# ABSTRACT

Title of Thesis: Synthesis of Cyclobutenyl Ketals

Atef Boulos, Master of Science, 1984

Thesis directed by: Dr. David Kristol, Professor of Chemistry

A series of dialkoxy derivatives of N,N'-di-tert-butyl-2-butylamino-3,3-dichloro-4-dichloromethylene cyclobutenyl carboxamidinum chloride, were prepared by dissolving either $Na^+$ or $K^+$ alkoxide in the appropriate alcohol, or by treatment with potassium hydroxide in the appropriate alcohols. Thus, the dimethoxy, diethoxy, di-isopropoxy, di-n-butoxy, di-tert-butoxy derivatives were obtained.

# SYNTHESIS OF CYCLOBUTENYL KETALS

BY

ATEF Z. BOULOS

Thesis submitted to the Faculty of the Graduate School of
the New Jersey Institute of Technology in partial fulfillment of
the requirements for the degree of
Master of Science, 1984

# APPROVAL SHEET

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# INTRODUCTION

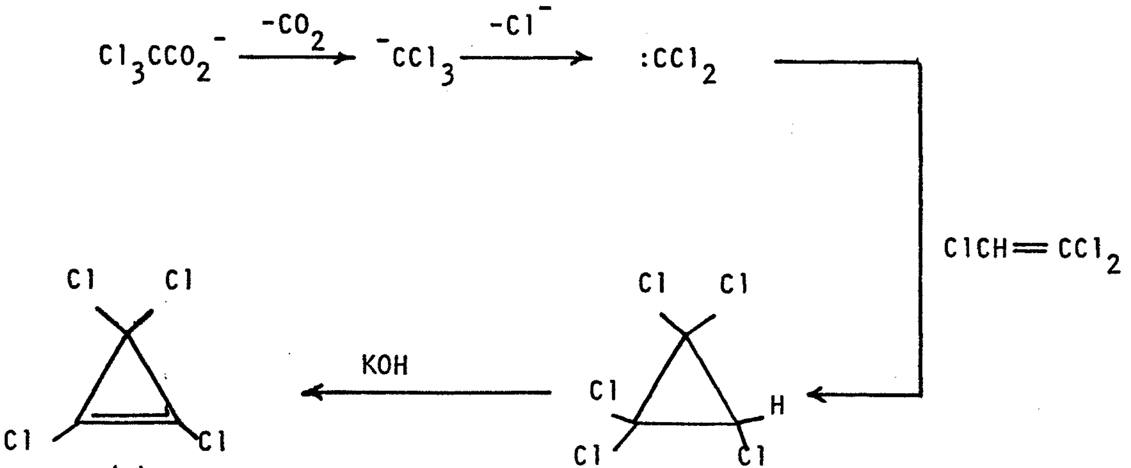
The study of the syntheses and reactions of chlorocarbons is a relatively new and unexplored area of organic chemical research. One reason for the existence of this unexplored frontier is the great investigative interest on the syntheses and reactions of the hydrocarbons because of both their greater availability and applicability to modern laboratory techniques, such as nmr spectroscopy. Reactions of organic compounds which contain few heteroatoms, such as chlorines, yield simple, readily characterized compounds when reacted with monofunctional reagents. By contrast, the reactions of polyhalo compounds may yield polyfunctional molecules produced by a variety of substitutions, additions and eliminations which may occur simultaneously.

Reactions involving chlorocarbons usually occur under milder conditions than their sister hydrocarbons because of (a) the more polarized carbon-chlorine bond as opposed to the carbon-hydrogen bond and (b) the fact that chlorine is a good leasing group. It is for this reason that a greater variety of reactions occur with chlorocarbons than with hydrocarbons. For instance, substitution and elimination reactions occur more readily with chlorocarbons than with their corresponding hydrocarbons.

Up to recent times, reactions with chlorocarbons have generally been limited to reactions with Lewis Acids or to free radical reactions. Very little work has been done on nucleophilic substitutions of chlorocarbons which is the topic of my thesis.

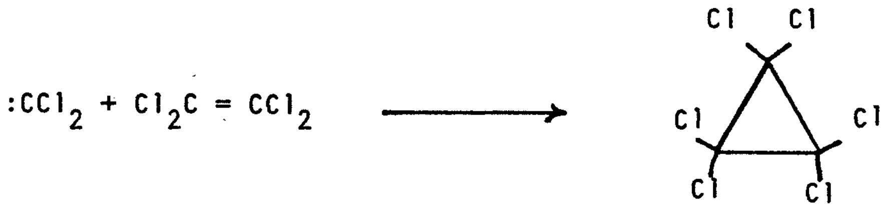
Syntheses of Small Ring Chlorocarbons

The availability of small ring chlorocarbons has significantly increased because of recent developments in organic chemical research. For example, dichlorocarbene (produced by thermal decarboxylation of sodium trichloroacetate) and trichloroethylene reacted together to produce pentachlorocyclopropane. Dehydrohalogenation of the latter afforded tetrachlorocyclopropene.[1] (1)



(1)

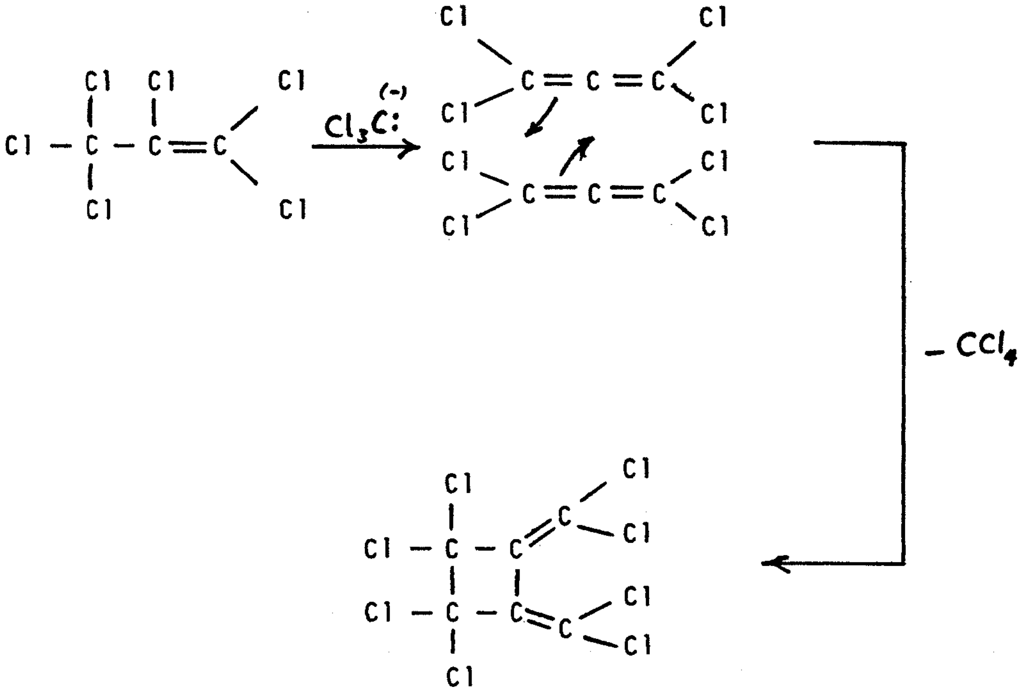
Hexachlorocyclopropane was prepared in a similar manner from tetrachloroethylene.[2] (2)



(2)

1,1,2,2-tetrachloro-3,4-bis(dichloromethylene) cyclobutane[3] (3), was synthesized by the treatment of hexachloropropene with sodium trichloroacetate with thermal decarboxylation.

The following mechanism was proposed for the synthesis of the product.

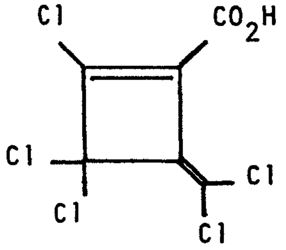


(3)

Reactions of 1,1,2,2-tetrachloro-3,4-bis (dichloromethylene) cyclobutane.

Compound (3):

Compound (3) has been reported to yield (4) with sulfuric acid[4] (5), with fuming nitric acid[5] (6), with a mixture of aluminum and aluminum chloride[6] (7), with diazomethane[7] (8), with aluminum chloride[8], and (9) upon heating at 230°.[9]



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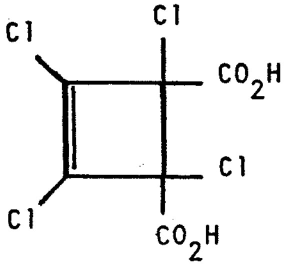

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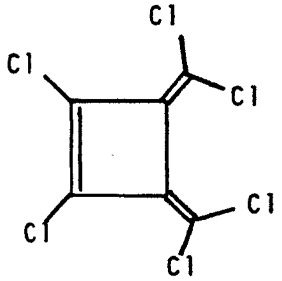

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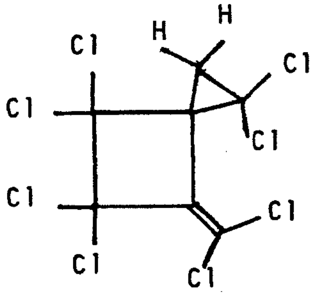

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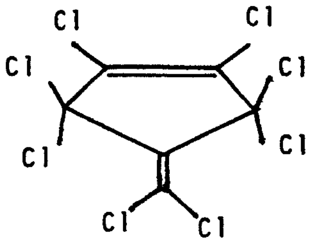

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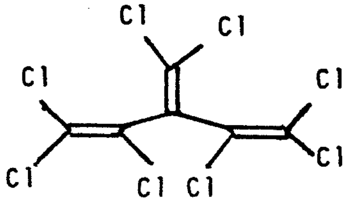
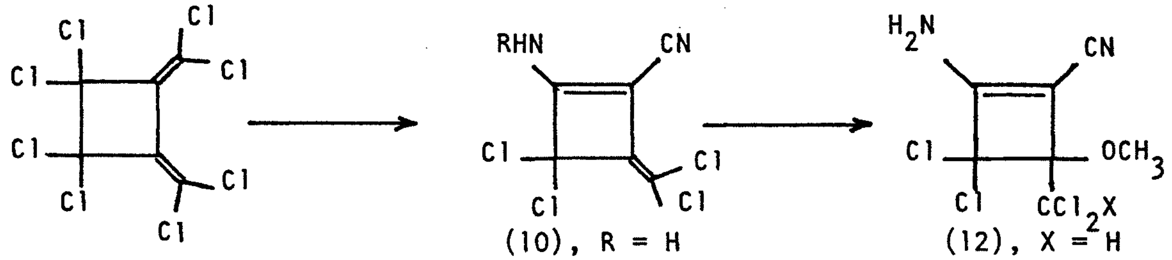


(9)

## Reactions of Halocarbons with Nucleophiles:

It was also reported that compound (3), reacts readily with ammonia[10] to give 2-amino-3,3-dichloro-4-dichloro-methylene-1-cyanocyclobutene,(10).



(3)

(10), R = H

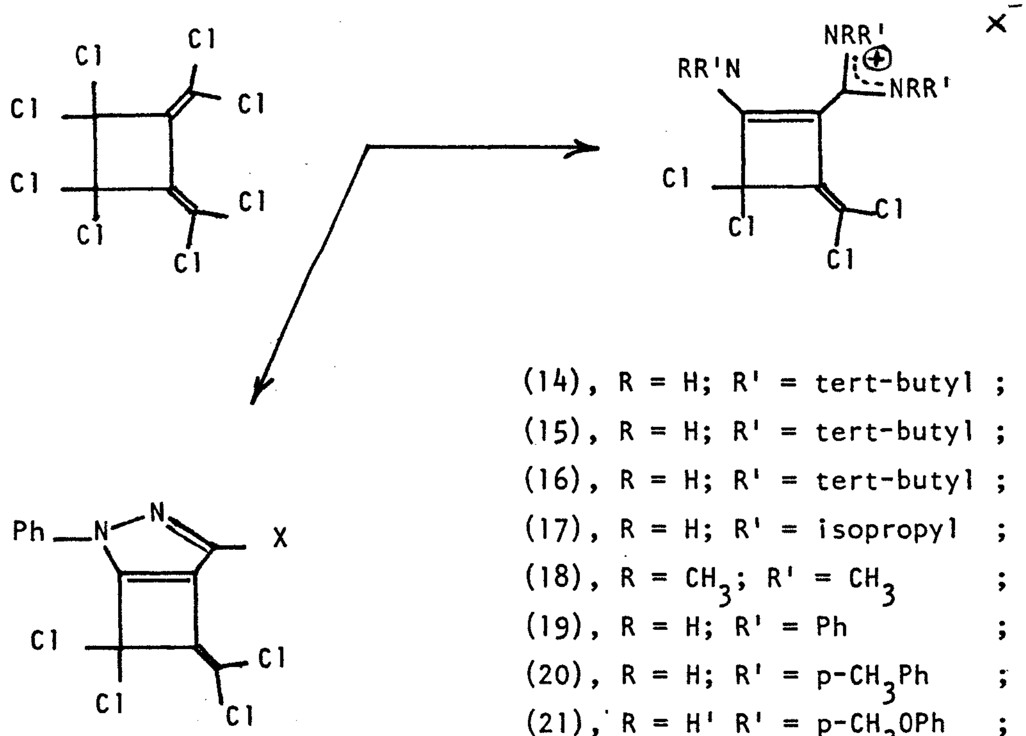
(11), R = AC

(12), X = H

(13), X = Bn

Compound (11) was produced from the reaction of (10) with acetic anhydride,[11] and compound (12) from the reaction of (10) with methyl alcohol and hydrochloric acid.[12]

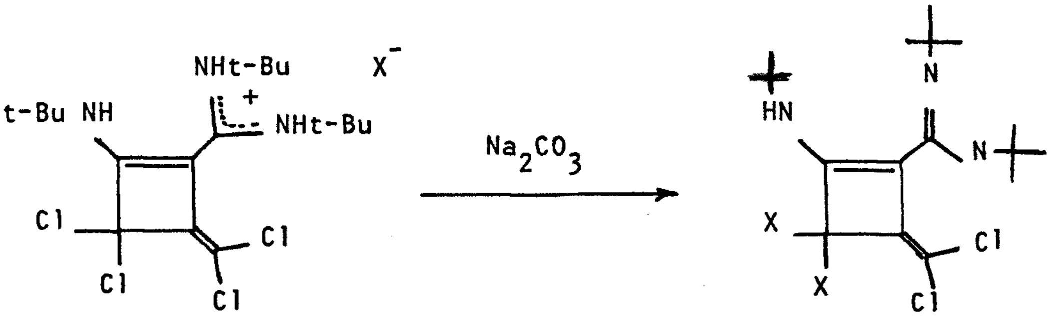
Compound (3) was also reacted with various primary or secondary aliphatic or aromatic amines[13] to form compounds (14) to (24).



