzhydryl, increasing yields of the alkyl halides (R'Cl) were obtained, being highest in the case of benzhydryl.[149] These results as well as the occasional reports[151] of olefin formation during the thermal elimination of N-t-alkyl imidoyl halides, are consistent with a fragmentation process involving an S_N1-like mechanism.



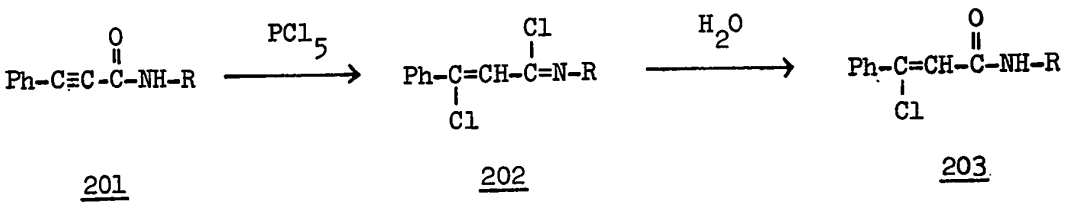
Only a few reports are available in the literature regarding the von Braun reaction of α,β-unsaturated amides. The inertness of such double bonds in amides has also been demonstrated by von Braun et al.[31-33] Cinnamanilide 199 reacts with phosphorus pentachloride to give the imidoyl halide 200 with preservation of the olefinic bond.



199 200

Only two α,β-acetylenic amides 201 (R = Ph, Et) have previously been studied. Von Braun and Ostermayer[30] have demonstrated

that in the reaction with phosphorus pentachloride, the triple bond suffered conjugate addition of HCl concurrent with the formation of the imidoyl chloride 202. This was shown to hydrolyze quantitatively to the β-chlorocinnamamides 203. In each case only one isomer of the



201 202 203

R = Ph, Et

β-chlorocinnamide (of undetermined stereochemistry) was obtained. In the present study it is shown that it is the trans isomer (H and Cl trans) in each case.

B. Reactions of α,β-Acetylenic Amides with Phosphorus Pentachloride.

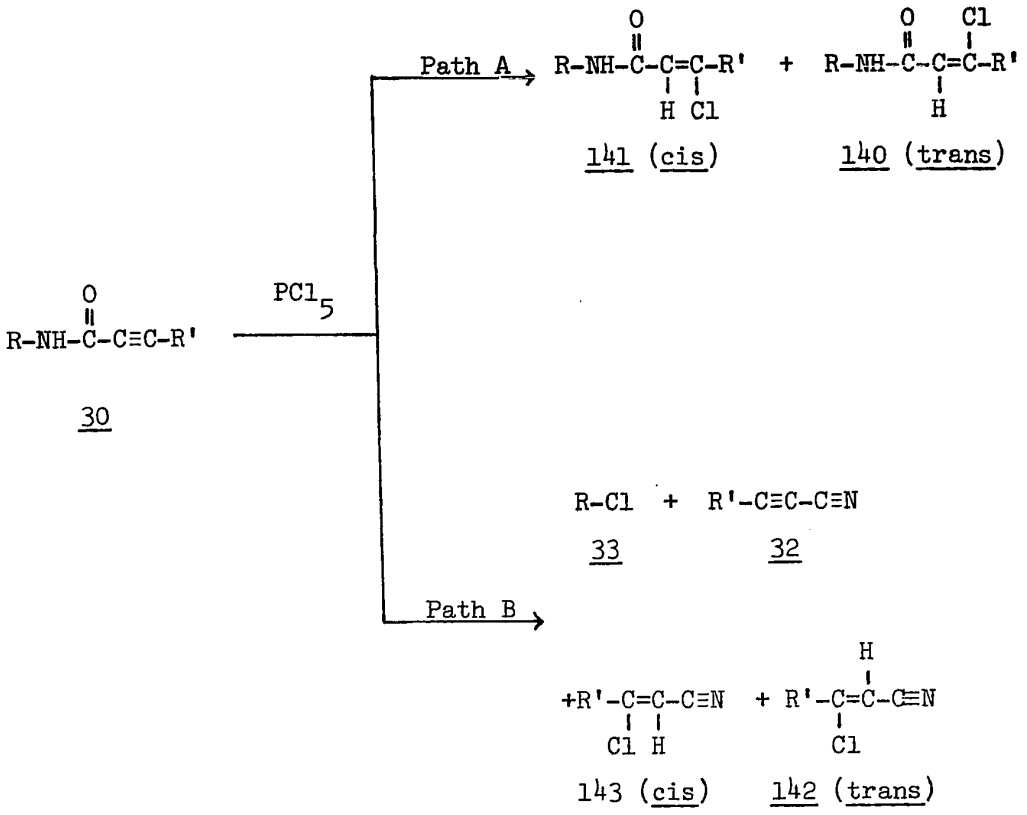
The paucity of data on α,β-acetylenic amides and their behavior towards phosphorus pentahalides and other halogenating agents such as thionyl chloride and phosgene, coupled with the novel results of the related acetylenic oximes with phosphorus pentachloride prompted the study of the reaction of phosphorus pentachloride with a series of α,β-acetylenic amides. Several new aliphatic and aromatic acetylenic amides of the type 30 (including some with a chiral substituent on the

nitrogen atom) were synthesized and were subjected to the action of phosphorus pentachloride.

All the amides examined reacted with phosphorus pentachloride under the conditions used for the reaction of the same reagent with the related acetylenic oximes. The results indicate that there are two pathways by which the reaction proceeds, depending on the nature of the R and R' groups in the amides 30(scheme 8).

The net result of the reaction by one pathway (path A) is the addition of the elements of HCl (one mole) to the triple bond of the starting amide. In the reaction of phosphorus pentachloride with

Scheme 8. Reactions of α,β-acetylenic amides with phosphorus pentachloride.

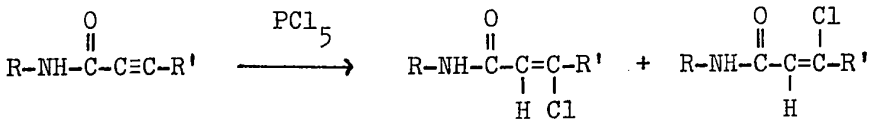


phenylpropiolanilide (30, R = R' = Ph) and ethylphenylpropiolamide (30, R = Et, R' = Ph), von Braun and Ostermayer[30] have isolated the precursor to the olefinic amides and have shown this to be the imidoyl halide of the type R-N=C(Cl)-CH=CCl-R' (on the basis of elemental analysis) which was shown to react with water and yield quantitatively the observed olefinic amides. The results of the reaction proceeding by path A are presented in Table XX.

Reaction by path B results in the fragmentation of the amide, 50% of the products being the chloride R-Cl 33, and the other 50% being made up of the nitriles 32, 142, and 143. The distribution of the nitriles seems to be determined by the groups R and R'. Table XXI represents the results of the reaction by path B. Reaction products were identified by comparison with authentic samples synthesized by alternate routes. For solid products the yields reported are those calculated from the actual amounts isolated by column chromatography; for liquid mixtures the product distributions were estimated directly from the nmr spectra of the mixtures.

TABLE XX

Von BRAUN REACTION (PATH A)



30 141 (cis) 140 (trans)

TABLE XX(cont'd)

Von BRAUN REACTION (PATH A)

Amides 30		Products (Amides 140 and 141)		
R	R'	Total Yield(%)	%cis(mp°)	%trans(mp°)
i-Pr	Ph	86	--	100 (97-8)
(R)-MeCH(Ph)	Ph	26*	--	100 (108-9)
(S)-MeCH(Ph)	Ph	19*	--	100 (107-8)
Ph	Me	90	82 (106-7)	18 (122-3)
i-Pr	Me	87	58 (85-6)	53 (74-5)
p-ClPh	Me	86	71 (128-9)	29 (135-6)
p-MePh	Me	79	77 (107-8)	23 (101-2)
(R)-MeCH(Ph)	Me	12*	56 (93-4)	44 (--**)
(S)-MeCH(Ph)	Me	27*	82 (92-3)	18 (--**)
i-Pr	Et	57	23 (50-1)	77 (71-2)

*Products corresponding to path B have also been identified.

**Products could not be purified; their identities were established by comparison of their ir and nmr spectra, as well as tlc characteristics with those of the authentic racemic products.

N.B. The R and S configurations are deduced from arguments presented in Section C.

TABLE XXI

Von BRAUN REACTION (PATH B)

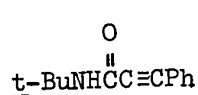
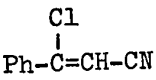
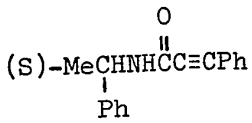
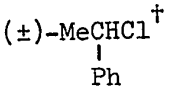
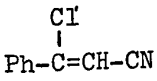
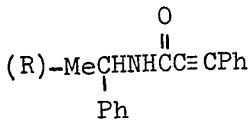
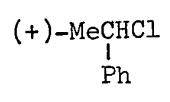
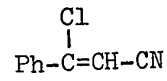
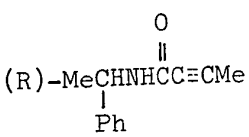
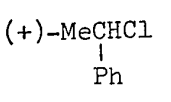
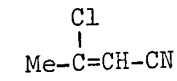
Amides	Total Yield(%)	Product Distribution	
	44§	PhC≡CCN (22%)	 (78%) (23% cis, 77% trans)
	41*	 (56%)	 (44%) (10% cis, 90% trans)
	68*	 (48%)	 (52%) (8% cis, 92% trans)
	58*	 (62%)	 (38%) (23% cis, 77% trans)

TABLE XXI(cont'd)

Von BRAUN REACTION (PATH B)

Amides	Total Yield(%)	Product Distribution	
(S)-MeCHNHCC≡CMe (Ph)	58*	(-)-MeCHCl (Ph) (60%)	Me-C(Cl)=CH-CN (40%) (12% cis, 88% trans)
(S)-MeCHNHCC≡CBu^t (Ph)	82	(-)-MeCHCl (Ph) (45%)	t-Bu-C(Cl)=CH-CN (55%) (91% cis, 9% trans)
(R)-MeCHNHCC≡CBu^t (Ph)	94	(+)-MeCHCl (Ph) (46%)	t-Bu-C(Cl)=CH-CN (54%) (79% cis, 21% trans)

TABLE XXI(cont'd)

Von BRAUN REACTION (PATH B)

Amides	Yield(%)	Product Distribution	
(R)-MeCHNHCC≡C-Et (Ph; O)	59**	(+)-MeCHCl (Ph) (50%)	Et-C(Cl)=CH-CN (50%) (18% cis, 82% trans)

§ t-BuCl was lost during the workup of the reaction mixture.

† α-Phenylethyl chloride racemized during distillation.

*Products corresponding to path A have also been identified.

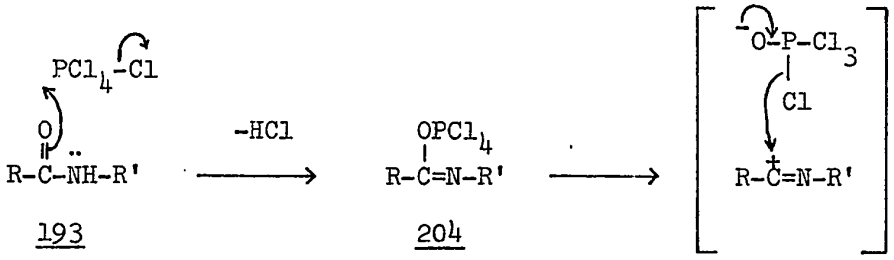
**Products corresponding to path A were isolated only in trace amounts. Their identities could not be fully established.

N.B. The (R) and (S) configurations are deduced from arguments presented in Section C.

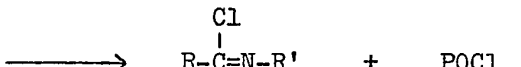
C. Aspects of the Mechanism of the Reaction of Phosphorus Pentachloride with α,β-Acetylenic Amides.

The reaction of saturated secondary amides 193 with phosphorus pentachloride (and other halogenating agents such as thionyl chloride) has attracted some attention in the past, and although all the details of the mechanism have not been unequivocally established,

there is evidence pointing to the intermediacy of imidoyl halides. The following has been suggested as a likely sequence in the formation of imidoyl chlorides from amides by the action of phosphorus pentachloride[144]:



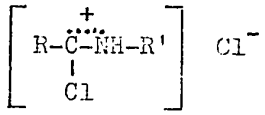
193 204



194

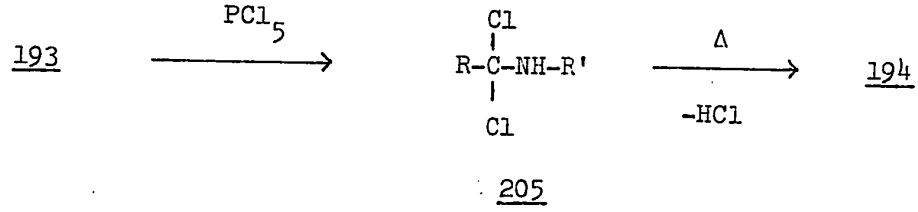
The isolation of the tetrachlorophosphonyl derivative 204, in some cases,[153] seems to support this mechanism. An alternative mechanism would require the intermediacy of an amidochloride 205,* which has been

*Also termed "imminium chloride" and formulated as 206.[156]



206

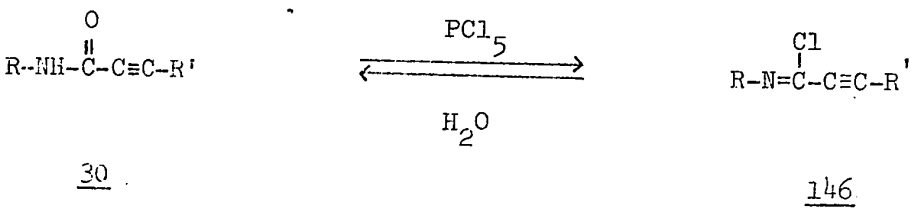
considered by early workers[154,155] as a precursor to the imidoyl chloride 194.



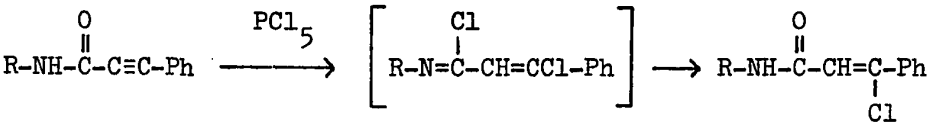
Imidoyl chlorides of the type 194 have been isolated and characterized by Vaughan and Carlson[149] from the reaction of amides with thionyl chloride; however, these authors hasten to point out that imidoyl chlorides cannot be postulated as a necessary intermediate in all cases, but rather, as a probable one under certain conditions.

1. Reaction by Path A.

In analogy with the results discussed above one would expect phosphorus pentachloride to react with an α,β-acetylenic amide 30 to produce initially an imidoyl chloride of the type 146. This imidoyl chloride, upon reaction with water would give the starting amide 30. However, von Braun and Ostermayer[30] have shown that the



reaction yields olefinic amides where the net result is the addition of HCl across the triple bond of the starting amide. The imidoyl chloride 202 was postulated[30] as a precursor to the amide 203 on the basis of the isolation of products whose analyses

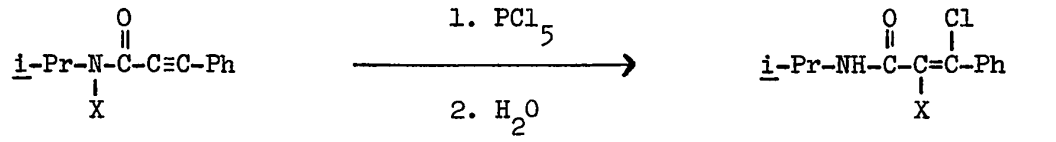


201 202 203

R = Ph, Et

approximated to compositions corresponding to the structure 202, and which upon hydrolysis yielded the amides 203.

The results of von Braun[30] and those obtained in the present study demonstrate that the net result of the action of phosphorus pentachloride on α,β-acetylenic amides is the addition of HCl to the acetylenic bond. Results from deuterium labelling studies in the present work seem to cast some doubts on the intermediacy of the imidoyl chloride 202 postulated by von Braun.[30] In one experiment the N-deuterated amide 207b was treated with phosphorus pentachloride and then quenched with H_2O and the product isolated was the amide 208a with no detectable deuterium (as estimated by nmr spectroscopy) either at the vinylic position or on the nitrogen atom. However, when the quenching was effected with D_2O, the amide obtained (208b) indicated deuterium incorporation at the vinylic position (ca. 33%) and not on the nitrogen. In another experiment the

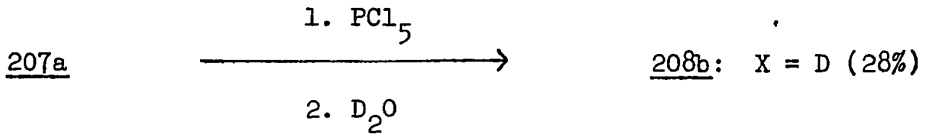


207a: X = H

b: X = D

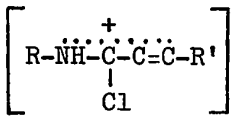
208a: X = H

b: X = D(33%)

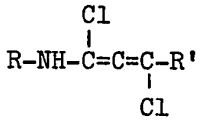


amide 207a on treatment with PCl_5 followed by treatment with D_2O, also gave the amide 208b with deuterium incorporation to the extent of ca. 28% at the vinylic position only. These results indicate that the deuterium in the amide 208b has its origin not in the deuterated amide 207b but in the D_2O used in the quenching step. These results also show that the intermediate, which in the final step reacts with water to produce the amide 208b, could not have been an imidoyl chloride of the type 202 postulated by von Braun.[30] It is highly unlikely that the vinylic hydrogen in 208a will exchange with D_2O under the conditions used.

Two other types of intermediates, 209 (or its "amidochloride" form) and 210 may be considered. These could also explain the

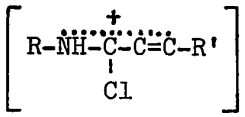


209

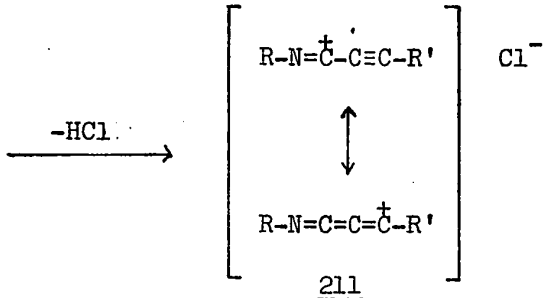


210

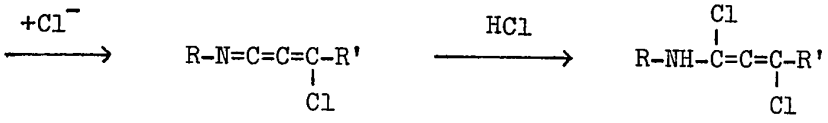
results of von Braun.[30] From 209 the following sequence seems plausible:



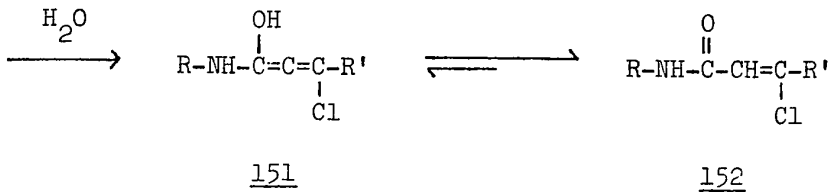
209



211

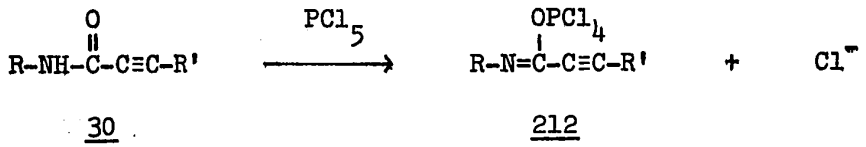


148 210

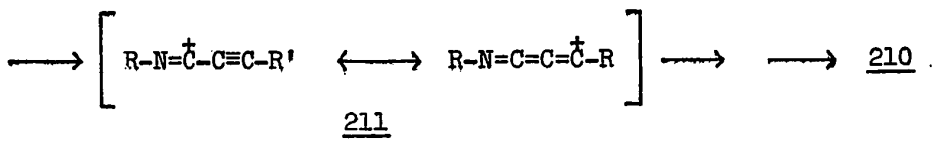


151 152

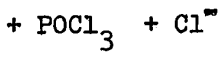
Intermediate 210 could also be visualized as arising from the amide in the following series of reactions.



30 212



211



It is also interesting to note that the elemental composition of either 209 or 210 is identical to that of the imidoyl chloride intermediate 202 postulated by von Braun. Intermediate 210 has the structural features of both an allene and an enamine. Normally an enamine with a hydrogen atom on the nitrogen is expected to be more stable in its tautomeric Schiff base form (which in this particular case will be the imidoyl chloride 202 postulated by von Braun). However, the incorporation of deuterium on the carbon atom in amide 208b is not easily explained if the intermediate is

in the imidoyl chloride form 202.

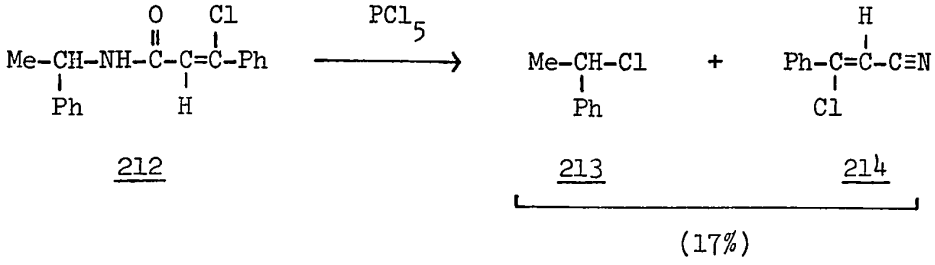
The stereochemistry of the products 152 cannot be readily predicted from the above schemes. When R' = Ph the "HCl addition" is exclusively trans. (Table XX). Initial formation of both cis and trans amides 152 followed by equilibration to the more stable trans isomer was ruled out on the basis of control experiments in which each isomer was subjected to the conditions of the reaction. The trans isomer was recovered unchanged and the cis isomer underwent only partial isomerization (42% trans product).

In one experiment the acetylenic amide 30 (R = i-Pr, R' = Ph) was treated with phosphorus pentachloride in ether in the presence of lithium bromide and the products obtained were the cis- and trans-dibromo amides 170 and 171. These results are identical to those obtained in the reaction of the amide with phosphorus pentabromide and similar to those in the reaction of the related oxime 1 with phosphorus pentabromide.

2. Reaction by Path B.

The reaction of α,β-acetylenic amides with phosphorus pentachloride by path B involves the cleavage of the amide to produce chlorides and nitriles, the chlorides resulting from the N-substituent and the nitriles from the remainder of the molecule. This is the typical von Braun reaction discussed briefly earlier (Sec. A). There are several cases in which the cleavage process is accompanied by the addition of the elements of HCl to the acetylenic function. One aspect of the problem is to decide the order in which the two events take place, that is, whether the N-alkyl fission precedes the addition of

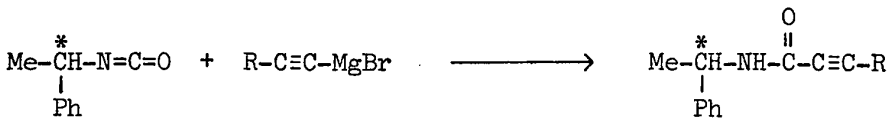
HCl to the acetylenic bond or vice versa. The chloroolefinic nitriles 142 and 143, do not seem to result from addition of HCl to the initially produced acetylenic nitrile 32 because there are several cases in which such acetylenic nitriles are produced to the exclusion of the chloroolefinic amides 140 and 141. In one experiment the chloroolefinic amide 212 was treated with phosphorus pentachloride under the conditions used for the acetylenic amides. It was found that this amide also underwent fragmentation to the extent of 17% and a major part of the starting material (ca. 58%) was recovered unchanged. The corresponding acetylenic amide 30



(R = MeCH(Ph), R' = Ph), under the same conditions, gave the chloride 213 and the nitrile 214 and its cis-isomer (together accounting for 68% fragmentation) and the amide 212 (26% based on starting material). It seems less likely that the HCl addition to the acetylenic bond precedes the N-alkyl fission. In cases where fragmentation occurs without HCl addition to the acetylenic bond one must conclude that the N-alkyl fission is a much faster process.

The other aspect of the problem concerns the manner in which the N-alkyl cleavage occurs and the formation of the chloride. In

this connection, since some data pertaining to the von Braun reaction involving optically active saturated amides were available,[149,150] it was decided to investigate the action of phosphorus pentachloride on the α,β-acetylenic amides with a chiral substituent on the nitrogen atom. It was especially interesting to see what effect the α,β-unsaturation provided by the triple bond would have on the N-alkyl fission during the reaction. A series of optically active propiolamides 215 were therefore synthesized from the corresponding acetylenic Grignard reagents and optically active α-phenylethylisocyanates according to the following scheme:



215

R = Me, Et, t-Bu, Ph

In this reaction the configurational identity of the chiral carbon atom of the isocyanate is expected to be retained in the acetylenic amide. The optically active (+) and (-)- α-phenylethylisocyanates used were supplied by Fluka AG, Buchs, Switzerland.

a. Stereochemical Identities of the Commercial "(+)" and "(-)"-α-Phenylethylisocyanates.

Where reactions of optically active compounds are considered,

a knowledge of the configurational and specific rotational relationships of the starting materials and the final products is among the prerequisites for mechanistic significance. It was therefore imperative that the configurational identities of the commercial samples of the "(+)" and "(-)"-α-phenylethylisocyanates be established.

Recent studies by Soviet workers[157,158] have established that the reaction of phosgene with (-)-α-phenylethylamine hydrochloride gives good yields of (-)-α-phenylethylisocyanate of high optical purity. In a detailed study of the optical rotary dispersion of this isocyanate these workers[158] have established that its optical rotation (sign as well as magnitude) is dependent on such variables as solvent, concentration, and temperature. For example, the optical rotation of this isocyanate is (-) when measured without solvent, but is (+) in benzene at low concentrations (10g/100 ml or less) and (-) in carbon tetrachloride as shown in Table XXII.

TABLE XXII

MOLECULAR ROTATIONS OF (-)-α-PHENYLETHYLISOCYANATE.[158]

λnm	Neat	C_6H_6			CCl_4
		c, 5.54	1.0	16.70	2.05
	ℓ 0.5	1.0	2.0	2.0	2.0
578	-14.5	+2.1	+3.1	-0.30	-11.55
546	-16.7	+2.5	+3.6	-0.36	-13.25
436	-30.2	+4.5	+6.1	-1.18	-25.0
405	-37.8	+5.2	+7.2	-1.8	-31.5

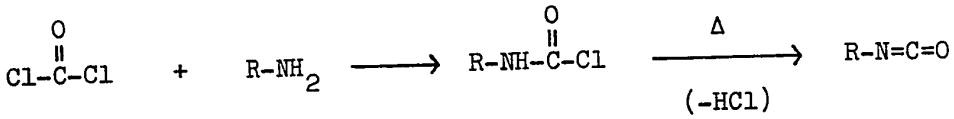
TABLE XXII(cont'd)

MOLECULAR ROTATIONS OF (-)-α-PHENYLETHYLISOCYANATE.[158]

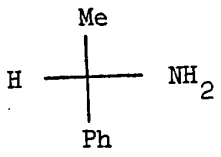
λnm	Neat	C_6H_6			CCl_4
		c, 5.54	1.0	16.70	2.05
	1, 0.5	1.0	2.0	2.0	2.0
365	-53.0	+6.7	+9.7	-3.2	-45.0
334	-71.5	+8.4	+12.6	--	-63.1

In this connection, it is interesting to note that in the first ever reported synthesis of optically active α-phenylethylisocyanate, Cairns[159] reacted (+)-α-phenylethylamine hydrochloride with phosgene and obtained an optically active α-phenylethylisocyanate whose sign of rotation was (-) when measured in benzene. In this report[159] benzene was the only solvent used and no measurement was made on the pure liquid. However, at the time of Cairns' study, the peculiar property of some solvents to invert the optical rotation of certain types of compounds was unknown. It is now known that optically active compounds such as atrolactic acid,[160] certain types of simple amides[161] and some peptides[162] exhibit different signs of rotation in different solvents. It is also interesting to note that these are all compounds containing the carbonyl function.

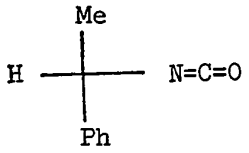
The reaction of a primary amine (aliphatic or aromatic) with phosgene is one of the general methods of preparing the corresponding isocyanate.[163] In this reaction phosgene converts the amine to the chloroformamide derivative, which at elevated temperatures loses HCl



to give the isocyanate. There is no reason to believe that at any stage of the reaction there is any severance of the carbon-nitrogen bond of the amine. Thus, to a high degree of probability, an optically active primary amine in which the NH_2 group is directly attached to a chiral carbon yields an isocyanate whose configuration is identical to that of the starting amine. The stereochemical relationships between optically active α-phenylethylamines and optically active α-phenylethylisocyanates are thus easily derived: the (S)-(-)-α-phenylethylamine gives the (S)-α-phenylethylisocyanate; by the same token, the (R)-α-phenylethylisocyanate has the same configuration as the R-(+)-α-phenylethylamine.



(S)-(-)-α-phenylethylamine[164]



(S)-α-phenylethylisocyanate

The optical rotatory characteristics of the "(+)" and "(-)" -α-phenylethylisocyanates (Fluka) in several solvents including

benzene were determined and are given in Tables XXIII and XIV.

TABLE XXIII

MOLECULAR ROTATIONS* OF "(-)"-1-PHENYLAETHYL ISOCYANAT PURUM (FLUKA)

λnm	C_6H_6	CCl_4	$CHCl_3$	Et_2O
	c,1.482	1.444	1.586	1.876
589	-3.87	+13.23	+21.40	+32.21
578	-3.87	+13.74	+22.71	+33.69
546	-4.75	+15.58	+26.05	+38.47
436	-7.04	+29.83	+47.64	+69.97
365	-9.63	+53.95	+83.23	+117.92

*cell length(ℓ) = 1.0 dm

TABLE XXIV

MOLECULAR ROTATIONS*OF "(+)"-1-PHENYLAETHYL ISOCYANAT PURUM (FLUKA)

λnm	C_6H_6	CCl_4	$CHCl_3$	Et_2O
	c,1.685	1.487	1.615	1.436
589	+2.44	-13.74	-21.12	-32.75
578	+2.70	-14.23	-22.39	-34.19
546	+2.97	-16.71	-25.75	-39.20
436	+4.28	-37.63	-47.33	-70.43
365	+5.41	-55.65	-82.55	-118.95

*cell length (ℓ) = 1.0 dm

These results, in conjunction with those of the Soviet workers,[158] clearly indicate that the material obtained from Fluka AG, labelled "(+)-1-phenylaethylisocyanat purum" must configurationally be identical to S-(-)-α-phenylethylamine and therefore must actually be S-(-)-α-phenylethylisocyanate; similarly the one labelled "(-)"-1-phenylaethylisocyanat purum" must actually be R-(+)-α-phenylethylisocyanate. In the discussions hereafter, these two isocyanates and the amides 215 derived from these will be referred to by their true configurations (R and S notation).

The phenomenon of the dependence of the sign of optical rotation on the nature of the solvent, was observed in the present study also in the cases of certain acetylenic and chloroolefinic amides. These observations are summarized in Table XXV.

TABLE XXV

MOLECULAR ROTATIONS OF AMIDES*

Amide	Rotation	Concn	Solvent
(R)-MeCH(Ph)NHCC≡CPh (O)	+13.35	0.971	CCl_4
	-156.60	0.900	EtOH
	-32.87	0.977	$CHCl_3$
(R)-MeCH(Ph)NHCC≡CBu^t (O)	+77.93	0.761	CCl_4
	+33.98	0.640	EtOH
	+70.76	0.940	$CHCl_3$
(R)-MeCH(Ph)NHCC(H)=C(Cl)-Ph (O)	-15.53	0.496	CCl_4
	+38.23	0.493	EtOH

TABLE XXIV(cont'd)

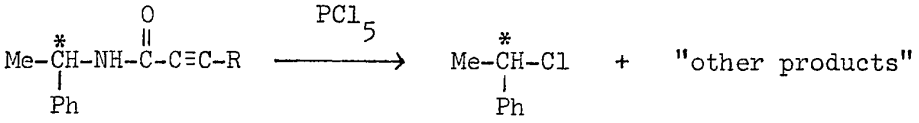
MOLECULAR ROTATIONS OF AMIDES*

Amide	Rotation	Concn	Solvent
(S)-MeCHNHC(=O)-C≡C-Me (Ph; H, Cl)	-60.01	0.985	$CHCl_3$
	-325.57	0.600	CCl_4
	-261.45	0.701	EtOH
	-234.90	1.140	$CHCl_3$

*cell length = 1.0 dm

b. The Mechanism of the N-Alkyl Fission: Reaction of Phosphorus Pentachloride with Optically Active N-(α-phenylethyl) propiolamides.

The optically active N-(α-phenylethyl) propiolamides 215 were treated with phosphorus pentachloride in anhydrous ether and the products were identified. In each case α-phenylethylchloride



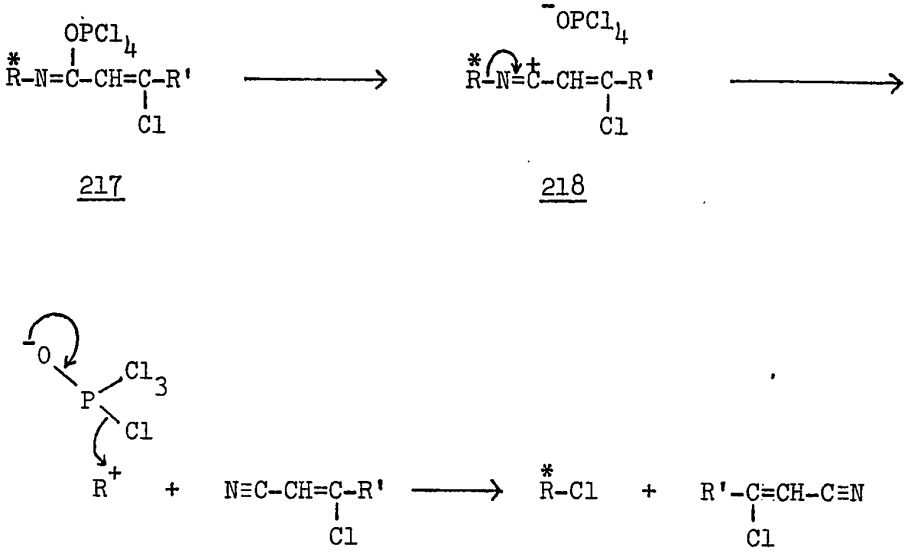
215 216

(R = Ph, Me, Et, t-Bu)

216 was one of the products, the other products were mainly chloroolefinic nitriles, and in some cases chloroolefinic amides resulting from reaction by path A (see Table XX). It was not possible to isolate the chloride free of all the other reaction products; however, column chromatography afforded the chloride mixed with the nitriles in each case. The solvent was removed at reduced pressure and the mixture was shown to be feebly but unmistakeably optically active. The mixtures of the nitriles present were such that they could not possess any optical activity and thus all the activity of the product is attributed to the α-phenylethylchloride 216. The sign of rotation was also shown to be unchanged in chloroform, carbon tetrachloride and benzene. As the material used in each case was a crude mixture it was not possible to ascertain the optical purity of the chloride. The results are summarized in Table XXI.

It is well established that (-)-α-phenylethylchloride has the S configuration and the (+) chloride the R configuration.[165] It is clear from Table XXI that, in the reaction of phosphorus pentachloride with the amides 215, there is retention of configuration in the α-phenylethylchloride 216 produced in the reaction. As the observed optical activities in the chloride were low there was only a small preference for retention of configuration over racemization. The observation of predominant racemization implies that the N-alkyl fission takes place in an S_N1-type process to produce the α-phenylethyl cation. The small preference for the retention of configuration can be rationalized if one invokes an S_Ni process in a manner reminiscent of the cleavage of chlorosulfites to produce

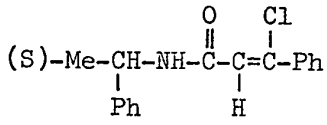
alkyl halides.[166] This mechanism as pictured below, requires the ionization of the substrate 217 to give a cation in the form of an



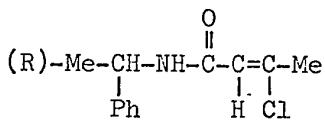
intimate ion pair, followed by substitution by part of the leaving group ($^{-}O\text{-}PCl_4$), which of necessity must approach from the same side as the leaving group, thereby resulting in retention of configuration in the product. This might well be a diffusion-controlled "cage" process. Another possibility to be considered, although not as attractive, is that the observed retention of configuration is the result of a double inversion on the alkyl group, especially when ether-type solvents are used. However, in such cases, retention of configuration is the predominant effect. A previous study[149] of the reaction of thionyl chloride in nitromethane with saturated amides having α-phenylethyl substituents on the nitrogen

atom indicated that the chloride produced was feebly optically active and from the correlation of optical activities, it was concluded that, to the extent that there was optical activity, inversion of configuration had occurred. Further studies in this area would be interesting.

