PART I
THE SYNTHESIS OF 2,5-DIOXO-CYCLOPENTANEPROPIONIC ACID
PART II
THE SYNTHESIS AND PHOTOREARRANGEMENT OF TWO β,γ-ENONES

Dissertation for the Degree of Ph. D.
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JEFFREY EARL TELSCHOW
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This is to certify that the

thesis entitled

I--The Synthesis of 2,5-Dioxo-cyclopentanepropionic Acid

II--The Synthesis and Photorearrangement of Two β,γ-Enones

presented by

Jeffrey Earl Telschow

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

William H Reusch

Major professor

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ABSTRACT

PART I

THE SYNTHESIS OF 2,5-DIOXO-CYCLOPENTANE-PROPIONIC ACID

PART II

THE SYNTHESIS AND PHOTOREARRANGEMENT OF TWO β,γ-ENONES

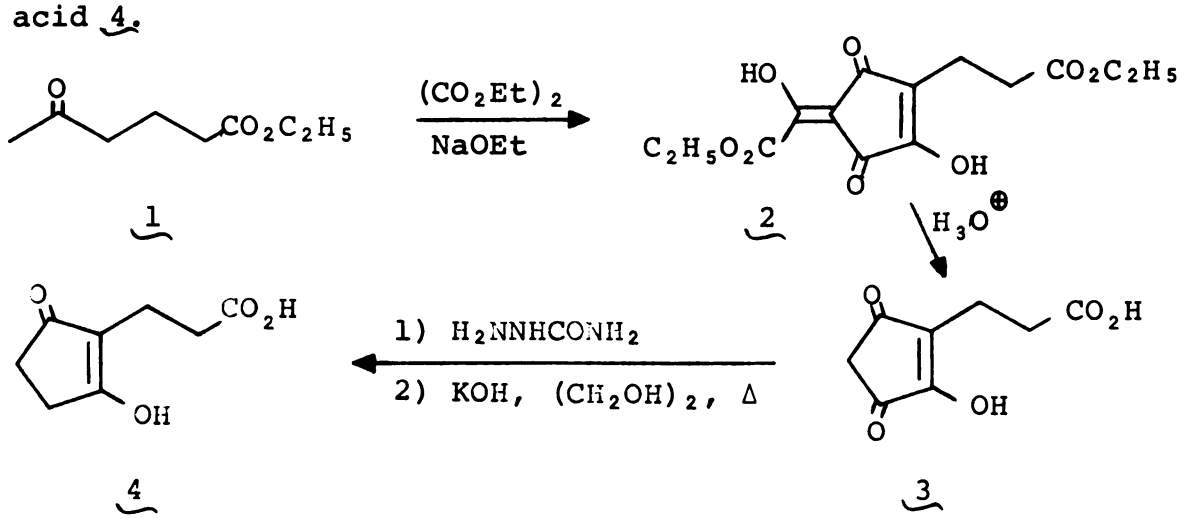
By

Jeffrey Earl Telschow

PART I

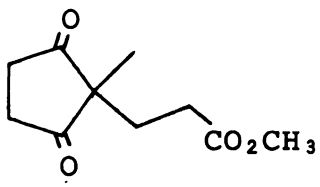
The title compound, 4, was desired as an intermediate in a proposed total synthesis of the alkaloid cephalotaxine. The successful synthesis of 4, via the cyclopentane-1,2,4-trione 3, and two unsuccessful approaches to 4 are described.

Base catalyzed condensation of diethyl oxalate and ethyl 5-oxo-hexanoate (1) yielded the ethoxalyl trione 2, which on hydrolysis gave 3. Wolff-Kishner reduction of the 1-semicarbazone of this trione yielded the desired dione acid 4.



1 2 3 4

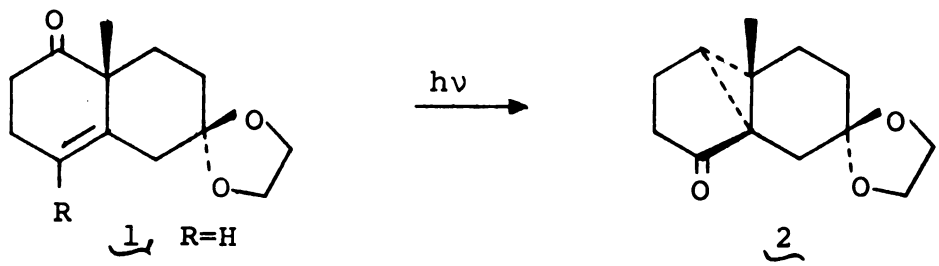
The structure of 4 was proven by methylation to give the known dione ester 5, which was independently synthesized from 2-methylcyclopentane-1,3-dione and methyl acrylate.



5

PART II

Initially, a new synthesis of the sesquiterpene bulnesol was to be developed, using as a key step the anticipated photorearrangement of β,γ-enone 1, R = H to its tricyclic isomer 2. This proposed 1,2-acyl shift failed to occur on photolysis of 1.

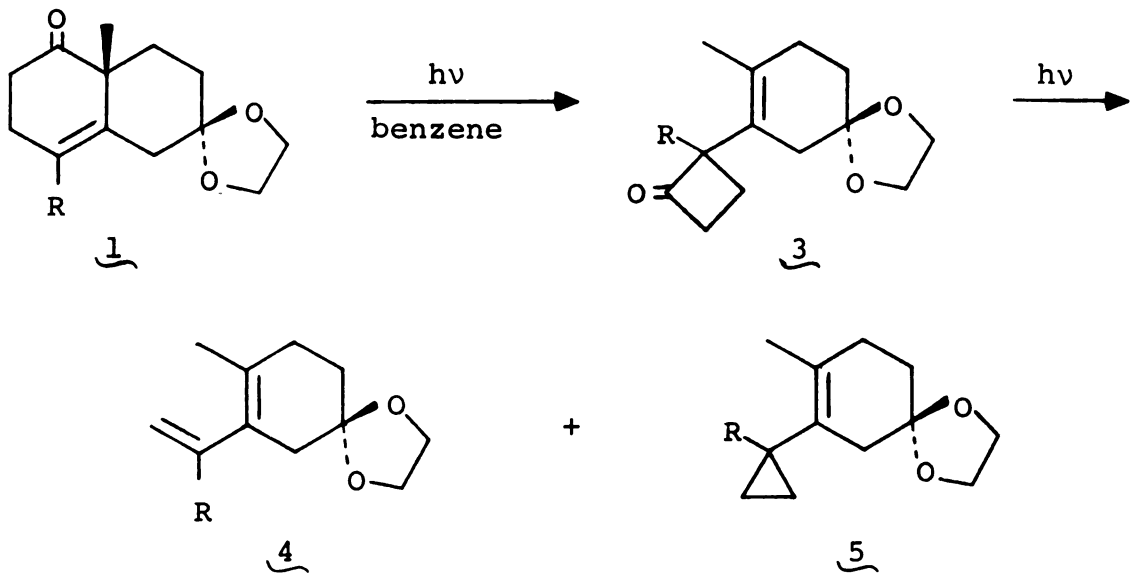


1, R=H 2

Because the photochemical consequences of minor structural changes in β,γ-enones are not well understood, the photochemistry of enone 1, R = CH_3 was investigated and compared to that of the unmethylated compound.

Direct photolysis of 1, R = H or CH_3 produced (via a 1,3-acyl shift) the cyclobutanone 3, which subsequently

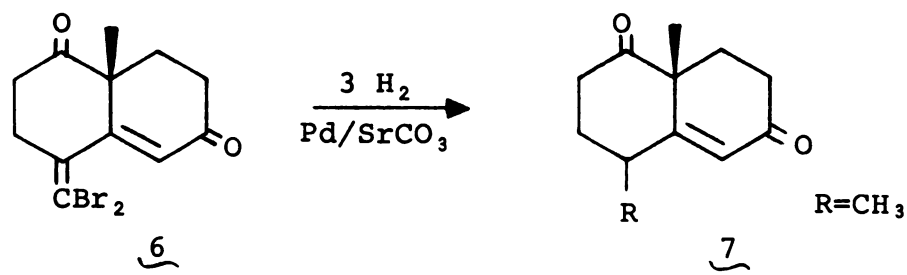
underwent photodecomposition to a diene 4 and a cyclopropane 5. In the case of R = CH_3, a substantial amount of



nonvolatile material was also produced.

Acetone sensitized irradiation of 1, R = H produced no new volatile products, but with R = CH_3, six or seven unidentified components were formed in addition to the usual photoproducts.

The synthesis of 1, R = H or CH_3 was achieved by selective ketalization of enedione 7 which, for R = CH_3, was prepared by hydrogenation of the dibromomethylene derivative 6.



PART I

THE SYNTHESIS OF 2,5-DIOXO-CYCLOPENTANE-PROPIONIC ACID

PART II

THE SYNTHESIS AND PHOTOREARRANGEMENT OF TWO β,γ-ENONES

By

Jeffrey Earl Telschow

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TABLE OF CONTENTS

TABLE OF CONTENTS--Continued

LIST OF FIGURES AND CHARTS

FIGURE Page

PART I

LIST OF FIGURES AND CHARTS--Continued

FIGURE Page

PART II

LIST OF FIGURES AND CHARTS--Continued

FIGURE Page

LIST OF FIGURES AND CHARTS--Continued

LIST OF FIGURES AND CHARTS--Continued

FIGURE

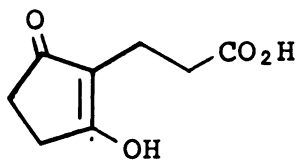
CHART

PART I

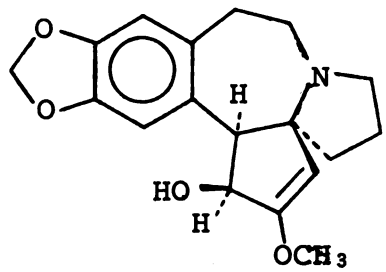
THE SYNTHESIS OF 2,5-DIOXO-CYCLOPENTANEPROPIONIC ACID

INTRODUCTION

The title compound 1 was desired as an intermediate in a projected total synthesis of the alkaloid cephalotaxine 2, natural esters of which possess potent antileukemic properties.[1]

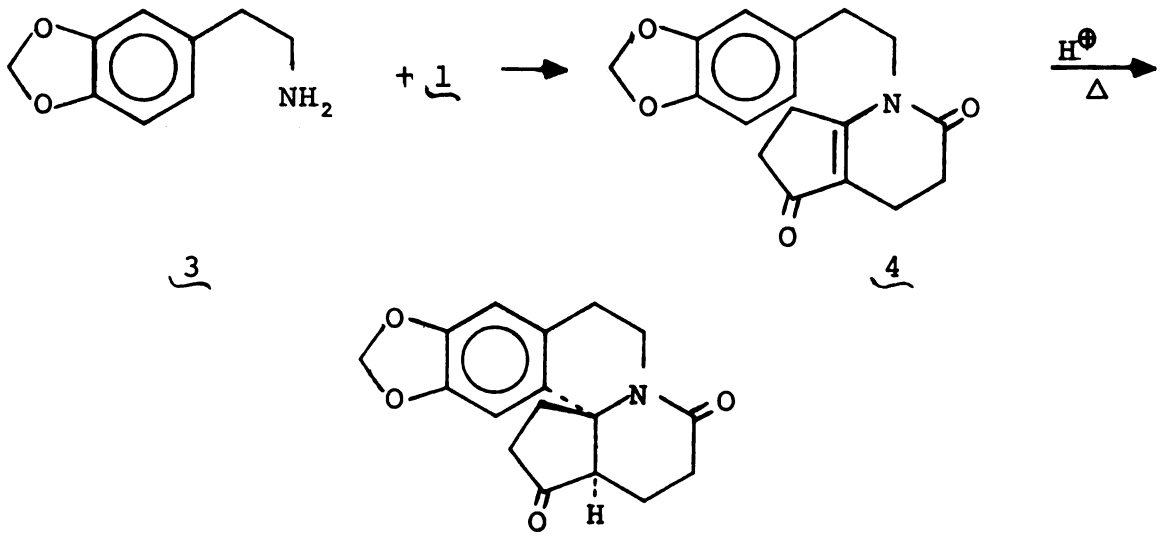


1



2

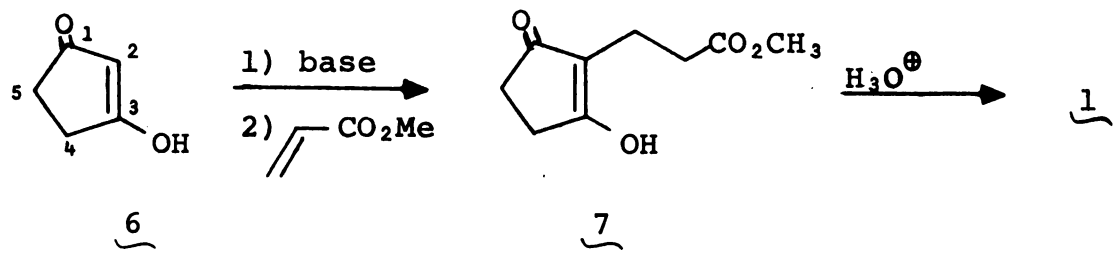
The proposed initial reactions using dione 1 are outlined below and are based on Mondon's work with a structurally analogous system in the synthesis of Erythrina alkaloids.[2] In the second stage of this study, the possibility of effecting rearrangement of the ring system in 5 to the cephalotaxine skeleton was to be explored.



3 4 5

Since cyclopentane-1,3-diones are relatively rare in contrast to the cyclohexane-1,3-diones, a brief discussion of some of the synthetic routes to the former compounds is desirable.

The synthesis of 2-substituted cyclopentane-1,3-diones could be achieved by alkylating the parent β-diketone 6, an approach that appears to be well suited for the preparation of 1. Michael addition of the enolate of 6 to methyl acrylate, for example, should give the desired product after hydrolysis of 7.

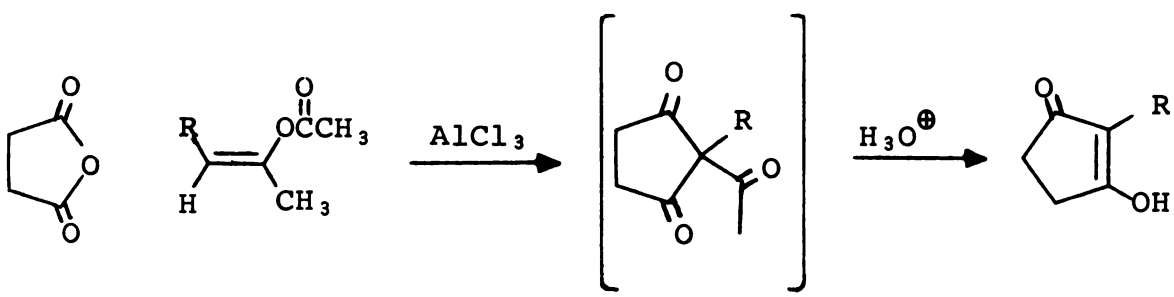


6 7

The drawback of this synthetic strategy is that the unsubstituted compound 6 is not readily available, and its syntheses suffer from a combination of many steps, difficult workup conditions, and low yields. A better route to alkylated cyclopentane-1,3-diones would incorporate all necessary carbon atoms at once.

There are two important condensation reactions which lead to 2-substituted cyclopentane-1,3-diones. The simpler method involves a reaction between succinic anhydride and an enol ester as illustrated in Scheme 1. The intermediate acetyl compound 10 can be isolated if R = H.[3]

Scheme 1



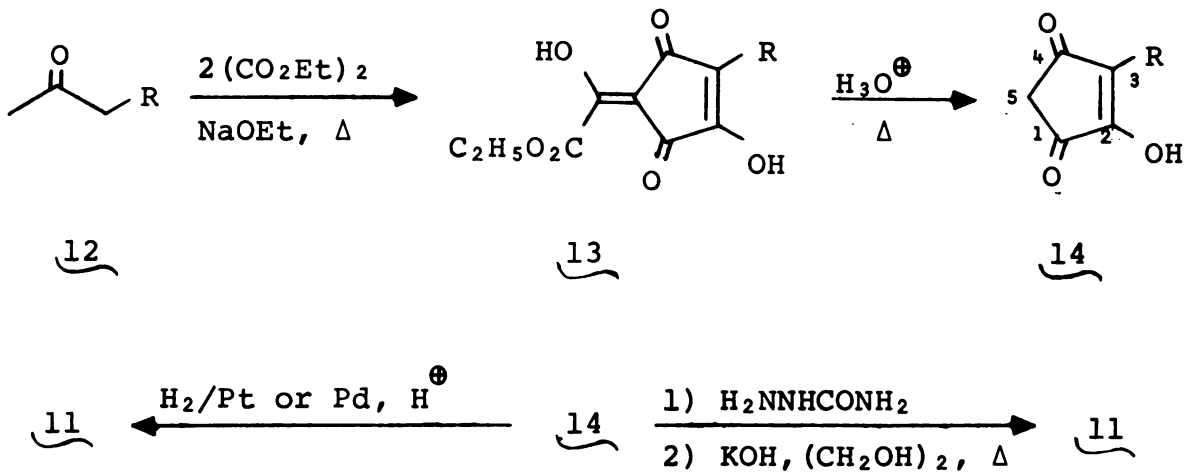
8 9 10 11

Although this condensation is direct and gives good yields when R = CH_3,[4] it has not been used for more complex R groups.

The other important route to 11 requires several steps (see Scheme 2) but is a well established pathway. A methyl ketone 12 is allowed to react with diethyl oxalate, and the

resulting tetraketo-ester 13 is de-ethoxalylated to a cyclopentane-1,2,4-trione 14. The 1-carbonyl function can be removed by Wolff-Kishner reduction of the corresponding semicarbazone[5] or by catalytic hydrogenolysis.[6]

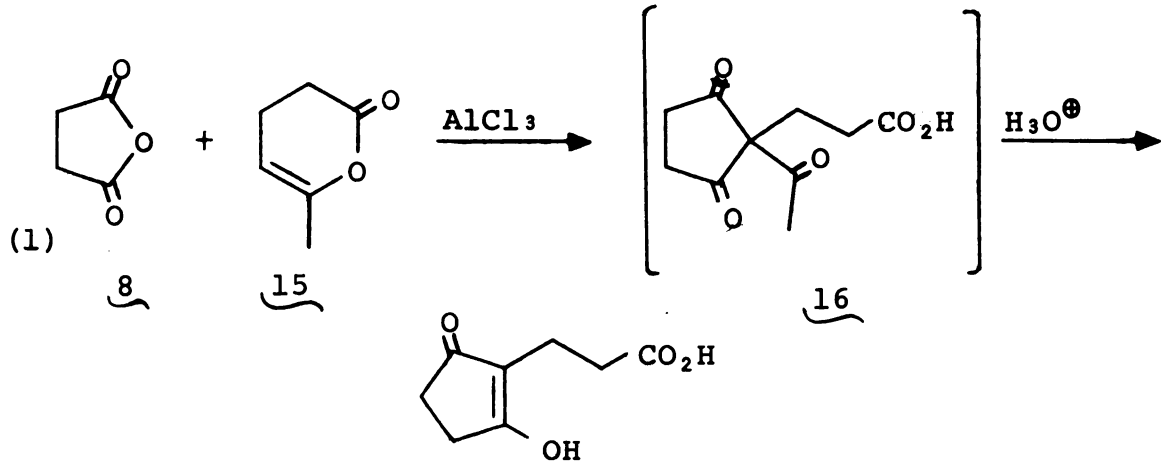
Scheme 2



The good to excellent yields in these reactions and the great synthetic versatility of the triones 14 in making a variety of substituted cyclopentanes makes the route in Scheme 2 particularly attractive. The synthesis of 1 was achieved using this general procedure.

RESULTS AND DISCUSSION

The first attempt to synthesize 2,5-dioxo-cyclopentane-propionic acid 1 used a modification of the route outlined in Scheme 1. Since an enol ester is required for this reaction, and since 1 contains a carboxyl group, the enol lactone 15 seemed to be a logical choice for the proposed condensation (equation 1).



(1)

8 15 16 1

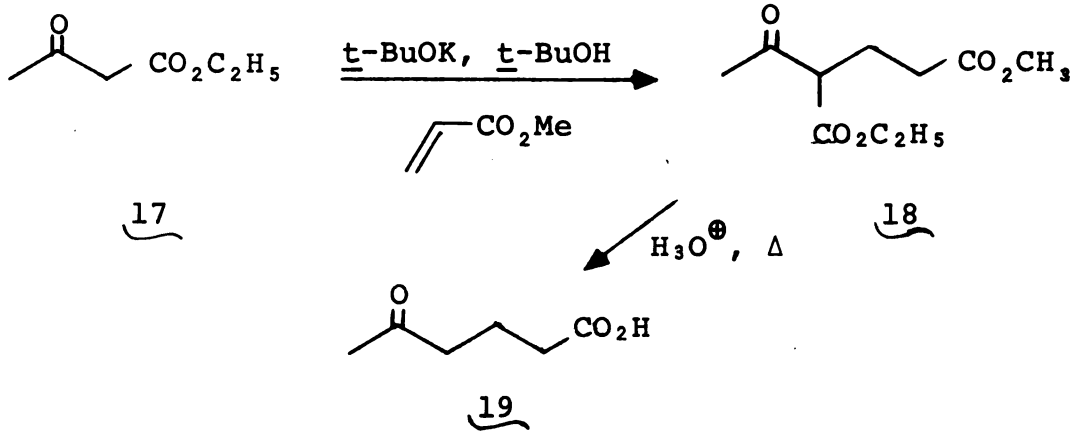
When 15 was subjected to reaction conditions analogous to those used in successful condensations of this type,[3,4] 1 could not be isolated from the many products produced. Therefore this approach was abandoned.

The dione acid 11, R = $(CH_2)_6CO_2H$ had been prepared previously by Collins et al.[6c] by the route outlined in Scheme 2, starting with 12, R = $(CH_2)_7CO_2H$. The 1-carbonyl

group of 14 was removed via catalytic hydrogenation (palladium on carbon) in an acetic acid solution containing sulfuric acid. The similarity between 11, R = $(CH_2)_6CO_2H$ and 1 suggested that the latter compound could be synthesized from 5-oxo-hexanoic acid 19, using Collins' methods.

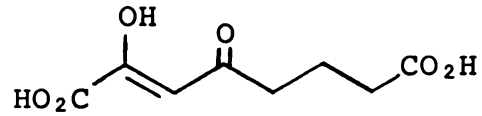
Compound 19 was prepared by a Michael addition of ethyl acetoacetate 17 to methyl acrylate, followed by hydrolysis and decarboxylation of 18[7,8] (equation 2).

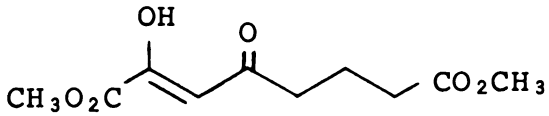
(2)



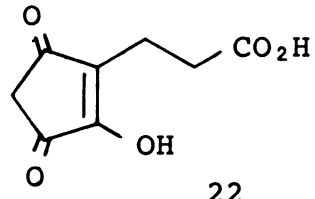
17 18 19

In an attempt to produce intermediate 22 directly, 19 was allowed to react with diethyl oxalate in the presence of potassium t-butoxide. Hydrolysis of the resulting crude mixture gave a small amount of diacid 20 as the only isolated product (equation 3). Cyclization to the desired product, 22, may have been prevented by the heterogeneity of the reaction medium in the first step.

(3) 19 —1) t-BuOK, $(CO_2Et)_2$ / 2) 2.5 N HCl, Δ→  20



21



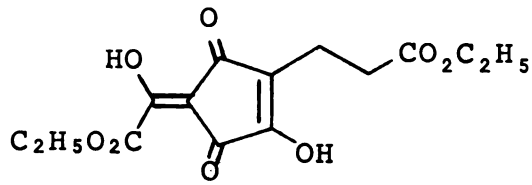
22

The dimethyl ester 21, formed by diazomethane treatment of 20, was more easily purified and characterized than the diacid. The fact that 21 shows the same nmr pattern as 19 for the three methylene groups in the chain indicates that 21 is still acyclic. The uv spectrum of 21 (λ_{max}^{acid} 284 nm, ε 7.7 x 10^3, λ_{max}^{base} 320 nm, ε 1.3 x 10^4) is consistent with the spectra of other 2,4-dioxo esters.[9]

The solubility problem associated with the use of 19 was overcome by using its ethyl ester 23 in the condensation reaction with diethyl oxalate. A good yield of the ethoxalyl-cyclopentane-1,2,4-trione intermediate 24 was obtained when sodium ethoxide was used as the base (equation 4).

(4)

23

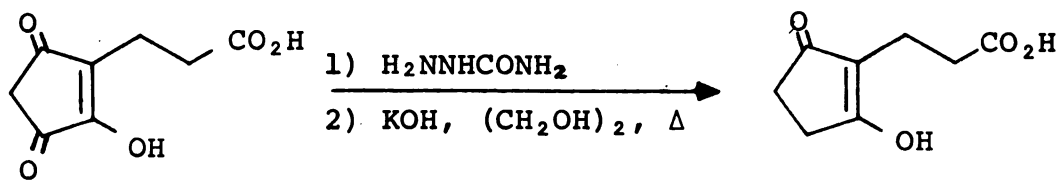


24

The spectral data for 24 agree with those expected for compounds of this type.[6c,10] The nmr is noteworthy, since the two methylene groups of the propionic acid side chain have, by chance, the same chemical shift and appear as a singlet at δ2.64.

Hydrolysis of 24 with hydrochloric acid gave 22, as expected. The remaining requirement for conversion to 1 was removal of the 1-keto function, but Collins' method of catalytic reduction failed when applied to 22 (no reaction occurred). However, Wolff-Kishner reduction of the semicarbazone derivative of 22 gave the desired dione acid 1 (equation 5).

(5)

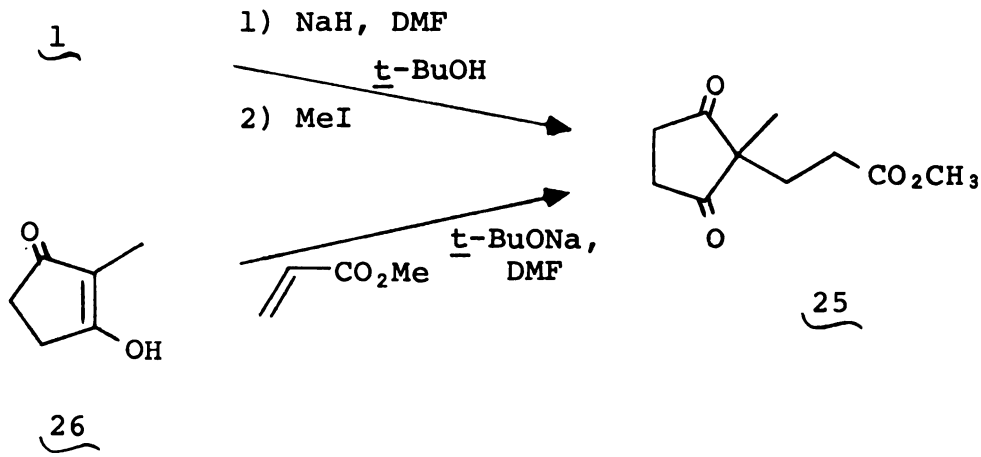


22 1

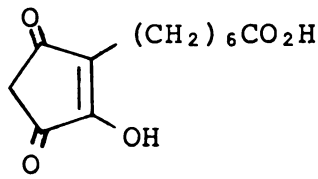
A remarkable feature of 1 is its unusually simple nmr spectrum. In d_6 acetone all eight methylene hydrogens appear as a singlet at δ2.42. In d_6 dimethyl sulfoxide the two sets of adjacent methylene groups occur as two equally intense singlets at δ2.31 and δ2.40. In neither spectrum was a signal corresponding to the enolic and carboxylic hydrogens detected.

Although the other spectral data were consistent with the assigned structure of 1, its peculiar nmr behavior prompted a chemical structure proof. Methylation of 1 gave the known dione ester 25, which was independently synthesized from commercially available 2-methylcyclopentane-1,3-dione 26 (equation 6). The nmr and ir spectra of 25 produced by the two pathways were superimposable, thus verifying the structure of 1.

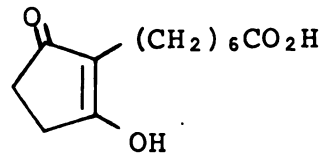
(6)



Because both 27 and 28 have previously been used for the synthesis of natural prostaglandins,[6c,10,11,12] compounds 1 and 22 should also be useful synthons for prostaglandin analogs. Furthermore, the discovery that several cyclopentanepropionic acid derivatives are metabolites of the natural prostaglandins E_2 and $F_{2\alpha}$[13,14,15] suggests that 1 and 22 would also be of interest as snythetic precursors of such metabolites.



27



28

EXPERIMENTAL

General

Infrared spectra were recorded on a Perkin-Elmer 237B spectrophotometer. Nuclear magnetic resonance spectra were taken on a Varian T-60 spectrometer, using tetramethylsilane as an internal standard. Ultraviolet spectra were recorded on a Unicam SP-800 spectrophotometer. A Hitachi RMU-6 mass spectrometer was used to obtain the mass spectra.

Melting points were taken on a Reichert hot stage microscope and are uncorrected.

Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee, or by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

All reactions were magnetically stirred and run under an inert atmosphere of nitrogen or argon. Organic extracts were dried over anhydrous sodium sulfate, and solvents were evaporated under reduced pressure unless otherwise indicated. Craig tubes were used for recrystallization in most cases.

All spectral data are described in this section except the mass spectra which appear in the Appendix only.

5-Oxo-hexanoic acid (19)[7,8]

To a solution of potassium t-butoxide, prepared from 0.3 g of potassium and 50 ml of dry t-butanol, was added 65.0 g (0.50 mol) of ethyl acetoacetate. Slow addition of 44.8 g (0.52 mol) of methyl acrylate to this solution was effected with rapid stirring and intermittent cooling to maintain the temperature at about 25°. This reaction mixture was stirred overnight at room temperature, acidified with 0.45 ml of acetic acid, and stripped of solvent. A chloroform solution of the residue was washed with water and brine and, after concentration of the dried extracts, the residue was distilled at 87°/1 mm, yielding 82.9 g (77%) of methyl 4-carbethoxy-5-oxo-hexanoate 18. This compound was hydrolyzed without further characterization by refluxing it for four hours in a solution containing 150 ml of concentrated hydrochloric acid and 100 ml of water. After evaporation of the solvent, the residue was dissolved in methylene chloride, and the resulting solution was washed twice with brine and evaporated. Distillation of this crude product (bp 95°/0.15 mm) gave 46.0 g (92.5%) of colorless 5-oxo-hexanoic acid 19.

On standing in moist air 19 formed a colorless hydrate, mp 32-35° (lit[16] mp 34-36°).

Anhydrous 19 showed nmr absorption (CCl_4) at δ1.82 (m, 2H, C-3 CH_2), 2.06 (s, 3H, $COCH_3$), 2.38 (m, 4H, C-2, C-4 methylene protons), 10.94 (s, 1H, CO_2H).

Ethyl 5-oxo-hexanoate (23)[7]

A solution consisting of 10.4 g (0.08 mol) of 19, 200 mg of p-toluenesulfonic acid, 25 ml of absolute ethanol, and 10 ml of benzene was refluxed for three hours through a Dean Stark trap. At 20 min intervals, 5 to 10 ml of distillate was drawn off from the trap. Finally the solvent was allowed to distill, leaving about 20 ml of concentrate which was diluted with methylene chloride, washed once with 10% sodium bicarbonate and twice with brine. Evaporation of all solvents left 11.2 g (88%) of colorless 23 which was pure enough to use in subsequent reactions.

Ester 23 showed nmr absorption (CCl_4) at δ1.20 (t, 3H, J 7Hz, $CH_2\underline{CH_3}$), 1.82 (m, 2H, C-3 $\underline{CH_2}$), 2.03 (s, 3H, $CO\underline{CH_3}$), 2.30 (m, 4H, C-2, C-4, methylene protons), 3.97 (q, 2H, J 7Hz, $\underline{CH_2}CH_3$).

2,4-Dioxo-octanedioic acid (20)

To a refluxing, mechanically stirred suspension of potassium t-butoxide, prepared by dissolving 13.5 g (0.345 g atom) of potassium in 200 ml of dry t-butanol, was added a solution of 13.0 g (0.10 mol) of keto acid 19 in 32.0 g (0.22 mol) of freshly distilled diethyl oxalate. After refluxing 3.5 hours, the thick orange mixture was acidified with 30 ml of concentrated hydrochloric acid, and the precipitated potassium chloride was filtered and washed with

chloroform. Evaporation of the filtrate left a brown oil, which was refluxed with 50 ml of 2.5 N hydrochloric acid for 90 min. The brown solution was concentrated, and the resulting solid was filtered, washed with water and ethyl acetate, and air dried to give 4.7 g (4.3%) of light brown diacid 20.

Compound 20 was very difficult to purify (recrystallization from acetone gave mp 155-175°, dec) and hence was characterized as its dimethyl ester 21.

Dimethyl 2,4-dioxo-octanedioate (21)

A solution of 184 mg of crude 20 in 2 ml of methanol was treated with an excess of ethereal diazomethane. After evaporation of the solvents the resulting yellow solid was recrystallized several times from ether to give white crystals: mp 66-67°; ir (KBr) 1725, 1635, 1600 cm^{-1}; nmr ($CDCl_3$) δ1.97 (m, 2H, C-6 $C\underline{H}_2$), 2.43 (m, 4H, C-5, C-7 methylene protons), 3.60 (s, 3H, $CH_2CO_2C\underline{H}_3$), 3.82 (s, 3H $=C(HO)-CO_2C\underline{H}_3$), 6.25 (s, 1H, vinylic proton), 13.65 (brd s, 1H, enolic proton)

Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13.
Found : C, 52.09; H, 6.13.

Ethyl 4-ethoxalyl-2,3,5-trioxo-cyclopentanepropionate (24)

To a chilled (0°) sodium ethoxide solution, prepared from 2.80 g (0.122 g atom) of sodium and 50 ml of absolute

ethanol, was added a solution of 8.70 g (0.055 mol) of keto ester 23 in 23.6 g (0.162 mol) of diethyl oxalate. The resulting solution was stirred at room temperature for 30 minutes, refluxed for 30 minutes, and then acidified with 9.6 ml of concentrated hydrochloric acid. The precipitated sodium chloride was filtered and washed with ethanol, and the filtrate was concentrated. Crystallization of a carbon tetrachloride solution of the residue gave 9.6 g of yellow-orange 24.

The concentrated mother liquors were dissolved in ethyl acetate and extracted with 10% sodium bicarbonate to remove the acidic 24. The aqueous solution, washed with ether, acidified, and extracted with chloroform, gave an additional 5.9 g of crystalline 24 for a total of 15.5 g (90%).

An analytical sample of 24 was obtained by recrystallization from ether: mp 80-81.5°; ir (KBr) 3180, 1750, 1725, 1625 cm^{-1}; nmr ($CDCl_3$) δ1.30 (overlapping triplets, 6H, J 7Hz, $CO_2CH_2C\underline{H}_3$), 2.64 (s, 4H, $C\underline{H}_2C\underline{H}_2$), 4.20 (overlapping quartets, 4H, J 7Hz, $CO_2C\underline{H}_2CH_3$), 9.85 (brd s, 2H, O<u>H</u>); uv max (95% EtOH) 258 nm (ε 12,600), 323 nm (ε 6500).

<u>Anal</u>. Calcd for $C_{14}H_{16}O_8$: C, 53.85; H, 5.16
Found : C, 53.98; H, 5.30.

<u>2,3,5-Trioxo-cyclopentanepropionic acid</u> (22)

A solution of 3.120 g (0.010 mole) of 24 in 30 ml of 3N hydrochloric acid was refluxed for five hours and then

concentrated. The solid residue was boiled twice with 40 ml of chloroform to give 1.728 g (94%) of crude 22.

Since trione acid 22 was difficult to purify, its methyl ester was prepared for analysis. The purest sample of 22 was obtained after several recrystallizations from acetone: mp 141-144°; ir (KBr) 3400-2900, 1740, 1685 cm^{-1}; nmr (d_6 acetone) δ2.68 (s, 4H, $C\underline{H}_2C\underline{H}_2$), 2.92 (s, 2H, $COC\underline{H}_2CO$), 9.06 (brd s, 2H, $CO_2\underline{H}$, $O\underline{H}$); uv max (95% EtOH) 274 nm (ε 9300), 316 nm (ε 4650).

Methyl 2,3,5-trioxo-cyclopentanepropionate

A solution consisting of 276 mg (1.5 mmol) of 22, 3 ml of methanol, 0.33 ml (3.0 mmol) of trimethyl orthoformate, and two crystals of p-toluenesulfonic acid was refluxed for three hours. The reaction mixture was distilled to remove 1.5 ml of solvent, diluted with water, and extracted with methylene chloride. The organic extracts were washed first with 5% hydrochloric acid and then twice with 10% sodium bicarbonate. The aqueous bicarbonate solution was acidified and extracted with methylene chloride to yield 124 mg (42%) of brown oil. Two bulb to bulb distillations (150°/0.05 mm) of this crude product gave nearly colorless methyl 2,3,5-trioxo-cyclopentanepropionate: ir (neat) 3600-2500, 1735, 1685, 1655 cm^{-1}; nmr ($CDCl_3$) δ2.65 (s, 4H, $C\underline{H}_2C\underline{H}_2$), 2.89 (s, 3H, $COC\underline{H}_2CO$), 3.64 (s, 3H, $CO_2C\underline{H}_3$),

8.05 (brd s, 1H, OH).

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09
Found : C, 54.39; H, 5.15

2,5-Dioxo-cyclopentanepropionic acid (1)

To a solution of 368 mg (2.0 mmol) of triketo acid 22 and 168 mg (2.0 mmol) of sodium bicarbonate in 3 ml of water was added a solution of 240 mg (2.15 mmol) of semicarbazide hydrochloride and 320 mg of sodium acetate trihydrate in 2 ml of water. The resulting suspension was stirred at room temperature for two hours, acidified to pH 2, cooled in ice, filtered, and washed with water. After drying in a vacuum the light yellow, powdery semicarbazone derivative weighed 407 mg (85%) and was used in the next step without further purification or characterization.

A solution of 560 mg (2.32 mmol) of the 3-semicarbazone derivative of 22 and 1.23 g of potassium hydroxide in 5.5 ml of ethylene glycol was heated at 200° for six hours and then concentrated. An aqueous solution (3 ml) of the residue was acidified, filtered, and extracted 14 times with ethyl acetate to afford 327 mg (83%) of 1. Several recrystallizations of 1 from methanol produced white crystals: mp 168-171°; ir (KBr) 3300-2500, 1690, 1595, 1560 cm^{-1}; nmr (d_6 acetone) 2.42 (s, 8H, methylene protons of ring and side chain), (d_6 DMSO) 2.31 (s, 4H), 2.40 (s, 4H); uv max (95% EtOH) 248 nm (ε 11,150).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92
Found : C, 56.50; H, 5.93

Methyl 2,5-dioxo-1-methylcyclopentanepropionate (25)

The known compound 25[17] was prepared by the method of Kessar et al.[18] and by the methylation of 1.

a) To a solution of sodium t-butoxide, prepared by dissolving 3 mg of sodium in 0.3 ml dry t-butanol, was added a solution of 224 mg (2.0 mmol) of 2-methylcyclopentane-1,3-dione in 4 ml of dry dimethylformamide (DMF) and 0.52 ml (5.8 mmol) of methyl acrylate. After heating at 140° for 12 hours the brown solution was concentrated, diluted with water, and extracted with methylene chloride. The organic extract was washed successively with 10% sodium bicarbonate, water, and brine, and then concentrated. Bulb to bulb distillation of the residue gave 50 mg (12.6%) of light yellow oil, and another bulb to bulb distillation (100°, 0.3 mm) gave 25 as a nearly colorless liquid: ir (neat) 1715-1745 cm^{-1}; nmr (CCl_4) δ1.03 (s, 3H, C-1 CH_3), 2.01 (A_2B_2, 4H, side chain methylene protons), 2.67 (s, 4H, ring methylene protons), 3.50 (s, 3H, CO_2CH_3).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12
Found : C, 60.69; H, 7.12

b) To a suspension of 0.69 mmol of sodium hydride (from 28 mg of 57% oil dispersion washed with pentane) in 0.8 ml of dry DMF was added a solution of 51 mg (0.30 mmol)

of dione acid 1 in 0.2 ml of dry DMF. After adding 0.070 ml of dry t-butanol and 0.040 ml (0.6 mmol) of methyl iodide, the solution was stirred at room temperature for 90 min, acidified, diluted with water, and extracted with ethyl acetate to give 40 mg of oil. Preparative thick layer chromatography (silica gel, ether) gave 6 mg (10.8%) of 25 having ir and nmr spectra superimposable on those of the compound as prepared in part (a).