(14), R = H; R' = tert-butyl ; X - Cl
(15), R = H; R' = tert-butyl ; X = $NO_3$
(16), R = H; R' = tert-butyl ; X = $HSO_4$
(17), R = H; R' = isopropyl ; X = Cl
(18), R = $CH_3$; R' = $CH_3$ ; X = Cl
(19), R = H; R' = Ph ; X = Cl
(20), R = H; R' = p-$CH_3$Ph ; X = Cl
(21), R = H' R' = p-$CH_3$OPh ; X = Cl

(23), X = Cl

(24), X = pH NHNH

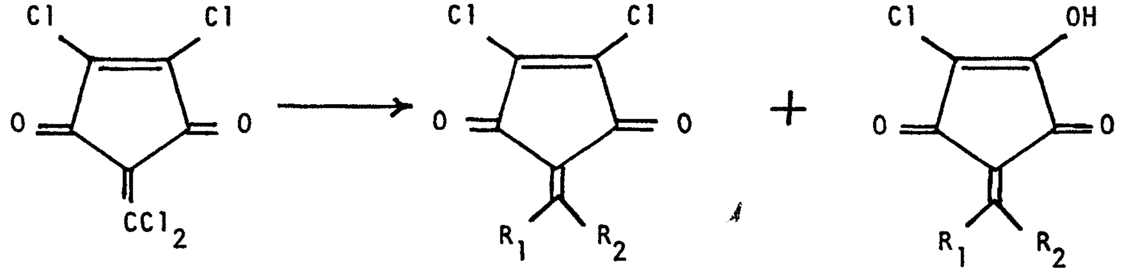


(22), X = Cl

Compound (22) was produced from the reaction of compound (14) with sodium carbonate,[14] and compounds (15) and (16) were also produced from the reaction of compound (14) with silver nitrate and sulfuric acid respectively.[15] David Kristol and R. Shapiro studied the spectroscopic properties of these compounds and the transformation products derived from them. A mechanism was also proposed for this reaction.

### Reaction of 4,5-dichloro-2-dichloromethylene-4-cyclopentene-1,3-dione, (25), with amines.[16]

These reactions gave high yields of (26) and (27)

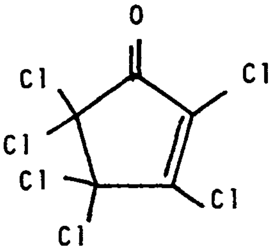


(25) (26) (27)

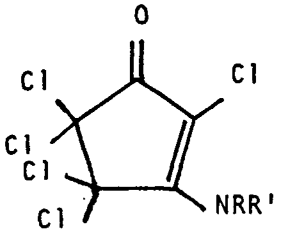
a : $R_1 = R_2 = NMe_2$
b : $R_1 = R_2 = NEt_2$
c : $R_1 = R_2$ = morpholino
d : $R_1 = R_2$ = piperidino

a : $R_1 = R_2 = NMe_2$
b : $R_1 = R_2 = NET_2$
c : $R_1 = R_2$ = piperidino

Reaction of perchloro-2-cyclopentene-1-one and perchloro-4-cyclopentene-1,3-dione with ammonia and aliphatic amines.[17]



(28)



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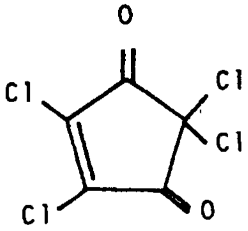
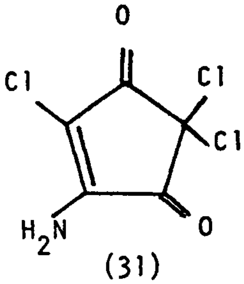


(30)



(31)

Reaction of (28), with $NH_3$ and unhindered aliphatic amines gave (29), and $Cl_2C{:}ClCCl{:}CClCONHRR'$ (e.g. R,R'= H,H;H,Me), secondary, more hindered amines also gave $Cl_2C{:}CClCCl{:}CClCO_2H$. RR' NH (eg. R = R'= Et). The basic direction of reaction of (30), with aliphatic amines was replacement of Cl at position 4, to give e.g., (31). In the presence of ACOH the perchloro Ketones formed the corresponding enolates.

# ETHER AND KETAL FORMATION

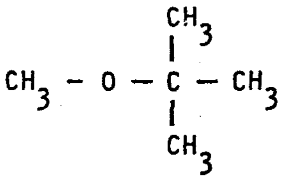
## HISTORY AND THE REACTION OF ETHERS

### Structure and nomenclature of ethers

Ethers are compounds of the general formula R-O-R, Ar-O-R, or Ar-O-Ar. To name ethers we usually name the two groups that are attached to oxygen, and follow these names by the word ether:

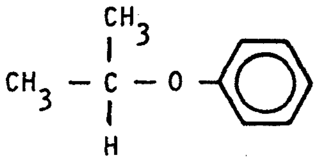
$$C_2H_5OC_2H_5$$

Ethyl ether



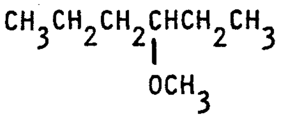
$$CH_3-O-\overset{CH_3}{\underset{CH_3}{C}}-CH_3$$

Methyl tert-butyl ether



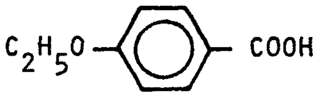
Isopropyl phenyl ether

If one group has no simple name, the compound may be named as an alkoxy derivative:

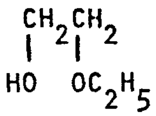


$$CH_3CH_2CH_2\underset{OCH_3}{CH}CH_2CH_3$$

3-Methoxyhexane



p-Ethoxybenzoic acid



$$\underset{HO}{CH_2}\underset{OC_2H_5}{CH_2}$$

2-Ethoxyethanol

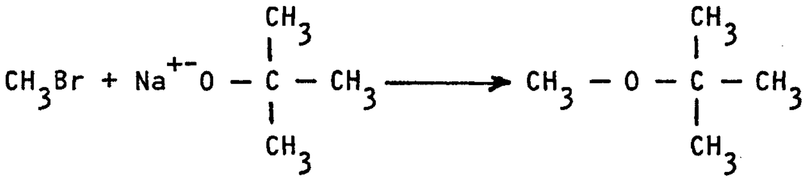
## PREPARATION OF ETHERS. WILLIAMSON SYNTHESIS[18]

In the laboratory, the Williamson synthesis of ethers is important because of its versatility: it can be used to make unsymmetrical ethers as well as symmetrical ethers, and aryl alkyl ethers as well as dialkyl ethers.

In the Williamson synthesis an alkyl halide (or substituted alkyl halide) is allowed to react with a sodium alkoxide or a sodium phenoxide:

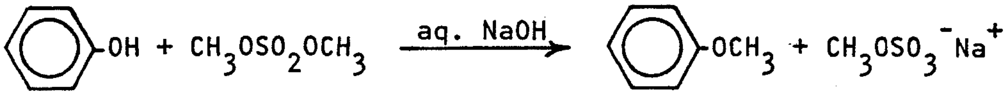
$$\mathrm{R{-}X + Na^{+-}O{-}R' \longrightarrow R{-}O{-}R' + Na^{+}X^{-}}$$

$$\mathrm{R{-}X + Na^{+-}O{-}Ar \longrightarrow R{-}O{-}Ar + Na^{+}X^{-}}$$

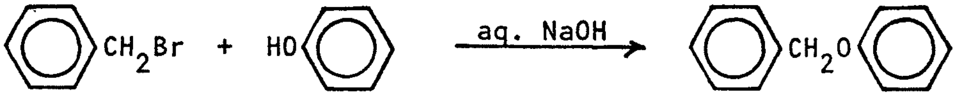


$$\mathrm{CH_3Br + Na^{+-}O - \underset{CH_3}{\overset{CH_3}{C}} - CH_3 \longrightarrow CH_3 - O - \underset{CH_3}{\overset{CH_3}{C}} - CH_3}$$

Sodium tert-butoxide Methyl tert-butyl ether



Phenol Methyl Sulfate Anisole



Benzyl Bromide Phenol Benzyl Phenyl Ether

The Williamson synthesis involves nucleophilic substitution of alkoxide ion or phenoxide ion for halide ion; it is strictly analogous to the preparation of alcohols by treatment of alkyl halides with aqueous hydroxide. Sodium alkoxides are made by direct action of sodium metal on dry alcohols:

$$\mathrm{ROH + Na \longrightarrow RO^{-}Na^{+} + 1/2\ H_2}$$

An Alkoxide

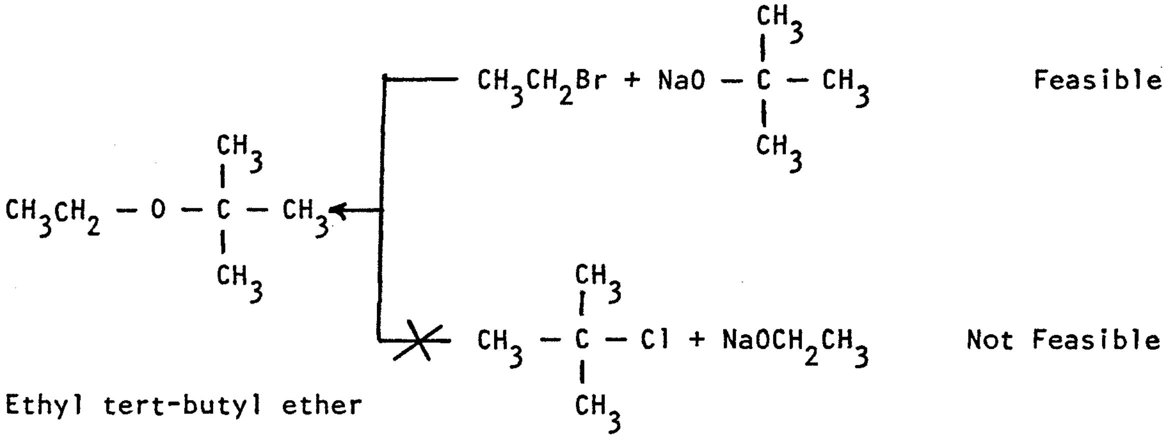
Sodium phenoxides, on the other hand, because of the appreciable acidity of phenols, are made by the action of aqueous sodium hydroxide on phenols:

$$ArOH + Na^{+}\,{}^{-}OH \longrightarrow ArO^{-}Na^{+} + H_2O$$

Stronger Acid   A phenoxide weaker acid

If we wish to make an unsymmetrical dialkyl ether, we have a choice of two combinations of reagents; one of these is nearly always better than the other.

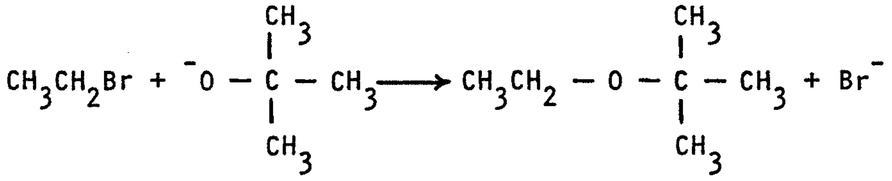
In preparation of ethyl tert-butyl ether, for example, the following combinations are conceivable:



$$CH_3CH_2-O-C(CH_3)_2-CH_3 \longleftarrow CH_3CH_2Br + NaO-C(CH_3)_2-CH_3$$

$$CH_3CH_2-O-C(CH_3)_2-CH_3 \not\longleftarrow CH_3-C(CH_3)_2-Cl + NaOCH_2CH_3$$

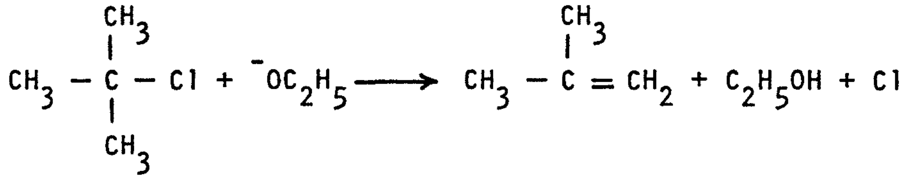
Which do we choose? As always, we must consider the danger of elimination competing with the desired substitution; elimination should be particularly serious here because of the strong basicity of the alkoxide reagent. We therefore reject the use of the tertiary halide which we expect to yield mostly - or all - elimination product; we must use the other combination. The disadvantage of the slow reaction between sodium and tert-butyl alcohol in the preparation of the alkoxide is more than offset by the tendency of the primary halide to undergo substitution rather than elimination. In planning a Williamson synthesis of a dialkyl ether, we must always keep in mind that the tendency for alkyl halides to undergo dehydrohalogenation is 3° > 2° > 1°.



$$CH_3CH_2Br + {}^-O-\overset{CH_3}{\underset{CH_3}{C}}-CH_3 \longrightarrow CH_3CH_2-O-\overset{CH_3}{\underset{CH_3}{C}}-CH_3 + Br^-$$

Substitution

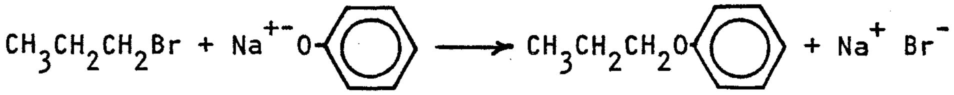
Ethyl tert-butyl ether



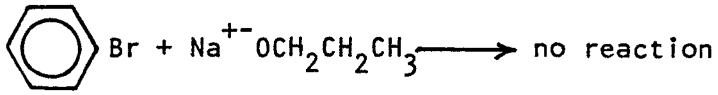
$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-Cl + {}^-OC_2H_5 \longrightarrow CH_3-\overset{CH_3}{C}=CH_2 + C_2H_5OH + Cl^-$$

Elimination

For the preparation of an aryl alkyl ether there are again two combinations to be considered; here, one combination can usually be rejected out of hand. n-Propyl phenyl ether (38), for example, can be prepared only from the alkyl halide and the phenoxide, since the aryl halide is quite unreactive toward alkoxides.



n-Propyl bromide Sodium phenoxide n-Propyl phenyl ether



Bromobenzene Sodium n-propoxide

Since alkoxides and phenoxides are prepared from the corresponding alcohols and phenols, and since alkyl halides are commonly prepared from the alcohols, the Williamson method ultimately involves the synthesis of an ether from two hydroxy compounds.

## Kinetics of nucleophilic aliphatic substitution. Second order and first order reactions:[19]

Example, the reaction of methyl bromide with sodium hydroxide to yield methanol:

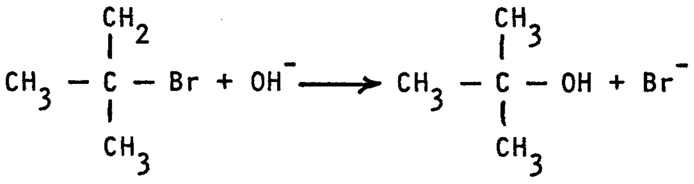
$$CH_3Br + OH^- \longrightarrow CH_3OH + Br^-$$

This reaction would probably be carried out in aqueous ethanol, in which both reactants are soluble. If reaction results from collison between a hydroxide ion and a methyl bromide molecule, the rate will depend upon the concentration of both these reactants. If either $[OH^-]$ or $[CH_3Br]$ is doubled, the collision frequency would be doubled and therefore, the reaction rate doubled. If either concentration is cut in half, the collision frequency, and consequently the rate, should be halved.

$$\text{rate} = k\ [CH_3Br]\ [OH^-]$$

k is the rate constant.

Now, let us look at other reactions between tert-butyl bromide and hydroxide ion:



$$CH_3 - \overset{\displaystyle CH_2}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}} - Br + OH^- \longrightarrow CH_3 - \overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}} - OH + Br^-$$

As before, if we doubled [RBr] the rate doubles; if we cut [RBr] in half the rate is halved. But, if we double $[OH^-]$, or if we cut $[OH^-]$ in half, there is no change in the rate. The rate of reaction is independent of $[OH^-]$.

