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SYNTHESIS OF BIOLOGICALLY ACTIVE SUBSTITUTED CHALCONES

by

Kiel Steven Hoff

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Master of Arts
Department of Chemistry

Western Michigan University
Kalamazoo, Michigan
June 1997

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1997

ACKNOWLEDGEMENTS

I wish to thank Professor R. E. Harmon for his guidance and counsel in this research work, my course work and in my personal life. I also appreciate Professor J. Howell's help with the NMR and Professor M. McCarville's help with the GC-MS. I also would like to thank my committe members Professors D. Schreiber and R. Steinhaus for their time in reviewing my research work and this thesis. I also would like to thank all of the Department of Chemistry faculty members for their efforts in expanding my knowledge of chemistry. The financial support provided by Western Michigan University during my graduate education was also appreciated.

Special thanks goes to my life long friend Po-Chang Chiang for both his knowledge of chemistry and friendship. I finally wish to thank my wife, Kimberly M. Carr-Hoff, for without her support and companionship I would never have achieved the things in life that I have.

Kiel Steven Hoff

SYNTHESIS OF BIOLOGICALLY ACTIVE SUBSTITUTED CHALCONES

Kiel Steven Hoff, M.A.

Western Michigan University, 1997

Two different synthetic routes to poly-hydroxylated chalcones are investigated. The wittig synthesis and protection of the hydroxyl functionalities by forming the methyl ether followed by the base catalyzed Claissen-schmidt reaction and then deprotection were investigated. It was demonstrated that the protection-condensation-deprotection route was more efficient. The antiviral activity of 2,2',4'-trihydroxychalcone against the HIV virus is also presented.

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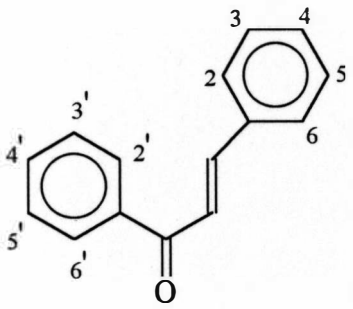
CHAPTER I

INTRODUCTION

Chalcones 1 are a class of naturally occurring compounds with the general structure as shown.



1

Alternative names given to chalcones are phenyl styryl ketone, benzalacetophenone, β-phenylacrylophenone, benzylideneacetophenone and α-phenyl-β-benzoylethylene. They come naturally occurring in a wide range of substitution patterns on both rings and across the double bond.

There are many synthetic routes published in the literature on the synthesis of chalcone and substituted chalcones. The most common and convenient method is the base catalyzed Claissen-schmidt reaction.[1] This reaction is a one step condensation reaction between the appropriate acetophenone and benzaldehyde in the presence of aqueous alkali and is usually run in an alcohol as the solvent. The acid catalyzed

condensation has also been published in the literature.[2] When attempting to prepare certain substituted chalcones in which the substituent groups may interact with the alkali and give undesirable side products or no reaction at all. Several other condensing agents have been published for use in the Claissen-schmidt reaction to form chalcones.[2]

Other synthetic pathways of interest have been reported in the literature to synthesize chalcone and various substituted chalcones. These include the reaction of Schiff's bases with acetophenone, the Wittig reaction, the copper catalyzed condensation of benzal chloride with acetophenone, the condensation of cinnamic acid with phenol in the presence of a Lewis acid and the ring opening of flavonoids. An excellent review of the various synthetic routes to substituted chalcones has been published by Dhar.[2]

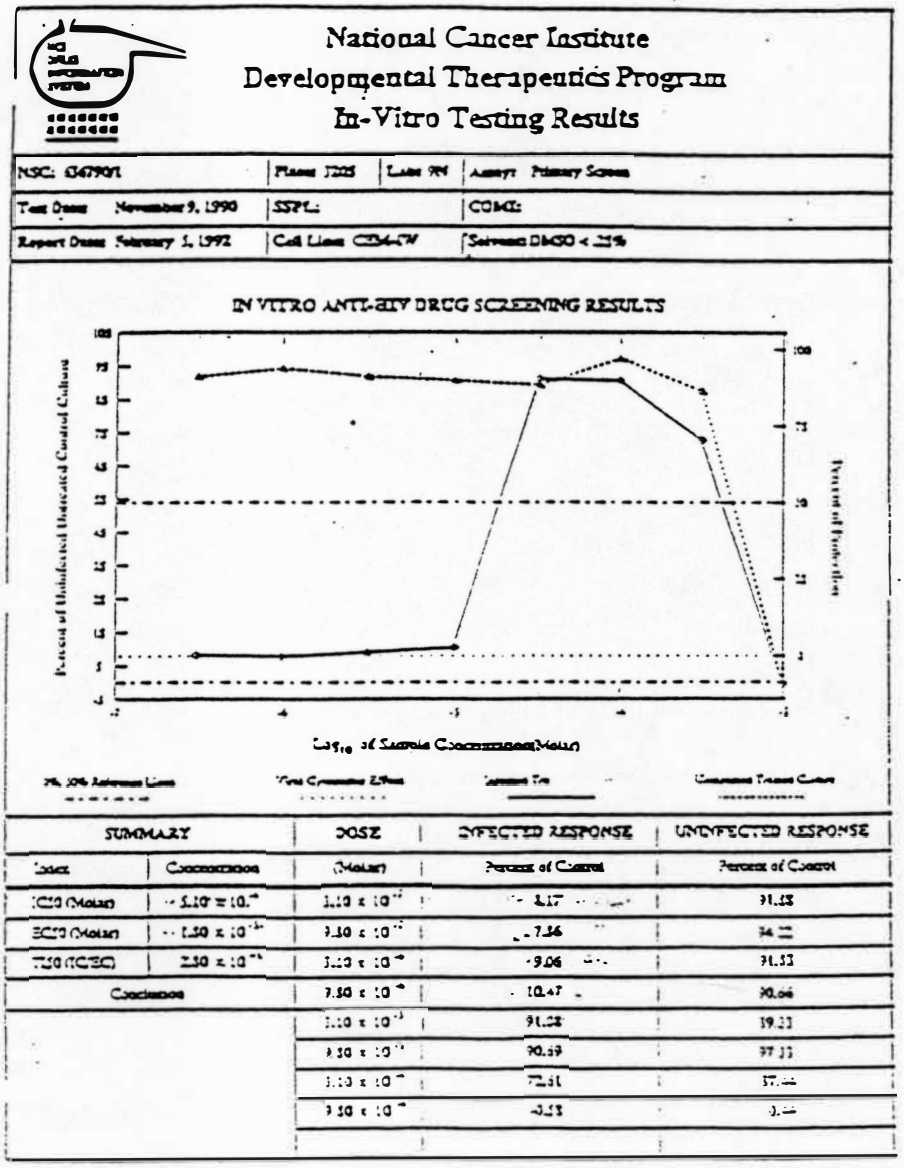
Chalcones are present in a large variety of plants and have been isolated from every part of a plant from the roots to the leaves and flowers. They serve several functions in plants including serving as anti-oxidants and enzyme cofactors but are most commonly used as pigments in plants.[3] They generally have a large molar absorbtivity and the wide variety of substituents found on chalcones along with the fact that they are a fully conjugated system gives them a wide range of λ_{max} values ranging from about 250 - 550 nm.[3] Their primary function as pigments are as U-V absorbers and as a vast array of coloring agents found usually in the flowering portion of the plant.[3]

Chalcones are also found in animals, mainly due to dietary uptake. They are also synthesized by some animals as coloring agents and other rare biological functions.[3]

Chalcones have been determined to have a wide range of biological activity including the following; acaricidal, analgesic, anesthetic, antibacterial, antibiotic, antiinflammatory, antimicrobial, antitubercular, antiparasitic, antimalarial, cytotoxic, fungicidal, herbicidal and insecticidal.[2] As seen in the literature chalcones have a wide range of biological activity, and the specific biological activity is usually imparted by substitution at a key position by a particular group. As the instrumentation for the separation and identification of components in plants continues to improve, more and more chalcone derivatives are being isolated and tested for their biological activity.

This research project focused on synthesizing 2,2',4'-trihydroxychalcone in high purity to examine its biological activity, specifically against the HIV virus. This research was first begun in Dr. R.E. Harmon's lab when an attempt was made to prepare this compound through what is believed to be the base catalyzed Claissen-schmidt reaction. No record of the reaction conditions or proof of structure was ever discovered by the author, only that this was the title compound in the attempted preparation and that Dr. Harmon believed that this was the route that was chosen. This compound was sent to the National Cancer Institute for screening against the HIV virus.

The National Cancer Institute screened this compound on three different occasions for an in vitro primary screen. An example of the results are given in Figure 1. A summary of the IC_{50}, EC_{50}, and TI_{50} data is given in Table 1.



National Cancer Institute
Developmental Therapeutics Program
In-Vitro Testing Results

IN VITRO ANTI-HIV DRUG SCREENING RESULTS

SUMMARY		DOSE	INFECTED RESPONSE	UNINFECTED RESPONSE
Index	Concentration	(Molar)	Percent of Control	Percent of Control
IC50 (Molar)	[illegible]	[illegible]	[illegible]	91.53
EC50 (Molar)	[illegible]	[illegible]	[illegible]	[illegible]
TI50 (IC/EC)	[illegible]	[illegible]	[illegible]	91.53
Conclusion		[illegible]	[illegible]	[illegible]
		[illegible]	91.28	19.23
		[illegible]	90.59	97.33
		[illegible]	[illegible]	[illegible]
		[illegible]	[illegible]	[illegible]

Figure 1. Invitro Test Results of 2,2',4'-Trihydroxychalcone for the HIV Virus.

Table 1

IC_{50}, EC_{50}, and TI_{50} Values for the Original 2,2',4'-Trihydroxychalcone Against the HIV Virus

	IC_{50} (M)	EC_{50} (M)	TI_{50} (IC/EC)
Oct 19,1990	4.5×10^{-4}	3.5×10^{-5}	13.0
Nov. 9, 1990	5.1×10^{-4}	1.8×10^{-5}	28.0
Dec. 28,1990	5.3×10^{-4}	1.4×10^{-4}	3.7
Feb. 26, 1991	2.6×10^{-4}	1.5×10^{-5}	17.0

The EC_{50} represents the dosage required in molar concentration to protect half of the infected treated cells from cell death by the virion. The IC_{50} represents the dosage required in molar concentration to kill half of the uninfected treated control cells with the particular anti-viral agent being screened. The TI_{50} represents the drugs ability to start cell protection from the virus at a lower concentration than when the drug begins to show toxic effects and kill cells. The higher the TI_{50} value, the wider the range between dosage levels that protect cells from the virus versus the dosage levels that begin to exhibit toxic effect and kill cells. At a TI_{50} value of 1, the drug exhibits toxic effects at the same dosage that it exhibits viral inhibitory effects.

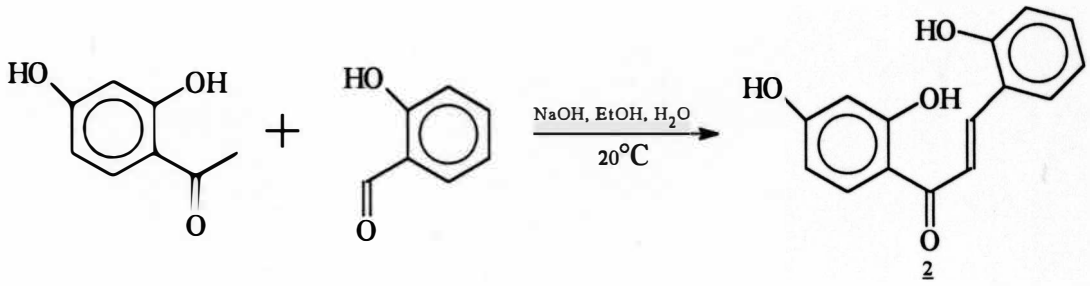
Unfortunately, the compound that showed promising primary screenings, had no preparation, no retained sample and no analytical data. The research described in this thesis proceeded forward under the assumption that the title compound was the compound sent to the National Cancer Institute. The current research project moved

forward with the goal of synthesizing a highly pure sample of 2,2',4'-trihydroxychalcone so that it could be sent to the National Cancer Institute for screening against the HIV virus.

CHAPTER II

RESULTS AND DISCUSSION

The synthesis of 2,2',4'-trihydroxychalcone 2 was initially attempted by the base catalyzed Claissen-schmidt reaction.



2

The product was never isolated from this route, only a dark yellow solid which was determined to be a mixture was recovered. Several attempts to purify and classify the material were attempted. Recrystallization from ethanol was attempted several times but did not improve the TLC assay of the material. Attempts were made to characterize this material by GC-MS, but the analysis gave many peaks on the GC and the MS spectra indicated only low molecular weight degradation products. The GC column continued to bleed off peaks at a high temperature for several hours after the run. This indicates that the material was being absorbed on the column material and slowly degrading and volatizing off at higher temperatures. Normal phase TLC was attempted on this solid employing an increasingly higher polarity mobile phase, but

but this only yielded one spot that remained on the baseline.

The probable reason for this reaction not yielding the expected product is that the interaction of the alkali, a strong base, with the fairly acidic hydroxyl groups on the phenyl rings was deprotonating some or all of the hydroxyl groups, Figure 2, and causing unwanted side reactions.

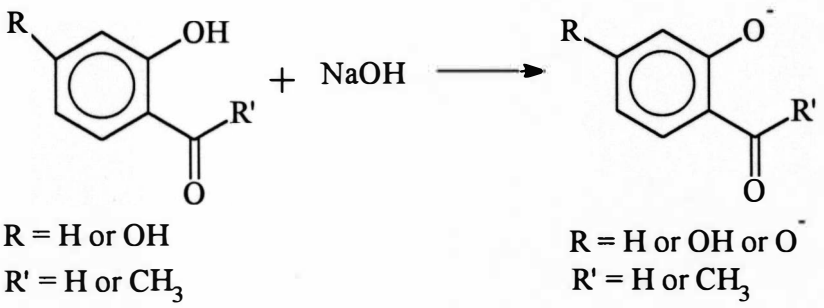


Figure 2. Base Catalyzed Deprotonation of the Benzylic Hydroxyl Groups in the Claissen-Schmidt Synthetic Route to 2,2',4'-Trihydroxychalcone.

