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Reduction of 1,2 cyclopentanedione with lithium aluminum hydride

David Curtis Winn
College of William & Mary - Arts & Sciences

REDUCTION OF 1,2 CYCLOPENTANEDIONE WITH LITHIUM ALUMINUM HYDRIDE

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Master of Arts

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by

David C. Winn

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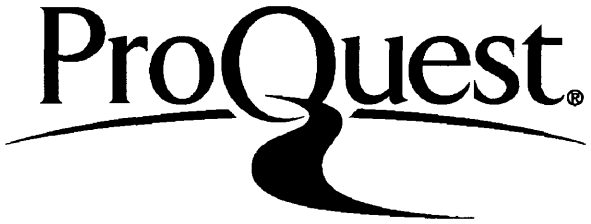

APPROVAL SHEET

This thesis is submitted in partial fulfillment of

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David C. Winn

Author

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Trevor B. Hill

Trevor B. Hill

Randolph A. Coleman

Randolph A. Coleman

Robert A. Orwoll

Robert A. Orwoll

Dedicated to Mr. and Mrs. James C. Larkin whose support throughout my academic career has kept my aspirations high and to Susan H. Gray whose moral support was a vital necessity in trying times and last, but not least, to Anne J. Hale who makes it all worth it.

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ABSTRACT

Reduction of 1,2 cyclopentanedione with excess lithium aluminum hydride in tetrahydrofuran solvent gave cis- and trans- 1,2 cyclopentanediols and 2-hydroxycyclopentanone as products. Diol yields were 30-35% with isomer distributions of 57% trans at 0° and 67-69% trans at -78°. The quantity of 2-hydroxycyclopentanone remains uncertain due to losses of this compound during workup.

An unexpected air oxidation of tetrahydrofuran in the presence of 1,2 cyclopentanedione was observed, giving rise to γ-butyrolactone and 1,4 butanediol in the reduction products. A 2.1% iron impurity was measured in freshly recrystallized 1,2 cyclopentanedione, and is suggested as a possible catalyst for the oxidation.

REDUCTION OF 1,2 CYCLOPENTANEDIONE WITH LITHIUM ALUMINUM HYDRIDE

CHAPTER I

INTRODUCTION

The literature involving stereoselective reduction of cyclic ketones is immense. Reductions with lithium aluminum hydride have shown this reducing agent to be a powerful reagent for the reduction of organic functional groups. Introduction of alkoxy groups on lithium aluminum hydride results in a milder reducing agent than the parent compound. These substituted aluminohydrides offer not only different reactivities, but increased steric influences. The reducing power can also be altered by the solvent used and the cation of the complex hydride. The overall result is a complete spectrum of reducing agents capable of steric control of many reductions in a desired direction.

The reduction of cyclic diketones, however, has received very little attention. These reductions offer a different aspect in stereoselective control. With two carbonyls on the ring, the reduction of one carbonyl may affect the reduction of the other carbonyl. Stereochemical studies involving the formation of the possible cis and trans glycols from a diketone have, for the most part, been ignored. Reductions of 1,2 cyclohexanedione using lithium aluminum hydride, lithium trimethoxyaluminohydride, and lithium tri-t-butoxy-aluminohydride have been reported (24,25,26) ; much of the literature has formed expectations for the research undertaken here.

One molecule receiving little attention as far as reductions are concerned is the 1,2 cyclopentanedione molecule. It was of interest

to us to reduce this molecule and observe any stereochemical effects exhibited. 1,2 Cyclopentanedione is unlike 1,2 cyclohexanedione or larger cyclic diketones in that it is a more rigid system. It cannot distort its shape to accommodate steric problems as can the larger cyclic diketones. It has been reported that 1,2 cyclopentanedione is like 1,2 cyclohexanedione in that both exist primarily in a monoenol form (38). This results in three adjacent sp^2 carbons. In the five membered ring, this would result in a nearly flat molecule which should show characteristics on reduction somewhat different than the six membered ring.

In the reduction of 1,2 cyclohexanedione, the predominant product of lithium aluminum hydride reduction was 2-hydroxycyclohexanone with small diol yields(26). The same mechanism that leads this molecule to the 2-hydroxycyclohexanone is expected to give the 2-hydroxyketone as the major product in lithium aluminum hydride reduction of 1,2 cyclopentanedione. Gas chromatographic analysis will be employed to determine product yields and distribution. It should be possible to determine the conditions necessary to achieve enhanced stereospecific control in these reductions.

CHAPTER II

REDUCING AGENTS

Lithium aluminum hydride was first synthesized in 1947 by reacting lithium hydride with aluminum trichloride in ether under dry nitrogen (1). After its discovery, it became one of the most versatile reducing agents known. It could easily be stored due to its indefinite stability at room temperature.

$$4LiH + AlCl_3 \xrightarrow{ether} LiAlH_4 + 3LiCl$$

Immediately following its discovery, it was characterized to some extent by Nystrom and Brown who reduced several different types of functional groups (2). In contrast to the relatively mild reducing agent, sodium borohydride discovered five years earlier (3), which reduced aldehydes, ketones, and acid chlorides, lithium aluminum hydride was found to be a much more reactive reagent. It fell short of reducing all reducible functional groups in reductions of olefinic double bonds. One exception, however, has been reported in the reduction of 2-cyclopentenone where saturation has occurred significantly (4).

It was later found that alkoxy substituents greatly effected the reducing characteristics of the hydrides. These new substituted hydrides became the subject of much study. Brown and McFarlin found that the addition of four moles of either methyl, ethyl, or isopropyl alcohol resulted in the precipitation of the tetraalkoxide, and four moles of hydrogen were evolved (5).

$$LiAlH_4 + 4ROH \xrightarrow{ether} LiAl(OR)_4 + 4H_2\uparrow$$

Using tertiary butyl alcohol, this was not quite the case. Reacting four moles of this alcohol resulted in three moles of hydrogen evolution with the fourth mole evolving only under prolonged reflux (6).

$$LiAlH_4 + 3C(CH_3)_3OH \xrightarrow[25^o]{THF} LiAlH(OC(CH_3)_3)_3 + 3H_2\uparrow$$

$$LiAlH(OC(CH_3)_3)_3 + C(CH_3)_3OH \xrightarrow[reflux]{THF} LiAl(OC(CH_3)_3)_4 + H_2\uparrow$$

Possibilities for this decreased rate in the addition of the fourth mole of t-butanol are steric factors, lower reactivity of the remaining hydridic hydrogen, and decreased acidity of the tertiary alcohol group.

The trisubstituted alkoxy aluminohydrides were studied extensively to determine the difference, if any, in their reducing activities over the parent compound. Three moles of methanol per mole of lithium aluminum hydride in tetrahydrofuran (THF) produced the trimethoxy-aluminohydride which was apparently readily soluble in THF. Brown and Weissman tested lithium trimethoxy aluminohydride on many representative functional groups and found that the trimethoxy aluminohydride's activity was very similar to the parent lithium aluminum hydride (6,7, 8). However, they also presented evidence to suggest that the trimethoxy derivative could be useful in more selective reductions than the parent compound.

Brown and McFarlin also undertook studies of the tri-t-butoxy aluminohydride, suggesting that the lack of the tri-t-butoxy derivative to pick up the fourth t-butoxy group might indicate a molecule of considerably different characteristics than the parent molecule. They found that the tri-t-butoxy aluminohydride was readily soluble in THF and that its reducing characteristics were considerably milder than the

parent compound. The alkoxy substituents appeared to decrease the reactivity of the lithium aluminum complex to resemble the milder reagent, sodium borohydride. This is in marked contrast to sodium borohydride where alkoxy substituents increase reactivity of the hydride (10). This contrast in the reducing agents seems best explained by H. C. Brown (11). The electron withdrawing effect of the alkoxy groups would be expected toweaken the borohydride as it apparently does in lithium aluminum hydride, but Brown suggests that resonance effects are greater than the electronic effects, satisfying boron electron deficiency. This would not necessarily be as important of an effect for the second row element aluminum, having increased atom size and decreased orbital overlap.

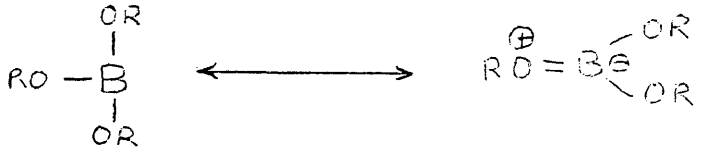


Table 1 shows the reducing ability of lithium aluminum hydride in comparison with the trimethoxy and tri-t-butoxy substituted aluminohydrides.

The alkoxy substituted aluminohydrides offer characteristics not typical of the parent lithium aluminum hydride (LAH). The parent reagent may produce a succession of reagents of different reactivities as the reduction proceeds, but with the single active hydrogen in the trialkoxy derivatives, this would seem an improbable consideration (12). The relative bulk of the trialkoxy derivatives would certainly be expected to produce a larger steric effect than the parent compound yielding different stereospecificity. A third difference has already been discussed in the apparent decreased activity in the parent compound compared to its alkoxy derivatives.

TABLE 1

Typical products of reductions on functional groups by lithium aluminum hydride and its trialkoxy derivatives in tetrahydrofuran at 0° C (11).

Functional group	$LiAlH_4$	$LiAlH(OMe)_3$	$LiAlH(O\text{-}tBu)_3$
Aldehyde	alcohol	alcohol	alcohol
Ketone	alcohol	alcohol	alcohol
Acid chloride	alcohol	alcohol	alcohol
Lactone	glycol	glycol	glycol (slow)
Epoxide	alcohol	alcohol (slow)	alcohol (slow)
Ester	alcohol	alcohol	slow reaction
Carboxylic acid	alcohol	alcohol	NR
Carboxylic acid salt	alcohol	alcohol	NR
Tert-amide	amine	amine	NR
Nitrile	amine	amine	NR
Nitro	azo	reaction	NR
Olefin	NR	NR	NR

The reduction of a functional group apparently involves transfer of a hydride from the aluminum anion to an electron deficient center on the reducible group. Brown and Trevoy suggested that lithium aluminum hydride is a nucleophilic reducing agent that reduces in a bimolecular displacement mechanism based on reductions of epoxides (13). Free hydride attack alone would not explain the difference between LAH and sodium borohydride.

CHAPTER III

REDUCTION STEREOCHEMISTRY

A. Concepts of Steric Approach Control and Product Developement Control

There has been much study on the subject of reduction of cyclic ketones by complex metal hydrides. In the reduction of a ketone such as the one in Figure 1, there are two possibilities for the products. The hydride may attack the axial side of the carbonyl resulting in the equatorial alcohol or the hydride may attack the equatorial side of the carbonyl resulting in the less stable axial alcohol.

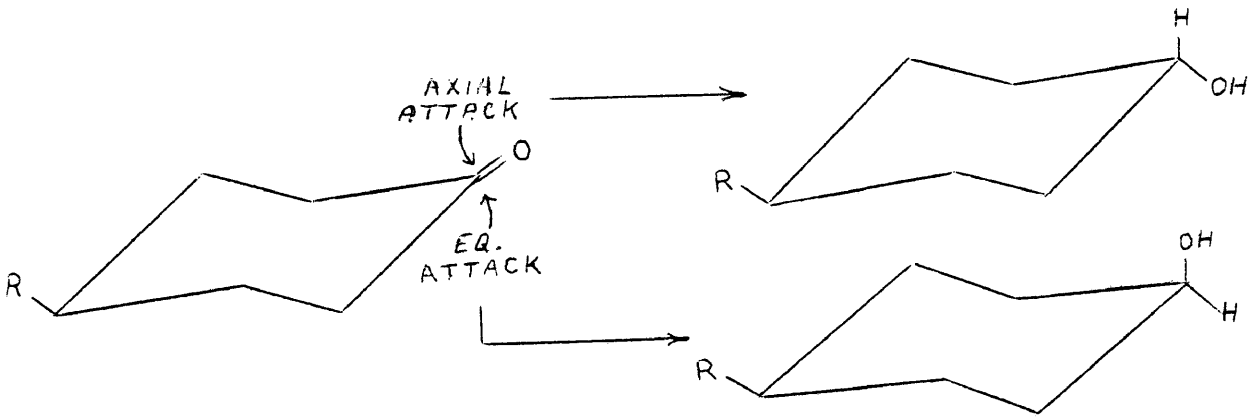


Figure 1: The two products resulting from hydride attack on a simple cyclic ketone.

Ashby and Boone carried out reductions on the molecule in Figure 1 where R was a t-butyl group. When $LiAlH_4$ was the reducing agent, 90% of the alcohol produced was the equatorial isomer-the more stable product (14). Haubenstock and Eliel carried out reductions on 3,3,5-trimethylcyclohexanone using LAH and attained quite different results (15). Their alcohol products consisted of only 25% of the equatorial isomer with the less stable axial alcohol predominating (Figure 2).

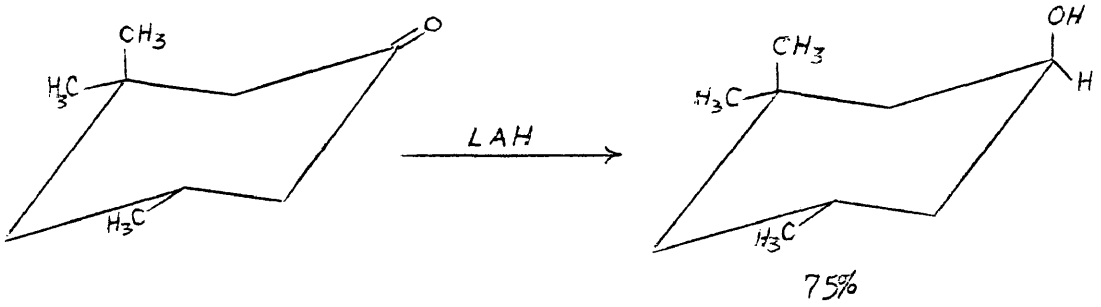


Figure 2: Reduction of 3,3,5 trimethylcyclohexanone with LAH showing major product as the axial alcohol.

It would appear that axial attack is inhibited by possible steric block by the methyl group on carbon 3 towards the attacking hydride.

In 1956, Dauben, Fonken, and Noyce suggested two concepts to explain the different isomeric ratios of the products in reductions such as the two just presented (Figures 1 & 2). One concept-the concept of steric approach control was introduced to describe the formation of products which reflect " competitive attacks from a favored (unhindered) side or unfavored (hindered) side," and a second concept-the concept of product developement control was introduced to describe the formation of products which reflect the relative thermodynamic stabilities of the possible products (16). They proposed that the isomeric ratios in reductions could be explained by these postulates with the stereochemistry argued in terms of the ease of formation of a metallo-organic complex and the energetics of the product formation.

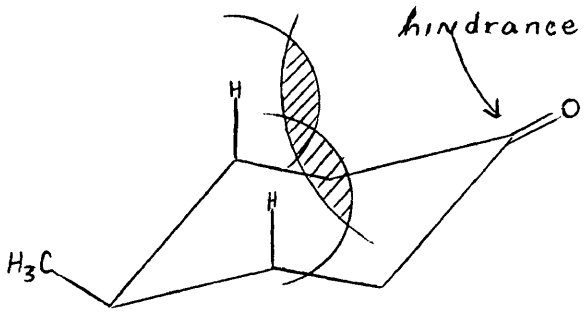
To apply these concepts, consider the two reductions previously mentioned. Ashby and Boone reduced 4-t-butylcyclohexanone with LAH and attained 90% of the more stable <u>trans</u> alcohol. The distant t-butyl group does not interfere with the attack of the relatively small LAH molecule. The metallo-organic complex formation is equally probable

for the LAH, and the predominance of equatorial isomer is directed by the relative energies of the products.

On the other hand, consider the reduction by Haubenstock and Eliel of 3,3,5-trimethylcyclohexanone (Figure 2). The steric interactions of the methyl group on carbon #3 and the LAH seem to direct the reduction to favor equatorial attack yielding the less stable alcohol. This shows the competition of the possible sites of attack with the unhindered or least hindered site being attacked 75% of the time.

Increasing the relative size of the reducing agent is comparable to increasing the steric environment of the carbonyl to be reduced. A closer look at the work of Dauben, Fonken, and Noyce will give an example of this as well as a more subtle example of product developement control (PDC) and the steric approach control (SAC).

Table 2 (pg. 12) shows the results that Dauben et. al. attained in reducing 2-methylcyclohexanone with lithium aluminum hydride and sodium borohydride. Instead of changing the environment around the carbonyl, a look down the 4-methylcyclohexanone column reflects only a change in the reducing agent. The considerably larger bulk of the sodium borohydride appears to give it more stereoselectivity for the cis isomer. This could be explained by the SAC concept where, with the relative bulk of the $NaBH_4$, steric interactions of the reducing agent with the axial hydrogens on carbons 3 and 5 hinder axial attack and increase the cis isomer.*



* See note 1, pg. 74

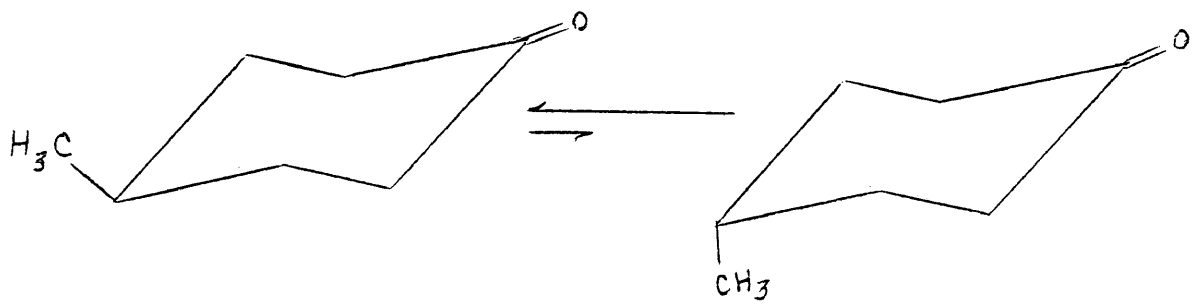
TABLE 2 Isomer distribution in reductions of cyclic ketones (16)
TABLE 2 Isomer distribution in reductions of cyclic ketones (16)

Reducing Agent	4-Methylcyclohexanone		2-Methylcyclohexanone	
	%trans	%cis	%trans	%cis
$LiAlH_4$	81	19	82	18
$NaBH_4$	75	25	69	31
Equilibrium	88	12	99	1

The results indicate that steric factors are now influencing the products more than in the reduction of the same molecule using LAH.

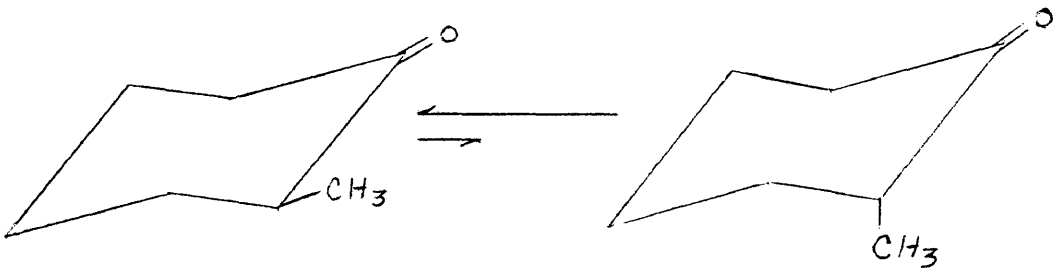
A more in depth view of the two compounds in Table 2 illustrates how PDC and SAC can be utilized to explain apparent differences in the stereochemistry of the reductions. The lack of difference in the isomer distribution for the two substrates using LAH is understandable in that the relatively small size of the reducing agent avoids steric interactions and the product distribution is guided by the relative stability of the products. It has already been mentioned that the larger bulk of the $NaBH_4$ is responsible for its higher stereoselectivity over LAH for the <u>cis</u> alcohol.

To consider the difference between the $NaBH_4$ reduction of the 4-methylcyclohexanone and the 2-methylcyclohexanone, it is necessary to look at the two conformers of each.



The distant position of the methyl group equates the conformers in terms of hydride attack, thus one would expect PDC to give the more stable equatorial alcohol. This would result in the trans alcohol for the left conformer and the cis for the right. The transition states for the two will determine the stereochemistry of the final products. The transition state for the axial methyl conformer is of higher energy than the equatorial methyl conformer giving the predominant product- the trans alcohol; however, more cis alcohol is produced than if the methyl group were locked into the equatorial position.

The equatorial position of the methyl in the conformers of 2-methylcyclohexanone (below) allows equal attack on either side of the carbonyl; therefore, it would be predicted that PDC would yield the most stable product as the major product. Equatorial attack, however, is hindered by the axial methyl group in the right conformer resulting in a higher amount of cis alcohol than for the 4-methylcyclohexanone.



B. Controversy Concerning Product Developement Control

Both SAC and PDC have come under some criticism with the latter concept receiving considerably more attention. If isomer distribution is governed by product stability as in PDC, then the transition states should be "product-like". With SAC, the transition state should be "reactant-like". Wigfield and Phelps used isotope effects to determine the degree of bond breakage in the transition states of

reactions exemplifying both concepts; reductions with sodium borodeuteride showed no evidence for such differences in the transition states (17).

Several alternatives have been proposed for product developement control, but the most supported at the present is a tortional strain postulate introduced by Chérest and Felkin (18). The postulate is based on the concept that the transition states are purely reactant-like which would be expected for reductions where steric interactions are minimal (19). Chérest and Felkin proposed that during equatorial attack, a partially eclipsed transition state is experienced which produces a tortional strain on the molecule (Figure 3). This tortional strain competes with a steric strain which may result from axial attack.

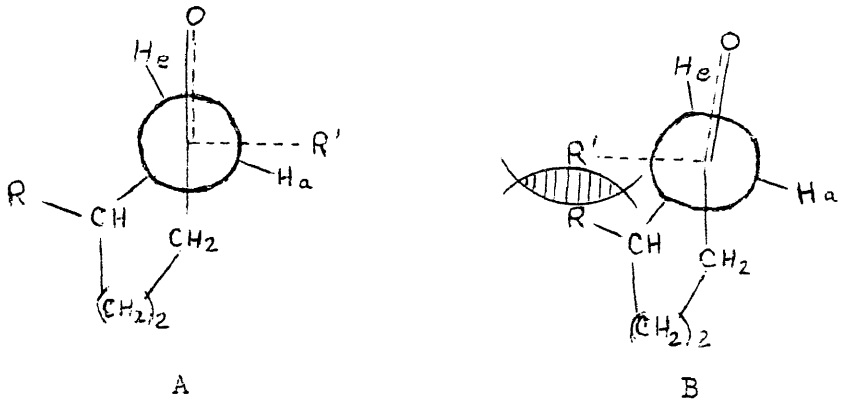


Figure 3. The two possibilities of hydride attack

In this concept, it is the relative strain of the partially eclipsed R' group and the bulk of the R and R' groups that determines the isomeric product ratios. With a relatively small reducing agent, the reduction would occur through the B transition state. As R and R' increase in size, the growing steric strain would encourage the reduction to favor A as a transition state. Thus, in the absence of steric

strain, it is tortional strain that directs the reduction to give the more stable product and not product stability.