The rate of reaction of tert-butyl bromides depends only upon [RBr]. This is indicated by the expression

$$\text{rate} = k\,[\text{RBr}]$$

The methyl bromide reaction is said to follow second-order kinetics since its rate is dependent upon the concentration of two substances. The tert-butyl bromide reaction is said to follow first-order kinetics; its rate depends upon the concentration of only one substance, tert-butyl bromide. It has been proposed that nucleophilic substitution can proceed by two different mechanisms.

### The $S_N2$ reaction: mechanism and kinetics[20]

The reaction between methyl bromide and hydroxide ion to yield methanol follows second-order kinetics; that is, the rate depends upon the concentrations of both reactants:

$$CH_3Br + OH^- \longrightarrow CH_3OH + Br^-$$

$$\text{rate} = k[CH_3Br][OH^-]$$

The simplest way to account for the kinetics is to assume that reaction requires a collision between a hydroxide ion and a methyl bromide molecule. It is known that in its attack the hydroxide ion stays as far away as possible from the bromine; that is to say, it attacks the molecule from the rear.

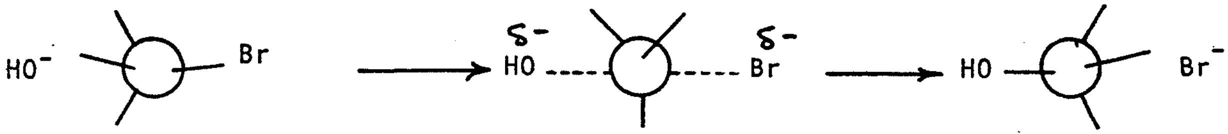


Figure 1, The $S_N2$ reaction: complete inversion of configuration. Nucleophilic reagent attacks back side.

The reaction is believed to take place as shown in Figure 1. When hydroxide ion collides with a methyl bromide molecule at the face most remote from the bromine, and when such a collision has sufficient energy, a C-OH bond forms and the C-Br bond breaks, liberating the bromide ion.

The transition state can be pictured as a structure in which carbon is partially bonded to both -OH and -Br; the C-OH bond is not completely formed, the C-Br bond is not yet completely broken. Hydroxide has a diminished negative charge, since it has begun to share its electrons with carbon. Bromine has developed a partial negative charge, since it has partly removed a pair of electrons from carbon. At the same time, of course, ion-dipole bonds between hydroxide ion and solvent are being broken and ion-dipole bonds between bromide ion and solvent are being formed.

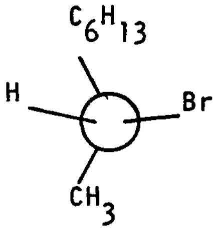
The -OH and -Br are located as far apart as possible; the three hydrogens and the carbon lie in a single plane, all bond angles being 120°. The C-H bonds are thus arranged like the spokes of a wheel, with the C-OH and the C-Br bonds lying along the axis.

This is the mechanism that is called $S_N2$: substitution nucleophilic bimolecular. The term bimolecular is used here since the rate-determing step involves collision of two particles.

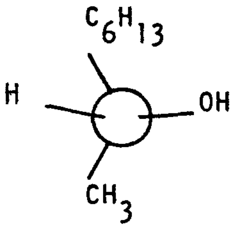
## The $S_N2$ reaction: sterochemistry[21]

Both 2-bromooctane and 2-octanol are chiral; that is, they have molecules that are not superimposable on their mirror images. Consequently, these compounds can exist as enantiomers, and can show optical activity.

The following configurations have been assigned



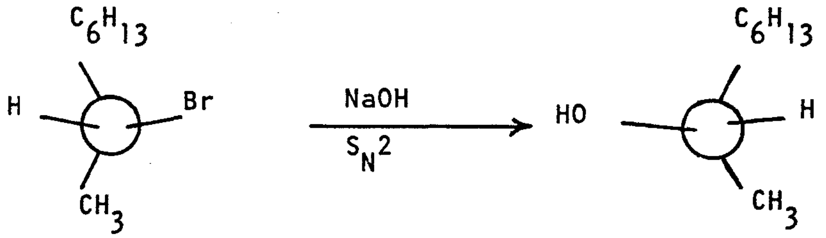
(-)-2-Bromooctane
[α] = -34.6°



(-)-2-Octanol
[α] = -9.9°

Both the (-)-bromide and the (-)-alcohol have similar configurations; that is, -OH occupies the same relative position in the (-)-alcohol as -Br does in the (-)-bromide.

When (-)-2-bromooctane is allowed to react with sodium hydroxide under conditions where second-order kinetics are followed, there is obtained (+)-2-octanol.

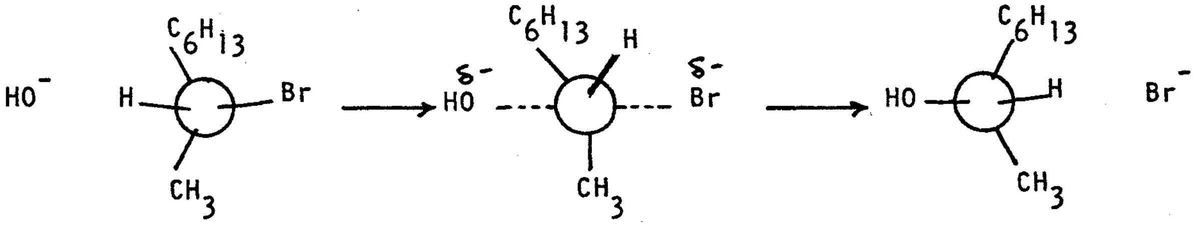


(-)-2-Bromooctane
Optical purity 100%

(+)-2-Octanol
Optical purity 100%

The -OH group has not taken the position previously occupied by -Br; the alcohol obtained has a configuration opposite to that of the bromide. A reaction that yields a product whose configuration is opposite to that of the reactant is said to proceed with inversion of configuration.

It was to account for inversion of configuration that back-side attack was first proposed for substitution of the $S_N2$ kind. As $OH^-$ becomes attached to carbon, three bonds are forced apart until they reach the planar "spoke" arrangement of the transition state; then as bromide is expelled, they move on to a tetrahedral arrangement opposite to the original one. This process has often been likened to the turning-inside-out of an umbrella in a gale.



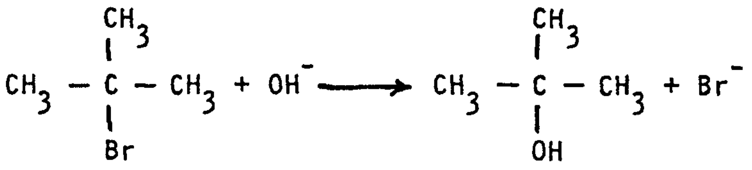
$S_N2$: Complete inversion

The stereochemistry of the 2-bromooctane reaction indicates back-side attack in accordance with the $S_N2$ mechanism; studies of other optically active compounds, under conditions where the reactions follow second-order kinetics, show similar results.

The $S_N2$ mechanism is supported, then, by stereochemical evidence. Indeed, the relationship between mechanism and stereochemistry is so well established that in the absence of other evidence complete inversion is taken to indicate an $S_N2$ reaction.

## The $S_N1$ reaction:[22] mechanism and kinetics. Rate-determining step

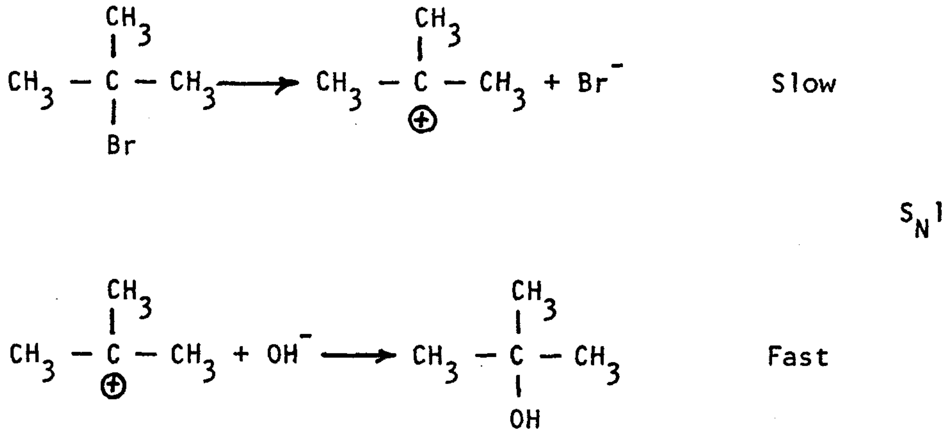
The reaction between tert-butyl bromide and hydroxide ion to yield tert-butyl alcohol follows first-order kinetics; that is, the rate depends upon the concentration of only one reactant, tert-butyl bromide.



$$CH_3-\underset{Br}{\overset{CH_3}{C}}-CH_3 + OH^- \longrightarrow CH_3-\underset{OH}{\overset{CH_3}{C}}-CH_3 + Br^-$$

$$\text{rate} = k\,[RBr]$$

The reaction proceeds with the following mechanism.



$$CH_3-\underset{Br}{\overset{CH_3}{C}}-CH_3 \longrightarrow CH_3-\underset{\oplus}{\overset{CH_3}{C}}-CH_3 + Br^- \qquad \text{Slow}$$

$$S_N1$$

$$CH_3-\underset{\oplus}{\overset{CH_3}{C}}-CH_3 + OH^- \longrightarrow CH_3-\underset{OH}{\overset{CH_3}{C}}-CH_3 \qquad \text{Fast}$$

tert-Butyl bromide slowly dissociates (step 1) into bromide ions and tert-butyl cations. The carbonium ions then combine rapidly (step 2) with hydroxide ions to yield tert-butyl alcohol.

The rate of the overall reaction is determined by the slow breaking of the C-Br bond to form the carbonium ion; once formed, the carbonium ion reacts rapidly to form the product. A single step whose rate determines the overall rate of a stepwise reaction is called a rate-determining step.

This is the mechanism that is called $S_N1$: substitution nucleophilic unimolecular. The term unimolecular is used here since the rate-determining step involves only one molecule (disregarding the many necessary solvent molecules). In general, an $S_N1$ reaction follows first-order kinetics. The rate of the entire reaction is determined by how fast the alkyl halide ionizes, and hence depends only upon the concentration of alkyl halide.

When (—)-2-bromooctane is converted into the alcohol under conditions (low $[OH^-]$) where first-order kinetics are followed, there is obtained (+)-2-octanol.

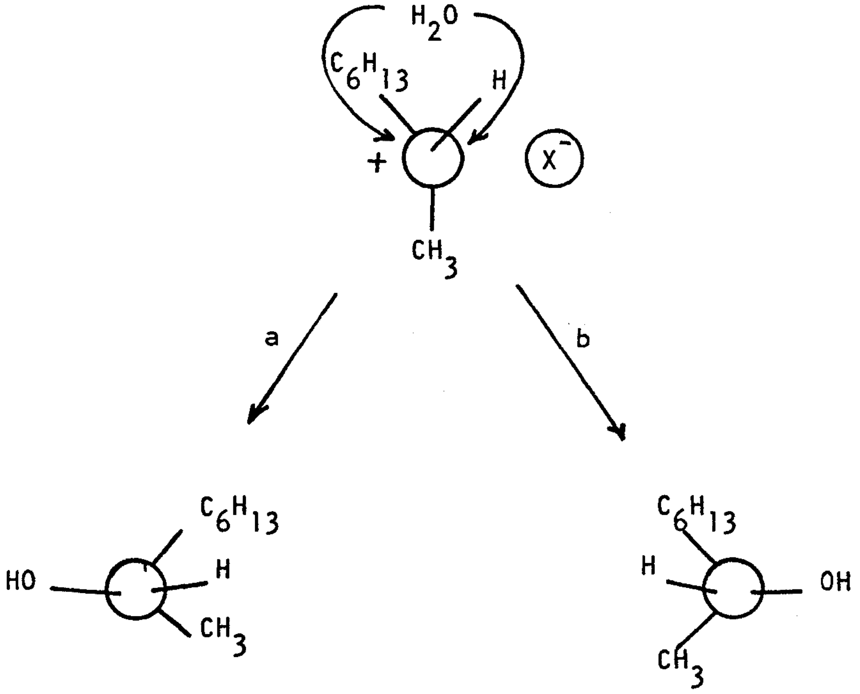
$$(-)\ \text{-}C_6H_{13}CHBrCH_3 \xrightarrow[S_N1]{OH^-,H_2O} (+)\ \text{-}C_6H_{13}CHOHCH_3$$

Lower optical purity

The product has the opposite configuration from the starting materials, as in the $S_N2$ reaction, but this time there is a loss in optical purity. The product is thus a mixture of the inverted compound and the racemic modification, and we say that the reaction has proceeded with partial racemization.

The carbonium ion, has a flat structure: carbon is bonded to three other atoms, and for this bonding uses $sp^2$ orbitals. Let us see how this shape affects the sterochemical course of the reaction.

In the first step the optically active 2-bromooctane ionizes to form bromide ion and the flat 2-octyl cation. The nucleophilic reagent $OH^-$ (or very possibly $H_2O$) then attaches itself to the carbonium ion. But it may attach itself to either face of this flat ion, and depending upon which face, yields one or the other of two products (see Fig. 2).



(a) Inversion
(Predominantes)

(b) Retention

Figure 2. The $S_N1$ reaction: racemization plus inversion. Nucleophilic reagent attacks both (a) back side and (b) front side of carbonium ion. Back-side attack predominates.

If the attack were purely random, we would expect equal amounts of the two isomers; that is to say, we would expect only the racemic modification. But the product is not completely racemized, for the inverted product exceeds its enantiomer. The attack by the nucleophilic reagent occurs before the departing halide ion has completely left the neighborhood of the carbonium ion; to a certain extent the departing ion thus shields the front side of the ion from attack. As a result, back-side attack is somewhat preferred.

In contrast to an $S_N2$ reaction, which proceeds with complete inversion, an $S_N1$ reaction proceeds with racemization.

## $S_N2$ vs. $S_N1$[23]

The strength of the evidence for the two mechanisms, $S_N1$ and $S_N2$, lies in its consistency. Nucleophilic substitutions that follow first-order kinetics also show racemization and rearrangement, and the reactivity sequence $3^o > 2^o > 1^o > CH_3X$. Reactions that follow second-order kinetics show complete stereochemical inversion and no rearrangement, and follow the reactivity sequence $CH_3X > 1^o > 2^o > 3^o$. Because there are two opposing reactivity sequences, we seldom encounter either of them in a pure form, but find instead a sequence that is a combination of the two. Most typically for halides, as we go along the series $CH_3$, $1^o$, $2^o$, $3^o$, reactivity passes through a minimum, usually at $2^o$:

$$\begin{array}{cccc} CH_3X > & 1^o > & 2^o > & 3^o \\ S_N2 & S_N2 & \text{Mixed} & S_N1 \end{array}$$

Reactivity by the $S_N2$ mechanism decreases from $CH_3$ to $1^o$, and at $2^o$ is so low that the $S_N1$ reaction begins to contribute significantly; reactivity now by $S_N1$, rises sharply to $3^o$. The change in mechanism at $2^o$ is confirmed by kinetics and other evidence.