In cases where chloroolefinic amides were isolated (reaction by path A, Table XX), these were strongly optically active as indicated below. In view of their strong optical activity it can be concluded that they were not produced by the reaction of the α-phenylethyl cation with the nitrile in a Ritter-type reaction.[103] It is also assumed that the configurations of the α-phenylethyl group in these amides are the same as those of the same group in the acetylenic amides from which they arose.



$$[\alpha]_D^{23} + 21.24^\circ \quad (c\ 0.998,\ CHCl_3)$$



$$[\alpha]_D^{23} + 106.2^\circ \quad (c\ 1.087,\ CHCl_3)$$

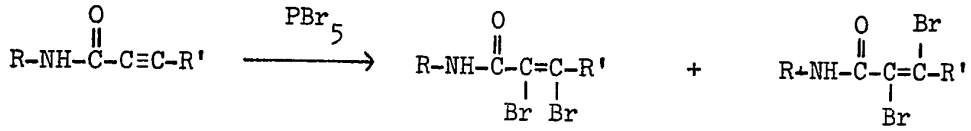
D. Reaction of α,β-Acetylenic Amides with Phosphorus Pentabromide.

In view of the observed differences in the behavior of phosphorus pentachloride and phosphorus pentabromide towards the related oximes, it

was of interest to see if the same trend would be exhibited in the α,β-acetylenic amides. The reaction of phosphorus pentabromide with some acetylenic amides was therefore examined and the results summarized in Table XXVI.

TABLE XXVI

REACTION OF α,β-ACETYLENIC AMIDES WITH PBr_5

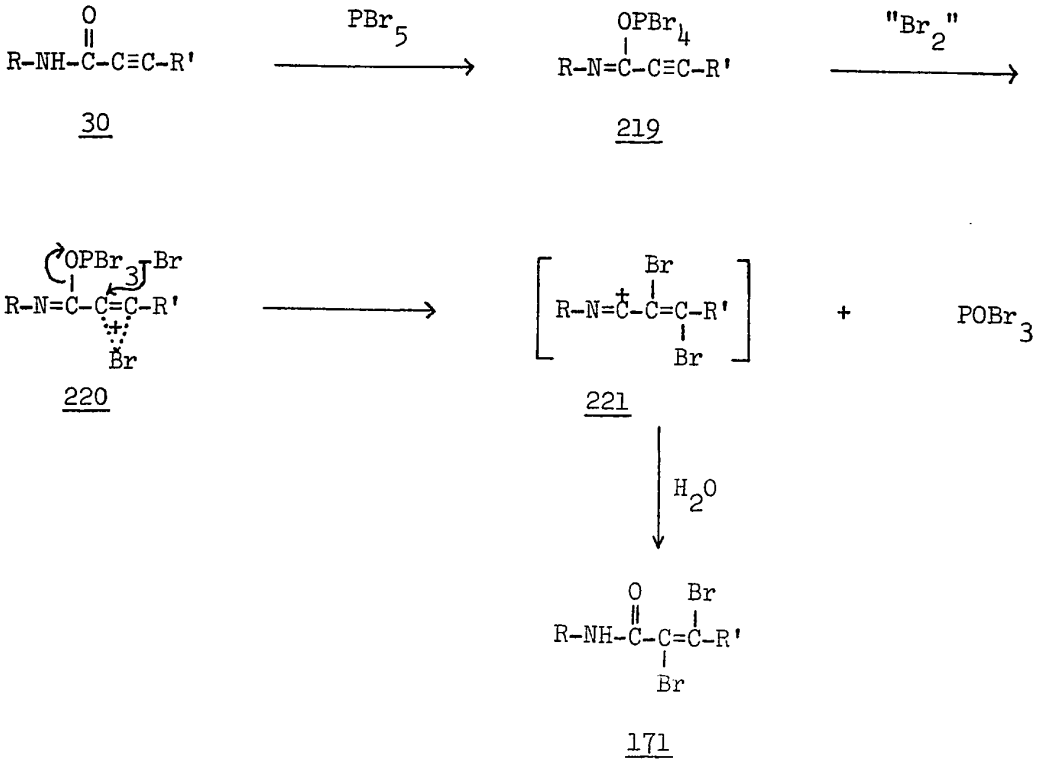


30 170 (cis) 171 (trans)

Acetylenic Amides(30)		Olefinic Amides (170 + 171)		
R	R'	Total Yield(%)	%cis(mp°)	%trans(mp°)
i-Pr	Ph	84	16 (117-8)	84 (145-6)
Ph	Ph	80	11 (127-8)	89 (167-8)
i-Pr	Me	80	--	100 (124-5)

Under the conditions employed no unreacted acetylenic amides were detectable in the reaction products. It will be recalled that in the Beckmann rearrangement of the related oximes with phosphorus pentabromide (Sec. IID), small amounts of the acetylenic amide

(rearrangement product) were always obtained, and that the addition of bromine to the acetylenic function was predominantly cis. In the reaction of the acetylenic amides with phosphorus pentabromide it is the trans-dibromo amide 171 that is the predominant product. It is highly probable that the mechanism operating in the case of the amides is different from that in the case of the related oximes. In view of the fact that the predominant product is the trans-dibromo amide, a bromonium ion intermediate of the type postulated by Pincock and Yates [137] seems attractive here and a scheme as given below can be considered:

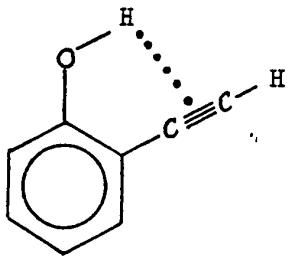


The addition of the second bromine atom to produce the trans dibromo product can be either intramolecular or intermolecular. It would be interesting to examine a wider range of amides including those that would fragment to give alkyl bromide and nitriles in reactions analogous to those with phosphorus pentachloride.

In one case in which an acetylenic amide (30, R = i-Pr, R' = Ph) was treated with phosphoryl bromide under conditions used for the phosphorus pentabromide reaction, the starting material was recovered unchanged. This is in contrast to the behavior of the related oxime with phosphoryl bromide where the rearrangement to the amide was accompanied by addition of Br_2 to the acetylenic bond (Sec. IIF).

IV. Intramolecular π-Hydrogen Bonding in α,β-Acetylenic Oximes.

There has been a considerable amount of study on the hydrogen bond in recent years using various spectroscopic techniques.[168] Perhaps the most straightforward method for the detection of hydrogen bonds is provided by ir spectroscopy. That the π-electron system of an acetylenic bond may function as the donor or the "base" in hydrogen bonding was first discovered in 1951 in the case of o-hydroxyphenyl-



222

acetylene 222.[169] Since then many examples of intramolecular π-hydrogen bonding involving double bonds and π-electron systems of the phenyl ring in several classes of compounds have been demonstrated.[168,170,171]

Intramolecular (chelated) hydrogen bonding can be readily distinguished from the intermolecular (associated) type by ir spectroscopy by virtue of the fact that the latter is concentration dependent while the former is not. As the intramolecular hydrogen bond is an internal effect it persists even at low concentrations, and the intermolecular hydrogen bonding is practically nonexistent at very high dilutions. This feature serves as the main guide in distinguishing between the two types of hydrogen bonding. That the difference between the stability or ease of formation of the inter- and intramolecular

hydrogen bonds is the difference in magnitude of the entropy change accompanying their formation was pointed out by Jaffe.[172] The entropy change in intermolecular bonds is much larger (of the order of 50 e.u.) than that accompanying the formation of the intramolecular bond. For this reason one might expect to observe very weak hydrogen bonds more easily when these are of the intramolecular type.

For compounds containing hydroxyl groups usually two absorption bands are observable (see Figure 1) in the "OH-stretching" region of the ir spectra of their solutions, the higher frequency narrower band being that due to the "free OH" (stretching vibration of the OH group not involved in hydrogen bonding), and the lower frequency broader band being that due to the "bonded OH" (vibration of the OH group involved in hydrogen bonding).[173]

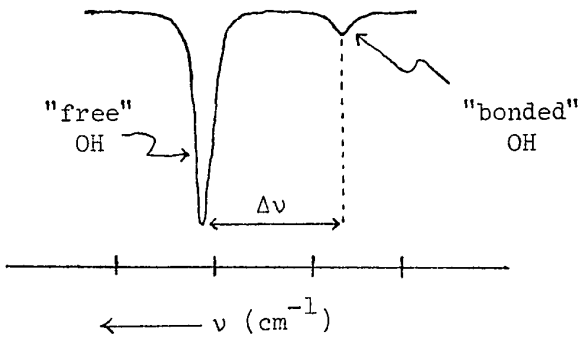


Figure 1. Ir spectrum of "free" and "bonded" OH region.

The ratio of the integrated intensities of the two bands is generally regarded as reflecting the ratio of the molecules existing in the non-hydrogen bonded and the hydrogen bonded forms, and the frequency separation ($\Delta\nu$) has been correlated with various physical and chemical properties and many workers have found it convenient to employ the frequency shift ($\Delta\nu$) as a measure of the strength of the hydrogen bond.[173-5]

Intramolecular hydrogen bonding has proved to be very useful in the elucidation of conformations in flexible systems, and the application of the phenomenon to problems in stereochemistry has been recently reviewed.[176] Comparisons of the double bond and the triple bond in their intramolecular hydrogen bonding capabilities has shown that the acetylenic bond forms stronger hydrogen bonds than the olefinic bond.[177] Both steric and conformational factors influence the formation of intramolecular π-hydrogen bonds. Thus, trans-2-alkynylcyclopentanol does not show the π-bonded hydroxyl absorption, whereas it is observed in trans-2-alkynylcyclohexanol (in the diequatorial conformation), and in trans-2-alkynylcycloheptanol.[178] The intensity of the π-bonded hydroxyl band is weaker in the cycloheptanol even though the π-hydrogen bond is stronger here ($\Delta\nu$ = 52 cm^{-1}) than in the cyclohexanol ($\Delta\nu$ = 41 cm^{-1}), which indicates that the probability of the conformation best suited for a π-bond is lower in the cycloheptanol.[178]

In the case of α,β-acetylenic ketoximes synthesized in the present work there was ample evidence that one was dealing with a single isomer in each case, and that the configuration of this isomer was such that the triple bond and the hydroxyl group were in a syn relationship. In each case the nmr spectrum (dilute solution in

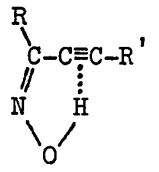
DMSO) revealed a single sharp signal for the hydroxyl proton and the chemical shift of the signal fell within a fairly narrow range (δ11.18 to δ12.23), and all of the solid oximes had sharp melting points. Each oxime also readily underwent ring closure to yield the expected isomerically pure 3,5-disubstituted isoxazole. In addition, these oximes readily underwent the well-known Beckmann rearrangement and/or fragmentation reactions yielding products whose structures indicated that the hydroxyl group must have been syn with respect to the triple bond in each case. The rearrangement in all cases, however, was accompanied by HCl (in phosphorus pentachloride reactions) or Br_2 (in phosphorus pentabromide reactions) additions to the acetylenic function.

The spatial relationship existing between the OH group and the acetylenic bond in o-hydroxyphenylacetylene 222,[169] is very nearly the same as that between the two groups in the α,β-acetylenic oximes in the syn configuration. In this configuration where the hydroxyl group is closer to the acetylenic bond some direct field effects are probably established, and since the hydrogen atom of the OH group is closer to the α-carbon atom of the triple bond, it is possible that some polarization, however small, of the triple bond will result and the OH group will interact with that part of the π-system in the region of the α-carbon. Moreover, the cylindrical symmetry of the π-system provides good overlap possibilities and thus a fairly strong π-hydrogen bond is expected to be produced.

This expectation was fully realized when the OH absorption characteristics of these oximes were examined as a function of concentration. In each case the two characteristic bands for the OH

stretching vibrations were observed but that due to the "bonded OH" persisted at dilutions where intermolecular hydrogen bonds were nonexistent. As a representative example, the ir spectra in the "OH region" of oxime 1 (R = i-Pr, R' = Ph) in CCl_4 at concentrations of 0.2 M, 0.02 M and 0.002 M using cell path lengths of 0.1 mm(A), 1.0 mm(B), and 10 mm(C) respectively are shown in Figure 2. In the first spectrum (A) bands due to both "free" and intermolecularly bonded OH groups can be observed. The very broad band, due to intermolecular association, decreases markedly in spectrum B and disappears entirely in spectrum C.

The more intense sharp band at higher frequency in each spectrum is ascribed to the "free OH" group. Its frequency (3588 cm^{-1}) is nearly the same as that of the OH frequency of anti-benzaldoxime (3595 cm^{-1}). The lower intensity broader band at 3367 cm^{-1} in C is ascribed to the "bonded OH" in the molecule, the bonding being of the type,



223

in which the OH group of the oxime function is bonded to the π-electrons of the acetylenic bond in 223 to give an average frequency shift (Δν) of 228 cm^{-1}.

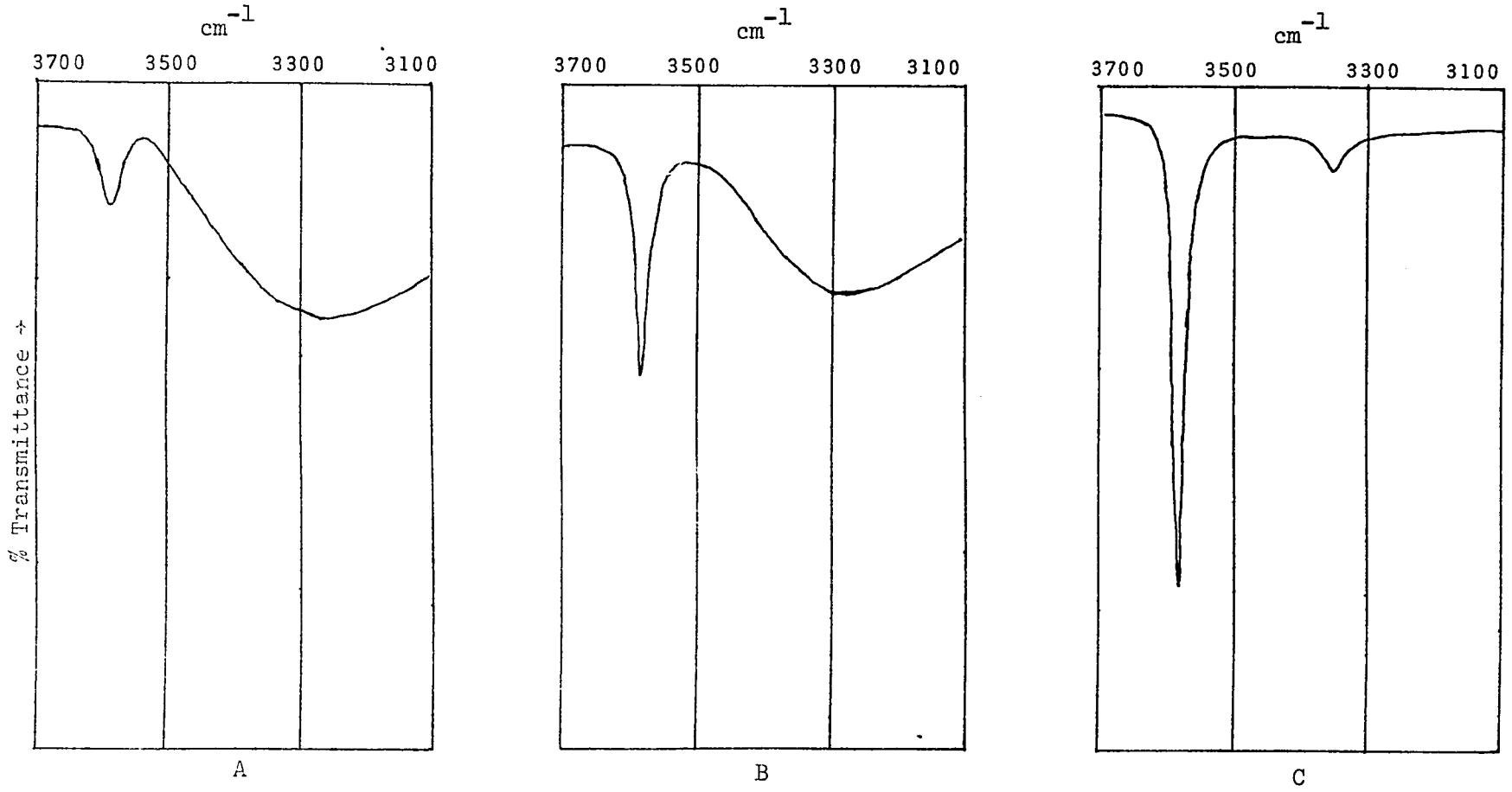


Figure 2. Ir spectra of the OH region of oxime 1 (R = i-Pr, R' = Ph): left to right, curves A, B and C at concentrations 0.2, 0.02 and 0.002 M, respectively. The cell path lengths are: A, 0.1 mm; B, 1.0 mm; C, 10 mm.

The intensity of the π-bonded OH band, however, is considerably smaller, indicating that the number of molecules of the oxime existing in a conformation having π-hydrogen bonds with the triple bond is far fewer than the number of molecules of the oxime in which there are no such intramolecular π-hydrogen bonds. The OH frequencies and the frequency separation of the two bands are listed in Table XXVII.

The frequency separations between the "free" and "bonded" OH bands ($\Delta\nu_{OH}$) in the α,β-acetylenic oximes vary between 220 and 234 cm^{-1}, and are among the largest observed for such intramolecular π-hydrogen bonding. There have been several attempts in the past to correlate the frequency separation $\Delta\nu_{OH}$ with the energy of the π-hydrogen bond (ΔH) and different workers have used different assumptions and different approaches. For example, Goldman and Crisler[179] suggested that the strengths of this kind of interaction in 2-phenylethanol and 2-(p-methoxy)phenylethanol are 0.88 and 0.98 kcal/mole respectively, on the basis of an earlier postulation of Badger and Bauer[180] that a frequency separation of 70 cm^{-1} represented 1 kcal/mole for the energy of the interaction. This relationship is no longer considered valid,[173] and Oki and Iwamura[181] have calculated the energy of the interaction in several π-hydrogen bonded systems from the temperature dependence of the integrated intensities of the "bonded" and "nonbonded" bands. In their study they found no linear relationship between the Δν and ΔH. Although several studies of π-hydrogen bonding[182] have demonstrated a systematic increase in $\Delta\nu_{OH}$ with increase in the electron density of the π-system by appropriate substitution at the multiple bond, there does not appear to be any general relation between $\Delta\nu_{OH}$ and ΔH.

The frequency shifts for the intramolecular π-interaction between acetylenic functions and OD groups have been observed to be smaller than those for the corresponding OH compounds.[177] As can be seen from Table XXVIII, the same trend is also observed in the O-deuterated α,β-acetylenic oximes. Several studies[183,184] have indicated that deuterium bonds are weaker than hydrogen bonds.

Whatever is the relation between the frequency separation and the strength of the interaction, it is clear that in these α,β-acetylenic oximes one has a set of $\Delta\nu_{OH}$ values that are among the largest observed for such π-hydrogen bonding, and there is little doubt as to the existence of this interaction in these molecules when the OH group is syn with respect to the triple bond. The case of t-butylpropiolaldoxime (38) is a very elegant example. This is the only α,β-acetylenic oxime synthesized in this study which consisted of a mixture of 31% syn (38a, H and OH "cis") and 69% anti (38b, H and OH "trans") as demonstrated by nmr spectroscopy. The ir spectrum of a very dilute solution of this mixture (0.002M) clearly showed the intramolecularly π-hydrogen bonded band at 3356cm^{-1} and the "free" OH bond at 3590cm^{-1}. The isomer in which the OH group is closer to the triple bond (38b) was found to cyclize to the expected 5-t-butylisoxazole (39) in the presence of sodium hydride and therefore a separation of the other isomer in which the OH group is directed away from the acetylenic bond was possible. However, it was observed that in solution this product (38a) slowly isomerized to the other isomer yielding a mixture of 78% 38a and 22% 38b after 2 days and 67% 38a and 33% 38b after 13 days. It is estimated that at the time of the ir measurement the material contained a maximum of 10% of

the isomer 38b. Nevertheless, in the ir spectrum of the dilute solution of the product in CCl_4 (0.002 M) the π-bonded band at 3356 cm^{-1} was not detectable.

Internal hydrogen bonding, such as the well-known case of o-nitrophenol, generally results in anomalous physical properties, particularly in volatility behavior. This is exemplified in the case of o-hydroxyphenylacetylene 222 which is more volatile (bp 75° at 15 mm) than its methoxy derivative (bp 99° at 15 mm). In this connection it is interesting to note that many of the α,β-acetylenic oximes made in this study (cf. Table III) are liquids at ambient temperature, whereas the saturated oximes of comparable molecular weights are generally solids.

TABLE XXVII

IR SPECTRA ("OH REGION") OF α,β-ACETYLENIC OXIMES

$$(R\text{-}\underset{\underset{NOH}{\|}}{C}\text{-}C{\equiv}C\text{-}R')$$

		ν_{OH}		
R	R'	"free"	"bonded"	$\Delta\nu_{OH}$
H	Me	3591	3360	231
H	t-Bu	3590	3356	234
H	Ph	3586	3362	224
i-Pr	Ph	3588	3367	221
sec-Bu	Ph	3590	3366	224
t-Bu	Ph	3588	3360	228
Ph	Ph	3584	3352	232

TABLE XXVII(cont'd)

IR SPECTRA ("OH REGION") OF α,β-ACETYLENIC OXIMES

$$(R\text{-}\underset{\underset{NOH}{\|}}{C}\text{-}C\equiv C\text{-}R')$$

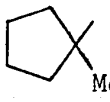
R	R'	ν_{OH} "free"	ν_{OH} "bonded"	$\Delta\nu_{OH}$
MeCH(Ph)	Ph	3587	3360	227
Ph-CH_2	Ph	3585	3365	220
p-MePh	Ph	3582	3354	228
p-MeOPh	Ph	3580	3353	227
i-Pr	Me	3590	3360	230
t-Bu	Me	3590	3360	230
Ph	Me	3585	3354	231
Me(CH)Ph	Me	3592	3362	230
p-MePh	Me	3598	3368	230
p-ClPh	Me	3581	3350	231
p-i-PrPh	Me	3584	3356	228
t-Bu	t-Bu	3588	3356	232
Ph	t-Bu	3580	3346	234
	Ph	3588	3360	228

TABLE XXVIII

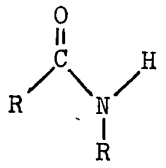
IR SPECTRA ("O-D REGION") OF α,β-ACETYLENIC KETOXIMES

$(R\text{-}\underset{\underset{NOD}{\|}}{C}\text{-}C\equiv C\text{-}R')$

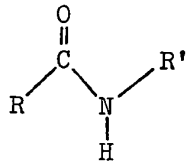
R	R'	$\Delta\nu_{OH}$ "free"	$\Delta\nu_{OH}$ "bonded"	$\Delta\nu_{OH}\ cm^{-1}$
i-Pr	Ph	2650	2495	155
Me(CH)Ph	Ph	2643	2485	158
Ph	Ph	2640	2482	158
p-i-PrPh	Ph	2643	2485	158
Ph	Me	2645	2480	165

V. Infrared Spectra of α,β-Acetylenic Amides in the N-H Stretching Region.

Although the hydrogen bonding involving the N-H group has not been as extensively studied as those involving the O-H group, both inter- and intramolecular hydrogen bonding in numerous amides and amines have been well established from ir spectroscopic studies.[185] A series of secondary amides, and their α-halogen or alkoxy derivatives have been recently studied by Nyquist.[186,187] The conclusions of these studies were that, in dilute solutions in nonpolar solvents, the N-alkyl acetamides exist in the trans configuration and that steric factors from the N-alkyl group affect the νNH but did not alter the trans configuration. Furthermore, the N-H proton in the

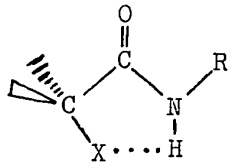


"cis"



"trans"

α-halogenated (or alkoxy) acetamides was weakly intramolecularly hydrogen bonded to the halogen (or oxygen) as shown below.



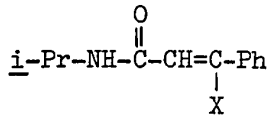
X = Cl, OR

It seems that in secondary amides the π-hydrogen bonding of the type encountered in many unsaturated hydroxylic compounds has not been unequivocally established. The intramolecular hydrogen bonding studies using ir spectroscopy as described for the α,β-acetylenic oximes was extended to the α,β-acetylenic amides. The N-H stretching region of the ir spectra of these amides in CCl_4 exhibited the characteristic sharp band due to the "free" N-H (band a) in the region of 3430 cm^{-1}, and the broad band due to intermolecular association between 3380 - 3200 cm^{-1}. It was consistently observed that upon progressive dilution the intermolecular association band in the region 3380 - 3200 cm^{-1} vanished and a "shoulder" (band b) persisted on the low frequency side of the "free" N-H band even at a concentration as low as 0.002M. The frequencies of the absorption bands a and b are listed in Table XXIX.

Within a given series the N-methyl amide shows the highest νNH, and the frequencies of the bulkier N-alkyl amides decrease progressively reaching a minimum value of 3433 cm^{-1} in the case of the N-t-butyl and α-phenylethyl groups. The same trend has been observed in N-alkylacetamides and their α-halo analogs.[186] This has been ascribed to a steric effect in which the protons of the branched alkyl group repel slightly the N-H proton, making the N-H bond slightly longer, thus lowering the force constant and hence the N-H stretching frequency. Table XXIX also shows that, within a given series, concurrent with the decrease in the N-H frequency there is a consistent enhancement of the carbonyl frequency. This trend was not shown by the N-alkylacetamides.[186] Regardless of these two trends with the N-H and C=O frequencies of the acetylenic amides the "$\Delta\nu_{NH}$" remains reasonably constant. Accurate values for "$\Delta\nu_{\overline{NH}}$" could not be obtained

for the N-t-butyl and the N-(α-phenylethyl) amides as the "shoulder" was unresolved.

The origin of this low intensity band on the low frequency side of the N-H stretching band (band b) is not certain at present. It seems highly unlikely that this band is an overtone (2 X νC=O) of the carbonyl frequency (cf. Table V) or a combination band. In the case of the N-deuterated amide (30 R = i-Pr, R' = Ph) the N-D stretching bands are very similar both in shape and relative intensities to those of the corresponding N-H compound; the shoulder is still present indicating that the band b is not a combination band or an overtone of a lower lying fundamental. The N-D shift ($\Delta\nu_{ND}$) is only 21 cm^{-1} as compared to the N-H shift ($\Delta\nu_{NH}$) of 27 cm^{-1}. There have been studies which indicated that deuterium bonding is weaker than hydrogen bonding.[183,184] Consistently lower frequency shifts in intramolecular π-deuterium bonding ($\Delta\nu_{OD}$) as compared to the corresponding shifts ($\Delta\nu_{OH}$) in hydrogen bonding have also been observed in some acetylenic alcohols.[177] The band b which is characteristic of all the α,β-acetylenic amides studied here is clearly absent in the NH bands of N-alkylacetamides and their analogs;[186] it is also absent in the ir spectra of the cis- and trans-olefinic amides of the type 224.



224

X = Cl or Br

A rationalization attributing this band to a weak intramolecular π-hydrogen bonding between the N-H proton and the acetylenic function would be an attractive one, however, consideration of bond angles in the acetylenic amides would tend to make this a weak argument. In this connection, it must be pointed out that propargyl alcohol is estimated to have a weak intramolecular π-hydrogen bond ($\Delta\nu_{OH}$≃18 cm^{-1}) between the OH and the acetylenic bond.[188] Clearly, further studies are required before a definite assignment for this band could be made.

TABLE XXIX

N-H AND C=O FREQUENCIES OF α,β-ACETYLENIC AMIDES

(R-NH-C(=O)-C≡C-R')

R	R'	νNH (cm^{-1}) a	νNH (cm^{-1}) b	$\Delta\nu_{NH}$ (cm^{-1})	νCO (cm^{-1})
Me	Ph	3460	3432	28	1640
Et	Ph	3446	3420	26	1640
i-Pr	Ph	3435	3408	27	1650
i-Pr	Ph	2545*	2524*	21*	1650
n-Bu	Ph	3444	3418	26	1640
t-Bu	Ph	3433	(sh)**	--	1655
Ph	Ph	3428	3403	25	1660
p-MePh	Ph	3429	3404	25	1660

TABLE XXIX(cont'd)

N-H AND C=O FREQUENCIES OF α,β-ACETYLENIC AMIDES

$(R\text{-}NH\text{-}\overset{O}{\overset{\|}{C}}\text{-}C\equiv C\text{-}R')$

R	R'	νNH (cm^{-1}) a	νNH (cm^{-1}) b	$\Delta\nu_{NH}$ (cm^{-1})	νCO (cm^{-1})
p-ClPh	Ph	3428	3404(sh)	24	1660
(R)-MeCH(Ph)	Ph	3434	(sh)**	--	1645
Me	Me	3463	3435	28	1650
Et	Me	3448	3420	28	1640
t-Bu	Me	3436	3408(sh)	28	1650
Ph	Me	3432	3406	26	1660
p-MePh	Me	3431	3402	29	1660
p-ClPh	Me	3431	3404(sh)	27	1665
MeCH(Ph)	Me	3435	(sh)**	--	1640
i-Pr	Et	3437	3408	29	1630
Ph	Et	3429	3403	26	1655
MeCH(Ph)	Et	3436	(sh)**	--	1640
(R)-MeCH(Ph)	t-Bu	3436	(sh)**	--	1640

*values for the N-D bond.

**unresolved shoulder.

EXPERIMENTAL

Melting Points and Boiling Points:- All melting points and boiling points reported are uncorrected. Melting points were taken with a Gallenkamp MF-370 instrument.

Elemental Analyses:- These were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, by Schwarzkopf Microanalytical Laboratory, Woodside, New York, and by Dr. R. T. Rye of this Department.

Thin Layer Chromatography (tlc):- Analytical tlc was accomplished on standard microscope slides coated in this laboratory with E. Merck Aluminium oxide GF-254 or E. Merck Silica Gel GF-254. Components were detected by using a MINERALIGHT Model SL 2537 uv lamp with short wave uv filter, supplied by Ultra-Violet Products, Inc., South Pasadena, California.

Dry Column Chromatography:- This was accomplished by the technique described by Loev and Goodman.[189] Fisher acidic alumina A-948 (deactivated to Brockman Activity II-III) was generally used as the adsorbent. A ratio of 1 g of reaction mixture to 60 g of adsorbent was usually used. Fractions (15 ml) were collected using an LKB Automatic Fraction Collector with a Type 3406A Turntable disk and a Rotator Type 3401B, and were monitored by tlc.

Optical Rotations:- These were measured (at 23°C) with a Perkin-Elmer 141 Automatic Polarimeter. Measurements are accurate to ± 0.002°.

UV Spectra:- These were recorded in 95% ethanol solution on a

Bausch and Lomb Spectronic 505 spectrometer.

Ir Spectra:- These were routinely recorded with a Beckmann IR-8 spectrometer or Perkin-Elmer Models 137 and 457 spectrometers. Spectra were taken in either chloroform or carbon tetrachloride and the intensities of the absorption bands are designated as strong (s), medium (m), weak (w), or shoulder (sh). For the more accurate measurements required in the hydrogen bonding work a Perkin-Elmer Model 225 Spectrometer was used. All spectra were taken as 0.002 to 0.007 M carbon tetrachloride solutions. Matched sets of 0.1 mm and 1.0 mm NaCl cells and 1.0 cm and 5.0 cm quartz (Beckman Red Label) cells were used. A slit program of 3.5 and scanning speeds fast x 0.5 or slow x 8.0 were used. Wavelengths are accurate to $\pm$ 2 cm^{-1}.

Nmr Spectra:- These were recorded with a Varian A-60A spectrometer. Spectra were taken in CCl_4, $CDCl_3$, DMSO or DMSO-d_6. Chemical shifts are expressed in ppm (δ) relative to TMS. Spin-spin coupling constants and the chemical shifts of the oxime hydroxyl protons were measured from spectra recorded at 50 Hz sweep widths.

Reagents and Chemicals:- The less common reagents and chemicals used in this study and their commercial sources are listed below:

Isocyanates:- isopropyl, p-chlorophenyl (Ald); methyl, phenyl (Can); ethyl, n-butyl (PB); t-butyl (KK); p-tolyl (Fis); (+) and (-)-α-phenylethyl (Fl).

Acetylenes:- phenyl (Ald, Far, PB); t-butyl (Far); methyl, ethyl (Math).

Other:- 2-pyridinealdoxime, Diazald (Ald); 1-methylcyclohexene (Chem); oxalyl chloride, α-phenylethyl chloride, α-phenylethyl bromide (Fis); phenylpropiolyl chloride (PB); m-chloroperbenzoic acid (Res).

Inorganics:- lithium iodide, sodium hydride (Alf); Sulfan (stabilized sulfur trioxide) (All); lithium bromide (Fis); phosphorus pentabromide (KK, PB); phosphoryl bromide (KK); phosphorus pentafluoride (USS).

Key:
- Ald - Aldrich Chemical Co.
- Alf - Alfa Inorganics Inc.
- All - Allied Chemicals (Canada) Ltd.
- Can - Canadian Laboratory Supplies Ltd.
- Chem - Chemical Samples Co.
- Far - Farchan Research Laboratories.
- Fis - Fisher Scientific Co., Ltd.
- Fl - Fluka A.G.
- KK - K and K Laboratories.
- Math - Matheson of Canada Ltd.
- PB - Pfaltz and Bauer.
- Res - Research Organic/Inorganic Chemical Co.
- USS - USS-Agri Chemicals.

General

Detailed procedures are given only for reactions that gave identifiable products and for those reactions that gave known compounds by new routes. Petroleum ether refers to the fraction with boiling range 60-75^{o} unless stated otherwise. The terms "reduced pressure" and "high vacuum" refer respectively to the vacuum obtained with a water aspirator and an oil pump. Column chromatography implies the technique of dry column chromatography described previously. Solutions are dried with sodium sulfate unless otherwise indicated.

α-Acetylenic aldoximes: The α-acetylenic aldoximes were prepared from the corresponding acetals according to the method of Claisen.[5] The spectral data of these oximes are given in Tables I and II (p 18). The following oximes were prepared:

Tetrolaldoxime[5] (37) yield 27%, mp 97-98° (benzene-petroleum ether).

Phenylpropiolaldoxime[4] (36) yield 66%, mp 104-105° (chloroform-petroleum ether).

Syn and anti t-butylpropiolaldoximes (38): A solution of 2.92 g (0.042 mol) of hydroxylamine hydrochloride in 10 ml of water was stirred (magnet) and cooled to 0° (ice-bath). Concentrated hydrochloric acid (3 drops) was added followed by the dropwise addition of 5.52 g (0.030 mol) of t-butylpropiolaldehyde diethyl acetal over a 5-min period, and the mixture was stirred overnight at 0°. The reaction mixture was then diluted with 25 ml of ether and the ether phase was separated, washed with saturated brine, dried, and evaporated to yield a pale yellow oil, 3.68 g (98%) that was found (by nmr spectroscopy) to consist of 31% syn and 69% anti aldoximes. The mixture had the following spectral properties: ir ($CHCl_3$) 3575, 3280, 2230, 1610 cm^{-1}; nmr (DMSO-d_6) δ 1.30 (9H, s), 6.75 (1H, s, -CH= anti), 7.32 (1H, s, -CH= syn), 11.47 (1H, s, OH syn), 11.75 (1H, s, OH anti). Preparation of the N-phenylcarbamate derivative[191] was attempted but the crude carbamate could not be purified for analysis. The crude product had the following properties: ir ($CHCl_3$) 3390, 2220, 1750 cm^{-1}.

Separation of syn and anti t-butylpropiolaldoximes (38): To a stirred (magnet) suspension of 0.31 g (0.013 mol) sodium hydride

(oil free) in 10 ml of anhydrous ether was added dropwise during 30 min a solution of 1.5 g (0.012 mol) of 38 in 5 ml of ether. The reaction mixture was stirred an additional 15 min and then poured on 30 g of crushed ice and the aqueous and ethereal phases separated. The ether phase was washed with saturated brine, dried and evaporated to give a yellow oil that was distilled yielding 0.44 g (42%) of 5-phenylisoxazole: bp 94-97° (97 mm) (lit.[190] bp 156° (760 mm)); ir ($CHCl_3$) 1580 cm^{-1}; nmr (CCl_4) δ 1.32 (9H, s), 5.85 (1H, d), 7.95 (1H, d). The aqueous layer was acidified with concentrated hydrochloric acid, extracted with ether and the ether extracts washed with saturated brine, dried, and evaporated to give 0.53 g of yellow oil: ir ($CHCl_3$) 3580, 3280, 2275, 2245, 2215, 1725, 1610 cm^{-1}. Tlc (on alumina using chloroform) showed two products. The oil was chromatographed on alumina (50 g) and the column was eluted with chloroform and 5 ml fractions were collected. The first product eluted yielded 0.28 g, crude crystalline α-cyanopinacolone, which was recrystallized from hexane to give 0.15 g: mp 67-68°; ir ($CHCl_3$) 2270, 1725 cm^{-1}; nmr ($CDCl_3$) δ 1.20 (9H, s), 3.72 (2H, s).

