STUDIES IN α-ACETYLENIC CARBONYL COMPOUNDS — ISOXAZOLE FORMATION

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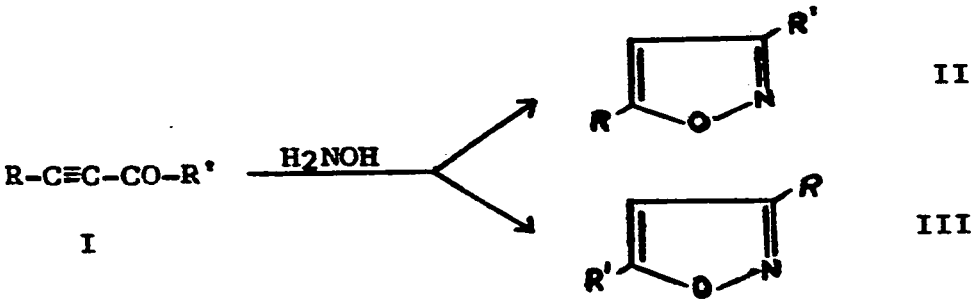
ABSTRACT

The isoxazole-forming reactions in basic medium of twenty α-acetylenic ketones with hydroxylamine were studied. Both 1,2- and 1,4-addition to the α-acetylenic ketone were observed for the majority of ketones studied with 1,2-addition predominating in base. Nuclear magnetic resonance (NMR) spectroscopy was used to determine the purity of the isomeric isoxazole products. It was found that steric factors play an important part in determining the ratio of 1,2- to 1,4-addition product.

α-Acetylenic ketoximes suggested as intermediates in the 1,2-addition mechanism for the reaction of acetylenic ketones with hydroxylamine were isolated for the first time from the reaction of hydroximyl chlorides with α-acetylenic Grignard reagents. α-Acetylenic oximes are very reactive and cyclize readily to the corresponding isoxazole by the action of a trace of alkali or heat. Using this method isoxazoles which could not be obtained isomerically pure from α-acetylenic ketones were prepared. The NMR spectra of dilute dimethyl sulfoxide solutions of the α-acetylenic oximes suggest that the hydroxyl group of α-acetylenic oximes has a <u>syn</u> (to triple bond) configuration.

INTRODUCTION

One of the many general methods of preparation of isoxazoles makes use of the reaction of α-acetylenic carbonyl compounds with hydroxylamine.[1,2] Acetylenic aldehydes (I a) yield 3-, or 5-substituted isoxazoles. Unsymmetrically substituted acetylenic ketones (I b) are known to yield isomeric isoxazoles II and/or III depending on reaction conditions.



I

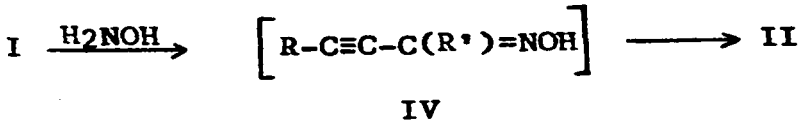
Ia, R' = H

Ib, R ≠ R' ≠ H

Ic, R = Ø ; R' = H

Id, R = CH_3 ; R' = H

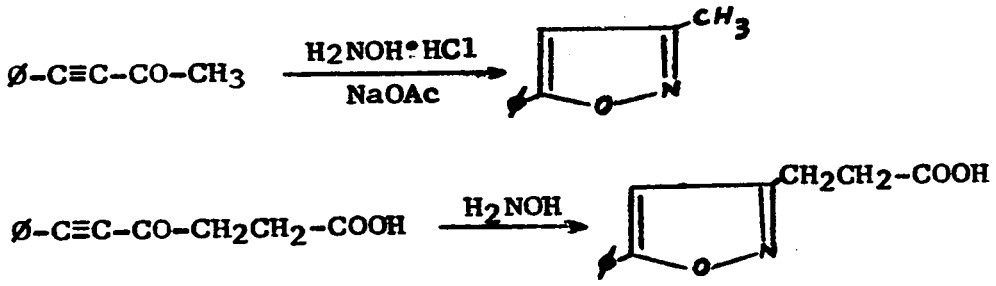
Isoxazole II may be considered as the product of 1,2-addition of hydroxylamine to I: i.e. the initial oximation of the carbonyl group followed by ring closure to the isoxazole:



IV

This mechanism of the formation of II assumes the formation of the oxime IV (the so-called "normal oxime" whose configuration, it is believed,[3-6] is such that the hydroxyl group is <u>syn</u> with respect to the triple bond, thus having the most favorable geometry for cyclization).

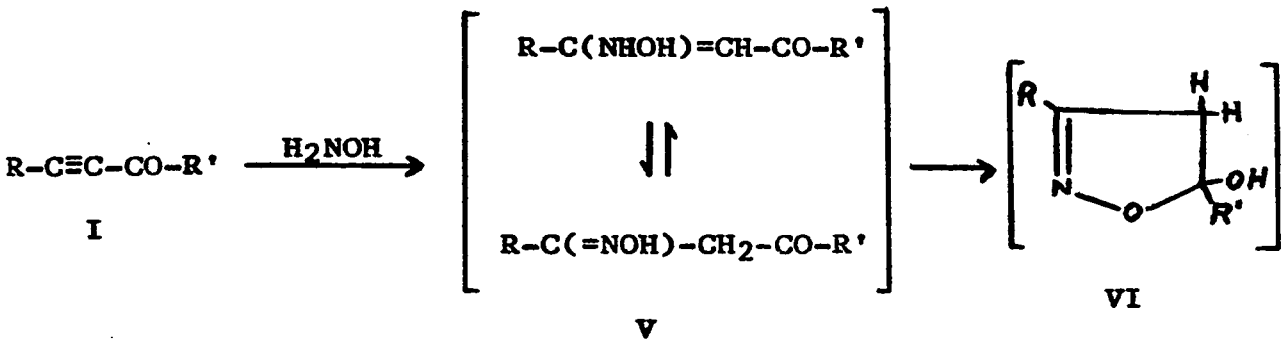
Although this "normal oxime" formation is implicit in the mechanism, no acetylenic ketoxime of the type IV has yet been isolated and fully characterized. However, it has been reported that phenylpropiolic aldehyde oxime has been isolated as an apparent intermediate in the reaction of hydroxylamine with phenylpropiolaldehyde (I c) and that the oxime has been converted to 5-phenylisoxazole by the action of a trace of alkali.[3,7] The other report in the literature[8] of the synthesis of an α-acetylenic oxime is that of the oxime of tetrol-aldehyde (I d). The configurations of both these aldoximes remain to be unequivocally established. If the 1,2-addition mechanism is operating, R' in I will be found in the 3-position of the isoxazole II (adjacent to the N-atom) as indicated in the examples given below.[9,10]



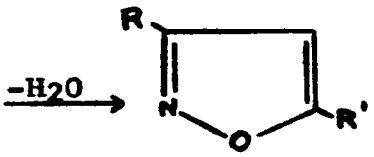
Thus the structure of the isoxazole formed in the reaction is also generally accepted as an evidence for this so-called 1,2-addition mechanism.

The isoxazole III maybe regarded as the product resulting from the initial 1,4-addition of hydroxylamine to the unsaturated system I. In this mechanism the hydroxylamine adds first across the triple bond to produce the monoxime of a 1,3-dicarbonyl compound V (or its tautomer) which then undergoes cyclization followed by the

elimination of a molecule of water to give III. If this mechanism is



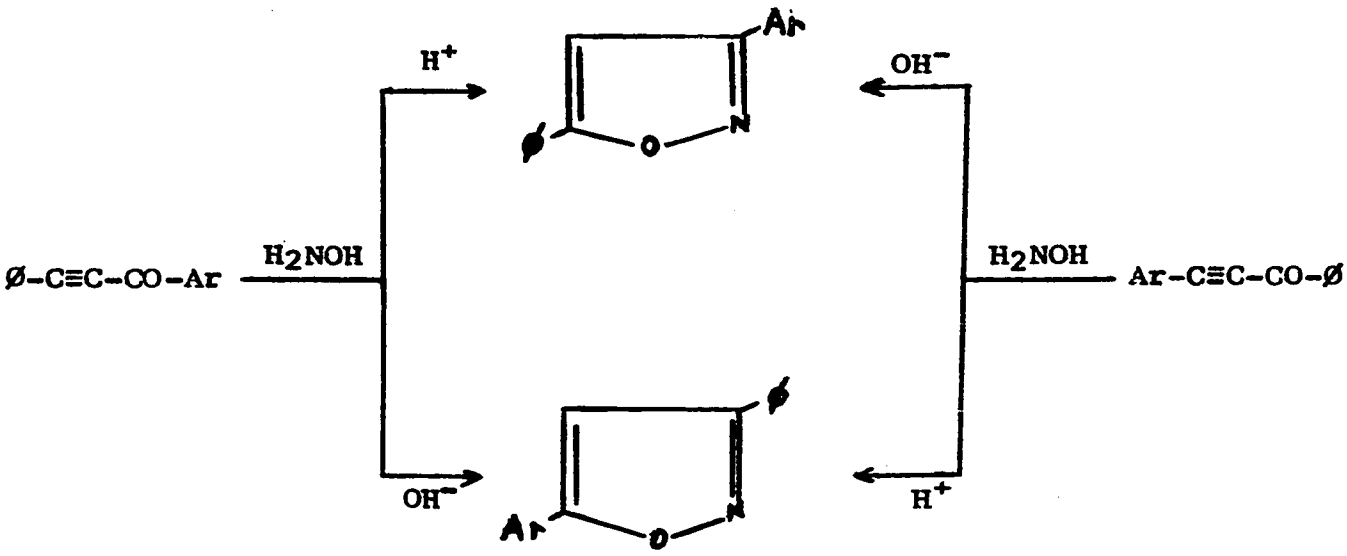
I V VI



III

operating the substituent R' in I will be found in the 5-position (adjacent to the O-atom) of the isoxazole III. The nature of the intermediate involved in this reaction has not been established unequivocally. There is even the conjecture that the intermediate might well be a 5-hydroxyisoxazoline VI.[11]

As the 1,4-addition is a Michael-type addition to the α,β -unsaturated system I it is generally believed that this is the process usually operating in basic medium, the 1,2-addition mechanism generally operating in acid medium.[2] Thus it has been demonstrated in the case of phenyl-(p-methoxybenzoyl)acetylene that the presence of base or acid in the reaction determines which of the two isomeric isoxazoles is formed.[12] However, it is a fact that most acetylenic ketones produce both the isomeric isoxazoles possible in any given

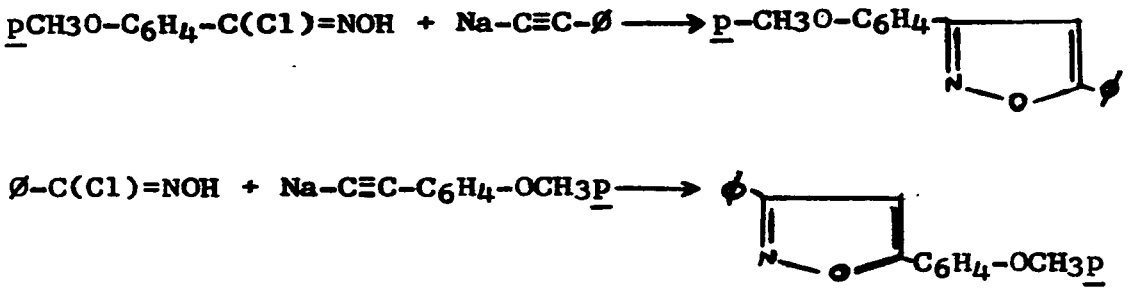


reaction with hydroxylamine indicating that the 1,2- and the 1,4- processes are in operation simultaneously, one or the other isomer predominating, depending on, among other factors, the conditions of the reaction.

Thus the problem of establishing the mechanism of the cyclization reaction of acetylenic ketones and hydroxylamine rests mainly on the identification of the structures of the isomeric isoxazoles produced. The earlier literature connected with this problem is, for the most part, not entirely reliable because the structural assignments were based on insufficient evidence and hypothetical mechanisms, thus resulting in improper indentification of the isomeric products produced in the reaction. The difficulty has been aggravated by the fact that the two isomeric isoxazoles usually have similar melting points and show little or no depression when the melting point of a mixture of the two isomers is determined. In many cases the isomers also have extremely similar infrared spectra so that it is easy to overlook a small amount of one isomer as a contaminant

in the other. Conventional techniques of separation such as fractional distillation, fractional crystallization, column or gas chromatography have proved to be useless in effecting the separation of a pair of the isomeric 3,5-disubstituted isoxazoles.[13,14]

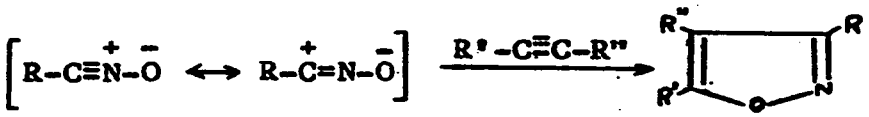
Another method that has been used for the synthesis of substituted isoxazoles involved reaction of the sodium salt of a substituted acetylene with a suitable hydroximyl chloride. In 1927 Weygand and Bauer[12] prepared a pair of the isomeric 3,5-disubstituted isoxazoles as shown below and believed that the structures of the isomeric isoxazoles to have been unequivocally established from their method of synthesis:-



However, it has later been demonstrated by Quilico and Speroni[15] that this reaction proceeds by the addition of the nitrile oxide (formed from the chloride by the elimination of HCl) to the triple bond of the acetylene and that the product isoxazole need not necessarily always have the structures expected from this reaction. It has also been demonstrated soon afterwards that acetylenic Grignard reagents can be used as a substitute for the sodium derivatives of the acetylenes in the reaction with hydroximyl chlorides[16,13] for the production of the isoxazoles.

Quilico and co-workers have developed a general method for

the preparation of substituted isoxazoles[15] from the reaction of nitrile oxides with acetylenic compounds of the type R'-C≡C-R".



This reaction is generally known to proceed smoothly and to produce good yields of the isoxazoles.

In the reaction between hydroximyl chlorides and sodium derivatives of acetylenes or acetylenic Grignard reagents or in the reaction between nitrile oxides and acetylenic Grignards, an α-acetylenic oxime of the type IV seems to be a logical immediate precursor for the cyclization reaction to the isoxazole. Although there have been allusions to the existence of these acetylenic oximes as intermediates in such reactions[16] there seems to have been no effort directed to actually isolate and characterize these oximes in reactions of acetylenic Grignard reagents and hydroximyl chlorides. Indeed acetylenic ketoximes of this type seem to be undescribed in the literature. An acetylenic ketoxime of the type IV (whether of the syn- or the anti-configuration) must give only one isoxazole if and when it undergoes cyclization (assuming no unusual rearrangements take place under the rather mild conditions used for cyclization, such as the use of dilute base). Thus if such acetylenic ketoximes can be prepared by methods that are straightforward and if their structures and configurations are established beyond doubt, and if these oximes are independently cyclized to the isoxazoles, then, one can safely assume the structures of such isoxazoles to have been unequivocally

established.

Another aspect of the problem which requires careful examination is the understanding of the various factors that determine the 1,2- as well as 1,4-addition of a nucleophile like hydroxylamine to the α-acetylenic ketones of the type I. As early as 1930 von Auwers[17] did investigate these factors in the case of chalcones (R-CH=CH-CO-R' with R and R' = Aryl) which are the ethylenic analogs of I. In the cases studied the groups R and R' were almost invariably benzene derivatives, and the factors that determined which way the neucleophilic reagent reacted with the chalcone were postulated to be the nature of the nucleophile, the degree of activation of the double bond, and the nature of the groups R and R'. It was found that the tendency of the double bond to undergo addition varied not only with the position of a substituent on the benzene nucleus in R and R' (i.e. ortho and para, or meta) but also on which one it was located.

Thus the groups R and R' in the chalcones seem to have been investigated with regard to their electronic effects but little or no study seems to have been directed towards ascertaining the steric effects of R and R'. However, no such systematic investigation of the factors that control the 1,2- and 1,4-addition of hydroxylamine and like reagents seems to have been undertaken in the case of α-acetylenic ketones. It will shed more light on the problem of 1,2- vs. 1,4-addition in α-acetylenic ketones if one is able to demonstrate the operation, if any, of the electronic or steric effects of R and R' in α-acetylenic ketones of the type I.

STATEMENT OF THE PROBLEM

The present investigation was initiated with the object of gaining insight into mechanisms of formation of the two isomeric isoxazoles from the reaction of α-acetylenic carbonyl compounds with hydroxylamine.

It was proposed to synthesize a series of α-acetylenic ketones of the type R-C≡C-CO-R' and to study their reactions with hydroxylamine with regard to the various factors that controlled the 1,2- and 1,4-addition of the nucleophile to the conjugated system. Among the factors that seemed of immediate interest were the reaction conditions and the electronic as well as the steric effects of the groups R and R'.

In the 1,2-addition mechanism for the formation of the isoxazole an α-acetylenic ketoxime (the "normal oxime" of the acetylenic ketone) has often been postulated but its existence and configuration remain conjectural. It was decided to attempt to synthesize these elusive intermediates independently and to demonstrate their subsequent cyclization to isoxazoles whose structures can thus be established beyond doubt.

DISCUSSION

Syntheses

As the first step towards the study of the isoxazole-forming reactions of α-acetylenic ketones and hydroxylamine, 20 different ketones of the type R-C≡C-CO-R' were synthesized, 6 of them for the first time. The syntheses involved the reaction of the so-called Iotsitch reagents(α-acetylenic Grignard reagents, R-C≡C-Mg-Br) with the appropriate aldehydes and the subsequent oxidation of the resulting secondary alcohols to the corresponding ketones by chromic acid treatment. The various steps involved are illustrated in the following scheme:

$$C_2H_5\text{-Mg-Br} \xrightarrow{\text{R-C}\equiv\text{C-H}} \text{R-C}\equiv\text{C-MgBr} \xrightarrow{\text{R'-CHO}} \text{R-C}\equiv\text{C-CHOH-R'}$$

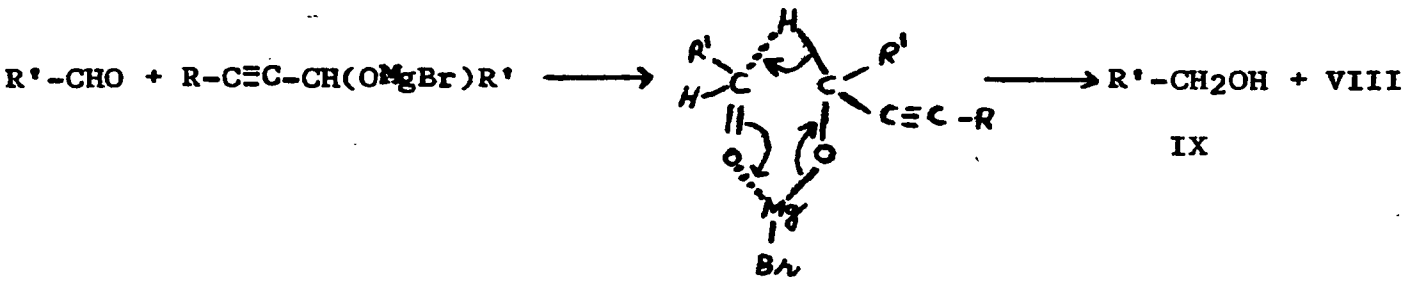
VII

$$\text{R-C}\equiv\text{C-CHOH-R'} \xrightarrow{CrO_4^{--}} \text{R-C}\equiv\text{C-CO-R'}$$

VIII

VII a, R = CH_3; R' = CH_3-CH=CH

This sequence has been used for the synthesis of α-acetylenic ketones[18] in good yields. During the synthesis of the acetylenic alcohols the formation of ketones (VIII) was observed. This was minimized by using slightly less than an equimolar amount of aldehyde. The formation of (VIII) and (IX) is reported to proceed through the cyclic, concerted rearrangement as shown.[19,20]



During storage the α-acetylenic alcohols underwent slow oxidation yielding some α-acetylenic ketones as was revealed by the IR spectra of many of the pure alcohols stored for about a year. There is also a report that α-acetylenic alcohols of the type (VII a) undergo dehydration on storage.[21]

For the final step, oxidation of the secondary alcohol to the ketone, the method used was a modification of the well-known "chromic acid oxidation" described by H. C. Brown and C. P. Garg.[22] This method entails using diethyl ether which extracts the ketone as it is formed from the chromic acid immiscible layer thus protecting it from further oxidation. The products obtained are highly pure containing none of the starting secondary alcohols and the yields are good.

α-Acetylenic ketones have been prepared by other methods, of which three will be discussed here: the action of acid chlorides[23] or anhydrides[10] on sodium acetylides; the dehydrohalogenation of α-halo ethylenic ketones;[24] the action of anhydrides on α-acetylenic Grignard reagents.[25] These methods are inferior compared to the method chosen when yields and purity of the final products are taken into account. Acid chlorides react with sodium phenylacetylide, for example, with variable yields and the products obtained usually contain halogen impurities. Anhydrides react with sodium acetylides with poor

yields and there remains the problem of separating the expected ketone from the tarry side products and unreacted anhydride. Dehydrobromination of α-bromo ethylenic ketones also poses problems in separating unreacted starting material from the expected product. The action of acetic anhydride on α-acetylenic Grignard reagents is complicated by the fact that the α-acetylenic ketone formed tends to react further with the α-acetylenic Grignard reagent.

Acetylenic Alcohols:

The infrared spectra of the α-acetylenic alcohols are summarized in Table I giving the absorption bands for the (-C≡C-) stretching vibrations. There is usually a weaker absorption band close to the main band which is attributed either to combination or isotopic effects, or to Fermi resonance if it is as intense as the main band.[18] The main band usually falls at 2225 cm^{-1} for those compounds with R = alkyl groups and the replacement of R by a phenyl ring produces a displacement of 20 cm^{-1} toward lower wave numbers for the (-C≡C-) main absorption band. When R' is also replaced by a phenyl ring a further shift toward lower wave numbers is usually observed. These shifts are analogous to those found for α-acetylenic ketones.[18]

The infrared spectra of the α-acetylenic alcohols are also characterized by their very intense absorption bands at approximately 3610 cm^{-1} (free OH stretching) and 3350-3410 cm^{-1} (intermolecularly hydrogen bonded OH stretching).

The nuclear magnetic resonance (NMR) spectra of the α-acetylenic alcohols are summarized in Table II. The chemical shift for the OH proton (not given in the table) varied from 2.4 to 5.2 ppm.[26]

Magnetic non-equivalence[27-29] of the methylene protons was not observed for alcohols of the type R-C≡C-CHOH-CH_2R" where R = Me or Ø and R" = Me or Ø under the conditions used for the NMR spectra. For these cases further work needs to be done under more favorable conditions to determine whether such non-equivalence indeed exists. However, magnetic non-equivalence[27,29,30] was observed for the case Ø-C≡C-CHOH-$CH(Me)_2$. The chemical shift difference between the two magnetically non-equivalent methyl groups was approximately 0.03 ppm. The methyl groups in H-C≡C-CHOH-$CH(Me)_2$ have also been reported to be magnetically non-equivalent with a chemical shift difference between the two methyl groups of 0.02 ppm.[31] For the case of Me-C≡C-CHOH-$CH(Me)_2$, magnetic non-equivalence was not observed under the conditions used for the NMR spectra, but, as mentioned above, further study is required.

