CHIRAL α-SUBSTITUTED SULFOXIDES: LIQUID CRYSTALS AND POTENTIAL ANTICANCER AGENTS

By

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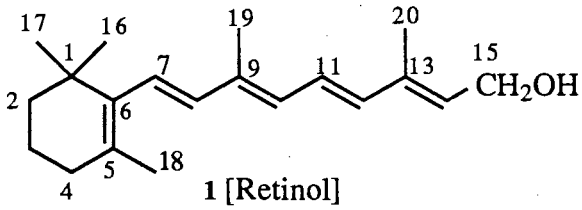
CHAPTER I

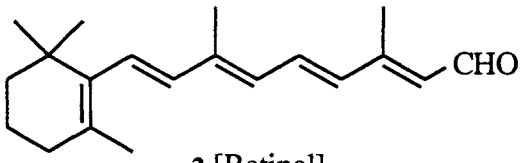
HISTORICAL

Introduction

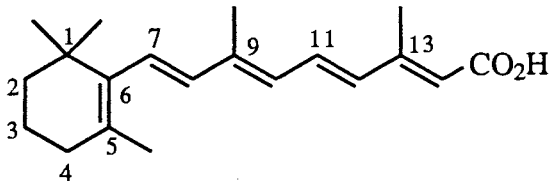
Retinoids are natural (like **1-6**) and/or synthetic derivatives like **7-11** of vitamin A (retinol-**1**). Although vitamin A and analogs are known to be involved in fetal development as well as in regulation of proliferation and differentiation of cells throughout life, it is the



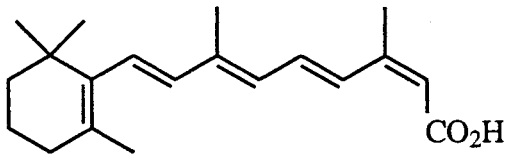
1 [Retinol]



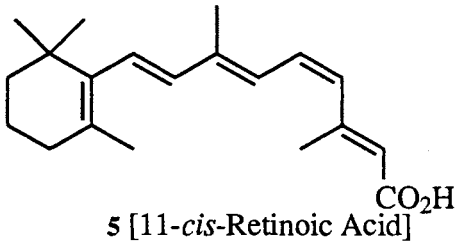
2 [Retinal]



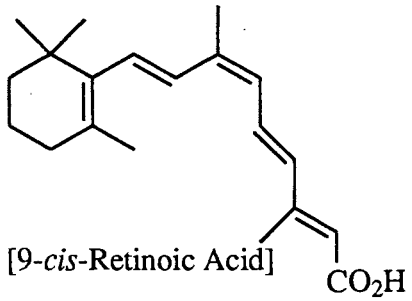
3 [all-*trans*-Retinoic Acid]



4 [13-*cis*-Retinoic Acid]

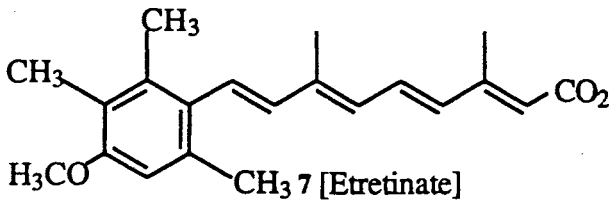


5 [11-*cis*-Retinoic Acid]

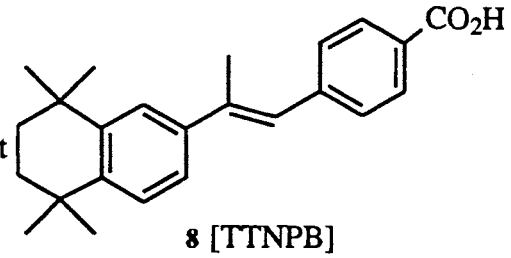


6 [9-*cis*-Retinoic Acid]