Anal. Calcd for $C_7H_{11}NO$: C, 67.16; H, 8.86; N, 11.19. Found: C, 67.27; H, 8.88; N, 11.13.

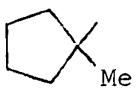
The second product eluted yielded 0.30 g (64%) of a yellow oil that was found (by nmr spectroscopy) to consist of a mixture of 90% syn and 10% anti t-butylpropiolaldoximes. The syn isomer slowly partially isomerized to the anti isomer yielding a mixture of 78% syn and 22% anti isomers after 2 days and 67% syn and 33% anti after 13 days.

Preparation of Aldoximes: The aldoximes that were required for the synthesis of hydroxamoyl chlorides were prepared either by the

methods of Wieland[39] or Vogel[40]. The yields as well as the relative amounts of the syn and anti isomers (as determined by nmr spectroscopy) of the aldoximes synthesized are shown in Table XXX.

TABLE XXX

ALDOXIMES (R-CH=NOH)

R	Total Yield(%)	% syn	% anti
Me	50	38	62
Et	81	60.	40
n-Pr	88	40	60
i-Pr	72	75	25
sec-Bu	89	72	28
t-Bu	77	100	--
MeCH(Ph)	91	73	27
$PhCH_2$	73	--	100
Ph	93	100	--
Ph	80	--	100
p-MePh	94	100	--
p-MeOPh	95	100	--
p-ClPh	87	100	--
p-i-PrPh	95	100	--
	82	100	--

Preparation of Hydroxamoyl Chlorides: The hydroxamoyl chlorides required for the synthesis of acetylenic ketoximes were prepared from the corresponding aldoximes either by the methods of Perold et al.[41] or Benn.[42] No attempts were made to isolate and characterize these compounds. They were used immediately as ether solutions in subsequent reactions.

General Procedure for the Preparation of α,β-Acetylenic Ketoximes: To a 1-liter 3-necked flask fitted with a mechanical stirrer, condenser and drying tube, and a pressure equalizing dropping funnel, were added 4.9 g (0.20 mol) magnesium turnings and 50 ml of anhydrous ether. A solution of 28.3 g (0.26 mol) ethyl bromide in 150 ml anhydrous ether was added dropwise during 30 min to the stirred suspension of magnesium. When the addition was completed, the mixture was refluxed for 15 min then a solution of 0.2 mol of the appropriate liquid acetylene (phenyl or p-methoxyphenylacetylene) in 100 ml of anhydrous ether was added and the resulting solution refluxed for ca. 3 hr, whereupon the acetylenic Grignard reagent formed and separated as a dark lower layer. (For methyl or ethylacetylenes, 100 ml of anhydrous ether was added before the gaseous acetylene was bubbled in at a rate of 0.15 liter per min for ca. 3 hr, whence the lower Grignard reagent layer separated. t-Butylacetylene, 0.24 mol in 100 ml of anhydrous ether, was added in one portion, then stirred for 1 hr and left standing for ca. 8 hr, whereupon the Grignard reagent formed as a white suspension. For these acetylenes a dry-ice condenser is required.) The reaction flask was cooled to 0° (ice-bath) and the appropriate ethereal solution (250 ml) of 0.1 mol of hydroxamoyl chloride was added dropwise during 1 hr, then stirred an additional 30 min and the

reaction mixture was slowly acidified by the dropwise addition of 150-200 ml of 10% sulfuric acid. The yellow ether layer was separated and the aqueous phase saturated with sodium chloride and ether extracted. The combined ether solutions were washed with saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure at room temperature to yield an oil. Further evacuation with a pump (1-2 mm) at room temperature removed the remaining ether and low boiling acetylenes. (Phenylacetylene was recovered in almost quantitative yields by this process). The acetylenic oximes either remained as a dark oil or solidified. Liquid oximes could be chromatographed on silica gel but yellow colored impurities always persisted. Solid oximes were carefully recrystallized yielding either colorless or pale yellow crystalline solids. The spectral data of these acetylenic ketoximes are given in Table III (p 30).

Some oximes were characterized as their N-phenyl-carbamates by reaction with phenylisocyanate according to standard procedures.[191] The following acetylenic oximes and carbamate derivatives were prepared:

4-Phenyl-3-butyn-2-ketoxime: Me-C(=NOH)-C≡C-Ph, crude amber oil (35%).

1-Phenyl-1-pentyn-3-ketoxime: Et-C(=NOH)-C≡C-Ph, crude amber oil (36%).

1-Phenyl-1-hexyn-3-ketoxime: n-Pr-C(=NOH)-C≡C-Ph, crude amber oil (45%).

2-Methyl-5-phenyl-4-pentyn-3-ketoxime: i-Pr-C(=NOH)-C≡C-Ph (61%), mp 89-90° (petroleum ether).

Anal. Calcd for $C_{12}H_{13}NO$: C, 76.95; H, 7.01; N, 7.48. Found: C, 75.88; H, 6.65; N, 7.62.

N-phenylcarbamate: mp 108-109°: (benzene-petroleum ether); ir ($CHCl_3$) 3390, 2220, 2200 (sh), 1750 cm^{-1}.

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.47; H, 5.92; N, 9.15. Found: C, 74.52; H, 5.85; N, 9.11.

4-Methyl-1-phenyl-1-hexyn-3-ketoxime: sec-Bu-C(=NOH)-C≡C-Ph (51%), mp 82-83° (petroleum ether).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.61; H, 7.51; N, 6.96. Found: C, 77.50; H, 7.43; N, 7.00.

2,2-Dimethyl-5-phenyl-4-pentyn-3-ketoxime: t-Bu-C(=NOH)-C≡C-Ph (69%), mp 102-103° (petroleum ether).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.61; H, 7.51; N, 6.96. Found: C, 77.75; H, 7.58; N, 6.94.

N-phenylcarbamate: mp 137-138° (benzene-petroleum ether); ir ($CHCl_3$) 3390, 2220, 1750 cm^{-1}.

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.99; H, 6.29; N, 8.75. Found: C, 74.90; H, 6.25; N, 8.74.

1-4-Diphenyl-1-pentyn-3-ketoxime: MeCH(Ph)-C(=NOH)-C≡C-Ph (39%), mp 81-82° (benzene-petroleum ether).

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.91; H, 6.09; N, 5.62. Found: C, 81.85; H, 6.53; N, 6.06.

N-phenylcarbamate: mp 92-93° (ether-petroleum ether); ir ($CHCl_3$) 3390, 2220, 1750 cm^{-1}.

Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.25; H, 5.47; N, 7.61. Found: C, 78.30; H, 5.55; N, 7.60.

1,4-Diphenyl-1-butyn-3-ketoxime: Ph-CH_2-C(=NOH)-C≡C-Ph (35%), mp 103-104° (benzene-petroleum ether).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.66; H, 5.57; N, 5.94. Found: C, 81.75; H, 5.50; N, 6.10.

1,3-Diphenyl-2-propyn-1-ketoxime: Ph-C(=NOH)-C≡C-Ph (70%), mp 100-101° (benzene).

Anal. Calcd for $C_{15}H_{11}NO$: C, 81.55; H, 5.03; N, 6.34. Found: C, 81.58; H, 4.92; N, 6.44.

N-phenylcarbamate: mp 149-150° (ether-petroleum ether); ir ($CHCl_3$) 3390, 2220, 1755 cm^{-1}.

Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.93; H, 4.79; N, 8.06.

3-Phenyl-1-tolyl-2-propyn-1-ketoxime: p-MePH-C(=NOH)-C≡C-Ph (45%) mp 95-96° (ether-petroleum ether).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.66; H, 5.57; N, 5.94. Found: C, 81.80; H, 5.60; N, 5.85.

3-Phenyl-1-(p-methoxyphenyl)-2-propyn-1-ketoxime: p-MeOPh-C(=NOH)-C≡C-Ph (60%), mp 110-112° (ether-petroleum ether).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.21; N, 5.58. Found: C, 76.60; H, 5.32; N, 5.55.

3-Phenyl-1-(p-isopropylphenyl)-2-propyn-1-ketoxime: p-i-PrPh-C(=NOH)-C≡C-Ph (34%), mp 90-91° (ether-petroleum ether).

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.08; H, 6.51; N, 5.32. Found: C, 82.25; H, 6.40; N, 5.28.

1-(1-Methylcyclopentyl)-3-phenyl-2-propyn-1-ketoxime:

C(=NOH)-C≡C-Ph, crude amber oil (70%).

N-phenylcarbamate: mp 122-123° (ether-petroleum ether); ir ($CHCl_3$) 3385, 2220, 1750 cm^{-1}.

Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.06; H, 6.44; N, 7.90.

4-Hexyn-3-ketoxime: Et-C(=NOH)-C≡C-Me, crude amber oil (55%).

2-Heptyn-4-ketoxime: n-Pr-C(=NOH)-C≡C-Me, crude amber oil (83%).

2-Methyl-4-hexyn-3-ketoxime: i-Pr-C(=NOH)-C≡C-Me, crude amber oil (47%).

3-Methyl-5-heptyn-4-ketoxime: sec-Bu-C(=NOH)-C≡C-Me, crude amber oil (69%).

2,2-Dimethyl-4-hexyn-3-ketoxime: t-Bu-C(=NOH)-C≡C-Me (68%), mp 81-82° (petroleum ether) (lit.[20] mp 85-86°).

2-Phenyl-4-hexyn-3-ketoxime: MeCH(Ph)-C(=NOH)-C≡C-Me (56%), mp 87-88° (benzene-petroleum ether).

Anal. Calcd for $C_{12}H_{13}NO$: C, 77.00; H, 7.00; N, 7.49. Found: C, 77.15; H, 6.80; N, 7.52.

N-Phenylcarbamate: mp 98-99° (ether-petroleum ether); ir ($CHCl_3$) 3390, 2235, 1750 cm^{-1}.

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.45; H, 5.96; N, 9.07.

1-Phenyl-2-butyn-1-ketoxime: Ph-C(=NOH)-C≡C-Me (40%), mp 88-89° (benzene-petroleum ether).

Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.32; H, 5.10; N, 9.17.

N-Phenylcarbamate: mp 123-124° (ether-petroleum ether); ir ($CHCl_3$) 3395, 2270(m), 2220(s), 1750 cm^{-1}.

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 72.99; H, 5.06; N, 10.25.

1-(p-Chlorophenyl)-2-butyn-1-ketoxime: p-ClPh-C(=NOH)-C≡C-Me (68%), mp 96-98° (ether-petroleum ether).

Anal. Calcd for $C_{10}H_8NClO$; C, 62.03; H, 4.16; N, 7.24.

Found: C, 62.25; H, 4.00; N, 7.15.

1-(p-Tolyl)-2-butyn-1-ketoxime: p-MePh-C(=NOH)-C≡C-Me, crude amber oil (75%).

1-(p-Isopropylphenyl)-2-butyn-1-ketoxime: p-i-PrPh-C(=NOH)-C≡C-Me, crude amber oil (74%).

2,6,6-Trimethyl-4-heptyn-3-ketoxime: i-Pr-C(=NOH)-C≡C-t-Bu, crude amber oil (65%).

N-Phenylcarbamate: mp 105-106° (petroleum ether); ir ($CHCl_3$) 3395, 2225, 1750 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.29; H, 7.74; N, 9.78. Found: C, 71.35; H, 7.70; N, 9.77.

3,7,7-Trimethyl-5-octyn-4-ketoxime: sec-Bu-C(=NOH)-C≡C-t-Bu, crude amber oil (69%).

N-Phenylcarbamate: mp 108-109° (pentane); ir ($CHCl_3$) 3385, 2220, 1745 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.08; H, 8.12; N, 9.41.

2,2,6,6-Tetramethyl-4-heptyn-3-ketoxime: t-Bu-C(=NOH)-C≡C-t-Bu, crude amber oil (67%).

N-Phenylcarbamate: mp 100-101° (pentane); ir ($CHCl_3$) 3385, 2220, 1745 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.89; H, 7.95; N, 9.48.

4,4-Dimethyl-1-phenyl-2-pentyn-1-ketoxime: Ph-C(=NOH)-C≡C-t-Bu, crude amber oil (85%).

N-Phenylcarbamate: mp 138-139° (petroleum ether); ir ($CHCl_3$) 3390, 2225, 1750 cm^{-1}.

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.74. Found: C, 74.67; H, 6.66; N, 8.62.

2-Methyl-4-heptyn-3-ketoxime: i-Pr-C(=NOH)-C≡C-Et, crude amber oil (78%).

1-Phenyl-2-pentyn-1-ketoxime: Ph-C(=NOH)-C≡C-Et, crude amber oil (71%).

2-Phenyl-4-heptyn-3-ketoxime: MeCH(Ph)-C(=NOH)-C≡C-Et, crude amber oil (70%).

2-Methyl-5-(p-methoxylphenyl)-4-pentyn-3-ketoxime: i-Pr-C(=NOH)-C≡C-(p-MeOPh), crude amber oil (68%).

Preparation of 1-phenyl-1-hexyn-3-ketoxime-O-trimethylsilyl ether. A mixture of 2.0 g (0.011 mol) of crude 1-phenyl-1-hexyn-3-ketoxime and 1.4 g (0.011 mol) of N-trimethyl-silylacetamide[48] in 10 ml of anhydrous ether was shaken vigorously for 10 min whereupon solid acetamide precipitated. The acetamide was removed by suction filtration and the yellow filtrate diluted with 30 ml of pentane and kept in a freezer overnight. The solution was then suction filtered to remove the precipitated acetamide and the filtrate was evaporated to a crude yellow oil. Distillation of this oil at reduced pressure afforded a light yellow oil 1.2 g (42%) of the trimethylsilyl ether; bp 150-155 (12mm); ir ($CHCl_3$) 2225 cm^{-1} (C≡C); nmr ($CDCl_3$) δ 0.25 (9H, s, Me_3Si).

Acidic hydrolysis of 1-phenyl-1-hexyn-3-ketoxime-O-trimethylsilyl ether. A solution of 1.2 g (0.005 mol) of the O-trimethylsilyl ether in 20 ml of pentane was stirred (magnet) with 20 ml of 10% sulfuric acid for 2 hr. The aqueous and organic phases

were separated and the aqueous phase was extracted with ether. The combined ether solutions were washed with saturated brine, dried and evaporated to a crude yellow oil, 1.1 g, that was shown (by ir and nmr spectroscopy) to be a mixture of the acetylenic oxime and trimethylsilanol: ir ($CHCl_3$) 3590, 3280, 2235 cm^{-1}; nmr ($CDCl_3$) δ 0.13 (9H, s, Me_3Si-).

Attempted preparation of 1-phenyl-1-hexyn-3-ketoxime-O-methyl ether. To a stirred solution of 6.4 g (0.034 mol) of crude 1-phenyl-1-hexyn-3-ketoxime in 15 ml of anhydrous ether at 0° was added 200 ml of a yellow ethereal solution of diazomethane (prepared[192] from 21.5 g (0.10 mol) of Diazald). The reaction mixture was stirred for 1 hr and left standing overnight in a fumehood. Excess unreacted diazomethane still remained and was destroyed by diluting the reaction mixture with 10 ml of acetic acid. The resulting mixture was washed with water, dried and evaporated to give 6.0 g of crude yellow oil, 3-n-propyl-5-phenylisoxazole: ir ($CHCl_3$) 1610, 1590, 1575, 1500 cm^{-1}.

Attempted preparation of anti-1-phenyl-2-butyn-1-ketoxime: The general procedure of acetylenic oxime synthesis was used (see p 178) and 16.1 g of a crude yellow solid was obtained: ir ($CHCl_3$) 3560, 3280, 2260, 2220 cm^{-1}. The ir spectrum of this product was identical to that of the syn isomer. However, the crude product decomposed violently after 30 min on the laboratory bench.

Attempted preparation of 3-phenyl-1-(2-pyridinyl)-2-propyn-1-ketoxime: Starting with 0.10 mol of 2-pyridinyl hydroxamoyl chloride[193] the general method of acetylenic oxime synthesis was used. The aqueous and ether phases obtained after decomposition of the Grignard complex with 10% sulfuric acid were separated and the

ether phase washed with water, dried and evaporated to give trace amounts (by nmr spectroscopy) of phenylacetylene. The aqueous phase was neutralized with 10% sodium bicarbonate, extracted with ether, and worked up in the usual way to give 20 g of a crude black solid. Analysis of this solid by tlc (on alumina using chloroform) showed two components. A portion of this product (4.0 g) was applied to a column of 180 g of alumina and eluted with chloroform. The first product eluted (1.7 g) was recrystallized from petroleum ether to give 1.4 g of 3,4-di-(2-pyridinyl)-furoxan: mp 143-144° (lit.[193] mp 145°). The second product eluted was recrystallized from petroleum ether to give 0.3 g of white crystals of 2-pyridine carboxamide: mp 104-105° (lit. [194] mp 106.5°); ir ($CHCl_3$) 3520, 3460(w), 3495, 1680 cm^{-1}.

The synthesis was repeated starting with 0.04 mol of the hydroxamoyl chloride. Saturated ammonium chloride was used instead of sulfuric acid. The usual workup afforded 9.0 g of a black solid from the ether phase. Analysis of this product by tlc (on alumina using benzene) indicated only one component. Chromatography on 230 g of alumina yielded a pale yellow solid which was recrystallized from petroleum ether to give 2.87 g of white crystals of 5-phenyl-3-(2-pyridinyl)-isoxazole: mp 95-96°; ir ($CHCl_3$) 1612, 1595, 1570, 1485 cm^{-1}; nmr (DMSO-d_6) δ 7.67 (5H, m), 8.10 (4H, m), 8.85 (1H,m).

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.61. Found: C, 75.68; H, 4.50; N, 12.68.

Attempted preparation of 1-(2-pyridinyl)-2-butyn-1-ketoxime: The same procedure was used as described above. 2-Pyridinyl hydroxamoyl chloride (0.07 mol) was used and the Grignard complex was

decomposed with saturated ammonium chloride solution. The usual workup afforded 9.0 g of a black oil. Distillation under high vacuum yielded 5.2 g (46%) of colorless oil, 5-methyl-3-(2-pyridinyl)-isoxazole: mp 92-94° (0.4 mm); ir ($CHCl_3$) 1610, 1590, 1570 cm^{-1}; nmr ($CDCl_3$) δ 2.45 (3H, s); 6.72 (1H, s); 7.33 (1H, m); 7.87 (1H, m); 8.73 (1H, m).

Preparation of α,β-Acetylenic Amides: These were prepared by two methods: 1) reaction of acetylenic Grignard reagents with the appropriate isocyanates and 2) reaction of the acetylenic acid chlorides with the appropriate amines.

1) Grignard reagent-Isocyanate Method: The Grignard reagents (0.10 mol) were synthesized in the manner described for the preparation of acetylenic ketoximes. To the vigorously stirred ethereal solution of the Grignard reagent was added dropwise during 20 min a solution of 0.08 mol of the appropriate isocyanate in 10 ml of anhydrous ether, the resulting mixture being gently refluxed for ca. 5 hr. The Grignard complex was decomposed with 100 ml of 10% sulfuric acid solution and the ether phase was separated, washed with water, dried and evaporated to give the crude acetylenic amide as an oil or brown solid. The liquid amides were distilled under high vacuum and the solid amides were recrystallized from appropriate solvents. In the case of optically active liquid acetylenic amides, these were chromatographed on alumina and used as such in subsequent reactions. The spectral data of these amides are given in Tables V and VI (pp 41 and 43).

The following acetylenic amides were prepared:

N-Methylphenylpropiolamide: Me-NH-CO-C≡C-Ph (45%), mp 97-98°

(chloroform-petroleum ether).

Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80 Found: C, 75.63; H, 5.70; N, 8.91.

N-Ethylphenylpropiolamide: Et-NH-CO-C≡C-Ph (60%), mp 62-63° (benzene-petroleum ether) (lit.[30] mp 63°).

N-Isopropylphenylpropiolamide: i-Pr-NH-CO-C≡C-Ph (72%), mp 85-86° (petroleum ether) (lit.[55] mp 81°).

N-(n-Butyl)phenylpropiolamide: n-Bu-NH-CO-C≡C-Ph (71%), bp 165-175° (1 mm).

N-(t-Butyl)phenylpropiolamide: t-Bu-NH-CO-C≡C-Ph (44%), mp 69-70° (petroleum ether bp 35-60°).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.37; H, 7.56; N, 6.93.

Phenylpropiolanilide: Ph-NH-CO-C≡C-Ph (92%), mp 127-128° (benzene) (lit.[55] mp 128°).

N-p-Tolylphenylpropiolamide: p-MePH-NH-CO-C≡C-Ph (39%), mp 141-142° (chloroform).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.77; H, 5.63; N, 5.67.

N-(p-Chlorophenyl)phenylpropiolamide: p-ClPh-NH-CO-C≡C-Ph (38%), mp 186-187° (chloroform) (lit.[55] mp 186°).

(R)-N-Phenylethylphenylpropiolamide: (R)-MeCH(Ph)-NH-CO-C≡C-Ph (70%), mp 110-111° (benzene-petroleum ether); $[\alpha]_D$-13.20° (c 0.977, $CHCl_3$).

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.82; H, 5.94; N, 5.62.

(S)-N-Phenylethylphenylpropiolamide: (S)-MeCH(Ph)-NH-CO-C≡C-Ph

(53%), mp 110-111° (benzene-petroleum ether); $[\alpha]_D$ +13.27° (c 0.972, $CHCl_3$).

N-methyltetrolamide: Me-NH-CO-C≡C-Me (17%), mp 58-59° (hexane).

Anal. Calcd for C_5H_7NO: C, 61.83; H, 7.27; N, 14.43. Found: C, 62.12; H, 7.33; N, 14.49.

N-Ethyltetrolamide: Et-NH-CO-C≡C-Me (50%), bp 80-95° (0.6 mm).

N-Isopropyltetrolamide: i-Pr-NH-CO-C≡C-Me (83%), bp 84-88° (0.5 mm).

N-(t-Butyl)-tetrolamide: t-Bu-NH-CO-C≡C-Me (61%), mp 101-102° (petroleum ether).

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.07. Found: C, 69.20; H, 9.43; N, 9.92.

Tetrolanilide: Ph-NH-CO-C≡C-Me (71%), mp 102-103° (benzene-petroleum ether).

Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 74.58; H, 5.77; N, 8.39.

N-(p-Tolyl)-tetrolamide: p-MePh-NH-CO-C≡C-Me (47%), mp 130-131° (benzene).

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.44; H, 6.50; N, 8.04.

N-(p-Chloro)-tetrolamide: p-ClPh-NH-CO-C≡C-Me (58%), mp 139-140° (benzene).

Anal. Calcd for $C_{10}H_8NClO$: C, 62.03; H, 4.16; N, 7.24. Found: C, 61.88; H, 4.18; N, 7.11.

(R)-N-phenylethyltetrolamide: (R)-MeCH(Ph)-NH-CO-C≡C-Me,

crude pale yellow oil (58%); $[\alpha]_D$+58.34° (c 1.042, $CHCl_3$).

(S)-N-Phenylethyltetrolamide: (S)-MeCH(Ph)-NH-CO-C≡C-Me, crude pale yellow oil (60%); $[\alpha]_D$-55.17° (c 1.024, $CHCl_3$).

N-Isopropylethylpropiolamide: i-Pr-NH-CO-C≡C-Et (82%), by 94-98° (0.5 mm).

Ethylpropiolanilide: Ph-NH-CO-C≡C-Et (75%), mp 78-79°, (petroleum ether).

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.44; H, 6.46; N, 8.07.

(R)-N-Phenylethylethylpropiolamide: (R)-MeCH(Ph)-NH-CO-C≡C-Et (78%), crude pale yellow oil; $[\alpha]_D$+39.44° (c 1.065, $CHCl_3$).

(S)-N-Phenylethyl-t-butylpropiolamide: (S)-MeCH(Ph)-NH-CO-C≡C-t-Bu (43%), mp 87-88° (petroleum ether); $[\alpha]_D$-29.70° (c 0.936, $CHCl_3$).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.88; H, 8.72; N, 5.94.

(R)-N-Phenylethyl-t-butylpropiolamide: (R)-MeCH(Ph)-NH-CO-C≡C-t-Bu (57%), mp 87-88° (petroleum ether); $[\alpha]_D$+30.90° (c 0.940, $CHCl_3$).

2) Acid chloride-Amine Method: To a stirred (magnet) suspension of 50 mmol of the sodium salt of the acetylenic aicd (prepared from sodium hydride) in 15 ml of dry benzene at room temperature, was added dropwise during 15 min a solution of 100 mmol of oxalyl chloride in 15 ml of dry benzene. When the evolution of carbon monoxide had subsided the reaction flask was warmed to 40° for 1 hr. The mixture was evaporated under reduced pressure to give a yellow oily residue which was extracted with 25 ml of dry benzene. The benzene extracts of the crude acid chloride were cooled to ca. 15°, then a solution of 100

mmol of the appropriate amine in 15 ml of benzene was added dropwise during 15 min, and the mixture stirred at 15° for 1 hr, then poured into 100 ml of cold water. The benzene phase was separated and washed successively with 5% hydrochloric acid, 5% sodium carbonate and water, dried and evaporated to give the crude amide as a yellow oil. The oil was passed through a small column of alumina (30 g) and after evaporation of the solvent (chloroform) the pale yellow solid amide was obtained. Recrystallization yielded pure white crystalline amide.

The following amides were prepared:

(±)-N-Phenylethyltetrolamide: MeCH(Ph)-NH-CO-C≡C-Me (12%), mp 79-80° (benzene-petroleum ether).

Anal. Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.13; H, 7.04; N, 7.56.

(±)-N-Phenylethylethylpropiolamide: MeCH(Ph)-NH-CO-C≡C-Et (31%), mp 79-80° (benzene-petroleum ether).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.73; H, 7.41; N, 6.89.

Preparation of N-Isopropylphenylpropiolamide: Phenylpropiolyl chloride (1.1g, 0.007 mol, Pfaltz and Bauer, Inc.) was dissolved in 10 ml of dry benzene and the solution was stirred and cooled to ca. 15°. To this was added dropwise during 10 min a solution of 0.79 g (0.013 mol) of isopropylamine in 10 ml of benzene whereupon the mixture was stirred for 1 hr and then poured into 50 ml of cold water. The benzene phase was separated and washed, dried, and evaporated to give 1 g of a yellow oil: ir ($CHCl_3$) 3420, 3280 (NH), 2200 (C≡C), 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.00 (Me_2, d), 1.15 (Me_2,d), 4.1 (-$\overset{|}{C}$H, m), 6.4 (NH, broad),

7.03 (=CH-, s), 7.35 (Ph, m). Analysis of this oil by tlc (on alumina using chloroform) indicated two products. The oil was chromatographed on 70 g of alumina and eluted with chloroform. The first component eluted was recrystallized from petroleum ether to afford 0.38 g of white crystalline N-isopropyl-α-bromo-cis-cinnamamide: mp 69-70°; ir ($CHCl_3$) 3430, 3290, 1655 cm^{-1}; nmr ($CDCl_3$) δ 1.08 (6H, d), 4.1 (1H, m), 5.6 (1H, broad s), 7.20 (1H, s), 7.38 (5H, s).

Anal. Calcd for $C_{12}H_{14}NBrO$: C, 53.74; H, 5.26; N, 5.22. Found: C, 5366; H, 5.31; N, 5.16.

The second product eluted was recrystallized from petroleum ether yielding 0.42 g of white crystalline N-isopropylphenyl-propiolamide: mp 83-84° (lit.[55] mp 81°; ir ($CHCl_3$) 3430, 3260, 2220, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.23 (6H, d), 4.2 (1H, m), 7.0 (1H, broad s), 7.45 (5H, m).

Preparation of N-isopropyltetrolamide: A mixture of 1.5 g (0.018 mol) of tetrolic acid[47] and 4.3 g (0.036 mol) of thionyl chloride in 30 ml of dry benzene was gently refluxed for 2 hr, cooled, and evaporated under reduced pressure to give a yellow oil. The oil was dissolved in 15 ml of dry benzene, stirred, and cooled to ca. 15°. To this solution was added dropwise during 10 min a solution of 2.1 g (0.036 mol) of isopropylamine in 15 ml of dry benzene. The mixture was stirred at 15° for 1 hr, poured into 100 ml of cold water, and the benzene phase was separated and washed, dried, and evaporated to yield 2.5 g of a yellow oil: ir ($CDCl_3$) 3425, 3280 (NH), 2240 (C≡C), 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.22 ($2Me_2$, d), 1.95 (Me, s), 2.23 (Me, d, trans), 2.62 (Me, d, cis), 4.15 (-CH, m), 6.15 (=CH-, m), 6.8 (NH, broad,s). It was estimated from the nmr data that the mixture consisted of 34%

N-isopropyltetrolamide and 66% cis-trans-N-isopropyl-β-chlorocrotonamides (27% cis; 73% trans).

Preparation of N-deuterio-N-isopropylphenylpropiolamide: The Grignard reagent-Isocyanate method was used except that in this case deuterium oxide was substituted for 10% sulfuric acid in the hydrolysis step. After the addition of deuterium oxide, the mixture was refluxed for 30 min, cooled and suction filtered, and the filter-cake washed with anhydrous ether. The filtrate was dried and evaporated to yield the crude brown crystalline amide. Two recrystallizations from petroleum ether afforded the pure white crystalline amide in 80% yield: mp 85-86°; ir (CCl_4) 3430, 3280 (NH), 2550, 2420 (ND), 2215, 1650 cm^{-1}. It was found (by nmr spectroscopy) to contain 74% deuterium.

Isomerization of cis-β-Chlorocrotonic acid: cis-β-chlorocrotonic acid (2.0 g) was sublimed at 35-40° (1 mm) during 40 min. The sublimed acid (1.97 g) was found (by nmr spectroscopy) to consist of 60% cis- and 40% trans- acids: nmr ($CDCl_3$) δ 2.32 (Me, d, trans-), 2.63 (Me, d, cis-), 6.07 (=CH-, q, trans-), 6.13 (=CH-, q, cis-), 12.55 (OH, s, cis- and trans-). The mixture of acids was steam distilled and the distillate cooled (ice-bath), whereupon the cis-acid readily crystallized. Suction filtration and air-drying of the crystals afforded 1.12 g of the cis-acid: mp 60-61° (lit.[68] mp 60.3-60.6°); nmr ($CDCl_3$) δ 2.58 (3H, d), 6.13 (1H, q), 11.77 (1H, s). The residue from the distillation flask was extracted with ether, the ether extracts dried, and evaporated to give a pale yellow solid which was recrystallized from petroleum ether to afford 0.65 g of the trans-acid: mp 93-94° (lit.[68] 93.8-94.0°); nmr ($CDCl_3$) δ 2.32 (3H, d), 6.13 (1H, q), 12.28 (1H, s).

Preparation of cis-3-Chloro-4,4-dimethyl-2-pentenoic acid (70): To a stirred (magnet) solution of 4.75 g (0.028 mol) of silver nitrate in 15 ml of water was added 4.48 g (0.056 mol) of sodium hydroxide solution (50 wt %). A black suspension of silver oxide immediately formed. To the mixture was added 2.0 g (0.014 mol) of cis-3-chloro-4, 4-dimethyl-2-pentenal (69) in one portion. The temperature of the reaction mixture rose to 40° after 10 min and slowly dropped back to room temperature after 1.5 hr. The mixture was stirred at this temperature overnight, then suction filtered and the filter cake washed with warm water. The clear filtrate was acidified with concentrated hydrochloric acid, and the precipitated acid was filtered, air dried, and then further dried overnight in a vacuum dessicator containing phosphorus pentoxide to give 2.01 g (88%) of white crystalline acid: mp 80-81°; ir ($CHCl_3$) 3300-2500 (broad, OH), 1700, 1625 cm^{-1}; nmr ($CDCl_3$) δ 1.25 (9H, s), 6.17 (1H, s), 11.72 (1H, s). The filtrate was extracted with ether and the ether extracts dried and evaporated to give an oil that was shown (by ir and nmr spectroscopy) to contain a trace amount of the corresponding acetylenic acid together with the olefinic acid 70: ir ($CHCl_3$) 3300-2500 (broad, OH), 2220 (C≡C), 1700 (C=O), 1625 (C=C).

Preparation of trans-β-chloro-p-methoxycinnamic acid (75): A solution of 8.0 g (0.036 mol) of ethylanisoylacetate [73] in 10 ml of phosphorus trichloride was added dropwise with stirring during 40 min to 16.0 g (0.075 mol) of powdered phosphorus pentachloride. A gentle evolution of hydrogen chloride occurred and the initially yellow reaction mixture changed to orange and then wine-red. The mixture was then heated on a steam-bath for 10 min and the excess phosphorus

trichloride was removed under reduced pressure to leave a dark brown oil which was cooled and poured on 100 g of crushed ice. A brown oil which separated as the lower layer and subsequently solidified after 30 min was extracted with ether. The ether extracts were washed with 20% ammonium hydroxide (200 ml) and the aqueous extracts treated with 100 ml of saturated barium chloride solution, whereupón the insoluble barium salt of the acid precipitated. This salt was vacuum filtered and washed with saturated barium chloride solution, then acidified with 10% hydrochloric acid to give the insoluble acid which was vacuum filtered, air dried, and recrystallized from ethanol-water to afford 2.0 g of pale yellow crystals of the trans-acid: mp 161-163° (dec) (lit.[71] mp 166°): ir ($CHCl_3$) 3300-2500 (broad, OH), 1690, 1600 cm^{-1}. The aqueous filtrate was acidified with concentrated hydrochloric acid and after filtration and recrystallization, yielded 0.6 g of the trans-acid: mp 160-162° (dec); total yield, 2.6 g (34%).

Preparation of Acrylic Amides: These amides were prepared by reaction of the acid chlorides and amines by two methods, A and B. In method A the acid chloride was prepared by the reaction of the acid with thionyl chloride and in method B by the reaction of the acid with oxalyl chloride.

Method A: A mixture of 2 mmol of acid and 4 mmol of thionyl chloride in 15 ml of dry benzene was refluxed for 1.5 hr, cooled, and the solvent and excess thionyl chloride evaporated under reduced pressure at room temperature to give the crude acid chloride as a yellow oil. This was dissolved in 10 ml of dry benzene and cooled to ca. 15°, whereupon 4 mmol of the appropriate amine in 10 ml of dry benzene was added dropwise with stirring during 10 min, the mixture

being stirred for 1 hr. The reaction mixture was poured into 100 ml of cold water, the benzene phase was separated and was washed successively with 5% hydrochloric acid, 5% sodium carbonate, water, was dried and was evaporated to give the crude solid amide which was recrystallized from the appropriate solvent or sublimed to give the pure white crystalline amide.

The following amides were prepared by this method:

N-Isopropyl-trans-β-chlorocinnamamide: i-Pr-NH-CO-CH=C(Cl)Ph (79%); mp 96-97° (petroleum ether).

Anal. Calcd for $C_{12}H_{14}NClO$: C, 64.42; H, 6.31; N, 6.26; Cl, 15.85. Found: C, 64.08; H, 6.41; N, 6.17; Cl, 15.73.

N-Isopropyl-cis-β-chlorocinnamamide: i-Pr-NH-CO-CH=C(Cl)Ph (65%); mp 118-119° (petroleum ether).

Anal. Calcd for $C_{12}H_{14}NClO$: C, 64.42; H, 6.31; N, 6.26. Found: C, 64.23; H, 6.45; N, 6.15.

N-Phenyl-trans-β-chlorocinnamamide: Ph-NH-CO-CH=C(Cl)Ph (81%); mp 130-131° (benzene-petroleum ether) (lit.[30] mp 129-130°).

N-sec-Butyl-trans-β-chlorocinnamide: sec-Bu-NH-CO-CH=C(Cl)Ph (72%); mp 85-86° (benzene-petroleum ether).

Anal. Calcd for $C_{13}H_{16}NClO$: C, 65.64; H, 6.80; N, 5.89; Cl, 14.91. Found: C, 65.80; H, 6.79; N, 5.87; Cl, 14.72.

N-Ethyl-trans-β-chlorocinnamamide: Et-NH-CO-CH=C(Cl)Ph (82%); mp 106-107° (benzene-petroleum ether) (lit.[30] mp 107-108°).

N-(n-Propyl)-trans-β-chlorocinnamamide: n-Pr-NH-CO-CH=C(Cl)Ph (60%); mp 57-58° (benzene-petroleum ether).

Anal. Calcd for $C_{12}H_{14}NClO$: C, 64.42; H, 6.31; N, 6.26. Found: C, 64.48; N, 6.61; N, 6.01.

N-Methyl-trans-β-chlorocinnamamide: Me-NH-CO-CH=C(Cl)Ph (75%); mp 113-114° (benzene-petroleum ether).

Anal. Calcd for $C_{10}H_{10}NClO$: C, 61.41; H, 5.15; N, 7.16. Found: C, 61.59; H, 5.32; N, 7.06.

N-(p-Methoxyphenyl)-trans-β-chlorocinnamamide: p-MeOPh-NH-CO-CH=C(Cl)Ph (80%); mp 144-145° (chloroform-petroleum ether).

Anal. Calcd for $C_{16}H_{14}NClO_2$: C, 66.78; H, 4.90; N, 4.87. Found: C, 66.83; H, 4.83; N, 4.88.

N-(p-Tolyl)-trans-β-chlorocinnamamide: p-MePh-NH-CO-CH=C(Cl)Ph (85%); mp 134-135° (benzene-petroleum ether).