Long range coupling was observed in the case of Me-C≡C-CHOH-R', where the coupling constant between the methyl group and the methine proton was approximately 2.5 Hz. This is in good agreement with the literature values (2.4-2.6 Hz.).[32]

Coupling between the methine proton and the hydroxyl proton occurred in dimethyl sulfoxide solution and the coupling constant amounted to approximately 5 Hz. for CH_3C≡C-CHOH-CH_3. Coupling constants of 3.5-5.0 Hz. have been reported for alcohols in dimethyl sulfoxide.[33]

TABLE I

INFRARED SPECTRA OF α-ACETYLENIC ALCOHOLS (R-C≡C-CHOH-R')

COMPOUND		INFRARED (cm^{-1}) (-C≡C-)	
R	R'		
Me	Me	2255	2225 weaker
Me	Et	2250 weaker	2220
Me	i-Pr	2270 weaker	2220
Me	CH_3-CH=CH	2295 weaker	2240
Me	CH_2=C(CH_3)	2295 weaker	2230
Me	t-Bu	2285 weaker	2225
Me	ØCH2	2285 weaker	2235
Me	Ø	2285 weaker	2230
CH_2=C(CH_3)	Me	2215	2195 weaker
t-Bu	Me	2250 equal	2220 equal
t-Bu	t-Bu	2230	2200 weaker
t-Bu	Ø	2235 weaker	2215
Ø	Me	-	2205
Ø	Et	2230 weaker	2200
Ø	i-Pr	2225 equal	2205 equal
Ø	CH_3-CH=CH	2235 equal	2215 equal
Ø	CH_2=C(CH_3)	2220	2205 weaker
Ø	t-Bu	2245 weaker	2225
Ø	ØCH2	-	2230
Ø	Ø	-	2200

TABLE II

NUCLEAR MAGNETIC RESONANCE (NMR) SPECTRA OF α-ACETYLENIC ALCOHOLS (R-C≡C-CHOH-R')

COMPOUND		^{1}H-NMR(δ UNITS) (ppm)		
R	R'	R	CH	R'
Me	Me	1.9 (CH_3)(doublet)	4.5 (mult.)	1.4(CH_3)(doublet)
Me	Et	1.9 (CH_3)(doublet)	4.4 (mult.)	1.0(CH_3)(triplet)
				1.7(CH_2)(mult.)
Me	i-Pr	1.9 (CH_3)(doublet)	4.2 (mult.)	1.0$(CH_3)_2$(doublet)
				1.8(CH)(mult.)
Me	CH3-CH=CH	1.9 (CH_3)(doublet)	4.8 (mult.)	1.8(CH_3)(mult.)
				5.8(CH=CH)(mult.)
Me	CH_2=C(CH_3)	2.0 (CH_3)(doublet)	5.0 (mult.)	1.9(CH_3)(mult.)
				5.2 and 5.5 (CH_2=)(2 mult.)
Me	t-Bu	2.1 (CH_3)(doublet)	4.5 (quartet)	1.1$(CH_3)_3$(singlet)
Me	ØCH_2	1.8 (CH_3)(doublet)	4.6 (mult.)	3.0(CH_2)(doublet)
				7.4(Ø)(singlet)
Me	Ø	1.8 (CH_3)(doublet)	5.4 (quartet)	7.4(Ø)(mult.)

TABLE II (CONTINUED)

R	R'	R	CH	R'
$CH_2=C(CH_3)$	Me	1.9 (CH_3)(mult.)	4.7 (quartet)	1.5(CH_3)(doublet)
		5.3$(CH_2=)$(mult.)		
t-Bu	Me	1.2 $(CH_3)_3$(singlet)	4.4 (quartet)	1.4(CH_3)(doublet)
t-Bu	t-Bu	1.2 $(CH_3)_3$(singlet)	3.9 (singlet)	1.0$(CH_3)_3$(singlet)
t-Bu	Ø	1.2 $(CH_3)_3$(singlet)	5.3 (singlet)	7.3(Ø)(mult.)
Ø	Me	7.3(?)(Ø)(mult.)	4.7(?)(quartet)	1.4(?)(CH_3)(doublet)
Ø	Et	7.5 (Ø)(mult.)	4.7 (triplet)	1.1(CH_3)(triplet
				1.8(CH_2)(mult.)
Ø	i-Pr	7.6 (Ø)(mult.)	4.5 (doublet)	1.1$(CH_3)_2$(mult.)
				2.0(CH)(mult.)
Ø	CH_3-CH=CH	7.7 (Ø)(mult.)	5.4 (mult.)	1.8(CH_3)(mult.)
				6.1(CH=CH)(mult.)
Ø	$CH_2=C(CH_3)$	7.6 (Ø)(mult.)	5.2 (mult.)	2.0(CH_3)(mult.)
				5.3 and 5.5 $(CH_2=)$(2 mult.)
Ø	t-Bu	7.4 (Ø)(mult.)	4.3 (singlet)	1.1$(CH_3)_3$(singlet)

TABLE II(CONTINUED)

R	R'	R	CH	R'
Ø	$ØCH_2$	7.3 (Ø)(mult.)	4.8 (triplet)	3.1(CH_2)(doublet)
				7.3(Ø)(singlet)
Ø	Ø	7.6(?)(Ø)(mult)	4.9(?)(singlet)	7.6(?)(Ø)(mult.)

α-Acetylenic Ketones

The oxidation of the α-acetylenic alcohols to α-acetylenic ketones is significantly affected by substituents at the triple bond. The acetylenic alcohol R-C≡C-CHOH-R' where R is an alkyl group gives much higher yields of ketones than when R is aromatic and conjugated with the triple bond. This has been explained by the fact that the triple bond, and thus a Ø-ring conjugated with it, takes an active part in the oxidative mechanism of the secondary alcoholic group.[34]

It has also been reported that acetylenic alcohols with electron-accepting substituents at the reaction center (R') are oxidized to ketones very slowly and principally undergo cleavage at the triple bond. This has been attributed to the fact that there is always a large excess of oxidizing agent present in the reaction medium that tends to attack the triple bond.[34] Since the method of oxidation used in the present study protects against cleavage due to a large excess of oxidizing agent, high yields were observed for most of the compounds studied.

The ketones could not be separated from traces of alcoholic starting material by distillation as confirmed by infrared spectra.[18,34] Thus,when necessary, reoxidation to remove the alcohol impurity was carried out. This reoxidation tended to cut down yields appreciably in these cases.

An excess of chromic acid was used in all cases but the reaction time had to be varied to suit the reactivity of the various alcohols being oxidized. No comprehensive study was made of reactivities, but in general bulky groups such as R' = t-Bu slowed down the oxidation and thus these sterically hindered alcohols had to be oxidized for a greater

length of time.

It has been reported that when alcohol CH_3-C≡C-CHOH-CH=CH-CH_3 is oxidized with chromic anhydride in acid medium, isomerization takes place and a mixture of ketones is obtained.[21] By the oxidation technique used in the present study this same alcohol gave the corresponding ketone $CH_3C{\equiv}C$-CO-CH=CH-CH_3 in 73% yield with little or no isomerization. The oxidation can be carried out using active manganese dioxide instead of chromic acid yielding the same ketone as determined by IR and NMR.[21] Ketones of the type R-C≡C-CO-C(CH_3)=CH_2 where R is a methyl or phenyl group undergo polymerization on storage.

The infrared spectra of the α-acetylenic ketones are characterized by very intense absorption bands at 1660-1675 cm^{-1} (C=O) for aliphatic substituents adjacent to the carbonyl and at 1625-1650 cm^{-1} for aromatic or unsaturated substituents conjugated with the carbonyl group. There is also a very intense band at 2200-2230 cm^{-1} (-C≡C-). The infrared spectral data for the α-acetylenic ketones are summarized in Table III. There is usually a weaker absorption band close to the main acetylenic band for α-acetylenic ketones as is the case for the α-acetylenic alcohols. This has been attributed either to combination, isotopic effects or to Fermi resonance if this band is as intense as the main band.[18] The main band usually falls at 2220 $cm^{-1}$for those compounds with R = alkyl groups and the replacement of R by a phenyl ring produces a displacement of 20 cm^{-1} towards lower wave numbers for the (C≡C) main absorption band. When R' is also replaced by a phenyl ring a further shift toward lower wave numbers is usually observed.[18] A few of the ketones had not one but two weak bands in addition to the main acetylenic absorption band.

The carbonyl band of the α-acetylenic ketones is not affected to any noticeable extent when alkyl substituents adjacent to the triple bond are replaced by a phenyl ring or a conjugated unsaturated group. However, it has been reported that the extinction coefficient ϵ does increase to a considerable extent with extending conjugation.[18] α-Acetylenic ketones of the type R-C≡C-CO-C(R")=CH-R"' where R, R", R"' can be H, alkyl or aryl groups, have doublets for their carbonyl peaks.[21]

The NMR spectra of the α-acetylenic ketones are summarized in Table IV and are in complete accord with the structures expected for these ketones. Table V summarizes the UV spectra of these ketones as well. α,β-Acetylenic ketones are now known to have low-lying n-π^* excited triplet states.[35,36] This is characterized by their oxetane forming photochemical reactions. Absorption maxima at approximately 290 to 310 mμ in 95% ethanol were observed in the UV spectra of several of the acetylenic ketones studied. The other acetylenic ketones studied had that portion of the UV spectrum masked by the strongly absorbing π-π^* transitions.[37] These n-π^* maxima are also summarized in Table V.

TABLE III

INFRARED SPECTRA OF α-ACETYLENIC KETONES (R-C≡C-CO-R')

COMPOUND		INFRARED (cm^{-1})			
R	R'	(C≡C)			(C=O)
Me	Me	2280 weaker	2250 weaker	2220	1670
Me	Et		2260 weaker	2225	1675
Me	i-Pr		2220	2150 weaker	1670
Me	CH_3-CH=CH	2270 weaker	2225	2130 weaker	1645 1628
Me	CH_2=C(CH_3)		2230		1640 1625
Me	t-Bu		2225	2090 weaker	1665
Me	ØCH_2		2220		1670
Me	Ø		2250 equal	2210 equal	1640
CH_2=C(CH_3)	Me		2200	2150 weaker	1675
t-Bu	Me		2220	2180 weaker	1675
t-Bu	t-Bu	2230 weaker	2205	2175 weaker	1670
t-Bu	Ø		2210		1640
Ø	Me		2203	2130 weaker	1665
Ø	Et		2200		1675
Ø	i-Pr		2203		1670
Ø	CH_3-CH=CH		2220		1647 1625
Ø	CH_2=C(CH_3)		2210		1640 1628
Ø	t-Bu		2200	2165 weaker	1663
Ø	ØCH_2		2203		1663
Ø	Ø		2210		1635

TABLE IV

NUCLEAR MAGNETIC RESONANCE (NMR) SPECTRA OF α-ACETYLENIC KETONES

COMPOUND (R-C≡C-CO-R')		^{1}H NMR(δ UNITS) (ppm)	
R	R'	R	R'
Me	Me	2.0 (CH_3)(singlet)	2.3(CH_3)(singlet)
Me	Et	2.1 (CH_3)(singlet)	1.1(CH_3)(triplet)
			2.6(CH_2)(quartet)
Me	i-Pr	2.0 (CH_3)(singlet)	1.1(CH_3)$_2$(doublet)
			2.5(CH)(septet)
Me	CH_3-CH=CH	2.1 (CH_3)(singlet)	2.0(CH_3)(mult.)
			6.2 and 7.3(CH=CH)(2 mult.)
Me	CH_2=C(CH_3)	2.3 (CH_3)(singlet)	2.0(CH_3)(mult.)
			6.4 and 6.9(CH_2=)(2 mult.)
Me	t-Bu	2.0 (CH_3)(singlet)	1.1(CH_3)$_3$(singlet)
Me	ØCH$_2$	2.0 (CH_3)(singlet)	3.9(CH_2)(singlet)
			7.4(Ø)(singlet)
Me	Ø	2.1 (CH_3)(singlet)	7.5 and 8.1(Ø)(2 mult.)
CH_2=C(CH_3)	Me	2.0 (CH_3)(mult.)	2.4(CH_3)(singlet)
		5.7 (CH_2=)(mult.)	
t-Bu	Me	1.3(CH_3)$_3$(singlet)	2.2(CH_3)(singlet)
t-Bu	t-Bu	1.3(CH_3)$_3$(singlet)	1.1(CH_3)$_3$(singlet)
t-Bu	Ø	1.4(CH_3)$_3$(singlet)	7.5 and 8.1(Ø)(2 mult.)
Ø	Me	7.3 (Ø)(mult.)	2.3(CH_3)(singlet)
Ø	Et	7.4 (Ø)(mult.)	1.2(CH_3)(triplet)
			2.6(CH_2)(quartet)

TABLE IV(CONTINUED)

R	R'	R	R'
Ø	i-Pr	7.6 (Ø)(mult.)	1.3(CH_3)$_2$(doublet)
			2.7(CH)(septet)
Ø	CH_3-CH=CH	7.8(Ø)(mult.)	2.1(CH_3)(mult.)
			6.5 and 7.6(CH=CH)(2 mult.)
Ø	CH_2=C(CH_3)	7.8 (Ø)(mult.)	2.0(CH_3)(mult.)
			6.3 and 6.8 (CH_2=)(2 mult.)
Ø	t-Bu	7.6 (Ø)(mult.)	1.3(CH_3)$_3$(singlet)
Ø	ØCH_2	8.1 (Ø)(mult.)	4.2(CH_2)(singlet)
			8.1(Ø)(singlet)
Ø	Ø	7.5 (Ø)(mult.)	7.4 and 8.1(Ø)(2 mult.)

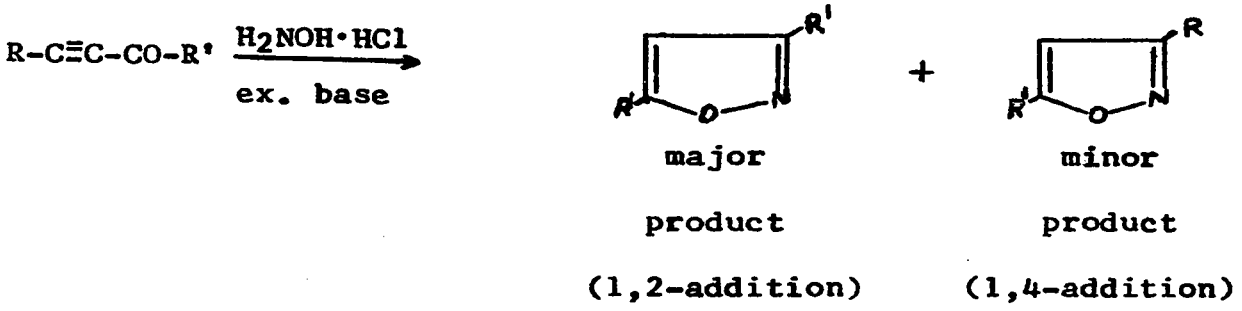
TABLE V

ULTRAVIOLET ABSORPTION SPECTRA OF α-ACETYLENIC KETONES IN 95% ETHANOL

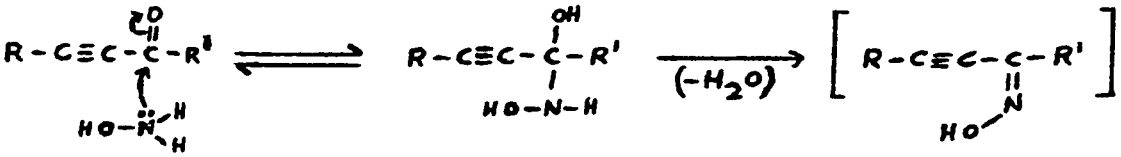
Compound (R-C≡C-CO-R')		UV			
R	R'	λmax(mμ)	ε	λmax(mμ)	ε
Me	Et	219.5	5100	shoulder at approx. 290 mμ	
Me	i-Pr	219.5	6200	292.0	45
Me	$CH_2=C(CH_3)$	225.5	7800	-	-
		shoulder at approx. 245 mμ			
Me	t-Bu	219.5	6300	306.5	40
Me	$ØCH_2$	207.5	9200	-	-
		shoulder at 220 mμ			
Me	Ø	261.5	13,600	-	-
$CH_2=C(CH_3)$	Me	258.0	7900	-	-
		shoulder at approx. 220 mμ			
t-Bu	Me	221.0	8200	299.5	25
t-Bu	t-Bu	222.0	5900	308.5	38
t-Bu	Ø	262.5	14,800	-	-
Ø	Me	273.5	10,000	-	-
Ø	Et	273.0	14,000	-	-
Ø	i-Pr	274.0	13,400	-	-
Ø	$CH_2=C(CH_3)$	227.5	13,000	-	-
		296.0	11,000		
Ø	t-Bu	274.0	14,600	-	-
Ø	Ø	223.0	12,600	-	-
		295.0 and 301.5	18,600		
		shoulder at approx. 275 mμ			

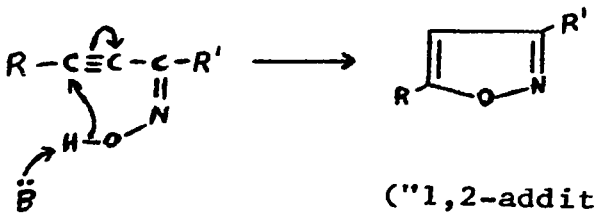
Reactions of Hydroxylamine with α-Acetylenic Ketones—Isoxazole Formation

α-Acetylenic ketones react with hydroxylamine in base to form 3,5-disubstituted isoxazoles:

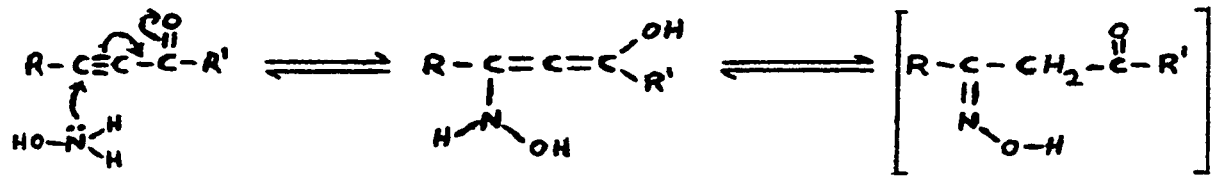


where R ≠ R'. Of course, when R = R' only one product is obtained whether the 1,2-addition or 1,4-addition or both mechanisms occur. The 1,2-addition mechanism is the usual mechanism for saturated ketone oximation and leads to an α-acetylenic oxime intermediate.

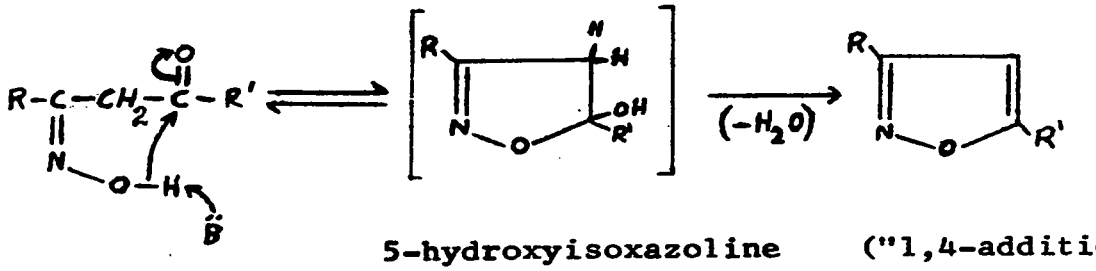




The 1,4-addition mechanism, however, leads to a β-diketone mono-oxime and a 5-hydroxyisoxazoline intermediate.



("1,4-addition") β-diketone mono-oxime intermediate



5-hydroxyisoxazoline intermediate ("1,4-addition product")

Both 1,2- and 1,4-addition occurred in base for many of the ketones studied. However, separation of the isomeric isoxazoles is difficult in all cases and impossible by methods available today for many cases. The physical constants for the isomers are very similar, differing only slightly or not at all in boiling point, melting point, refractive index, rf value using TLC, retention time on a gas chromatographic column, UV, IR, etc.[13,14] Thus, if a mixture occurs there is little hope of separating the two isomers and obtaining each pure. If the pure isomers are required the only hope is either to find the proper reaction conditions that give only one isomer or to use another method of synthesis which eliminates this problem.

In order to determine when mixtures of the two isomeric isoxazoles occurred and their ratio, the NMR spectroscopic method was

used.[13] The chemical shift difference for the protons in the 4-position of the isomeric isoxazoles was sufficient to determine when mixtures occurred and from the relative peak areas for the 4-protons a quantitative estimation of the two isomers was possible. 3-Methyl-5-phenylisoxazole and 5-methyl-3-phenylisoxazole have been fully characterized in the literature[38] and their melting points are different. Each of the two isomers was independently synthesized by unequivocal methods. Comparison of the NMR spectra of the two isomers indicated clearly the chemical shift difference for the proton in the 4-position. It was also observed that the coupling constant between the 4-H and the 5-Me protons was approximately 1 Hz. while that between the 4-H and the 3-Me was practically nil. This coupling behavour was found to be quite general and hence this additional criterion could be used in establishing the identity of an unknown isoxazole with suitable substituents. Further evidence for the identities of the isomers of the methylphenylisoxazoles was obtained from the mass spectrometric fragmentation patterns of the two isomers (see page35).

It was found that in aqueous alcoholic sodium hydroxide Ø-C≡C-CO-Me yielded exclusively 3-methyl-5-phenylisoxazole (the "1,2-addition product",) while MeC≡C-CO-Ø yielded approximately 70% 3-phenyl-5-methylisoxazole (the "1,2-addition product") and 30% of 3-methyl-5-phenylisoxazole (the "1,4-addition product") as determined by NMR. The 1,4-product impurity in the latter case had little effect on the melting point of the mixture. In fact the mixture melted sharply and at the same temperature as did pure 3-phenyl-5-methylisoxazole. This lack of depression in the melting point of isoxazole mixtures is common and has led to the inability to detect isomeric impurities in the isoxazole

products before the advent of NMR spectroscopy. Thus the 3,5-disubstituted isoxazoles that were obtained from α-acetylenic ketones in earlier work could easily have been contaminated with isomeric isoxazoles in large quantities without being detected. Since products and product ratios which were obtained in the past are in doubt, the mechanisms and factors affecting the reaction of α-acetylenic ketones with hydroxylamine which were concluded from these results are therefore also open to criticism.

Using the isomeric methylphenylisoxazoles as a guideline, the major products obtained from the other α-acetylenic ketones with hydroxylamine in basic solution should also be due to 1,2-addition. The ratio of the two isomers and their identities were established by employing the NMR method described above. In order to obtain absolute proof as to the assignment, some of these isoxazoles were prepared by an unequivocal method and the NMR spectra of these compounds checked.

Thus, the NMR method coupled with melting point assignments, mass spectral data, and independent syntheses were deemed sufficient for the unequivocal establishment of the structures of the isomeric 3,5-disubstituted isoxazoles and the determination of their ratios in a given reaction.

The 3,5-disubstituted isoxazoles were obtained from α-acetylenic ketones by refluxing them with a slight excess of hydroxylamine hydrochloride in an approximately 50% aqueous alcoholic solution usually containing a two molar excess of sodium hydroxide. The results obtained under these conditions are summarized in Table VI, as determined by the NMR spectroscopic method.

Since the reaction of α-acetylenic ketones with hydroxylamine hydrochloride was carried out in base to form 3,5-disubstituted isoxazoles, other side reactions such as condensation were possible. Those compounds with hydrogens α to the carbonyl group could undergo aldol condensation and thus reduce the yield of isoxazole. This is reflected by the yields shown in Table VI where the highest yields are for acetylenic ketones where R' = tertiary group and the lowest yields are where R' = Me group.

The ratio of % 1,2-addition to % 1,4-addition is affected by steric factors. If R is a bulky group and R' a small group, only 1,2-addition seems to occur. However, if R' is a bulky group whether R is large or small, there is always a mixture of products resulting from both 1,2- and 1,4-additions.

No isoxazole products could be isolated from the reaction of α-acetylenic ketones with R' = propenyl or isopropenyl groups. For these compounds 1,4-addition involving the double bond as well as the triple bond can occur and thus yield isoxazolines among other products.

In an attempt to produce pure 3-phenyl-5-methylisoxazole from tetrolophenone (CH_3-C≡C-CO-Ø), the reaction conditions were varied to see if 1,4-addition could be eliminated. These results are summarized in Table VII. In Table VIII are the results for 2,2-dimethyl-4-hexyn-3-one.

When the basicity is increased the ratio of 1,2- to 1,4-additon is increased as can be seen from Tables VII and VIII. On the other hand as the reaction mixture is made more acid with acetic acid, 1,4-addition begins to predominate. By using highly basic conditions 1,4-addition almost can be eliminated with tetrolophenone but not with

2,2-dimethyl-4-hexyn-3-one. This is probably due to the greater steric hindrance of a t-butyl group compared to a phenyl ring.

