This is to certify that the

dissertation entitled

SYNTHETIC UTILITY OF
ALPHA-LITHIO SULFOXIDES

presented by

John B. Dickenson

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of the requirements for

Ph.D. degree in Chemistry

William Reusch
Major professor

Date 1-28-83

SYNTHETIC UTILITY OF ALPHA-LITHIO SULFOXIDES

By

John B. Dickenson

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ABSTRACT

SYNTHETIC UTILITY OF ALPHA-LITHIO SULFOXIDES

By

John B. Dickenson

Interest in organosulfur chemistry has grown explosively in the past decade. Researchers have shown that many synthetic transformations once difficult to achieve can now readily be accomplished by means of organosulfur reagents or sulfur-containing intermediates.

We have been interested in studying some synthetic applications of sulfoxides; in particular, our research has centered on reactions made possible by the ability of the sulfoxide group to stabilize adjacent carbanions.

Two syntheses of general interest have evolved from this research. The first allows the transformation of cyclic ketones into exocyclic allylic alcohols. Phenylsulfinylmethyllithium, formed by metallation of phenylmethyl sulfoxide, is condensed with a ketone, and the resulting

β-hydroxysulfoxide is dehydrated to afford an allylic sulfoxide. Treatment of this allylic sulfoxide with a thiophilic reagent yields an allylic alcohol by intercepting a {2,3} sigmatropic rearrangement.

The second synthetic method developed here permits elaboration of a cyclohexanone to a tetralin system. This reaction sequence also makes use of the phenylsulfinylmethyllithium reagent, and it is interesting to note that the methyl group of phenylmethylsulfoxide eventually becomes one of the aromatic ring carbons. The cyclic aliphatic ketone is first converted to a masked β-ketoaldehyde, in this study the α-methoxymethylene derivative. Condensation of phenylsulfinylmethyllithium with this enol ether, followed by acid hydrolysis, yields a β-(phenylsulfinylmethyl) unsaturated aldehyde. Deprotonation of this aldehyde, followed by a Michael addition to ethyl acrylate, aldol condensation and a pyrolytic elimination, gives the desired tetralinic ester. Overall yields are good in a simple model system, but apparently the reaction scheme is sensitive to steric factors, since yields drop greatly in hindered systems.

DEDICATION

To my parents, Joseph and Pauline;

and to my wife Andrea

ACKNOWLEDGEMENTS

I wish to thank Professor William Reusch for his guidance throughout my stay at Michigan State. Appreciation is also extended to the MSU Department of Chemistry and the MHESLA for financial support.

Special thanks to Marge Dunn, who prepared the final manuscript on the word processor, and to my wife Andrea, who typed the initial draft and provided much love and understanding. And many thanks to my parents, whose gift of a chemistry set led to all this.

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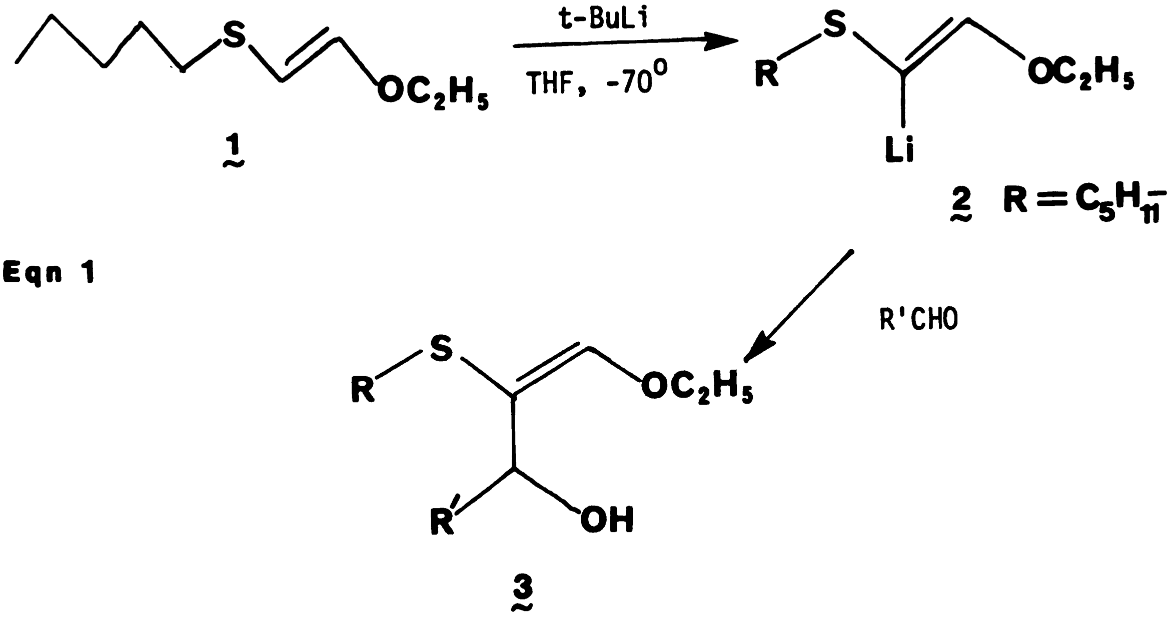
INTRODUCTION

Achieving carbon-carbon bond formation is a vital part of any total synthesis; it is in this way that complex molecules are assembled from simple building blocks. Almost all common carbon-carbon bond formation reactions involve reaction of a carbanion with an electrophilic species,[1] although electrocyclic reactions are a noteworthy exception. Thus it is the ability to form a specific carbanion and cause it to react with a suitable electrophile that allows the synthetic organic chemist to perform a myriad of reactions -- a Grignard addition, an aldol condensation, alkylation of an enolate, and so on.

In a few cases, such as Grignard reagents and organolithiums, no extra stabilization is afforded to the carbanion. In a majority of carbanions, however, the negative charge on carbon is alleviated to some degree by inductive or resonance delocalization of charge. The benefit is twofold: the reagent is more stable, and the product of the reaction may then contain additional desired functionality.

Among the class of carbanions stabilized only by an α-heteroatom, those containing silicon, sulfur, and phosphorus are generally the most stable and synthetically useful. Oxygen and nitrogen provide limited stabilization due to their lesser polarizability.[2] Equation 1 provides a vivid example of the superior effect of sulfur in the metallation of 2-ethoxy-1-pentylthioethylene **1**.[3]



Eqn 1

Sulfur-containing carbanions are especially valuable in synthesis, due to the flexibility provided by the many oxidation states available to sulfur. Three major classes of organosulfur compounds are capable of stabilizing an adjacent negative charge. These are sulfides, sulfones, and sulfoxides. Each will be discussed in turn.

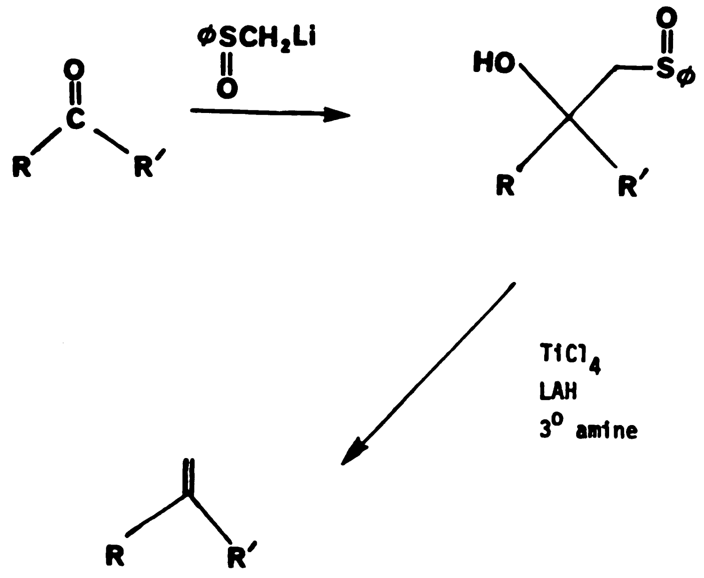
Sulfides

Sulfides represent the lowest oxidation state of organosulfur compounds, and may be synthesized easily by displacement of halide by the conjugate base of a thiol or thiophenol.[4]

Eqn 2 $$RS^- + R'X \longrightarrow RSR' + X^-$$

Compared to sulfoxides and sulfones, a sulfide provides the least stabilization to an adjacent carbanion. The pKa of thioanisole in DMSO (dimethyl sulfoxide) solution is 49.[5] Nevertheless, even simple dialkyl or arylalkyl sulfides can be metallated with very strong bases. Thus thioanisole can be lithiated by n-butyllithium-diazabicyclooctane (n-BuLi-DABCO),[6] and even methylthiomethyllithium has been formed _via_ reaction of dimethyl sulfide with n-butyllithium-tetramethylethylenediamine (n-BuLi-TMEDA).[7]

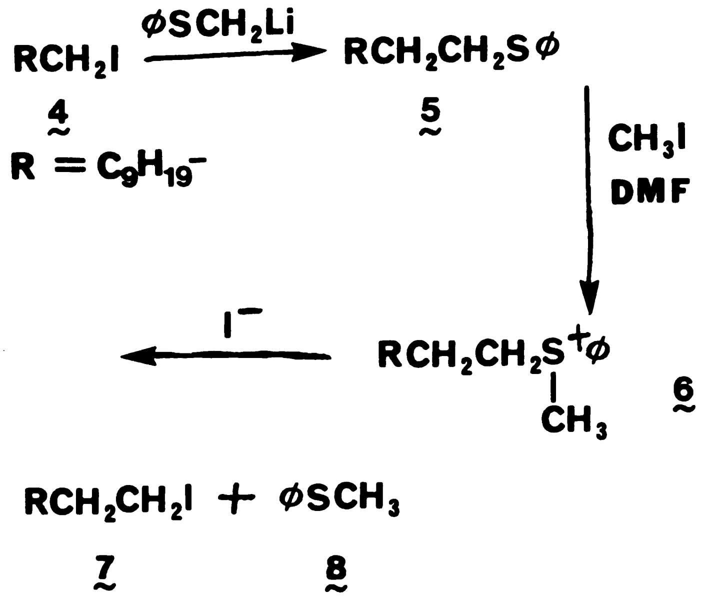
Once formed, these powerful nucleophiles can react with a variety of substrates. For example, phenylthiomethyllithium adds to ketones in good yields. The adducts can be eliminated to methylene compounds,[8] thus providing an alternative to the Wittig reaction for ketones which are highly hindered or prone to enolization.



Eqn 3

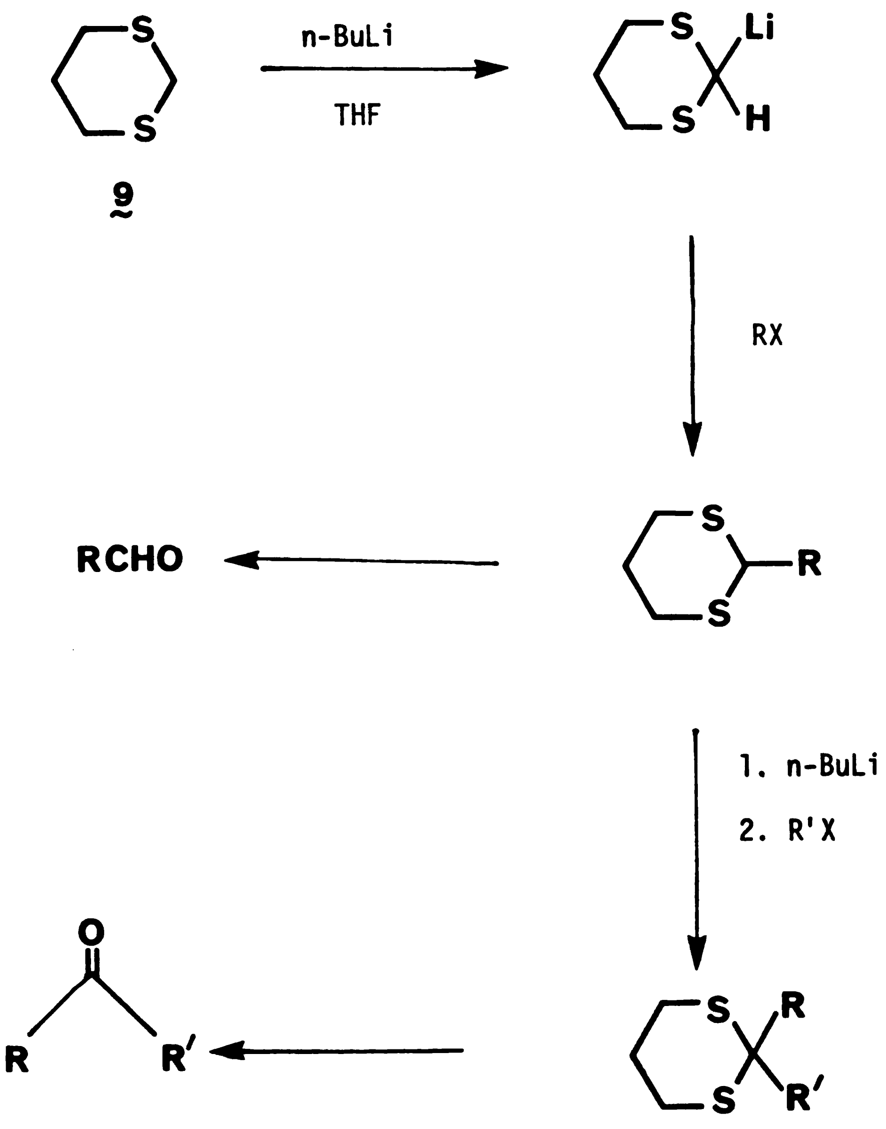
Phenylthiomethyllithium has also been used in a one-carbon homologation of primary alkyl halides, as reported by Corey.[9] This homologation proceeds in high yield and in only two steps. Phenylthiomethyllithium is alkylated by the primary halide, and the resulting sulfide is then heated with excess methyl iodide in dimethyl formamide (DMF). The overall yield for the transformation of 1-iododecane to 1-iodoundecane is 76 per cent.

Eqn 4



Perhaps the most renowned application of sulfide-stabilized carbanion chemistry is Corey and Seebach's 1,3-dithiane synthesis.[10] Here, 1,3-dithiane 9 serves as an "acyl anion equivalent" because of its reactivity toward electrophiles and because alkylated 1,3-dithianes can be transformed into aldehydes or ketones. Typically, 1,3-dithiane is lithiated by n-butyllithium in tetrahydrofuran at -20°; the anion is then alkylated by alkyl halide, and the resulting 2-alkyl-1,3-dithiane can be hydrolyzed to an aldehyde, or alkylated once again. A 2,2-dialkyl-1,3-dithiane yields a ketone upon hydrolysis.

SCHEME I

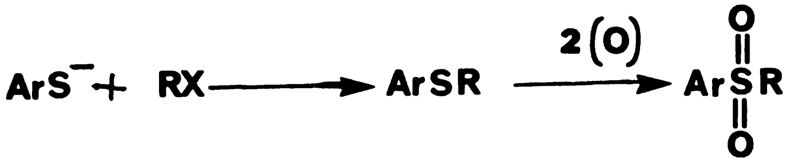


Yields of alkylated 1,3-dithianes are high with primary and secondary halides; hydrolysis, however, is not trivial. Many different hydrolysis reagents and conditions have been used, but none were found to be general.

Sulfones

The higher oxidation states of sulfur are often synthesized from the corresponding sulfide. Thus displacement of halide by thiophenoxide, followed by treatment with two equivalents of an oxidant, yields a sulfone.[11]

Eqn 5



$$ArS^- + RX \longrightarrow ArSR \xrightarrow{2(O)} Ar\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}R$$

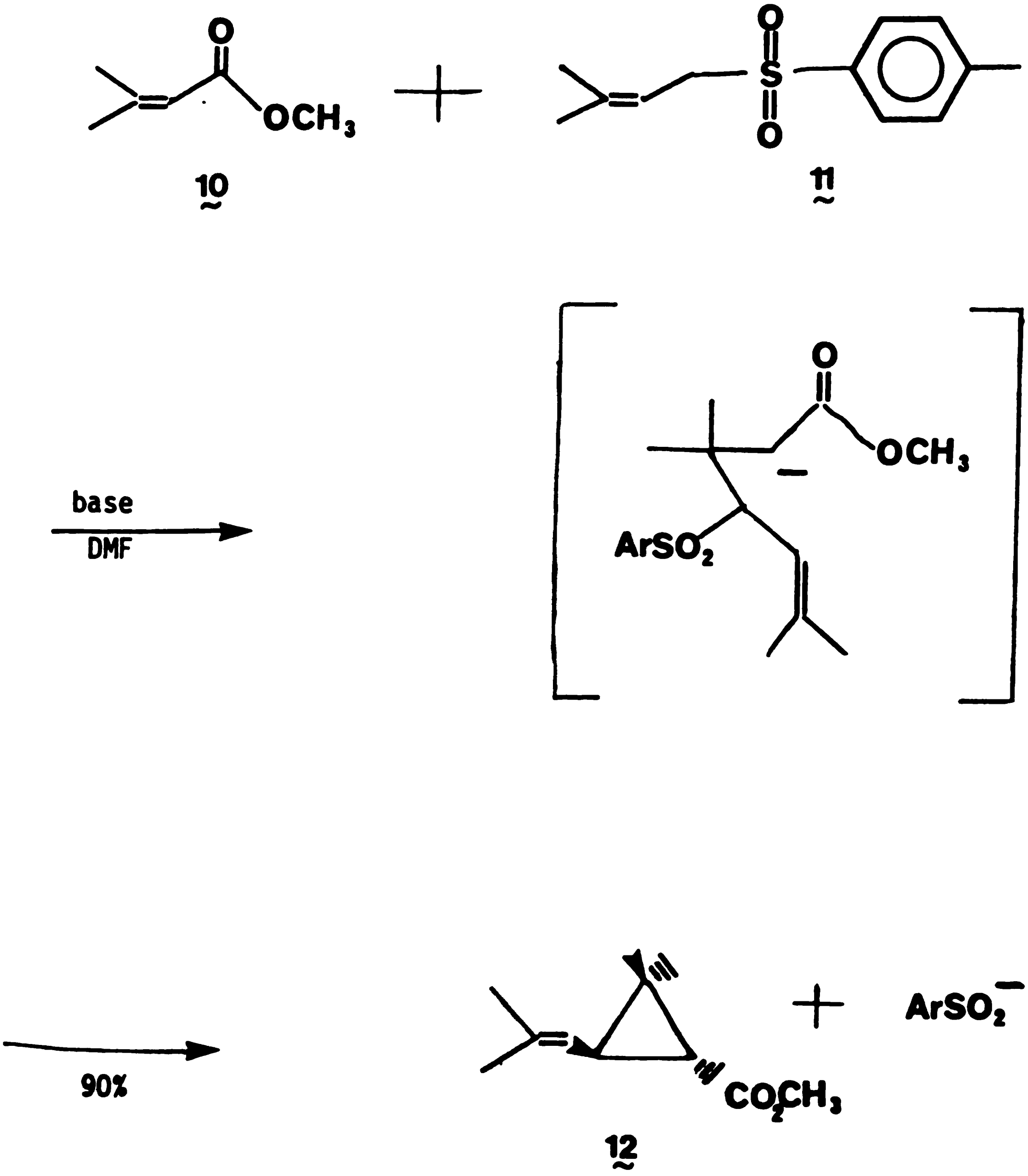
Alternatively, sulfones may be prepared directly by alkylation of sodium aryl sulfinates.[12]

Eqn 6

$$ArSO_2^-Na^+ + RX \longrightarrow Ar\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}R$$

Sulfones are more acidic than sulfides and sulfoxides. Most sulfones have pKa's in the range of 23-27.[13] Due to their "soft" nature, sulfone anions often add to unsaturated carbonyl compounds in a 1,4 fashion. For example, Schatz has reported a convergent synthesis of methyl chrysanthemate 12 which is so straightforward that he recommends it for inclusion in an undergraduate laboratory course.[14] The key step in this synthesis is a conjugate addition of a sulfone-derived anion followed by an intramolecular displacement of arylsulfinate.

SCHEME II

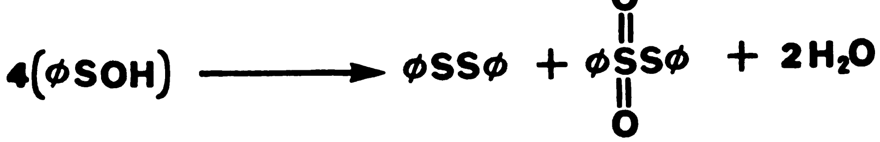


Sulfoxides

Sulfoxides are intermediate in acidity between sulfides and sulfones, having pKa's in the neighborhood of 35.[13] The simplest sulfoxide, DMSO, has found extensive use as an industrial solvent,[15] and lately has received much publicity concerning its medicinal properties.[16] The sodium salt of DMSO, known as "dimsyl sodium", is often used as a strong base.[17] Until recently, few sulfoxides more complex than DMSO were studied. A review of the current literature, however, reveals a dramatic increase of interest in sulfoxide chemistry. Pioneering researchers such as Evans and Trost have demonstrated the synthetic utility of sulfoxides.

It was perhaps the difficulty of synthesis and instability of sulfoxides which deterred earlier chemists from studying them. It is known that the sulfoxide oxidation state is unstable with respect to sulfides and sulfones. For example, thiophenol and benzenesulfinic acid are stable compounds, but attempts to synthesize benzenesulfenic acid led only to disproportionation products.[18]

Eqn 7



$$4(\phi SOH) \longrightarrow \phi SS\phi + \phi\overset{\text{O}}{\underset{\text{O}}{\overset{\|}{\underset{\|}{\text{S}}}}}S\phi + 2H_2O$$

Fortunately, recent developments have greatly facilitated sulfoxide synthesis. Some of the effective methods include:

1. Oxidation of a sulfide. In the past, this has been the most common method, but has suffered from over-oxidation to sulfones. However, aqueous sodium metaperiodate oxidizes sulfides to sulfoxides in near-quantitative yield, with no sulfone contaminants.[19] A somewhat less satisfactory alternative oxidant is meta-chloroperbenzoic acid at very low temperatures.[20]

2. Reaction of a Grignard reagent with an aryl sulfinate ester. Because this reaction proceeds with 100% inversion of the sulfur configuration, it is useful in the synthesis of chiral sulfoxides.[21]

3. Friedel-Crafts acylation of suitable aromatic substrates with an aryl sulfinyl halide.[22]

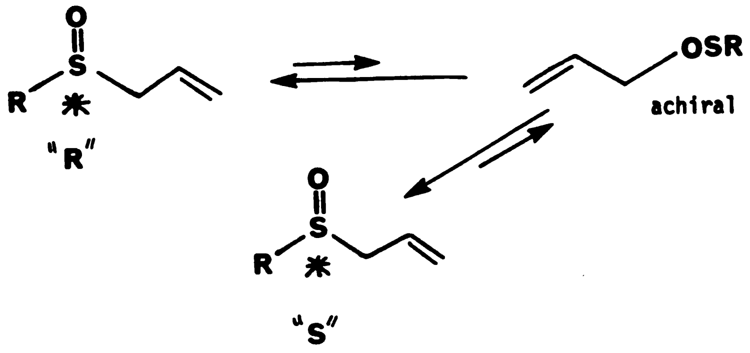
4. Sulfenylation of an allylic alcohol. Reaction of allylic alcohols with benzenesulfenyl chloride has been used as a synthesis of allylic sulfoxides.[23] This last method of sulfoxide synthesis exemplifies a unique aspect of sulfoxide chemistry, the {2,3} sigmatropic rearrangement of allylic sulfoxides. The first evidence for this rearrangement was noted by Mislow.[24] Observing that chiral sulfoxides with a

β-γ double bond slowly racemized, he postulated that such sulfoxides were in equilibrium with an achiral sulfenate ester (Eqn 8).

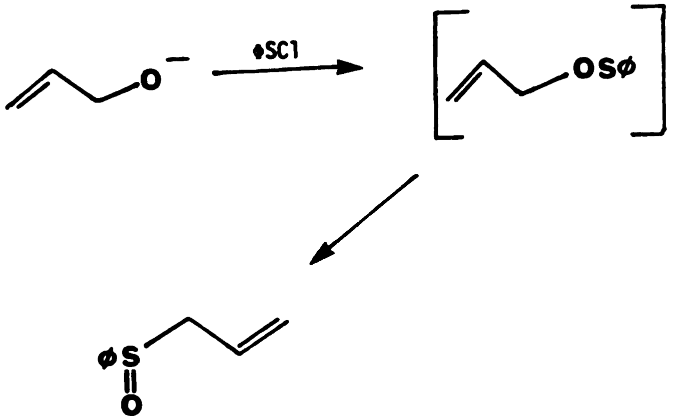
This hypothesis was later proved by Evans, who showed that allylic sulfoxides were converted to allylic alcohols by reagents which cleaved the sulfur-oxygen bond of the intermediate sulfenate ester.[25] Such reagents are known as "thiophiles" and include trimethyl phosphite, thiophenoxide, and secondary amines.

Owing to the lesser stability of sulfenate esters _vis-à-vis_ allylic sulfoxides, the equilibria do not favor formation of sulfenate esters, and such compounds are not normally present in detectable concentrations.[26] Thus sulfenylation of allylic alkoxides proceeds _via_ a transient sulfenate ester, the end product being a sulfoxide.

Eqn 8

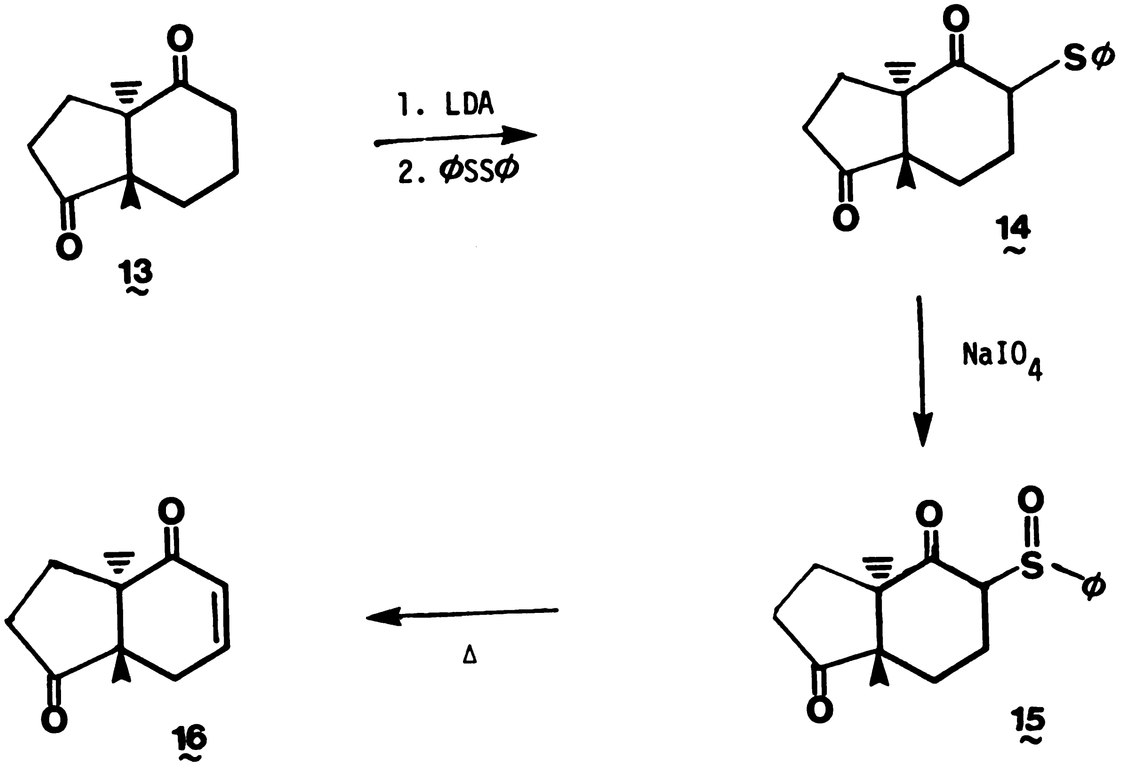


Eqn 9



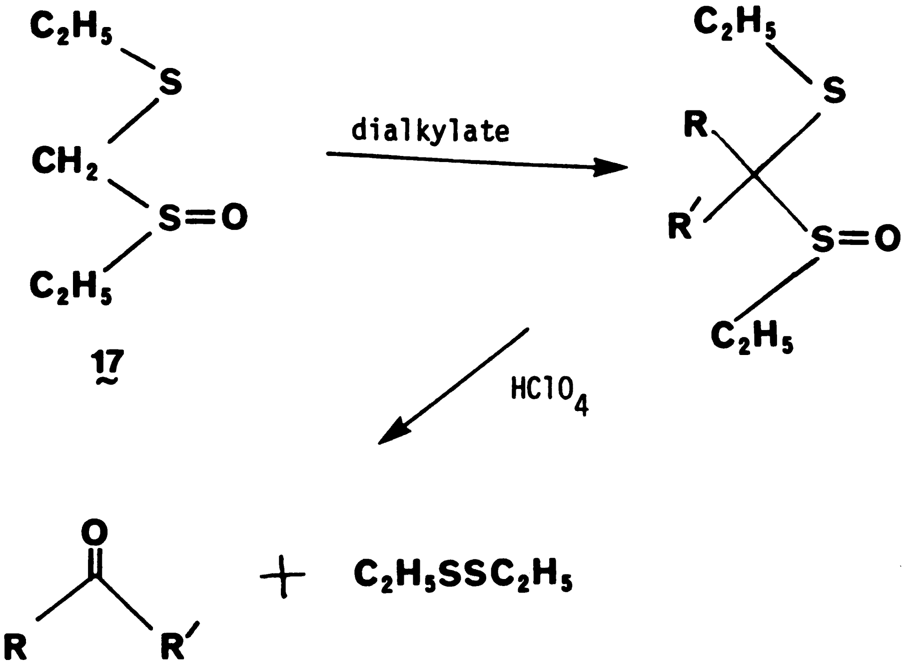
The technique of enolate sulfenylation is useful in the synthesis of enones from ketones. The intermediate β-ketosulfide is oxidized to the sulfoxide; thermolysis then yields an α,β unsaturated ketone.

SCHEME III



The hydrolysis problem alluded to earlier in the 1,3-dithiane synthesis has been alleviated completely by Schlessinger *et al.* with a mixed sulfoxide-sulfide reagent 17.[28] This system has been shown to alkylate in the same manner as 1,3-dithiane, and hydrolysis proceeds with excellent yields in the presence of a catalytic amount of perchloric acid.

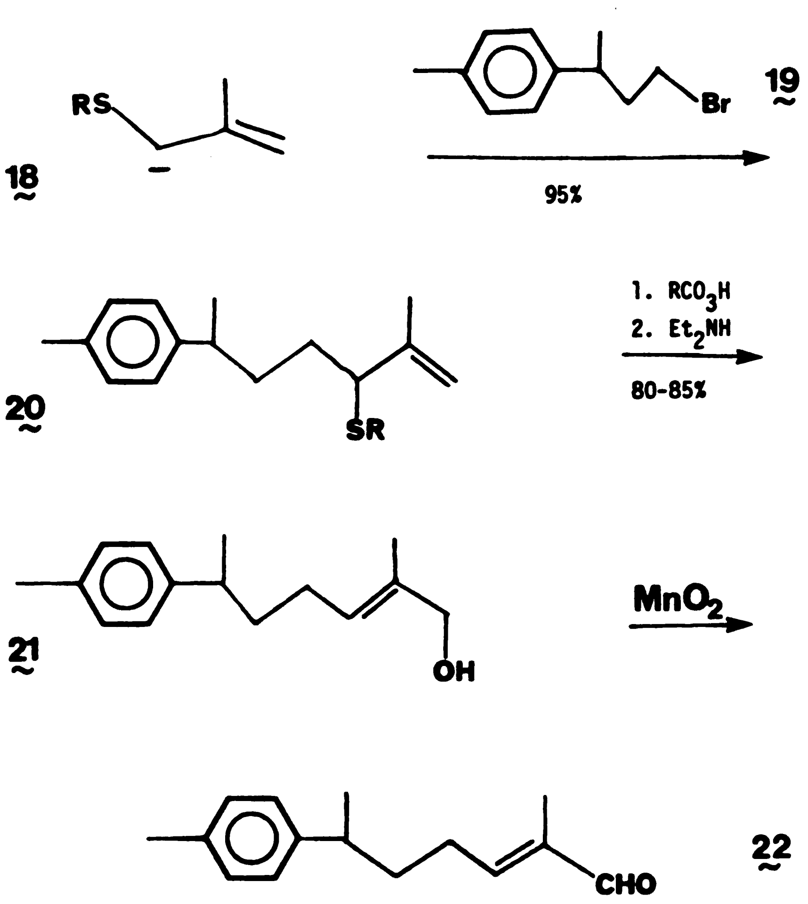
SCHEME IV



Furthermore, in contrast with the exclusive 1,2 additions exhibited by 1,3-dithianes, this mixed sulfide-sulfoxide adds 1,4 to unsaturated carbonyls, thus providing an efficient synthesis of 1,4-dicarbonyl compounds, which are difficult to produce by classical methods. It is interesting to note that the dimethyl analog of **17** alkylates with difficulty and will not dialkylate at all.

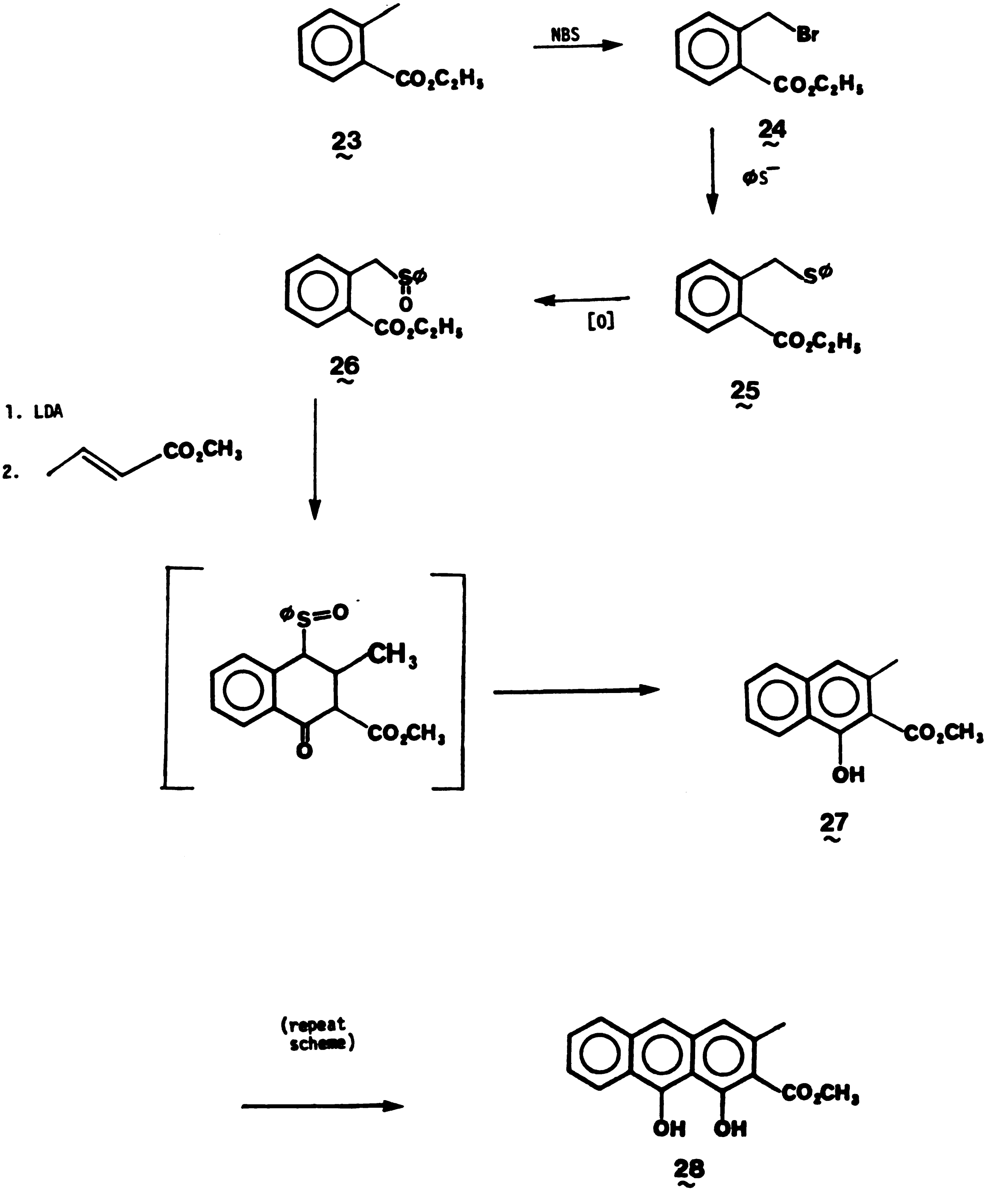
The synthetic utility of allylic sulfoxides has received much attention, and forms a major part of this thesis. Evans used an allylic sulfoxide in his elegant synthesis of nuciferal (Scheme V).[29] Alkylation of sulfide 18 with bromide 19 gave sulfide 20. Oxidation to the sulfoxide followed by 2,3 sigmatropic rearrangement afforded allylic alcohol 21. Nuciferal 22 was then obtained by a manganese dioxide oxidation. It can be seen that allylic sulfoxides serve as a γ-allylic alcohol anion equivalent.

SCHEME V



Finally, Hauser has reported a method by which a toluate ester can be elaborated to an α-naphthol.[30] Repetition of this reaction sequence would, in principle, lead to linear aromatic systems of any length; for example, compound 28. Part of this thesis describes an aromatic annulation scheme which complements Hauser's nicely, allowing saturated ring systems to be converted to tetralins bearing a variety of substituents.

Scheme VI

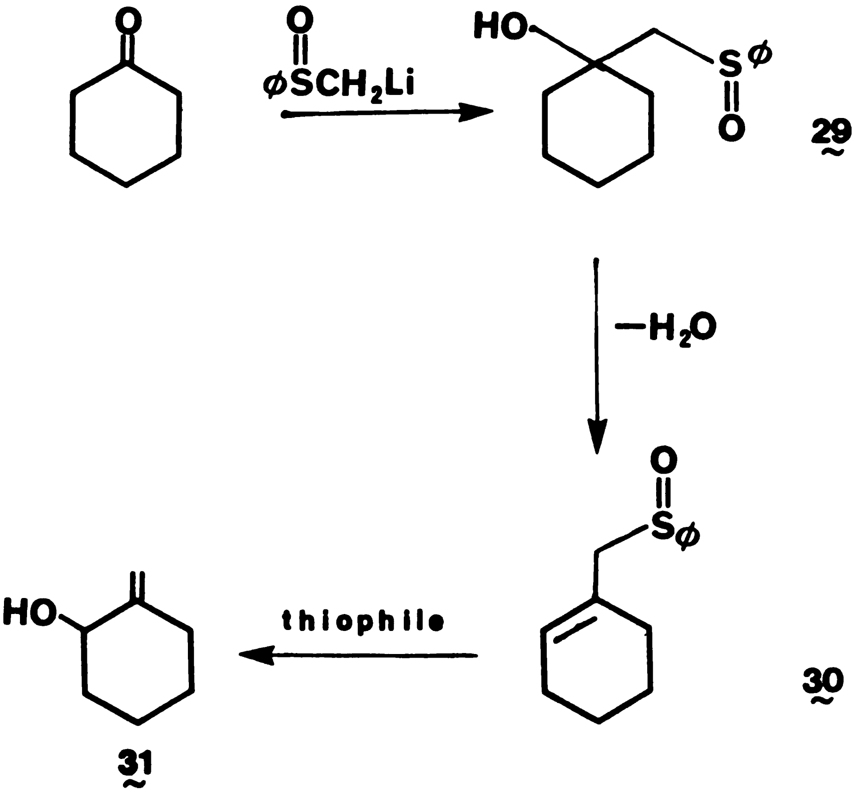

CO2C2H5
23
NBS
Br
CO2C2H5
24
ϕS⁻
Sϕ
CO2C2H5
25
[O]
Sϕ
O
CO2C2H5
26
1. LDA
2.
CO2CH3
ϕS=O
CH3
CO2CH3
O
CO2CH3
OH
27
(repeat scheme)
CO2CH3
OH
OH
28

RESULTS AND DISCUSSION

A. Conversion of Cyclic Ketones to Exocyclic Allylic Alcohols

We have developed a reaction sequence whereby a cyclic ketone may be elaborated to an allylic alcohol, as indicated in Scheme VII.

