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Studies toward the Total Synthesis of a Colchicine Analog

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STUDIES TOWARD THE TOTAL SYNTHESIS OF A COLCHICINE ANALOG

by

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Jacob Shya Tou

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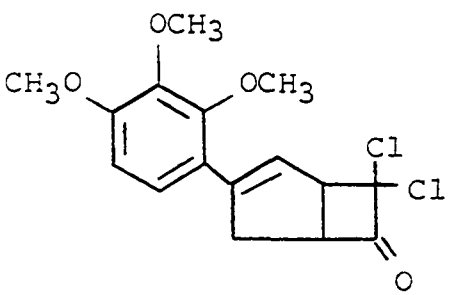
CHAPTER I

INTRODUCTION

The objective of this work was to synthesize the compound 3-(2,3,4-trimethoxyphenyl) 7,7-dichlorobicyclo-[3,2,0]hept-2-en-6-one (1). This compound could probably be used to synthesize a colchicine analog (structure 2) by opening the bicyclic ring.



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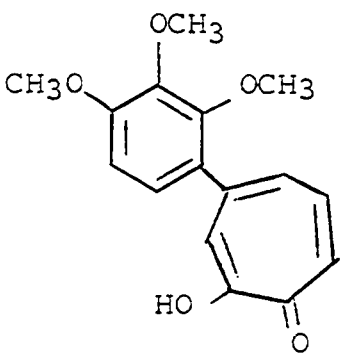
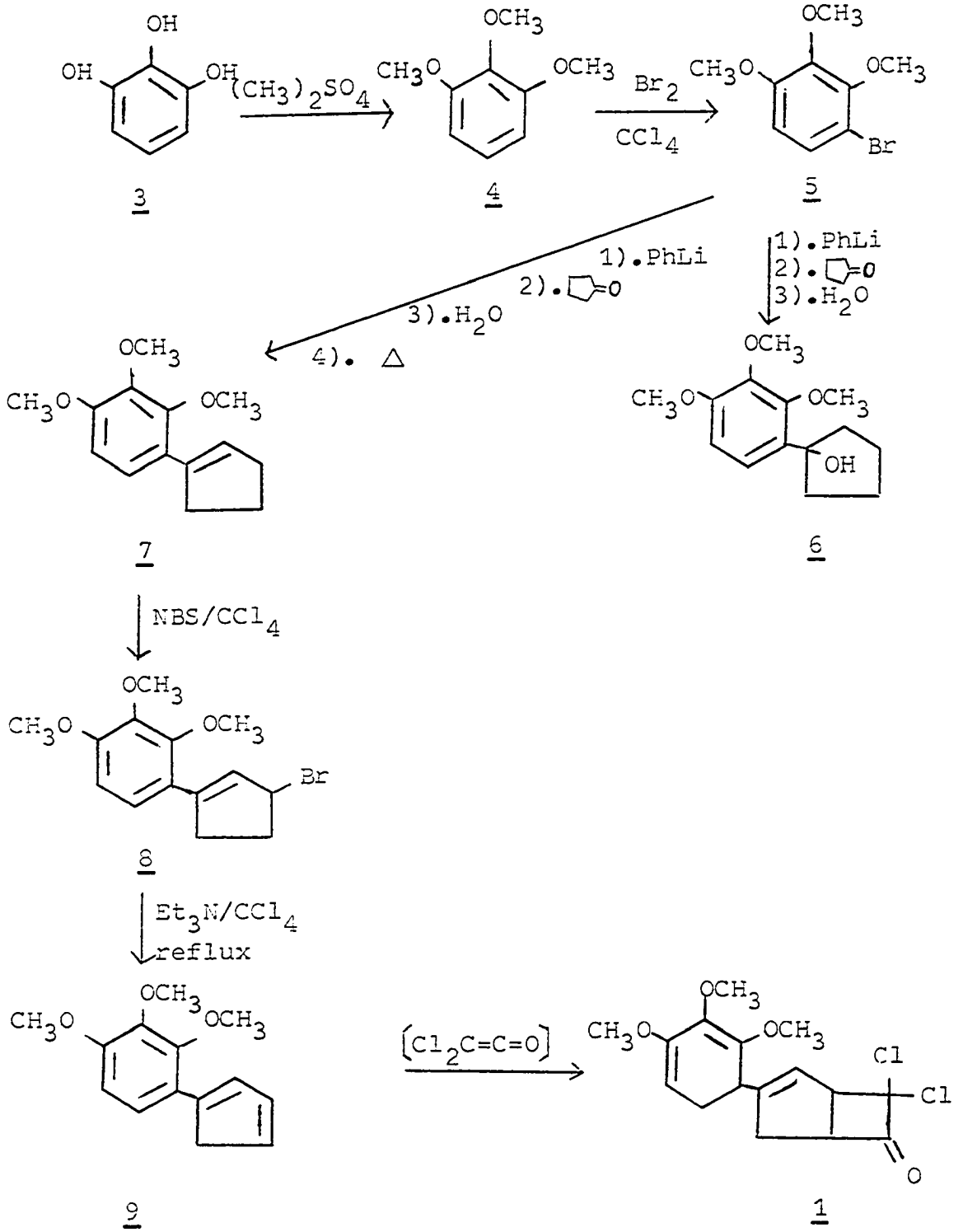


2

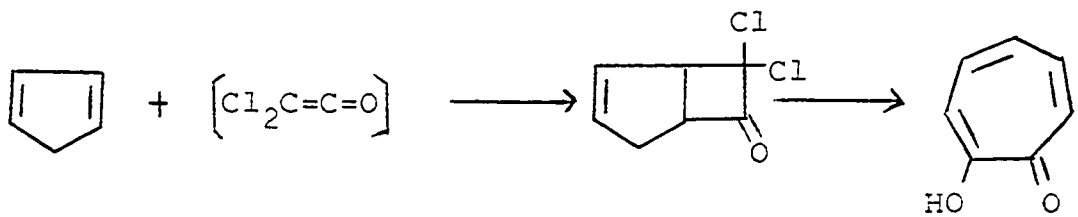
Compound 1 was synthesized in several steps from pyrogallol (3). The overall synthetic route to 1 is shown in the accompanying scheme:



CHAPTER II

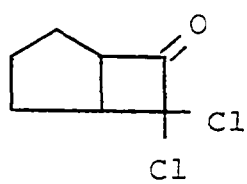
HISTORICAL

In 1965, Stevens and co-workers[1] reported a new route for synthesizing tropolone, 13, via dichloroketene, 11. They reported that the 1:1 adduct (structure 12) obtained by the reaction of cyclopentadience, 10, with dichloroketene was a precursor of tropolone.



10 11 12 13

Ghosez et. al.[2] reported, independently, the reaction of dichloroketene with cyclopentene and cyclopentadiene which yields compounds with structures, 14 and 12, respectively.



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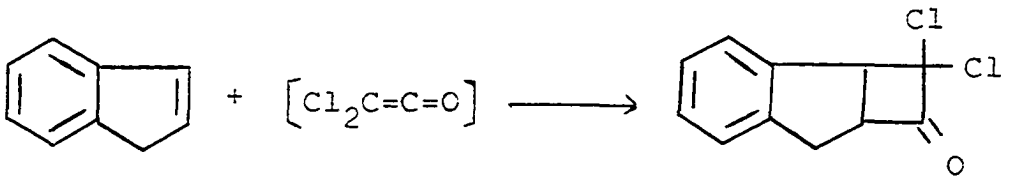
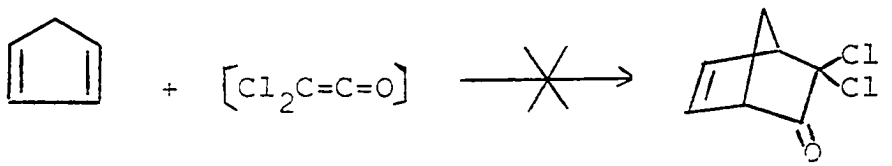
Potts and Harmon[3] studied the addition of dichloroketene to indene, 15, and obtained a compound having structure 16.



15 11 16

These investigators had discussed the mechanism of dichloroketene addition to a double bond. The products were assigned structures 12 and 16 resulting from $2\pi_a+2\pi_s$ cycloaddition reactions in preference to the $4\pi+2\pi$ Diels-Alder addition product 17, and it was further suggested that the reaction was regiospecific and proceeded via route A to give compound 12 instead of via route B to give compound 18.