In the past, 1,2-addition and 1,4-addition were explained on the basis of electronic effects alone.[12] With the methods available then it was impossible to know whether the isoxazole obtained was a single isomer or a mixture of the two isomers. In most cases the purity was established exclusively from melting points and this could be misleading. Electronic effects probably play a part in determining product ratios but this remains to be seen. Studies using phenyl substituted α-acetylenic ketones with electron-donating and electron-withdrawing groups on the rings would give a good indication as to whether electronic effects actually do affect the product ratios.

TABLE VI

$$R\text{-}C{\equiv}C\text{-}CO\text{-}R' + H_2NOH \xrightarrow{OH^-} \text{isoxazole(s)}$$

R	R'	% total yield of isoxazoles based on ketones	% 1,2-addition	% 1,4-addition
Me	Me	< 2	-	-
Me	Et	18	100	0
Me	i-Pr	48	90	10
Me	CH_3-CH=CH-	?	-	-
Me	CH_2=C(CH_3)-	?	-	-
Me	t-Bu	66	74	26
Me	ØCH_2	42	100	0
Me	Ø	64	86	14
CH_2=C(CH_3)	Me	14	100	0
t-Bu	Me	24	100	0
t-Bu	t-Bu	84	-	-
t-Bu	Ø	90	78	22
Ø	Me	17	100	0
Ø	Et	44	100	0
Ø	i-Pr	55	> 98	< 2
Ø	CH_3CH=CH	?	-	-
Ø	CH_2=C(CH_3)	?	-	-
Ø	t-Bu	76	83	17
Ø	ØCH_2	40	100	0
Ø	Ø	72	-	-

TABLE VII

$CH_3-C\equiv C-CO-\phi \xrightarrow{H_2NOH\cdot HCl}$ methylphenylisoxazoles

REACTION CONDITIONS						YIELDS		
moles of ketone	moles of $H_2NOH\cdot HCl$	type and moles of acid or base		ml. H_2O	ml. EtOH	% total yield based on ketone	% 1,2-addition	% 1,4-addition
0.025(acid imp.)	0.025	NaOH	0.075	30	30	-	68	32
0.025	0.035	NaOH	0.050	30	30	34	86	14
0.025	0.035	NaOH	0.075	33	30	22	85	15
0.025	0.035	NaOH	0.125	35	30	64	86	14
0.025	0.035	NaOH	0.250	40	30	58	89	11
0.0086	0.050	NaOH	0.50	20	30	0	-	-
0.025	0.050	NaOAc	0.050	50	30	73	17	83
0.0086	0.050	HOAc	0.525	0	0	51	33	67
0.0086	0.050	HOAc	0.525	30	0	59	30	70
		NaOAc	0.050					
0.0086	0.050	KOH	0.41	0	100	33	100	0
0.029	0.10	KOH	0.36	0	100	-	91	9
0.0086	0.05	KOH	0.41	0	100	33	>98	<2

TABLE VIII

$CH_3-C\equiv C-CO-t-Bu \xrightarrow{H_2NOH\cdot HCl}$ t-butylmethylisoxazoles

REACTION CONDITIONS						YIELDS		
moles of ketones	moles of $H_2NOH\cdot HCl$	type and moles of base		ml. H_2O	ml. EtOH	% total yield based on ketone	% 1,2-addition	% 1,4-addition
0.03	0.04	NaOH	0.15	36	30	66	74	26
0.03	0.10	KOH	0.36	0	100	70	82	18
0.03	0.10	KOH	0.50	0	500	53	84	16
0.0086	0.05	KOH	0.41	0	100	50	87	13
0.012	0.08	KOH	1.8	0	500	39	92	8
0.01	0.05	Et_3N	0.03	40	0	0	-	-

3, or 5-Monosubstituted and 3,5-Disubstitued Isomeric Isoxazoles

The NMR spectra of the isoxazoles are summarized in Table IX. The peak assignments were made on the basis of long range coupling constants as mentioned previously (see page 27). For those cases where no coupling is possible such as 3,5-di-t-butylisoxazole the peaks could not be assigned.

The NMR coupling between the 5-alkyl groups and the 4-hydrogen was found to be general for 3,5-disubstituted isoxazoles and the coupling constant was found to be approximately 1.0 Hz. No coupling was observed between 3-alkyl groups and the 4-hydrogen for all the cases studied. 5-Phenylisoxazole has a coupling constant between the 3-hydrogen and 4-hydrogen of approximately 2.0 Hz., while 5-methylisoxazole gives a more complicated spectrum since the 5-methyl group is coupled to both the 4-H and the 3-H. The 3-H,4-H coupling in isoxazole is similar.[79]

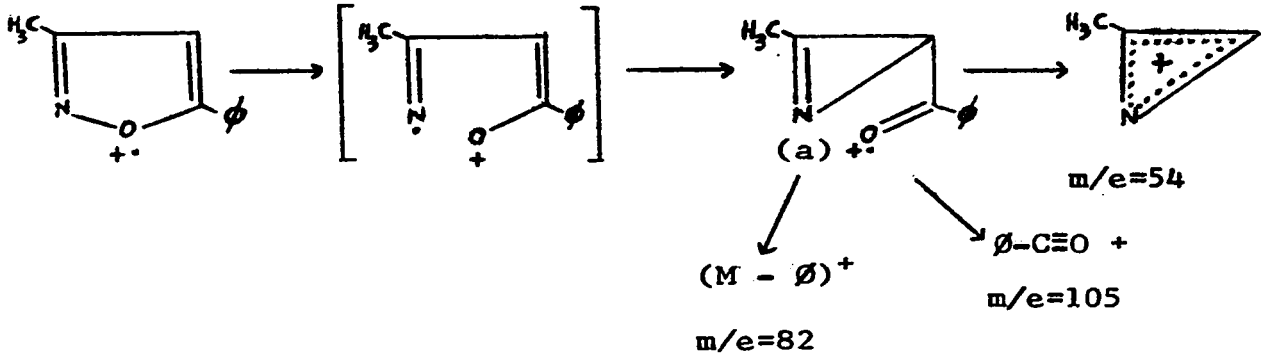
The NMR coupling constants of 3,5-disubstituted isoxazoles are analogous to those of 2-or 3-substituted furans.[39]

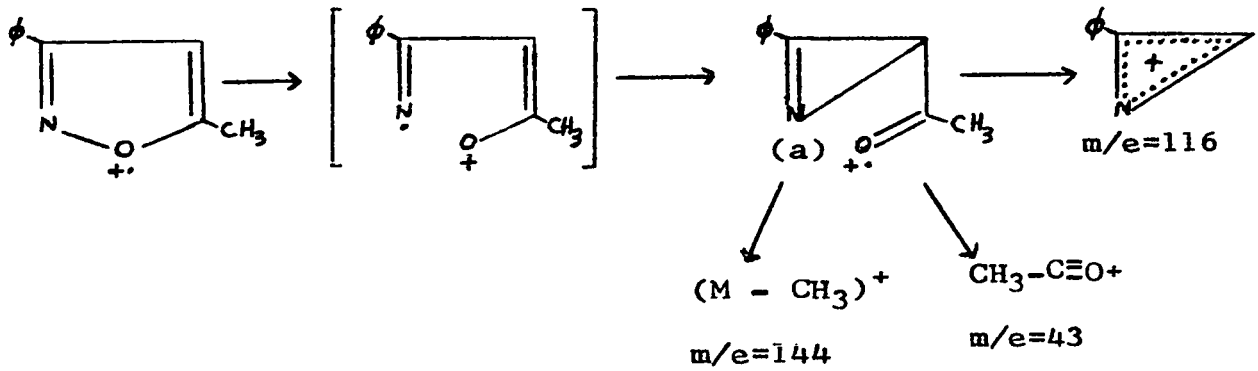
The ultraviolet absorption spectra of the 3,5-disubstituted isoxazoles are summarized in Table X. The λmax for those isoxazoles with a phenyl ring in the 5-position is shifted to longer wave lengths than for those with a phenyl ring in the 3-position. This shift occurs because of greater conjugation in the 5-position than in the 3-position for isoxazoles.[40,41]

The IR spectra of some isoxazoles have been studied intensively.[42] The infrared spectrum of a compound containing the isoxazole ring can be broken down into vibrational modes of the ring which fall in the 2000-800 cm^{-1} region. Thus ring stretching and breathing modes can be assigned to specific absorption peaks in the spectrum. However, these frequency

assignments are dependent upon substituents on the ring and thus the absorption peaks can only be assigned arbitrarily for the isoxazoles studied. For this reason, no attempt has been made to assign any peaks even though the infrared spectra of most of the compounds fitted well with the previous assignments. Three of the compounds were the same as those studied previously[42] and their infrared spectra were very similar to the others.

The mass spectra of two isomeric 3,5-disubstituted isoxazoles were run in order to verify the previous assignment of structures. 3-Methyl-5-phenylisoxazole and 5-methyl-3-phenylisoxazole gave a cracking pattern which can be interpreted easily according to the mechanism proposed recently for isoxazoles.[43]





The mass spectra of the two isomers tend to support this scheme. The peak at m/e=144 is negligible for 3-methyl-5-phenylisoxazole but it is the peak with the strongest relative abundance for 5-methyl-3-phenylisoxazole.

TABLE IX

NUCLEAR MAGNETIC RESONANCE (NMR) SPECTRA OF ISOXAZOLES

COMPOUND  ^{1}H NMR (δ UNITS) (ppm)

R	R'	R(5)	4-H	R'(3)
Me	H	2.4(CH_3)(mult.)	5.9(mult.)	8.0(mult.)(H)
Me	Me	2.3(CH_3)(doublet)	5.7(quartet)	2.2 (CH_3)(singlet)
Me	Et	2.3(CH_3)(doublet)	5.8(quartet)	1.2(CH_3)(triplet)
				2.6(CH_2)(quartet)
Me	i-Pr	2.4(CH_3)(doublet)	6.0(quartet)	1.3(CH_3)$_2$ (doublet)
				3.0(CH)(septet)
Me	t-Bu	2.4(CH_3)(doublet)	6.0(quartet)	1.3(CH_3)$_3$(singlet)
Me	ØCH$_2$	2.2(CH_3)(doublet)	5.6(quartet)	3.8(CH_2)(singlet)
				7.1(Ø)(singlet)
Me	Ø	2.4(CH_3)(doublet)	6.2(quartet)	7.3 and 7.7(Ø)
				(2 mult.)
CH_2=C(CH_2)	Me	2.1(CH_3)(mult.)	6.2(singlet)	2.3(CH_3)(singlet)
		5.3 and 5.8(CH_2=)(2 mult.)		
CH_2=C(CH_3)	t-Bu	2.0(CH_3)(mult.)	6.0(singlet)	1.3(CH_3)$_3$(singlet)
		5.2 and 5.7(CH_2=)(2 mult.)		
t-Bu	Me	1.3(CH_3)$_3$(singlet)	5.7(singlet)	2.2(CH_3)(singlet)
t-Bu	t-Bu	1.3(?)(CH_3)$_3$(singlet)	5.8(singlet)	1.3(?)(CH_3)$_3$
				(singlet)
t-Bu	Ø	1.4(CH_3)$_3$(singlet)	6.3(singlet)	7.5 and 7.5 (Ø)
				(2 mult.)
Ø	H	7.3 and 7.7(Ø)(2 mult.)	6.4(doublet)	8.1(H)(doublet)
Ø	Me	7.4 and 7.7(Ø)(2 mult.)	6.3(singlet)	2.3(CH_3)(singlet)

TABLE IX (CONTINUED)

R	R'	R(5)	4-H	R'(3)
Ø	Et	7.3 and 7.7(Ø)(2 mult.)	6.3(singlet)	1.3(CH_3)(triplet) 2.7(CH_2)(quartet)
Ø	i-Pr	7.3 and 7.7(Ø)(2 mult.)	6.4(singlet)	1.3$(CH_3)_2$(doublet) 3.1(CH)(septet)
Ø	t-Bu	7.5 and 7.9(Ø)(2 mult.)	6.7(singlet)	1.4$(CH_3)_3$(singlet)
Ø	ØCH_2	7.3 and 7.6(Ø)(2 mult.)	6.1(singlet)	3.9(CH_2)(singlet) 7.2(Ø)(singlet)
Ø	Ø	7.4 and 7.8(Ø)(2 mult.)	6.9(singlet)	7.4 and 7.8 (Ø) (2 mult.)

TABLE X

ULTRAVIOLET ABSORPTION SPECTRA OF ISOXAZOLES

COMPOUND

U.V.

R	R'	Solvent	λ Max (mμ)	ε
Me	H	EtOH	216.5	5300
Me	Me	H_2O	216.0	5900
Me	Et	H_2O	216.0	6200
Me	i-Pr	H_2O	216.5	6100
Me	t-Bu	H_2O	216.0	6200
Me	$ØCH_2$	H_2O	209.5*	11,500
		EtOH	210.5*	12,400
Me	Ø	EtOH	240.0	17,200
$CH_2=C(CH_3)$	Me	EtOH	248.0	13,100
$CH_2=C(CH_3)$	t-Bu	EtOH	248.0	14,500
t-Bu	Me	H_2O	217.0	5900
t-Bu	t-Bu	H_2O	217.0	6600
t-Bu	Ø	EtOH	240.5	14,400
Ø	H	EtOH	261.0	18,900
Ø	Me	EtOH	261.5	20,800
Ø	Et	EtOH	264.0	16,200
Ø	i-Pr	EtOH	261.0	17,200
Ø	t-Bu	EtOH	261.0	20,500
Ø	$ØCH_2$	EtOH	264.0	21,000
			212.0	13,200
Ø	Ø	EtOH	244.5 267.0	20,200 23,800

*Shoulder at 217 mμ

α-Acetylenic Oximes

α-Acetylenic oximes have been postulated as intermediates in the 1,2-addition mechanism of hydroxylamine to α-acetylenic ketones but have never been isolated.[3-6] Only two α-acetylenic aldoximes seem to be known. Tetrolaldehyde oxime was prepared from tetrolaldehyde diethyl acetal by the method of L. Claisen.[8] Phenylpropiolic aldehyde oxime[7] was prepared from phenylpropiolaldehyde diethyl acetal by an analogous method. These α-acetylenic aldoximes were prepared in an attempt to check the configuration of the hydroxyl group. The hydroxyl group of the α-acetylenic oximes has been assigned a syn (to triple bond) configuration[3] since the oxime readily cyclized to the isoxazole but no unequivocal assignment has been made as yet.

α-Acetylenic ketoximes have been prepared for the first time using the general method of Palazzo[16] as slightly modified by Feuer and Markofsky.[13] This involves the reaction of hydroximyl chlorides with acetylenic Grignard reagents($R-C\equiv C-MgX$) at 0° C. and subsequent decomposition of the Grignard product with 10% H_2SO_4 or saturated ammonium chloride solution. Instead of further treatment with base to form the isoxazole, the mixture was worked up yielding the α-acetylenic oxime.

$$R-C\equiv C-MgBr + R-C(Cl)=NOH \xrightarrow{0^{\circ}\ C.} R-C\equiv C-C(R')=NOH$$

α-acetylenic oxime

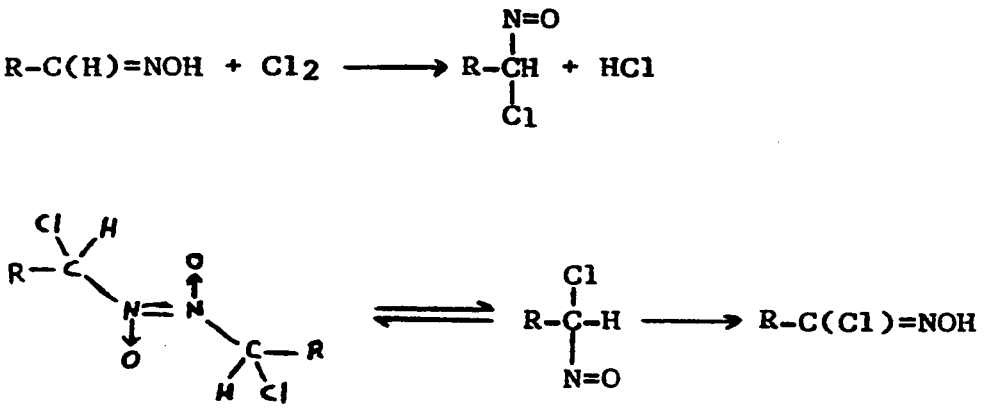
The method gives good yields and seems to be quite general[44] but problems occur if purification of someof the isolated oximes is required. The α-acetylenic ketoximes tend to cyclize on distillation or sublimation. When eluted on an alumina chromatographic column they also tend to cyclize to the corresponding isoxazoles.

Preparation of Aldoximes (for hydroximyl chlorides)

The aliphatic aldoximes were prepared by the method of Wieland[45] from the respective aldehydes and hydroxylamine hydrochloride in aqueous base at 0° C. Trimethylacetaldoxime was prepared by a method of Vogel[46] using aqueous alcohol and sodium acetate rather than base since trimethylacetaldehyde is almost insoluble in water. Benzaldehyde oxime was also prepared by a method of Vogel.[47] The configuration of the aldoximes as well as the amounts of syn- and anti-isomers were determined by NMR. The aldehyde hydrogen of the aldoxime is at higher field in the NMR for the anti (to H) than for the syn (to H) isomer.[48] In dilute dimethyl sulfoxide solution separate signals for the hydroxyl protons can be observed in the NMR for a mixture of syn and anti oximes, the anti (to H) hydroxyl proton being at lower field than in the syn (to H) hydroxyl proton.[49] These chemical shifts were demonstrated to be concentration independent.

Hydroximyl Chlorides (Acyl Chloride Oximes)

The hydroximyl chlorides were prepared from aldoximes by passing chlorine gas through a dilute hydrochloric acid solution of the oxime of 0° C. for approximately 15 minutes.[45,50] The configuration of the hydroximyl chlorides was not determined since NMR studies of the chemical shift of the hydroxyl proton in dimethyl sulfoxide for this series of compounds have not been undertaken as yet. Also the reaction to form the hydroximyl chlorides has been postulated to pass through a chloro-nitroso intermediate[76] and therefore the question of retention of configuration in the final product is subject to criticism.



α-Acetylenic Ketoximes

The infrared spectra of the α-acetylenic ketoximes are summarized in Table XI. The solution spectra of the α-acetylenic ketoximes are also characterized by their very intense absorption bands at approximately 3600 cm^{-1} (free OH stretching) and 3300 cm^{-1} (intermolecularly hydrogen bonded OH stretching).

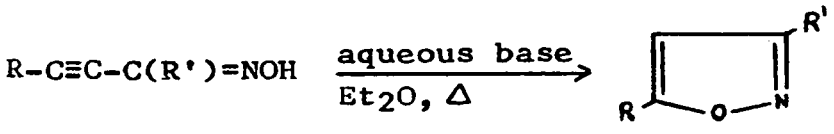
The NMR spectra of the α-acetylenic ketoximes are summarized in Table XII. The chemical shift of the OH proton in carbon tetrachloride (not given in the table) varied from 9.8-10.0 ppm.[49] The NMR spectra were also run on 5% w/w dimethyl sulfoxide solutions of the α-acetylenic ketoximes. Most simple oximes and many containing an additional functional group exhibit a hydroxyl proton resonance signal whose chemical shift value is essentially concentration independent and thus characteristic of the particular oxime.[49] Since oximes with the hydoxyl group <u>syn</u> to the t-butyl group are virtually unknown,[49] the α-acetylenic ketoximes of the type R-C≡C-C(t-BU)=NOH must have their OH <u>anti</u> to the t-butyl group (i.e. <u>syn</u> to the triple bond). Further work[44] has indicated that α-acetylenic ketoximes in general have the OH most probably <u>syn</u> to the triple bond. This is indicated by the ease of cyclization to the corresponding isoxazole and also by

NMR spectra in dilute dimethyl sulfoxide solution where the chemical shift of the hydroxyl proton falls within a narrow range.

The ultraviolet absorption spectra of the α-acetylenic ketoximes are summarized with Table XIII. There is a shift of λmax to longer wave lengths and an increase in extinction coefficients for the α-acetylenic oximes as compared to the corresponding isoxazoles. This shift is similar to that observed for α-ethylenic oximes as compared to the corresponding isoxazoles.[40]

Cyclization of α-Acetylenic Ketoximes to the Isoxazoles

The α-acetylenic ketoximes were cyclized to the corresponding isoxazoles by using a dilute aqueous base-ether two phase system with refluxing. If the reaction is carried out in alcoholic KOH, the reaction proceeds almost explosively with CH_3-C≡C-C(t-Bu)=NOH.



Only one isoxazole was obtained which corresponded to the 1,2-product in the hydroxylamine reaction with R-C≡C-CO-R' as determined by the NMR spectra. Since the α-acetylenic ketoximes can be isolated and their structures determined and since the cyclization reaction is a straightforward reaction, this method of preparation of 3,5-disubstituted isoxazoles can be regarded as an unequivocal synthesis and thus this method of formation can be used as structural proof for the isomer produced.[51]

α-Acetylenic Aldoximes

The syntheses of both the known α-acetylenic aldoximes were carried out and the products demonstrated to be authentic. The diethyl acetals of tetrolaldehyde and phenylpropiolaldehyde were prepared and subsequently reacted with hydroxylamine hydrochloride and a trace of hydrochloric acid at 25° C. to form the corresponding α-acetylenic aldoximes.[7,8,52]

$$CH_3\text{-}CH{=}CH\text{-}CHO + Br_2 \longrightarrow CH_3\text{-}CHBr\text{-}CHBr\text{-}CHO \xrightarrow{KOAc} CH_3\text{-}CH{=}C(Br)\text{-}CHO$$

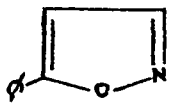
$$CH_3\text{-}CH{=}C(Br)CHO \xrightarrow[EtOH]{HC(OEt)_3} CH_3\text{-}CH{=}C(Br)\text{-}CH(OEt)_2$$

$$CH_3\text{-}CH{=}C(Br)\text{-}CH(OEt)_2 \xrightarrow[EtOH]{KOH} CH_3\text{-}C{\equiv}C\text{-}CH(OEt)_2$$

$$CH_3\text{-}C{\equiv}C\text{-}CH(OEt)_2 \xrightarrow[HCl,H_2O]{H_2NOH\cdot HCl} CH_3\text{-}C{\equiv}C\text{-}C(H){=}NOH \xrightarrow{\Delta}$$

$$\text{Ø-}C{\equiv}C\text{-}MgBr \xrightarrow{HC(OEt)_3} \text{Ø-}C{\equiv}C\text{-}CH(OEt)_2$$

$$\text{Ø-}C{\equiv}C\text{-}CH(OEt)_2 \xrightarrow[HCl,EtOH,H_2O]{H_2NOH\cdot HCl} \text{Ø-}C{\equiv}C\text{-}C(H){=}NOH \xrightarrow{\Delta}$$



The temperature of the oximation reaction must remain low since heating causes cyclization of the α-acetylenic oxime product to the corresponding isoxazole.

The NMR spectra of the two diethyl acetals are summarized in

Table XIV. The methylene protons of acetals are magnetically non-equivalent and the chemical shift difference between them was approximately 0.07 ppm in both cases.[27, 52] Long range coupling was also observed between the methyl hydrogens adjacent to the triple bond and the methine proton adjacent to the oxygens in tetrolaldehyde diethyl acetal. The coupling constant was approximately 2.0 Hz.[32,52]

The NMR spectra of the α-acetylenic aldoximes are summarized in Table XV. The spectra were also run using 5% w/w dimethyl sulfoxide solutions of the α-acetylenic aldoximes. As was the case with α-acetylenic ketoximes the OH proton resonance of the α-acetylenic aldoximes was diagnostic of a configuration with OH <u>syn</u> to the triple bond. Long range coupling was observed in tetrolaldoxime with a coupling constant of approximately 2.0 Hz.[32]

The infrared absorption spectra of the α-acetylenic aldoximes are summarized in Table XVI. The solution infrared spectra of the α-acetylenic aldoximes are also characterized by their very intense absorption bands at approximately 3580 cm^{-1}(free OH stretching) and a doublet at approximately 3290 and 3210 cm^{-1} (intermolecularly hydrogen bonded OH stretching).

The ultraviolet absorption spectra of the α-acetylenic aldoximes are summarized in Table XVII. As was the case with α-acetylenic ketoximes there is a shift of λmax to longer wave length and an increase in ε for α-acetylenic aldoximes as compared to the corresponding isoxazoles.[40] <u>Trans</u>-cinnamaldehyde oxime has a λmax at 288 mμ and 5-phenylisoxazole has a λmax at 260 mμ. However phenylpropiolic aldehyde oxime has a λmax at 275.5 mμ with a shoulder at 292.0 mμ.