Scheme VII



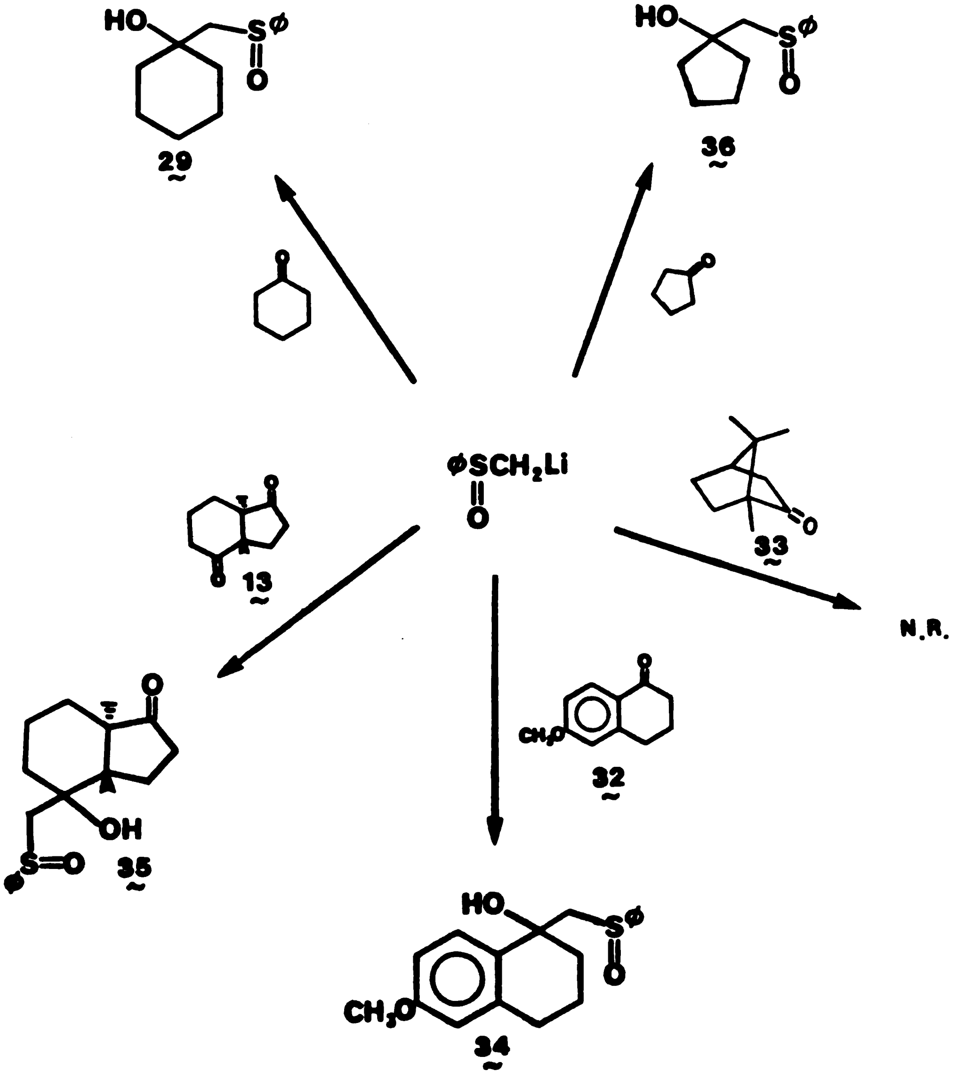
Overall yields are good. It should be noted that the transformation is not equivalent to α-methylenation followed by reduction; rather, the carbonyl carbon becomes part of the methylene group. Thus this method also involves a 1,2 transposition of oxygen functionality, which may prove useful in certain cases.

The first step is the condensation of the ketone with an α-metallated sulfoxide. To this end, phenyl methyl sulfoxide was prepared in high yield by oxidation of thioanisole with aqueous sodium metaperiodate.[31] The sulfoxide was treated with lithium diisopropylamide (LDA) in THF solution to afford the lithium salt, which was then reacted with a variety of ketones.

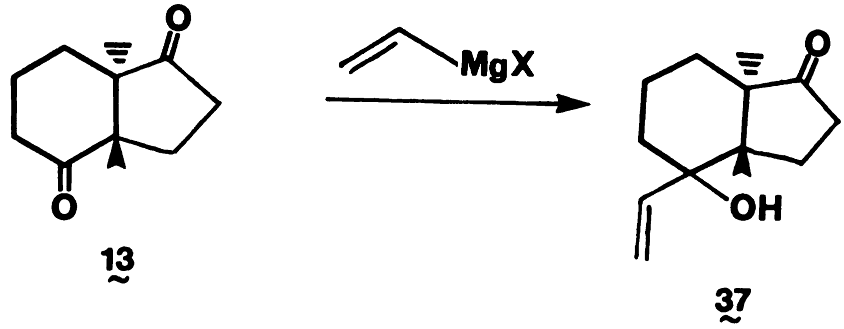
The yields in this addition were highly dependent upon the structure of the ketone substrate. Addition to cyclohexanone and cyclopentanone went smoothly; 6-methoxytetralone 32 also gave good yields of the adduct. When the reaction was attempted with sterically hindered ketones, however, the results were less satisfactory. Camphor 33 failed to react at all; apparently enolization took place. The bicyclic ketone 13 gave only moderate yields of adduct. This is not surprising, as the small, reactive reagent vinyl magnesium bromide is reported to add to 13 in only fifty per cent yield.[32] The best conversions to 35 were achieved when the reaction was carried out at -78° and then quenched. When the reaction mixture was refluxed in an attempt to force further reaction, only starting material was isolated. Finally, we observe that the lithium salt of 35 reverts to ketone 13 and sulfoxide under reflux (Eqn 11).

Recently another experimenter has reported a similar method, developed independently from ours. The author also cites an example of elimination of β-hydroxysulfoxide anions derived from hindered ketones.[33]

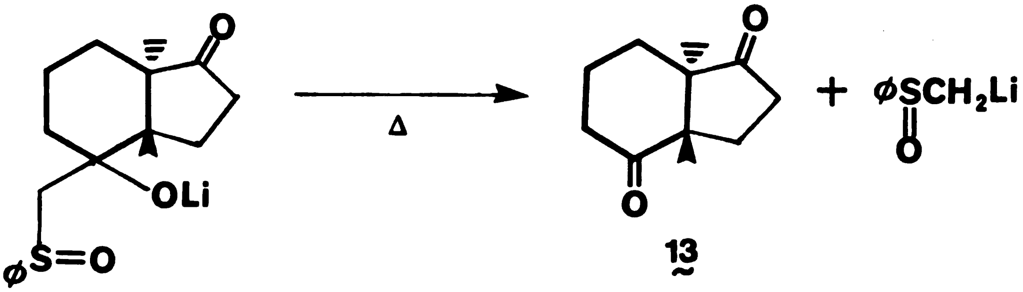
SCHEME VIII



Eqn 10



Eqn 11



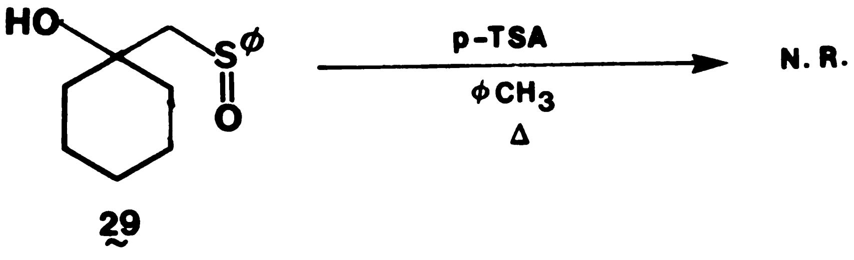
Once formed, the highly polar β-hydroxysulfoxides were isolated and recrystallized. It was observed that the methylene group gave rise to an AB system in the proton NMR because the protons are diastereotopic and thus exhibit mutual spin-spin splitting. Another interesting phenomenon occurs in the mass spectra; in most cases, these β-hydroxysulfoxides show a prominent M+1 peak instead of a parent ion. This may be rationalized as the result of an ion-molecule reaction whereby the basic sulfoxide oxygen is protonated. When the mass spectra are obtained *via* chemical ionization (reagent gas: methane), the same M+1 peak is observed, indicating the correct mass for the compound. The corresponding β-hydroxysulfides do not exhibit this proton transfer phenomenon.

Dehydration of the β-hydroxysulfoxide products presented some challenges. For instance, the initial compound studied, 1-phenylsulfinyl-1-cyclohexanol 29, was resistant to a large number of conventional dehydration reagents; in fact, 29 was recovered unchanged after prolonged reflux with p-toluenesulfonic acid in toluene solution. Other reagents either failed to induce a reaction, or gave tars.

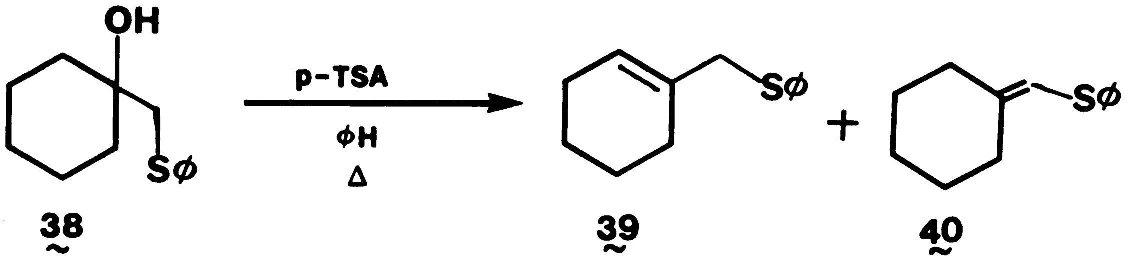
In contrast to the unreactivity of 29, β-hydroxysulfide 38 (prepared from cyclohexanone and phenylthiomethyl lithium) dehydrates readily, as one might expect a normal tertiary alcohol to do. Refluxing 38 in benzene with p-toluenesulfonic acid gave a mixture of the two isomeric alkenes 39 and 40.

It is not obvious why the presence of the sulfoxide oxygen so greatly attenuates the reactivity at the tertiary alcohol site. I propose that intramolecular hydrogen bonding might hinder the approach of reagents to the hydroxyl group. Some support for this theory was obtained from a study of acetylation reactions of 29 and 38. Thus 38 reacted with acetic anhydride in pyridine at room temperature to give acetate 41 in good yield. Sulfoxide 29, on the other hand, required long periods of reflux with acetic anhydride/pyridine in the presence of dimethylaminopyridine (DMAP) to achieve even partial conversion to its acetate derivative 42. DMAP is an acylation catalyst which has been reported to increase acetylation reaction rates by factors of 1,000 or more.[34]

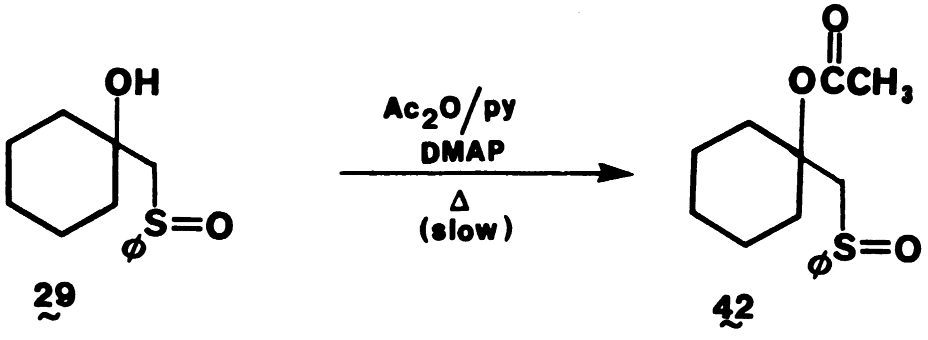
Eqn 12



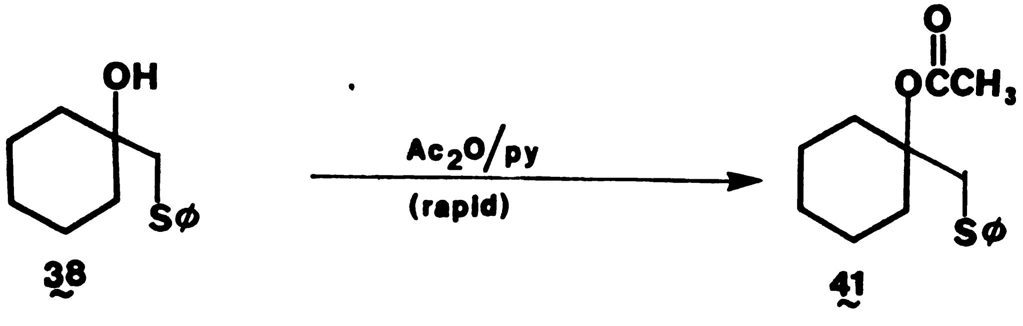
Eqn 13



Eqn 14

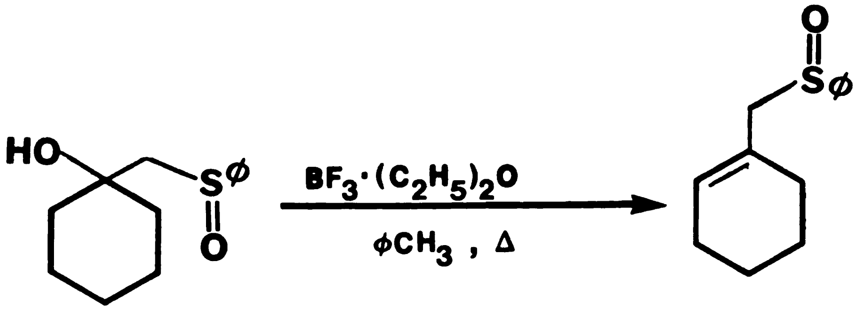


Eqn 15



Dehydration of 29 to 30 was finally effected in high yield by boron trifluoride etherate in refluxing toluene. It proved important to quench the reaction after forty minutes to one hour, as prolonged reflux led to extensive decomposition.

Eqn 16

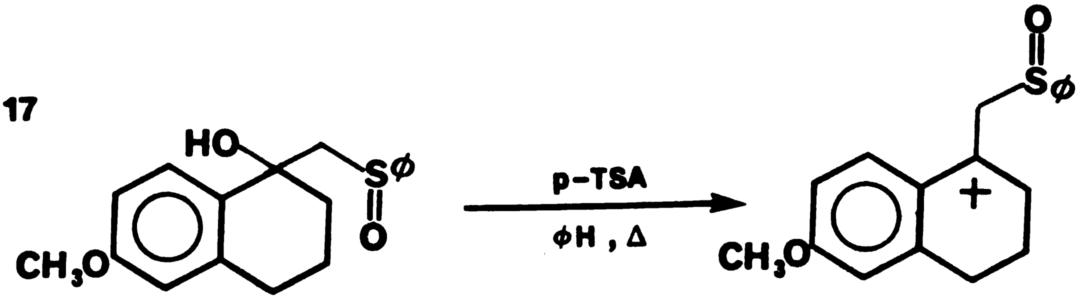


29

30

In contrast, the product 34 derived from phenylmethylsulfoxide and 6-methoxytetralone was dehydrated quantitatively by p-toluenesulfonic acid in refluxing benzene. The facility of this reaction is no doubt due to the increased stabilization afforded the tertiary carbocation by the electron-rich aromatic ring.

Eqn 17



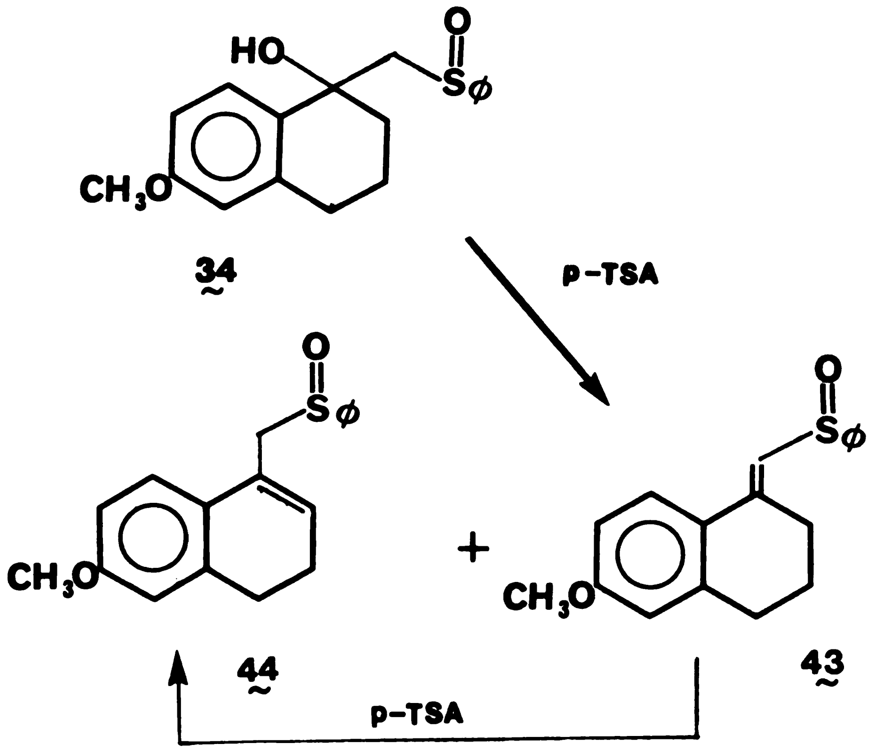
34

When the dehydration reaction was allowed to proceed at reflux for twenty minutes or longer, only the β,γ-unsaturated product 44 was observed. However, by quenching the reaction mixture with sodium bicarbonate after only five minutes, a mixture of unsaturated sulfoxides 43 and 44 was obtained. The ratio of the β, γ isomer 44 to α, β isomer 43 was approximately 2/1 by pmr analysis (Figure 1).

Figure 1. Comparison of vinyl region of pmrs showing effect of reaction time on isomer ratio.

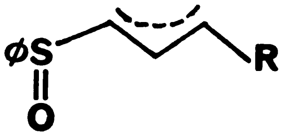
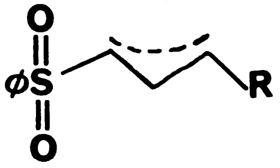
Thus it seems that isomer 43 is the kinetically favored dehydration product, but is converted to the thermodynamically more stable 44 under the reaction conditions.

Eqn 18



Although it may seem surprising that the less-conjugated isomer is thermodynamically more stable, there is ample evidence for this in the literature. O'Connor and Lyness measured the equilibrium concentrations of α,β- and β,γ-unsaturated sulfides, sulfoxides, and sulfones.[35] Their data are summarized in Table 1.

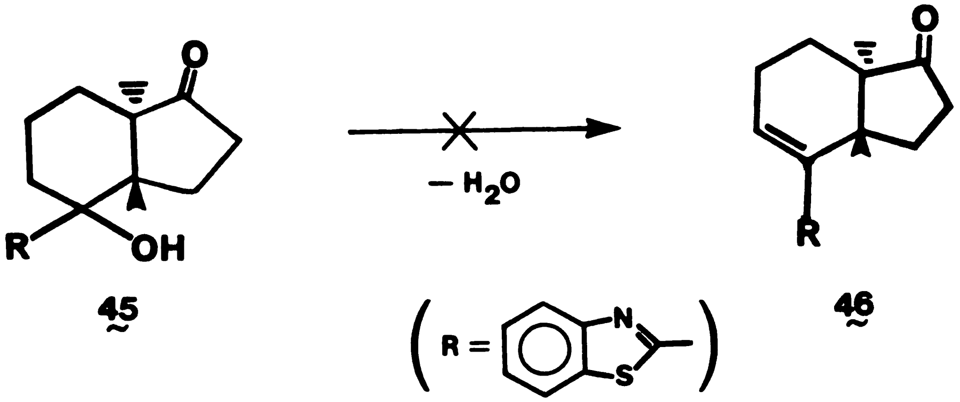
TABLE 1

Type of Sulfur Moiety	Equilibrium Product Distribution	
	% α,β	% β,γ
	66	34
	5	95
	<1	>99

Of course, other variables such as differences in double bond substitution and the presence of rings (endocyclic or exocyclic) may perturb these ratios, but our work is in qualitative agreement with the findings of O'Connor and Lyness. Hence, sulfoxides tend to be almost entirely β,γ-unsaturated, whereas sulfides exhibit only a slight preference for the α,β form.

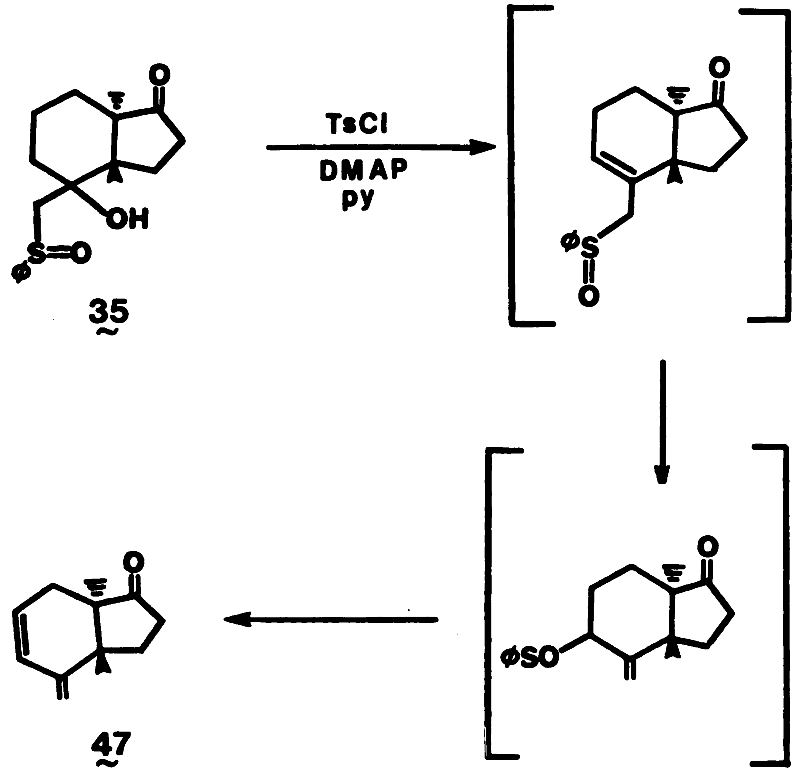
In the case of alcohol 35 no conditions were found to accomplish dehydration. This is not entirely unexpected, inasmuch as the structurally similar benzthiazole adduct 45 had previously been shown not to dehydrate under a variety of conditions.[36]

Eqn 19



Over 85% of 35 could be recovered after five days of reflux with p-toluenesulfonic acid in benzene. A subsequent attempt to form the tosylate ester of 35 gave an interesting result. Reaction of 35 with tosyl chloride and DMAP in refluxing pyridine gave a complex reaction mixture, the major component of which was identified as 47. This diene is most likely formed *via* the desired allylic sulfoxide 48. Since 48 would be in equilibrium with an allylic sulfenate ester, a sulfenate elimination could take place. Recently a synthesis of dienes from allylic sulfoxides has been reported;[37] and in one instance an intermediate allylic sulfoxide was not observed, but apparently eliminated directly to the diene, much as we have observed here.

Eqn 20

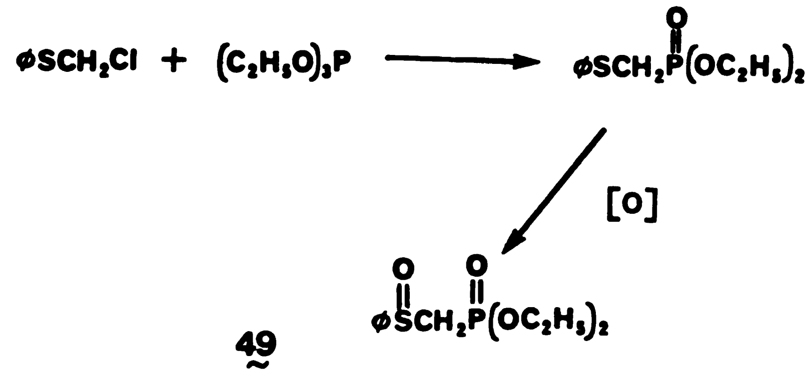


In light of the difficulties encountered in this dehydration step, a Wittig-like reagent might offer an effective alternative route to unsaturated sulfoxides, particularly for certain small-scale reactions. Phenyl sulfinylmethylphosphonate 49 has been shown to be effective in converting aldehydes and ketones to α, β-unsaturated sulfoxides,[38] which could then be isomerized to the more stable β,γ isomers.[39] This reagent is readily available by oxidation of sulfide

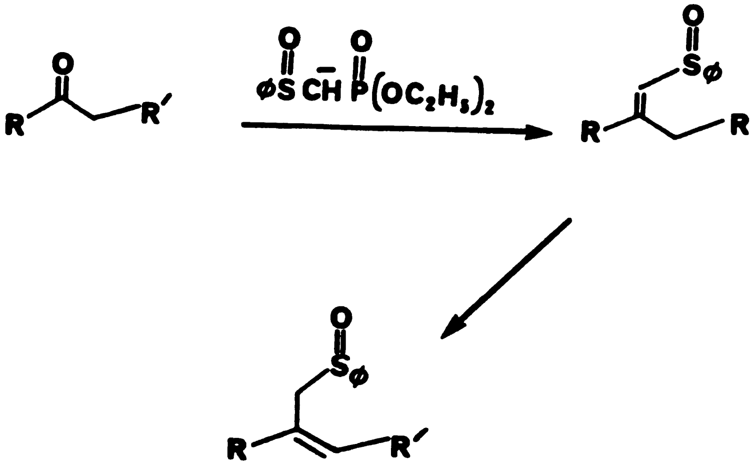
50,[40] which is formed *via* a Michaelis-Arbuzov reaction of phenylchloromethylsulfide and triethyl phosphite.[41]

Although the use of such ylides avoids problems associated with the dehydration of intermediate β-hydroxysulfoxides, the reagent derived from 49 does not react with sterically hindered ketones. Thus no reaction was observed with ketone 13.

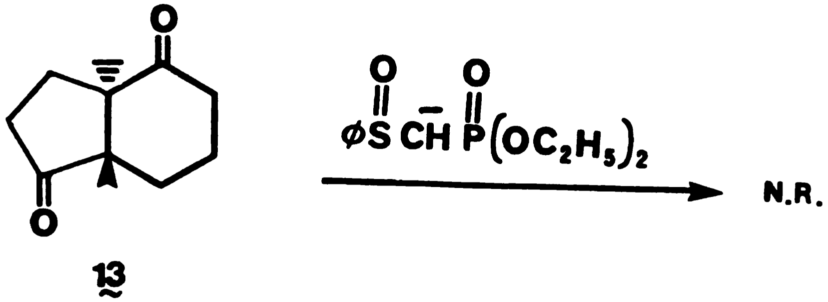
Eqn 21



Eqn 22

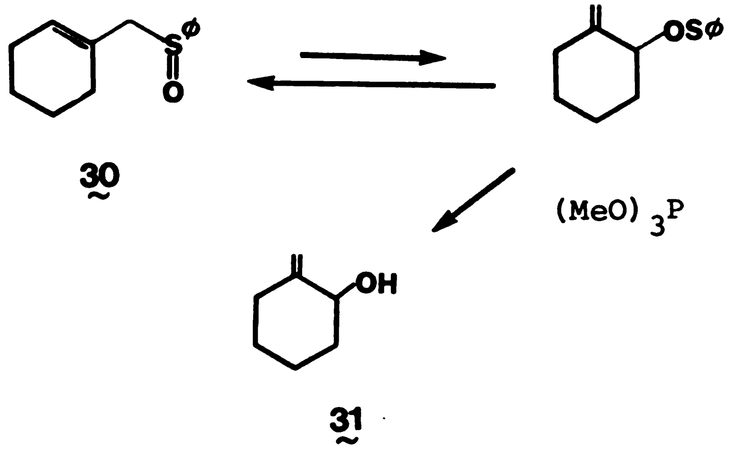


Eqn 23

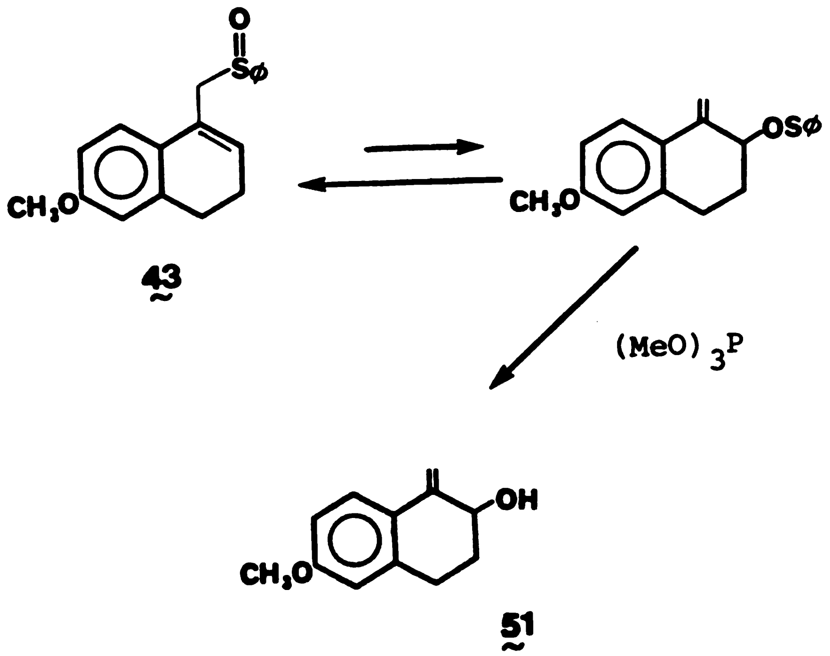


Once formed, the allylic sulfoxides were treated with trimethyl phosphite to generate allylic alcohols.[42] It was important to distill the trimethyl phosphite from sodium metal to remove dimethyl phosphonate, which tended to result in by-product formation and lower yields of the desired allylic alcohols.

Eqn 24

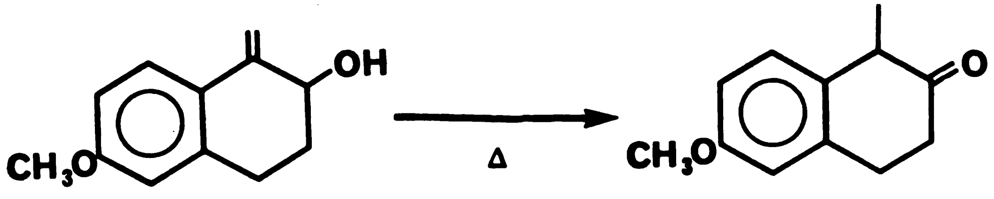


Eqn 25



Allylic alcohol 51 proved to be unstable. Upon Kugelrohr distillation, crude 51 was completely isomerized to β-tetralone 52.

Eqn 26

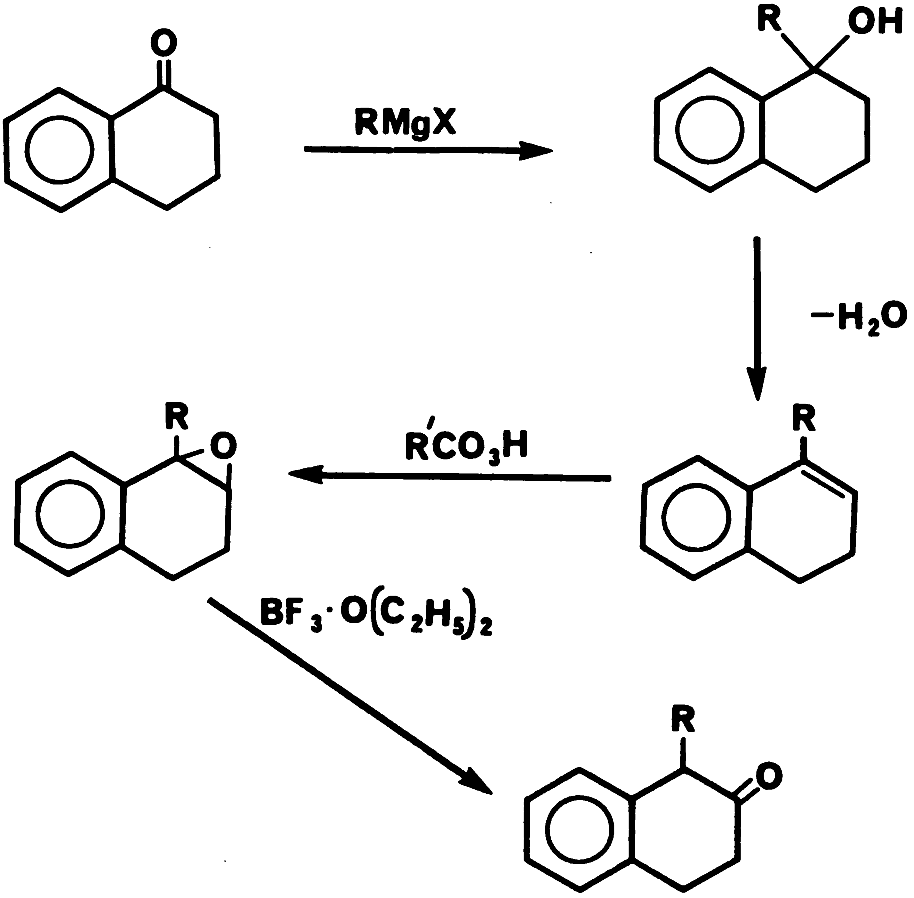


51

52

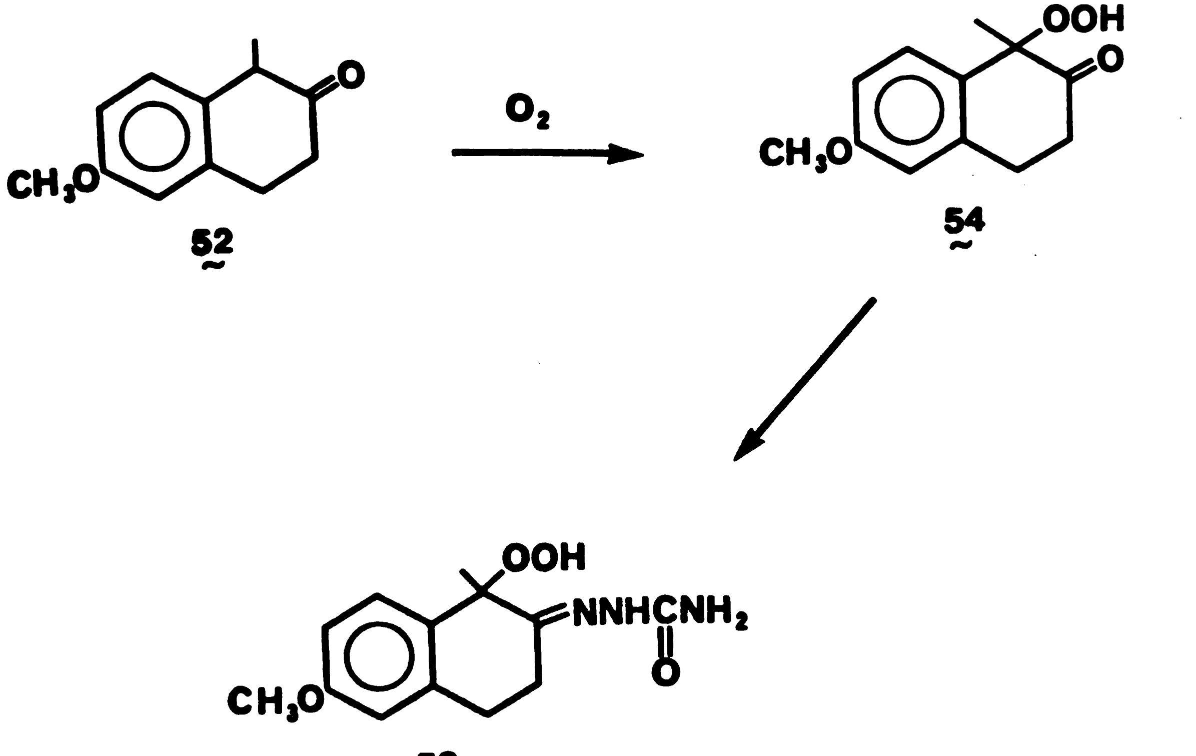
This unexpected result suggests an alternative to Stork's classic synthesis of α-monoalkyl-β-tetralones. Because β-tetralones are notoriously prone to dialkylation, Stork chose to proceed from a α-tetralone (Scheme IX).[43]

SCHEME IX



Ketone 52 is a clear, mobile liquid, but on exposure to air it was rapidly transformed into a viscous, blood-red material. As a consequence of this reaction, the methyl doublet in the pmr of 52 became a singlet and shifted downfield slightly. The crude reaction product yielded a crystalline semicarbazone derivative (53), and the mass spectrum of this derivative showed a parent ion 32 mass units higher than expected for the semicarbazone of 52. This confirmed our suspicions that 52 had reacted with molecular oxygen to give a hydroperoxide of structure 54.

Eqn 27



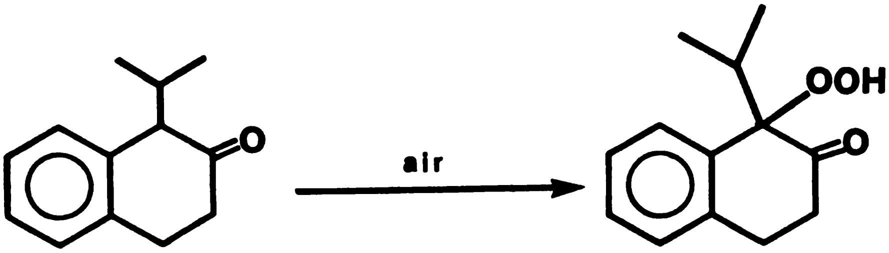
52

54

53

There is certainly precedent for this type of auto-oxidation, including the important industrial preparations of cumene hydroperoxide and t-butylhydroperoxide. Since the α-proton in 52 is at once tertiary and benzylic and activated by the carbonyl group, it should be easily attacked by oxygen. A group of Polish researchers have reported a similar auto-oxidation of an α-alkyl-β-tetralone (Eqn 28).[44]

Eqn 28

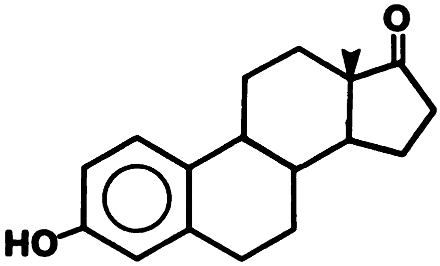


55

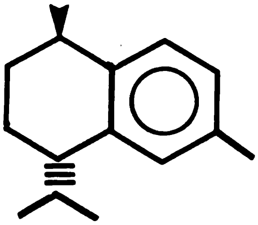
56

B. Aromatic Annulation of Cyclic Ketones

Many naturally occurring compounds contain an aromatic ring fused to one or more saturated rings, examples being estrone 57 and calamenin 58.