Either a much weaker base was needed in the reaction in order to eliminate the anion formation or the hydroxyl groups would need to be protected so they would not react in the presence of alkali.

It was then decided to attempt to synthesize this compound by the Wittig pathway, Figure 3. This would give two advantages. First, hopefully obtain a quick route to the substituted chalcone without encountering the problems associated with using the strong base, alkali, because the Wittig route uses a much weaker base, sodium carbonate. Second, demonstrate a new methodology of synthesizing substituted chalcones where the substituent on the chalcones does not affect the

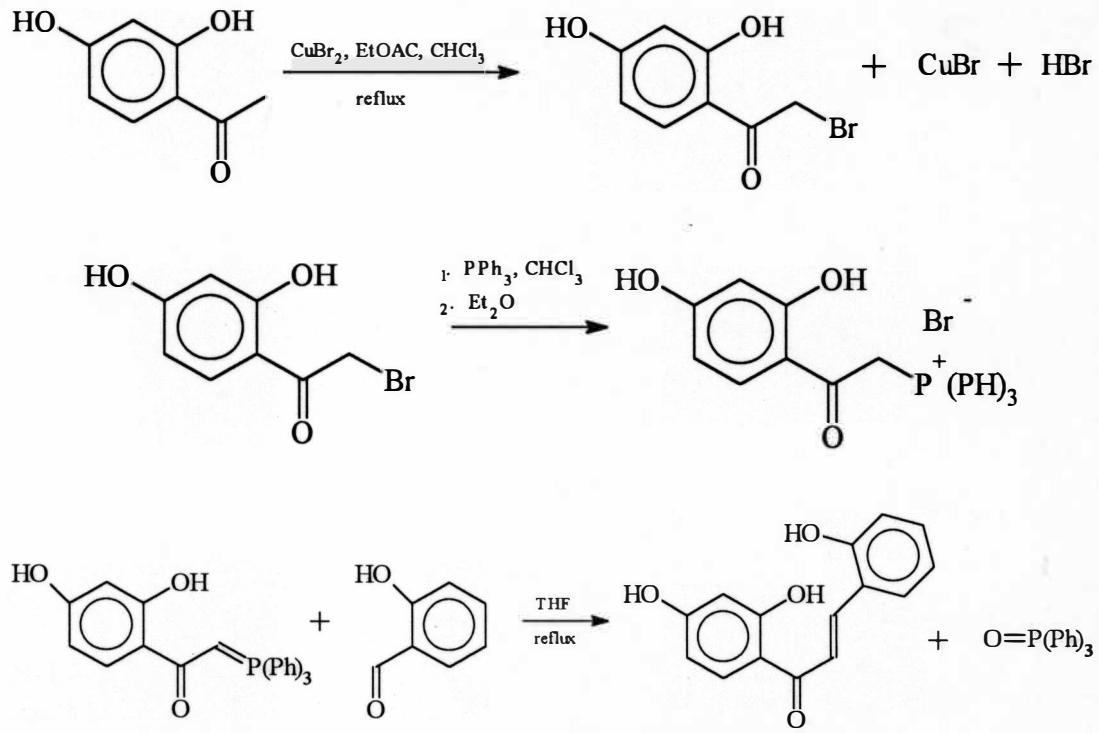


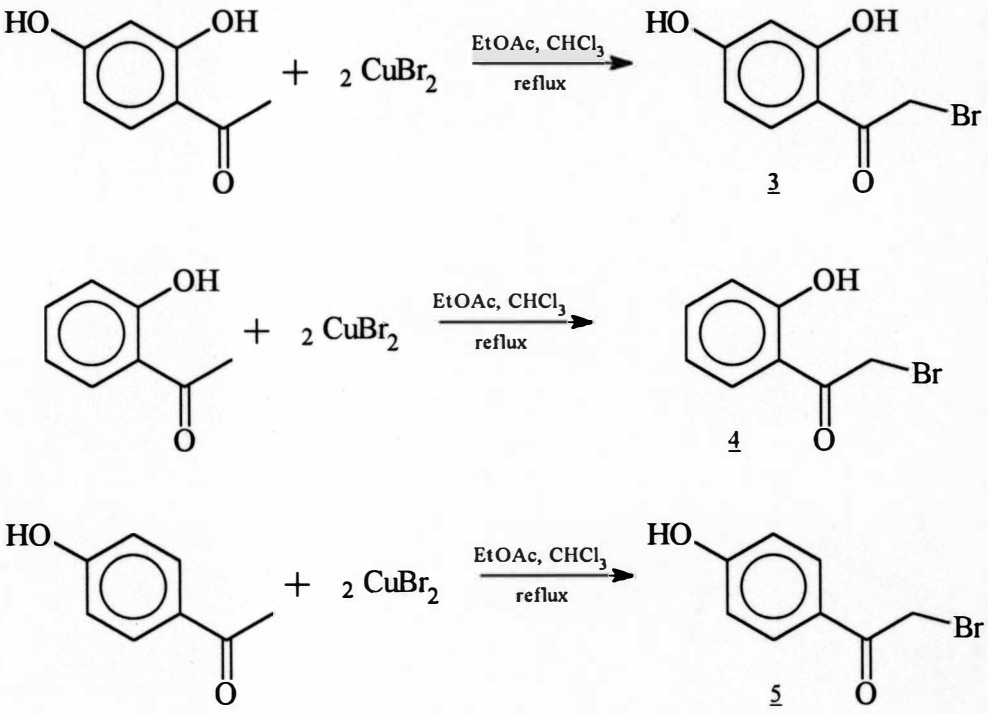
Figure 3. Wittig Synthetic Pathway for 2,2',4'-Trihydroxychalcone.

synthetic pathway or methodology synthesizing the compound.

The first step in the reaction is the formation of the halide at the α carbon position. Bromine was chosen as the halide for two reasons. First, bromide is generally considered a better halogen to use than chloride in the Wittig reaction because it acts as a better leaving group in the phosphonium salt formation step. Second, a preparation of the brominated compound was found using cupric bromide which matched the substituted acetophenones that were being prepared.[4]

The α-bromo acetophenones were prepared by the reaction of cupric bromide, 2 molar excess, with the corresponding acetophenone in refluxing chloroform/ethyl

acetate. The reaction was determined to be complete when hydrobromic acid evolution ceased and when no more white cuprous bromide, insoluble in the reaction mixture, was seen to be formed. After workup, the reaction afforded 2-bromo-2',4'-dihydroxyacetophenone, 3, 2-bromo-2'-hydroxyacetophenone, 4, and 2-bromo-4'-hydroxyacetophenone, 5.



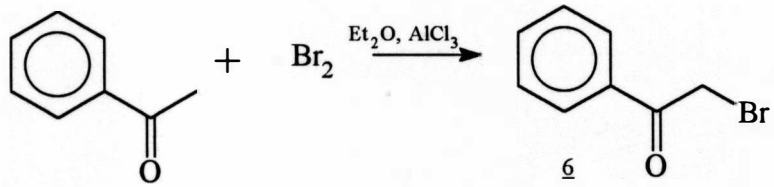
The yield and melting point data for these compounds are listed in Table 2.

2-Bromoacetophenone, 6, was also prepared but by a different route. 2-Bromoacetophenone was prepared by reacting acetophenone with bromine, in a 1:1 mole ratio, in diethyl ether in the presence of a catalytic amount of aluminum chloride. After workup the reaction afforded the desired product.

Table 2

Yield and Melting Point Data for Hydroxylated 2-Bromoacetophenones

I	Yield (%)	Literature Melting Point (°C)	References	Melting Point (°C)
3	47	144-145	4	142-144
4	42	40	4	39-40
5	41	124-126	4	127-128



6

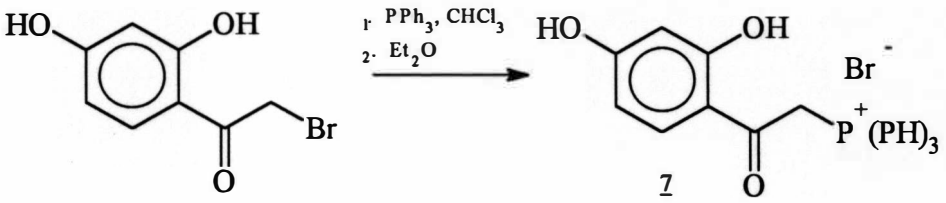
The yield and melting point data for 2-bromoacetophenone is listed in Table 3.

The next step in the synthesis of chalcones by the Wittig route is the formation of the phosphonium salt. The preparation of 2',4'-dihydroxyphenacyltriphenyl-phosphonium bromide, 7, was attempted by reacting 2-bromo-2',4'-

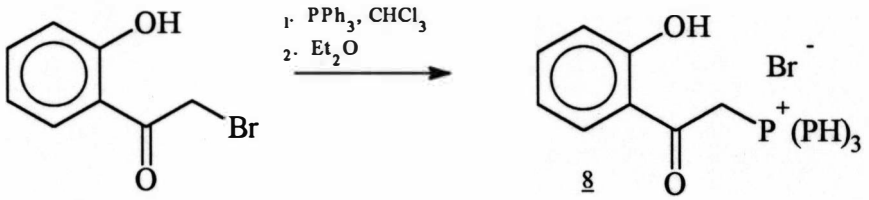
Table 3

Yield and Melting Point Data for 2-Bromoacetophenone

I	Yield (%)	Literature Melting Point (°C)	References	Melting Point (°C)
6	31%	48-50°C	3	47-49°C

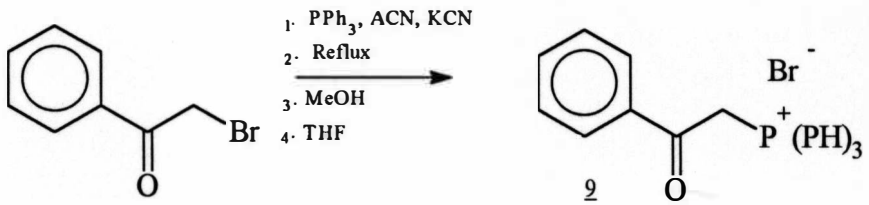


dihydroxyacetophenone with triphenylphosphine in chloroform. This solution is added to diethyl ether and a white precipitate is formed. Filtration of the solid yielded a material which quickly turned an amber color and hardened. Repeated attempts at synthesizing this compound, including under nitrogen, yielded the same results. The preparation of 2'-hydroxyphenacyltriphenylphosphonium bromide, 8, was attempted



by the above procedure and yielded the same results.

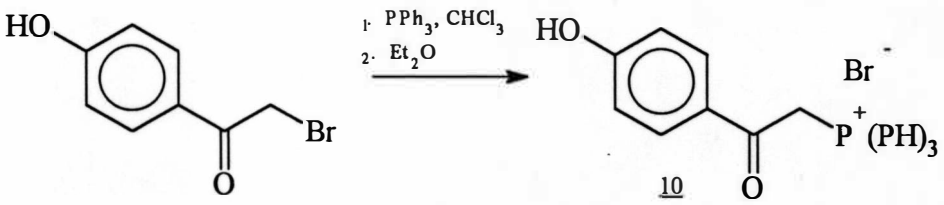
The synthesis of phenacyltriphenylphosphonium bromide, 9, was attempted



using a different procedure. The phenacylbromide, and the triphenylphosphine, were refluxed in acetonitrile with a catalytic amount of potassium cyanide present. Methanol was then added to dissolve the solids. The product was then isolated from tetrahydrofuran. This method yielded the desired product. This showed that it was

possible to isolate these types of compounds, as was also indicated by the literature.

Next the 4'-hydroxyphenacyltriphenylphosphonium bromide, 10, was



prepared by the same method that was used to try to prepare 2'-hydroxyphenacyl-triphenylphosphonium bromide and 2',4'-dihydroxyphenacyltriphenylphosphonium bromide. This synthesis proved to be successful, the product was isolated, dried and did not decompose. The yield and melting point data for 9 and 10 are listed in Table 4.

Table 4

Yield and Melting Point Data for 9 and 10

I	Yield (%)	Literature Melting Point (°C)	References	Melting Point (°C)
9	86%	269-271°C	5	276-277°C
10	90%	N/A		295-301°C

The ability to synthesize and isolate the unsubstituted phosphonium salt and the phosphonium salt hydroxylated at the 4' position, while not being able to isolate the phosphonium salts hydroxylated at the 2' positions, indicates that hydroxylation at the 2' position is the probable cause for the degradation of the product. Several factors could be put forth to explain this phenomena.

First, an intermolecular reaction could be taking place between the positively charged phosphorous atom and the oxygen atom in the 2' hydroxyl group. The oxygen atom possesses two free lone pairs of electrons, one of which could attack the highly electrophilic positively charged phosphorous atom, Figure 4.

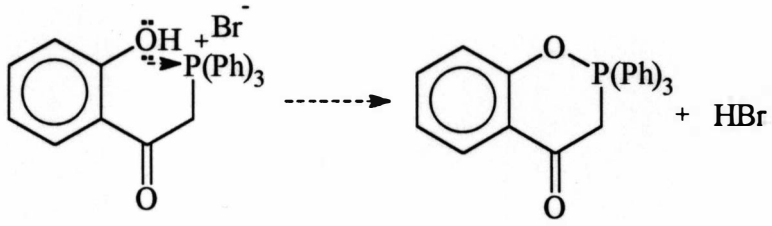


Figure 4. Possible Cyclization Mechanism for the Degradation of 2'-Hydroxy-phosphonium Salts.