C. Alkoxy Substituted Aluminohydrides

Table 3 shows the percent equatorial alcohol attained on reduction of three ketones using $LiAlH_4$ and the trimethoxy and tri-t-butoxy derivatives. These are results from Brown and Deck (12).

TABLE 3 Reductions of Cyclic Ketones with $LiAlH_4$ and its Alkoxy Derivatives at 0° C in Tetrahydrofuran (20)

KETONE	REAGENT	%EQU. ALCOHOL
2-Methyl Cyclohexanone	$LiAlH_4$	75
	$LiAlH(OMe)_3$	31
	$LiAlH(O\text{-}tBu)_3$	70
2-Methyl Cyclopentanone	$LiAlH_4$	76-79
	$LiAlH(OMe)_3$	56
	$LiAlH(O\text{-}tBu)_3$	72
2-t-Butyl Cyclohexanone	$LiAlH_4$	42
	$LiAlH(OMe)_3$	36
	$LiAlH(O\text{-}tBu)_3$	46

In all three cases the trimethoxy derivative showed more selectivity for the less stable alcohol than did the tri-t-butoxy derivative or the parent compound. It would appear that the trimethoxy derivative is a bulkier reducing agent than the tri-t-butoxy derivative. It was certainly expected that the bulkier trimethoxy compound should exhibit more selectivity for the less stable alcohol, but it would follow

that the tri-t-butoxy compound should exhibit more selectivity than the trimethoxy derivative. Brown and Deck proposed that the stereochemical outcome might be explained by disproportionation of the reducing agent (12).

$$\underset{\text{A}}{LiAlH(O\text{-}t\text{-}Bu)_3} \longrightarrow \underset{\text{B}}{HAl(O\text{-}t\text{-}Bu)_2} + Li(O\text{-}t\text{-}Bu)$$

They suggested that the less bulky B could be the reducing species.

The discrepancy in the isomer distribution seems better justified by the work of Ashby, Sevenair, and Dobbs (21) who studied the associative properties of the reducing agents. They found through ebullioscopic techniques that the trimethoxy derivative at high concentrations associates considerably more than either the tri-t-butoxy reagent or the parent reagent, LAH. See Figure 4. They used this fact to explain the results from the reduction of 2-methylcyclohexanone (Table 4).

TABLE 4 Effect of Hydride Concentration on the Reduction of 2-Methylcyclohexanone (Ashby, Sevenair, & Dobbs (21))

Reagent	Initial Conc.	% Axial Alcohol
$LiAl(O\text{-}t\text{-}Bu)_3H$	.01	23
	.10	25
	.30	25
	.50	26
$LiAl(OCH_3)_3H$	.01	28
	.10	61
	.30	62
	.50	63

At low concentrations of $LiAl(OCH_3)_3H$ where association is at a minimum, the products resemble reductions with $LiAl(O\text{-}t\text{-}Bu)_3H$. At higher concentrations, where association is greater, selectivity for the less

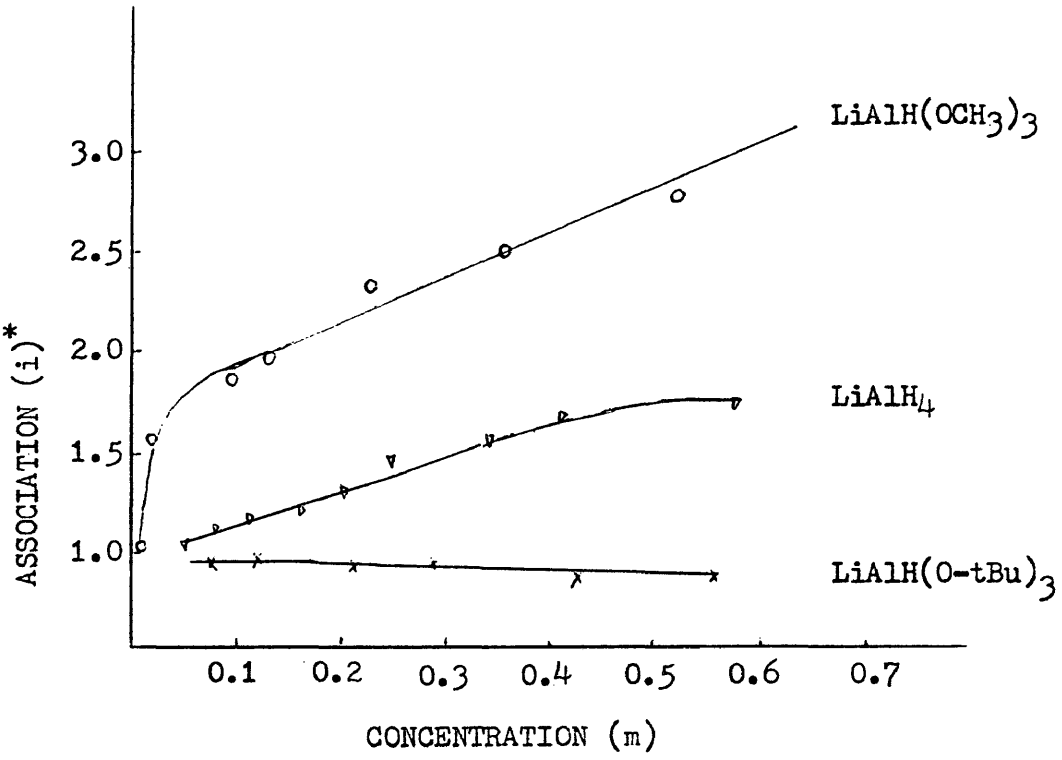


Figure 4: Association of lithium trialkoxyaluminum hydrides in tetrahydrofuran (21)

* The association was monitored by the apparent change in the vapor pressure above the solutions compared to the vapor pressure of the pure solvent. Increased association would result in a small change in the vapor pressure. Decreased association is indicated by a greater change.

stable alcohol is increased. The association data seems to adequately explain the results attained by Ashby et. al.; however, conflicting evidence appeared in the work of Ashby and Boone (14). They reduced 2-methylcyclohexanone with the same two reagents as did Ashby et. al. but attained slightly different results. See Table 5. They did not experience any difference in the isomer ratios as a function of the concentration of the reducing agent. Based on conductance experiments, Ashby and Boone suggested that the difference in stereoselectivity between the trimethoxy and tri-t-butoxy aluminohydrides in THF is best explained by their finding that the trimethoxy derivative is more solvated than its tri-t-butoxy counterpart. This recent finding appears to be the best supported explanation for the increased steric demand of the the trimethoxy aluminohydride.

TABLE 5 Effect of Hydride Concentration on the Reduction of 2-Methylcyclohexanone (Ashby and Boone (14))

Reagent	Initial Conc.	% Axial Alcohol
$LiAl(O\text{-}t\text{-}Bu)_3H$	.0051	35
	.055	34
	.51	36
$LiAl(OCH_3)_3H$	.0032	65
	.0051	63
	.0053	68
	.0080	66
	.055	65
	.58	63

D. Cyclic Diketones

Reduction of diketones requires additional considerations over monoketones in that reduction of one carbonyl group may influence the reduction of the remaining carbonyl. Another factor to be dealt with is that cyclic diketones are usually more acidic than simple cyclic monoketones resulting in a greater possibility of reducing agent decomposition; tautomeric equilibria must also be considered since the reducing agent may encounter conjugated enolic species.

As mentioned earlier, Ashby and Boone found no relationship between hydride concentration and stereochemistry (14). Snyder, however, attained stoichiometric control of stereochemistry using aluminum isopropoxide in a Meerwein-Ponndorf-Verley reduction of both 1,2-cyclohexanedione and 1,2-cyclopentanedione (22,23). Snyder attained a linear relationship between the percent cis glycol and the dione:aluminum isopropoxide molar ratio. His results are illustrated in Figure 5 (pg. 20). At low ratios-excess reducing agent, stereoselectivity is high for 1,2-cyclopentanedione but low for 1,2-cyclohexanedione. At high ratios, the stereoselectivity is reversed for the respective diketones. Synder proposed a "one aluminum" reduction pathway for reductions where there is a limited amount of reducing agent resulting in reduction of both carbonyls by the same reducing agent molecule. He proposes a "two aluminum" reduction pathway for excess reducing agent conditions where the position of the first attached aluminum complex influences the attack of the second. He correlates these two hypotheses to explain the relative distribution of the isomer ratios at different diketone: reducing agent molar ratios.

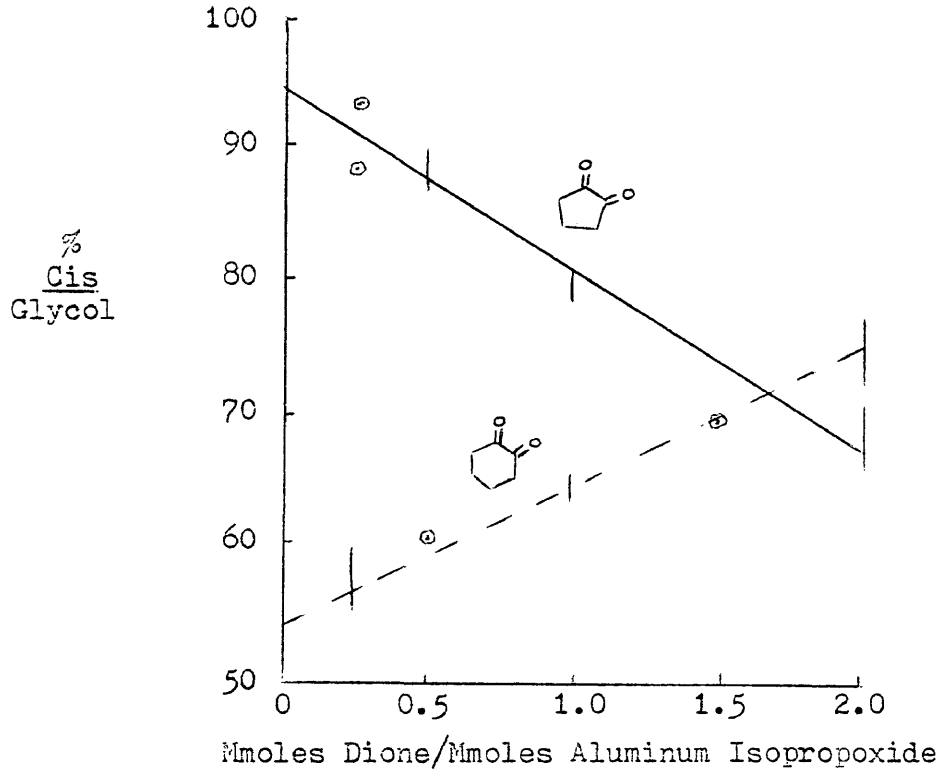


Figure 5: Snyder's Stoichiometric Control of Stereoselectivity (22,23)*

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* The Meerwein-Ponndorf-Verley reduction is not completely analogous to the alkoxy aluminohydride reduction in that a methyl group is the hydride source. It is important, however, that he attained a linear relatioship between isomer distribution and dione:alkoxide molar ratio.

E. Reductions of 1,2-Cyclohexanedione

The reduction of 1,2-cyclohexanedione by sodium borohydride in water was carried out by Dale who identified the products in 58-75% yields to be the isomeric cis and trans glycols (24). He found that at 20-25°, the cis isomer comprised 48% of the diols and at 6-10°, the cis isomer comprised 15% of the diols. In contrast, Trevoy and Brown had already reduced 1,2-cyclohexanedione with LAH, but they identified only 2-hydroxycyclohexanone as a product (41% yield)(25).

R. E. Baker undertook the reduction of 1,2-cyclohexanedione using LAH and and its trimethoxy and tri-t-butoxy derivatives. Through gas chromatographic analysis of the products, he studied the steric course of these reductions, and he investigated the possibility of stoichiometric control of stereoselectivity as reported by Snyder in the Meerwein-Ponndorf-Verley reduction of 1,2-cyclohexanedione with aluminum isopropoxide (22,23).

In reductions using LAH, Baker got mostly the 2-hydroxycyclohexanone as did Trevoy and Brown (25), but he also attained diols in as high as 25% yields, unlike Trevoy and Brown. In reductions using lithium trimethoxy aluminohydride, Baker again attained the 2-hydroxy ketone as the major product, but this reducing agent appeared more stereoselective for the 2-hydroxy ketone (95-99% yield) with traces of diols present.

The milder lithium tri-t-butoxy aluminohydride gave considerably different results. The major product was the diols (as high as 80%) with small amounts of the 2-hydroxy ketone present.

Perhaps the most consistant finding by Baker was that regardless of hydride concentration, mode of addition, reaction time, or reducing agent, the diol products consisted of 59±3% cis isomer.

Spectral evidence indicates that 1,2-cyclohexanedione exists mainly in the mono-enol form (27). Baker used this factor to explain his results. The more reactive LAH and lithium trimethoxy aluminohydride react preferentially with the hydroxyl group of the enol to evolve hydrogen which Baker measured and found to support hydroxy attack quantitatively. See Figure 6. Following hydrolysis, ketonization yields the observed product of 2-hydroxycyclohexanone.

The less reactive lithium tri-t-butoxy aluminohydride attacks the carbonyl initially, allowing tautomerism of the enolate. This allows reduction of the second carbonyl to yield the observed diols as major products. See Figure 7.

Thus Baker showed that 1,2-cyclohexanone reacts as a mono-enol and reduction to 1,2-cyclohexanediol can only occur by initial attack of the carbonyl over the enol group. The more reactive agents attack the hydroxyl group first effecting no reduction of that carbon, resulting in 2-hydroxy cyclohexanone. Baker did not, however, achieve stoichiometric control over the isomer distribution, getting 59±3% cis isomer in all cases.

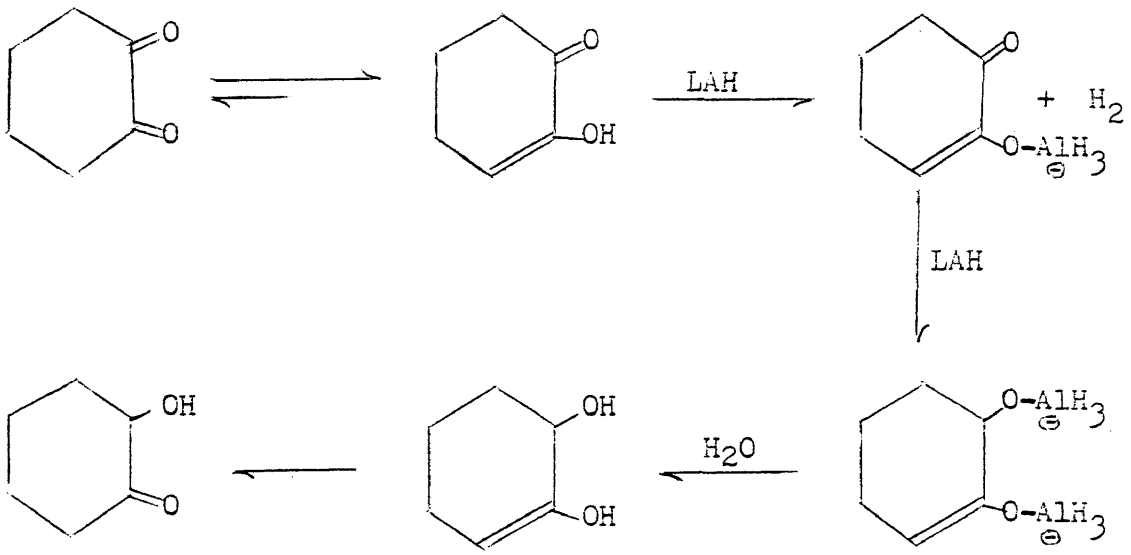


Figure 6: Reductive Pathway to 2-Hydroxycyclohexanone

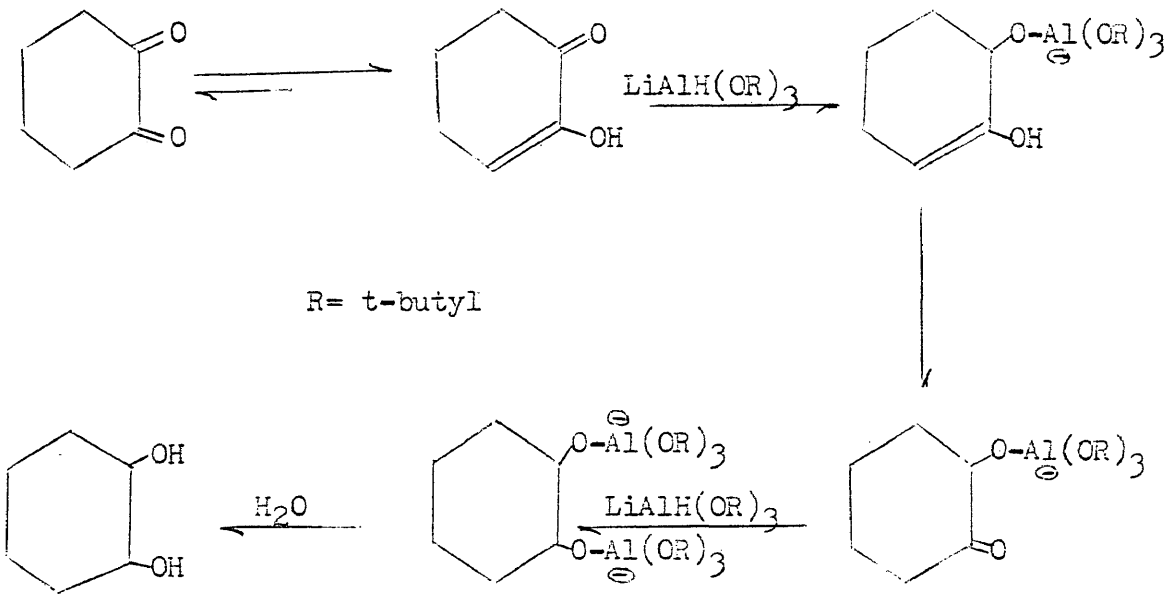


Figure 7: Reductive Pathway to 1,2-Cyclohexanediol

CHAPTER IV

RESULTS AND DISCUSSION

The reduction of 1,2 cyclopentanedione (1,2-CPD) with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) solvent was complicated by several factors. The results here will deal with 1) the preparation and properties of reagents, 2) the results of LAH reductions, and 3) an unexpected oxidation of THF solvent to γ-butyrolactone.

A. Preparation and Properties of Reagents

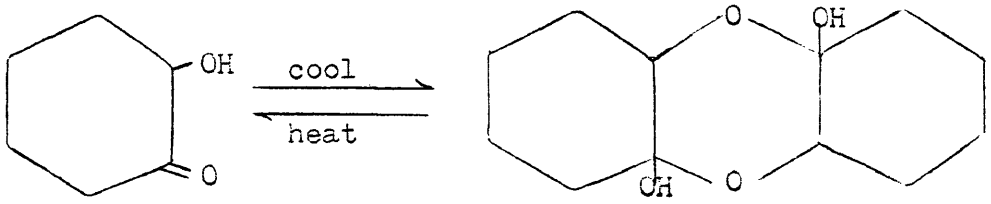
The reagents prepared were those to be expected on the basis of products formed in previous work (26) on the reduction of 1,2-cyclohexanedione with LAH.

The cis- and trans- 1,2-cyclopentanediols were prepared by the appropriate oxidations of cyclopentene (34).

The starting diketone (1,2-CPD) was prepared by the aqueous ferric chloride oxidation of 2-bromocyclopentanone (29a). The product was purified by final vacuum distillation under nitrogen followed by a recrystallization from petroleum ether to give a sharp melting crystalline white solid (m.p. 55-56.5°). This material, homogeneous by glpc decomposed rapidly to a brown tar at room temperature even under nitrogen. Leaching the brown tar with light petroleum ether furnished more white crystalline material, and freshly crystallized samples had to be prepared before each reduction. The 1,2-CPD was, however, fairly stable on refrigeration. That the 1,2-CPD exists as the monoenol (38) was confirmed by infrared (Figure A1) and NMR (Figure A2) analysis. The intense brown stains that were reported (33) on skin contact were (inadvertently)

confirmed.

2-Hydroxycyclopentanone was an expected, and found, product in the reduction of 1,2-CPD with LAH. For purposes of glpc analysis, an authentic sample was prepared, but the stability of this material is a confusing issue. Literature reports (36,40) on the stability of 2-hydroxycyclohexanone are clear in that it dimerizes to the tricyclic dihemiketal (II) with the monomer material generated on distillation.



I II

Reports (33) on 2-hydroxycyclopentanone (IV), however, are confused as to the differing degrees of polymerization of the material on standing. Schrapler and Ruhlman (33) noted an increase in viscosity while Sheehan, O'Neill, and White (40) reported production of solid polymer. In this research, based on infrared analysis, the compound was found to be very stable on setting 28 days at room temperature (Figures A3 & A4). Attempted preparations of the compound via hydrolysis of 2-bromo- (29) and 2-chloro- (30) cyclopentanone were unsuccessful; however, the compound was prepared through an acyloin condensation of dimethyl glutarate (III) in the presence of chlorotrimethylsilane (31,32). See **Figure** 8 (pg. 26).