57



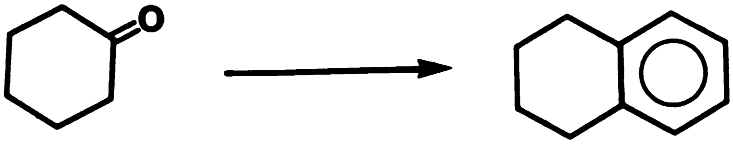
58

Figure 2. Estrone and Calamenin

In almost all cases, synthesis of such compounds begins with an aromatic precursor and the other rings are then added by well-established annulation methods.[45] In many instances, however, it would be convenient to begin with the saturated rings and then attach the aromatic ring. This is especially true in cases where either the aromatic ring is not highly functionalized with respect to the remainder of the molecule, or when a synthon for the non-aromatic portion of the molecule is readily available.

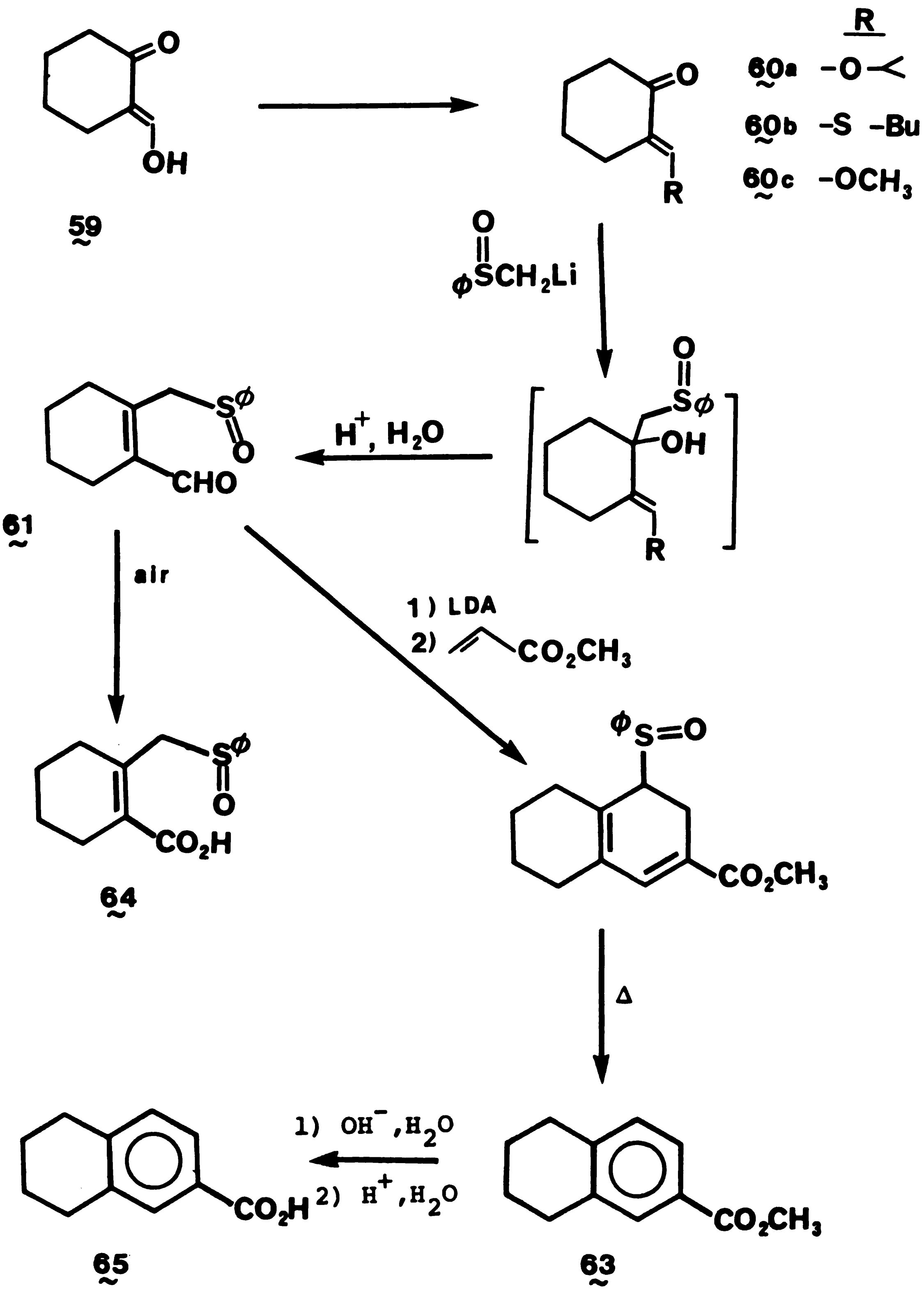
With this in mind, we set out to develop a synthetic sequence capable of converting a cyclic ketone to a tetralin.

Eqn 29



Our aromatic annulation route is outlined in Scheme X. 2-hydroxymethylenecyclohexanone $\underset{\sim}{59}$, prepared from cyclohexanone and ethyl formate according to the procedure of Ainsworth[46], was converted to an enol ether derivative. Several different protecting groups were evaluated for this purpose.

SCHEME X


59
R
60a -O-<
60b -S -Bu
60c -OCH$_3$
ϕS(O)CH$_2$Li
H$^+$, H$_2$O
61
air
1) LDA
2) CO$_2$CH$_3$
64
Δ
63
1) OH$^-$, H$_2$O
2) H$^+$, H$_2$O
65

The first derivative to be considered was the isopropyl enol ether. It is reported that α-hydroxymethylene ketones can be converted to isopropyl ethers by O-alkylation with 2-bromopropane in dimethylformamide solution.[47] However, reaction of 2-hydroxymethylene cyclohexanone under these conditions afforded only a 15% yield of isopropyl ether 60a, after distillation, along with a large residue of tarry material.

Reaction of 60a with phenylsulfinylmethyllithium followed by hydrolysis afforded 61 in moderate yield. On exposure to air, this aldehyde was found to be slowly oxidized to the corresponding carboxylic acid 64. Once contaminated with acid, the aldehyde could be purified by dissolution in tetrahydrofuran and filtration, leaving the insoluble acid behind. Pure aldehyde was stored under nitrogen or argon to prevent oxidation.

Although the conversion of 60a to unsaturated aldehyde-sulfoxide 61 proceeded in poor overall yield, sufficient 61 was obtained to test the proposed aromatic annulation sequence. Optimization of the synthesis of 61 was thus deferred.

Based on reports of Lansbury that γ-arylsulfonyl groups directed alkylation of α,β unsaturated ketones to the

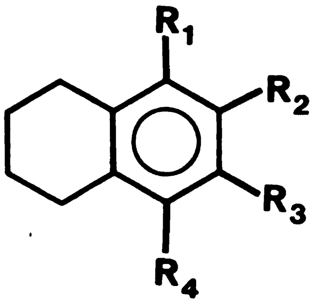
γ-site [48], it was believed that the phenylsulfinyl group in 61 might promote Michael addition α to the sulfoxide function.

When a THF solution of 61 was treated at low temperature with one equivalent of LDA, a bright yellow solution of the derived anion resulted. Reaction of this anion with methyl acrylate led to 62, presumably through Michael addition followed by a Knoevenagel condensation-dehydration reaction. Compound 62 then underwent a mild pyrolytic elimination (THF, reflux) to yield tetralinic ester 63. Saponification of 63 yielded the known tetralin carboxylic acid 65.

In this synthesis, the sulfoxide moiety serves several purposes; first, the methyl group of phenyl methyl sulfoxide ultimately becomes one of the aromatic ring carbons; secondly, the arylsulfinyl group serves to direct the Michael addition to the carbon atom γ to the aldehyde; and lastly, the facile elimination of the sulfoxide from the cyclohexadiene brings about aromatization.

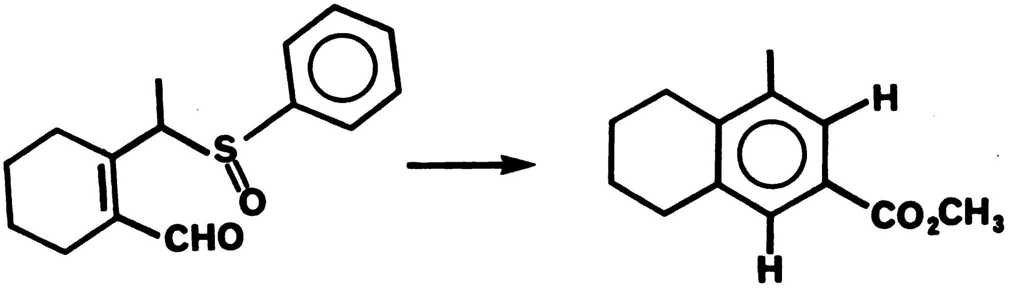
Many variations of this scheme are possible, which in principle could be used to introduce a variety of substituents on the aromatic ring.

Figure 3. Numbering of tetralin aromatic ring.



One can envision the introduction of an R_1 group in two distinct ways; first, one could begin with a substituted sulfoxide. Utilizing phenylethylsulfoxide, for example, would yield aldehyde 66. The Michael reaction would then lead to a product bearing a methyl substituent on the new ring (67).

Eqn 30



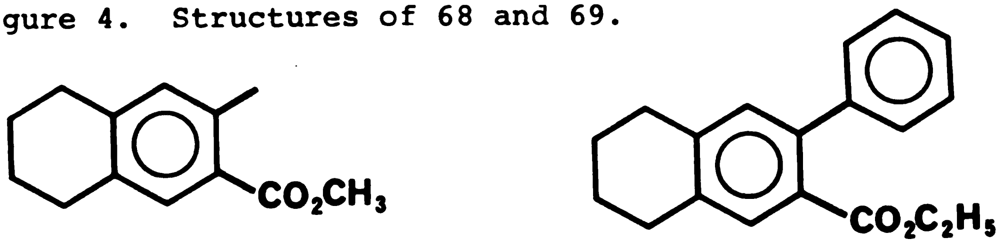
66

67

An alternative involves alkylation of the unsubstituted sulfoxide 61. It was expected that alkylation of the anion from 61 would take place γ to the aldehyde, in analogy to the Michael addition. However, the anion of 61 failed to react with methyl iodide at -78°. When the reaction mixture was warmed to 0°, self-condensation of the aldehyde took place, resulting in polymeric material. An attempt to form the anion at 0° also produced a polymer.

R_2 substituents may be introduced by a suitable choice of Michael acceptor. A drawback here is that the yields are lower, due to steric factors. We have been able to synthesize 68 by using methyl crotonate; but a similar attempt to synthesize the biphenyl 69 by using ethyl cinnamate failed.

Figure 4. Structures of 68 and 69.



68

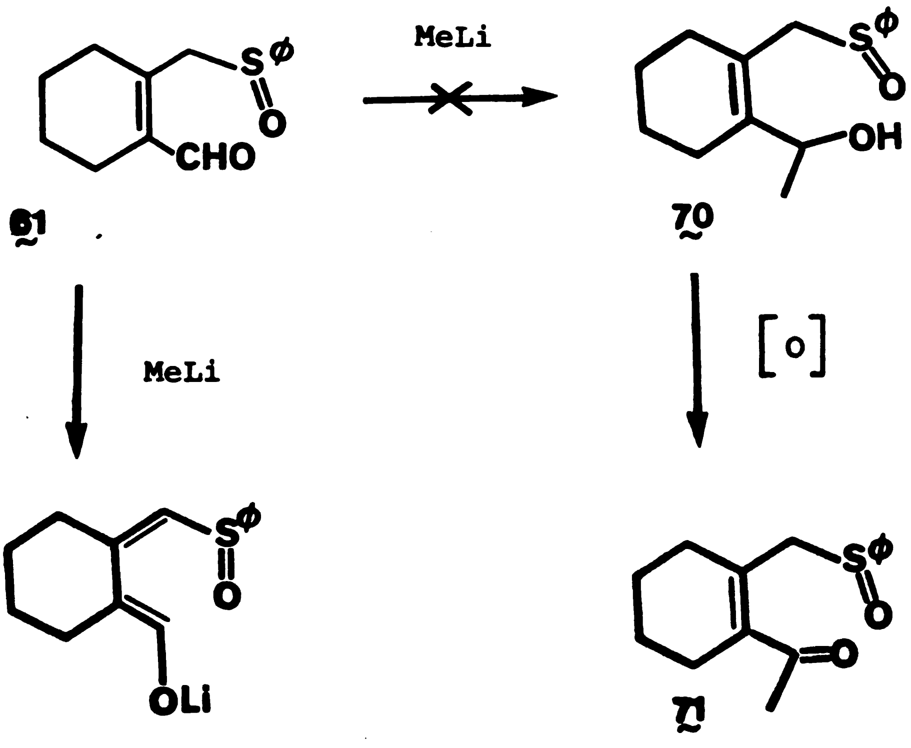
69

In a similar fashion, varying the Michael acceptor would afford products with different R_3 substituents. Here, obviously, the choices are limited to vinyl compounds bearing strong electron-withdrawing groups. Ester, ketone, cyano, and nitro are all possibilities; nitroethene would be a particularly interesting candidate for further study as reduction followed by diazotization could lead to a large number of "Sandmeyer" products.

Finally, the carbonyl moiety in 61 could be modified. For example, an ester function would lead to phenols in the manner demonstrated by Hauser.[30] Furthermore, reaction of 61 with methyllithium might yield 70, which could then be oxidized to 71.

This keto sulfoxide would then yield R_4-substituted tetralins. Such a route proved infeasible, however, when it was discovered that 61 was rapidly converted to its enolate on addition of methyllithium.

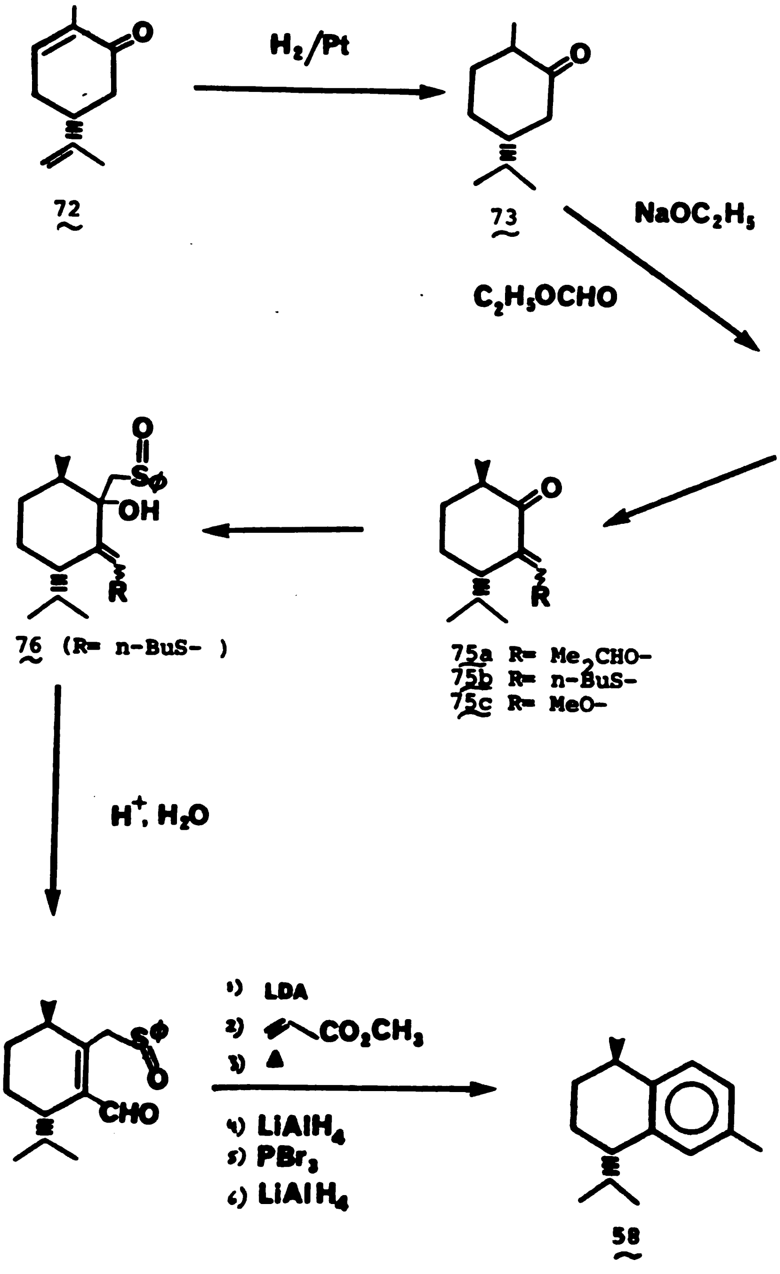
SCHEME XI



This behavior corresponds to that of other active methylene compounds bearing two electron-withdrawing groups, such as acetoacetic ester.

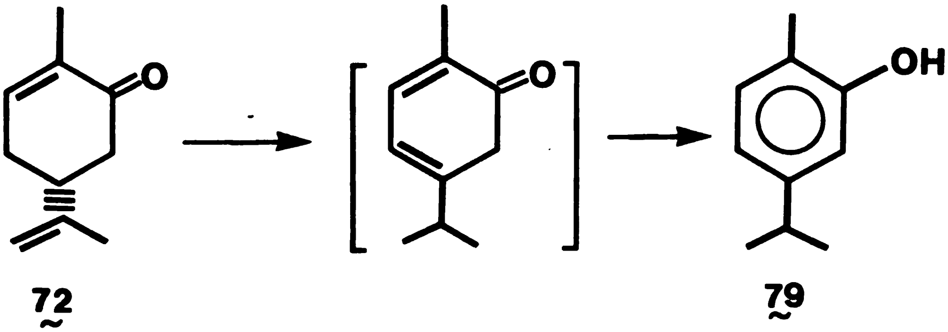
It was hoped that this aromatic annulation procedure might provide a stereoselective synthesis of calamenin 58 from l-carvone 72. The proposed synthesis is shown in Scheme XII.

SCHEME XII


H2/Pt
72
73
NaOC2H5
C2H5OCHO
74
OH
O
75a R= Me2CHO-
75b R= n-BuS-
75c R= MeO-
R
76 (R= n-BuS-)
Sφ
OH
H+, H2O
CHO
1) LDA
2) CO2CH3
3) Δ
4) LiAlH4
5) PBr3
6) LiAlH4
58

The first step in this synthesis requires hydrogenation of l-carvone. During initial attempts at hydrogenation over a palladium on carbon catalyst in ethanol solution, it was observed that only a small percentage of the stoichiometric amount of hydrogen was consumed before all reaction ceased. Isolation of the product showed that most of the carvone 72 was converted to carvacrol 79 by way of a double bond migration and subsequent aromatization of the resulting cyclohexadienone.

Eqn 31



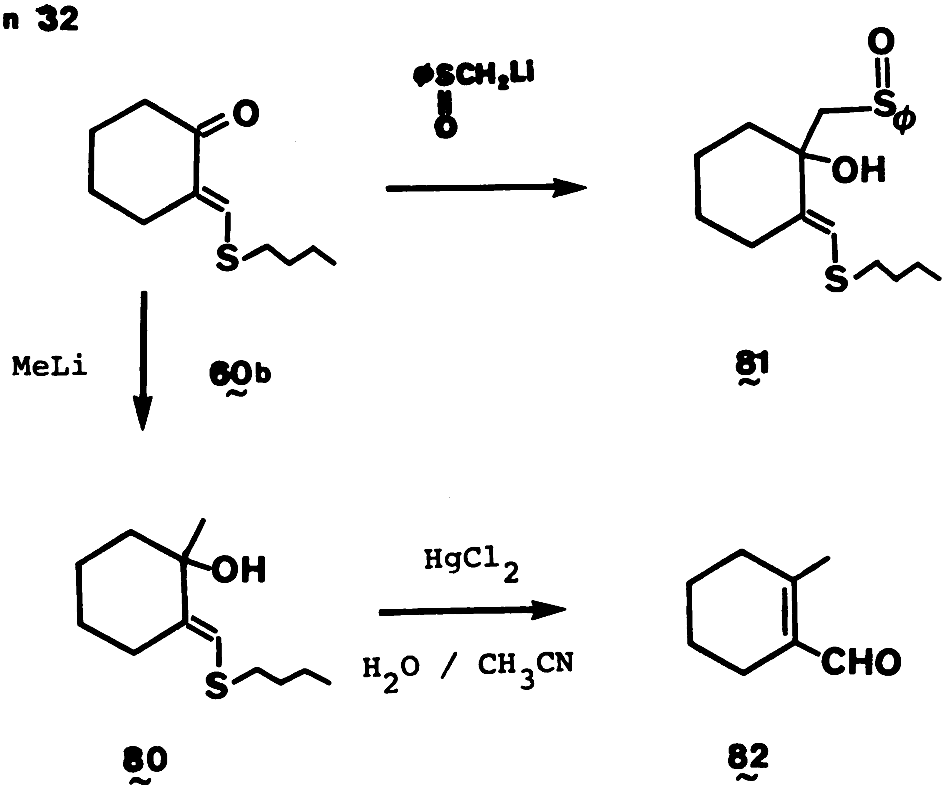
Fortunately, hydrogenation could be performed readily with a platinum catalyst, and the completely saturated compound 73 was isolated in high yields.

Treatment of 73 with ethyl formate in the presence of sodium ethoxide provided the formyl derivative 74. Reaction of this crude enol with 2-bromopropane in DMF afforded enol ether 75a in 59% yield. This yield was encouraging, since cyclohexanone itself had given a rather poor yield of the corresponding enol ether, 60a, together with substantial amounts of a tarry residue. Since α-hydroxymethylene ketones are known to polymerize readily [46], and should be protected immediately as their enol ethers, the long reaction times necessary for the reaction with secondary alkyl halide may have contributed to the decomposition observed. The increased alkyl substitution on 74 apparently provides enough steric hindrance to retard polymerization.

During exposure to base in the enol ether synthesis, the methyl group in 73 is presumably epimerized so that it and the isopropyl group can assume a trans-diequatorial configuration. A ^{1}H nmr study of 73 using europium shift reagents was inconclusive, however, and we were unable to assign an unequivocal configuration to the methyl group in 75a. In any event, our synthesis of calamenin suffered a major setback when enol ether 75a proved to be completely inert toward our nucleophilic sulfoxide base.

Because addition to the carbonyl carbon of 75a was vital to the proposed synthesis of calamenin, many experiments under varying reaction conditions were conducted. One of the first strategies to be tried involved varying the nature of the enol ether group. Since Ireland had reported enhanced reactivity of n-butylthiomethylene ketones, compared to the corresponding alkyloxymethylene ketones, we decided to evaluate the n-butylthio protecting group.[49] In the model system, treatment of hydroxymethylene compound 59 with n-butylthiol/p-TSA in refluxing benzene gave the desired thioenol ether 60b without complications. This compound reacted readily with methyllithium to yield 80, and with phenylsulfinylmethyllithium to give 81. These products were characterized by spectral analysis, and in addition a sample of 80 was hydrolyzed to the known aldehyde 82.[50]

Eqn 32



60b

81

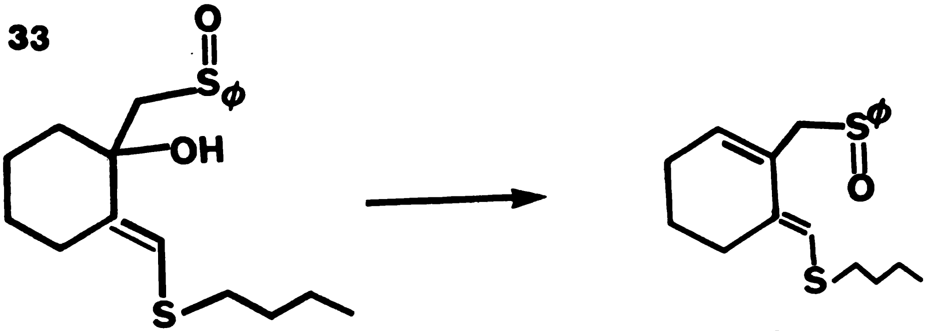
80

82

A disadvantage of the n-butylthio protecting group was soon discovered; whereas the alkoxy enol ethers were readily hydrolyzed with dilute aqueous mineral acid at room temperature, the thioenol ethers required days of reflux with mercury (II) chloride in aqueous acetonitrile.[51] Under these rigorous conditions the yield of aldehyde 61 was greatly reduced.

An interesting phenomenon was observed during vacuum distillation of 81. Crude 81, a dark brown oil, on Kugelrohr distillation afforded a straw-colored distillate which solidified upon standing. Analysis showed this material to be diene 83. Indeed, the 250 MHz proton nmr spectrum of 83 is remarkable in that every unique set of protons appears as a well-defined and distinct signal.

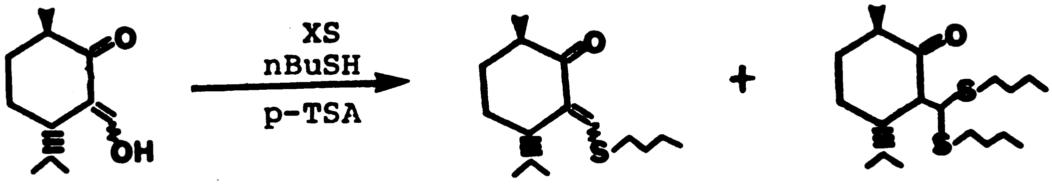
Eqn 33



81 83

Reaction of hydroxymethylene carvomenthone 74 with n-butylthiol/p-TSA proceeded more slowly than with the model system. It was observed that equimolar amounts of thiol and enol produced some polymeric material along with the expected 75b, whereas excess n-butylthiol gave a mixture of 75b and thioacetal 84.

Eqn 34



74 75b 84

The best yield of 75b, after distillation, was about 65%. This n-butyl thiomethylene derivative of tetrahydrocarvone also proved to be disappointingly unreactive in the subsequent step of the proposed synthesis. After trying the phenylsulfinylmethyllithium reaction under many different conditions, it was observed that prolonged reaction of 75b at room temperature with an excess of phenylsulfinylmethyllithium gave a mixture containing a small amount of adduct 76 along with a large amount of unreacted 75b. Extensive purification and recrystallization afforded a 2% yield of 76. Many attempts to force this reaction to completion were fruitless. In light of this poor reactivity and the difficulty in hydrolyzing thioenol ethers, this approach was abandoned.

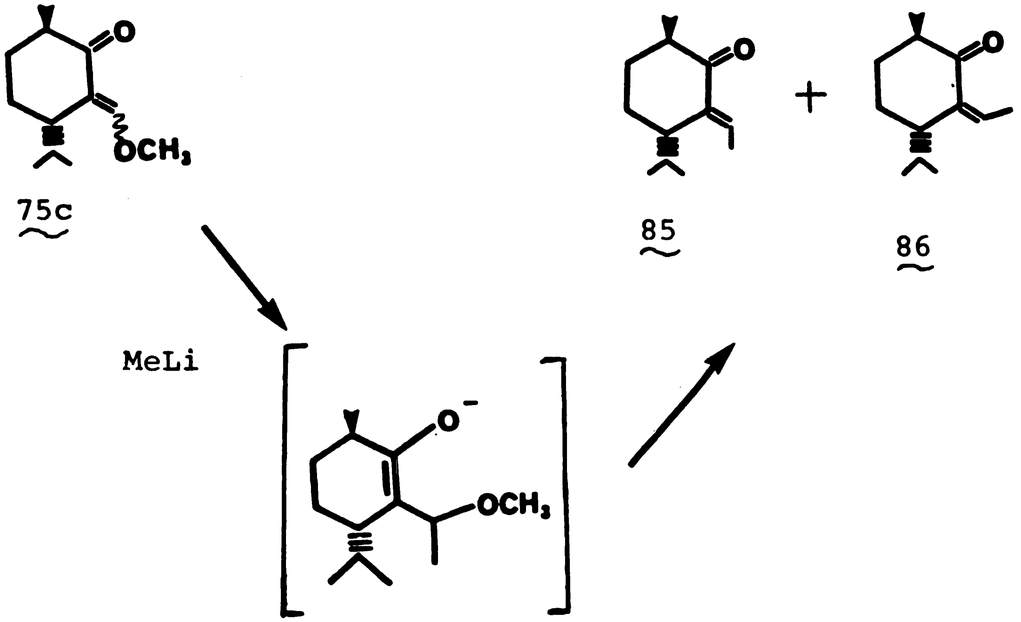
Speculating that it may have been steric effects rather than electronic effects which were causing the low reactivity of 75b, we searched for a smaller blocking group. To this end a preparation for α-methoxymethylene ketones was devised. The O-methyl derivative 60c had been previously prepared by Belanger, but in low yields of about 34%.[52] This method required the use of toxic dimethyl sulfate, and in our hands afforded only a 15% yield of 60c after two tedious distillations. However, the discovery that 60c reacted instantly with phenylsulfinylmethyllithium, and that hydrolysis of the adduct gave a 77% overall yield of 61, stimulated a search for a better synthesis of 60c.

Eventually we discovered that by dissolving **59** in anhydrous methanol and adding a catalytic amount of p-toluenesulfonic acid, a near quantitative yield of **60c** could be obtained.[53] Moreover, the only impurity was a small amount of starting material, easily removed by washing with dilute aqueous caustic. The high yields of pure product make this the method of choice for synthesis of methoxy enol ethers.

Returning to the calamenin system, we prepared α-methoxy methylenecarvomenthone **75c** in high yield. This product was a mixture of the two possible geometric isomers, as indicated by two signals in the vinyl region of the pmr spectrum and two almost overlapping signals for the methoxy group. Attempts to condense **75c** with phenylsulfinylmethyllithium were all unsuccessful. When dimsylsodium was substituted for phenylsulfinylmethyllithium, enolization of **75c** resulted. In an experiment to determine whether the ketone group in **75c** was reactive toward *any* nucleophiles, it was treated with 1.1 equivalents of methyllithium. Under these conditions, **75c** was completely consumed but the product was not the expected adduct.

The ^1H nmr spectrum of the product showed a complex vinyl region, and GC/MS indicated that two compounds of identical mass, sixteen atomic mass units less than that of **75c**, were present. Furthermore, the infrared spectrum showed a prominent carbonyl band. Based on this evidence, we have assigned structures 85 and 86 to the product mixture. Thus it seems that this reaction represents a novel 1,4 addition of an alkyl lithium, followed by a β-elimination of methoxide.

Eqn 35



In the literature there are many examples of 1,4 addition of Grignard reagents to systems such as alkoxymethylene ketones, but to our knowledge this represents the first example of conjugate addition of an alkyllithium reagent to an unsaturated carbonyl compound. It is likely that severe steric hindrance at the carbonyl function forces the addition to take place at the less-hindered β carbon.

Later it was discovered that under forcing conditions (HMPA-TMEDA-reflux) 75c reacted with phenylsulfinylmethyllithium to yield a mixture of products. Spectral analysis indicated that these products had undergone a complete loss of the methoxy group. It appears that the major product here was also the result of a conjugate addition.

We have shown that a simple ketone can easily be elaborated to a fused bicyclic tetralin system. In order for this technique to be generally useful, however, the problems we observed in sterically hindered systems will have to be dealt with.

EXPERIMENTAL

General

Reactions were conducted in standard laboratory glassware. Most non-aqueous reactions were carried out under a dry argon atmosphere. Magnetic stirrers and teflon-coated magnetic stir bars were used for agitation. Most reactions were worked up by extraction into ether and drying of the organic layer over anhydrous sodium sulfate.

The progress of most reactions was followed by thin-layer chromatography or gas chromatography. Thin layer plates were silica with fluorescent indicator, and were visualized either by UV light or by spraying with dilute sulfuric acid followed by charring. A Varian 1200 gas chromatograph equipped with either a 4% QF-1 or 10% SE-30 column was used for GC analysis.

Melting points were determined on a Hoover-Thomas apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 237B grating spectrophotometer and were measured relative to a polystyrene standard. Proton magnetic resonance spectra were recorded on either a Varian

T-60 or a Bruker 250 spectrometer. Carbon-13 spectra were obtained on a Varian CFT-20 spectrometer. All nuclear magnetic resonance samples were dissolved in deuterochloroform containing tetramethylsilane as an internal standard.

Mass spectra were obtained on a Finnegan 4000 gas chromatograph/mass spectrometer.

Micro-combustion analyses were performed by Spang Microanalytical Labs, Ann Arbor, Michigan.

Preparation of 1-[(phenylsulfinyl)methyl]-1-cyclohexanol 29.

To a cold (-78^{o}) solution of lithium diisopropylamide (LDA) in THF (30 mL), prepared from 1.01 g of diisopropylamine and 4.35 mL of 2.3 M n-BuLi, was added a solution of 1.4 g (10 mmol) phenyl methyl sulfoxide in a small amount of dry THF.

This solution was stirred for fifteen minutes, 1 mL (10 mmol) of cyclohexanone was added, and the resulting mixture was warmed to room temperature and stirred for two hours. The reaction mixture was quenched with 5 mL water, then extracted with three 15-mL portions CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, and after removal of the solvent yielded a cream-colored oil which solidified upon standing. Recrystallization from 1:1 CH_2Cl_2/ether afforded 1.60 g (67%) of white needles; mp 94.5-97.0°; IR ($CHCl_3$) 3425 (br), 1450, 1190 cm^{-1}; PMR ($CDCl_3$) δ7.3-7.7 (m, 5H), 3.77 (s, 1H), 2.98 (d, J=14 Hz, 1H), 2.70 (d, J=14 Hz, 1H), 1.3-2.1 (m, 10H); MS (70 eV) m/e 239 (3), 126 (24), 113 (29), 95 (100), 78 (24), 77 (20), 67 (20), 55 (25), 43 (32), 41 (29); MS (CI, CH_4) m/e 239.

Preparation of 1-[(phenylsulfinyl)methyl]-1-cyclohexene 30.

A solution of 1-(phenylsulfinylmethyl)-1-cyclohexanol 29 (1.27 g) in 50 mL dry toluene was treated with 6.35 mL BF_3 Et_2O and refluxed for one hour. The reaction mixture was then cooled to 0^{o} and quenched with 50 mL 10% aqueous sodium hydroxide. The layers were separated and the aqueous layer was discarded. The organic layer was washed twice with water, once with brine, and then dried over anhydrous sodium sulfate. Removal of the solvent gave 1.14 g (97%) of an oil. A small non-polar impurity was removed via column chromatography (silica, 1:1 ether/hexanes) to yield a solid product, melting point $50\text{-}52^{o}$. The product could be crystallized from ether-pentane; melting point $50.5\text{-}52.5^{o}$; IR (CCl_4) 1450, 1085, 1060 cm^{-1}; PMR ($CDCl_3$) 7.5 δ(m, 5H), 5.4 (br s, 1H), 3.49 (d, J=13 Hz, 1H), 3.21 (d, J=13 Hz, 1H), 1.9 (m, 4H), 1.4 (m, 4H); MS (70 eV) m/e 221 (0.8), 126 (17), 95 (100), 77 (24), 67 (33), 55 (20), 41 (26); MS (CI, CH_4) m/e 221. Analysis: Calc. for $C_{13}H_{18}SO_2$: C, 70.86%; H, 7.32%. Found: C, 71.32%; H, 7.37%.

Preparation of 2-methylidene-1-cyclohexanol 31.

To a solution of 1-(phenylsulfinylmethyl)-cyclohexene (920 mg) in 20 mL dry THF was added 0.5 g $(MeO)_3$ P (freshly distilled from sodium metal) and 2 mL dry MeOH. The resulting mixture was then stirred for four days at room temperature. Removal of solvents yielded 440 mg of crude 2-methylidene cyclohexanol 31. Column chromatography (pentane/ether on silica) afforded 395 mg of pure 31 (yield 84%): PMR ($CDCl_3$) δ4.77 (m, 1H), 4.63 (m, 1H), 3.8-4.2 (m, 2H), 1.2-2.4 (m, 8H).[54]

Condensation of 6-methoxy-1-tetralone with phenylsulfinylmethyllithium (Preparation of β-hydroxysulfoxide 34.)

A solution of 10 mmol LDA in THF was prepared from 1.01 g (1.40 mL) of diisopropylamine and 6.25 mL of 1.6 M n-BuLi at 0°. Phenyl methyl sulfoxide (1.4 g, 10 mmol) was added as a solution in 5 mL of THF and the reaction mixture stirred thirty minutes at 0°. A solution of 6-methoxytetralone (1.762 g, 10 mmol) in 5 mL THF was then added, the ice bath removed, and the reaction stirred four hours at room temperature. The reaction was quenched with saturated ammonium chloride and extracted with diethyl ether. Drying over anhydrous sodium sulfate and removing the ether yielded 3.18 g (100%) of adduct 34: IR (neat) 3350 (br), 2920, 1675, 1605, 1500, 1250 cm^{-1}; PMR ($CDCl_3$) δ7.2-7.6 (m, 6H), 6.4-6.8 (m, 2H), 3.63 (s, 3H), 1.8-3.2 (m); MS m/e 299 (3), 192 (13), 191 (100), 174 (21), 173 (81), 172 (35), 158 (34).

Condensation of diene 13 with phenylsulfinylmethyllithium (Preparation of β-hydroxysulfoxide 35.)

To a cold (0°) solution of LDA prepared from 10 mmol of diisopropylamine and 10 mmol of 2.6 M n-butyllithium in 30 mL dry THF, was added a solution of 1.4 g (10 mmol) phenylmethylsulfoxide in 5 mL THF.

This solution was stirred 15 minutes, cooled to -78°, and then a solution of 1.8 g (10 mmol) of 13 in 10 mL THF was added and the resulting solution stirred at -78° for a period of thirty minutes.

The reaction mixture was neutralized with saturated ammonium chloride and the organic layer was separated. The aqueous layer was extracted with two 10 mL portions of ether. The combined extracts were dried over anhydrous sodium sulfate; removal of the solvents gave 2.68 g of a tan solid, which was shown to be approximately a 1:1 mixture of 13 and 35. Compound 35 was conveniently isolated by stirring the mixture overnight in a small amount of diethyl ether; 13 dissolved, leaving sparingly soluble 35 behind as a solid: Yield 1.42 g, 42%, mp 154-156°; IR ($CDCl_3$) 3425 (br), 2950, 2250, 1740 cm^{-1}; PMR ($CDCl_3$) 7.5 (s, 5H), 4.42 (s, 1H), 3.03 (d, J=13 Hz, 1H) , 2.64 (d, J=13 Hz, 1H), 1.4-2.4 (m), 1.32 (s, 3H), 0.83 (s, 3H); MS m/e 321 (4), 305 (22), 303 (41), 195 (37), 193 (45), 177 (28), 162 (21), 137 (30), 135 (40), 126 (100), 125 (48), 124 (23), 123 (47), 122 (37), 121 (23); MS (CI, CH_4) m/e 321.

Preparation of 1-(phenylsulfinylmethyl)-1-Cyclopentanol 36.

To a cold (0°) solution of 2.2 mmoles of phenylsulfinylmethyllithium (prepared in the usual fashion) was added 168 mg (2 mmol) of cyclopentanone. The resulting solution was stirred overnight at ambient temperatures.

After standard work-up, the crude product was recrystallized from ether/CH_2Cl_2. The first crop of crystals weighed 160 mg and had a melting point of 102-106°. Upon concentration of the mother liquors a second crop of 35 mg was obtained for a 63% yield: PMR ($CDCl_3$) δ7.42 (s, 5H), 3.82 (s, 1H) 3.14 (d, J=13 Hz, 1H), 2.76 (d, J=13 Hz, 1H), 1.4-2.2 (m, 8H); MS m/e 225 (7), 126 (40), 99 (64), 81 (100).

Preparation of 1-(phenylthiomethyl)-1-cyclohexanol 38.

To a solution of 5.8 g TMEDA and 20.7 mL of 2.42 M n-BuLi in hexane at 0° was added 5.8 g of thioanisole. After this mixture had stirred for four hours, 10 mL dry THF was added to dissolve the solid which had formed, and the resulting solution was cooled to -78°. A solution of 5 mL cyclohexanone in 20 mL dry THF was added dropwise, and this mixture was warmed to room temperature and stirred for two hours. After quenching with saturated ammonium chloride solution, the reaction mixture was extracted with diethyl ether, washed with dilute aqueous hydrochloric acid, saturated aqueous $NaHCO_3$, and then dried over anhydrous sodium sulfate. Kugelrohr distillation yielded 4.65 g of 1-(phenylthiomethyl)-1-cyclohexanol (45%), as well as substantial amounts of unreacted thioanisole and cyclohexanone: IR (neat) 3425 cm^{-1} (br); PMR ($CDCl_3$) δ 6.9-7.3 (m, 5H), 3.00 (s, 3H), 2.2 (s, 1H), 1.3-1.7 (m, 10H); MS (70 eV) m/e 222 (17), 124 (100), 123 (35), 109 (41), 99 (29), 81 (35), 77 (22), 55 (24), 41 (30).