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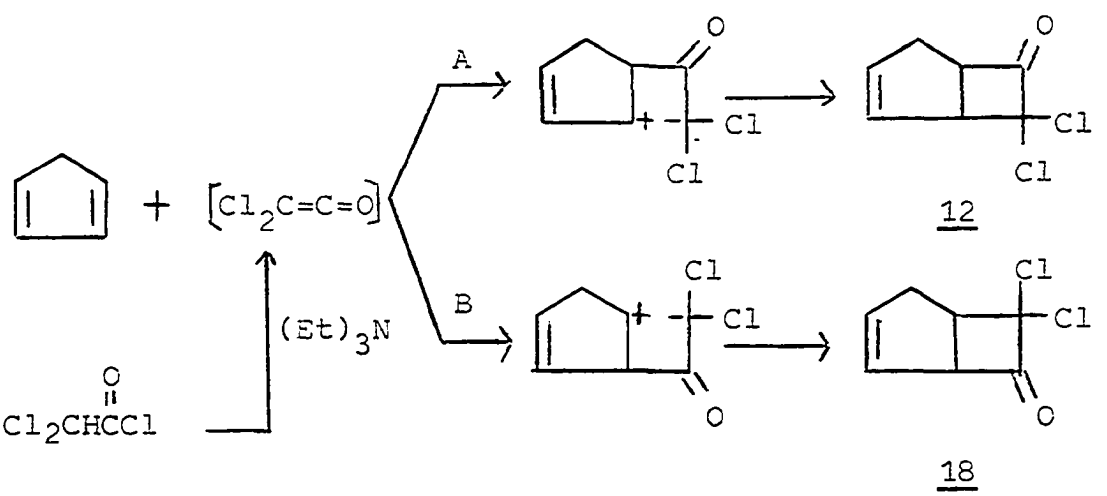


12 18

CHAPTER III

EXPERIMENTAL

Infrared spectra were obtained with a Perkin-Elmer model 21 spectrophotometer and the absorption maxima are expressed in cm^{-1}. The samples were dissolved in chloroform and placed in KBr cells. The Nuclear Magnetic Resonance spectra were obtained with a Varian A-60 spectrometer using carbon tetrachloride as solvent and tetramethylsilane as an internal reference. The δ values of the nmr data are expressed in ppm.

Some of the mass spectra were determined on a DuPont 20-490B mass spectrometer, and the remainder, obtained with the direct probe technique, were taken with a Varian MAT CH4B mass spectrometer with the ion source temperature regulated at 250° and the electron current at 60 μa. The gas chromatography-mass spectrometry studies were carried out with an LKB 9000 gas chromatograph-mass spectrometer unit, equipped with a dual jet separator. The temperatures of the ion source and the jet separator were kept at 270° and 250°, respectively, and the electron current was kept at 20 μa. A 10 feet long stainless steel column containing a 10%, UCW-98 gas chromatographic column was employed and programmed from 60° to 200° at a rate of 8°/min.. The column was kept

at 200°, after that temperature was reached, until the analysis was completed.

Gas chromatographic studies were carried out with use of a Hewlett-Packard 402 high efficiency gas chromatograph, using carbowax as the packing material. The vacuum distillation was accomplished by using a 24 inches Nester/Faust (patent no. 2712520) spinning band distillation column.

The separation of compounds 6, 7 and 1 from their crude reaction mixtures was carried out by means of a chromatographic column which was packed with 70-230 mesh silica gel. Methylene chloride was used as an eluent. The compounds of interest eluted separately and were monitored by thin layer chromatography using methylene chloride as a developing solvent. The fractions which contained the desired products as indicated by thin layer chromatography were combined. The products were then isolated by evaporation of the solvent.

All the microanalyses were carried out by The Midwest Microlaboratory, Indianapolis, Indiana.

A. Preparation of pyrogallol trimethyl ether (4).

This compound was originally prepared by Chapman, Perkin and Robinson[4] in 1927 with a yield of 86%. The reaction was carried out under nitrogen

instead of under hydrogen, as used by the previous workers.

One hundred-fifty milliliters of 40% aqueous sodium hydroxide was gradually added over a period of four hours from a pressure-equalized dropping funnel to a mixture of 42.0 g, 0.33 mole of pyrogallol, 142 ml, 1.5 mole of dimethyl sulfate and 100 ml of ethanol. The reaction mixture was stirred vigorously under a nitrogen atomosphere. After the reaction was completed, the flask was cooled in an ice-bath, and 200 ml cold water was added to the reaction flask. This caused compound 4 to crystallize as glistening, white prisms which were then filtered and dried in air for several days, or dried by means of a water pump vacuum for several hours. The isolated product, 52.5 g, 92% yield, melted at 40-41°. (lit[4]. m.p. 47°)

B. Preparation of 4-bromopyrogallol trimethyl ether (5).

This compound was prepared according to the method of Bruce and Sutcliffe[5].

Bromine (51.6 ml, 1 mole) in 500 ml of dry carbon tetrachloride was added over a period of 7 to 8 hours to a vigorously stirred solution of 168 g, 1 mole of pyrogallol trimethyl ether in 500 ml of dry carbon tetrachloride. The temperature was kept at 4-5° and

the reaction flask was connected to a water trap in order to dissolve the hydrogen bromide gas generated during the reaction. After the bromine solution had been added, the mixture was kept overnight at room temperature. The solvent was removed by means of a rotatory evaporator and the residual yellow oil was distilled through a spinning band distillation apparatus. The fraction 95-98° (0.2 mm) was collected and weighed 206 g, 83.4%. (lit[5]. b.p. 95-100°/0.2mm).

C. Preparation of 1-(2,3,4-trimethoxyphenyl) cyclopentanol (6) and 1-(2,3,4-trimethoxyphenyl) cyclopentene (7).

2,3,4-trimethoxyphenyllithium was prepared by adding a solution of compound 5 (99 g, 0.4 mole) in 200 ml anhydrous ether under a nitrogen atomosphere during 1 hour, to a vigorously stirred solution of 2M phenyllithium in benzene (220 ml, 0.44 mole) at 0°. When about half of the solution of 5 had been added, the reaction mixture turned milky white. After the completion of the addition, the reaction mixture was stirred at 0° for another 30 minutes before the temperature was raised to room temperature for one hour; the reaction mixture was then again cooled to 0°. Cyclopentanone (45.4 ml, 0.51 mole, purified by distillation), was dissolved in 150 ml of ether, and added to the above solution over a period of one

hour. The reaction mixture was stirred overnight at room temperature. The reaction mixture was then cooled to 0° and decomposed by the dropwise addition of 200 ml of ice-cold water. The yellow ether layer was separated and washed four times with 5% NaOH solution and sequentially with water and saturated salt. The resulting ether phase was dried with sodium sulfate. After the ether was removed with a rotatory evaporator, a yellow viscous oil was left which was then separated by column chromatography. Compound 6 was obtained in 40.3 g, 40% yield.

The crude reaction mixture was dehydrated during spinning band distillation to yield 35 g, 38% of compound 7, a clear colorless viscous oil with b.p. 130-133° (0.15 mm).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.76; H, 7.76. Found: C, 71.42; H, 7.53.

D. Purification of N-bromosuccinimide (NBS).

The purification was done using the procedure developed by Dauben and McCoy[6].

The commercial grade NBS had a deep yellow color, presumably due to occluded bromine. Purification of the crude material was accomplished by adding thirty grams of NBS to boiling water (300 ml) in a flask; the

flask was swirled in order to rapidly dissolve the NBS. The solution was filtered rapidly into another flask immersed in an ice-bath and allowed to stand in the ice-bath for an hour. White crystals of NBS were formed, washed thoroughly with ice water, and then dried by means of a water pump for about 10 hours. The purified NBS was stored in a desiccator.

E. Preparation of 1-(2,3,4-trimethoxyphenyl) cyclopentadiene (9).

Compound 7 (11.7 g, 0.05 mole), dissolved in 200 ml of dry carbon tetrachloride, was added to 9 g of NBS (in 50 ml anhydrous ether) under nitrogen. The solution was irradiated with a 100 W light bulb placed near the reaction flask (about 10 inches) for about 4 hours. As the bromination proceeded, succinimide appeared on the surface of the carbon tetrachloride solution in the reaction flask. The solution turned yellow indicating completion of the reaction. The insoluble imide and the excess NBS were collected by filtration. The resulting solution containing compound 8 was found to oxidize very easily, turning black after a few hours. Therefore this solution was quickly placed in a pressure-equalized dropping funnel and added dropwise, in 20 minutes, to 10 ml (99%) triethylamine in 100 ml carbon tetrachloride. After

the completion of the adding, the reaction mixture was refluxed for 1 hour, and then stirred overnight at room temperature. The precipitated salt, triethylamine hydrobromide, was collected using vacuum filtration. The filtrate was a brown solution, and was found to be easily oxidized in air, turning dark green after few hours. This crude mixture was analyzed by mass spectrometry and showed the presence of the expected molecular ion at m/e 232 ($M^{\ddagger}$) and fragment ions at 217 ($M^{\ddagger}-CH_3$), and 201 ($M^{\ddagger}-OCH_3$). Compound 9 was found to be the major component in the mixture.