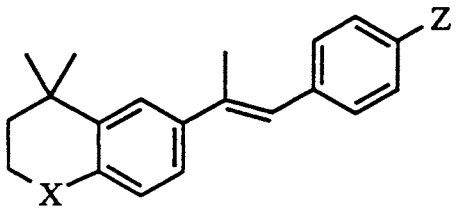
activity of vitamin A as a potent anticancer agent which first led to the immense interest and subsequent development of retinoids.[52] Toxic side effects exhibited by retinol (**1**) and its naturally occurring derivatives, retinal (**2**) and retinoic acid (**3**), led to structural modifications and development of more active aromatic retinoids (arotinoids; **7**, **8**) with variable toxicity.[10,34] Additional modification via substitution of C-4 in **3** by a heteroatom (O, S, N) has produced both potent but less toxic derivatives known as heteroarotinoids (**9** and **10** are common examples)[11, 62]



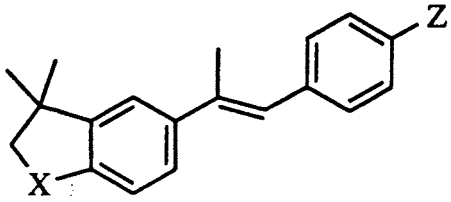
7 [Etretinate]



8 [TTNPB]

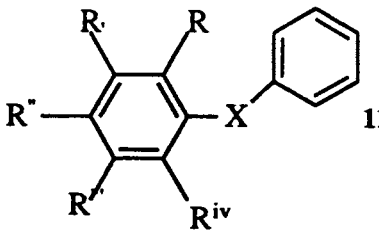


9 [X = O, S, SO_2, NR
Z = CO_2H, CO_2Me, CO_2Et]



10 [X = O, S, SO_2,
Z = CO_2H, CO_2Me, CO_2Et]

Retinobenzoic acids **11**, although structurally and physically very different from conventional retinoids, are a series of benzoic acid derivatives with potent retinoid



11 [X = NHC(O), C(O)NH, C(O)CH=CH, N=N]

action.[27] Note that a variety of ring-bridging groups have been used.

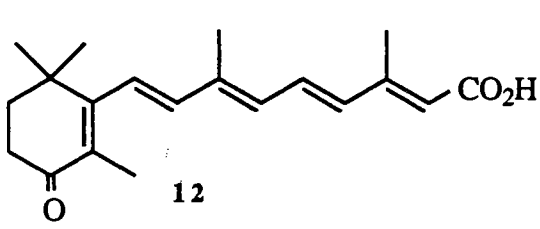
The recent discoveries of retinoic acid (**3**) as a morphegen and that retinoic acid/retinoid receptors exist has sparked a new interest in structure-activity relationship of retinoids.[42]

Retinoids have now been redefined (in a biological sense) as substances that elicit specific responses [this refers to a specific activity of retinoic acid (**3**)] through binding to a specific receptor.[52] It has been found that retinoic acid/retinoid receptors respond differently to various forms of retinoic acid/metabolites.[31,42] Thus, it is important to study the different metabolic pathways and metabolites in order to understand the specificity of action of specific retinoids.

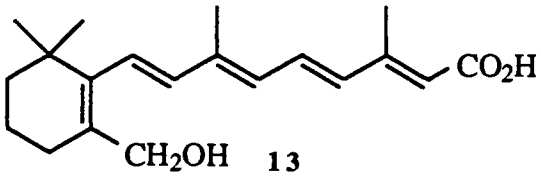
Metabolism of Retinoic Acid

Studies of metabolites of retinoic acid (**3**) have shown that degradation takes place by two possible pathways - oxidative and non-oxidative.[12,17] Both are discussed below, with some exmples of metabolites found in humans.

Oxidative Pathway.[17] The oxidative metabolism of retinoic acid (**3**) includes



12



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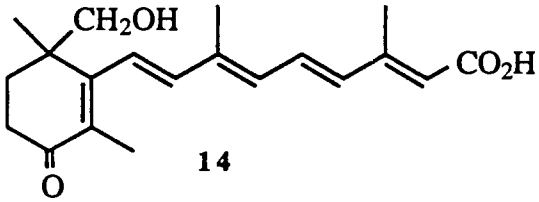

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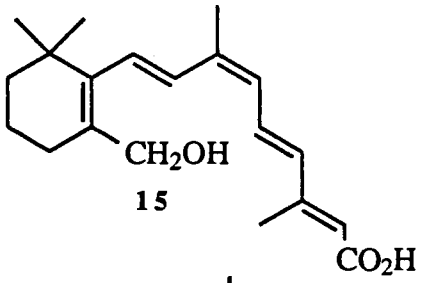