APPENDIX

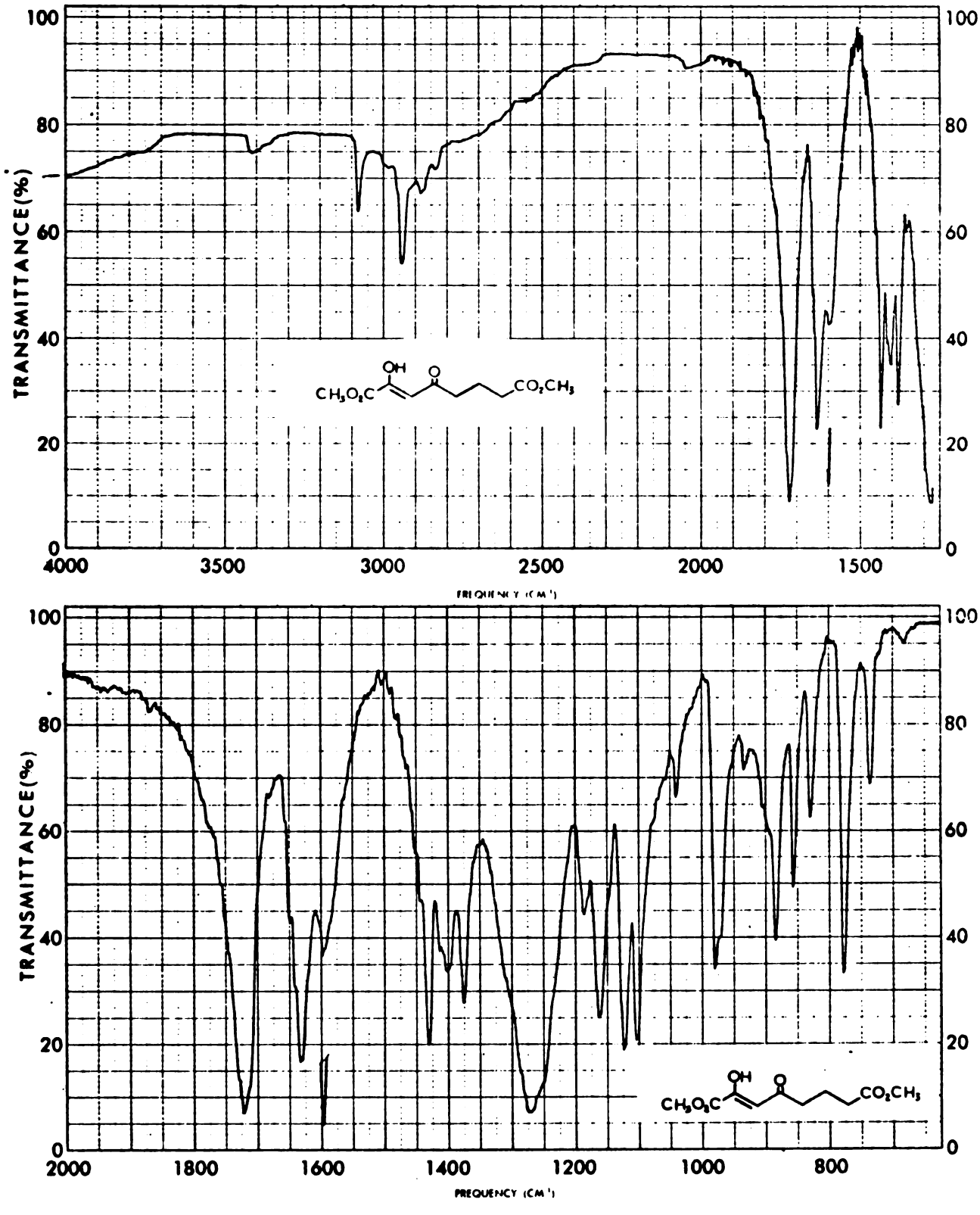


Figure 1. Infrared spectrum of dimethyl 2,4-dioxo-octanedioate (21).

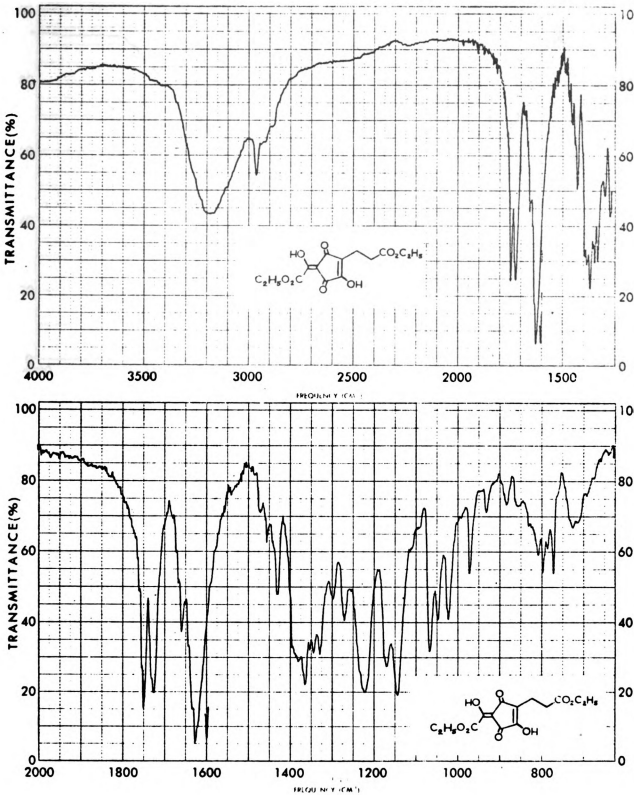


Figure 2. Infrared spectrum of ethyl 4-ethoxalyl-2,3,5-trioxo-cyclopentanepropionate (24).

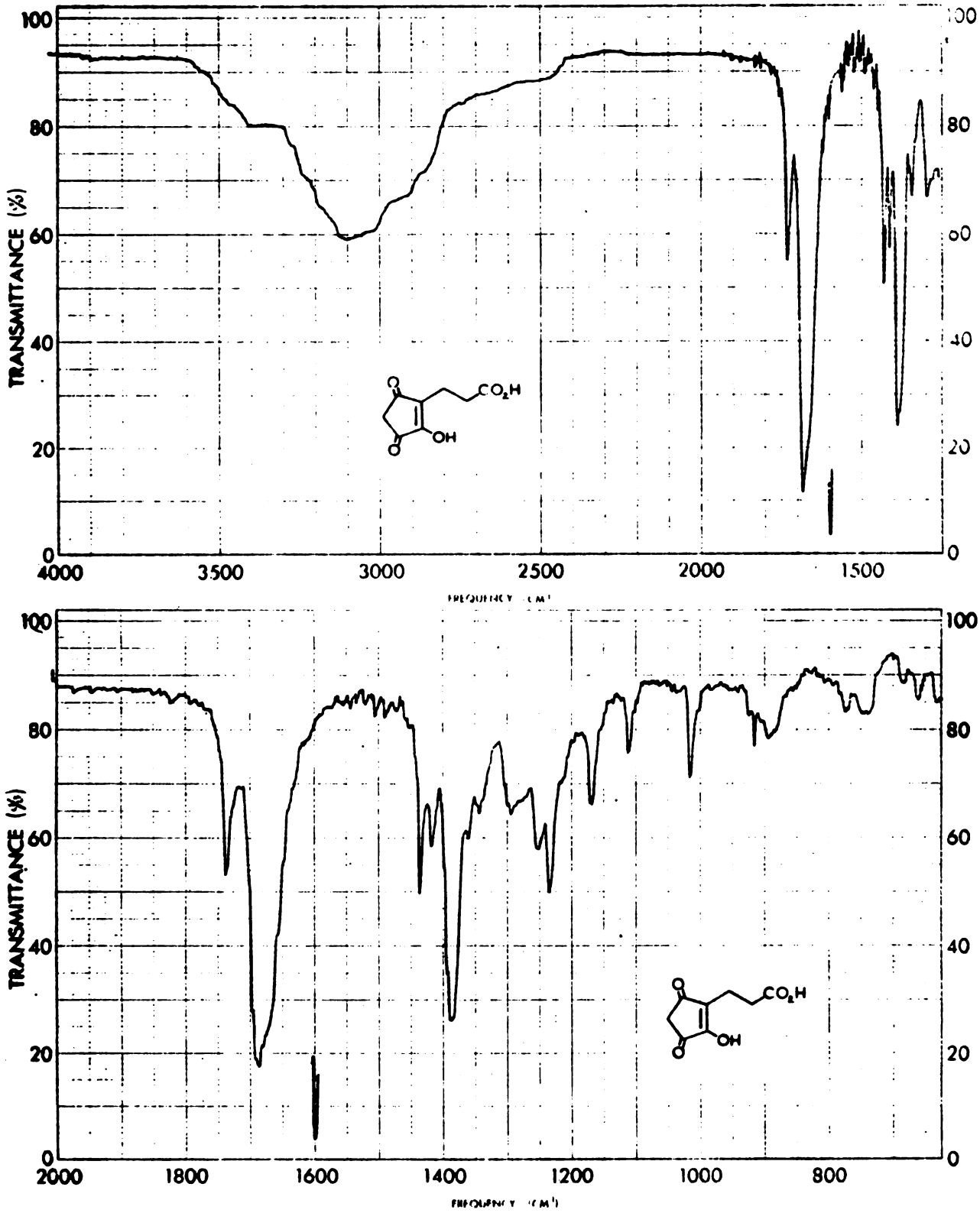


Figure 3. Infrared spectrum of 2,3,5-trioxo-cyclopentane-propionic acid (22).

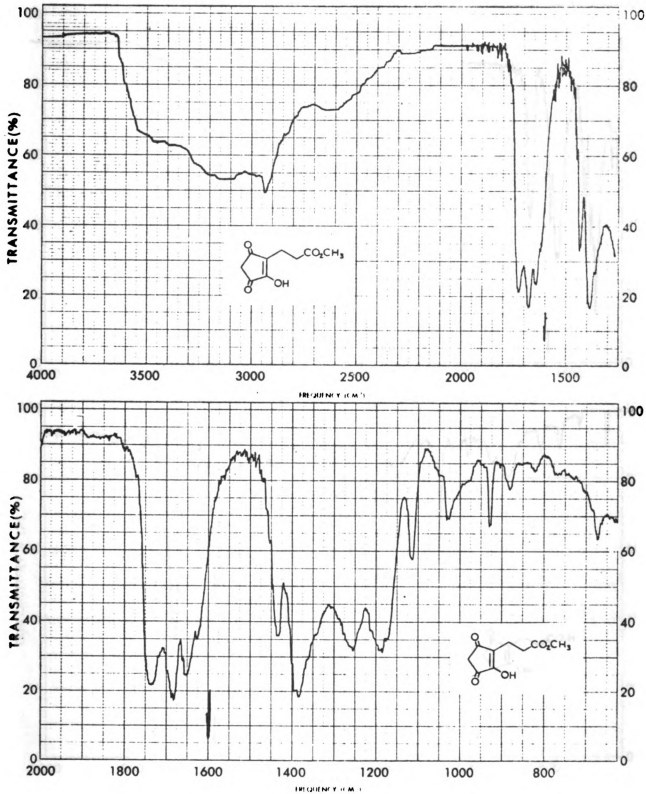


Figure 4. Infrared spectrum of methyl 2,3,5-trioxo-cyclopentanepropionate.

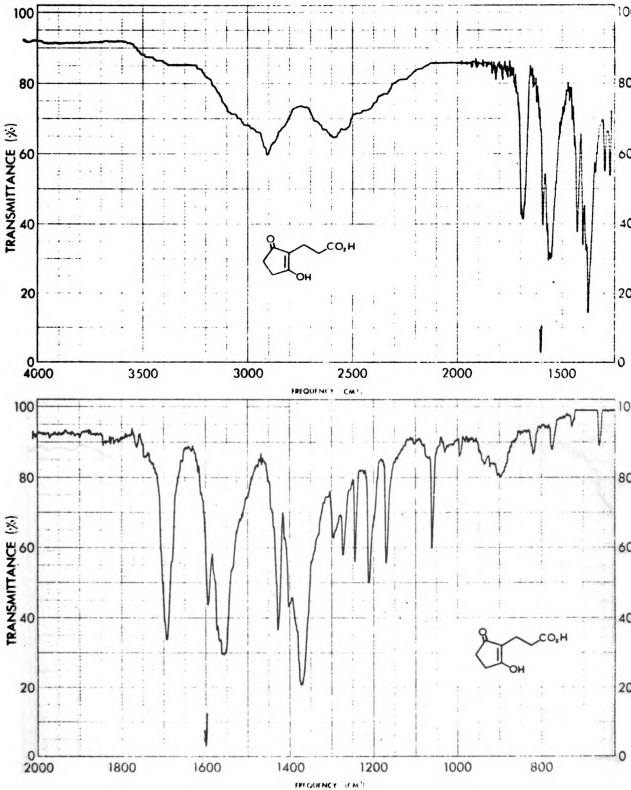


Figure 5. Infrared spectrum of 2,5-dioxo-cyclopentane-propionic acid (1).

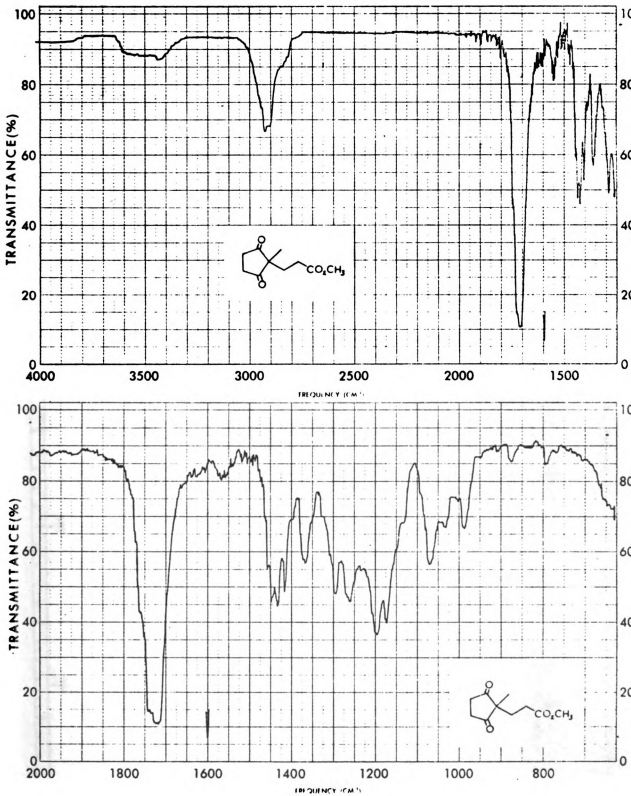


Figure 6. Infrared spectrum of methyl 2,5-dioxo-1-methyl-cyclopentanepropionate (25).

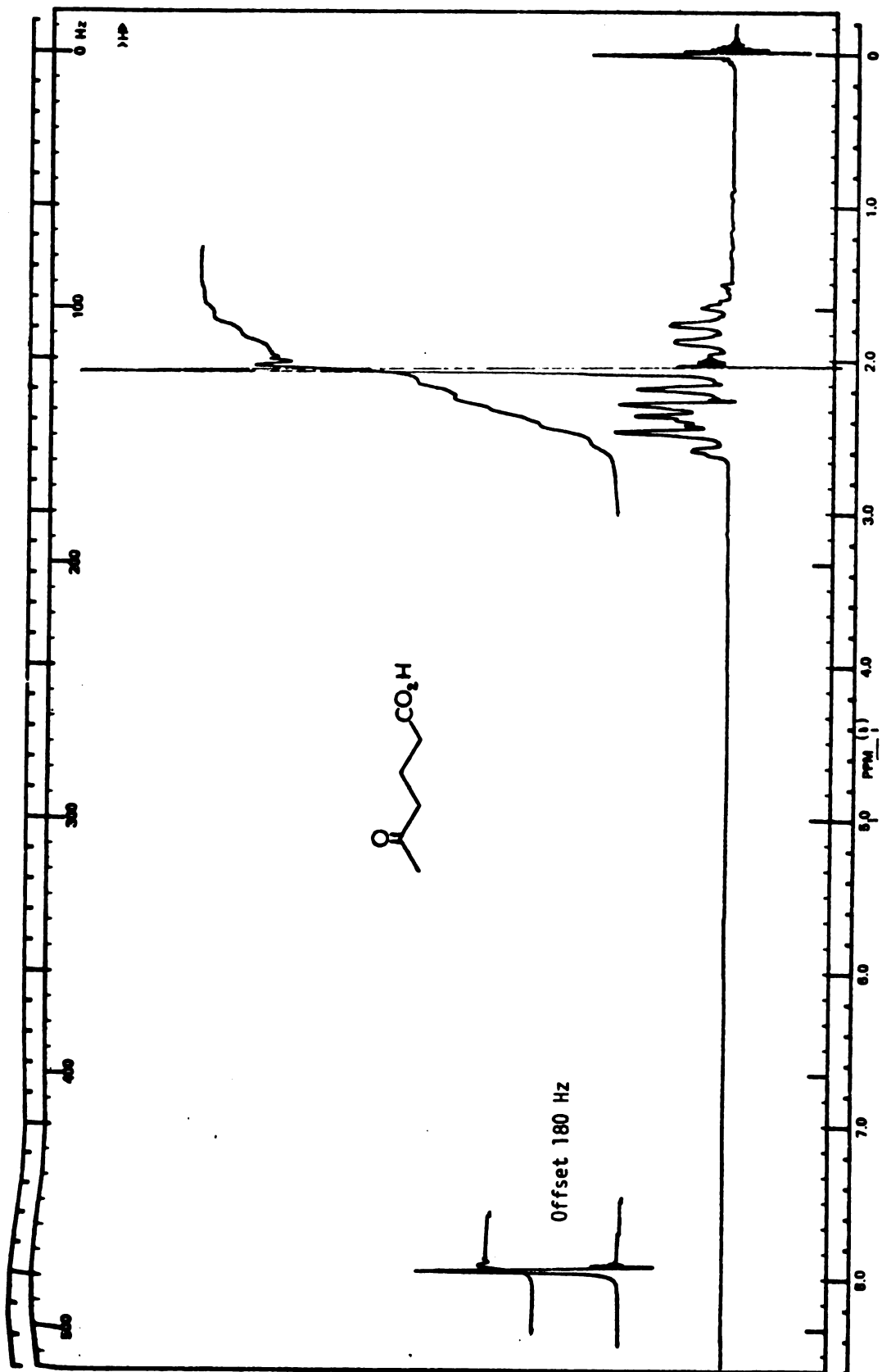


Figure 7. Nmr spectrum of 5-oxo-hexanoic acid (19) (CCl_4).

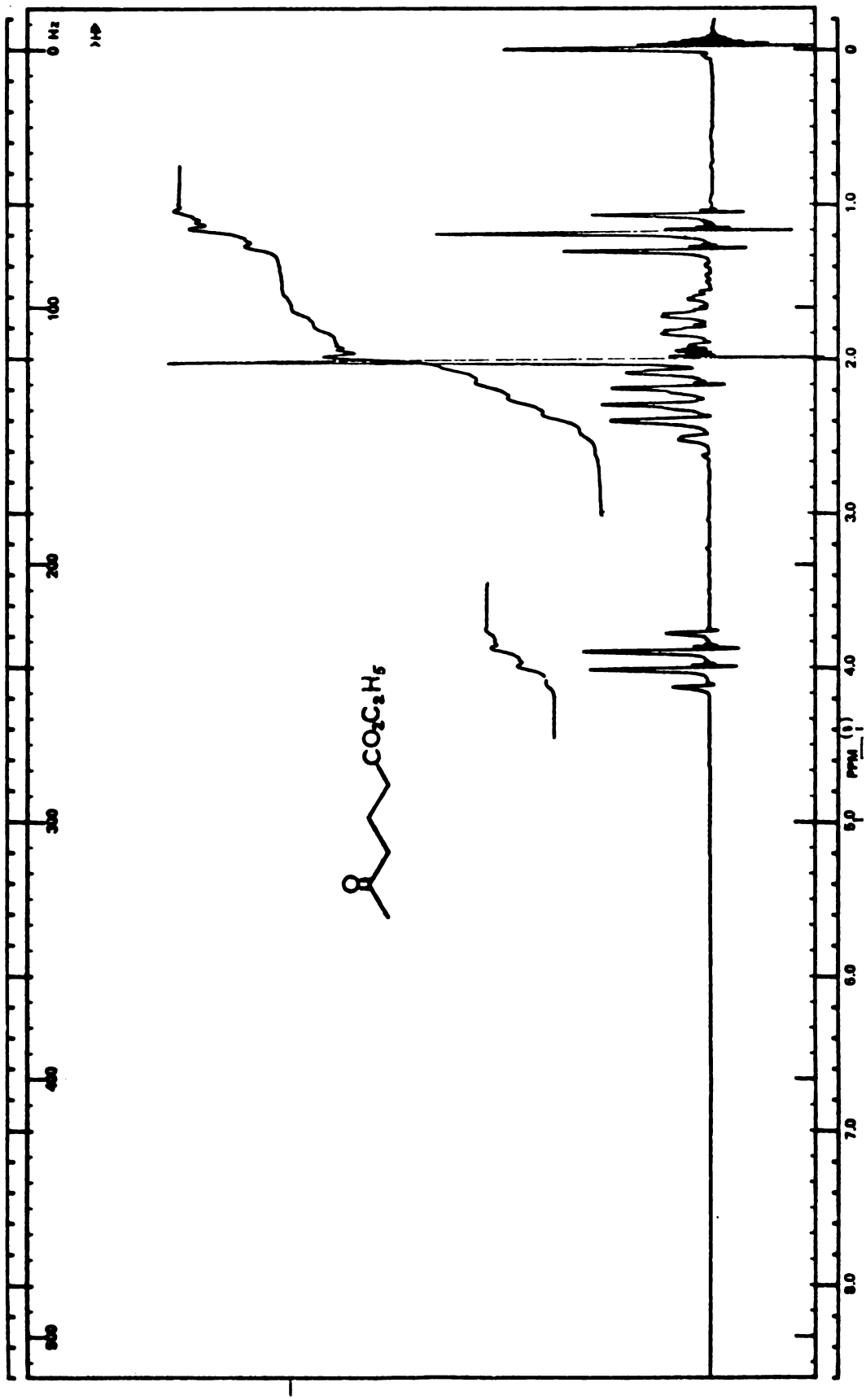


Figure 8. Nmr spectrum of ethyl 5-oxo-hexanoate (23) (CCl_4).

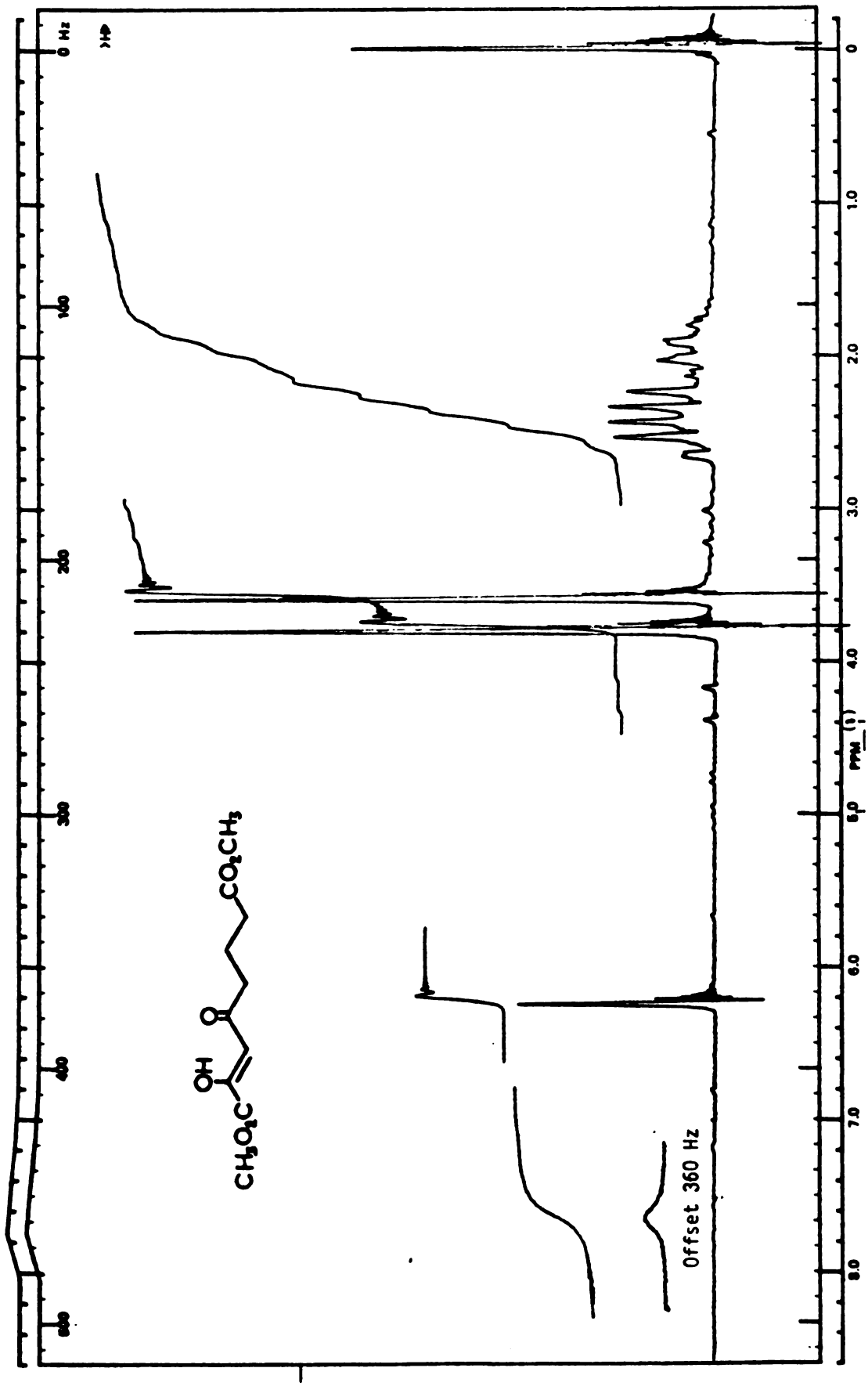


Figure 9. Nmr spectrum of dimethyl 2,4-dioxo-octanedioate (21) ($CDCl_3$).

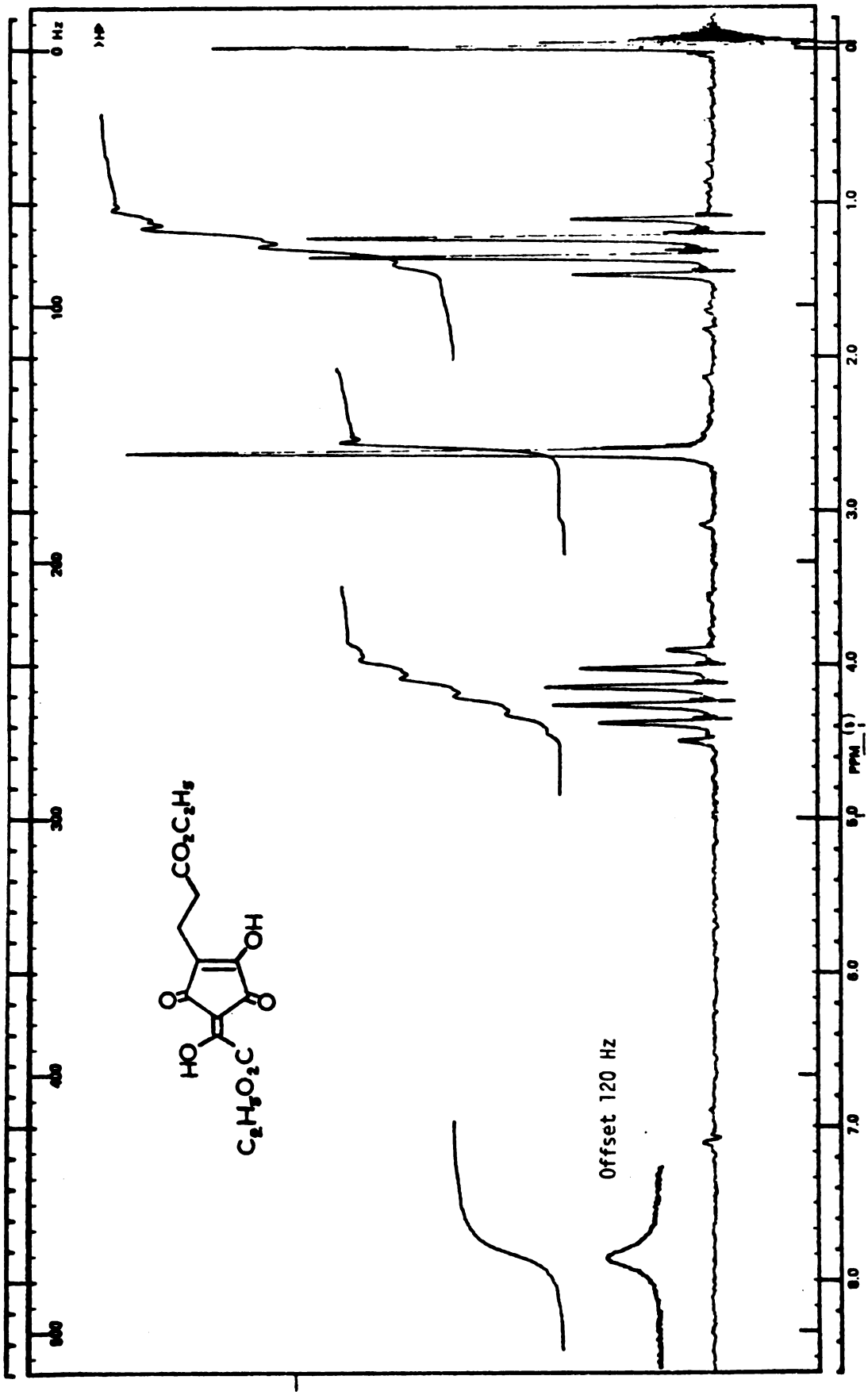


Figure 10. Nmr spectrum of ethyl 4-ethoxalyl-2,3,5-trioxo-cyclopentane-propionate (24) ($CDCl_3$).

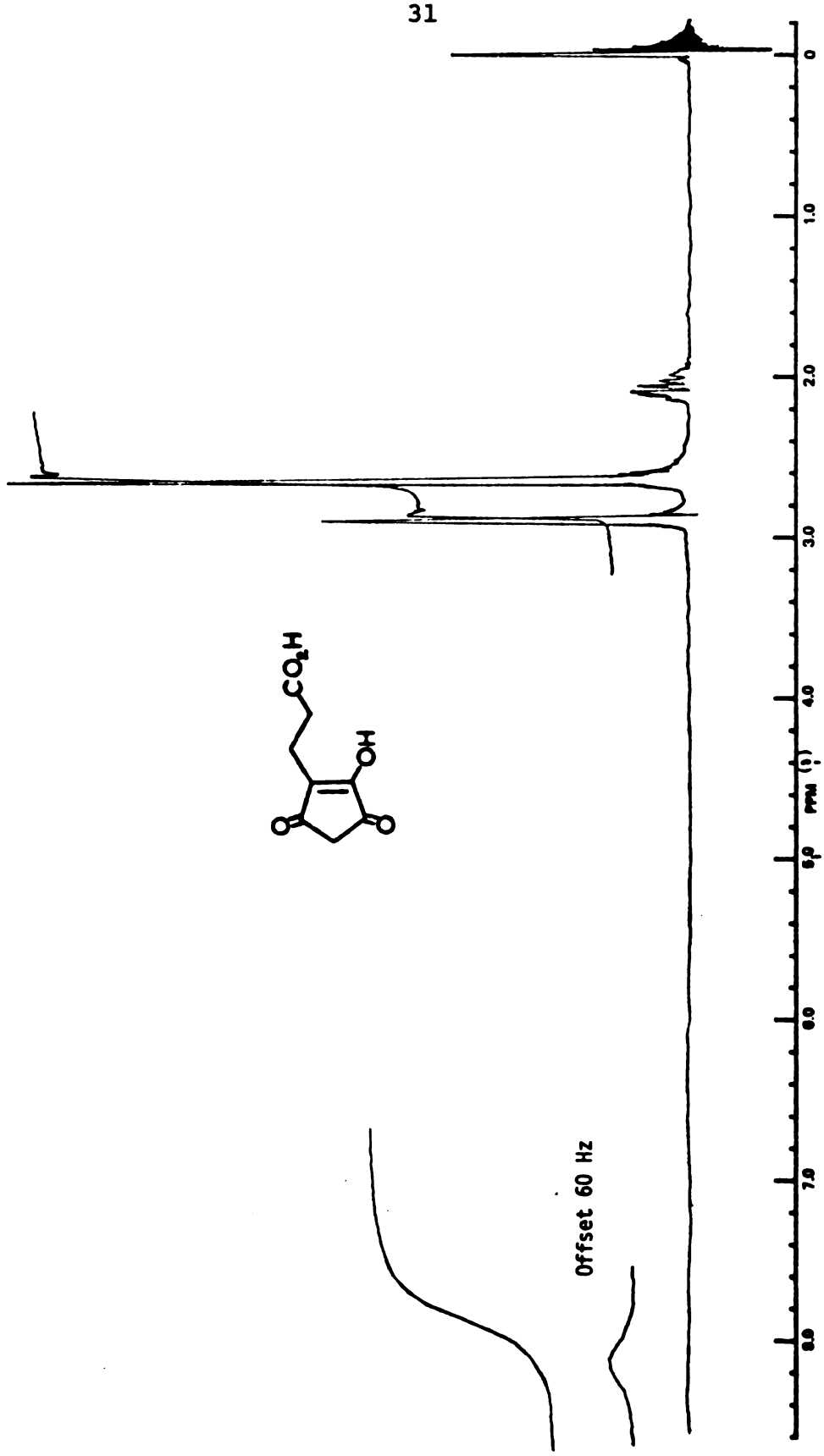


Figure 11. Nmr spectrum of 2,3,5-trioxo-cyclopentanepropionic acid (22) (CD_3COCD_3).

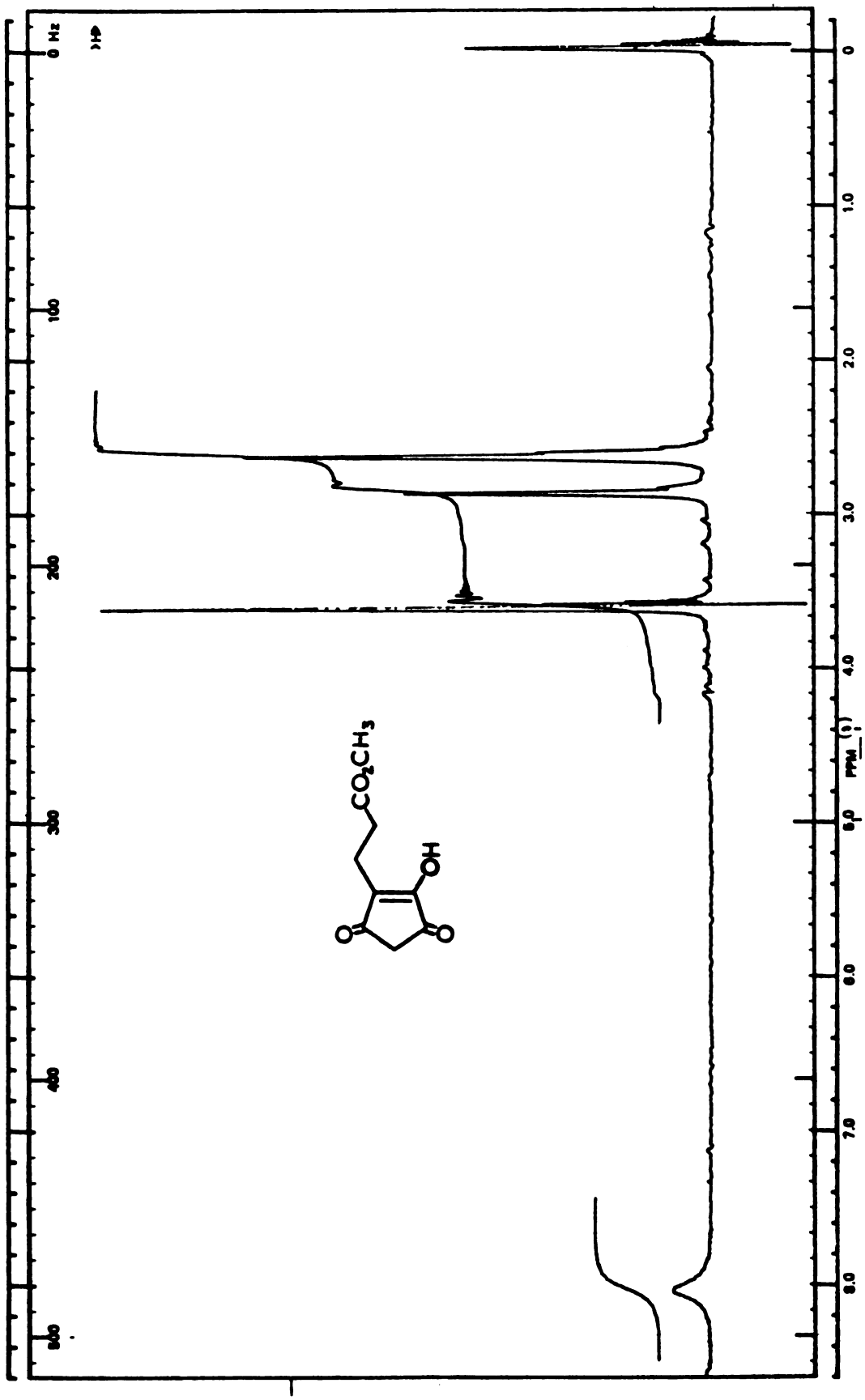


Figure 12. Nmr spectrum of methyl 2,3,5-trioxo-cyclopentanepropionate ($CDCl_3$).

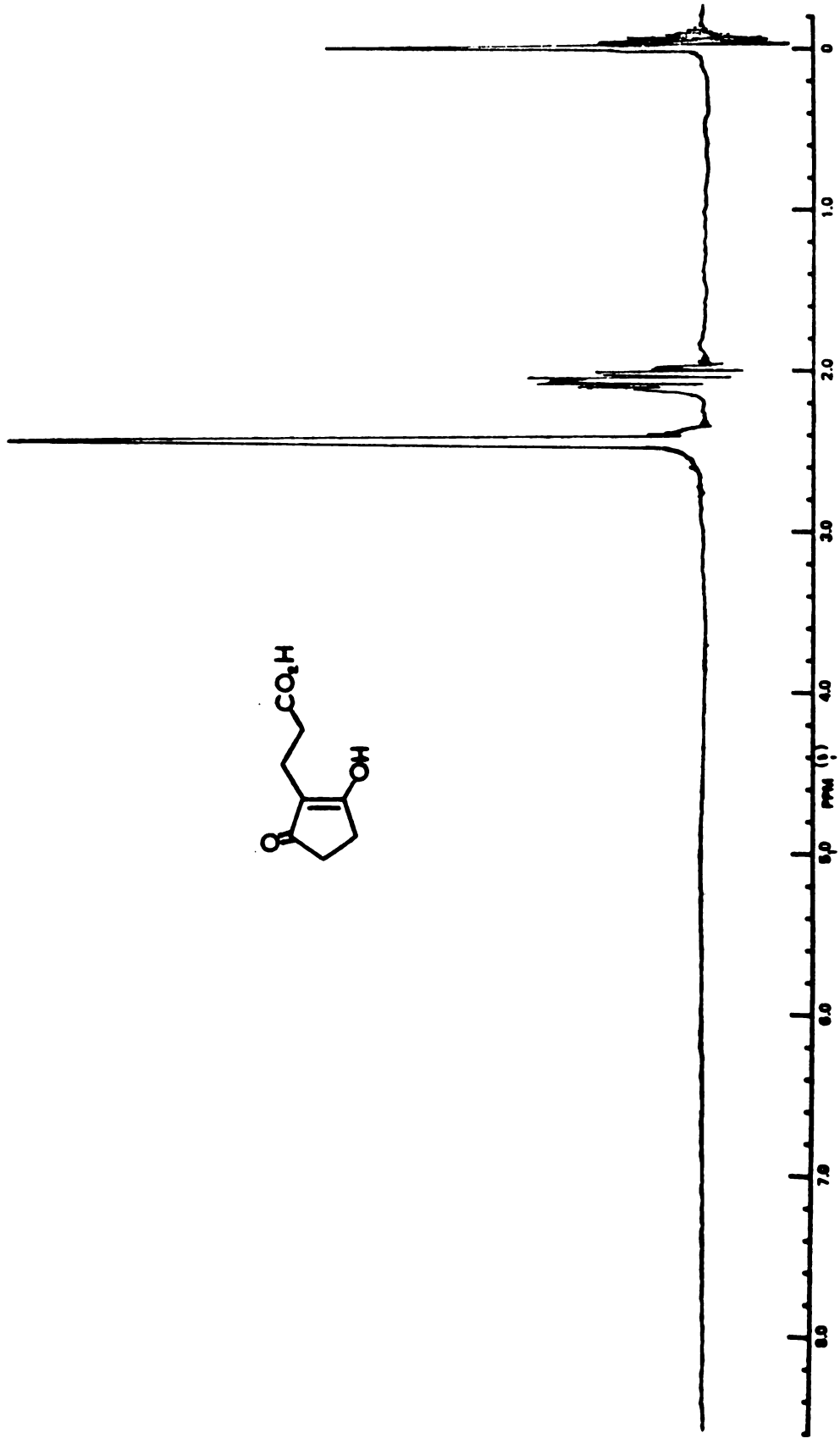


Figure 13. Nmr spectrum of 2,5-dioxo-cyclopentanepropionic acid (1) (CD_3COCD_3).

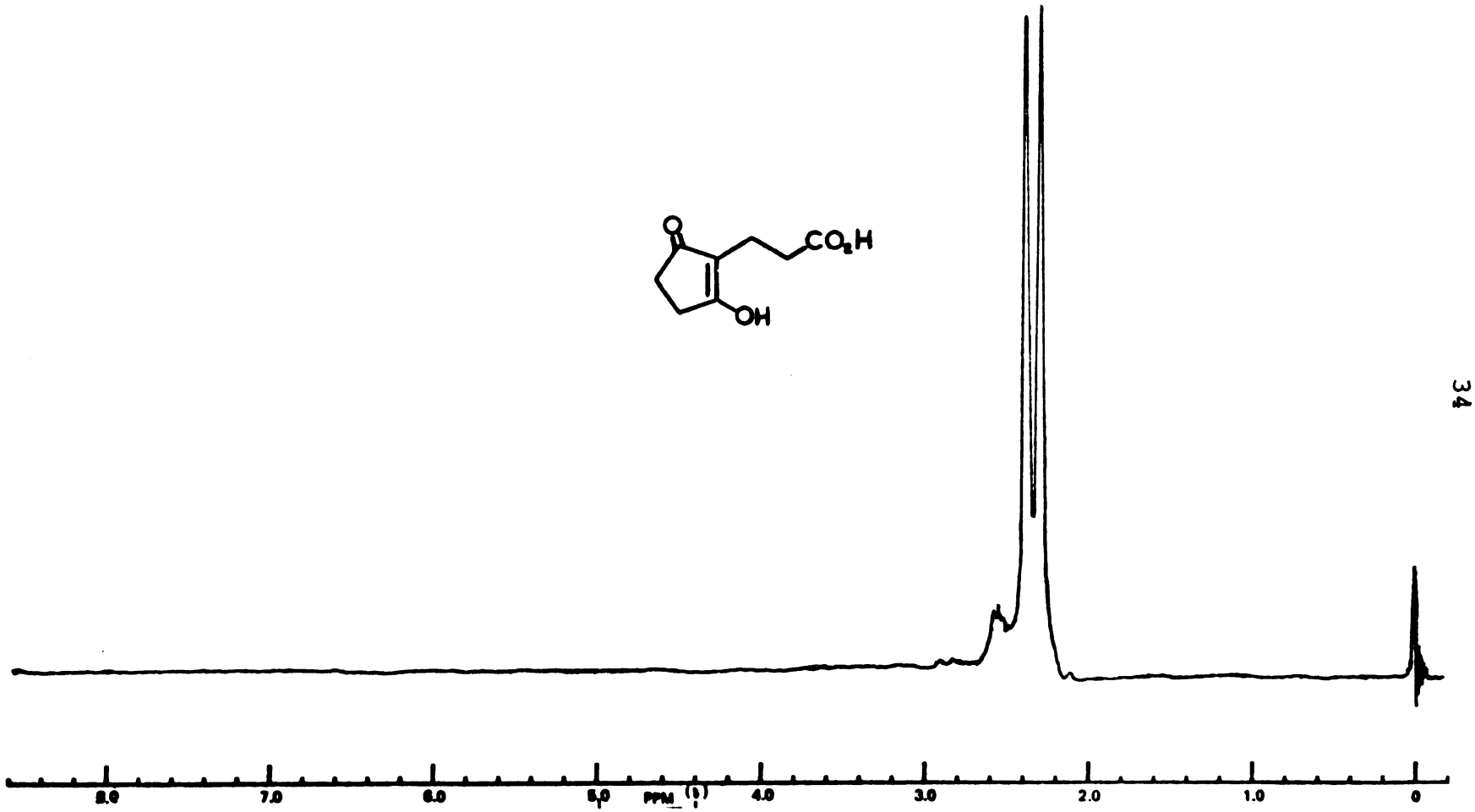


Figure 14. Nmr spectrum of 2,5-dioxo-cyclopentanepropionic acid (1) (CD_3SOCD_3).