F. Preparation of 3-(2,3,4-trimethoxyphenyl) 7, 7-dichlorobicyclo-[3,2,0] hept-2-en-6-one (1).

The crude reaction mixture containing compound 9 (approximately 0.05 mole) and 6.5 ml excess Et_3N was quickly transfered with a pressure-equalized dropping funnel to a 1000 ml 3-neck reaction flask, under nitrogen, containing 4.8 ml (0.05 mole) dichloroacetyl chloride in 200 ml carbon tetrachloride. The addition was carried out over a period of 1.5 hours and the reaction mixture was then heated to 50° over 1 hour. The brown solution turned dark green. The stirring was continued over another 40 hours. The final reaction mixture was cooled in an ice-bath, and the

precipitated triethylamine hydrochloride was collected by filtration. The solvent was removed with a rotatory evaporator. Purification by distillation was found to be unsatisfactory because polymerization of the reaction mixture was observed to take placed at high temperature, which resulted in the formation of tar. Instead, column chromatography was employed, and a yellow sticky oil was obtained which was flushed overnight with nitrogen. Yellow crystals were obtained and then analyzed by TLC; only one spot was observed.

The compound was found to be unstable and sensitive to heat and light. Therefore, after the solvent had been evaporated, the product was placed in a refrigerator in a sample vial wrapped with aluminum foil. Otherwise the color of this compound changed to a dark green. Upon being heated, compound 1 decomposed to its starting material, compound 9, with a loss of dichloroketene as shown by gas chromatography-mass spectrometry. The overall yield of compound 1 from compound 7 was 10.7 g (63%).

Anal. Calcd. for $C_{16}H_{16}O_4Cl_2$: C, 55.98; H, 4.66; Cl, 20.70.

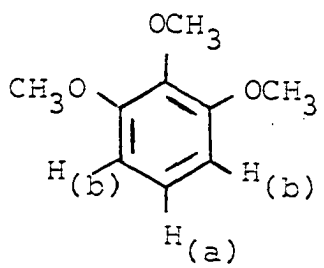
Found: C, 55.27; H, 4.73; Cl, 21.54.

CHAPTER IV

IDENTIFICATION OF STRUCTURES

The determinations of the structures of compound 4 through compound 1 were made on the basis of elemental analysis, nmr spectra, infrared spectra, mass spectra, chromatography and other physical properties. All the analytical data are discussed below.

A. Pyrogallol trimethyl ether (4).



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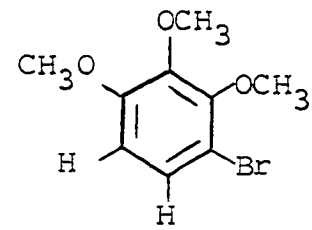
The nmr spectrum of compound 4 is consistent with that found in the literature[7].

The multiplet centered at δ 7.10 shows the H_a proton in the benzene ring. The other two H_b protons are shown slightly upfield as a multiplet. The region of δ 3.90 gives a singlet of the nine methyl protons.

B. 4-bromopyrogallol trimethyl ether (5).



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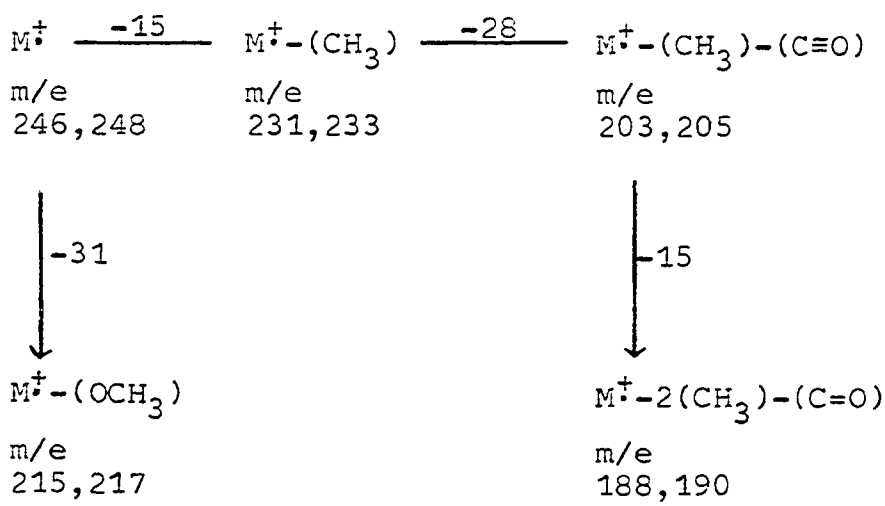
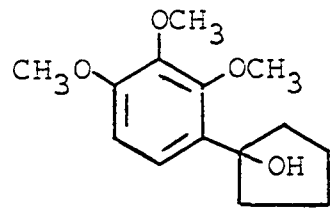
The nmr spectrum shows AB type (J=9 cps) absorptions in the downfield indicating the presence of the two ring protons. The methyl protons are shown as a singlet with a chemical shift δ 3.80.

The mass spectrum shows the presence of the expected molecular ion peaks at m/e 246 and 248, carrying one bromine pattern. The peaks at m/e 231, 233 and 215, 217 are generated from the loss of methyl and methoxyl groups from the molecular ions.

The structure is also confirmed by the peaks m/e 203, 205, 188, 190. The major fragmentation scheme is rationalized as follows:



C. 1-(2,3,4-trimethoxyphenyl) cyclopentanol (6) and 1-(2,3,4-trimethoxyphenyl) cyclopentene (7).



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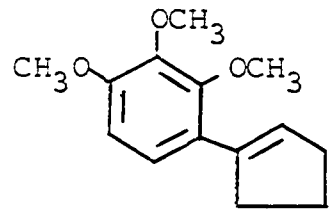


7

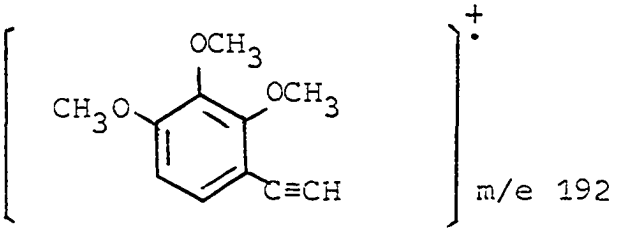
The ir, nmr and mass spectra of compound 7 are shown in Figure I, II and III, respectively.

The strong absorption at 1600 cm^{-1} in the infrared spectrum shows a typical C=C group. Other assignments are: 2950 cm^{-1} (asymmetric stretching of CH_3, CH_2), 2850 cm^{-1} (symmetric stretching of CH_3 and CH_2), 1495 cm^{-1} (scissoring vibration of CH_3), 1465 cm^{-1} (asymmetric vibration of CH_3 and scissoring vibration of CH_2), 1416 cm^{-1} (olefinic C-H bending vibration), 1110 cm^{-1} (asymmetrcal C-O-C stretching vibration).

The nmr spectrum shows the three methyl groups (m, at δ 3.75), the two phenyl protons (δ 6.35-6.85, AB quartet, J=9 cps). The vinyl proton is shown as a multiplet at δ 6.15 and the broad region at δ 1.80-2.80 is related to the six methylene protons.

The expected molecular ion of compound 7 is m/e 234 as shown in the mass spectrum. After losing

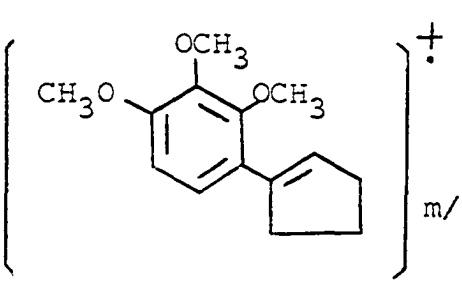
a methyl and a methoxyl group, the spectrum gives peaks at m/e 219 and 203, respectively. The fragment ion at m/e 192 results from the loss of a C_3H_6 group and possibly has the structure 19.



19

Compound 6, was isolated by column chromatography instead of by spinning band distillation. The structure of compound 6 is confirmed by the infrared and mass spectra.

The absorption at 3600 cm^{-1} in the infrared spectrum indicates the presence of a hydroxyl group. The mass spectrum shows the molecular ion at m/e 252. The fragment ions at m/e 234 and 195 are generated from the molecular ion by the loss of H_2O and a C_4H_9 radical, respectively. They may have the following stable structures 20 and 21.