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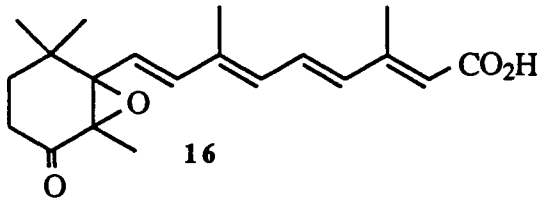
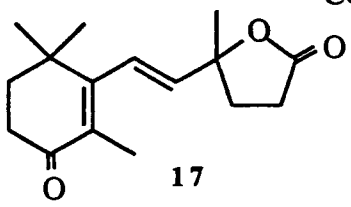


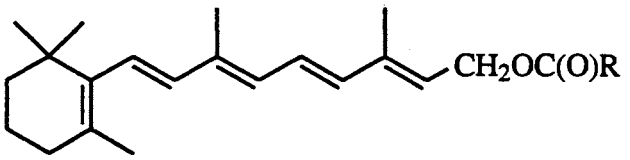
16



17

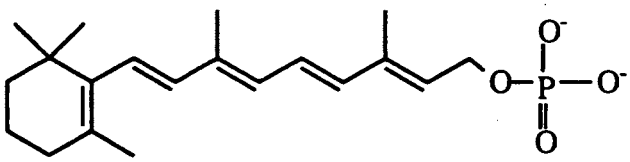
the oxidation of C-4 [as in **12**,**14**, **16**, **17**], oxidation of the methyl groups on the cyclohexenyl ring [as in **13**, **14**, **15**], epoxidation of C(5)-C(6) double bond [as in **16**] and shortening of the side chain [as in **17**]. These data are from studies on rats[45] and humans.[22]

Non-oxidative Pathway.[12,17] A non-oxidative pathway has been reported for retinol (**1**) which, in the presence of fatty acyl-CoA: retinol acyltransferase, forms esters with long chain fatty acids [as in **18**, **19**], phosphates [as in **20**], and mannosyl phosphates [as in **21**]. These studies were conducted in rats.[18] Retinol palmitate is stored in the liver.[46]

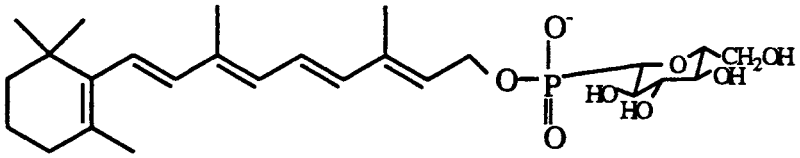


18 [Retinyl palmitate, R = $(CH_2)_{14}CH_3$]

19 [Retinyl stearate, R = $(CH_2)_{16}CH_3$]



20 [Retinyl phosphate]



21 [Retinyl-β-mannosylphosphate]

Isomerization.[17] All *trans*-retinoic acid (**3**) is isomerized to the 13-*cis*-isomer **4** and 9-*cis*-isomer **6**. The 9-*cis*-isomer **6** has been recently identified as a ligand for a novel retinoic acid response pathway.[4,31]

Structure-Activity and Structure-Toxicity Relationships and Rationale For The Synthises of Retinoic Acid Analogs

The undesireable toxic effects[50]and inadequate tissue distribution of naturally occurring retinoids, which prevent retinol (**1**) from reaching the desired target sites, led to the synthesis of modified retinoic acid analogs[50] (Table I).[11] Specific parts (the hydrocarbon ring, the polyene side chain, and terminal polar group) of the retinoic acid molecule were targeted for modification in order to identify new structural features that would increase activity while decreasing toxicity. For example, prevention of oxidation at C-4 by methylation and of the side chain by retaining the major skeletal features in a aromatic ring, as expected, deactivated the major oxidative metabolic pathways of vitamin A (**1**).[34] The polar end group is important also in controlling metabolic pathways as evidenced by the fact while retinol (**1**) is stored in the liver, the carboxyl analog **3** is not.[51]

Replacement of the hydrocarbon ring by an aromatic ring was found to increase potency.[34] Substitution by a tetrahydronaphthyl moiety further increased the activity.[10,34] Indeed, the most active retinoid found is TTNPB (**8**), but it is also by far the most toxic (Table II).[34] Studies of TTNPB (**8**) showed that the presence of the methyl groups was essential for activity, but toxicity was increased via a decrease in the hydrophilicity which was suggested to disrupt transfer profiles.[34] Retinoids are transported *in vivo* by various proteins, and thus any change in structural features that would prevent binding of a retinoid to such proteins would cause accumulation of the retinoid in certain tissues.