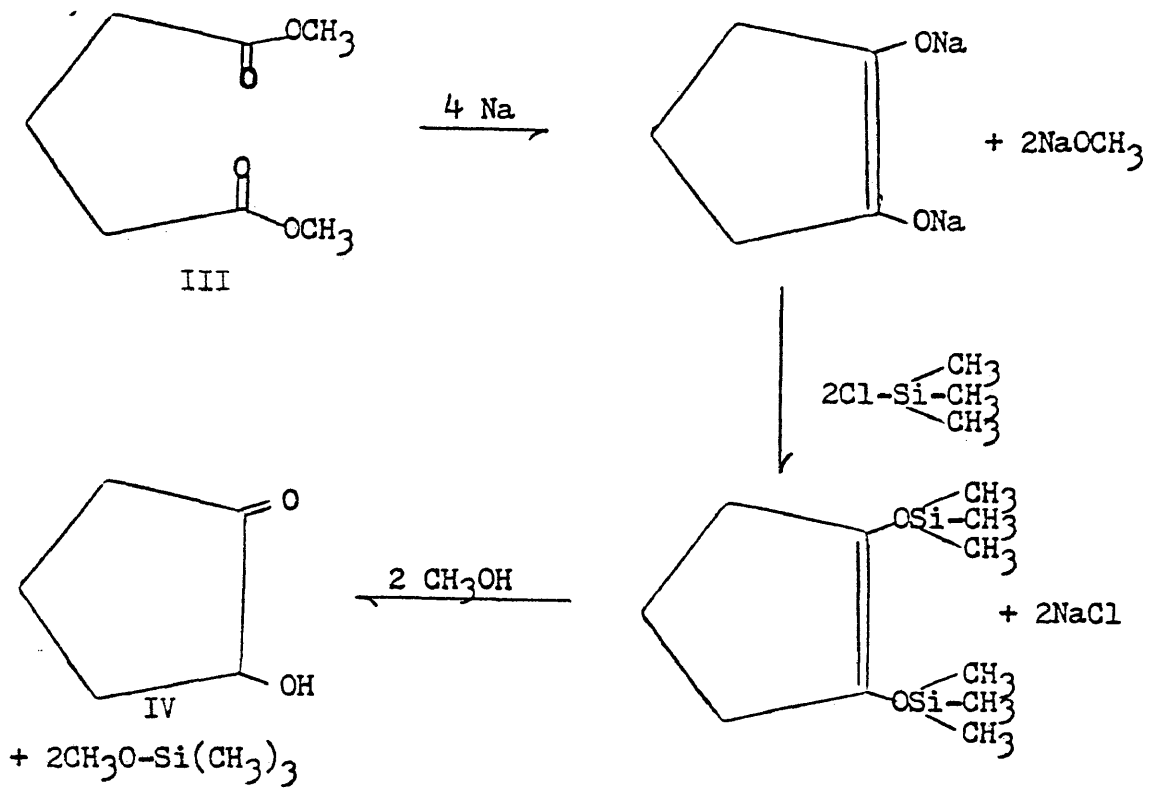


Figure 8: The Acyloin Condensation of Dimethyl Glutarate

B. Results of LAH Reduction

The diketone was reduced by addition of a THF solution of 1,2-CPD to excess standardized LAH in THF at temperatures of 0° and -78°. After three hours stirring at these temperatures, the reaction mixture was hydrolyzed with 100% excess H_2O in THF (based on LAH). The mixture was treated with 50/50 magnesium sulfate/silicic acid, and the solid mass was leached six times with THF. The THF extracts were combined, evaporated under nitrogen, treated with p-cymene standard, and analyzed by glpc. Hydrogen evolution was measured on addition of LAH and on hydrolysis (apparatus Figure 12, pg. 42).

Glpc analysis of reduction products on a carbowax 20M column gave five distinct peaks (Figure A5). Infrared analysis of the trapped

materials and spiking with authentic samples gave positive identification of the products to be the cis- and trans- 1,2-cyclopentanediols (Figures A6 to A9), γ -butyrolactone (Figures A10 & A11), 1,4 butanediol (Figures A12 & A13), and 2-hydroxycyclopentanone (Figures A14 & A15).

Table 6 is a summary of reductions. As in Baker's results (pg. 21), the hydrogen evolution was expected to indicate enolic attack by the reducing agent to give VI, followed by reduction of the remaining carbonyl to give VII, followed by hydrolysis and ketonization to give 2-hydroxycyclopentanone (IV) (Figure 9).

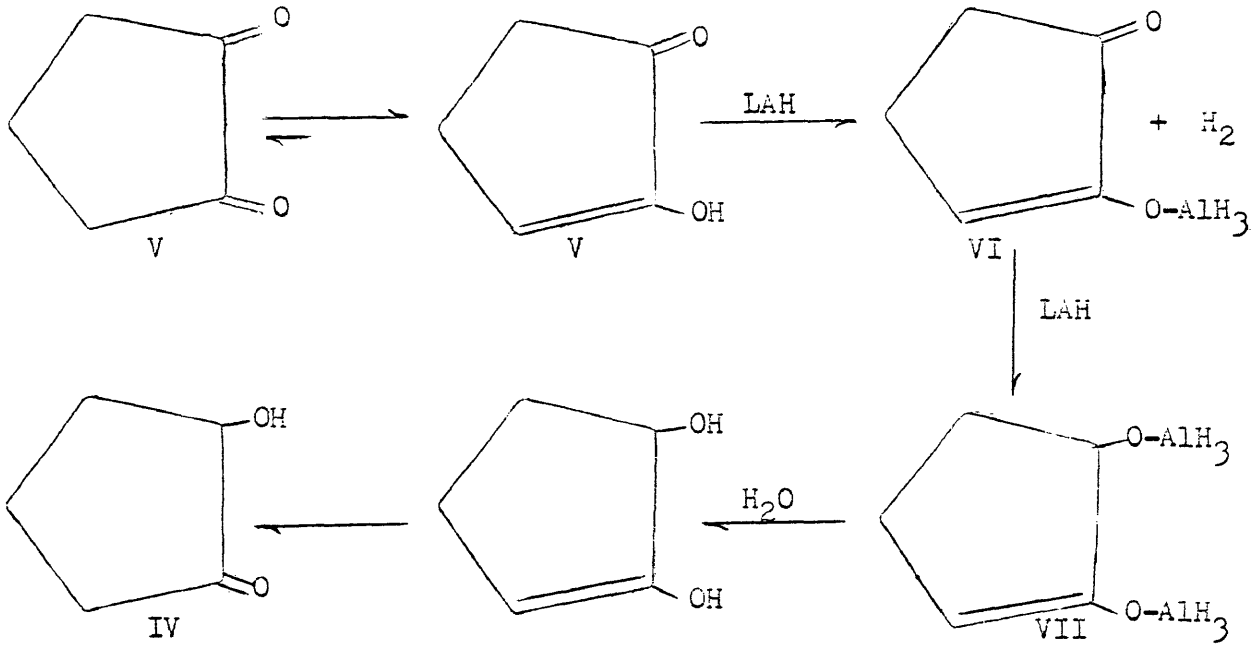


Figure 9: Reductive Pathway to 2-Hydroxycyclopentanone

Diol composition appeared constant in reductions differing only in reducing agent concentration. Diol yields were low but were considered accurate based on recovery experiments. Thus, a known mixture of diols, subjected to treatment with LAH, followed by the workup described,

TABLE 6

Reductions of 1,2 Cyclopentanedione using $LiAlH_4$ (I) and $Li(O\text{-}t\text{-}Bu)_3AlH$ (II) in Tetrahydrofuran at 0^o and -78^o C.

Reducing Agent	mmoles Red. Agent	mmoles Diketone	Al-H / c=o	Temp °C	mmoles H_2 on add.	% Diol Yield	%Trans
I	5.0	5.0	2/1	0	4	35	57
I	5.0	5.0	2/1	-78	4	30	69
I	15.	5.0	6/1	0	4	33	57
I	15.	5.0	6/1	-78	4	30	67
II	10.	5.0	1/1	0	3	23	100
II	10.	5.0	1/1	-78	3	24	100

gave 95-99% recovery of starting materials in the same ratio.

Reductions using $Li(O\text{-}t\text{-}Bu)_3AlH$ showed stereoselective preference for only the trans diol in 24% yields.

Addition of a known amount of authentic 2-hydroxycyclopentanone to a hydrolyzed mixture of LAH in THF, resulted in only 20% recovery of this material using the workup procedure described. Thus while hydroxyketone is produced in the reduction, its quantitative amount remains uncertain. At least, this amount is less than 65-70% of starting material based on diols produced.

Hydrogen evolution measurements gave 70-80% of theoretical hydrogen based on starting diketone, if assumed 100% enolic. It is suspected that no hydrogen would be evolved on addition of diketone to LAH if diols were the exclusive products.

Figure 9 (pg. 27) shows that 1 mmole H_2 should be produced for every mmole diketone proceeding to the hydroxyketone (IV), assumming the pathway shown. The production of diols should not give hydrogen gas on mixing of reagents, if it is assumed the carbonyl group is first attacked by AlH_4^- (Figure 10) as Baker postulated. Reduction to enol (VIII), followed by ketonization and subsequent reduction to (IX) should give diols (X) on hydrolysis but with no H_2 evolved on mixing. See Figure 10 (pg. 30).

C. Oxidation of THF Solvent

A considerable quantity of 1,4 butanediol (1,4-BD) was found among the products of reduction of 1,2-CPD with LAH (Figure A5), and no reason for the production of 1,4-BD was apparent, at least initially. One obvious source of diol is the LAH reduction of γ-butyrolactone which is a known contaminant of THF arising from its air oxidation,

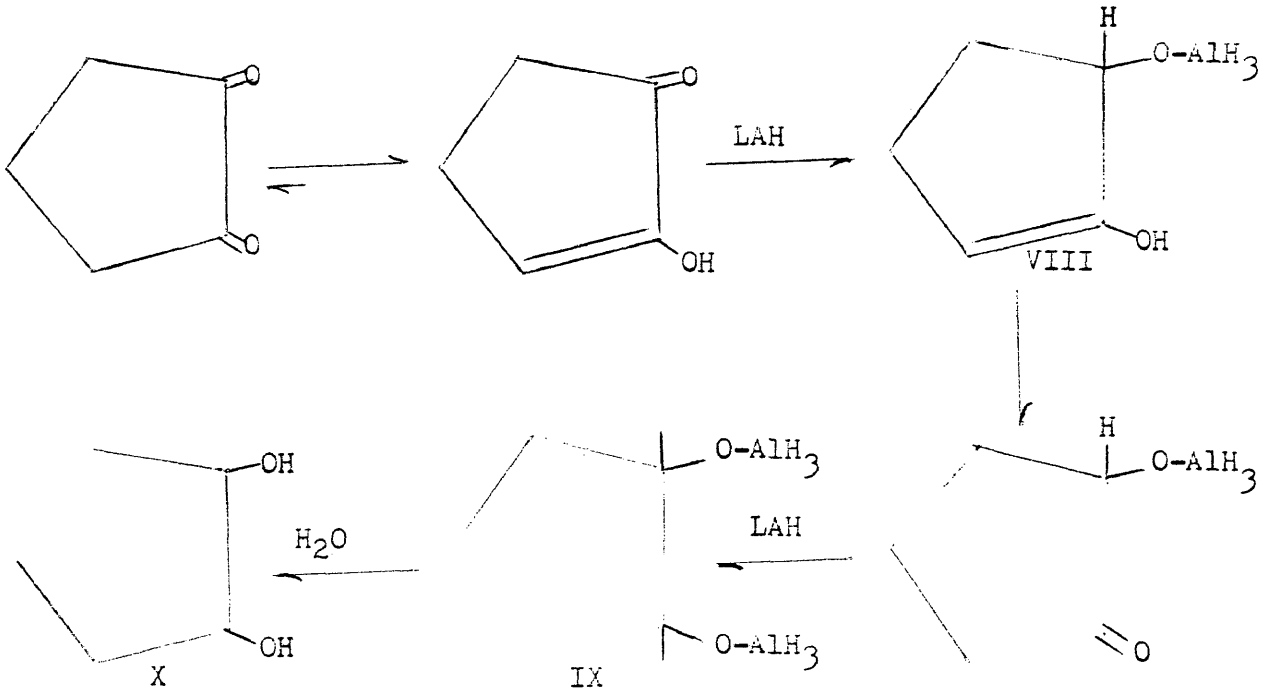


Figure 10: Reductive Pathway to 1,2-Cyclopentanediol

particularly in the absence of di-t-butylphenol inhibitor. Practically all chromatograms from LAH reductions show a small peak for γ-butyrolactone. All THF solvent used in these reductions was distilled from LAH and stored over molecular seives before use, and is presumably inhibitor-free at this stage. Thus the solvent may be susceptible to air oxidation under these circumstances. All transfers before experiments were effected with dry syringes flushed with nitrogen to limit air oxidation.

Another more likely reason for γ-butyrolactone production would arise during workup, in which the same THF solvent was used for leaching products (after hydrolysis) from magnesium sulfate/silicic acid (however, no diol could be produced after hydrolysis of LAH). A centrifuge was used in these separations and no special effort was made to exclude air. Final evaporation of THF, prior to gas chromatography, was performed under nitrogen.

Figure A16 shows a reduction run with a 6/1 hydride to carbonyl ratio, showing presence of 1,4-BD. Figure A17 is a blank (having no diketone), run under exact conditions as the run shown in Figure A16, both containing the same amount of p-cymene. It is apparent that for the quantity of 1,4-BD produced, insufficient butyrolactone is present, initially, in the solvent. The generation of lactone from THF in the presence of LAH was simply untenable as the blank run also confirms.

The investigation of lactone generation from THF in the presence of the starting diketone was finally considered. When a small amount of 1,2-CPD was dissolved in pure THF (no LAH), glpc analysis over a period of 70 minutes showed a steady increase in the butyrolactone at no apparent expense of diketone (Figures A18 & A19).

Oxygen uptake by a mixture of 1 mmole diketone, 3 mmoles THF, and p-cymene (internal standard) dissolved in hexane was monitored over 70 minutes. Glpc analysis before and after this period (Figures A20 & A21) showed formation of lactone. Absorption of 1.8 mmoles O_2 was observed with the concomitant decrease of 1.8 mmoles THF. This result is contrasted with a blank in which absorption of 0.22 mmoles O_2 with a corresponding decrease of 0.22 mmoles THF was observed (Figures A22 & A23). The relative heights of lactone and THF clearly establish the enhanced oxidation of THF in the presence of diketone (Figure A24). Of particular interest is the fact that in both oxidations undertaken, no change in diketone concentration was observed. Thus it appears that the diketone catalyzes the oxidation of THF to γ-butyrolactone.

The possibility of an impurity (serving as the oxidation catalyst) in the starting diketone was considered. 1,2-CPD was prepared by aqueous ferric chloride oxidation of 2-bromocyclopentanone (31,32). It was decided to investigate the possibility of trace iron impurities present in the diketone. A qualitative test involving destruction of the organic sample and subsequent addition of KSCN yielded a faint red color indicating trace amounts of ferric ions.

Quantitative analysis of a freshly recrystallized diketone sample was performed by a method in Skoog and West (35) with some modification (details pg. 44). A 2.1 $\pm$0.3% iron content was found to exist in the diketone despite a sharp melting point of the material before analysis. Earlier, the presence of iron was never considered in view of the fact that the workup procedure for 1,2-CPD involved vacuum distillation and recrystallization following the $FeCl_3$ oxidation.

CHAPTER V

SUMMARY AND CONCLUSIONS

A. This Research

1,2-Cyclopentanedione was reduced with $LiAlH_4$ to give 2-hydroxycyclopentanone plus cis- and trans- 1,2-cyclopentanediols. The quantitative amounts of 2-hydroxycyclopentanone is uncertain at this time, but its quantity can be speculated by considering the hydrogen evolved on addition (See Figure 9). Thus LAH reduction of 5 mmoles of 1,2-CPD resulted in 4 mmoles of H_2 evolution. This H_2 measurement reflects attack on the enol by the hydride which would result in the predominant production of 2-hydroxycyclopentanone.

Isomer distribution did not change in runs differing only in reducing agent concentration. However, a notable change (10-12%) occurred in the distribution at lower temperatures. The fact that more trans was produced at lower temperatures would suggest that the trans diol is the kinetic product. Literature could not be found to indicate which of the two diols is most stable.

The unusual production of γ-butyrolactone is due to rapid air oxidation of THF. The enhanced effect in the presence of 1,2-CPD on air oxidation is well supported. Oxidation is catalyzed either by 1,2-CPD or associated impurities arising in the synthesis. This impurity could be iron or its ions since metal ions are known to catalyze air oxidations (39).

B. Future Work

Future work concerning reductions should involve devising a suitable workup procedure which results in high percentage recovery of the hydroxyketone. This may prove to be a formidable task in view of the possibility that the hydroxyketone may not stand up to the basicity of the hydrolyzed reaction mixture before the actual workup procedure is incurred.

Another subject for future investigation is the apparent confusion between the literature and this research concerning the stability of 2-hydroxycyclopentanone. This research found no evidence of polymerization occurring on setting 28 days at room temperature, contrasted with reports (33,40) finding considerable polymerization.

The problem of generation of γ-butyrolactone during normal reduction procedures may be resolved in the improvement of the purification process of the diketone. Perhaps the use of an agent at some suitable point in the synthesis, harmless to the diketone, could be found that complexes with any iron impurities present. Removal of the iron may give some insight concerning the enhanced oxidation observed here.

CHAPTER VI

EXPERIMENTAL

A. Preparation of Major Materials

1. 1,2-Cyclopentanedione was prepared by the method of R. M. Acheson (29a). The compound had to be refrigerated immediately upon isolation by vacuum distillation. A typical procedure follows.

A 1 liter, 3-necked, round bottom flask was fitted with a condenser, thermometer, dropping funnel, and motor driven paddle stirrer. Into the 1 liter flask was put 60 mls. of cyclopentanone, 31 mls. of glacial acetic acid, and 135 mls. of deionized water. 39 mls. of bromine were put in the dropping funnel. A few drops of bromine were added and the mixture was heated to 65° with very vigorous stirring. At approximately 65°, the bromine color dissipated and the remaining bromine was added over 20 minutes maintaining the temperature to 55-59° C (not to exceed 60°).

The reaction mixture was cooled to room temperature and neutralized with solid anhydrous Na_2CO_3 to congo red indicator paper (when paper no longer turns blue). The bottom, yellow, oily layer was separated from the aqueous layer and washed twice with 10-15 mls. of water.

This 58 gms. of yellow oil was added to 375 mls. water in the 1 liter flask and heated to 94-96° while stirring vigorously (temperature should not exceed 96°). A hot $FeCl_3$ solution was added over 20 minutes. The solution was cooled to 40° and saturated with ammonium sulfate. The solution was then put on a continuous extraction apparatus and extracted with ethyl ether for 13 hours.

The title compound was vacuum distilled over N_2 (81° at 5mm Hg) and collected in a dry ice-acetone cooled flask to avoid decomposition.

When the freezing procedure was followed immediately upon collection, one recrystallization from low boiling petroleum ether was sufficient to attain fairly sharp melting points. This method is relatively easy to follow but yields never exceeded 54%. Precautions must be taken to avoid temperatures in excess of those prescribed, to avoid noxious HBr vapors, and to avoid skin contact with the title compound.

2. Preparation of 2-hydroxycyclopentanone was attempted via bromination (29) and chlorination (30) of cyclopentanone followed by hydrolysis. These attempts were unsucessful, plagued by low yields in halide substitution and suspected decomposition of the hydroxy ketone before its isolation from the hydrolysis mixture.

A sucessful method was found in utilizing an acyloin reaction to isolate a stable intermediate, 1,2-bis trimethylsiloxycyclopentene, which could be stored until its hydrolysis to the 2-hydroxycyclopentanone was needed (32). The complete path for 1,2-hydroxycyclopentanone synthesis is presented in Figure 8. A typical procedure follows.

A 1 liter round bottom flask was fitted with a motor driven stirrer, condenser, N_2 gas inlet, and a dropping funnel. See Figure 11. All glassware was bone dry. 300 mls. of toluene was put in the flask and brought to a boil. 9.2 gms. of Na metal was added and the stirrer was started, with vigorous stirring until a fine Na dispersion was attained. 16 gms. of dimethyl glutarate and 43.6 gms. of chlorotrimethyl silane were added together in 125 mls. toluene and put in the dropping funnel. The solution was added dropwise to the Na dispersion over 2 hours and 40 minutes with continued stirring (addition must be

very slow to avoid diester buildup which has been reported to cause explosions). When addition was complete, the reaction mixture was transfered over N_2 to a closed sintered glass funnel to remove any excess Na. The toluene was removed under pressure and the bis-1,2-trimethylsiloxy cyclopentene was distilled (80-81° at 4.2mm Hg) in 66% yield. This is a convenient point to stop and store the potential 2-hydroxy ketone. The chlorotrimethylsilane has been found to yield this stable five membered ring and produce the hydroxy ketone in higher yields than previous methods.

The only step left in the synthesis is hydrolysis of the siloxy compound which proved sucessful in 50% yields (33).