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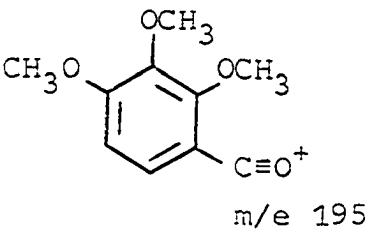

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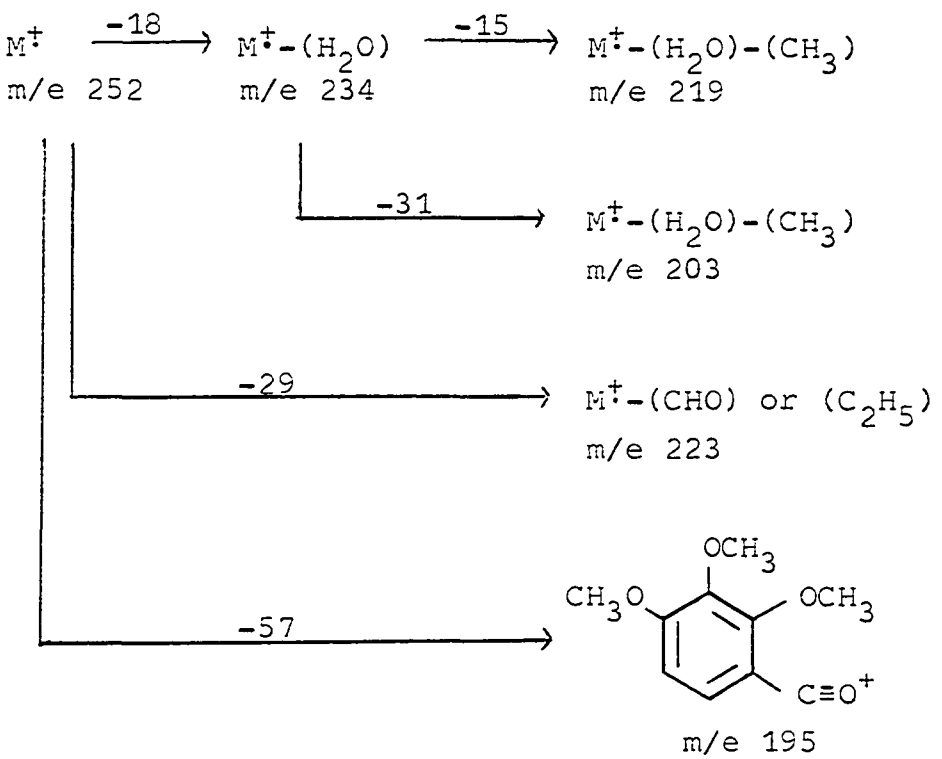
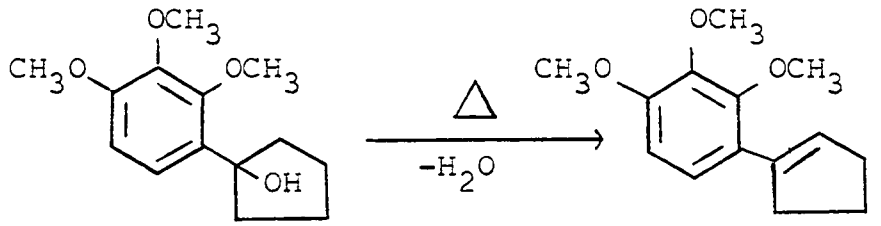
The fragment ions at m/e 223, 195 are not present in the mass spectrum of compound 7. On the other hand, the characteristic fragment ion at m/e 192 of compound 7 does not exist in the mass spectrum of compound 6. The above evidence indicates that compound 7 is the dehydrated form of compound 6.

The following fragmentation is suggested:



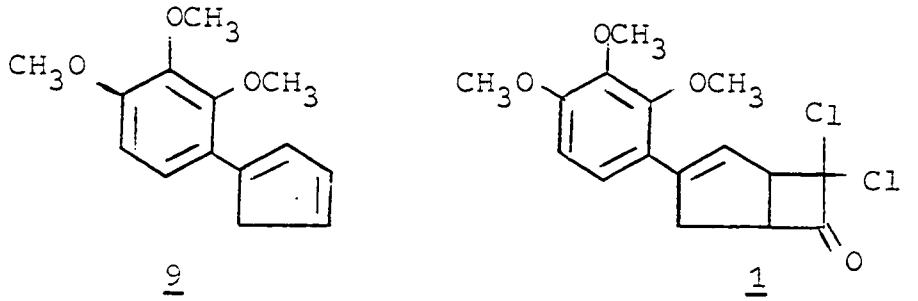
It is realized from this study that the method of separation of the compound in the reaction mixture is very critical in obtaining compound 6 or compound 7. If the compounds in the crude mixture are separated by column chromatography, compound 6 is isolated. On the

other hand, if the spinning band distillation apparatus is used at a higher temperature, compound 6 will be dehydrated to form compound 7 as shown below:



6 7

D. 1-(2,3,4-trimethoxyphenyl) cyclopentadiene (9) and 3-(2,3,4-trimethoxyphenyl) 7, 7-dichlorobicyclo-[3,2,0]hept-2-en-6-one (1).



9 1

Compound 9 is the precursor of compound 1. It is easily oxidized in air and then turns dark green. No attempt was made to isolate compound 9 from the crude reaction mixture. Gas chromatography-mass spectrometry was first employed for analyzing both of the crude reaction mixtures. The total ion chromatograms of these two reaction mixtures are shown in Figures IV and VI, respectively. The mass

fragmentograms of the expected molecular ion of compound 9 are shown in Figures V and VII, respectively. No evidence was found for the presence of the expected molecular ion of compound 1. The mass spectrum taken of this chromatographic peak is shown in Figure VIII. The peak at m/e 232 is due to the molecular ion of compound 9. The loss of 15 and 31 mass units, giving ion peaks at m/e 217 and 201, indicates the presence of methyl and methoxyl groups. The above data confirm that the gas chromatographic peak with the retention time of 12 minutes is due to compound 9.

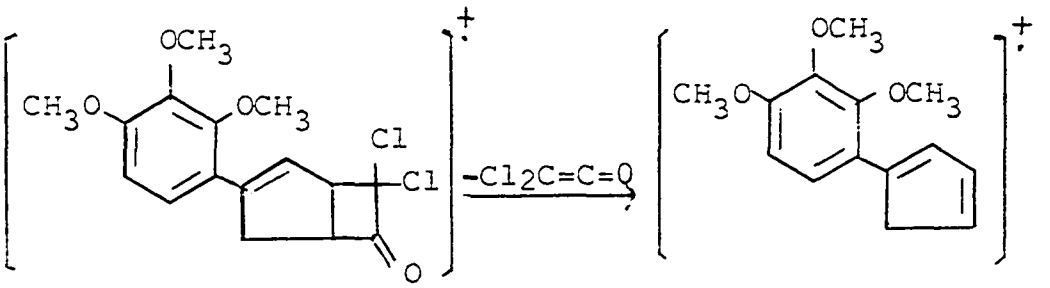
It can be seen from Figures IV and VI that all the gas chromatographic peaks are the same except the one having a retention time of 12 minutes. This peak in the chromatogram of compound 9 crude reaction mixture is sharp while that of compound 1 crude reaction mixture is broad and tailing. This indicates that the observed compound 9, which contributes to the peak at the retention time of 12 minutes shown in Figure VI, is generated from the thermal decomposition of an unknown compound in the gas chromatographic injection port.

When the mass spectrometric direct probe technique was used, where the thermal energy

transfered to the molecule from the surrounding is much reduced, the molecular ion of compound 1 at m/e 342, 344, 346 having the pattern of two chlorine atoms is observed. The relative abundances of the peaks in the mass spectra taken at different probe temperatures are shown in the table:

Probe Temperature °C	Relative abundances %		
	m/e 342	m/e 232	m/e 217
200	11	100	36
280	11	100	36
300	9.1	100	37
450	9	100	37

The consistency of the relative abundances at different probe temperatures clearly indicates that the peaks are generated from a common origin, namely the molecular ion of compound 1. The following fragmentation scheme is proposed.



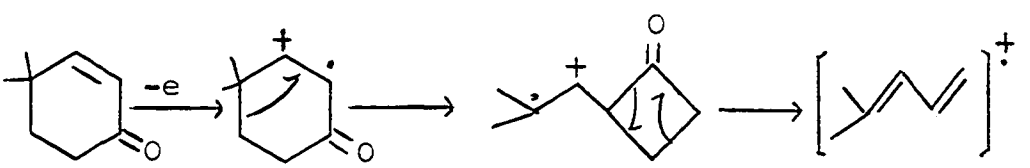
m/e 342 m/e 232

-15

$M^{+\cdot}-(Cl_2C=C=O)-(CH_3)$

m/e 217

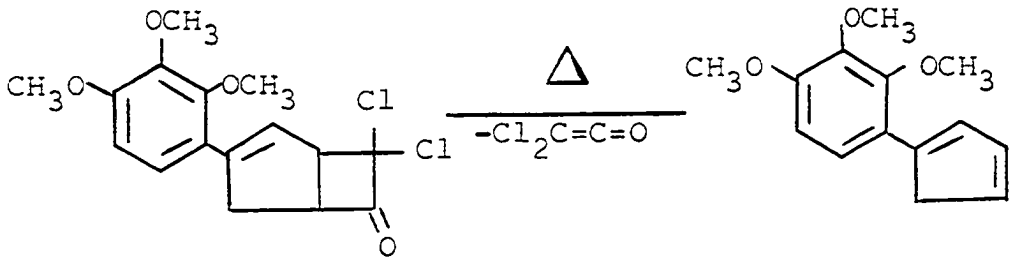
The ketene elimination from cyclic α,β-unsaturated ketones and substituted cyclobutanones is very common in mass spectrometry. Budzikiewicz, Djerassi and Williams[8] indicate the following mechanism for formation of the species observed in the mass spectrum of cyclic α,β-unsaturated ketones.