TABLE XI

INFRARED SPECTRA OF ∝-ACETYLENIC KETOXIMES (R-C≡C-C(R')=NOH)

COMPOUND		INFRARED (cm^{-1})		
R	R'	(C≡C)		(C=N)
Me	t-Bu	2238	2170 weaker	1595
$CH_2=C(CH_3)$	t-Bu	2208	2180 weaker	1610
ø	t-Bu	2220	2178 weaker	1595

TABLE XII

NUCLEAR MAGNETIC RESONANCE (NMR) SPECTRA OF ∝-ACETYLENIC KETOXIMES

COMPOUND(R-C≡C-C(R')=NOH)		^1H NMR(δ UNITS) (ppm)		
R	R'	R	R'	OH*
Me	t-Bu	2.2(CH_3)(singlet)	1.2(CH_3)3(singlet)	11.2(singlet)
$CH_2=C(CH_3)$	t-Bu	2.0(CH_3)(mult.) 5.5 and 5.6(CH_2=) (2 mult.)	1.3(CH_3)3(singlet)	11.2(singlet)
ø	t-Bu	7.5 and 7.7 (ø) (2 mult.)	1.3(CH_3)$_3$(singlet)	11.6(singlet)

*Solvent dimethyl sulfoxide 5% w/w solution.

TABLE XIII

ULTRAVIOLET ABSORPTION SPECTRA OF α-ACETYLENIC KETOXIMES(R-C≡C-C(R')=NOH)

COMPOUND		U.V.	
R	R'	λmax (mμ)	ε
Me	t-Bu	226.0	8,800
$CH_2=C(CH_3)$	t-Bu	258.0	11,200
Ø	t-Bu	273.5	17,500

TABLE XIV

NUCLEAR MAGNETIC RESONANCE (NMR) SPECTRA OF α-ACETYLENIC ACETALS

COMPOUND (R-C≡C-CH(OEt)$_2$)		1H NMR (δ UNITS)(ppm)		
R	R	CH	CH_2	CH_3
Me	1.9(CH_3)(doublet)	5.2(quartet)	3.7(mult.)	1.2(triplet)
Ø	7.3(Ø)(mult.)	5.4(singlet)	3.7(mult.)	1.2(triplet)

TABLE XV

NUCLEAR MAGNETIC RESONANCE (NMR) SPECTRA OF α-ACETYLENIC ALDOXIMES

COMPOUND (R-C≡C-CH=NOH)		^{1}H NMR(δ UNITS)(ppm)	
R	R	CH	OH*
Me	2.1(CH_3)(doublet)	6.9(quartet)	11.7(singlet)
Ø	7.5(Ø)(mult.)	7.2(singlet)	12.1(singlet)

*Solvent dimethyl sulfoxide 5% w/w solution.

TABLE XVI

INFRARED ABSORPTION SPECTRA OF α-ACETYLENIC ALDOXIMES(R-C≡C-CH=NOH)

COMPOUND	λmax(cm^{-1})	
R	(C≡C)stretching	(C=N)stretching
Me	2230	1607
Ø	2210 2170	1605

TABLE XVII

ULTRAVIOLET ABSORBANCE SPECTRA OF α-ACETYLENIC ALDOXIMES(R-C≡C-CH=NOH)

COMPOUND	U.V.	
R	λmax(mμ)	ε
Me	228.0	9400
Ø	275.5	19,500
	292.0	15,500

EXPERIMENTAL

Reagents and Chemicals:- The reagents and chemicals used in the present study were obtained from various commercial sources as indicated below:

Aldrich Chemical Co., Inc., Milwaukee, Wisconsin: phenylacetylene, phenylacetaldehyde, isopropenylacetylene

Allied Chemicals Canada, Ltd.: cadmium chloride, potassium acetate, benzaldehyde

Anachemia Chemicals Ltd., Montreal, Quebec: sodium sulfate anhydrous

British Drug Houses (Canada) Limited: hydroxylamine hydrochloride, sodium acetate anhydrous

Canadian Laboratory Supplies Limited(Matheson Coleman and Bell): bromoethane, sodium dichromate dihydrate, acetaldehyde, iso-butyraldehyde, crotonaldehyde, methacrylaldehyde, triethyl orthoformate

Fisher Scientific Co., Ltd. (Eastman): magnesium, anhydrous diethyl ether, molecular sieve, propionaldehyde, phosphorus pentachloride, paraffin oil, hydroxylamine hydrochloride, alumina chromatographic grade

K & K Laboratories, Inc., Plainview, N. Y.: phenylacetylene, pivaldehyde, pinacolone

Mallinckrodt Chemical Works Ltd., Pointe Claire, Quebec: ammonium chloride, chloroform, carbon tetrachloride, calcium chloride anhydrous

Matheson of Canada Limited, Whitby, Ontario: methylacetylene, chlorine, hydrogen chloride, carbon dioxide

Most reagents were freshly distilled or recrystallized before use.

Melting Points and Boiling Points: All melting points and boiling points reported are uncorrected. Melting points were taken on a Gallenkamp MF-370, and/or Mettler FP 1 instrument.

IR and UV Spectra: All IR spectra were obtained using a Perkin-Elmer Model 137 spectrometer and a Beckman IR-8 double-beam recording spectrometer with sodium chloride optics. UV spectra were recorded on a Cary 14 instrument using 95% Ethanol or H_2O as solvents.

Mass Spectra: Mass spectra reported herein were taken on a Perkin-Elmer Hitachi Model #RMU-6E, single focussing instrument by Dr. T. J. Adley of this Department.

Elemental Analyses: Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York and by Dr. R. T. Rye of this Department using an F & M Model 185 CHN Analyser.

NMR Spectra: All NMR spectra were recorded by the author using a Varian A-60A spectrometer on undegassed samples (either as neat liquids or as solutions in CCl_4, $CDCl_3$ or dimethylsulfoxide). All chemical shifts are expressed in ppm relative to tetramethylsilane (TMS) used as an internal standard. Spin-spin coupling constants were measured from spectra recorded at 50 Hz. sweep widths.

Preparation of α-Acetylenic Alcohols

A one liter 3-necked flask was fitted with mechanical stirrer, efficient reflux condenser, dropping funnel, and drying tube and contained 300 mmoles of ethyl magnesium bromide in 300 ml. of anhydrous diethyl ether (prepared from 370 mmoles of ethyl bromide and 300 mmoles of magnesium). To this was added 300 mmoles of the appropriate acetylene and the mixture allowed to stir with gentle refluxing for 3

hours until a lower layer separated. When the acetylene was a gas an excess of it was allowed to bubble through—approximately 250 ml./min. for 2-3 hours—and a Dewar condenser with crushed Dry Ice was used. A solution of the appropriate aldehyde (290 mmoles) was then added slowly at room temperature and the mixture then was refluxed for one hour. After decomposition of the resulting Grignard reagent with saturated ammonium chloride solution, the aqueous layer was extracted with diethyl ether and the ether layers combined. The combined ether layers were washed with saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The ether was removed by distillation by means of a steam bath and the crude product was distilled under reduced pressure. The infrared and NMR spectra of the alcohols are summarized in Tables I and II respectively(p.14 and p.15). t-Bu-C≡C-CHOH-t-Bu can be considered as a representative sample (IR Spectrum No. 1 ; NMR Spectrum No. 1). The UV spectrum of CH_3-C≡C-CHOH-t-Bu was recorded in 95% ethanol and gave a λmax at 219.0 mμ with an extinction coefficient ϵ of 3400. Using water as solvent the same compound gave λmax at 222.5 mμ and an ϵ of 3100.

The following alcohols were prepared:-

<u>3-pentyl-2-ol</u>: $CH_3C{\equiv}C\text{-}CHOH\text{-}CH_3$;[53] yield = 60% based on Mg;
b.p. = 67-73° at 35 mm.

<u>4-hexyn-3-ol</u>: $CH_3\text{-}C{\equiv}C\text{-}CHOH\text{-}CH_2CH_3$;[54] yield - 72% based on Mg;
b.p. = 70-90° at 22 mm.

<u>2-methyl-4-hexyn-3-ol</u>: $CH_3\text{-}C{\equiv}C\text{-}CHOH\text{-}CH(CH_3)_2$;[55] yield = 80% based on Mg;
b.p. = 76-83° at 17 mm.

<u>2-heptene-5-yn-4-ol</u>: $CH_3\text{-}C{\equiv}C\text{-}CHOH\text{-}CH{=}CH\text{-}CH_3$;[21] yield = 74% based on Mg;
b.p. = 52-60° at 1.7 mm.

2-methyl-1-hexene-4-yn-3-ol: $CH_3-C\equiv C-CHOH-C(CH_3)=CH_2$;
yield = 77% based on Mg; b.p. = 86-96° at 20 mm.

2,2-dimethyl-4-hexyn-3-ol: $CH_3-C\equiv C-CHOH-C(CH_3)_3$;[20]
yield = 78% based on Mg; b.p. = 90-99° at 50-65 mm.

1-phenyl-3-pentyn-2-ol: $CH_3-C\equiv C-CHOH-CH_2-\emptyset$;[55] yield = 91% based on Mg;
b.p. = 115-130° at 2.0 mm.

1-phenyl-2-butyn-1-ol: $CH_3-C\equiv C-CHOH-\emptyset$;[56] yield = 79% based on Mg;
b.p = 92-106° at 1.0 mm.

2-methyl-1-hexene-3-yn-5-ol: $CH_2=C(CH_3)-C\equiv C-CHOH-CH_3$;[57]
yield = 63% based on Mg; b.p. = 80 -92° at 50 mm.

5,5-dimethyl-3-hexyn-2-ol: $(CH_3)_3C-C\equiv C-CHOH-CH_3$;[58]
yield = 65 % based on Mg; b.p.= 35-60° at 1.6 mm.

2,2,6,6-tetramethyl-4-heptyn-3-ol: $(CH_3)_3C-C\equiv C-CHOH-C(CH_3)_3$
yield = 65% based on Mg; b.p.= 52-60° at 1.6 mm.;m.p.=39-41°(from Ligroin)

4,4-dimethyl-1-phenyl-2-pentyn-1-ol: $(CH_3)_3C-C\equiv C-CHOH-\emptyset$;[20]
yield = 54% based on Mg; b.p.= 100-110° at 1.9 mm.

4-phenyl-3-butyn-2-ol: $\emptyset-C\equiv C-CHOH-CH_3$;[59]
yield not calculated;crude product not distilled prior to oxidation

1-phenyl-1-pentyl-3-ol: $\emptyset-C\equiv C-CHOH-CH_2CH_3$;[60]
yield = 61% based on Mg; b.p. = 113-120° at 1.6 mm.

4-methyl-1-phenyl-1-pentyn-3-ol: $\emptyset-C\equiv C-CHOH-CH(CH_3)_2$; [34]
yeild = 78% based on Mg; b.p. = 113-121° at 2.0 mm.

1-phenyl-4-hexene-1-yn-3-ol: $\emptyset-C\equiv C-CHOH-CH=CH-CH_3$;[61]
yield = 57% based on Mg; b.p.= 140-146° at 1.5 mm.

2-methyl-5-phenyl-1-pentene-4-yn-3-ol: $\emptyset-C\equiv C-CHOH-C(CH_3)=CH_2$;[61]
yield=60% based on Mg; b.p. = 120-126° at 1.5 mm.

4,4-dimethyl-1-phenyl-1-pentyn-3-ol: $\emptyset-C\equiv C-CHOH-C(CH_3)_3$;[62]
yield = 60% based on Mg; b.p. = 109-112° at 2.0 mm.

1,4-diphenyl-3-butyn-2-ol: Ø-C≡C-CHOH-CH_2-Ø;[63]

yield = 67% based on Mg; b.p. = 155-166° at 0.4 mm.

1,3-diphenyl-2-propyn-1-ol: Ø-C≡C-CHOH-Ø;[56]

yield not calculated; crude product not distilled prior to oxidation

Preparation of α-Acetylenic Ketones

A 500 ml. 3-necked flask was fitted with mechanical stirrer, thermometer, and dropping funnel and contained 100 mmoles of the appropriate α-acetylenic alcohol and 150 ml. of diethyl ether. To this was added dropwise 100 mmoles of chromic acid solution (prepared from 100 mmoles of sodium dichromate dihydrate and 22.3 ml. (400 mmoles) of sulfuric acid and diluted to 161 ml. with water). The temperature of the reaction mixture was maintained throughout the reaction between 25 and 30° C. After stirring for a minimum of two hours (longer for sterically hindered alcohols) the two layers were separated and the water layer extracted with diethyl ether. The ether extracts were combined with the ether layer and washed with 10% sodium bicarbonate solution until neutral and finally washed with saturated sodium chloride solution. The combined ether layer was dried over anhydrous sodium sulfate and the ether removed by distillation by means of a steam bath. If all the acetylenic alcohol was oxidized to the ketone as determined by IR, then the crude ketone was distilled under reduced pressure. If not the crude ketone containing the unreacted alcohol was reoxidized with more chromic acid solution as described and worked up as usual.

The infrared, NMR, and UV spectra of the acetylenic ketones are summarized in Tables III, IV, and V respectively (pp.21,22 and 24).

The following ketones were prepared:-

3-pentyn-2-one: $CH_3-C\equiv C-CO-CH_3$;[64] yield = 62% based on alcohol; b.p. = 28-35° at 41 mm.

4-hexyn-3-one: $CH_3-C\equiv C-CO-CH_2CH_3$;[65] yield = 70% based on alcohol; b.p. = 64-73° at 21 mm.

2-methyl-4-hexyn-3-one: $CH_3-C\equiv C-CO-CH(CH_3)_2$; yield = 71% based on alcohol; b.p. = 70-77° at 19 mm.

2-heptene-5-yn-4-one: $CH_3-C\equiv C-CO-CH=CH-CH_3$;[21] yield = 73% based on alcohol; b.p. = 94-102° at 16 mm.

2-methyl-1-hexene-4-yn-3-one: $CH_3-C\equiv C-CO-C(CH_3)=CH_2$; yield = 69% based on alcohol; b.p. = 73-78° at 16 mm.

2,2-dimethyl-4-hexyn-3-one: $CH_3-C\equiv C-CO-C(CH_3)_3$; yield = 62% based on alcohol; b.p. = 73 - 81° at 35 mm.

1-phenyl-3-pentyn-2-one: $CH_3-C\equiv C-CO-CH_2-\emptyset$; yield = 61% based on alcohol; b.p.=97-103° at 1.9 mm.

1-phenyl-2-butyn-1-one;tetrolophenone: $CH_3-C\equiv C-CO-\emptyset$;[56] yield = 83% based on alcohol; b.p = 84-92° at 1.0 mm.

2-methyl-1-hexene-3-yn-5-one: $CH_2=C(CH_3)-C\equiv C-CO-CH_3$;[66] yield = 40% based on alcohol(reoxidized to remove traces of starting alcohol); b.p. = 60-68° at 45 mm.

5,5-dimethyl-3-hexyn-2-one: $(CH_3)_3C-C\equiv C-CO-CH_3$;[58] yield = 64% based on alcohol; b.p.=50-60° at 12 mm.

2,2,6,6-tetramethyl-4-heptyn-3-one: $(CH_3)_3C-C\equiv C-CO-C(CH_3)_3$; yield = 74% based on alcohol; b.p=52-60° at 1.5 mm.

4,4-dimethyl-1-phenyl-2-pentyn-1-one: $(CH_3)_3C-C\equiv C-CO-\emptyset$;[20] yield = 83% based on alcohol; b.p = 100-112° at 1.6 mm.

4-phenyl-3-butyn-2-one: $\emptyset-C\equiv C-CO-CH_3$;[67] yield = 50% based on Mg(alcohol not distilled prior to oxidation); b.p.=88-108° at 1.0 mm.

1-phenyl-1-pentyn-3-one: Ø-C≡C-CO-CH_2CH_3;[68]

yield = 42% based on alcohol(reoxidized to remove traces of starting alcohol); b.p. = 81-91° at 1.3 mm.

4-methyl-1-phenyl-1-pentyn-3-one: Ø-C≡C-CO-$CH(CH_3)_2$;[34]

yield = 56% based on alcohol; b.p.= 100-113° at 2.0 mm.

1-phenyl-4-hexene-1-yn-3-one: Ø-C≡C-CO-CH=CH-CH_3;[61]

yield = 55% based on alcohol; b.p. = 115-126° at 1.5 mm.

2-methyl-5-phenyl-1-pentene-4-yn-3-one: Ø-C≡C-CO-$C(CH_3)$=CH_2;[61]

yield = 52% based on alcohol; m.p.=47-48° (from ligroin).

4,4-dimethyl-1-phenyl-1-pentyn-3-one: Ø-C≡C-CO-$C(CH_3)_3$;

yield = 46% based on alcohol(reoxidized to remove traces of starting alcohol); b.p.=88-93° at 0.8 mm.

1,4-diphenyl-3-butyn-2-one: Ø-C≡C-CO-CH_2-Ø;[69]

yield = 26% based on alcohol(reoxidized to remove traces of starting alcohol); b.p.=165-175° at 0.8 mm.

1,3-diphenyl-2-propyn-1-one(3-phenylpropiolophenone): Ø-C≡C-CO-Ø;[70]

yield = 50% based on Mg(alcohol not distilled prior to oxidation); b.p.=160-172° at 1.5 mm.; m.p. = 46.5-47.0° (from ligroin).

Aldoximes

The yields and configuration of the aldoximes as well as the relative amounts of the *syn* and *anti* isomers as determined by NMR are summarized in Table XVIII.

TABLE XVIII

ALDOXIMES(R'-C(H)=NOH)

R'	% yield based on aldehyde	% syn(to H)	% anti (to H)
t-Bu	56	100	0
Me	53	40	60
i-Pr	63	75	25
$CH_2=C(CH_3)$	75	100*	
ø	83	100	0

*The configuration of this oxime has not been established.

Preparation of α-Acetylenic Ketoximes

A one liter 3-necked flask was fitted with mechanical stirrer, efficient reflux condenser, dropping funnel, and drying tube, and contained 300 mmoles of ethyl magnesium bromide in 300 ml. of anhydrous diethyl ether (prepared from 370 mmoles of ethyl bromide and 300 mmoles of magnesium). To this was added 300 mmoles of the appropriate acetylene and the mixture allowed to stir with gentle refluxing for 3 hours until a lower layer separated. The appropriate hydroximyl chloride (150 mmoles) in ether was then added slowly over a one hour period while maintaining the reaction mixture at 0^{o} C. The mixture was stirred for 5 more minutes and then 150 ml. of saturated ammonium chloride solution was carefully added to the mixture. The aqueous layer was extracted with ether. The combined ether layers were washed with saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The ether was removed by film evaporation at room temperature yielding an oil that crystallized on refrigeration.

The crude α-acetylenic oxime was recrystallized from ligroin (35-60°). In some cases the oil did not crystallize and only the crude product could be obtained.

The IR and NMR spectra of the α-acetylenic ketoximes are given in the Appendix (pp. 83-85 and pp. 72-74).

The following ketoximes were prepared:-

Oxime of 2,2-dimethyl-4-hexyn-3-one: $CH_3-C\equiv C-C(t\text{-}Bu)=NOH$; yield = 68% based on trimethylacetaldoxime; m.p. = 85-86° (from ligroin); Anal. calcd. based on $C_8H_{13}NO$, C=69.0%, H=9.41%, N=10.1%; found, C=69.6%, H=9.27%, N=9.91%

Oxime of 2,6,6-trimethyl-1-heptene-3-yn-5-one: $CH_2=C(CH_3)-C\equiv C-C(t\text{-}Bu)=NOH$; yield = 57% based on trimethylacetaldoxime; m.p.=47.2° (from ligroin)

Oxime of 4,4-dimethyl-1-phenyl-1-pentyn-3-one: $\text{Ø}-C\equiv C-C(t\text{-}Bu)=NOH$; yield = 42% based on trimethylacetaldoxime; m.p=101.5-102.5°

Preparation of α-Acetylenic Aldoximes from α-Acetylenic Acetals

The α-acetylenic oximes were prepared from the corresponding acetals according to the method of Claisen.[8] The IR and NMR spectra of these oximes are given in the Appendix.(pp.86-87 and.pp.75-76)

The following aldoximes were prepared:-

Tetrolaldehyde Oxime(Oxime of 2-butynal): $CH_3-C\equiv C-C(H)=NOH$;[8] m.p.= 98-99° (from benzene-ligroin)

3-phenylpropiolaldehyde Oxime (Oxime of 3-phenylpropynal): $\text{Ø}-C\equiv C-C(H)=NOH$;[7] yield = 66% based on α-acetylenic acetal; m.p=104.5-105.0°(from chloroform-ligroin).

Preparation of 3,5-Disubstituted Isoxazoles from α-Acetylenic Ketones

To a 100 mL flask fitted with reflux condenser and magnetic stirrer and cooled by an ice bath was taken the α-acetylenic ketone (30 mmoles) in 30 ml. of 95% ethanol. To a cold solution of 50 mmoles of NaOH in 30 ml. of water was slowly added hydroxylamine hydrochloride (40 mmoles) and the mixture stirred until solution was complete. This cold solution was then slowly added to the cold solution of the ketone and the resulting mixture stirred rapidly and gradually warmed up to room temperature. The mixture was then brought to reflux temperature by using a heating mantle. After refluxing for 2 hours the mixture was cooled in an ice bath. If no precipitate or oil formed the mixture was diluted with water. If a precipitate formed it was filtered by suction and then washed with water. The resulting crude isoxazole was then recrystallized from ligroin (35-60°)or chromatographed on alumina using ligroin (35-60°) as solvent. If no precipitate formed on dilution of the reaction mixture, it was extracted with ligroin (35-60°) and the combined ligroin extracts were washed with water. The solution was dried over anhydrous sodium sulfate and the ligroin removed by distillation by means of a steam bath leaving a crude oil. This oil was then distilled under reduced pressure to yield the isoxazole product.

Pure Isomers of Isoxazoles from α-Acetylenic Ketones:-

1. 3-ethyl-5-methylisoxazole: (from Me-C≡C-CO-Et);[13]
yield = 18%(reaction medium aqueous alcoholic base);b.p.=53° at 20 mm.

2. 3-benzyl-5-methylisoxazole:(from Me-C≡C-CO-CH_2-Ø);
yield = 42%(see 1); b.p.=112-113° at 2.5 mm.

3. 5-isopropenyl-3-methylisoxazole: (from $CH_2=C(CH_3)-C\equiv C-CO-Me$);[71]
yield=14%(see 1.); b.p.=88° at 50 mm.

4. 5-t-butyl-3-methylisoxazole: (from t-Bu-C≡C-CO-Me);[72]
yield=24%(see 1.); b.p.=66-67° at 27 mm.

5. 3,5-di-t-butylisoxazole: (from t-Bu-C≡C-CO-t-Bu);[73]
yield=84%(see 1.); m.p.= 96-97°

6. 3-methyl-5-phenylisoxazole:(from Ø-C≡C-CO-Me);[74]
yield=17% (see 1.); m.p. = 66.4°

7. 3-ethyl-5-phenylisoxazole: (from Ø-C≡C-CO-Et);[75]
yield = 44% (see 1.); b.p. = 115-120° at 2.0 mm.

8. 5-phenyl-3-isopropylisoxazole: (from Ø-C≡C-CO-i-Pr);[76]
yield = 55% (see 1.); b.p.=116-127° at 1.7 mm.

9. 3-benzyl-5-phenylisoxazole: (from Ø-C≡C-CO-CH_2-Ø);
yield = 40% (see 1.); m.p.=86.5°; Anal. calcd. based on $C_{16}H_{13}NO$,
C=81.7%, H=5.57%, N=5.95%; found, C=81.2%, H=5.29%, N=6.04%

10. 3,5-diphenylisoxazole: from Ø-C≡C-CO-Ø);[9]
yield = 72% (see 1.); m.p.=139-140°

11. 3,5-dimethylisoxazole:(from CH_3-C≡C-CO-CH_3);[77]
yield = 22% (powdered KOH and mineral oil used as reaction medium since this isoxazole is highly soluble in aqueous alcoholic base);
b.p.=140-143° at 760 mm.