We have already seen an example of this: high concentration of the nucleophilic reagent favors the $S_N2$ reaction; low concentration favors the $S_N1$ reaction.

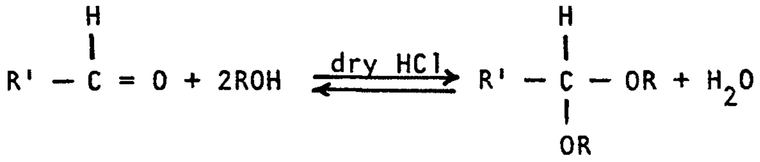
The nature of the nucleophilic reagent also plays an important role: for example, neopentyl bromide reacts with ethoxide ion by the $S_N2$ mechanism and with ethyl alcohol by the $S_N1$ mechanism. The strongly nucleophilic (strongly basic) ethoxide ion pushes halogen from the molecule, whereas the weakly nucleophilic ethanol waits to be invited in.

Finally, the polarity of the solvent can often determine the mechanism by which reaction occurs. Increasing the polarity of the solvent slows down the $S_N2$ reaction slightly. Other things being equal, the more polar the solvent, the more likely it is that an alkyl halide will react by the $S_N1$ mechanism.

## Other Related Reactions

Acetal formation:[24]

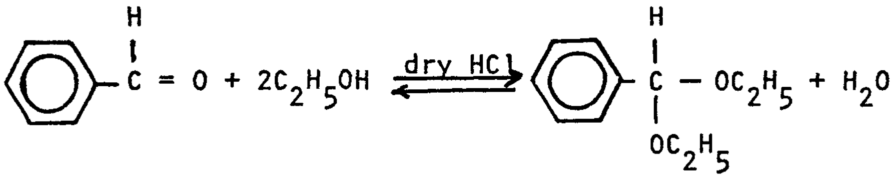
Alcohols add to the carbonyl group of aldehydes in the presence of anhydrous acids to yield acetals:



$$R' - \overset{H}{\overset{|}{C}} = O + 2ROH \xrightleftharpoons{\text{dry HCl}} R' - \underset{OR}{\underset{|}{\overset{H}{\overset{|}{C}}}} - OR + H_2O$$

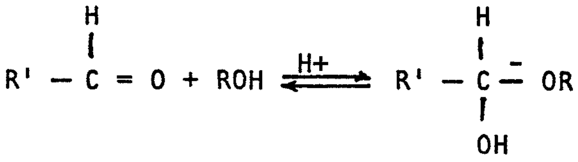
Aldehyde Alcohol Acetal

The reaction is carried out by allowing the aldehyde to stand with an excess of the anhydrous alcohol and a little anhydrous acid, usually hydrogen chloride. In the preparation of ethyl acetals the water is often removed as it is formed by means of the azeotrope of water, benzene, and ethyl alcohol (b.p. 64.9°,). (Simple ketals are usually difficult to prepare by reaction of ketones with alcohols, and are made in other ways.)



Benzaldehyde Ethyl alcohol Diethyl acetal of benzaldehyde

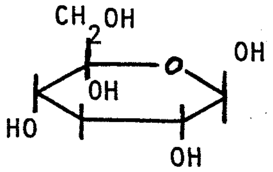
There is good evidence that in alcoholic solution an aldehyde exists in equilibrium with a compound called a hemiacetal:



$$R' - \overset{\displaystyle H}{\overset{|}{C}} = O + ROH \underset{}{\overset{H+}{\rightleftharpoons}} R' - \underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle H}{|}}{C}} - OR$$

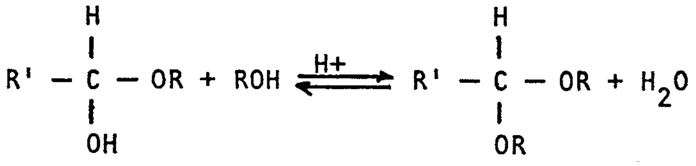
A hemiacetal

A hemiacetal is formed by the addition of the nucleophilic alcohol molecule to the carbonyl group; it is both an ether and an alcohol. With a few exceptions, hemiacetals are too unstable to be isolated. Glucose, as well as other sugars, exists predominantly as a hemiacetal.



β-D-glucose

In the presence of acid the hemiacetal, acting as an alcohol, reacts with more of the solvent alcohol to form the acetal, an ether:



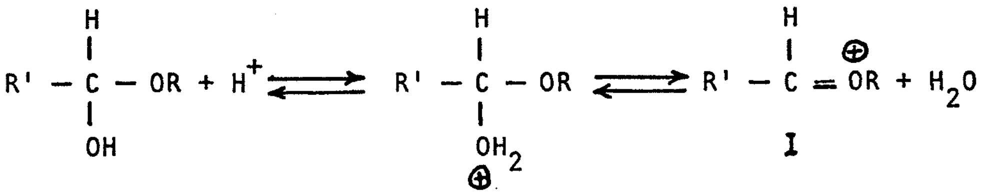
$$R' - \underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle H}{|}}{C}} - OR + ROH \overset{H+}{\rightleftharpoons} R' - \underset{\underset{\displaystyle OR}{|}}{\overset{\overset{\displaystyle H}{|}}{C}} - OR + H_2O$$

Hemiacetal
(An alcohol)

Acetal
(An ether)

The reaction involves the formation (step 1) of the ion I, which then combines (step 2) with a molecule of alcohol to yield the protonated acetal, as in the following equations:

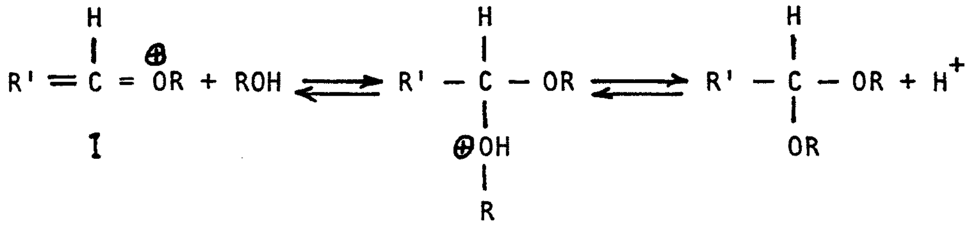
(1)



$$R'-\overset{H}{\underset{OH}{C}}-OR + H^{+} \rightleftharpoons R'-\overset{H}{\underset{\underset{\oplus}{OH_2}}{C}}-OR \rightleftharpoons R'-\underset{I}{\overset{H}{C}}=\overset{\oplus}{O}R + H_2O$$

Hemiacetal

(2)

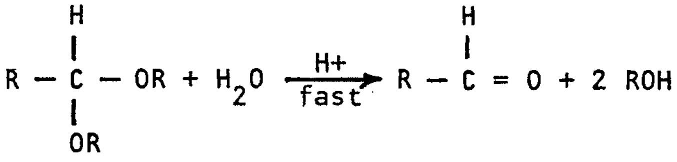


$$R'=\underset{I}{\overset{H}{C}}=\overset{\oplus}{O}R + ROH \rightleftharpoons R'-\overset{H}{\underset{\underset{R}{\oplus OH}}{C}}-OR \rightleftharpoons R'-\overset{H}{\underset{OR}{C}}-OR + H^{+}$$

Acetal

Acetal formation thus involves (a) nucleophilic addition to a carbonyl group, and (b) ether formation via a carbonium ion.

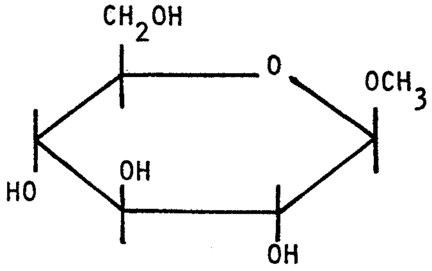
Acetals have the structure of ethers and, like ethers, are cleaved by aqueous acids and are stable toward bases. Acetals differ from ethers, however, in the extreme ease with which they undergo acidic cleavage; they are rapidly converted even at room temperature into the aldehyde and alcohol by dilute mineral acids. The mechanism of hydrolysis is exactly the reverse of that by which acetals are formed.



$$R-\overset{H}{\underset{OR}{C}}-OR + H_2O \xrightarrow[fast]{H+} R-\overset{H}{C}=O + 2\ ROH$$

Acetal Aldehyde Alcohol

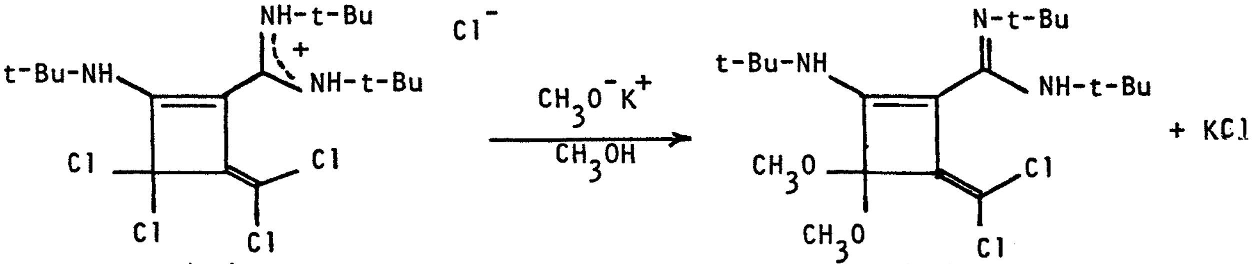
Methyl D-glucosides are formed when D-(+)-glucose treated with methanol and HCl. Although the products contain only one mole of methanol, they are nevertheless full acetals, the other mole of alcohol being D-(+)-glucose itself through the C-5 hydroxyl group. They are fairly stable in aqueous solution. On being heated with aqueous acids they undergo hydrolysis to yield the original hemiacetals. Toward bases glycosides, like acetals generally, are stable.



Methyl β-D-glucoside

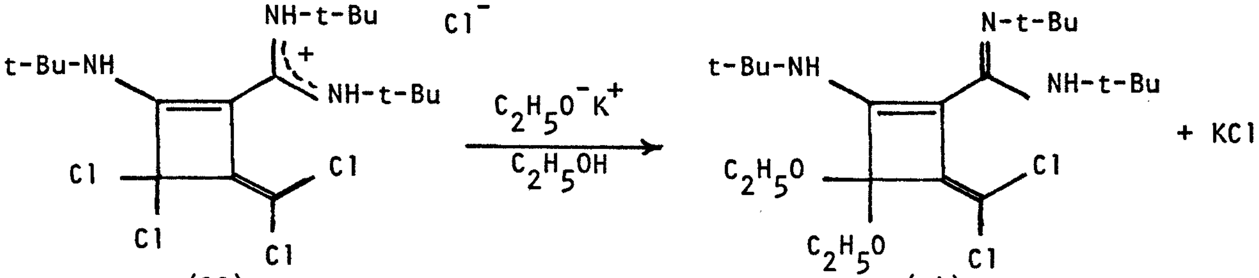
The equations of the five syntheses performed are listed below.

I The Reaction of the Amidinium Salt (32) with Potassium Methoxide



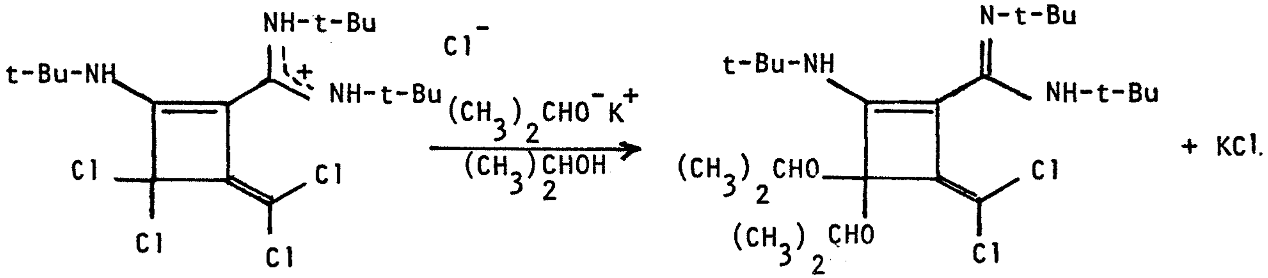
(32) (33)

II The Reaction of the Amidinium Salt (32) with Potassium Ethoxide



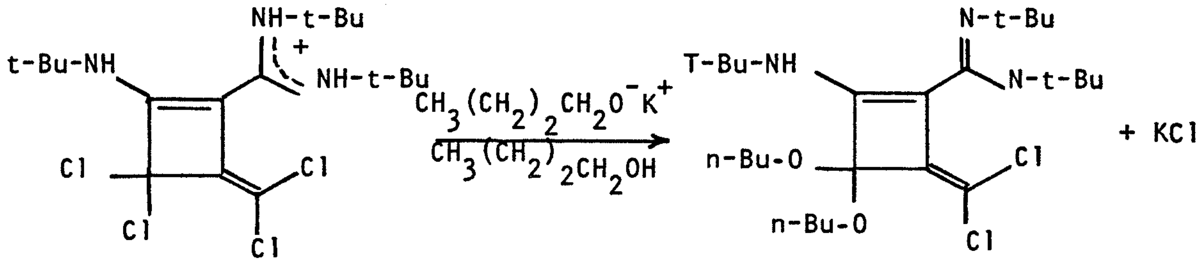
(32) (34)

III The Reaction of the Amidinium Salt (32) with Potassium Isopropoxide



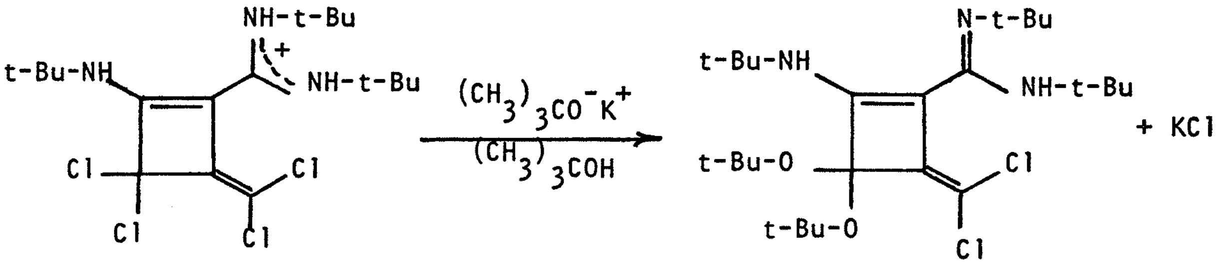
(32) (35)

## IV The Reaction of the Amidinium Salt (32) with Potassium n-Butoxide



(32) (36)

## V The Reaction of the Amidinium Salt (32) with Potassium tert-Butoxide



(32) (37)

## EXPERIMENTAL PROCEDURE

### N,N'-Di-tert-butyl-2-tert-butylamino-3,3-dichloromethylene cyclobutenyl cyclobutenyl carboxamidinium chloride (32)

Compound (3), 1,1,2,2-tetrachloro-3,4-bis (dichloromethylene) cyclobutane 11.0 grams (30.8 mmoles) was reacted with 66 ml (630 mmoles) of tert-butylamine.