The structure below illustrates that the arotinoids (like **7** and **8**) can still be regarded as retinoic acid derivatives containing a carbon skeleton in a rigid conformeric fixation.

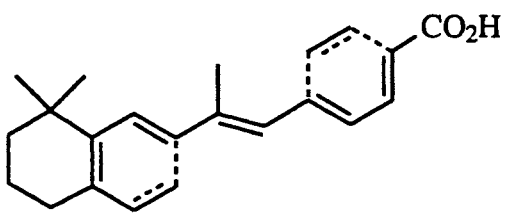
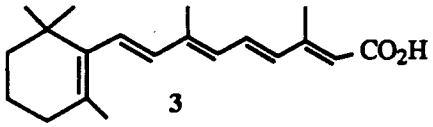
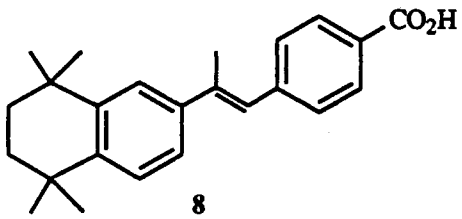
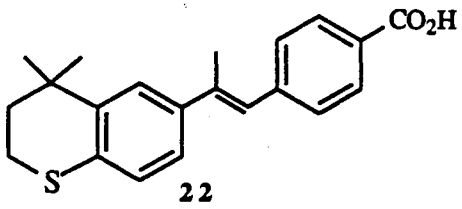


TABLE I

Structure-Toxicity and Structure-Activity Relationships of Selected Retinoids[a]

Retinoid	Toxicity		Activity
	Dose $\mu mol\ kg^{-1}day^{-1}$	Survivors Day 15	TOC Assay[b] [ED_{50}[c]]
 3	300	0	1×10^{-11}
 8	100	0	1×10^{-12}
 22	100	100	5×10^{-11}

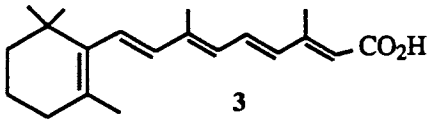
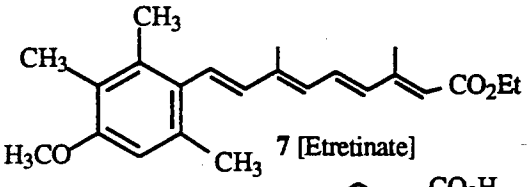
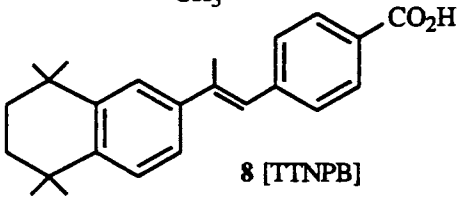
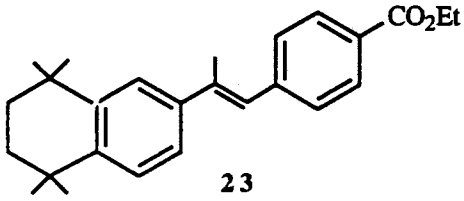
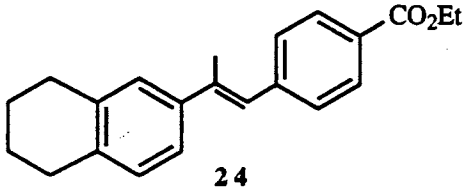
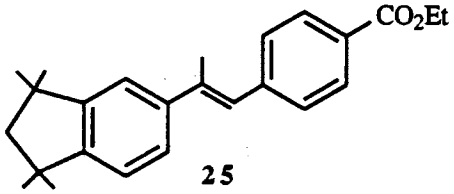
[a]Reference 11.