Anal. Calcd for $C_{16}H_{14}NClO$: C, 70.72; H, 5.19; N, 5.16. Found: C, 70.62; H, 4.97; N, 5.16.

N-(p-Isopropylphenyl)-trans-β-chlorocinnamamide: p-i-PrPh-NH-CO-CH=C(Cl)Ph (90%); mp 116-117° (benzene-petroleum ether).

Anal. Calcd for $C_{18}H_{18}NClO$: C, 72.11; H, 6.05; N, 4.67. Found: C, 71.55; H, 6.08; N, 4.79.

N-Benzyl-trans-β-chlorocinnamamide: $Ph-CH_2-NH-CO-CH=C(Cl)Ph$ (93%); mp 88-89° (benzene-petroleum ether).

Anal. Calcd for $C_{16}H_{14}NClO$: C, 70.72; H, 5.19; N, 5.16. Found: C, 70.99; H, 5.12; N, 5.08.

(±)-N-Phenylethyl-trans-β-chlorocinnamamide: MeCH(Ph)-NH-CO-CH=C(Cl)Ph (90%); mp 106-107° (benzene-petroleum ether).

Anal. Calcd for $C_{17}H_{16}NClO$: C, 71.45; H, 5.64; N, 4.90. Found: C, 71.08; H, 5.87; N, 4.81.

N-Isopropyl-trans-β-bromocinnamamide: i-Pr-NH-CO-CH=C(Br)Ph (85%); mp 98-99° (hexane).

Anal. Calcd for $C_{12}H_{14}NBrO$: C, 53.73; H, 5.26; N, 5.22.

Found: C, 53.96; H, 5.24; N, 5.23.

N-Isopropyl-cis-β-bromocinnamamide: i-Pr-NH-CO-CH=C(Br)Ph (72%); mp 130-131° (hexane).

Anal. Calcd for $C_{12}H_{14}NBrO$: C, 53.73; H, 5.26; H, 5.22. Found: C, 53.90; H, 5.23; N, 5.01.

N-sec-Butyl-cis-β-bromocinnamamide: sec-Bu-NH-CO-CH=C(Br)Ph (64%); mp 123-124° (hexane).

Anal. Calcd for $C_{13}H_{16}NBrO$: C, 55.31; H, 5.71; N, 4.96. Found: C, 55.45; H, 5.60; N, 5.04.

N-sec-butyl-trans-β-bromocinnamamide: sec-Bu-NH-CO-CH=C(Br)Ph (40%); mp 77-78° (hexane).

Anal. Calcd for $C_{13}H_{16}NBrO$: C, 55.31; H, 5.71; N, 4.96. Found: C, 55.45; H, 5.74; N, 5.10.

N-Isopropyl-trans-β-chlorocrotonamide: i-Pr-NH-CO-CH=C(Cl)Me (32%); mp 74-75° (sublimed).

Anal. Calcd for $C_7H_{12}NClO$: C, 52.02; H, 7.49; N, 8.67. Found: C, 51.83; H, 7.29; N, 8.57.

N-Isopropyl-cis-β-chlorocrotonamide: i-Pr-NH-CO-CH=C(Cl)Me (50%); mp 85-86° (sublimed).

Anal. Calcd for $C_{17}H_{12}NClO$: C, 52.02; H, 7.49; N, 8.67. Found: C, 52.00; H, 7.39; N, 8.52.

N-t-Butyl-trans-β-chlorocrotonamide: t-Bu-NH-CO-CH=C(Cl)Me (60%) mp 83-84° (sublimed).

Anal. Calcd for $C_8H_{14}NClO$: C, 54.69; H, 8.03; N, 7.98. Found: C, 55.15; H, 8.04; N, 7.89.

N-t-Butyl-cis-β-chlorocrotonamide: t-Bu-NH-CO-CH=C(Cl)Me (27%); mp 94-95° (sublimed).

Anal. Calcd for $C_8H_{14}NClO$: C, 54.69; H, 8.03; N, 7.98. Found: C, 54.82; H, 8.21; N, 7.84.

(±)-N-Phenylethyl-trans-β-chlorocrotonamides: MeCH(Ph)-NH-CO-CH=C(Cl)Me (53%); mp 115-116° (sublimed).

Anal. Calcd for $C_{12}H_{14}NClO$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.54; H, 6.39; N, 6.01.

(±)-Phenylethyl-cis-β-chlorocrotonamide: MeCH(Ph)-NH-CO-CH=C(Cl)Me (47%); mp 93-94° (sublimed).

Anal. Calcd for $C_{12}H_{14}NClO$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.62; H, 6.22; N, 6.32.

N-sec-Butyl-trans-β-chlorocrotonamide: sec-Bu-NH-CO-CH=C(Cl)Me (52%); mp 62-63° (sublimed).

Anal. Calcd for $C_8H_{14}NClO$: C, 54.70; H, 8.03; N, 7.98. Found: C, 54.72; H, 8.02; N, 7.95.

N-sec-Butyl-cis-β-chlorocrotonamide: sec-Bu-NH-CO-CH=C(Cl)Me (48%); mp 68-69° (sublimed).

Anal. Calcd for $C_8H_{14}NClO$: C, 54.70; H, 8.03; N, 7.98. Found: C, 54.92; H, 8.12; N, 8.00.

N-Ethyl-trans-β-chlorocrotonamide: Et-NH-CO-CH=C(Cl)Me (14%); mp 54-55° (sublimed).

Anal. Calcd for $C_6H_{10}NClO$: C, 48.82; H, 6.83; N, 9.49. Found: C, 49.10; H, 6.89; N, 9.45.

N-Ethyl-cis-β-chlorocrotonamide: Et-NH-CO-CH=C(Cl)Me (42%); mp 57-58° (sublimed).

Anal. Calcd for $C_6H_{10}ClO$: C, 48.82; H, 6.83; N, 9.49. Found: C, 48.83; H, 6.78; N, 9.54.

N-Methyl-cis-β-chlorocrotonamide: Me-NH-CO-CH=C(Cl)Me (25%); mp 81-82° (sublimed).

Anal. Calcd for C_5H_8NClO: C, 44.96; H, 6.03; N, 10.49. Found: C, 44.79; H, 6.08; N, 10.51.

N-Phenyl-trans-β-chlorocrotonamide: Ph-NH-CO-CH=C(Cl)Me (54%); mp 122-123° (sublimed).

Anal. Calcd for $C_{10}H_{10}NClO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.41; H, 5.19; N, 7.15.

N-Phenyl-cis-β-chlorocrotonamide: Ph-NH-CO-CH=C(Cl)Me (24%); mp 106-107° (sublimed).

Anal. Calcd for $C_{10}H_{10}NClO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.41; H, 5.17; N, 7.20.

N-(p-Isopropylphenyl)-trans-β-chlorocrotonamide: p-i-PrPh-NH-CO-CH=C(Cl)Me (28%); mp 76-77° (petroleum ether).

Anal. Calcd for $C_{13}H_{16}NClO$: C, 65.68; H, 6.79; N, 5.89. Found: C, 65.85; H, 6.58; N, 5.76.

N-(p-Isopropylphenyl)-cis-β-chlorocrotonamide: p-i-PrPh-NH-CO-CH=C(Cl)Me (30%); mp 113-114° (petroleum ether).

Anal. Calcd for $C_{13}H_{16}NClO$: C, 65.68; H, 6.79; N, 5.89. Found: C, 65.78; H, 6.81; N, 5.70.

N-(p-Chlorophenyl)-trans-β-chlorocrotonamide: p-ClPh-NH-CO-CH=C(Cl)Me (39%); mp 130-131° (petroleum ether).

Anal. Calcd for $C_{10}H_9NCl_2O$: C, 52.19; H, 3.94; N, 6.09. Found: C, 51.92; H, 3.90; N, 6.02.

N-(p-Chlorophenyl)-cis-β-chlorocrotonamide: p-ClPh-NH-CO-CH=C(Cl)Me (18%); mp 135-136° (petroleum ether).

Anal. Calcd for $C_{10}H_9NCl_2O$: C, 52.19; H, 3.94; N, 6.09. Found: C, 52.22; H, 3.85; N, 6.07.

N-(p-Tolyl)-trans-β-chlorocrotonamide: p-MePh-NH-CO-CH=C(Cl)Me (47%); mp 107-108° (petroleum ether).

Anal. Calcd for $C_{11}H_{12}NClO$: C, 63.01; H, 5.73; N, 6.68. Found: C, 63.08; H, 5.90; N, 6.67.

N-(p-Tolyl)-cis-β-chlorocrotonamide: p-MePh-NH-CO-CH=C(Cl)Me (28%); mp 101-102° (petroleum ether).

Anal. Calcd for $C_{11}H_{12}NClO$: C, 63.01; H, 5.73; N, 6.68; Found: C, 62.89; H, 5.69; N, 6.72.

N-Isopropyl-cis-β-chloro-β-(t-butyl)-acrylamide: i-Pr-NH-CO-CH=C(Cl)-t-Bu (51%); mp 123-124° (hexane).

Anal. Calcd for $C_{10}H_{18}NClO$: C, 58.96; H, 8.91; N, 6.88. Found: C, 59.16; H, 9.00; N, 7.01.

N-sec-Butyl-cis-β-chloro-β-(t-butyl)-acrylamide: sec-Bu-NH-CO-CH=C(Cl)-t-Bu (87%); mp 119-120° (sublimed).

Anal. Calcd for $C_{11}H_{20}NClO$: C, 60.68; H, 9.26; N, 6.43. Found: C, 60.45; H, 9.37; N, 6.71.

N-(t-Butyl)-cis-β-chloro-β-(t-butyl)-acrylamide: t-Bu-NH-CO-CH=C(Cl)-t-Bu (90%); mp 151-152° (sublimed).

Anal. Calcd for $C_{11}H_{20}NClO$: C, 60.68; H, 9.26; N, 6.43. Found: C, 60.40; H, 9.61; N, 6.40.

N-Phenyl-cis-β-chloro-β-(t-butyl)-acrylamide: Ph-NH-CO-CH=C(Cl)-t-Bu (60%); mp 155-156° (sublimed).

Anal. Calcd for $C_{13}H_{16}NClO$: C, 65.68; H, 6.79; N, 5.89. Found: C, 65.27; H, 6.87; N, 5.84.

(±)-N-Phenylethyl-cis-β-chloro-β-(t-butyl)-acrylamide: (63%); mp 140-141° (petroleum ether).

Anal. Calcd for $C_{15}H_{20}NClO$: C, 67.78; H, 7.59; N, 5.27. Found: C, 67.81; H, 7.57; N, 4.91.

N-Isopropyl-trans-β-chloro-p-methoxycinnamamide: i-Pr-NH-CO-CH=C(Cl)-p-MeOPh (69%); mp 117-118° (petroleum ether).

Anal. Calcd for $C_{13}H_{16}NClO_2$: C, 61.54; H, 6.36; N, 5.52.

Found: C, 61.86; H, 6.47; N, 5.64.

N-Isopropyl-trans-α,β-dibromocinnamamide: i-Pr-NH-CO-CBr=C(Br)Ph (72%); mp 143-144° (petroleum ether).

Anal. Calcd for $C_{12}H_{13}NBr_2O$: C, 41.51; H, 3.77; N, 4.03. Found: C, 41.63; H, 3.82; N, 4.08.

N-Isopropyl-cis-α,β-dibromocinnamamide: i-Pr-NH-CO-CBr=C(Br)Ph (95%); mp 117-118° (petroleum ether).

Anal. Calcd for $C_{12}H_{13}NBr_2O$: C, 41.51; H, 3.77; N, 4.03. Found: C, 41.67; H, 3.86; N, 3.98.

N-sec-Butyl-trans-α,β-dibromocinnamamide: sec-Bu-NH-CO-CBr=C(Br)Ph (81%); mp 143-144° (petroleum ether).

Anal. Calcd for $C_{13}H_{15}NBr_2O$: C, 43.22; H, 4.19; N, 3.88. Found: C, 43.20; H, 3.97; N, 3.63.

N-sec-Butyl-cis-α,β-dibromocinnamamide: sec-Bu-NH-CO-CBr=C(Br)Ph (92%); mp 131-132° (petroleum ether).

Anal. Calcd for $C_{13}H_{15}NBr_2O$: C, 43.22; H, 4.19; N, 3.88. Found: C, 43.06; H, 4.31; N, 3.76.

N-Phenyl-trans-α,β-dibromocinnamamide: Ph-NH-CO-CBr=C(Br)Ph (84%); mp 169-170° (benzene-petroleum ether).

Anal. Calcd for $C_{15}H_{11}NBr_2O$: C, 47.25; H, 2.91; N, 3.67. Found: C, 47.24; H, 2.75; N, 3.62.

N-Phenyl-cis-α,β-dibromocinnamamide: Ph-NH-CO-CBr=C(Br)Ph (66%); mp 129-130° (benzene-petroleum ether).

Anal. Calcd for $C_{15}H_{11}NBr_2O$: C, 47.25; H, 2.91; N, 3.67. Found: C, 47.21; H, 2.75; N, 3.87.

N-Isopropyl-trans-α-chlorocinnamamide: i-Pr-NH-CO-CCl=C(H)Ph (71%); mp 84-85° (petroleum ether).

Anal. Calcd for $C_{12}H_{14}NClO$: C, 64.42; H, 6.32; N, 6.26. Found: C, 63.96; H, 6.24; N, 5.98.

N-Isopropyl-trans-α-bromocinnamamide: i-Pr-NH-CO-CBr=C(H)Ph (83%); mp 110-111° (pentane).

Anal. Calcd for $C_{12}H_{14}NBrO$: C, 53.73; H, 5.26; N, 5.22. Found: C, 53.83; H, 5.31; N, 5.00.

Method B: To a stirred (magnet) solution of 2 mmol of the α-halo-acid in 15 ml of dry benzene was added in one portion 4 mmol of oxalyl chloride. Vigorous evolution of carbon monoxide was initially observed. This gradually subsided after 30 min whereupon the mixture was heated at 40° for 1 hr. Removal of the solvent and excess oxalyl chloride under reduced pressure gave the crude acid chloride as a yellow oil. This was dissolved in 10 ml dry benzene and the benzene solution cooled to ca. 15° and treated with isopropylamine in the manner described in Method A. The crude solid amide obtained was recrystallized from petroleum ether to give the pure white crystalline amide.

The following amides were prepared by this method:

N-Isopropyl-cis-α-chlorocinnamamide: i-Pr-NH-CO-CCl=C(H)Ph (62%); mp 56-57° (petroleum ether).

Anal. Calcd for $C_{12}H_{14}NClO$: C, 64.42; H, 6.32; N, 6.26. Found: C, 64.29; H, 6.40; N, 6.14.

N-Isopropyl-cis-α-bromocinnamamide: i-Pr-NH-CO-CBr=C(H)Ph (70%); mp 69-70° (petroleum ether).

Preparation of cis-α-chlorocinnamoyl chloride: A mixture of 2 mmol of cis-α-chlorocinnamic acid and 4 mmol of thionyl chloride in 15 ml of dry benzene was refluxed for 2 hr, cooled, and evaporated under reduced pressure at room temperature to give a mixture of 35% cis-

and 65% trans- acid chlorides as a yellow oil: nmr ($CDCl_3$) δ 7.08 (Ph, s, cis-), 7.33, 7.83 (Ph, m, trans-), 7.47 (=CH-, s, cis-), 8.17 (=CH-, s, trans-). (The nmr spectra ($CDCl_3$) of cis- and trans-acids are as follows: cis-acid, δ 7.40 (Ph, s), 7.47 (=CH-, s), 11.23 (OH, s); trans-acid, δ 7.47, 7.92 (Ph, m), 8.05 (=CH-, s), 11.53 (OH, s)). A solution of 2 mmol of the cis-acid in 15 ml of dry benzene was refluxed for 2 hr, cooled, and the solvent evaporated to give the pale yellow crystalline cis-acid: nmr ($CDCl_3$) δ 7.40 (Ph, s), 7.47 (=CH-, s), 12.0 (OH, s). A mixture of 2 mmol of the cis-acid and 4 mmol of oxalyl chloride was stirred at room temperature for 30 min until the evolution of carbon monoxide had subsided, then the mixture was heated at 40° for 1 hr. The solvent and excess oxalyl chloride were removed under reduced pressure to give the cis-acid chloride as a pale yellow oil: nmr ($CDCl_3$) δ 7.10 (Ph, s), 7.47 (=CH-, s).

Preparation of acetylenic nitriles: A solution of 0.03 mol of the acetylenic aldoxime in 10 ml of acetic anhydride was stirred (magnet), and heated (water bath) to 80° for 30 min, then gently refluxed for 30 min, cooled, and poured on 50 g of crushed ice. The aqueous and ether phases were separated, the aqueous phase saturated with sodium chloride, and then ether extracted. The combined ether solutions were washed with saturated sodium carbonate then saturated brine, dried, and the ether removed by distillation to give a yellow oil. Distillation afforded the pure acetylenic nitrile.

The following acetylenic nitriles were prepared:

Tetrolonitrile: Me-C≡C-C≡N (87%); bp 104-112° (760 mm) (lit.[194] bp 101.5° (754 mm)).

Phenylpropiolonitrile: Ph-C≡C-C≡N (51%); bp 74-75° (3.0 mm)

(lit.[194] bp 105-196° (13 mm)).

t-Butylpropiolonitrile: t-Bu-C≡C-C≡N (66%); bp 82-94° (760 mm).

Preparation of cis- and trans-β-chlorocinnamaldehyde: Phosphoryl chloride (133.1 g, 1.25 mol) was added dropwise during 30 min to a vigorously stirred (mechanical) 109.5 g (1.50 mol) of dimethylformamide, while maintaining the reaction temperature at ca. 22°. To this was added dropwise during 30 min 60.0 g (0.50 mol) of acetophenone, the reaction temperature being kept at ca. 55° with a water bath. After 3 hr the temperature dropped back to room temperature and the reaction mixture was allowed to stand overnight. The viscous oil was poured on 1 kg of crushed ice and stirred (glass rod), then neutralized with solid sodium acetate. The resulting milky solution was ether extracted, and the ether extracts washed first with 10% sodium bicarbonate then water, dried, and evaporated to give 79 g of a yellow oil. Distillation of this oil under high vacuum yielded 54.8 g (66%) of a yellow oil that was found (by nmr spectroscopy) to consist of 13% cis- and 87% trans-aldehydes: bp 100-105° (0.2 mm); ir ($CHCl_3$) 2870, 2750, 1665 cm^{-1}; nmr ($CDCl_3$) δ 6.75 (=CH-, d, cis-), 6.90 (=CH-, d, trans-), 7.80 (Ph, m, cis- and trans-), 9.80 (CHO, d, cis-), 10.58 (CHO, d, trans-).

Preparation of cis-β-chloro-β-(t-butyl)-acrylaldehyde diethyl acetal (79): A mixture of 29.3 g (0.20 mol) of 3-chloro-4,4-dimethyl-2-pentenal, 44.4 g (0.30 mol) of triethylorthoformate, and 0.5 g of ammonium chloride in 40 ml of absolute ethanol was refluxed for 30 min, cooled and the ethanol distilled out at atmospheric pressure. The residue was distilled at reduced pressure to give 36.5 g (83%) of the acetal as a

colorless oil: bp 112-116° (24 mm); nmr ($CDCl_3$) δ 1.2 (t-Bu, s), 1.3 (Me, t), 3.6 ($-CH_2-$, m), 5.5 (AB quartet, J = 7 Hz).

Preparation of t-Butylpropiolaldehyde diethyl acetal (80): To a solution of 12.9 g (0.23 mol) of potassium hydroxide in 150 ml of absolute ethanol was added 33.1 g (0.15 mol) of 79 and the mixture was refluxed for 55 hr. The precipitated solids were filtered off by suction and the filtrate diluted with 500 ml of water and ether extracted. The ether extracts were washed with water, dried, and evaporated to yield a pale yellow oil. This was distilled at reduced pressure to give 15.0 g (63%) of the acetylenic acetal as a colorless oil: bp 95-97° (28 mm); ir (neat) 2250 cm^{-1}; nmr ($CDCl_3$) δ 1.23 (t-Bu, s), 1.3 (Me, t), 3.65 ($-CH_2-$, m), 5.23 ($-CH-$, s).

Preparation of 1-methylcyclopentane carboxaldehyde (87): To a solution of 22.0 g (0.25 mol) of lithium bromide in 45.0 g (0.25) of hexamethylphosphoramide was added 27.2 g (0.24 mol) of 1-methylcyclohexene oxide 86 (prepared[83,84] from 1-methylcyclohexene) and the mixture was refluxed for 5 days. The reaction mixture was then cooled and diluted with water and the benzene phase was separated, washed with water, dried and the benzene removed by atmospheric pressure distillation. The residue was distilled at reduced pressure to give 12.9 g (48%) of the aldehyde 87 as a colorless oil: bp 65-75° (48 mm); ir ($CHCl_3$) 2870, 2740, 1725 cm^{-1}; nmr ($CDCl_3$) δ 1.1 (Me, s), 1.7 ($-CH_2-$, broad m), 9.50 (CHO, s).

Preparation of p-Isopropylbenzoic acid (89): A solution of 102 g (0.6 mol) of silver nitrate in 180 ml of water was added to a stirred solution of 96 g (1.2 mol) of 50 weight % sodium hydroxide in 350 ml of water to immediately form a black suspension of silver oxide. To

this was added 44.4 g (0.3 mol) of p-isopropylbenzaldehyde (88) and the mixture was heated (water-bath) to 55°. The resulting exothermic reaction caused the reaction temperature to rise to 75°. The water-bath was removed and the mixture stirred for an additional 30 min and then suction filtered and the filter-cake was washed with hot water. The clear filtrate was acidified with concentrated hydrochloric acid and the precipitated acid was suction filtered and dried in a vacuum oven at 70° to give 44.8 g (91%) of the acid: mp 118-119° (lit.[194] mp 115-117°).

Preparation of p-isopropylbenzamide (91): A mixture of 16.4 g (0.1 mol) of p-isopropylbenzoic acid (89) and 23.8 g (0.2 mol) of thionyl chloride in 100 ml of dry benzene was refluxed for 2 hr, cooled and evaporated to yield the crude yellow acid chloride (90) as an oil. This was dissolved in 50 ml of anhydrous ether and cooled to ca. -10° (ice-salt bath) and ammonia gas was introduced above the liquid surface. Considerable fuming occurred, the ether solution became cloudy, and after 15 min a white solid separated. Ammonia addition was continued for a further 15 min and the reaction mixture was allowed to warm up to room temperature and was then poured into 500 ml of water. The precipitated amide was extracted with chloroform and the chloroform extracts dried and evaporated to give the crude amide which was recrystallized from benzene to afford 9.7 g (60%) of white crystalline amide: mp 151-152° (lit.[194] mp 153°); ir ($CHCl_3$) 3530, 3500, 3410, 3350(w), 3280(w), 3190, 1665 cm^{-1}.

Preparation of p-Isopropylaniline (92): A solution of 24.0 g (0.30 mol) of 50 weight % of sodium hydroxide in 120 ml of water was cooled to 0° and 9.6 g (0.06 mol) of bromine was added. To the resulting

yellow solution was added portionwise during 5 min 8.2 g (0.05 mol) of powdered amide (91). The amide dissolved after 20 min and the reaction mixture turned orange after 40 min. The mixture was then heated to 70-80° for 1 hr and the resulting dark solution was cooled, saturated with sodium chloride, and ether extracted. The ether extracts were washed with saturated brine, dried, and evaporated to give a black oil which was distilled under reduced pressure to give 3.8 g (57%) of the amine: by 118-124° (28 mm); ir ($CHCl_3$) 3470, 3440 cm^{-1}.

Preparation of methylenecyclopentane (95): To 75 ml of stirred dimethyl sulfoxide (DMSO) was added 3.84 g (0.16 mol) of oil free sodium hydride. Evolution of hydrogen immediately occurred and the rapidly stirred slurry was heated to 70-75° for 1.5 hr until the evolution of hydrogen had ceased. The resulting greenish-black solution was cooled to 0° and a warm solution of 53.6 (0.15 mol) of methyltriphenylphosphonium bromide in 150 ml of DMSO was added to it, yielding a reddish-brown solution. This solution was stirred at room temperature for 10 min, 12.6 g (0.17 mol) of cyclopentanone was added to it, and the reaction mixture was stirred at room temperature for 40 min then immediately distilled to give 13.6 g of a colorless liquid (bp 74-90°). This was redistilled to give 9.14 g (74%) of methylenecyclopentane (95): bp 76-77° (lit.[194] bp 75-76°); nmr ($CDCl_3$) δ 1.63 (m), 3.07 (m), 4.82 ($=CH_2$, m).

Preparation of α-cyanopinacolone (101): To a stirred solution of 0.54 g (0.011 mol) of sodium cyanide in 5 ml of ethanol and 2 ml of water was added dropwise during 5 min 1.79 g (0.010 mol) of α-bromopinacolone (100).[93] The clear solution immediately turned yellow and then black. The mixture was then gently refluxed for

14 hr, diluted with 25 ml of benzene and cooled and diluted with 50 ml of water. The phases were separated, the aqueous phase was saturated with sodium chloride and was extracted with benzene. The combined benzene solutions were washed with saturated brine, dried and evaporated to yield 1.3 g of a black oil. Analysis by tlc (on alumina using chloroform) showed only one product. This oil was passed through a column of alumina (70 g), using chloroform, and after evaporation of the solvent yielded pale yellow crystals. Recrystallization from hexane yielded 0.58 g (46%) of white crystalline α-cyanopinacolone: mp 66-67°; ir ($CHCl_3$) 2270, 1725 cm^{-1}; nmr ($CDCl_3$) δ 1.20 (9H, s), 3.72 (2H, s).

Preparation of 5-phenyl-3-(2-pyridinyl)-isoxazole (53): A mechanically stirred solution of 3.0 g (0.0192 mol) of 2-pyridine hydroxamoyl chloride (50) in 50 ml of anhydrous ether was cooled to 0° and 9.79 g (0.096 mol) of phenyl acetylene was added in one portion. To this was added dropwise during 45 min a solution of 1.67 g (0.0192 mol) of triethylamine in 10 ml of anhydrous ether to produce a cloudy solution. The mixture was stirred at room temperature for 4 hr, then suction-filtered to remove the precipitated solids and the filter-cake was washed with anhydrous ether. The filtrate was evaporated to yield a greenish-black oil, which was evacuated under high vacuum to remove the phenylacetylene impurity. The oily residue (4.6 g) was analyzed by tlc (on alumina using benzene) and showed only one component. The oil was chromatographed on 230 g of alumina and elution with benzene yielded a pale yellow solid, which was sublimed to give 2.64 g (62%) of the isoxazole: mp 95-96°; ir ($CHCl_3$) 1612, 1595, 1570, 1485 cm^{-1}; nmr (DMSO-d_6) δ 7.67 (5H, m), 8.10 (4H, m), 8.85 (1H, m).

General procedure for the Beckmann rearrangement of acetylenic oximes with Phosphorus halides: A mechanically stirred solution of 10 mmol of acetylenic oxime in 50 ml of anhydrous ether was cooled to 0° and 20 mmol of powdered phosphorus pentachloride, phosphorus pentabromide or phosphoryl bromide was added portionwise during 1-2 min. (When 10 mmol of phosphorus pentachloride was used the yield of product decreased by ca. 10%). The suspension was stirred at 0° for 1 hr then at room temperature for 4 hr and the mixture was poured on 100 g of crushed ice. (The alternative procedure of adding 10% sodium bicarbonate to the cooled reaction mixture did not alter the yield or the nature of the product). The phases were separated and the aqueous phase saturated with sodium chloride and ether extracted. The combined ether solutions were washed with saturated brine, dried, and evaporated to yield a yellow oil. In the cases in which rearrangement occurred tlc analysis of the oil (on alumina using benzene) revealed only trans- or cis- and trans-haloacrylic amides. Chromatography on alumina yielded crude haloamides which were recrystallized from appropriate solvents. In the cases in which fragmentation exclusively occurred, the product was distilled to give the alkyl halide and the nitrile. When both rearrangement and fragmentation simultaneously occurred, the products were chromatographed on alumina as previously described.

The acetylenic oximes rearranged by this procedure and the nature of the products obtained are shown in Tables XVII, XVIII and XIX (pp 94, 96 and 113 respectively), and on p 119.

Beckmann rearrangement of 1-(1-methylcyclopentyl)-3-phenyl-2-propyn-1-ketoxime with PCl_5 : The general procedure was used.

Distillation of the crude oil at atmospheric pressure yielded 0.75 g (50%) of 1-methylcyclopentene (94); bp 72-76° (lit.[194] bp 72°); nmr ($CDCl_3$) δ 5.3 (=CH-). The residue was further distilled at 1 mm pressure to give 1.47 g (50%) of an oil that was shown (by nmr spectroscopy) to be a mixture of 12% cis- and 88% trans-β-chlorocinnamonitriles: bp 102-138° (1 mm); ir ($CHCl_3$) 2230 cm^{-1}; nmr ($CDCl_3$) δ 6.0 (=CH-, s, cis-), 6.2 (=CH-, s, trans-), 7.5 (Ph, m, cis- and trans-).

Beckmann rearrangement with PCl_5 in the presence of LiBr: A solution of 2.0 g (0.011 mol) of 2-methyl-5-phenyl-4-pentyn-3-ketoxime in 50 ml of anhydrous ether was added to a solution of 2.0 g of lithium bromide in 100 ml of anhydrous ether. The mixture was stirred and cooled to 0°. To this pale yellow solution was added portionwise during 1-2 min 4.6 g (0.022 mol) of powdered phosphorus pentachloride, whereupon the solution immediately turned orange. The reaction mixture was kept at 0° for 1 hr then at room temperature for 4 hr and the product worked up as previously described to yield 3.15 g of a brown oil. Analysis by tlc (on alumina using benzene) revealed three products. Chromatography on 118 g of alumina and elution with benzene afforded the following products. The first product eluted was recrystallized from petroleum ether to give 1.44 g of white crystalline N-isopropyl-cis-α,β-dibromocinnamamide (162): mp 116-117°; ir ($CHCl_3$) 3430, 3300, 1655 cm^{-1}. The second product eluted was recrystallized from petroleum ether to give 0.56 g of white crystalline N-isopropyl-trans-α,β-dibromocinnamamide (163): mp 143-144°; ir ($CHCl_3$) 3430, 3300, 1665 cm^{-1}. The third product eluted was recrystallized from petroleum ether to afford 0.14 g of white

crystalline N-isopropylphenylpropiolamide: mp 85-86°; ir ($CHCl_3$) 3435, 3260, 2220, 1650 cm^{-1}.

Beckmann rearrangement with PCl_5 in the presence of LiI: A solution of 1.5 g (0.008 mol) of 2-methyl-5-phenyl-4-pentyn-3-ketoxime in 50 ml of anhydrous ether was added to a solution of 2.2 g (0.016 mol) of lithium iodide in 100 ml of anhydrous ether and the mixture was stirred and cooled to 0°. Powdered phosphorus pentachloride (3.3 g, 0.016 mol) was added, whereupon the pale yellow solution immediately turned purple. The reaction mixture was kept at 0° for 1 hr, then at room temperature for 4 hr, and was worked up as previously described to give 2.0 g of a brown oil. Analysis by tlc (on alumina using benzene) revealed only one product. Chromatography on 150 g of alumina and elution with benzene yielded a pale yellow solid which was recrystallized from petroleum ether to afford 0.31 g (17%) of white crystalline N-isopropyl-trans-β-chlorocinnamamide: mp 95-96°; ir ($CHCl_3$) 3430, 3300, 1650 cm^{-1}.

Beckmann rearrangement of 2-methyl-5-phenyl-4-pentyn-3-ketoxime-OD with PCl_5: A solution of 2.0 g (0.011 mol) of the deuterated oxime in 50 ml of anhydrous ether was stirred and cooled to 0° and to it was added portionwise during 2 min 0.022 mol of powdered PCl_5. The reaction mixture was stirred at 0° for 1 hr and then at room temperature for 4 hr and slowly quenched at 0° by the addition of 20 ml of D_2O. The phases were separated and the aqueous phase saturated with sodium chloride and ether extracted. The combined ether solutions were washed with saturated brine, dried, and evaporated to give a pale yellow oil which was recrystallized from petroleum ether to afford 1.0 g (41%) of N-isopropyl-trans-β-chloro-α-deuteriocinnamamide: mp 97-98°; ir ($CHCl_3$)

3430, 3300, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.2 (Me, d), 4.2 (-CH, m), 6.6 (=CH-, s), 6.7 (NH, broad), 7.5 (Ph, m). The deuterium content was estimated (by nmr spectroscopy) to be 81%.

The experiment was repeated under the same conditions except that the mixture was quenched with 20 ml of H_2O instead of D_2O. Workup afforded 1.1 g (45%) of 86% deuterated amide. The deuterated oximes treated by this method as well as the percent deuterium in the products are shown on p 102.

Beckmann rearrangement of a mixture of 2-methyl-5-phenyl-4-pentyn-3-ketoxime-OD and 1,3-diphenyl-2-propyn-1-ketoxime with PCl_5: A mixture of 0.9 g (0.0048 mol) of the deuterated oxime and 1.05 g (0.0048 mol) of the non-deuterated oxime in 70 ml of anhydrous ether was stirred and cooled to 0°. To this was added 0.019 mol of powdered PCl_5 and the reaction mixture was stirred at 0° for 1 hr then at room temperature for 4 hr, quenched with water, and worked up to give 1.3 g of a crude oil. Analysis of the crude oil by tlc (on alumina using benzene) indicated a mixture of the corresponding β-chlorocinnamamides. Chromatography with 120 g of alumina and elution with benzene gave, in order of elution, 1) 0.52 g (42%) of N-phenyl-trans-β-chlorocinnamamide: mp 131-132° (benzene-petroleum ether), and 2) 0.5 g (46%) of N-isopropyl-trans-β-chloro-α-deuteriocinnamamide: mp 96-97° (petroleum ether). Deuterium analysis by nmr spectroscopy indicated 38% D in the latter product.

Beckmann rearrangement of a mixture of 2-methyl-5-phenyl-4-pentyn-3-ketoxime and 3-phenyl-1-(p-isopropylphenyl)-2-propyn-1-ketoxime-OD with PCl_5: A mixture of 0.9 g (0.0048 mol) of the nondeuterated oxime and 1.27 g (0.0048 mol) of the deuterated oxime

in 100 ml of anhydrous ether was treated with 0.0019 mol of powdered PCl_5 in the manner previously described. Workup of the reaction mixture afforded 1.4 g of crude β-chlorocinnamamides as indicated by tlc analysis. Chromatography with 140 g of alumina and elution with benzene afforded, in order of elution, 1) 0.52 g (36%) of N-(p-isopropylphenyl)-trans-β-chloro-α-deuteriocinnamamide containing 20% D: mp 117-118°, and 2) 0.46 (43%) of N-isopropyl-trans-β-chlorocinnamamide.

Beckmann rearrangement of 4-methyl-1-phenyl-1-hexyn-3-ketoxime with PBr_5: A solution of 2.2 g (0.011 mol) of oxime in 70 ml of anhydrous ether was treated with 9.48 g (0.022) mol of powdered PBr_5 as previously described (p 210). The usual workup afforded 2.5 g of a brown oil which contained 3 compounds as determined by tlc analysis (on alumina using benzene). This oil was chromatographed on 190 g of alumina using benzene, and the following products were obtained. The first compound eluted gave, after recrystallization from petroleum ether, 1.2 g (60% cis) of N-sec-butyl-cis-α,β-dibromocinnamamide: mp 131-132°; ir ($CHCl_3$) 3430, 3300, 1665 cm^{-1}. The second component eluted gave 0.8 g (40% trans) of N-sec-butyl-trans-α-β-dibromocinnamamide: mp 143-144° (petroleum ether); ir ($CHCl_3$) 3430, 3300, 1665 cm^{-1}. The third component eluted gave 0.04 g (2%) of N-sec-butylphenylpropiolamide: mp 90-91° (petroleum ether); ir ($CHCl_3$) 3430, 3300, 2220, 1650 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.88; H, 7.46; N, 6.94.

Beckmann rearrangement of 2-methyl-4-hexyn-3-ketoxime with PBr_5: A solution of 0.5 g (0.0037 mol) of oxime in 40 ml of anhydrous

ether was treated with 3.19 g (0.0074 mol) of powdered PBr_5 in the usual manner to give 0.6 g of a crude black oil. Analysis of the crude oil by tlc (on alumina using benzene) indicated only one product. This oil was chromatographed on 40 g of alumina and elution with benzene afforded, after recrystallization from petroleum ether, 0.24 g (23%) of N-isopropyl-trans-α,β-dibromocrotonamide: mp 124-125°; ir ($CHCl_3$) 3430, 3300, 1655 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (6H, s), 2.35 (3H, s), 3.9 (1H, m), 5.8 (1H, broad, s).

Anal. Calcd for $C_7H_{11}NBr_2O$: C, 29.48; H, 3.89; N, 4.91. Found: C, 29.42; H, 4.03; N, 4.90

Bromination of 1,3-diphenyl-2-propyn-1-ketoxime: A solution of 0.5 g (0.0023 mol) of the oxime in 10 ml of anhydrous ether was stirred and to it was added dropwise during 20 min a solution of 0.4 g (0.0024 mol) of bromine. The mixture was stirred for 1 hr and evaporated to give 1.3 g of crude oil. Analysis by tlc (on alumina with chloroform) showed one component. This was chromatographed on 90 g of alumina. Elution with chloroform gave a yellow solid, which was recrystallized from petroleum ether to yield 0.31 g (35%) of pale yellow crystalline dibromooxime: mp 134-136° (dec); ir ($CHCl_3$) 3570, 3270 cm^{-1}; uv (95% EtOH) λ_{max} 206 (ε 22,150), 242 nm (ε 9,270).