The tert-butylamine was placed in a dropping funnel. Compound (3) was placed in 250 ml conical flask and dissolved in a 100 ml tetrahydrofuran, which was distilled from lithium aluminum hydride. tert-Butylamine was added gradually (over one hour) to the solution of compound (3) in THF, while stirring using a magnetic stirrer. During the addition the batch temperature kept under 40°C. After the addition of the tert-butylamine, the reaction mixture became cloudy and a white precipate was formed. The reaction mixture left overnight, then filtered to remove the white precipitate (tert-butylamine hydrochloride). The filtrate was then transferred into 250 ml round bottom flask, and rotary evaporated under vacuum (about 20 psi) to dryness to yield a brown mass. This brown mass was treated with carbon tetrachloride to dissolve the unreacted Compound (3) and grease, then the product was crystallized from chloroform-hexan to one spot on thin layer chromatography using 5% methanol in chloroform as a solvent.

A total of 6.4 grams of a pure colorless compound was recovered to yield 44.5% with melting point range of 258-265°C (decomposition).

For the elemental analysis, the calculated percentages for $C_{18}H_{30}N_3Cl_5$ were: carbon: 46.42%, hydrogen: 6.49%, nitrogen: 9.02%.
The actual percentages found were: carbon: 45.95%, hydrogen: 6.56%, nitrogen: 9.12%.

## Compound (33), N,N'-di-tert-butylamino-3,3-di-(methoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine.

Reaction of Compound (32) with potassium methoxide: A 1.5 N potassium hydroxide in methanol was freshly prepared and filtered by dissolving 7.0 grams of potassium hydroxide in 100 ml absolute methanol. A 1.6 grams (3.4 mmoles) of Compound (32) were dissolved in 25 ml methanol. Twenty milliliters of the potassium methoxide solution were placed in a dropping funnel, which was added gradually to the solution of Compound (32) at room temperature, and while stirring using the magnetic stirrer. The reaction mixture was kept for five days during which time a solid precipitated. The solid (potassium chloride) was removed by suction filtration, The filtrate was then transferred to 100 ml round bottom flask and rotary evaporated until dryness to yield 1.2 grams of a light brown material. This was crystallized from chloroform to yield 650 mg (48%) colorless crystals, which gave one spot on thin layer chromatography using 5% methanol in chloroform as solvent. Its melting point range, determined by Fisher Johns melting point apparatus was 218-222°C.

Samples of this product were placed in vials and submitted for elemental analysis, and NMR spectroscopy. Infrared spectrum was also performed. For elemental analysis, the calculated percentages for $C_{20}H_{35}N_3O_2Cl_2$ were: carbon: 57.14%, hydrogen: 8.33%, nitrogen: 10.0%, chlorine: 16.90%.

The actual percentages found were: carbon: 56.94%, hydrogen: 7.99%, nitrogen: 10.12%, chlorine: 17.64%.

### Compound (34), N,N'-di-tert-butylamino-3,3-di-(ethoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine

Reaction of Compound (32) with potassium ethoxide: A 1.5 N potassium hydroxide in anhydrous ethanol, was prepared by dissolving 7.0 grams of KOH in 100 ml 200 proof ethanol, then filtered. 3.2 grams (6.87 mmoles) of Compound (32) (the amidinium salt) was dissolved in 75 ml anhydrous ethanol. A 40 ml portion of the freshly prepared and filtered potassium ethoxide solution was placed in a dropping funnel, and was added slowly to the amidinium salt solution while stirring at room temperature. After the addition of potassium ethoxide, the reaction mixture became cloudy. The reaction mixture was left at room temperature for seven days, during which a solid potassium chloride was precipitated. The solid was removed by filtration. The filtrate was accurately transferred to 250 ml round bottom flask and rotary evaporated to about one fifth of its original volume. Distilled water was added. A precipitate was formed, filtered, then dried, to give 960 mg off white material with melting point range 205-208°C. The off white material was crystallized from carbon tetrachloride to yield 310 mg (10% yield) of colorless crystals. The melting point range of these crystals was 236-239°C.

An infrared spectra was determined and samples of this product were submitted for elemental analysis and NMR spectroscopy. For the elemental analysis, the calculated percentages for $C_{22}H_{39}N_3O_2Cl_2 \cdot 2\ H_2O$ were: carbon: 54.54%, hydrogen: 8.05%, nitrogen: 8.67%.

The actual percentages found were: carbon: 53.45%, hydrogen: 8.04%, nitrogen: 8.68%. The reaction gave also the same product when sodium hydroxide was used in place of potassium hydroxide in the preparation of ethoxide solution.

## Compound (35), N,N'-di-tert-butylamino-3,3-di-(2-propoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine

Reaction of Compound (32) (the amidinium salt) with potassium iso-propoxide:

Again and in the same way 1.5 N freshly prepared and filtered potassium hydroxide solution in isopropanol was prepared. A 3.2 grams (6.87 mmoles) of the amidinium salt (Compound 46) was dissolved in 150 ml isopropanol. The amidinium salt took about half hour to be dissolved in the isopropyl alcohol at room temperature, using a magnetic stirrer. A 40 ml portion of the potassium isopropoxide solution was added dropwise over a period of 60 minutes, to the amidinium salt solution, and while stirring.

The reaction mixture was kept stirring for two hours, then left at room temperature for five days, during which a solid of potassium chloride was precipitated. The solid was removed by filtration. The filtrate was accurately transferred to a 500 ml round bottom flask. The filtrate was then concentrated by rotary evaporation at a temperature about 50°C and 20 psi vacuum, to about one fourth of its original volume. Distilled water was added. The precipitate which formed was filtered off via suction filtration, then dried to give an off white material. This solid off white material was crystallized from carbon tetrachloride to yield 780 mg (23.8%) off white material. Its melting point range was 220-222°C. Infrared spectrum was determined and samples were submitted for elemental analysis and NMR spectroscopy. For elemental analysis, the calculated percentages for the isopropoxy derivative $C_{24}H_{43}N_3O_2Cl_2 \cdot H_2O$ were: carbon: 58.30%, hydrogen: 8.70%, nitrogen: 8.50%, chlorine: 14.37%.

The actual percentages found were: carbon: 58.79%, hydrogen: 8.75%, nitrogen: 8.48%, chlorine: 14.65%.

### Compound (36), N,N'-di-tert-butylamino-3,3-di-(n-butoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine.

Reaction of amidinium salt (Compound 32) with potassium n-butoxide: Potassium butoxide was freshly prepared by dissolving 7.0 gm of potassium hydroxide in 100 ml 1-butanol, then filtered. 3.2 grams (6.87 mmoles) of the amidinium salt (Compound 32) were dissolved in 75 ml of 1-butanol. A 50 ml of the freshly prepared potassium, n-butoxide was added dropwise from a dropping funnel into the amidinium salt solution at room temperature, and while stirring. After the addition was completed the reaction mixture kept stirring for three hours, which became cloudy. The batch kept at room temperature for 72 hours, during which a white solid was precipitated. The solid (potassium chloride) was removed by suction filtration. The solid weighed about 1.2 gm. The filtrate was accurately transferred to 250 ml round bottom flask. The filtrate was then concentrated by rotary evaporation at about 55°C-60°C and 20 psi vacuum. Another solid material was precipitated out; first it seemed to be a product. This solid material was filtered off, washed with chloroform. The filtrate was saved, and the white solid material was weighed and tested for its solubility in water and also to determine its melting point. It was found that this white solid material might be potassium chloride, it is soluble in water, and did not have a melting point and weighed about 1.2 grams.

The filtrate was rotary evaporated again, to give a light brown liquid. Extensive trials were performed to purify this material using chloroform, carbon tetrachloride, hexanes, ethanol, methanol and ethers. Difficulty has become encountered to obtain a solid material. The light brown liquid that was obtained has one spot with tailing on thin layer chromatography. The liquid product weighed 1.8 grams (52%), its infrared spectra was determined, and samples were submitted for elemental analysis and NMR spectroscopy.

For elemental analysis, the calculated percentages for $C_{26}H_{47}N_3O_2Cl_2$ were: carbon: 61.91%, hydrogen: 9.32%, nitrogen: 8.33%, chlorine: 14.08%. The actual percentages found were: carbon: 61.88%, hydrogen: 9.84%, nitrogen: 8.39%.

Compound (37), N,N'-di-tert-butylamino-3,3-di-(tert-butoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine.

Reaction of the amidinium salt (Compound 32) with potassium tert-butoxide: Potassium tert-butoxide solution was prepared by dissolving 8.4 grams of Potassium tert-butoxide into 100 ml of tert-butyl alcohol.

3.2 g (6.87 mmoles) of amidinium salt was dissolved into 200 ml tert-butyl alcohol at 50°C, and the reaction took place at the same temperature. A 100 ml of tert-butyl alcohol containing 8.4 grams of potassium tert-butyl was added gradually with stirring to the warm solution (50°C) of the Compound (32). The reaction mixture kept stirring at 50°C for three hours then left at room temperature for five days during which a solid was precipitated. The solid was removed by suction filtration. The filtrate was transferred to 500 ml round bottom flask. The filtrate was then concentrated by rotary evaporation to about one fifth of its original volume. Distilled water (100 ml) was added, and a solid was precipitated. The precipitate which formed, was filtered by suction filtration and then dried to give an off white material. This off white material was crystallized from methanol/water, to yield 350 mg (10%) off white product. Its melting point range was 110-115°C.

Infrared spectra was performed. For elemental analysis, the calculated percentages for $C_{26}H_{47}N_3O_2Cl_2$ were: carbon: 61.91%, hydrogen; 9.32%, nitrogen: 8.33%, chlorine: 14.08%.

(Sample for elemental analysis was mistakenly destroyed.)

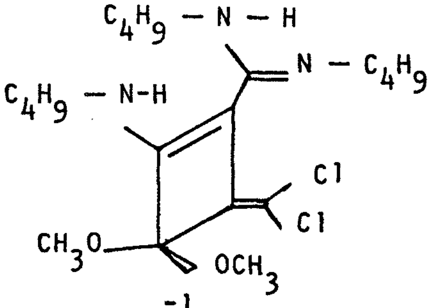
## DISCUSSION AND RESULTS

The infrared spectrum, NMR spectrum and elemental analysis of N,N'-di-tert-butylamino-3,3-di-(methoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine. N,N'-di-tert-butylamino-3,3-di-(ethoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine, N,N'-di-tert-butylamino-3,3-di-(2-propoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine, N,N'-di-tert-butylamino-3,3-di(-n-butoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine and N,N'-di-tert-butylamino-3,3-di-(tert-butoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine were performed at Beecham Products Research, Parsippany, New Jersey, New Jersey Institute of Technology, and MIC-ANAL Laboratory, Tuscon, Arizona, respectively. The infrared spectra were obtained by use of a Perkin-Elmer Spectrophotometer, Model 267. Potassium bromide dispersion pellets for the solids and sodium chloride cells for the liquid were used for the infrared spectra; the concentration of the product was about 0.5%. The NMR spectra were obtained by use of a Varian EM-360 60MHZ NMR Spectrometer. The solvent used was deutero chloroform. The elemental analysis, consisting of carbon, hydrogen, nitrogen and chlorine determinations, were performed by MIC ANAL Organic Microanalysis Laboratories. The melting points were performed on Fisher-Johns melting point apparatus.

Reaction of the amidinium salt (46) with a series of alkoxides ranging from methyl, ethyl, isopropyl, n-butyl and tert-butyl were performed. It is known that aliphatic halogens can be replaced by strong neucluphiles, and in fact that if there is a second halogen already present on the carbon, it would be more easily displaced. It was expected that the saturated carbon of four membered ring would lose halogen more easily than would the vinylic carbon which also bears halogens.

### N,N'-di-tert-butylamino-3,3-di-(methoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine

Treatment of the N,N'-di-tert-butyl-2-tert-butylamino-3,3-dichloromethylene cyclobutenyl carboxamindinum chloride (32, amidinium salt) with a solution of methanol and potassium methoxide in methanol at room temperature for five days yielded a precipitate which was identified subsequently as potassium chloride. Present in solution was a compound that was obtained by thin layer chromatography and was purified to one spot on a TLC by 5% methanol in chloroform. The product thus obtained displayed an infrared spectrum consistent with the following structure.



Prospective view of Compound (33)

Strong absorption at 3000 $cm^{-1}$ for C-H absorption was indicated, a medium absorption at 3200 $cm^{-1}$ which may be due to the N-H vibration of the amino groups present in the product. Significantly multiple bond absorption at 1680 $cm^{-1}$, 1610 $cm^{-1}$ and 1580 $cm^{-1}$ which is due to 3-multiple bond absorptions in the product, the dichloromethylene, the cyclobutenyl and the amidine double bonds, all should absorb in that region. The tert-butyl absorption is displayed at 1370 $cm^{-1}$ and 1450 $cm^{-1}$ with pronounced two methoxy absorption due to the methoxy groups at the four membered ring at 1400 $cm^{-1}$ and 1490 cm-1. Further characteristic absorption for C-O-C of the ether at 1180 $cm^{-1}$ is present reasonably strong. The infrared spectrum, therefore, is very much consistent with the proposed structure.

The NMR spectrum of the dimethoxy amidinium Compound (33) in deuterochloroform ($CDCl_3$) was quite revealing. It displayed two singlets centered around 1.5 δ in a ratio of almost 1:2 as indicated by the integration curve, for the tert-butyl groups protons. This spectrum may be explained by assuming that the tert-butyl groups occupy a less crowded external amidinium positions causing them to be magnetically equivalent. If the enamine tert-butyl preferentially occupies one position, or undergoes rapid free rotation about the enamine nitrogen, a 1:2 ratio would be observed.

The spectrum showed an equivalent methoxy group proton resonance around 3.6 δ, whose area indicated an approximately 1:5 ratio, consistent with two equivalent methyls and three tert-butyls. The spectrum also showed the amino group protons which appeared in two different positions; one may be deshielded (shifted) at approximately 1.7 δ and the second is a broad peak at 5.6 δ. In general, the IR, NMR spectra and the elemental analysis appear to agree with the proposed structure.

### N,N'-di-tert-butylamino-3,3-di-(ethoxy)-4,4-dichloromethylene cyclobutenyl carboxamine, (34).

There is a marked similarity between the methoxide derivative compound and the ethoxide amidinium derivative compound. The ethoxide product was obtained from the treatment of the amidinium salt (32) with ethanol and potassium hydroxide. This mixture was kept at room temperature for five days. The expected undesolved potassium chloride salt was them removed by filtration. The reaction mixture filtrate contained both the ethoxide, and the hydroxide ions, and the amidine. Work up the filtrate generated the product which, like the methoxide product, has one spot on TLC with 5% methanol in chloroform as the solvent.

The infrared absorption spectrum is similar to the methoxide product. There is very strong C-H absorption in the 3000 $cm^{-1}$ region as expected. Three peaks appear in the multiple bond region as well, medium absorption at 1680 $cm^{-1}$ and also two strong absorptions at 1580 $cm^{-1}$ and 1610 $cm^{-1}$ which are due to the three multiple bonds in the molecule. The peaks which are due to tert-butyl groups appeared at 1365 $cm^{-1}$ and 1450 $cm^{-1}$. The ethyl absorption also appeared at 1400 $cm^{-1}$ and 1480 $cm^{-1}$, very much like the methyl absorption.