[b]Tracheal organ culture assay, reference 16.

[c]ED_{50} refers to the molarity of the retinoid required to effect reversal of keratinization in 50% of the cultures.

TABLE II

Structure-Activity Relationships of Selected Arotinoids[a]

Retinoid	Papilloma avtivity [ED_{50},[b] mg/kg]	Hypervitaminosis A dose[c] [mg/kg]	Therapeutic Index[d]
 **3**	400	80	5
 **7** [Etretinate]	50	200	0.25
 **8** [TTNPB]	>0.8	>0.1	>0.8
 **23**	0.05	0.1	0.5
 **24**	200	200	1
 **25**	<0.2	<0.2	1

[a]Reference 11.

[b]ED_{50} refers to dose (mg/kg) that causes 50% regression of skin papillomas in Swiss mice.

[c] Lowest daily dose causing hypervitaminosis A in a 2-week period.

[d]Therepeutic Index = The ratio of dose (mg/kg) that induced 50% regession of papillomas in Swiss mice to that of the dose (mg/kg) which induced hypervitaminoses.

High potencies are exhibited when the terminal polar function is a carboxyl group, although methyl and ethyl esters also show good activity.[11] It should be noted that toxicity of natural retinoids is mainly due to the propensity of the liver to sequester and accumulate retinol as retinyl esters which can result in severe hepatatic dysfunction.[33] This accumulation also likely prevents retinoids from reaching intended target sites. While retinal (**2**) could be converted to both retinol (**1**) and retinoic acid (**3**), **3** cannot be reduced to **2** *in vivo*.[51]

The replacement of C-4 of TTNPB with a heteroatom, as shown by Berlin and co-workers[62] and Dawson and co-workers,[11] produced highly active but less toxic heteroarotinoids (Table III). All the data were compared to that with **3**. The heteroatom at the 4-position confers increased hydrophilicity to the molecule while at the same time preventing oxidation of the carbon atom at the 4-position.

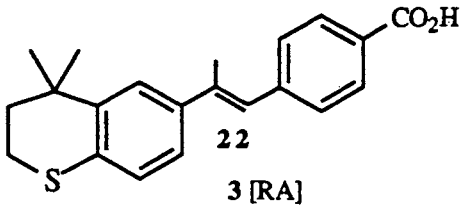
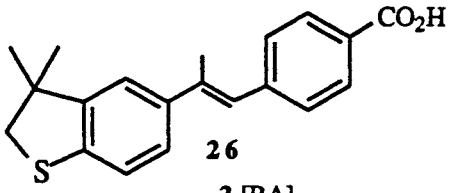
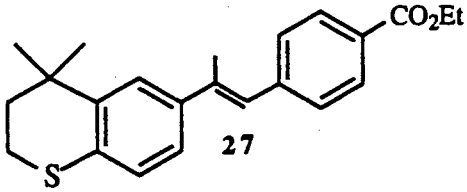
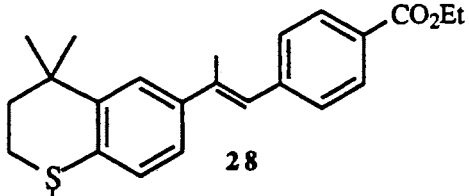
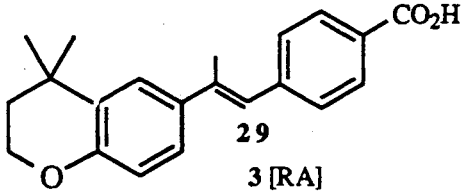
Assays

One relatively recent method to appraise retinoid activity has been via a determination of ability to induce cell differentiation.[7,16,60] Three most commonly used assays are the assessment of cell differentiation of HL-60 cells (human leukemic cell line),[7] the ODC (ornithine decarboxylase)[60] and the TOC (tracheal organ culture) (Table III) assays.[16] The recent isolation of retinoic acid/retinoid receptors allows one to measure binding abilities or specific responses [retinoid response elements are transfected with a promoter of a particular reporter gene, for example, using a promoter containing a reporter gene for chloramphenicol acetyl transferase (CAT) and measuring the CAT activity] elicited from specific retinoid receptor interactions.[35]