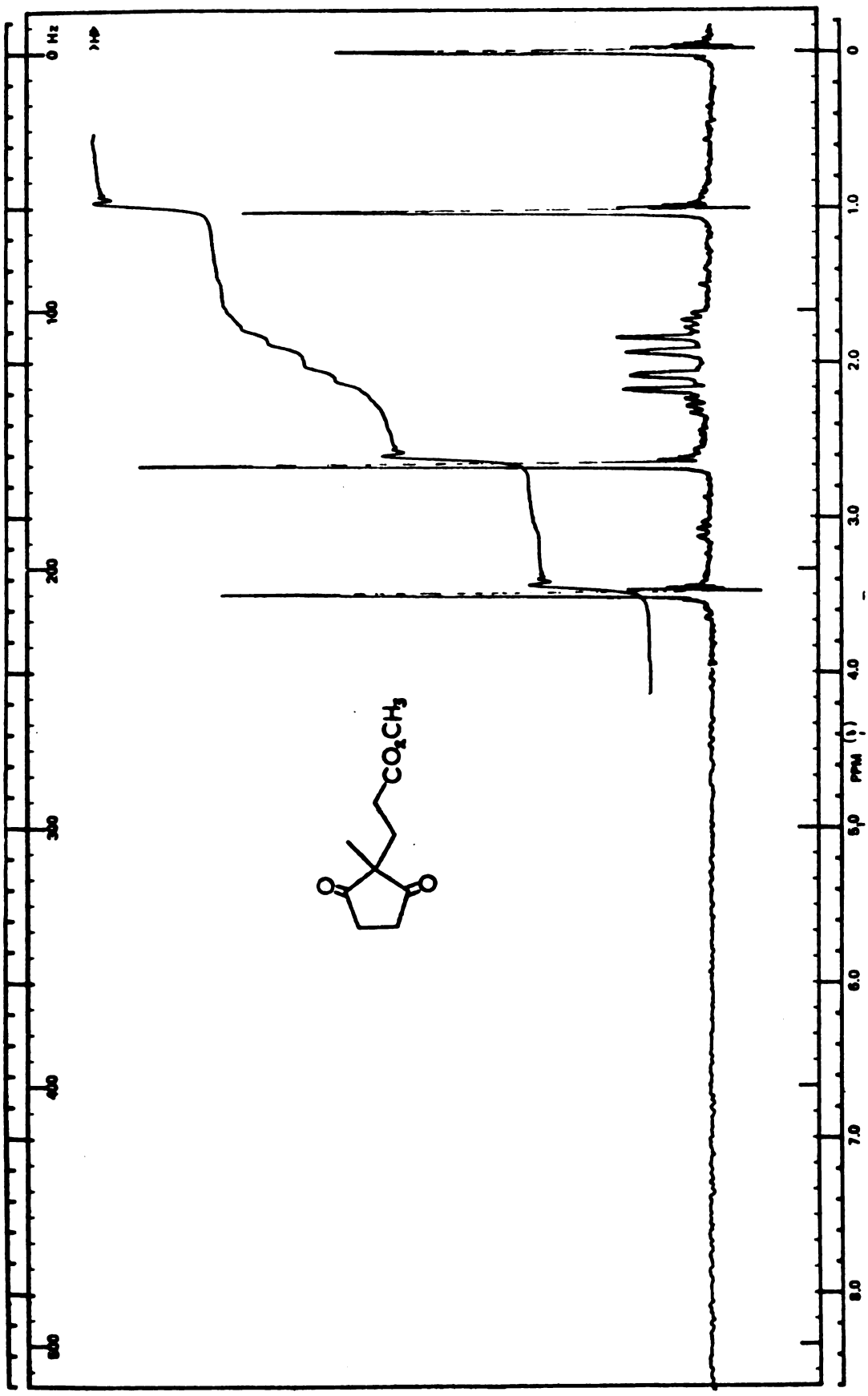


Figure 15. Nmr spectrum of methyl 2,5-dioxo-1-methylcyclopentanepropionate (25) (CCl_4).

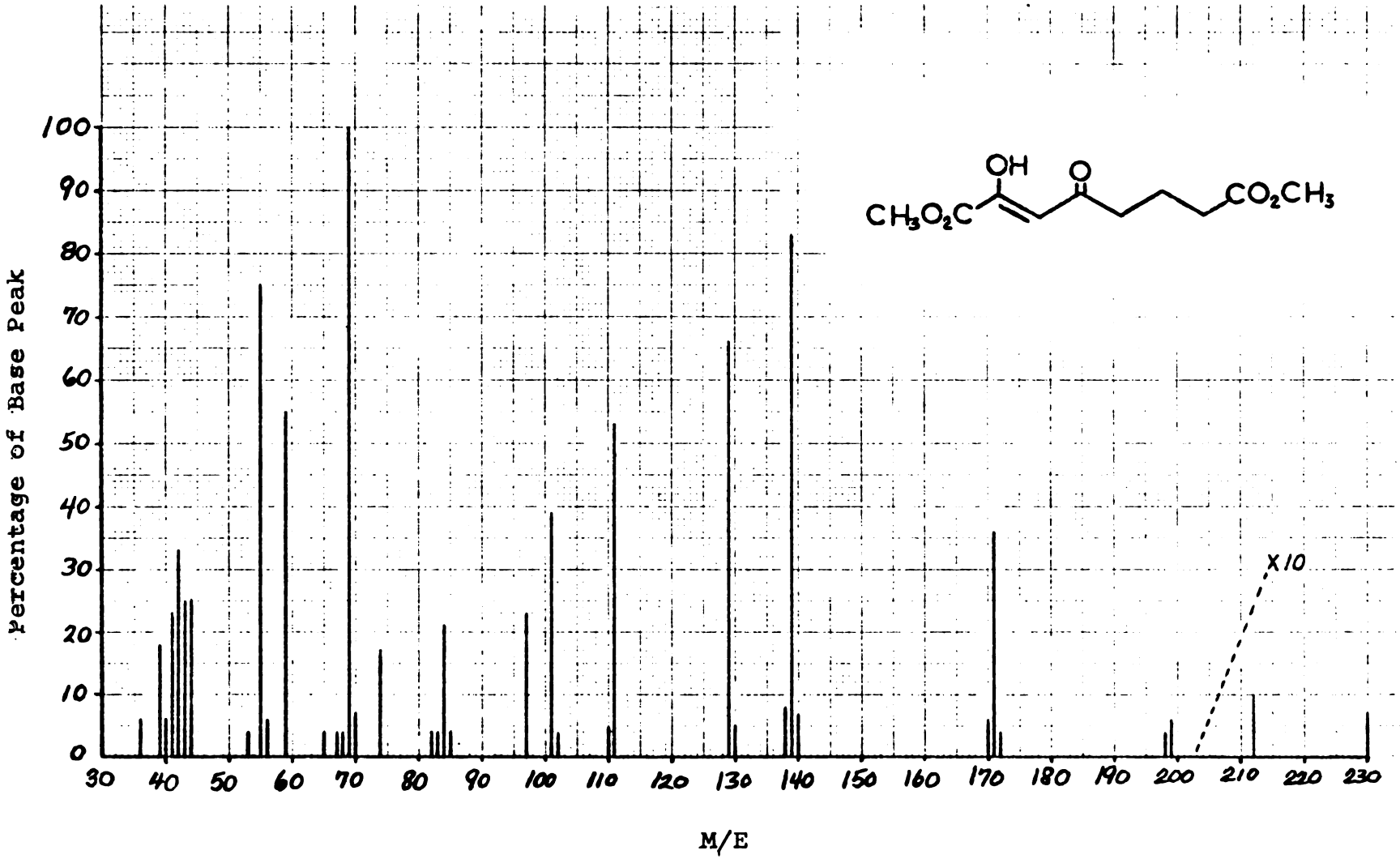


Figure 16. Mass spectrum of dimethyl 2,4-dioxo-octanedioate (21).

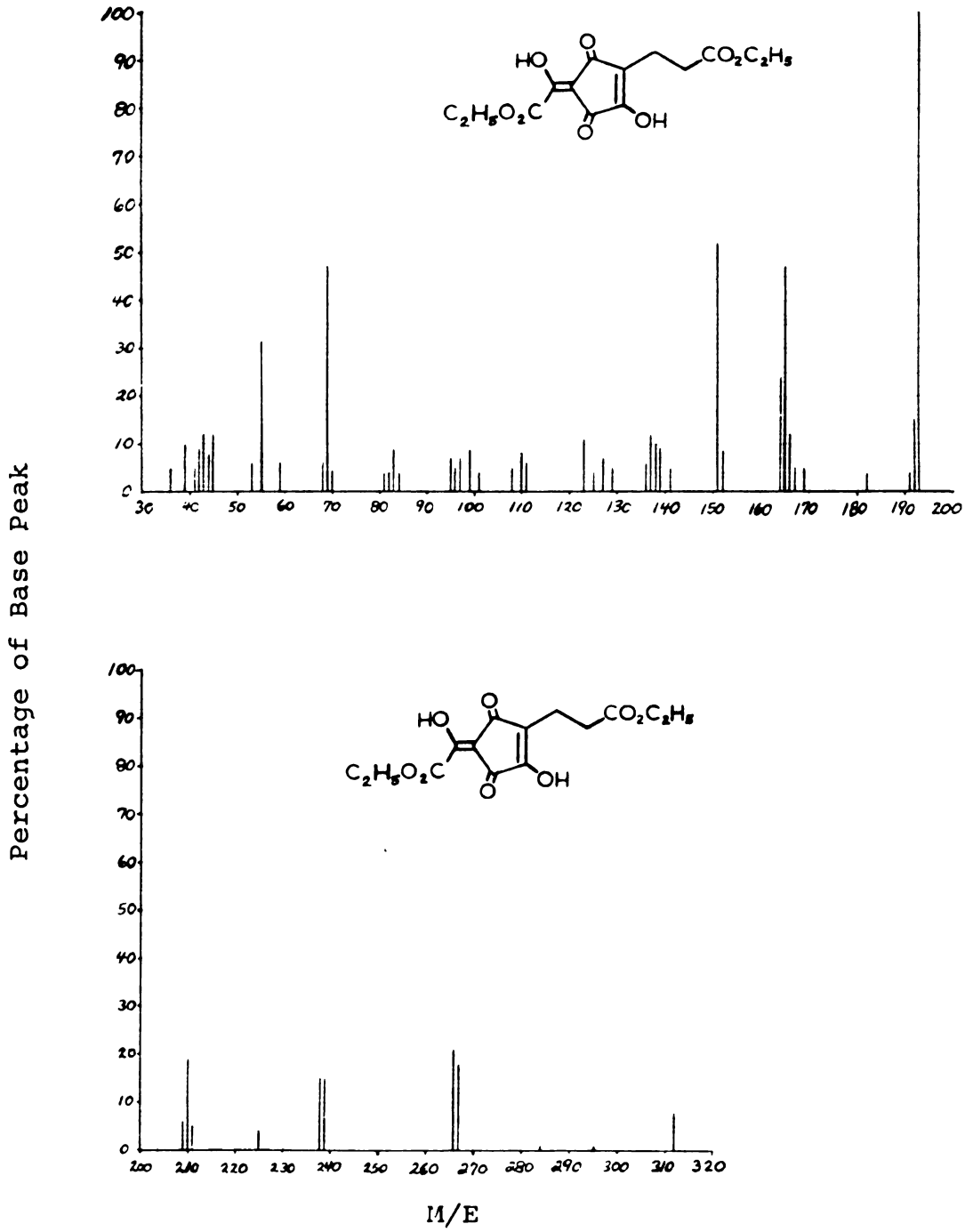


Figure 17. Mass spectrum of ethyl 4-ethoxalyl-2,3,5-trioxo-cyclopentanepropionate (24).

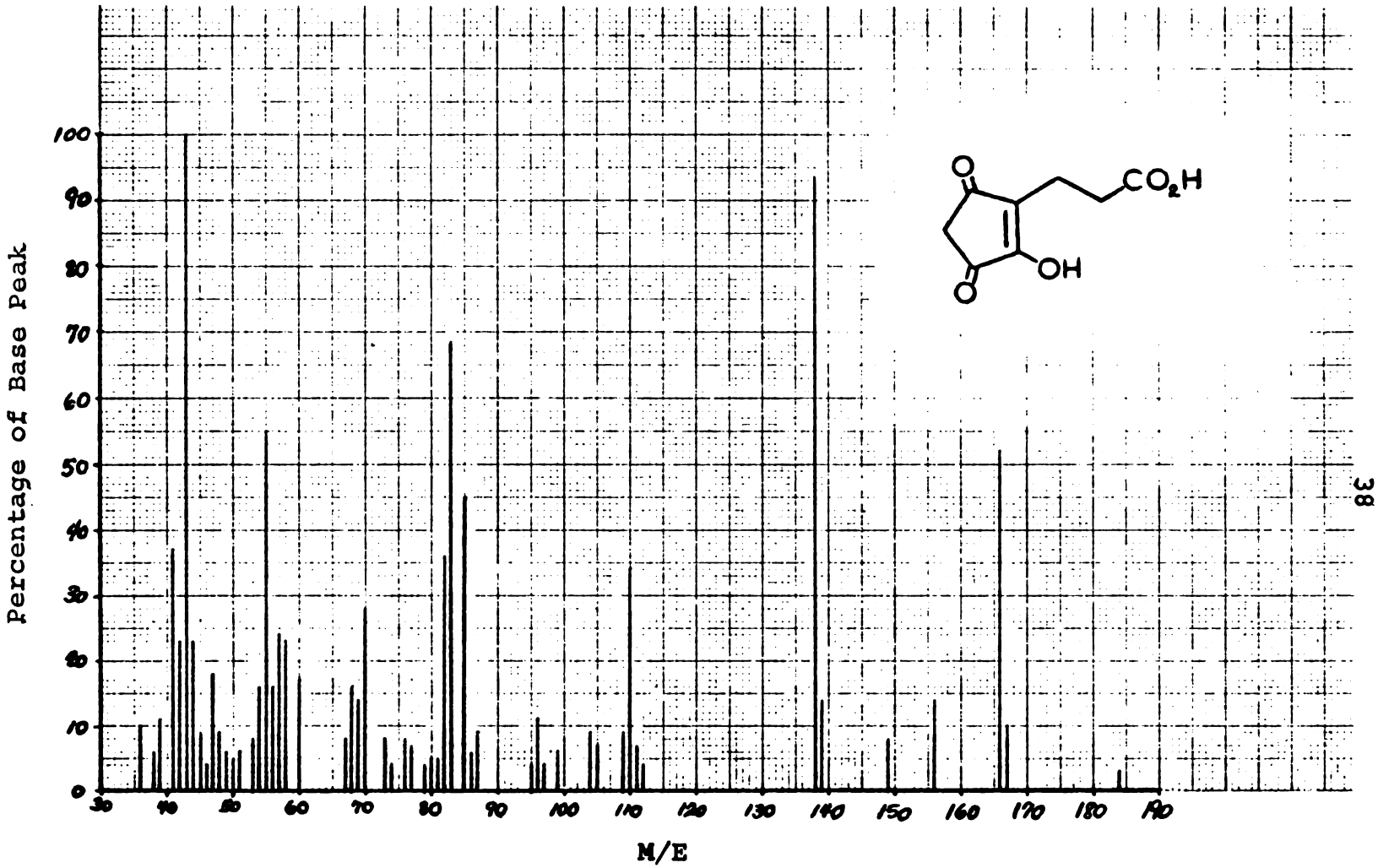


Figure 18. Mass spectrum of 2,3,5-trioxo-cyclopentanepropionic acid (22).

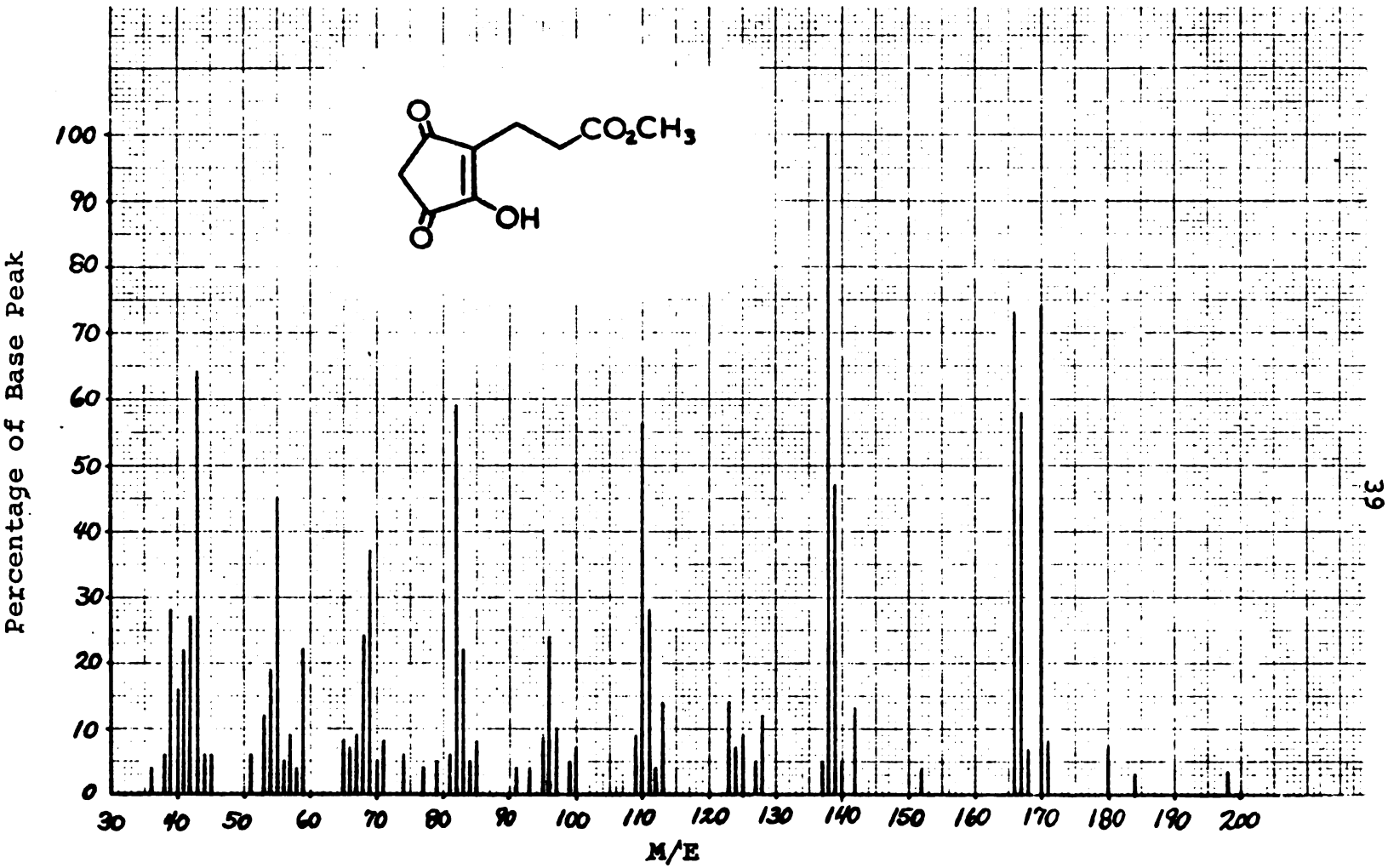


Figure 19. Mass spectrum of methyl 2,3,5-trioxo-cyclopentanepropionate.

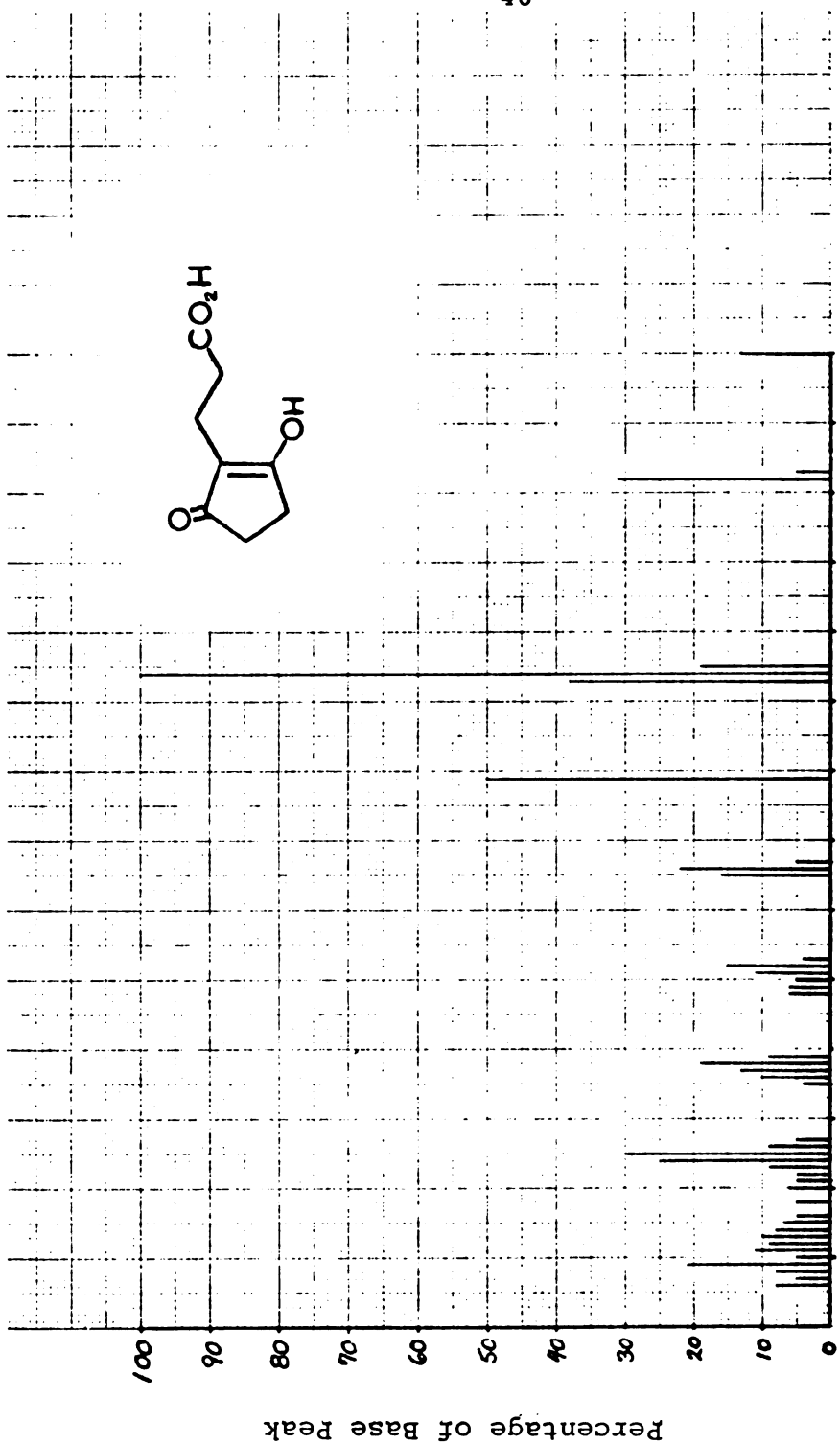


Figure 20. Mass spectrum of 2,5-dioxo-cyclopentanepropionic acid (1).

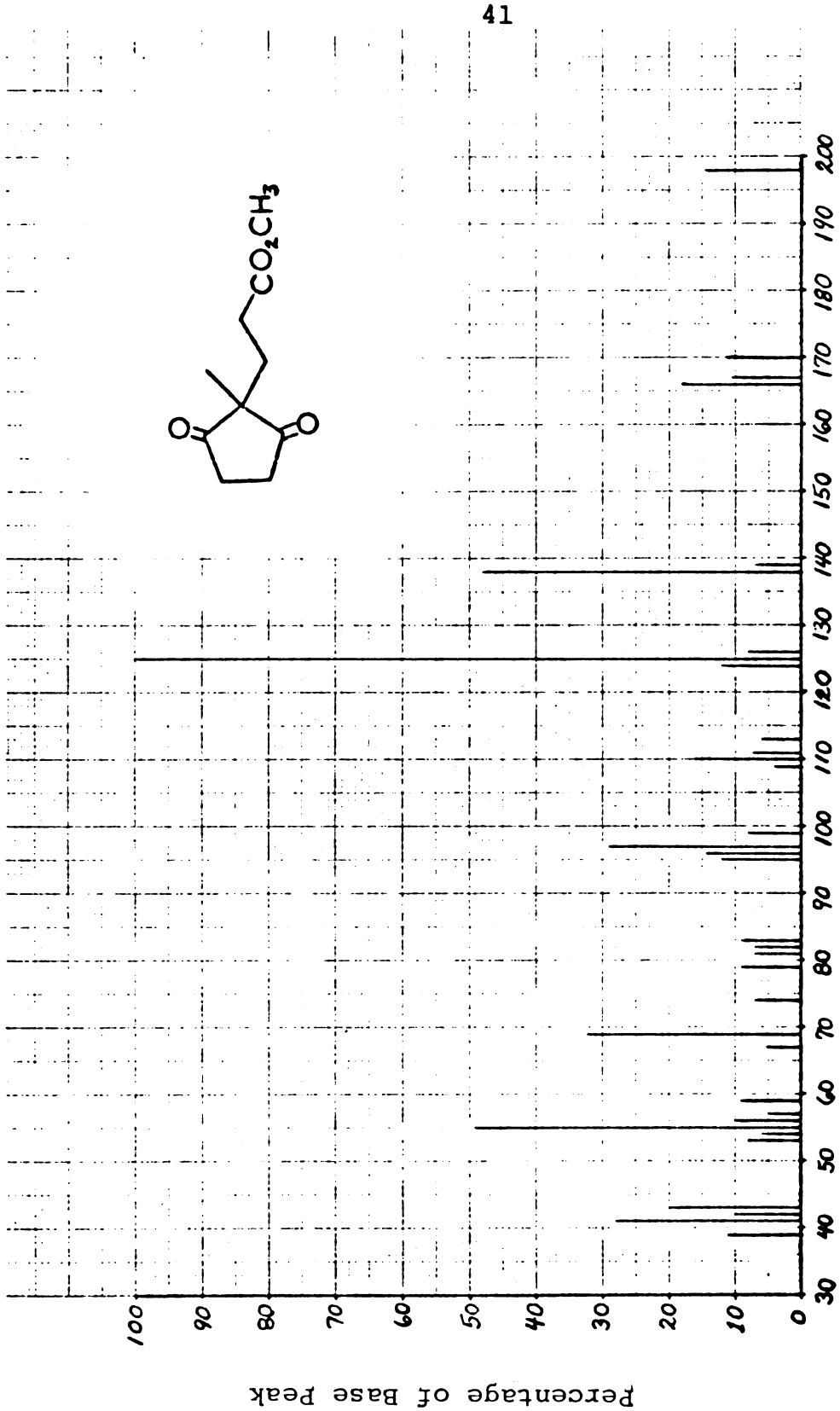


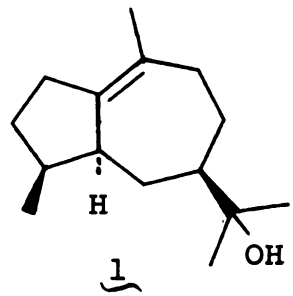
Figure 21. Mass spectrum of methyl 2,5-dioxo-1-methylcyclopentane-propionate (25).

PART II

THE SYNTHESIS AND PHOTOREARRANGEMENT OF TWO β,γ-ENONES

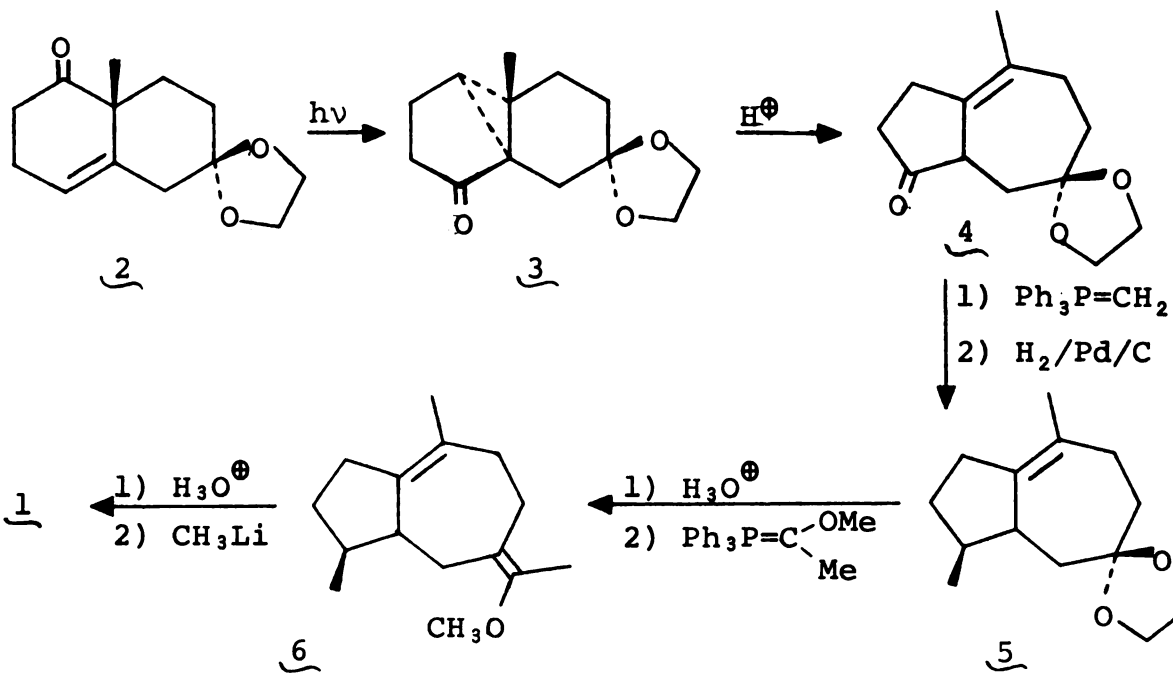
INTRODUCTION

The initial goal of this study was development of a new and facile synthesis of the sesquiterpene bulnesol, 1. A key step in the proposed synthesis (Scheme 1) was the anticipated photorearrangement of β,γ-unsaturated ketone 2 to the tricyclic isomer 3.



1

Scheme 1

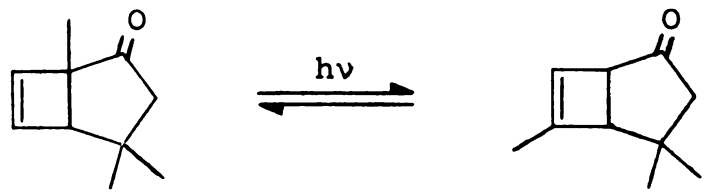


2 3 4 5 6 1

Although photorearrangement of β,γ-enones is well established, the factors controlling the course of these rearrangements have not been completely elucidated. Before proceeding further, therefore, a survey of the "state of the art" is necessary.

Interest in this area of photochemistry originated in Büchi's observation in 1960[19] of the photointerconversion of 7 and 8 by a 1,3-acyl shift (equation 1). One of the

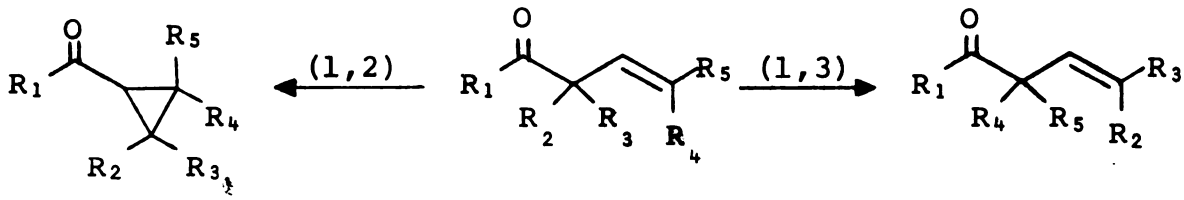
(1)



7 8

first examples of a 1,2-acyl shift, corresponding to that desired for the bulnesol synthesis, was noted by Williams and Ziffer in 1967.[20] These two types of rearrangement are usually the major photoreactions of β,γ-unsaturated ketones (Scheme 2); however, other transformations such as decarbonylation,[21,22] hydrogen abstraction,[23] and reduction[24,25] are frequently encountered and may even predominate in certain cases.

Scheme 2



9 10 11

The 1,3- and 1,2-shifts normally arise respectively, from the n,π* singlet and triplet excited states.[23,26] The mechanisms of these rearrangements and the structural features which influence them generally remain poorly defined. Some β,γ-enones show exclusive 1,3- or 1,2-shifts, whereas others exhibit both reactions simultaneously. In many cases a 1,3-shift is obtained on direct irradiation (presumably via the n,π* singlet) and a 1,2-shift is the major product on sensitized irradiation (via a triplet state). These facts illustrate the complexity of β,γ-enone photochemistry and the difficulty in predicting how a particular compound will behave on exposure to light.

Chart 1 contains several examples of structurally related β,γ-unsaturated ketones which, with the exception of 12, undergo exclusively one type of photoreaction on direct irradiation. The rare examples of direct triplet 1,2-shifts

Chart 1. Direct Irradiation of Some β,γ-Enones

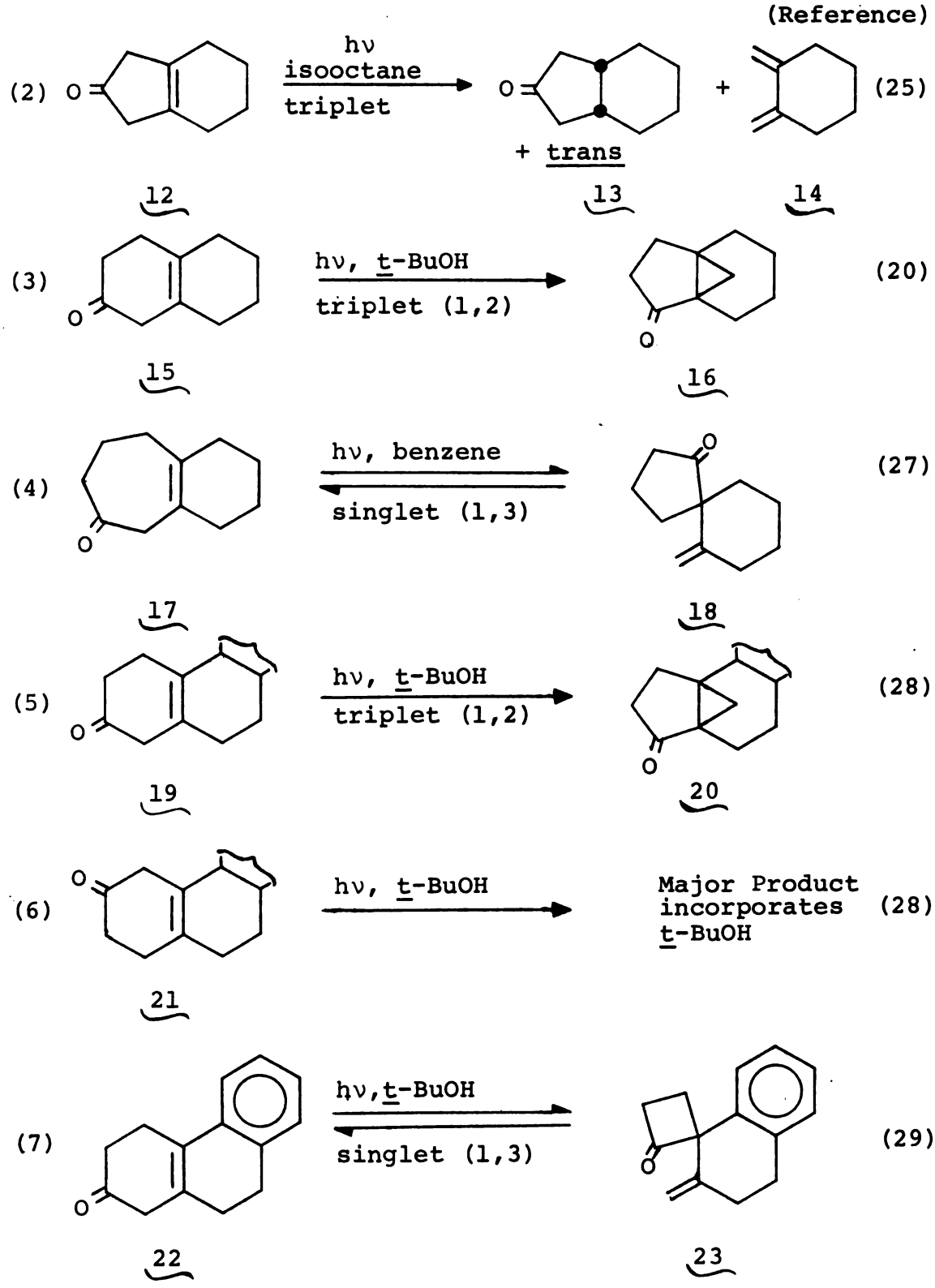
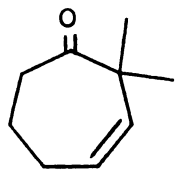
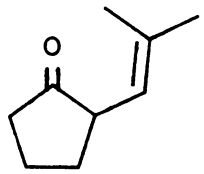
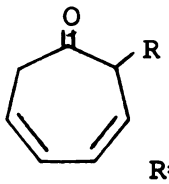
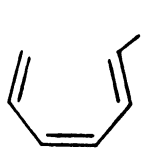


Chart 1 (cont'd.)

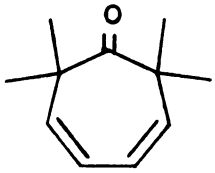
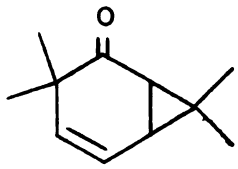
(Reference)

(8)  hν, ether ⇌ singlet (1,3)  (22)

24 25

(9)  R=H,CH_3 hν, ether → singlet  + CO (22)

26 27

(10)  hν, ether → triplet(?) (1,2)  (22)

28 29

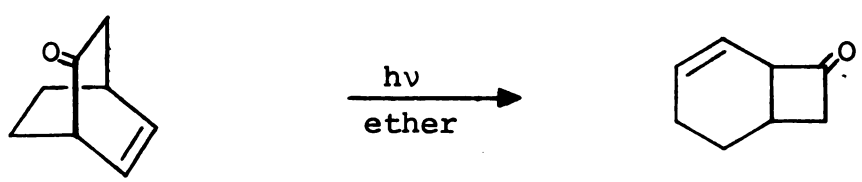
for compounds 15, 19, and (probably) 28 must occur via fairly rapid intersystem crossing (isc) of the initial n,π* singlet excited state of the ketone. As expected of typical triplet reactions, these exhibit quenching (except 28 which is unaffected) and increased rate on triplet sensitization (e.g., acetone). The fact that the reaction of 28 cannot be quenched with piperylene but can be sensitized is unusual. Either product 29 can arise from both a singlet and a triplet intermediate (which would be exceptional), or isc occurs, and subsequent rearrangement from the triplet state is faster than diffusion control.

In comparing equations 2, 3, and 4, one sees a marked variance in reaction pathway with changes in ring size of the enone. Excessive ring strain probably prevents product formation via a 1,2- or 1,3-shift for 12. Compound 17 neither undergoes isc (as 15 does) nor produces a cyclopropyl ketone (1,2-shift) on triplet sensitization. This lack of similarity between the photoisomerizations of 15 and 17 is difficult to explain.

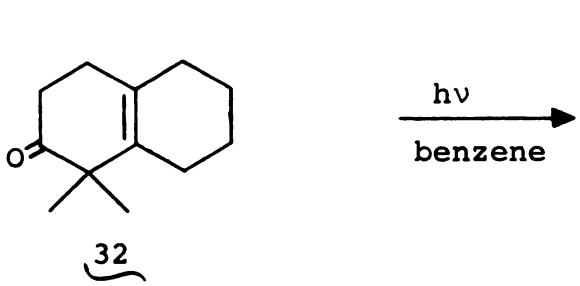
The triplet rearrangement of steroid 19 is analogous to reaction 3. But surprisingly, the isomeric steroid 21 incorporates solvent on photolysis; no cyclopropyl ketone was detected. Compound 22, although structurally similar to 19 and 21, has increased conjugation with the aromatic ring, which seems to retard isc and favor a singlet 1,3-shift. A triplet 1,2-shift is observed, however, on

photosensitized irradiation of 22.[26g] It is apparent from Chart 1 that rather subtle factors must contribute to the variation in reactivity among similar molecules.

It should be noted that the 1,3-acyl shifts illustrated in equations 1,4,7, and 8 are reversible. Such photoisomerizations frequently reach a steady state in which the equilibrium favors the isomer having the lower molar absorptivity, ε. The magnitude of ε reflects the probability of electronic transition and hence is proportional to the rate of reaction. Molecular geometry can greatly affect the position of such equilibria[29] since ε becomes more intense as the degree of π-orbital interaction between the carbonyl and double bond increases.[30] Some 1,3-acyl shifts are irreversible as the conversions of 30 to 31[26e] and 32 to 33[26h] illustrate.