While this mechanism is feasible, it would not explain the polymeric properties that are exhibited by the degradation product unless the hydrobromic acid that is liberated is further degrading the compound to a polymeric type substance.

Another possibility could be an intermolecular reaction between the free lone pairs of electrons and the positively charged phosphorous atom, Figure 5. This mechanism is very similar to that of Figure 4, however it does not form the cyclic product. It does form a more reactive intermediate, which could further polymerize at the enol portion of the molecule or be further attacked intermolecularly by a hydroxyl group from another molecule to form a polymeric type material.

A third rearrangement is a modification of the Perkow reaction. In this reaction the electron rich carbonyl group attacks the positive phosphorous atom,

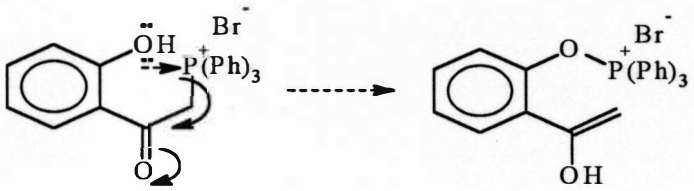


Figure 5. Possible Rearrangement Mechanism for the Degradation of 2'-Hydroxy-phosphonium Salts.

Figure 6. While this also is a very feasible mechanism and the intermediate ene compound formed would be reactive and could further form a polymeric material, it is unclear why hydroxyl substitution at the 2' position would cause this compound to form while unsubstituted compounds would not form this intermediate.

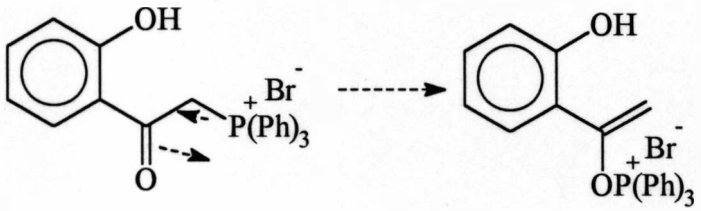
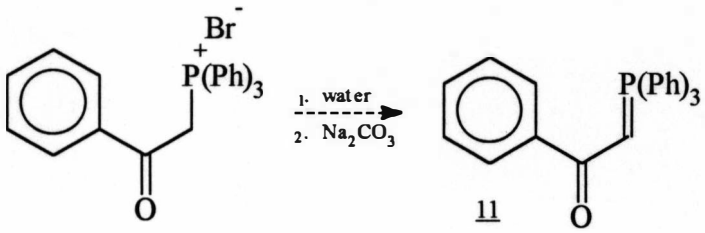


Figure 6. Possible Perkow Rearrangement Mechanism for the Degradation of 2'-Hydroxyphosphonium Salts.

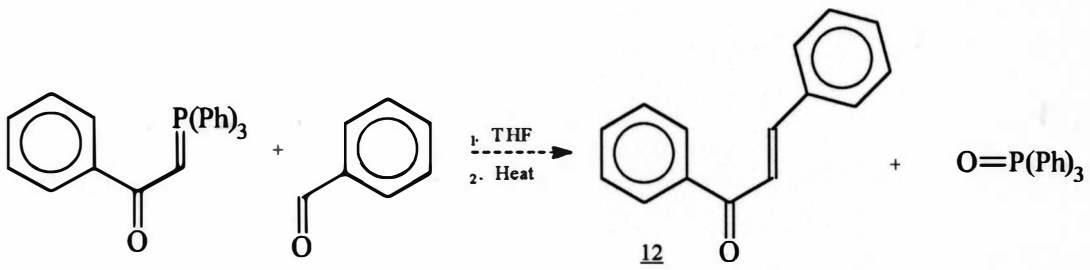
The next step in the synthesis of chalcones by the Wittig route is the formation of the ylide. The triphenylphosphinebenzoylmethyline, 11, was prepared by reacting the phenacyltriphenylphosphonium bromide with aqueous sodium carbonate. Filtration of the solution after five minutes yielded the product in quantitative yield,



11

mp 181-182°C (lit. 178-180°C)[5].

The final step in the synthesis of chalcones by the Wittig route is the condensation of the ylide with the aldehyde. Chalcone, 12, was prepared by reacting



12

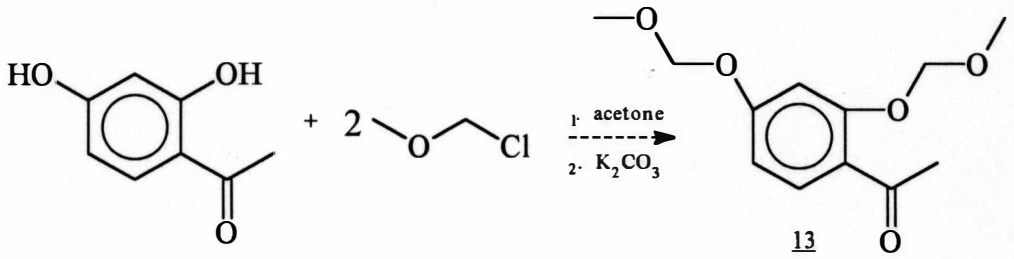
triphenylphosphinebenzoylmethyline with benzaldehyde in refluxing tetrahydrofuran. The product was recrystallized from ethanol in 62% yield mp 54-57°C (lit. 55-57°C).[1]

While it was demonstrated that the Wittig synthesis is a useful route for synthesizing chalcone, as was also demonstrated in the literature,[2] it was not useful in preparing chalcones regardless of substituents and specifically preparing 2,2',4'-trihydroxychalcone. Another route would have to be selected to prepare the title compound.

The next route selected would be to protect the hydroxyl groups before the condensation step, perform the base catalyzed condensation and then deprotect the resulting chalcone. The first protecting group selected was to make the

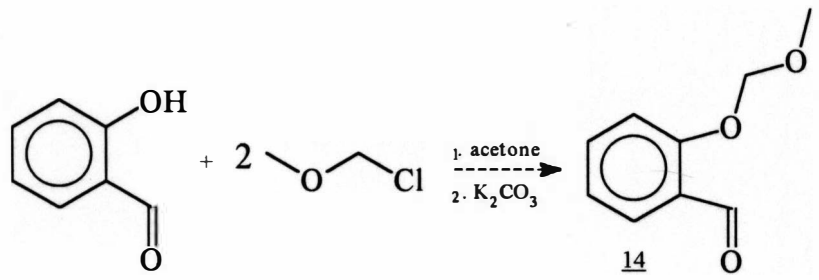
methoxymethyl ether using methoxymethyl chloride. These types of groups have been used in the literature in synthesizing other hydroxylated chalcones[6].

The preparation of 2,4-di(methoxymethoxy)acetophenone, 13, was attempted



by reacting 2,4-dihydroxyacetophenone with methoxymethyl chloride in dry acetone in the presence of potassium carbonate under reflux. The resulting product was worked up from petroleum ether:ethyl acetate. The product was determined to be the single methoxymethylated compound by G.C.-M.S. Repeated attempts, including increasing the reaction time and the methoxymethyl chloride to acetophenone ratio, yielded only the single protected product.

The preparation of 2-methoxymethoxybenzaldehyde, 14, was attempted by

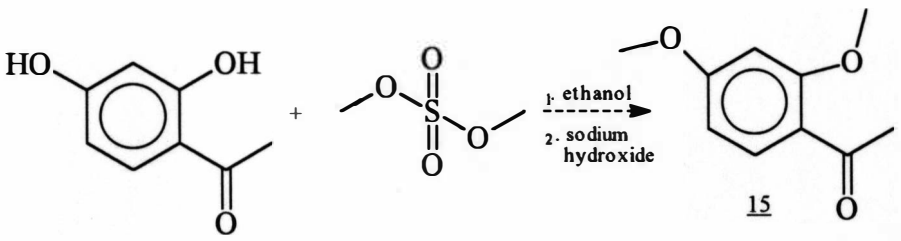


reacting 2-hydroxybenzaldehyde with methoxymethyl chloride in dry acetone in the presence of potassium carbonate under reflux. The resulting product was worked up from diethyl ether. The product was determined to be the starting material,

benzaldehyde, by G.C.-M.S. Repeated attempts, including increasing the reaction time and the methoxymethyl chloride to benzaldehyde ratio, failed to yield the desired product.

The next protecting groups tried were methylating groups. These groups were selected because they are much smaller and may not have the steric hindrance problems that could have been the problem with the methoxymethyl chloride reagents, and are also much smaller than other common protecting groups like benzyl chloride.

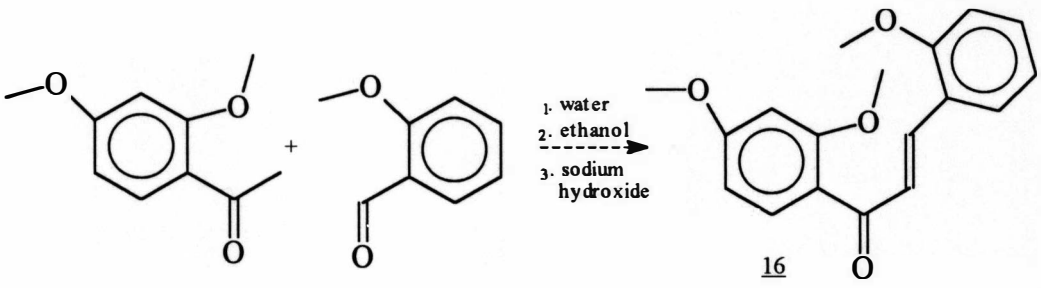
The preparation of 2,4-dimethoxyacetophenone, 15, was performed by



reacting 2, 4-dihydroxyacetophenone with dimethyl sulfate in absolute ethanol in the presence of sodium hydroxide under reflux. The resulting product was extracted and distilled. This gave 2,4-dimethoxyacetophenone in 63% yield mp 38-41°C (lit. 39-41°C).

The 2-methoxybenzaldehyde, *o*-anisaldehyde, is readily available from Aldrich and was on-site in the Western Michigan University chemistry department stockroom.

The next step in the synthesis was to perform the base catalyzed condensation reaction on the two protected compounds. The preparation of 2,2',4'-trimethoxychalcone, 16, was performed by reacting 2',4'-dimethoxyacetophenone



16

with *o*-anisaldehyde in a water ethanol mixture in the presence of sodium hydroxide in an ice bath. The product is filtered and recrystallized from ethanol. The 2,2',4'-trimethoxy chalcone was isolated in 80% yield mp 102.5-104°C (lit N/A). The G.C.-M.S., NMR and combustion analysis confirmed the product to be 16.

The M.S. of 16, Figure 7, shows a moderate peak at 298 and a smaller peak at 299. These are the largest molecular weight peaks in the spectrum and would match the molecular ion peak and the M + 1 peak for 16. A small peak at 283 would indicate loss of a methyl group from one of the methyl ethers on the aromatic rings. The largest peak on the spectrum occurs at 267, this would have a molecular weight 31 amu's below that of 16 and be attributed to the loss of one of the three methyl ether functionalities from one of the aromatic rings. The other moderate peak on the spectrum occurs at 165, this would indicate cleavage between the ene and carbonyl functionality's and would be the molecular weight of the disubstituted benzoyl ion. This is further supported by the small cluster of peaks around 135, which would be close to the mass of the ene half of the molecule, 134 amu's. The smaller peaks in the spectra, 91 and 77, are indicative of the tropylium ion and the benzyl ion, respectively, common to the M.S. spectra of most substituted aromatic compounds.

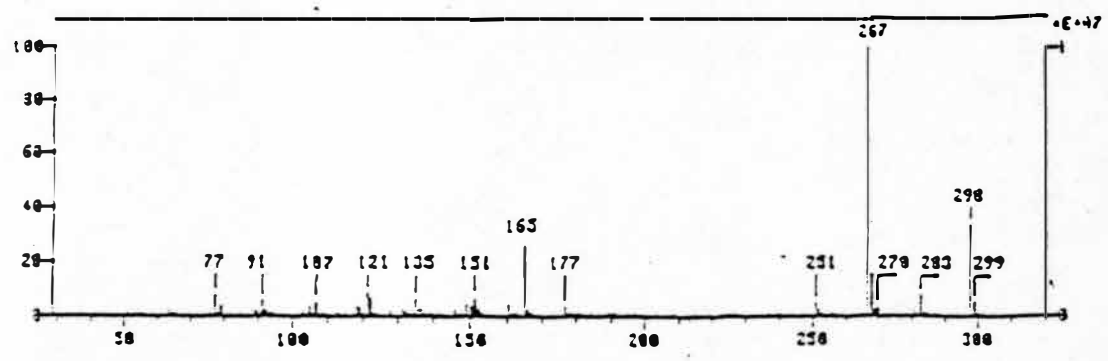


Figure 7. Mass Spectrum of 2,2',4'-Trimethoxychalcone.

The H^1 NMR, Figure 8, shows a strong peak at 0 ppm, this is the TMS peak and indicates that the spectrum is aligned properly. The first major peak, and the strongest peak in the spectrum, is the peak located at 3.85 δ. This peak is a doublet whose integration is assigned 9 hydrogens, the integration of all peaks are based on the hydrogen count and integration value for this peak. It is in the position where the hydrogens on the methyl ethers would be. The other major peak in the sprectrum our the groups of peaks located between 6.5 - 8.0 δ. This grouping of peaks are in the position where the aromatic hydrogens and the ene hydrogens would be located and gives an integration correlating to 7 hydrogens. While the integration is off by 2 hydrogens, this spectrum is believed to represent 16 due to the placement of the peaks correlates exactly to the structure of 16, and peak integration is a factor that can be less than ideal and can even be manipulated by simple manual integration. The peaks at 1.6 δ and 3.4 δ represent either solvent impurities such as water, $CDCl_3$ or DMSO or could be peaks from trace impurities in the sample.