Preparation of 1-(phenylthiomethyl)-1-cyclohexene 39 and (phenylthiomethylidene)-cyclohexane 40.

To a solution of 1.37 g of 1-(phenylthiomethyl)-1-cyclohexanol 38 in 50 mL of dry benzene was added 50 mg of p-toluenesulfonic acid monohydrate (p-TSA) and this mixture was then refluxed through a Dean-Stark trap for 48 hours. The solution was cooled, then washed with saturated sodium bicarbonate, water, and dried over anhydrous sodium sulfate. Removal of the solvent gave 1.01 g (80%) of a mixture of the two possible dehydration products. Integration of the pmr spectrum showed the ratio of endocyclic isomer 39 to exocyclic isomer 40 to be 2:1: IR (neat) 2935, 1590, 1485, 1445 cm^{-1}; PMR($CDCl_3$) δ7.2 (m, 5H), 5.83 (s, 1/3H), 5.47 (br s, 2/3H), 3.4 (s, 2H of endocyclic isomer), 1.4-2.4 (m);
MS (70 eV) Endocyclic isomer 39 m/e 204(60), 110(33), 95(100), 79(37), 67(36);
Exocyclic isomer 40 m/e 204(100), 110(18), 95(57), 91(19), 79(25), 67(22).

Preparation of Allylic Sulfoxide 44.

A solution of 3.18 g (10 mmol) of alcohol 34 in 50 mL dry benzene was treated with 50 mg p-TSA and refluxed for twenty minutes. The solution was then cooled and the benzene removed. The residue was dissolved in diethyl ether and washed with three portions saturated $NaHCO_3$, once with brine, and then dried over anhydrous sodium sulfate. Removal of the ether gave 2.792 g (94%) alkene 44, all β,γ: IR (neat) 1675, 1600, 1500, 1250 cm^{-1}; PMR ($CDCl_3$) δ6.5-7.4 (m, 8H), 5.50 (t, J=5 Hz, 1H), 3.70 (s, 3H), 1.9-3.1 (m, 4H); MS m/e 298 (1), 173 (100), 172 (95), 158 (37).

Preparation of 1-methylidene-1,2,3,4-tetrahydro-6-methoxy naphthalen-2-ol 51.

To a solution of 63 mg of allylic sulfoxide 44 in 5 mL THF and 0.5 mL methanol was added 0.2 mL of trimethyl phosphite. The reaction was monitored by thin-layer chromatography, and was found to be essentially complete within 2 to 4 hours, although longer reaction times had no adverse effect on the observed yields.

The solvents were removed under reduced pressure and the residual oil was subjected to column chromatography (ether/silica gel). Yield of crystalline allylic alcohol 51 was 33 mg (82%), mp 81-82°.

IR (KBr) 3350 (br), 1600, 1500, 1320, 1265, 1225, 1075, 1045, 1025 cm^{-1}; PMR ($CDCl_3$) δ6.4-7.5 (m, 3H), 5.33 (br s, 1H), 5.07 (br s, 1H), 4.2-4.5 (m, 1H), 3.70 (s, 3H), 2.6-3.1 (m, 2H), 1.7-2.1 (m, 2H); MS m/e 190 (100), 175 (28), 173 (25), 172 (42), 163 (38), 159 (20), 147 (35), 131 (26), 129 (58), 128 (36), 115 (60), 103 (52), 102 (26), 91 (46), 77 (48), 63 (37), 51 (28).

Analysis:Calculated: 75.76% C, 7.42% H.
Found: 75.73% C, 7.49% H.

Preparation of 6-methoxy-α-methyl-β-tetralone 52.

Upon Kugelrohr distillation of 2.79 g of crude 51, 1.30 g of a clear mobile liquid was collected. Analysis of the distillate showed it to be tetralone 52, the result of a thermally induced double bond migration. Bp: 200° (0.1 mm Hg); IR (neat) 1710, 1495 cm^{-1}; PMR ($CDCl_3$) δ6.6-7.6 (m, 3H), 3.72 (s, 3H), 2.3-3.6 (m, 5H), 1.42 (d, J = 8 Hz, 3H); MS m/e 190 (52), 147 (100), 91 (35).

Auto-oxidation of 52.

Compound 52 was found to react rapidly with atmospheric oxygen to yield a viscous, blood-red oil. PMR analysis of the crude oil showed that the methyl doublet at δ1.42 in 52 had been replaced by a singlet at δ2.40. On that basis, it was believed that the product 53 was a hydroperoxide. This was confirmed when it was found that upon treatment with semicarbazide 53 yielded a semicarbazone 54 which showed a parent ion in the mass spectrograph 32 units higher than that expected for 52 semicarbazone.

Preparation of 2-hydroxymethylenecyclohexanone 59.

2-Hydroxymethylenecyclohexanone 59 was prepared from cyclohexanone and ethyl formate according to the *Organic Synthesis* procedure using the sodium metal method.[46] The crude product was not distilled, and was used directly in the preparation of isopropoxymethylenecyclohexanone 60a, methoxymethylenecyclohexanone 60b, and 2-(n-butylthiomethylene)cyclohexanone 60c.

Preparation of 2-isopropoxymethylenecyclohexanone 60a.

A solution of 10 g 2-hydroxymethylenecyclohexanone 59, 10 g 2-bromopropane, and 20 g anhydrous potassium carbonate in 30 mL dry dimethylformamide (DMF) was heated overnight on a steam bath. The reaction mixture was filtered and the filter cake was washed with several portions of ether. The combined filtrates were washed sequentially with water, cold dilute caustic, and brine. After the solution was dried over sodium sulfate, the solvents were removed under reduced pressure, affording a crude yield of 10.43 g. Fractional vacuum distillation gave 2.0 g of product, bp 80-85^{o} at 0.25 mm Hg. There was a small forerun and a large amount of gummy polymeric material remained in the pot. The distillate was analyzed by pmr: PMR($CDCl_3$) δ 8.33 (s, 1/3H), 7.2-7.4 (t, 2/3H), 3.9-4.6 (m, 1H), 2.0-2.6 (m, 4H), 1.4-1.9 (m, 4H), 1.1-1.3 (d, J=6Hz, 6H).

Preparation of 2-(n-butylthiomethylene)-cyclohexanone 60b.

A solution of 109 g of crude 2-hydroxymethylenecyclohexanone 59 in 500 mL benzene was refluxed through a Dean-Stark trap to remove any water present. The solution was cooled to ambient temperature, and 92.5 mL of n-butanethiol and 150 mg of p-TSA were addded. The reaction mixture was then refluxed through the Dean-Stark trap for an additional two hours. The benzene and excess n-butanethiol were removed at reduced pressure. The crude product was dissolved in ether, washed with dilute caustic, water, and brine. After drying and removal of solvent, the crude product was distilled under vacuum. The cut boiling at 162-164^{o} at 13 mm Hg weighed 71 g (41%) and was shown to be pure 60b: IR (neat) 2930, 2860, 1675, 1550, 1310, 1150, 815 cm^{-1}; PMR ($CDCl_3$) δ 7.38 (t, J=2Hz, 1H), 2.80 (t, J=7Hz, 2H), 2.1-2.4 (m, 4H), 1.2-1.8 (m,8H), 0.8-1.0 (m, 3H); MS (70 ev) m/e 198 (27), 141 (100).

Preparation of 2-methoxymethylenecyclohexanone 60c.

Crude 2-hydroxymethylenecyclohexanone from 49 g of cyclohexanone was dissolved in 500 mL of absolute methanol containing 25 mg of p-TSA. Equilibrium was established within fifteen minutes; the ratio of 60c to 59 was determined to be approximately 5:1 by gas chromatographic analysis. One gram of anhydrous Na_2CO_3 was added to neutralize neutralize the sulfonic acid catalyst, and the mixture was then filtered. After the methanol was removed by distillation at reduced pressure, the resulting oil was dissolved in ether and filtered again. The ether solution was washed with small portions of 5% NaOH solution until gas chromatographic analysis showed that 59 was absent. The ether solution was then washed with brine and dried over sodium sulfate. Following removal of the ether, bulb-to-bulb distillation of the residual oil gave 26 g of 60c (37% from cyclohexanone); IR (neat) 1720, 1675, 1595, cm^{-1}; PMR ($CDCl_3$) δ 7.13 (t, J=2Hz, 1H), 3.80 (s, 3H), 2.2-2.6 (m, 4H), 1.8-2.0 (m, 4H).

Preparation of **61**.

A solution of 1.01 g (10 mmol) diisopropylamine in 10 mL dry THF was cooled to 0°. To this solution was added 10 mmol of n-BuLi (6.25 mL of a 1.6 *M* solution in hexane), and this mixture was stirred fifteen minutes at 0°. Phenyl methyl sulfoxide (1.4 g, 10 mmol) in 10 mL THF was added *via* a syringe, and the resulting yellow solution was stirred thirty minutes at 0°. The ice bath was then replaced with a dry ice-ether bath and 1.4 g (10 mmol) of 2-methoxymethylene cyclohexanone, **60b**, dissolved in 10 mL THF was added in one portion. This solution was stirred at -80° for five minutes and then allowed to warm to room temperature and stirred twenty-four hours.

The reaction was quenched with saturated ammonium chloride solution and the organic layer separated. The THF was removed under reduced pressure and the residue taken up in ether. This ether solution was washed sequentially with 6 N HCl, water, saturated $NaHCO_3$, and brine. At this point the product may crystallize as it is sparingly soluble in dry ether. The combined aqueous layers were extracted with three 25-mL portions of methylene chloride, and the combined ether and methylene chloride extracts were dried over anhydrous sodium sulfate. Removal of the solvents and recrystallization from either CH_2Cl_2/ether or THF/ether afforded 1.92 g (77%) of product: mp 118.5-119.5°; IR (KBr) 1660, 1620, 1440, 1160, 1085, 1030 cm^{-1}; PMR ($CDCl_3$) δ 9.48 (s, 1H), 7.37 (s, 5H), 3.87 (s, 2H), 2.0-2.4 (m, 4H), 1.4-1.8 (m, 4H); MS m/e 248 (1), 126 (23), 123 (100), 95 (35). Analysis: Calc. for $C_{14}H_{16}SO_2$: C, 67.71%; H, 6.50%. Found: C, 66.87%; H, 6.46%.

A portion of 61 was reacted with 2,4-dinitrophenylhydrazine in acidic aqueous ethanol and afforded an orange-red 2,4-D derivative: mp 185°. Analysis: Calc. for $C_{20}H_{20}N_4SO_5$: C, 56.06%; H, 4.71%. Found: C, 55.92%, H, 4.57%.

Isolation of Cyclohexadiene Intermediate 62.

To a solution of 100 mg (0.11 mmol) of 61 in 5 mL dry THF at -78° was added a solution of 0.4 mmol LDA in hexane. This solution was stirred thirty minutes, during which time the bright yellow color of the anion became evident. Methyl acrylate (63 μl, 0.6 mmol) was then added, and the reaction mixture was stirred fifteen minutes at -78°, followed by twenty-four hours at ambient temperature. After quenching with saturated ammonium chloride solution, the organic layer was separated and the aqueous layer was extracted twice with 10 mL portions of diethyl ether. The combined organic layers were then washed sequentially with 1% hydrochloric acid, water, and brine. The solution was dried over sodium sulfate, and the solvents were removed under reduced pressure taking care that the bath temperature did not exceed 30°. Compound 62 was a light yellow unstable solid: mp 133-134°; IR (KBr) 1730, 1425 cm^{-1}; PMR ($CDCl_3$) δ7.47 (m, 5H), 7.17 (s, 1H), 3.62 (s, 3H), 3.2-4.2 (m, 3H), 1.4-2.8 (m, 8H); MS m/e 250 (1) (Ø$_2$S$_2$O$_2$ decomposition product), 218 (2) (Ø$_2$S$_2$ decomposition product), 191 (25), 190 (33), 149 (27), 131 (100), 126 (45), 107 (47); MS (CI, CH_4) m/e 317 (M+1).

Preparation of 6-carbomethoxy-1,2,3,4-tetrahydronaphthalene 63.

The cyclohexadiene 62 (prepared from 100 mg 61) was dissolved in dry THF and refluxed for two hours. The reaction was conveniently followed by TLC. At the end of the reaction period, the solvent was removed and the products (diphenyl disulfide, S-phenyl phenylthiolsulfonate, and 63) were separated by column chromatography (CH_2Cl_2/silica). Yield of 63 was 65 mg (86% overall from 61): IR (neat) 1720, 1430, 1270 cm^{-1}; PMR ($CDCl_3$) δ7.4-7.8 (m, 2H), 7.0 (d, 1H), 3.87 (s, 3H), 2.7-3.0 m, 4H), 1.7-2.0 (m, 4H); MS m/e 190 (28), 159 (40), 131 (93), 87 (30), 85 (100).

Saponification of ester 63 to known tetralincarboxylic acid 65.

To a solution of 30 mg of ester 63 in 5 mL 95% ethanol was added 0.5 mL of 40% sodium hydroxide solution. The resulting solution was refluxed for two hours, and then cooled to room temperature. Acidification with 6 N hydrochloric acid yielded a fluffy white precipitate, which was collected by filtration and washed with water. The product correlated with the known 5,6,7,8-tetrahydronaphthalene-2-carboxylic acid, and had mp 152-153° (literature mp 154°):[55] MS m/e 176 (37), 131 (100), 91 (18).

Preparation of Methyl-substituted Tetralinic Ester 68.

Ester 68 was prepared by substituting methyl crotonate for methyl acrylate in the preparation of 62. Thus 61 (0.5 mmol) was treated with LDA (0.5 mmol) at -78° in THF. Methyl crotonate (0.75 mmol) was added and the mixture stirred 24 hours at room temperature.

In contrast to 62, no solid material was obtained but rather a mixture of the expected cyclohexadiene and a considerable amount of polymeric material. Thermolysis (refluxing THF, 4 hours) followed by column chromatography (CH_2Cl_2/silica gel) afforded 24 mg of 68 as an oil (24% yield from 61): PMR

($CDCl_3$) δ7.8 (s, 1H), 7.2 (s, 1H), 3.87 (s, 3H), 2.8-3.0 (m, 4H), 2.6 (br s, 3H), 1.8-2.0 (m, 4H); MS m/e 204 (38), 186 (23), 172 (45), 145 (100); Analysis:Calculated: 76.44% C, 7.40% H; Found: 76.61% C, 7.41% H.

Preparation of 2-methyl-5-(1-methylethyl)-cyclohexanone 73.

Method A. One-step method. A Parr bottle was charged with 30 g of l-carvone, 100 mg of platinum (IV) oxide (Adam's catalyst), and sufficient absolute ethanol to bring the total volume to 250 mL. The bottle was alternately evacuated and purged with hydrogen gas to remove air, and then agitated under 3-4 atmosperes of hydrogen for two hours at ambient temperature. The platinum catalyst was very finely divided and removal by filtration was difficult. Yield of carvomenthone 73 containing traces of olefinic contaminants was 27.1 g, 88%.

Method B. Pre-reduced catalyst method. The Parr bottle was charged with 100 mg Adam's catalyst and 100 mL of absolute ethanol. Air was removed as in Method A and then the catalyst was agitated for a few minutes under 4 atmospheres of hydrogen. The flask was vented, 30 g of l-carvone was added, and diluted to 250 mL with additional absolute ethanol. After two hours of reduction at 3-4 atmospheres pressure, the product was isolated by filtration and removal of solvent. In this case, filtration was easier and the product contained no residual olefin. Yield of 73 was 29.3 g, 95%. IR(neat) 1720 cm^{-1}; PMR δ 1.3-2.6 (m, 9H), 1.0-1.3(m,9H); MS m/e 154(27), 112(13), 111(100), 110(11), 97(16), 95(23), 83(24), 69(26), 55(98),41(60).

Preparation of α-hydroxymethylenecarvomenthone 74.

Carvomenthone (19.5 g) and ethyl formate (28.8 g) were dissolved in 500 mL of dry ether. Sodium metal (9 g) and 1 mL of absolute ethanol were added and the reaction mixture was stirred for 24 hours. Work-up,[46] followed by bulb-to-bulb distillation, gave 15.2 g of α-hydroxymethylene-carvomenthone 74, 66% yield.

Preparation of isopropyl enol ether 75a.

A solution of 14.92 g enol 74 and 10.09 g 2-bromopropane in 150 mL dry DMF was treated with 20.7 g anhydrous potassium carbonate and heated at 100° overnight. The reaction mixture was filtered and the filter cake washed with ether. The combined organic layers were washed several times with dilute caustic to remove unreacted starting material. Drying of the organic layer followed by removal of the solvents yielded 13.10 g (73%) of crude enol ether 75a. Kugelrohr distillation afforded 11.41 g of pure material: PMR($CDCl_3$) δ7.0-7.2 (m,1H), 3.8-4.3 (m,1H), 0.7-2.9 (m,22H).

Preparation of α-(n-butylthiomethylene)-carvomenthone 75b.

A solution of 21.47 g of enol 74, 12.74 g n-butyl thiol, and 30 mg of p-TSA in 400 mL dry benzene was refluxed through a Dean-Stark trap until no more water came over (about 48 hours). The benzene solution was washed sequentially with saturated aqueous sodium bicarbonate, water, brine, and dried over sodium sulfate. Removal of solvent yielded 25.33 g of thioenol ether 75b, 85%: IR(neat) 2955, 2930, 2870, 1680, 1550, 1470 cm^{-1}; PMR 7.20 (br s, 1/2H), 6.93 (s, 1/2H), 0.8-3.0 (m, 23H); MS m/e 254 (25), 212 (12), 211 (100), 209 (17), 197 (16).

Preparation of α-methoxymethylenecarvomenthone 75c.

A solution of 15.2 g of α-hydroxymethylenecarvomenthone 74 in 500 mL of dry methanol was treated with 50 mg of p-TSA. Gas chromatographic analysis showed that equilibrium was reached in thirty minutes. Approximately 1 g of anhydrous sodium carbonate was added to neutralize the catalyst. The reaction mixture was filtered, and the solvent stripped off at reduced pressure. The resulting semi-solid was dissolved in dry ether, and filtered again. The ether solution was washed with dilute caustic until gas chromatographic analysis showed no traces of residual enol 74. Drying and removal of solvent afforded 12.4 g of 75c, 76% yield, as a mixture of two geometric isomers: IR (neat) 1680, 1605, 1245 cm^{-1}; PMR (CDCl$_3$) δ7.00 and 6.90 (2s, 1H), 3.75 and 3.72 (2s, 3H), 1.3-2.6 (m, 7H), 1.10 (d, J=6 Hz, 3H), 0.7-1.0 (m, 6H); MS m/e 196 (7), 154 (10), 153 (100), 125 (30), 93 (17).

Preparation of 1-methyl-2-(n-butylthiomethylidene)-cyclohexan-1-ol 80.

A solution of 3.68 g of 60b in 50 mL of THF was cooled to -78^{o}. To this solution was added 14.6 mL of 1.4 M methyllithium solution in ether. The reaction mixture was stirred for 10 minutes at -78^{o}, and then warmed to room temperature. Analysis of an aliquat of the reaction mixture showed complete conversion of 60b to 80. Yield of 80 after work-up was 3.87 g, 97%: IR (neat) 3500 (br), 2950, 2890, 1675, 1550 cm^{-1}; PMR δ5.92 (s, 1H), 1.4-3.0 (m, 15H), 1.35 (s, 3H), 0.8-1.1 (m, 3H); ^{13}C NMR δ143.51, 116.29, 73.23, 42.38, 33.64, 32.40, 28.10, 27.25, 26.76, 23.44, 21.81, 13.67; MS m/e 196 (M$^+$-H$_2$O, 90), 140 (14), 139 (33), 125 (13), 111 (13), 108 (34), 107 (100), 106 (37), 105 (57), 97 (14), 95 (20), 93 (32), 91 (68).

Preparation of sulfoxide diene 83 and intermediate β-hydroxysulfoxide 81.

A solution of 7.92 g thioenol ether 60c in THF was added to a cold (-78°) solution of phenylsulfinylmethyl lithium in THF. The reaction mixture was allowed to stir for 5 minutes at -78°, and then slowly warmed to room temperature. The reaction was quenched with water and extracted into ether. Crude yield of β-hydroxysulfoxide 81 was 97%.

A portion of the crude adduct was subjected to bulb-to-bulb distillation. A forerun of excess phenyl methyl sulfoxide was observed, followed by more volatile material as the temperature reached 180° at 0.1 mm Hg. The bulk of the material failed to distill under these conditions. Upon cooling, the residue solidified. Recrystallization from ether afforded 83 as white needles. Overall yield from thioenol ether 60c was 51%: mp 74-76°; PMR (250 MHz) δ 7.52 (m, 5H), 6.09 (s, 1H), 5.31 (br s, 1H), 3.90(d, J=13 Hz, 1H), 3.42 (d, J=13 Hz, 1H), 2.75 (t, J=8 Hz, 2H), 2.30 (t, J=6 Hz, 2H), 2.0 (m, 2H), 1.5-1.6 (m, 6H), 0.95 (t, J=6 Hz, 3H); ^{13}C NMR δ 144.03, 132.25, 131.84, 131.15, 128.75, 126.52, 124.50, 122.25, 63.62, 34.03, 32.55, 27.35, 25.92, 21.73, 21.57, 13.68; MS m/e 320 (3), 196 (11), 195 (92), 139 (27), 138 (39), 137 (100), 110 (17), 106 (10), 105 (76), 97 (31).

Reaction of methyllithium with α-methoxymethylenecarvomenthone 75c (Preparation of E- and Z- isomers of ethylidenecarvomenthone 85 and 86).

To a solution of 196 mg of 75c in 10 mL dry THF at -78° was added 1.1 mmol of 1.6 M methyllithium in ether. After 15 minutes, the reaction was quenched with saturated aqueous ammonium chloride and worked up. Spectral analysis idicated that the product was predominantly a mixture of isomers 85 and 86. A small amount of alcohol was formed, owing to the excess methyllithium used: IR (neat) 3450 (br, wk), 2950, 1700, 1630 cm^{-1} ; PMR δ6.0-6.6 (complex multiplet); GC/MS Isomer I: m/e 180 (4), 152 (43), 138 (31), 137 (91), 109 (94), 96 (100); Isomer II: m/e 180 (18), 152 (24), 138 (40), 137 (100), 109 (81), 96 (98).

APPENDIX

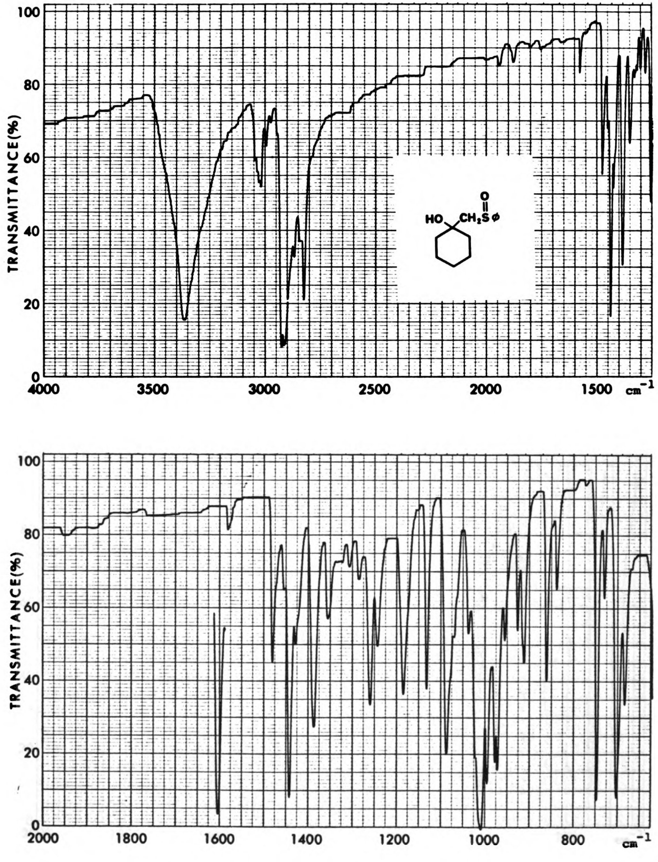


Figure 5. IR spectrum of 29.

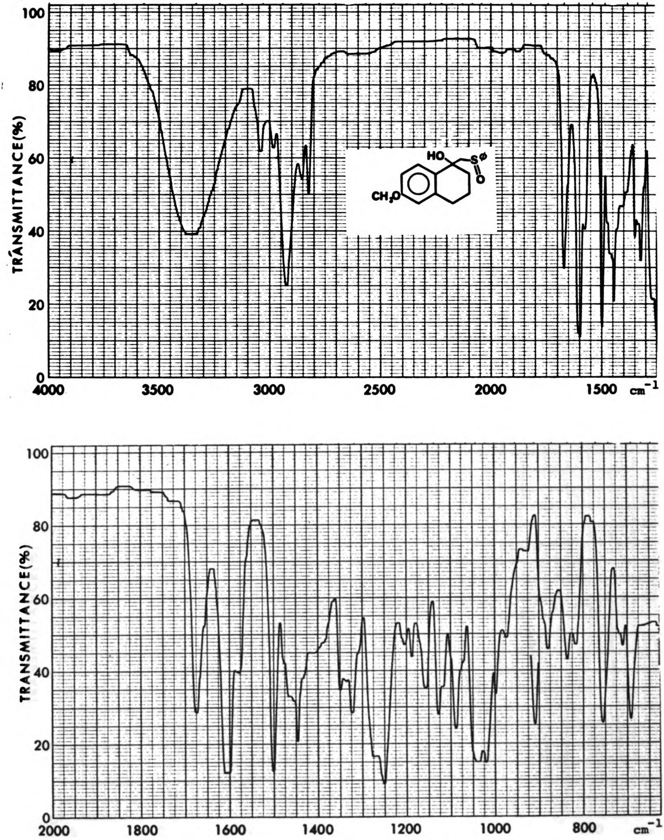


Figure 7. IR spectrum of 34.

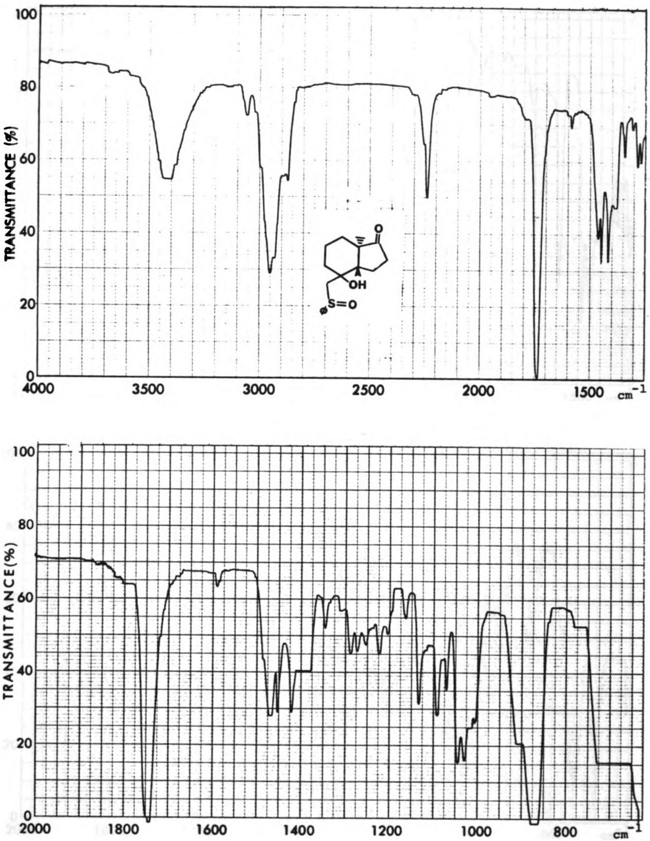


Figure 8. IR spectrum of 35.

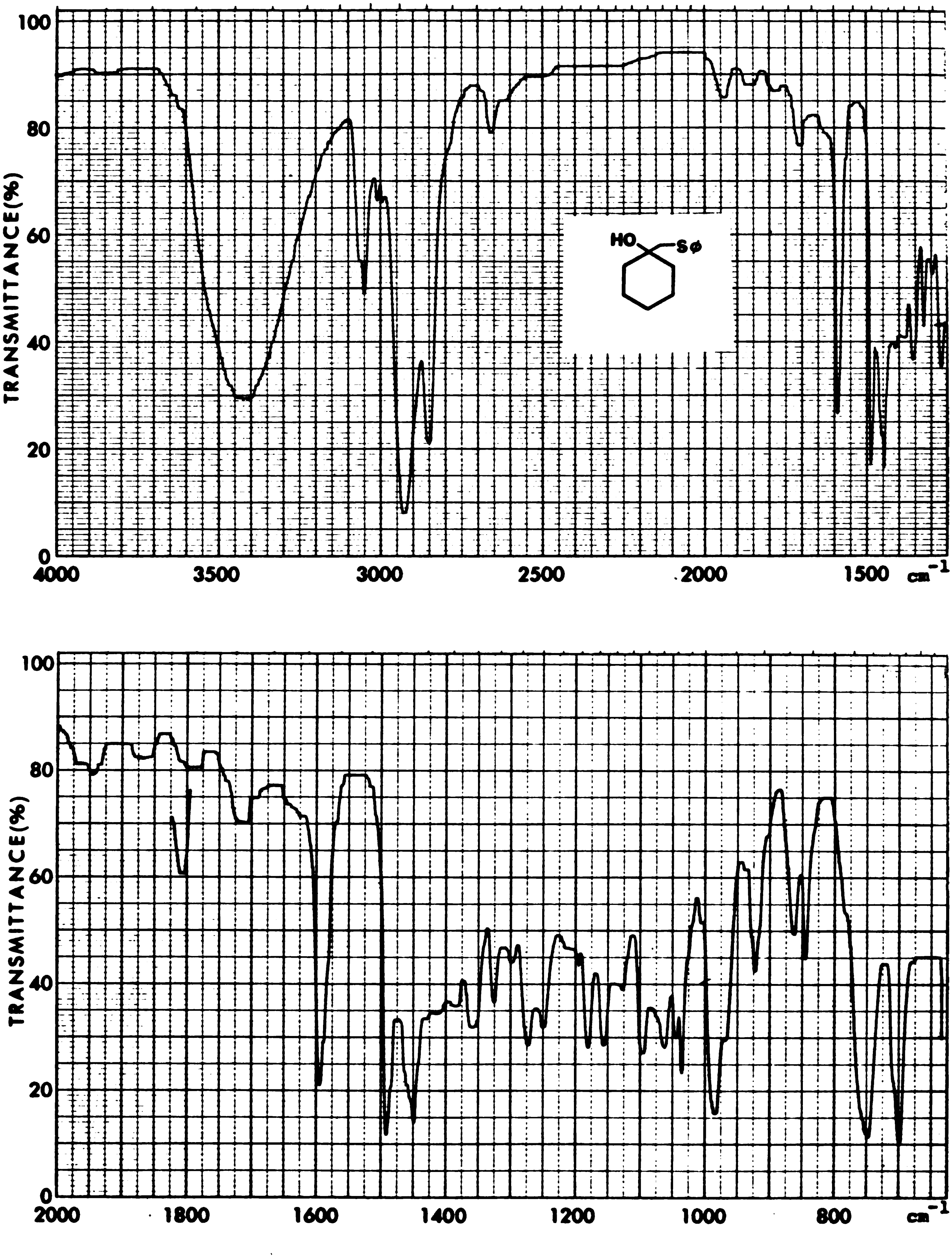


Figure 9. IR spectrum of 38.

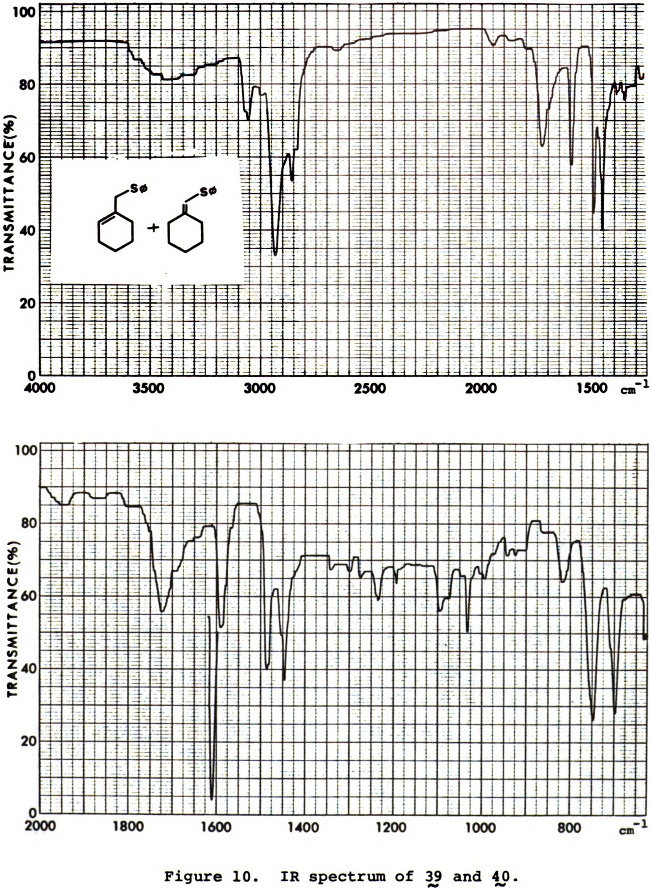


Figure 10. IR spectrum of 39 and 40.

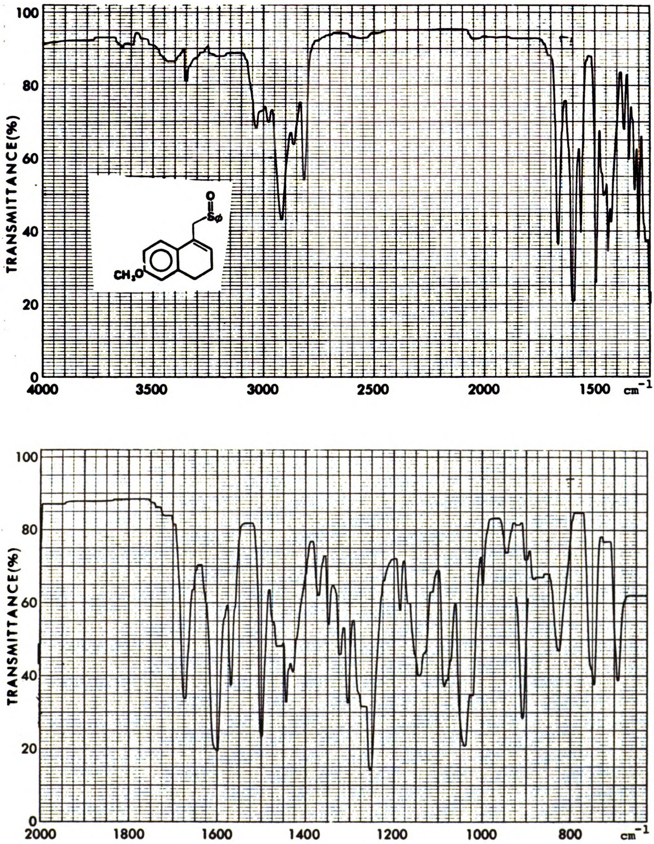


Figure 11. IR spectrum of 44.

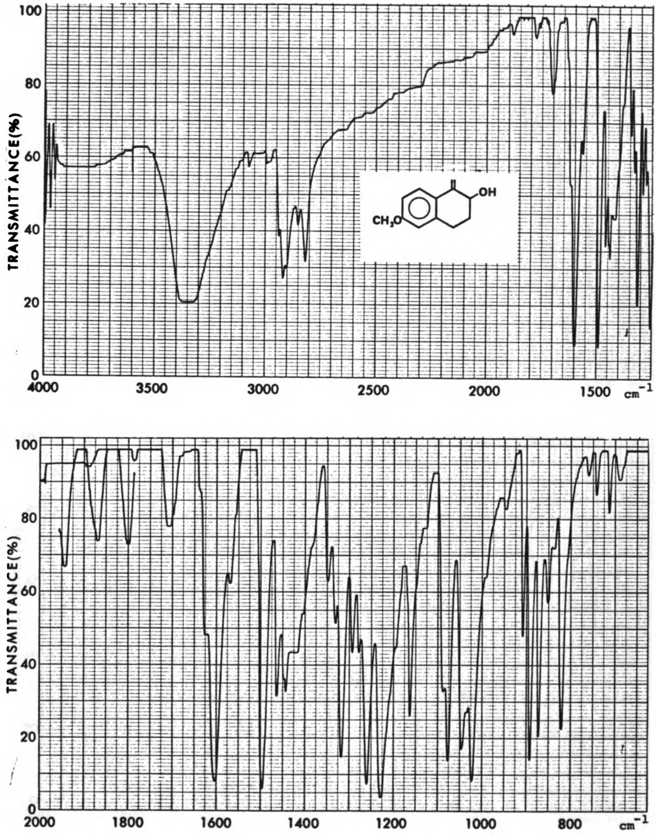


Figure 12. IR spectrum of 51.

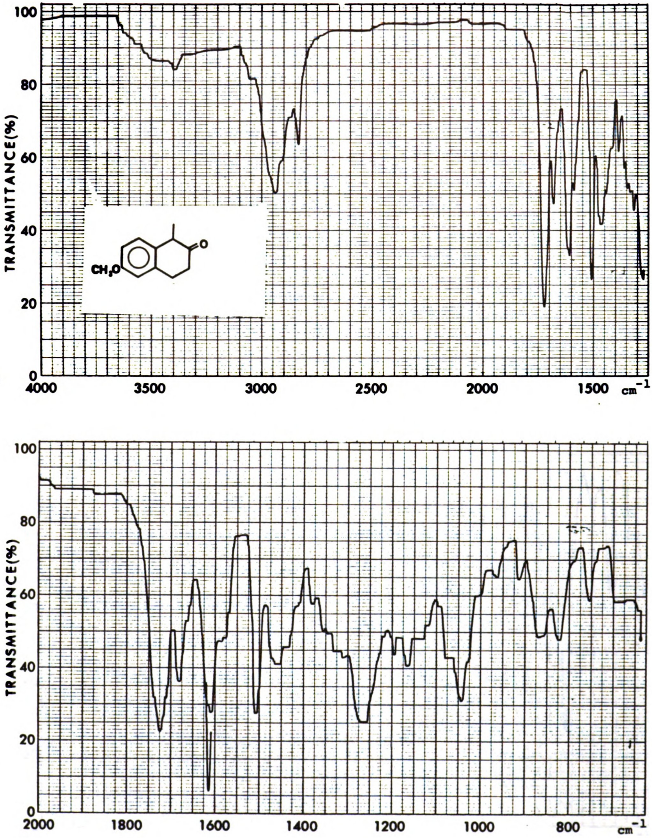


Figure 13. IR spectrum of 52.