Anal. Calcd for $C_{15}H_{11}NBr_2O$: C, 47.25; H, 2.91; N, 3.67. Found: C, 47.60; H, 2.87; N, 3.83.

Bromination of 1,3-diphenyl-2-propyn-1-ketoxime: A solution of 1.5 g (0.0068 mol) of oxime in 15 ml of chloroform was treated with a solution of 1.08 g (0.0069 mol) of bromine in 25 ml of chloroform as described in the previous experiment to give 3.8 g of a crude solid. Analysis by tlc (on alumina using chloroform) indicated two partially

resolved components. Resolution could not be improved by using silica gel or a mixture of solvents. The crude oil was passed through a column of alumina (150 g) by elution with chloroform to give 1.89 g (73%) of a pale yellow crystalline solid, which was recrystallized from petroleum ether to give a pale yellow solid: mp 100-119° (dec); ir ($CHCl_3$) 3570, 3270 cm^{-1}; uv (95% EtOH) λ_{max} 207 (ε 30,400), 250 nm (ε 12,620).

Beckmann simulation of N-isopropyl-trans-β-bromo-cinnamamide with PBr_5: A solution of 0.3 g (0.0011 mol) of amide in 30 ml of anhydrous ether was stirred and cooled to 0°. Powdered PBr_5 (0.95 g, 0.0022 mol) was added during 1 min and the mixture was stirred at 0° for 1 hr and then at room temperature for 4 hr. The usual workup afforded 0.28 g of a mixture of 20% cis- and 80% trans-amides: mp 90-96°; ir ($CHCl_3$) 3430, 3300, 1640 cm^{-1}; nmr ($CDCl_3$) δ 0.9 (Me_2, d, cis-), 1.2 (Me_2, d, trans-), 4.1 (-CH-, m), 5.9 (NH, broad), 6.6 (=CH-, s, cis-), 6.7 (=CH, s, trans-), 7.5 (Ph, m, cis- and trans-).

Beckmann simulation of N-isopropyl-cis-β-bromo-cinnamamide: A solution of 0.3 g (0.0011 mol) of the cis-amide was treated in the same manner described above for the trans isomer to give 0.27 g of a mixture of 60% cis- and 40% trans-amides.

Attempted Beckmann rearrangement with concentrated sulfuric acid: Concentrated sulfuric acid (15 g) was cooled to -10° (ice-salt bath) and stirred and to this was added portionwise during 5 min 1.5 g (0.008 mol) of powdered 2-methyl-5-phenyl-4-pentyn-3-ketoxime. Stirring was continued at this temperature for 2.5 hr, then the reaction mixture was poured on 100 g of crushed ice, whereupon a yellow oil separated at the bottom of the flask. The oil was extracted with ether, the

ether extracts were washed with saturated brine, dried, and the solvent evaporated under reduced pressure at room temperature to give 1.45 g of crude yellow 3-isopropyl-5-phenylisoxazole: ir ($CHCl_3$) 1615, 1495, 1470 cm^{-1}.

Attempted Beckmann rearrangement with polyphosphoric acid (PPA): To stirred and cooled PPA (30 g) was added portionwise during 10 min 1.5 g (0.008 mol) of powdered 2-methyl-5-phenyl-4-pentyn-3-ketoxime. Stirring was continued at 0° for 2 hr and the reaction mixture was then poured on 200 g of crushed ice. A yellow oil separated and was extracted with ether, the ether extracts were washed with water, dried, and evaporated to give 1.48 g of a mixture of 3-isopropyl-5-phenyl-isoxazole and unreacted oxime: ir ($CHCl_3$) 3590, 3280, 2220, 1615, 1495, 1470 cm^{-1}.

Attempted Beckmann rearrangement with thionyl chloride: Thionyl chloride (10 ml) was stirred and cooled to 0° and 1.0 g (0.0045 mol) powdered 1,3-diphenyl-2-propyn-1-ketoxime was added in one portion. The oxime readily dissolved with the evolution of gas. After 5 min the reaction mixture was poured on 150 ml of crushed ice and a yellow oil separated. The oil was extracted with ether and the usual workup afforded 0.95 g of unreacted oxime: ir ($CHCl_3$) 3590, 3290, 2220 cm^{-1}.

Attempted Beckmann rearrangement with a 1:1 dioxane-sulfur trioxide complex: A suspension of 0.91 g (0.0054 mol) of the dioxane-sulfur trioxide complex[144] in 10 ml of 1,2-dichloroethane was stirred (magnet) and cooled to 0°. To this was added dropwise during 15 min a solution of 1.0 g of 2-methyl-5-phenyl-4-pentyn-3-ketoxime in 10 ml of 1,2-dichloroethane and the mixture kept at 0° for an additional 5 min, then allowed to warm up to room temperature and heated at 70-

80° for 45 min. The yellow solution gradually darkened on heating. Evaporation of the solvent at reduced pressure afforded 1.8 g of an unidentifiable viscous black oil.

Attempted Beckmann rearrangement with PF_5: A solution of 1.0 g (0.0054 mol) of 2-methyl-5-phenyl-4-pentyn-3-ketoxime in 30 ml of anhydrous ether was stirred and cooled to 0° and PF_5 gas was bubbled into the solution for 20 min. The reaction mixture became cloudy, and a pale yellow oil separated at the bottom of the flask and solidified after 15 min. Stirring was continued at 0° for 1 hr during which time the solidified material reverted to an oil. The reaction mixture was allowed to warm up to room temperature and stirred for 4 hr then poured on ice and worked up in the usual manner to give 0.98 of pale yellow crystalline unreacted oxime: ir ($CHCl_3$) 3590, 3280, 2220 cm^{-1}.

Preparation of 2-methyl-5-phenyl-4-pentyn-3-ketoxime tosylate: The procedure of House and Berkowitz[195] was used. A solution of 2.8 g (0.015 mol) of oxime in 15 ml of pyridine was stirred and cooled to 0° and to it was added portionwise during 10 min 3.1 g (0.016 mol) of powdered p-toluenesulfonyl chloride. The mixture was stirred at 0° for 1 hr, then at room temperature for 1.5 hr, and then poured into 200 ml of cold water whereupon an oil initially separated and solidified after 5 min. The crude tosylate was suction-filtered, washed with water, and dried overnight in a vacuum desicator containing phosphorus pentoxide. Recrystallization from petroleum ether (bp 35-60°) yielded 4.4 g (87%) of the pale yellow tosylate: mp 118-119°; ir ($CHCl_3$) 2230, 2200 (sh), 1375, 1180 cm^{-1}; nmr ($CDCl_3$) 1.2 (Me_2, d), 2.45 (Me, s), 2.72 (-$\dot{C}$H, m), 7.5 (Ph, m and AB quartet, J_{AB}= 8 Hz).

Anal. Calcd for $C_{19}H_{19}NO_3S$: C, 66.83; H, 5.62; N, 4.10.

Found: C, 67.24; H, 6.10; N, 4.48.

Attempted Beckmann rearrangement of 2-methyl-5-phenyl-4-pentyn-3-ketoxime tosylate: A solution of 1.0g (0.002 g mol) of the oxime tosylate in 5 ml of benzene was applied to a column of 25 g of alumina and the column was developed with benzene and allowed to stand for 2 hr. The column was then eluted with chloroform to give 0.97 g of unreacted oxime tosylate: mp 117-118°; ir ($CHCl_3$) 2230, 2220 (sh), 1375, 1180 cm^{-1}.

Beckmann fragmentation of α,β-acetylenic aldoximes with PCl_5: α,β-Acetylenic aldoximes were treated with PCl_5 under the same conditions described for the Beckmann rearrangement of α,β-acetylenic ketoximes with PCl_5. Acetylenic nitriles were exclusively obtained. These results are shown on p 122.

General procedure for the von Braun reaction of acetylenic amides with Phosphorus halides: The conditions of the reaction were similar to those used in the Beckmann rearrangement of the corresponding acetylenic ketoximes. In the cases in which HCl or Br_2 addition occurred exclusively the products were chromatographed on alumina and recrystallized from the appropriate solvents. In those cases where fragmentation occurred exclusively the product was distilled to give the alkyl halide and nitrile. When both halide addition and fragmentation occurred simultaneously (for optically active amides) the products were chromatographed on alumina.

The acetylenic amides that were subjected to the von Braun reaction conditions and the nature of the products obtained are shown in Tables XX, XXI and XXVI (pp 130, 132 and 153 respectively).

Attempted addition of HCl to acetylenic amides: A solution

of 0.2 g of N-isopropylphenylpropiolamide in 10 ml of anhydrous ether was saturated with hydrogen chloride at 0°. The mixture was stirred at 0° for 1 hr, then at room temperature for 1 hr, and then diluted with 50 ml of water. The usual workup gave, after recrystallization, 0.11 g of unreacted acetylenic amide: mp 84-85°; ir ($CHCl_3$) 3430, 3300, 2220, 1650 cm^{-1}.

Beckmann simulation of N-isopropyl-cis-β-chlorocinnamamide with PCl_5: A solution of 0.3 g (0.0014 mol) of amide in 35 ml of anhydrous ether was stirred and cooled to 0° and to it was added 0.6 g (0.0028 mol) of powdered PCl_5. The reaction mixture was stirred at 0° for 1 hr, then at room temperature for 4 hr. The usual workup afforded 0.24 g of a mixture of 58% cis- and 42% trans-amides: mp 75-105°; ir ($CHCl_3$) 3430, 3300, 1650 cm^{-1}; nmr ($CDCl_3$) δ 0.9 (Me_2, d, cis-), 1.2 (Me_2, d, trans-), 4.1 (-CH-, m, cis- and trans-), 6.4 (=CH-, s, cis-), 6.6 (=CH-, s, trans-), 6.1 (NH, broad), 7.5 (Ph, m, cis- and trans-).

Beckmann simulation of N-isopropyl-trans-β-chlorocinnamamide with PCl_5: A solution of 0.3 g of the trans-amide was treated under the same conditions described above for the cis- isomer to give 0.28 g of unchanged trans-amide: mp 96-97°; ir ($CHCl_3$) 3430, 3300, 1650 cm^{-1}.

Von Braun reaction with PCl_5 in the presence of LiBr: A solution of 2.0 g (0.011 mol) of N-isopropylphenylpropiolamide was treated with 4.6 g (0.022 mol) of PCl_5 and 2.0 g of LiBr as described for the corresponding ketoxime (p 211). Similar workup afforded 3.09 g of a mixture of cis- and trans-α,β-dibromoamides as indicated by tlc analysis (on alumina using benzene). Chromatography on 190 g of alumina and elution with benzene afforded 1.57 (60%) of N-isopropyl-cis-

α,β-dibromocinnamamide: mp 117-118°, and 1.04 g (40%) of N-isopropyl-trans-α,β-dibromocinnamamide: mp 142-143°. Total yield (cis- and trans-amides) is 2.61 g (68%).

Von Braun reaction of N-isopropylphenylpropiolamide with PCl_5. A solution of 1.0 g (0.0054 mol) of the amide in 40 ml of anhydrous ether was treated with 2.2 g (0.011 mol) of powdered PCl_5 under the general conditions described for the von Braun reaction. The reaction mixture was cooled to 0° and quenched with 20 ml of water and the usual workup afforded after recrystallization from petroleum ether 1.04 g (86%) of N-isopropyl-trans-β-chlorocinnamamide: mp 97-98°; ir ($CHCl_3$) 3430, 3300, 1650 cm^{-1}.

The reaction was repeated, but the reaction mixture was quenched with 20 ml of D_2O to give,after workup, 1.0 g (83%) of N-isopropyl-trans-β-chloro-α-deuteriocinnamamide containing 28% D; mp 97-98°.

When the N-deuterated acetylenic amide (74% D) was treated under these conditions and D_2O was used in the quenching step, 0.87 g (73%) of N-isopropyl-trans-β-chloro-α-deuteriocinnamamide containing 33% D was obtained.

The reaction was repeated on the N-deuterated acetylenic amide but the reaction mixture was quenched with H_2O. Workup afforded 0.81 g (68%) of N-isopropyl-trans-β-chlorocinnamamide.

Von Braun reaction of optically active acetylenic amides with PCl_5: The general procedure was used and the details of the results obtained are given below. (The general results are also summarized in Tables XX and XXI on pp 130 and 132 respectively).

(S)-N-phenylethylphenylpropiolamide (1.5 g, 0.006 mol) yielded

1) a mixture of 0.82 g (41%) of 56% (±) phenylethyl chloride and 44% β-chlorocinnamonitriles (10% cis-, 90% trans-): bp 35-100° (0.5 mm); ir ($CHCl_3$) 2230 cm^{-1} and 2) 0.33 g (19%) of (S)-N-phenylethyl-trans-β-chlorocinnamamide: mp 107-108° (benzene-petroleum ether); $[\alpha]_D$ +21.24° (c 0.998 g, $CHCl_3$).

(R)-N-phenylethylphenylpropiolamide (1.5 g, 0.006 mol) yielded 1) a mixture of 1.82 g (68%) of 48% (R)-phenylethyl chloride and 52% β-chlorocinnamonitriles (8% cis-, 92% trans-): ir ($CHCl_3$) 2230 cm^{-1}; α_D + 0.098° (c 0.3402 g/ 5ml $CHCl_3$), and 2) 0.44 g (26% of (R)-N-phenylethyl-trans-β -chlorocinnamamide: mp 108-109°; $[\alpha]_D$-21.02° (c 0.985 g, $CHCl_3$).

(R)-N-phenylethyltetrolamide (2.4 g, 0.013 mol) yielded 1) a mixture of 1.84 g (58%) of 62% (R)-phenylethyl chloride and 38% β-chlorocrotononitriles (23% cis-, 77% trans-); ir ($CHCl_3$) 2235 cm^{-1}; α_D +0.076° (c 0.5651 g/ 5 ml $CHCl_3$), and 2) 0.34 g (12%) of (R)-N-phenylethyl-β-chlorocrotonamides (56% cis-, 44% trans-): cis-amide, mp 93-94° (petroleum ether); $[\alpha]_D$ + 106.2° (c 1.087 g, $CHCl_3$); trans-amide (crude): $[\alpha]_D$ +38.22° (c 1.517 g, $CHCl_3$).

(S)-N-Phenylethyltetrolamide (2.1 g, 0.011 mol) yielded 1) a mixture of 1.54 g (58%) of 60% (S)-phenylethyl chloride and 40% β-chlorocrotonitriles (12% cis-, 88% trans-): ir ($CHCl_3$) 2235 cm^{-1}; α_D -0.066° (c 0.5690 g/ 5 ml $CHCl_3$), and 2) 0.67 g (27%) of (S)-N-phenylethyl-β-chlorocrotonamides (82% cis-, 18% trans-): cis-amide, mp 92-93° (petroleum ether); $[\alpha]_D$ -105.1° (c 1.085, $CHCl_3$); trans-amide (crude): $[\alpha]_D$ -28.38° (c 1.209 g, $CHCl_3$).

(R)-N-phenylethyl-t-butylpropiolamide yielded a mixture of 3.2 g (94%) of 46% (R)-phenylethyl chloride and 54% β-chloro-t-

butyl-acrylonitriles (79% cis-, 21% trans-): ir ($CHCl_3$) 2235 cm^{-1}; α_D +0.036° (c 0.4939 g/ 5 ml $CHCl_3$).

(S)-N-phenylethyl-t-butylpropiolamide yielded a mixture of 1.03 g (82%) of 45% (S)-phenylethyl chloride and 55% β-chloro-t-butyl-acrylonitriles (91% cis-, 9% trans-): ir ($CHCl_3$) 2235 cm^{-1}; α_D -0.087° (c 0.4182 g/ 5 ml $CHCl_3$).

(R)-N-Phenylethylethylpropiolamide yielded a mixture of 2.7 g (59%) of 50% (R)-phenylethyl chloride and 50% β-chloroethylacrylonitriles (18% cis-, 82% trans-): ir ($CHCl_3$) 2235 cm^{-1}; α_D +0.096° (c 0.5753 g/ 5 ml $CHCl_3$).

SUMMARY

The reaction of acetylenic Grignard reagents with hydroxamoyl chlorides was found to be a convenient and general procedure for the synthesis of α,β-acetylenic ketoximes 1. Methyl-, ethyl-, t-butyl-, phenyl- and p-methoxyphenylacetylenes were used with various alkyl and aromatic hydroxamoyl chlorides. Reaction of these oximes with PCl_5, PBr_5 or $POBr_3$ under the conditions of the Beckmann rearrangement established the syn oxime configuration. The main reaction products were the corresponding cis- and trans-β-chloro olefinic amides from PCl_5 and α,β-dibromo olefinic amides from PBr_5. However, the expected amide product 30 was obtained in low yields only with PBr_5 and $POBr_3$. In oximes in which R = t-Bu, MeCH(Ph), fragmentation to the alkyl halides and α,β-acetylenic nitriles predominated. Some aspects of the mechanism of the Beckmann rearrangement with these oximes are discussed.

The syn oxime configuration was also established by strong intramolecular π-hydrogen bonding observed between the hydroxyl hydrogen and the acetylenic function in the ir spectra of the OH stretching region of these oximes. An average frequency separation of 228 cm^{-1} between the "free" and "bonded" OH bands was measured. Further evidence for the syn oxime configuration was deduced from the narrow range of chemical shifts of the hydroxyl proton in DMSO.

The reaction of acetylenic Grignard reagents with isocyanates provided α,β-acetylenic amides in good yields. Methyl-, ethyl-, t-butyl- and phenylacetylenes were used with various alkyl and aromatic isocyanates. Reaction of these amides with PCl_5, PBr_5 and $POBr_3$ (von Braun reaction) gave similar products to those obtained in the

Beckmann rearrangement of the corresponding oximes. Optically active amides (30, R = $CH_3CH(Ph)$) gave alkyl chlorides with retention of configuration. Some aspects of the von Braun reaction are presented. An ir study of the NH stretching region revealed a frequency separation of 27 cm^{-1}. The possibility of intramolecular π-hydrogen bonding is discussed.

BIBLIOGRAPHY

1. H. G. Viehe, Ed., "Chemistry of Acetylenes," Marcel Dekker, New York, 1969.
2. T. F. Rutledge, "Acetylenic Compounds. Preparation and Substitution Reactions," Reinhold Book Corporation, New York, 1968.
3. T. F. Rutledge, "Acetylenes and Allenes. Additions, Cyclization and Polymerization Reactions," Reinhold Book Corporation, New York, 1969.
4. L. Claisen, Chem. Ber., 36, 3665 (1903).
5. L. Claisen, ibid., 44, 1164 (1911).
6. A. Quilico in "The Chemistry of Heterocyclic Compounds," R. H. Wiley, Ed., Interscience, New York, 1962, Vol. 17, pp 14-15.
7. R. A. Barnes in "Heterocyclic Compounds," R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, 1957, Vol. 5, p 457.
8. K. von Auwers and B. Ottens, Chem. Ber., 58, 2060 (1925).
9. K. von Auwers, ibid., 1320 (1929).
10. K. von Auwers and M. Seyfried, Ann., 484, 212 (1930).
11. A. H. Blatt, Chem. Rev., 12, 234 (1933).
12. L. Lopez and J. Barrans, Compt. Rend., 263, 557, 1088 (1966).
13. H. Ulrich, "The Chemistry of Imidoyl Halides," Plenum Press, New York, 1968, p 157.
14. C. Weygand and E. Bauer, Ann., 459, 127 (1927).
15. A. Quilico and G. Speroni, Gazz. Chim. Ital., 76, 148 (1946).

16. G. Palazzo, ibid., 77, 214 (1947).

17. F. Gaudiano, A. Ricca, and L. Merlini, ibid., 89, 2466 (1959).

18. H. Feuer and S. Markofsky, J. Org. Chem., 29, 935 (1964).

19. Reference 1, p 527.

20. D. J. Shearing, M.Sc. Thesis, Sir George Williams University (1968).

21. S. Morrochi, A. Ricca, A. Zanarotti, G. Bianchi, R. Gandolfi and P. Grunanger, Tetrahedron Lett., 3329 (1969).

22. J. M. J. Tronchet, A. Jotterand and N. LeHong, Helv. Chim. Acta., 52, 2569 (1969).

23. A. Battaglia and A. Dondoni, Tetrahedron Lett., 1221 (1970).

24. Z. Hamlet, M. Rampersad and D. J. Shearing, ibid., 2101 (1970).

25. Z. Hamlet and M. Rampersad, Chem. Commun., 1230 (1970).

26. W. Z. Heldt and L. G. Donaruma, Organic Reactions, 11, 1 (1960).

27. P. A. S. Smith in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, 1963, Vol. 1, p 483.

28. F. Uhlig and H. R. Snyder, Advan. Org. Chem., 1, 35 (1960).

29. C. G. McCarthy in "The Chemistry of the Carbon-Nitrogen Double Bond," S. Patai, Ed., Interscience Publishers, New York, 1970, Chapter 9.

30. J. von Braun and H. Ostermayer, Chem. Ber., 70, 1002 (1937).

31. J. von Braun and W. Rudolph, ibid., 67, 269 (1934).

32. J. von Braun and W. Rudolph, ibid., 67, 1735 (1934).

33. J. von Braun and P. Kurtz, ibid., 70, 1009 (1937).

34. R. Mantione, M. L. Martin, G. J. Martin, and H. Normant, Bull. Soc. Chim. Fr., 2912 (1967).

35. K. Bodendorf and R. Mayer, Chem. Ber., 98, 3554 (1965).

36. R. A. Hoffman and S. Gronowitz, Arkiv Kemi, 16, 471 (1961).

37. G. G. Kleinspehn, J. A. Jung, and S. A. Studniarz, J. Org. Chem., 32, 460 (1967).

38. B. Rickborn and R. M. Gerkin, J. Amer. Chem. Soc., 93, 1693 (1971).

39. H. Wieland, Chem. Ber., 40, 1676 (1907).

40. A. I. Vogel, "Practical Organic Chemistry," 1st ed, Longmans, Green and Co., London, 1948, p 685.

41. G. W. Perold, A. P. Steyn and F. V. K. von Reiche, J. Amer. Chem. Soc., 79, 462 (1957).

42. M. H. Benn, Can. J. Chem., 42, 2395 (1964).

43. O. Piloty and H. Steinbock, Chem. Ber., 35, 3112 (1902).

44. G. Casnati and A. Ricca, Tetrahedron Lett., 327 (1967).

45. J. M. J. Tronchet, Br. Baehler, N. Le-Hong and P. F. Livio, Helv. Chim. Acta, 54, 921 (1971).

46. C. R. Kinney, E. W. Smith, B. L. Wooley and A. R. Willey, J. Amer. Chem. Soc., 55, 3418 (1933).

47. M. S. Kharasch and O. Reinmuth, "Grignard reactions of Nonmetallic substances," Prentice-Hall Inc., New York, 1954.

48. L. Birkofer, A. Ritter and H. Dickopp, Chem. Ber., 96, 1473 (1963).

49. C. C. Sweeley, R. Bently, M. Makita and W. W. Wells, J. Amer. Chem. Soc., 85, 2497 (1963).

50. Ch. Grundmann and P. Grunager, "The Nitrile Oxides," Springer-Verlag, New York, 1971, p 173.

51. K. N. Campbell, B. K. Campbell, J. F. McKenna and E. P. Chaput, J. Org. Chem., 8, 103 (1943).

52. J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill Book Company, New York, 1968, p 274.

53. A. Battaglia, A. Dondoni and A. Mangini, J. Chem. Soc., (B), 554 (1971).

54. P. Beltrame, P. Sartirana and C. Vintani, ibid., (B) 814 (1971).

55. A. Yokoyama, K. Ashida and H. Tanaka, Chem. Pharm. Bull. Jap., 12, 690 (1964).

56. A. Yokoyama and H. Tanaka, ibid., 12, 683 (1964).

57. J. R. Johnson and W. L. McEwen, J. Amer. Chem. Soc., 48, 469 (1926).

58. A. L. Wilds and C. H. Shunk, ibid., 70, 2427 (1948).

59. Ch. R. Engel and G. Just, Can. J. Chem., 33, 1515 (1955).

60. J. R. Dyer in "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., New Jersey , 1965, p 14.

61. L. M. Jackman and S. Sternhell in "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, London, 1969, p 216.

62. T. C. James, J. Chem. Soc., 99, 1620 (1911).

63. J. J. Sudborough and T. C. James, ibid., 89, 105 (1906).

64. J. J. Sudborough and K. J. Thompson, ibid., 83, 1153 (1903).

65. J. J. Sudborough and K. J. Thompson, ibid., 83, 666 (1903).

66. R. Stoermer and P. Heymann, Chem. Ber., 46, 1249 (1913).

67. A. Mangini and F. Montanari, Gazz. Chim. Ital., 88, 1081 (1958).

68. D. E. Jones, R. O. Morris, C. A. Vernon and R. F. M. White, J. Chem. Soc., 2349 (1960).

69. E. Campaigne and W. A. LeSuer, "Organic Syntheses," Coll. Vol. IV, Wiley, New York, 1963, p 919.

70. I. A. Pearl, ibid., p 972.

71. M. Vo. Q. Yen, Ann. Chim. (Paris), 7, 785 (1962).

72. D. V. Gardner and D. E. McGreer, Can. J. Chem., 48, 2110 (1970).

73. V. H. Wallingford, A. H. Homeyer, and D. M. Jones, J. Amer. Chem. Soc., 63, 2252 (1941).

74. K. von Auwers and R. Hugel, J. Prakt. Chem., 143, 179 (1935).

75. K. Bodendorf and R. Mayer, Chem. Ber., 98, 3554 (1965).

76. Z. Arnold and J. Zemlicka, Proc. Chem. Soc., 227 (1958).

77. E. Eliel, "Stereochemistry of Carbon Compounds," McGraw Hill Book Company, Inc., New York, 1962, p 348 and references cited therein.

78. S. Stallberg-Stenhagen, J. Amer. Chem. Soc., 69, 2568 (1947).

79. J. E. H. Hancock and P. P. Linstead, J. Chem. Soc., 3490 (1953).

80. Reference 77, p 329.

81. H. Plaut and J. J. Ritter, J. Amer. Chem. Soc., 73, 4076 (1951).

82. a) Reference 1, p 40.

b) I. Iwai and N. Nakamura, Chem. Pharm. Bull., 14, 1277 (1966).

83. J. K. Crandall and L. Ho. C. Lin, J. Org. Chem., 33, 2375 (1968).

84. N. A. Lebel and G. G. Ecke, ibid., 30, 4316 (1965).

85. E. S. Wallis and T. F. Lane, Organic Reactions, 3, 267 (1946).

86. A. L. J. Beckwith in "The Chemistry of Amides," J. Zabicky, Ed., Interscience Publishers, New York, 1970, p 79.

87. C. H. Collins and G. S. Hammond, J. Org. Chem., 25, 698 (1960).

88. W. Huckel and E. Magle, Ann., 649, 13 (1961).

89. C. Cross and G. H. Whitham, J. Chem. Soc., 3892 (1960).

90. R. Greenwald, M. Chaykovsky, and E. J. Corey, J. Org. Chem., 28, 1128 (1963).

91. G. Wittig and U. Schoellkopf, "Organic Syntheses," Vol. 40. Wiley, New York, 1960, p 66.

92. H. C. Brown and R. S. Fletcher, J. Amer. Chem. Soc., 71, 1845 (1949).

93. J. H. Boyer and D. Straw, ibid., 74, 4506 (1952).

94. R. C. Fuson and N. Rabjohn, "Organic Syntheses," Coll. Vol. III, Wiley, New York, 1955, p 557.

95. E. Beckmann, Chem. Ber., 19, 988 (1886).

96. B. Jones, Chem. Rev., 35, 335 (1944).

97. R. T. Conley and S. Ghosh in "Mechanisms of Molecular Migrations," Vol. 4, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, 1971, p 197.

98. J. Meisenheimer, Chem. Ber., 54, 3206 (1921).

99. O. Wallach, Ann., 259, 309 (1890).

100. G. Schroeter, Chem. Ber., 44, 1201 (1911).

101. R. F. Brown, N. M. van Gulick, and G. H. Schmidt, J. Amer. Chem. Soc., 77, 1094 (1955).

102. R. K. Hill, R. T. Conley, and O. T. Chortyk, ibid., 87, 5646 (1965).

103. J. Kenyon and D. P. Young, J. Chem. Soc., 263 (1941).

104. A. Campbell and J. Kenyon, ibid., 25 (1946).

105. A. J. Nunn, K. Schofield, and R. S. Theobald, ibid., 2797 (1952).

106. P. Oxley and W. E. Short, ibid., 1514 (1948).

107. R. L. Burke and R. M. Herbst, J. Org. Chem., 20, 726 (1955).

108. R. E. Lyle and G. G. Lyle, ibid., 18, 1058 (1953).

109. a) H. K. Hall, Jr., J. Amer. Chem. Soc., 82, 1209 (1960).

109. b) R. C. Elderfield and E. T. Losin, J. Org. Chem., 26, 1703 (1961).

110. A. Hassner and E. G. Nash, Tetrahedron Lett., 525 (1965).

111. P. J. Balling, Ph.D. Dissertation, Seton Hall University, 1966.

112. C. A. Grob, H. P. Fischer, W. Raudenbusch, and J. Zergenyi, Helv. Chim. Acta, 47, 1003 (1964).

113. H. P. Fischer, ibid., 48, 1279 (1965).

114. E. D. Hughes, Trans. Faraday Soc., 34, 202 (1938).

115. W. von E. Doering and H. H. Zeiss, J. Amer. Chem. Soc., 75, 4733 (1953).

116. E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, 1959, pp 269-270.

117. A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Company, New York, 1962, p 69.

118. A. H. Blatt and J. F. Stone, Jr., J. Amer. Chem. Soc., 53, 4134 (1931).

119. R. C. Morris and A. V. Snider, U. S. Patent 2,462,009 (Feb. 15, 1949).

120. E. C. Horning, V. L. Stromberg, and H. A. Lloyd, J. Amer. Chem. Soc., 74, 5153 (1952).

121. R. S. Montgomery and G. Dougherty, J. Org. Chem., 17, 823 (1952).

122. C. S. Barnes, D. H. R. Barton, J. S. Fawcett, and B. R. Thomas, J. Chem. Soc., 2339 (1952).

123. G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, J. Org. Chem., 21, 520 (1956).

124. F. J. Donat and A. L. Nelson, ibid., 22, 1107 (1957).

125. R. H. Mazur, J. Amer. Chem. Soc., 81, 1454 (1959).

126. J. Romo and A. Romo de Vivar, ibid., 81, 3446 (1959).

127. R. H. Mazur, J. Org. Chem., 26, 1289 (1961).

128. C. Beauté, N. Thoai and J. Wiemann, Bull. Soc. Chim. Fr., 3327 (1971), and references therein.

129. T. Sato, H. Wakatsuka and K. Amano, Tetrahedron, 27, 5381 (1971).

130. K. von Auwers and H. Brink, J. Prakt. Chem., 133, 154 (1932).

131. A. Stephen and B. Staskun, J. Chem. Soc., 980 (1956).

132. W. Zielinski and S. Goszczynski, Zesz. Nauk. Politech. Slask. Chem. (39), 59 (1967); Chem. Abstr., 69, 66676f (1968).

133. P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier, New York, 1966, p 210.

134. H. G. Richey, Jr., in "The Chemistry of Alkenes," Vol. 2, J. Zabicky, Ed., Interscience Publishers, New York, 1970, p 39.

135. R. C. Fahey, in "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Interscience Publishers, New York, 1968, p 237.

136. J. A. Pincock and K. Yates, Can. J. Chem., 48, 3332 (1970).

137. D. S. Payne, in "Topics in Phosphorus Chemistry," Vol. 4, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, New York, 1967, p 85.

138. J. R. Van Wazer, "Phosphorus and its Compounds," Vol. 1, Interscience Publishers, New York, 1958, p 236.

139. T. M. Tencza, Ph.D. Dissertation, Seton Hall University, 1966.

140. C. W. Shoppee, G. Kruger, and R. N. Mirrington, J. Chem. Soc., 1050 (1962).

141. B. S. Ahmad and A. H. Siddiqi, Aust. J. Chem., 21, 1371 (1968).

142. M. E. Brokke, G. E. Lukes, and D. R. Arneklev, U. S. Patent 3375277 (1968); Chem. Abstr., 68, 113551c (1968).

143. K. K. Kelly and J. S. Matthews, J. Org. Chem., 36, 2159 (1971).

144. R. Bonnett, in "The Chemistry of the Carbon-Nitrogen Double Bond," S. Patai, Ed., Interscience Publishers, New York, 1970, Chapter 13.

145. B. C. Challis and T. Challis, in "The Chemistry of Amides," J. Zabicky, Ed., Interscience Publishers, New York, 1970, Chapter 13.

146. H. von Pechmann, Chem. Ber., 33, 611 (1900).

147. J. von Braun, Angew. Chem., 47, 611 (1934).

148. H. A. Hageman, Organic Reactions, 7, 198 (1953).

149. W. R. Vaughan and R. D. Carlson, J. Amer. Chem. Soc., 84, 769 (1962).

150. N. J. Leonard and E. W. Nommensen, ibid., 71, 2808 (1949).

151. R. F. Merritt and F. A. Johnson, J. Org. Chem., 32, 416 (1967).

152. A. Sonn and E. Muller, Chem. Ber., 52, 1927 (1919).

153. H. Ulrich, E. Kober, H. Schroeder, R. Ratz, and C. Grundmann, J. Org. Chem., 27, 2585 (1962).

154. O. Wallach, Ann. Chem., 184, 1 (1877).

155. H. Klinger, Chem. Ber., 8, 310 (1875).

156. H. Ulrich, "The Chemistry of Imidoyl Halides," Plenum Press, New York, 1968, p 55.

157. A. P. Terent'ev, R. A. Gracheva, V. T. Bezruchko, and O. G. Poltava, Zh. Obsch. Khim., 37, 1473 (1967); J. Gen. Chem. USSR, 37, 1397 (1967).

158. R. A. Gracheva, A. P. Terent'ev, and V. T. Bezruchko, Zh. Org. Khim., 5, 1058 (1969); J. Org. Chem. USSR, 5, 1044 (1969).

159. T. L. Cairns, J. Amer. Chem. Soc., 63, 871 (1941).

160. Reference 77, p 8.

161. V. M. Potapov, V. M. Dem'anovich, and A. P. Terent'ev, Zh. Obsch. Khim., 35, 1340 (1965); J. Gen. Chem. USSR, 35, 1346 (1965).

162. I. Z. Siemion, Tetrahedron Lett., 4807 (1966).

163. R. G. Arnold, J. A. Nelson, and J. J. Verbanac, Chem. Rev., 57, 47 (1957).

164. Reference 77, p 121.

165. Reference 77, pp 93 and 119.

166. E. L. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, 1956, p 61.

167. C. E. Boozer and E. S. Lewis, J. Amer. Chem. Soc., 75, 3182 (1953).

168. A. S. N. Murthy and C. N. R. Rao, Appl. Spectrosc. Rev., 2, 69 (1968).

169. V. Prey and H. Berbalk, Monatsch., 89, 990 (1951).

170. J. Grundy and L. J. Morris, Spectrochim. Acta, 20, 695 (1964).

171. A. W. Baker and A. T. Shulgin, J. Amer. Chem. Soc., 81, 4524 (1959).

172. H. H. Jaffe, ibid., 79, 2373 (1959).

173. G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Company, San Francisco, 1960.

174. C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, 1963.

175. "Infra-Red Spectroscopy and Molecular Structure," M. Davies, Ed., Elsevier Publishing Company, New York, 1963.

176. M. Tichy, Advan. Org. Chem., 5, 115 (1965).

177. B. Jordanov, A. Jovtscheff, S. Spassor, B. Blagoev, and M. Agova, Tetrahedron, 20, 903 (1964).

178. C. R. Eddy, J. S. Showell, and T. E. Zell, J. Amer. Oil Chem. Soc., 40, 92 (1963).

179. I. M. Goldman and R. O. Crisler, J. Org. Chem., 23, 751 (1958).

180. R. M. Badger and S. H. Bauer, J. Chem. Phys., 5, 839 (1937).

181. M. Oki and H. Iwamura, Bull. Chem. Soc. Jap., 33, 717 (1960).

182. L. J. Bellamy, "Advances in InfraRed Group Frequencies," Methuen and Co. Ltd., London, 1969, p 246.

183. L. J. Bellamy and P. F. Rogasch, Proc. Roy. Soc. (London), A257, 98 (1960).

184. G. Dahlgram and F. A. Long, J. Amer. Chem. Soc., 82, 1303 (1960).

185. Reference 182, p 283.

186. R. A. Nyquist, Spectrochim. Acta, 19, 509 (1963).

187. R. D. McLachlan and R. A. Nyquist, ibid., 20, 1397 (1964).

188. P. von R. Schleyer, D. S. Trifan and R. Bacskai, J. Amer. Chem. Soc., 80, 6692 (1958).

189. B. Loev and M. M. Goodman, Intra-Science Chemistry Reports, 4, 283 (1970).

190. O. Mumm and H. Hornhardt, Chem. Ber., 70B, 1930 (1937).

191. N. D. Cheronis and J. B. Entrikin, "Identification of Organic Compounds," Interscience Publishers, New York, 1963, p 252.