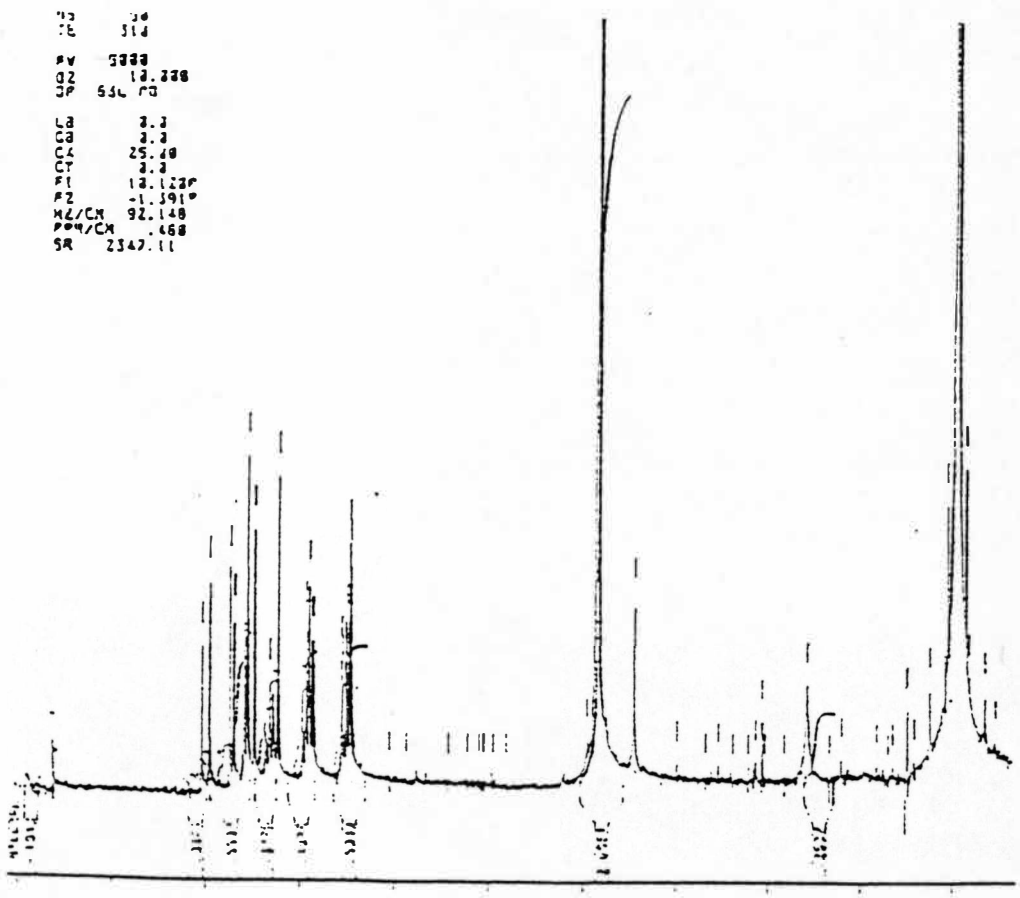


Figure 8. H^1 NMR Spectrum of 2,2',4'-Trimethoxychalcone.

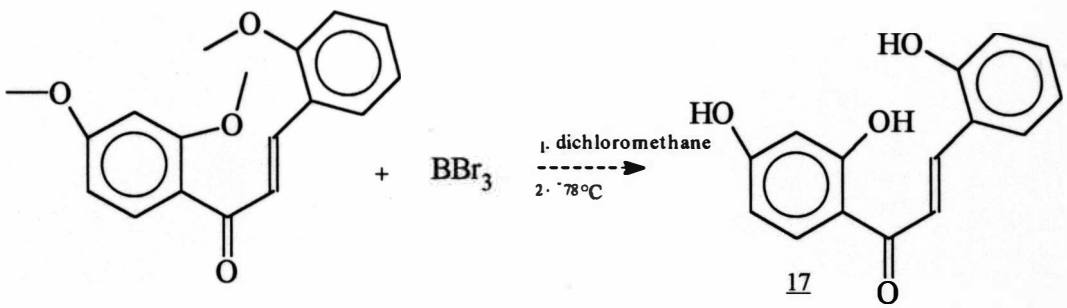
The combustion analyses, Table 5, matches the Carbon, Hydrogen and Oxygen percent of 16, with the largest deviation being < .13% from the calculated value of 16. The absence of ash or residue in the combustion analyses sample indicates that no inorganic salts are present in the sample.

The final step in the synthesis was to deprotect the chalcone. The preparation of 2,2',4'-trihydroxychalcone, 17, was performed by reacting 2,2',4'-trimethoxychalcone with boron tribromide in dichloromethane under nitrogen in a dry

Table 5

Combustion Analyses of 2,2',4'-Trimethoxychalcone

Analysis	Theory	% Found
Carbon	72.47%	72.34%
Hydrogen	6.08%	6.11%
Oxygen	21.45%	21.46%



17

ice/isopropyl alcohol bath. The product was worked up by extracting it out of salty ice water with dichloromethane and then recrystallized from ethanol. The 2,2',4'-trihydroxychalcone was isolated in 73% yield mp 176.5-178.5°C (lit. N/A). The M.S., NMR and combustion analysis confirmed the product to be 17.

The liquid chromatograph of 17, Figure 9, shows 3 peaks. The first peak at 2.70 is a small sharp peak and integrates to 0.2% of the total area. The second peak is a very large broad peak at 3.53 and integrates to 99.3% of the total area. The last peak in the chromatogram is a small broad peak at 8.33 and integrates to 0.5% of the total area. It is presumed that the peak at 3.53 is 17. However any sort of purity

determination cannot be determined from the chromatogram because it is difficult to determine whether the peak at 3.53 is a singlet or many peaks bunched together because the top of the peak is not visible. The other two peaks in the chromatogram are unidentified.

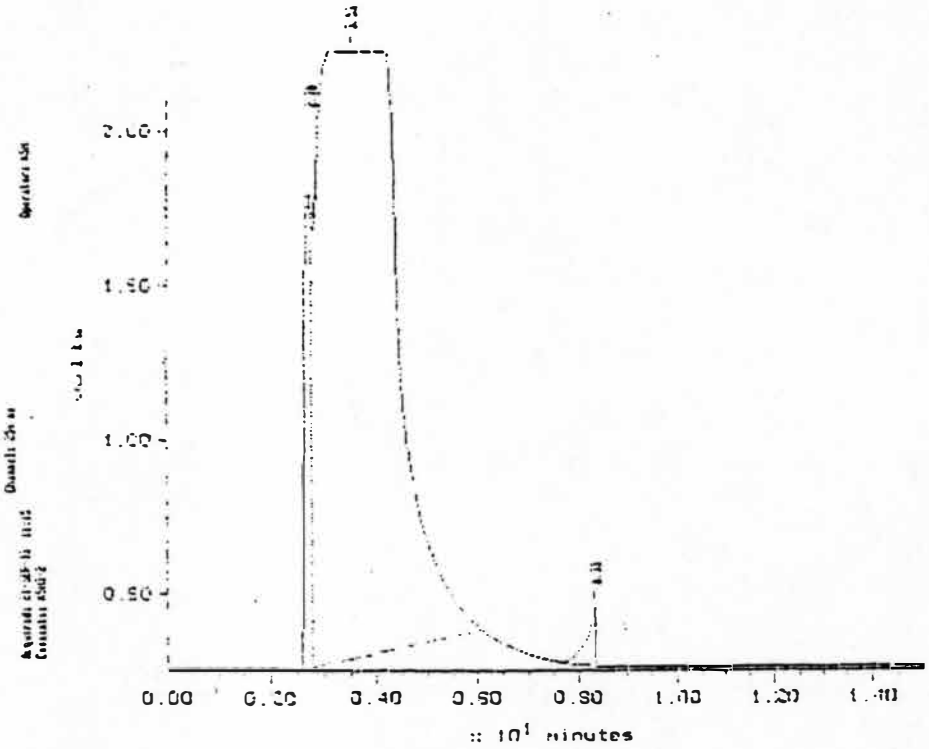


Figure 9. Liquid Chromatogram of 2,2',4'-Trihydroxychalcone.

The M.S. of 17, Figure 10, shows a moderate peak at 256 and a smaller peak at 257. These are the largest molecular weight peaks in the spectrum and would match the molecular ion peak and the M + 1 peak for 17. The peaks at 238, the largest peak in the spectra, and 239 would indicate the loss of water from 17 and its M + 1 peak, respectively. The small peak at 210 would indicate the loss of two water

molecules from 17. The small peak at 163 would indicate cleavage between the ene functionality and the monosubstituted aromatic ring. The peak other strong peak in the spectrum, 137, would indicate cleavage between the ene and the carbonyl functionality's and would be the molecular weight of the disubstituted benzoyl ion. The other identified peak in the spectra, 91, is indicative of the tropylium ion, common to the M.S. spectra of most substituted aromatic compounds.

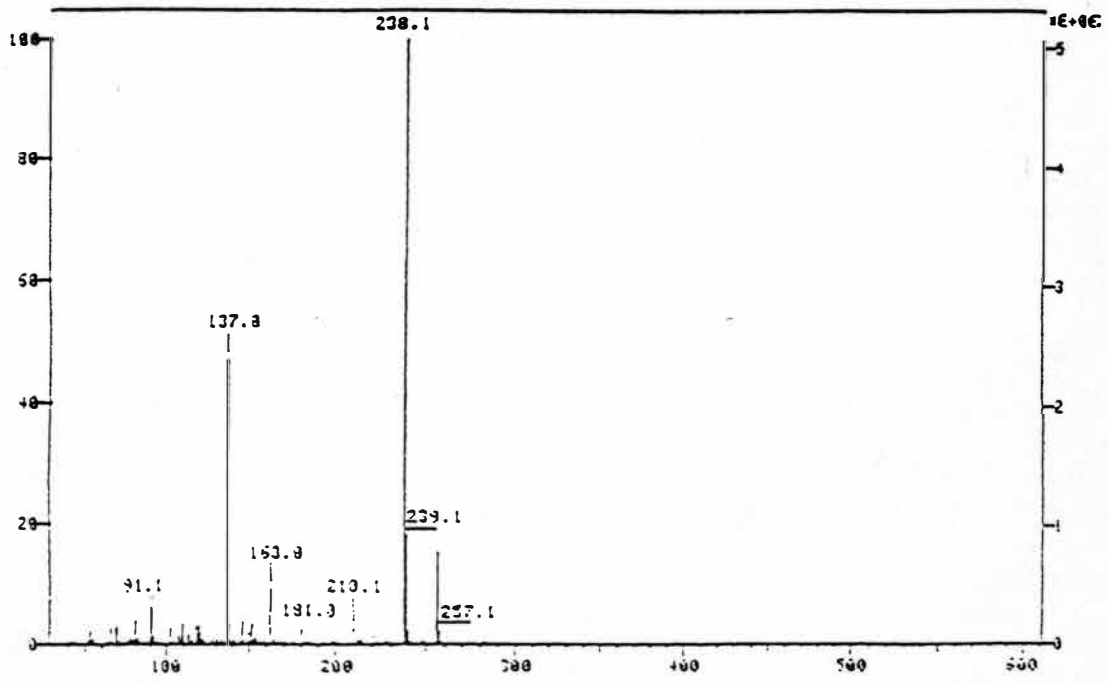


Figure 10. Mass Spectrum of 2,2',4'-Trihydroxychalcone.

The H^1 NMR, Figure 11, shows a strong peak at 0 ppm, this is the TMS peak and indicates that the spectrum is aligned properly. The group of peaks from 6.3 - 8.2 δ represent the aromatic hydrogens and the ene hydrogens and they have a total integration assigned as 9 hydrogens, the integration of all peaks are based on the

hydrogen count and integration value for this peak. The peak at 10.5 δ correlates to the 2-hydroxy hydrogen and has an integration correlating to .8 hydrogens which