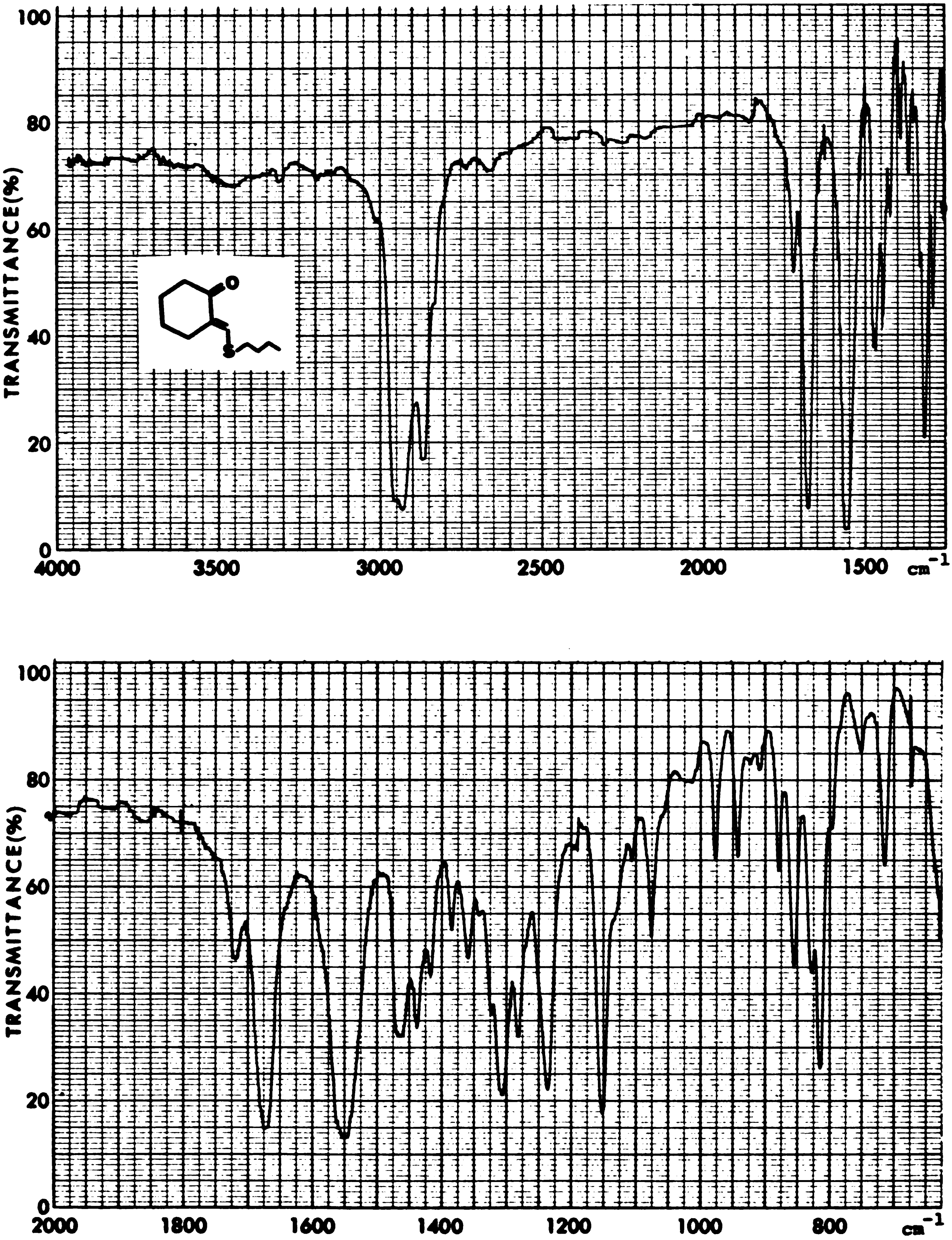


Figure 15. IR spectrum of 60b.

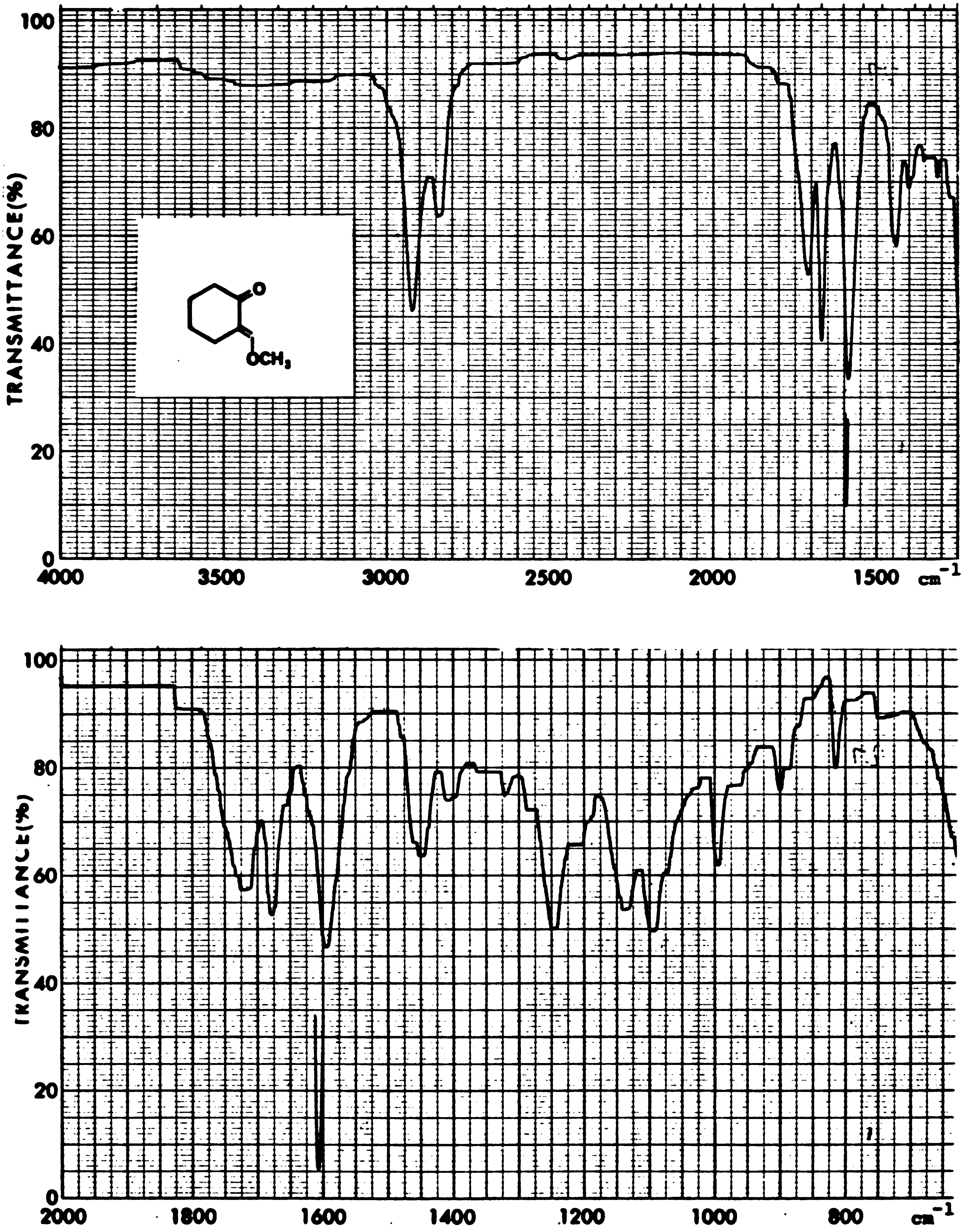


Figure 14. IR spectrum of 60c.

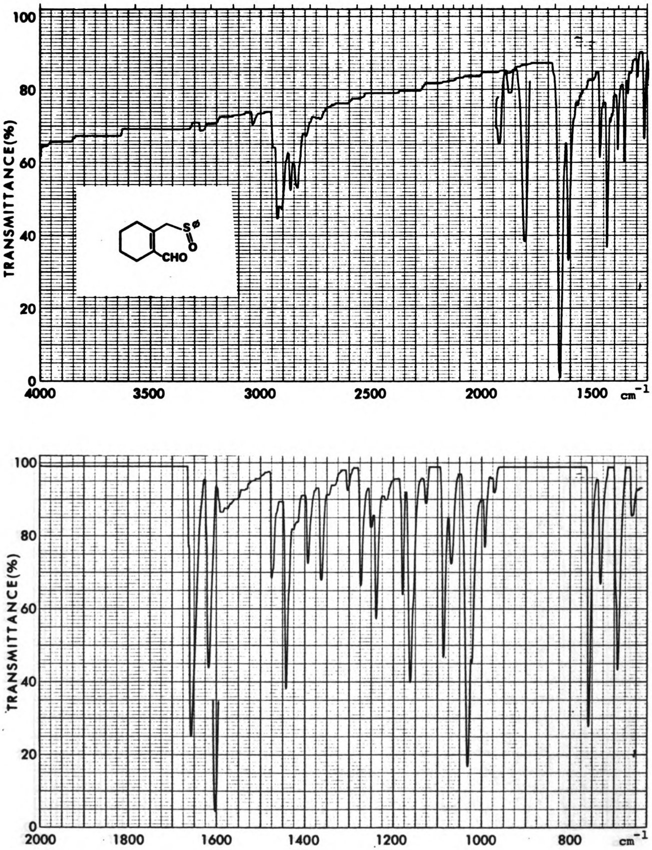


Figure 16. IR spectrum of 61.

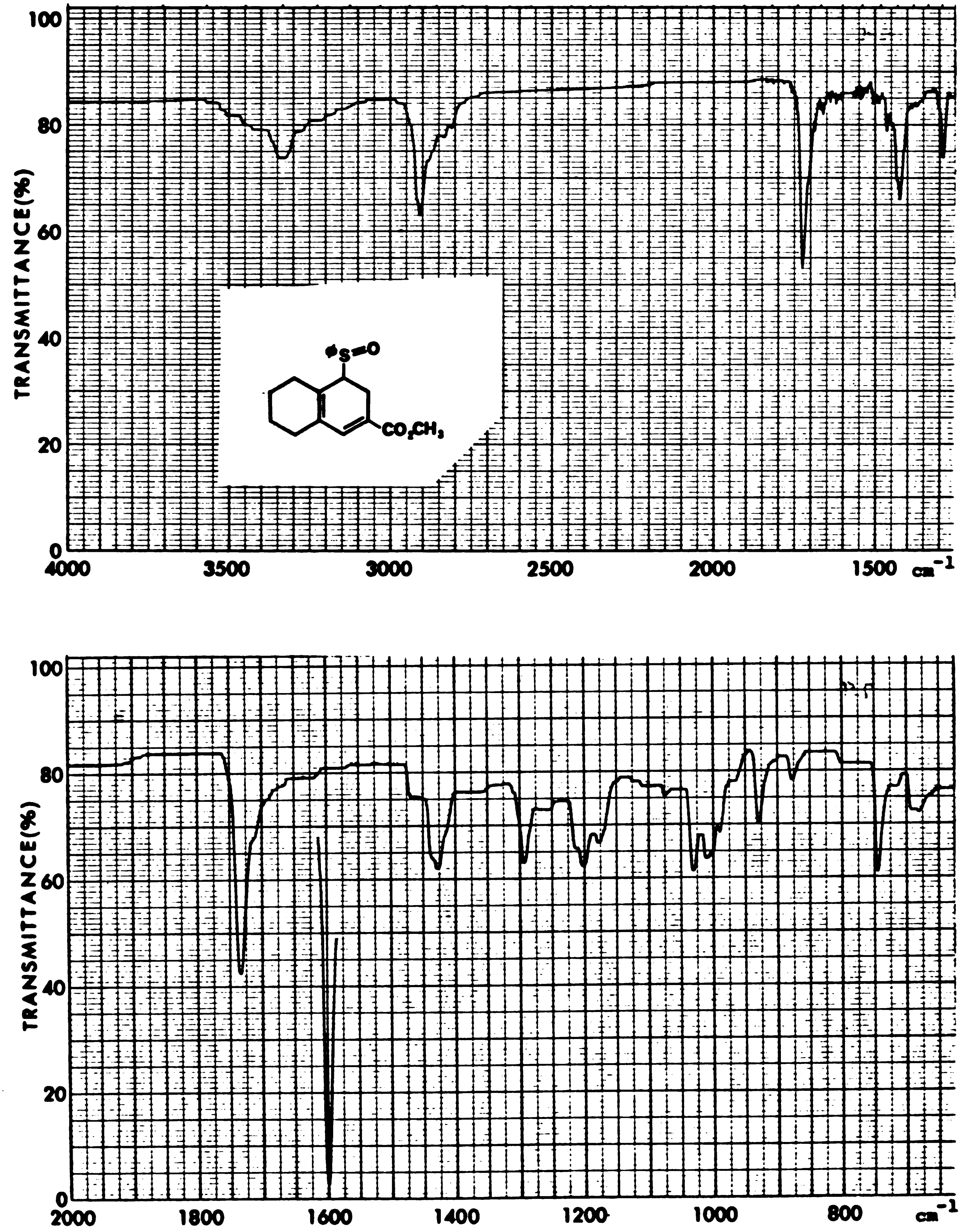


Figure 17. IR spectrum of 62.

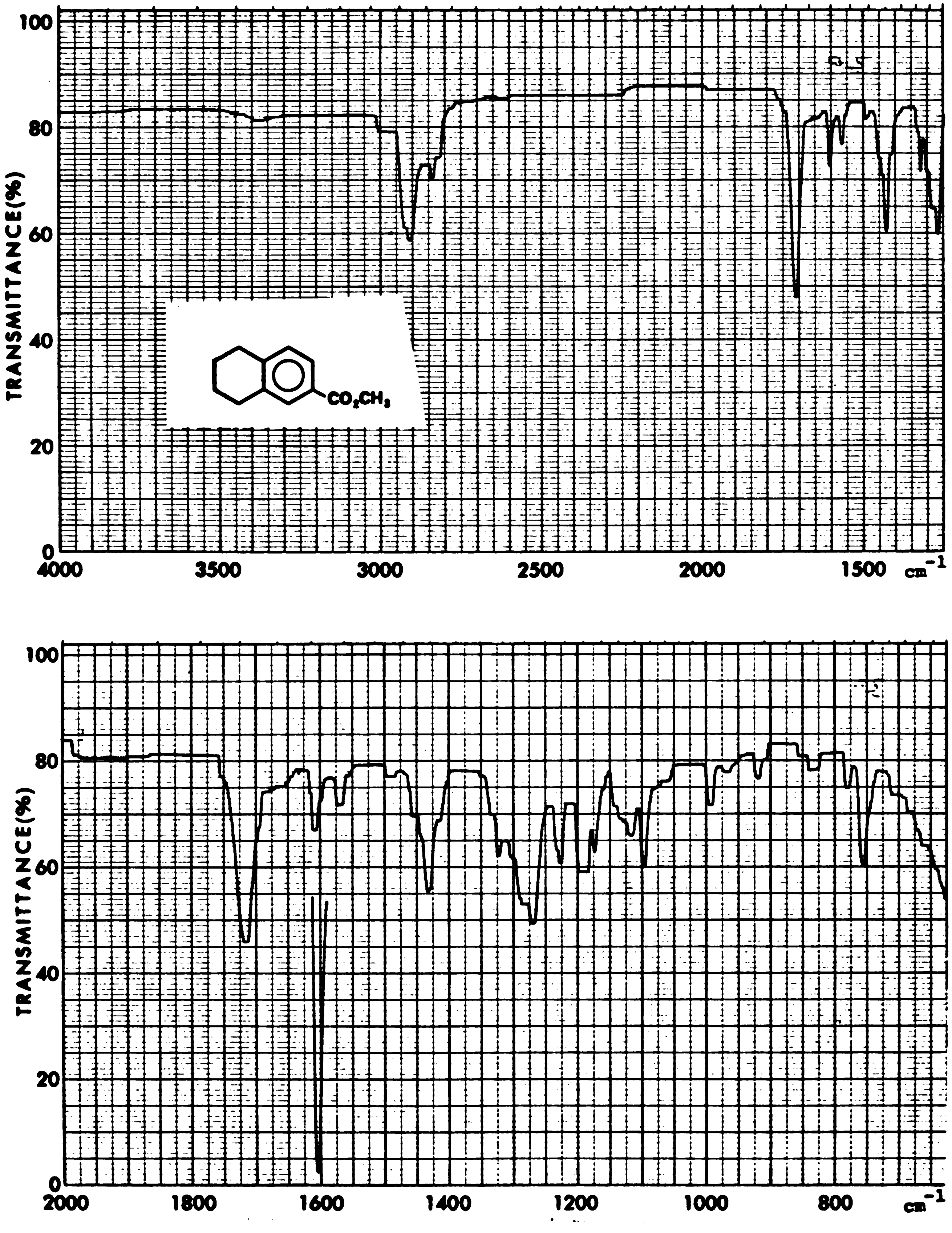


Figure 18. IR spectrum of 63.

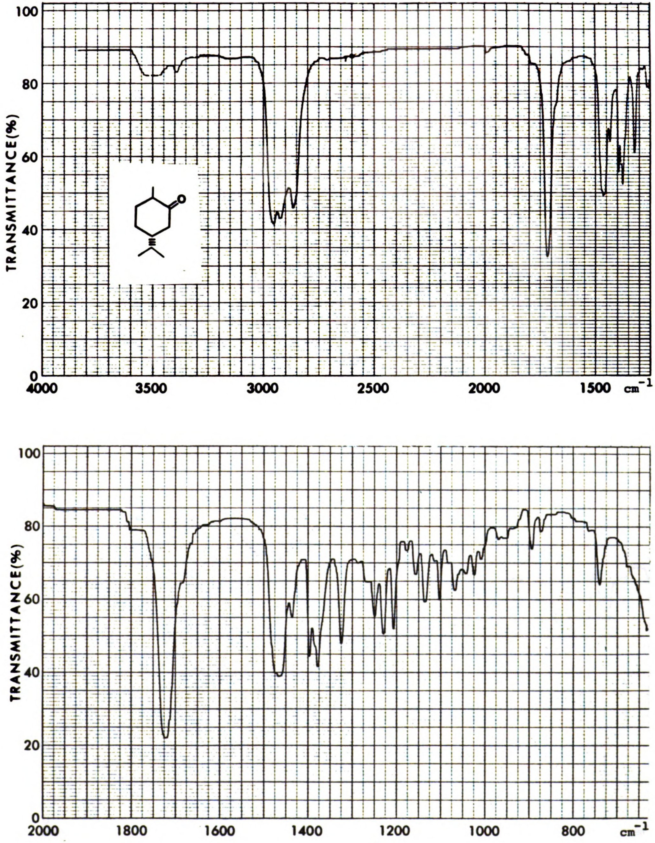


Figure 19. IR spectrum of **73**.

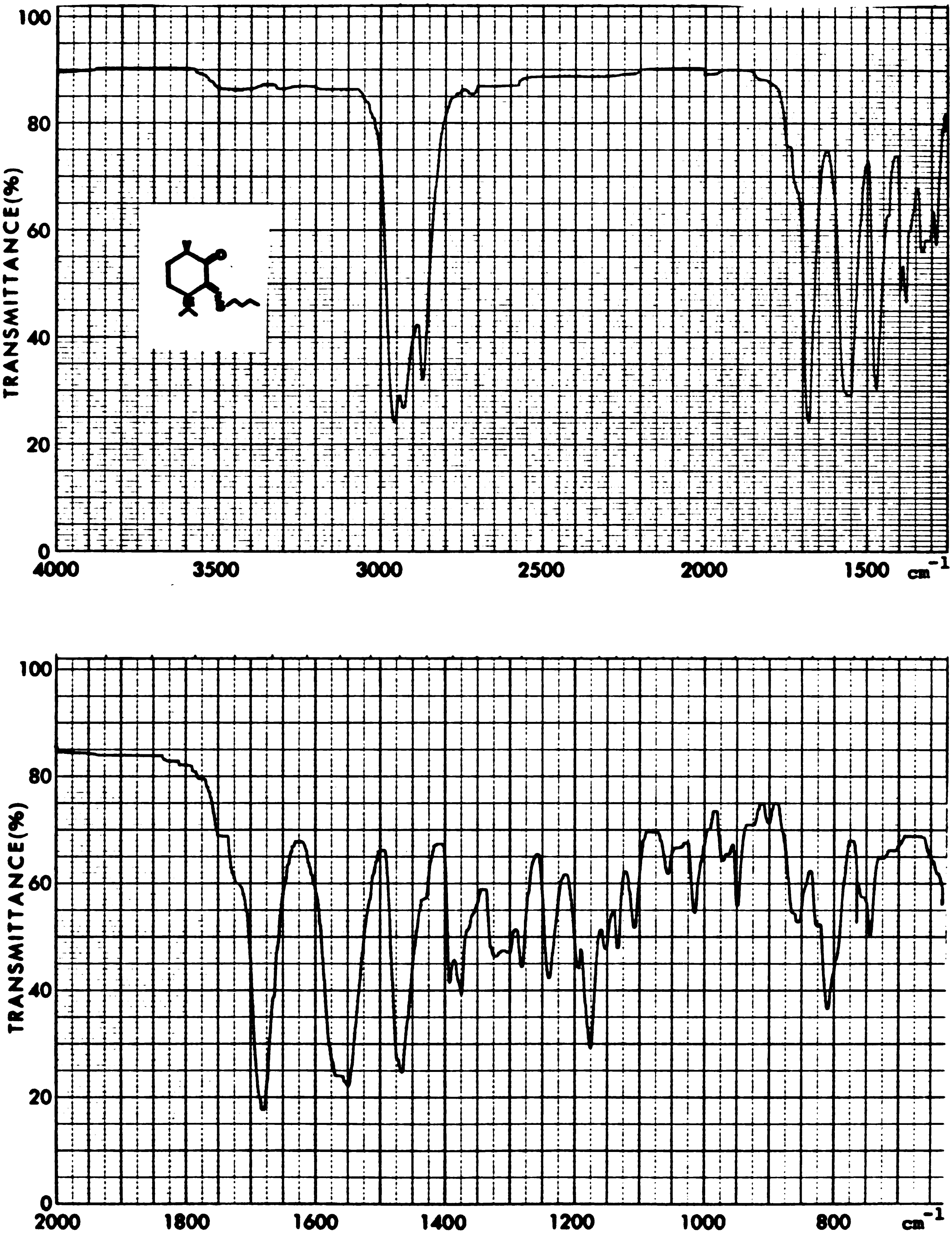


Figure 20. IR spectrum of **75b**.

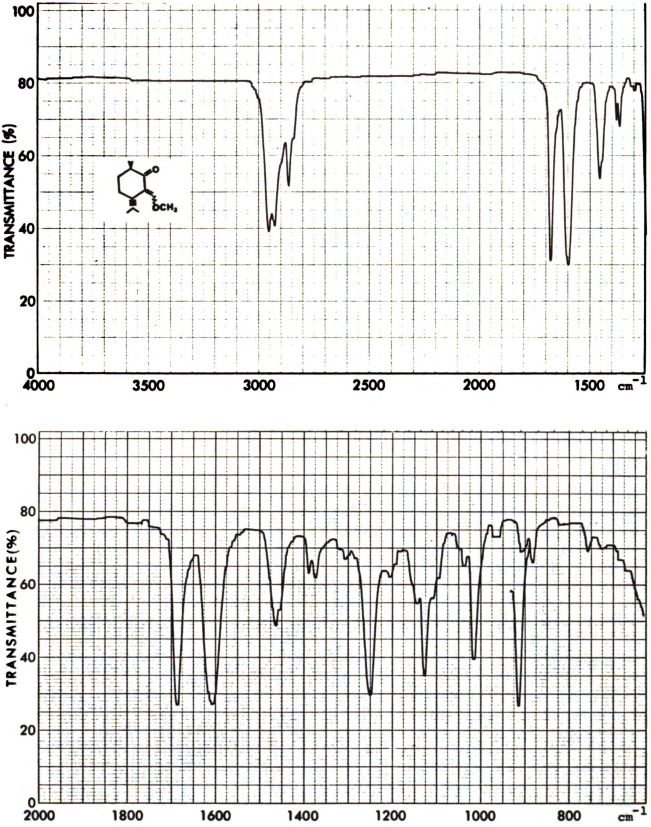


Figure 21. IR spectrum of 75c.

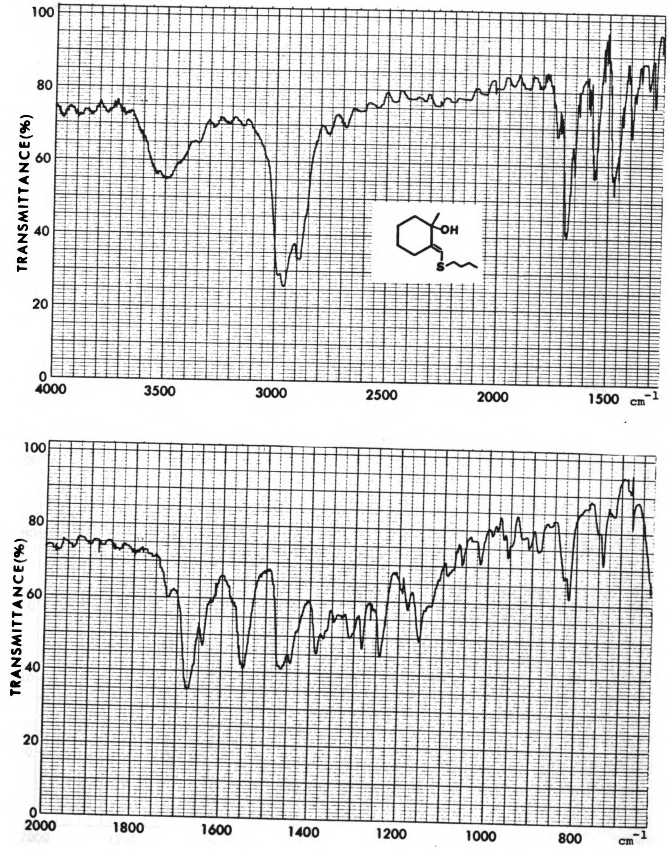


Figure 22. IR spectrum of 80.

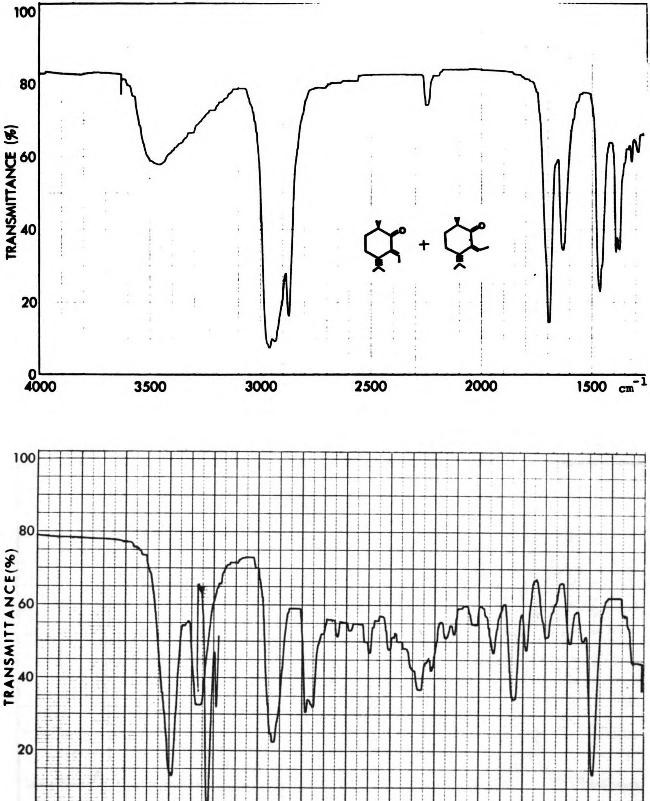


Figure 23. IR spectrum of 85 and 86.

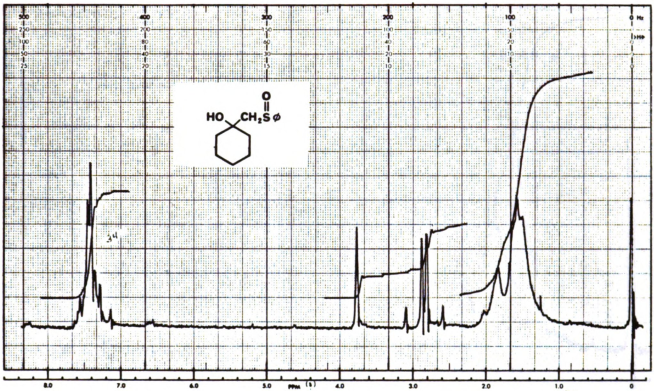


Figure 24. PMR spectrum of 29.

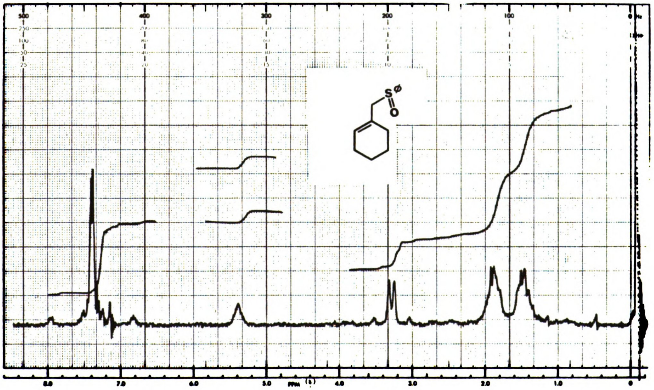


Figure 25. PMR spectrum of 30.

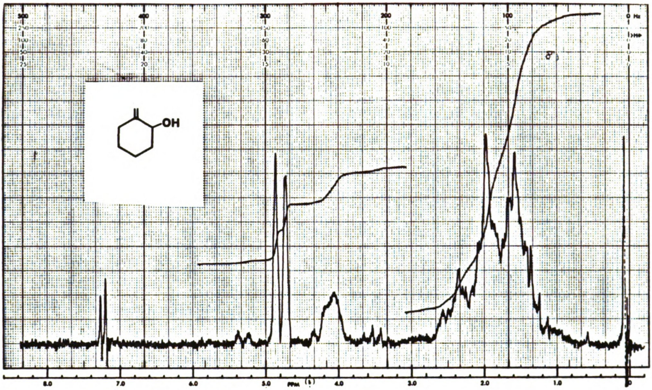


Figure 26. PMR spectrum of 31.

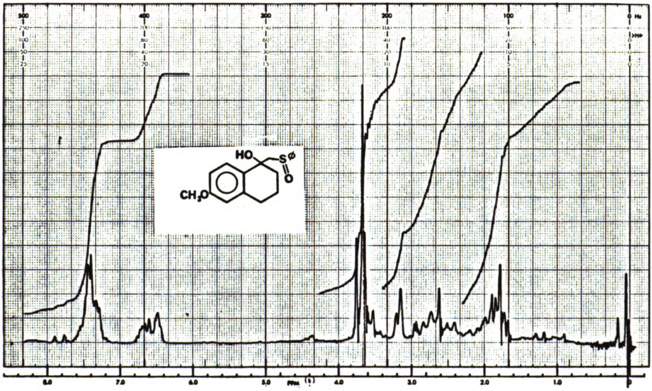


Figure 27. PMR spectrum of 34.

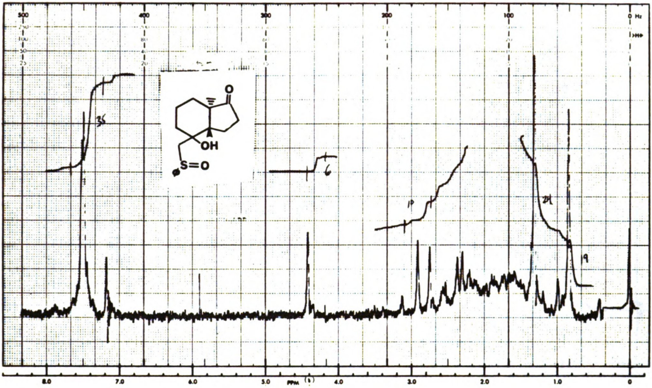


Figure 28. PMR spectrum of 35.

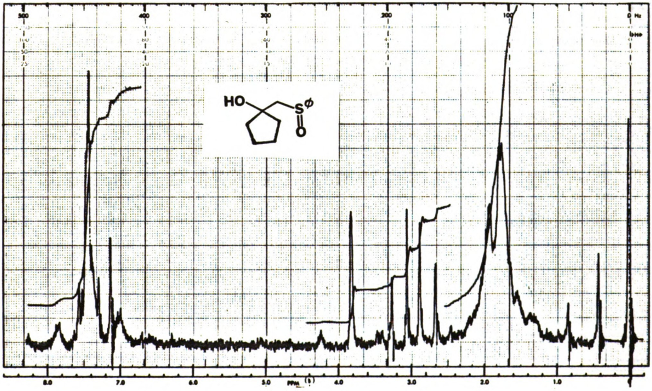


Figure 29. PMR spectrum of 36.

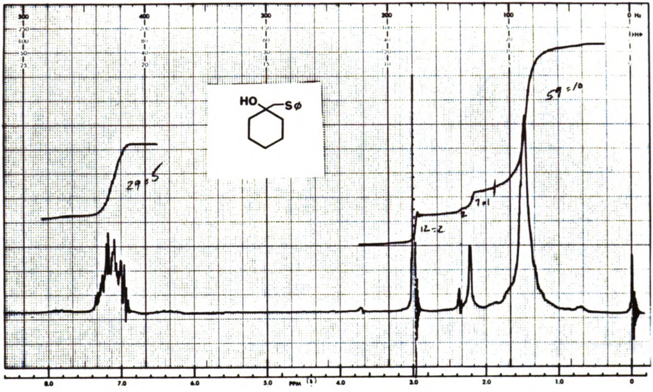


Figure 30. PMR spectrum of 38.

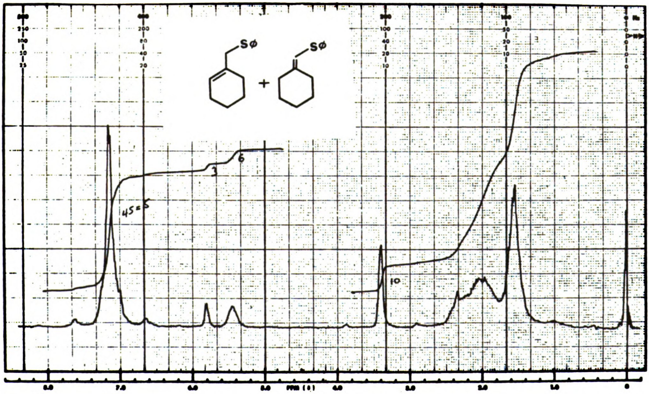


Figure 31. PMR spectrum of 39 and 40.

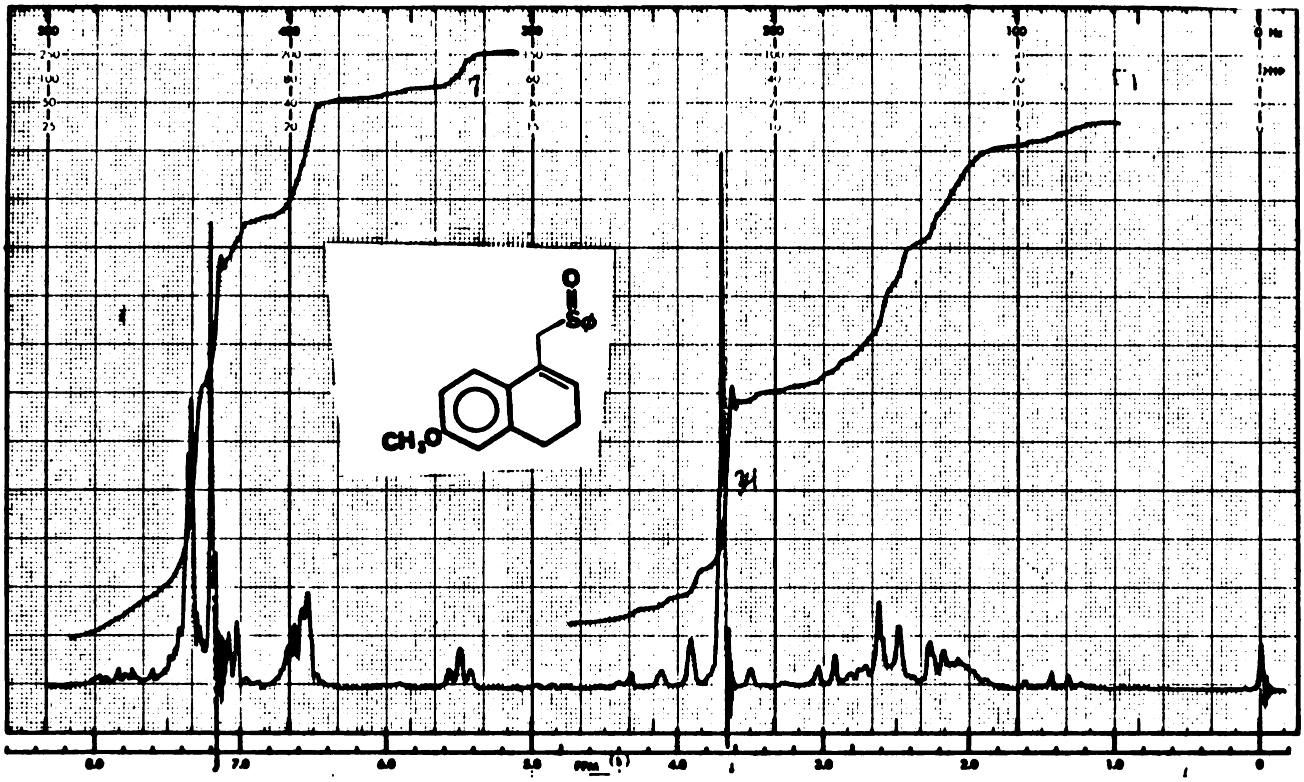


Figure 32. PMR spectrum of **44**.

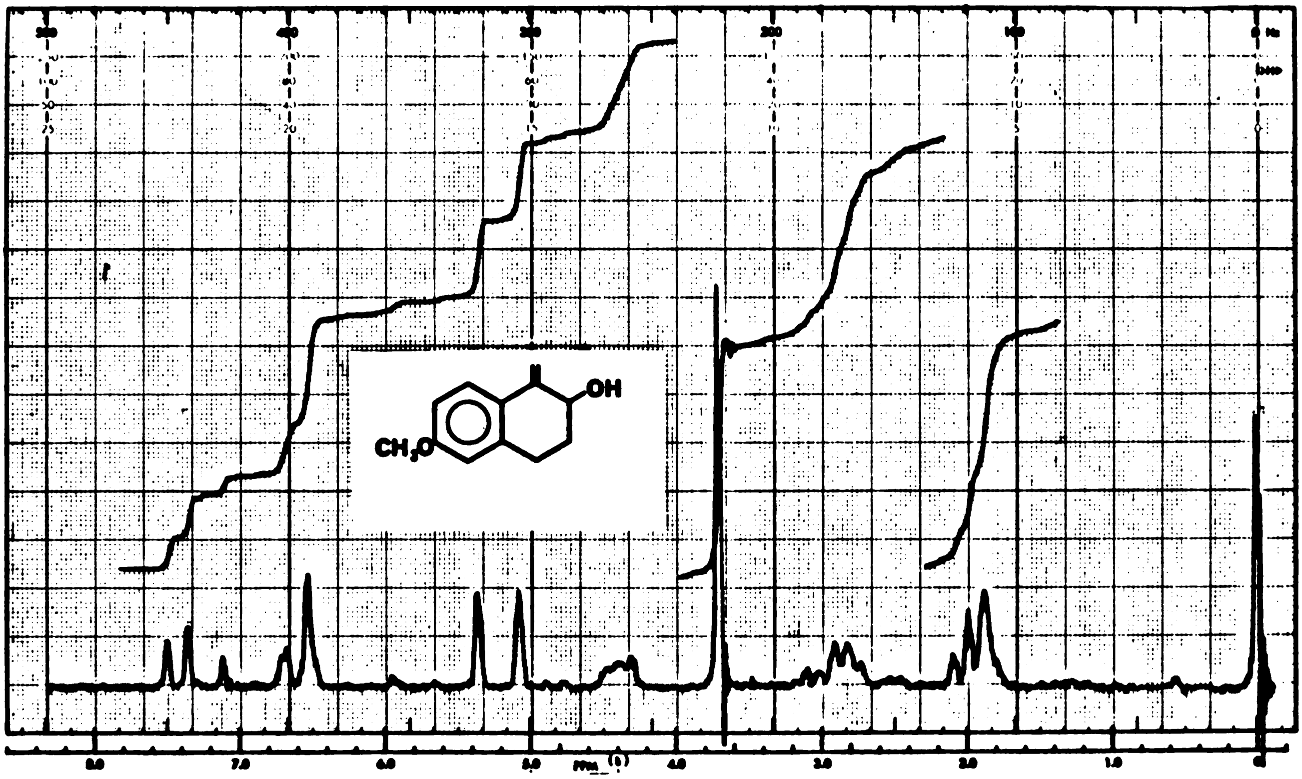


Figure 33. PMR spectrum of **51**.