30 31

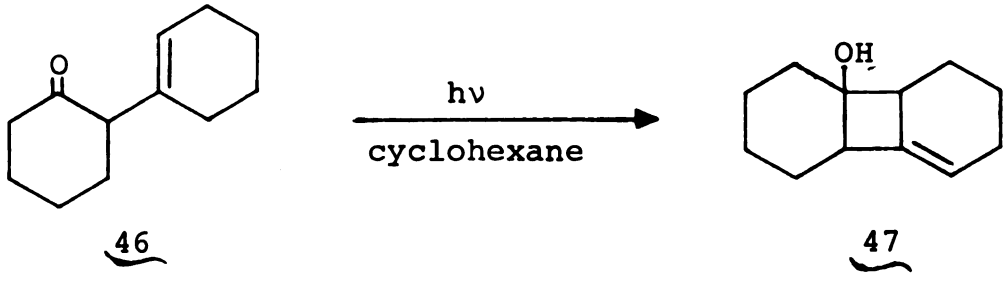


32 33

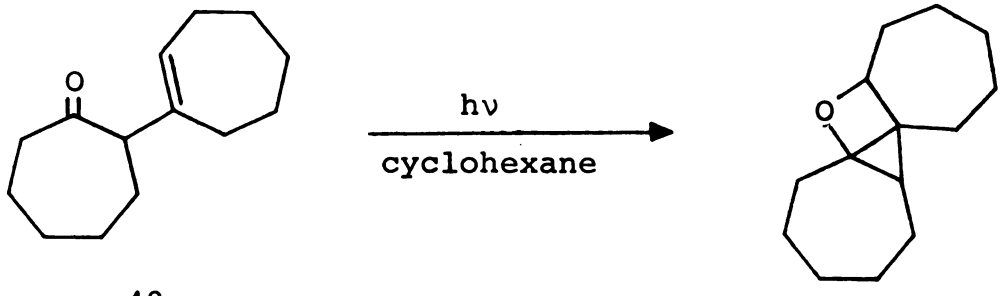
Much of the photochemistry of β,γ-enones suggests that, ordinarily, direct irradiation produces a 1,3-shift, and sensitization produces a 1,2-shift.[26] Some typical examples of this behavior are found in Chart 2.

The reactions of 44 are particularly instructive since the singlet pathway creates the skeleton of the guiane sesquiterpenes (e.g., bulnesol), and the triplet route yields a structure (45) similar to proposed intermediate 3 (Scheme 1). The synthetic utility of 43 as a guiane precursor is limited, however, by its low yield (50% based on recovered 44) and the unsatisfactory location of functionality.

In contrast with the photochemistry of 44 are the related systems 46 and 48, which give only cyclobutanol 47 and oxetane 49, respectively, on direct irradiation.[31]



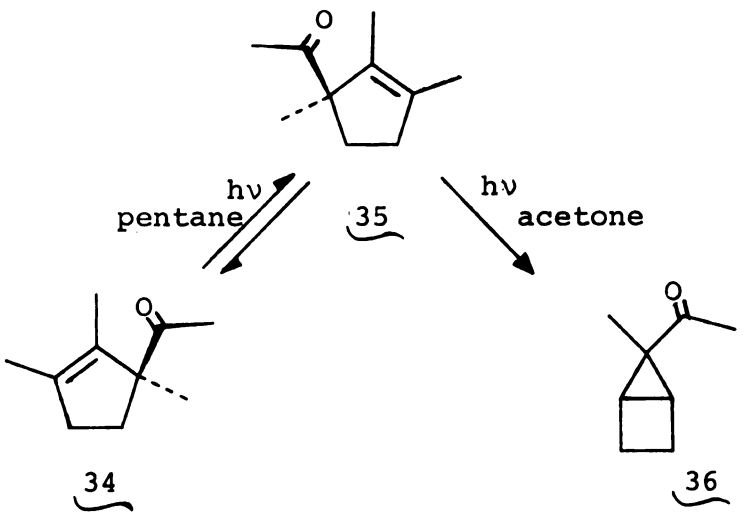
46 47



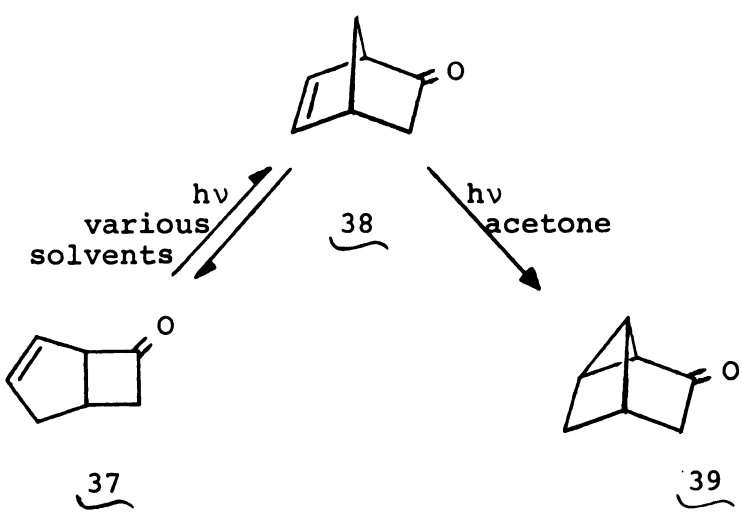
48 49

Chart 2. Examples of β,γ-Enones Which Give Both 1,2- and 1,3-Shifts.

1,3 Product	1,2 Product	(Reference)



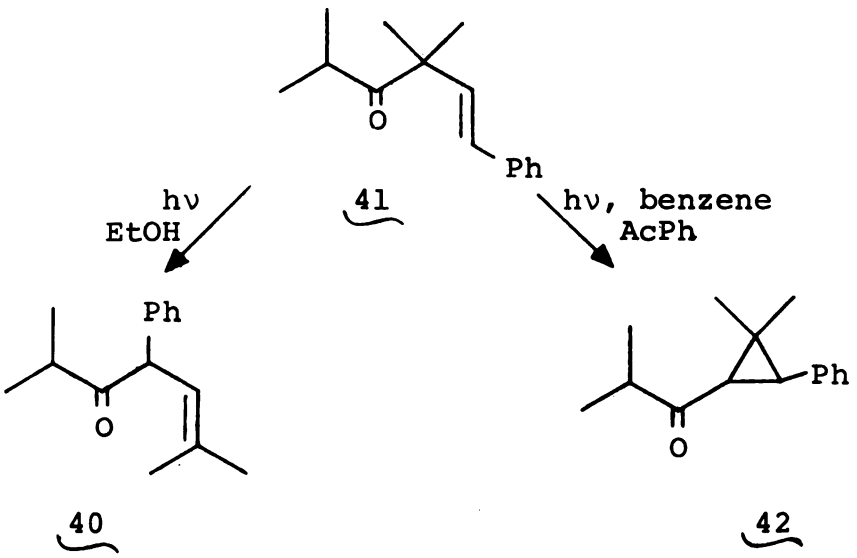
(26a)



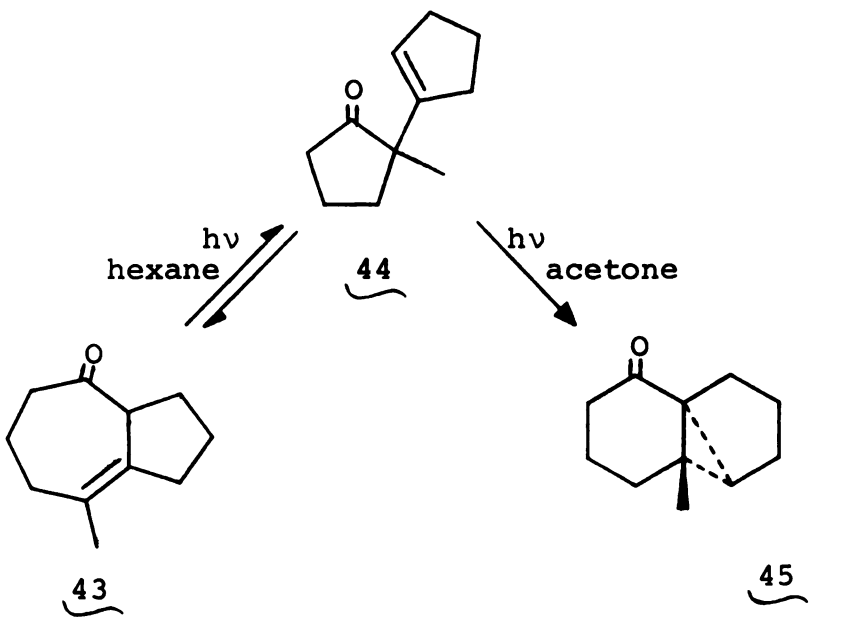
(26b)

Chart 2 (cont'd.)

1,3 Product	1,2 Product	(Reference)



(26d)

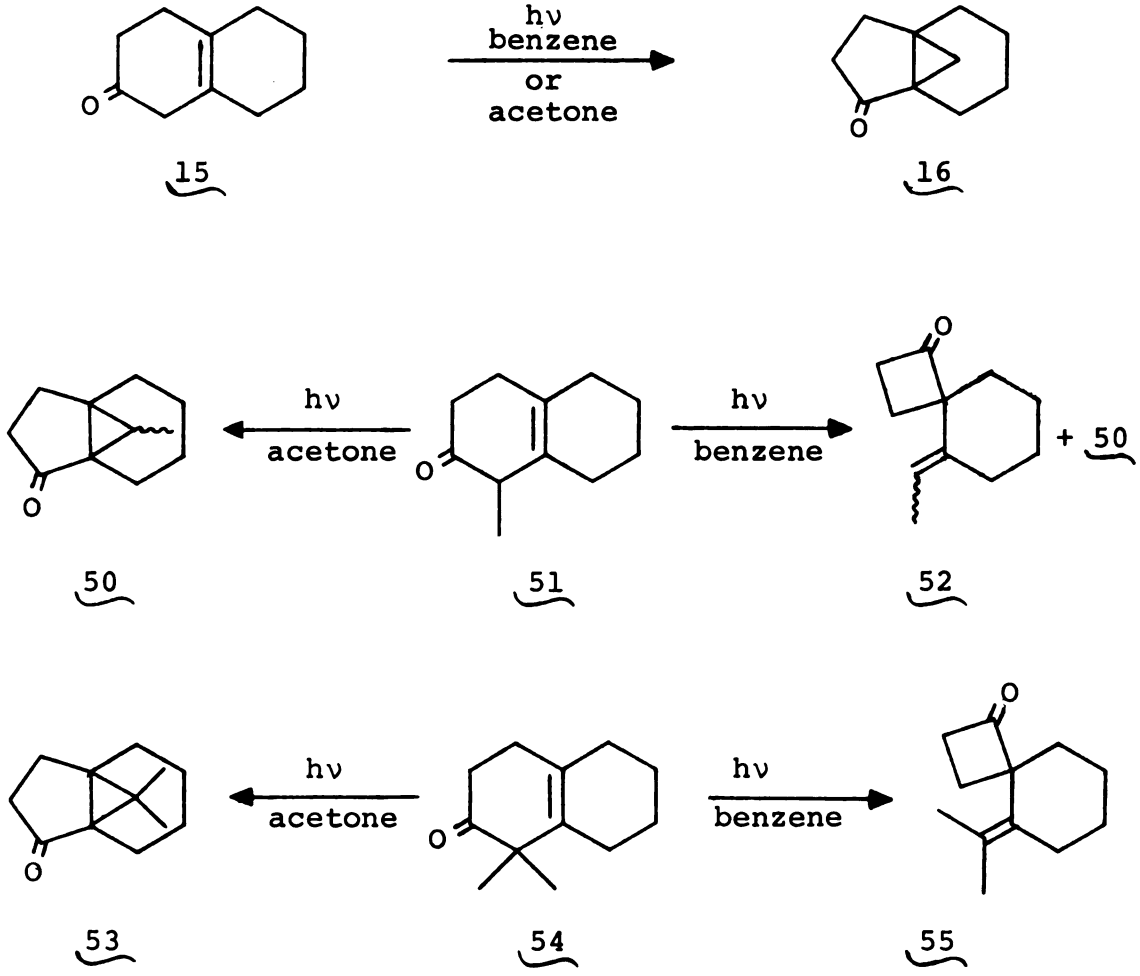


(26f)

In acetone solution, 46 and 47 merely photoisomerized to the corresponding α,β-enones. Again we note the striking effect of ring size on the course of reaction.

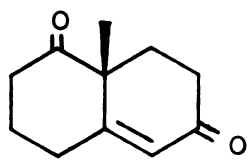
A recent study[26h] reveals that the number of α-alkyl substituents influences the competition between isc and 1,3-acyl shift. In particular, the rate of singlet reaction seems to be enhanced by α-methylation (Scheme 3).

Scheme 3

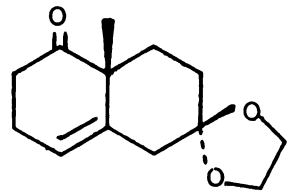


Compound 15, as previously noted, undergoes isc and exhibits no singlet reaction. Addition of one α-methyl group (51) reduces the amount of 1,2-shift, and rearrangement to 52 begins to occur from the singlet state. Two α-methyl substituents further increase the rate of the 1,3 shift leading to 55. An alternative explanation wherein α-substitution is said to decrease the rate of isc is considered unlikely by the authors. Moreover, differences in the geometry and ε values of these ketones are small and provide no adequate explanation for the observed differences in photochemical behavior. At present, the above results await both a theoretical interpretation and a correlation with other β,γ-enones.

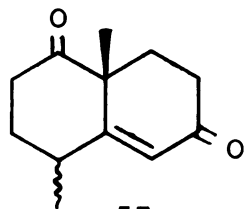
Because the photochemical consequences of minor structural changes in β,γ-enones are not well understood, the photorearrangements of both 2 and 58 were investigated. Presumably, only the influence of the γ-methyl group in 58 would account for any differences in photochemistry between these two ketones. The objective of this comparison was to gain some knowledge about the effects of double bond substitution on photorearrangement, rather than to use 58 in a synthesis.



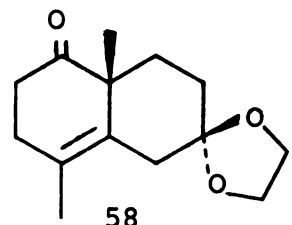
56



2

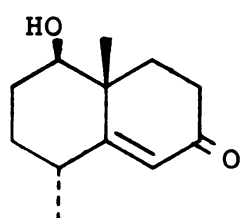


57



58

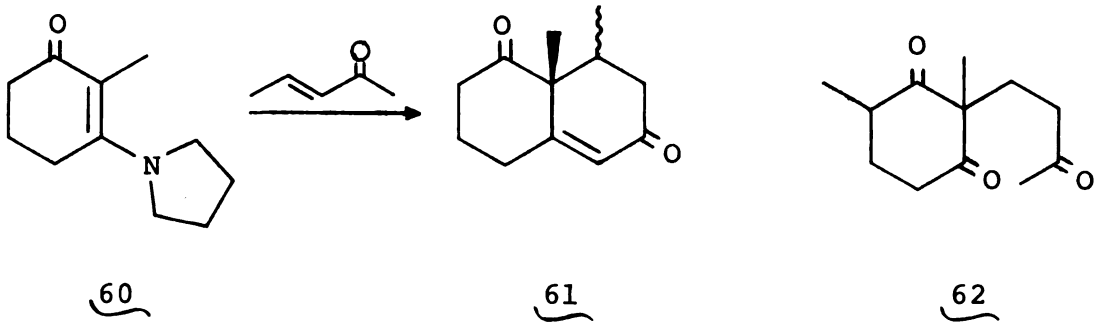
Some background regarding the synthesis of both 2 and 58 is in order. Ketal 2 can be prepared from Wieland-Miescher ketone 56,[32] but neither 58 nor its logical precursor enedione 57 has been reported. Enone alcohol 59 has been synthesized from 56 in eight steps[33] and could be oxidized to afford 57. However, a more direct route to the latter compound was sought.



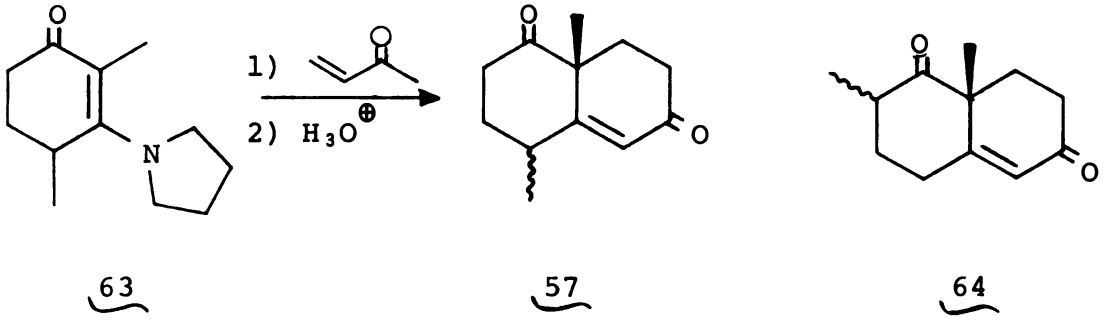
59

Modification of 56 is less efficient than incorporation of the 5-methyl group early in the synthesis of enedione 57. Consideration of a synthetic method used by Coates[34] (Scheme 4) suggested a possible approach to the problem.

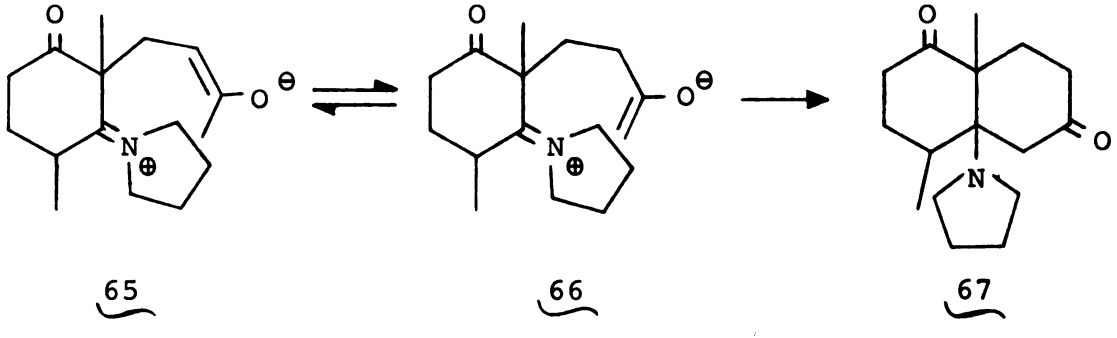
Scheme 4



60 61 62



63 57 64



65 66 67

Coates devised conditions for the conversion of enamino ketone 60 to enedione 61. A synthesis of 57 might proceed via the methylated enamino ketone 63, provided that cyclization could be made selective. If trione 62 is the precyclization intermediate, then differentiation between

the cyclohexanedione carbonyls will be lost, and cyclization would be expected to give mainly the isomeric enedione 64.

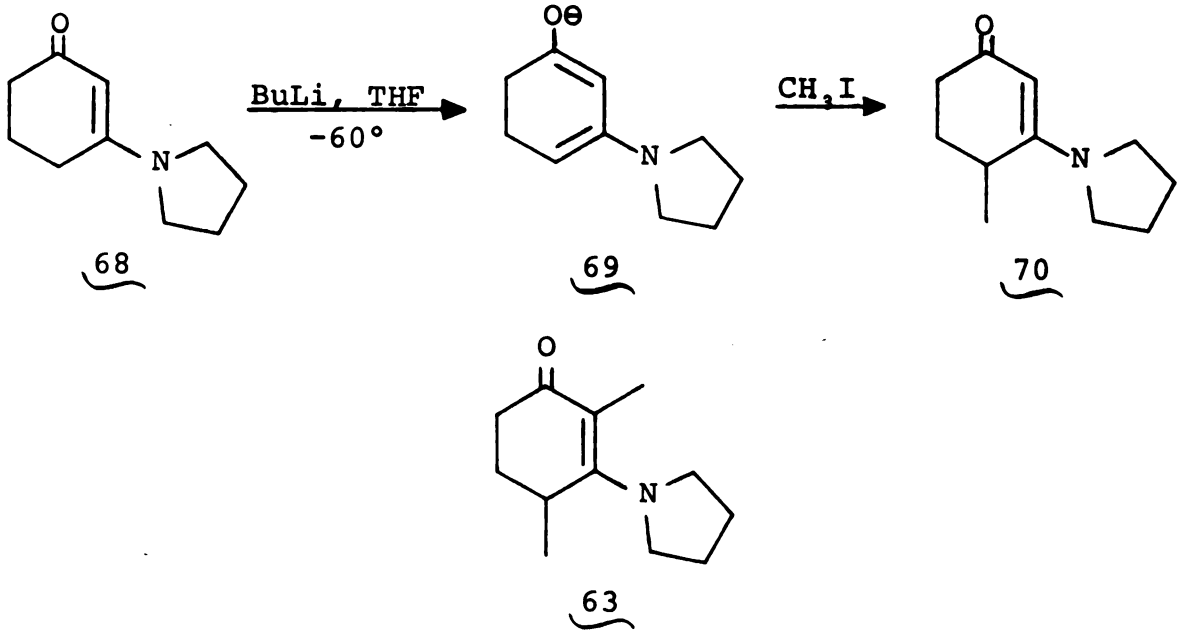
However, if 65 and 66 are the precyclization intermediates, selective cyclization to dione 67 would ultimately yield 57 exclusively, since the necessary differentiation of carbonyls would be maintained.

Both modification of 56 and the enamino ketone route were explored as potential synthetic pathways to 57.

RESULTS AND DISCUSSION

Much of the synthetic effort in the course of this research was directed toward the preparation of enedione 57. Therefore, investigations related to its synthesis will be described first.

The enamino ketone 63, required for the proposed route to 57 outlined in the Introduction, has not been reported in the literature. However, the recently described preparation[35] of 70 by γ-methylation of a conjugate base derived from the parent pyrrolidino enone 68 suggested a means of effecting a synthesis of 63.



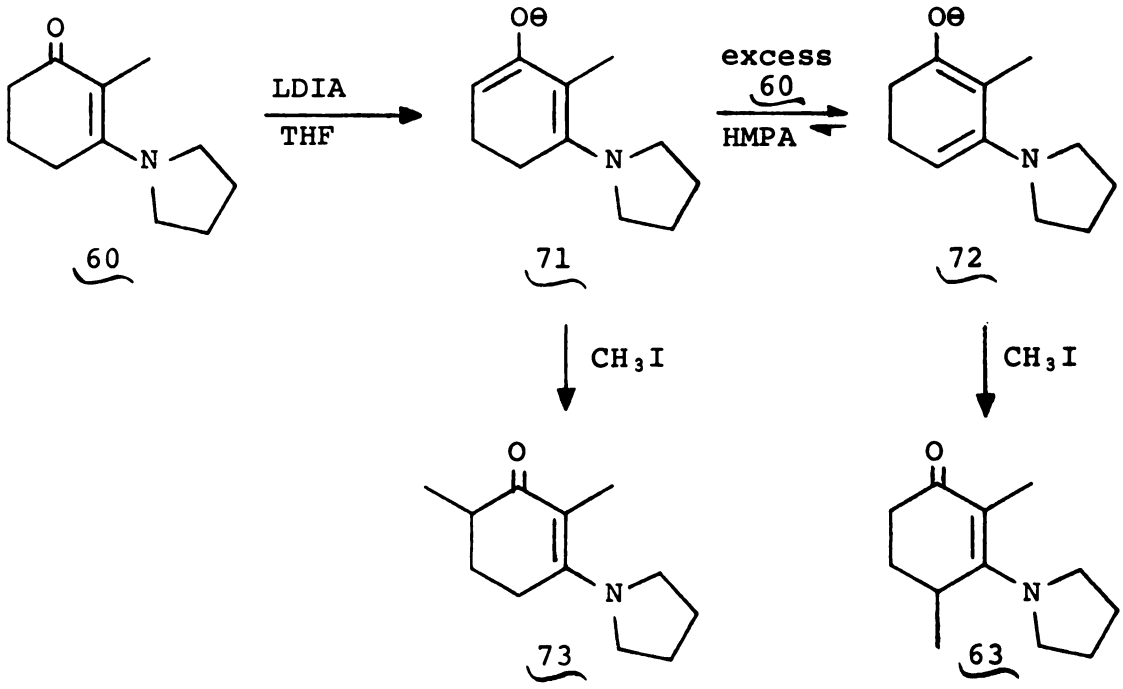
68 69 70

63

Alkylation of dienolate anion 69 at the γ-position is unusual, inasmuch as the fully-conjugated dienolates of α,β-unsaturated ketones react with alkylating agents exclusively at the α-position.[36]

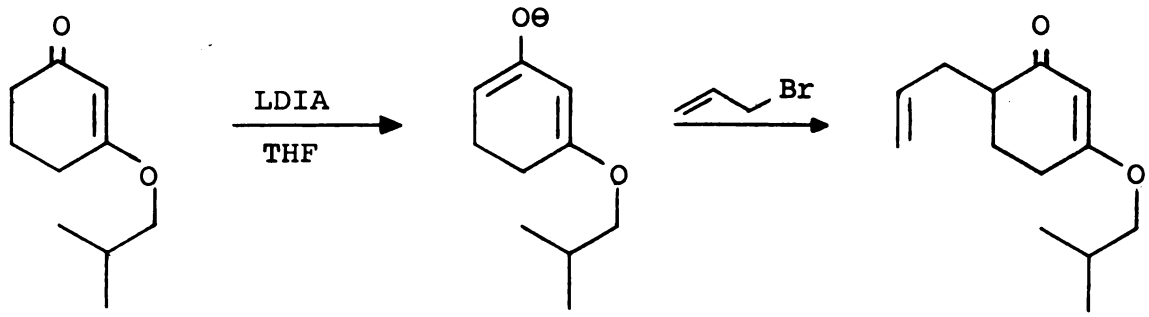
Unfortunately, the reported conversion of 68 to 70, with n-butyl lithium at low temperature, could not be duplicated, nor did these conditions, when applied to 60, yield 63. Previous successful application of 2°-amide bases in the formation of enolate anions[37] suggested their use here, and lithium diisopropyl amide (LDIA) was found to be effective under equilibrating conditions (Scheme 5).

Scheme 5



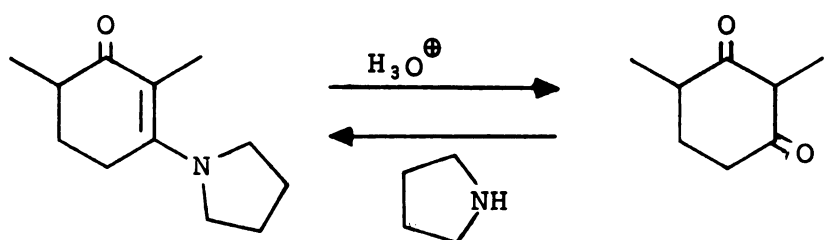
60 71 72 73 63

Initial formation of the kinetically favored cross-conjugated dienolate 71 was expected from previous work in this laboratory[37] as well as Stork's α'-allylation of enol ether 74 using this amide base.[38]



74 75 76

Compound 73 was distinguished from its isomer 63 by hydrolysis to 2,4-dimethylcyclohexane-1,3-dione 77, followed by reaction with pyrrolidine (at the less hindered carbonyl) to regenerate 73. The nmr spectra of 73 produced by methylation of 60 and by the above procedure were superimposable.

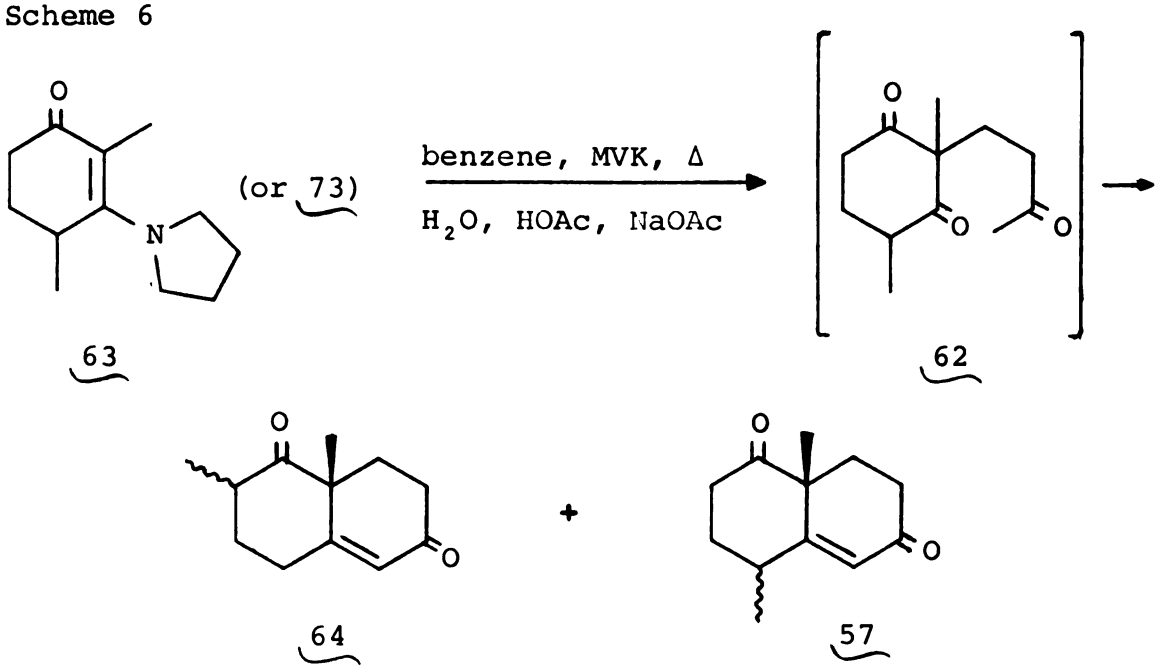


73 77

The equilibrium between the cross- and fully-conjugated dienolates (Scheme 5) was expected to favor the latter, since the additional charge delocalization in 72 should enhance its thermodynamic stability. Methylation of the equilibrated conjugate base did in fact take place at the γ-position, giving 63 essentially uncontaminated with the α'-isomer 73.

Scheme 6 illustrates the results of using Coates' reaction conditions[34] for the condensation of vinylogous amide 63 (or 73) with methyl vinyl ketone (MVK).

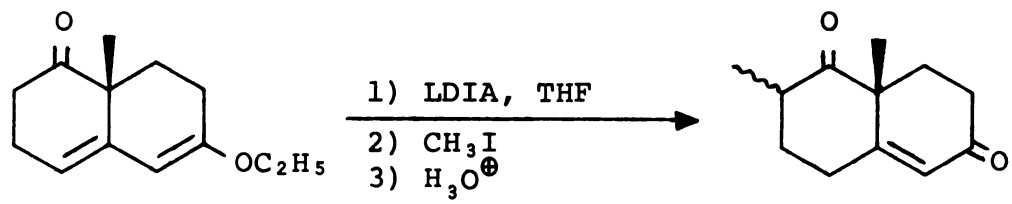
Scheme 6



Both 63 and 73 yielded a mixture of isomeric enediones 64 and 57 in a ratio of 5:1, respectively. Compound 57 was identified by comparison of its glpc retention time with a known sample prepared by an alternative route. Both 62 and

64 were isolated by preparative glpc and tentatively identified by their ir and mass spectra. In addition, 64 was synthesized *via* methylation of the known dienol ether 78[39] (equation 11). Samples of 64 produced by these two routes had the same glpc retention times and ir spectra.

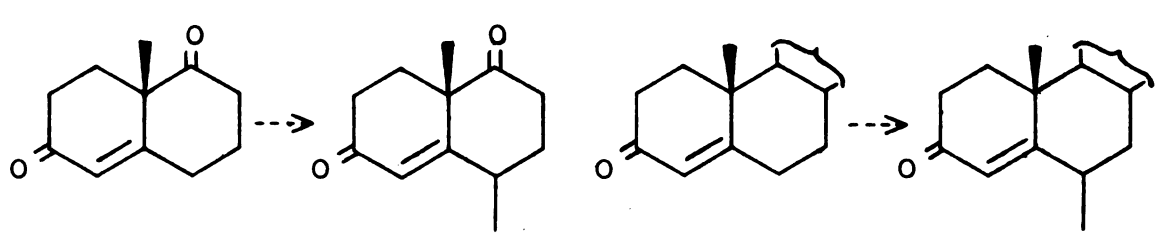
(11)



78 64

Unfortunately, under a variety of anhydrous conditions (to prevent formation of 62) the reaction of 63 with methyl vinyl ketone failed to produce significant amounts of the annelation product 57 (or 64). A different synthetic approach was ultimately successful.

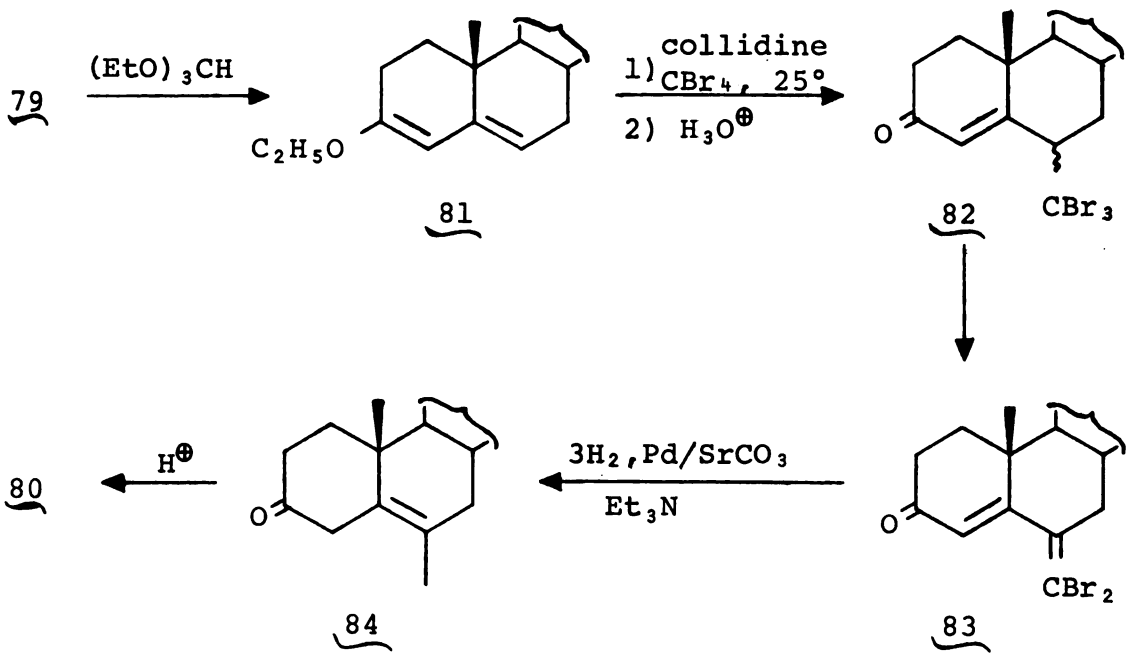
The structural similarity between Wieland-Miescher ketone 56 and the A- and B-rings of Δ^4-3-ketosteroids 79 is obvious. Therefore, modification of 56 to yield 57 should be possible by methods paralleling the synthesis of 6-methyl-Δ^4-3-ketosteroids (80 from 79).



56 57 79 80

One method which reportedly effects this transformation, without the need to protect other carbonyl functions, is the reaction of a dienol ether derivative (81) with carbon tetrabromide[40] (Scheme 7). The mechanism whereby 82 is formed is unknown.

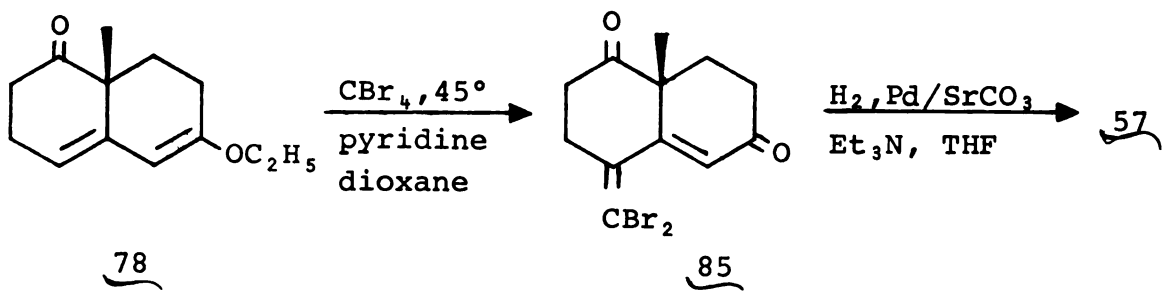
Scheme 7



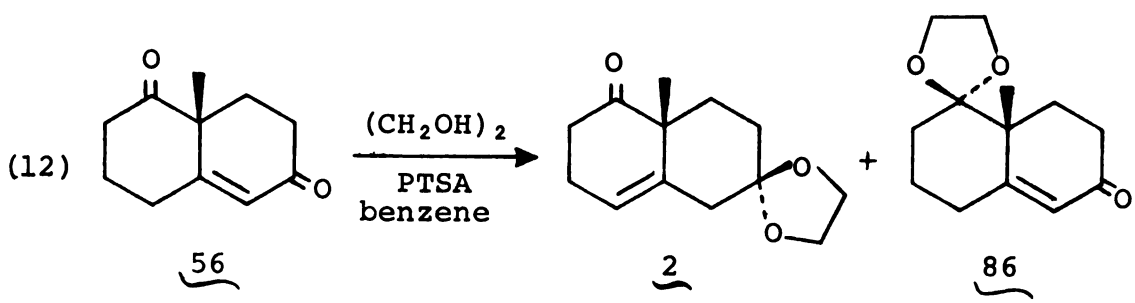
When applied to 56 this approach did provide some 57, although the yields were poor. The expected tribromomethyl and unconjugated enones, analogous to 82 and 84, were not isolated in our sequence, which began with the dienol ether 78 (Scheme 8). Incomplete reaction presented difficulties in the conversion of 78 to 85, and the separation of 57 from

six or seven other hydrogenation products required careful chromatography.

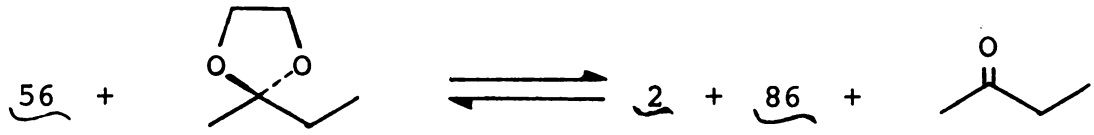
Scheme 8



The final synthetic requirement was selective ketalization of enediones 56 and 57. Ketal 2 has been prepared from 56 by two rather limited methods.[32] Direct ketalization (equation 12) gives a mixture of 2 and 86 which can be separated by chromatography. However, the reaction is not reproducible and generally favors the thermodynamically more stable ketal 86.

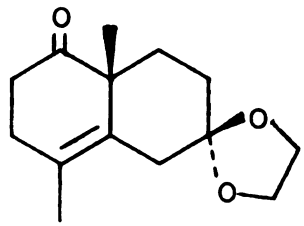


A selective cross-ketalization procedure was developed using 2-ethyl-2-methyl-1,3-dioxolane 87. When 56 was refluxed in excess 87 with an acid catalyst, ketal 2 could be crystallized from the crude product mixture in 43% yield. No chromatography is necessary, and the mother liquors can be hydrolyzed to 56 for recycling. Use of 87 as the



87 88

reaction solvent helps to shift the equilibrium to the right. Similar conditions were used to prepare the methylated ketal 58 in 68% yield from 57.

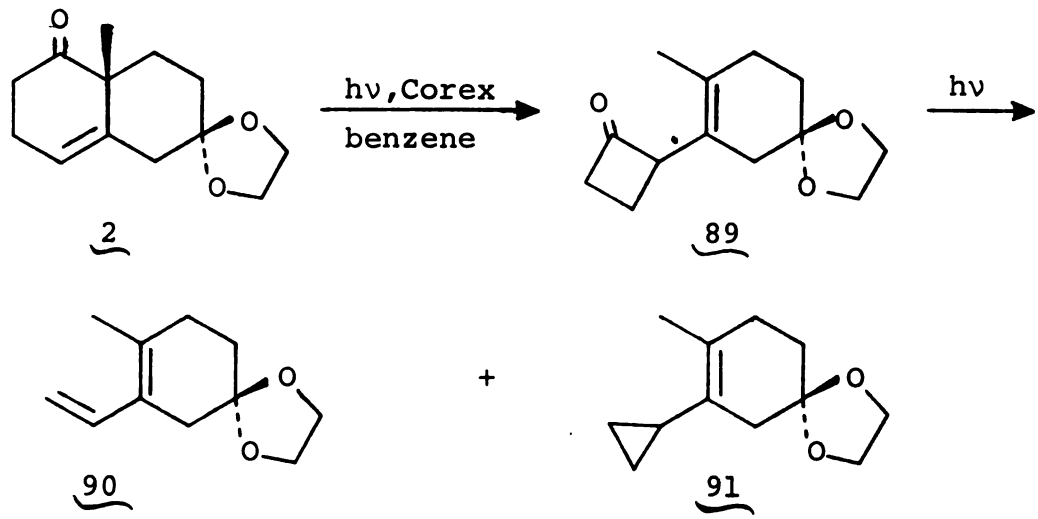


58

Photolysis of the β,γ-unsaturated ketone 2, either directly or with acetone sensitization, gave none of the desired 1,2-acyl shift product. Only products derived from a 1,3-shift were observed. On prolonged irradiation with a 400-W Hanovia lamp fitted with a Corex filter, a 0.05 M benzene (or ether) solution of enone 2 yielded two photoproducts, identified as diene 90 and cyclopropane 91 (equation 13). Use of an internal standard revealed that

90 and 91 were the only significant products and were produced in a ratio of 2.2:1, respectively. At shorter irradiation times the 1,3-acyl shift product cyclobutanone 89 was also observed. Its concentration increased initially and then decreased gradually as the reaction continued.

(13)



Since cycloelimination and decarbonylation are principal photoreactions of cyclobutanones,[41] the formation of these two products is not surprising.

The absence of a 1,2-shift on direct photolysis of 2 is also not unusual, since β,γ-enones ordinarily require triplet sensitization for this type of rearrangement. However, enone 2 gave no detectable 1,2-shift product when irradiated in 0.05 M acetone solution. The disappearance of starting material was much slower in acetone than in benzene, and sizable amounts of nonvolatile, polar materials were produced, as evidenced by tlc. Cyclobutanone 89 and cyclopropane 91 were present, but only a trace of diene 90

was detected by glpc analysis.