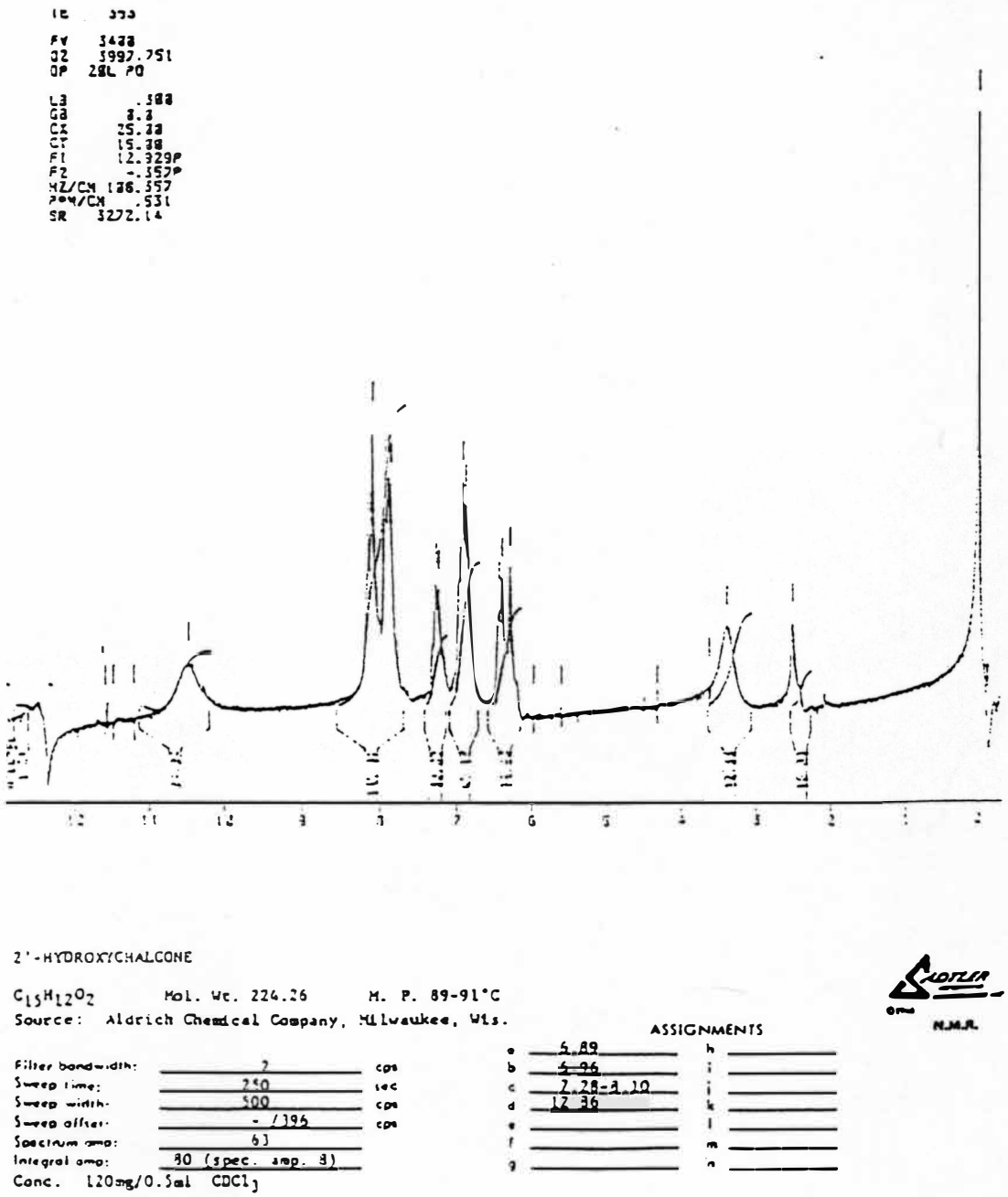
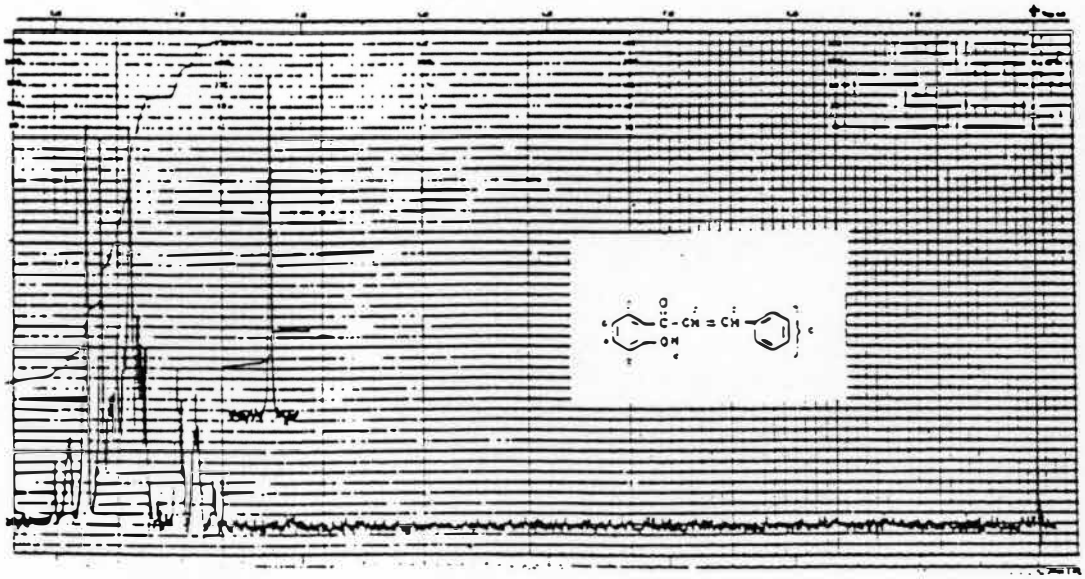


Figure 11. H^1 NMR Spectrum of 2,2',4'-Trihydroxychalcone.

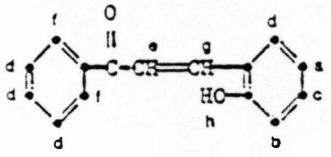
Figure 11—Continued

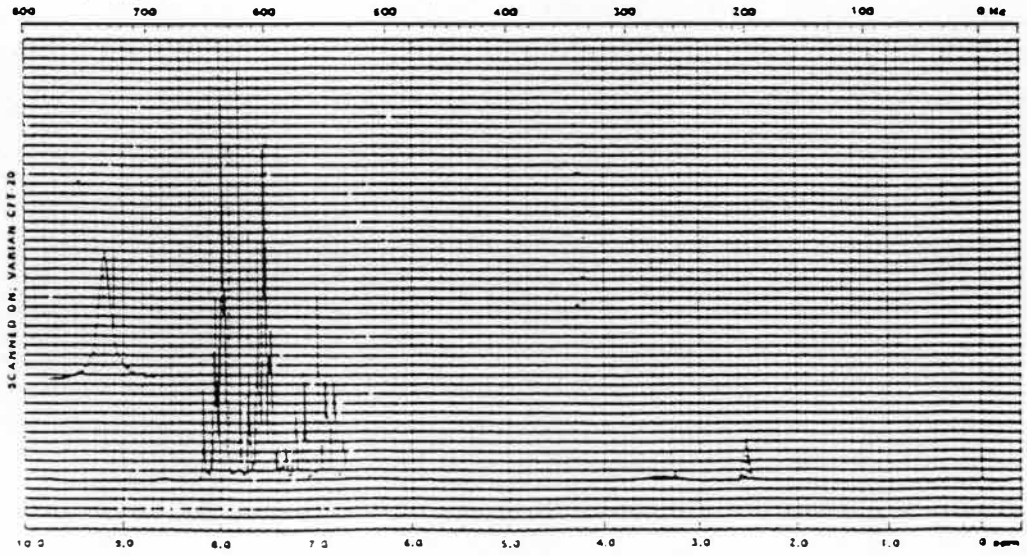


ASSIGNMENTS

5758

a	6.83	f	8.03	k		p	
b	6.95	g	8.09	l		q	
c	7.19	h	10.00	m		r	
d	7.35-7.75	i	2.50 DMSO-d_5	n		s	
e	7.70	j	3.45 H_2O	o		t	





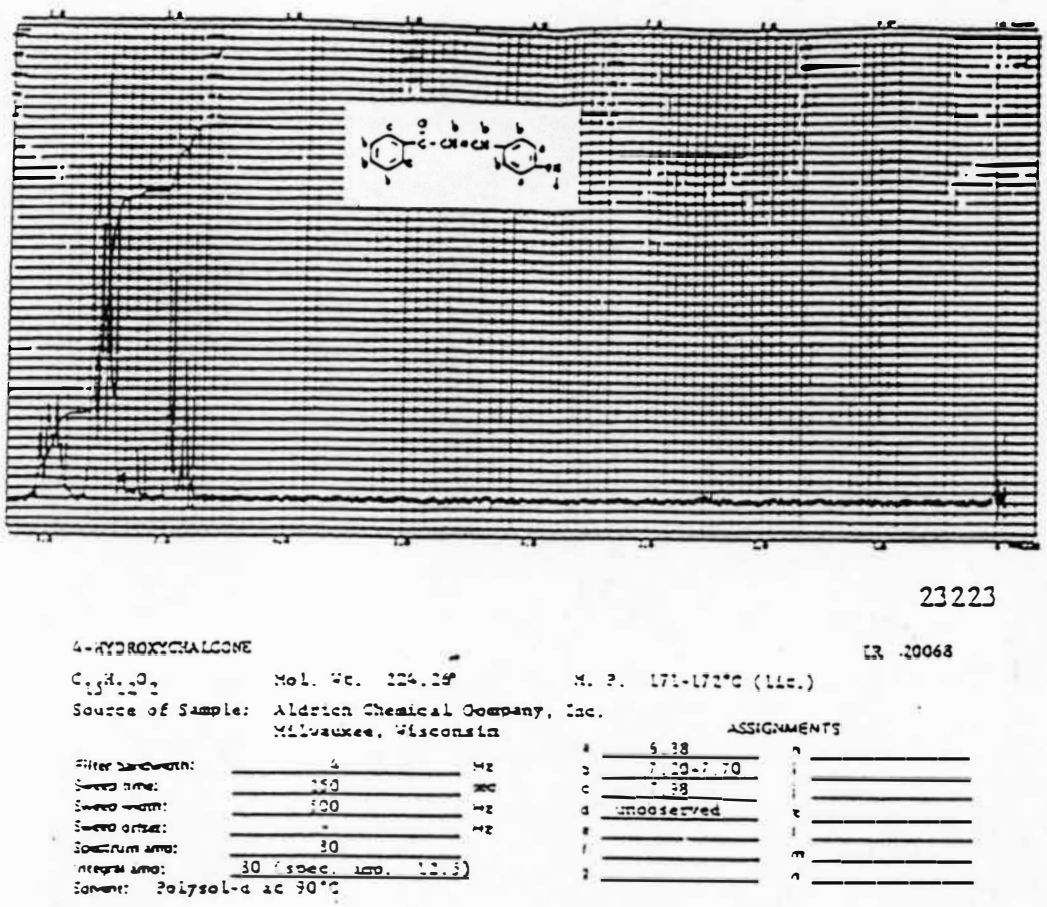


Figure 12. Reference H^1 NMR Spectra for 2'-Hydroxychalcone, 2-Hydroxychalcone and 4-Hydroxychalcone.

closely matches the actual hydrogen count of 1. Other peaks in the spectra include the peak at 2.5 δ, which probably is a trace impurity from either the solvent or the sample. The peak at 3.4 δ correlates to the 4'-hydroxy hydrogen and has an integration correlating to 1.3 hydrogens which closely matches the actual hydrogen count of 1. The peak at 12.5 δ, a small peak followed by a large negative peak, is from the 2'-hydroxy hydrogen. This peak was not integrable due to its shape. Reference spectra, Figure 12, are provided for 2'-hydroxychalcone, 2-hydroxychalcone and 4-

hydroxychalcone. The reference spectra for 2,2',4'-trihydroxychalcone was unavailable, therefore each hydroxyl group has to be viewed on separate reference spectra.

The combustion analyses, Table 6, matches the Carbon, Hydrogen and Oxygen percent of 17, with the largest deviation being < .9% from the calculated value of 17. The absence of ash or residue in the combustion analyses sample indicates that no inorganic salts are present in the sample.

Table 6

Combustion Analyses of 2,2',4'-Trihydroxychalcone

Analysis	**Theory**	**% Found (#1)**	**% Found (#2)**
Carbon	70.31%	71.19%	71.13%
Hydrogen	4.72%	4.70%	4.72%
Oxygen	24.97%	24.16%	24.18%

The analytical data presented gives very good qualitative proof of structure. Due to the lack of good chromatography data, the level of purity of the compound is not able to be quantified. The accuracy of the combustion analyses data presented for the title compound would indicate that the compound is of reasonably purity, however.

CHAPTER III

EXPERIMENTAL PROCEDURE

The melting points were determined in open capillaries using a Thomas Hoover (Philadelphia, Pennsylvania) Uni-melt capillary melting point apparatus. The gas chromatograph used was a Hewlett Packard (San Fernando, California) 5890 series with a crosslinked methyl silicone gum column (12 m x 0.2 mm x 0.33 μm thickness, 400 plates/m) and it was attached to a 5970 series mass selective detector. The gas chromatography conditions were an injector temperature of 240°C with an oven temperature starting at 70°C and holding for 2 minutes, followed by a 10°C/min ramp for 13 minutes, followed by a hold time of varying length. Samples were diluted approximately 1:10 in methanol and a 1 - 2 μl injection was made. The mass spectra of 2,2',4'-trimethoxychalcone and 2,2',4'-trihydroxychalcone were performed on a Finnigan (San Jose, California) series I triple quadrapole mass spectrometer at Michigan State University using a solid probe for sample introduction. The liquid chromatographs were performed on a Waters 600E Millipore system with a C18 column (25 cm x 4.6 mm x 5 μm) and it was attached to a 486 UV detector set at 254 nm. The liquid chromatography conditions were an isocratic mobile phase consisting of 60% acetonitrile and 40% 40 mM Dibasic Sodium Phosphate with a flow rate of 0.7 ml/min. Liquid chromatography samples were diluted approximately 1:100

in mobile phase and a 20 µl injection was made. Nuclear magnetic resonance spectra (NMR) were determined on a Brucker (Silberstreifen, Germany) 200 Mhz instrument. Samples were dissolved in Deuterated Chloroform. Infrared Spectra were determined on a Nicolet (Madison, Wisconsin) single beam infrared spectrophotometer. The combustion analyses were done by the Midwest Microlab Company (Indianapolis, Indiana).

All reagents used were purchased from the Aldrich Chemical company, Milwaukee, Wisconsin.

1. Attempt to prepare 2,2',4'-trihydroxychalcone. The following procedure is a modification of the method of Kohler and Chadwell.[1] To a 250 mL erlenmeyer flask 2.2 g of sodium hydroxide, 19.6 g of water and 10 g of absolute ethanol were added. This solution was stirred and cooled in an ice bath to 15°C. 6.5 g of 2,4-dihydroxyacetophenone and 5.2 g of 2-hydroxybenzaldehyde were added to the flask slowly in order. The solution is stirred for three hours controlling the temperature between 15-30°C. After three hours the solution is transferred to the freezer and allowed to sit overnight. The solution is recrystallized twice from 95% ethanol.

This gave 5.8 g (53% yield) of a mixture mp 114-118°C (ref. N/A).

2. Preparation of 2-Bromoacetophenone. This follows the literature procedure of Cowper and Davidson.[7] To a 500 mL, three necked round bottom flask, 20.0 g of acetophenone in 20 mL of anhydrous diethyl ether were added. The flask was cooled in an ice bath and 0.2 g of aluminum chloride was added, followed by 26.8 g of Bromine added through a dropping addition funnel at a rate of 1 mL/minute. The

solution was transferred to a 250 mL round bottom flask and most of the ether and Hydrobromic acid were removed on the rotary evaporator. Vacuum filtration was used to filter the wet solid. The solid was then washed with a 1:1 mixture of petroleum ether and water. The solid was then recrystallized the solid from methanol.