The loss of dichloroketene from the molecular ion of compound 1 is, therefore, expected.

The rest of the mass spectrum at masses below m/e 232 is very similar to that of compound 9

discussed previously. Therefore the ion at m/e 232 generated from compound 1 has the same structure as the molecular ion of compound 9. This is in agreement with the above fragmentation scheme. Because of the similarity between the two energetic processes, namely electron impact and thermolysis, the tailing peak at retention time 12 minutes in Figure VI is interpreted to be due to the following thermal decomposition of compound 1 taking place in the gas chromatographic injection port by loss of a molecule of dichloroketene.



M.W. 342 M.W. 232

The ir, nmr and mass spectra of the isolated and pure compound 1 are shown in Figures IX, X and XI, respectively.

Usually the carbonyl group of a ketone shows a strong C=O stretching vibration band in the region of 1870-1540 cm^{-1}. The C=O absorption frequency of a carbonyl group in a strained ring will shift to a high frequency as in the case of cyclobutanone, which absorbs in the region of 1775 cm^{-1}. If chlorine is in the α position to a strained carbonyl group the

absorption will shift to an even higher frequency[9]. Potts and Harmon[3] reported in 1969 that compound 16 showed an intense C=O band at 1821 cm^{-1}. Stevens et. al.[1] and Ghosez et. al.[2] published independently that the C=O absorption band of compound 12 were at 1806 cm^{-1} and 1807 cm^{-1}, respectively.

The infrared spectrum of compound 1 shows the presence of a strong C=O peak at 1808 cm^{-1} which is good evidence for the expected structure.

The absorption due to the olefinic unsaturation of compound 12 was reported at 1609 cm^{-1} and that of compound at 1608 cm^{-1} by Stevens[1] and Ghosez[2], respectively. The observation of an absorption at 1600 cm^{-1} in the infrared spectrum of compound 1 correlates very well with those from the previous studies.

The assignments for the other important peaks are 2950 cm^{-1} (asymetric stretching of CH_3 and CH_2), 1495 cm^{-1} (scissoring vibration of CH_3), 1465 cm^{-1} (asymmetric vibration of CH_3, scissoring vibration of CH_2), 1416 cm^{-1} (olefinic C-H bending vibration), 1110 cm^{-1} (asymmetrical C-O-C strentching vibration). The above infrared observations confirm the structure of compound 1.

Stevens[1] also reported that the nmr spectrum of

compound 12 exhibited a complex multiplet centered at δ 5.90 which was interpreted as due to the olefinic protons. Ghosez[2] also observed the multiplet centered at δ 5.93, and he reported two complex multiplets at δ 4.43-3.88 and δ 2.83-2.52 which were thought to be due to bridgehead tertiary protons and the two allylic methylene protons, respectively. In the present case, the nmr spectrum of compound 1 contains a multiplet at δ 6.25, a complex multiplet centered at δ 4.20 and a broad complex multiplet at δ 3.20-2.90 indicating the presence of one vinyl proton, two bridgehead tertiary protons and two allylic protons. Also the AB quartet, centered at δ 6.55 and δ 6.90 (J=9 cps), and a singlet at δ 3.80 were found. The relative peak area ratios of the above absorptions confirm the presence of two ring protons and nine methyl protons.

The mass spectrum also provides a strong evidence for the structure of compound 1. This spectrum has been discussed previously.