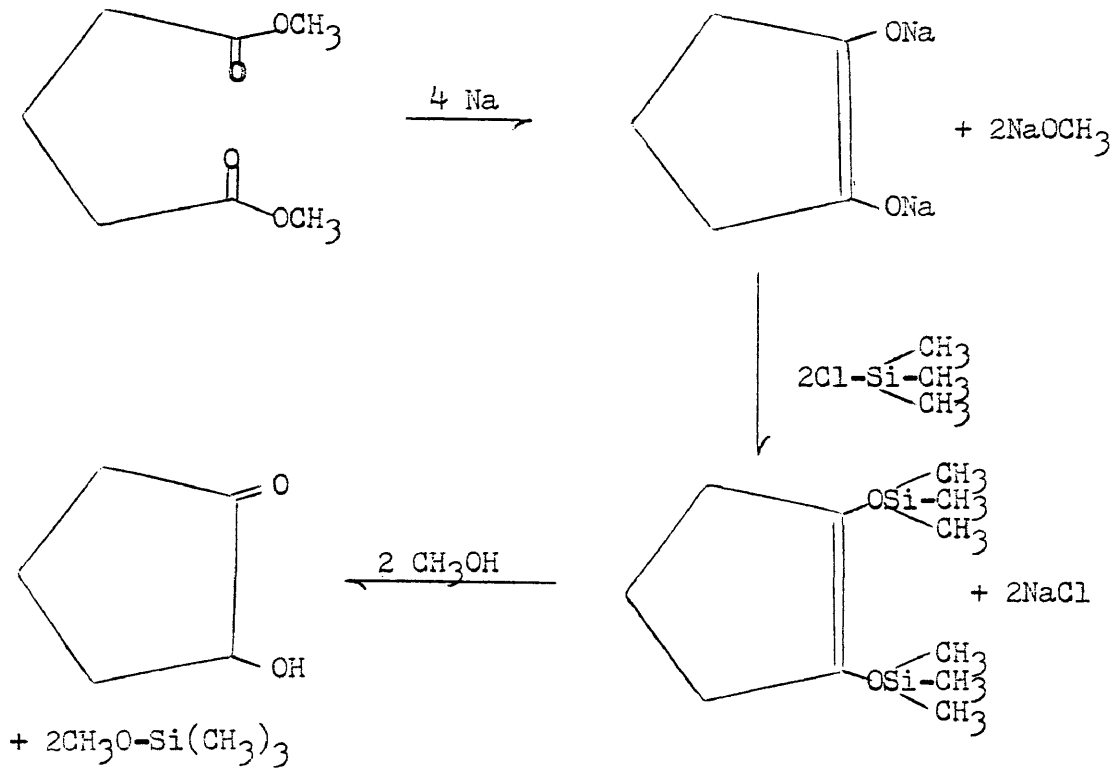


Figure 8 : The Acyloin Condensation of Dimethyl Glutarate

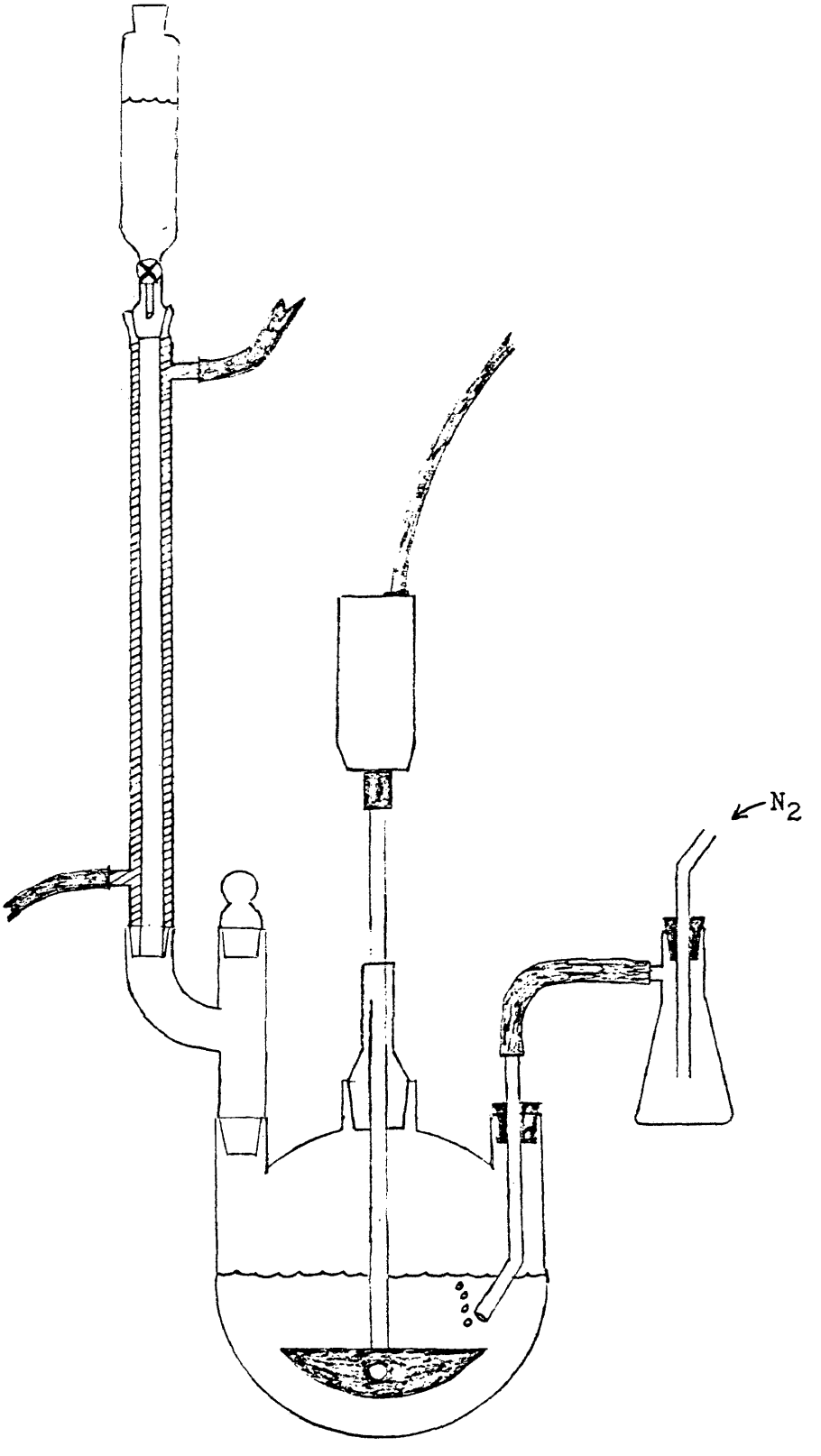


Figure 11: Apparatus for Acyloin Condensation

3. Cis-1,2-Cyclopentanediol was prepared by the method of Owen and Smith (34). A representative procedure follows. A solution of cyclopentene (22.1 gms.) in ethanol (600 cc.) was cooled to -40°. A solution of $KMnO_4$ (40 gms.) and anhydrous $MgSO_4$ (30 gms.) in water (800 mls.) was added with vigorous stirring during two hours. Afterwards, the MnO_2 was filtered off and washed with hot water; combined filtrates were evaporated down to ≈200 mls. and continuously extracted with ethyl ether for 68 hours. Vacuum distillation gave the title compound in 28% yield (b.p. 88-92° at 2mm Hg).

4. Trans-1,2-Cyclopentanediol was also synthesized by a method of Owen and Smith (34). A representative procedure follows. A mixture of 30% H_2O_2 and 231 mls. of 88% formic acid was added to cyclopentene with much heat being generated. The temperature was allowed to fall to 40° and so maintained for four hours. The formic acid was removed under reduced pressure (61° at 117mm Hg) and the residue was dissolved in 120 mls. of 10% NaOH solution. The mixture was refluxed for 40 minutes, diluted to 280 mls., and continuously extracted with ethyl ether for 64 hours. The dried extract ($MgSO_4$) was distilled and the trans glycol was collected in 29% yield (110° at 2mm Hg).

B. Preparation and Standardization of THF and LAH Solutions

The solvent used for all reductions and workup procedures was tetrahydrofuran (THF). The ether was distilled in the presence of lithium aluminum hydride and stored in a 2 liter flask over molecular sieves (type 3A) with a nitrogen atmosphere above the solvent at all times. The flask was fitted with a rubber septum and syringes were always cleaned, dried, and filled with N_2 before taking samples from the flask.

An apparatus similar to the one used in reductions (Figure 12) was used to standardize the solvent. This was necessary to account for any hydrogen evolution due to water and any other impurites still present after distillation and possible buildup of impurities on setting between new distillations. The following standardization is typical. 2 mls. of the LAH solution (1.1M) was put in a 100 ml. round bottom flask and cooled to -78°. 5 ml. aliquots of the dry distilled THF were injected via syringe and the H_2 evolution was measured. Solvent corrections were taken in consideration in all reduction data.

The lithium aluminum hydride solutions were made by introduction of 25 gms. of LAH into 500 mls. of dry, distilled THF and allowed to stir overnight under a N_2 atmosphere. The solution was then filtered under N_2 through a 3"x2"diam. bed of celite and standardized.

For standardization purposes, a hydrolysis mixture was made consisting of 25 mls. H_2O and 25 mls. glycerol. Small aliquots of the LAH solution were introduced via syringe, and H_2 evolution allowed calculation of the molarity of the LAH solution using the following equation:

$$M = \frac{(P_1-P_2)\ (273^\circ K)\ (V_1-V_2)}{(760\ mm)\ (T)\ (22.4\ ml/mmole)\ V_2\ X}$$

where P_1 = atmospheric pressure (mm Hg)
P_2 = vapor pressure of H_2O at T (mm Hg)
V_1 = volume of H_2 evolved (ml)
V_2 = volume of LAH injection (ml)
T = room temperature (°K)
X = mequ. of active hydride/mequ. of LAH
e.g. $LiAlH_4$: X=4

C. Reduction Procedures

1. The apparatus used in reductions is illustrated in Figure 12. The reaction flask, dropping funnel, and syringes were rigorously cleaned and oven dried under vacuum for 1 hour prior to reductions. Before each reduction, the apparatus was flushed with N_2 and checked for leaks.

2. In all reductions, the diketone was recrystallized from petroleum ether to a sharp melting point (55-56.5°) just prior to reactions. A typical reduction procedure follows.

490 mgs. of diketone (5 mmoles) were dissolved and diluted with dry THF to 5 mls. in the dropping funnel. The funnel was flushed with N_2. 4.5 mls. of 1.1 M LAH (5 mmoles) was introduced into the 100 ml. flask through the septum and chilled to -78° while stirring. The system was allowed to equilibrate , and the system was brought to atmospheric pressure. The diketone solution was slowly added to the reducing agent solution and the H_2 evolution on addition, if any, was measured. After this initial measurement, the reaction was allowed to continue for three hours. After this time, the flask was warmed to room temperature for hydrolysis.

Hydrolysis was accomplished by slow introduction of a hydrolysis solution (water diluted with THF to 88 mgs./ml sol'n) in a 100% stoichiometric excess. The H_2 evolution was again measured and recorded. The reaction mixture was now ready for workup.

D. Workup Procedures

The workup procedure involved taking the hydrolyzed reaction mixture, transfering it to a 4 inch test tube, adding a 50/50 mixture of $MgSO_4$ and silicic acid (total 6 gms.), and mixing well. By

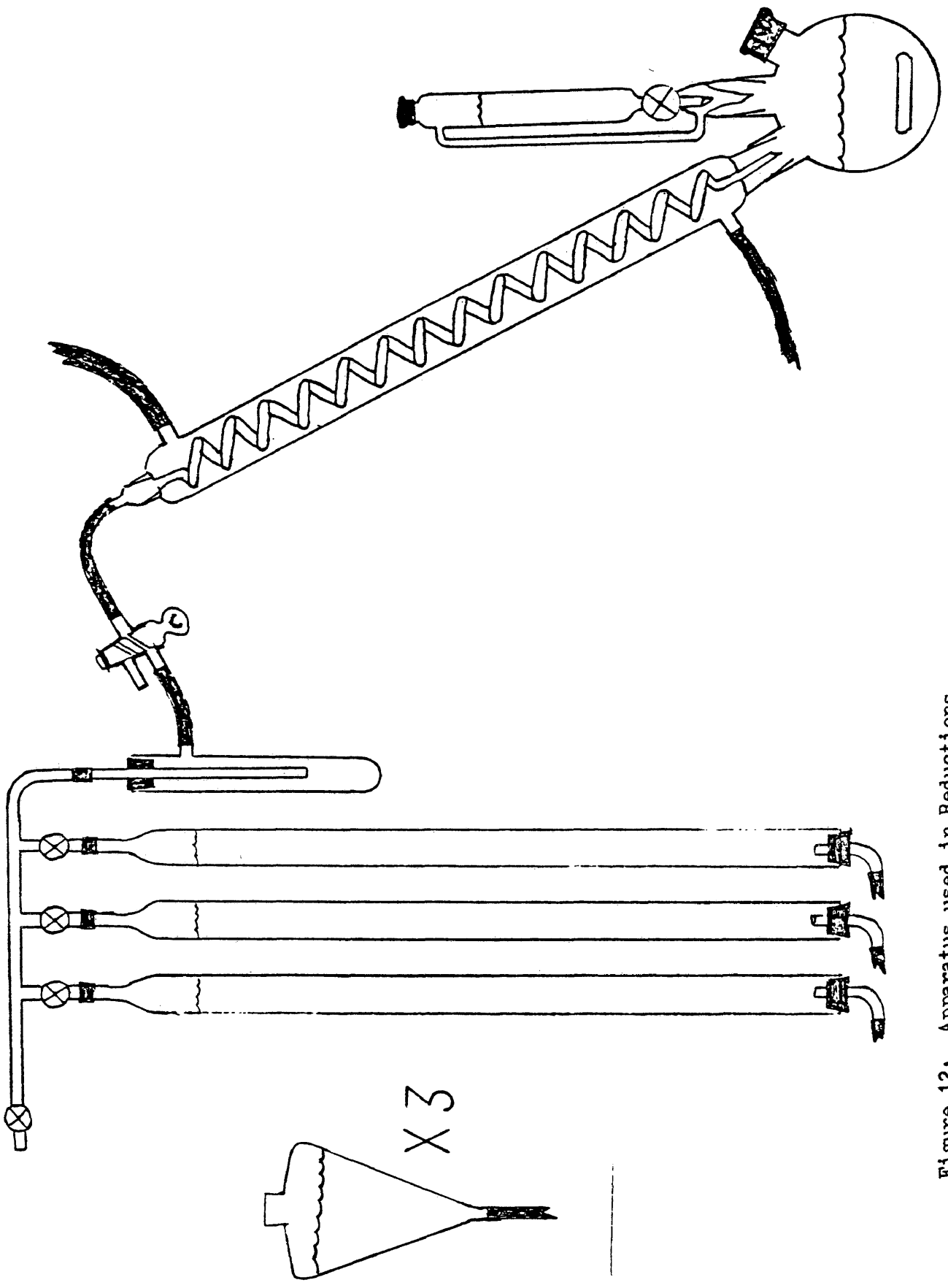


Figure 12: Apparatus used in Reductions

centrifugation, 6 leaches (2.5 mls.) were effected, and combined extracts were evaporated down to 1 ml. An appropriate amount of paracymene internal standard was added, and the sample was ready for gc analysis.

E. Gas Chromatographic Analysis

Yields of glycols as well as isomer distribution could be determined by gc analysis. By determining relative response factors of each glycol with paracymene, the mgs. of glycols could be calculated using the following equation.

$$\text{diol wt.} = R_f \frac{(\text{diol area})}{(\text{P.C. area})} \text{ P.C. wt.}$$

The general method for determining the response factor was to make up several solutions of glycol standards having different cis:trans ratios. With the addition of the internal standard, these solutions were chromatographed and areas under each diol peak would be measured. A plot of diol wt./P.C. wt vs. diol area/P.C. area would yield a slope equal to the response factor. These factors were found to be consistant over the different isomeric ratios i.e. plots just mentioned had good correlation coefficients.

All determinations involving reductions were made in triplicate. A study in the reproducibility showed that for the cis diol measurements, 95% of the data fell within $\pm$2.4% of the mean (99% within $\pm$3.7%). For the trans diol data, 99% of the data fell within $\pm$1.3% of the mean.

The important measurement of the paracymene standard solution was made with a one hundred microliter syringe. The ideal conditions for gc analysis of the reduction products were as follows.

Column : 10% Carbowax 20M, 80% Chromosorb D-370 (6'x$\frac{1}{8}$")

Ref Col : Silicone Rubber (2'x$\frac{1}{4}$")

Oven : Isothermal 115° C

Det : 315° (dial at 340)

Inj : 210° (38 on dial)

Bridge : 150 ma

Flow : 30 ml/min.

Chart : 2 in/min (for first 2.5 ins. or 1 min. 15 secs.)
0.25 in/min (to end of chromatograph)

Sample : 1-1.5 microliters

Att : 2 or 4

A faster chart speed initially was necessary to attain a sufficient area under the rather sharp paracymene peak.

F. Iron Analysis

Analysis of the iron impurity in the diketone sample was accomplished by a method explained in Skoog and West (35). A three part procedure was followed for the iron determination. The diketone was decomposed by the action of sulfuric acid and hydrogen peroxide; the ferric ions present were reduced to ferrous ions; the ferrous ions were titrated with a $KMnO_4$ solution. The typical procedure follows.

200 mgs. of the diketone were added to 1 ml. of H_2SO_4. Slowly, 3 mls. of 30% H_2O_2 were added dropwise and the mixture was brought to boiling and so maintained for 15 minutes. A check with starch-iodine paper indicated no peroxide present. Complete oxidation of all organics was assumed at this point. While still hot, 7 drops of a 0.16 M $SnCl_2$ solution was added to effect total reduction of ferric ions. The solution was cooled and 10 mls. of 0.018 M $HgCl_2$ is added rapidly. 25 mls.

of the Zimmermann-Reinhardt reagent (35) were added. The solution was diluted to 250 mls. and titrated with a 3.0×10^{-3} N solution of $KMnO_4$. A blank sample is titrated also and considered in the calculations.

The Zimmermann-Reinhardt reagent consists of manganese II ions in fairly concentrated sulfuric and phosphoric acids. The Mn ions inhibit oxidation of the chloride ion and the phosphoric acid complexes with the ferric ions produced to prevent the yellow color of the iron III chloride from interfering with the endpoint.

The iron analysis was performed in triplicate giving an average value of $2.1 \pm .3$ % iron impurity in the sample.

G. Instrumentation

1. All gas chromatographic data was obtained using a Honeywell F & M Model 720 Dual Column Programmed Temperature Gas Chromatograph.

2. Infrared spectra were obtained utilizing either a Perkin-Elmer 337 Grating Infrared Spectr photometer or a Baush and Lomb Spectronic 250 (Shimadru).

3. All melting points were obtained on a Thomas Hoover Capillary Melting Point Apparatus (Uni-melt).

4. NMR spectra were obtained on a Hitachi Perkin-Elmer R-20B High Resolution NMR Spectrometer.

H. Reagents

1. Acetic Acid (Glacial), Reagent ACS, Cd. 1019, Baker and Adamson.
2. Ammonium Sulfate (Crystal), Reagent ACS, Cd. 1316, Baker and Adanson.
3. Bromine B-385, Reagent ACS, Lot 770436, Fisher Scientific Company.
4. Calcium Sulfate (Anhydrous powder) 1458, Lot 31221, Baker Analyzed.
5. Chlorotrimethylsilane (98%), Cat. #69111, Lot 061677, Alfa Products.
6. Cyclopentanone 2543, Lot A7A, Eastman
7. Cyclopentene (99%), Cat. #C11,260-7, Lot 110837, Aldrich Chem. Comp.
8. Cymene (para) Certified Reagent, Cat. #C-560, Lot 760597, Fisher Scientific Comp.
9. Ethyl Ether (anhydrous) E-138, Lot 755308, Fisher Scientific Comp.
10. Formic Acid (88%) A-118, Certified ACS, Lot 781990, Fisher Scientific Comp.
11. Glutaric Acid 564, Lot 1340, Eastman
12. Hydrochloric Acid A-144, Reagent ACS, Fisher Scientific Comp.
13. Lithium Aluminum Hydride (95% LAH), Lot G-5, Alfa Products.
14. Manganous Sulfate (monohydrate) M-113, Certified ACS,Lot 723906, Fisher Scientific Comp.
15. Para-Toluenesulfonic Acid A-320, Lot 726642, Fisher Scientific Comp.
16. Petroleum Ether E-139, Certified ACS, Lot 771819, Fisher Scientific Comp.
17. Phosphoric Acid (Ortho 85%), Certified ACS, Lot 793261, Fisher Scientific Comp.
18. Potassium Permanganate P-279, Certified ACS, Lot 762127, Fisher Scientific Comp.
19. Silicic Acid A-288, Lot 730944, Fisher Certified Reagent
20. Silver Acetate , Cd. 2172, Lot 162, Baker and Adamson
21. Sodium Carbonate (Anhydrous), Lot 1.946, C. P. Baker's Analyzed.
22. Sodium Hydroxide (Sol'n, 50%), Analytical Reagent, Mallinckrodt 7705.
23. Sodium Oxalate (powder) C-140, Reagent ACS, Cd. 2270, Baker and Adamson.