This last fact may indicate that triplet sensitization of 89 favors decarbonylation (to give 91), or that 90 forms but is subsequently consumed by reaction with solvent.

Because the photorearrangement of 2 was slightly faster in benzene than in ether, an experiment was performed to determine whether benzene was sensitizing this reaction. Benzene (λ_{max} 256 nm) absorbs light of 253.7 nm strongly, but ether is transparent at this wavelength. During irradiation of 2 with a mercury resonance lamp (253.7 nm), the initial rate of reaction was about four times faster in a 0.05 M benzene solution than in an equimolar ether solution. Glpc analysis revealed that the usual photoproducts were produced in benzene, but that diene 90 was absent in ether, although 89 and 91 were present. Tlc showed substantial amounts of nonvolatile substances in the benzene solution but not in the ether solution.

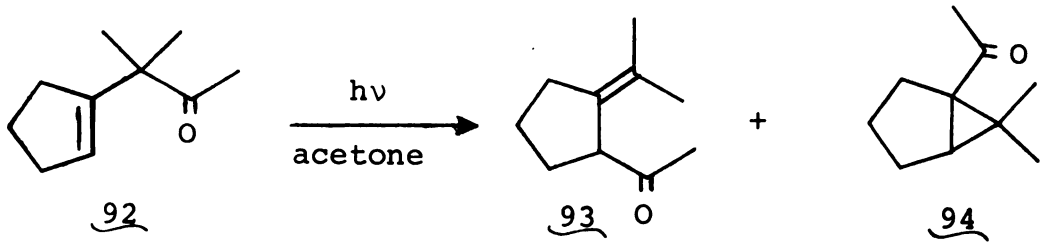
The above facts suggest that the rate of consumption of 2 during irradiation at 253.7 nm may be faster in benzene because of energy transfer from, and/or reaction with, this solvent.

The rate of the 1,3-acyl shift of 2, on irradiation in benzene or ether with the Hanovia lamp, was compared for reactions with and without added 1,3-pentadiene. The enone reacted about 1/2 as fast in benzene and 1/5 as fast in ether when 2M piperylene was present. The photodecomposition

of cyclobutanone 89 seemed to be less retarded by the added diene.

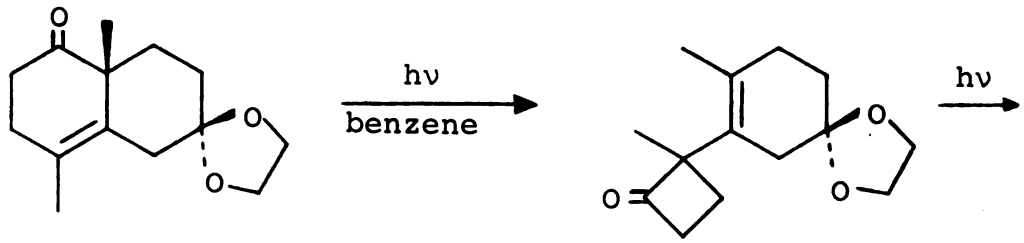
Because this photorearrangement appears to be sensitized by benzene and partially quenched by piperylene, some of the 1,3-shift may arise from the triplet excited state of 2. However, there is evidence that benzene (in fluid solution) can act as a singlet sensitizer[42] because its singlet and triplet lifetimes are about the same ($\backsim 2 \times 10^{-8}$ sec),[42] and its intersystem crossing efficiency is low (0.24, based on 1.00 for benzophenone).[43] In addition, concentrated solutions (1-10 M) of 1,3-pentadiene have been shown to quench the excited singlet states of ketones.[44] Thus, the assumption that piperylene acts exclusively as a triplet quenching agent is not always justified. The apparent inability of acetone to sensitize the photoreaction of 2 is also inconsistent with the occurrence of a triplet 1,3-shift in this case.

The nature of the excited state from which 2 undergoes rearrangement remains unclear, but one would certainly expect a singlet 1,3-acyl shift based on the work described earlier in this thesis. There seems to be no report of a simple triplet 1,3-shift, although both a triplet 1,2- and 1,3-shift occur concurrently in the sensitized photolysis of enone 92[23] (equation 14).

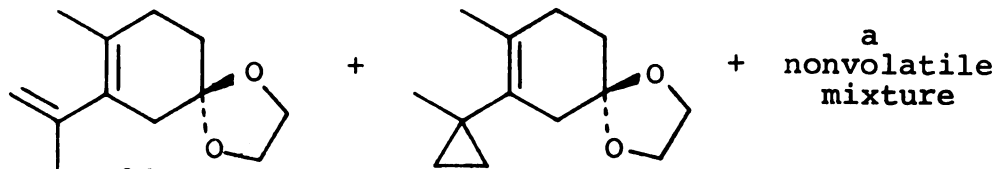
(14) 

92 93 94

The photoreactions of the methylated enone 58 (equation 15) were conducted in the manner already described for 2. After complete reaction in benzene solution, the volatile photoproducts were diene 96 and cyclopropane 97 in a 1:1 ratio, and a small amount (<1%) of a mixture of at least two unidentified components.

(15) 

58 95



96 97

In contrast to the relatively clean reaction of 2, about 40% of the total product mixture from 58 consisted of nonvolatile substances of unknown composition (tlc shows only a streak near the origin). As expected, cyclobutanone 95 was isolated after short irradiation.

As noted with 2, the photoreaction of 58 in benzene was slowed but not stopped by the addition of 1,3-pentadiene (2M).

In acetone solution, the disappearance of 58 was very slow relative to irradiation of an equimolar benzene solution. Both 96 and 97 were produded, but the latter compound predominated. In addition, six or seven new volatile photoproducts were detected by glpc, which suggests that additional reactions, probably with solvent, were taking place. The possibility that some 1,2-shift occurs in the photoreactions of 58 cannot be ruled out.

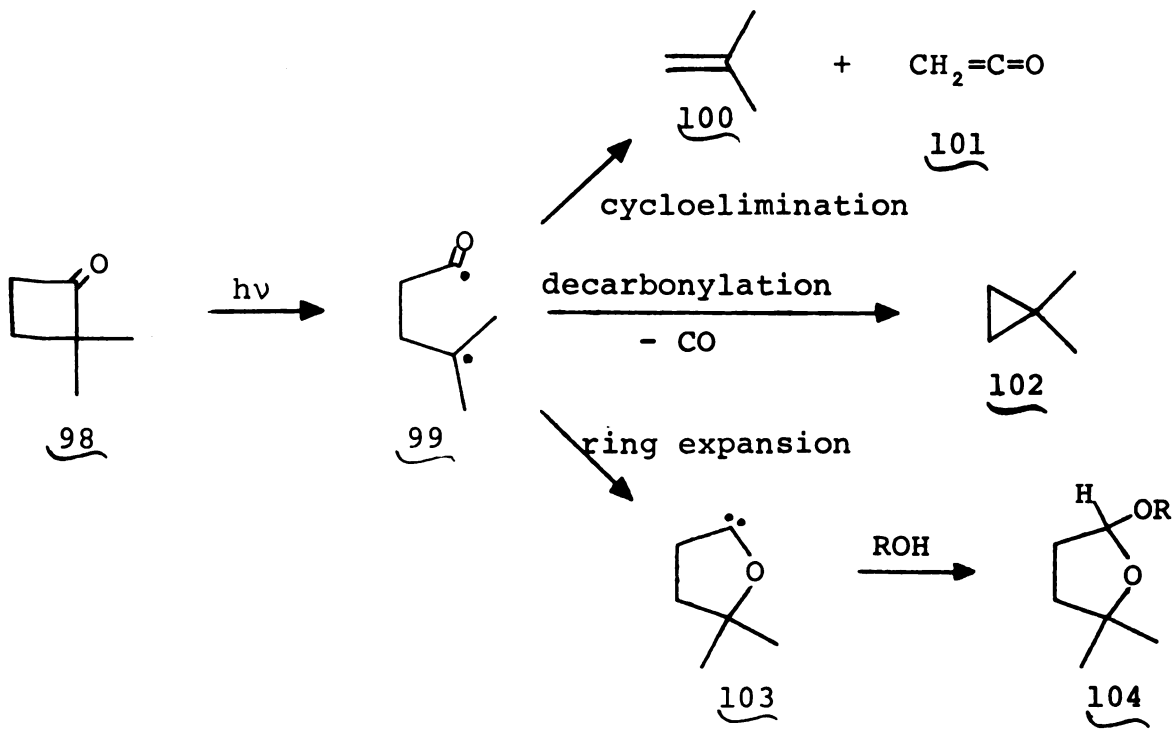
It is evident from the data presented here that the photochemistry of β,γ-unsaturated ketones 2 and 58 has both similarities and differences. The products of the 1,3-photorearrangement of each enone are analogous, although their relative amounts differ. Photolysis of 2 is a "clean" process, whereas 58 yields substantial amounts of unknown by-products. The reaction of each enone is slower in acetone than in benzene solution; but 58, unlike 2, produces new volatile substances on photosensitization.

Compounds 2 and 58 have very similar ultraviolet absorption spectra (λ_{max} (2) 290 nm [ε 31], λ_{max} (56) 290 nm [ε 30]). Consequently, the different photochemical behavior of 58 is almost certainly due to the influence of its extra methyl group on steps subsequent to the absorption of light.

One can only speculate about what processes are modified by this substitution factor.

One effect of the γ-methyl substituent might be that an additional photoreaction pathway is created. Studies of cyclobutanones have shown that successive introduction of α-alkyl substituents changes the proportions of the photoproducts.[41] Besides decarbonylation and cycloelimination, cyclobutanones may also undergo ring enlargement via carbenes (Scheme 9), and this process is enhanced by α-alkyl substitution.[41]

Scheme 9



Without added nucleophiles (e.g., ROH), a high energy intermediate such as 103 could conceivably give rise to a variety of products (such as dimers). Therefore, it is possible that cyclobutanone 95, because of its extra α-substituent, may produce some nonvolatile photodecomposition products derived from a carbene, even though 89 does not.

EXPERIMENTAL

General

In addition to the instruments described in Part I, a Cary 17 Spectrophotometer was used to record two of the ultraviolet spectra, and the Varian Aerograph 90-P3 and Series 1200 gas chromatographs were used for glpc work.

All mass spectral data can be found in the Appendix.

2-Methyl-3-(1-pyrrolidyl)-2-cyclohexene-1-one (60)

The procedure of Coates[34] was used and the product was purified by crystallization from ether, mp 37-39°. Enamino ketones 60, 63, and 73 are deliquescent and air sensitive, so careful handling is necessary.

2,6-Dimethyl-3-(1-pyrrolidyl)-2-cyclohexene-1-one (73)

To a chilled (0°) solution of 0.31 ml (2.2 mmol) of diisopropylamine in 1 ml of dry tetrahydrofuran (THF) was added 1.0 ml of a 2.15 M solution of n-butyl lithium in hexane. The resulting solution of lithium diisopropylamide (LDIA) was stirred at 0° for 30 min before a solution of 358 mg (2.0 mmol) of enamino ketone 60 in 1 ml of THF was added.

This enolate solution was stirred at 0° for 30 min, following which 0.15 ml (2.4 mmol) of methyl iodide was added. The resulting mixture was warmed to room temperature, stirred for 15 min, and then diluted with a little water before being concentrated.

An ethyl acetate solution of the residue was extracted three times with small amounts of water, and the aqueous layer was re-extracted with ethyl acetate. The combined organic extracts were washed with brine and evaporated to leave 351 mg (91%) of light brown oil which crystallized when chilled.

Compound 73 was also synthesized by treatment of its hydrolysis product, dione 77, with pyrrolidine. A solution of 96.5 mg (0.5 mmol) of enamino ketone 73 (prepared as described above) in five drops of 5% hydrochloric acid was heated at 110° for 10 min and then extracted with ethyl acetate. The organic extract was washed with brine and evaporated to give 65 mg of yellow crystals of 77. A solution of 77 in 3 ml of benzene and 0.075 ml of pyrrolidine was refluxed through a Dean Stark trap for 75 min and then concentrated. An nmr spectrum of this crude product was superimposable on that of 73 produced by methylation of 60.

Several recrystallizations of 73 from ether gave colorless deliquescent crystals: mp 27-35°; ir (neat) 1540, 1605 cm^{-1}; nmr ($CDCl_3$) δ1.04 (d, 3H, J 6.5 Hz, C-6 $C\underline{H}_3$), 1.77 (brd m, 7H, C-5 $C\underline{H}_2$, C-6 $C\underline{H}$, C-3' and C-4'

pyrrolidine methylenes), 1.86 (s, 3H, C-2 $C\underline{H}_3$), 2.50 (brd t, 2H, C-4 $C\underline{H}_2$), 3.45 (m, 4H, C-2' and C-5' pyrrolidine methylenes); uv max (95% EtOH) 317 nm (ε 2.63 x 10^4).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25
Found: C, 74.66; H,10.01; N, 7.29

2,4-Dimethyl-3-(1-pyrrolidyl)-2-cyclohexene-1-one (63)

To a solution of 4.6 mmol of LDIA in 2.5 ml of THF at 0° was added a solution of 895 mg (5.0 mmol, 8.7% excess) of 60 and 2.5 ml of dry hexamethylphosphoramide (HMPA) in 2.5 ml of THF. The resulting enolate solution was stirred at room temperature for 21 hr and then at 40° for 3 hr.

After the solution was cooled to 0°, 0.35 ml (5.6 mmol) of methyl iodide was added, and the mixture was allowed to return to room temperature for 1.5 hr.

This mixture was concentrated, diluted with 10 ml of water, and extracted six times with ethyl acetate, giving 986 mg of yellow oil (contaminated with a little HMPA) on evaporation of the solvent.

Column chromatography (silica gel, 10% methanol-ether) of 748 mg of this oil gave 403 mg (63% based on LDIA and normalized to account for material not chromatographed) of light tan oil. Several recrystallizations from ether gave colorless crystals: mp 27-35°; ir (neat) 1540, 1605 cm^{-1}; nmr ($CDCl_3$) δ1.20 (d, 3H, J 7Hz, C-4 $C\underline{H}_3$), 1.87 (brd m, 6H, C-5 $C\underline{H}_2$, C-3' and C-4' pyrrolidine methylenes), 1.91 (s, 3H,

C-2 CH_3), 2.36 (brd t, 2H, C-6 CH_2), 2.55 (brd m, 1H, C-4 CH), 3.56 (m, 4H, C-2' and C-5' pyrrolidine methylenes); uv max (95% EtOH) 323 nm (ϵ 2.63 x 10^4).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25
Found: C, 74.56; H, 9.95; N, 7.18

Reaction of 63 with methyl vinyl ketone

To a solution consisting of 0.13 ml of water, 0.13 ml of acetic acid, and 62 mg of sodium acetate was added 0.070 ml of methyl vinyl ketone and 193 mg (1.0 mmol) of 63 in 1 ml of benzene. The mixture was refluxed for 4.5 hr, cooled, diluted with benzene, and extracted four times with 5% hydrochloric acid.

The organic phase was washed successively with water, 10% sodium bicarbonate, and brine, and gave 142 mg of yellow oil on concentration.

Glpc analysis (5' 4% QF-1, 175°) of this oil revealed three components. Enediones 64 and 57 were present in a ratio of about 5:1 respectively. The concentration of the third constituent, trione 62, diminished greatly in the final product compared to its concentration after only 3 hr of reaction. Both 62 and 64 were isolated by preparative glpc (10' 4% QF-1, 190°) and were tentatively identified by their mass and ir spectra. In addition, enedione 64 was synthesized via methylation of dienol ether 78, and both samples of 64 were shown to have the same glpc retention

times and ir spectra. Enedione 57 was identified in the mixture by comparing its glpc retention time with that of an authentic sample. Spectral characteristics for 62 and 64 are given below.

2,4-Dimethyl-2-(3-oxobutyl)-cyclohexane-1,3-dione (62)

ir (CCl_4) 1695, 1720 cm^{-1}; mol wt 210

1,3-Dimethylbicyclo-[4.4.0]-dec-6-ene-2,8-dione (64)

ir (CCl_4) 1615, 1675, 1710 cm^{-1}; mol wt 192

Reaction of 73 with methyl vinyl ketone

To a solution consisting of 0.13 ml of water, 0.13 ml of acetic acid, and 62 mg of sodium acetate was added 0.100 ml of methyl vinyl ketone and 215 mg (1.11 mmol) of 73 in 1 ml of benzene. The mixture was refluxed for 4 hr and worked up as described in the previous section, giving 179 mg of a yellow oil. Glpc analysis of this oil indicated that only enediones 64 and 57 were present in a ratio of about 5:1.

1,3-Dimethylbicyclo-[4.4.0]-dec-6-ene-2,8-dione (64)

To a solution of 0.50 mmol of LDIA in 0.5 ml of THF at -78° was added a solution of 103 mg (0.50 mmol) of dienol ether 78 in 0.7 ml of THF. The resulting greenish

solution was stirred at -78° for 20 min, and then treated with 0.035 ml (0.60 mmol) of methyl iodide. This solution was stirred at -78° for 10 min and at room temperature for 30 min, and then it was diluted with water and ether. The organic phase was washed successively with 5% hydrochloric acid, water, and brine giving 103 mg of methylated dienol ether after evaporation of the solvent.

This crude product was hydrolyzed in a solution containing 1 ml of THF, one drop of 6N hydrochloric acid, and several drops of water. After standing for 3 hr at room temperature, the solution was worked up as usual to give 83 mg (87%) of methylated enedione 64. Purification via preparative glpc (10' 4% QF-1, 200°) gave a light yellow oil: ir (neat) 1615, 1670, 1710 cm^{-1}; nmr (CCl_4)-mixture of epimers, main peaks are δ1.02 (d, 3H, J 6.5 Hz C-3 CH_3), 1.41 (s, 3H, C-1 CH_3), 1.46-3.07 (brd m, 9H, C-4, C-5, C-9, C-10 methylenes, C-3 CH), 5.61 (m, 1H, vinyl proton).

8-Ethoxy-1-methylbicyclo-[4.4.0]-dec-5,7-diene-2-one (78)

A solution consisting of 35 ml of benzene, 9 ml (54 mmol) of distilled triethyl orthoformate, 15 mg of p-toluenesulfonic acid (PTSA), and 8.9 g (50 mmol) of Wieland-Miescher ketone 56 was stirred at room temperature for 4 hr. Analysis by glpc indicated complete conversion of 56 to a new product.

The reaction mixture was neutralized with three drops of triethylamine, diluted with 35 ml of ether, and extracted successively with 15 ml of 10% sodium bicarbonate, 20 ml of water, and 20 ml of brine. Evaporation of the solvents left a yellow oil, which could be used without further purification or crystallized from ether, mp 39-43°.

5-Dibromomethylene-1-methylbicyclo-[4.4.0]-dec-6-ene-2,8-dione (85)

A solution containing 618 mg (3.0 mmol) of dienol ether 78, 2.00 g (6.0 mmol) of carbon tetrabromide, 3 ml of pyridine, and 3 ml of dioxane was maintained at room temperature for 24 hr and then heated at 45° for 24 hr.

The resulting dark solution was filtered to remove the crystalline pyridinium hydrobromide-carbon tetrabromide complex, and the filtrate was concentrated, acidified, and extracted with ethyl acetate. The organic extract was washed three times with 6N hydrochloric acid to remove colored impurities and then with 10% sodium bicarbonate and brine. Evaporation of solvents gave 954 mg of a brown semisolid which was chromatographed (silica gel, ether) to yield 514 mg (50%) of brown 85. Several recrystallizations from methylene chloride-ether gave white crystals: mp 85-86°, ir (KBr) 1565, 1610, 1665, 1720 cm^{-1}; nmr ($CDCl_3$) δ1.36 (s, 3H, CH_3), 1.87-2.84 (m, 8H, C-3, C-4, C-9, C-10 methylenes), 6.25 (s, 1H, vinyl proton); uv max (95% EtOH) 260 nm (shoulder) (ε 5,700), 287 nm (ε 7,600).

Anal. Calcd for $C_{12}H_{12}Br_2O_2$: C, 41.41; H, 3.48
Found: C, 41.44; H, 3.38

1,5-Dimethylbicyclo-[4.4.0]-dec-6-ene-2,8-dione (57)

To a suspension of 800 mg of 2% $Pd/SrCO_3$ catalyst (saturated with hydrogen) in 6 ml of dry THF was added a solution of 1.740 g (5.0 mmol) of 85 and 1.4 ml (10 mmol) of triethylamine in 8 ml of THF. The suspension was stirred vigorously and allowed to absorb 376 ml (15.0 mmol) of hydrogen at atmospheric pressure.

After filtration, the catalyst was washed well with THF, and the filtrate was concentrated. An ether solution of the residue was extracted with water and brine and evaporated to give 987 mg of a yellow oil which was chromatographed (silica gel, 30% ethyl acetate-hexane). The fractions containing 57 were evaporated, leaving 312 mg (32%) of a light yellow oil.

An nmr spectrum of this product showed that it was a mixture of epimers. The more stable equatorial methyl epimer could be isolated after equilibration of the product in a carbon tetrachloride solution containing gaseous hydrogen chloride. Recrystallization of the equilibrated product from ether-petroleum ether solution gave white needles: mp 28-34°, ir (KBr) 1605, 1665, 1710 cm^{-1}; nmr (CCl_4) δ1.18 (d, 3H, J 6.5 Hz, C-5 CH_3), 1.39 (s, 3H, C-1

CH_3), 1.50-2.90 (m, 9H, C-3, C-4, C-9, C-10 methylenes and C-5 CH), 5.60 (d, 1H, J 2 Hz, vinyl proton).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39
Found: C, 74.83; H, 8.31

1-Methylbicyclo-[4.4.0]-dec-5-ene-2,8-dione-8-ethylene ketal (2)

A solution of 356 mg (2.0 mmol) of 56 and 10 mg of PTSA in 5 ml of 2-ethyl-2-methyl-1,3-dioxolane (87) was distilled (bp 68-80°) slowly for 2 hr to remove methyl ethyl ketone. The cooled solution was diluted with 5 ml of benzene and extracted twice with 10% sodium bicarbonate and once with brine. Evaporation of the solvents left 430 mg of a yellow oil which, when crystallized from ether-petroleum ether, gave 191 mg (43%) of ketal 2. Recrystallization from the same solvent mixture produced white needles, mp 68-70° (lit[32] mp 63-64.5°). The ir and nmr spectra agree with those reported[32] for 2.

1,5-Dimethylbicyclo-[4.4.0]-dec-5-ene-2,8-dione-8-ethylene ketal (58)

A solution of 515 mg (2.68 mmol) of enedione 57 and 12 mg of PTSA in 5 ml of 87 was refluxed for 11 min (duration of reflux is critical). The solution was cooled, stirred for 10 min with ten drops of 10% sodium bicarbonate, and diluted with 5 ml of ether.

The ether solution was washed with water and brine, and, after concentration, yielded 633 mg of an orange oil. Crystallization of this oil from ether afforded 318 mg of 58. The mother liquors were purified by preparative thick layer chromatography (silica gel, 60% ether-petroleum ether) and yielded an additional 110 mg of 58 for a total yield of 68%. Recrystallization from ether gave colorless needles: mp 86-88°, ir (KBr) 1710 cm^{-1}; nmr (CCl_4) δ1.18 (s, 3H, C-1, CH_3), 1.60 (m, 7H, C-5 CH_3, C-9 and C-10 methylenes), 2.30 (m, 6H, C-2, C-3, and C-7 methylenes), 3.79 (s, 4H, dioxolane methylenes), uv max (95% EtOH) 290 nm (ε 30).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53
Found: C, 71.04; H, 8.68

Photolysis of 1-methylbicyclo-[4.4.0]-dec-5-ene-2,8-dione-8-ethylene ketal (2) and 1,5-dimethylbicyclo-[4.4.0]-dec-5-ene-2,8-dione-8-ethylene ketal (58)

General Procedure:

Except as noted, all photolyses were conducted using a 500-W medium pressure Hanovia lamp suspended in a water cooled quartz housing and fitted with a Corex filter. Solutions of ketals 2 and 58 in spectral grade solvents were placed in quartz test tubes and degassed by bubbling nitrogen through them for about 10 min. After sealing with a rubber septum, the test tubes were affixed to the side of

the quartz housing, and the apparatus was partially immersed in an ice water bath. At specified intervals during irradiation, samples were removed from the test tubes and analyzed by glpc, using a 6 ft 4% SE-30 column at 130-150°.

Preparation of 4-methyl-3-vinyl-3-cyclohexene-1-one ethylene ketal (90) and 4-methyl-3-cyclopropyl-3-cyclohexene-1-one ethylene ketal (91)

A total of 9 ml of a 0.05 M solution of 2 in benzene was irradiated for 2 hr and then concentrated. Compounds 90 and 91 were collected by glpc (10' 4% SE-30, 160°) as colorless liquids, having spectral data as follows.

90: ir (neat) 1590, 1635 cm^{-1}; nmr (CCl_4) δ1.67 (t submerged under other signals, 2H, C-6 $C\underline{H}_2$), 1.80 (s, 3H, C-4 $C\underline{H}_3$), 2.26 (m, 4H, C-2 and C-5 methylenes), 3.93 (s, 4H, dioxolane methylenes), 4.98 (overlapping d of d, 2H, $C=C\underline{H}_2$), 6.76 (d of d, 1H, J 17 Hz, J 18 Hz, $C\underline{H}=CH_2$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95
Found: C, 73.33; H, 8.90

91: nmr (CCl_4) δ0.43 (m, 4H, cyclopropane methylenes), 160 (m, 5H, cyclopropane C<u>H</u>, C-2 and C-6 methylenes), 1.77 (s, 3H, C-4 $C\underline{H}_3$), 2.10 (brd t, 2H, C-5 $C\underline{H}_2$), 3.86 (s, 4H, dioxolane methylenes).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34
Found: C, 74.13; H, 9.42

Preparation of 4-methyl-3-(2-oxocyclobutyl)-3-cyclohexene-1-one ethylene ketal (89)

A 0.10 M solution of 2 in benzene (5 ml) was irradiated for 90 min and then concentrated. Preparative glpc (5' 4% QF-1, 160°) afforded 89 as a light yellow oil: ir (neat) 1770 cm^{-1}; nmr (CCl_4) δ1.60 (m, 5H, C-4 CH_3, C-6 CH_2), 2.17 (m, 6H, C-2, C-5, and C-4' [cyclobutanone ring] methylenes), 2.87 (m, 2H, $COCH_2$), 3.78 (s, 4H, dioxolane methylenes), 4.17 (t, 1H, J 9 Hz, C-1' COCH).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16
Found: C, 70.05; H, 8.22

Photolysis of 2 with a mercury resonance lamp

Two 15-W fluorescent lamps producing greater than 99% of their light at 253.7 nm were situated so as to face each other a few inches apart. Quartz test tubes containing 1 ml of a 0.05 M solution of ketal 2 in benzene or ether was positioned between the lamps.

The course of the photolysis was monitored by glpc at varying intervals for 4 hr. No starting material remained in the slightly yellow benzene solution, and substantial amounts of nonvolatile materials were detected by tlc (silica gel, 2:1 ether-petroleum ether). Glpc analysis indicated that the initial rate of disappearance of 2 was about four times faster in benzene than in ether solution and that diene 90 was absent in the ether solution, although

89 and 91 were produced (after 4 hr the ratio of 2:89:91 was 1.5:1.3:1).

Photolysis of 2 in acetone

A 0.05 M solution of 2 in acetone (3 ml) was irradiated by the Hanovia lamp for 9.5 hr. Glpc analysis at the end of this time showed about equal amounts of 2 and 89, a smaller amount of cyclopropane 91, and only a trace of diene 90. Much polar, nonvolatile material was evident by tlc.

Photolysis of 2 in the presence of 1,3-pentadiene

The rate of disappearance of 2 was compared for 0.05 M solutions of 2 (absorbance at 290 nm is about 1.5) in benzene and ether, both with and without added 1,3-pentadiene (2 M, absorbance at 290 nm is about 0.3). The rate of consumption of starting material was reduced by a factor of five in ether, and a factor of two in benzene, by photolysis in the presence of piperylene.

Photolysis of 2 with added internal standard

Known quantities of the pure products 90 and 91 were mixed with known amounts of pure dodecane ($C_{12}H_{26}$, mol wt 170.33), and the relative peak areas of the standard and each product were determined via glpc (5' 4% SE-30, 140°).

A solution of 11.1 mg (0.050 mmol) of 2 and 5.15 mg of dodecane in 1 ml of benzene was irradiated until only 90 and 91 remained. The peak areas of these two products were compared with the peak area of the added standard, and the molar amounts of each product were calculated. For two trials the combined amounts of 90 and 91 were 5.01 and 4.90×10^{-2} mmol. Within experimental error, products 90 and 91 account for all 5.0×10^{-2} mmol of starting material.

Photolysis of 58 in benzene solution

A total of 10 ml of a 0.05 M solution of 58 in benzene was irradiated for 50 min, concentrated, and then chromatographed of a 2 mm layer of silica gel (30% ether-petroleum ether) to give the following amounts of products: a 1:1 mixture of diene 96 and cyclopropane 97, 25 mg; cyclobutanone 95, 23.5 mg; recovered 58, 28.5 mg; a nonvolatile mixture, 23 mg.

The mixture of 96 and 97 was separated by glpc (10' 4% QF-1, 138°) to afford these two products as colorless liquids. Cyclobutanone 95 was rechromatographed and obtained as a yellowish oil. The mixture of nonvolatile compounds was found by glpc analysis to contain small amounts of three or four unidentified volatile components (thermal degradation products?). Characteristics of 95, 96, and 97 are given below.

4-Methyl-3-(1-methyl-2-oxocyclobutyl)-3-cyclohexene-1-one ethylene ketal (95)

Light yellow oil: ir (neat) 1765 cm^{-1}; nmr (CCl_4) δ1.28 (s, 3H, C-1' $COCCH_3$), 1.57 (m, 5H, C-4 $C=CCH_3$, C-6 CH_2), 2.03 (m, 6H, C-2, C-5, and C-4' [cyclobutanone ring] methylenes), 2.86 (t, 2H, J 8 Hz, $COCH_2$), 3.81 (s, 4H, dioxolane methylenes).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53
Found: C, 71.15; H, 8.60

4-Methyl-3-(2-propenyl)-3-cyclohexene-1-one ethylene ketal (96)

Colorless liquid: ir (neat) 1630 cm^{-1}; nmr (CCL_4) δ1.60 (s, 3H, $CH_2=C-CH_3$), 1.63 (m, 2H, C-6 CH_2), 1.70 (s, 3H, C-4 CH_3), 2.08 (m, 4H, C-2, C-5 methylenes), 3.80 (s, 4H, dioxolane methylenes), 4.18 (s, 1H, vinyl proton trans to ring), 4.78 (s, 1H, vinyl proton cis to ring).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34
Found: C, 74.03; H, 9.33

4-Methyl-3-(1-methylcyclopropyl)-3-cyclohexene-1-one ethylene ketal (97)

Colorless liquid: nmr (CCl_4) δ0.38 (m, 4H, cyclopropane methylenes), 1.03 (s, 3H, cyclopropane CH_3), 1.55 (m, 2H, C-6 CH_2), 1.68 (s, 3H, C-4 CH_3), 1.97 (m, 4H, C-2, C-5 methylenes), 3.78 (s, 4H, dioxolane methylenes).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68
Found: C, 75.08; H, 9.65

Photolysis of 58 in acetone

After irradiation of 0.5 ml of a 0.05 M acetone solution of 58 for 5.5 hr, glpc analysis showed the presence of six or seven new products in addition to the usual photoproducts and starting material. The new materials constituted at least half of the total volatile product.

Photolysis of 58 in the presence of 1,3-pentadiene

Conditions and results for the quenched photolysis of 58 in benzene were the same as those described earlier for ketal 2.

APPENDIX

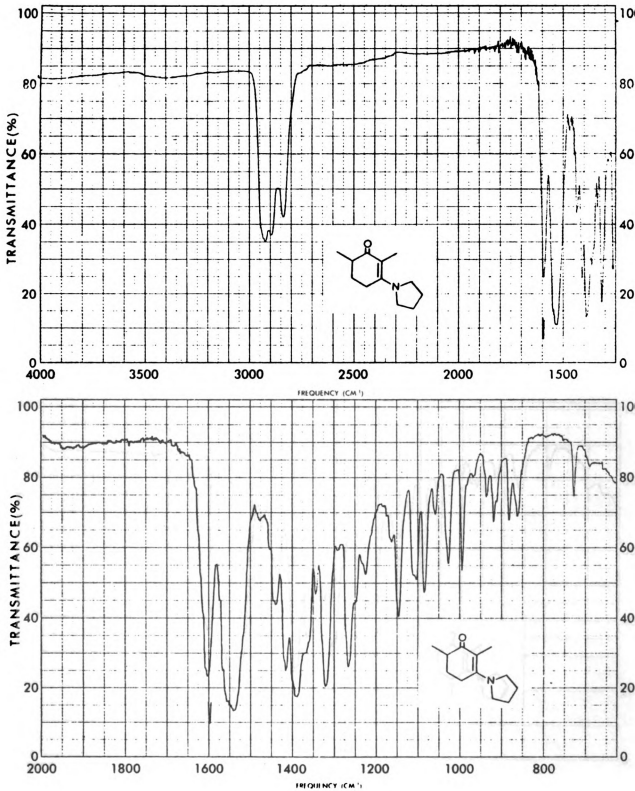


Figure 22. Infrared spectrum of 2,6-dimethyl-3-(1-pyrrolidyl)-2-cyclohexene-1-one (73).

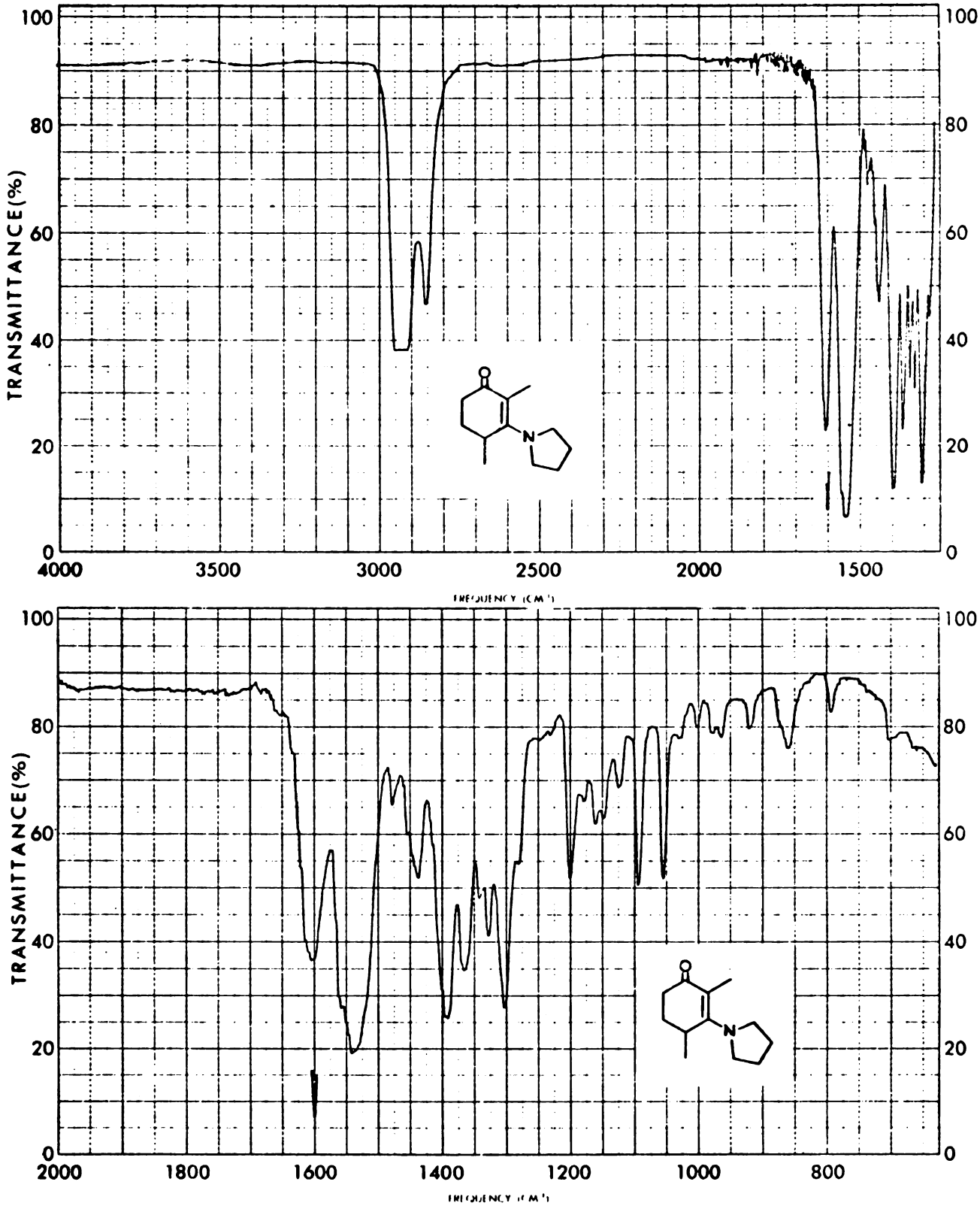


Figure 23. Infrared spectrum of 2,4-dimethyl-3-(1-pyrrolidyl)-2-cyclohexene-1-one (63).

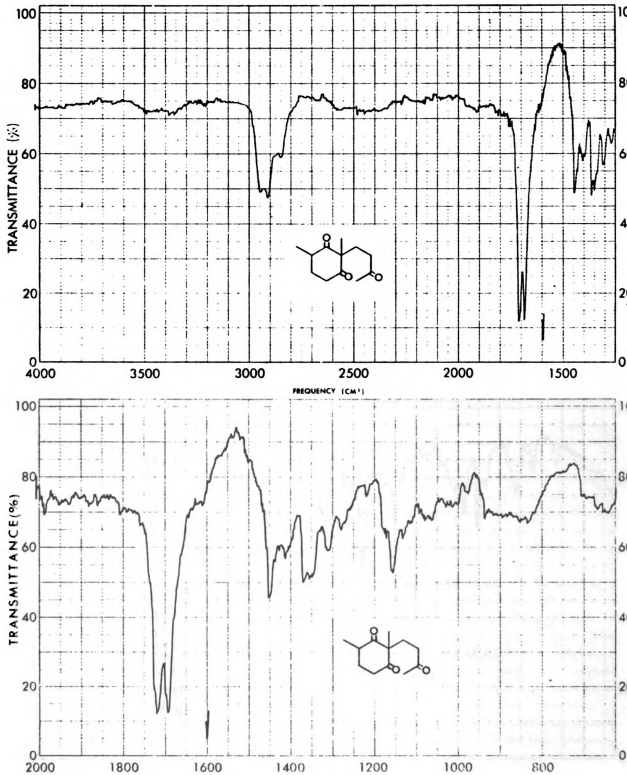


Figure 24. Infrared spectrum of 2,4-dimethyl-2-(3-oxobutyl)-cyclohexane-1,3-dione (62).

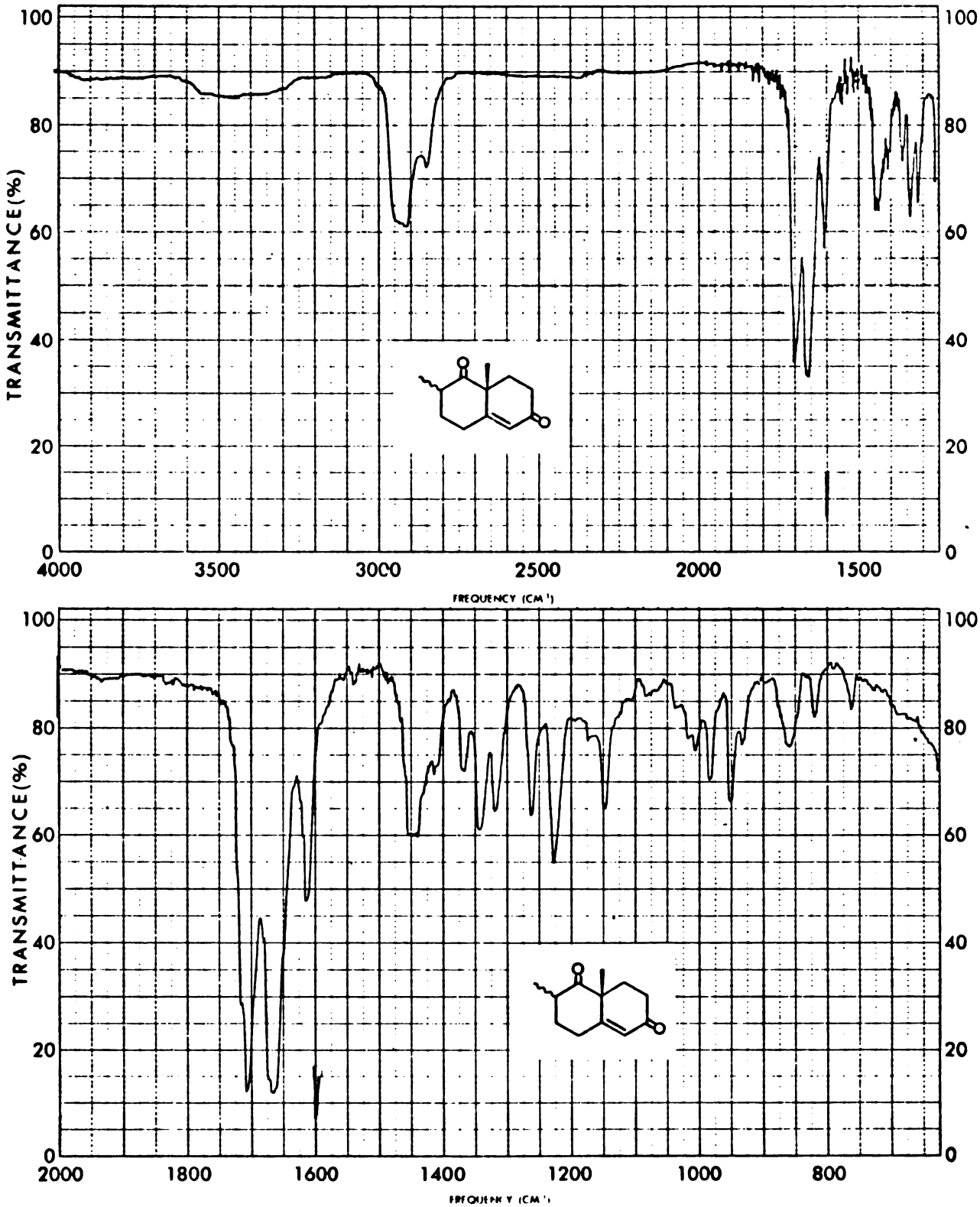


Figure 25. Infrared spectrum of 1,3-dimethylbicyclo-[4.4.0]-dec-6-ene-2,8-dione (64).