12. 5-methyl-3-phenylisoxazole: (from CH_3-C≡C-CO-Ø);[74]
yield = 33% (alcoholic KOH used as reaction medium to minimize 1,4-addition); m.p.=41.6°

Preparation of 3,5-Disubstituted Isoxazoles from α-Acetylenic Oximes

The crude α-acetylenic oxime (17 mmoles) was dissolved in

20 ml. of diethyl ether and cooled in an ice bath. To this was added an ice-cold solution of 20 mmoles of NaOH in 20 ml. of water. The two-phase system was rapidly stirred by means of a magnetic stirrer and gradually warmed and finally refluxed for one hour. After cooling, the aqueous layer was extracted with ether. The combined ether layers were washed with water and dried over anhydrous sodium sulfate. The ether was removed by distillation by means of a steam bath yielding the crude isoxazole. The isoxazole if liquid was distilled under reduced pressure, or, if solid, recrystallized from ligroin (35-60°).

Pure Isomers of Isoxazoles from α-Acetylenic Oximes:-

13. 5-methyl-3-isopropylisoxazole: (from CH_3-C≡C-C(i-Pr)=NOH); yield = 47% based on isobutyraldoxime (reaction medium: aqueous base-ether); b.p.=75-77° at 40 mm.

14. 3-t-butyl-5-isopropenylisoxazole: (from CH_2=C(CH_3)-C≡C-C(t-Bu)=NOH); m.p.=34.6°;(see 13.)

15. 5-t-butyl-3-phenylisoxazole: (from t-Bu-C≡C-C(Ø)=NOH);[78] b.p.=161-165° at 3.0 mm.; m.p.=41.5-43.0°;(see 13)

16. 3-t-butyl-5-phenylisoxazole: (from Ø-C≡C-C(t-Bu)=NOH);[78] yield=60% based on acetylenic oxime (see 13.); m.p.=50-51°

17. 3-t-butyl-5-methylisoxazole:(from CH_3-C≡C-C(t-Bu)=NOH); yield=39% based on acetylenic oxime (reaction medium alcoholic KOH); b.p.=81-82° at 42 mm.

18. 5-methylisoxazole: (from CH_3-C≡C-C(H)=NOH);[8] (reaction medium: chloroform and aqueous potassium carbonate).

19. 5-phenylisoxazole: (from Ø-C≡C-C(H)=NOH);[7] (reaction medium: carbon tetrachloride and aqueous potassium carbonate).

The infrared spectra of several representative 3,5-disubstituted isoxazoles are reproduced in the Appendix(IR spectra Nos.4-6). The NMR spectra of the 3,5-disubstituted isoxazoles have been summarized in Table IX(p.37). Some typical NMR spectra are given in the Appendix (NMR Spectra Nos. 5 and 8). NMR spectrum No.4 is that of a mixture of the two isomers of the 3,5-disubstituted isoxazoles obtained from CH_3-C≡C-CO-t-Bu. The UV spectra of the 3,5-disubstituted isoxazoles are summarized in Table X (p.39).

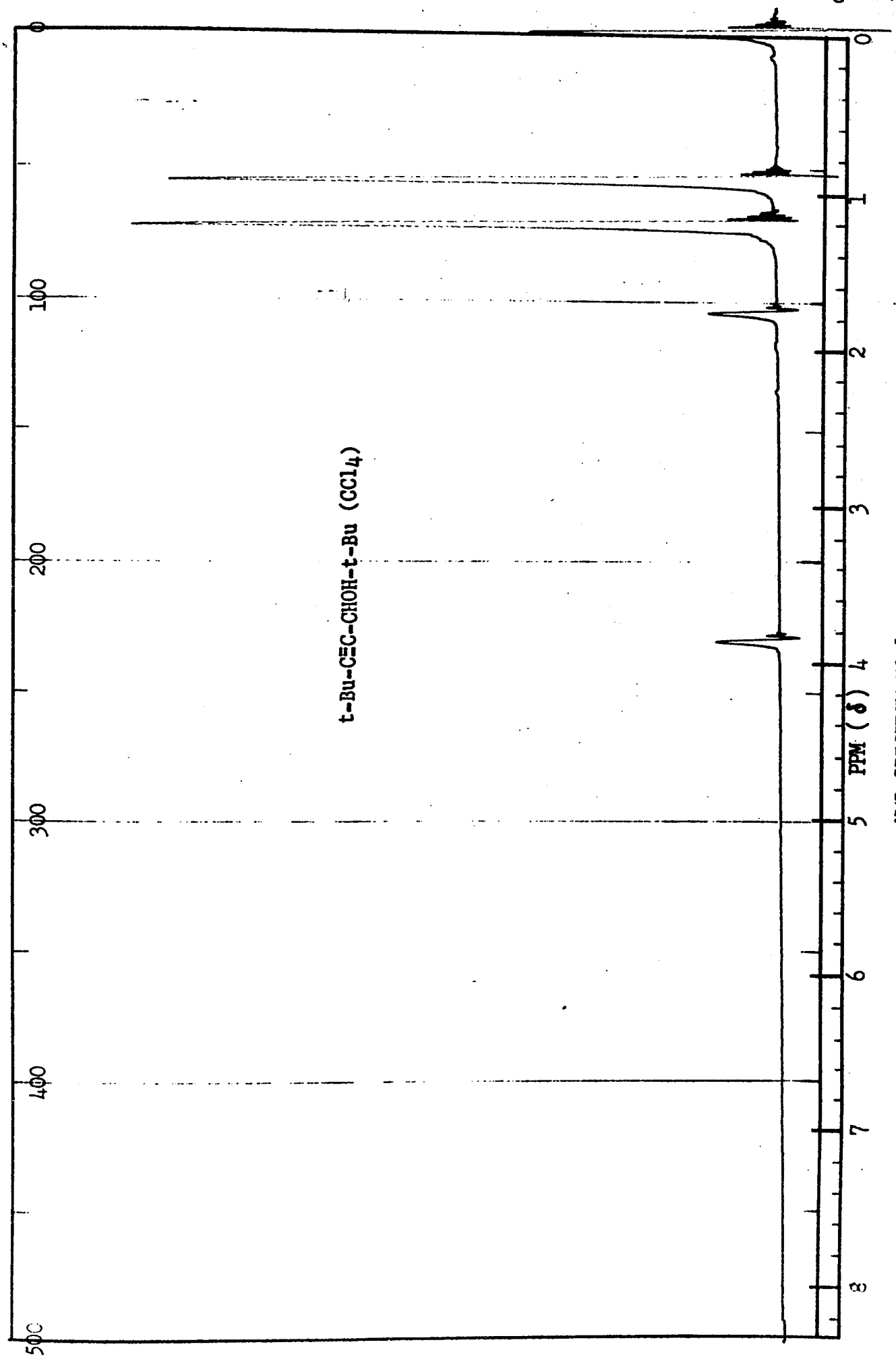
SUMMARY

The reaction of α-acetylenic ketones with hydroxylamine in base yields mainly isoxazoles formed by 1,2-addition, however, in the majority of cases some 1,4-addition product also is obtained. Steric factors were found to play an important part in determining the ratio of 1,2- to 1,4-addition. Further studies using phenyl substituted α-acetylenic ketones with electron-donating and electron-withdrawing groups on the rings would give a better indication as to whether electronic effects actually do affect the product ratios. Examination of the NMR spectra of the product isoxazoles led to a useful method for determining relative amounts of isomeric 3-5-disubstituted isoxazoles produced in a reaction.

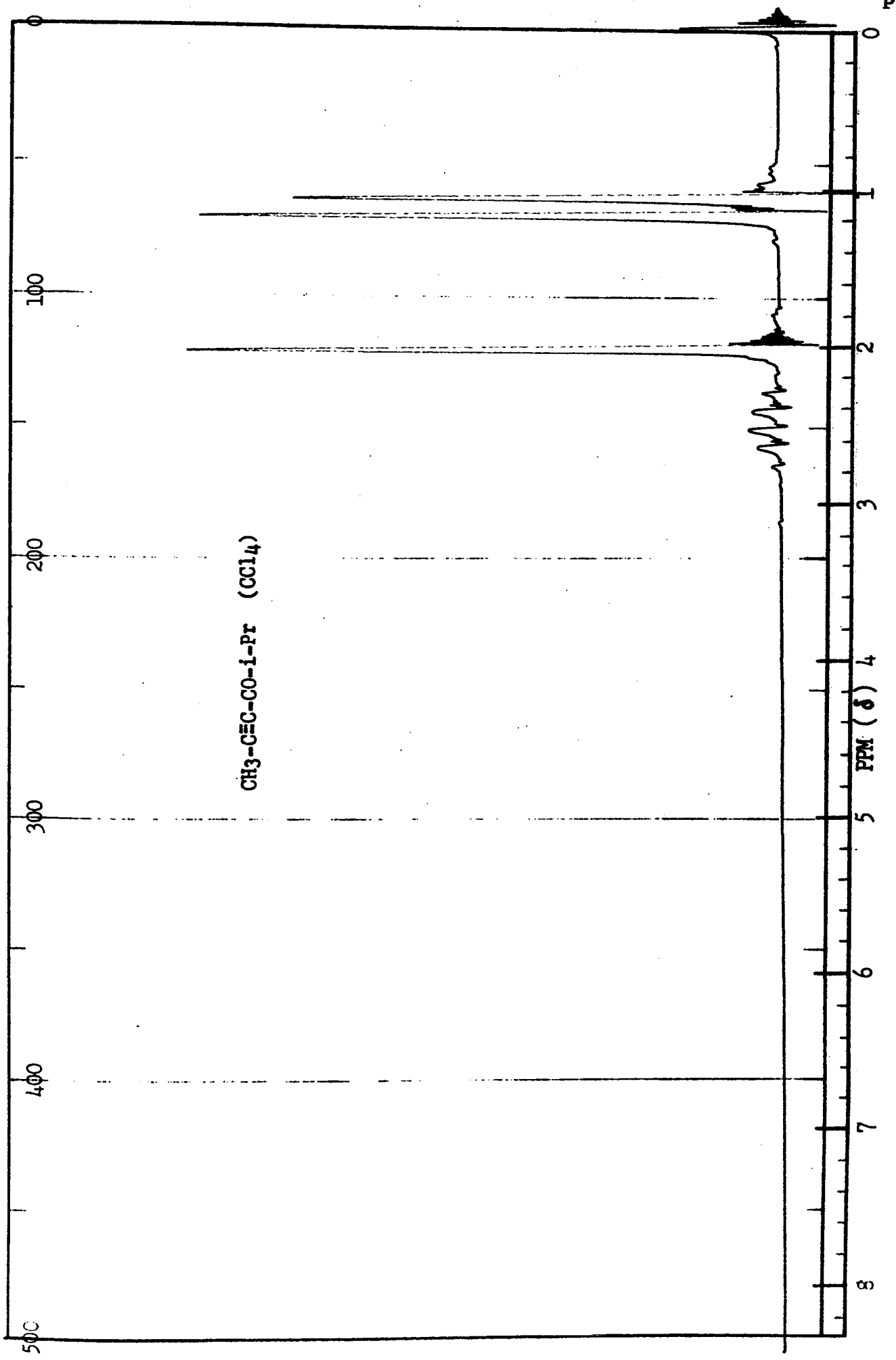
α-Acetylenic ketoximes which were only postulated as intermediates so far were isolated for the first time, and a general method for their preparation has been developed. α-Acetylenic oximes were cyclized independently using base catalysis to yield a single isoxazole in each case. Using this method isoxazoles which could not be obtained isomerically pure from α-acetylenic ketones were prepared. This method of preparation of 3,5-disubstituted isoxazoles can be regarded as an unambiguous synthesis of the particular isomer.

From chemical shift values (in dimethyl sulfoxide solutions) of the hydroxyl protons of the oximes, and from their ease of base catalyzed cyclizations to isoxazoles of known structure as well as from other evidence it is concluded that in these oximes the hydroxyl groups are syn to the triple bonds. However, additional work in this area is indicated to unambiguously establish their configurations.