This gave 10.6 g (31% yield) of 2-Bromoacetophenone mp 47-49°C (lit. 48-50°C). GC-MS (m/e) 200 (m^+), 198 (m^-), 105, 77. The peaks at 200 and 198 represent the molecular weight of the compound when using 81 and 79 amu's, respectively, as the atomic weight for bromine. The peak at 105 represents the loss of methyl bromide alpha to the ketone to form the $C_6H_5CO^+$ ion. The peak at 77 represents the loss of carbon monoxide from the peak at 105 to form the $C_6H_5^+$ ion.

3. Preparation of 2-Bromo-2'-hydroxyacetophenone. This follows the literature procedure of King and Ostrum.[4] To a 500 mL three necked round bottom flask, 22.3 g of cupric bromide and 50 mL of ethyl acetate were added. The resulting mixture was brought to reflux and then 7.2 mL of 2'-hydroxyacetophenone in 50 mL of hot chloroform was added to the refluxing mixture. The mixture was allowed to reflux for 3 hours. The reaction was determined to be complete when no more white cuprous bromide was formed. Drive off approximately one half of the solvent on the rotary evaporator. Filter the solution by vacuum filtration. Drive off the rest of the solvent from the mother liquor on the rotary evaporator and then recrystallize from benzene.

This gave 5.4 g (42% yield) of 2-bromo-2'-hydroxyacetophenone mp 39-40°C (lit. 40°) GC-MS (m/e) 216 (m^+), 214 (m^-), 121, 77. The peaks at 216 and 214

represent the molecular weight of the compound when using 81 and 79 amu's, respectively, as the atomic weight for bromine. The peak at 121 represents the loss of methyl bromide alpha to the ketone to form the $(OH)C_6H_5CO^+$ ion. The peak at 77 represents the $C_6H_5^+$ ion.

4. Preparation of 2-bromo-4'-hydroxyacetophenone. The procedure used was the same as described in Experiment 2. 4'-Hydroxyacetophenone (8.2 g), 22.3 g of cupric bromide, 50 mL of ethyl acetate and 50 mL of chloroform were combined in a 500 mL three necked round bottom flask.

This gave 5.3 g (41% yield) of 2-bromo-4'-hydroxyacetophenone mp 127-128°C (lit. 124-126°C). GC-MS (m/e) 216 (m), 214 (m^-), 121, 77. The peaks at 216 and 214 represent the molecular weight of the compound when using 81 and 79 amu's, respectively, as the atomic weight for bromine. The peak at 121 represents the loss of methyl bromide alpha to the ketone to form the $(OH)C_6H_5CO^+$ ion. The peak at 77 represents the $C_6H_5^+$ ion.

5. Preparation of 2-bromo-2',4'-dihydroxyacetophenone. The procedure used was the same as described in Experiment 2. 2',4'-Dihydroxyacetophenone (9.2 g), 22.3 g of cupric bromide, 50 mL of ethyl acetate and 50 mL of chloroform were combined in a 500 mL three necked round bottom flask.

This gave 6.5 g (47% yield) 2-bromo-2',4'-dihydroxyacetophenone mp 142-144°C (lit. 144-145°C). GC-MS (m/e) 233 (m^+), 232 (m), 231 (m^-, m^+), 230, 138, 137, 77. The peaks at 232 and 230 represent the molecular weight of the compound when using 81 and 79 amu's, respectively, as the atomic weight for bromine. The

peaks at 233 and 231 represent the molecular weight plus 1 amu of the compound when using 81 and 79 amu's, respectively, as the atomic weight for bromine. The peaks at 138 and 137 represent the loss of methyl bromide alpha to the ketone to form the $(OH)_2C_6H_5CO^+$ ion. The peak at 77 represents the $C_6H_5^+$ ion.

6. Preparation of phenacyltriphenylphosphonium bromide. This follows the literature procedure of Fukui, Sudo, Masaki and Ohta.[5] To a 250 mL, three necked round bottom flask, 5.24 g of triphenylphosphine, 100 mL of acetonitrile, 5 drops of a 33% solution of KCN in water and 3.98 g of 2-bromoacetophenone in 60 mL of acetonitrile were added. The mixture was stirred at a gentle reflux for 3 hours. Twenty mL of methanol was added to the cooled solution, the precipitate in solution dissolved, and the solution was placed on the rotary evaporator and as much solvent was driven off as possible. The remaining residue was treated with 40 mL of tetrahydrofuran and filtered by vacuum filtration.

This gave 7.9 g (86% yield) of phenacyltriphenylphosphonium bromide mp 276-277°C (lit. 269-271°C). IR (cm^{-1}) 2600 (m), 1660 (s), 1580 (m), 1470 (m), 1425 (s), 1375 (w), 1310 (m), 1290 (m), 1100 (m), 1000 (m). The peak at 2600 corresponds to absorption due to Alkyl-Phosphorous stretching in the phosphonium salt. The peak at 1660 corresponds to absorption due to the carbonyl stretch. The peaks at 1580 and 1470 correspond to absorption due to aromatic ring stretching. The other peaks listed in the sprectrum are mostly due to C-H bending and are not as interpretively useful as the peaks at the higher frequencies.

7. Attempt to Prepare 2'-hydroxyphenacyltriphenylphosphonium bromide. The following procedure is a modification of the method of Ramirez and Dershowitz.[8] To a 125 mL erlenmeyer flask was added 15 mL of chloroform, 1.8 g of triphenylphosphine and 1.4 g of 2-bromo-2'-hydroxyacetophenone in three portions. Stir the solution for 5 minutes. This solution was gravity filtered into 175 mL of anhydrous diethyl ether. A white precipitate was formed in the ether solution. The solution was then filtered by vacuum filtration. The white precipitate that was collected immediately turned to an amber colored mush which hardened quickly to a polymeric material. Attempts to analyze this material were unsuccessful. Several other attempts were made by following the same procedure and a modification of the procedure of Fukui et al.[5] The reaction was attempted to be run and filtered under nitrogen, but only the polymeric material was obtained. The reaction was run and the product left in the ether solution, it remained a white precipitate suspended in solution when stored under nitrogen.

8. Attempt to prepare 2',4'-dihydroxyphenacyltriphenylphosphonium bromide. The procedure used was the same as described in Experiment 6. 2-bromo-2'4'-dihydroxyacetophenone (1.5 g), triphenylphosphine (1.8 g), 15 mL chloroform and 175 mL of anhydrous diethyl ether were combined in a 250 mL erlenmeyer flask. This also yielded an unknown polymeric material.

9. Preparation of 4'-hydroxyphenacyltriphenylphosphonium bromide. The following procedure is a modification of the method of Ramirez and Dershowitz.[8] To a 125 mL erlenmeyer flask was added 15 mL of chloroform, 1.8 g of

triphenylphosphine and 1.4 g of 2-bromo-4'-hydroxyacetophenone in three portions. Stir the solution for 5 minutes. This solution was gravity filtered into 175 mL of anhydrous diethyl ether. A white precipitate was formed in the ether solution. Filter the solution by vacuum filtration.

This gave 2.8 g (90% yield) mp 295-301°C (lit N/A). IR (cm^{-1}) 3350 (m), 1660 (s), 1560 (m), 1475 (m), 1425 (s), 1375 (w), 1310 (m), 1280 (m), 1100(m), 1000 (m). The peak at 3350 corresponds to absorption due to O-H stretching. The peak at 1660 corresponds to absorption due to the carbonyl stretch. The peaks at 1560 and 1475 correspond to absorption due to aromatic ring stretching. The other peaks listed in the sprectrum are mostly due to C-H bending and are not as interpretively useful as the peaks at the higher frequencies.

10. Preparation of triphenylphosphinebenzoylmethyline. This follows the literature procedure of Ramirez and Dershowitz.[8] To a 250 mL beaker 2.5 g of phenacyltriphenylphosphonium bromide and 100 mL of 10% aqueous sodium carbonate were added with agitation. Allow the solution to stir for 5 minutes. Filter the solution by vacuum filtration.

This gave 2.1 g (100% yield) of triphenylphosphinebenzoylmethyline mp 181-182°C (lit. 178-180°C). IR (cm^{-1}) 1660 (m), 1585 (m), 1520 (s), 1475 (m), 1430 (m), 1380 (s), 1100 (m). The peak at 1660 corresponds to absorption due to the carbonyl stretch. The peaks at 1585 and 1475 correspond to absorption due to aromatic ring stretching. The other peaks listed in the sprectrum are mostly due to C-H bending and are not as interpretively useful as the peaks at the higher frequencies.

11. Attempt to prepare 2'-hydroxytriphenylphosphinebenzoylmethyline. The following procedure is a modification of the method of Ramirez and Dershowitz.[8] To a 600 mL beaker a solution containing approximately 2.7 g of 2'-hydroxyphenacyltriphenylphosphonium bromide in 175 mL of anhydrous diethyl ether and 15 mL of chloroform, and 100 mL of 10% aqueous sodium carbonate were added. Allow the solution to stir for 5 minutes. Filter the solution by vacuum filtration. The white precipitate that was collected immediately turned to an amber mush which hardened quickly to a polymeric material. Attempts to analyze this material were unsuccessful.

12. Preparation of chalcone. The following procedure is a modification of the method of Ramirez and Dershowitz.[8] To a 250 mL round bottom flask 50 mL of tetrahydrofuran and 1.5 g of triphenylphosphinebenzoylmethyline were added. The solution was stirred and brought to reflux. To the refluxing mixture was added .4 g of benzaldehyde and the mixture is refluxed for 30 hours. The solvent is removed on the rotary evaporator. The remaining residue was treated with ethanol and filtered by vacuum filtration.

This gave .5 g (62% yield) of chalcone mp 54-57°C (lit. 55-57°C). GC-MS (m/e) 208 (m), 207 (m^-), 131, 130, 105, 103, 77. The peaks at 208 and 207 represent the molecular weight of the compound and the molecular weight of the compound minus 1 amu, respectively. The peaks at 131 and 130 represents the loss of C_6H_5 due to cleavage of either of the benzene rings. The peak at 105 represents the $C_6H_5CO^+$ ion due to cleavage of the bond between the carbonyl and ene functionalities. The

peak at 103 represents the $C_6H_5C_2H_2^+$ ion due to cleavage of the bond between the carbonyl and ene functionalities. The peak at 77 represents the $C_6H_5^+$ ion.

13. Attempt to prepare chalcone. The procedure used was an original idea by the author. To a 250 mL, three necked round bottom flask, 100 mL of dimethylformamide, 2.3 g of phenacyltriphenylphosphonium bromide, .5 g of benzaldehyde and 10 drops of triethylamine were added. The solution is stirred under reflux for 48 hours. The phenacyltriphenylphosphonium bromide was recovered in almost quantitative yields.

14. Attempt to prepare chalcone. The procedure used was an original idea by the author. To a 250 mL, three necked round bottom flask, 100 mL of absolute ethanol, 2.3 g of phenacyltriphenylphosphonium bromide, .5 g of benzaldehyde, 8.5 mL of fresh .6 M sodium ethoxide in ethanol were added. The solution is stirred under reflux for 24 hours. The phenacyltriphenylphosphonium bromide was recovered in almost quantitative yields.

15. Attempt to prepare chalcone. The following was an original idea by the author. To a 250 mL, three necked round bottom flask, 100 mL of tetrahydrofuran, 1.0 g of benzaldehyde, 4.6 g of phenacyltriphenylphosphonium bromide and .6 g of 1,4-diazabicyclo[2.2.2]octane were added. The solution is stirred under reflux for 24 hours. The phenacyltriphenylphosphonium bromide was recovered in almost quantitative yield.

16. Attempt to prepare 2,4-di(methoxymethoxy)acetophenone. The following procedure is a modification of the method of Nabaei-Bidhendi and Bannerjee.[6] To a

500 mL, three necked round bottom flask, 200 mL of dry acetone, 6.4 g of 2,4-dihydroxyacetophenone, 20 g of potassium carbonate and 8 g of methoxymethyl chloride in 20 mL of dry acetone were added. The resulting mixture was stirred under reflux for 1.5 hours. Filter the solution by vacuum filtration. Drive off the solvent on the rotary evaporator. The remaining residue was filtered by vacuum filtration and washed with a 1:1 mixture of petroleum ether and ethyl acetate. The 2-hydroxy-4-methoxymethoxy-acetophenone product was formed instead of the expected product.

17. Attempt to prepare 2-methoxymethoxybenzaldehyde. The following procedure is a modification of the method of Nabaei-Bidhendi and Bannerjee.[6] To a 500 mL, three necked round bottom flask, 180 mL of dry acetone, 5.2 g of 2-hydroxybenzaldehyde, 10 g of potassium carbonate and 5 g of methoxymethyl chloride in 20 mL of dry acetone were added. The resulting mixture was stirred under reflux for 1.5 hours. Filter the solution by vacuum filtration. Drive off the solvent on the rotary evaporator. To the remaining residue was added 20 ml of diethyl ether. The ether was removed on the rotary evaporator and the resulting light yellow liquid dried in a vacuum desiccator overnight. The benzaldehyde starting material was recovered instead of the expected product.

18. Preparation of 2,4-dimethoxyacetophenone. The following procedure is a modification of the method of Vyas and Shah.[9] To a 500mL, three necked round bottom flask, was added 30 g of 2,4-dihydroxyacetophenone in 150mL of absolute ethanol. The solution is agitated and 60 g of dimethyl sulfate in 70 g of 25% sodium hydroxide is added slowly dropwise. After the addition was complete, 15 g of 35%

sodium hydroxide was added to the flask and the solution was heated to reflux for 3 hours. The solution was cooled, then placed on the rotary evaporator where most of the alcohol was removed. The resulting liquid was steam distilled. The distillate was cooled in an ice bath and extracted with ether. The ether was dried. The solution was then distilled at reduced pressure to yield the product.