CHAPTER V

SPECTRAL DATA

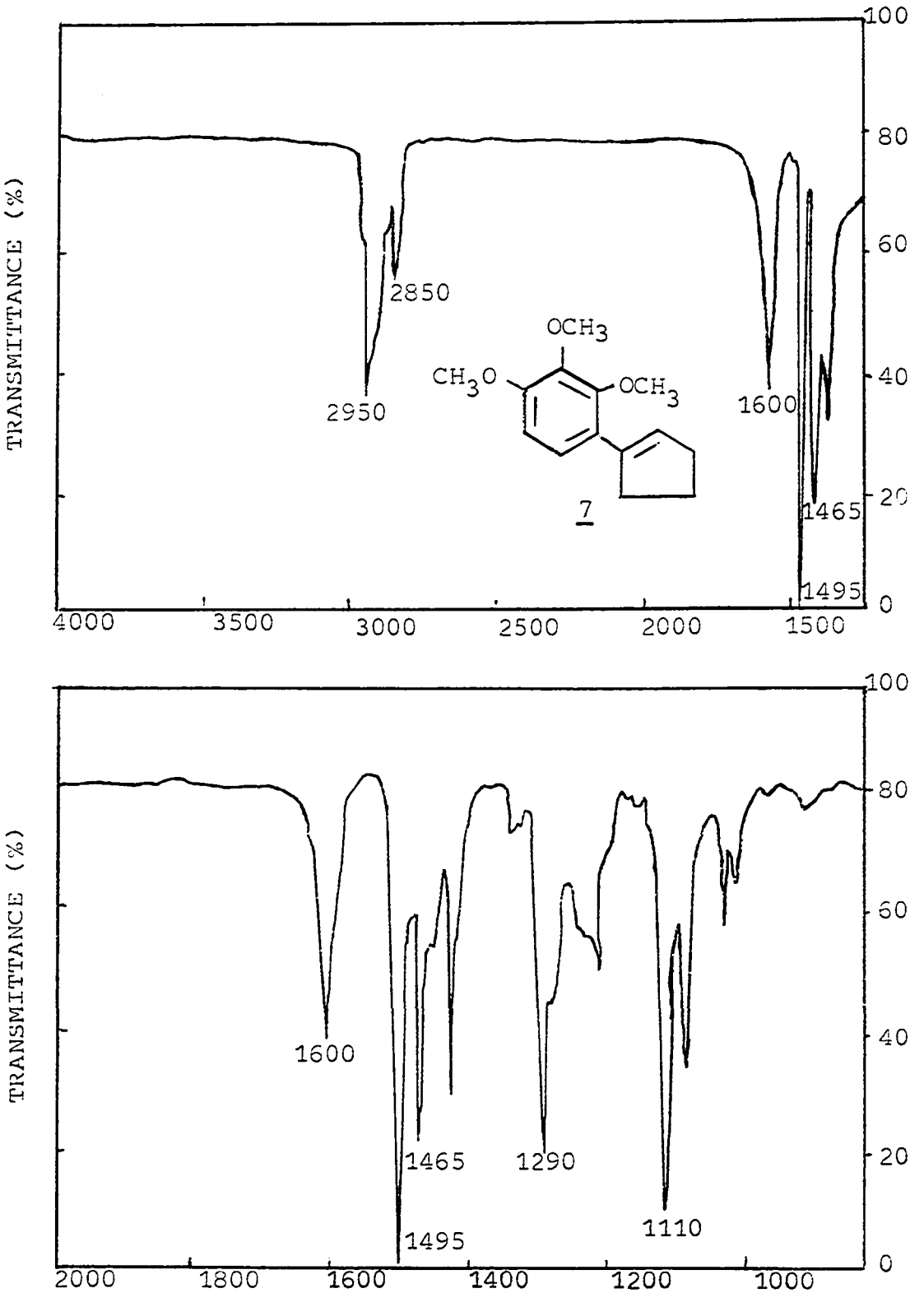


Figure I. Infrared spectrum of 7

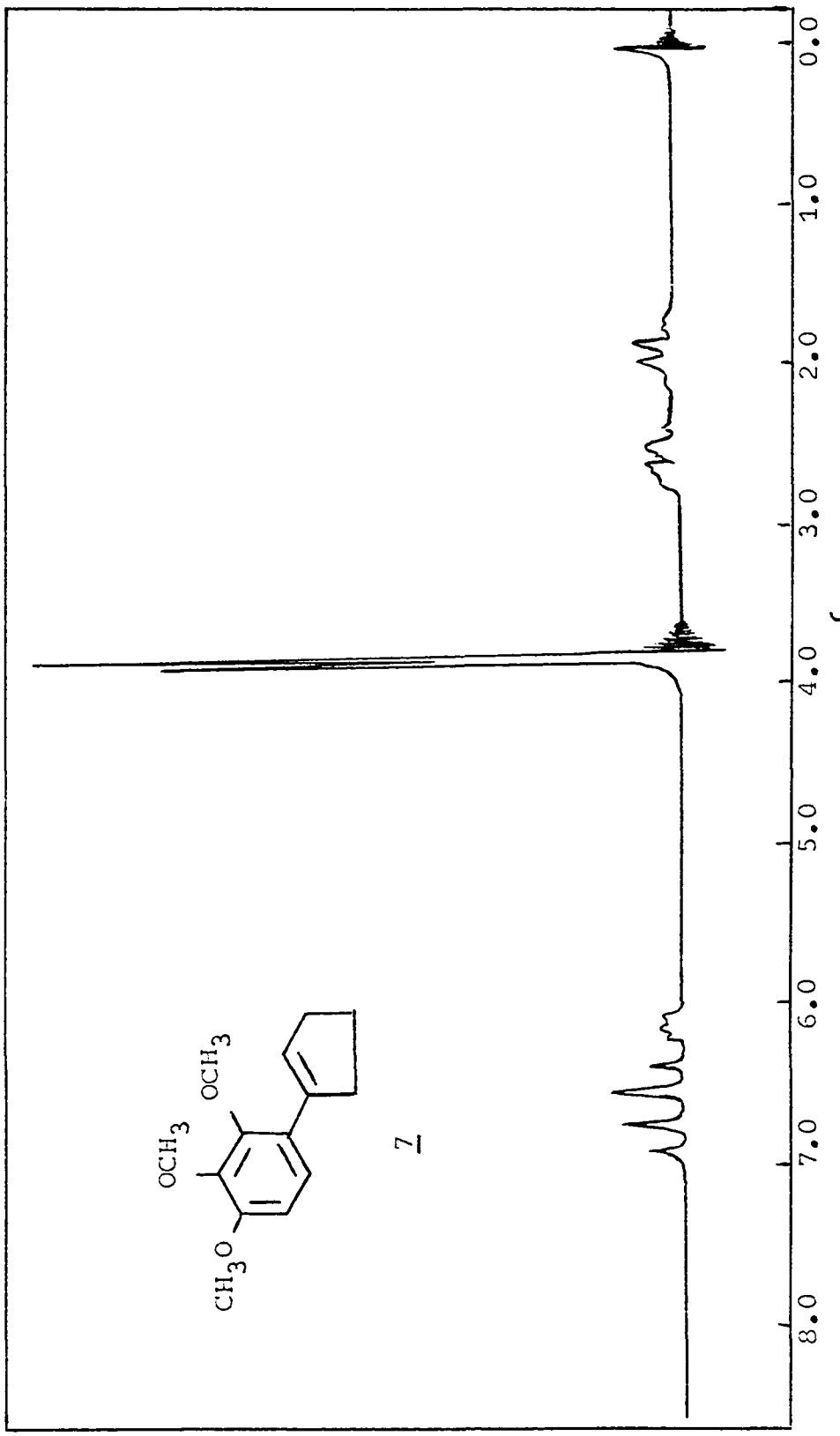


Figure II. Nmr spectrum of 7

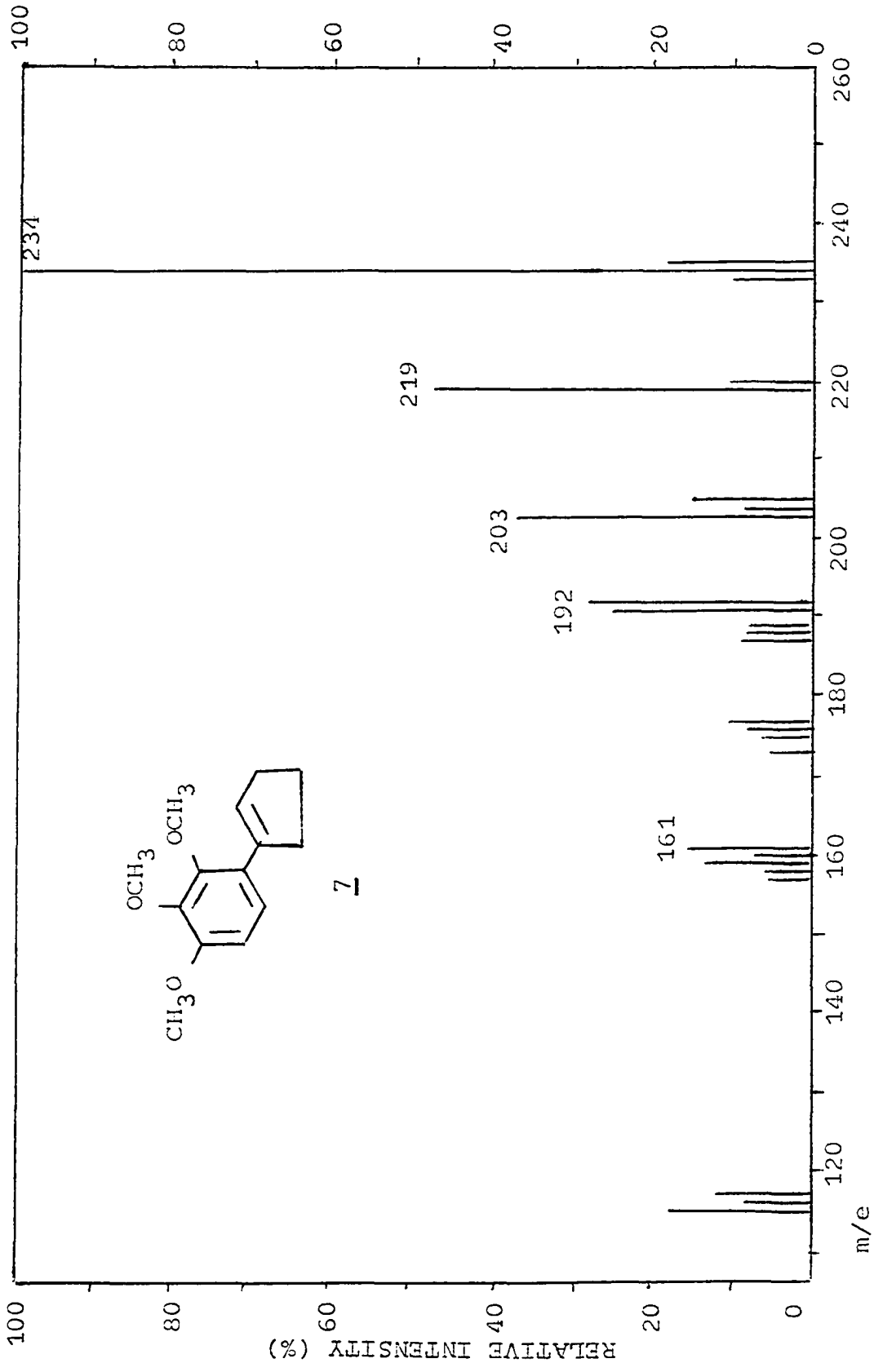


Figure III. Mass spectrum of 7

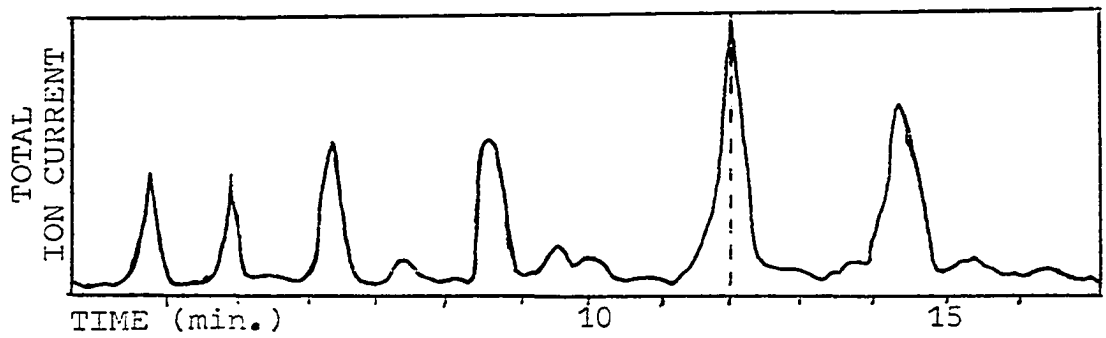


Figure IV. Total ion chromatogram of crude compound 9