24. Stannous Chloride (crystal) T-142, Certified ACS, Lot 780830, Fisher Scientific Comp.

25. Tetrahydrofuran T-397, Certified, Lot 770080, Fisher Scientific Comp.

APPENDIX A

Gas Chromatograms, Infrared Spectra, and Nuclear Magnetic Resonance Spectra

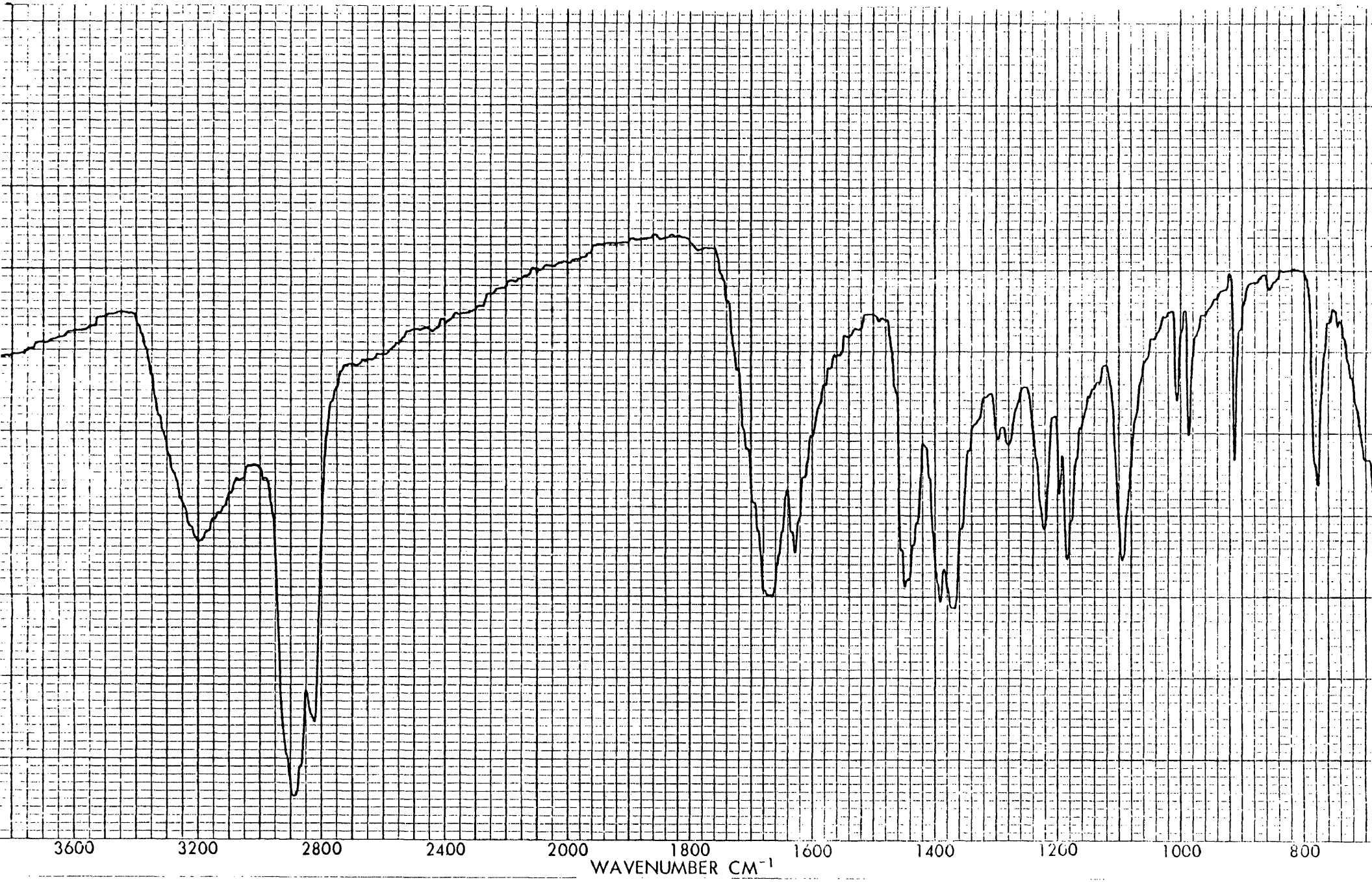


Figure A1: Infrared Spectrum of 1,2-Cyclopentanedione in a Nujol Mull

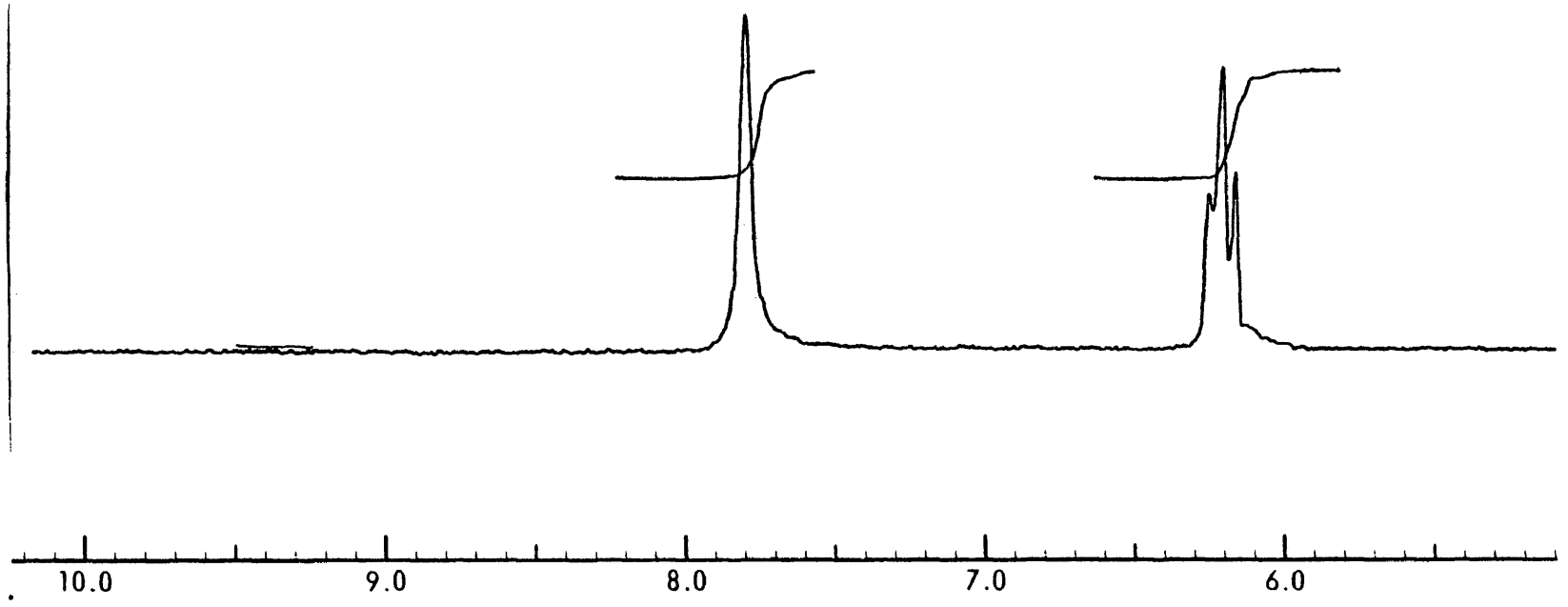


Figure A2: NMR Spectrum of 1,2-Cyclopentanedione in THF. An initial NMR in CCl_4 indicated that the THF Signals (two largest pg. 51) do not interfere with the diketone signals.

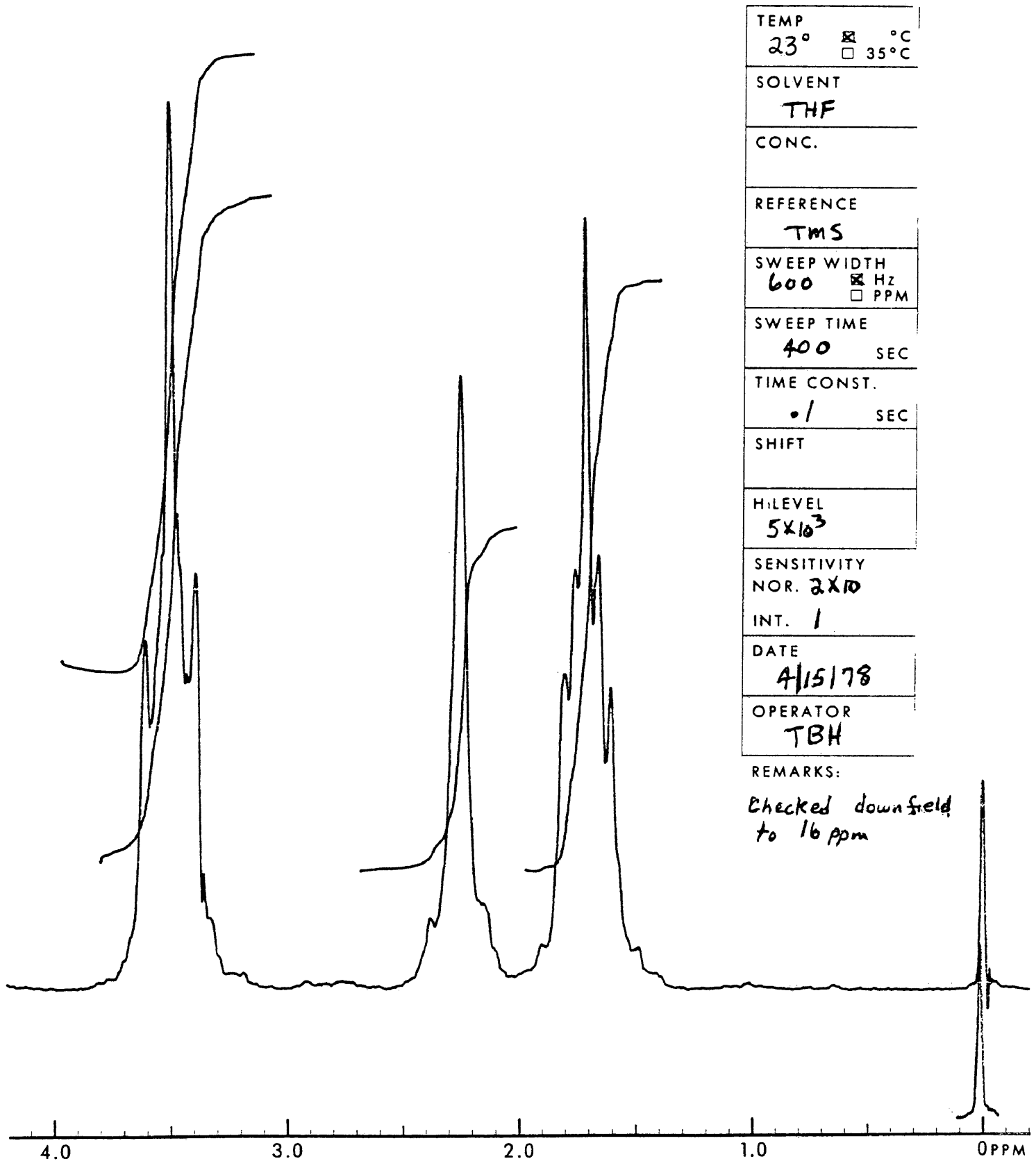


Figure A2: con't

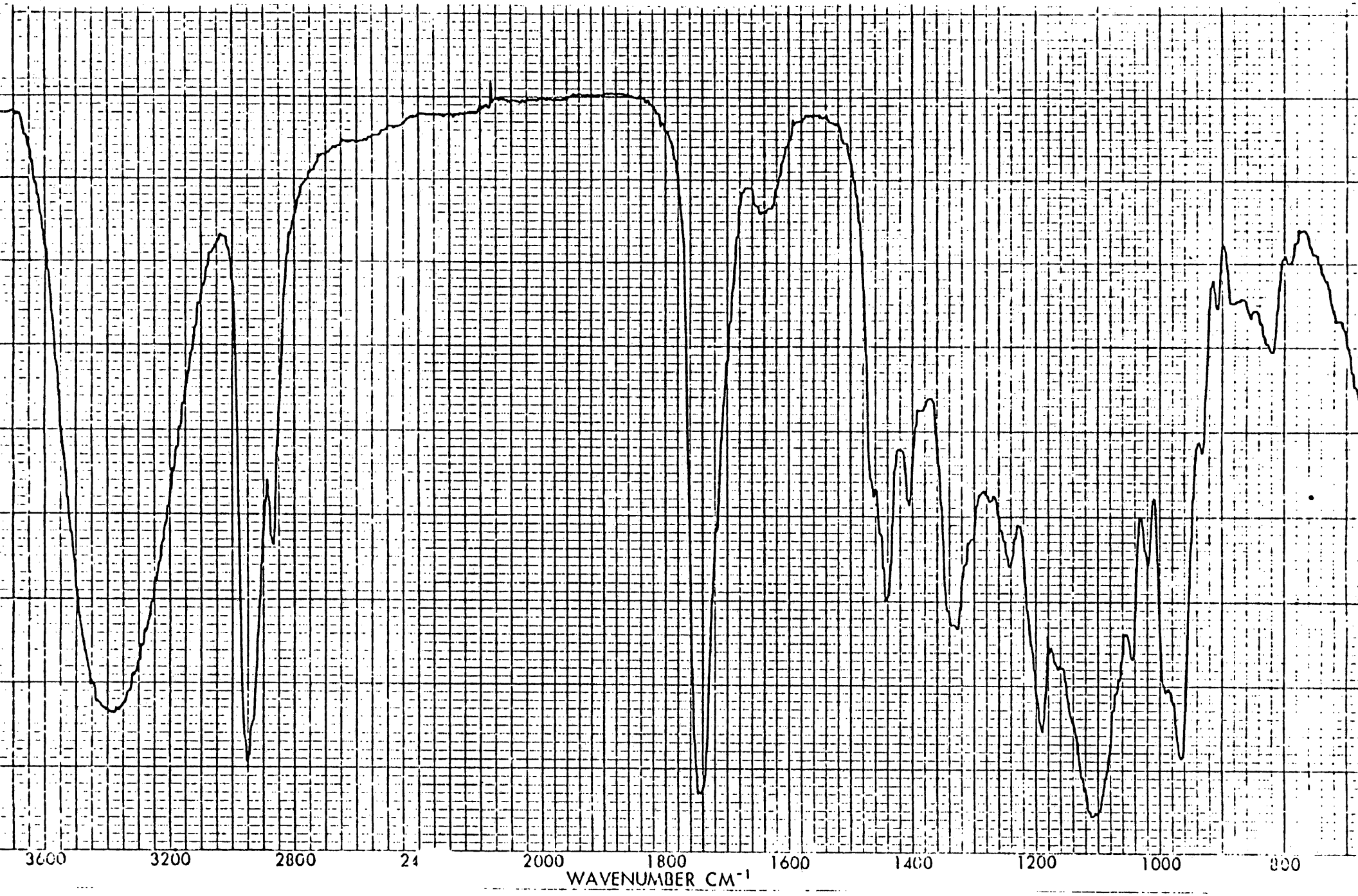


Figure A3: Infrared Spectrum of Freshly Distilled 2-Hydroxycyclopentanone

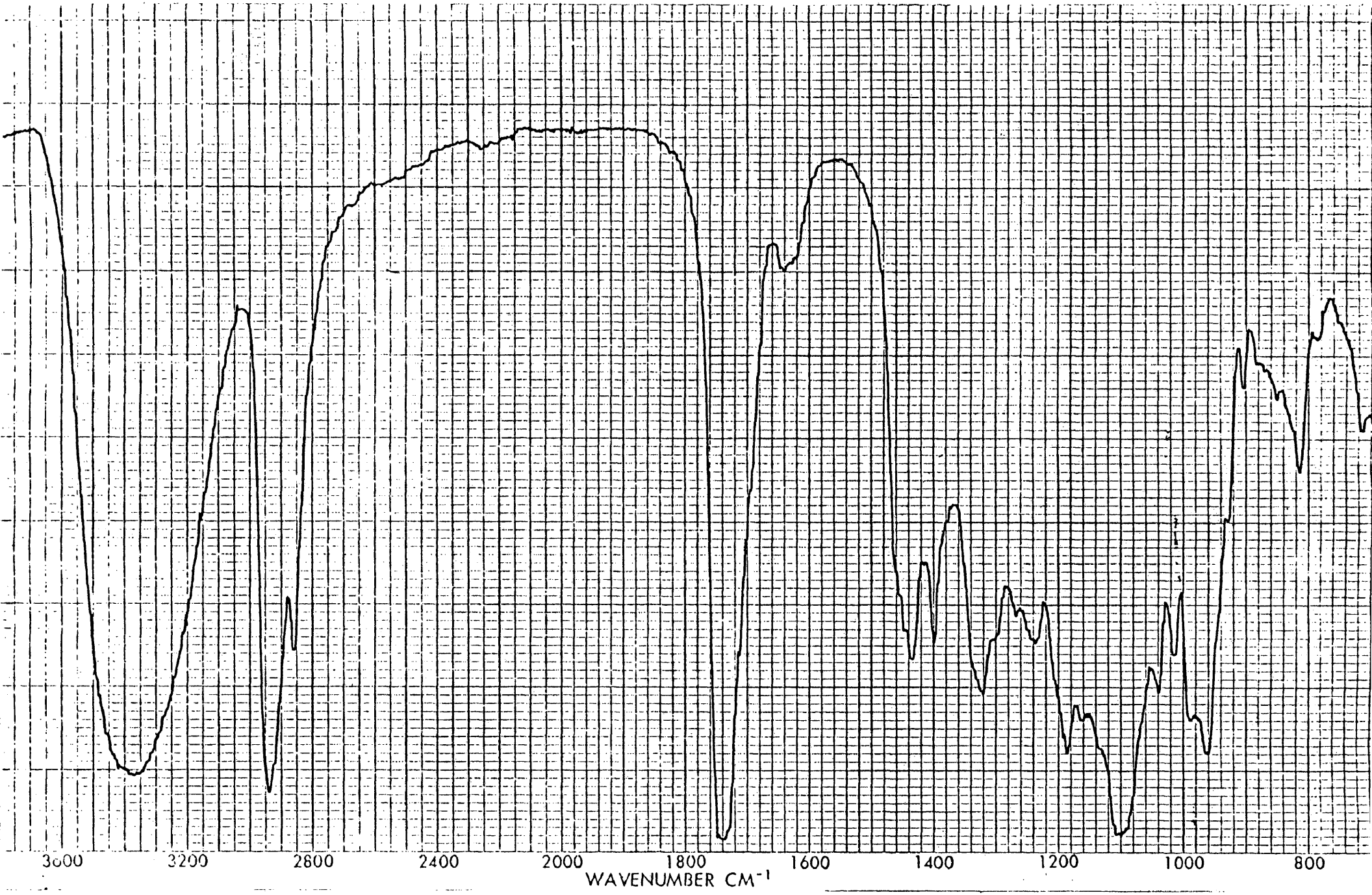


Figure A4: Infrared Spectrum of 2-Hydroxycyclopentanone after Setting 28 Days at Room Temperature

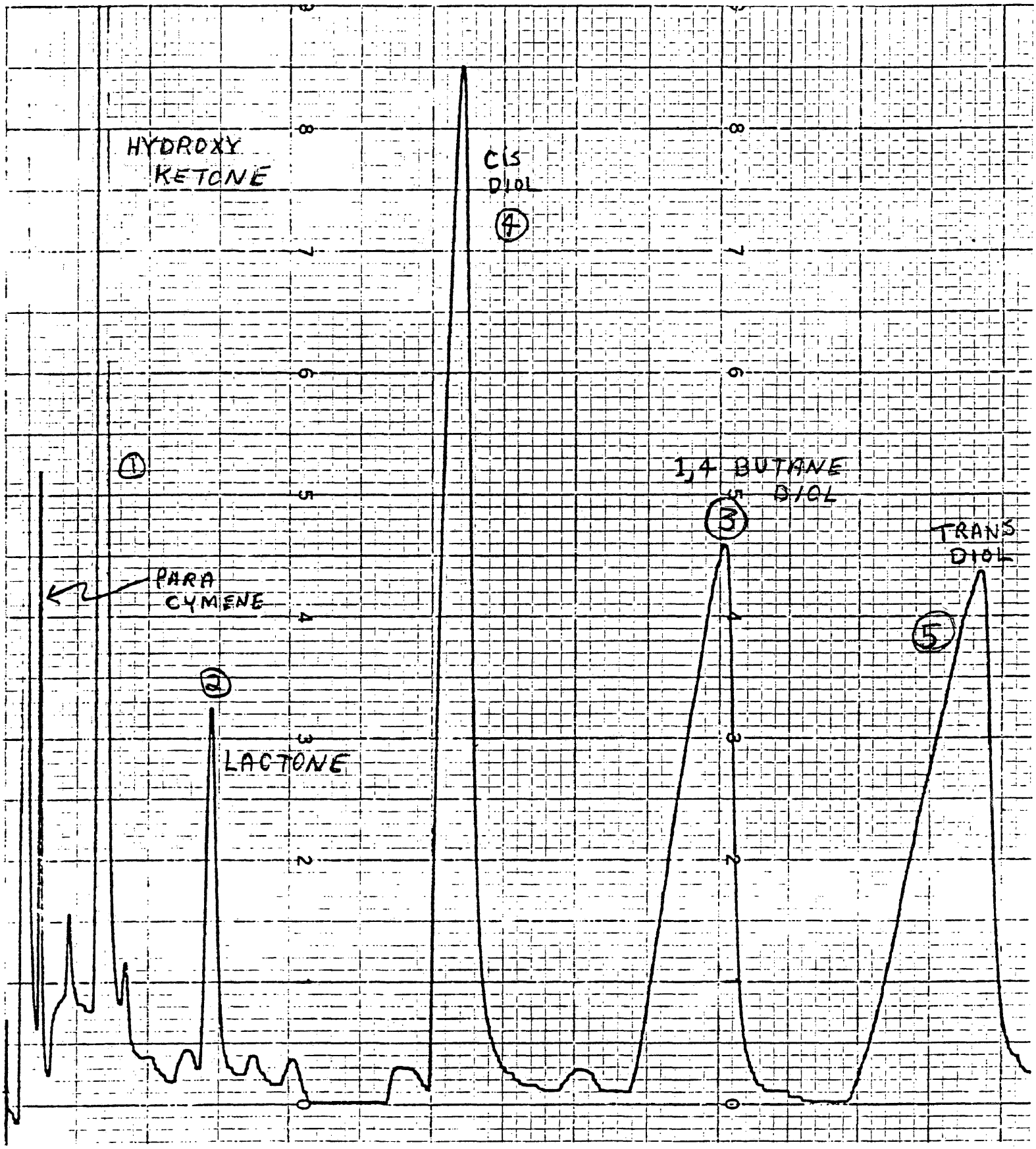


Figure A5: Typical Gas Chromatogram on Reduction products on Carbowax 20M Column

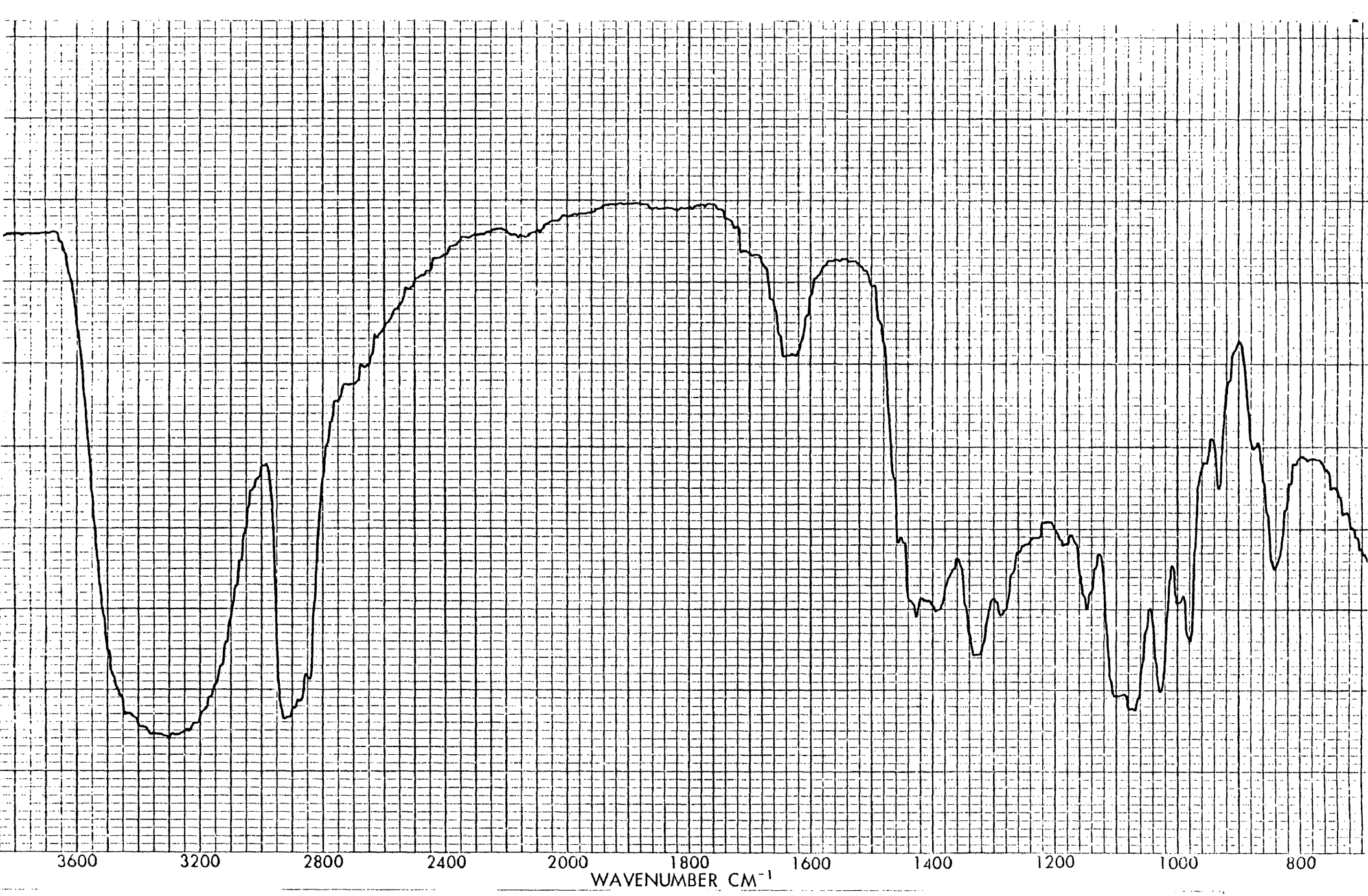


Figure A6: Infrared Spectrum of Peak 4 (Fig. A5) Expected to be Cis-1,2-Cyclo pentanediol