This gave 22.4g (63% yield) of 2',4'-dimethoxyacetophenone mp 38-41°C (lit. 39-41°C).

19. Preparation of 2,2',4'-trimethoxychalcone. The following procedure is a modification of the method of Kohler and Chadwell.[1] To a 250 mL erlenmeyer flask 2.2 g of sodium hydroxide, 19.6 g of water and 10 g of absolute ethanol were added. This solution was stirred and cooled in an ice bath to 15°C. 7.7 g of 2',4'-dimethoxyacetophenone and 5.8 g of *o*-anisaldehyde are added to the flask slowly in order. The solution is stirred for 3 hours controlling the temperature between 15-25°C. After 3 hours the solution was transferred to the freezer and allowed to sit overnight. Filter the wet solid by vacuum filtration and recrystallize twice from absolute ethanol.

This gave 10.2 g (80% yield) of 2,2',4'-trimethoxychalcone mp 102.5-104°C (lit. N/A). The analysis calculated value Carbon = 72.47%, Hydrogen = 6.08% and Oxygen = 21.45%, the analysis found Carbon = 72.34%, Hydrogen = 6.11% and Oxygen = 21.46%. GC-MS (m/e) 299 (m^+), 298 (m), 267, 165, 107, 77. ^{1}H NMR ($CDCL_3$) δ 8-6.5 (m), 3.85 (d), 3.45 (s), 1.58 ppm (s).

20. Preparation of 2,2',4'-trihydroxychalcone. The following procedure is a modification of the method of Vickery, Pahler and Eisenbraun.[10] To a 50 mL erlenmeyer flask 5.4 g of 2,2',4'-trimethoxyacetophenone and 5 mL of methylene chloride were added. The flask was purged with nitrogen and then sealed with a septum. This mixture was immersed in a dry ice/IPA bath and 1.9 mL of boron tribromide was added through the septum. This mixture was removed from the cold bath after 10 minutes and the mixture was stirred for 30 minutes. The resulting solution was poured into 25 mL of ice water, stirred for 30 minutes, saturated with sodium chloride and extracted 3 times with methylene chloride. The extract was dried, concentrated on the rotary evaporator and recrystallized twice from absolute ethanol.

This gave 3.4 g (73% yield) of 2,2',4'-trihydroxychalcone mp 176.5-178.5°C (lit. N/A). The analysis calculated value Carbon = 70.31%, Hydrogen = 4.72% and Oxygen = 24.97%, the analysis found Carbon = 71.13%, Hydrogen = 4.72% and Oxygen = 24.18%. GC-MS (m/e) 257 (m^+), 238, 163, 137, 91. ^{1}H NMR ($CDCl_3$) δ 10.49 (b), 8.2-6.3 (m), 3.39 (b), 2.51 ppm (s).

CHAPTER IV

CONCLUSION

This work demonstrated that 2,2',4'-trihydroxychalcone could be successfully synthesized and characterized. Several synthetic routes to poly-substituted chalcones were attempted. This is the first presentation in the literature where the Wittig route to poly-substituted chalcones was compared to the protection-condensation-deprotection route.

Different protecting groups were explored in an attempt to protect hydroxylated acetophenones and benzaldehydes. The successful synthesis of 2',4'-dimethoxyacetophenone along with the ready availability of *o*-anisaldehyde allowed for the synthesis of 2,2',4'-trimethoxychalcone via the well defined method of base catalyzed condensation. This allowed different deprotecting agents to be examined and the history of boron tribomide to completely deprotect the hydroxyl groups allowed for the synthesis of the title compound, 2,2',4'-trihydroxychalcone. This allowed for the biological screening of this promising candidate against the HIV virus.

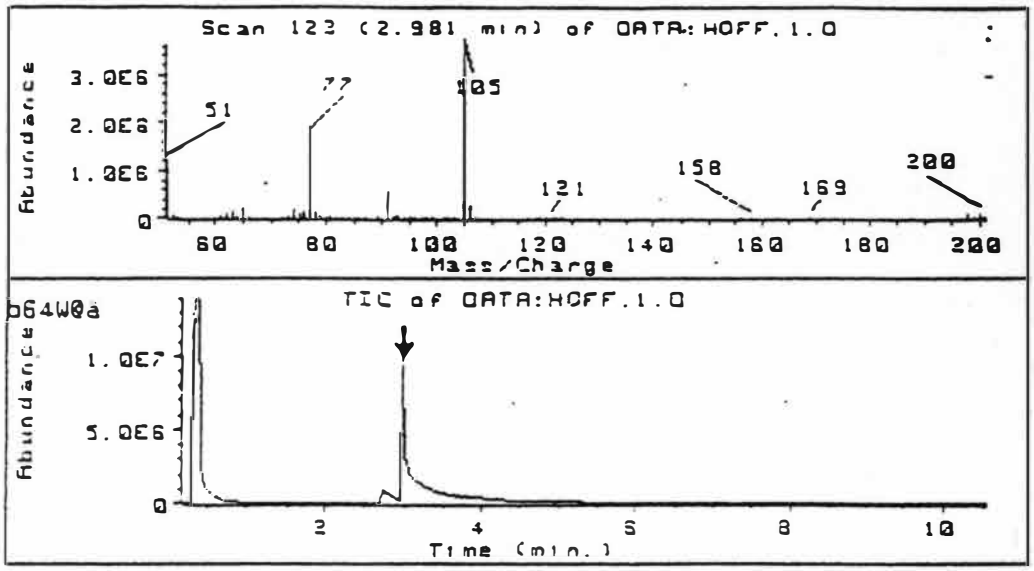
While the Wittig synthetic route proved not to be useful for this particular compound, it did show some promise in some other substituted chalcone derivatives. As cited in the literature, it was possible to synthesize unsubstituted chalcone and the 4'-hydroxychalcone could probably also be synthesized.

Further work is needed in two areas of this research project. First, more compounds that are structurally similar to the title compound need to be prepared to determine if any of these biosteres have the biological activity against the HIV virus that the original sample sent in had. Second, the Wittig synthesis of poly-substituted chalcones needs to be further explored to determine if this a facile route for the synthesis of many poly-substituted chalcones. The effect of substitution at the 2' position should also be studied.

Appendix A

Analytical Data

G.C.-M.S of 2-Bromoacetophenone



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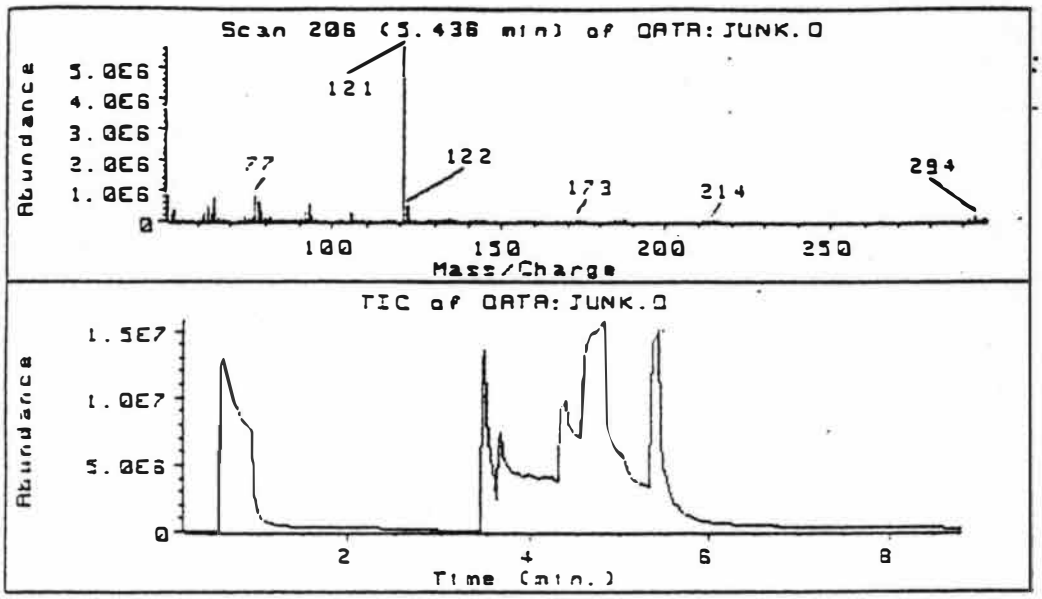
X: Scan 123 (2.981 min) of DA

G.C.-M.S of 2-Bromo-2'-hydroxyacetophenone



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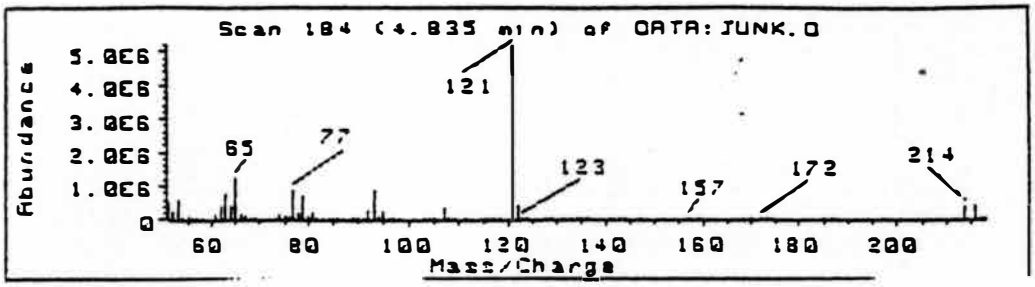
Y: Scan 140 (3.664 min) of DA
X: Scan 206 (5.436 min) of DA

[DE]

Tot Ion Chromat | Spectrum | Zoom In | New Data File | SPECTRUM KEYS | CHROMAT KEYS | ENVIRON KEYS | QUIT