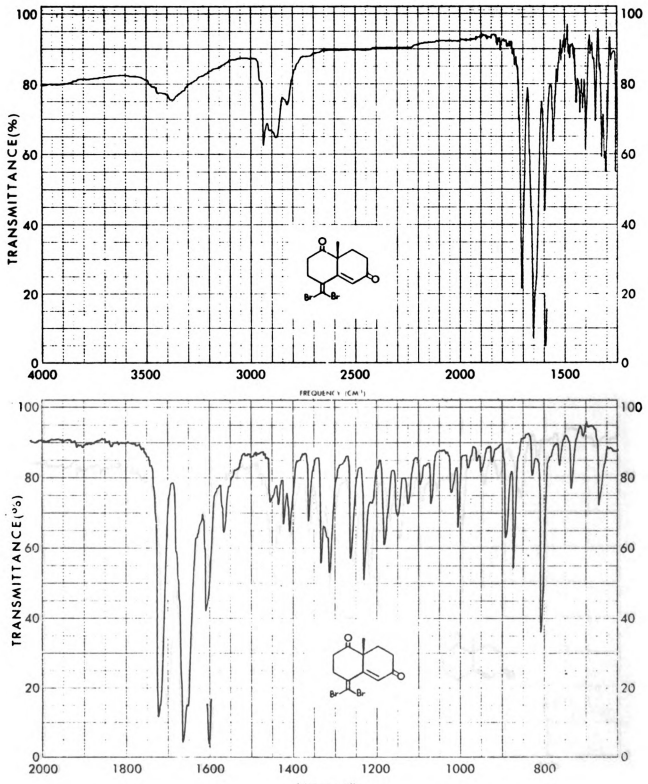


Figure 26. Infrared spectrum of 5-dibromomethylene-1-methyl-bicyclo-[4.4.0]-dec-6-ene-2,8-dione (85).

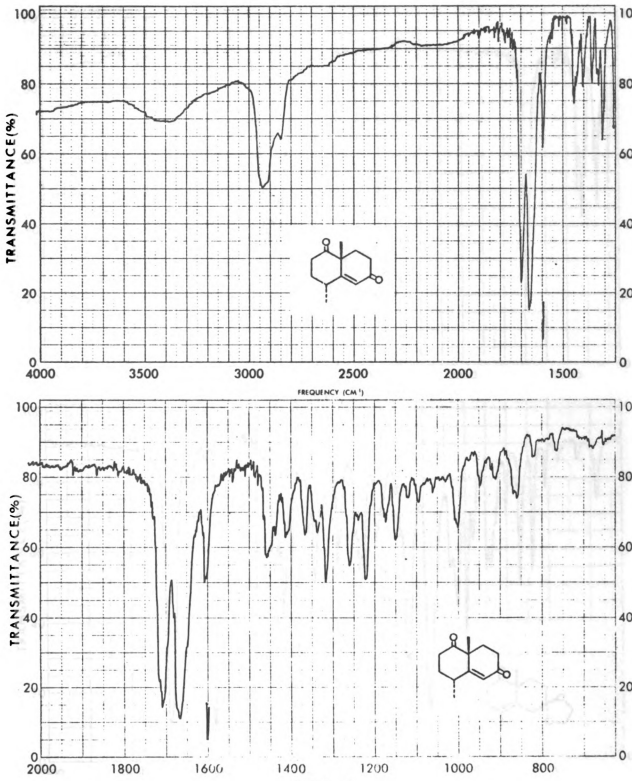


Figure 27. Infrared spectrum of 1,5-dimethylbicyclo-[4.4.0]-dec-6-ene-2,8-dione (57).

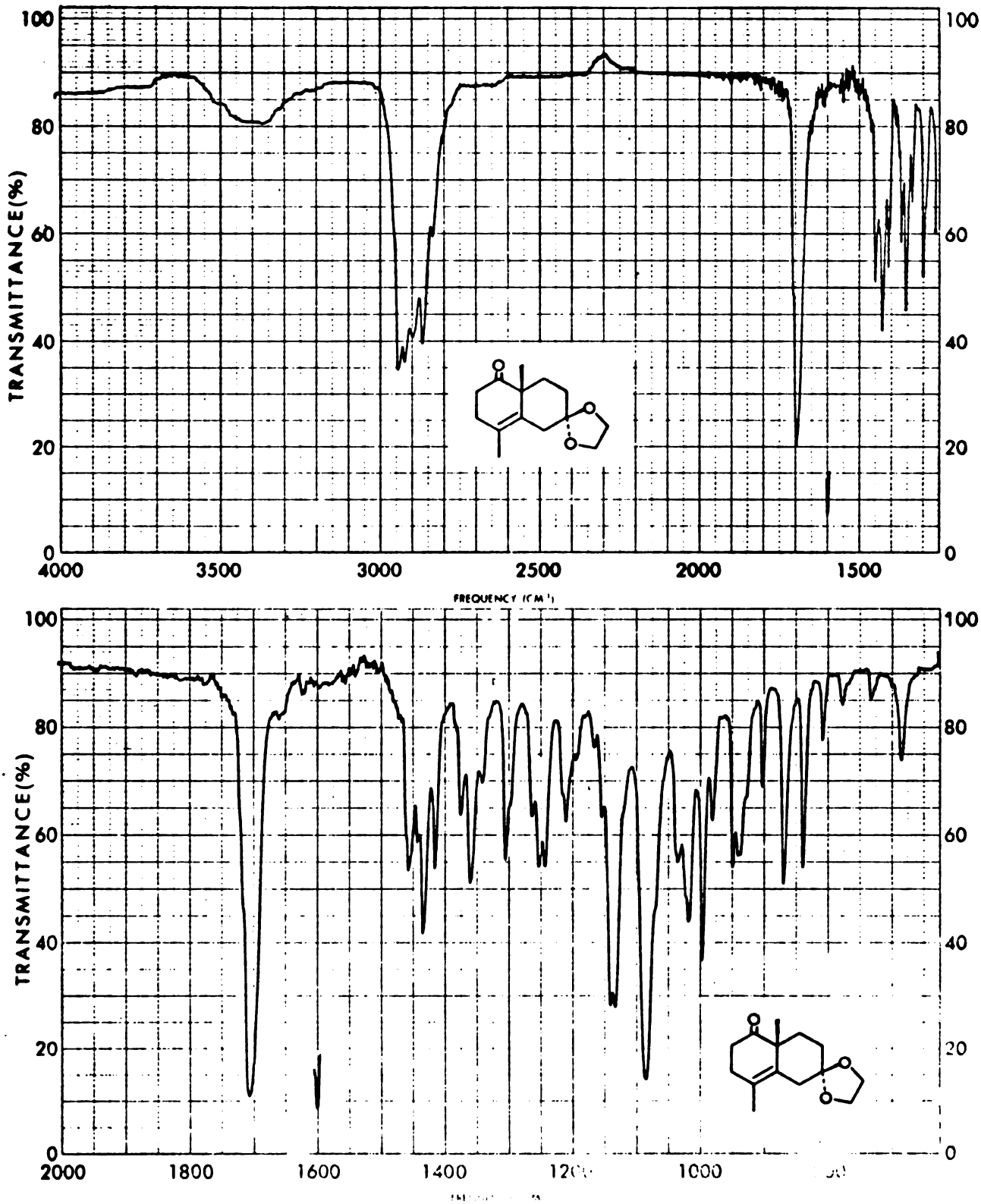


Figure 28. Infrared spectrum of 1,5-dimethylbicyclo-[4.4.0]-dec-5-ene-2,8-dione-8-ethylene ketal (58).

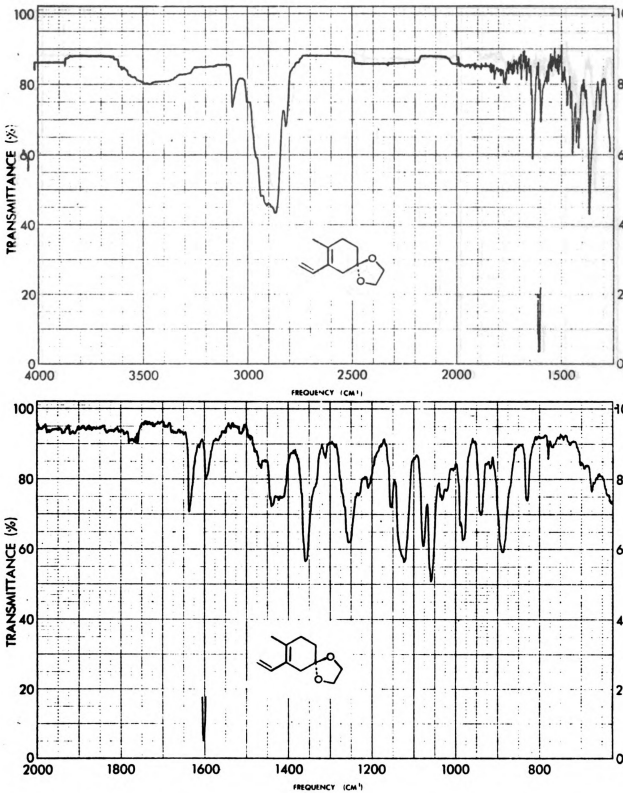


Figure 29. Infrared spectrum of 4-methyl-3-vinyl-3-cyclohexene-1-one ethylene ketal (90).

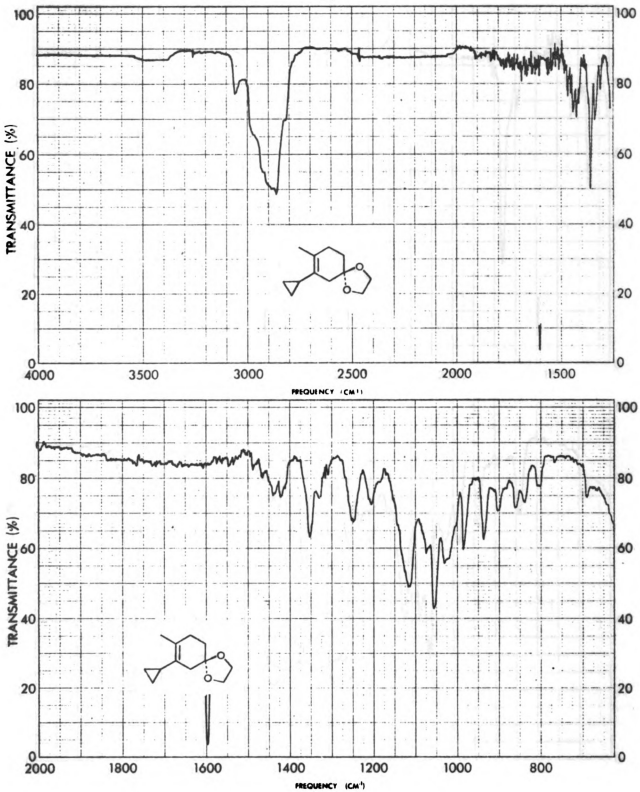


Figure 30. Infrared spectrum of 4-methyl-3-cyclopropyl-3-cyclohexene-1-one ethylene ketal (91).

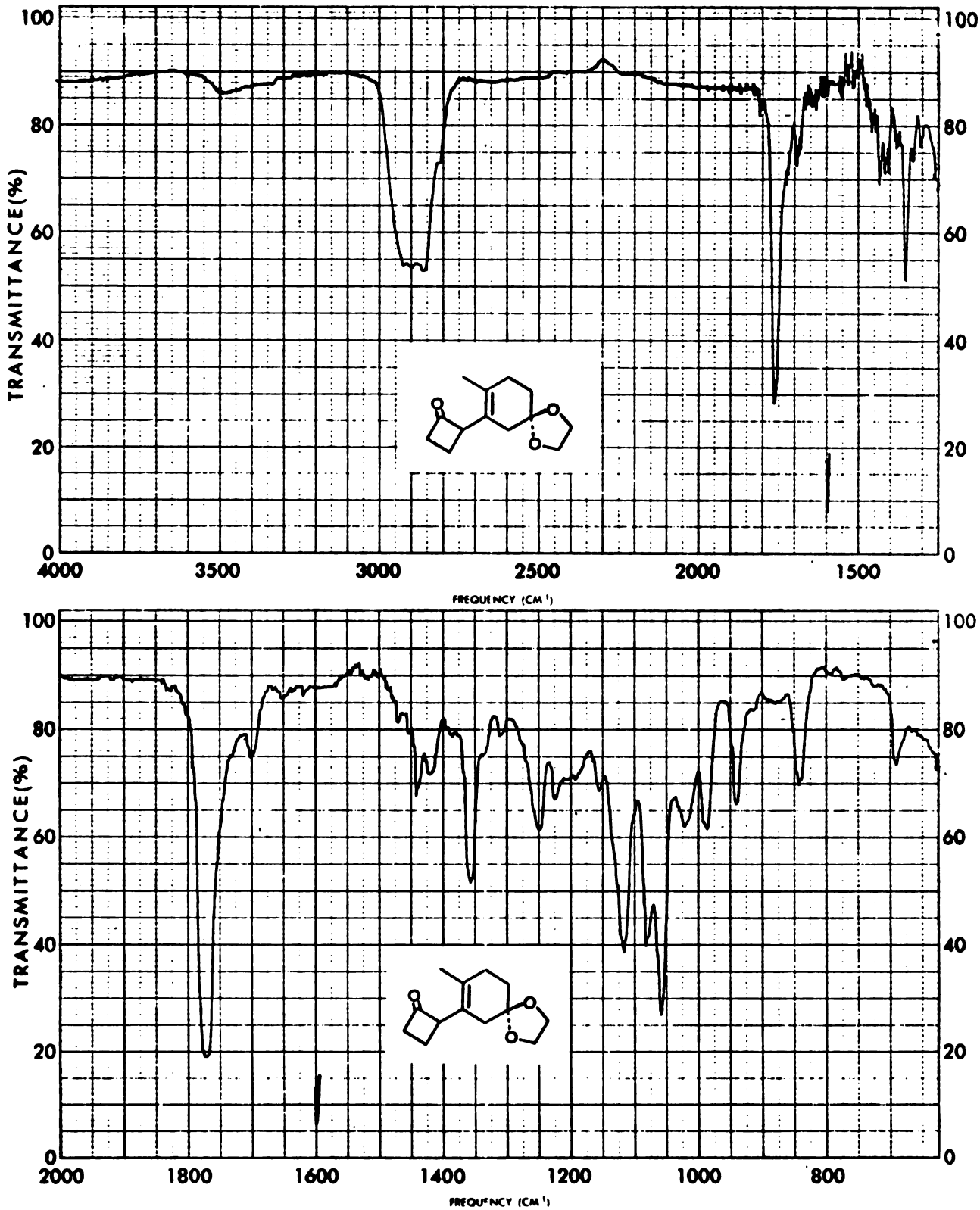


Figure 31. Infrared spectrum of 4-methyl-3-(2-oxocyclobutyl)-3-cyclohexene-1-one ethylene ketal (89).

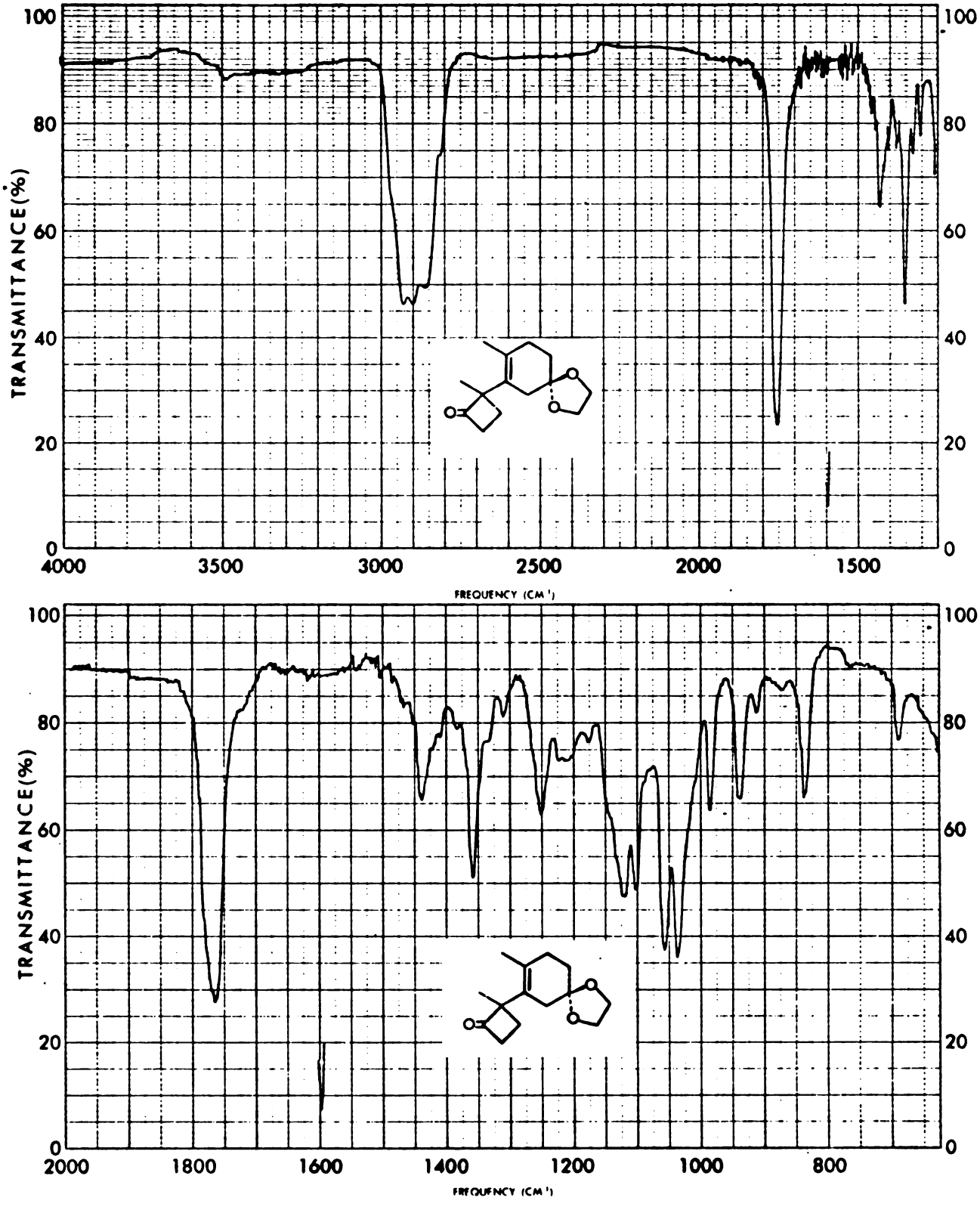


Figure 32. Infrared spectrum of 4-methyl-3-(1-methyl-2-oxocyclobutyl)-3-cyclohexene-1-one ethylene ketal (95).

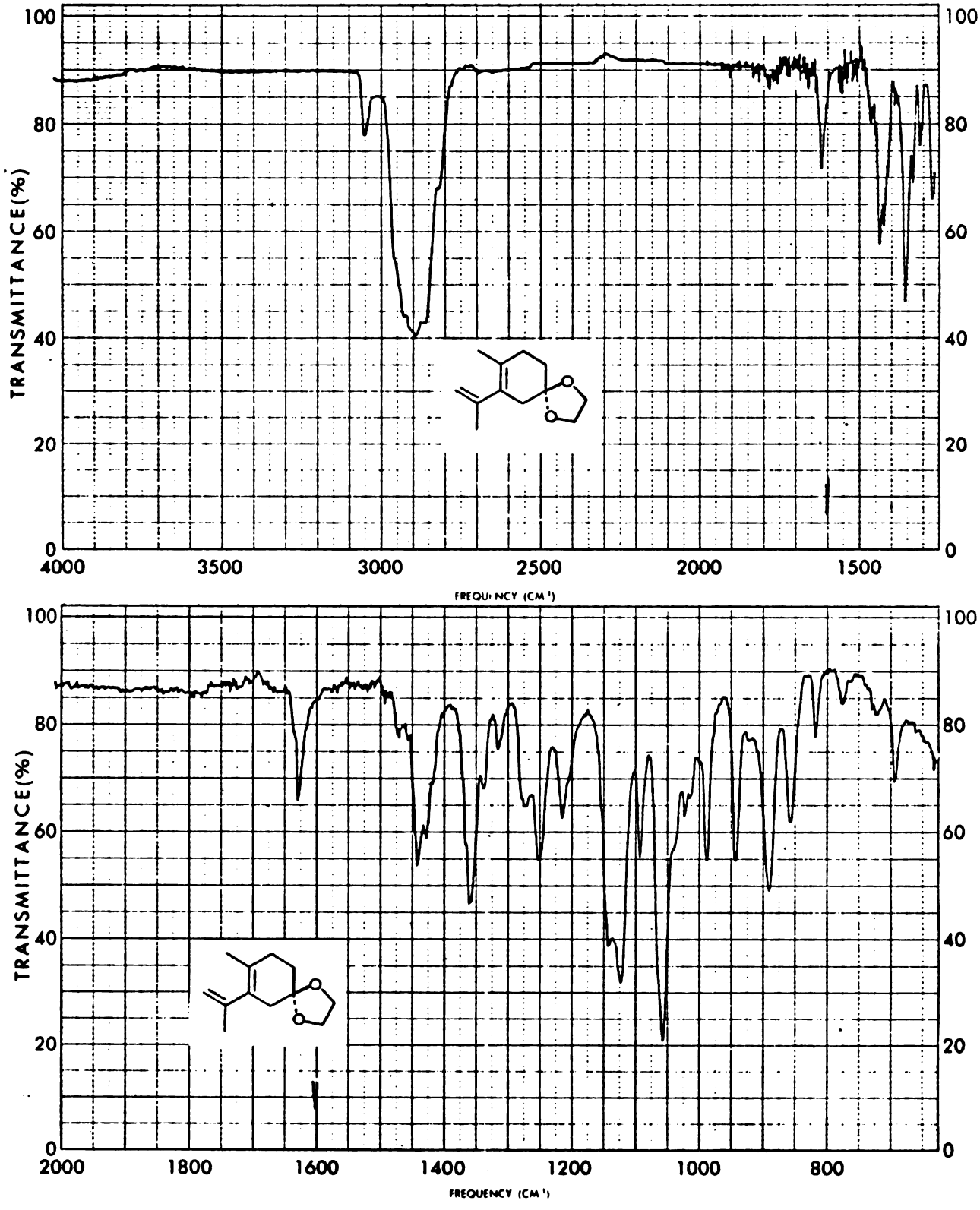


Figure 33. Infrared spectrum of 4-methyl-3-(2-propenyl)-3-cyclohexene-1-one ethylene ketal (96).

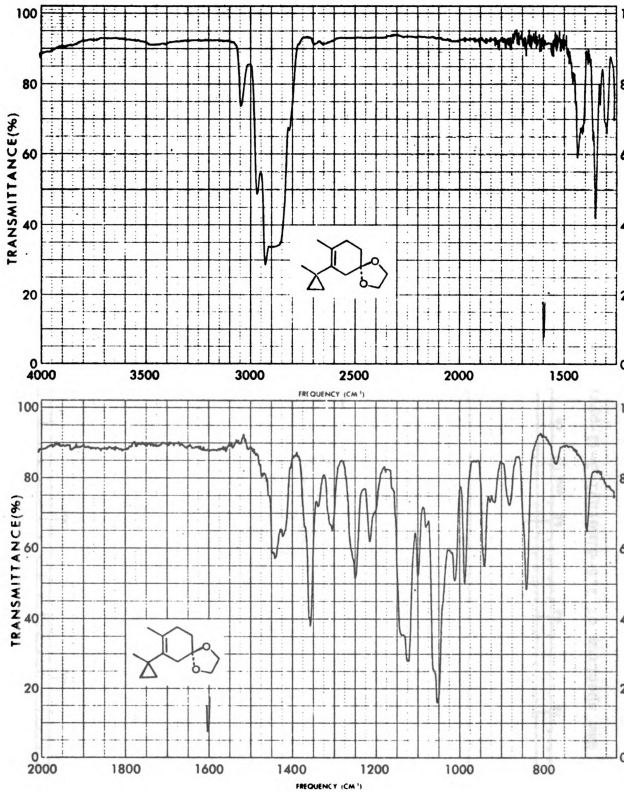


Figure 34. Infrared spectrum of 4-methyl-3-(1-methylcyclopropyl)-3-cyclohexene-1-one ethylene ketal (97).

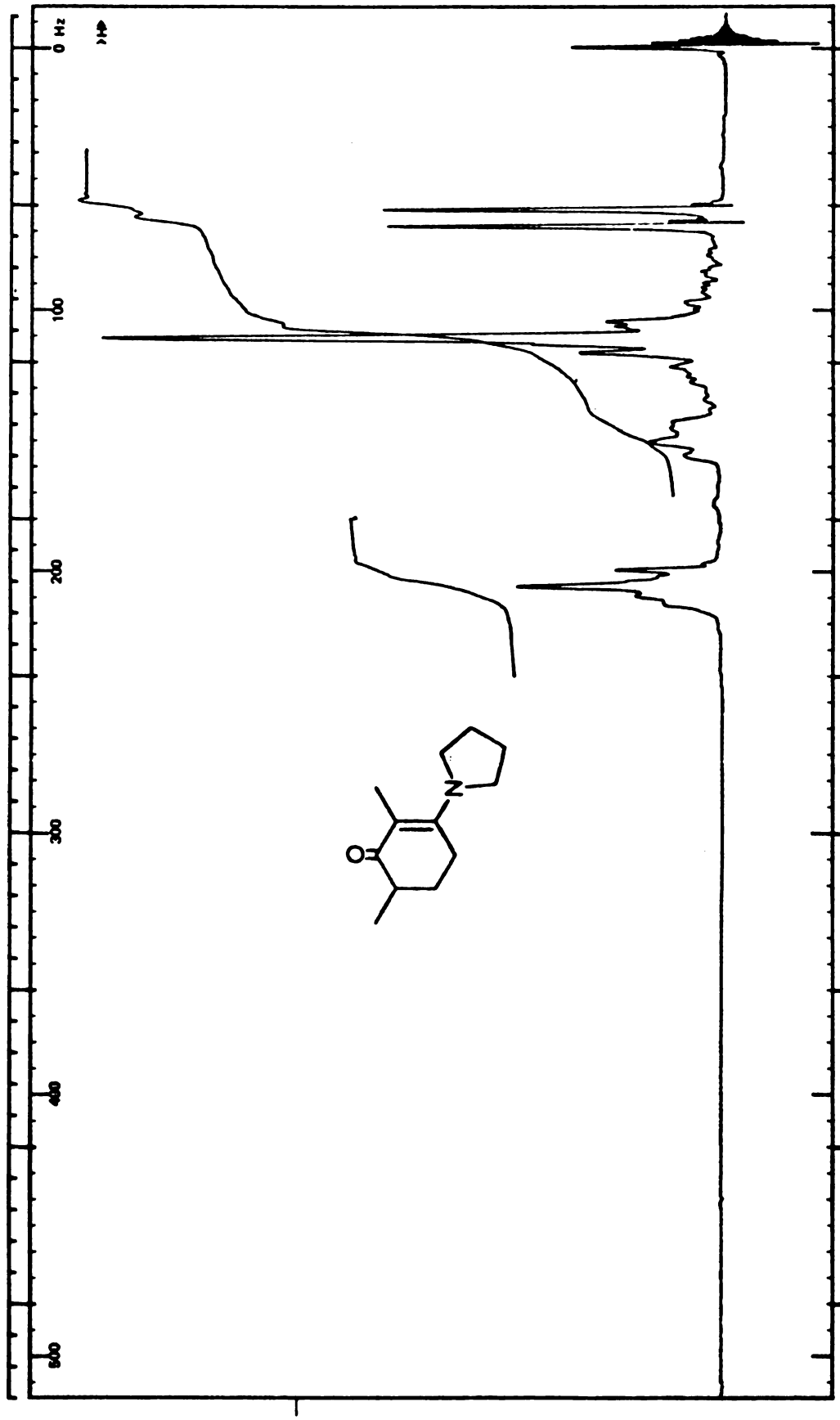


Figure 35. Nmr spectrum of 2,6-dimethyl-3-(1-pyrrolidyl)-2-cyclohexene-1-one (73), ($CDCl_3$).

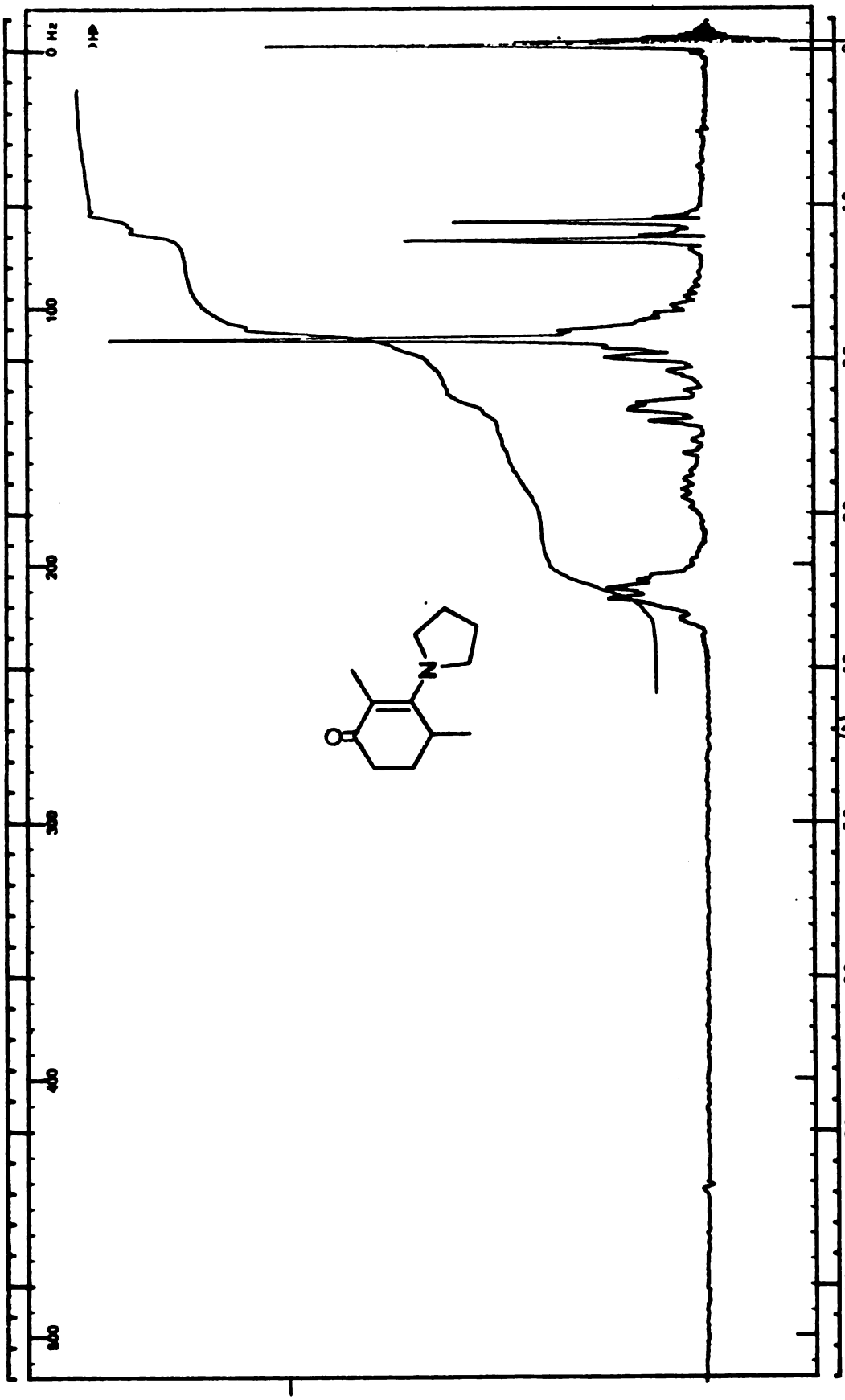


Figure 36. Nmr spectrum of 2,4-dimethyl-3-(1-pyrrolidyl)-2-cyclohexene-1-one (63), ($CDCl_3$).

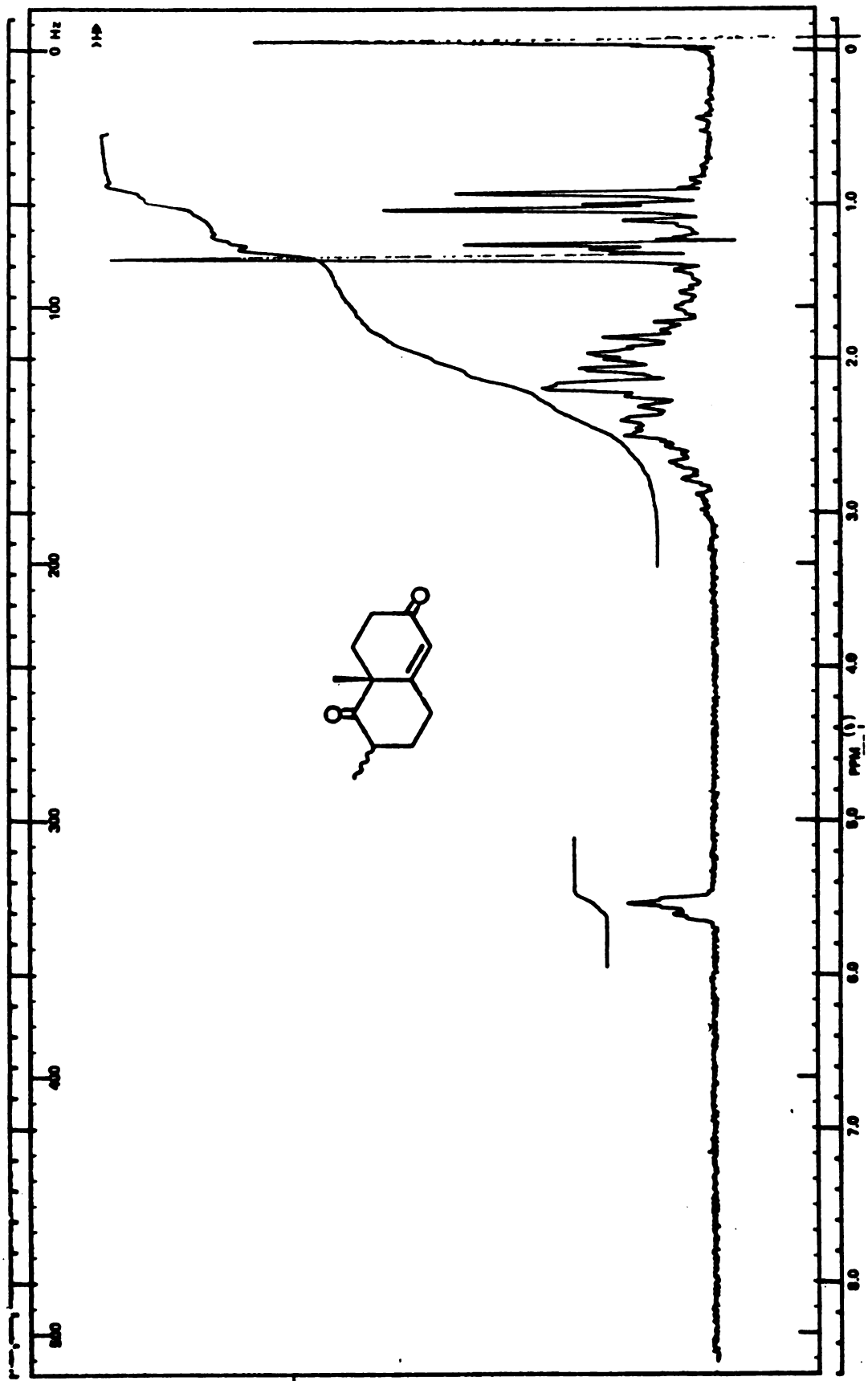


Figure 37. Nmr spectrum of 1,3-dimethylbicyclo-[4.4.0]-dec-6-ene-2,8-dione (64), (CCl_4).

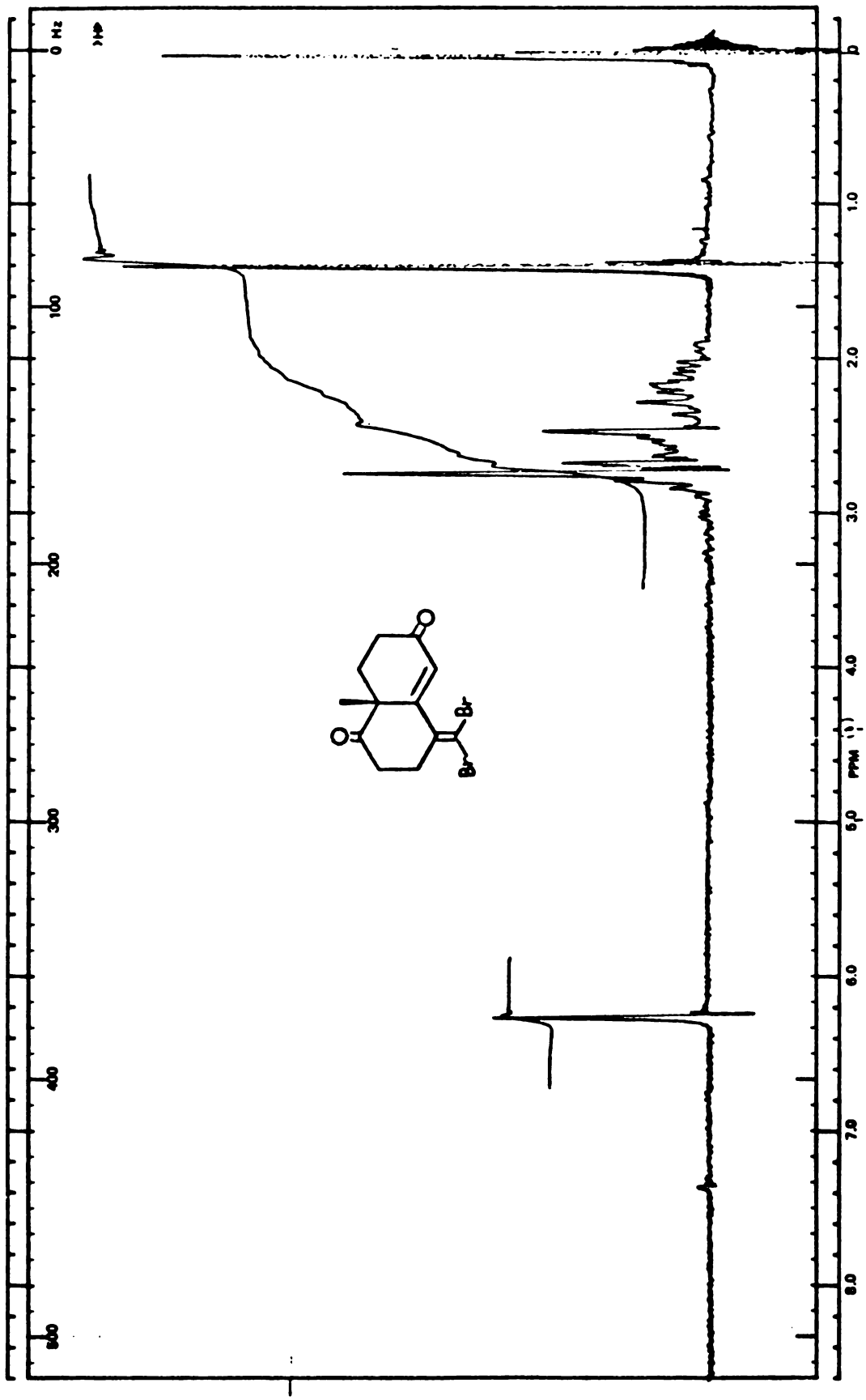


Figure 38. Nmr spectrum of 5-dibromomethylene-1-methylbicyclo-[4.4.0]-dec-6-ene-2,8-dione (85), ($CDCl_3$).

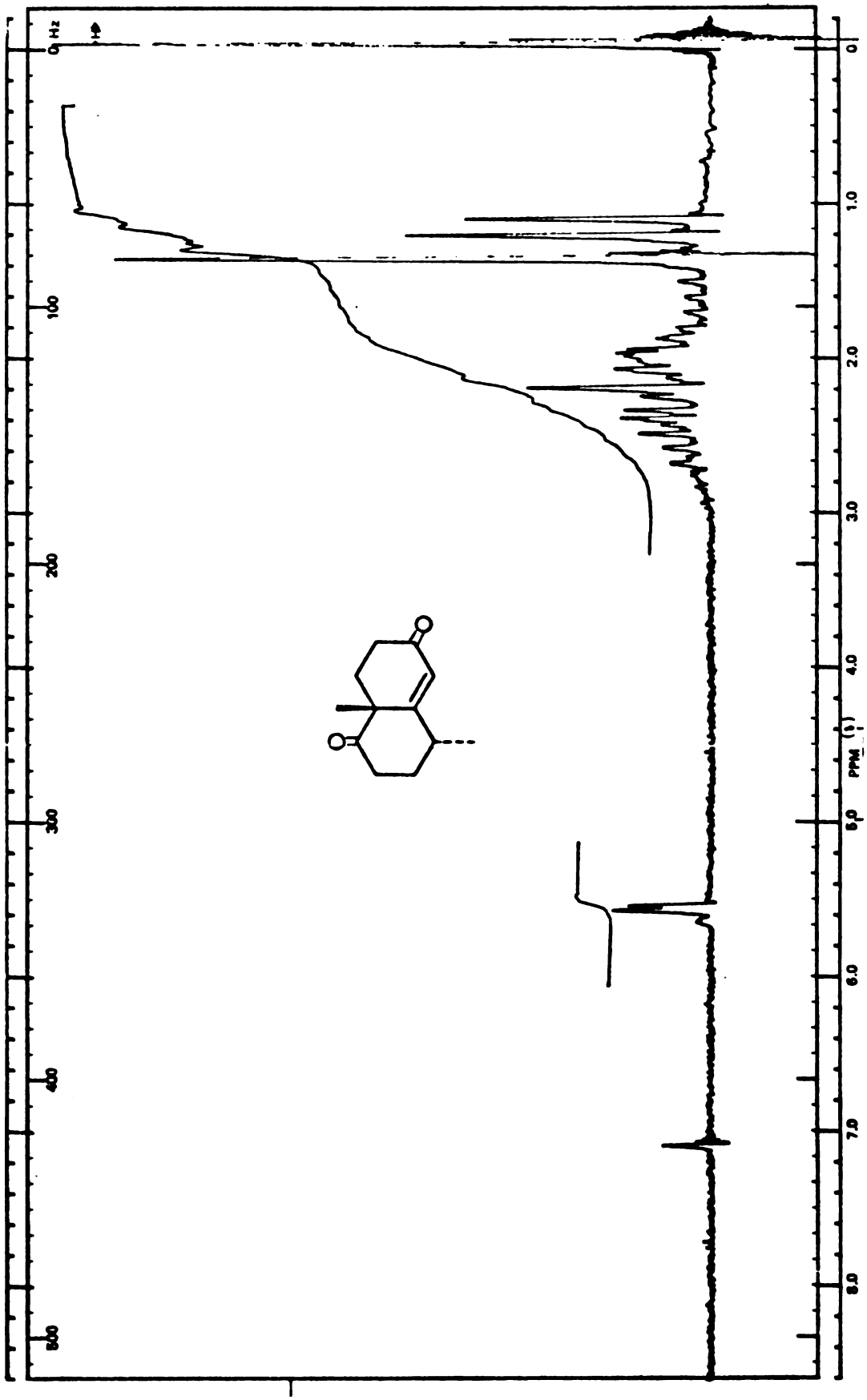


Figure 39. Nmr spectrum of 1,5-dimethylbicyclo-[4.4.0]-dec-6-ene-2,8-dione (57), (CCl_4).