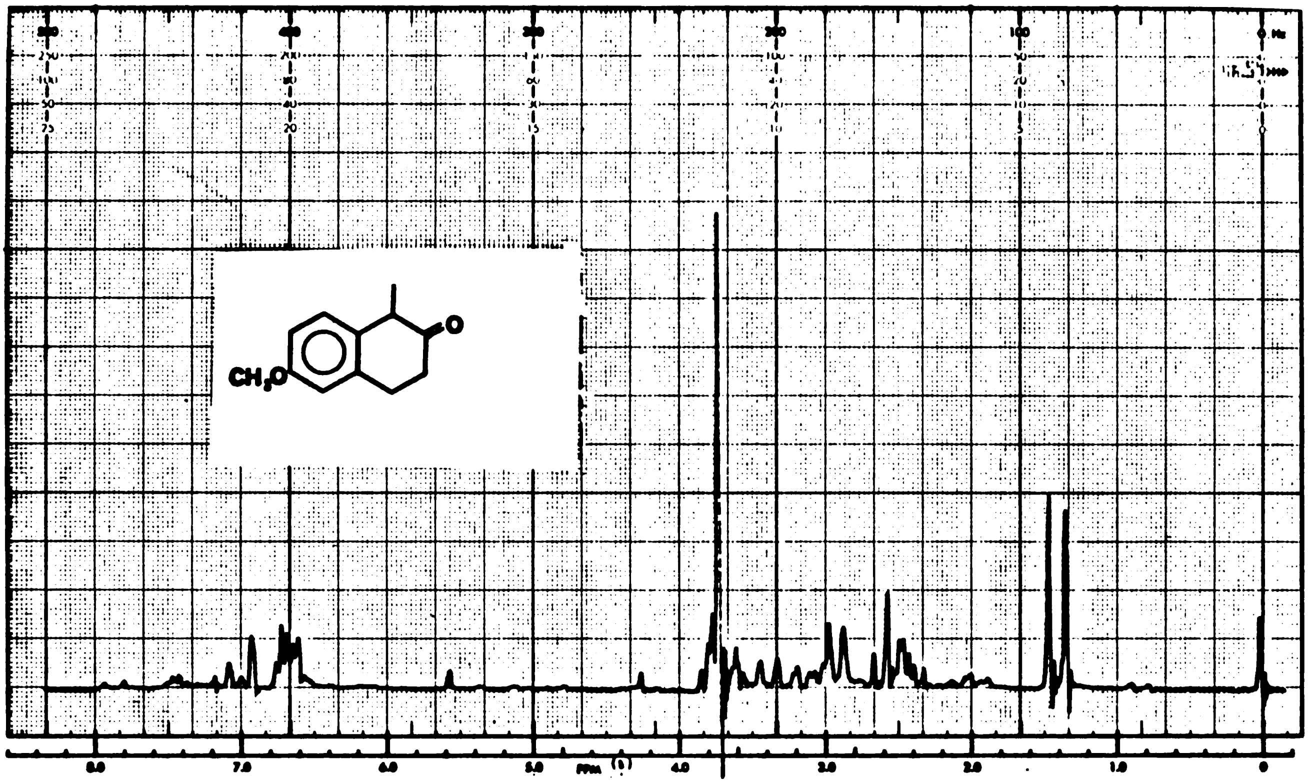


Figure 34. PMR spectrum of 52.

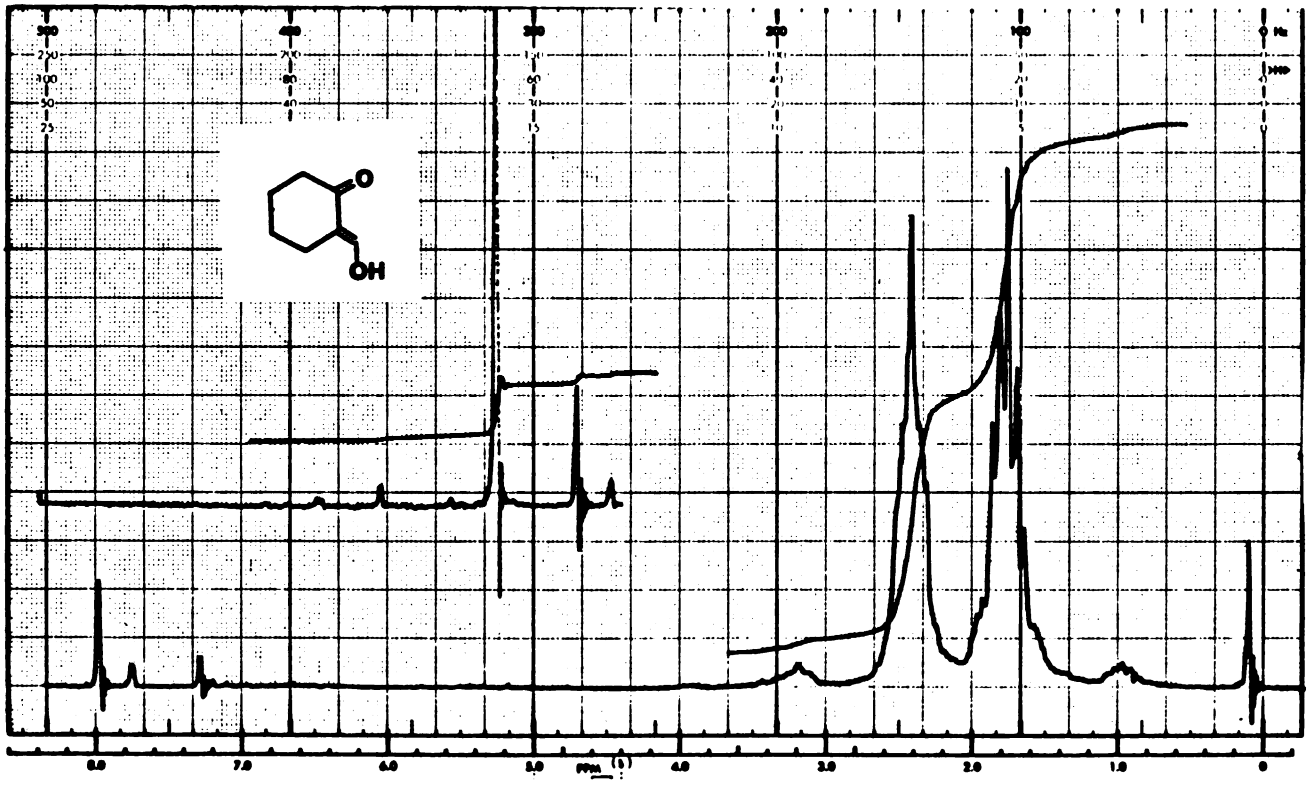


Figure 35. PMR spectrum of 59.

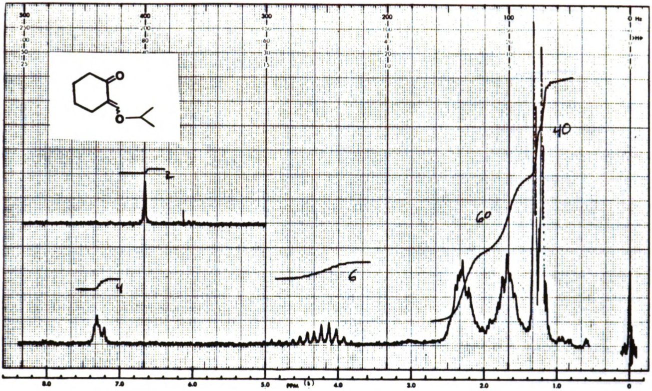


Figure 36. PMR spectrum of 60a.

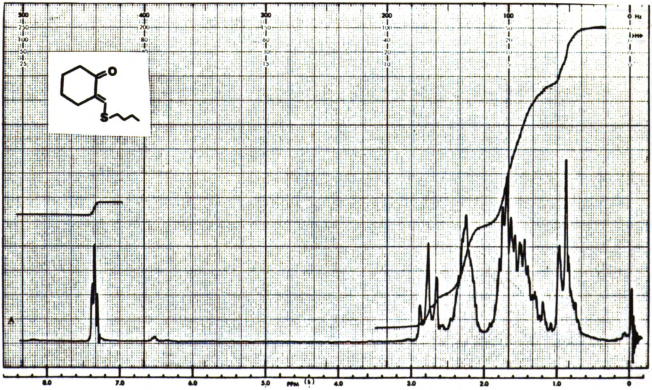


Figure 37. PMR spectrum of 60b.

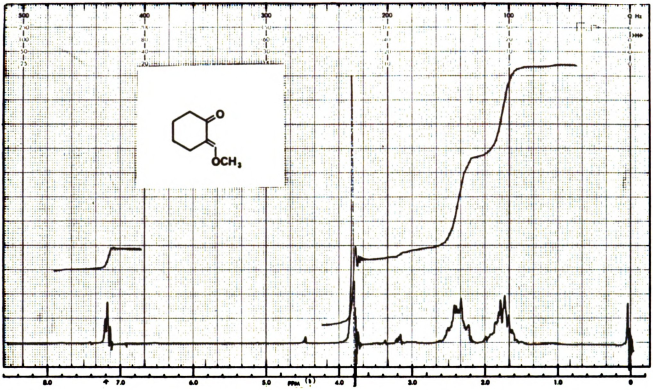


Figure 38. PMR spectrum of 60c.

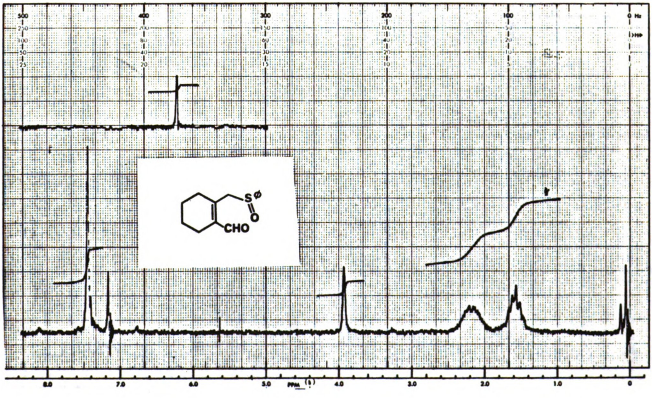


Figure 39. PMR spectrum of 61.

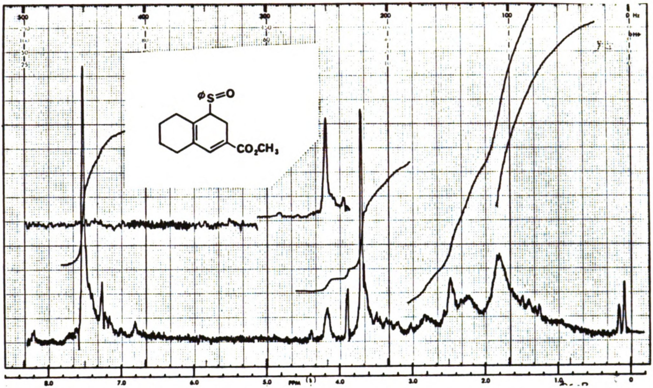


Figure 40. PMR spectrum of 62.

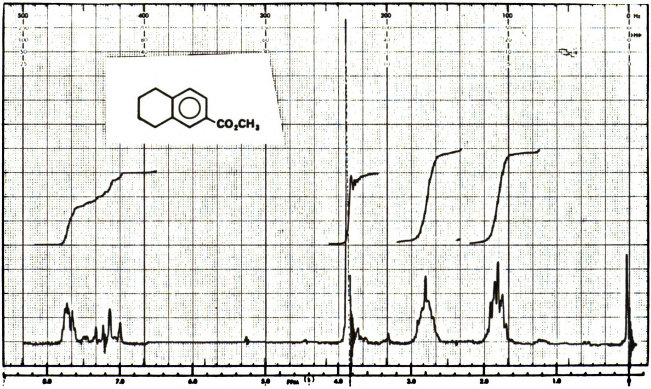


Figure 41. PMR spectrum of 63.

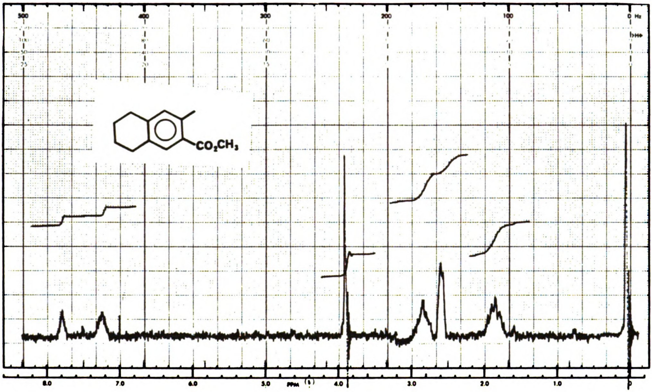


Figure 42. PMR spectrum of 68.

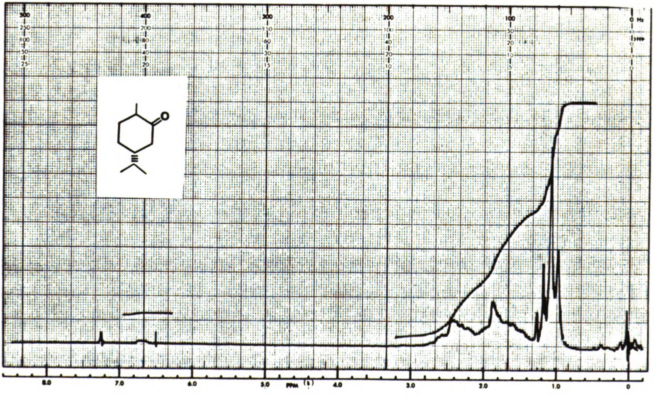


Figure 43. PMR spectrum of 73.

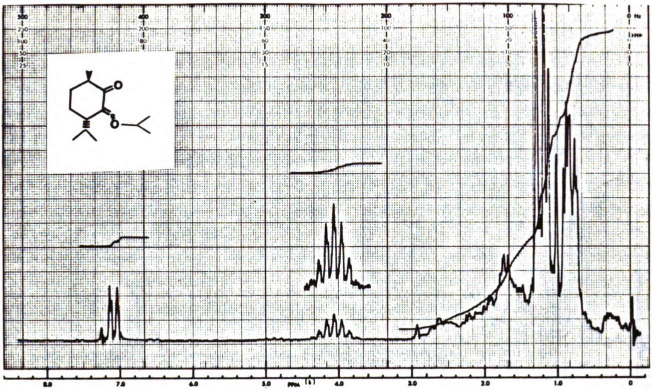


Figure 44. PMR spectrum of 75a.

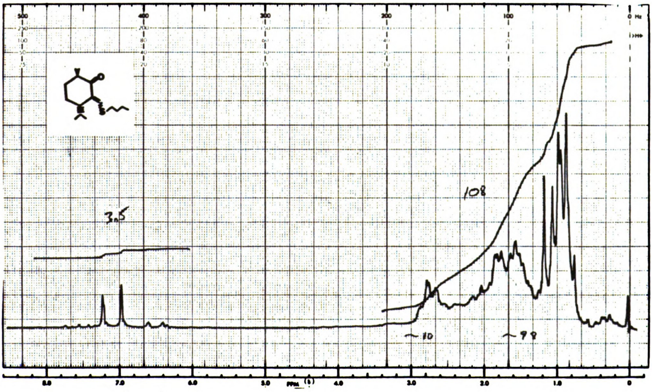


Figure 45. PMR spectrum of 75b.

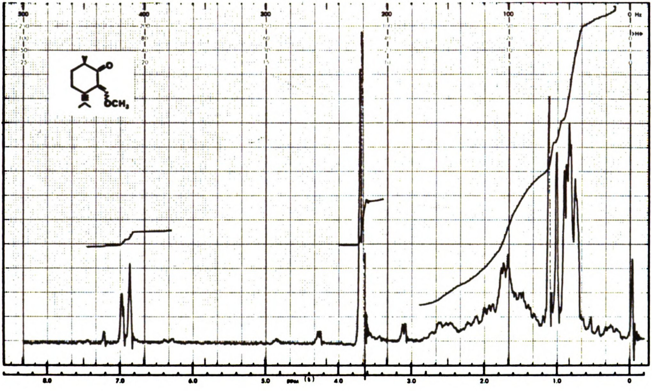


Figure 46. PMR spectrum of 75c.

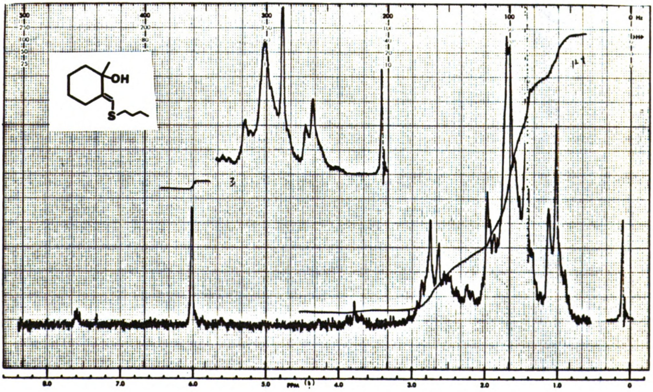


Figure 47. PMR spectrum of 80.

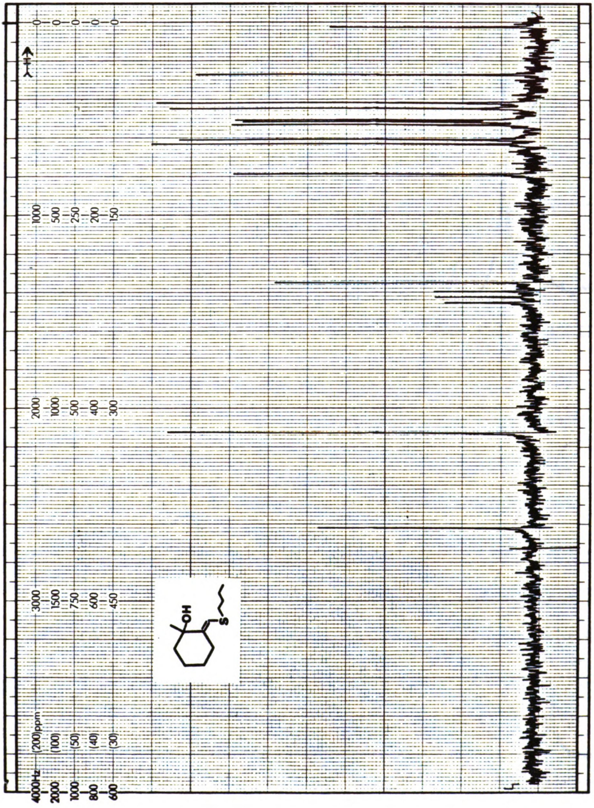


Figure 48. ^{13}C NMR spectrum of 80.

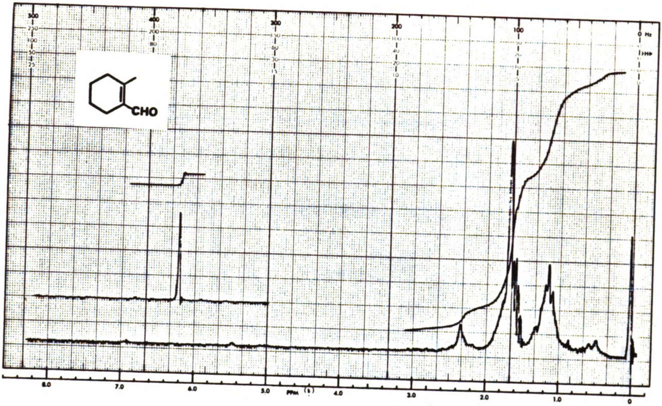


Figure 49. PMR spectrum of 82

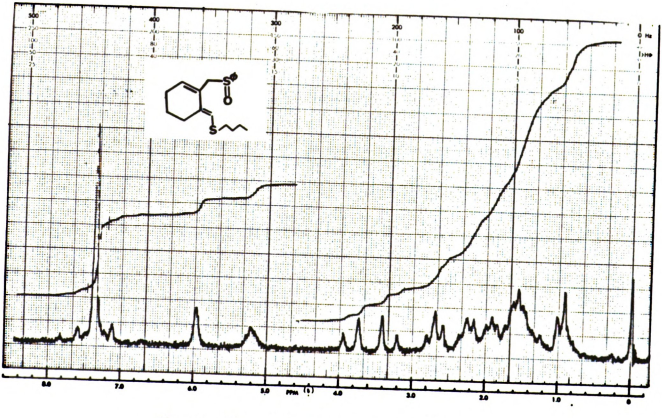


Figure 50. PMR spectrum of 83.

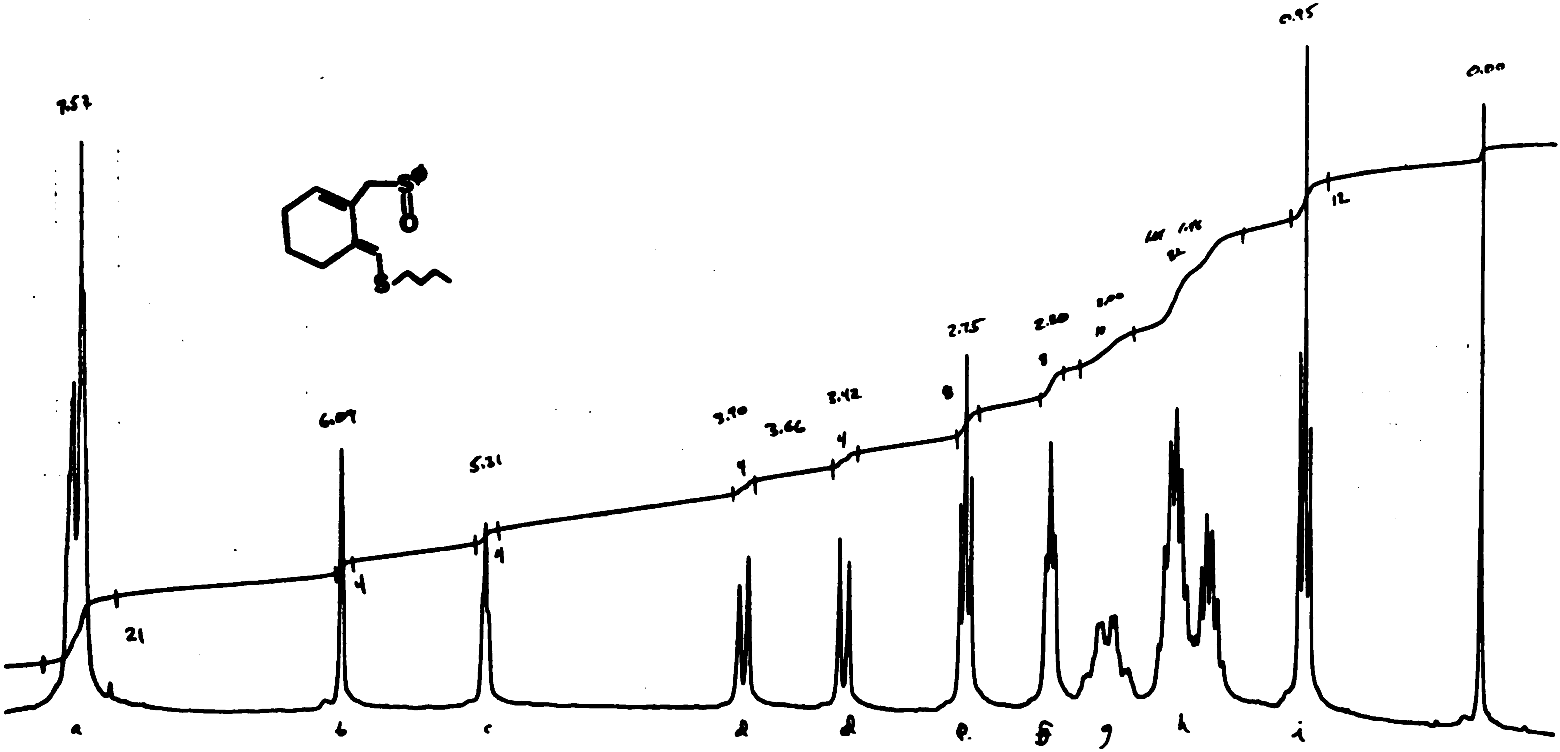


Figure 51. 250 MHz PMR spectrum of 83.

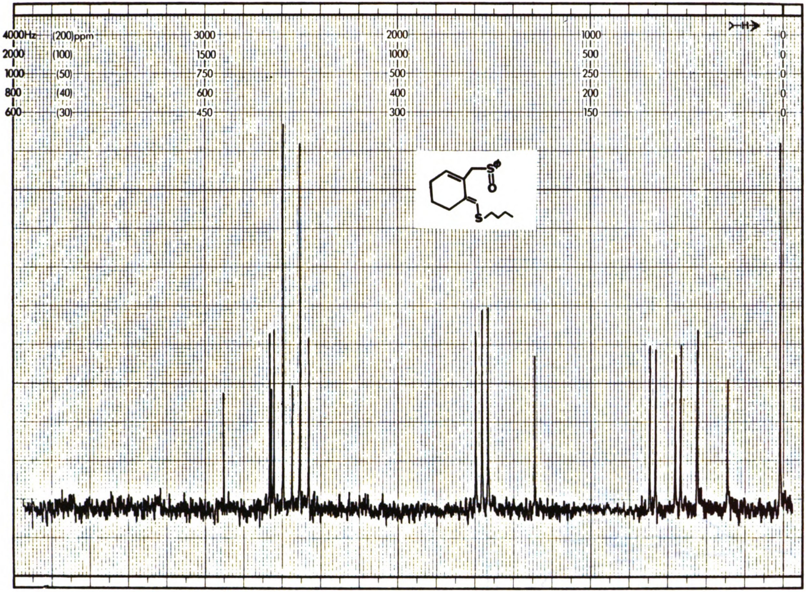


Figure 52. ^{13}C NMR spectrum of 83.

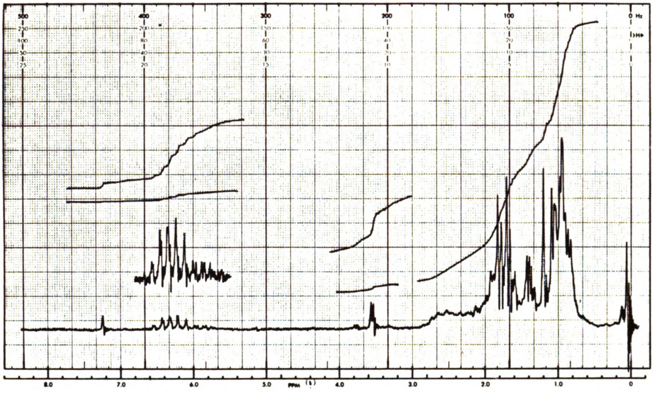


Figure 53. PMR spectrum of 85 and 86.

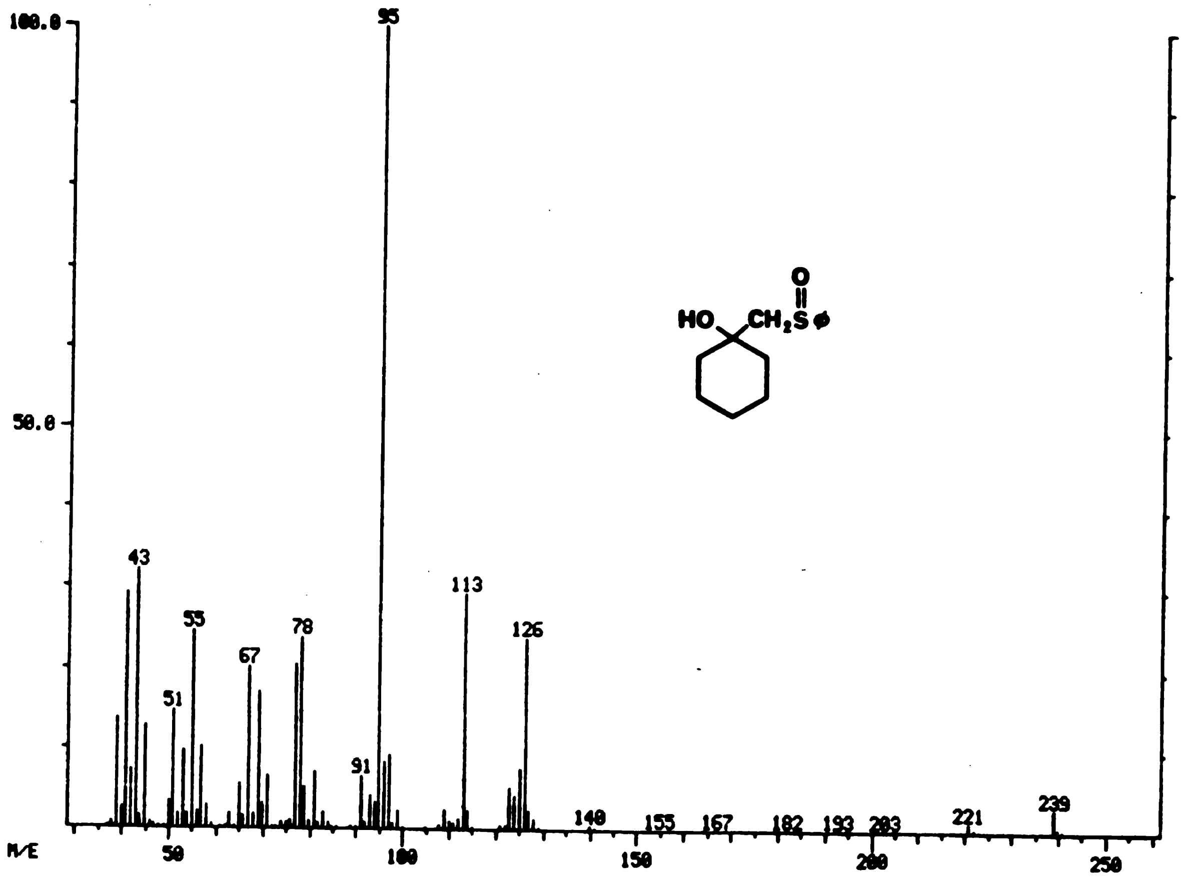


Figure 54. Mass spectrum of **29**.

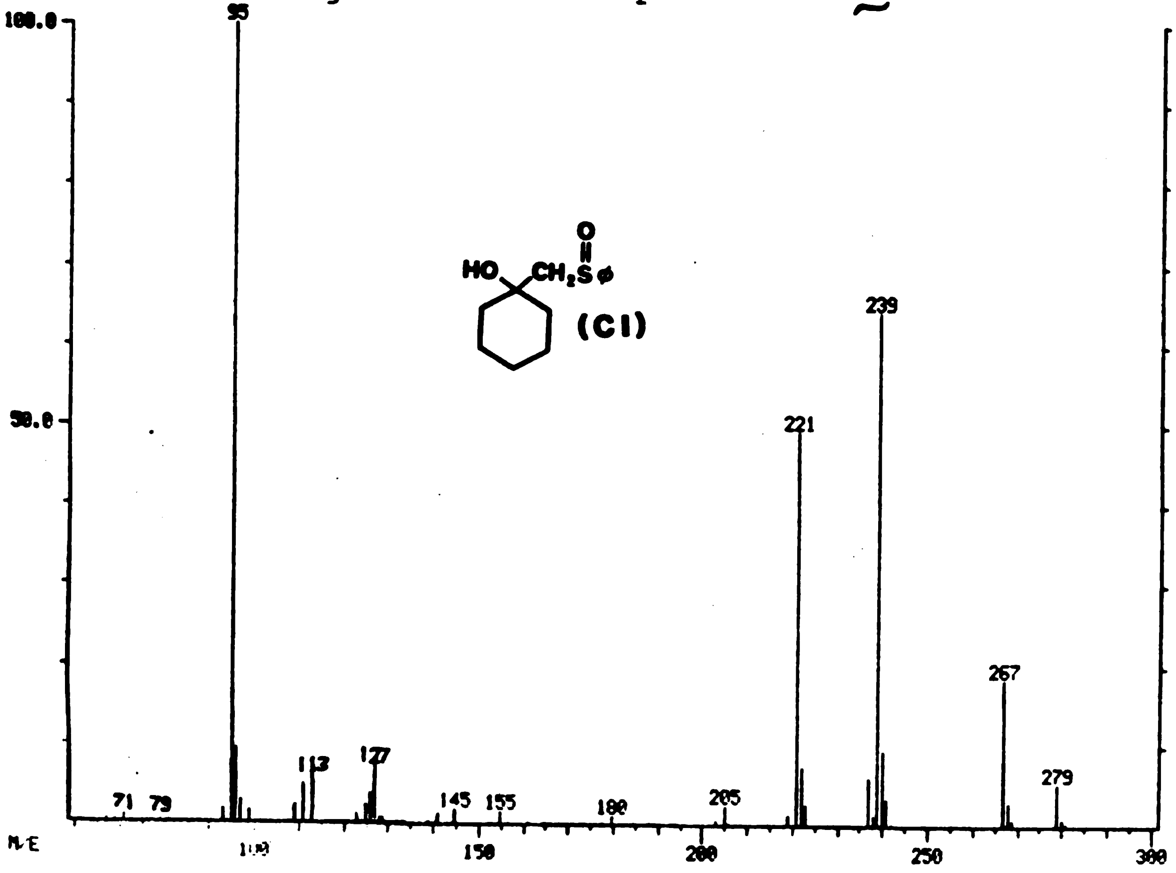


Figure 55. Mass spectrum of **29** (CI).

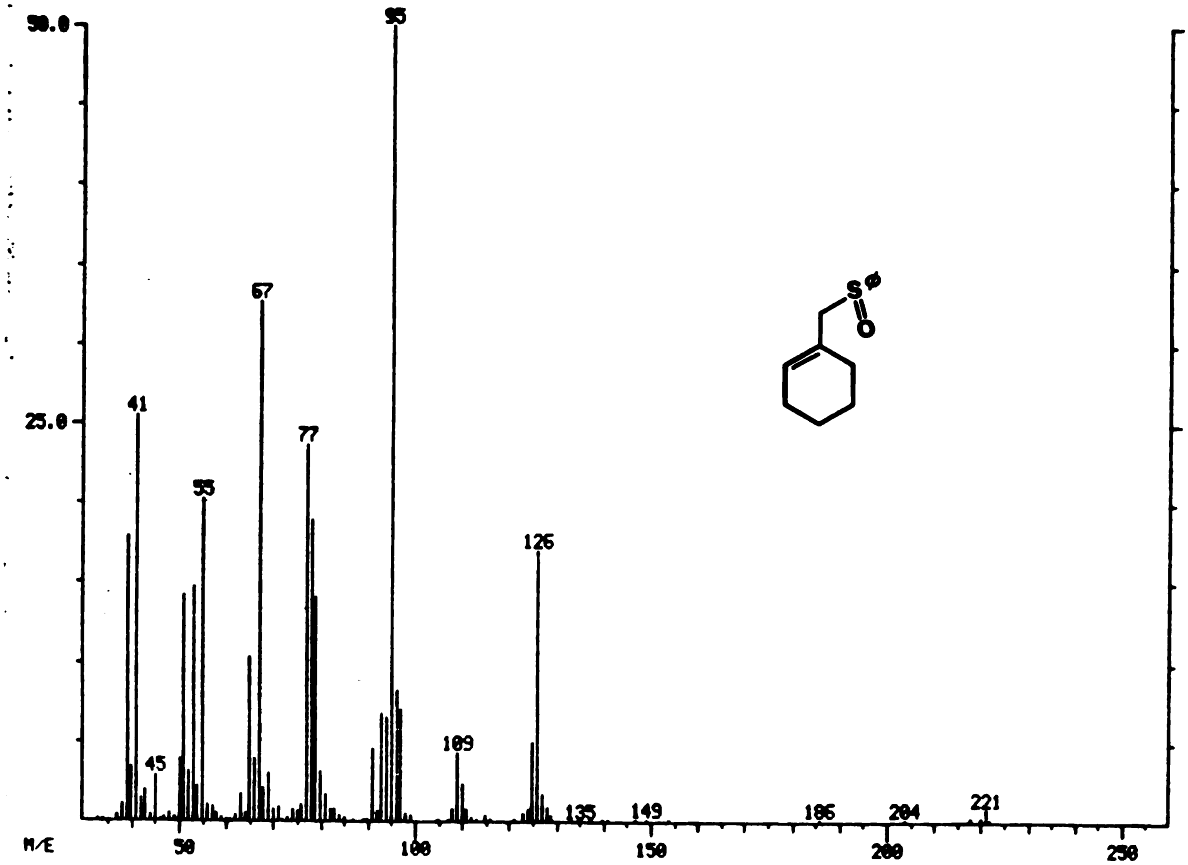


Figure 56. Mass spectrum of 30.

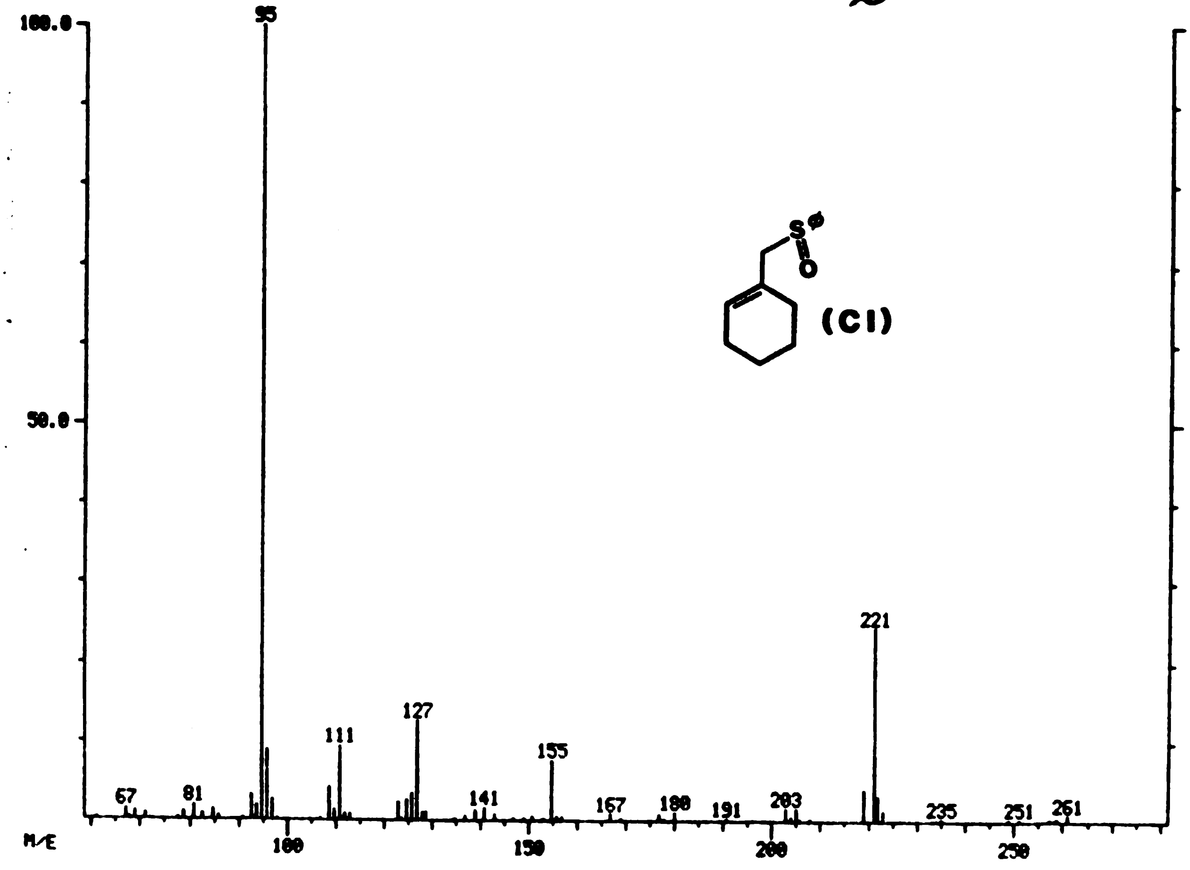


Figure 57. Mass spectrum of 30 (CI).