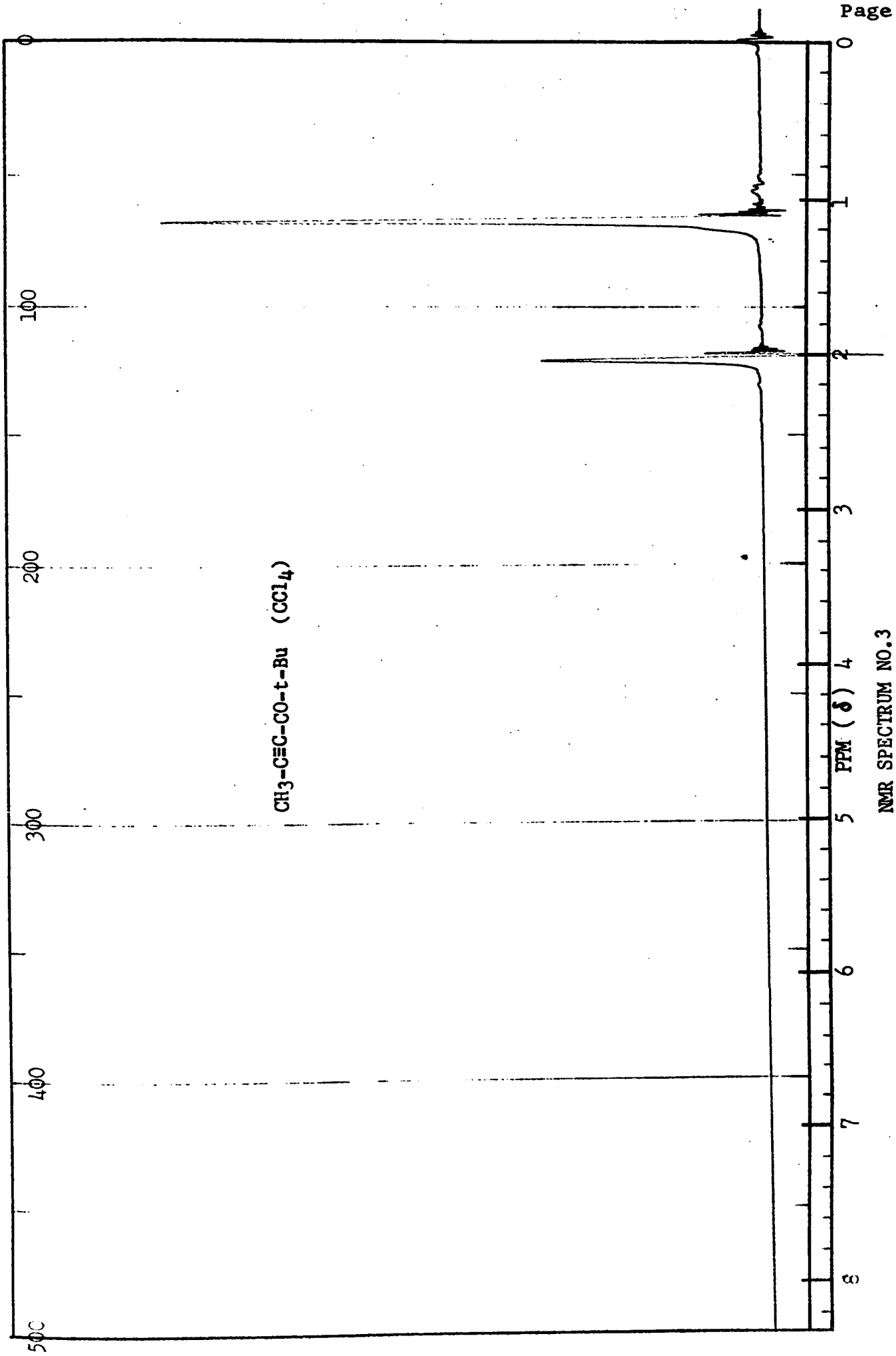
APPENDIX



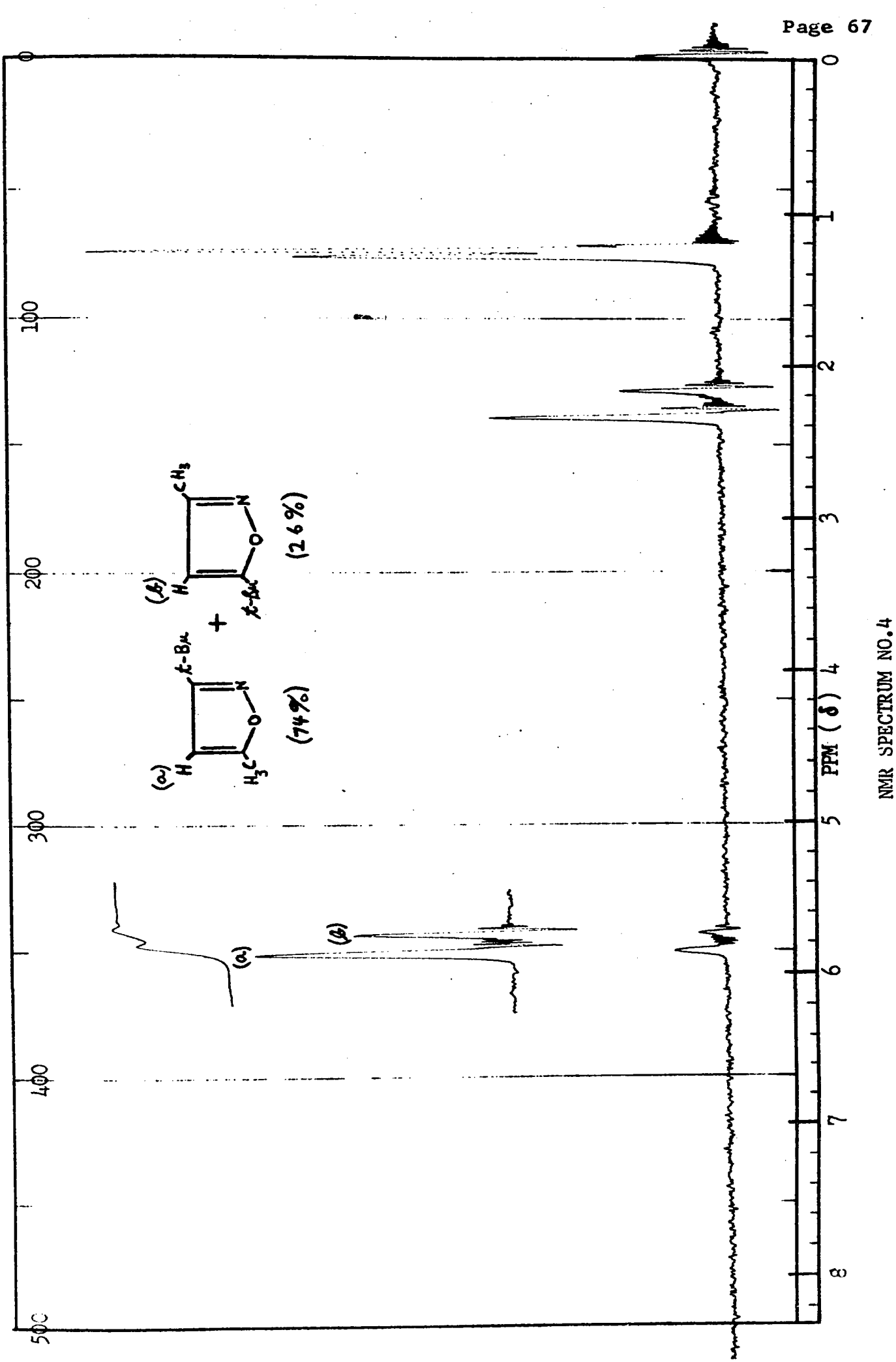
NMR SPECTRUM NO.1



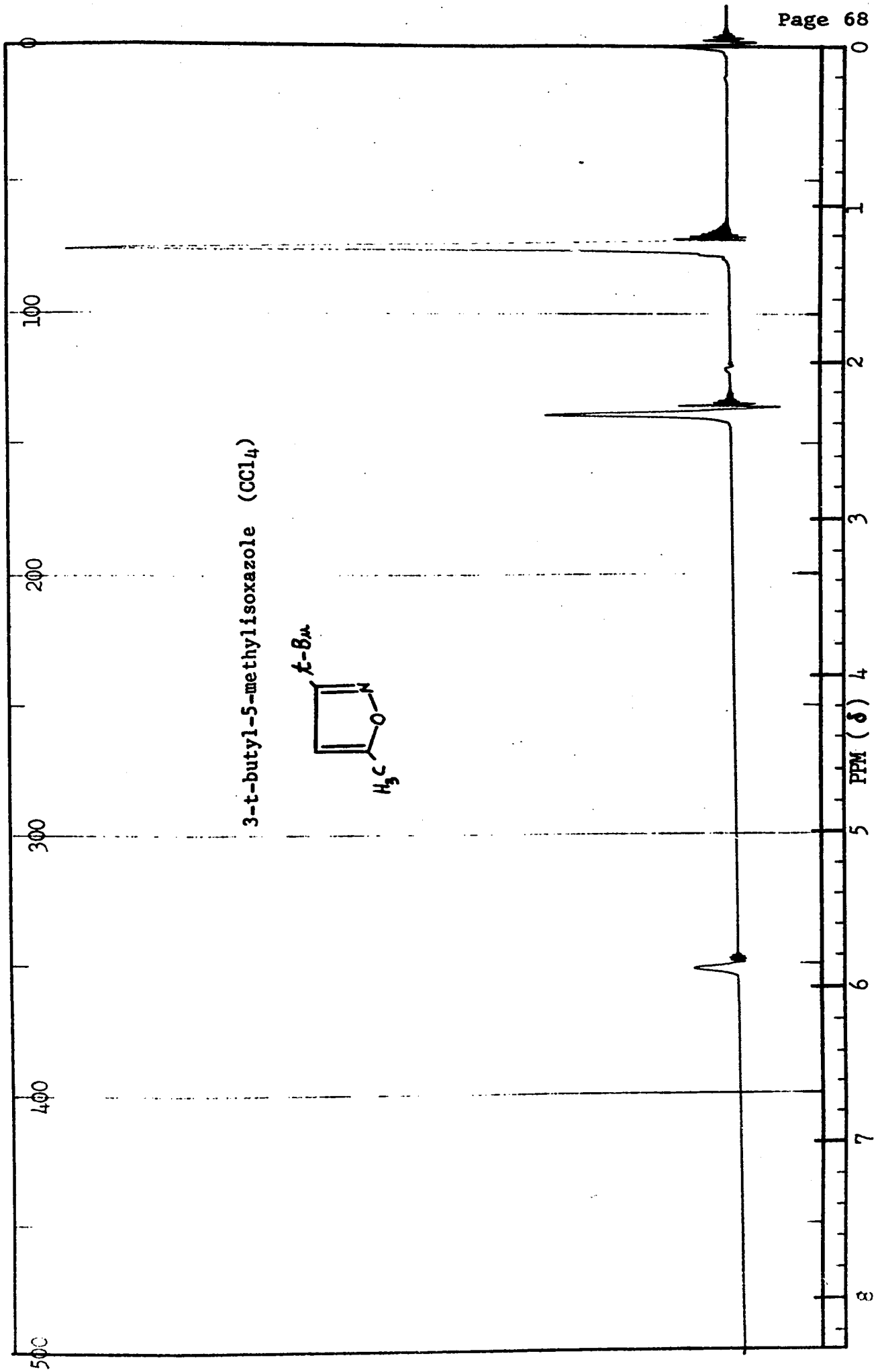
NMR SPECTRUM NO.2



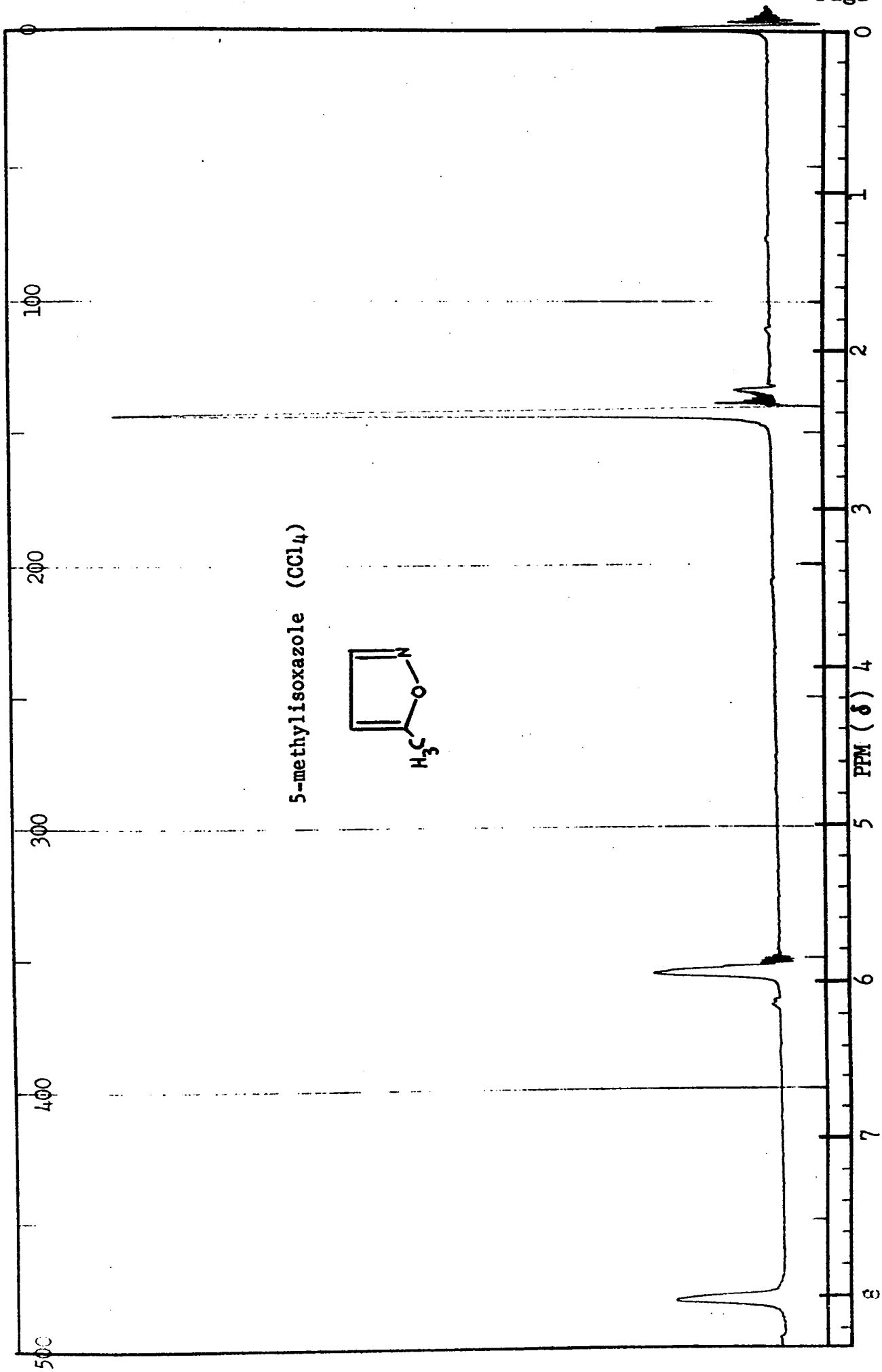
NMR SPECTRUM NO.3



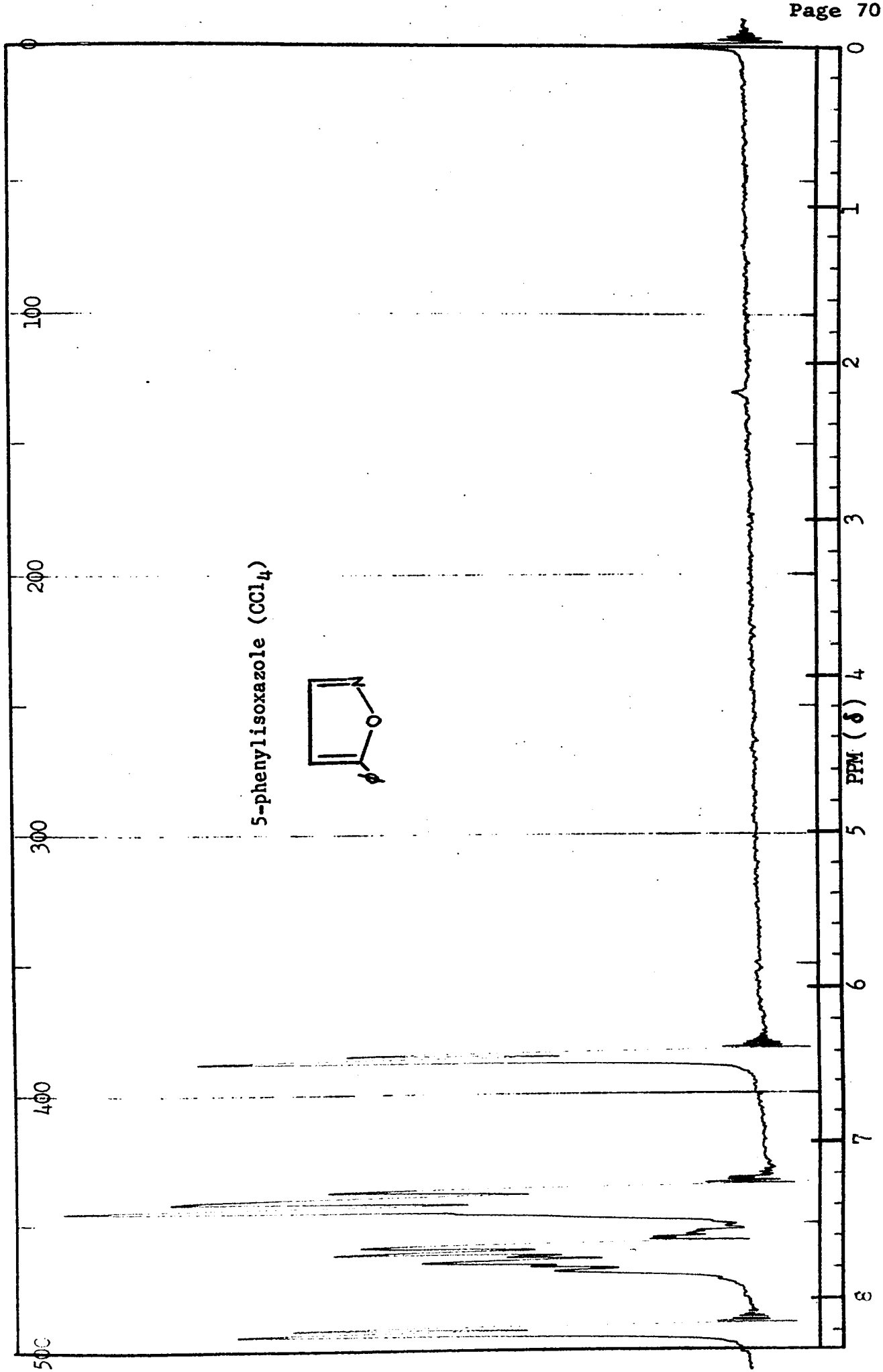
NMR SPECTRUM NO.4



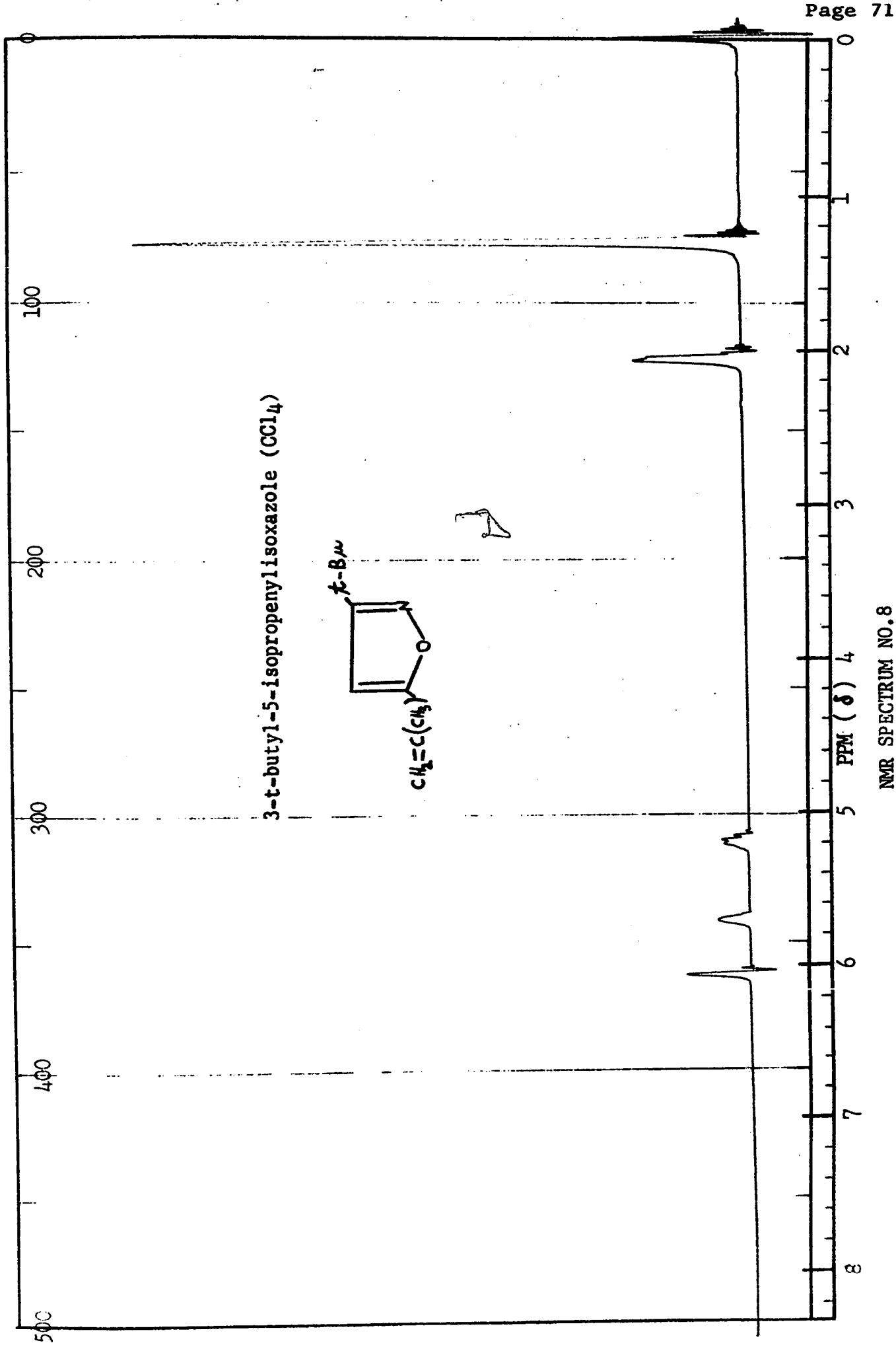
NMR SPECTRUM NO.5



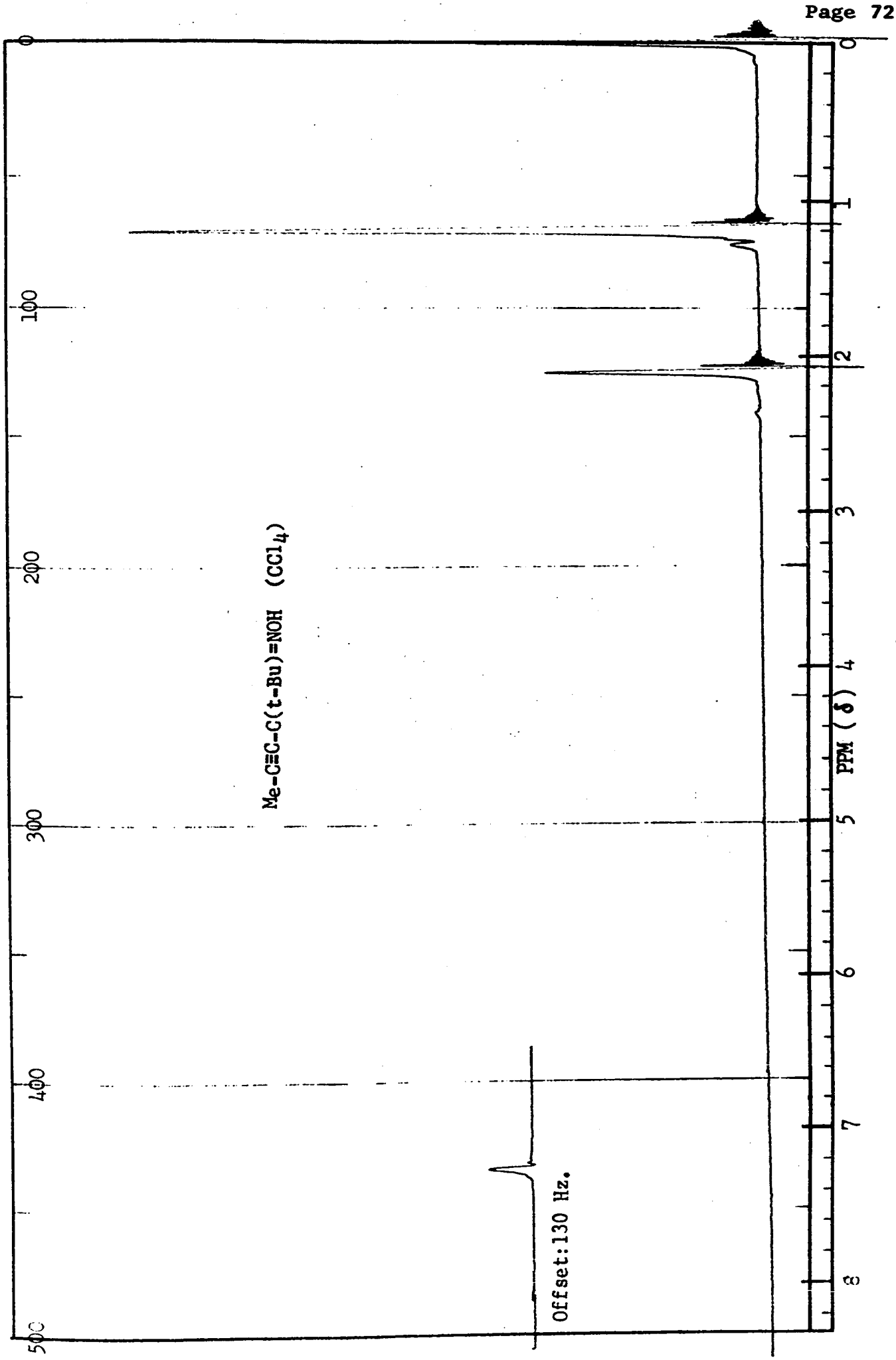
NMR SPECTRUM NO.6



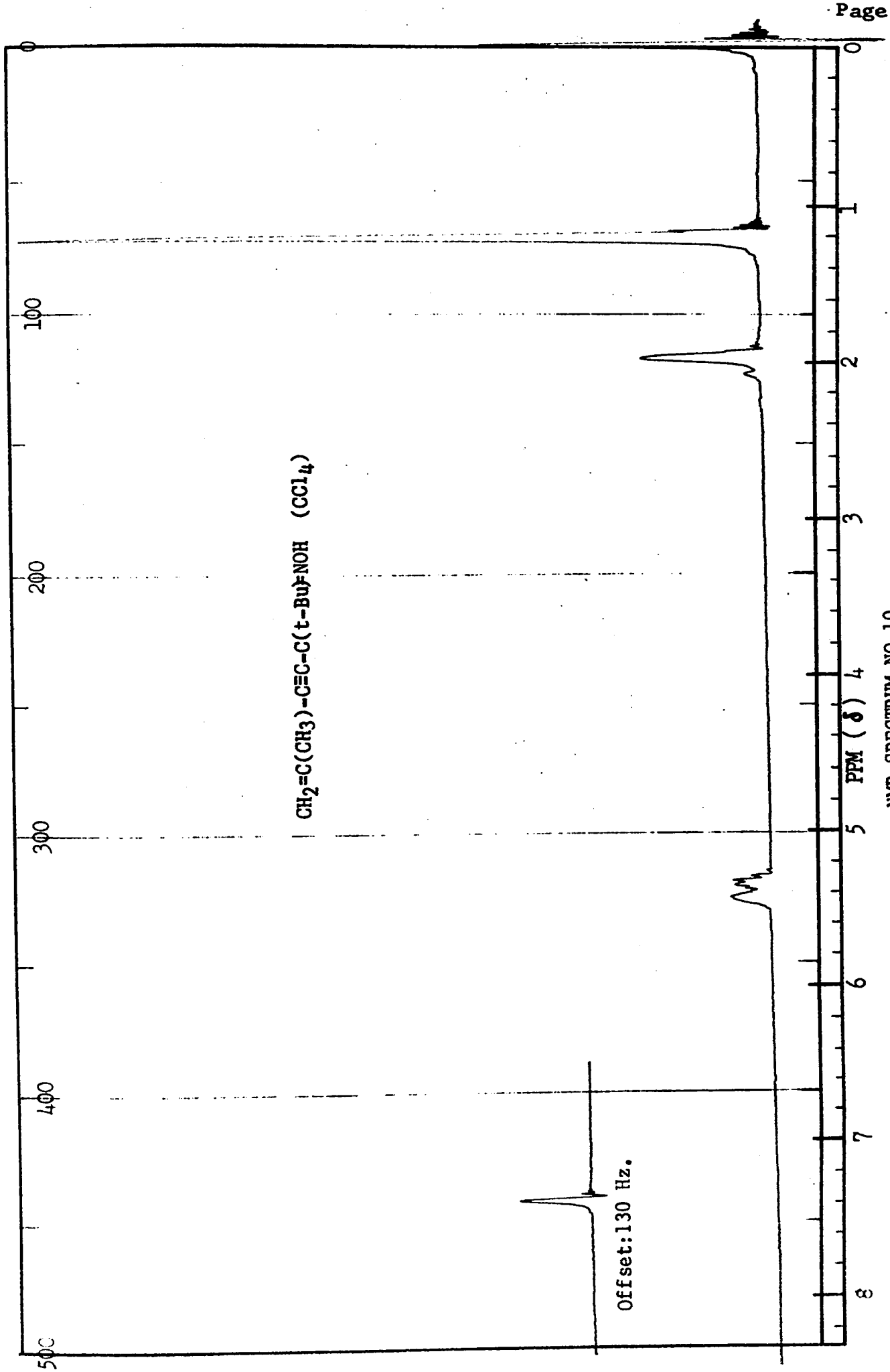
NMR SPECTRUM NO.7



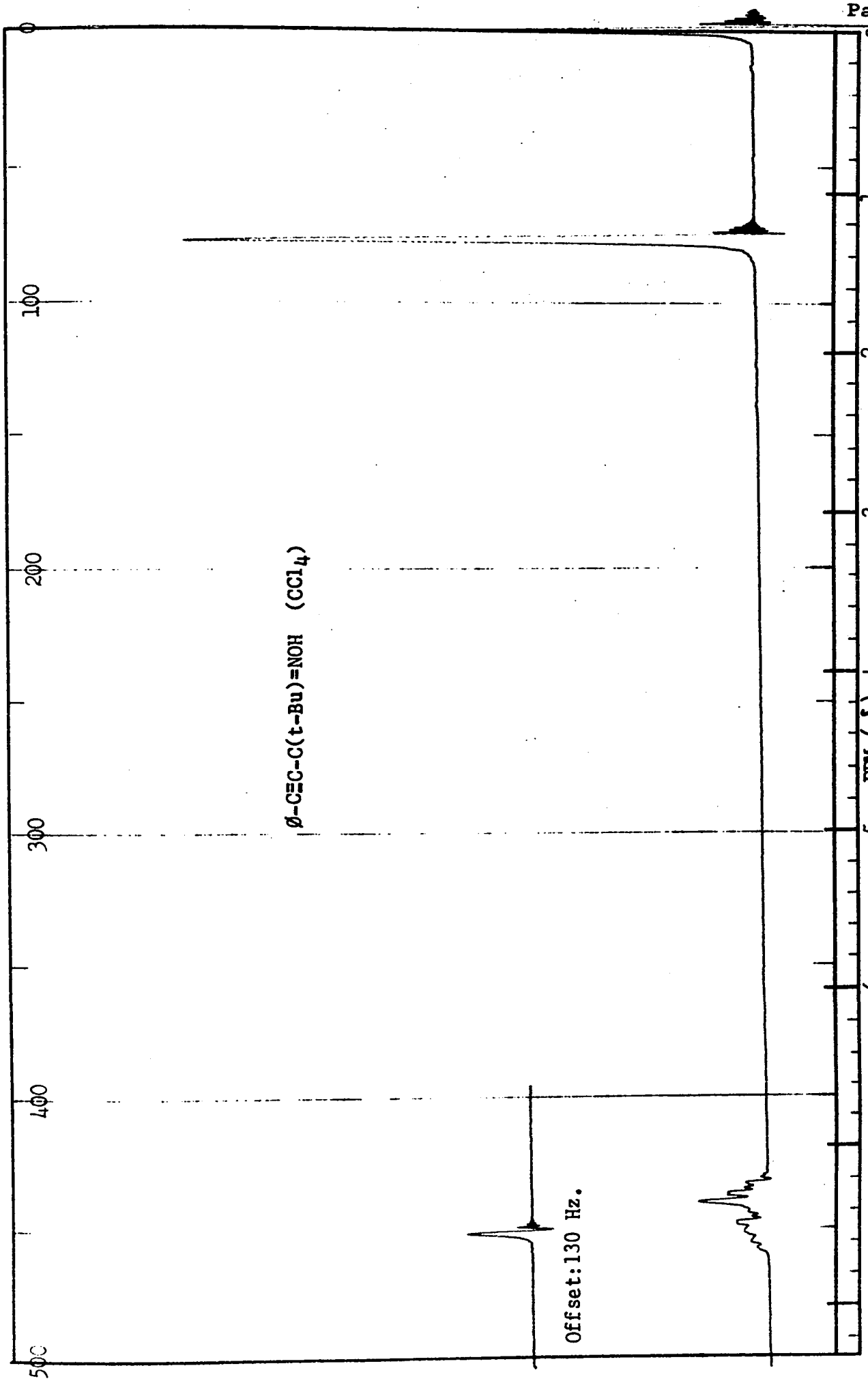
NMR SPECTRUM NO.8



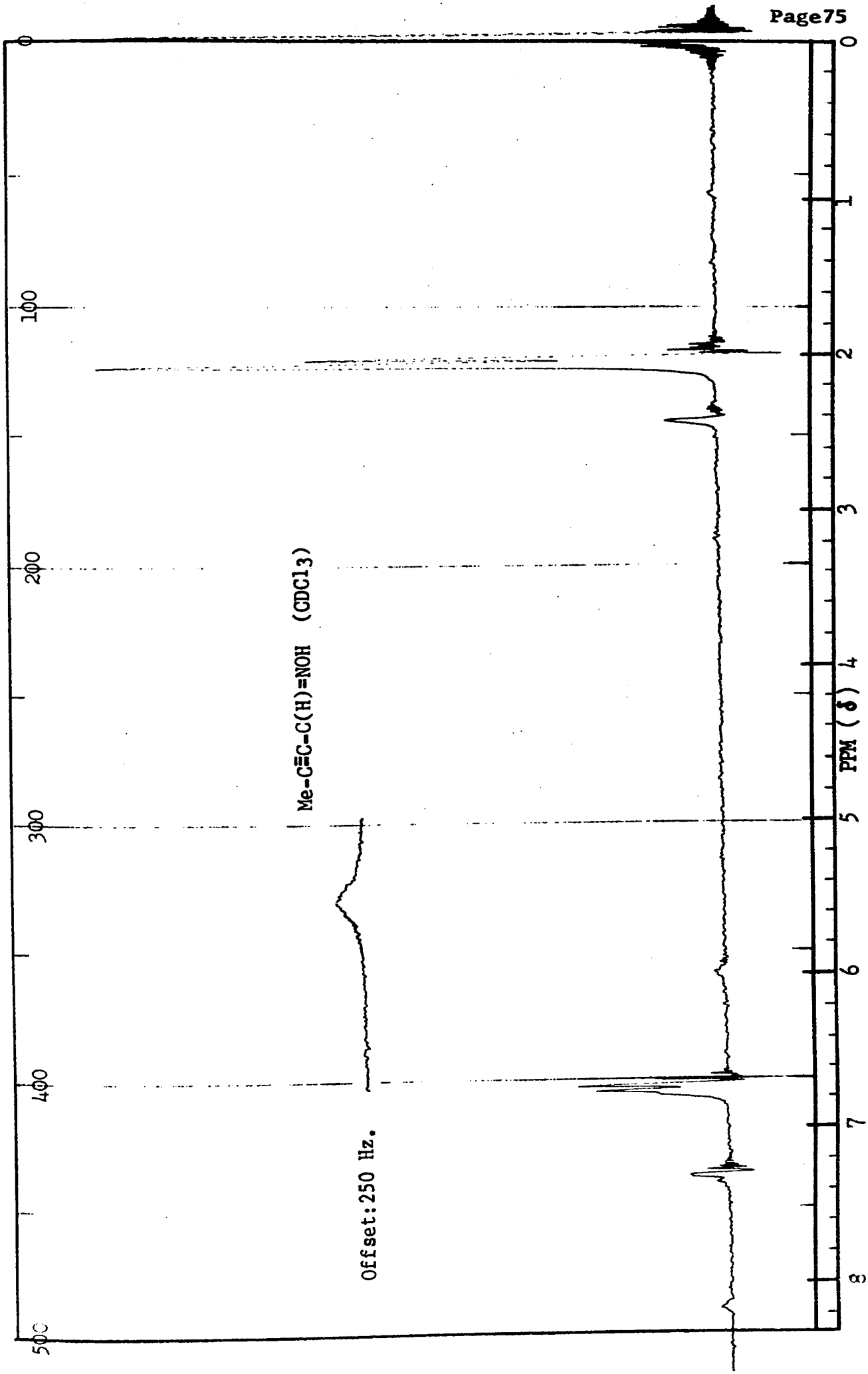