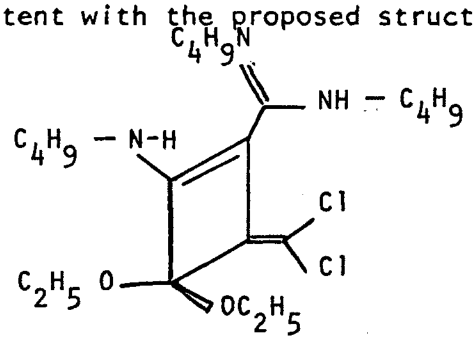
An ethyl absorption which should appear between 1000 $cm^{-1}$ and 1100 $cm^{-1}$ region, does appear strongly at 1030 $cm^{-1}$ and also at 780 $cm^{-1}$. These absorptions are consistent with an ethyl substitution vibration, in addition to the absorption at 1200 $cm^{-1}$ most likely to the absorption of ethoxy group.

The ether absorption C-O-C of the ethoxy group strongly appears at 1180 $cm^{-1}$. This was also similar to the 1180 $cm^{-1}$ peak of the methoxy derivative. Therefore, this spectrum is also consistent together with its N-H absorption at 3300 $cm^{-1}$ with the proposed compound structure.

NMR Spectrum of the Ethoxy derivative

The ethoxy derivative product (34) displayed the two singlets centered around 1.5 δ in a ratio of almost 1:2 indicating the tert-butyl groups, which we assumed that the tert-butyl amino groups are in an equivalent magnetic field around the enamine nitrogen. The area under the curve as indicated by the integration curve, covers approximately 5.8 : 2.7 large boxes. A triplet at about 1.2 δ suggests a methyl group spin coupled to a neighboring methylene, which part of it overlaped with tert-butyl singlets. The quartet appears at 3.8 δ which covers an area of approximately one large box, could be a methylene group spin coupled by a methyl group protons. The methylene quartet is deshielded considerably, which indicates that it is bound to oxygen. The quartet and triplet are immediately recognized as characteristics of an ethyl group. Two singlets appeared at 2 δ and at 5.2 δ were assigned to the tert-amine protons. The area under the curve is three small boxes.

The infrared, NMR interpretation and the elemental analysis appear to be very much consistent with the proposed structure (34).



(34)

### N,N'-di-tert-butylamino-3,3-di-(2-propoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine (35).

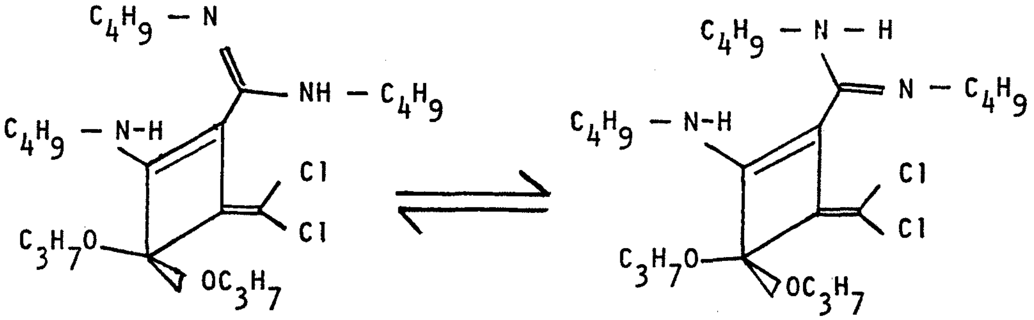
The isopropoxy derivative was prepared in similar way, by treating the amidinium salt in isopropanol with potassium hydroxide in isopropanol solution. The reaction mixture was left at room temperature for five days, during which time a solid (potassium chloride) was precipitated. The filtrate was worked up to yield the product. The product was crystallized from carbon tetrachloride to give the isopropoxy compound. The infrared absorption of the isopropyl group is little different from the previous spectra, which still appeared at 1190 cm-1. The 3-peaks are due to carbon-carbon multiple bonds in the product, still appeared in the same position 1680 $cm^{-1}$, 1610 $cm^{-1}$ and 1580 $cm^{-1}$.

The tert-butyl and isopropyl absorption are properly overlapped and look stronger at 1365 $cm^{-1}$ and 1460 $cm^{-1}$, because isopropyl is very much like the tert-butyl on its absorptions. Again, C-O-C ether absorptions appear between 1100 - 1200 $cm^{-1}$ and start to coalesce. There is a medium bond between 910 $cm^{-1}$ and 930 $cm^{-1}$ doublet for the isopropyl, consistent with the isopropyl derivative structure. We found also another weak band between 960 - 980 $cm^{-1}$ for the isopropyl.

NMR Spectrum of iso-propoxy derivative:

Insepction of the spectrum reveals that there are four types of protons and three groups show spin coupling. The spectrum displayed the two singlets for the tert-butyl protons located at almost 1.5 δ as they were seen in the previous spectra, which still has a ratio of 1:2 indicated by the integration curve. We observe a doublet and a low signal gain septet, which of course, spin coupled. The chemical shifts of the coupled multiplets suggests the possibility of a methyl resonance around 1.25 δ and a methine resonance at 4.4 δ. The methine septet deshielded considerably, which indicates that it is bound to an oxygen. It should be noted that if a second trace was run at a higher gain and concentration, would give a larger spin coupling peaks specially with the methine septet.

The spectrum also displayed broad singlets at 1.7 δ and 5.15 δ which would be assigned to the exchangeable protons of the tert-amino groups. The exchangeable protons give resonances for which both position and width are quite variable.



The NMR spectra assignments, IR interpretation and the elemental analysis agreed with postulated compound structure.

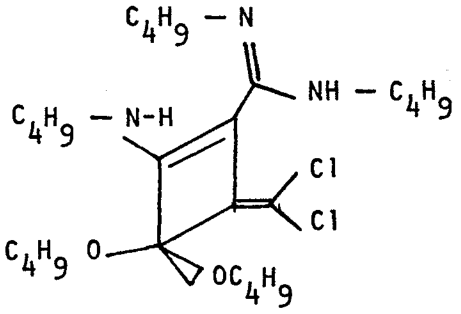
### N,N'-di-tert-butylamino-3,3-di-(n-butoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine, (36).

The reaction of n-butoxide in n-butyl alcohol with the amidinium salt took a course different from the methoxide, ethoxide, and isopropoxide, that the product isolated after the removal of potassium chloride salt is apparently a liquid, and cannot be solidified even after extensive purification. Thin layer chromatography shows in addition to the one spot tailing and difficulty of removal of this compound has been encountered. However, the material that was isolated, although fairly pure is liquid rather than solid as in the case of the previous compounds. The infrared spectrum likewise looks somewhat different, there is a relatively weak N-H absorption in the liquid state. The C-H absorption that is located at 2900 - 3000 $cm^{-1}$ is present, also there is the three absorption peaks in the 1600 - 1700 $cm^{-1}$ region, which would again agree with the proposed structure. Tert-butyl absorption appears at 1360 $cm^{-1}$ and 1470 $cm^{-1}$. Strong ether absorption and tert-butyl absorption appears at 1100 $cm^{-1}$ and 1200 $cm^{-1}$, and a butyl absorption at 750 $cm^{-1}$ is likewise present.

The unsatisfactory details in the infrared spectrum are most likely due to the liquid state and possible small impurity present in the material that has been isolated.

## NMR Spectrum of n-butoxide derivative

The NMR spectrum of n-butoxide derivative is quite difficult to interpert. However, the spectrum showed the two singlets of the tert-butyl group protons at approximately 1.35 δ. The spectrum displayed a triplet at 0.85 δ suggesting a methyl group spin coupled to a neighboring methylene, while a triplet at about 3.5 S could be a methylene group coupled to a second methylene and also bonded to oxygen to account for the observed deshielding. A multiplet centered (overlapped with singlets of tert-butyl group protons) at approximately 1.5 δ is a methylene group between two methylenes with equivalent spin coupling. So far, we have postulated the tert-butyl and n-butoxy groups. The assignment for the broad singlet at 2.25 δ and another singlet at 5.15 δ for the tert-amino protons completes the interpretation of the spectrum to agree with the proposed structure for the n-butoxy derivative of the amidinine compound.



(36)

### N,N'-di-tert-butylamino-3,3-di-(tert-butoxy)-4,4-dichloromethylene cyclobutenyl carboxamidine.

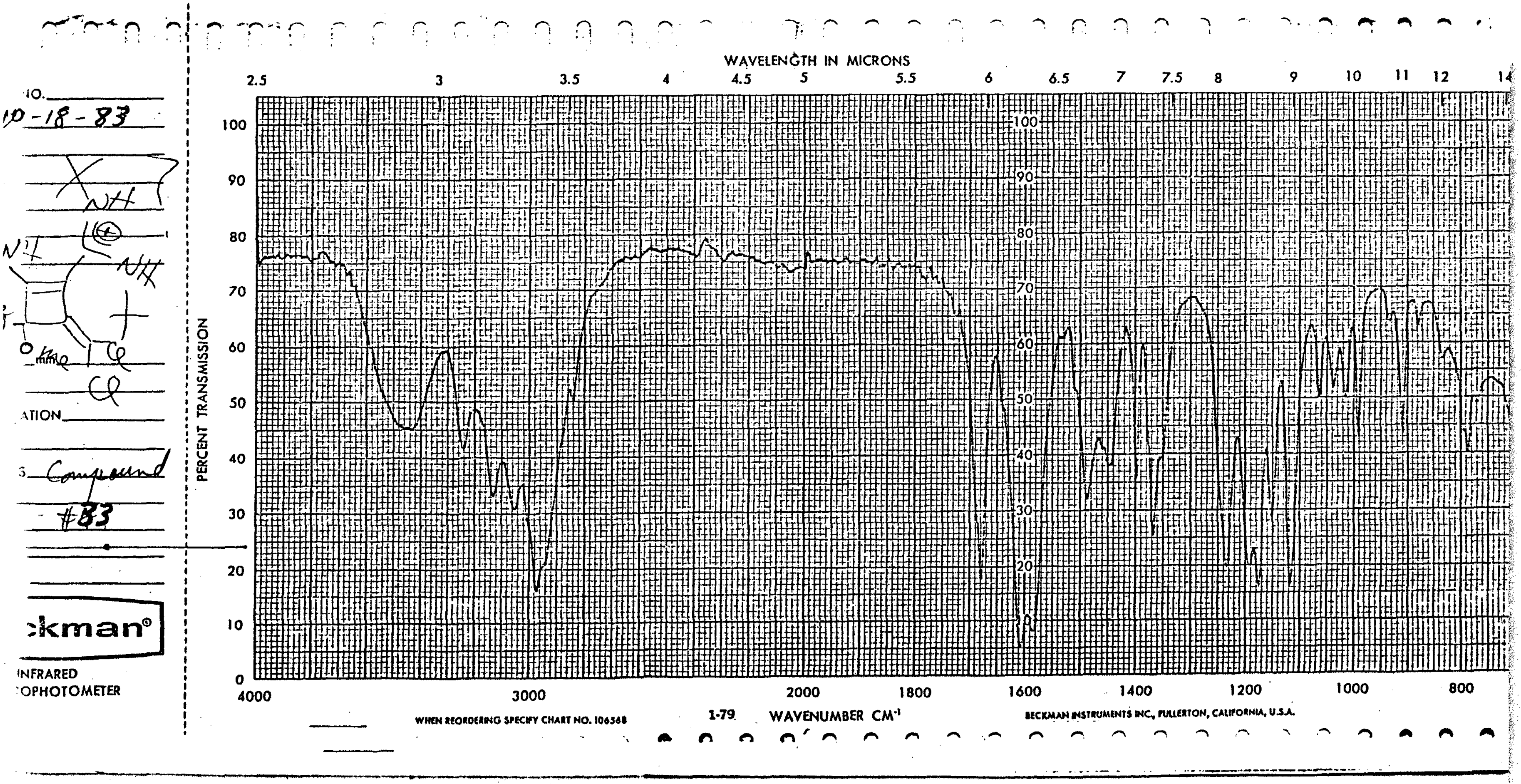
The tert-butoxy derivative was synsthesized by dissolving the potassium tert-butoxide in tert-butyl alcohol, and allowing the reaction to run at 50°C over a period of one hour. The elevated temperature was necessary to dissolve the N,N'-di-tert-butyl-2-tert-butylamino-3,3-dichloromethylene cyclobutenyl carboxamidinium chloride (amidinium salt) in tert-butyl alcohol, since the amidinium salt is slightly soluble at room temperature. After three hours at the elevated temperature, a copious quantity of potassium chloride had deposited. This was removed. The filtrate was worked up in the same manner as in the previous reactions. A solid compound was isolated and purified from methanol/water, and infrared spectrum was obtained. The infrared spectrum shows a broad N-H absorption at 3300 $cm^{-1}$, distinct C-H absorption between 2900 - 3000 $cm^{-1}$. Again three peaks between 1600 $cm^{-1}$ and 1720 $cm^{-1}$ for the three carbone, carbone double bond absorptions. Strong tert-butyl absorptions at around 1360 $cm^{-1}$ and 1450 $cm^{-1}$. Ether absorption C-O-C at 1200 $cm^{-1}$ is also present. In general, this infrared spectrum is relatively simple. This is in fact, attributed to the fact that the only alkyl substitutions are the five tert-butyl groups. The only other absorptions are the N-H and C-C stretching type vibrations. So, the spectrum that was obtained is as expected. Unfortunately, the sample for NMR spectrum and elemental analysis was mistakenly destroyed. This reaction should be repeated under identical conditions for final verification.

# CONCLUSION

This thesis helped to further advance the findings of many researchers who reacted cyclobutenyl amidinium compounds with alkoxides to form various cyclobutenyl ketals. Even though some of these alkoxides were bulky, steric effect did not inhibit formation of the ketals. In fact, these products were relatively stable as evidenced by their elevated melting points. In addition, the reaction of the amidinium salt with methoxide, ethoxide, propoxide, n-butoxide and t-butoxide produce the correspondent ketal derivatives.

The reaction of the amidinium compound with tert-butoxide should be repeated under identical conditions for final verifications.