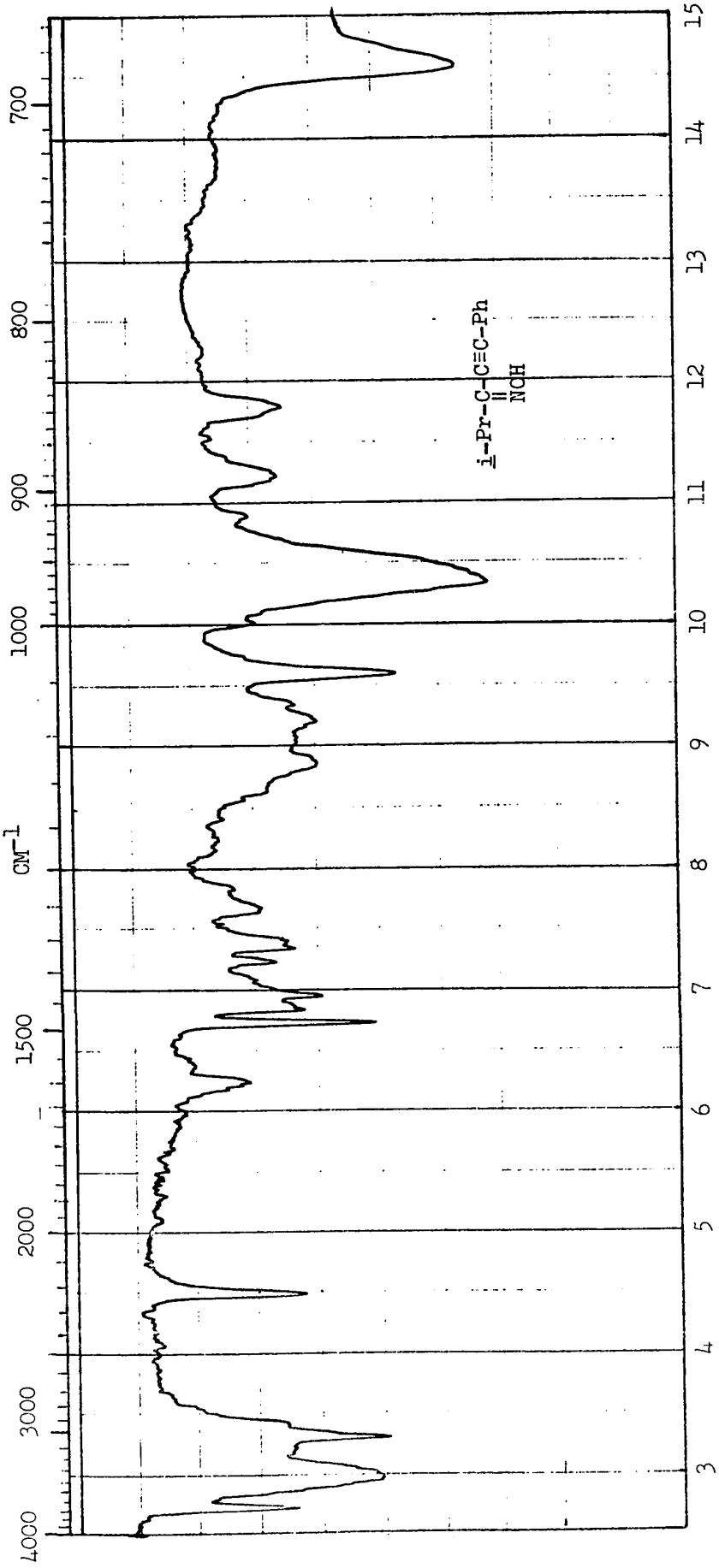
192. Th. J. De Boer and H. J. Backer, "Organic Syntheses," Coll. Vol. IV, Wiley, New York, 1963, p 225.

193. R. Paul and S. Tchelitcheff, Bull. Chem. Soc. Fr., 2215 (1962).

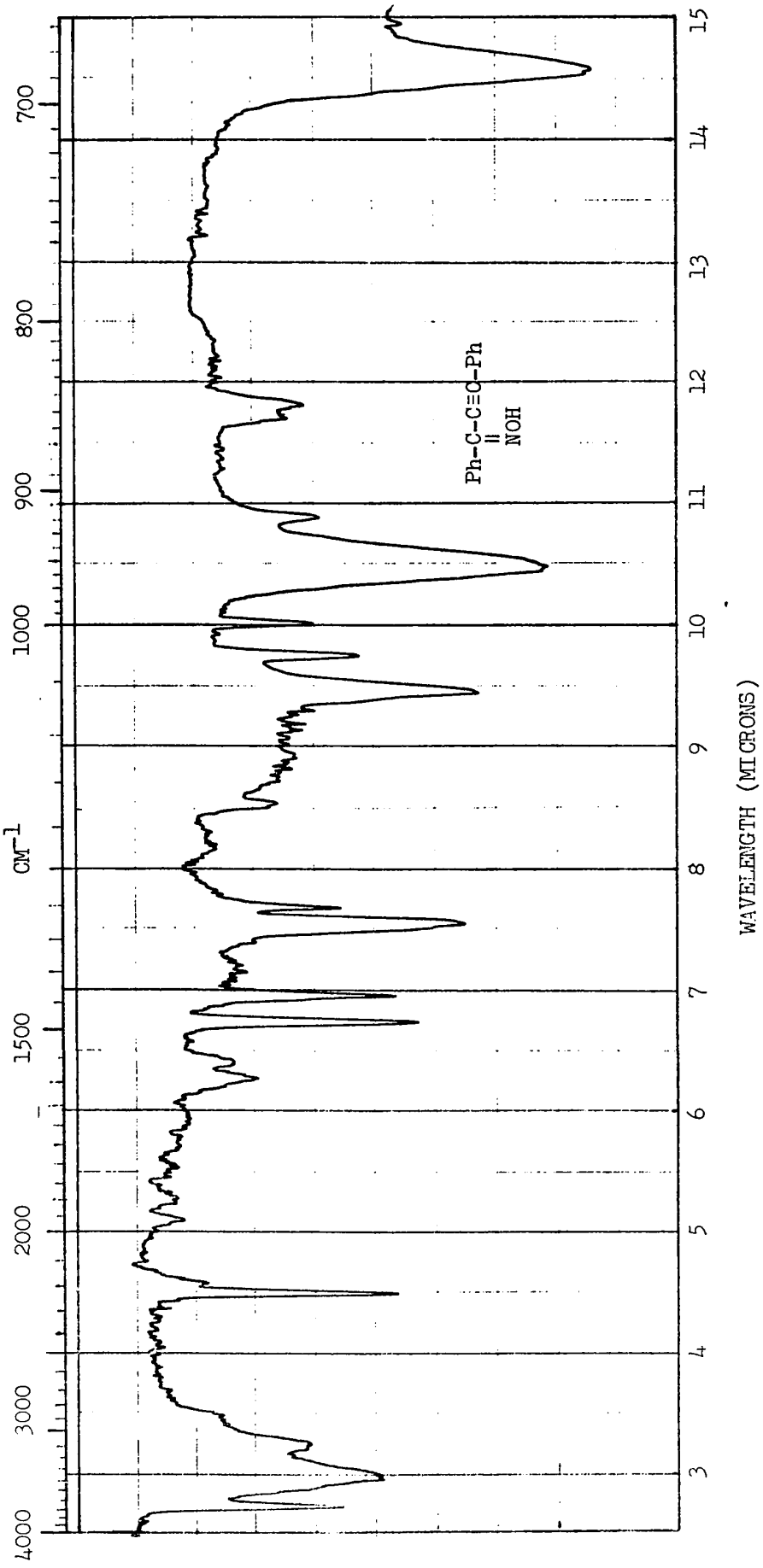
194. "Dictionary of Organic Compounds," Vol. I-V, J. R. A. Pollock and R. Stevens, Ed., Eyre and Spottiswoode Publishers Ltd., London, 1965.