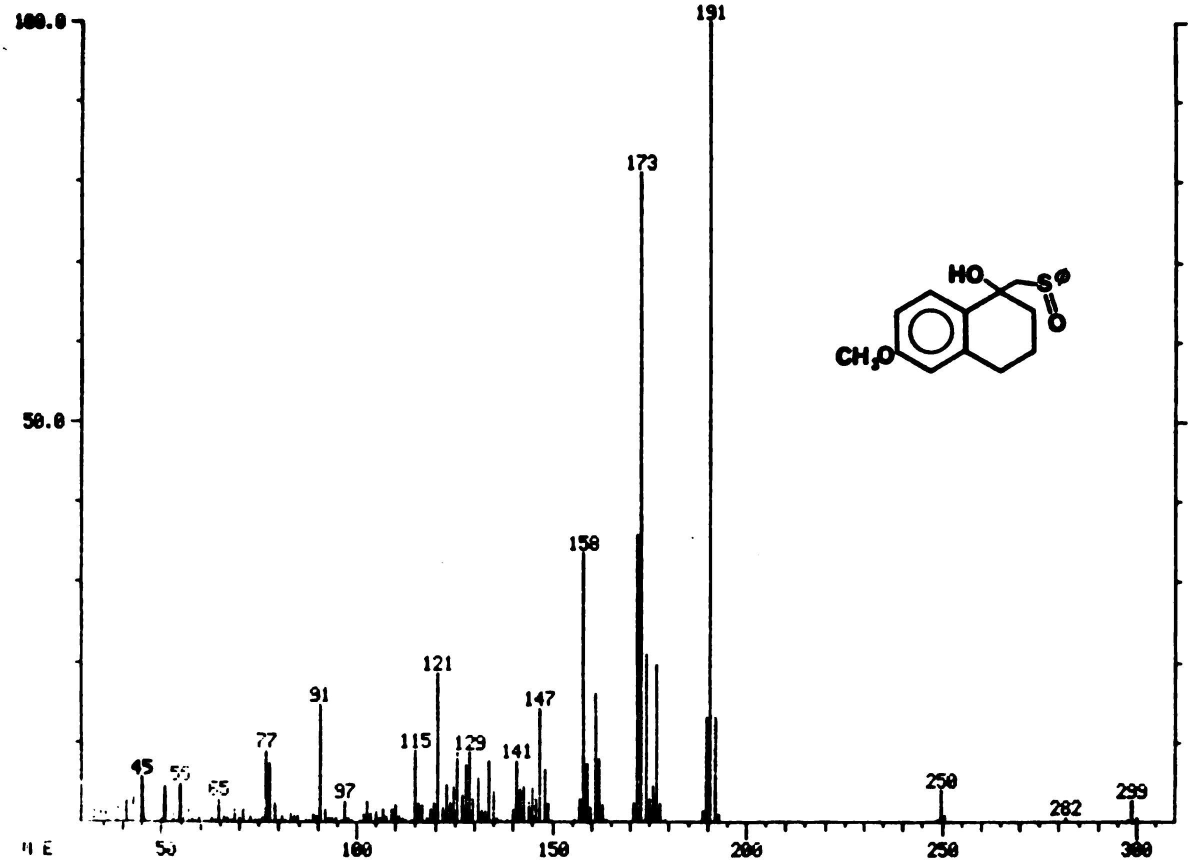


Figure 58. Mass spectrum of 34.

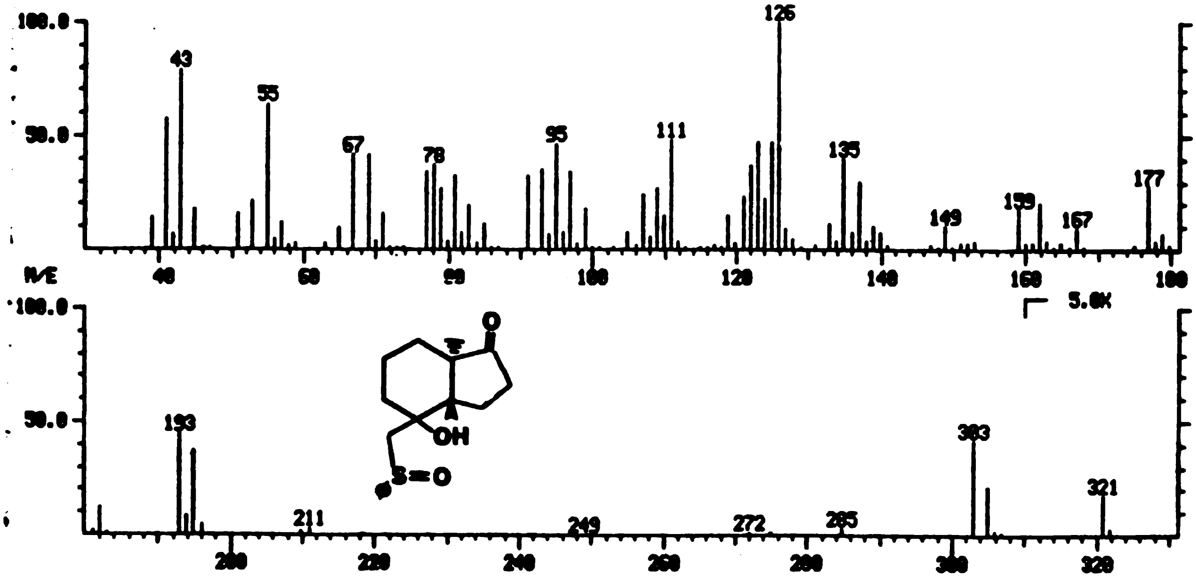


Figure 59. Mass spectrum of 35.

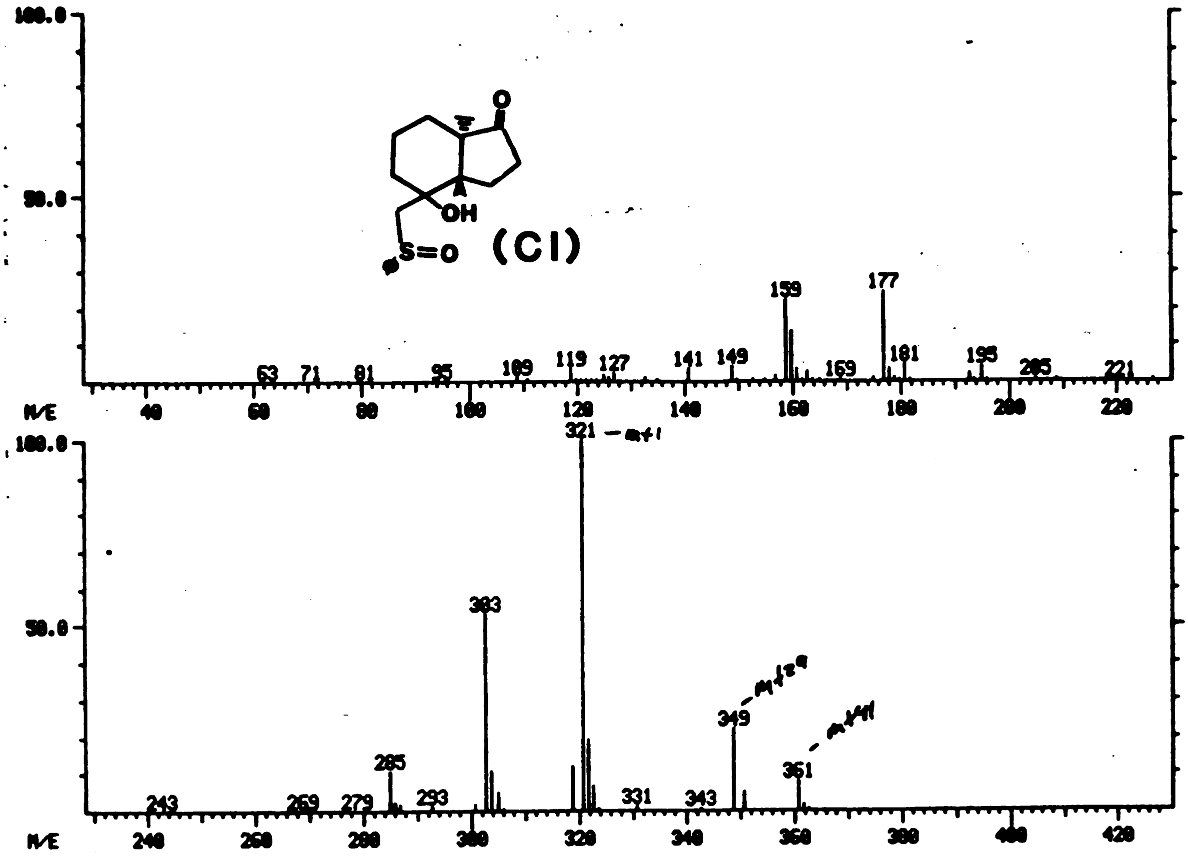


Figure 60. Mass spectrum of 35 (CI).

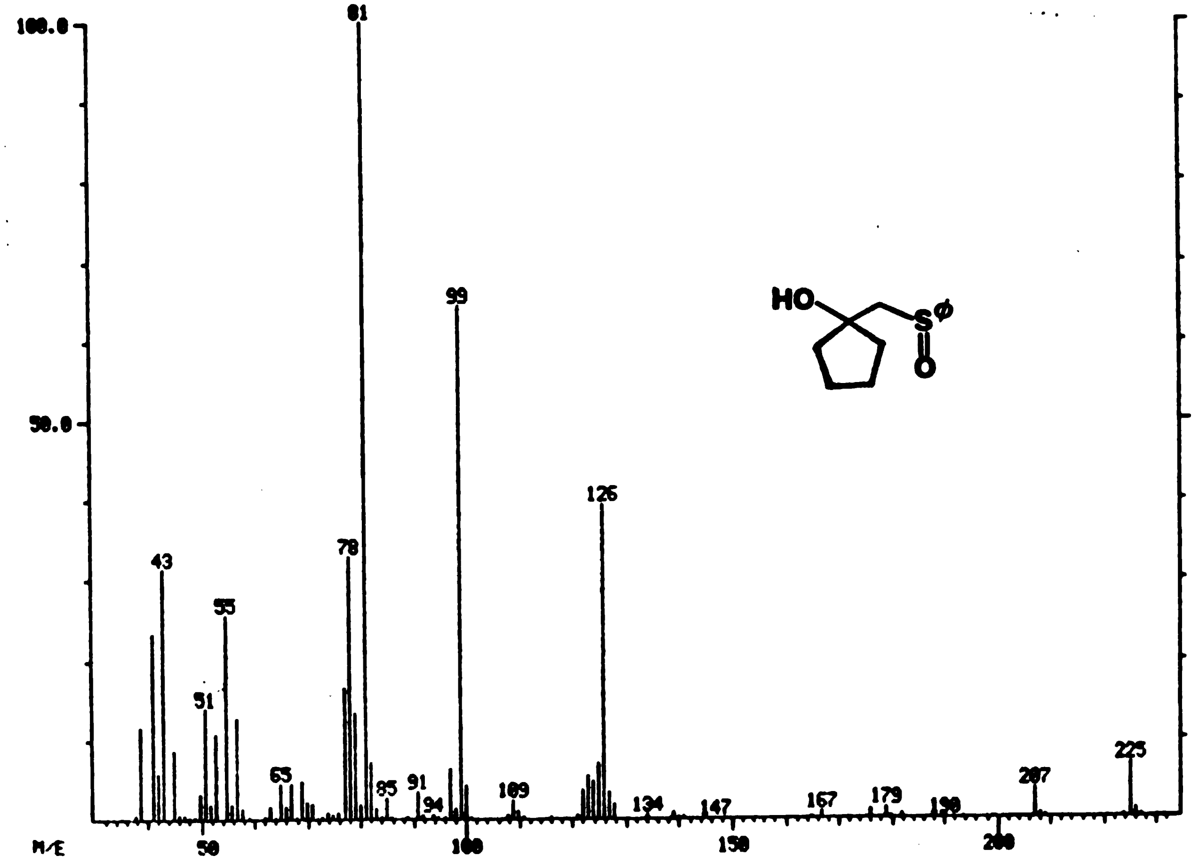


Figure 61. Mass spectrum of 36.

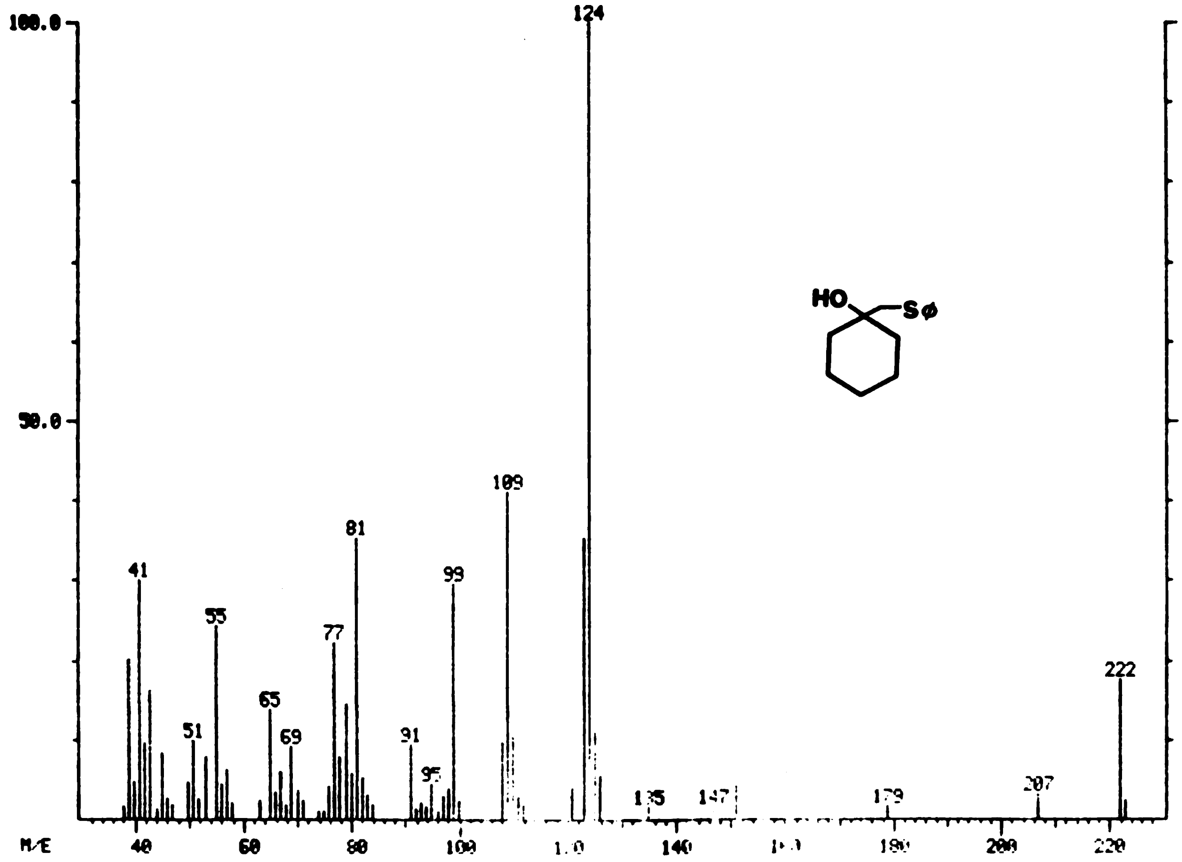


Figure 62. Mass spectrum of 38.

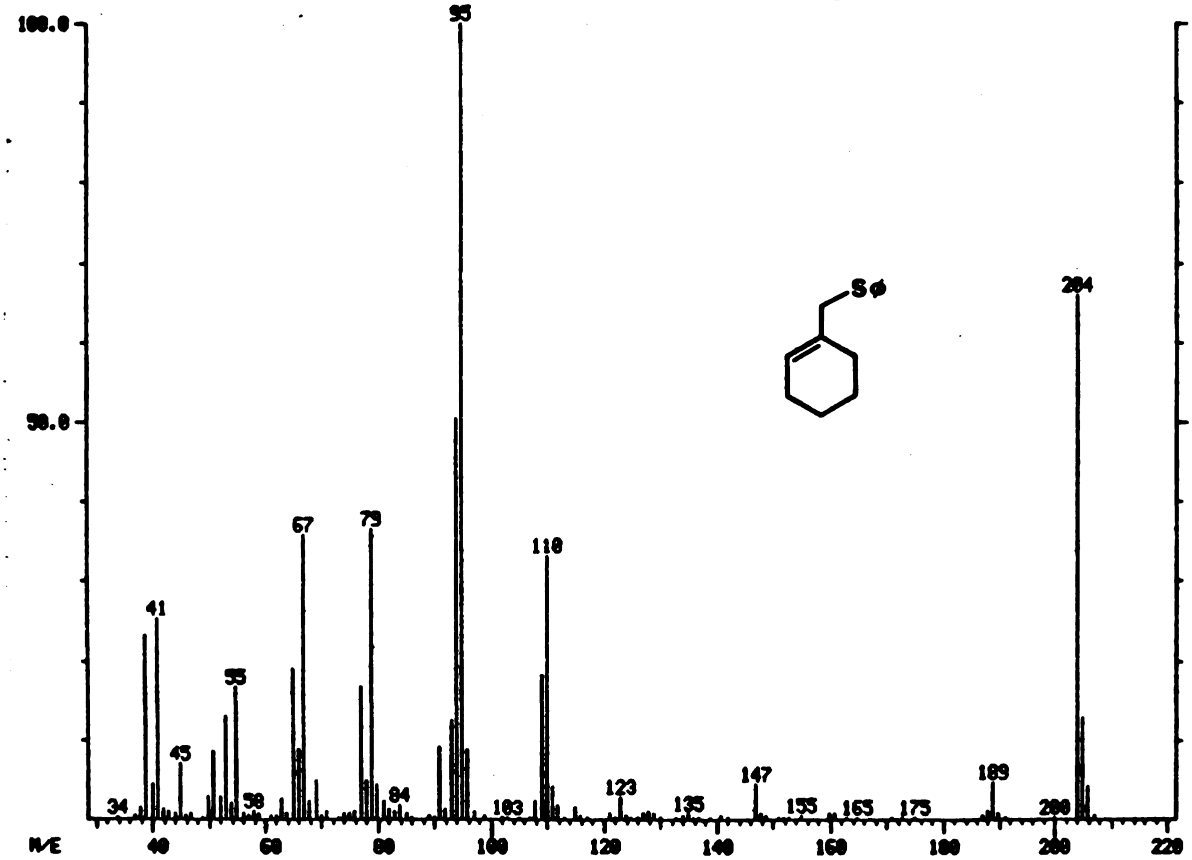


Figure 63. Mass spectrum of 39.

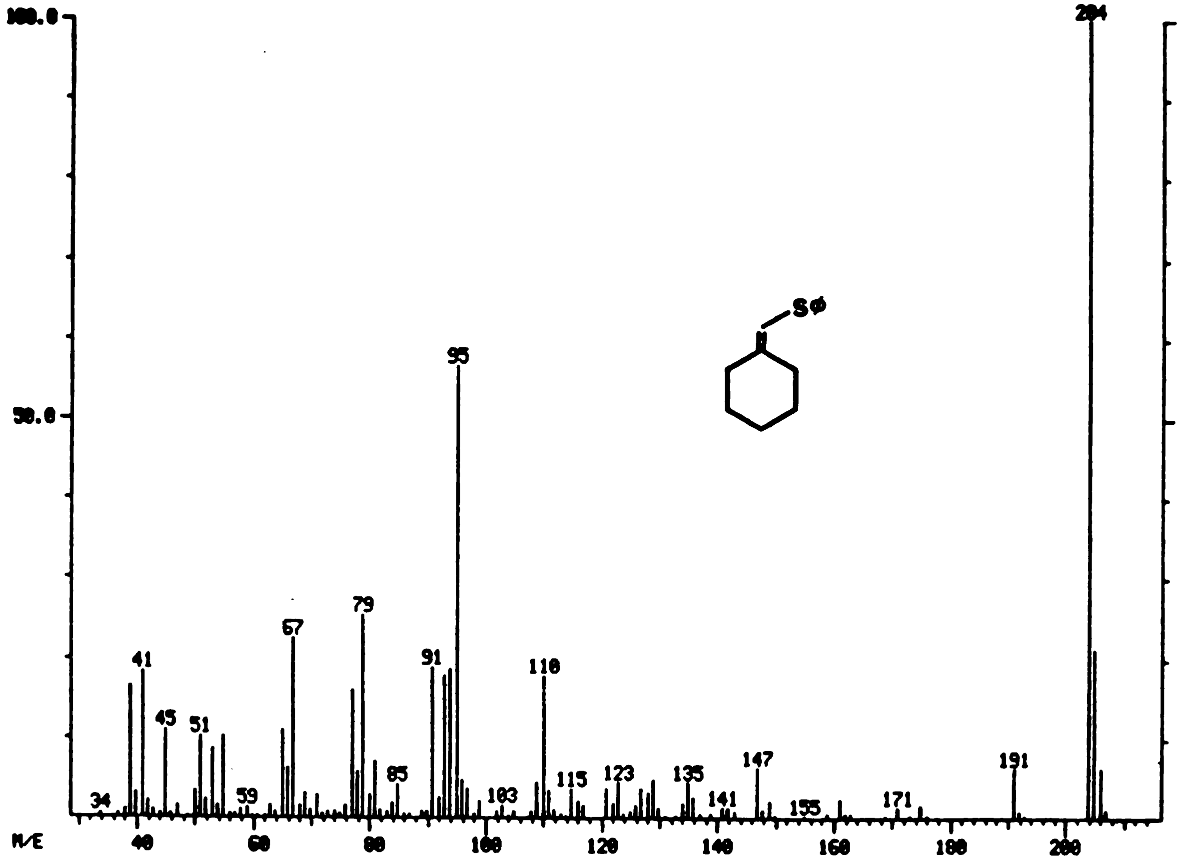


Figure 64. Mass spectrum of 40.

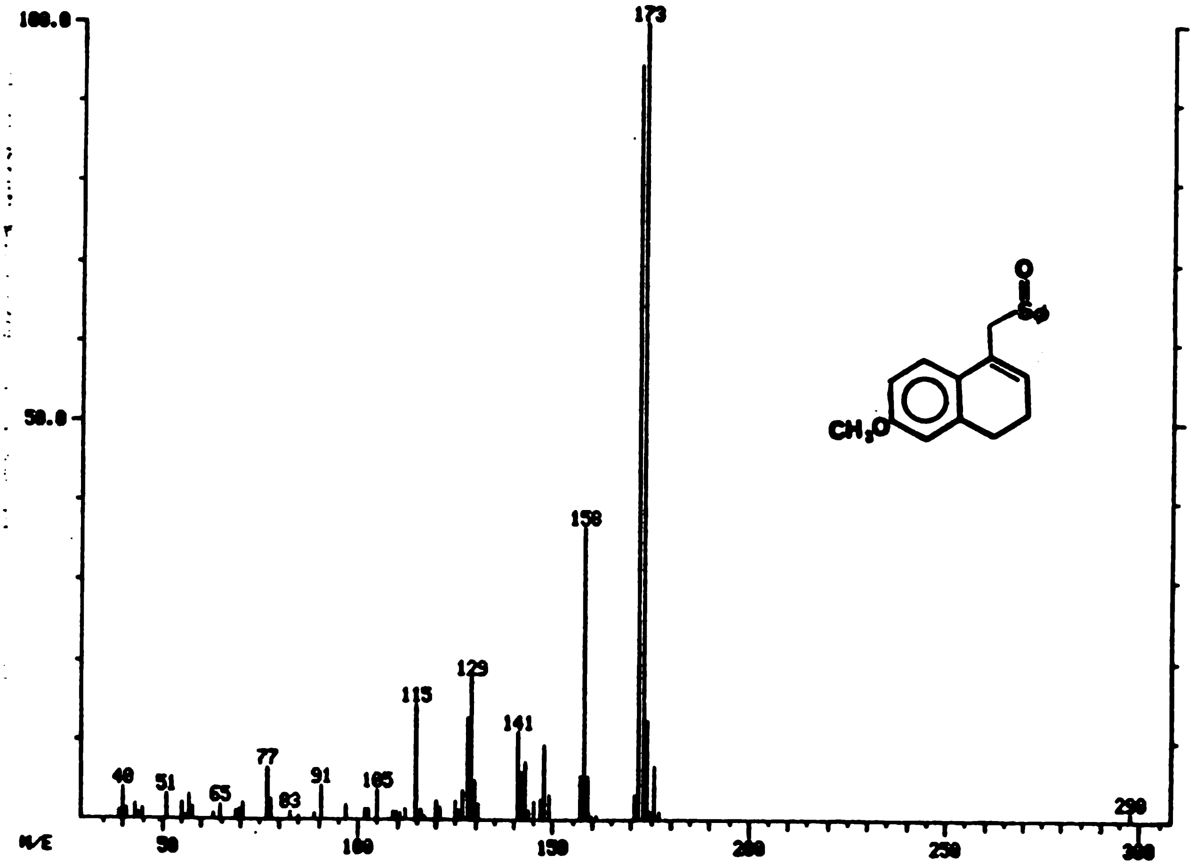


Figure 65. Mass spectrum of 44.

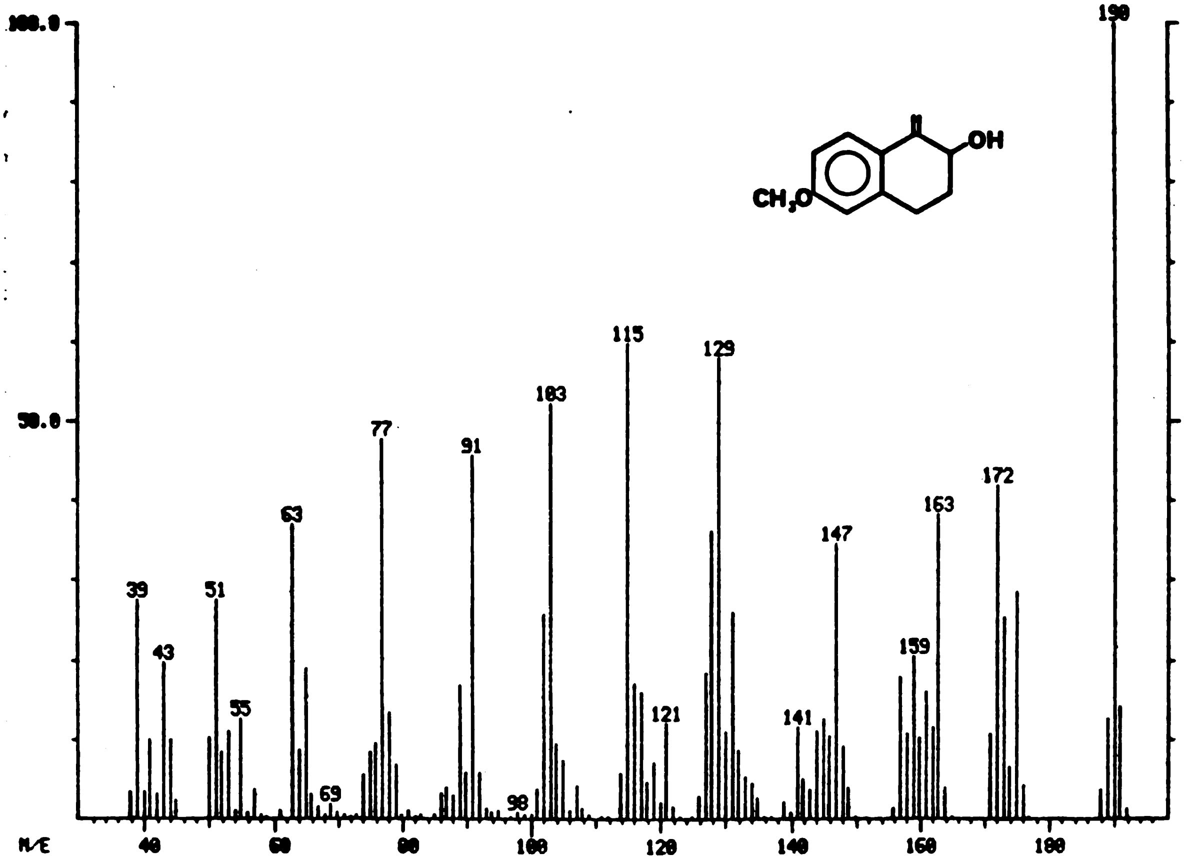


Figure 66. Mass spectrum of 51.

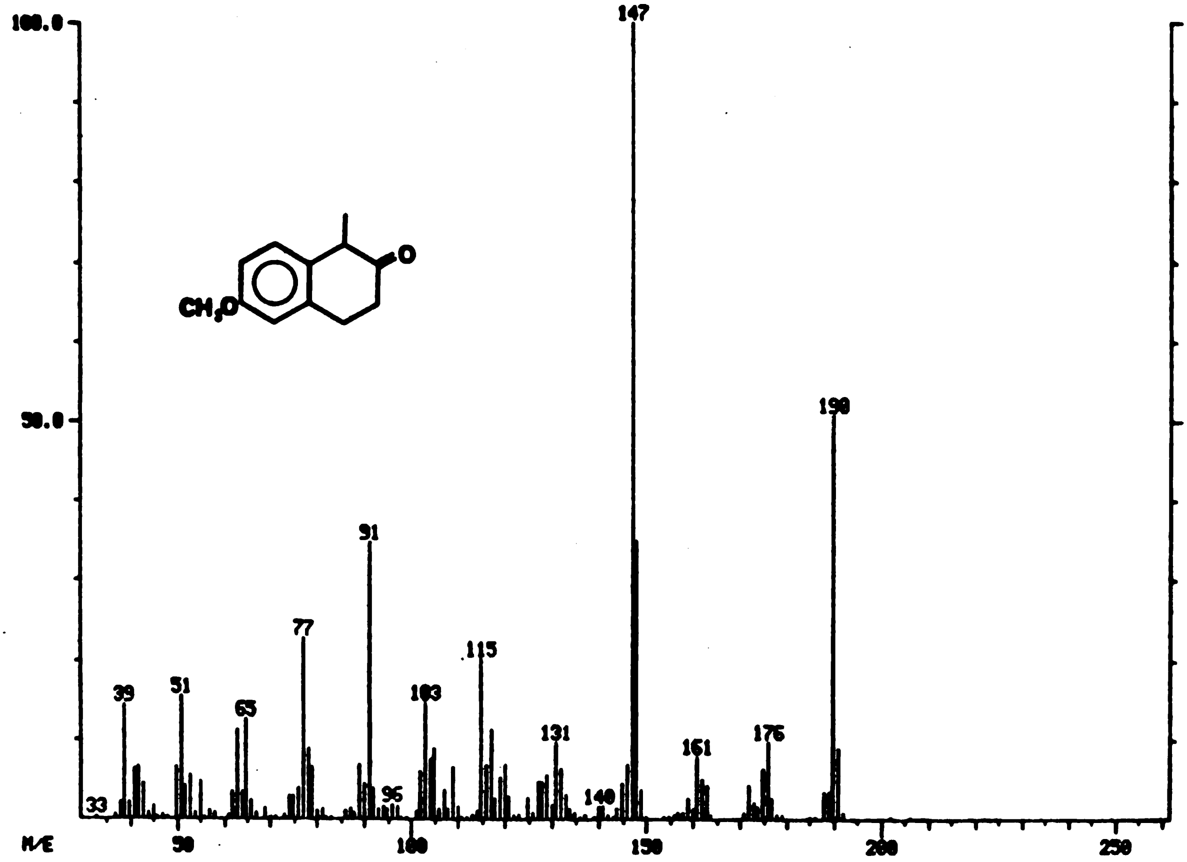


Figure 67. Mass spectrum of 52.

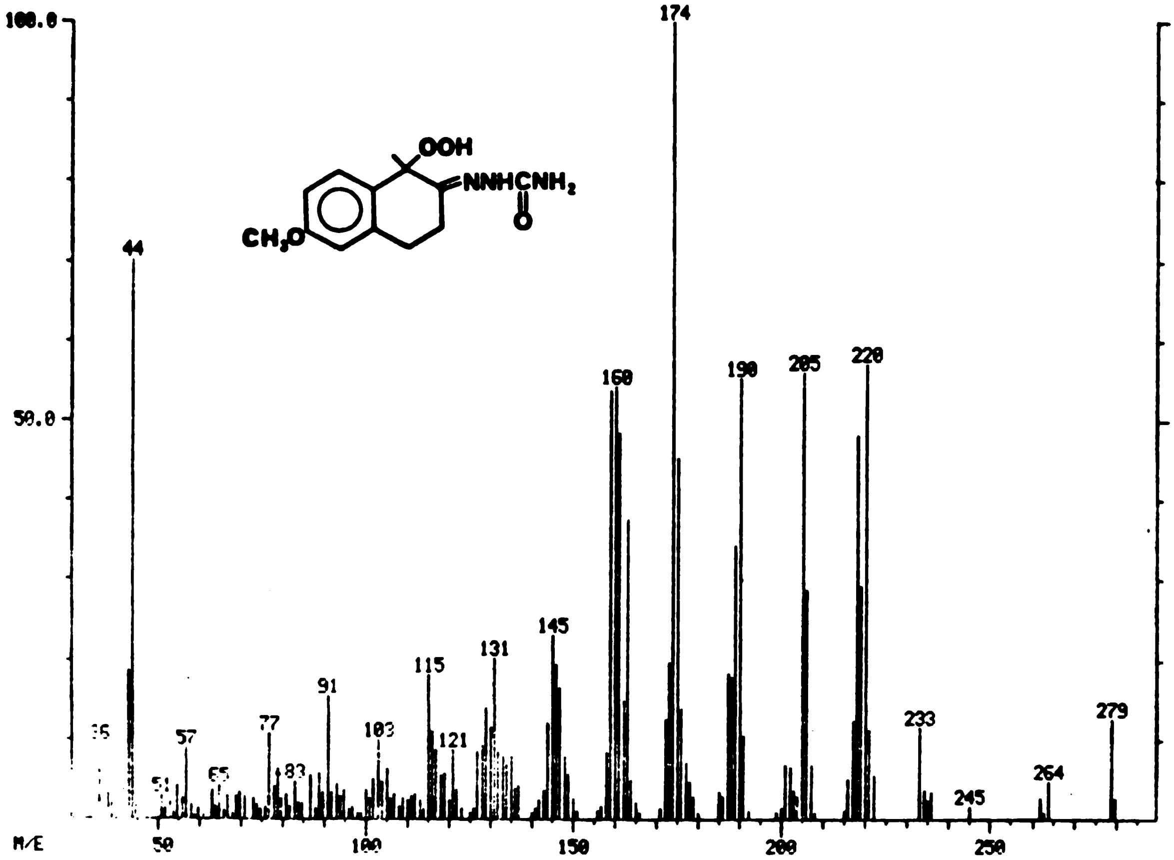


Figure 68. Mass spectrum of 53.

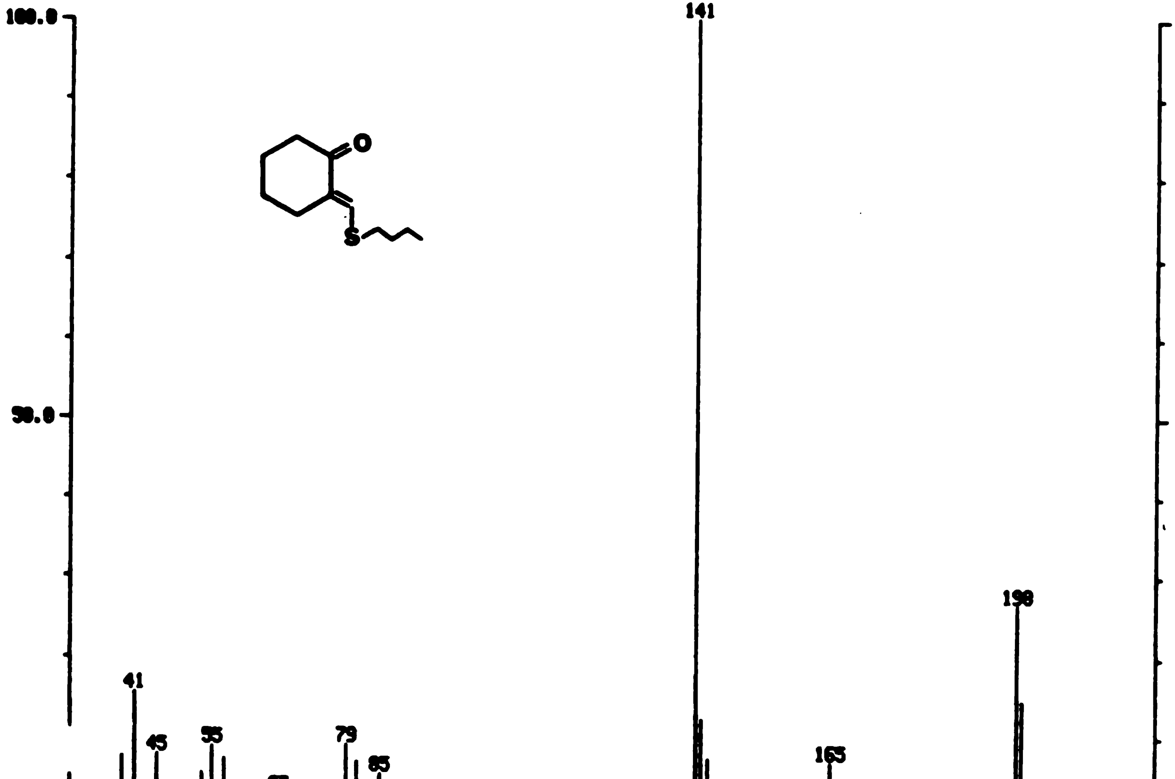


Figure 69. Mass spectrum of 60b.