HL-60 Assay (*In Vitro*). Differentiated HL-60 cells, after stimulation with 12-*O*-tetradecanoylphorbol-13-acetate (TPA), a known cancer promoter, produces superoxides which change the color of a test dye (nitroblue tetrazolium) from yellow to blue.[7] Normal

TABLE III

ODC and TOC Assays of Selected Heteroarotinoids [a]

Retinoid	ODC [b] [% Inhibition of control[c]]	TOC[d] [ED_{50},[e] M]
 **22**	85	5×10^{-11}
3 [RA]	88	1×10^{-11}
 **26**	91	
3 [RA]	89	
 **27**		6×10^{-11}
3 [RA]		2×10^{-11}
 **28**		60×10^{-11}
3 [RA]		1×10^{-11}
 **29**	81	10×10^{-11}
3 [RA]	88	1×10^{-11}

[a]References 11 and 62. RA refers to *trans*-retinoic acid (3).

[b]Ornithine decarboxylase assay; reference 60.

[c]% inhibition = 100 x[activity (ODC with acetone + TPA) - activity (ODC with retinoid/-activity (ODC with acetone + TPA)].

[d]Tracheal organ culture assay; reference 16.

[e] ED_{50} refers to the dose that causes reversal of keratinization in epithelia in cultures of retinoid-deficient hamster tracheas.

HL-60 cells do not produce superoxides on teatment with TPA. Retinoid activity is measured as the amount of test retinoid required for differentiation of 50% of the cells (effective dose, ED_{50}).[7]

ODC Assay (*In Vivo*). Tumor promotion by TPA is concurrent with production of the enzyme ornithine decarboxylase.[60] A solution of the test retinoid and TPA is applied to the shaven skin of a mouse. The mice are killed at appropriate times, and a suspension of the epidermis is treated with DL-[1-^{14}C] ornithine hydrochloride. The amount of $^{14}CO_2$ released is measured. Retinoid activity (reported as ID_{50}, or the concentration at which 50% of the ODC activity is inhibited) is thus related to the ability of a test retinoid to inhibit biosynthesis of ornithine decarboxylase.[60] The greater the ability of a retinoid to promote normal cell differentiation the smaller the amount of CO_2 released.

TOC Assay (*In Vitro*). The reversal of keratinization of cells is correlated with the ability of a retinoid to initiate normal cell differentiation.[16] Hence, the activity of a retinoid (ED_{50}) is measured in terms of concentration required for reversal of keratinization in 50% of the cells from a tracheal organ culture of vitamin A starved hamsters.

Retinoid Response Mechanism in Gene Regulation

Retinoic acid (**3**) and its analogs affect a wide array of biological processes. Retinal (**2**) participates in the visual cycle in association with the protein opsin.[41] Retinol (**1**) maintains reproduction by causing the proper development of the germinal epithelium [rats (both male and female) fed on low diets of retinol (**1**) showed disordered reproduction].[58] Retinoic acid (**3**) is essential fo normal cell growth and differentiation of many epithelial cell forms.[13]

Although retinoic acid (**3**) has long been known to be directly involved in certain gene expression, it is only recently with the discovery of nuclear retinoid receptors, through which retinoic acid/retinoid action is proposed to be mediated, has a mechanism of action been suggested.[14,42] These receptors are suggested to act as transcription activators by

binding resultant ligand-receptor complexes to specific nucleotide sequences in the response elements of the target genes.[14]

Retinoic acid/retinoid receptors show homology to a super family of steroid and thyroid hormone receptors and regulate gene expression by a similar ligand-dependent mechanism.[35,47] Two distinct types of nuclear receptors have been identified, namely retinoic acid receptors (RARs) and the retinoid X receptors (RXRs), both of which have three distinct subtypes, RARα, –β, –γ and RXRα, –β, –γ.[14,42] Classification of the subfamilies is based on:[4]

1) amino acid structure,

2) responsiveness to different naturally occurring and synthetic retinoids, and

3) ability to modulate expression of different target genes.