NMR SPECTRUM NO.9



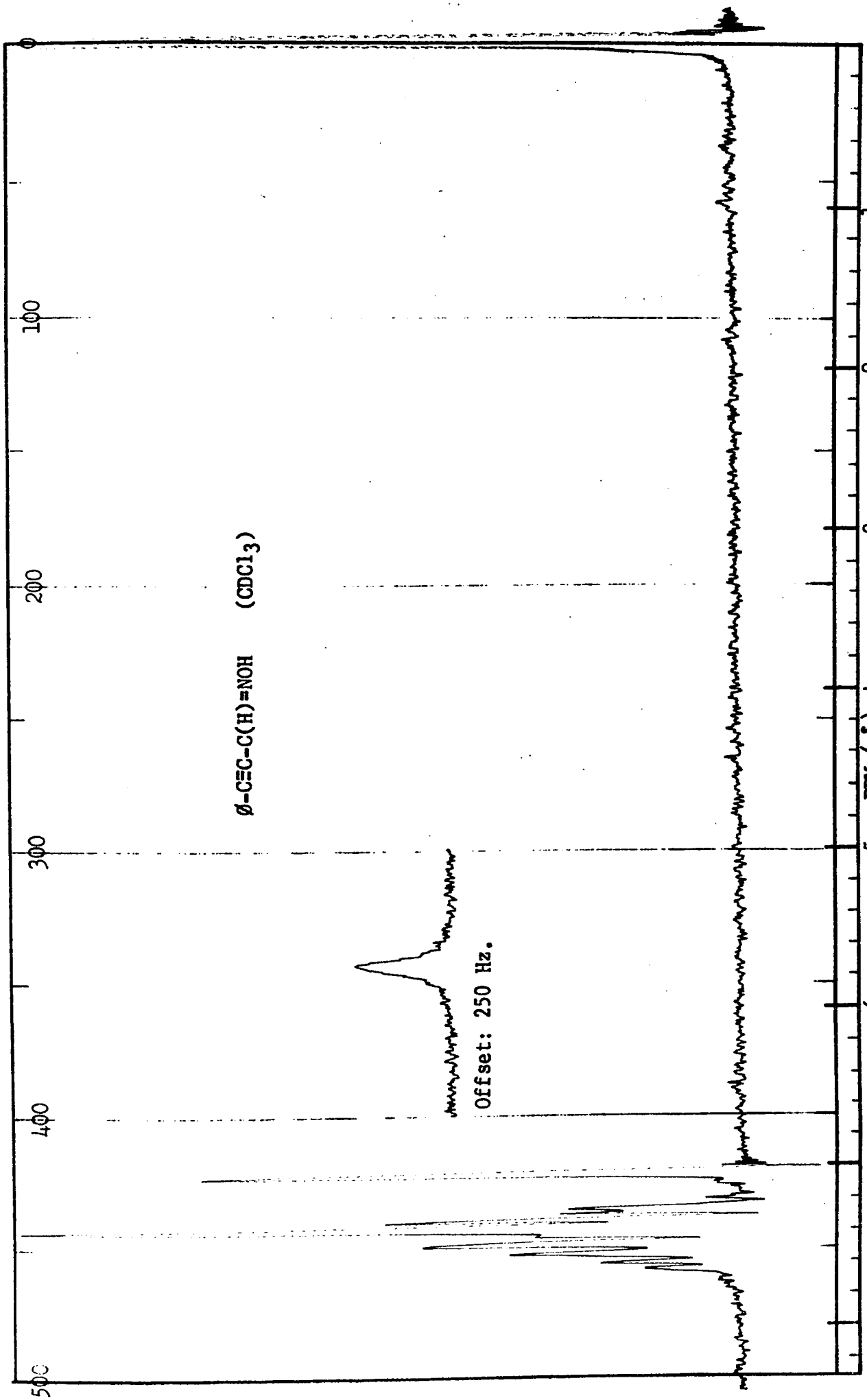
NMR SPECTRUM NO.10



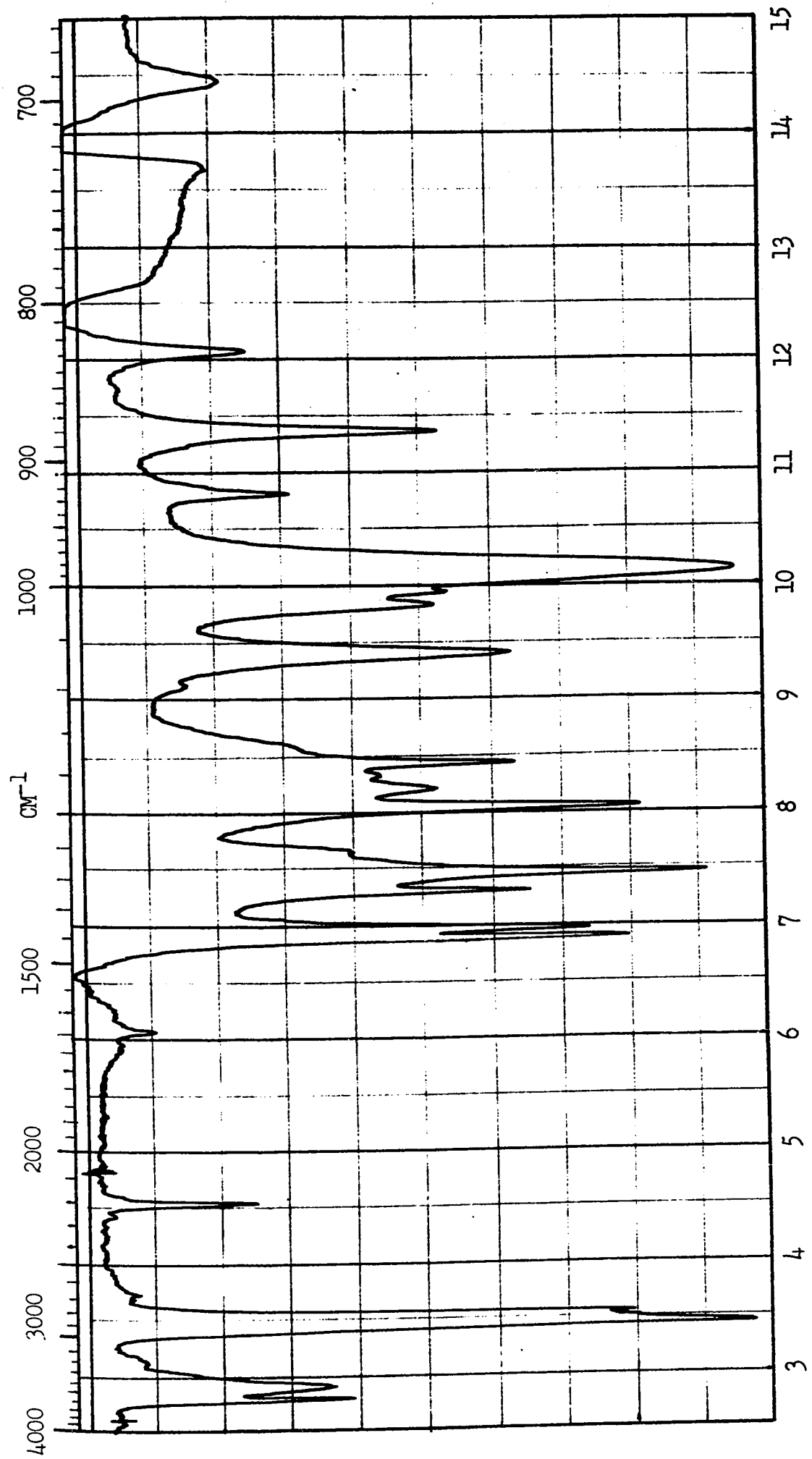
NMR SPECTRUM NO.11



NMR SPECTRUM NO.12

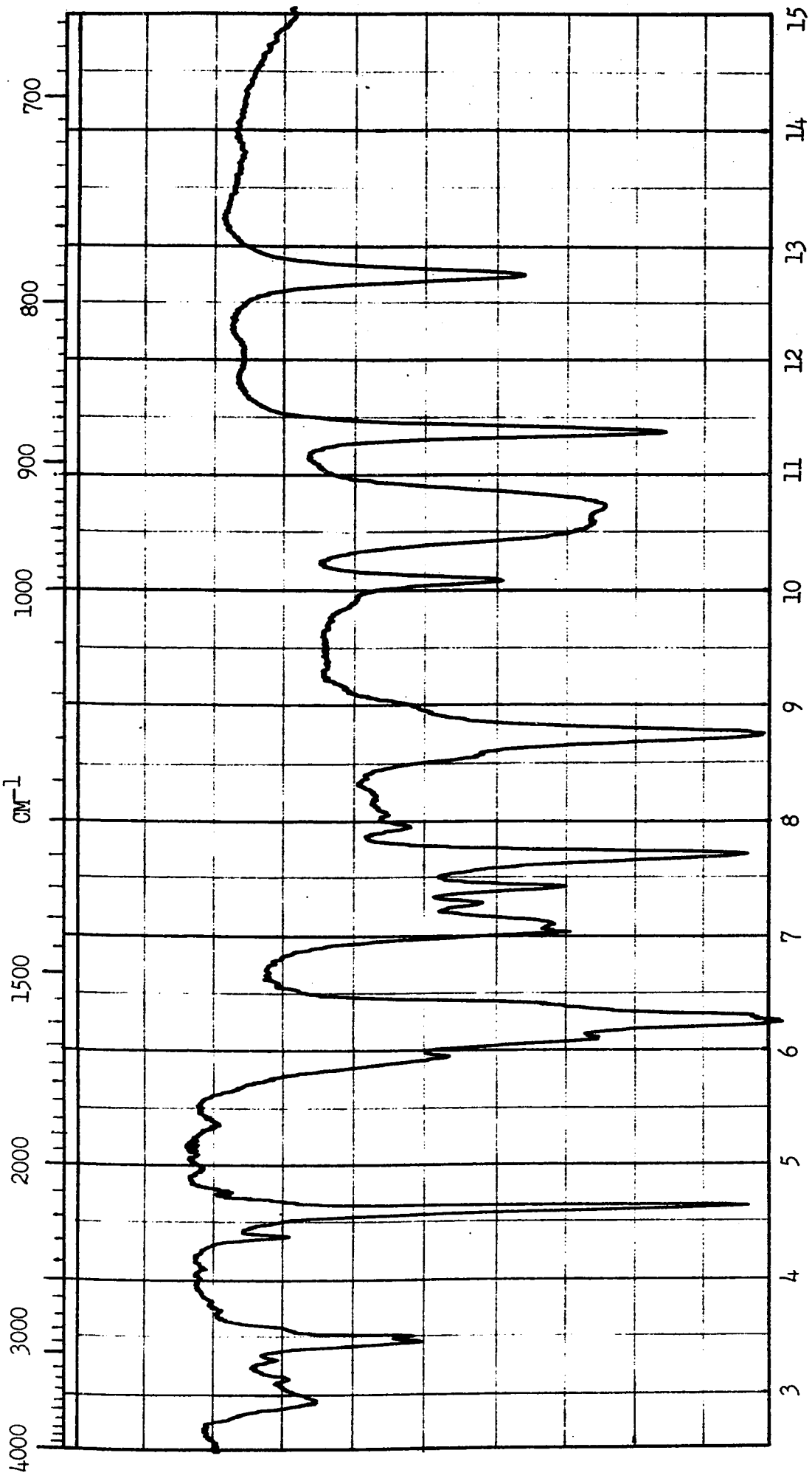


NMR SPECTRUM NO.13



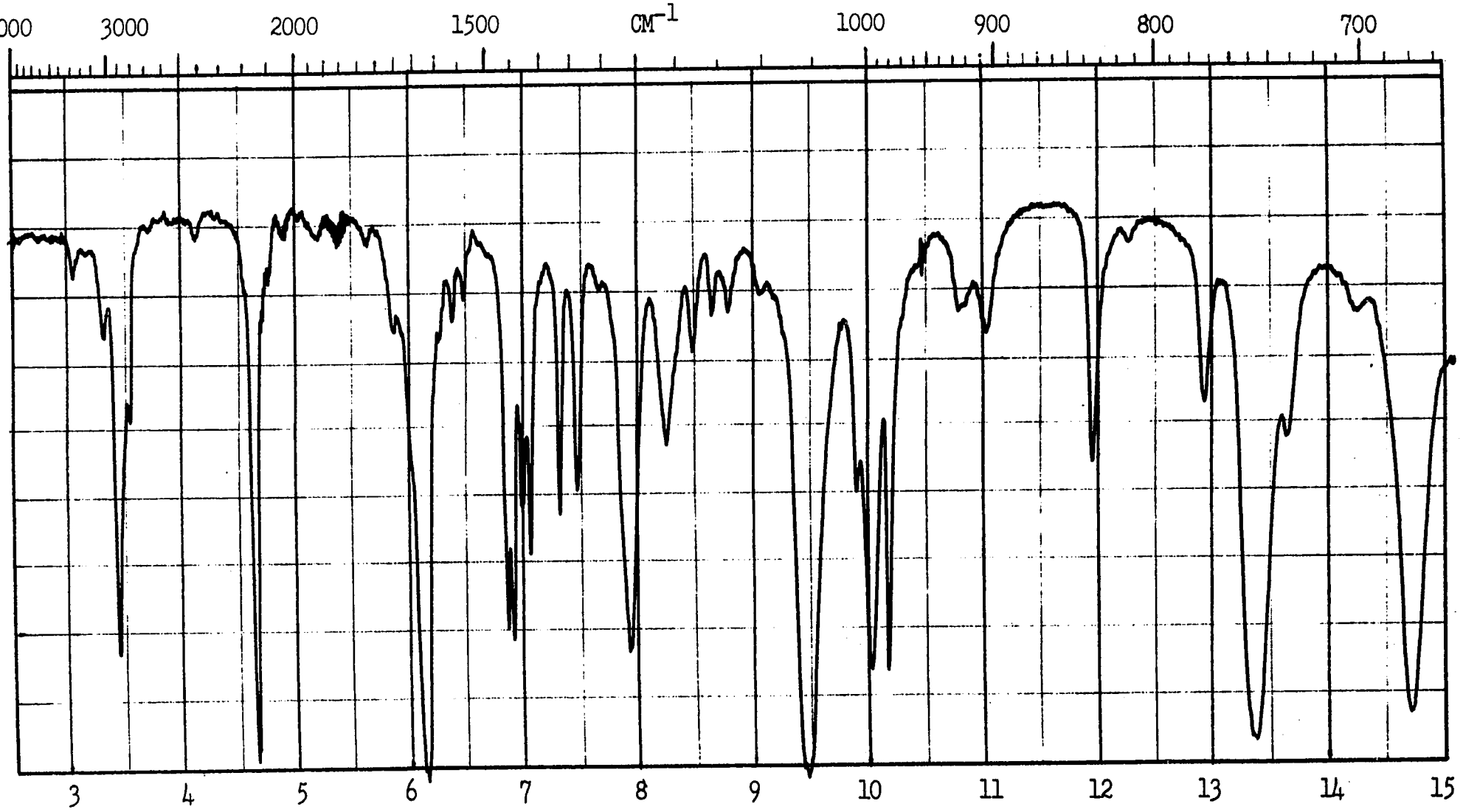
t-Bu-C≡C-CHOH-t-Bu (CCl_4)

IR SPECTRUM NO.1



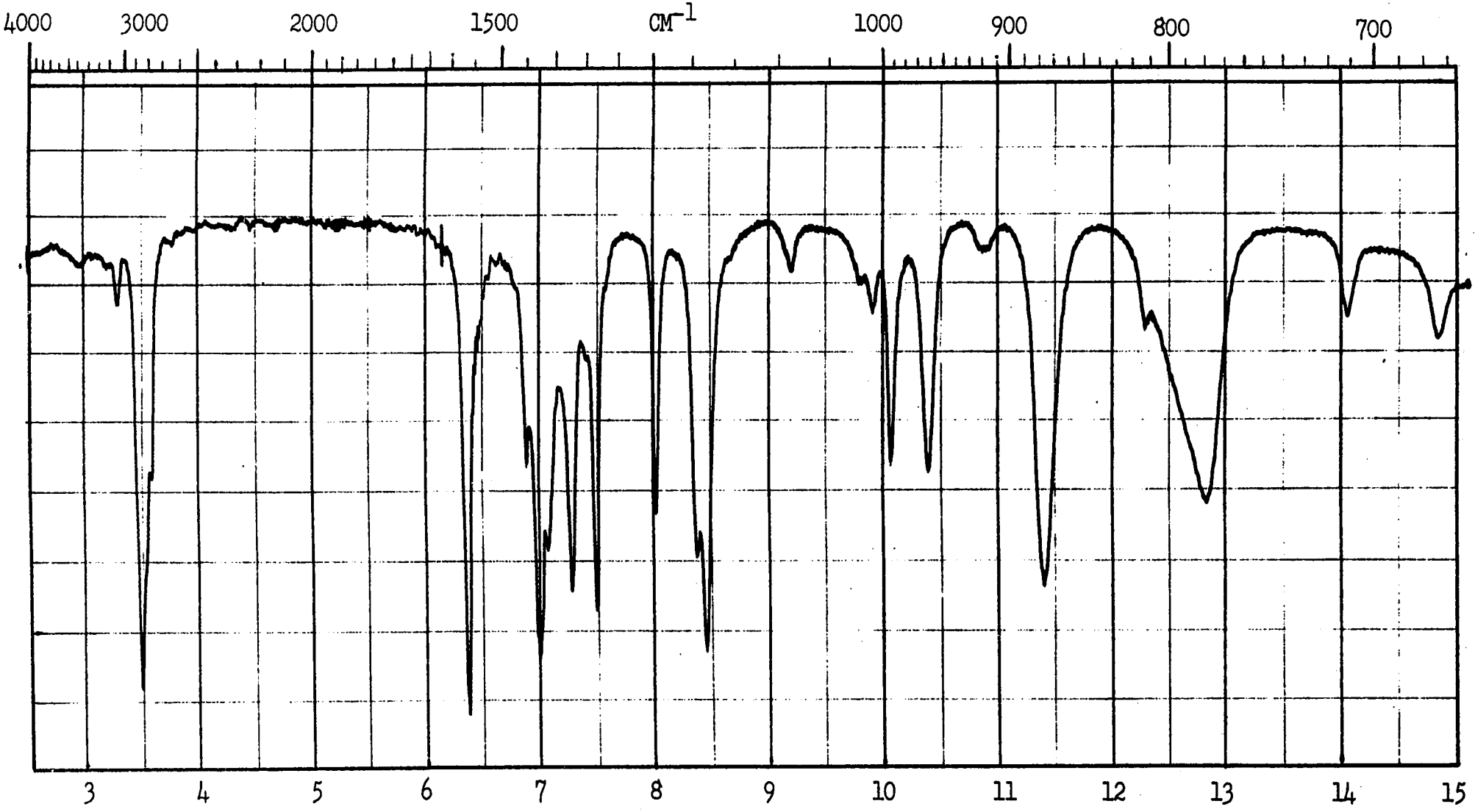
$CH_3-C\equiv C-CO-C(CH_3)=CH_2$ (neat)

IR SPECTRUM NO.2



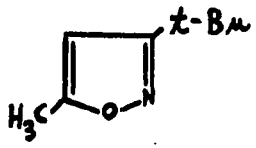
Ø-C≡C-CO-t-Bu (neat)

IR SPECTRUM NO.3

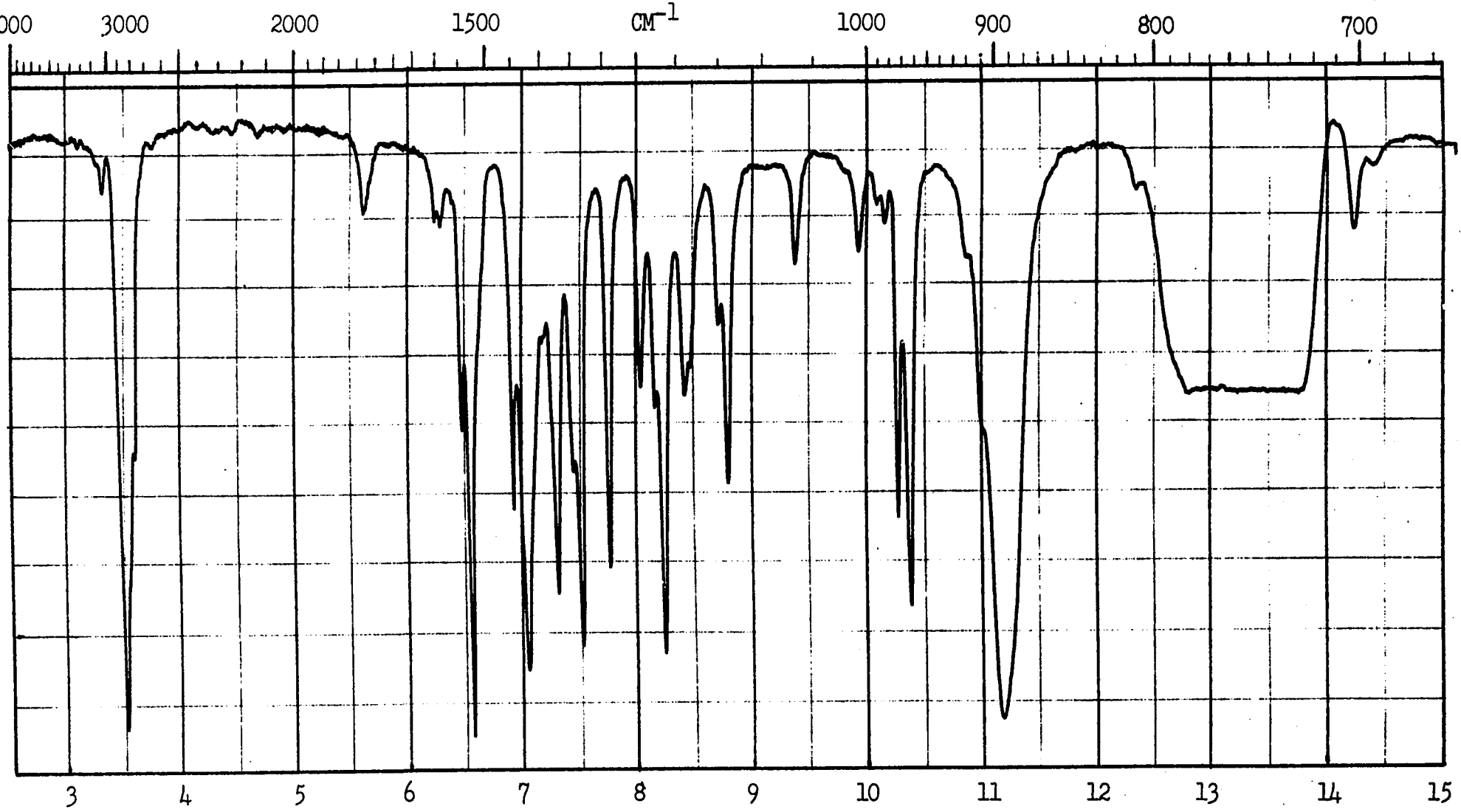


WAVELENGTH (MICRONS)