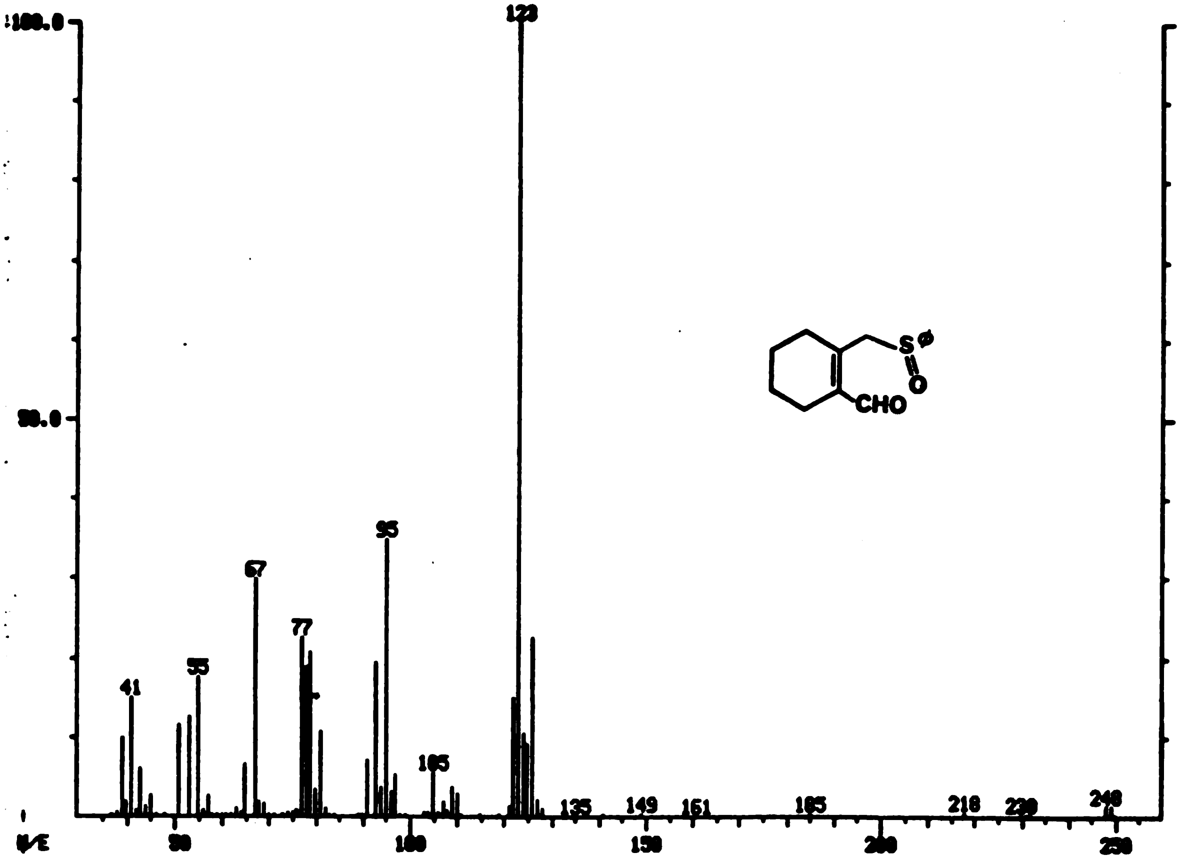


Figure 70. Mass spectrum of 61.

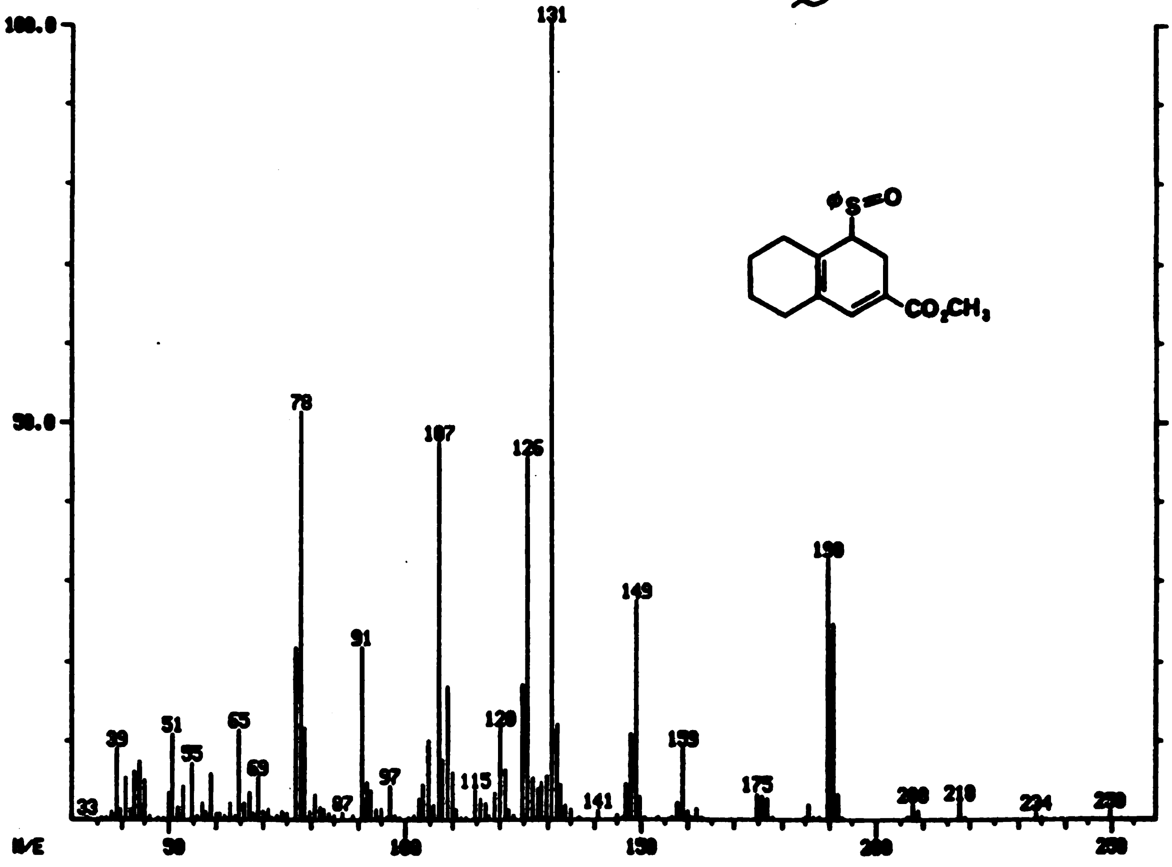


Figure 71. Mass spectrum of 62.

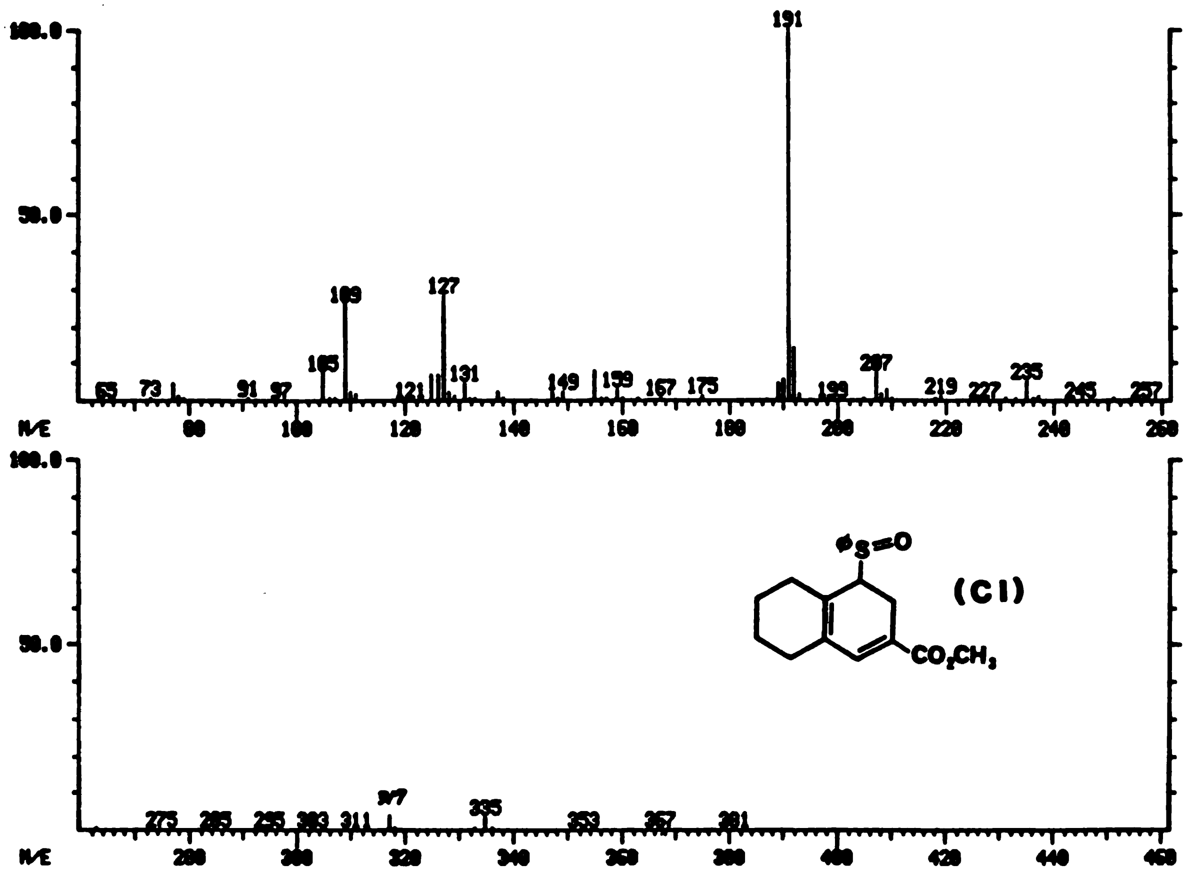


Figure 72. Mass spectrum of 62 (CI).

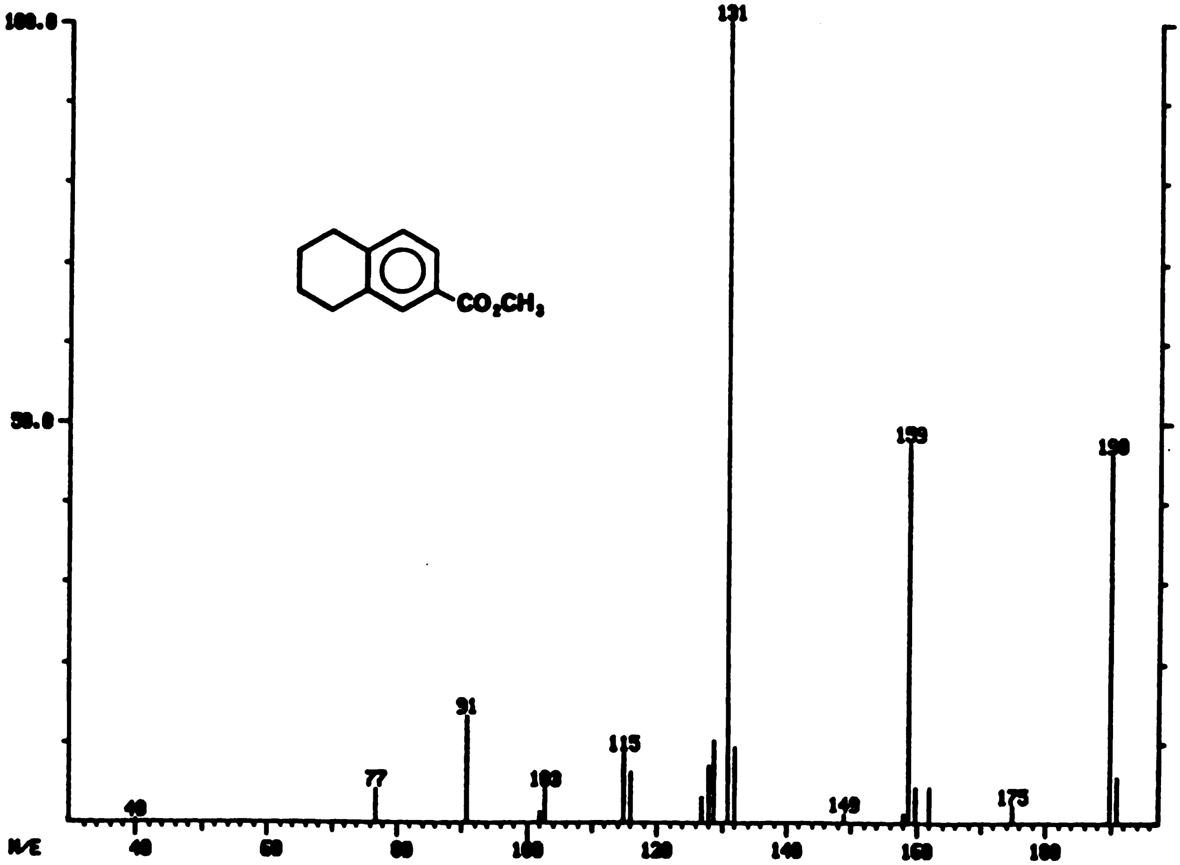


Figure 73. Mass spectrum of 63.

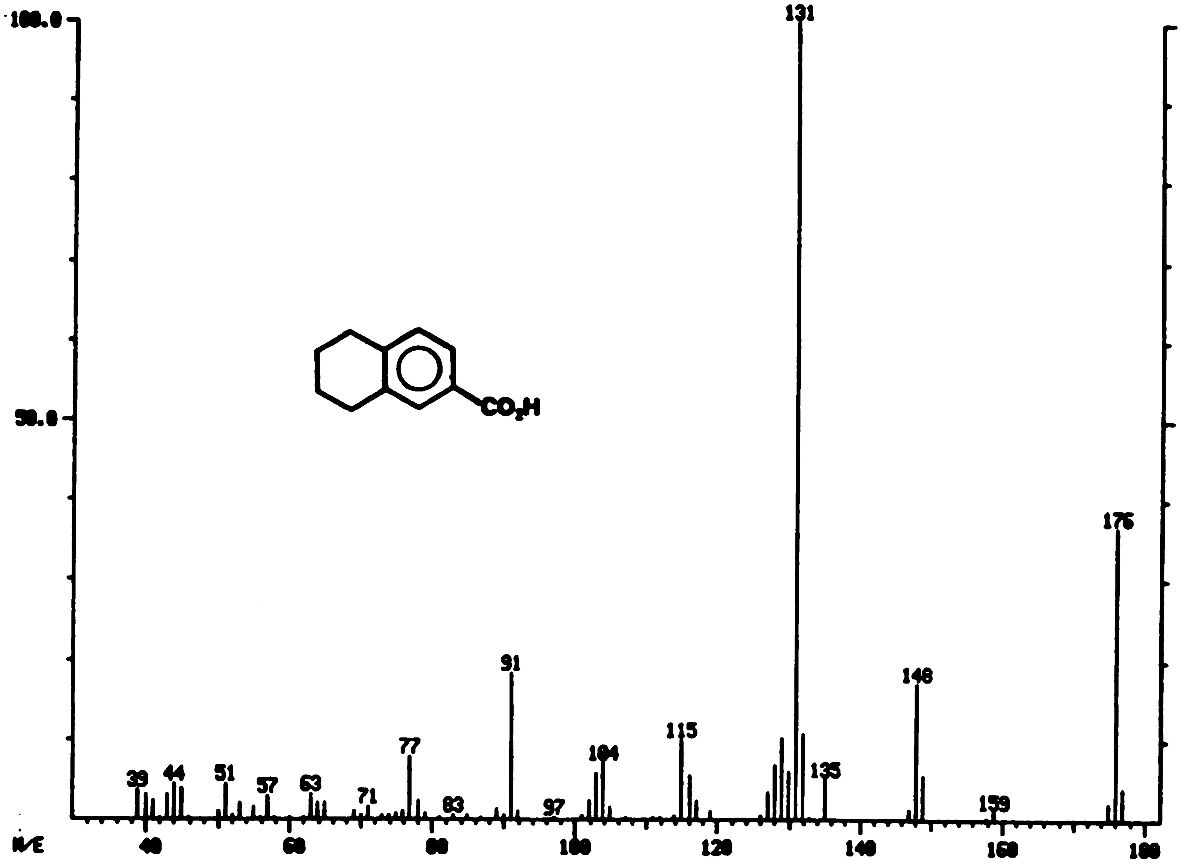


Figure 74. Mass spectrum of 65.

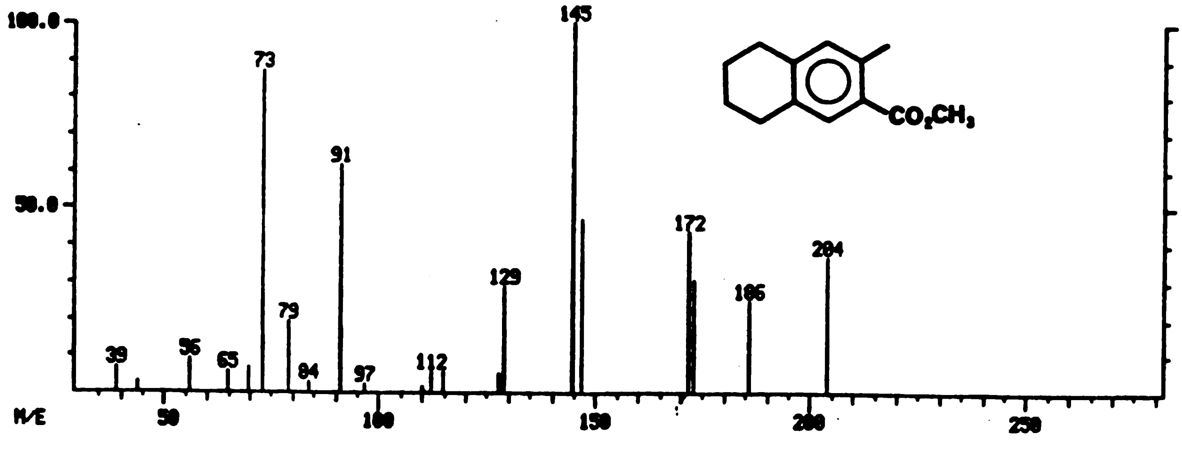


Figure 75. Mass spectrum of 68.

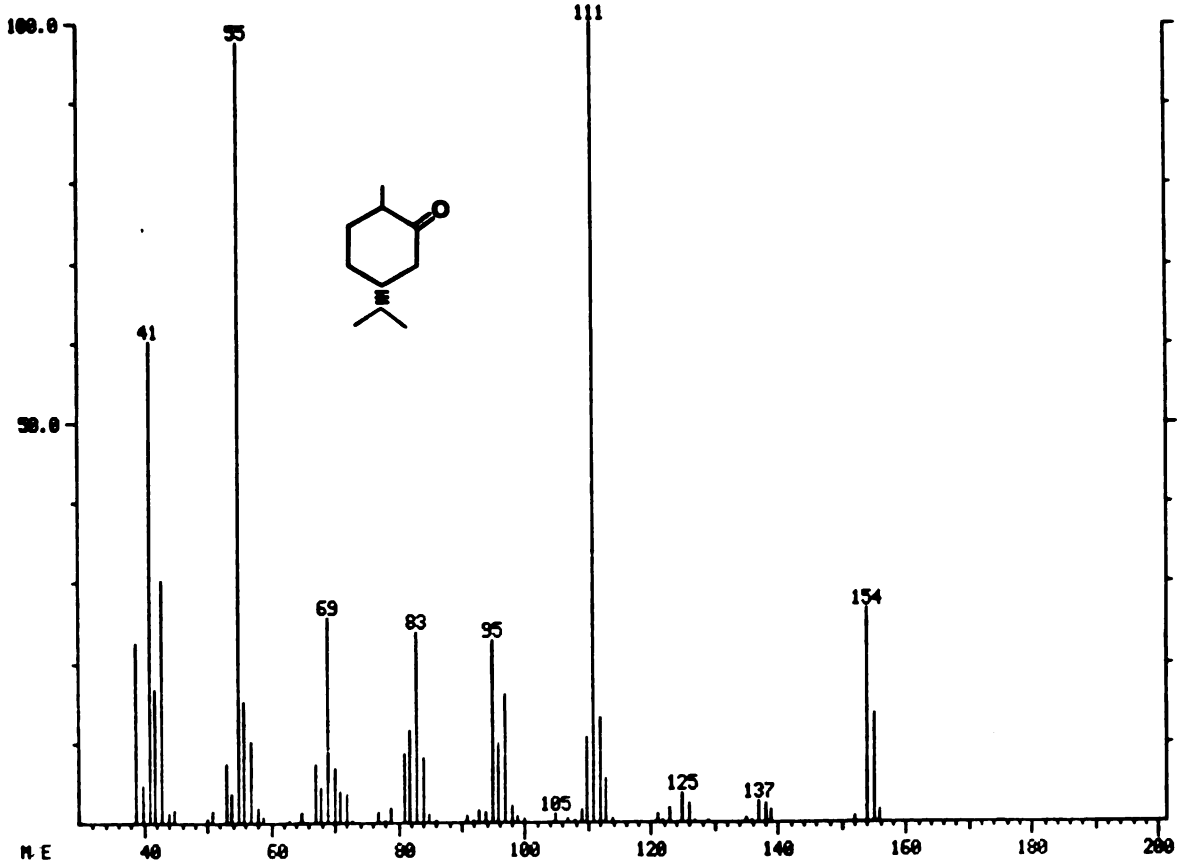


Figure 76. Mass spectrum of 73.

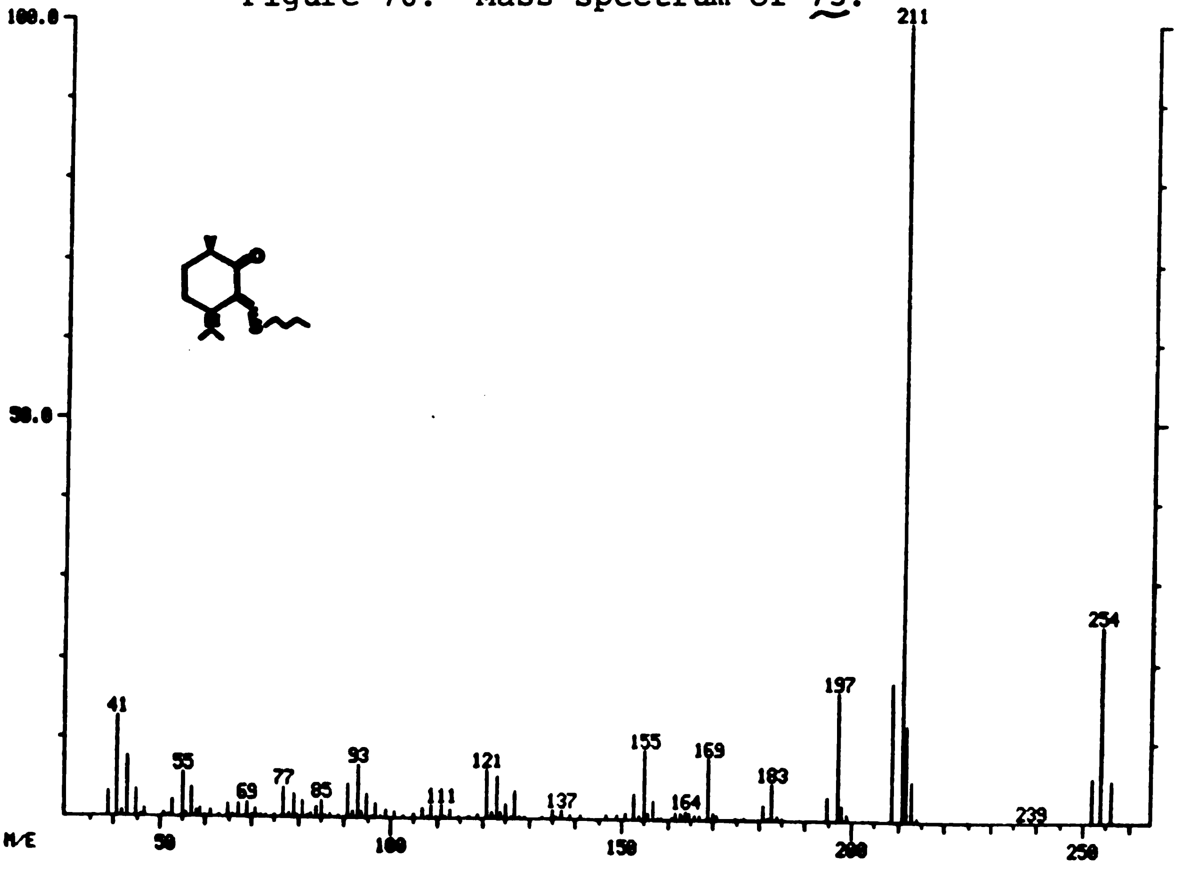


Figure 77. Mass spectrum of 75b.

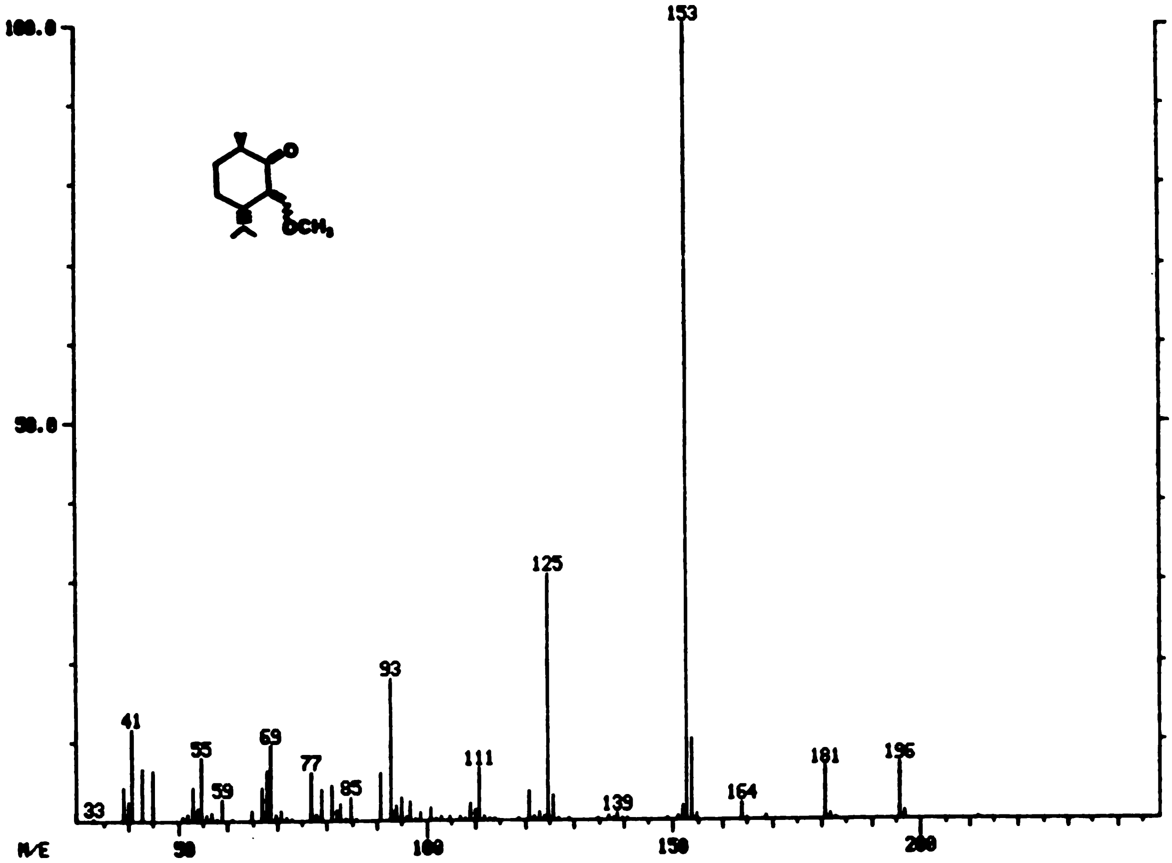


Figure 78. Mass spectrum of 75c.

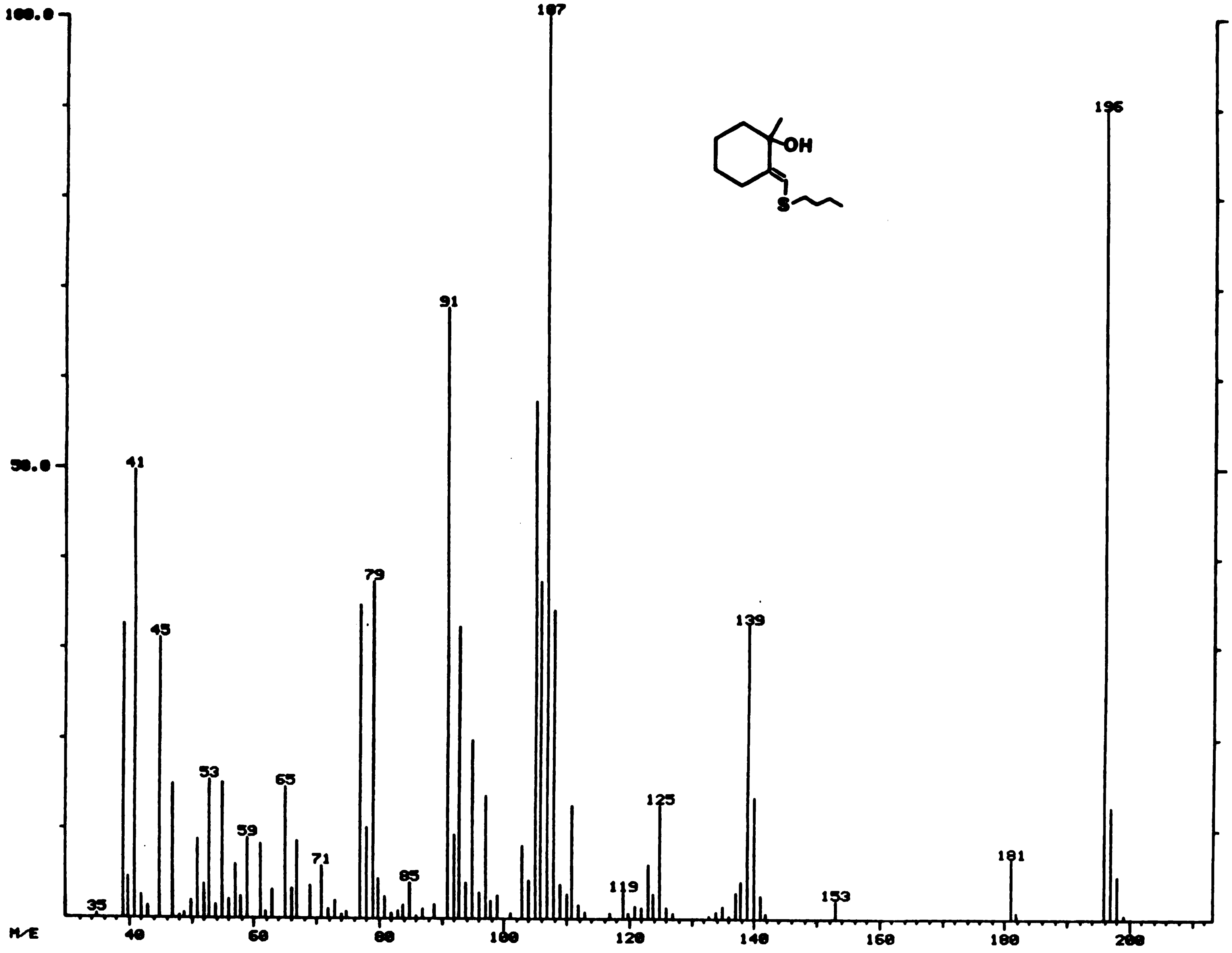


Figure 79. Mass spectrum of 80.

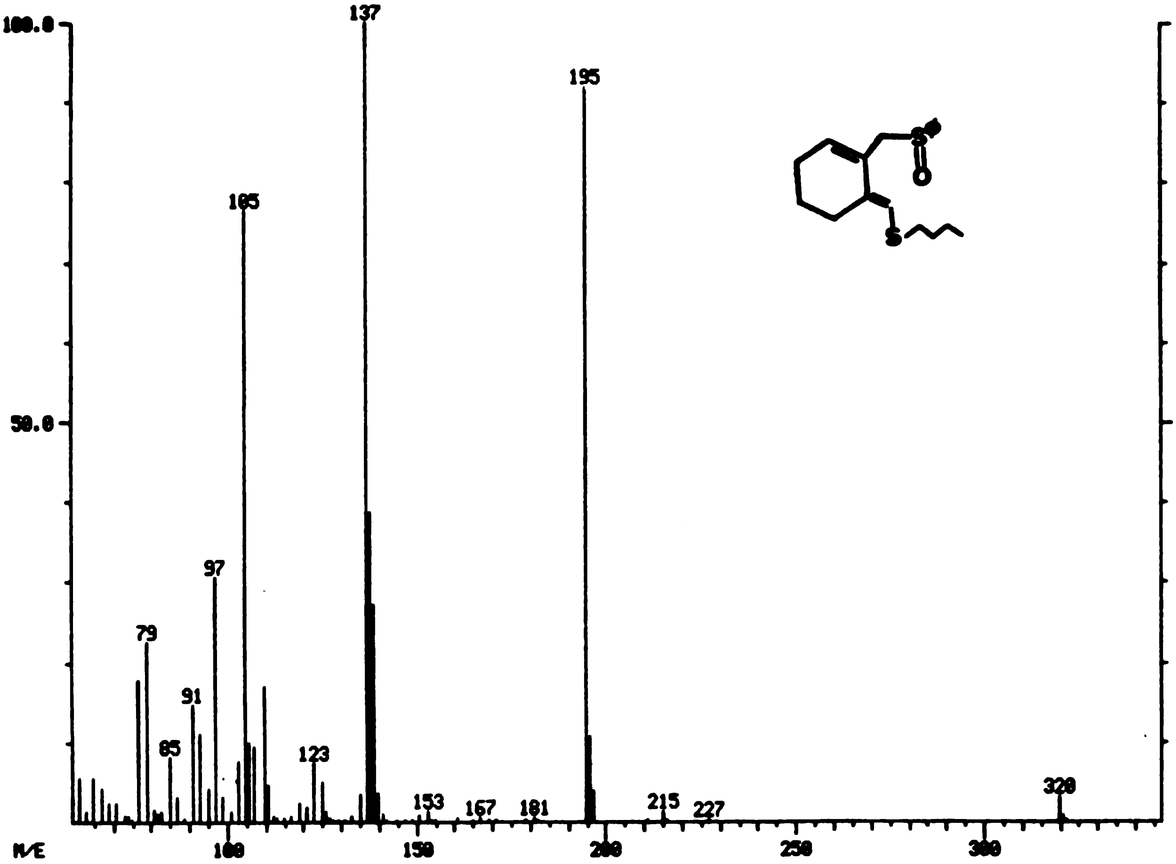


Figure 80. Mass spectrum of 83.

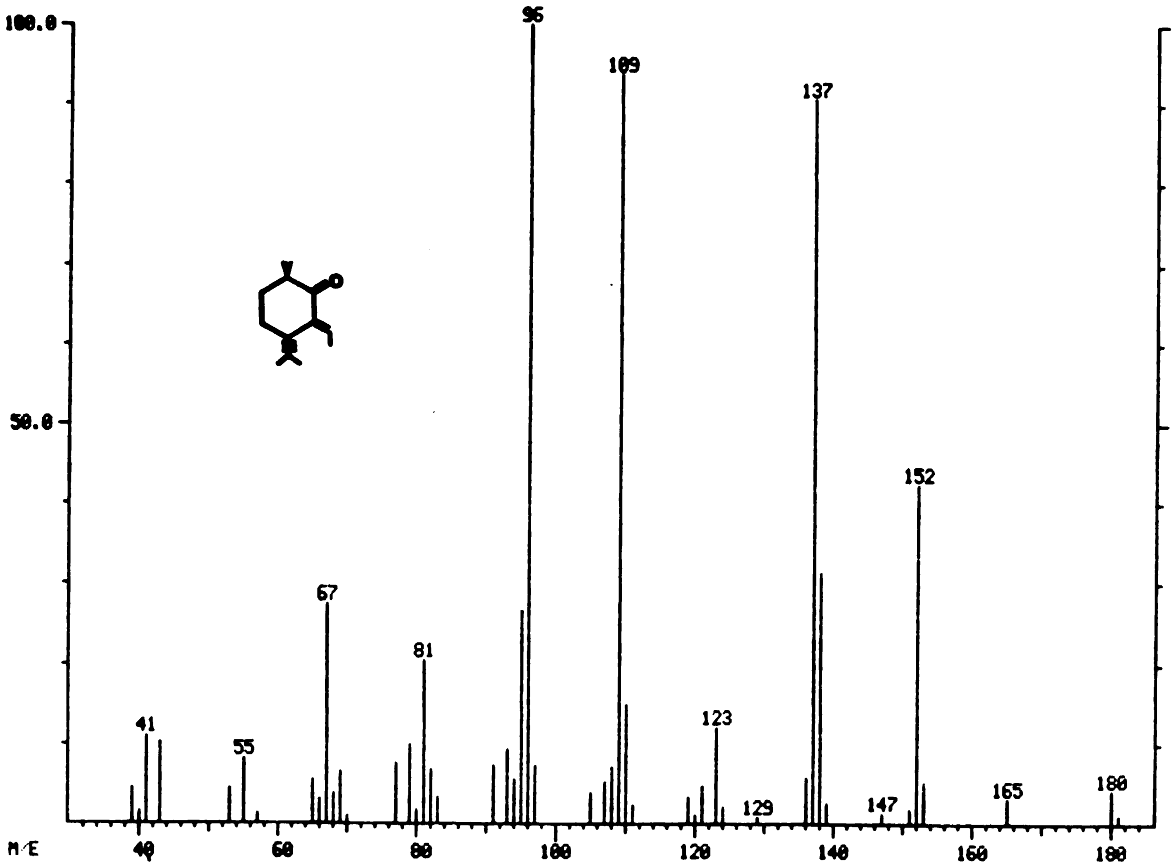


Figure 81. Mass spectrum of 85.

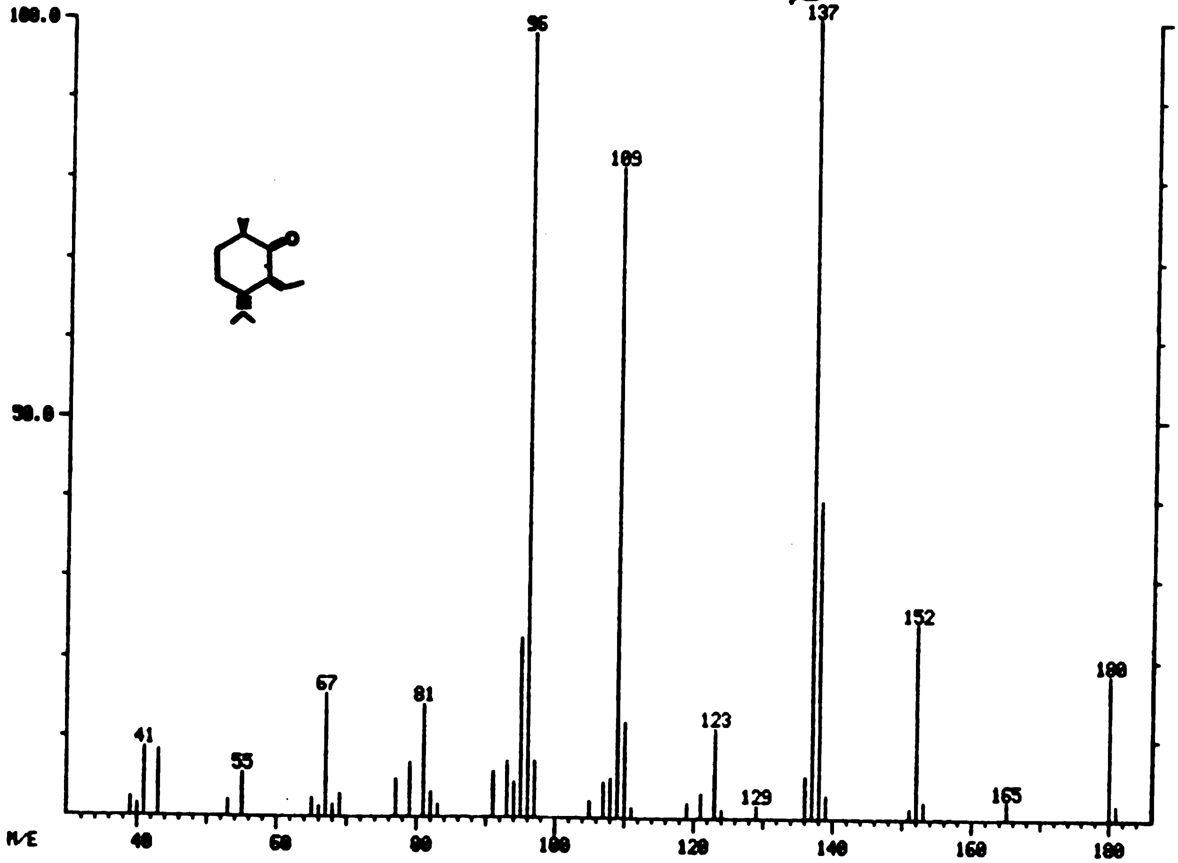


Figure 82. Mass spectrum of 86.

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