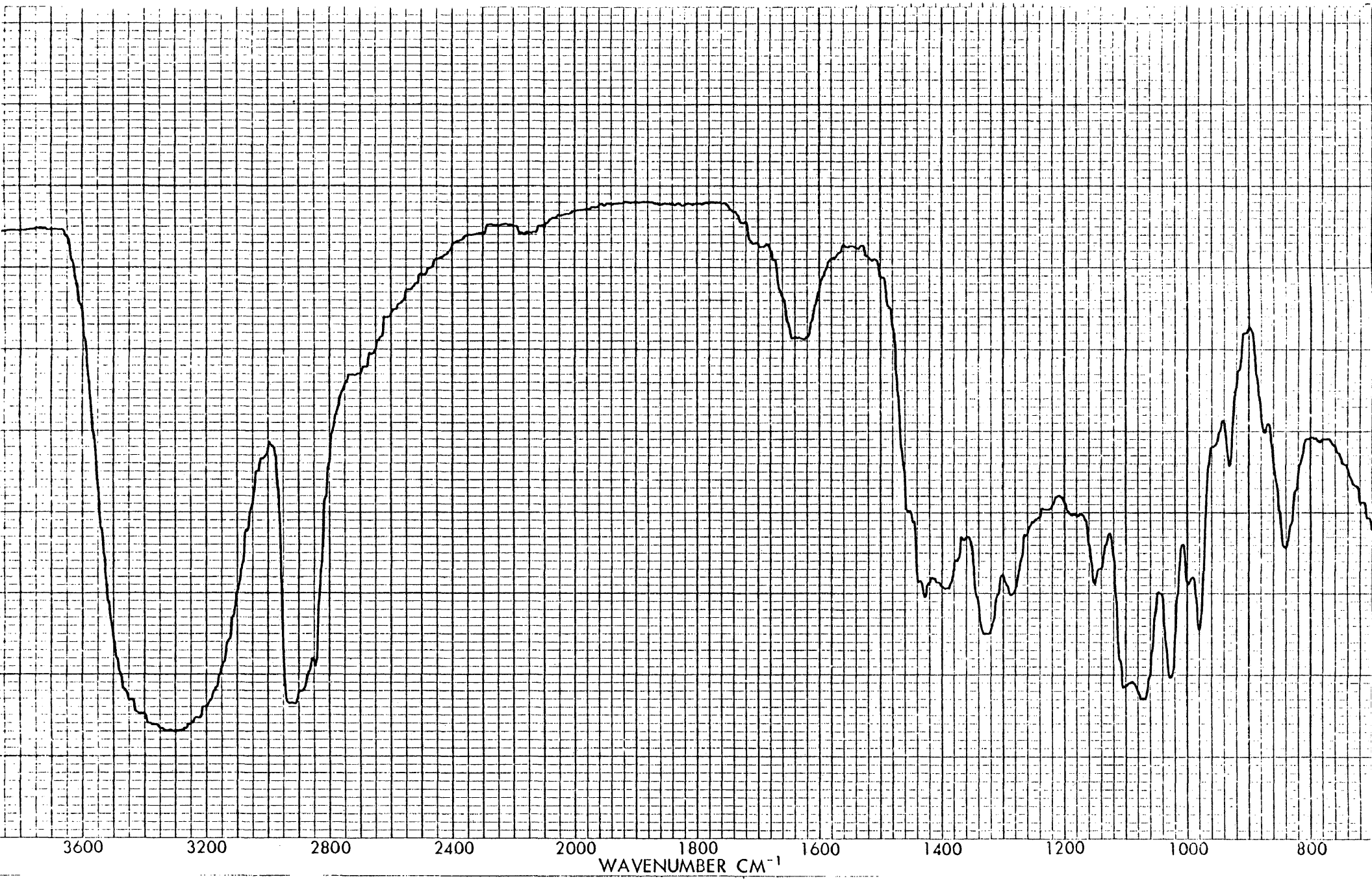


Figure A7: Infrared Spectrum of Authentic Cis-1,2-Cyclopentanediol

Figure A8: Infrared Spectrum of Peak 5 (Fig. A5) Expected to be Trans-1,2-Cyclopentanediol