# FIGURE I

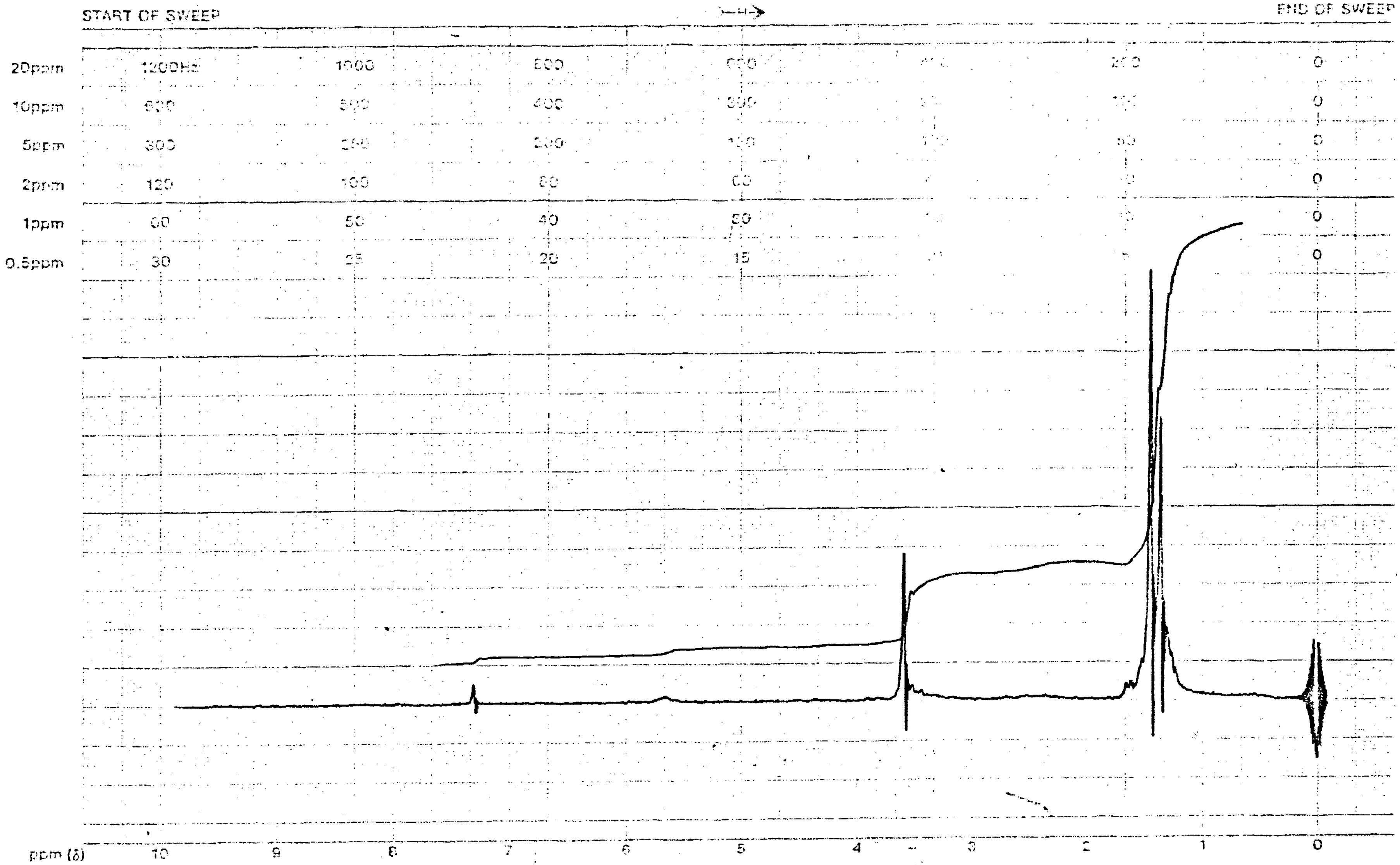


IO. 10-18-83

ATION

S Compound #83

# FIGURE 11



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DECOUPLING POWER________mG

SPECTRUM AMPL.________
FILTER________sec
RF POWER________mG

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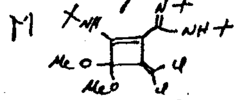
SWEEP WIDTH________ppm
END OF SWEEP________ppm

NUCLEUS________
ZERO REF. TMS
SAMPLE TEMP. RT C

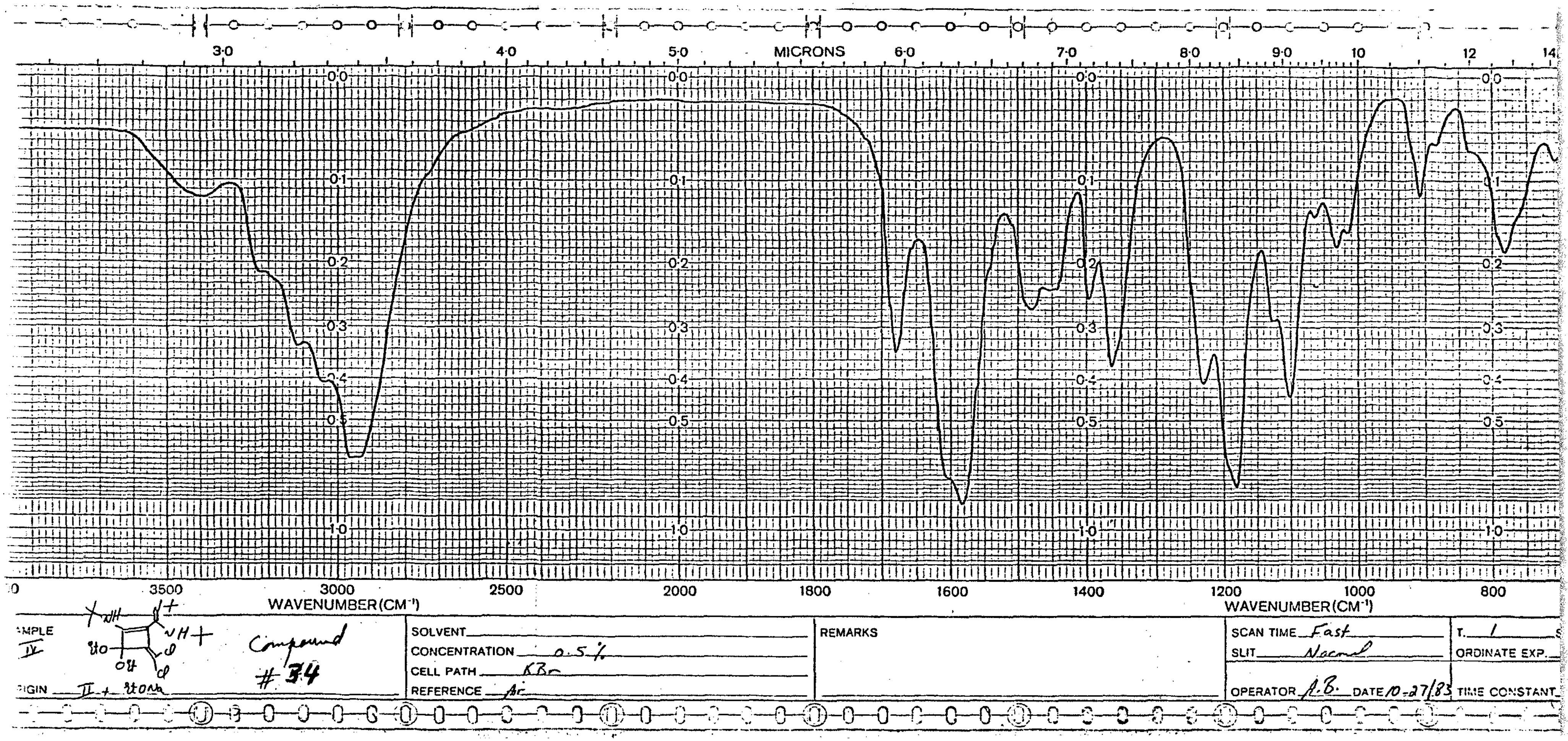
SAMPLE: Compound #33



SOLVENT: CDCl3

OPERATOR________
DATE April, 84
SPECTRUM NO.________

# FIGURE III



MPLE IV

Compound # 34

IGIN II + EtONa

SOLVENT

CONCENTRATION 0.5%

CELL PATH KBr

REFERENCE Air

REMARKS

SCAN TIME Fast

SLIT Normal

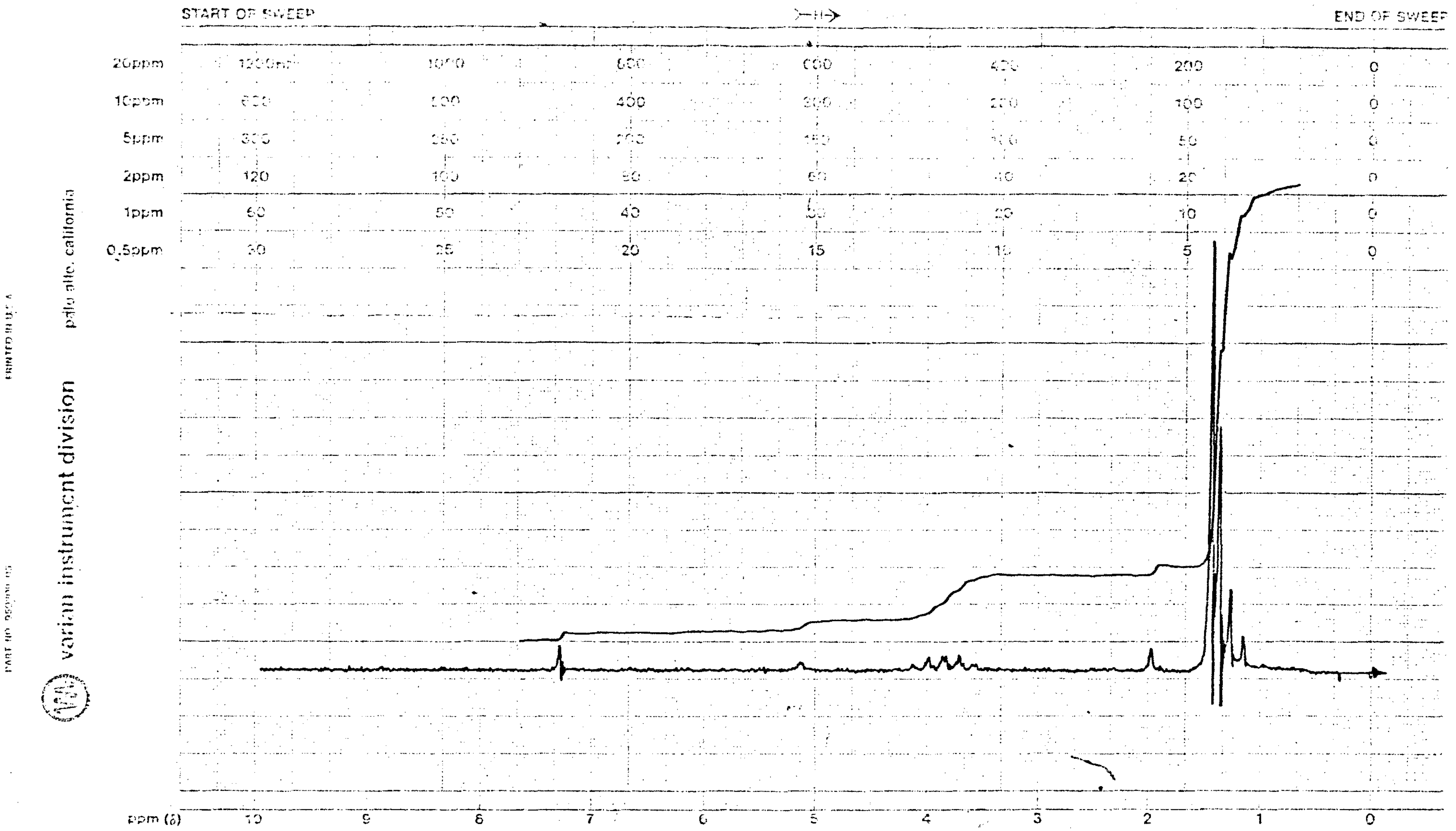
OPERATOR A.B. DATE 10-27/83

T. 1

ORDINATE EXP.

TIME CONSTANT

## FIGURE IV



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DECOUPLING POWER mG

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RF POWER .015 mG

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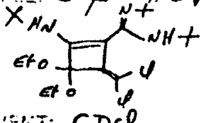
END OF SWEEP 0 ppm

NUCLEUS
ZERO REF. TMS
SAMPLE TEMP. room Tem °C

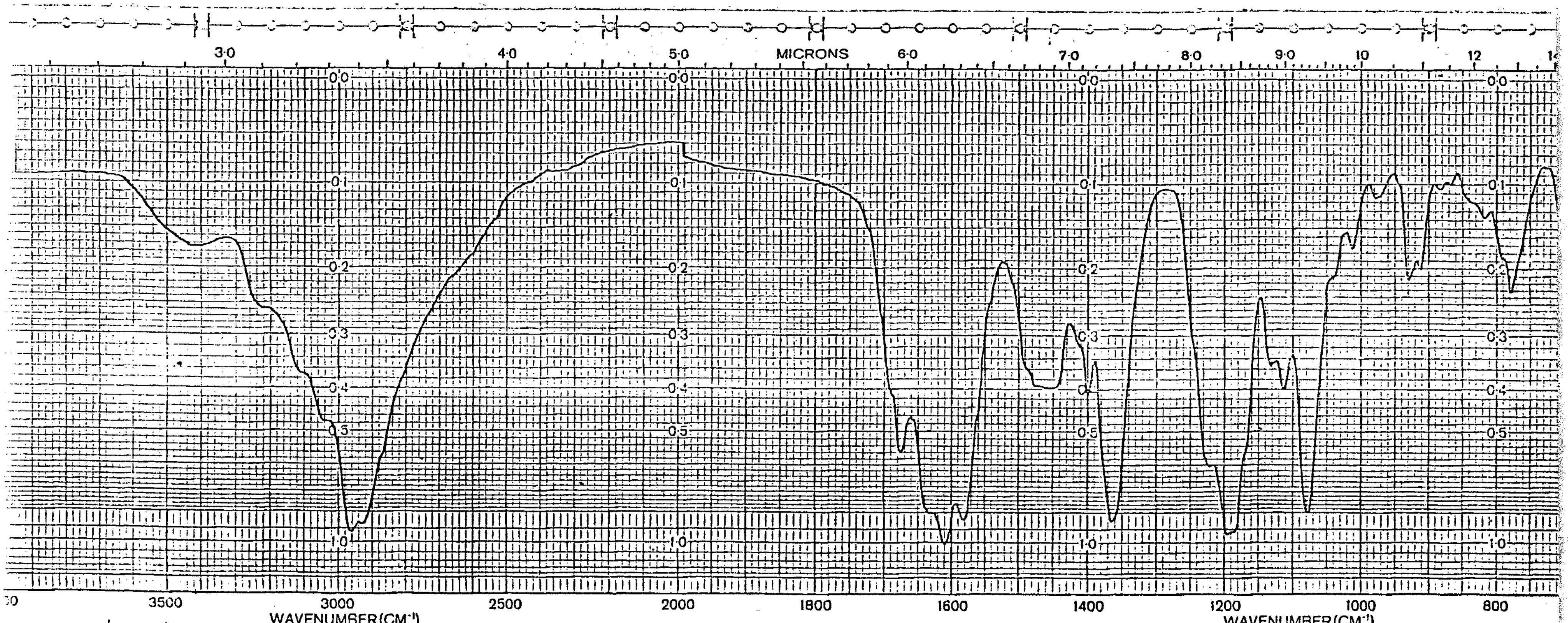
SAMPLE: Compound # 34



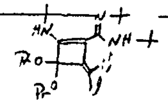
SOLVENT: CDCl3

OPERATOR
DATE April, 84
SPECTRUM NO.