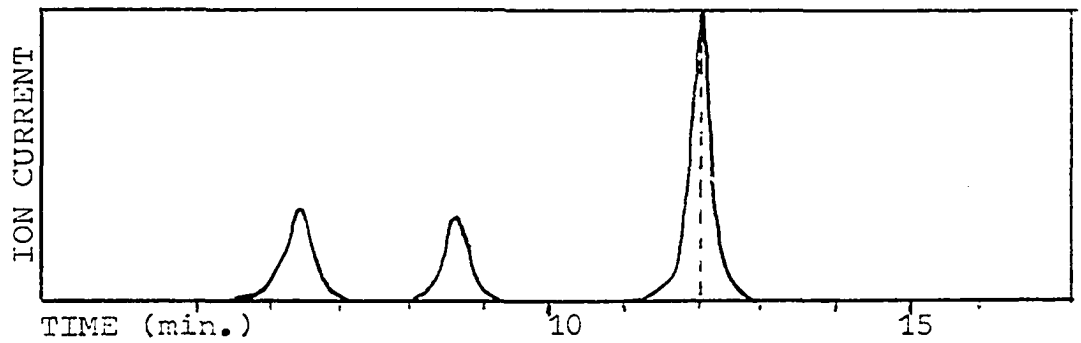


Figure V. Mass fragmentogram of m/e 232 from crude compound 9

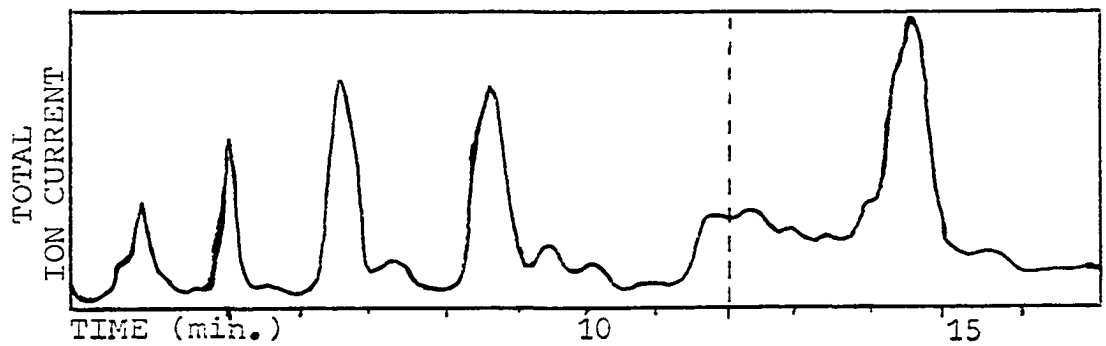


Figure VI. Total ion chromatogram of crude compound 1

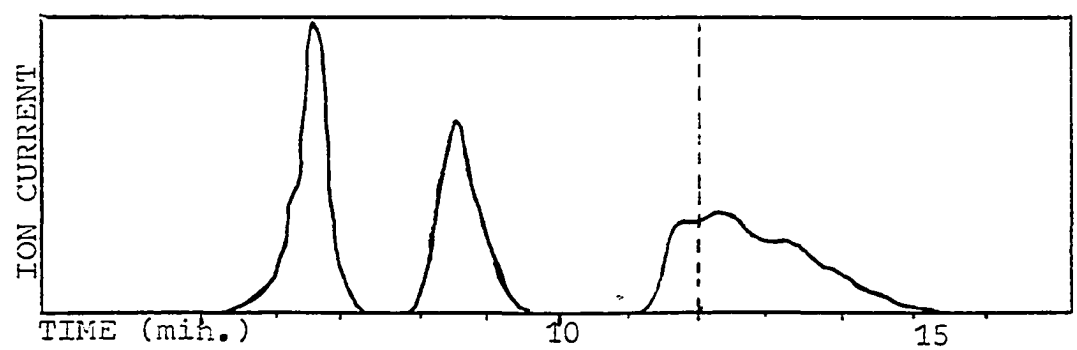


Figure VII. Mass fragmentogram of m/e 232 from crude compound 1

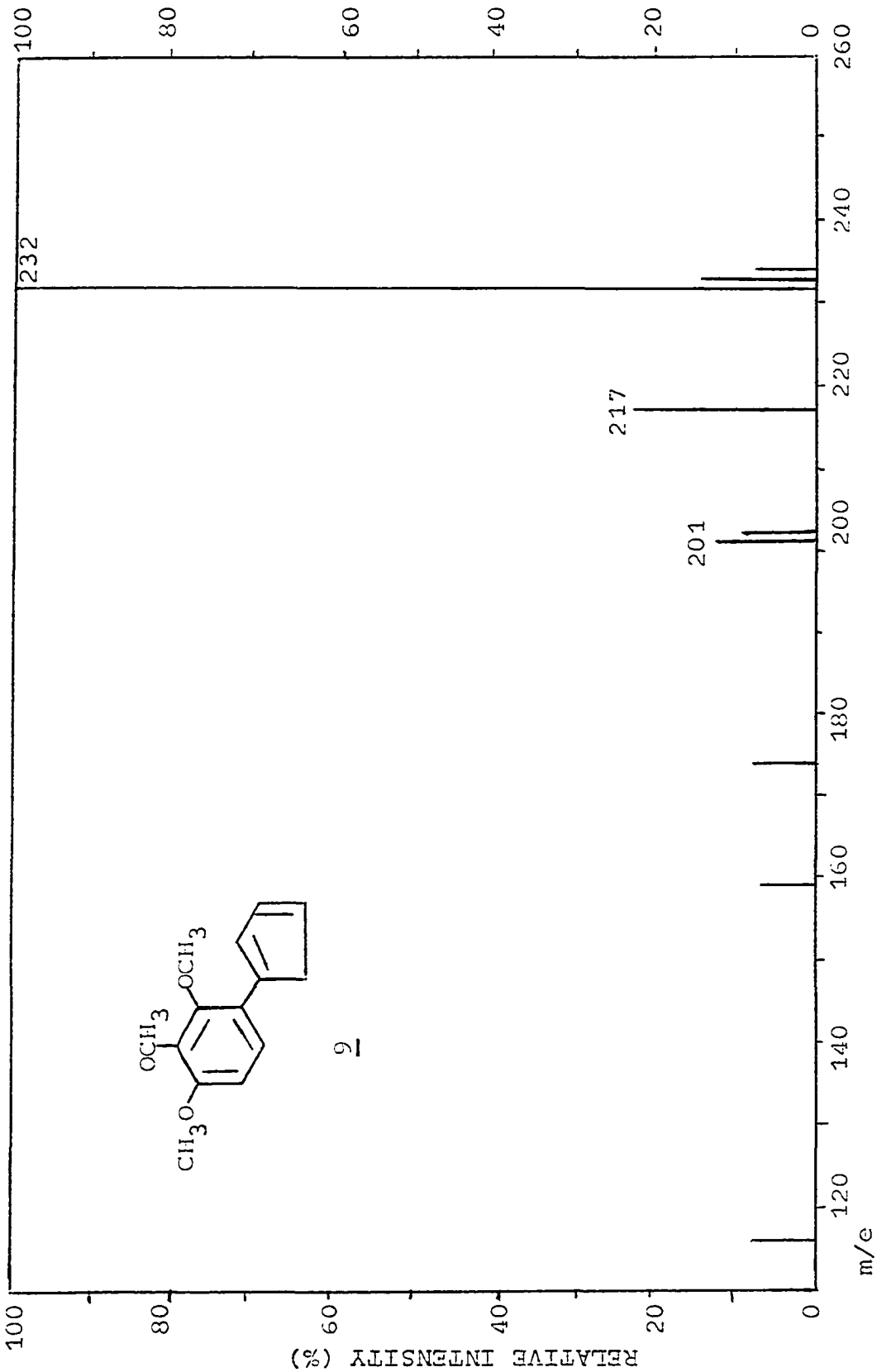