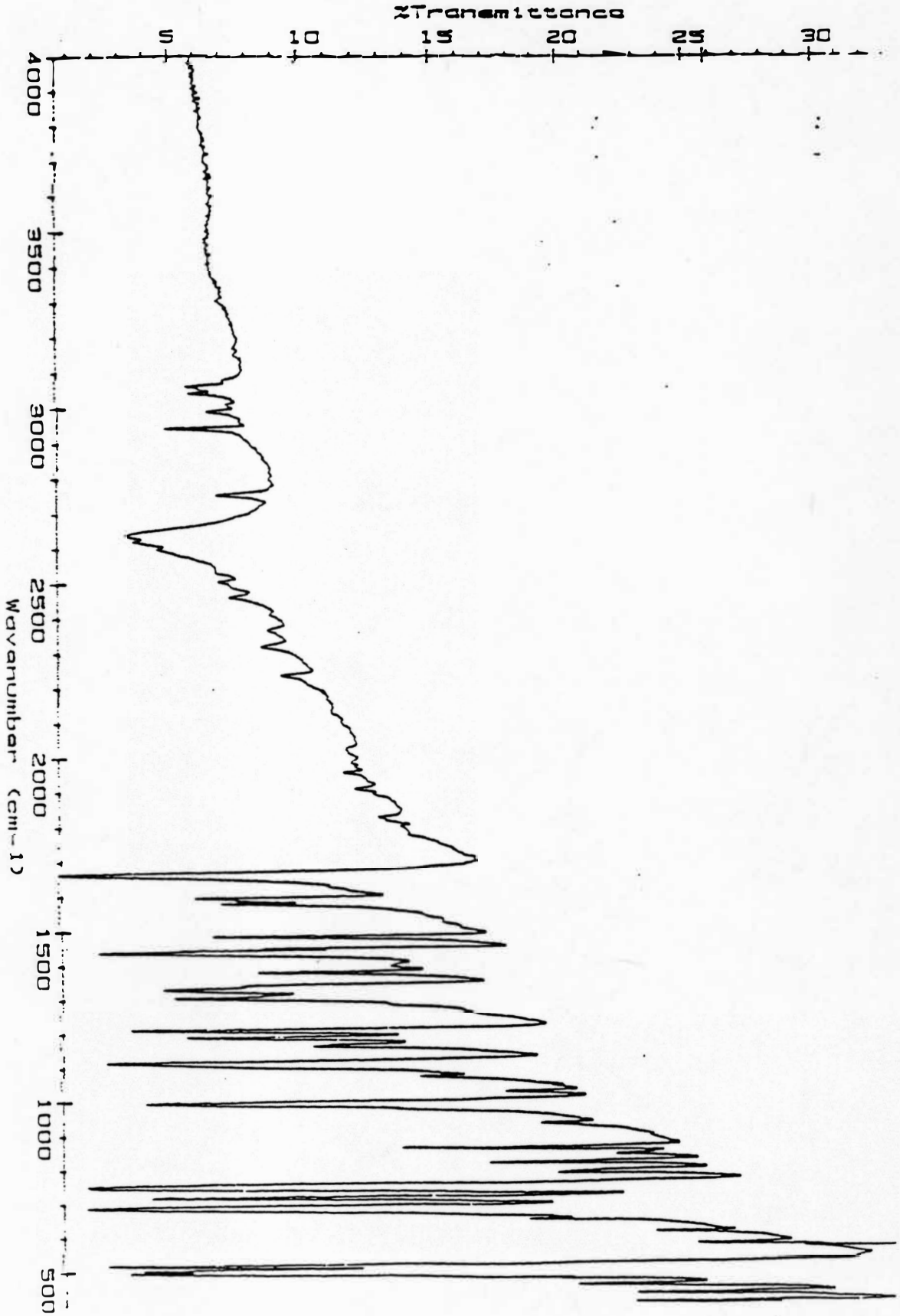
M.S. of 2-Bromo-4'-hydroxyacetophenone



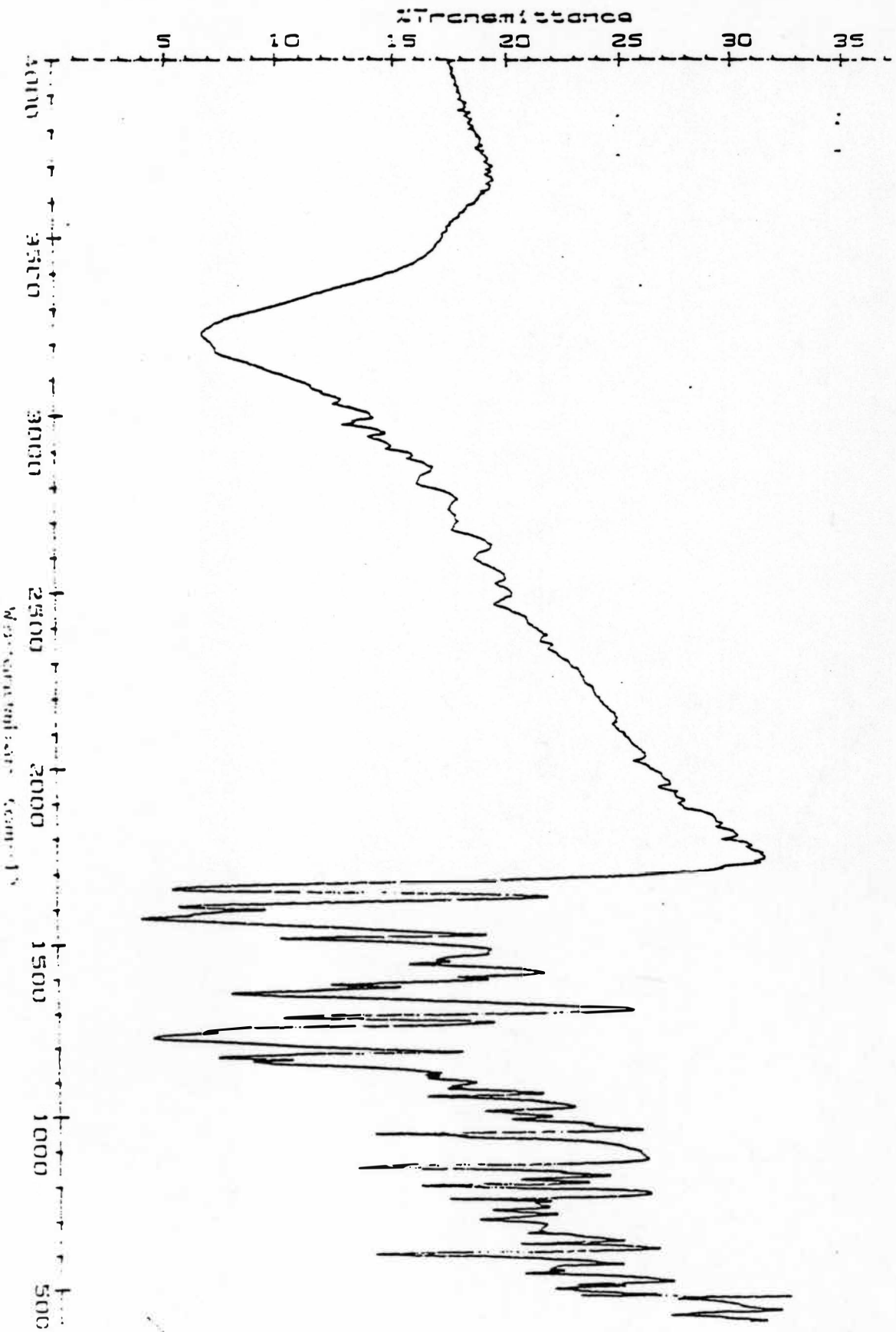
M.S. of 2-Bromo-2',4'-dihydroxyacetophenone

Spectrum Unavailable

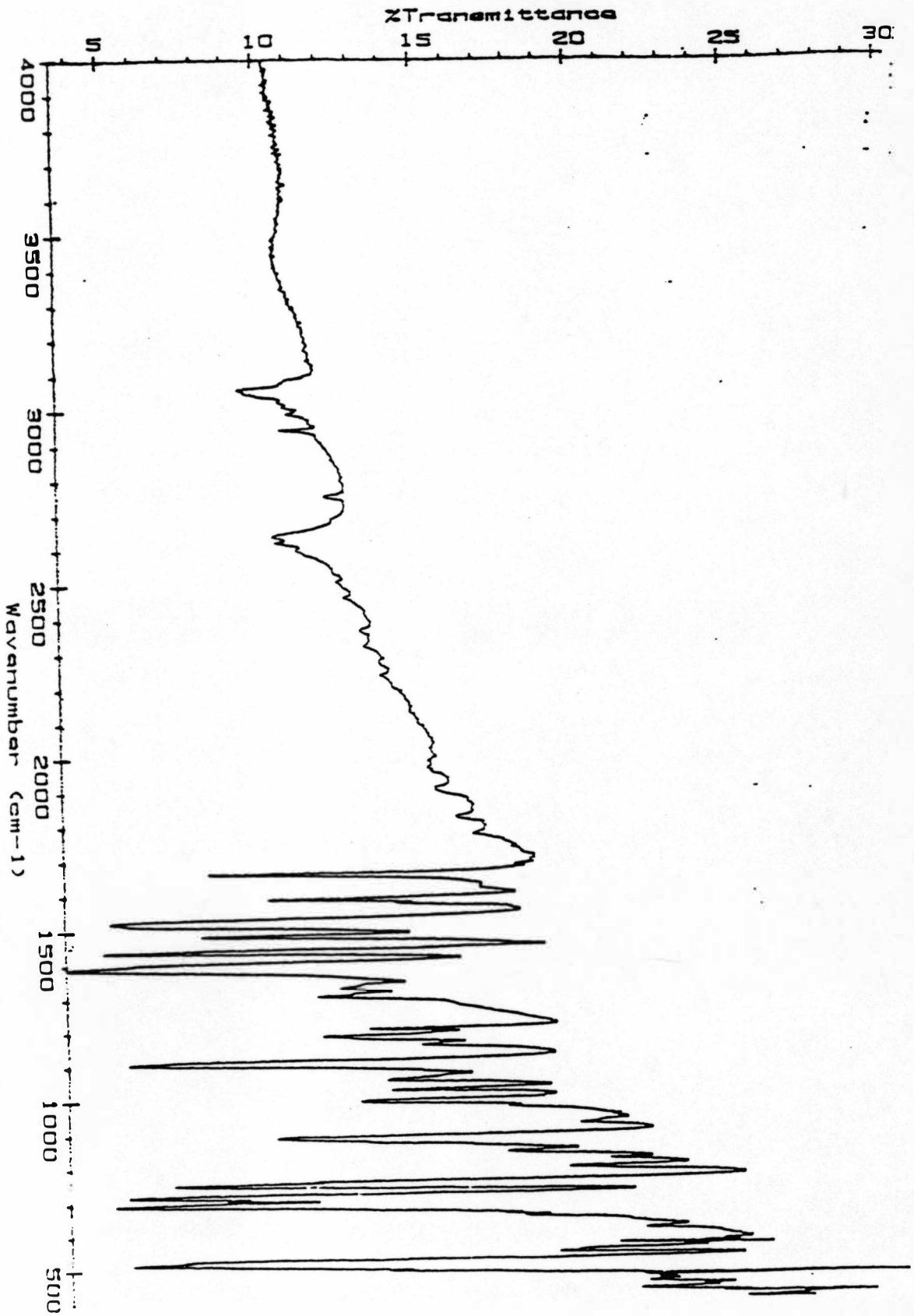
Infrared Spectrum of Phenacyltriphenylphosphonium bromide



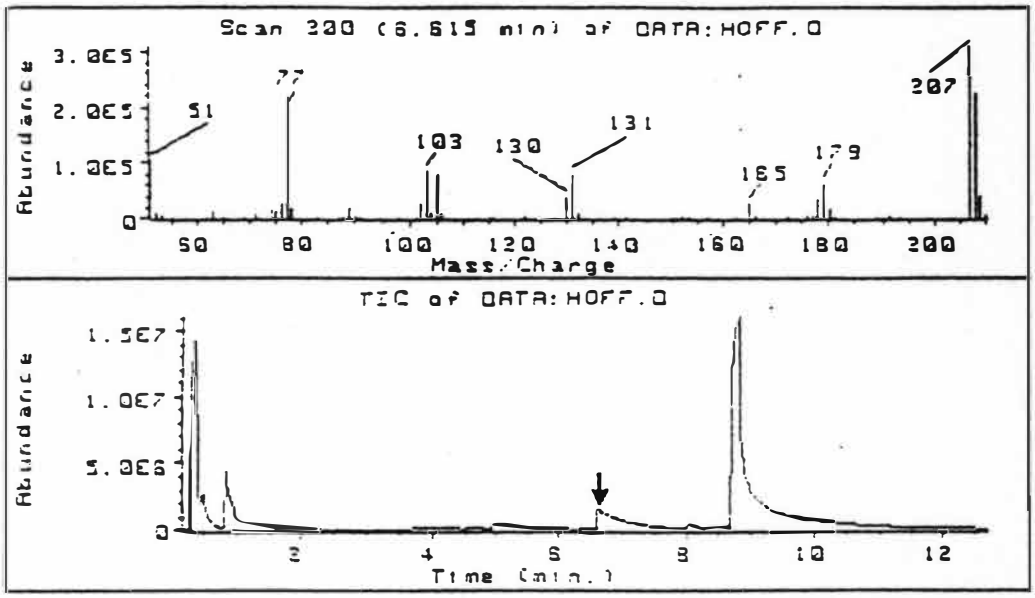
Infrared Spectrum of 4'-Hydroxyphenacyltriphenylphosphonium bromide



Infrared Spectrum of Triphenylphosphinebenzoylmethyline



G.C.-M.S. of Chalcone



(6.62, 1574588.0)
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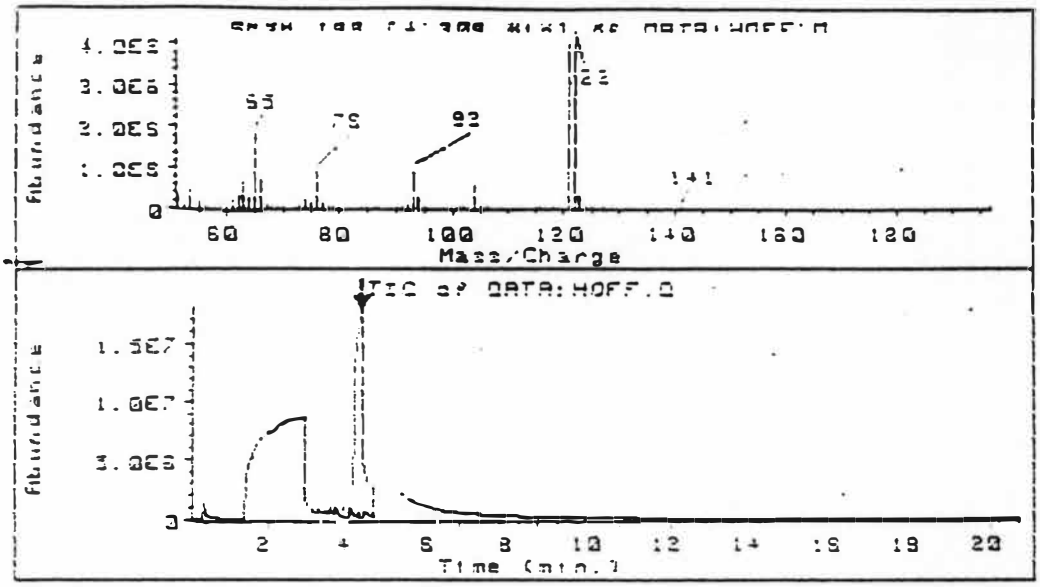
G.C.-M.S. of Recovered Benzaldehyde



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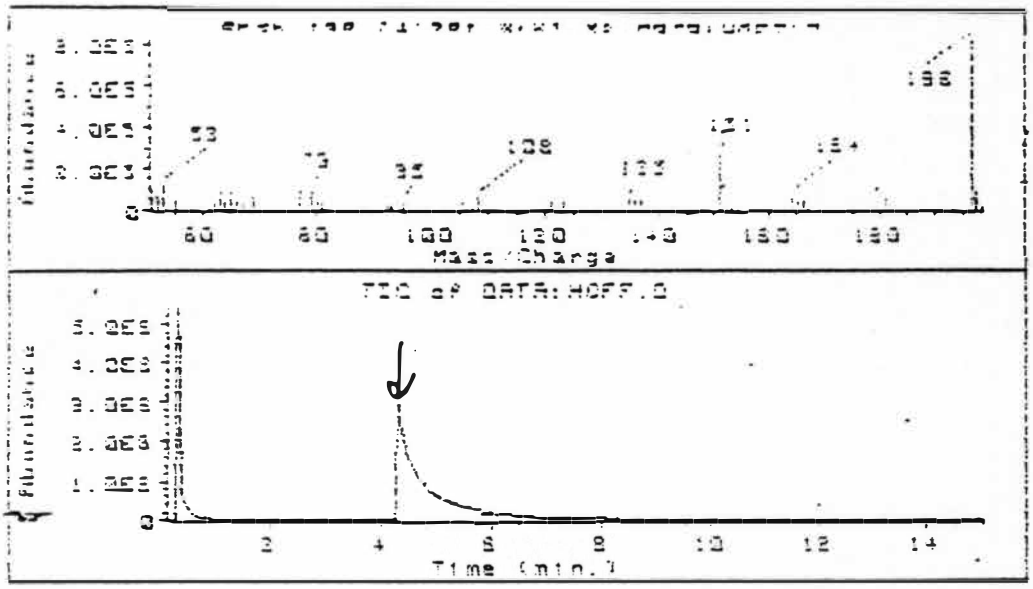

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[DE] \

Chromat | Spectrum | Zoom In | New Data File | SPECTRUM KEYS | CHROMAT KEYS | ENVIRON KEYS | QUIT

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