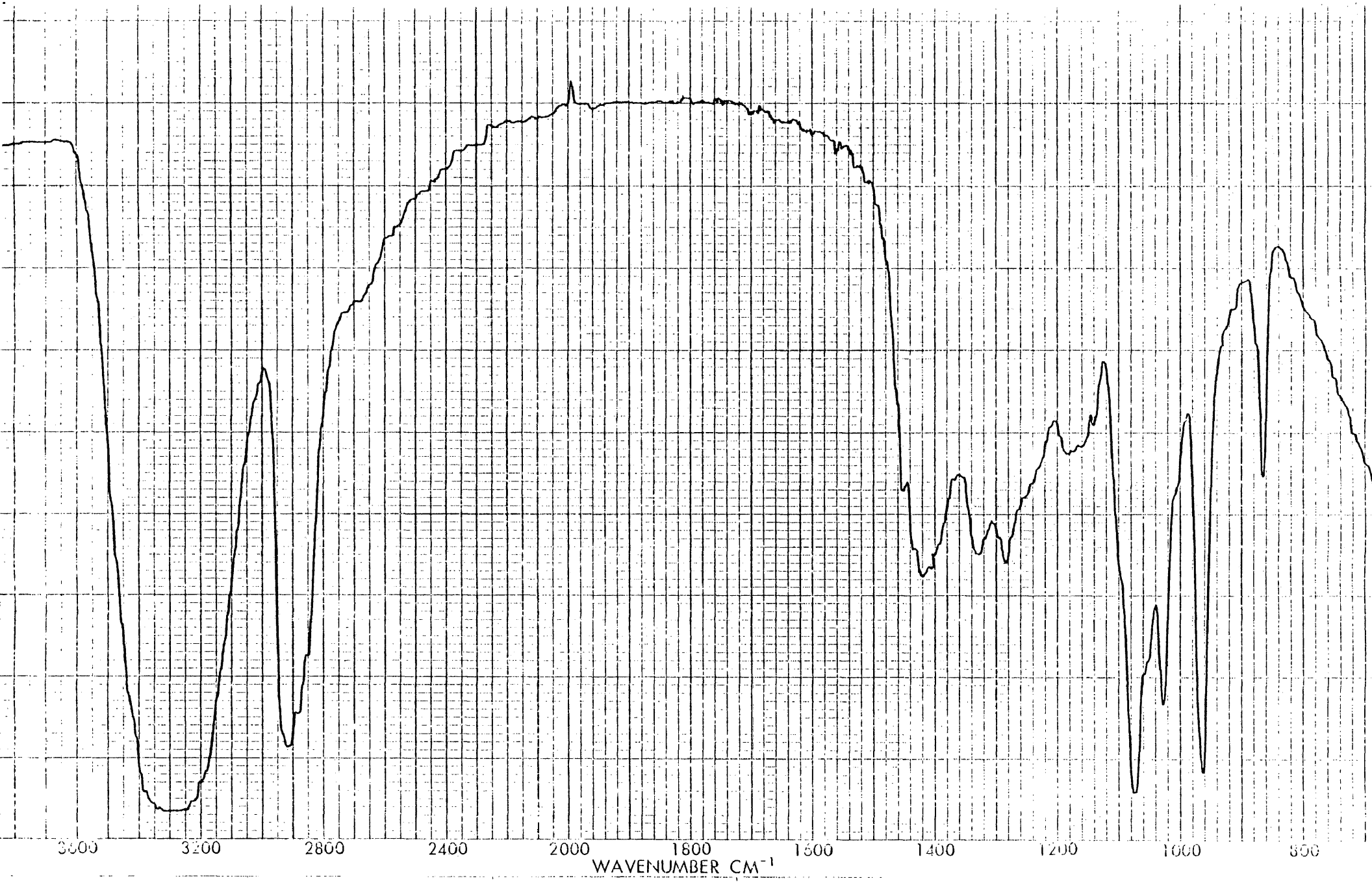


Figure A9: Infrared Spectrum of Authentic Trans-1,2-Cyclopentanediol

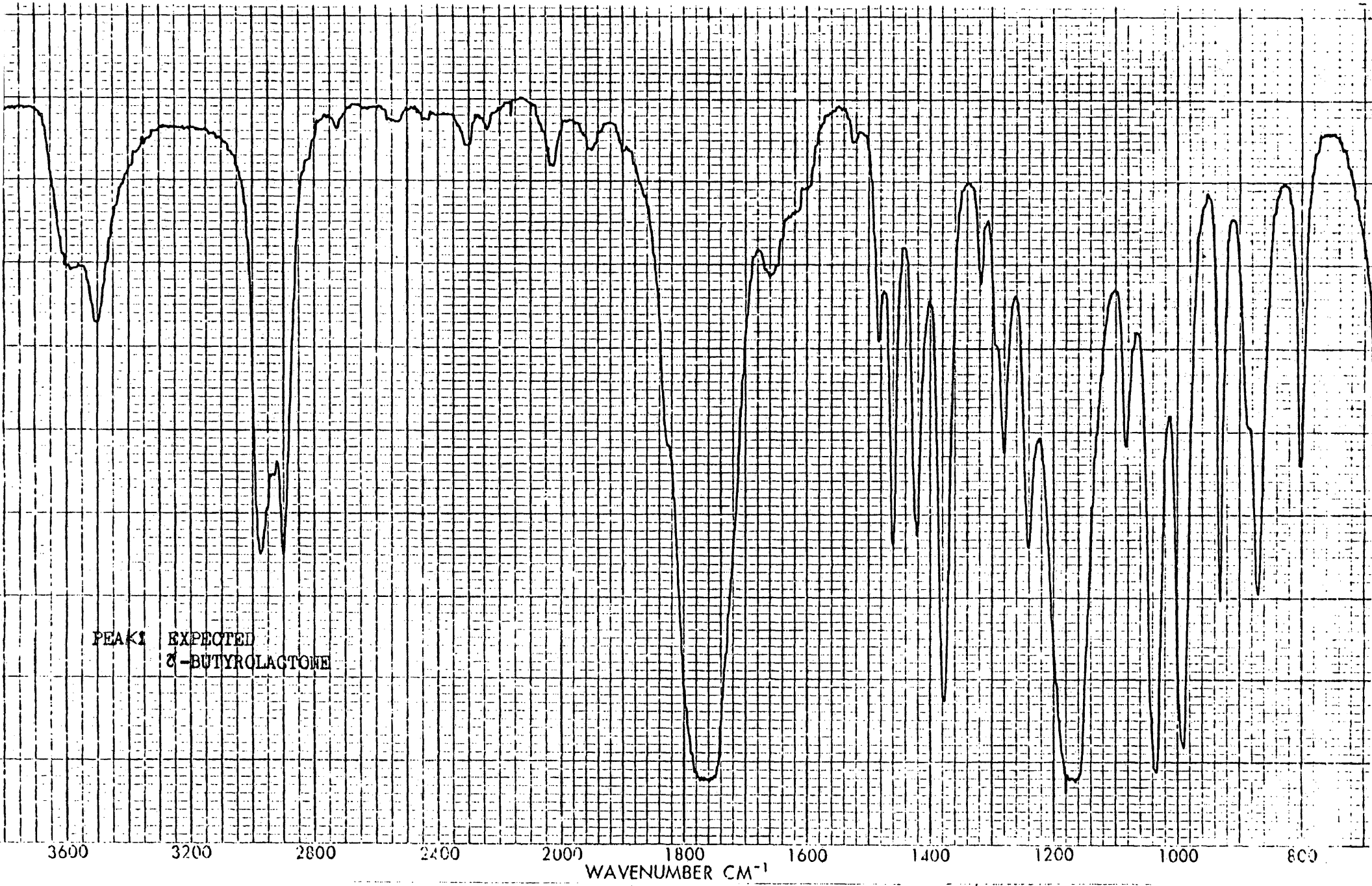


Figure A10: Infrared Spectrum of Peak 2 (Fig. A5) Trappings

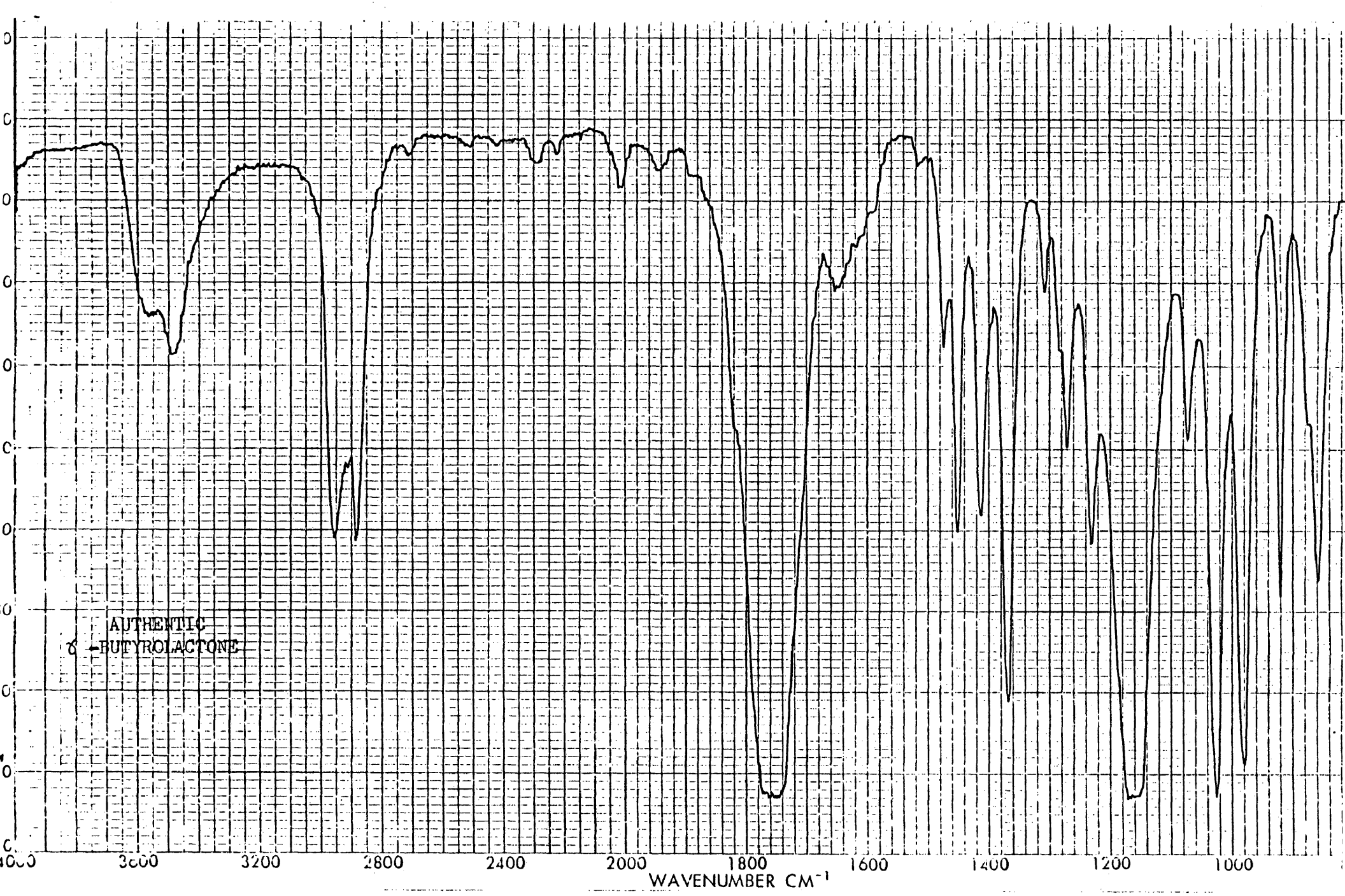


Figure A11: Infrared Spectrum of Authentic γ-Butyrolactone

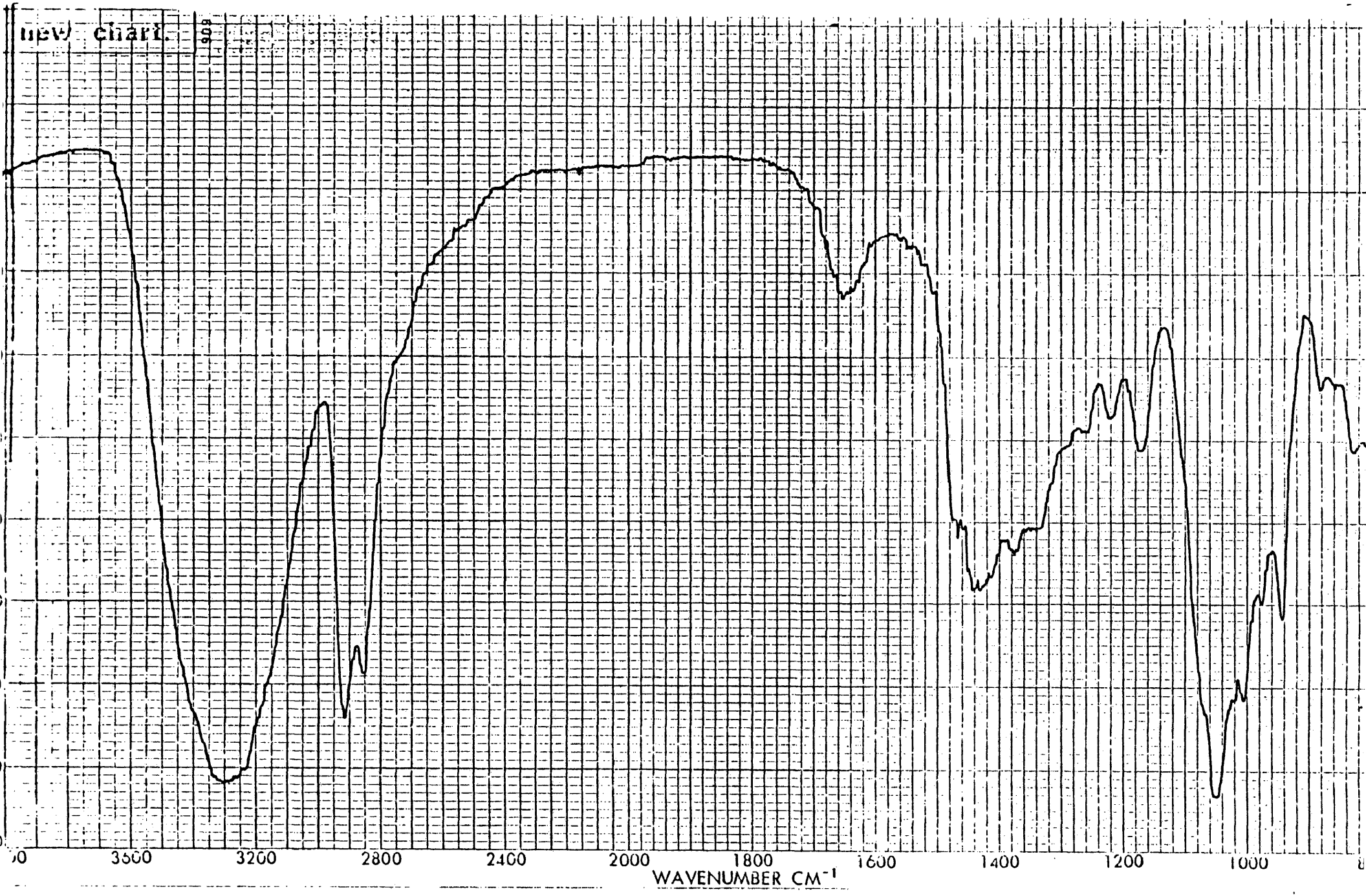


Figure A12: Infrared Spectrum of Peak 3 (Fig. A5) Trappings

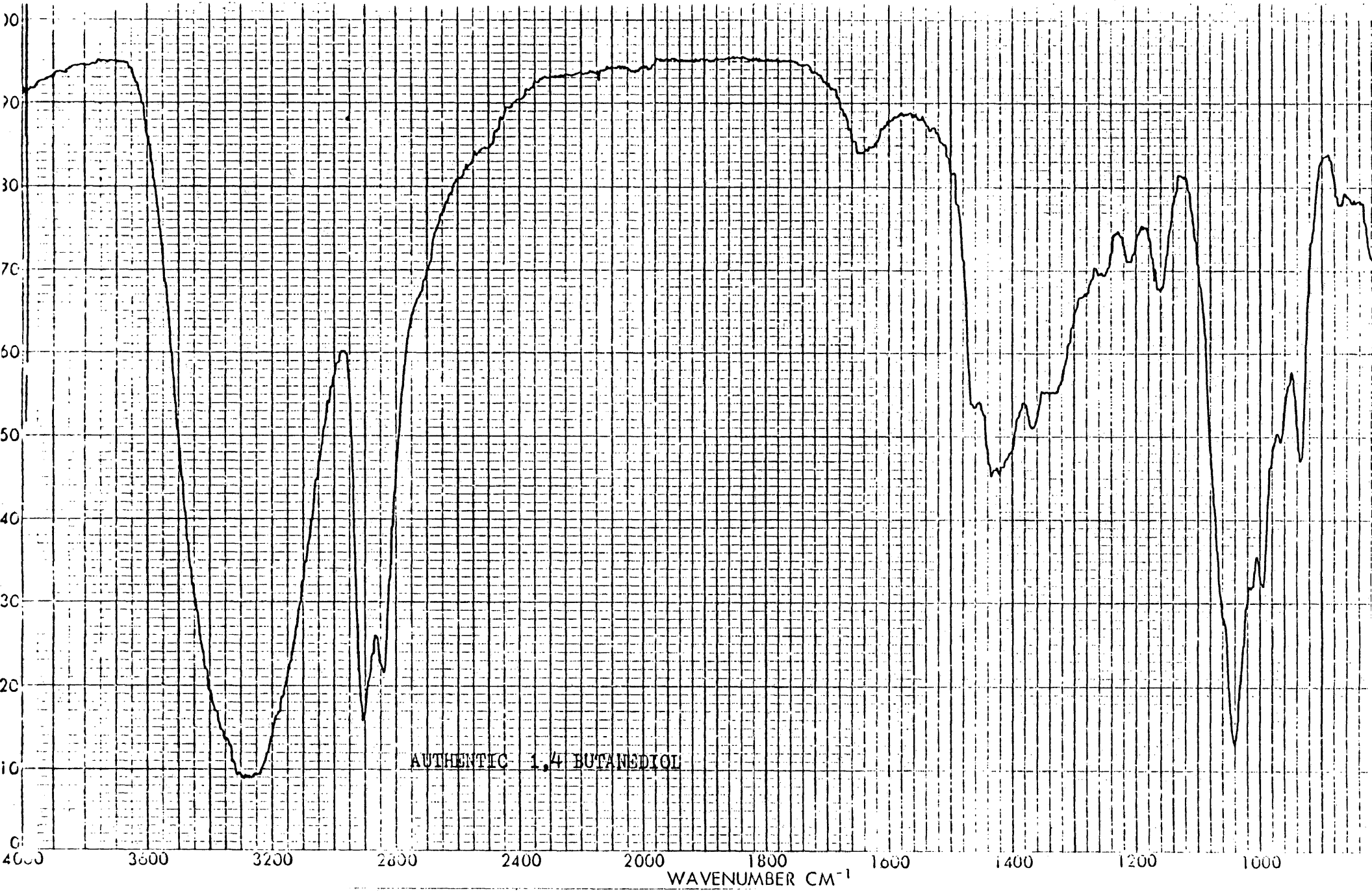


Figure A13: Infrared Spectrum of Authentic 1,4 Butanediol

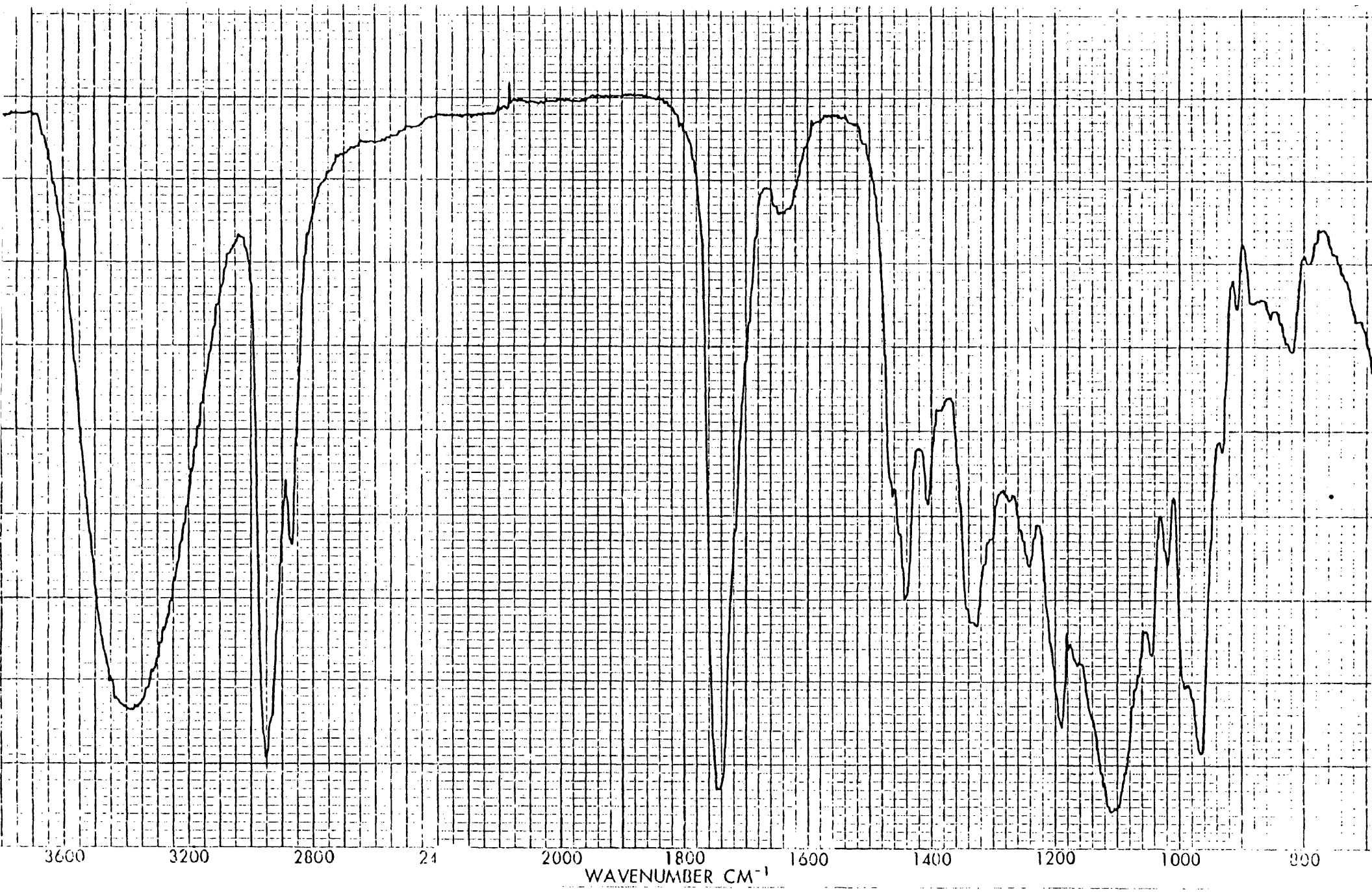


Figure A14: Infrared Spectrum of Peak 1 (Fig. A5) Trappings

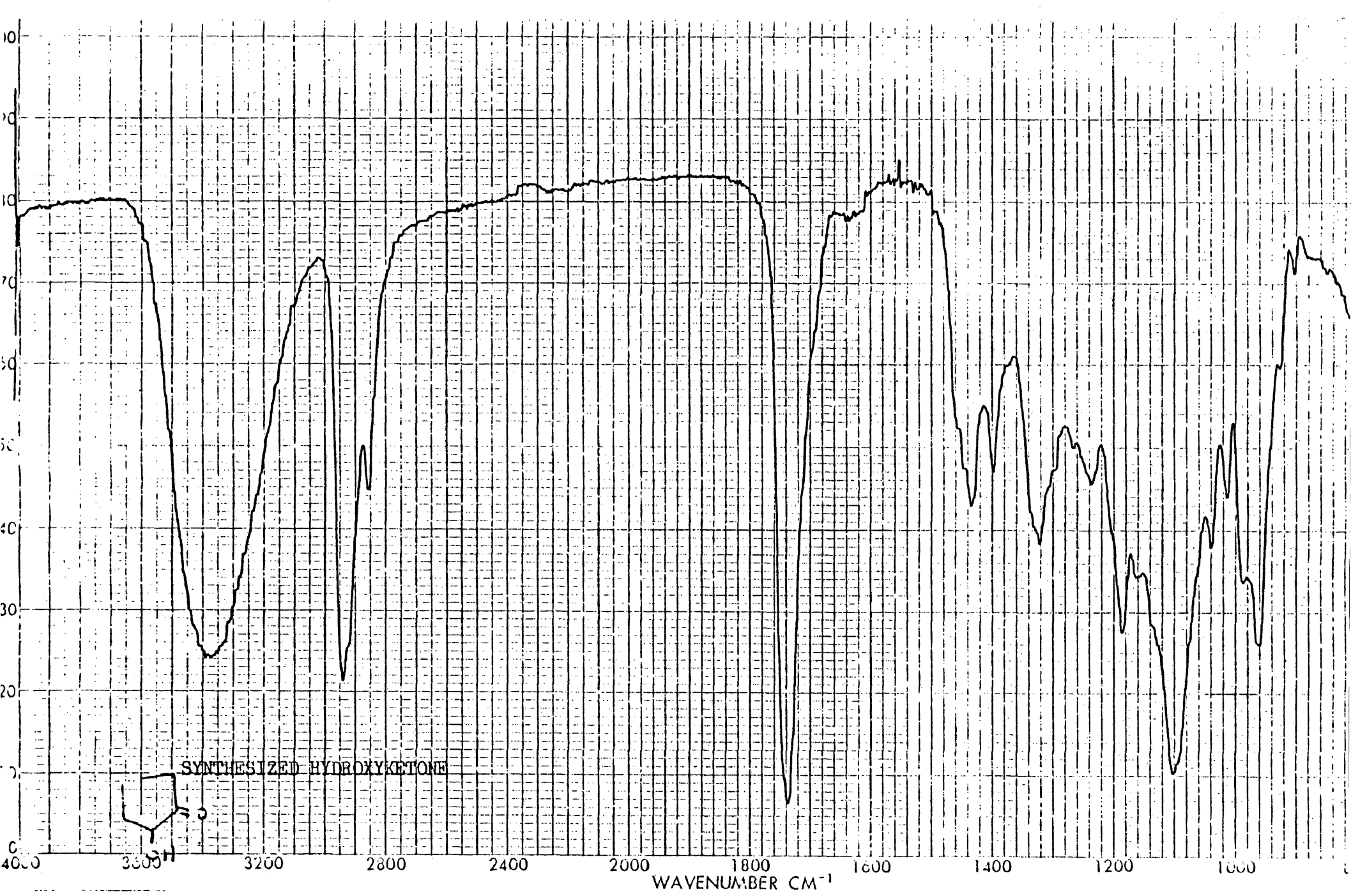


Figure A15: Infrared Spectrum of Authentic 2-Hydroxycyclopentanone

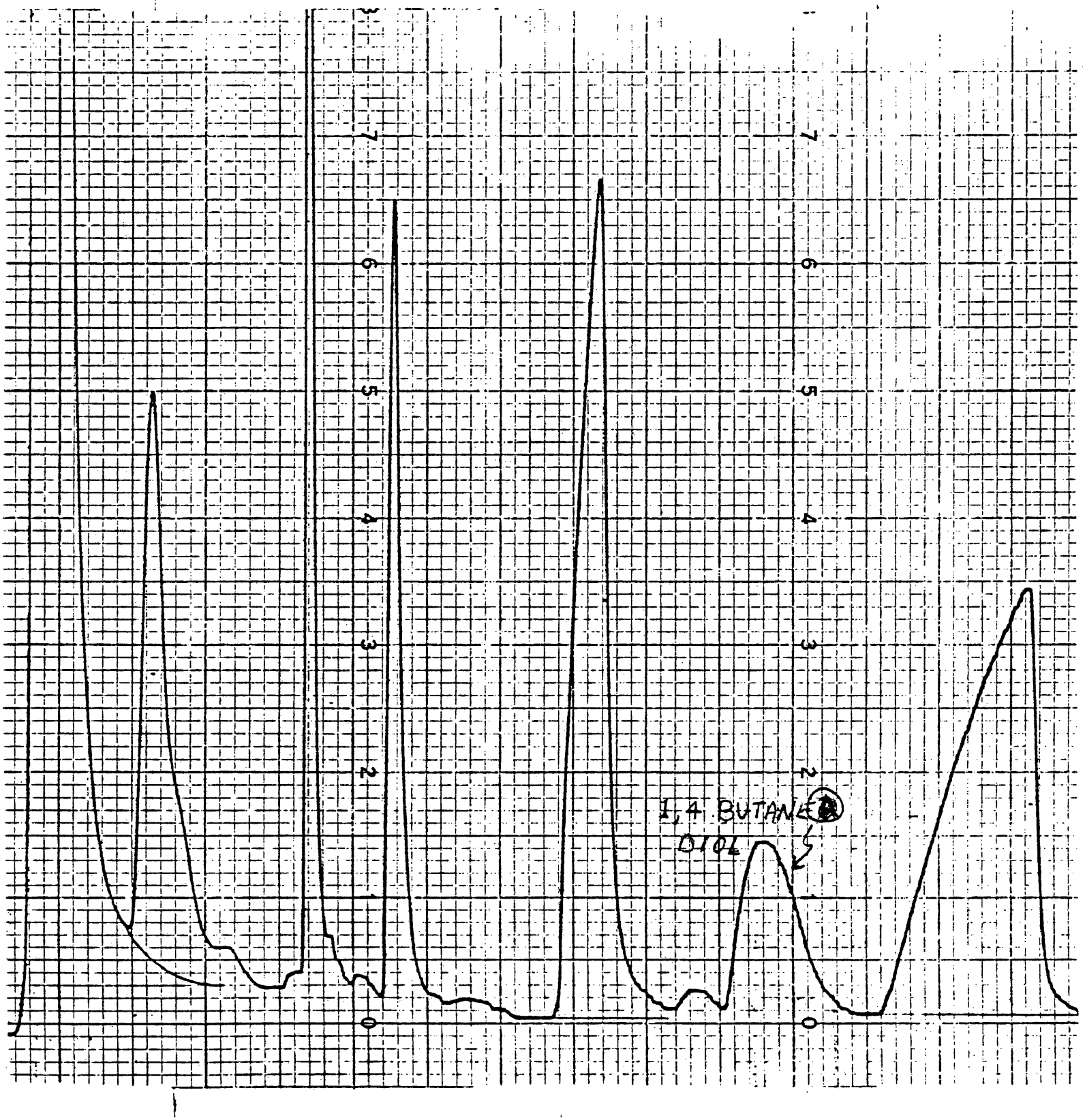


Figure A16: Gas Chromatograph of Reduction products of a 6:1 (hydride:carbonyl) run at 0°

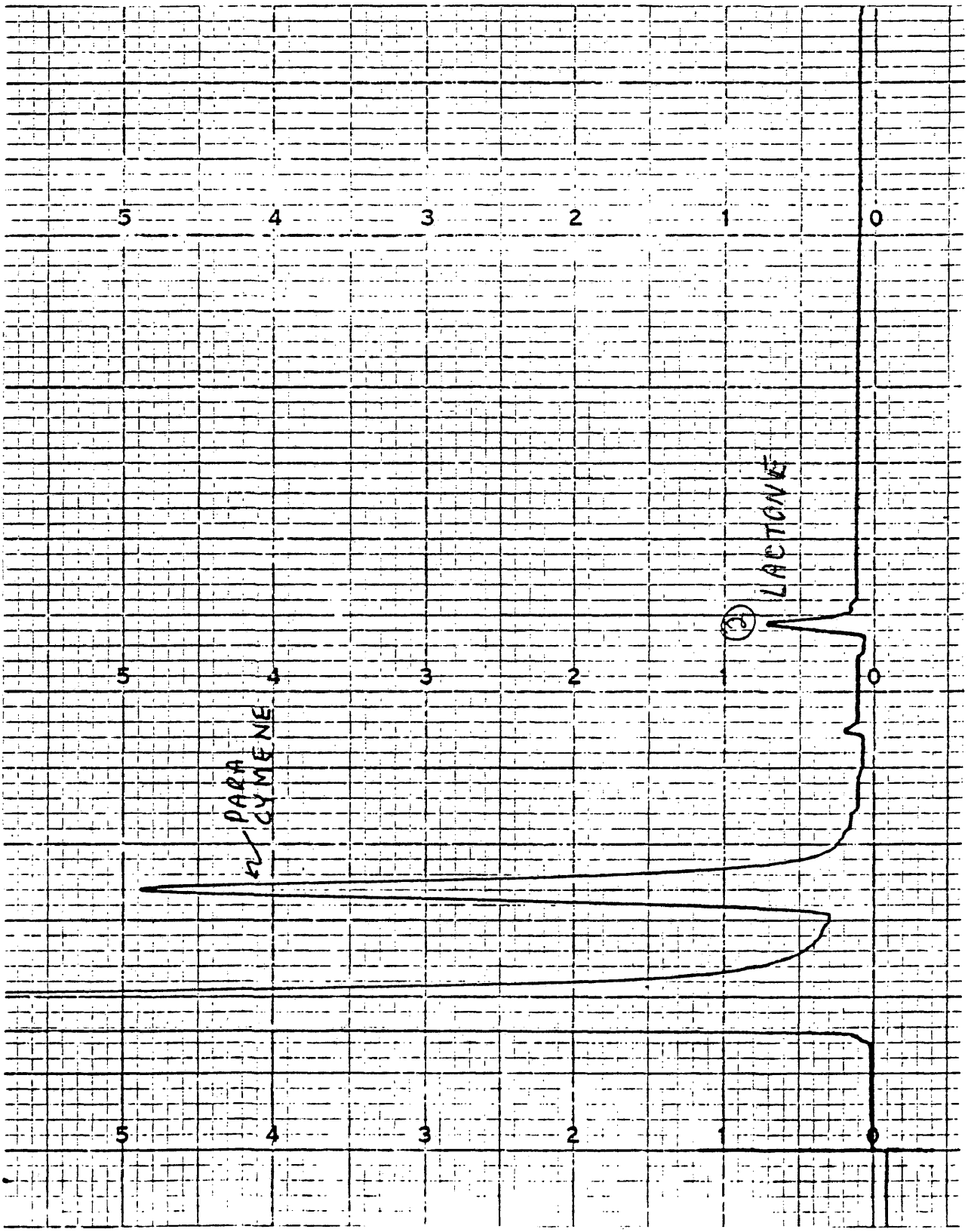


Figure A17: Gas Chromatograph of Blank Run (having no diketone) at the same reducing agent Concentration and p-cymene content as in Figure A16.

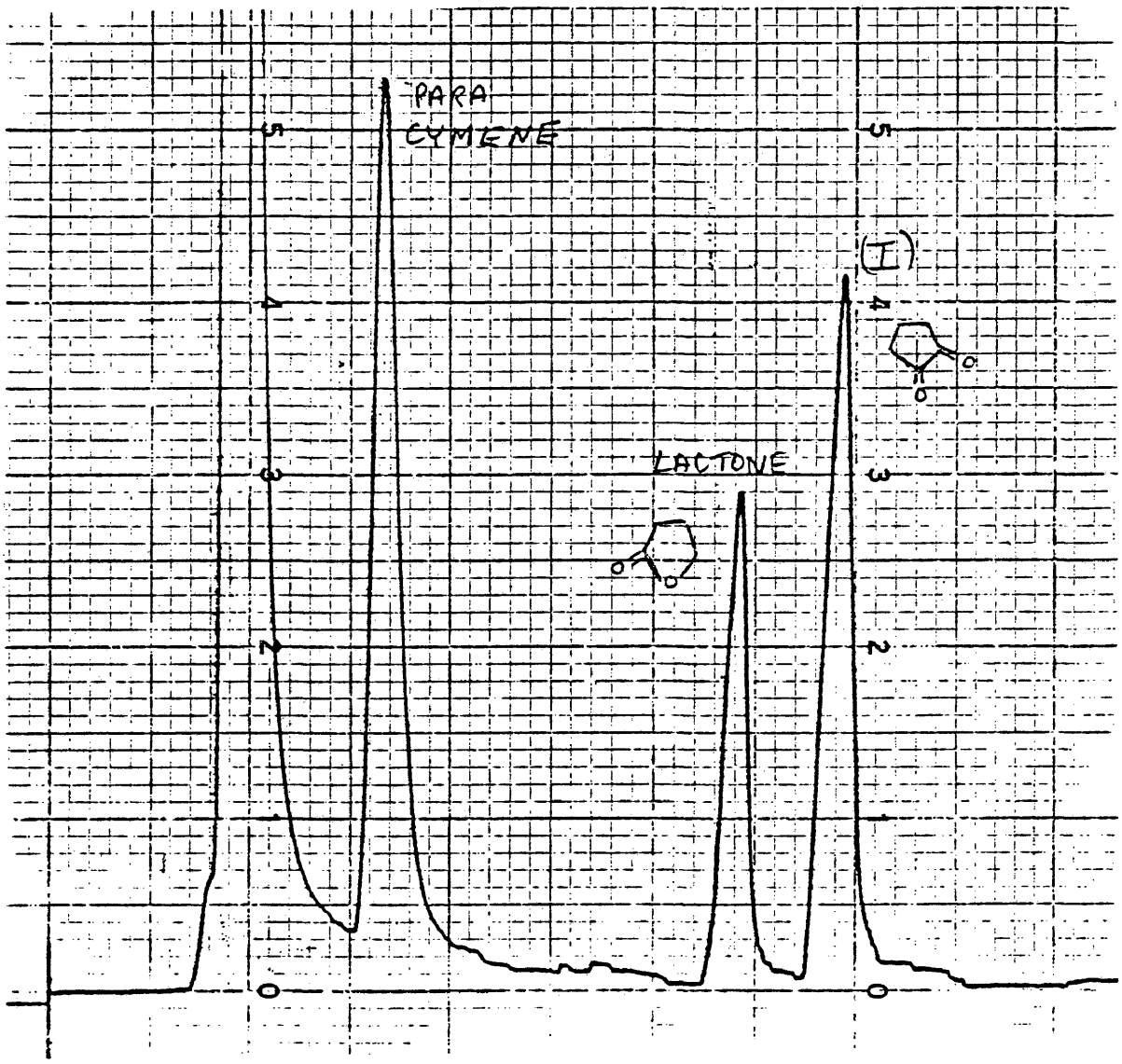


Figure A18: Gas Chromatograph of Air Oxidation Mixture After 30 Minutes when 1,2-Cyclopentanedione (I) is present

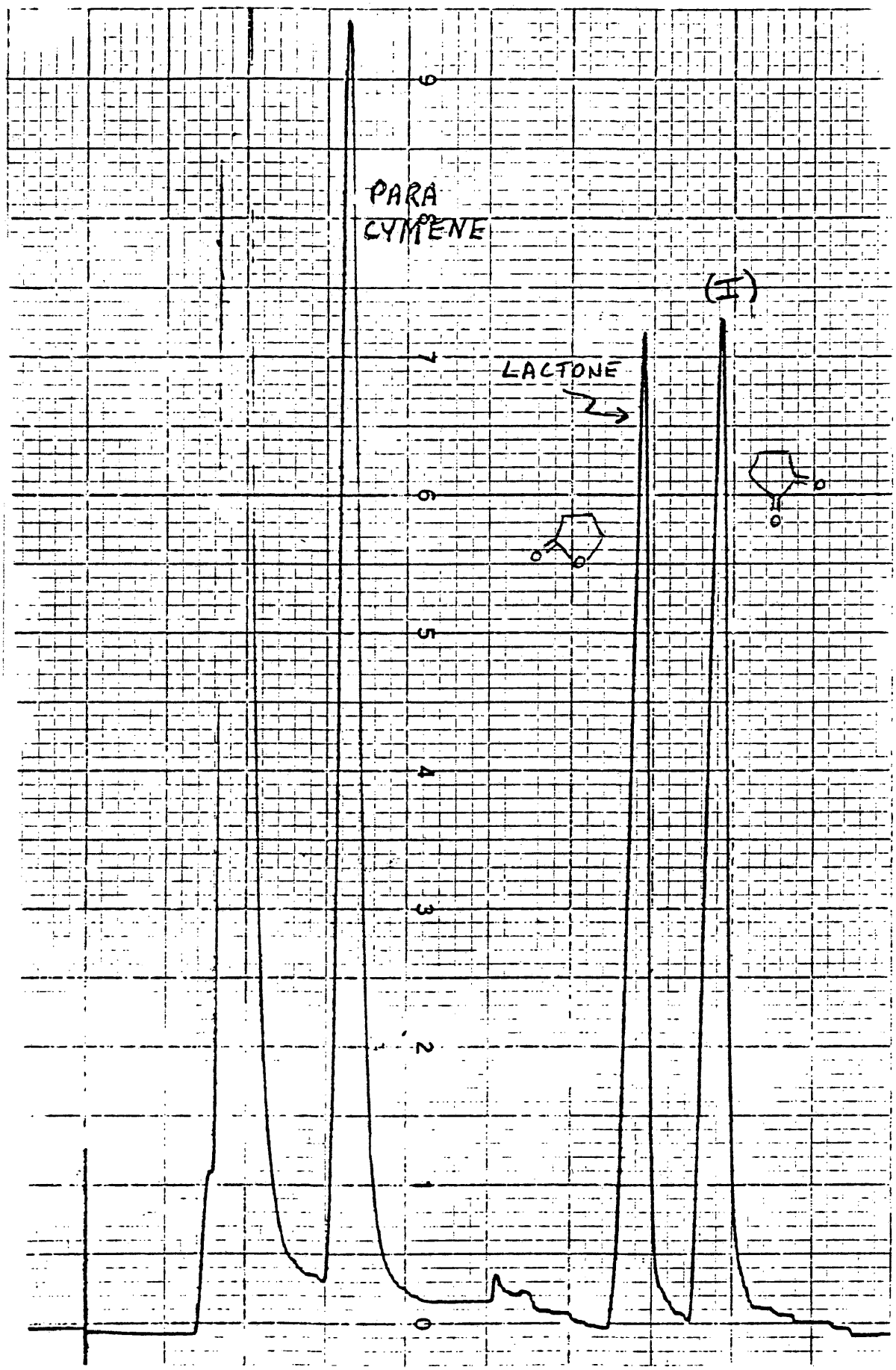


Figure A19: Gas Chromatograph of Air Oxidation Mixture After 60 Minutes when 1,2-Cyclopentanedione (I) is present.