# FIGURE V



AMPLE V



IGIN II + PrOK

Compound #35

SOLVENT

CONCENTRATION 0.5%

CELL PATH KBr

REFERENCE Air

REMARKS

SCAN TIME Fast

SLIT Normal

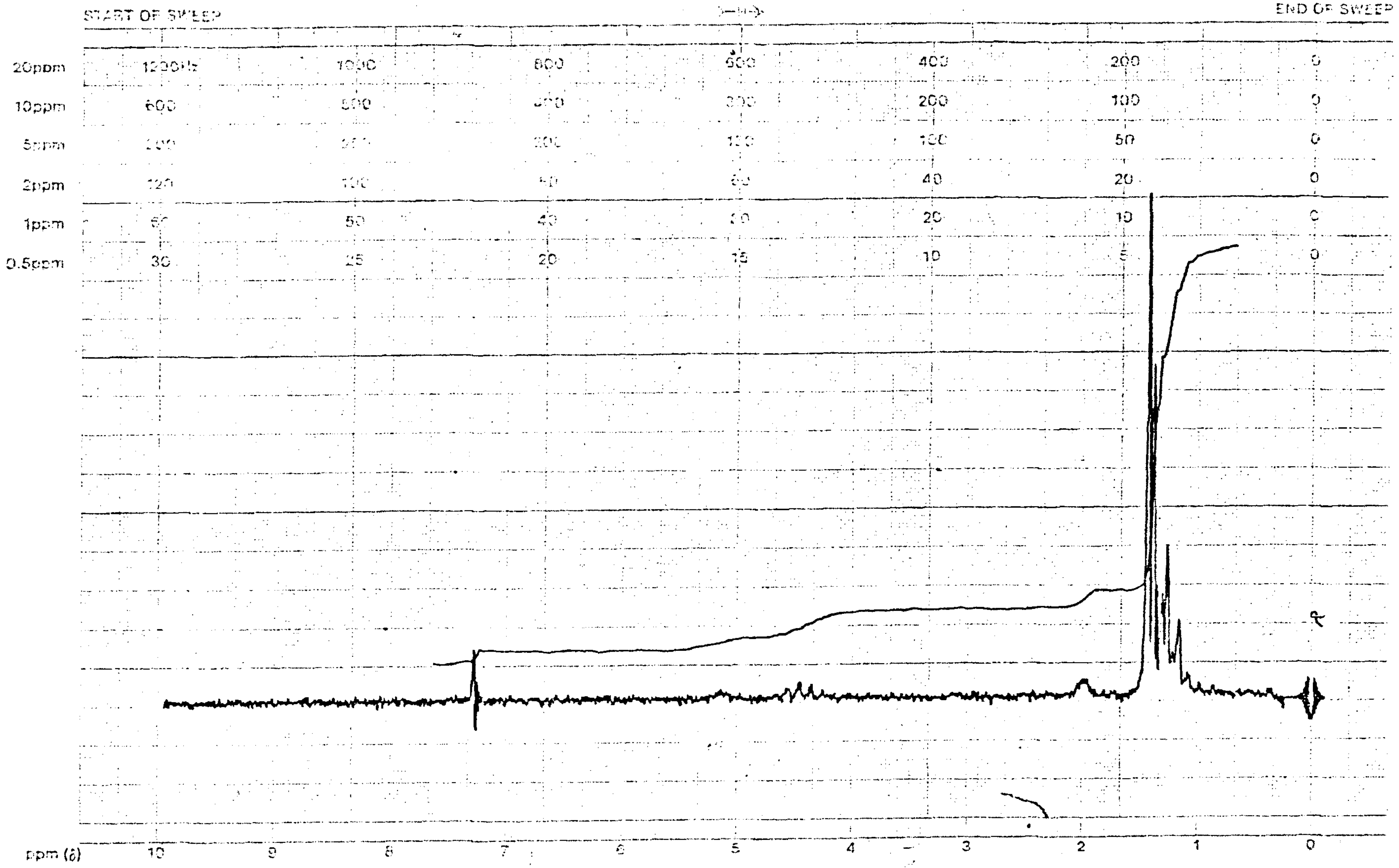
OPERATOR AB DATE 11/29/83

T. 1

ORDINATE EXP.

TIME CONSTANT

# FIGURE VI



varian instrument division

palo alto, california

PRINTED IN U.S.A.

LOCK POS.______ppm

LOCK POWER______mG

DECOUPLE POS.______ppm

DECOUPLING POWER______mG

SPECTRUM AMPL. 4000

FILTER______sec

RF POWER______mG

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SWEEP WIDTH______ppm

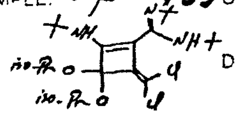
END OF SWEEP______ppm

NUCLEUS______

ZERO REF. TMS

SAMPLE TEMP. RT °C

SAMPLE: Compound #35



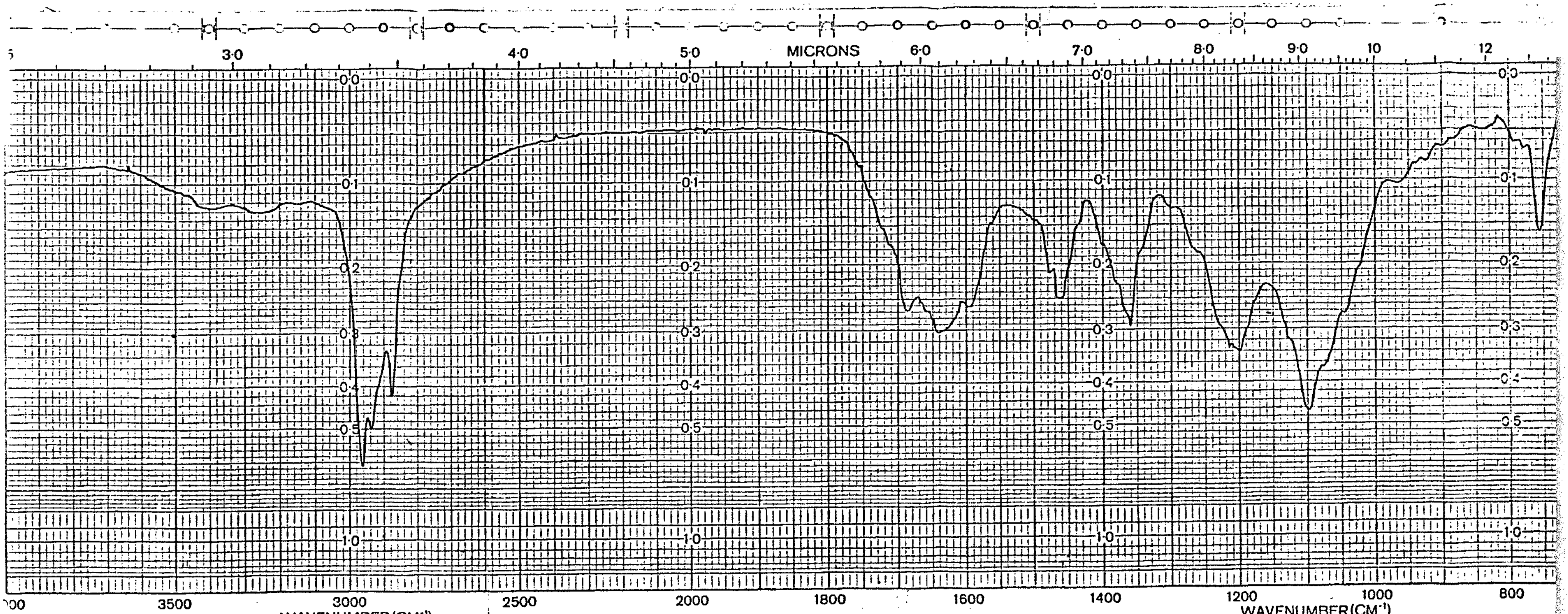
SOLVENT:

OPERATOR______

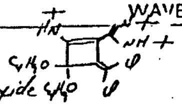
DATE. April, 94

SPECTRUM NO.______

# FIGURE VII



SAMPLE Cmpd. VII



II + n-butoxide

Compound #36

ORIGIN

SOLVENT

CONCENTRATION 100 %

CELL PATH Sod. chloride

REFERENCE air

REMARKS Liquid

SCAN TIME Fast

SLIT Normal

OPERATOR

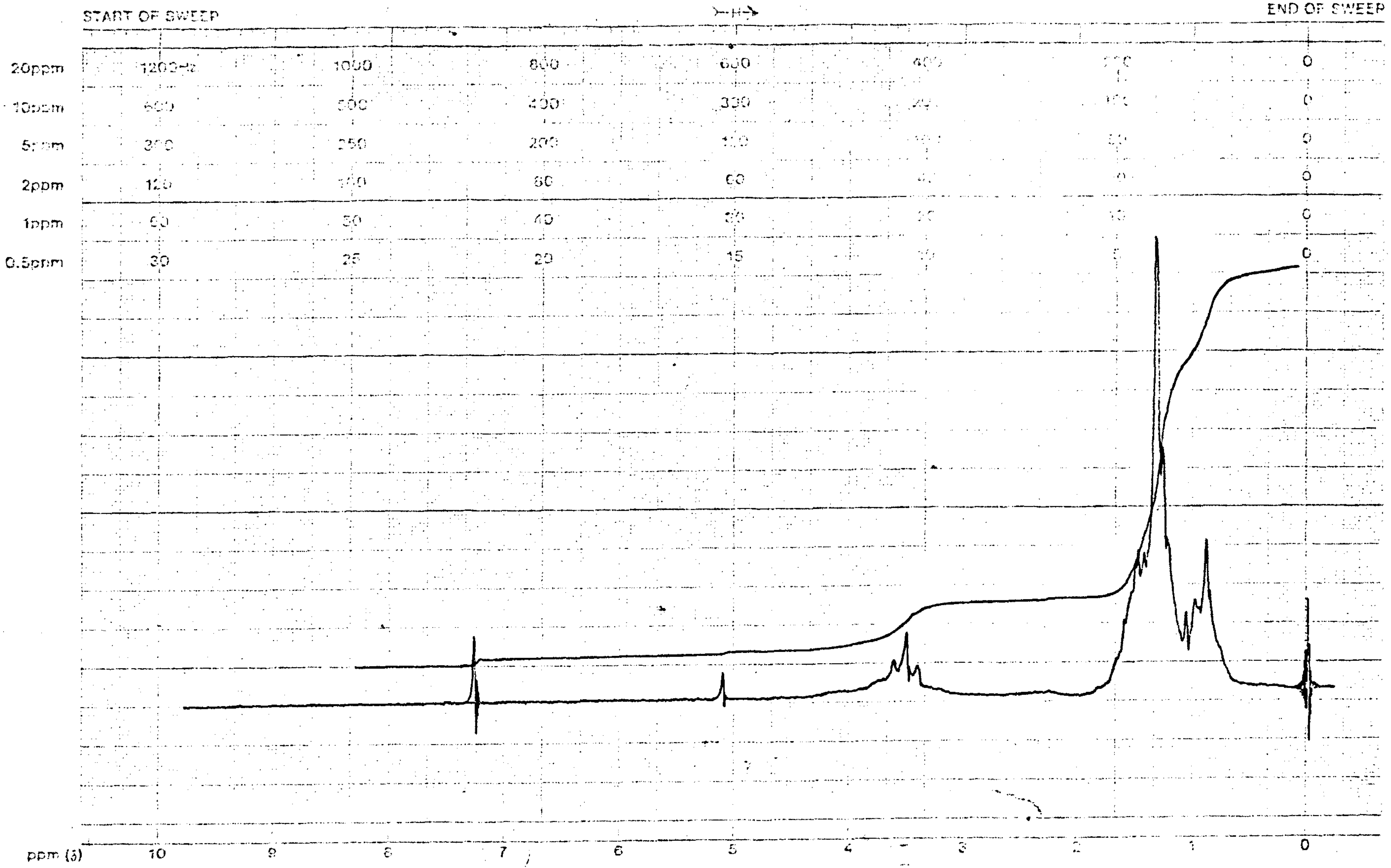
DATE 4/18/84

T. 1

ORDINATE EX

TIME CONSTA

# FIGURE VIII



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DECOUPLING POWER ______ mG

SPECTRUM AMPL. 600
FILTER ______ sec
RF POWER ______ mG

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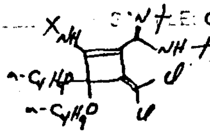
SWEEP WIDTH ______ ppm
END OF SWEEP ______ ppm

NUCLEUS ______
ZERO REF. TMS
SAMPLE TEMP. RT °C

SAMPLE: Compound #36

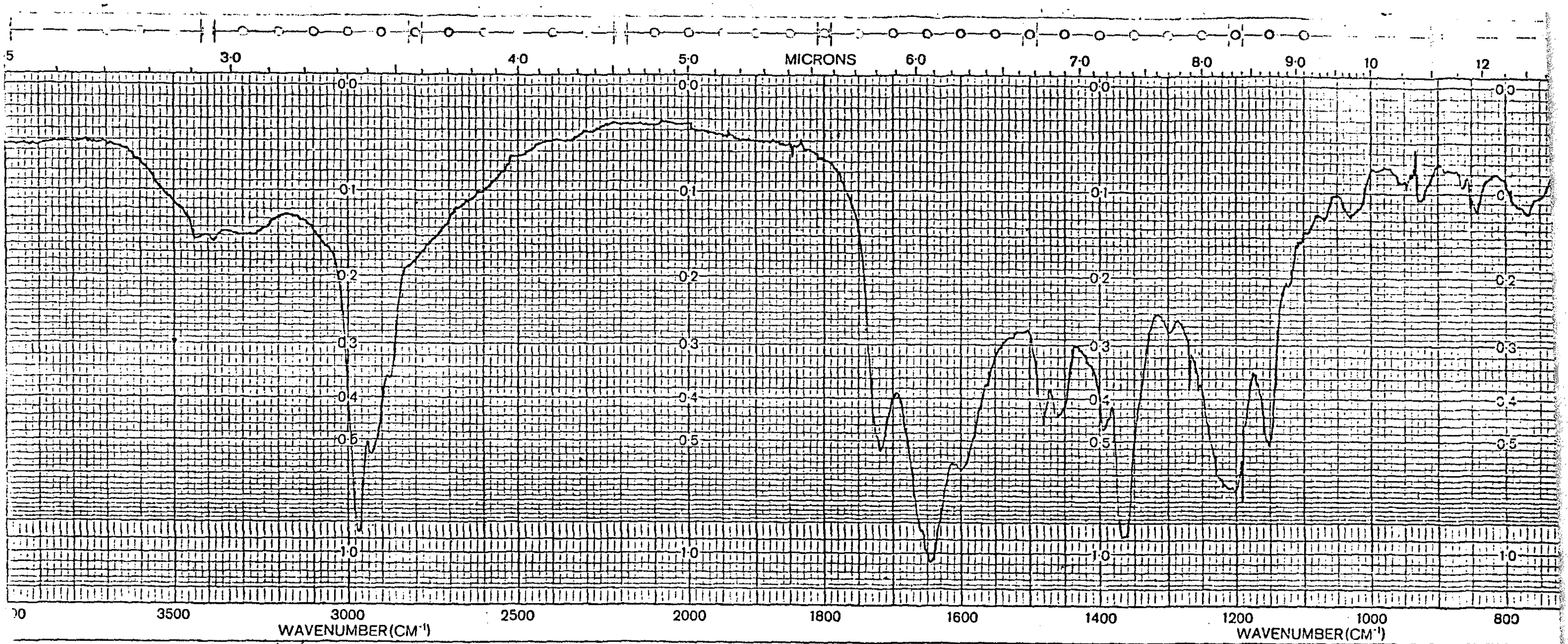


VII

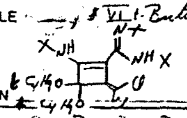
SOLVENT: CDCl3

OPERATOR ______
DATE 4/84
SPECTRUM NO. ______

## FIGURE IX



SAMPLE — # VI t-Butoxide Derivative



Compound #37

ORIGIN II + tBuOK

SOLVENT

CONCENTRATION 0.5 %

CELL PATH KBr

REFERENCE Air

REMARKS

SCAN TIME fast

SLIT Normal

OPERATOR AB DATE 11/11/74

T. 1

ORDINATE EXP.

TIME CONSTAN

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