Figure VIII. Mass spectrum of 9

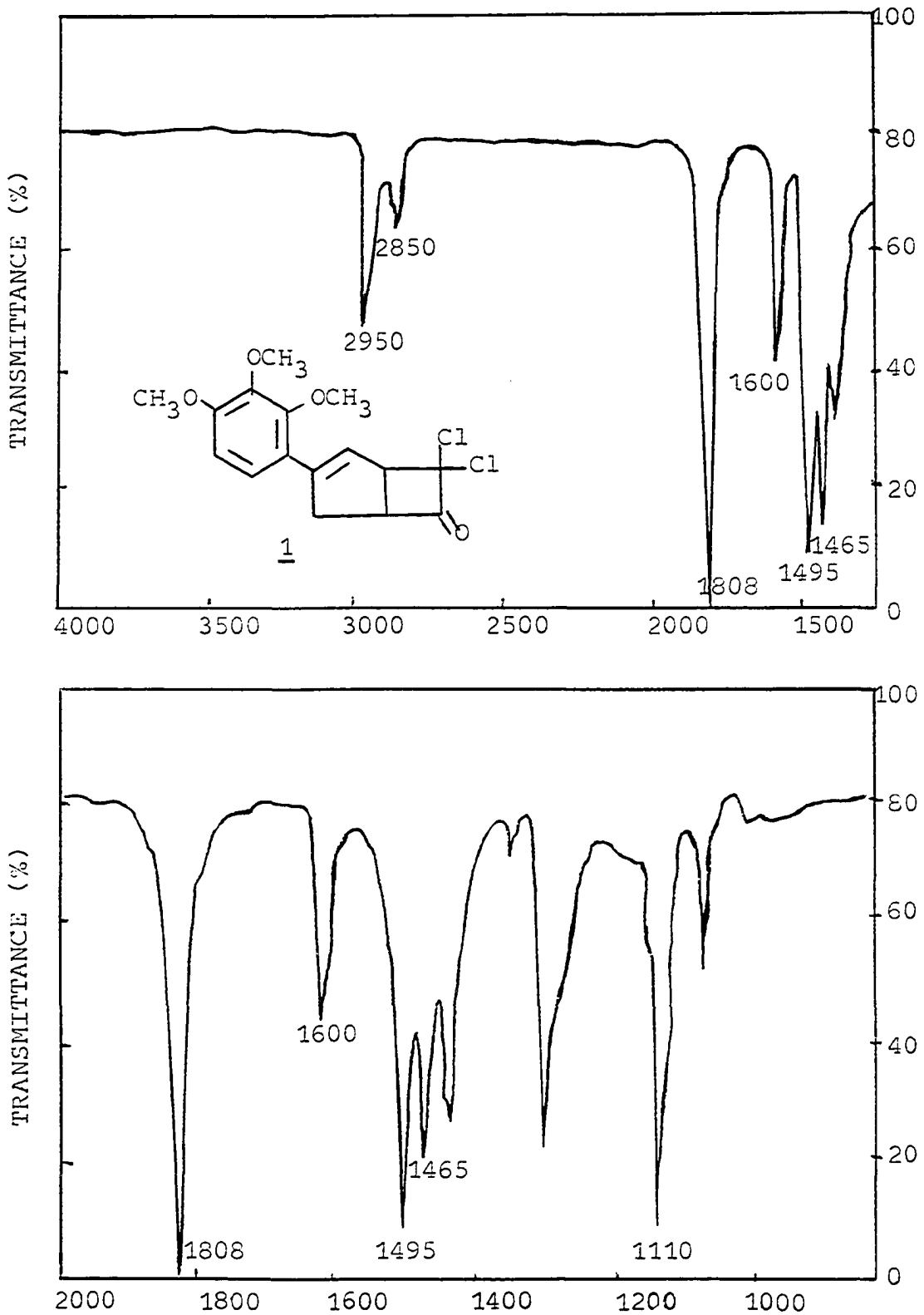


Figure IX. Infrared spectrum of 1

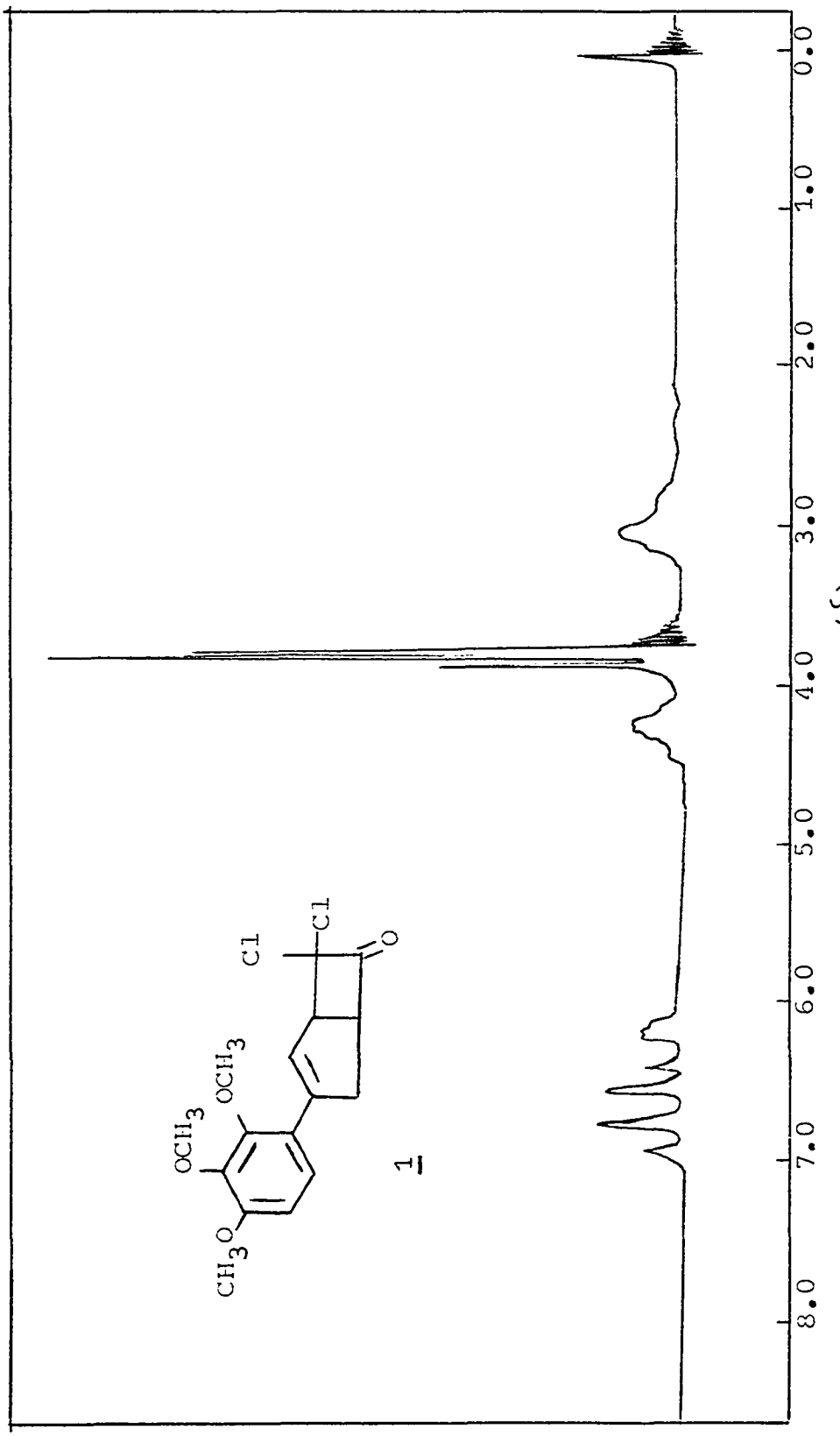


Figure X. Nmr spectrum of 1

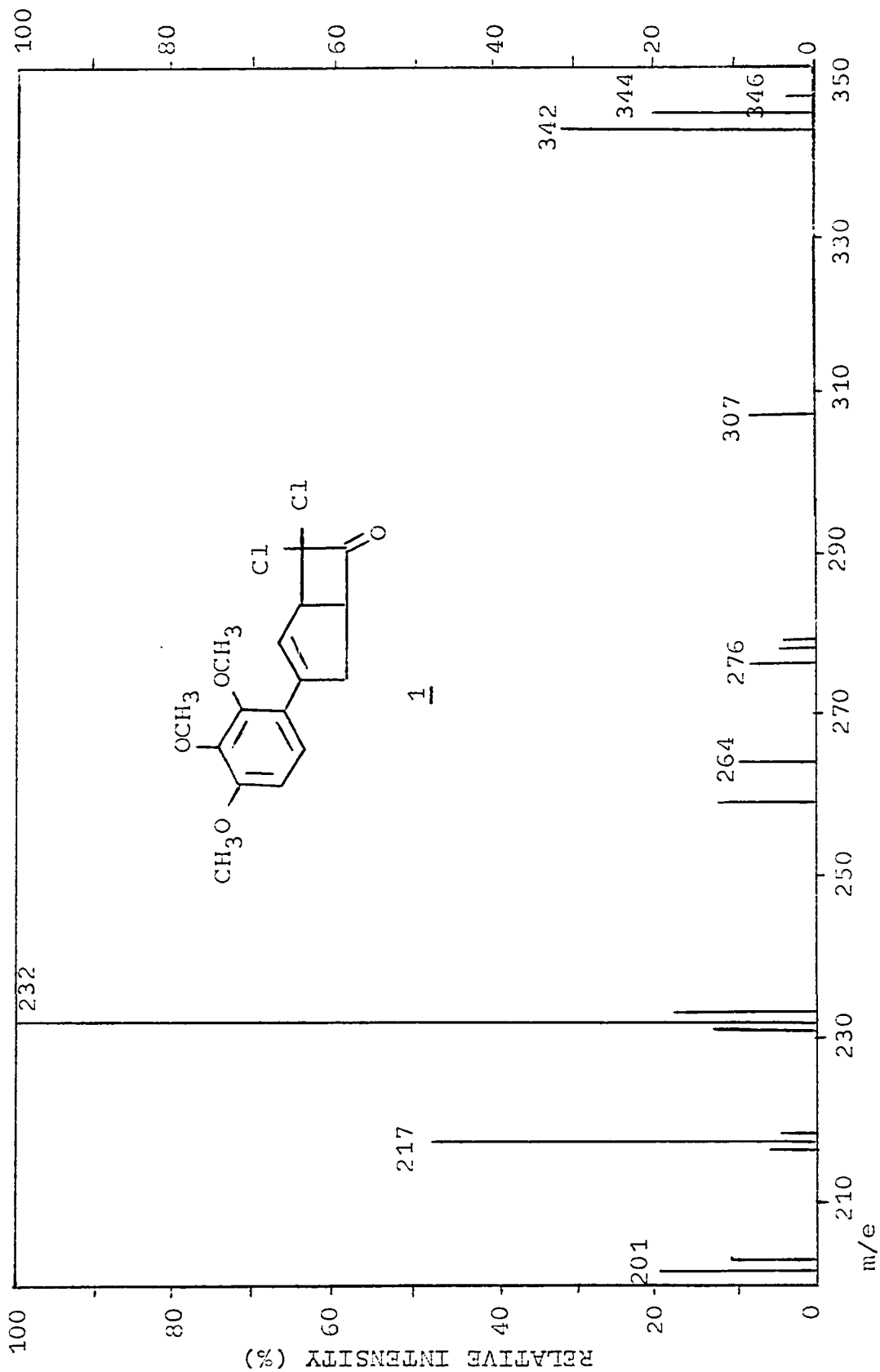


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Figure XI. Mass spectrum of 1

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