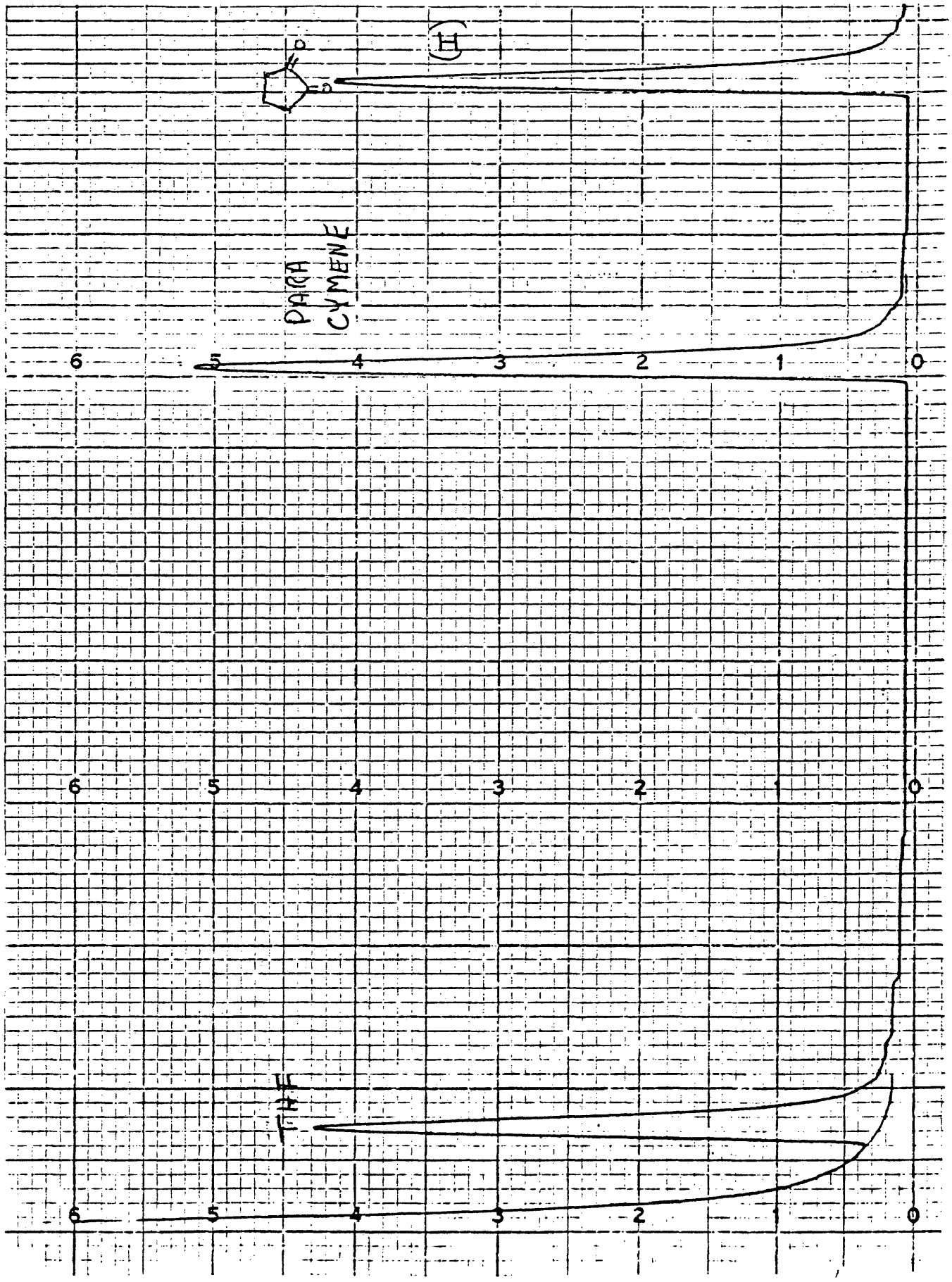


Figure A20: Gas Chromatograph of Hexane Solution in Oxygen Uptake Experiment Prior to O_2 exposure (1,2-Cyclopentanedione present, I)

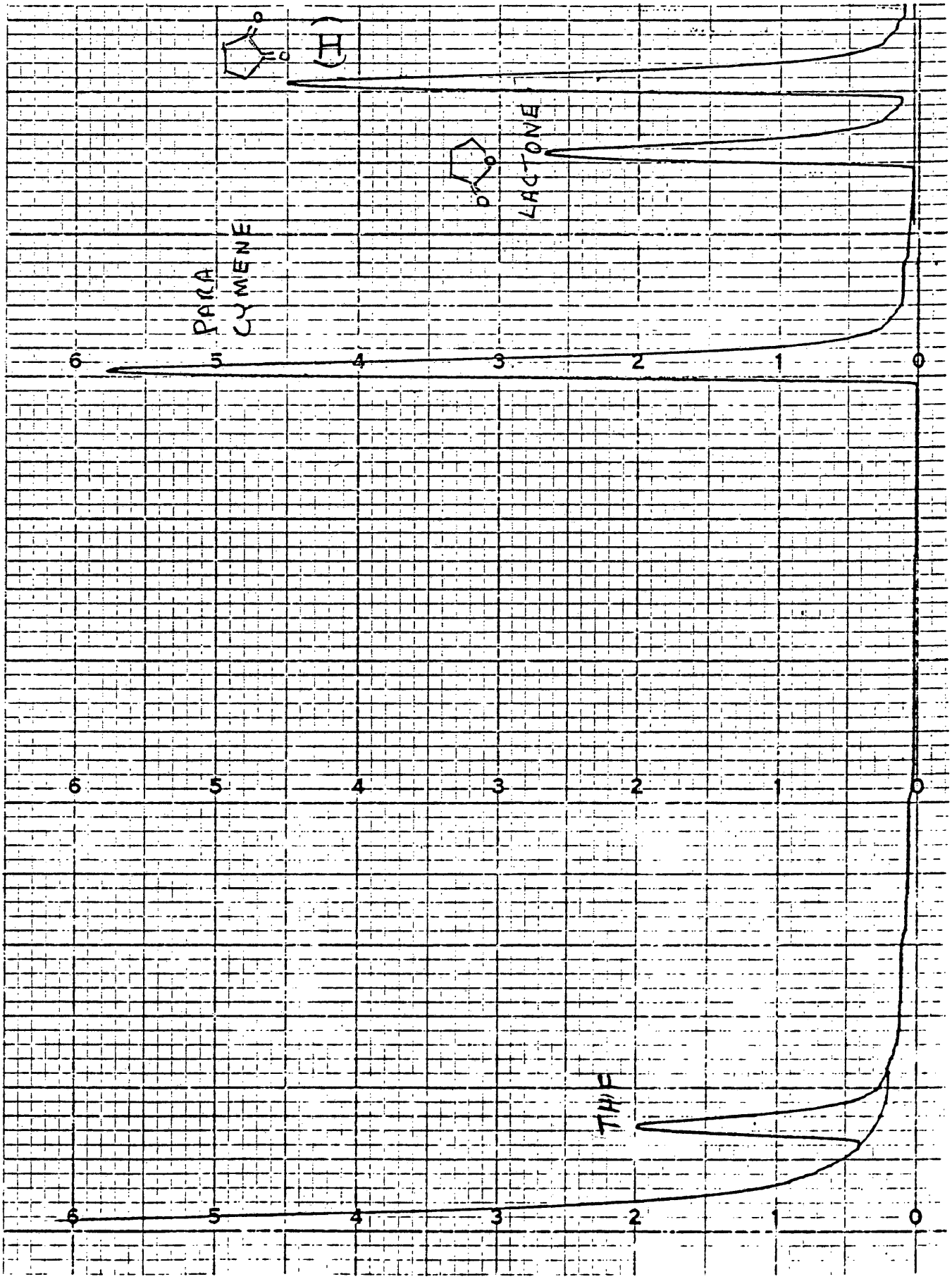


Figure A21: Gas Chromatograph of Hexane Solution in Oxygen Uptake Experiment Following 72 Minutes O_2 Exposure (1,2-Cyclopentanedione present, I)

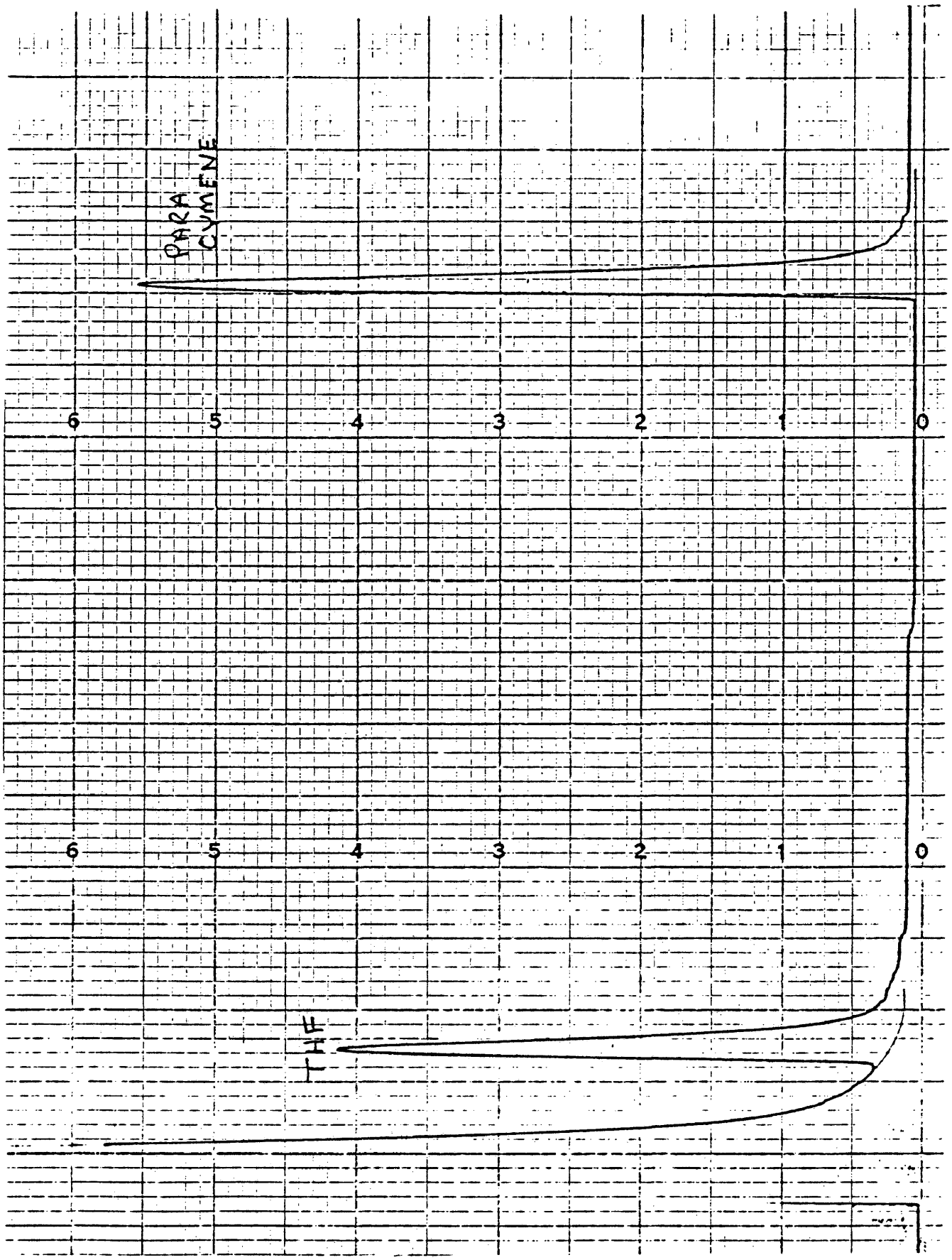


Figure A22: Gas Chromatograph of Hexane Blank (no diketone) in Oxygen Uptake Experiment Prior to O_2 Exposure.

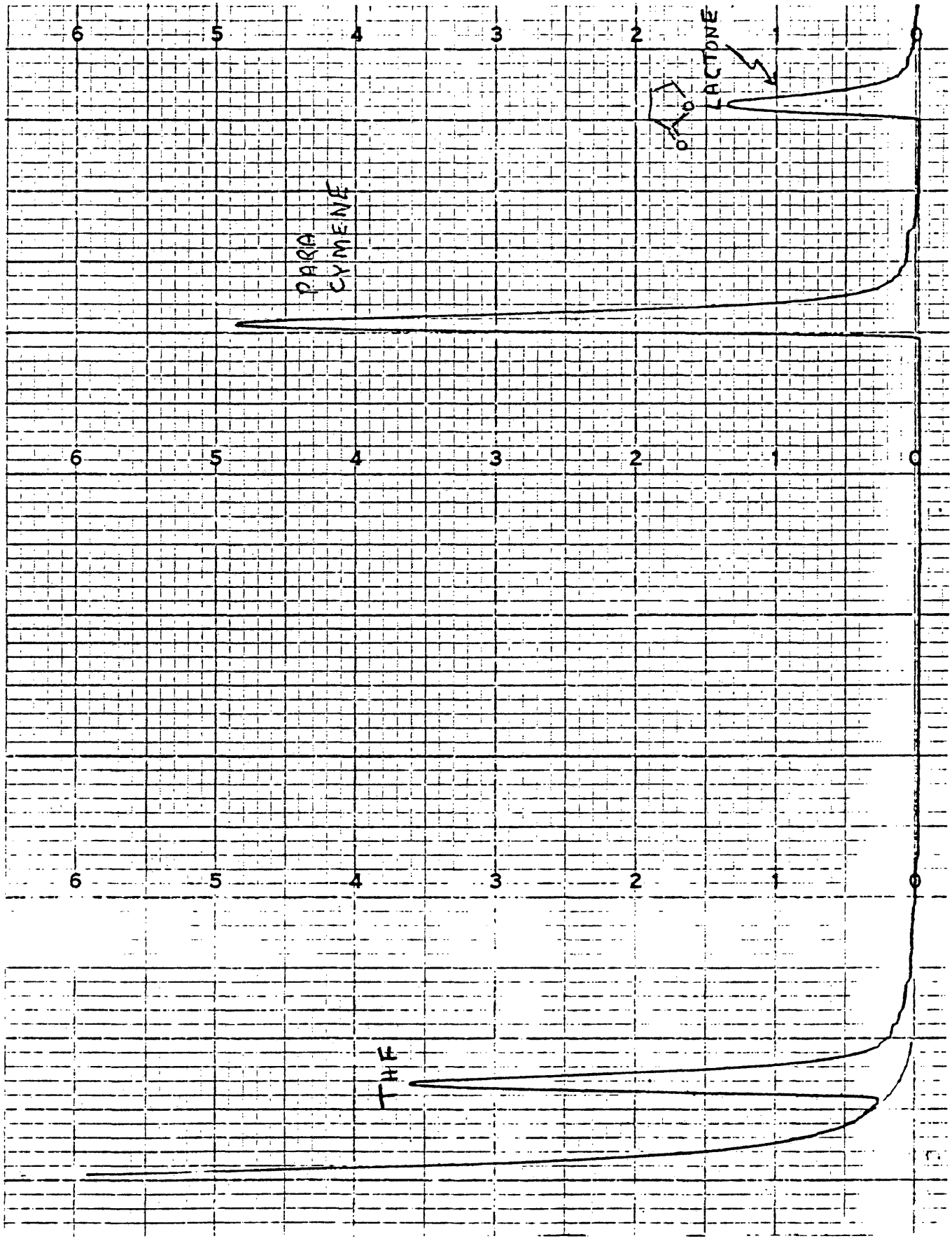


Figure A23: Gas Chromatograph of Hexane Blank (no diketone) in Oxygen Uptake Experiment Following O_2 Exposure.

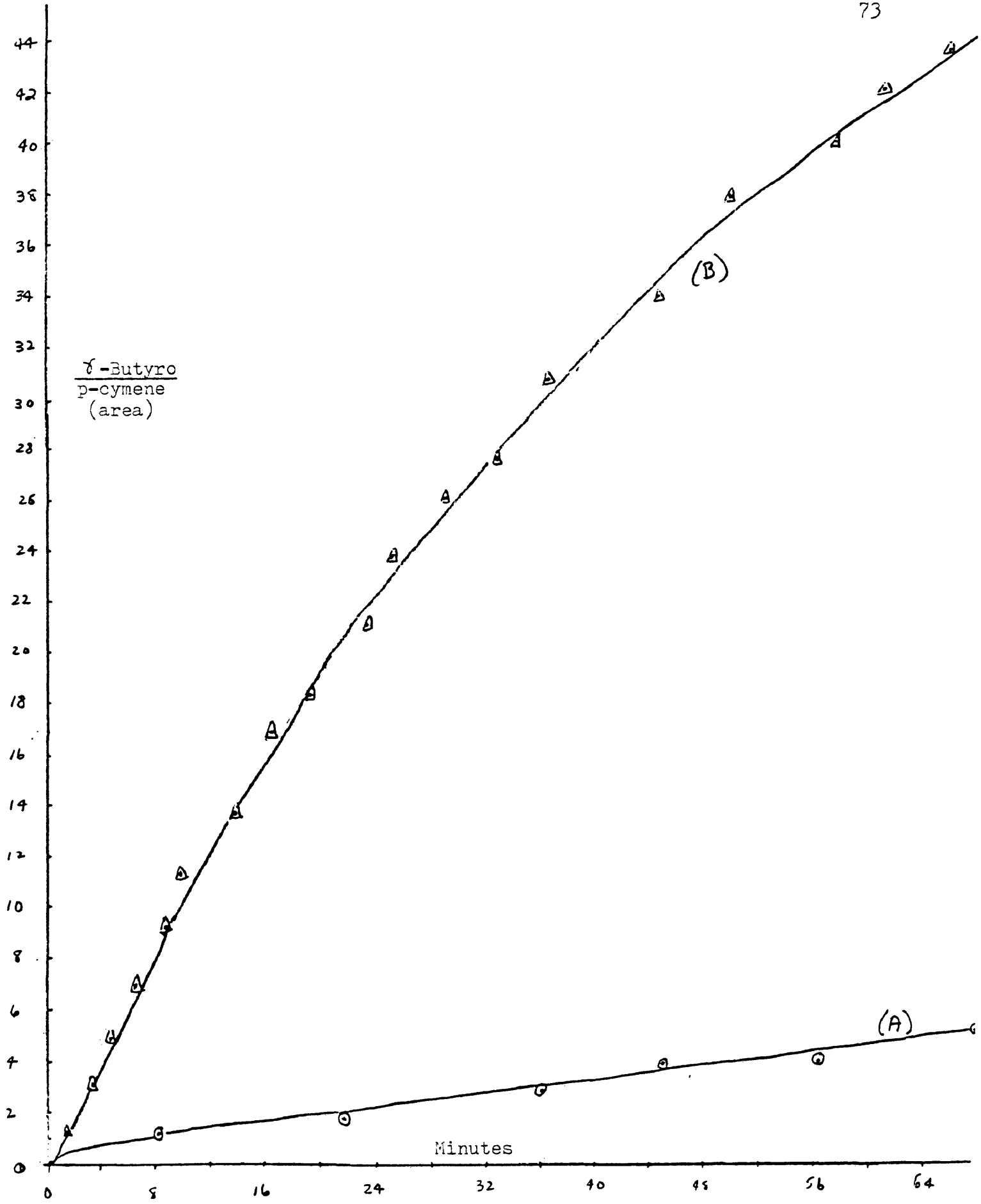


Figure A24: Oxygen Uptake by THF in Hexane Solvent at 0° in the Absence of ,(A), and the presence of, (B), 1,2-CPD

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VITA

David Curtis Winn

Born in Norfolk, Virginia, May 7, 1954. Graduated from Maury High School in Norfolk, June 1972. B.S. in Chemistry, Old Dominion University, August 1976. Entered the graduate program of the Department of Chemistry of the College of William and Mary, September 1976. With course requirements completed, became a M.A. candidate, May 1978.