195. H. O. House and W. F. Berkowitz, J. Org. Chem., 28, 2271 (1963).

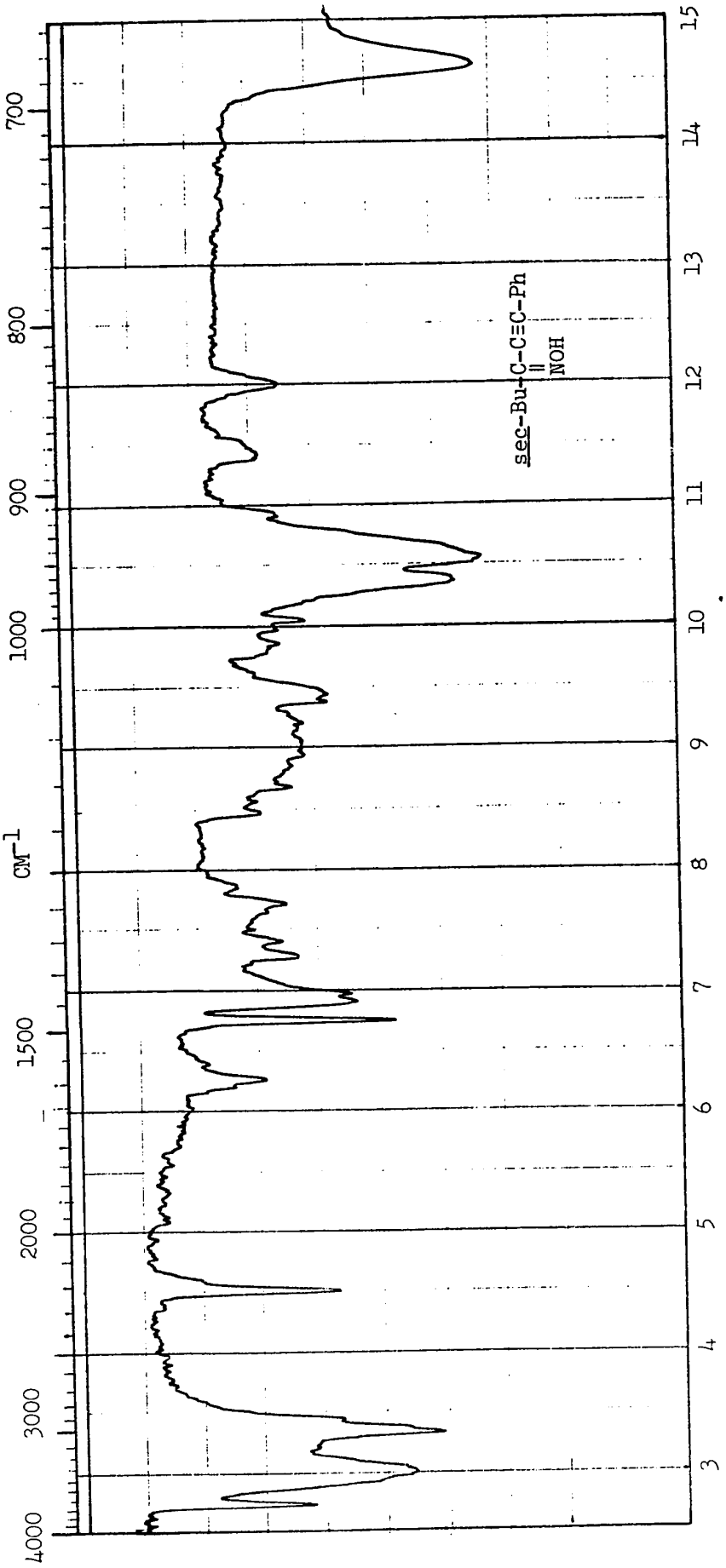
APPENDIX



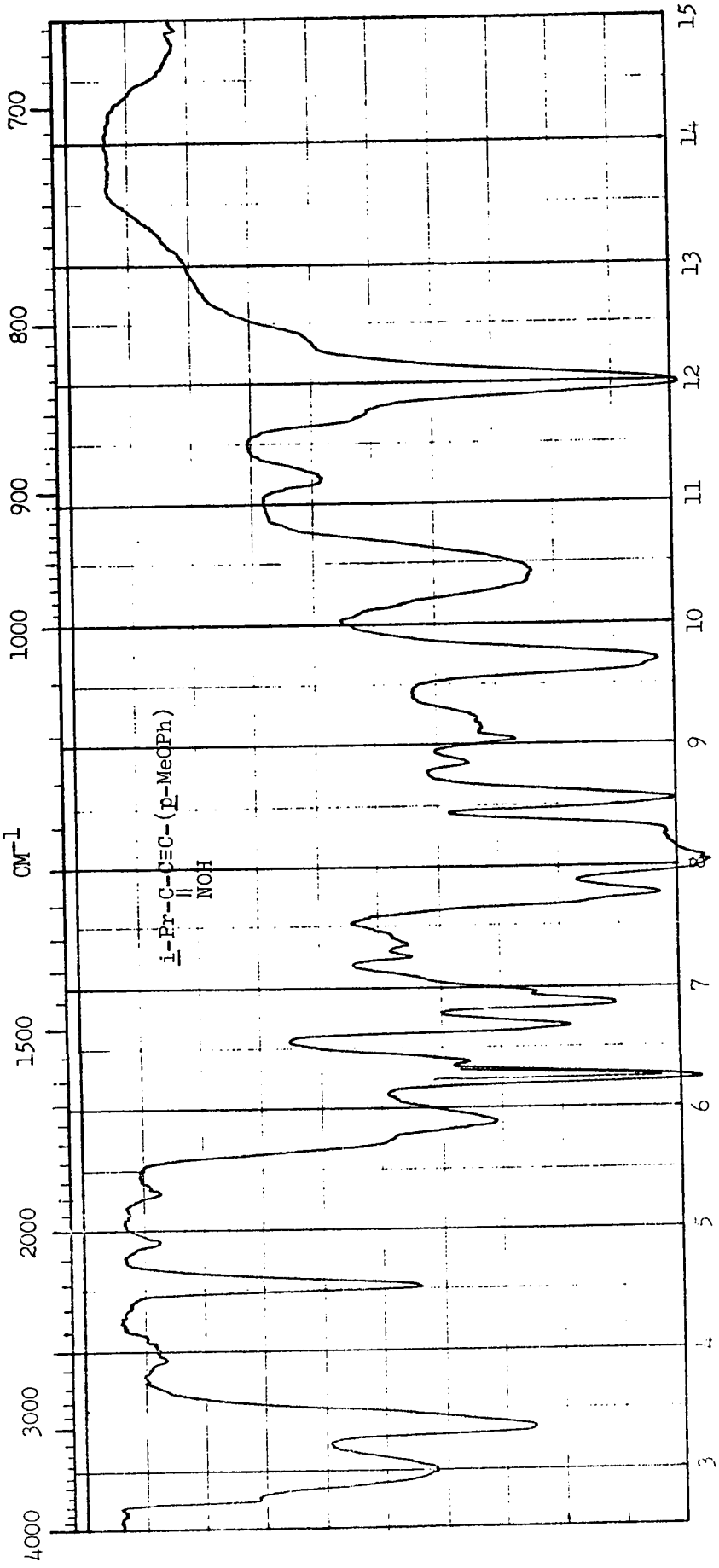
IR SPECTRUM 1



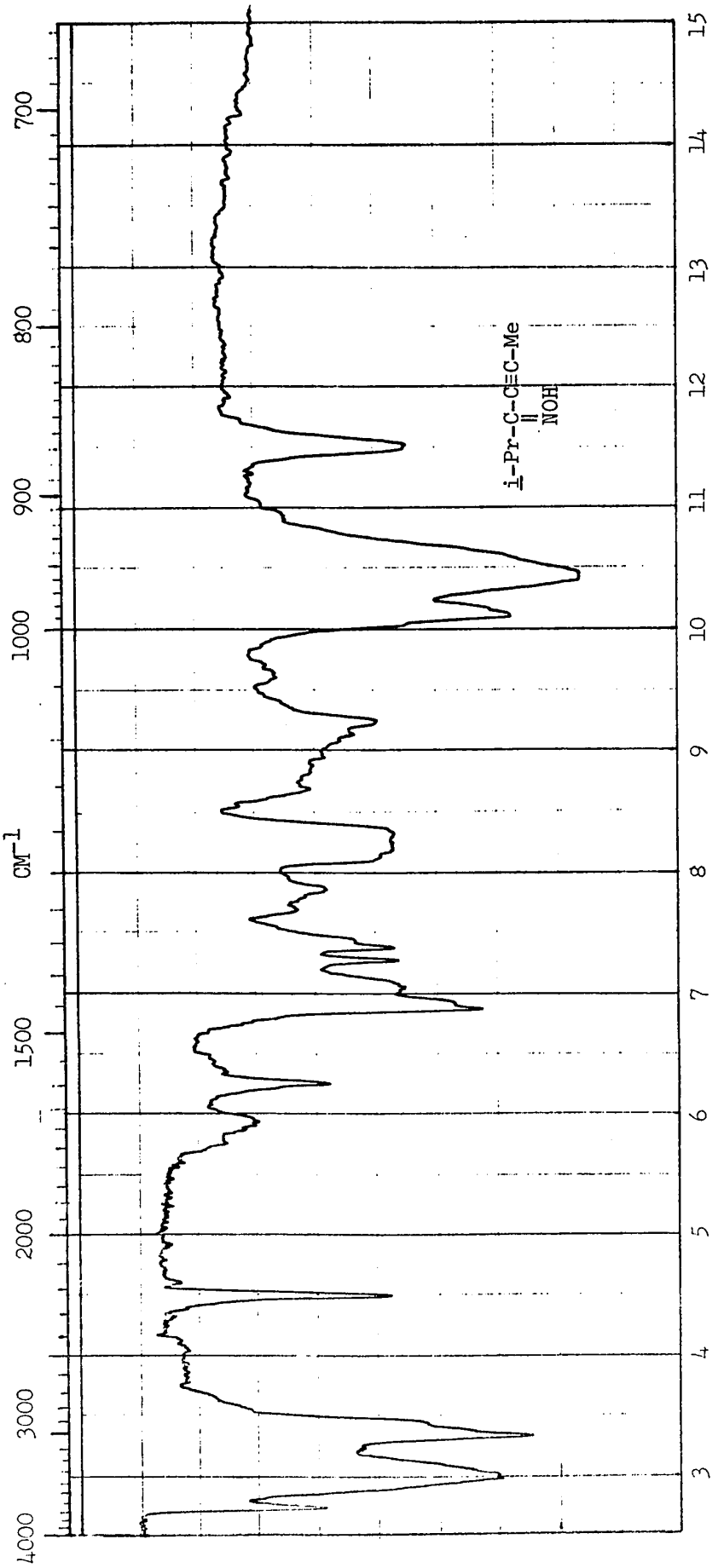
IR SPECTRUM 2



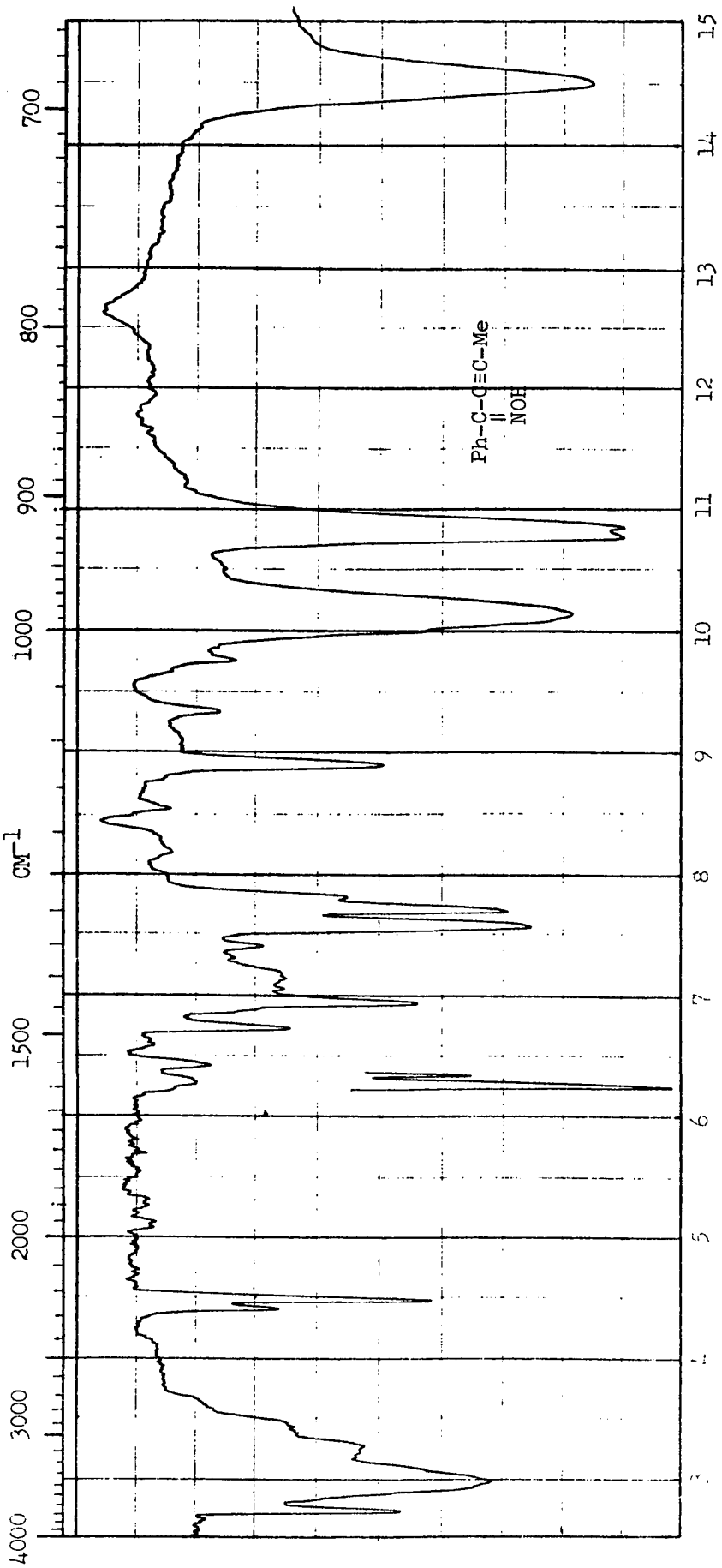
IR SPECTRUM 3



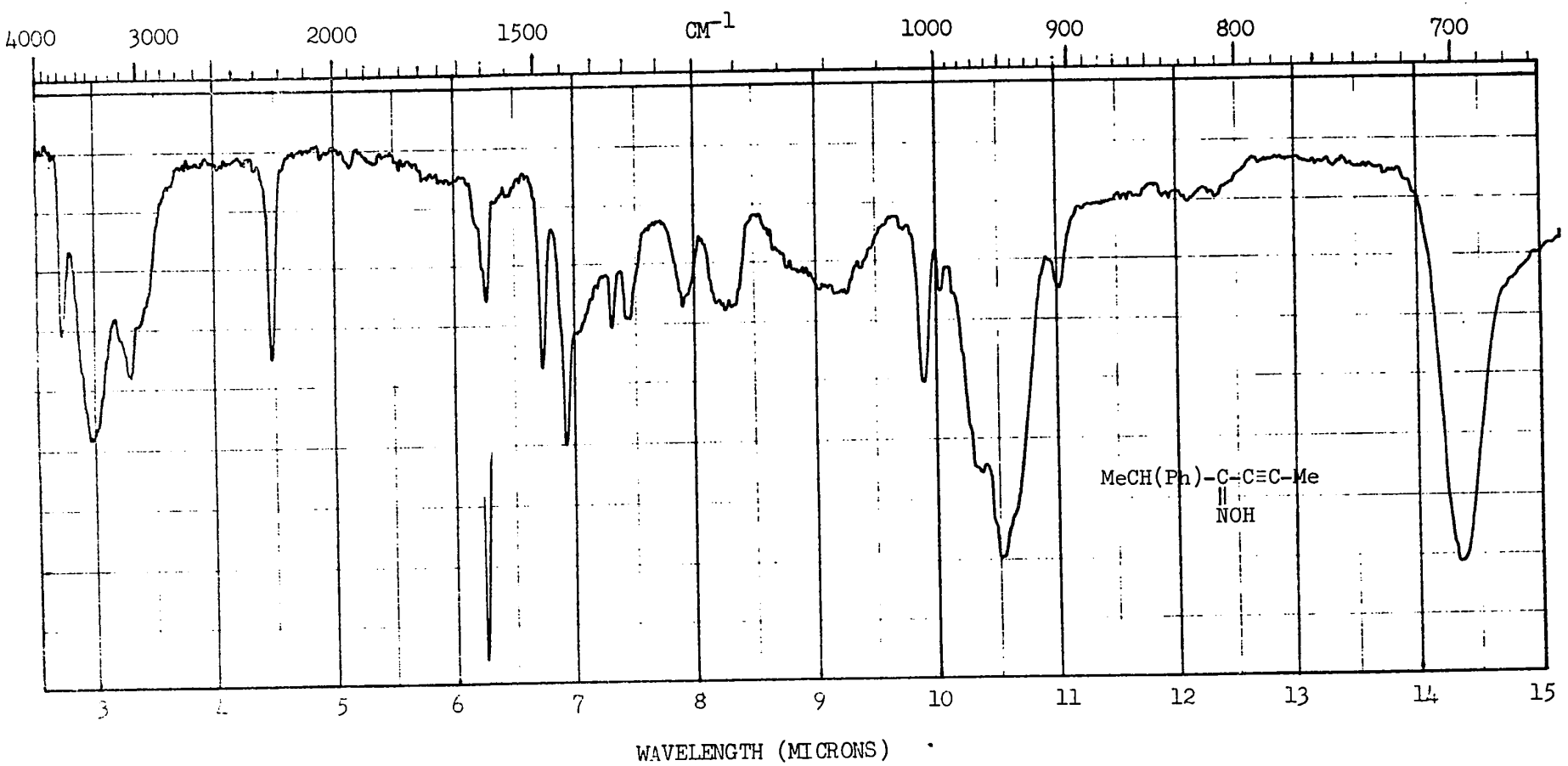
IR SPECTRUM 4



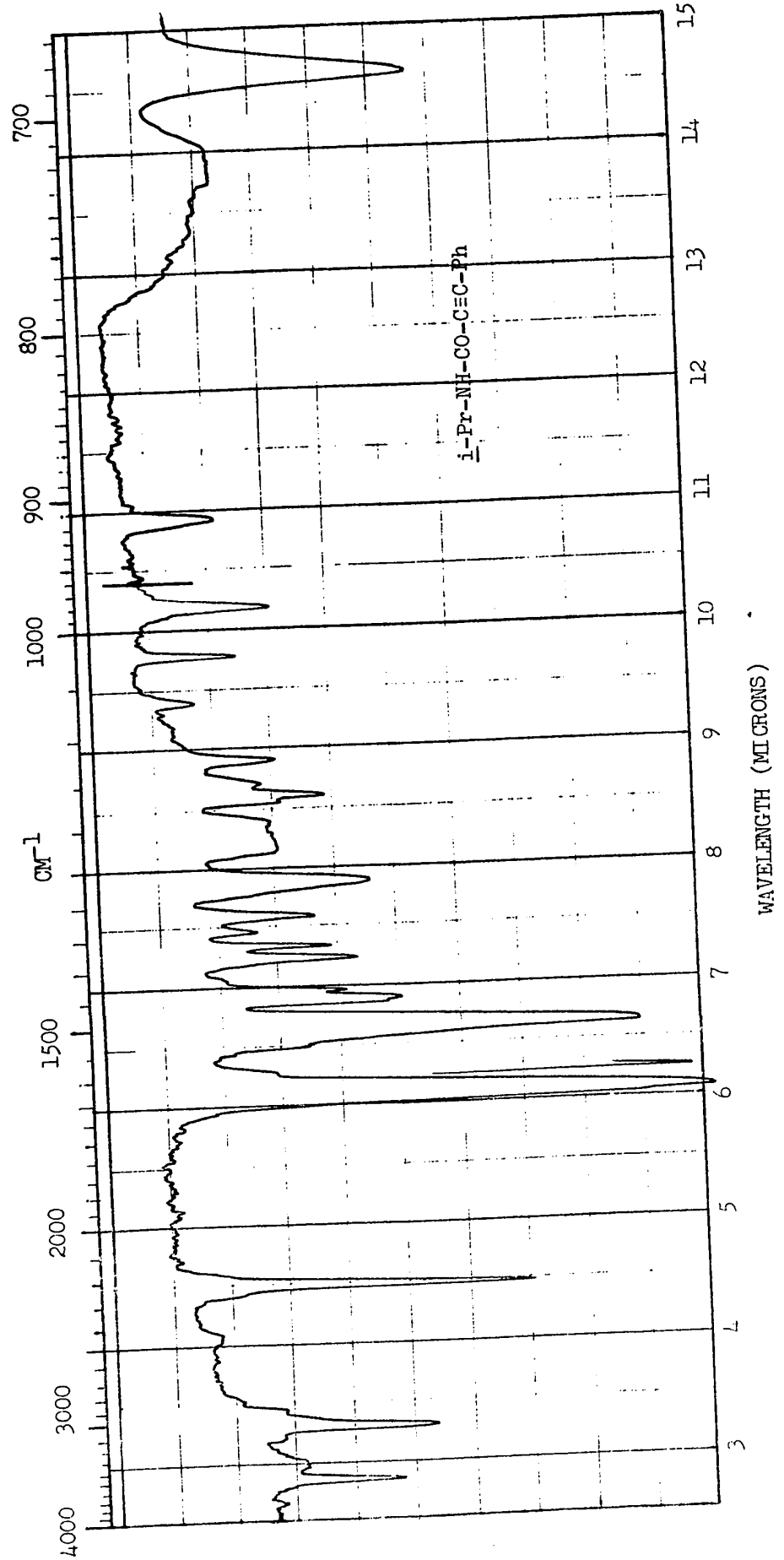
IR SPECTRUM 5



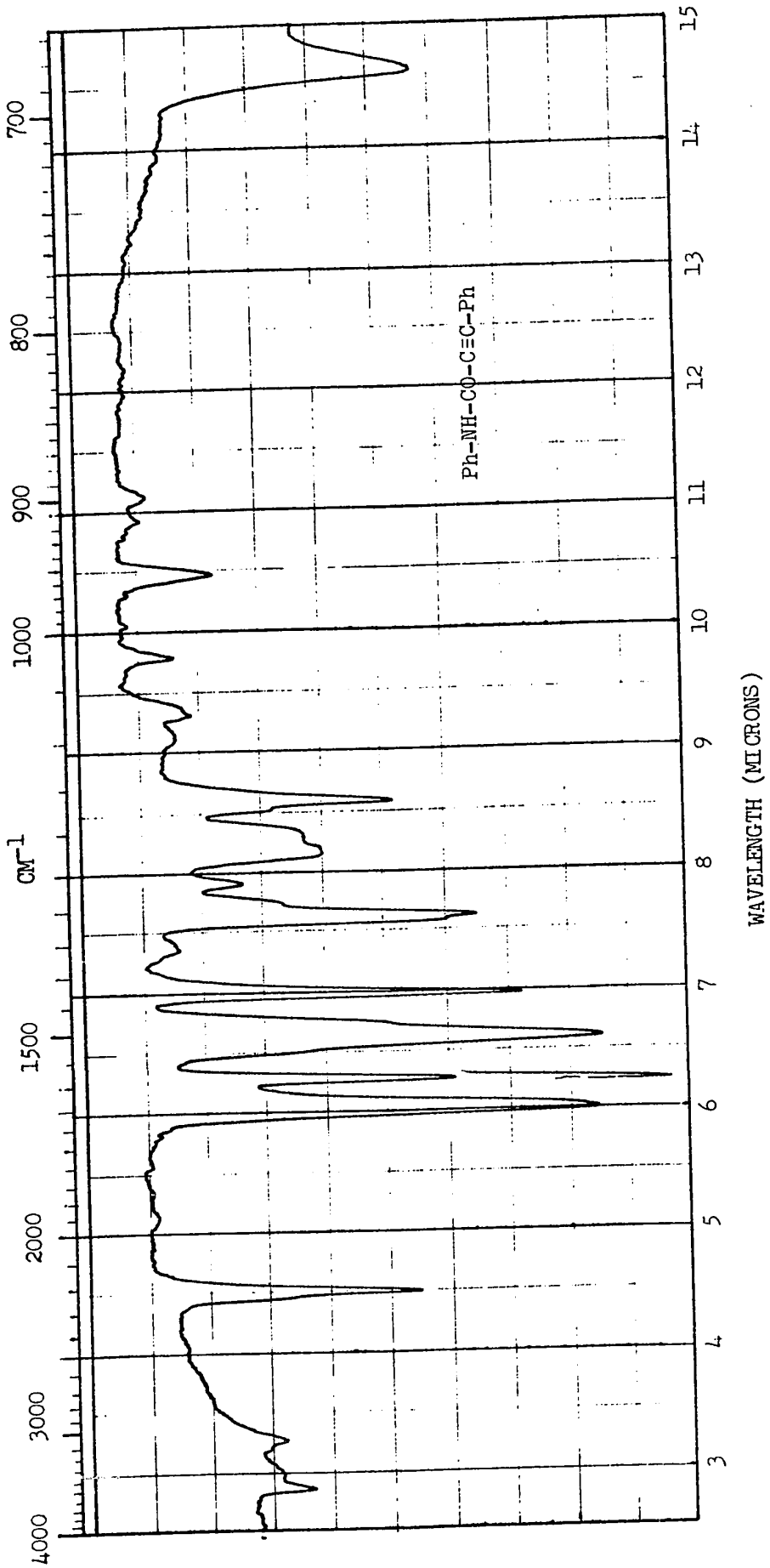
IR SPECTRUM 6



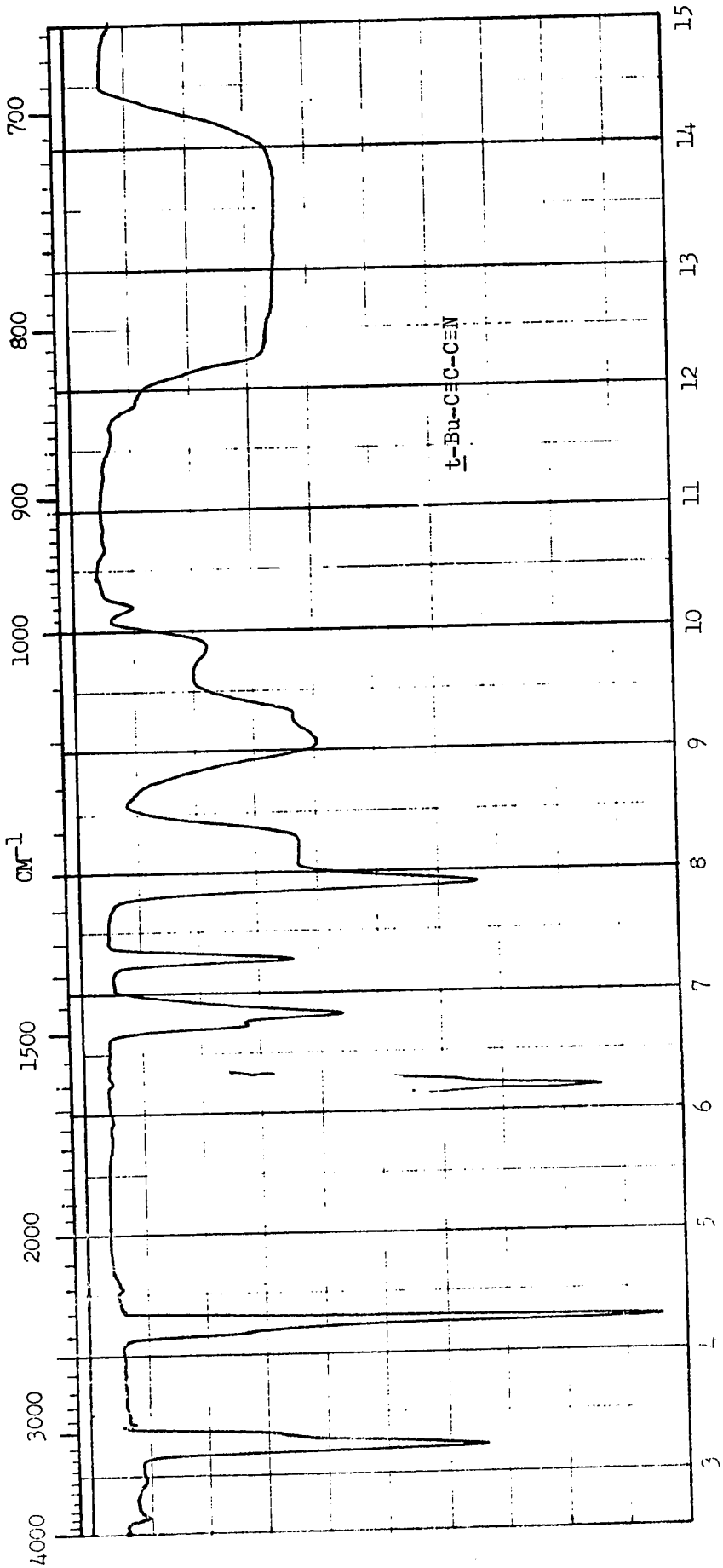
IR SPECTRUM 7



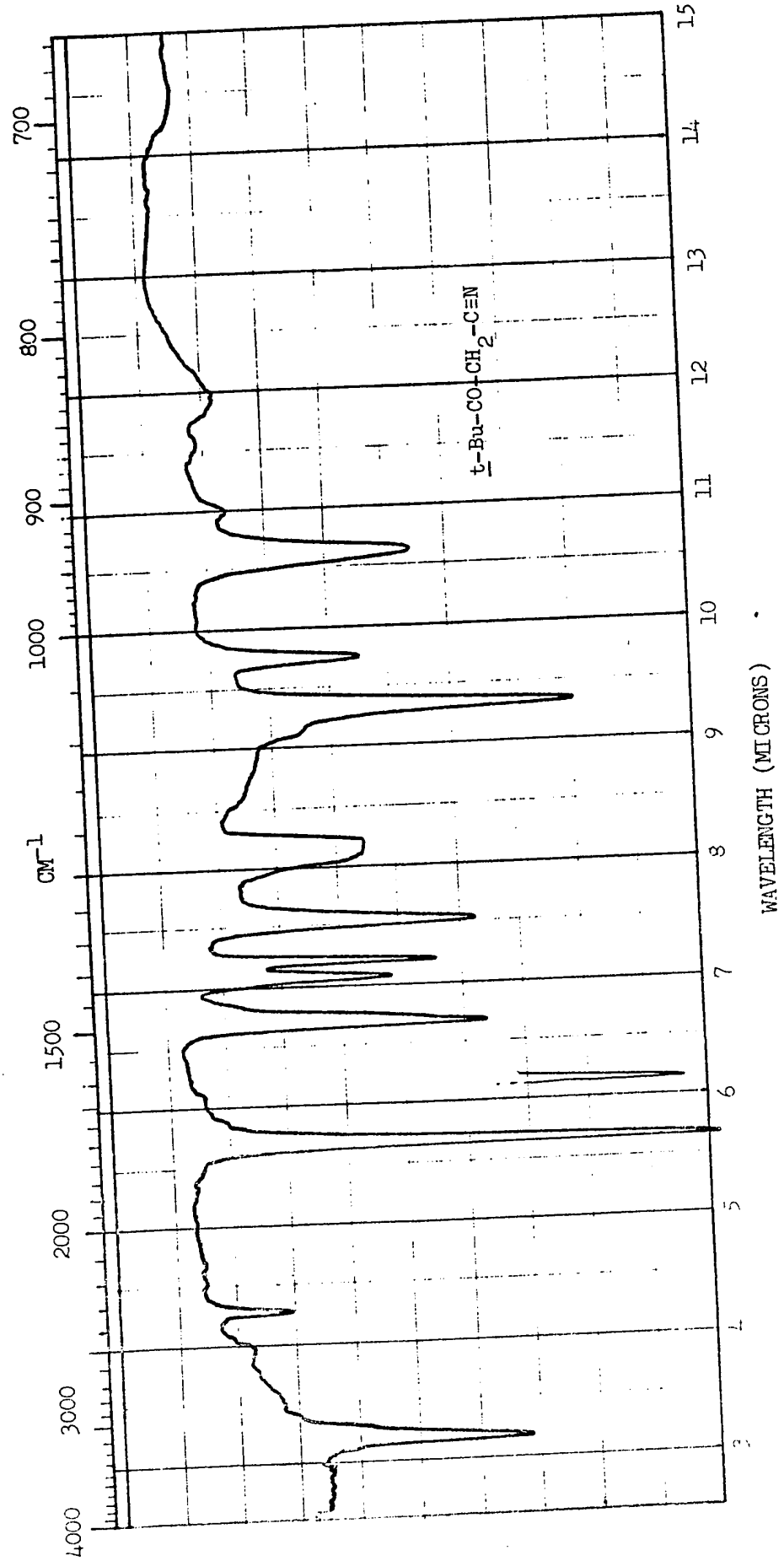
IR SPECTRUM 8



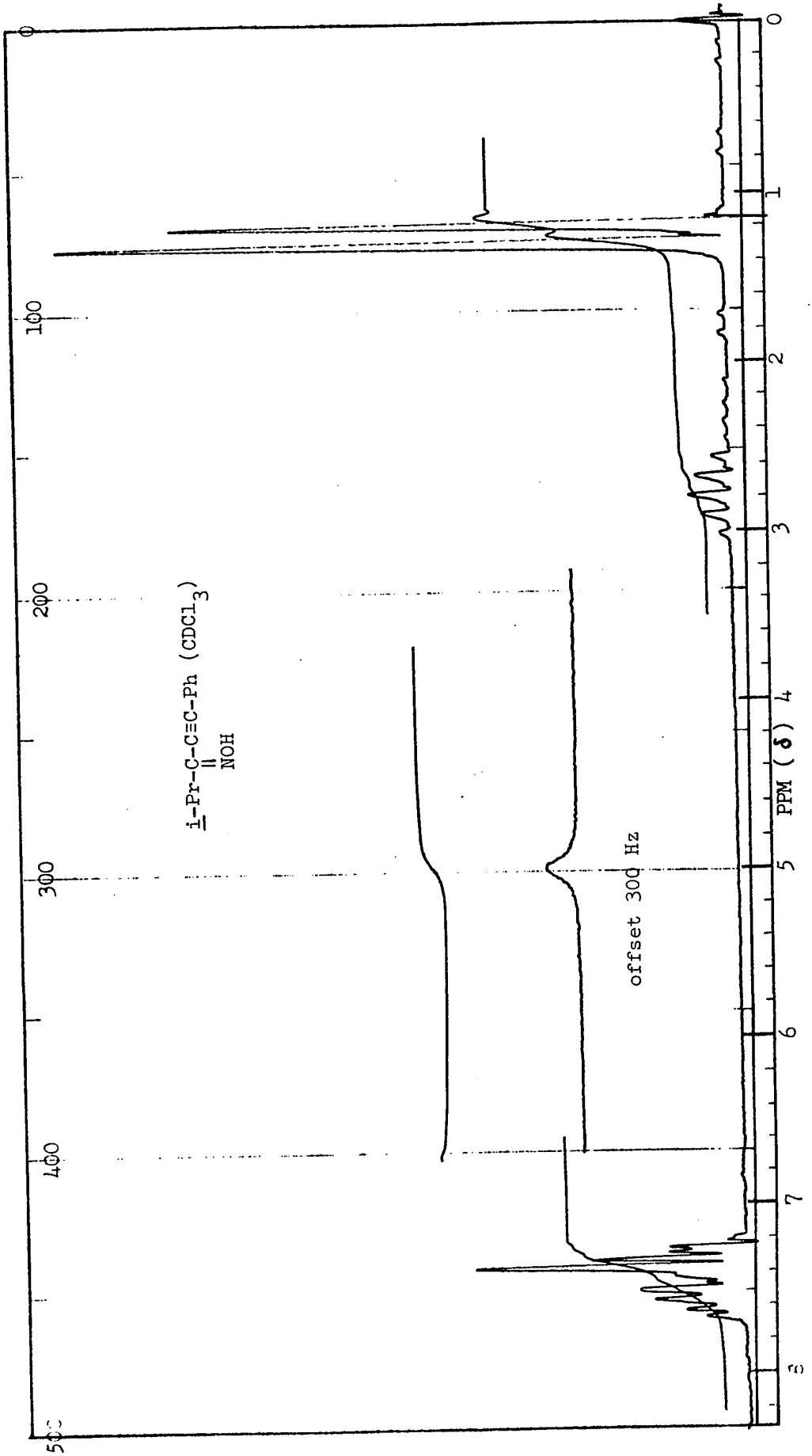
IR SPECTRUM 9



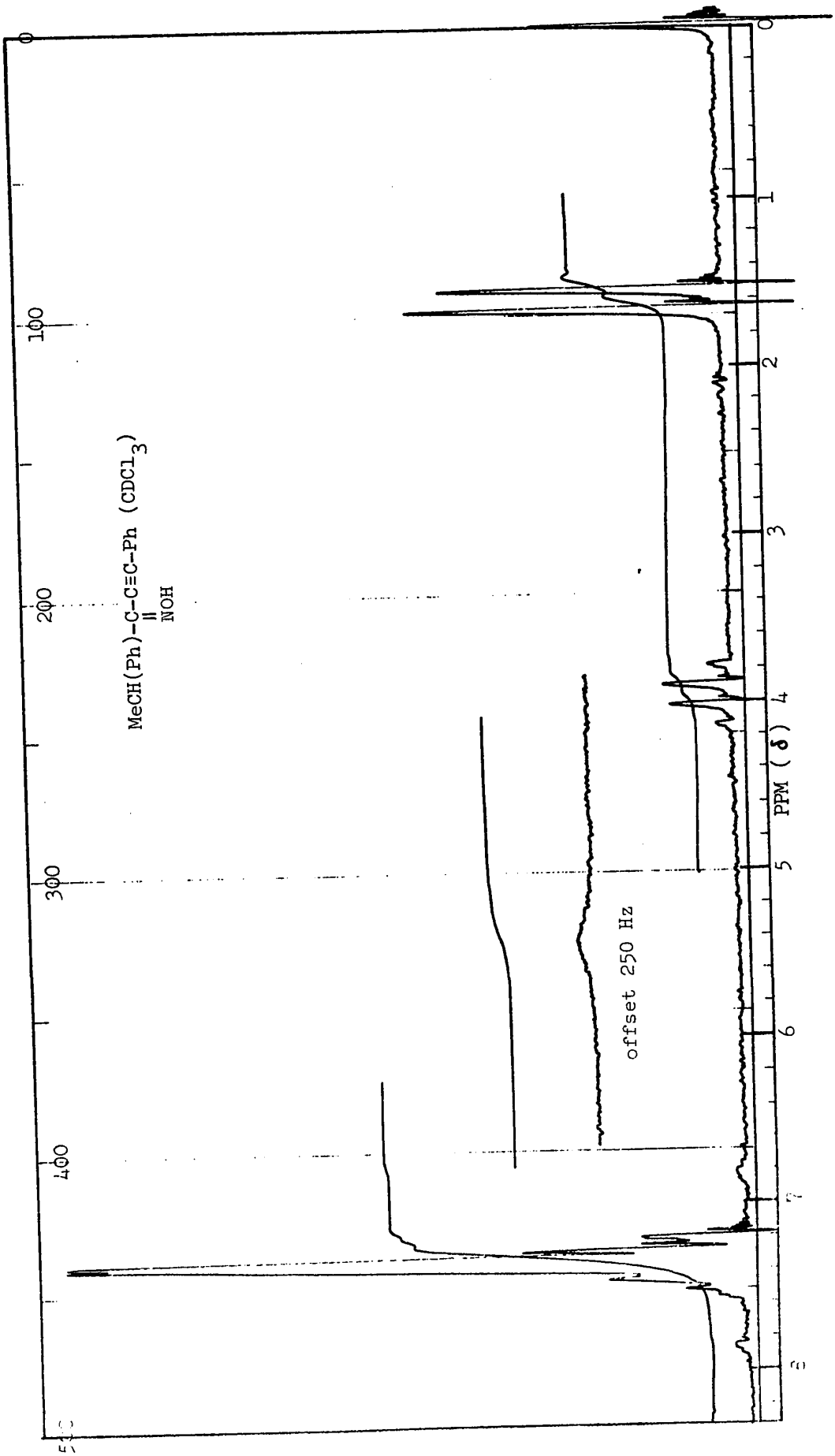
IR SPECTRUM 10



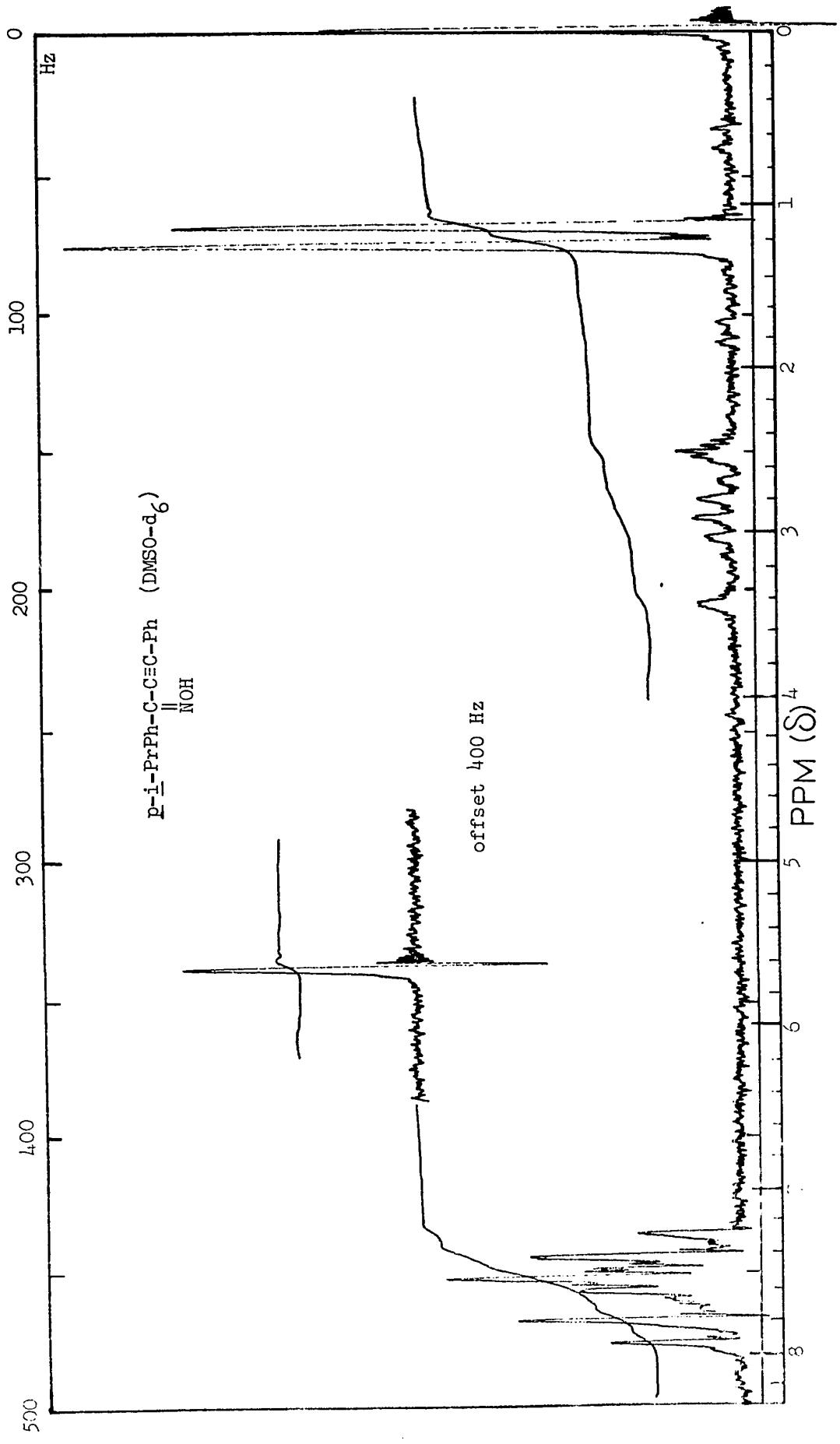
IR SPECTRUM 11



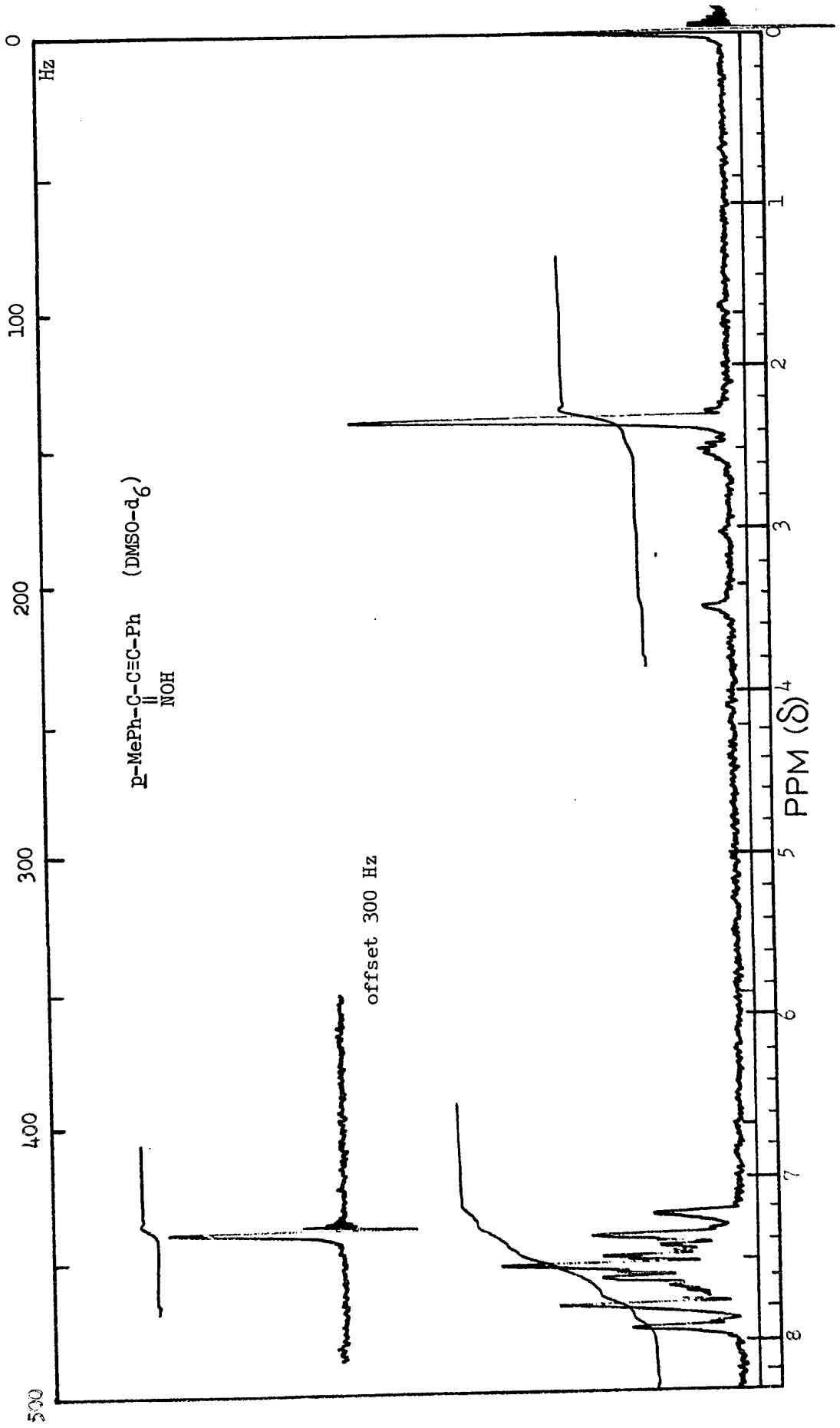
NMR SPECTRUM 1



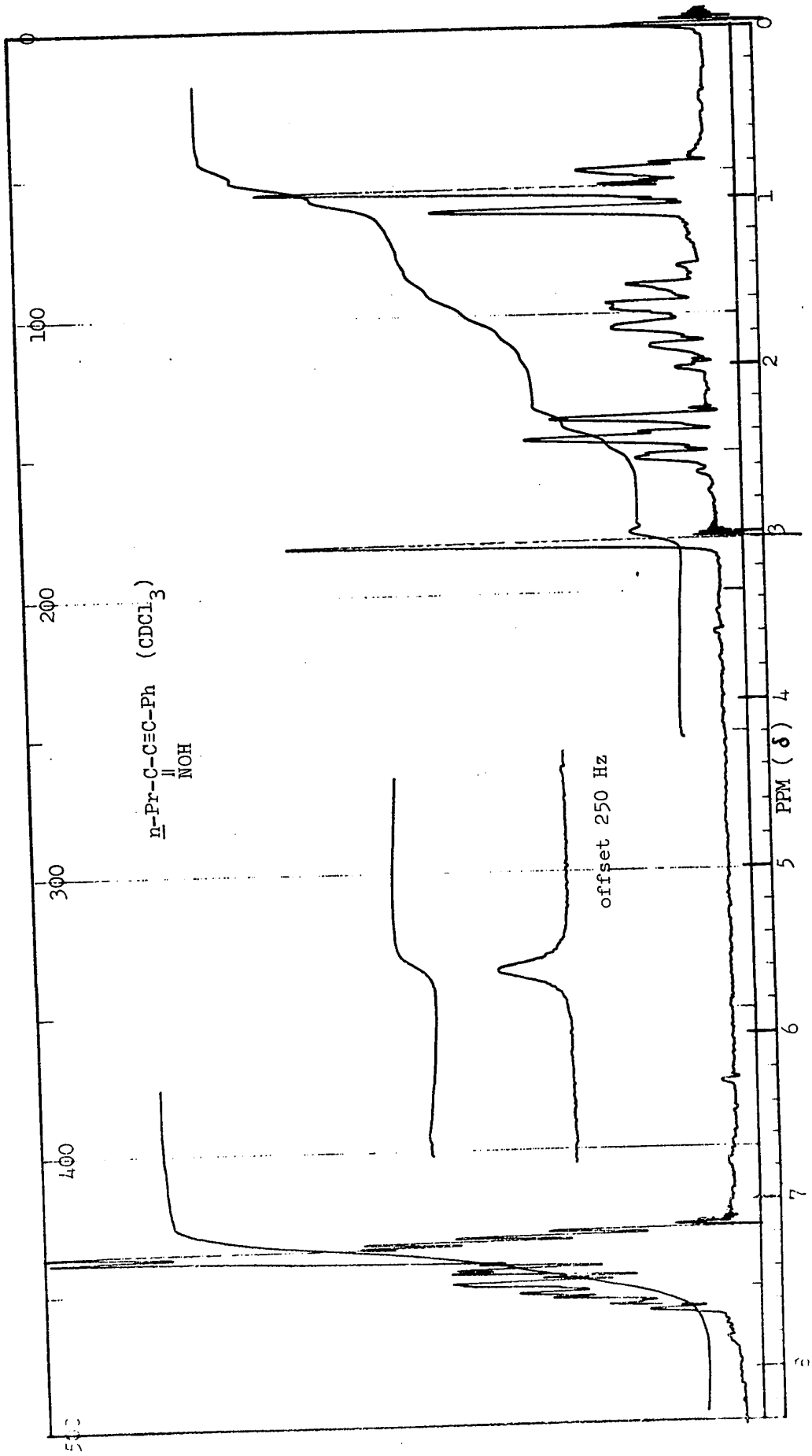
NMR SPECTRUM 2