3-t-butyl-5-methylisoxazole (neat)

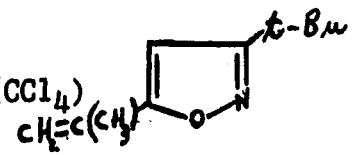


IR SPECTRUM NO.4

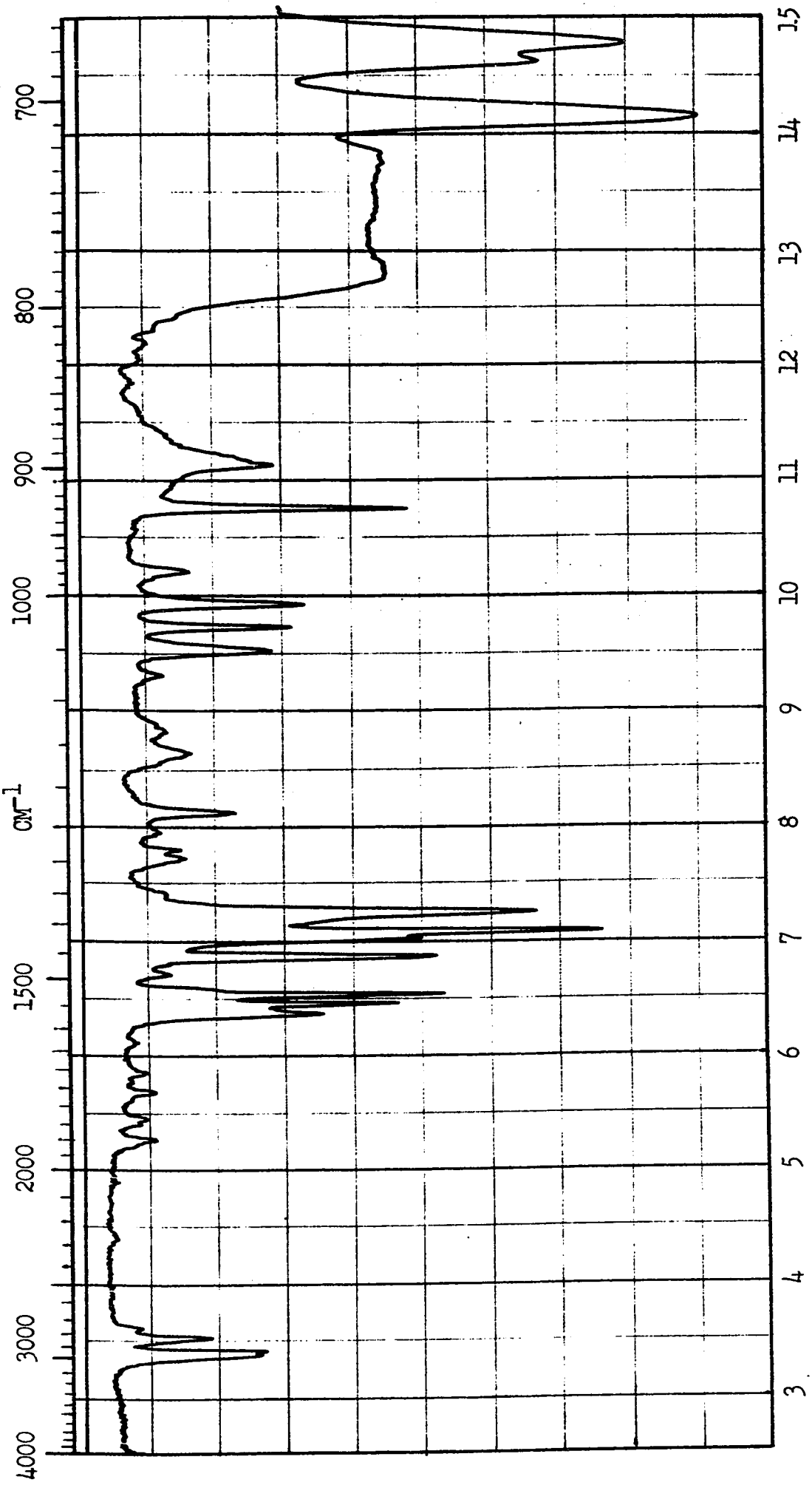


WAVELENGTH (MICRONS)

3-t-butyl-5-isopropenylisoxazole (CCl_4)

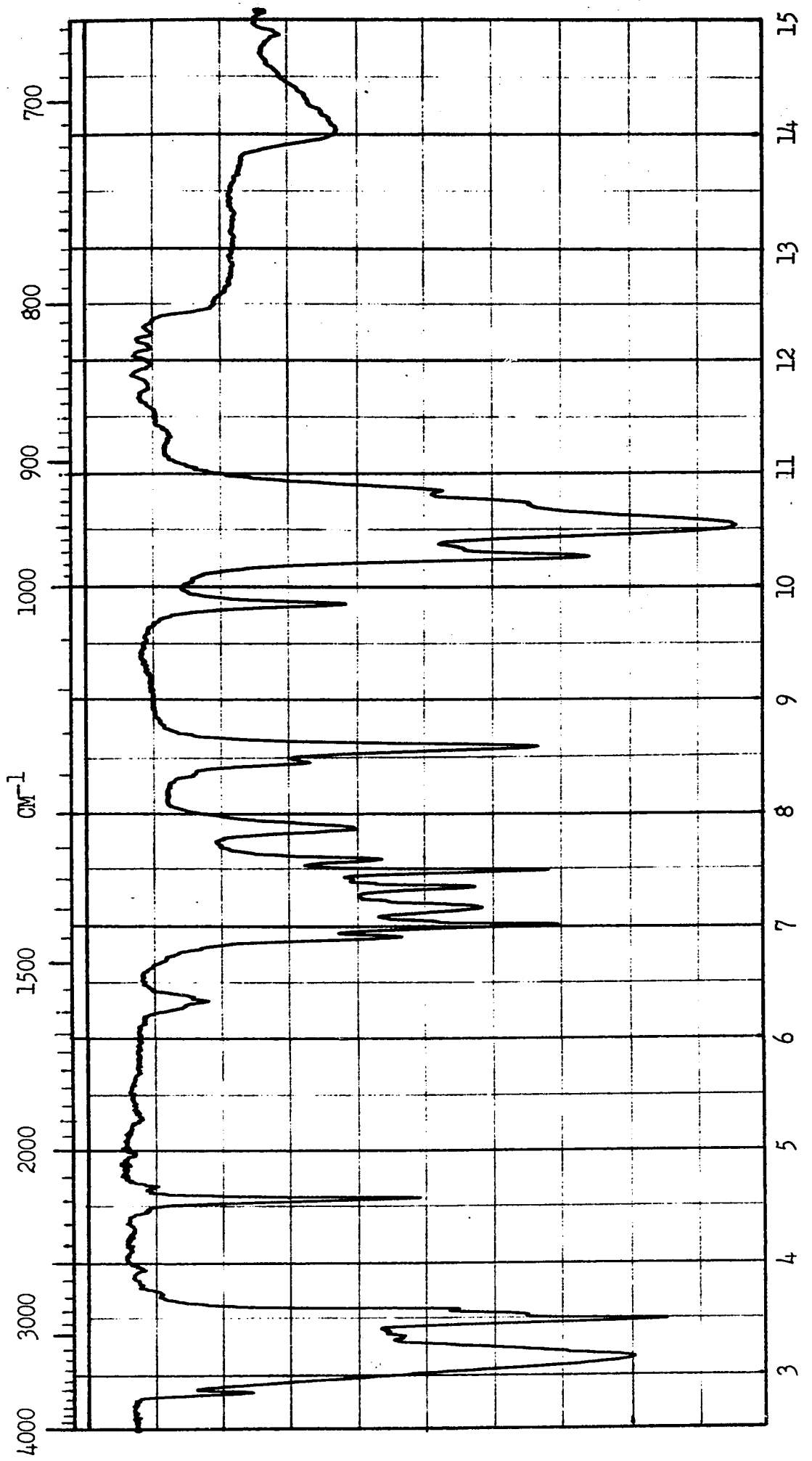


IR SPECTRUM NO.5



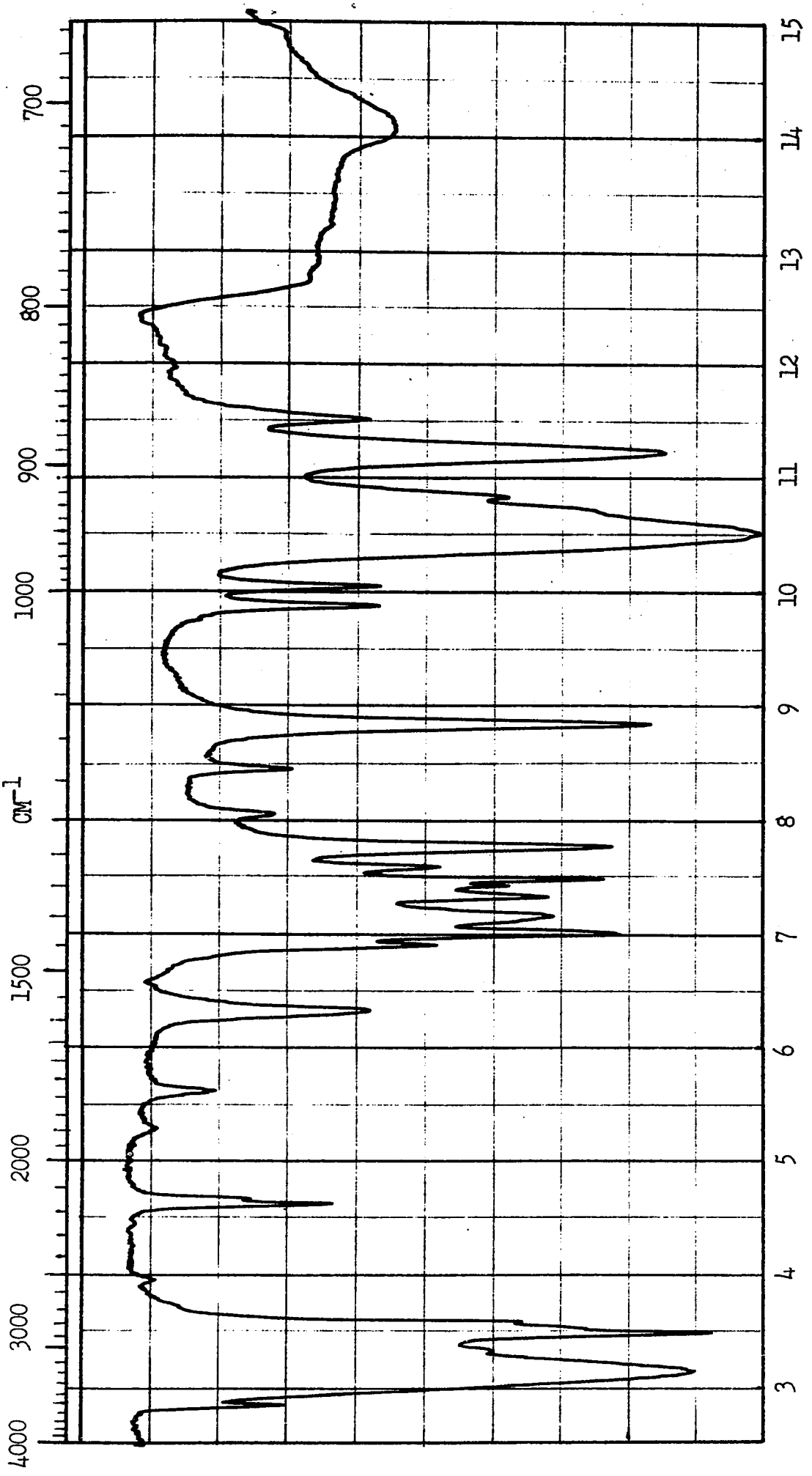
3-benzyl-5-phenylisoxazole (CCl_4)

IR SPECTRUM NO.6



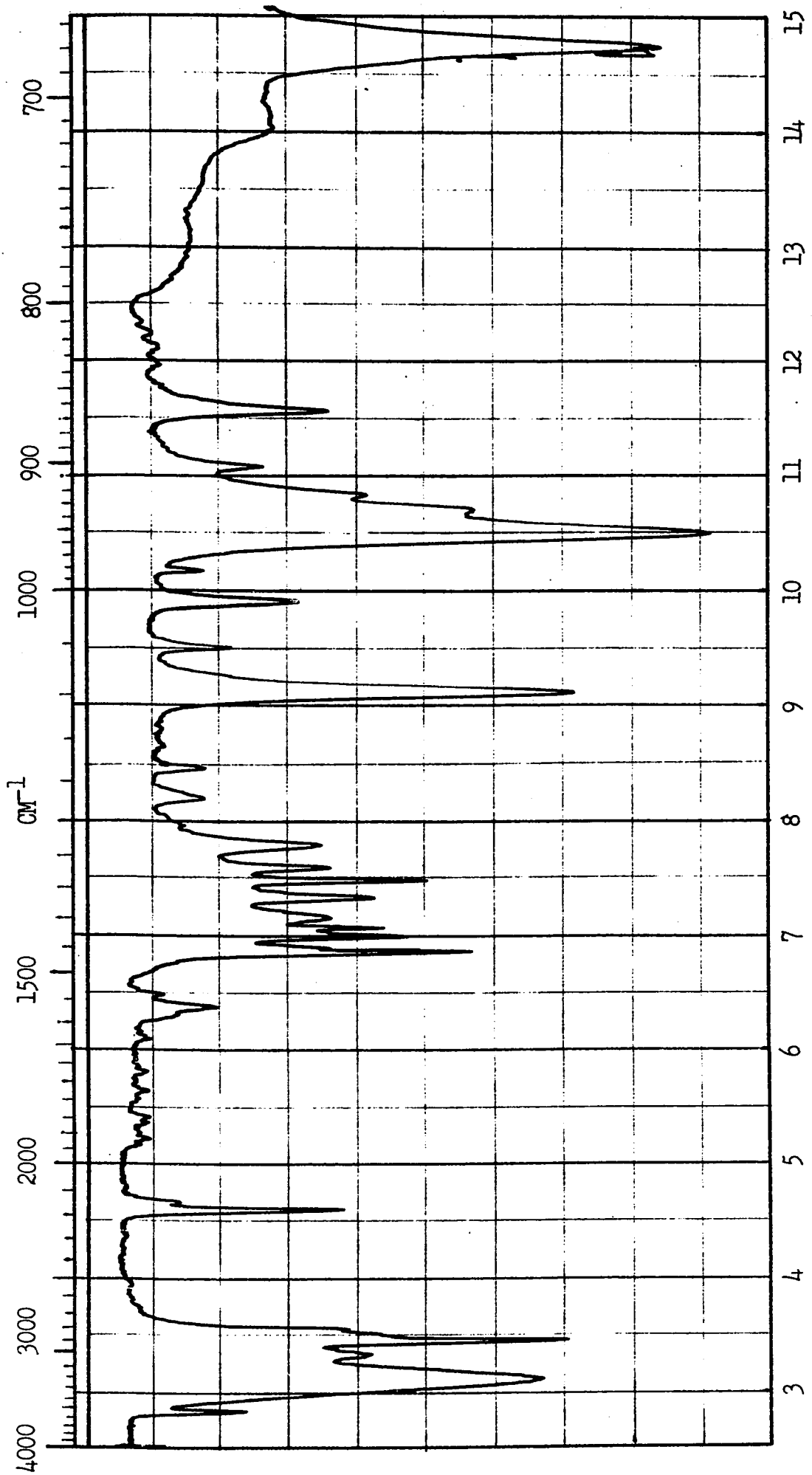
$CH_3-C\equiv C-C(t\text{-}Bu)=NOH$ (CCl_4)

IR SPECTRUM NO.7



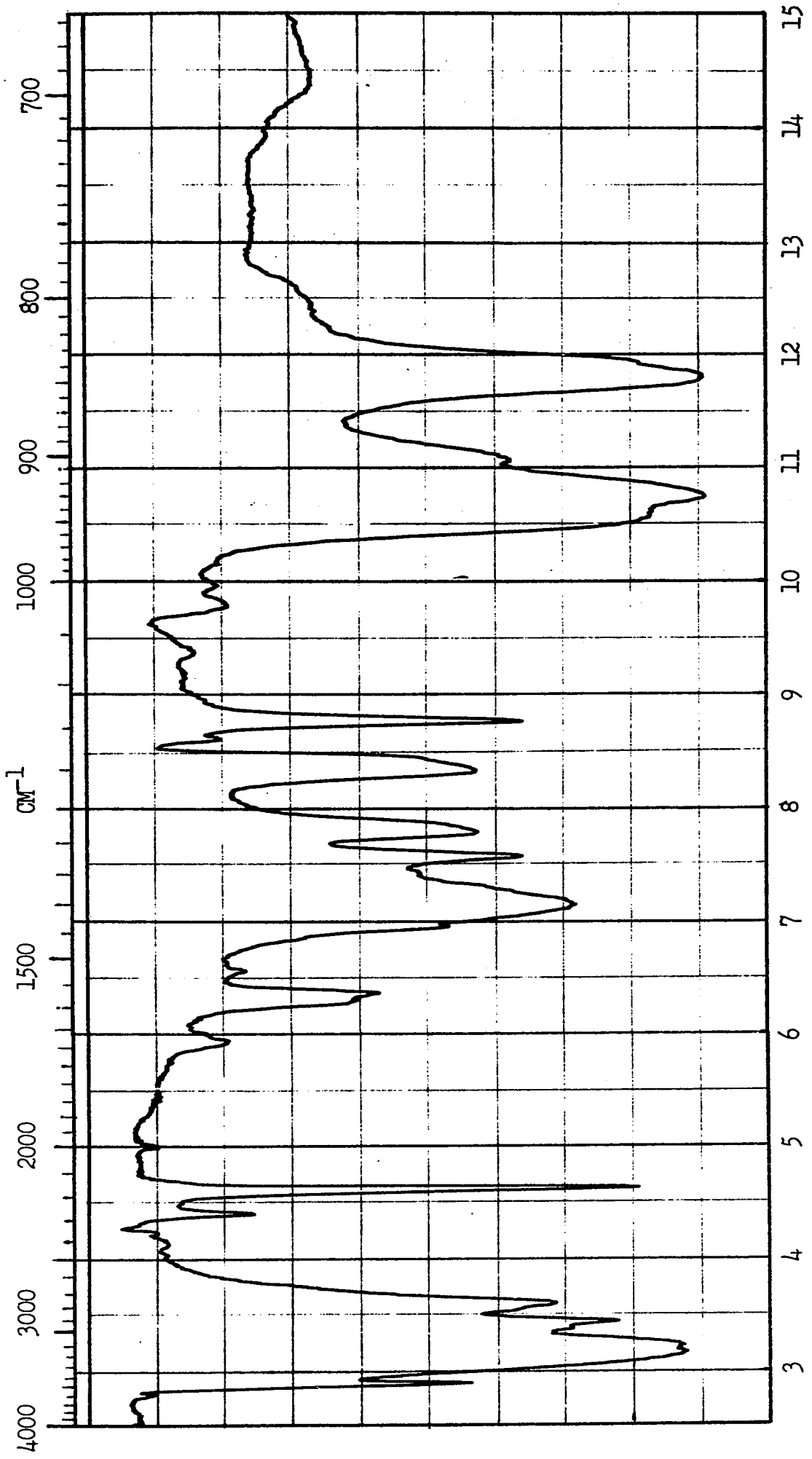
$CH_2=C(CH_3)-C\equiv C-C(t\text{-}Bu)=NOH$ (CCl_4)

IR SPECTRUM NO.8



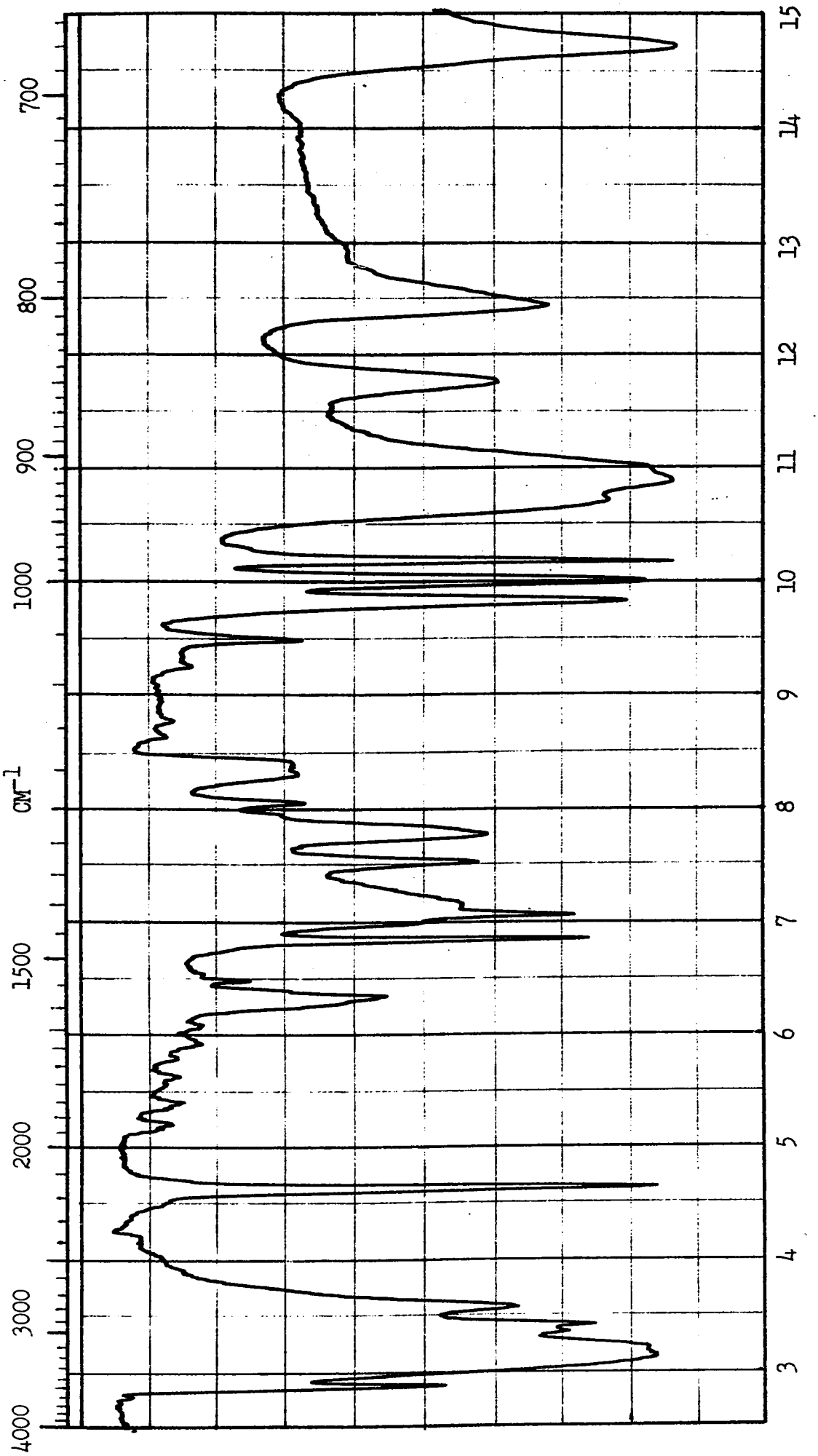
Ø-C≡C-C(t-Bu)=NOH (CCl_4)

IR SPECTRUM NO.9



Me-C≡C-C(H)=NOH (CHCl$_3$)

IR SPECTRUM NO.10



WAVELENGTH (MICRONS)

Ø-C≡C-C(H)=NOH ($CHCl_3$)

IR SPECTRUM NO.11

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