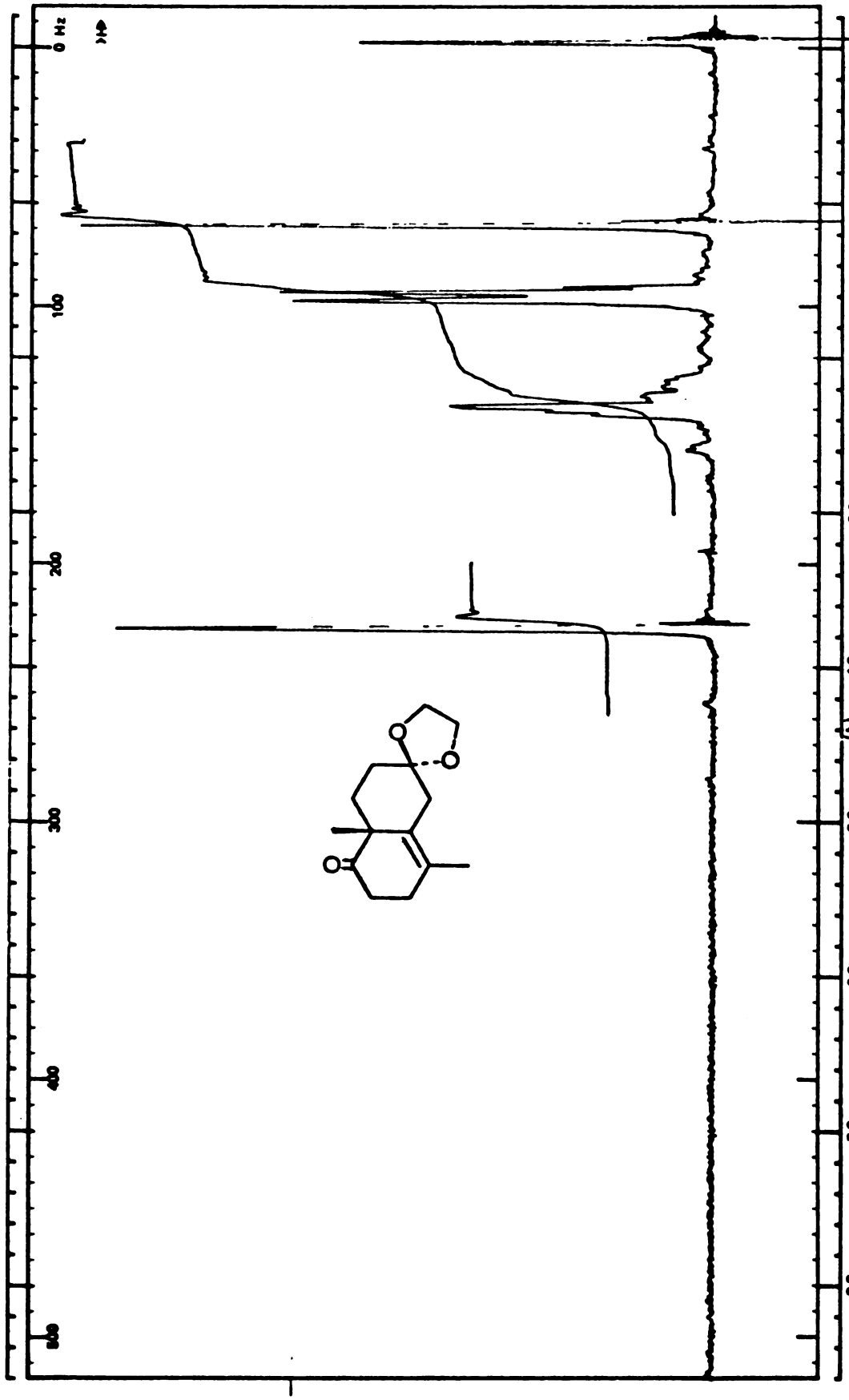


Figure 40. Nmr spectrum of 1,5-dimethylbicyclo-[4.4.0]-dec-5-ene-2,8-dione-8-ethylene ketal (58), (CCl_4).

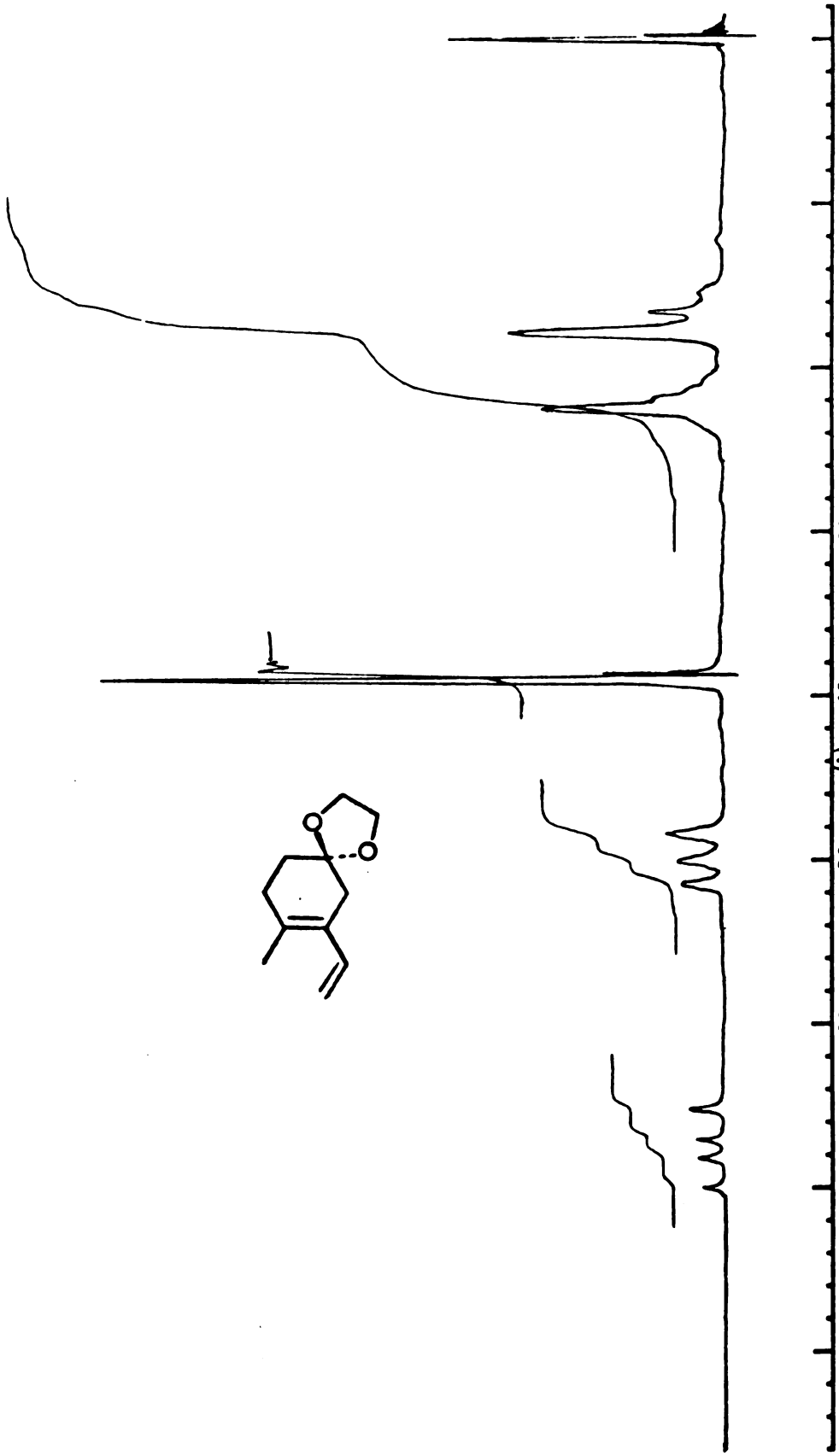


Figure 41. Nmr spectrum of 4-methyl-3-vinyl-3-cyclohexene-1-one ethylene ketal (90), (CCl_4).

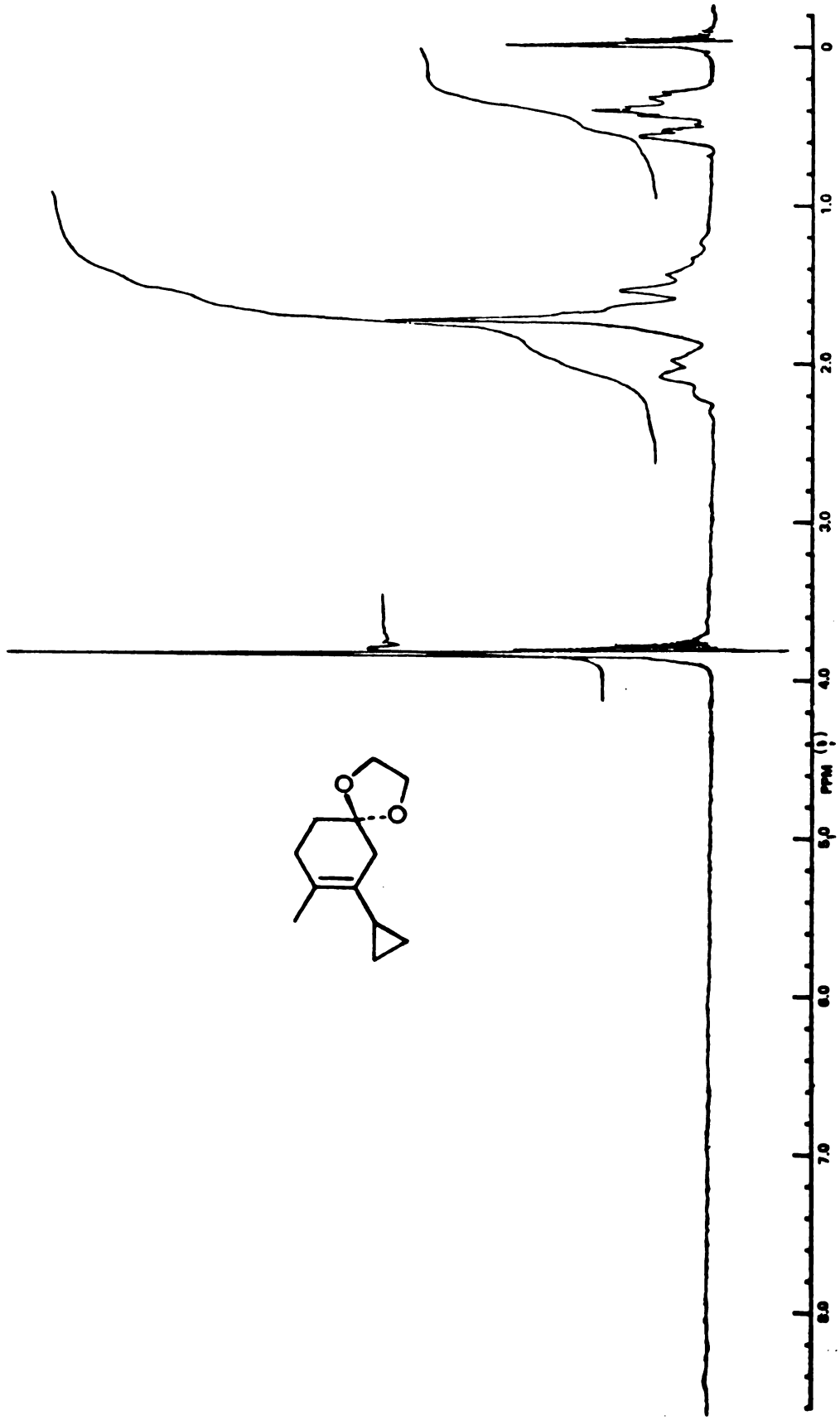


Figure 42. Nmr spectrum of 4-methyl-3-cyclopropyl-3-cyclohexene-1-one ethylene ketal (91), (CCl_4).

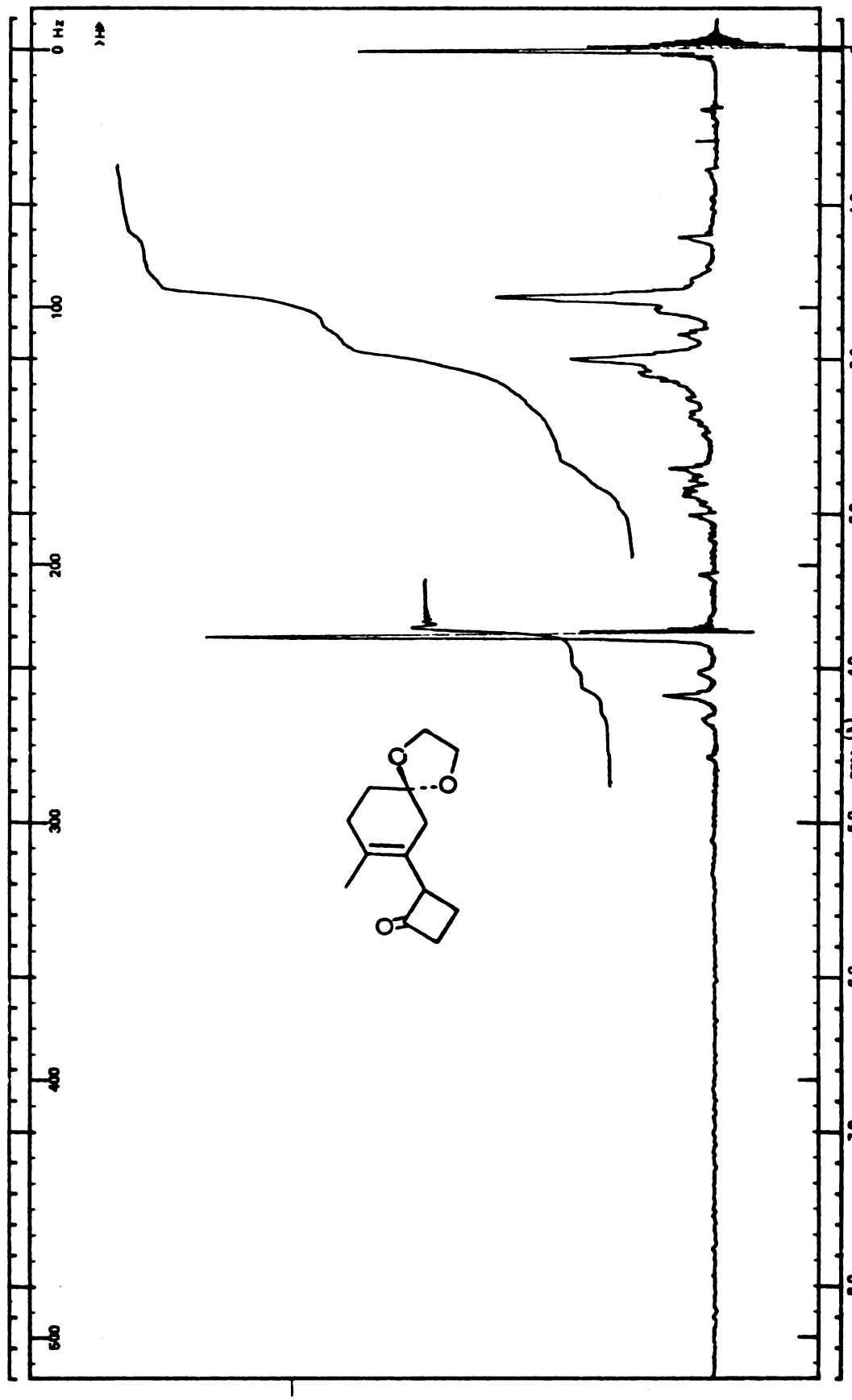


Figure 43. Nmr spectrum of 4-methyl-3-(2-oxocyclobutyl)-3-cyclohexene-1-one ethylene ketal (89), (CCl_4).

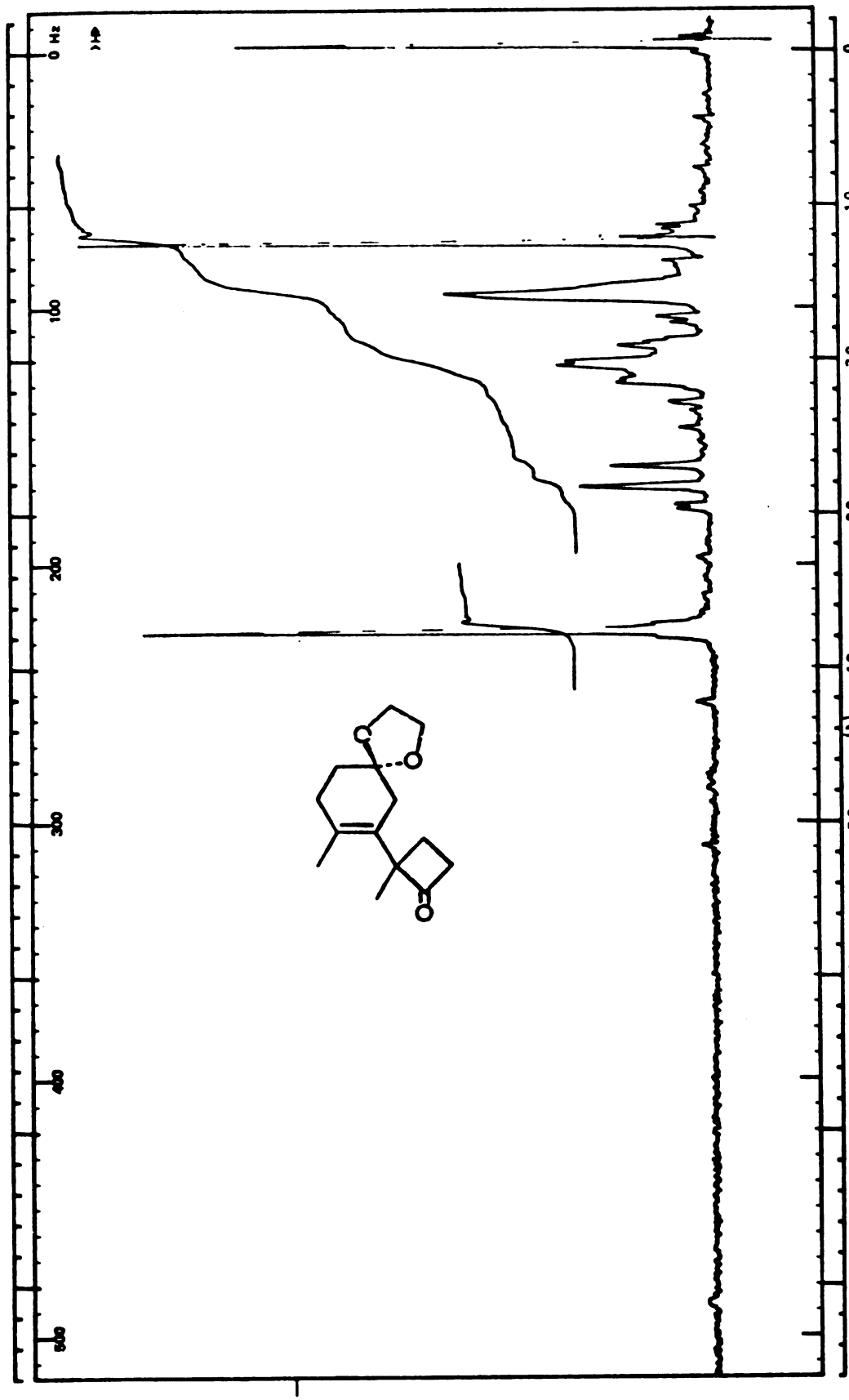


Figure 44. Nmr spectrum of 4-methyl-3-(1-methyl-2-oxocyclobutyl)-3-cyclohexene-1-one ethylene ketal (95), (CCl_4).

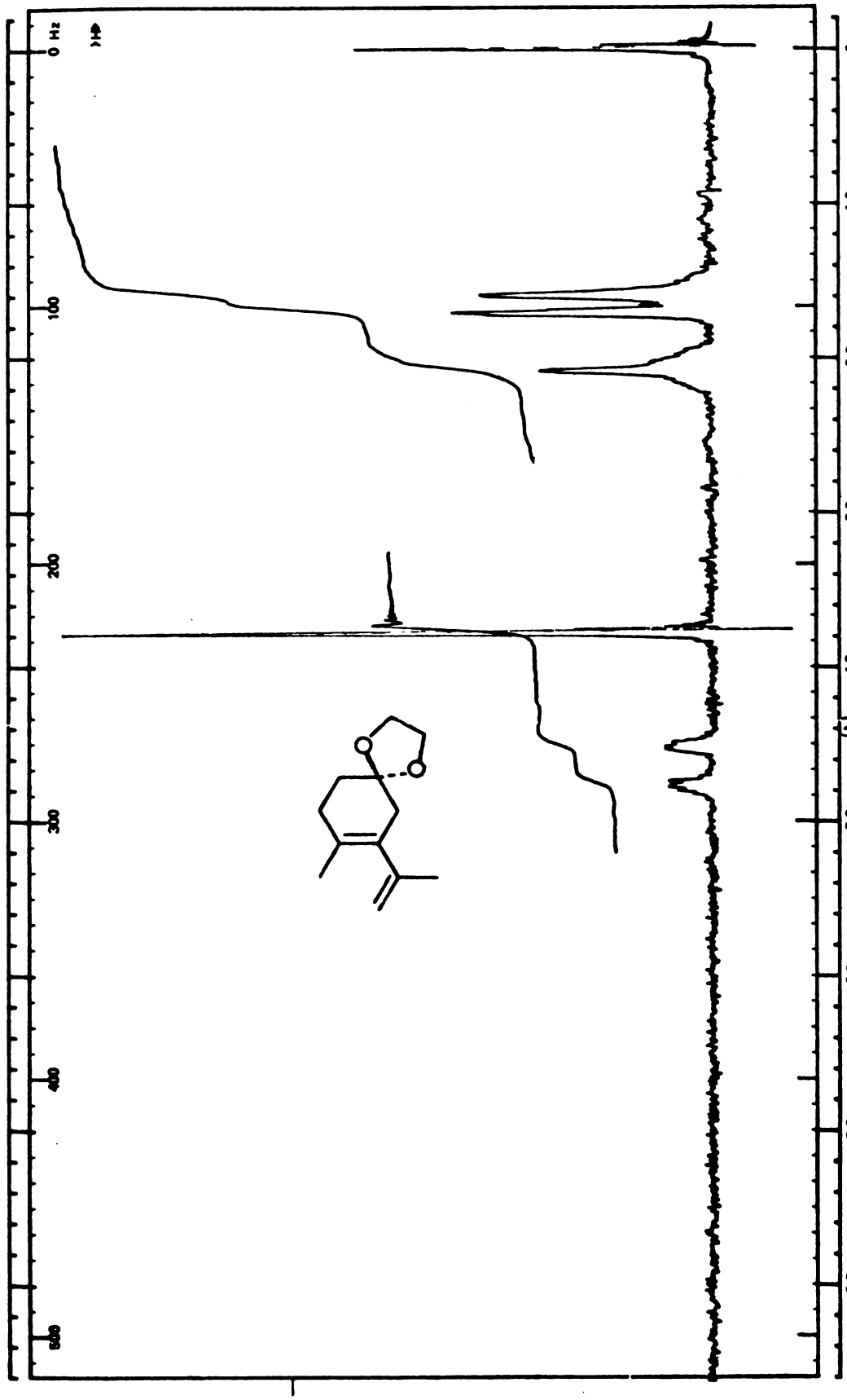


Figure 45. Nmr spectrum of 4-methyl-3-(2-propenyl)-3-cyclohexene-1-one ethylene ketal (96), (CCl_4).

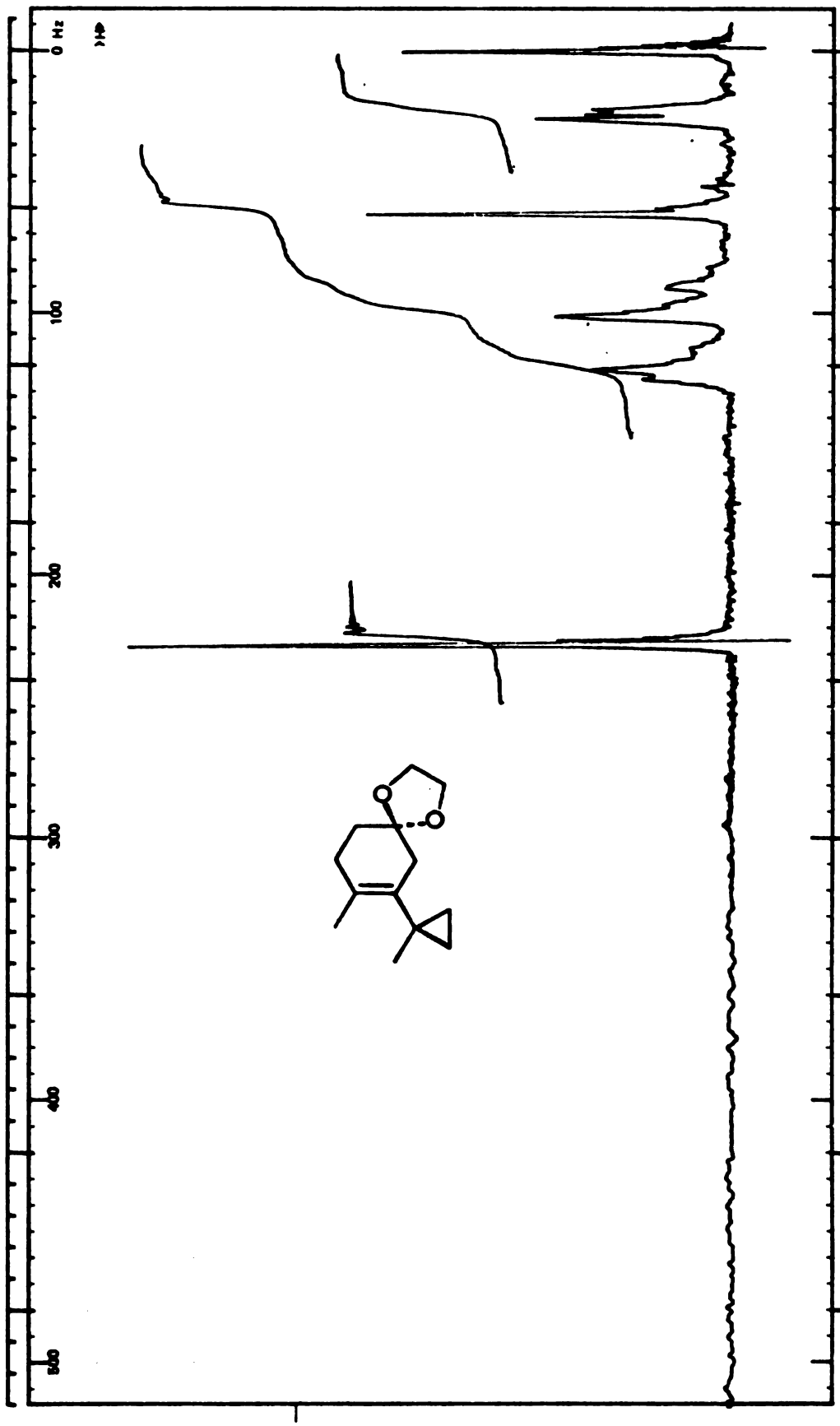


Figure 46. Nmr spectrum of 4-methyl-3-(1-methylcyclopropyl)-3-cyclohexene-1-one ethylene ketal (97), (CCl_4).

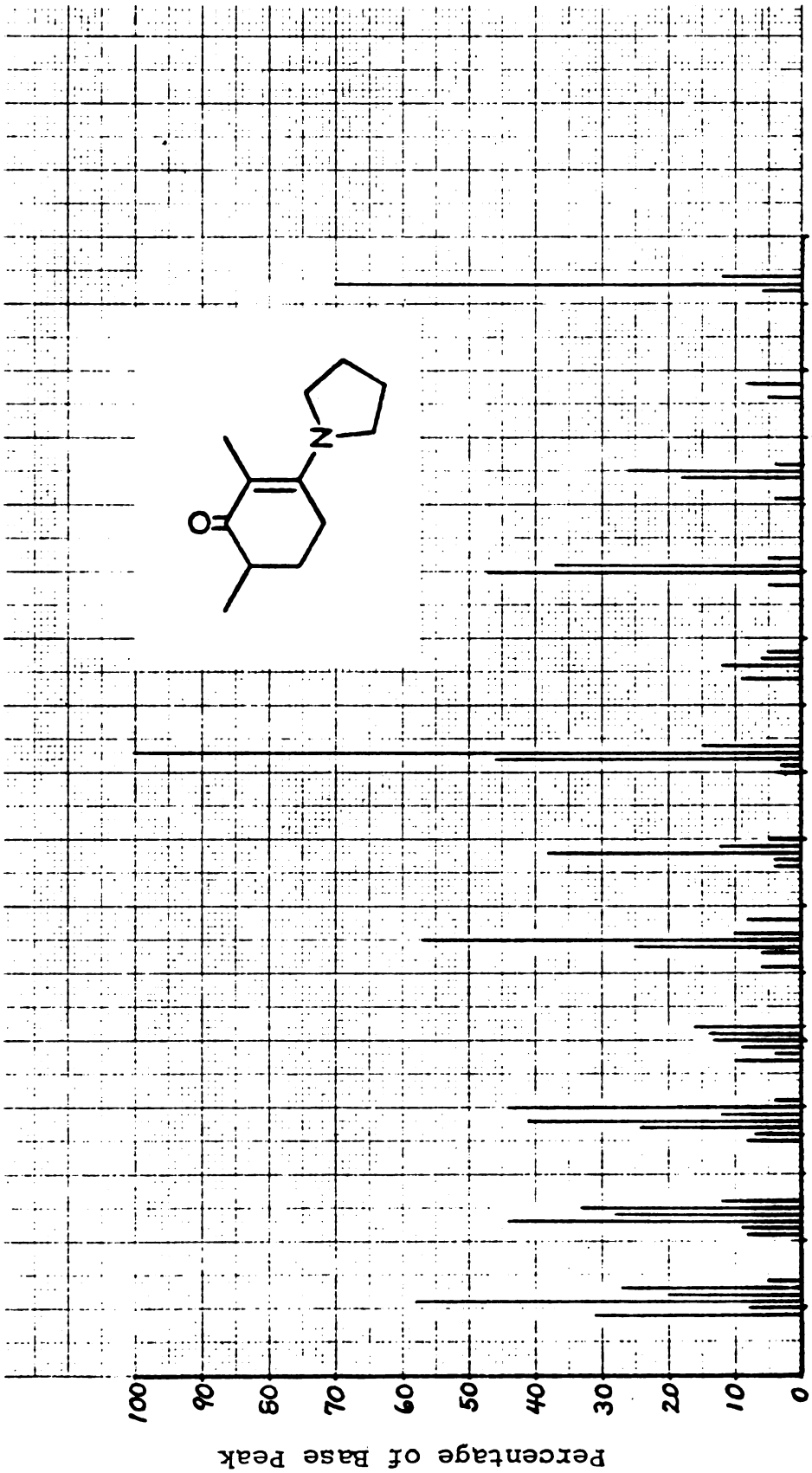


Figure 47. Mass spectrum of 2,6-dimethyl-3-(1-pyrrolidyl)-2-cyclohexene-1-one (73).

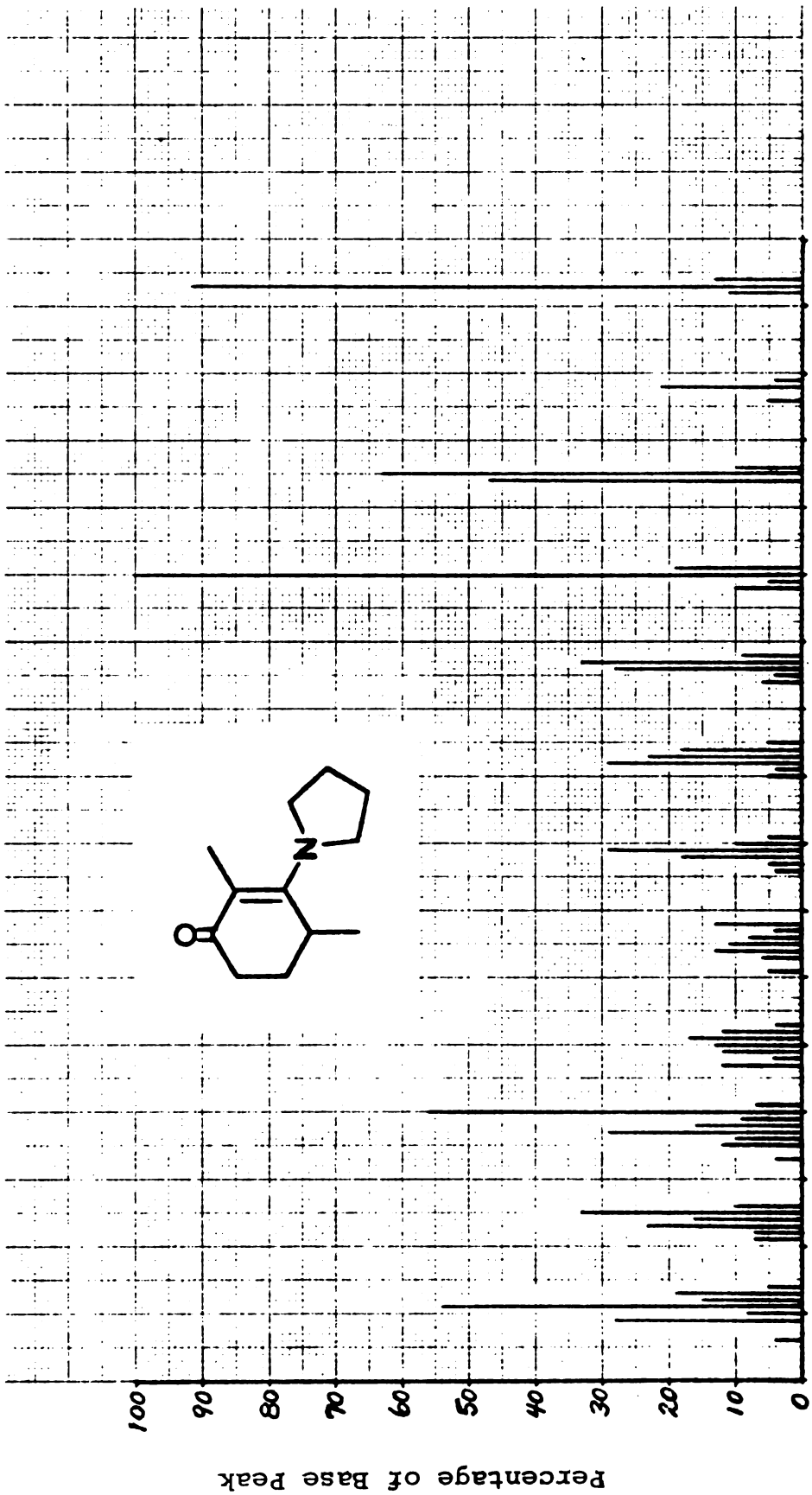


Figure 48. Mass spectrum of 2,4-dimethyl-3-(1-pyrrolidyl)-2-cyclohexene-1-one (63).

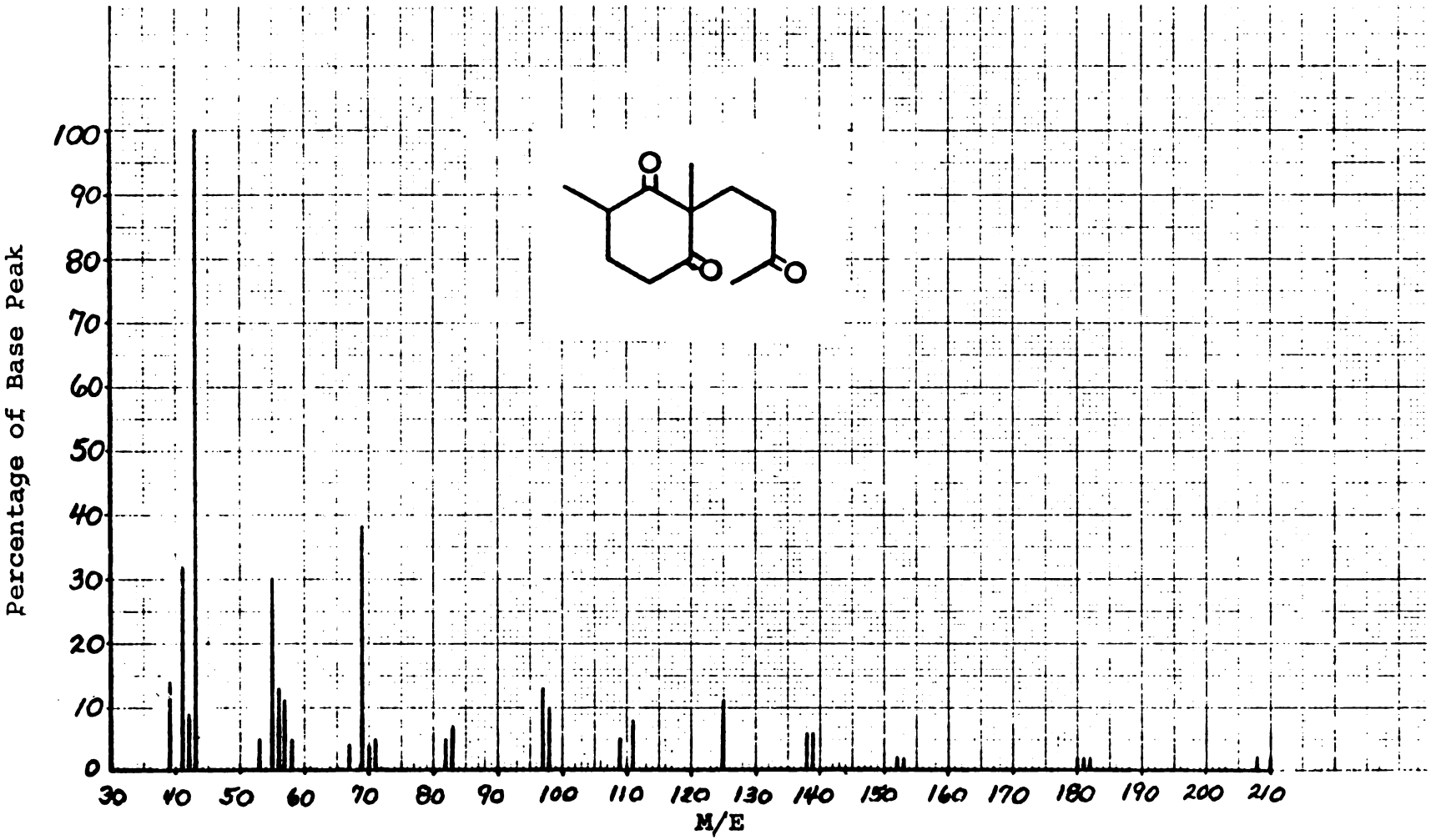


Figure 49. Mass spectrum of 2,4-dimethyl-2-(3-oxobutyl)-cyclohexane-1,3-dione (62).

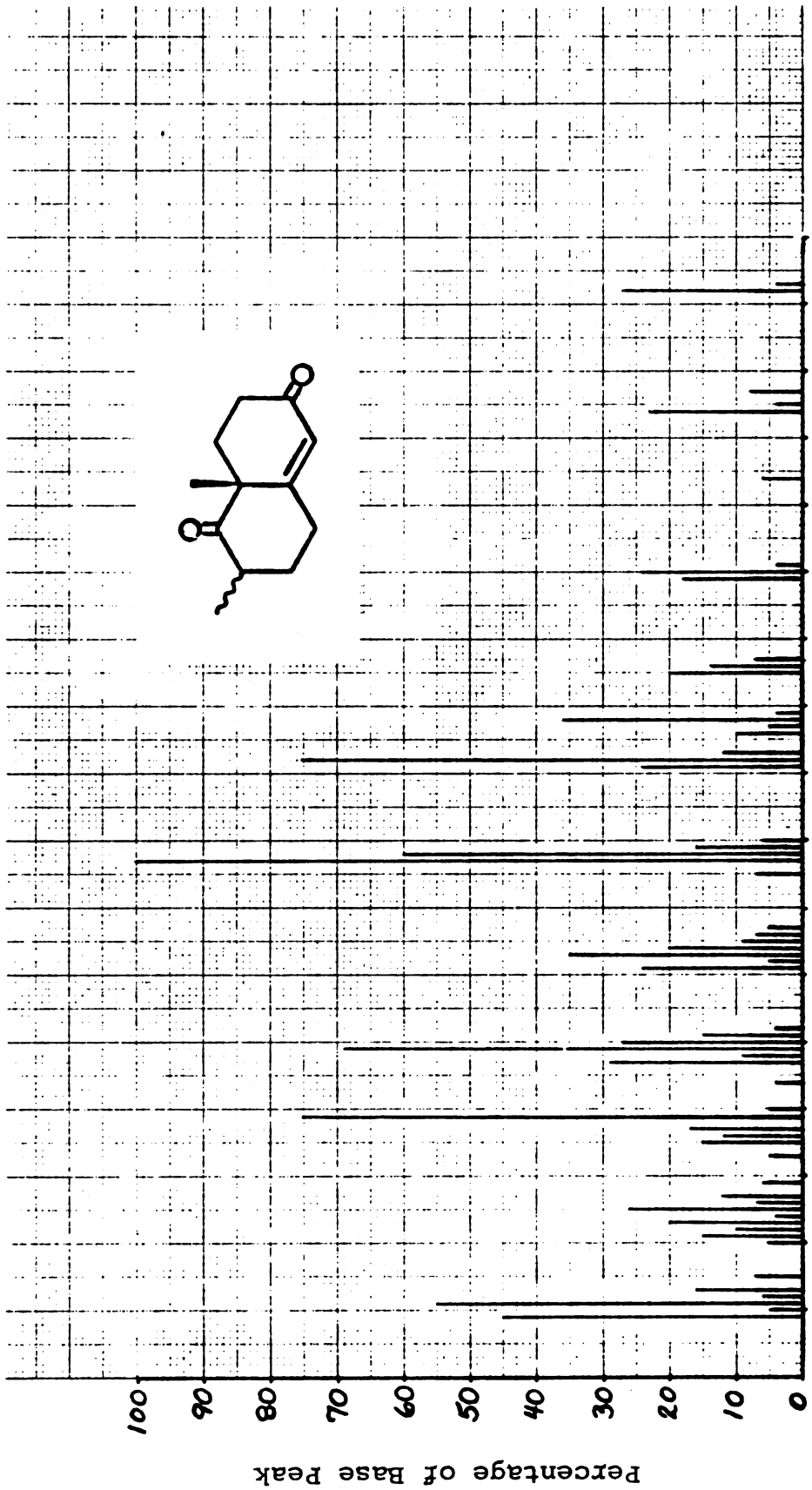


Figure 50. Mass spectrum of 1,3-dimethylbicyclo-[4.4.0]-dec-6-ene-2,8-dione (64).