Thirty members of the nuclear receptors have been identified.[42] Little variation is found among the different subtypes in the linear arrangement of the modular structure which comprises six domains (Figure 1).[14,42] Region C, the DNA binding domain, and Region E, the ligand binding domain, are apparently the most important in gene transcription. A study of RARs during mouse development has shown that although RAR expression is widespread among developing organs and tissues, the subtypes are restricted in a tissue

Figure 1. The Basic Linear Organization of Retinoic Acid Receptor Functional Domains.

A-B - Cell and promoter specific activation function

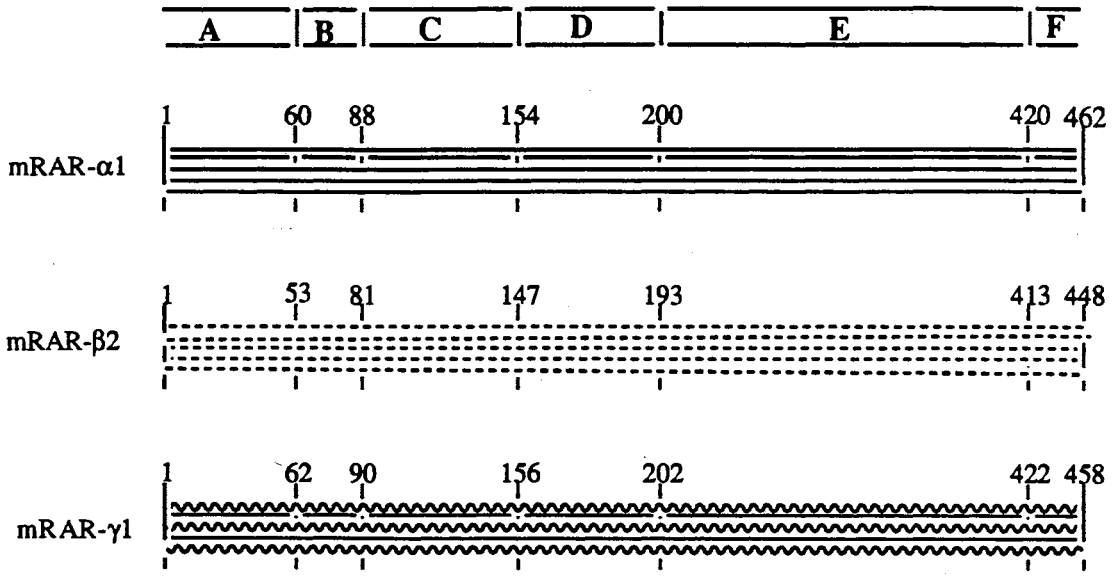
C - DNA binding

D - Hinge Region

E - Ligand Binding

F - Dimerization

specific manner.[14,42] For example, skin is an important target for retinoic acid (3) and it is the subtype RARγ which is predominantly expressed in this region.[14,42] In the tracheal epithelium, retinoic acid RARβ is the most predominantly expressed subtype.[14,42] This implies that each subtype performs different functions.



	A	B	C	D	E	F
% Homology						
α1/β2	18	79	95	74	90	20
α1/γ2	25	75	95	72	85	16
β2/γ1	16	86	95	61	90	23

Figure 2. Homology Comparison of Mouse RAR Subtypes with Each Other.
The primary amino acid sequences, numbered above the protein structure, have been aligned on the basis of identity. The data under the diagram indicates the percentage of homology between the subtypes.[42]

Structural and Functional Domains of the RARs

The DNA Binding (C) Domain. The C region is the most highly conserved in all cell types examined, showing 93-95% identity of the amino acid sequence (Figure 2) involving RARs α,β,γ.[14,42] This region of the protein comprises 166 amino acids with 8 cysteine residues which are bound to two zinc atoms to form two "zinc fingers". It is the two zinc fingers which interact with the specific DNA responsive elements *upstream* of the target gene for retinoid action. Mutational analysis of the C region has confirmed its action as the DNA binding domain.[14] However, it was shown that the binding of the ligand (retinoid) was not altered in the mutants since the binding of the ligand was dependent on the E region, the ligand binding domain.[14] Nevertheless, interaction of the C region of the receptors with the ligand response element is essential for the transcriptional activities to occur. This similarity in the degree of amino acid identity between physiologically unrelated receptors in the DNA binding region (Figure 2) implies conservation of function. Another important similarity is the remarkable conservation of the C region. Comparing zebra fish RARγ and mouse RARs illustrates that the basic function of retinoic acid (3) in gene function has remained unchanged for many years.[42] Comparison of the amino acid