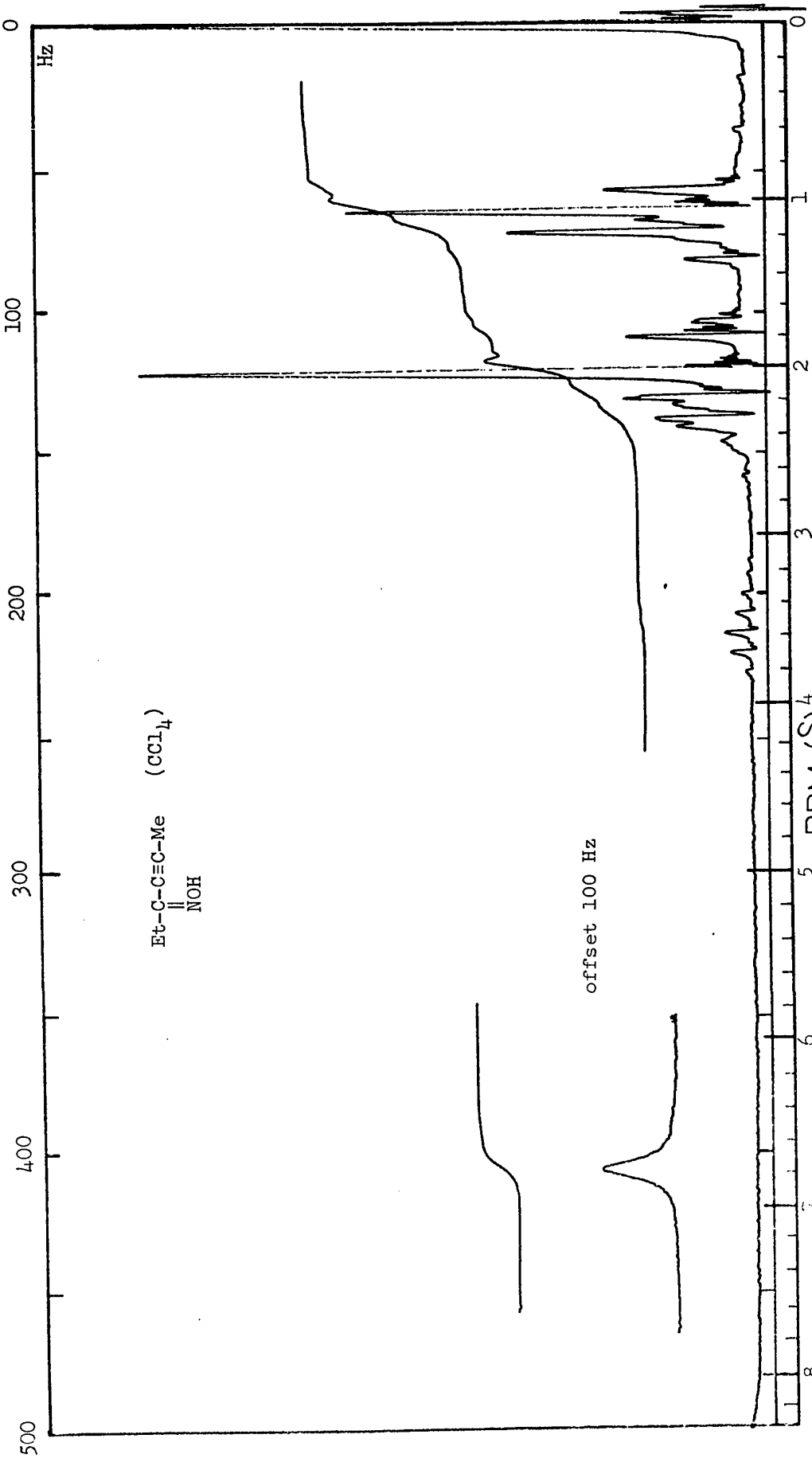
NMR SPECTRUM 3



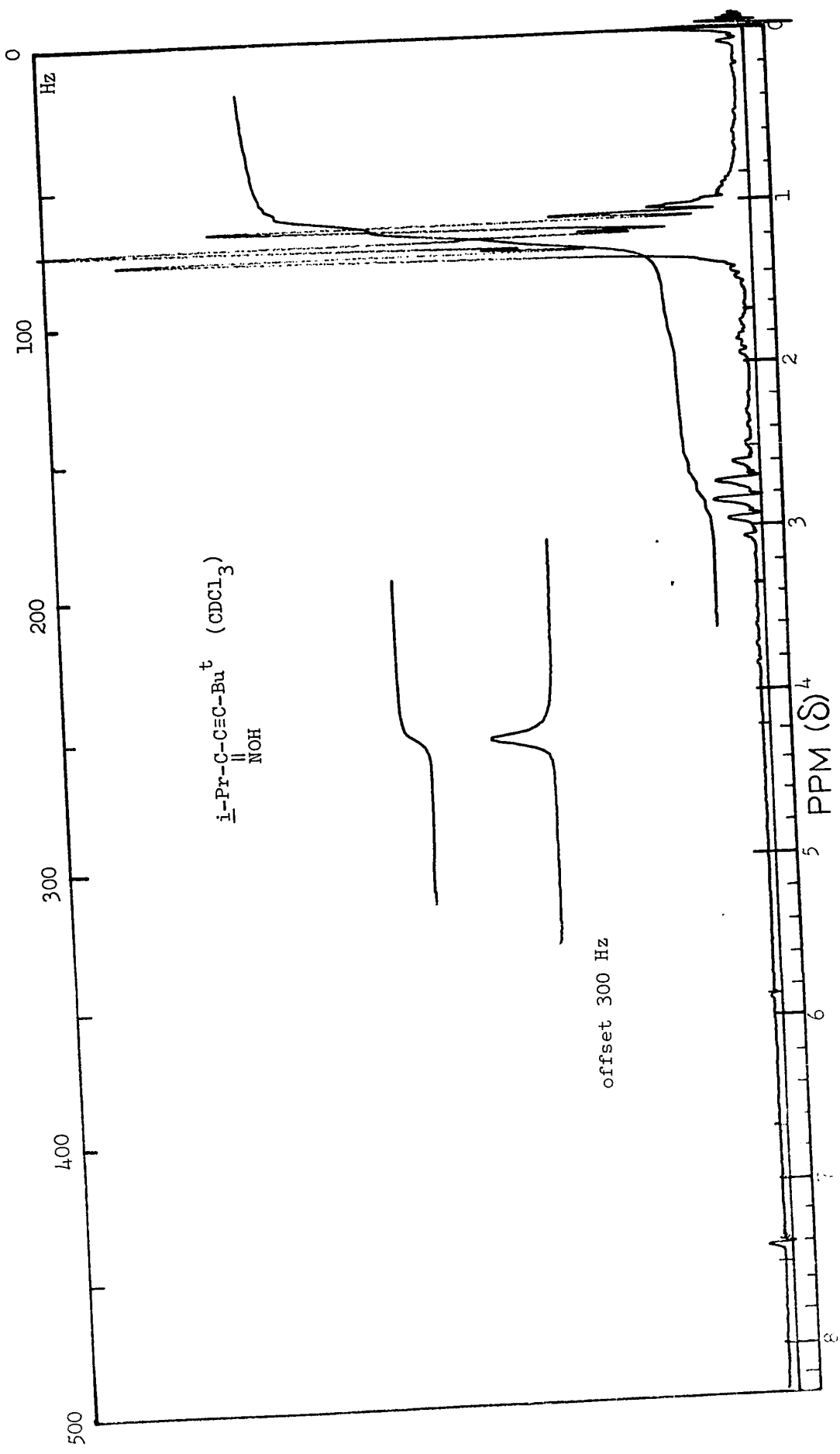
NMR SPECTRUM 4



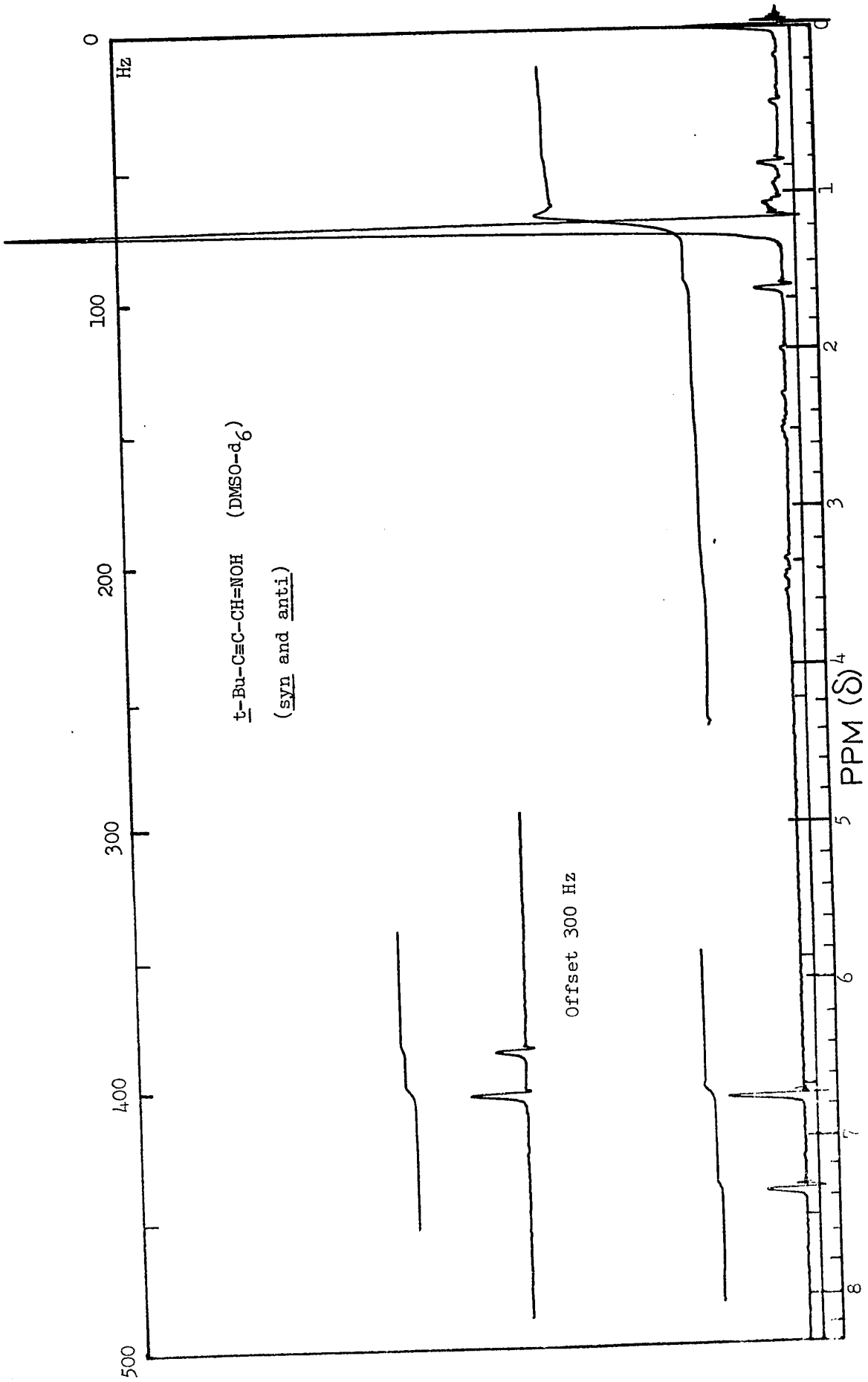
NMR SPECTRUM 5



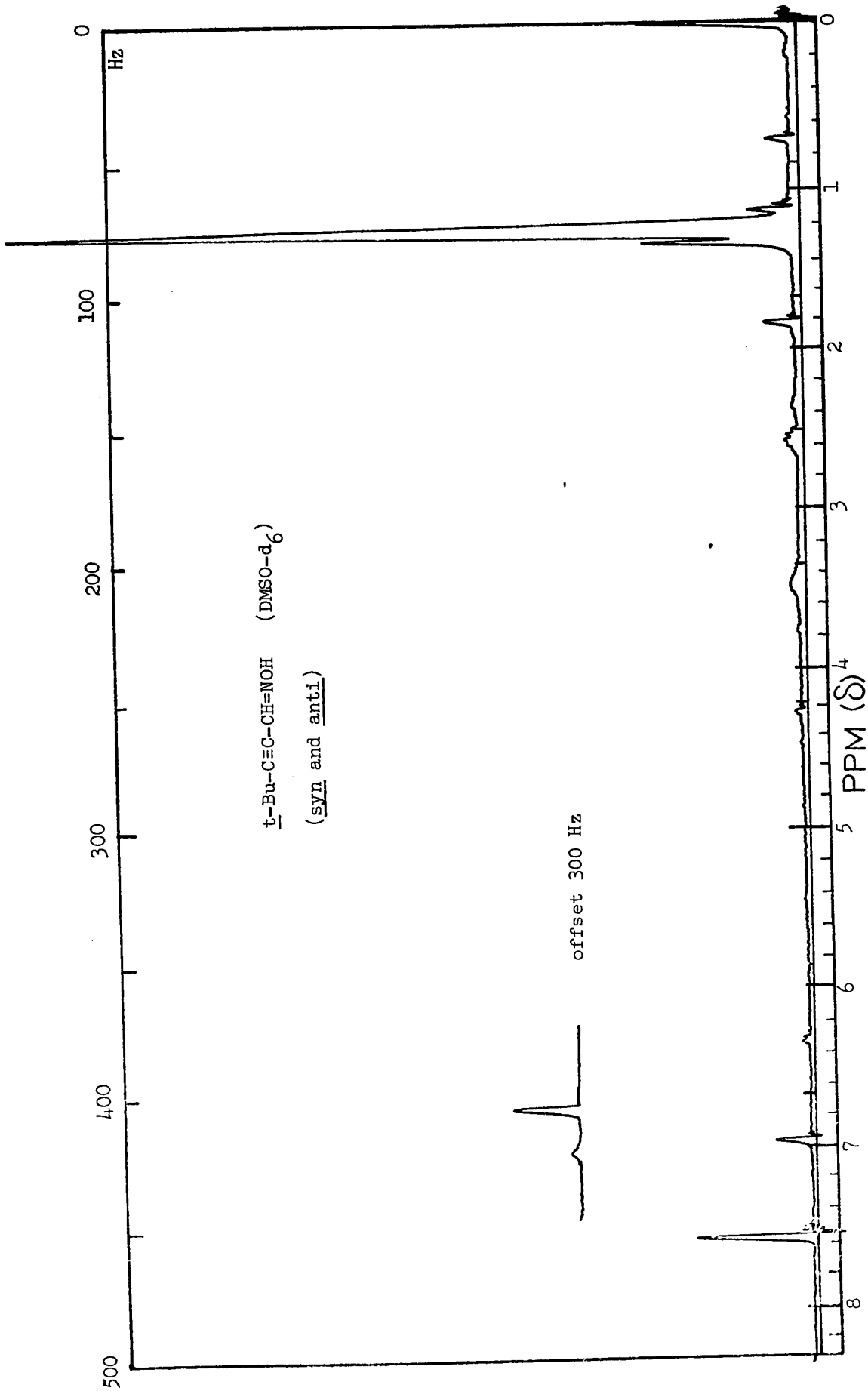
NMR SPECTRUM 6



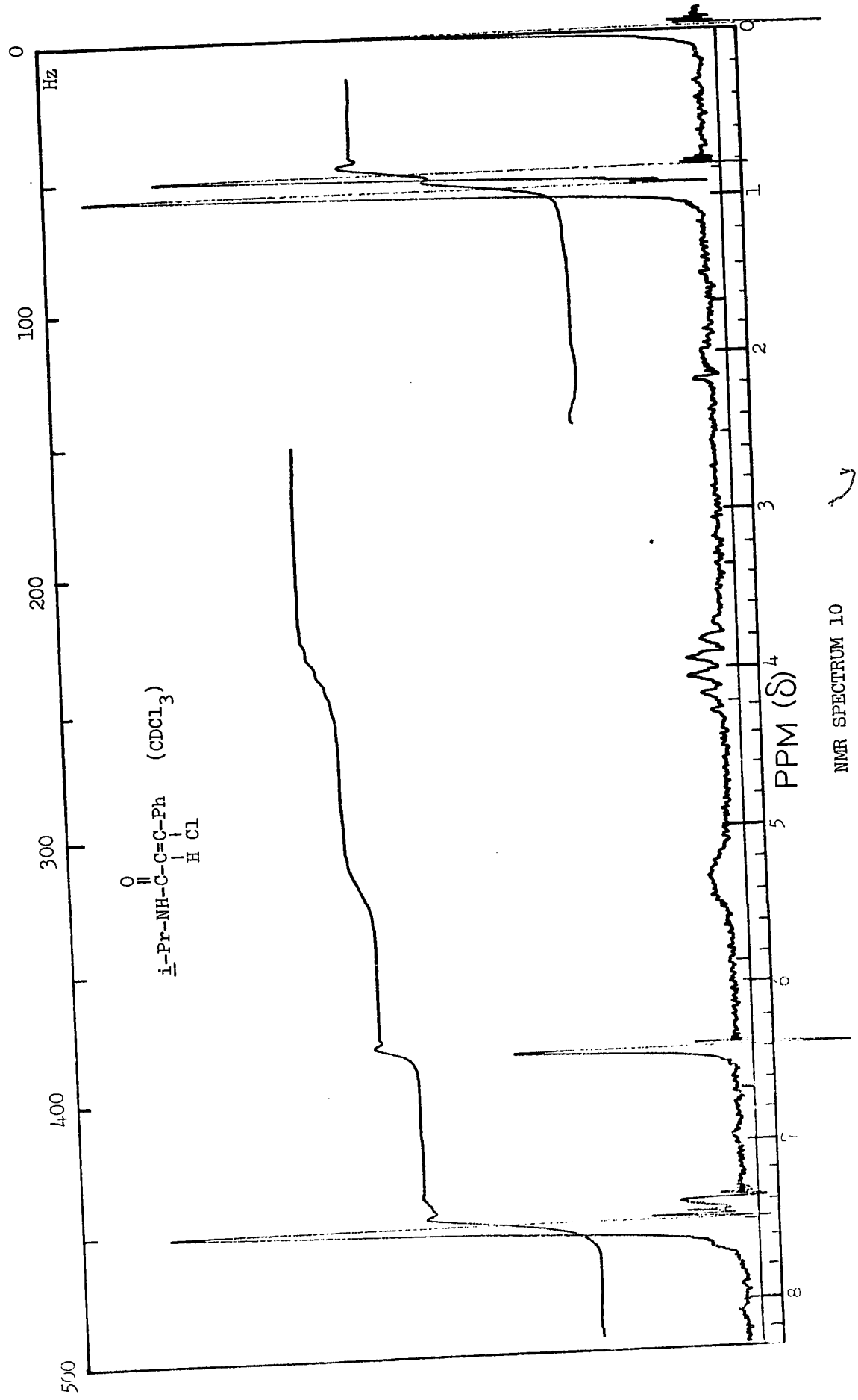
NMR SPECTRUM 7



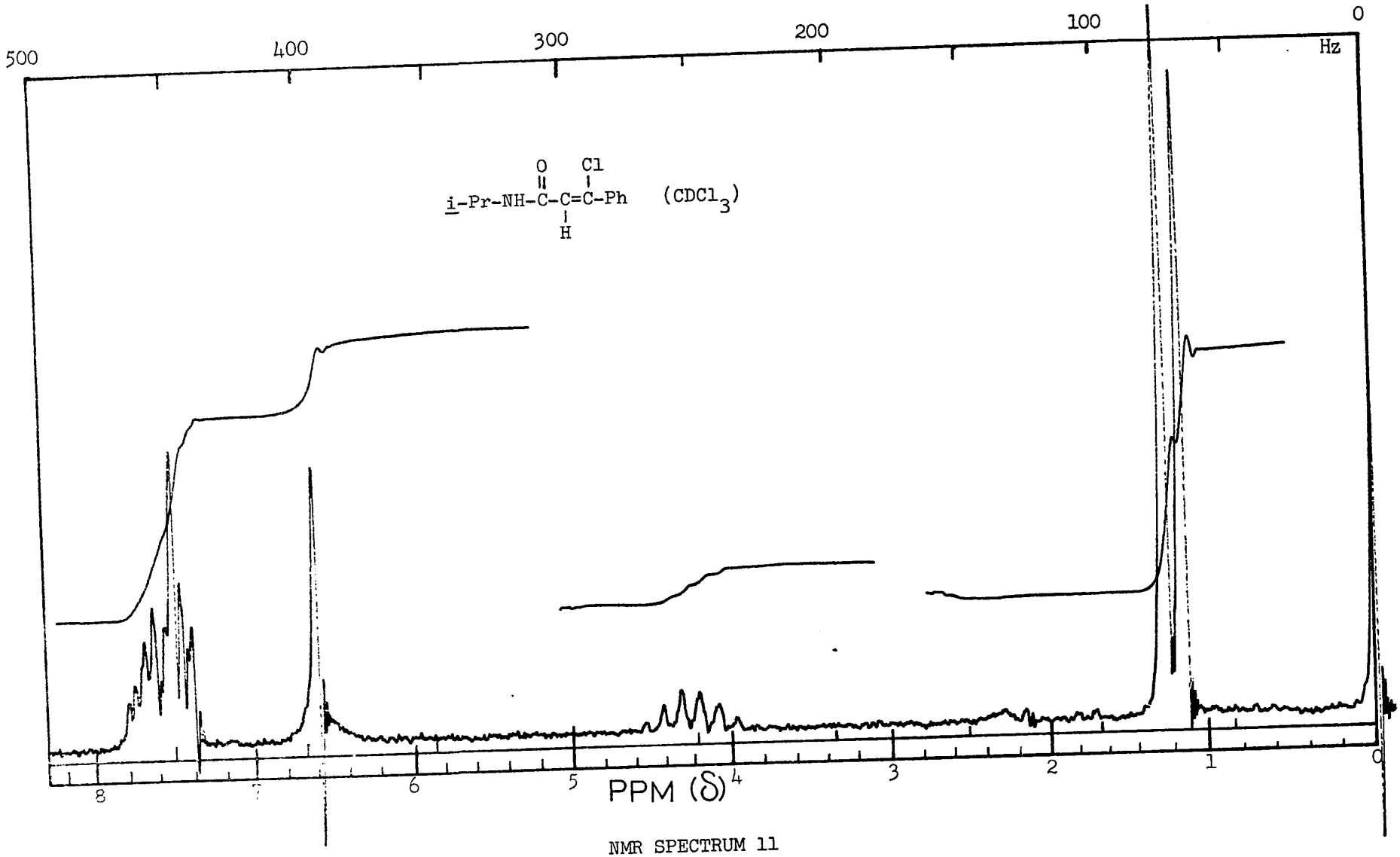
NMR SPECTRUM 8



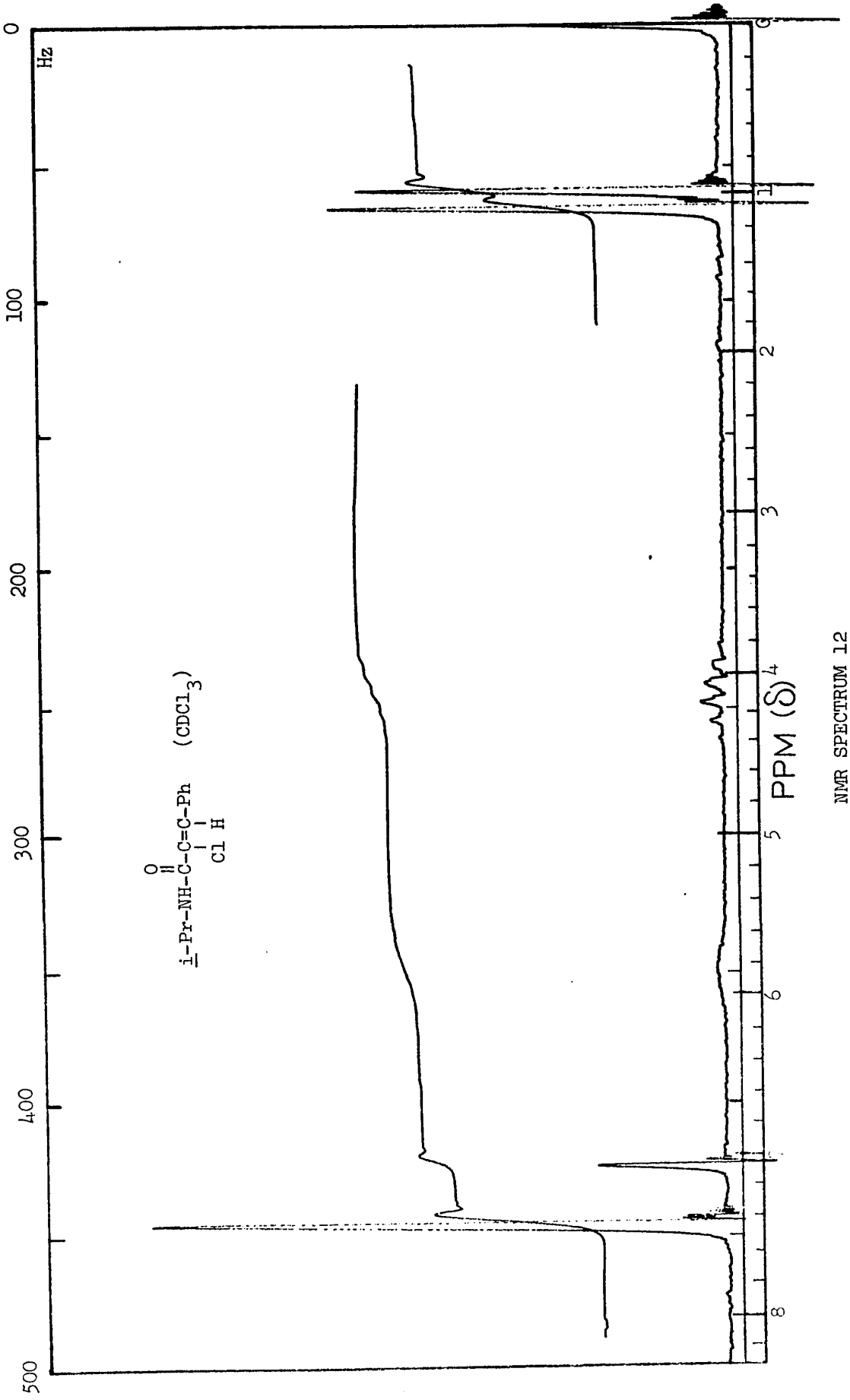
NMR SPECTRUM 9



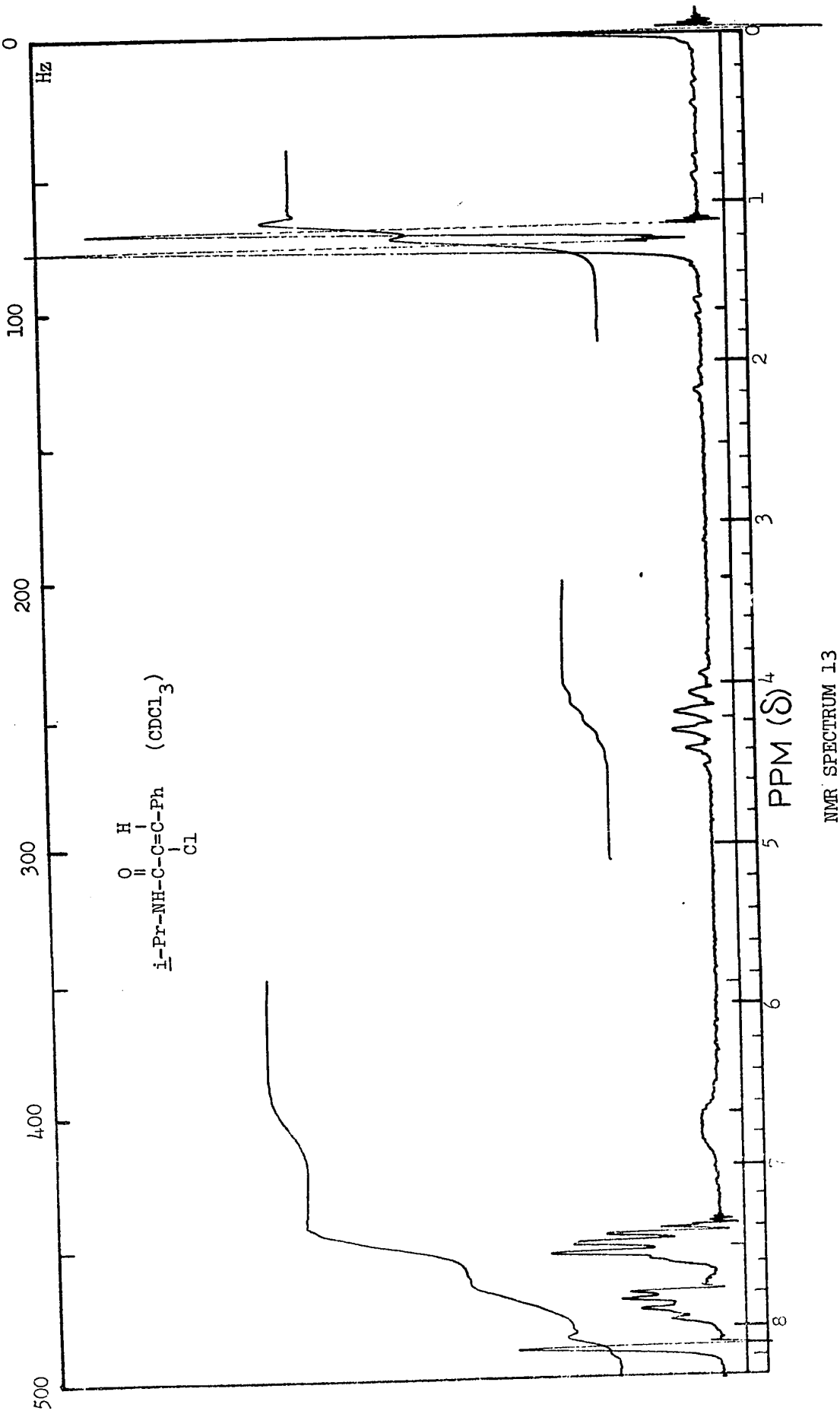
NMR SPECTRUM 10



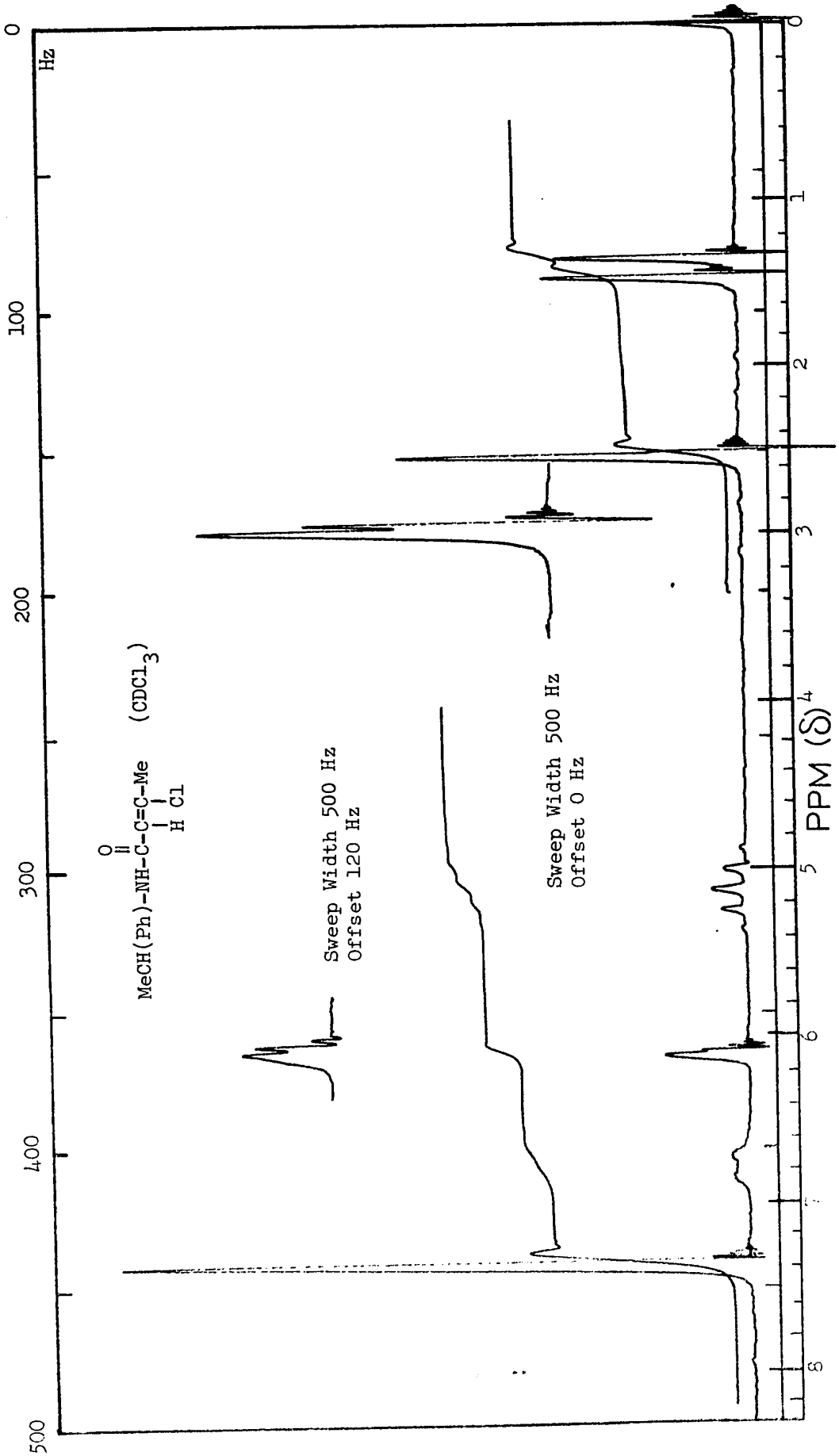
NMR SPECTRUM 11



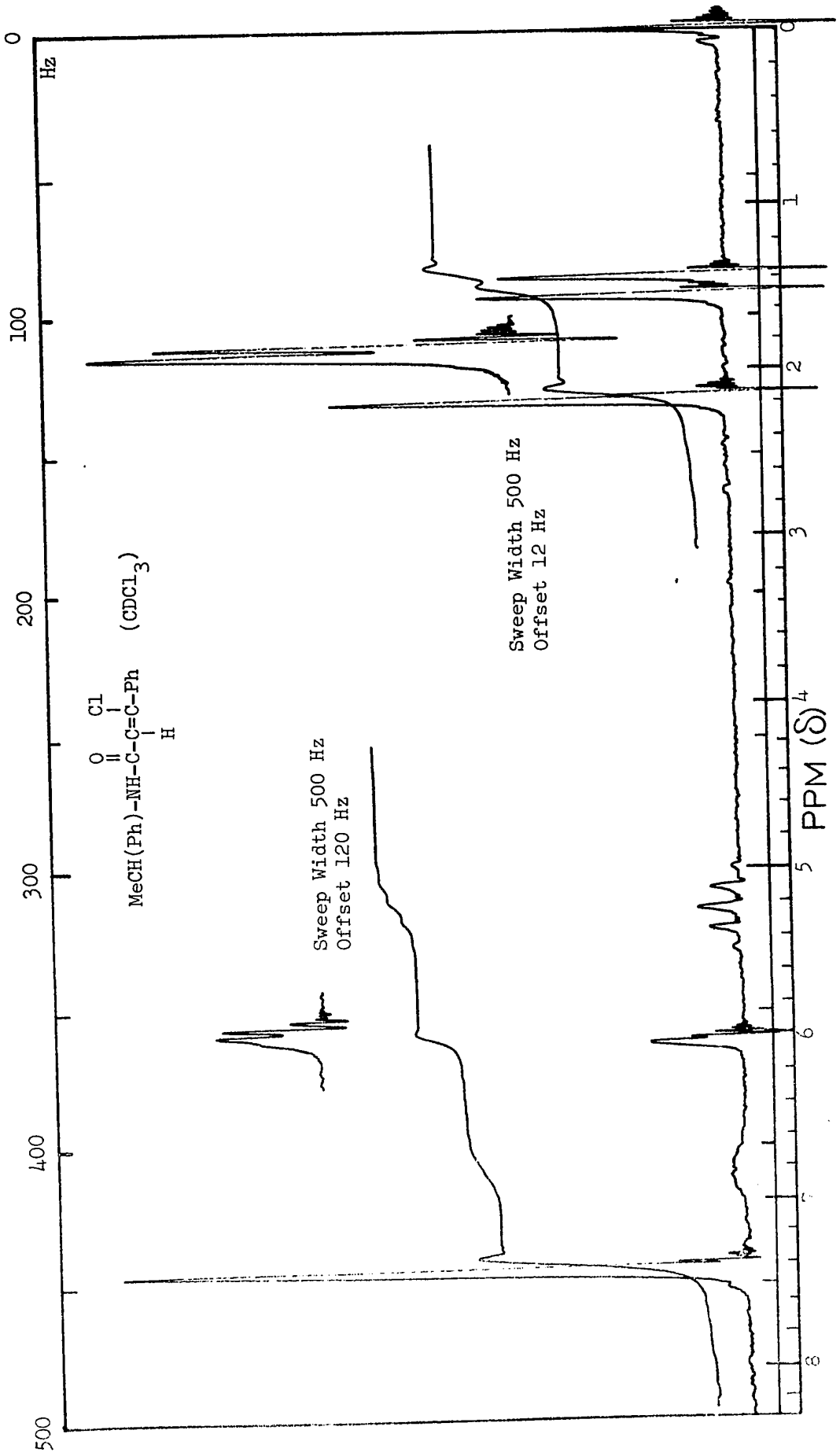
NMR SPECTRUM 12



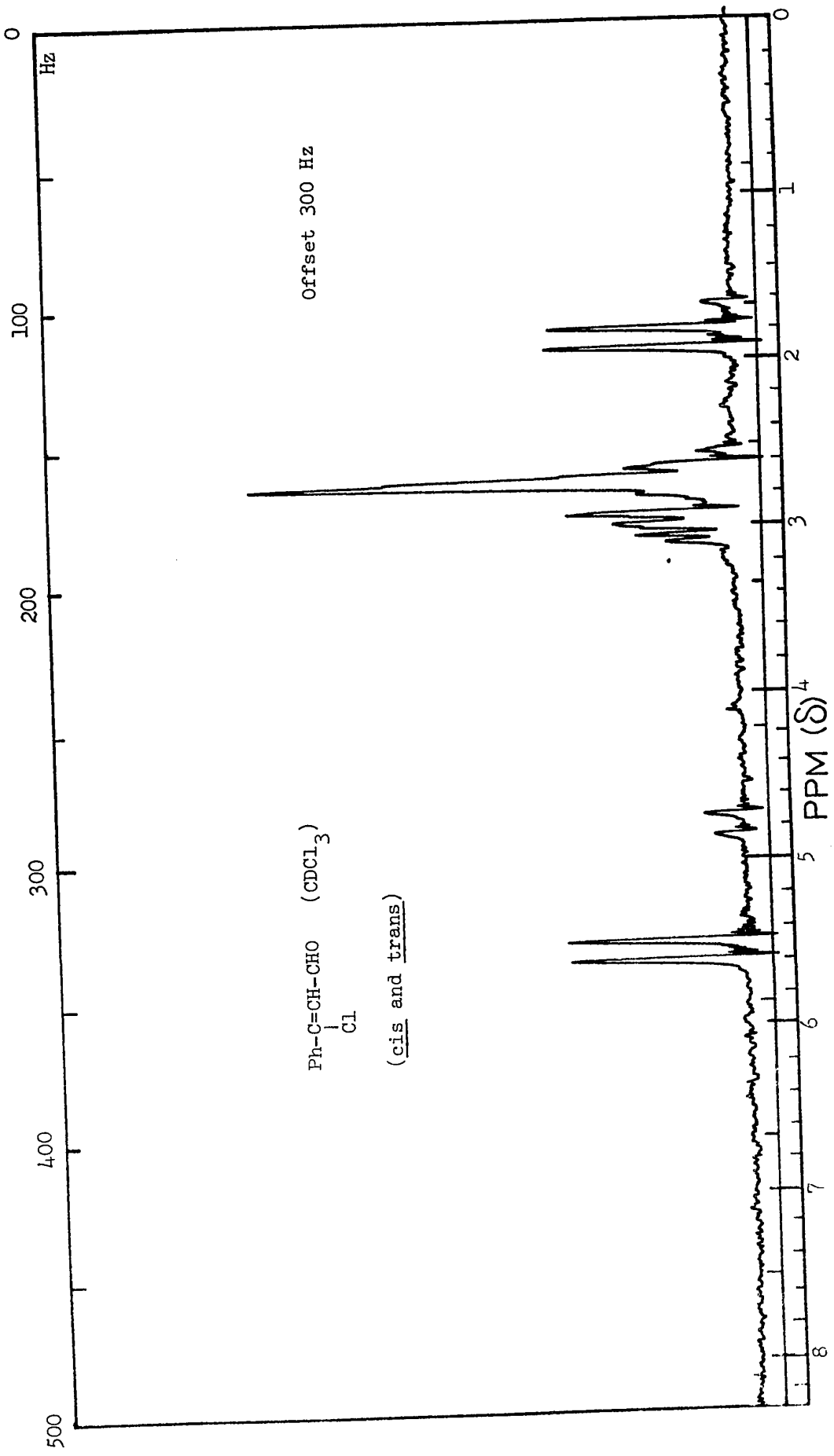
NMR SPECTRUM 13



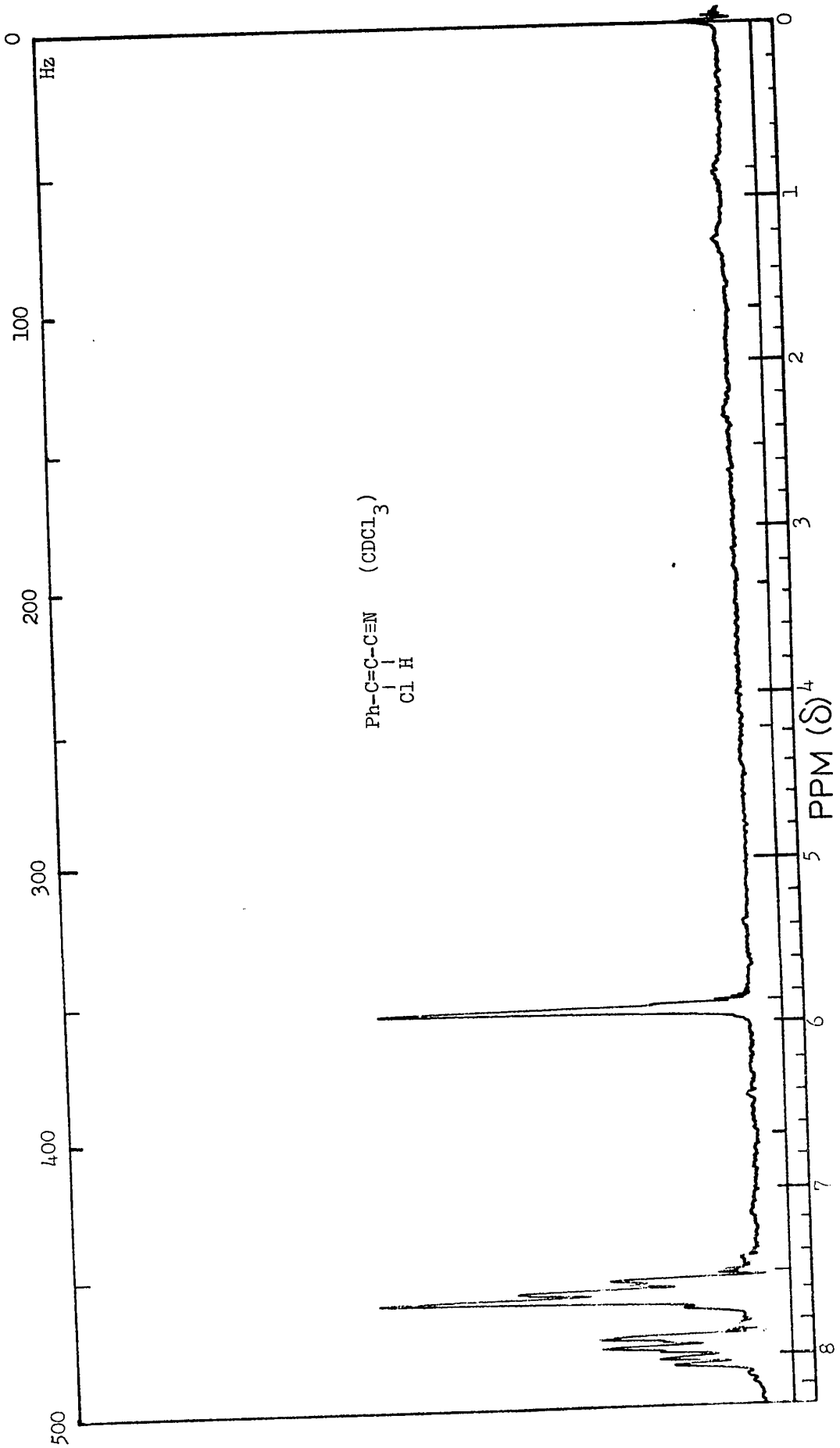
NMR SPECTRUM 14



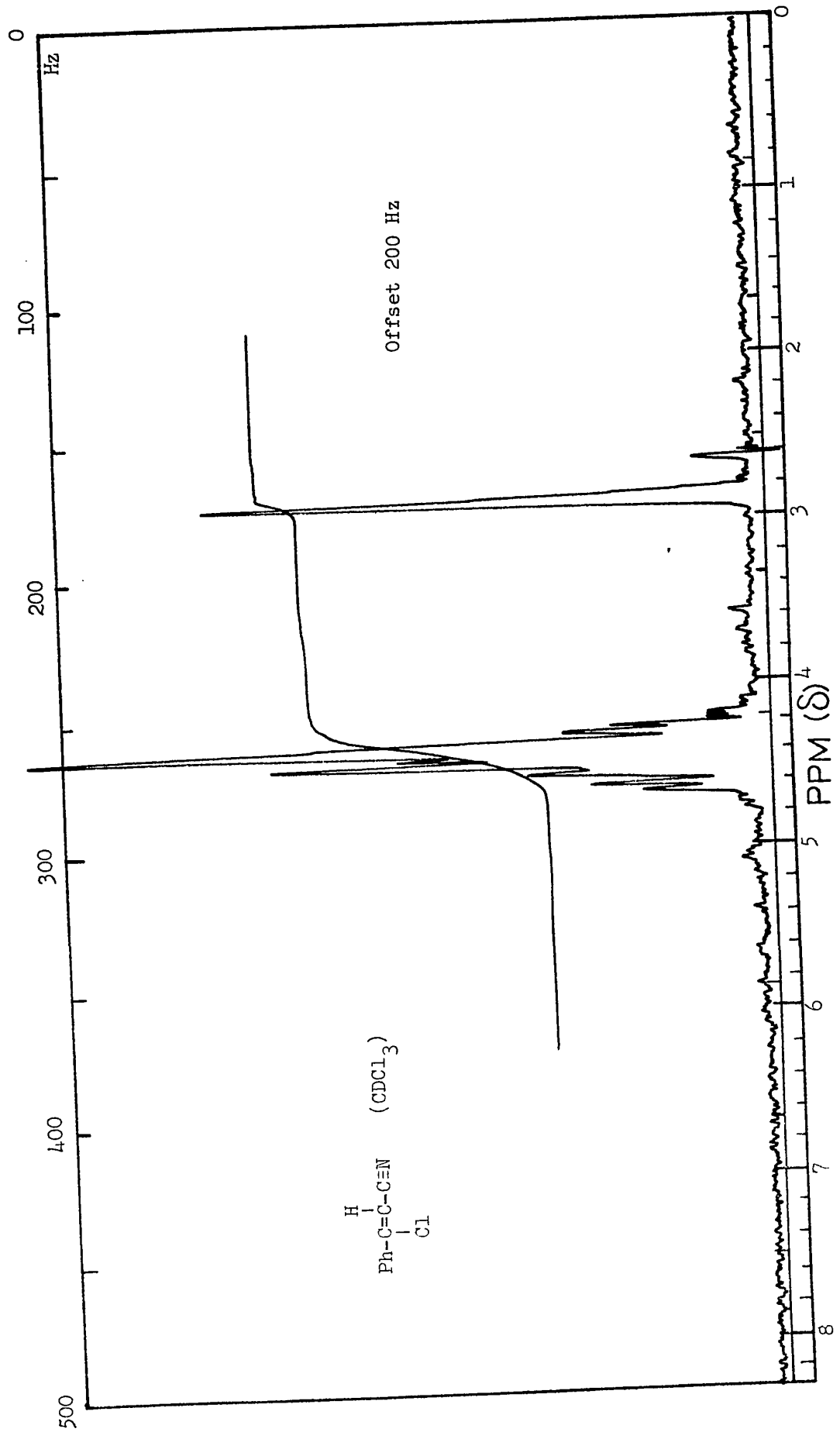
NMR SPECTRUM 15



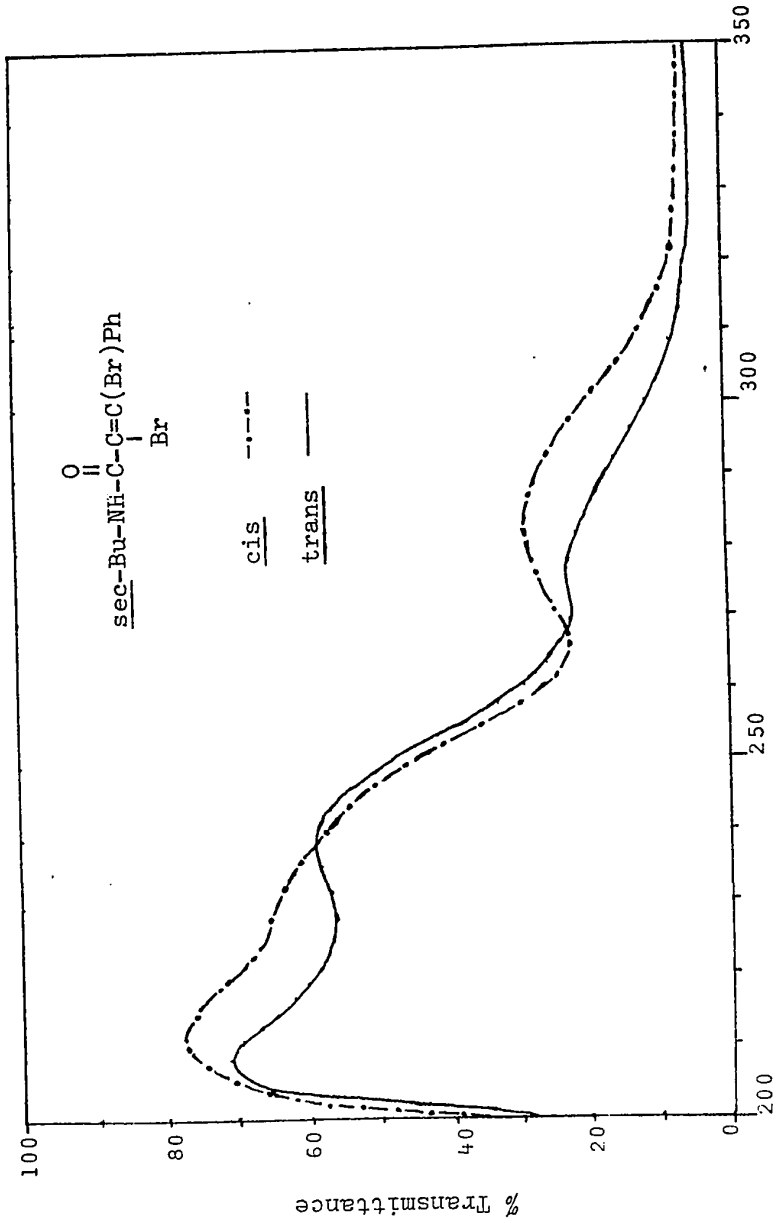
NMR SPECTRUM 16



NMR SPECTRUM 17



NMR SPECTRUM 18



UV SPECTRA OF CIS- AND TRANS-DIBROMO AMIDES