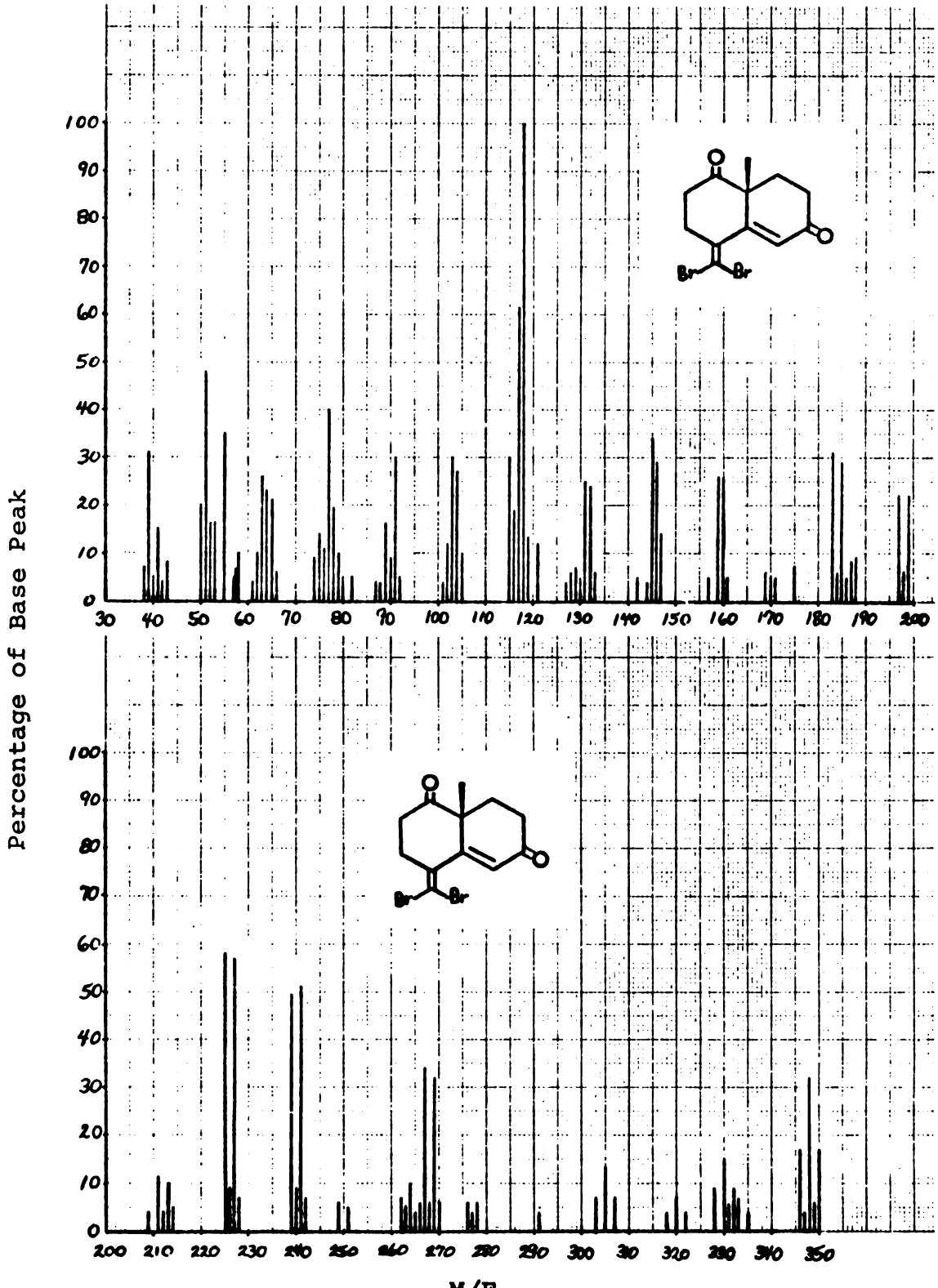


Figure 51. Mass spectrum of 5-dibromomethylene-1-methyl-bicyclo-[4.4.0]-dec-6-ene-2,8-dione (85).

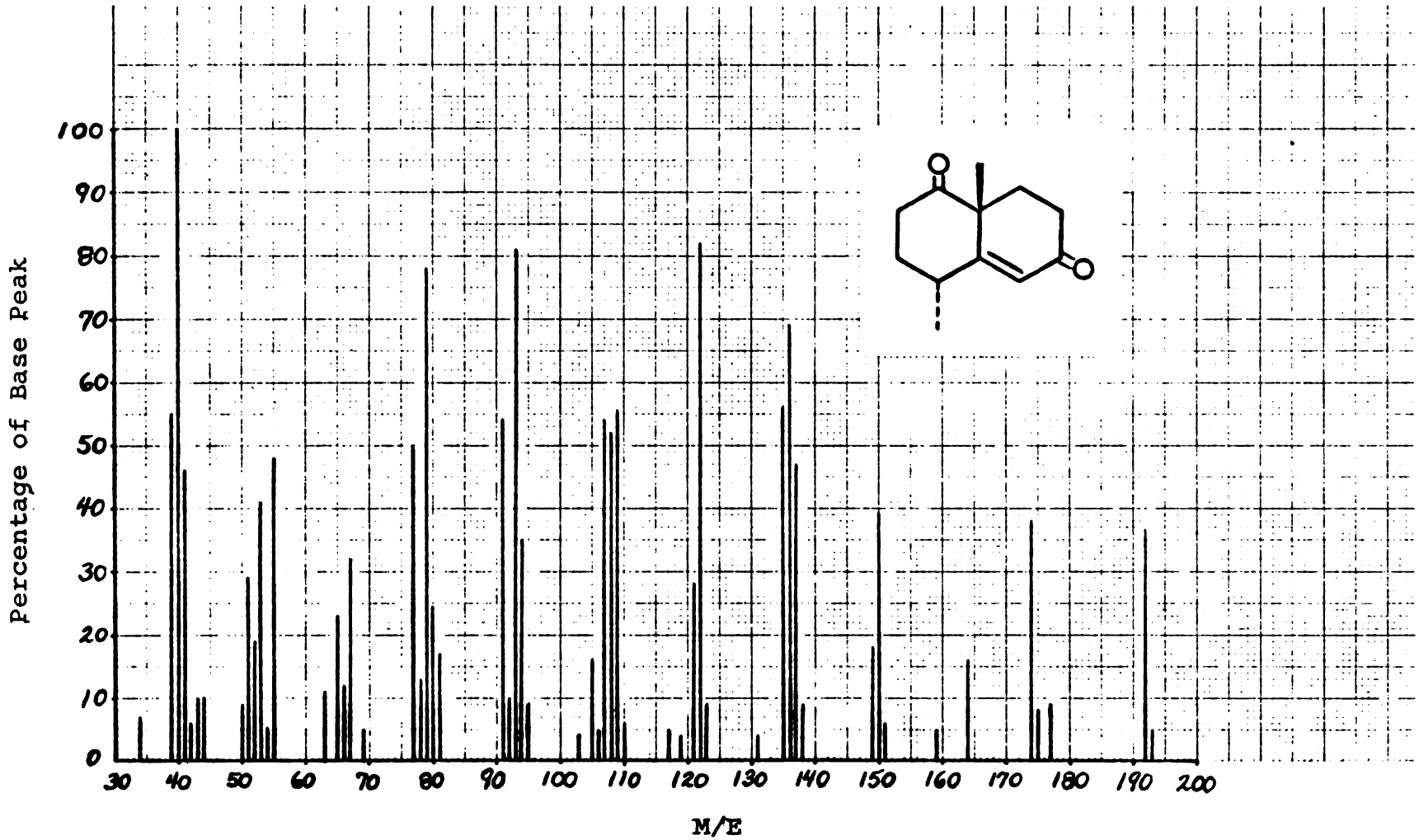


Figure 52. Mass spectrum of 1,5-dimethylbicyclo-[4.4.0]-dec-6-ene-2,8-dione (57).

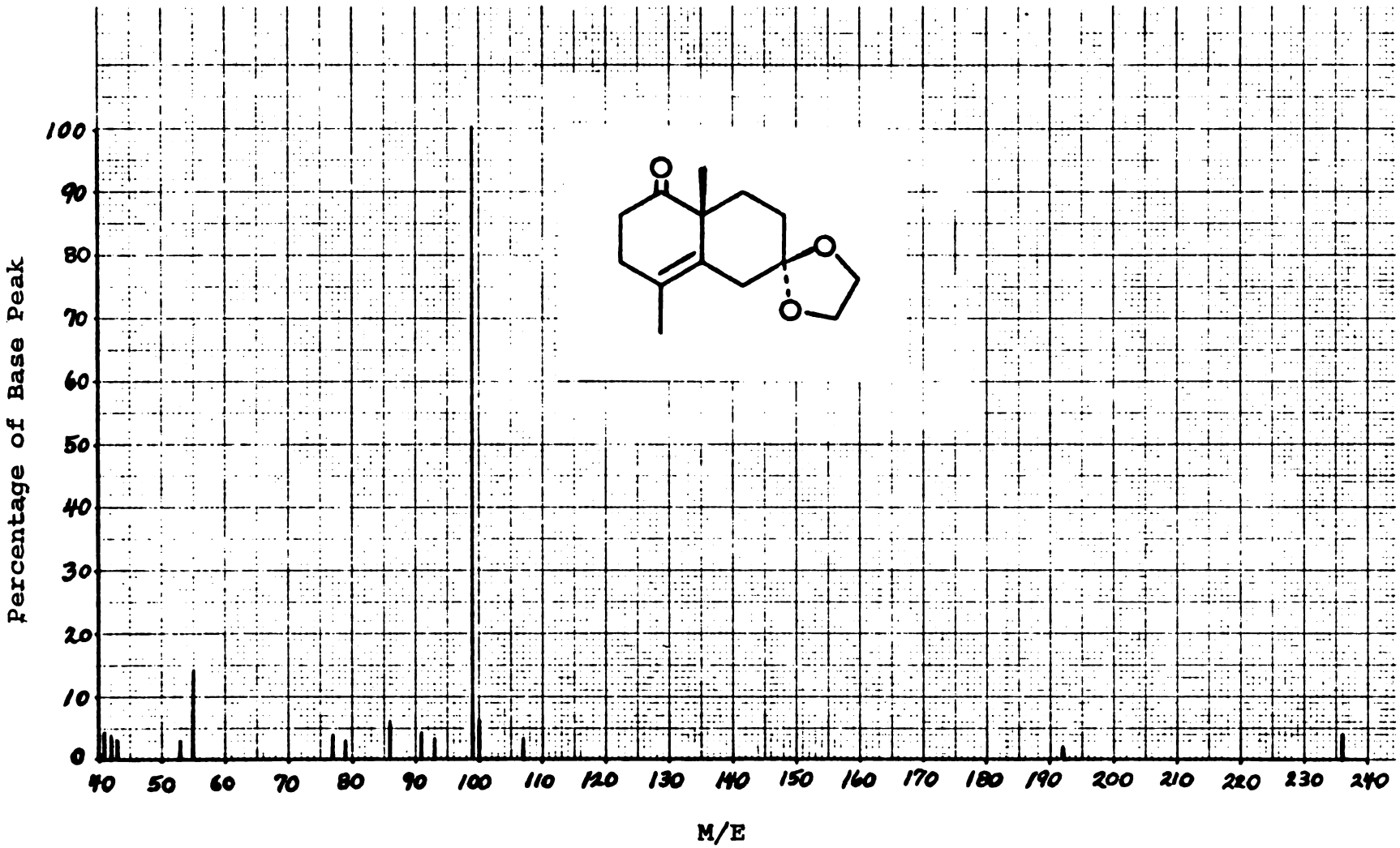


Figure 53. Mass spectrum of 1,5-dimethylbicyclo-[4.4.0]-dec-5-ene-2,8-dione-8-ethylene ketal (58).

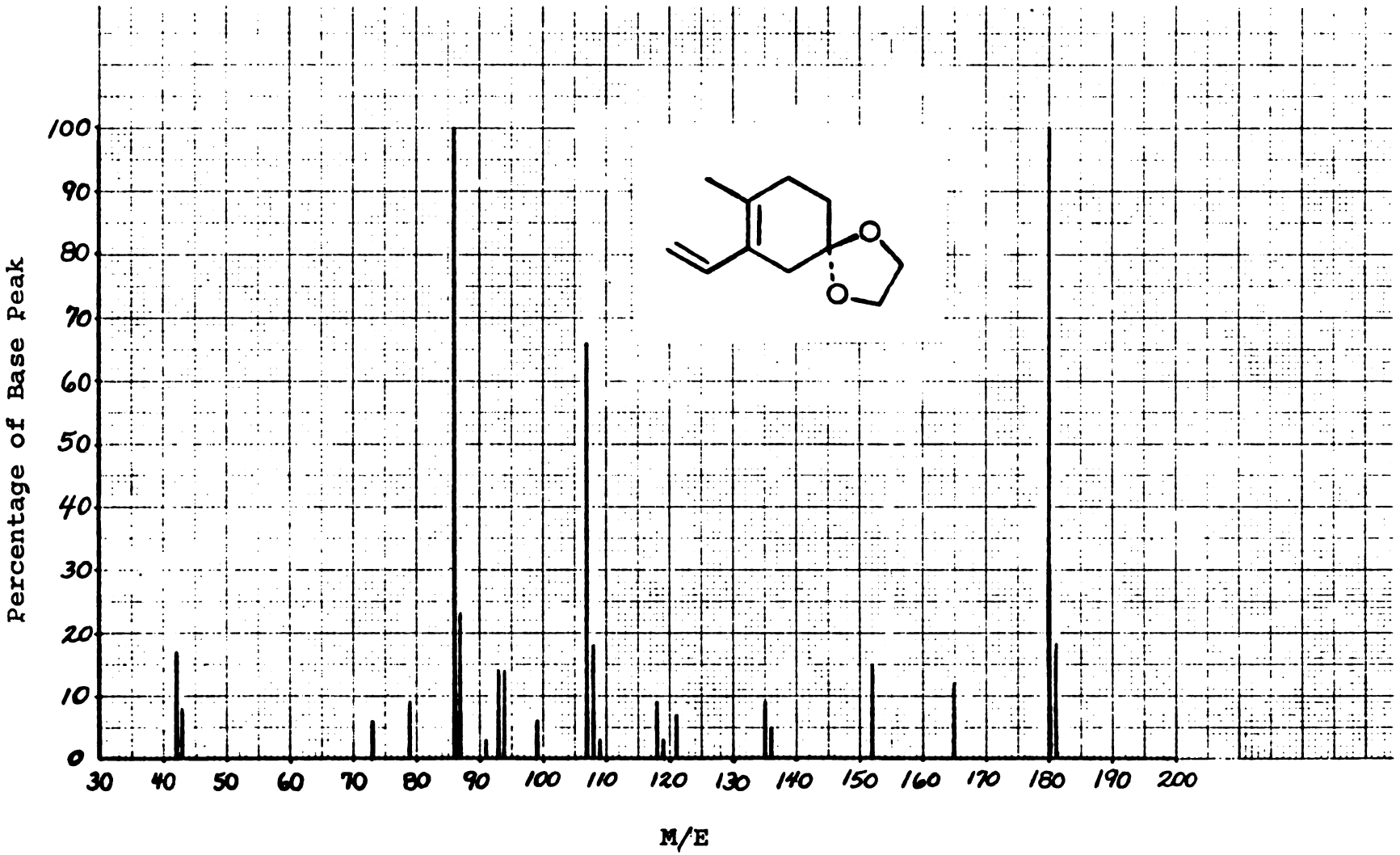


Figure 54. Mass spectrum of 4-methyl-2-vinyl-3-cyclohexene-1-one ethylene ketal (90).

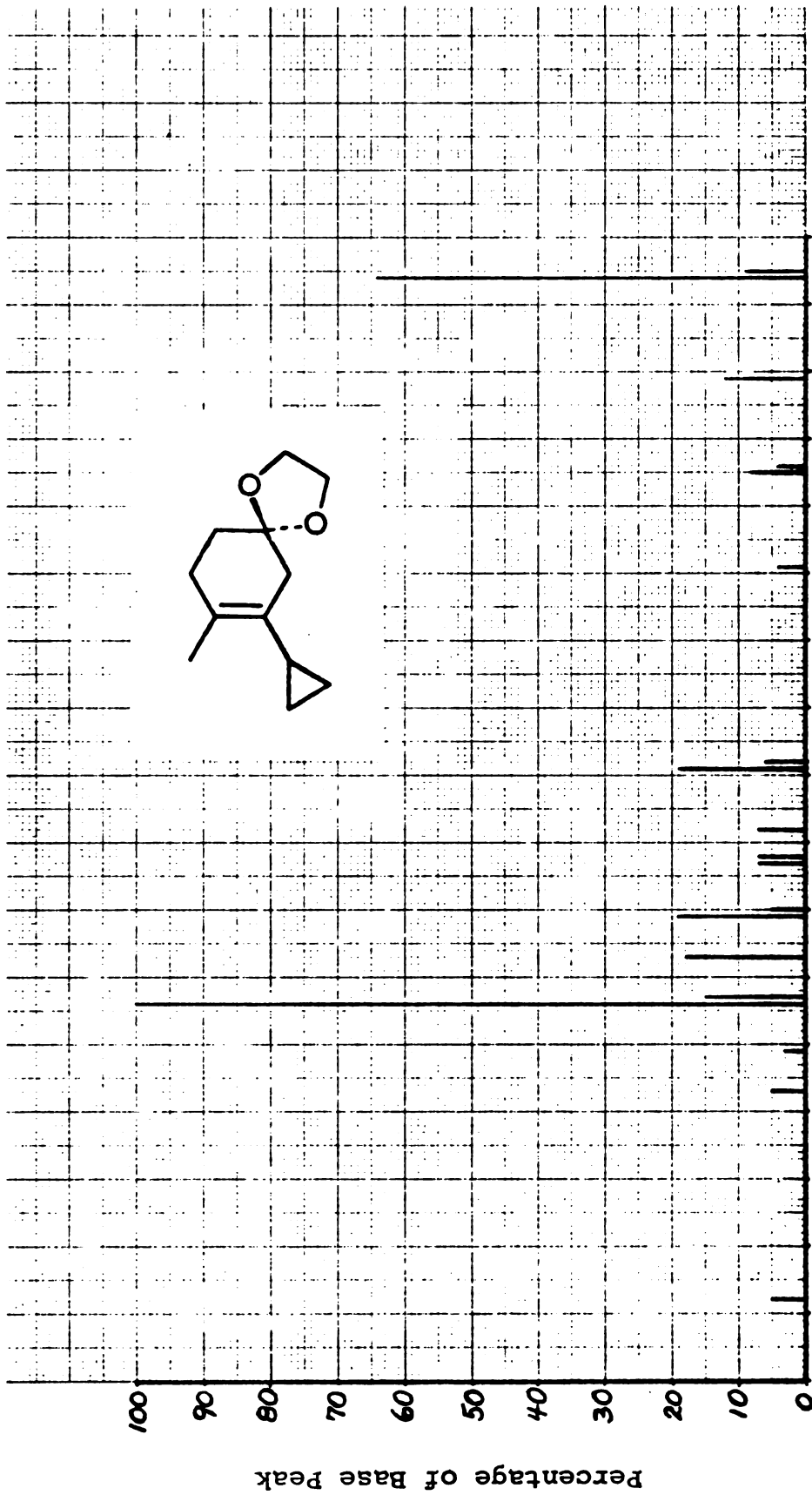


Figure 55. Mass spectrum of 4-methyl-3-cyclopropyl-3-cyclohexene-1-one ethylene ketal (91).

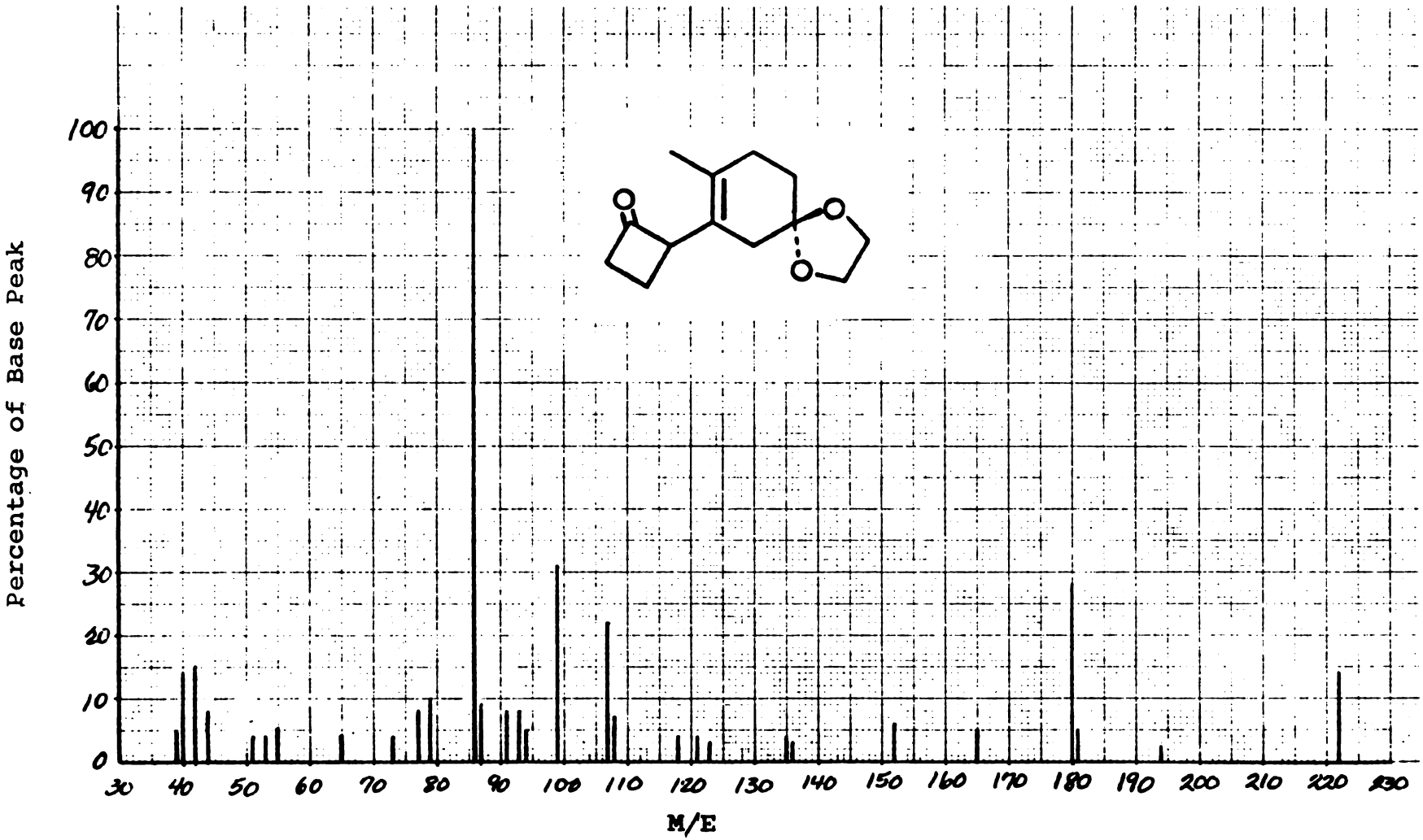


Figure 56. Mass spectrum of 4-methyl-3-(2-oxocyclobutyl)-3-cyclohexene-1-one ethylene ketal (89).

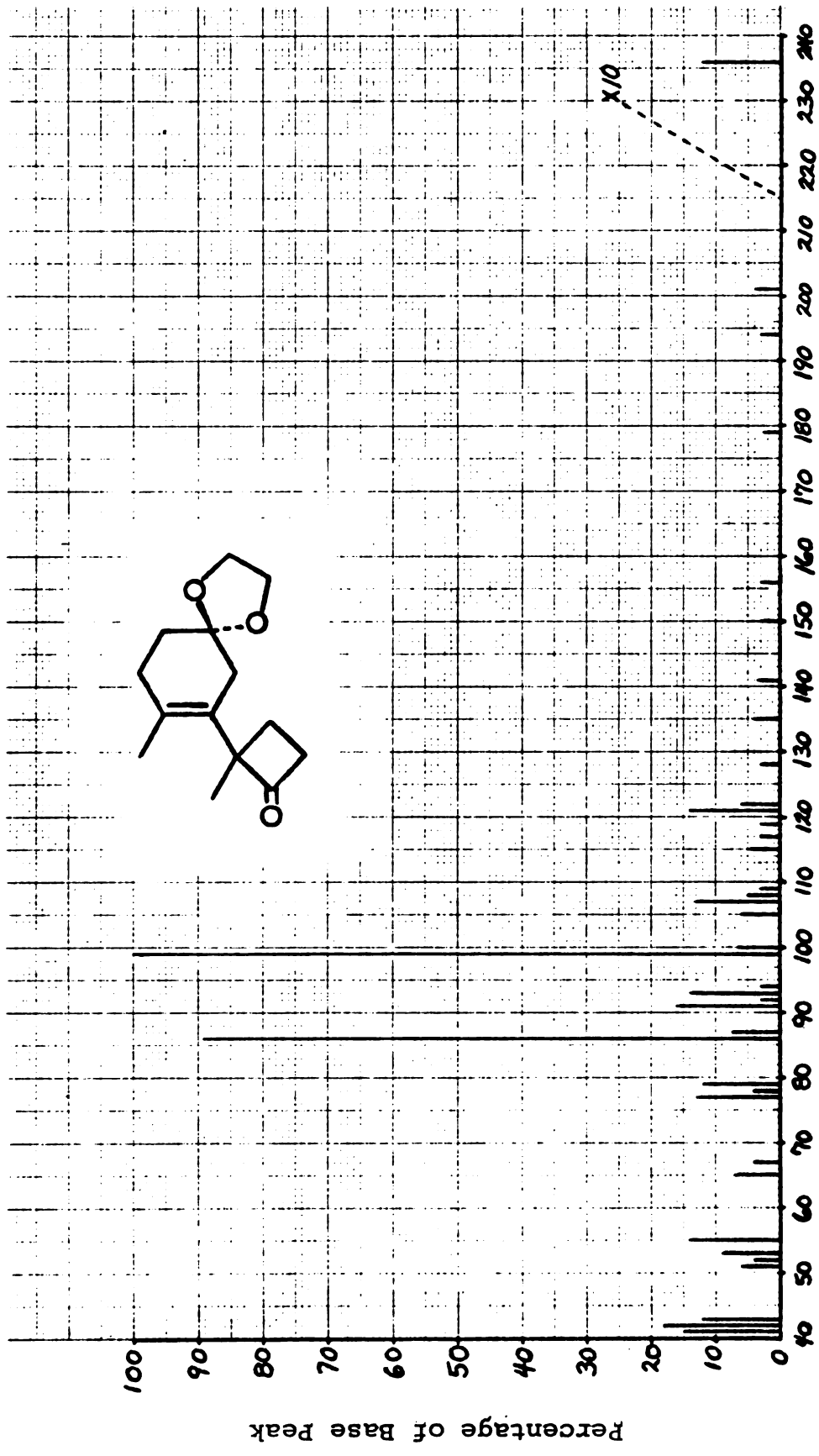


Figure 57. Mass spectrum of 4-methyl-3-(1-methyl-2-oxocyclobutyl)-3-cyclohexene-1-one ethylene ketal (95).

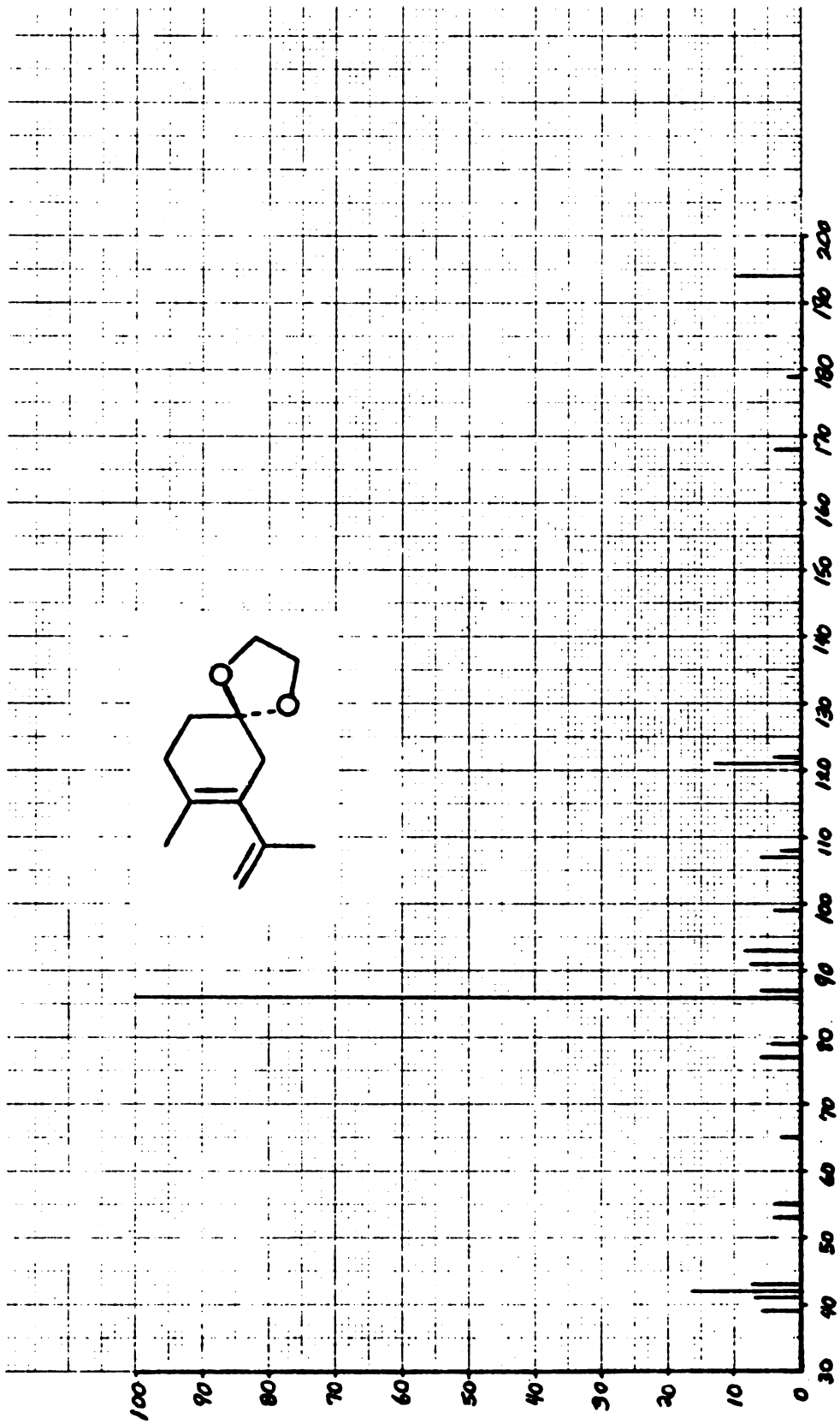


Figure 58. Mass spectrum of 4-methyl-3-(2-propenyl)-3-cyclohexene-1-one ethylene ketal (96).

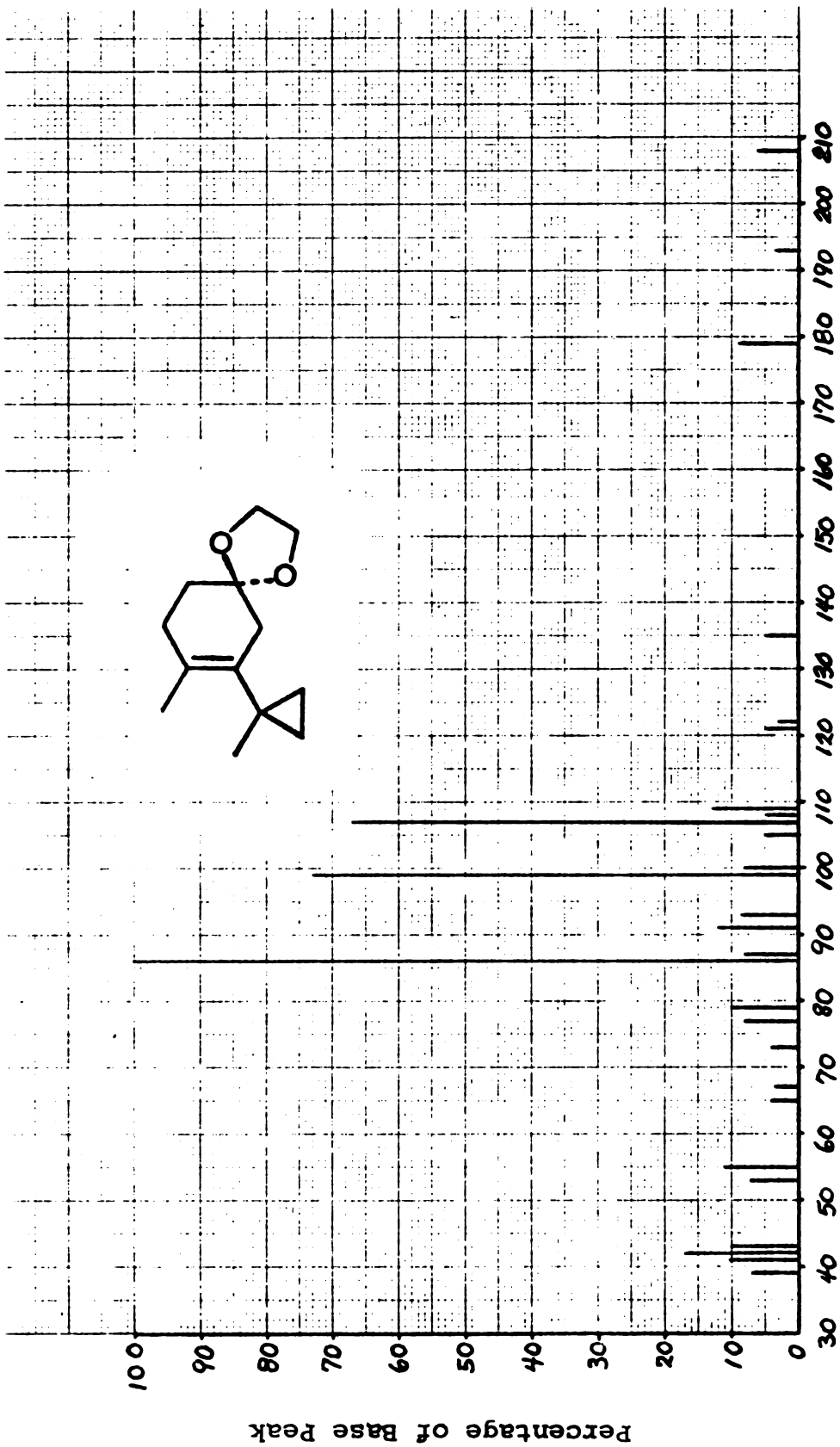


Figure 59. Mass spectrum of 4-methyl-3-(1-methylcyclopropyl)-3-cyclohexene-1-one ethylene ketal (97).

BIBLIOGRAPHY

BIBLIOGRAPHY

1. K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., Tetrahedron, 28, 1995 (1972).

2. A. Mondon and K. Böttcher, Chem. Ber., 103, 1512 (1970).

3. F. Merényi and M. Nilsson, Acta Chem. Scand., 17, 1801 (1963).

4. V. J. Grenda, G. W. Lindberg, N. L. Wendler, and S. H. Pines, J. Org. Chem., 32, 1236 (1967).

5. J. J. Panouse and C. Sannié, Bull. Soc. Chim. Fr., 1036 (1955).

6. For three methods of catalytic removal of the 1-Keto group see:
   a) M. Orchin and L. W. Butz, J. Amer. Chem. Soc., 65, 2296 (1943).
   b) M. Vandewalle and F. Compernolle, Bull. Soc. Chim. Belges, 75, 349 (1966)
   c) P. Collins, C. J. Jung, and R. Pappo, Israel J. Chem., 6, 839 (1968).

7. F. Korte and H. Machleidt, Chem. Ber., 88, 1676 (1955).

8. The specific reaction conditions used are taken from S. Dev and C. Rai, J. Indian Chem. Soc., 34, 266 (1957).

9. A. Meister and J. P. Greenstein, J. Biol. Chem., 573 (1948).

10. J. Katsube and M. Matsui, Agr. Biol. Chem., 33, 1078 (1969).

11. C. J. Sih, J. B. Heather, G. P. Peruzzotti, P. Price, R. Sood, and L. H. Lee, J. Amer. Chem. Soc., 95, 1676 (1973).

12. F. Van Hulle, V. Sipido, and M. Vandewalle, Tetrahedron Lett., 24, 2213 (1973).

13. K. Green, Acta Chem. Scand., 23, 1453 (1969).

14. K. Green, Biochim. Biophys. Acta, 231, 419 (1971).

15. K. Green, Biochemistry, 10, 1072 (1971).

16. O. Wichterle, Coll. Czech. Chem. Comm., 12, 93 (1947).

17. R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, J. Org. Chem., 31, 1489 (1966).

18. S. V. Kessar, A. L. Rampal, K. Kumar, and R. R. Jogi, Indian J. Chem., 2, 240 (1964).

19. G. Büchi and E. M. Burgess, J. Amer. Chem. Soc., 82, 4333 (1960).

20. J. R. Williams and H. Ziffer, Chem. Commun., 194 (1967).

21. J. E. Starr and R. H. Eastman, J. Org. Chem., 31, 1393 (1966).

22. L. A. Paquette, R. F. Eizember, and O. Cox, J. Amer. Chem. Soc., 90, 5153 (1968).

23. P. S. Engel and M. A. Schexnayder, ibid., 94, 9252 (1972) and references to H-abstraction cited therein.

24. R. Cargill, J. Damewood, and M. Cooper, ibid., 88, 1330 (1966).

25. P. S. Engel and H. Ziffer, Tetrahedron Lett., 5181 (1969).

26. a) E. Baggiolini, K. Schaffner, and O. Jeger, Chem. Commun., 1103 (1969).
    b) J. Ipaktschi, Tetrahedron Lett., 2153 (1969)
    c) J. Ipaktschi, ibid., 3179 (1970).
    d) W. G. Dauben, M. S. Kellogg, J. I, Seeman, and W. A. Spitzer, J. Amer. Chem. Soc., 92, 1786 (1970).
    e) R. S. Givens, W. F. Oettle, R. L. Coffin, and R. G. Carlson, ibid., 93, 3957 (1971)
    f) R. G. Carlson, R. L. Coffin, W. W. Cox, and R. S. Givens, Chem. Commun., 501 (1973)
    g) H. Sato, K. Nakanishi, J. Hayashi, and Y. Nakadaira, Tetrahedron, 29, 275 (1973).
    h) P. S. Engel, M. A. Schexnayder, H. Ziffer, and J. I. Seeman, J. Amer. Chem. Soc., 96, 922 (1974).

27. J. R. Williams and G. M. Sarkisian, ibid., 1564 (1971).

28. J. R. Williams and H. Ziffer, Tetrahedron, 24, 6725 (1968).

29. H. Sato, N. Furutachi, and K. Nakanishi, J. Amer. Chem. Soc., 94, 2150 (1972).

30. R. C. Cookson and N. S. Wariyar, J. Chem. Soc., 2302 (1956).

31. R. C. Cookson and N. R. Rogers, Chem. Commun., 809 (1972).

32. J. B. Jones, J. D. Leman, and P. W. Maar, Can. J. Chem., 49, 1604 (1971).

33. M. Kato, H. Kosugi, and A. Yoshikoshi, Chem. Commun., 185 (1970).

34. R. M. Coates and J. E. Shaw, J. Amer. Chem. Soc., 92, 5657 (1970).

35. M. Yoshimoto, N. Ishida, and T. Hiraoka, Tetrahedron Lett., 39 (1973).

36. H. O. House, "Modern Synthetic Reactions," 2nd ed., W. A. Benjamin, New York, N. Y., 1972, pp. 555-558.

37. R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, Tetrahedron Lett., 965 (1973).

38. G. Stork, and R. L. Danheiser, J. Org. Chem., 38, 1775 (1973).

39. B. C. Boyce and J. S. Whitehurst, J. Chem. Soc., 2680 (1960).

40. S. Liisberg, W. O. Godtfredsen, and S. Vangedal, Tetrahedron, 9, 149 (1960).

41. N. J. Turro and R. M. Southham, Tetrahedron Lett., 545 (1967).

42. J. T. Dubois and F. Wilkinson, J. Chem. Phys., 38, 2541 (1963).

43. N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1965, p. 131.

44. F. S. Wettack, G. D. Renkes, M. G. Rockley, N. J. Turro, and J. C. Dalton, J. Amer. Chem. Soc., 92, 1793 (1970).