TABLE IV

% homology Comparison of Each RAR Subtype Between Mouse (m) and Human (h)[a]

% Homology	A	B	C	D	E	F
hα1/mα1	98	100	98	98	99	90
hβ2/mβ2	94	100	100	98	99	92
hγ1/hγ2	98	100	100	100	100	58

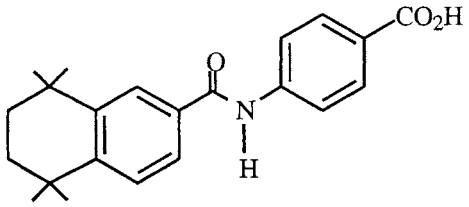
[a]Reference 14

content of the human RARs with mouse RARs also showed that the interspecies conservation of the RAR sub-family is much higher than that of conservation of all three receptors within a given species (Table IV).[14]

The Ligand Binding (E) Domain. As in the DNA binding domain, the three RARs, while showing subtle differences between the three RAR subtypes in a given species, shows remarkable interspecies conservation, (85-90%, Figure 2) This is again postulated to be indicative of specific functions regulated by the three different subtypes. The ligand binding region is involed in three main funtions, namely:[42]

1) ligand binding,
2) receptor dimerization, and
3) trancription activation.

These functions were demonstrated to be ligand dependent. It was found that the retinoid binding capabilities of the RARs were different. For example, human RARα required five times as much as retinoic acid (**3**) for activation as compared to RARβ. In contrast, RARγ was found to show the highest affinity for retinoic acid (**3**). Interestingly, retinobenzoic acid (**30**, a synthetic retinoid) showed preference for RARα over RARβ.[42] Such ligand selectivites exhibited by RARs encourages the syntheses of ligands with specific characteristics eliciting specific responses.



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Regions A, B, D, F. The N terminal region of the receptor, that is the A/B regions in Figure 2, shows cell and promoter specific transcription activation functions.[14,42] Studies with hormone receptors have demonstrated that regions important to transcriptional

activation are found in the A/B domains (Table IV) as well as in the ligand binding domain. However, the A/B region can function independently of the ligand region while E activation is ligand dependent.[42]

The F region, along with DNA binding and ligand binding regions, plays an imporatnt role in receptor dimerization.[14,32] Dimerization in this instance refers to the creation of combinations like RAR-RXR, for example. Formation of dimers was found to be an essential step in any trancriptional regulation in this superfamily of receptors.[32] It has been found that RAR-RXR heterodimers bind more effectively to RAREs than do homodimers of the either receptors.[32,35] RARE refers to "retinoic acid receptor element" which is a short DNA sequence found *upstream* of a target gene. The most variable regions among the RARα, –β, and –γ are the A and F regions. While region B, like regions C and E, shows remarkable conservation (79-86%) between the three RARs in a given species, region D shows 61-74% conservation, implying that regions A, D, and F contribute funtional distinction even though the role of region D is yet to be fully delineated.[14]

Retinoid X Receptors (RXRs)

The second family of retinoic acid active nuclear receptors are called RXRs and mediate cellular responses to retinoids.[35] RXRs, in some case, appear to be activated by 9-*cis*-retinoic acid (**6**).[4] Unlike the RARs, which showed limited expression in the adult, RXRs were found to be highly expressed in the liver which is a major site for vitamin A storage, metabolism, and mobilization. RXRs have also been discovered to occur extensively with CRBP (cellular retinol binding protein) expression.[19] Hence, RXRs are suggested to be involved in vitamin A metabolism.[19] The first isolated RXR, the human hRXRα, though still a member of the steroid/thyroid hormone receptor superfamily, did not exhibit any significant homology to RARα, –β or -γ in the retinoic acid binding (E) domain (Figure 3).[42] This suggested an evolutionarily distinct retinoid acid response pathway. However, similarity in the DNA binding (C) domain of the RXRα to the RARs implied that the

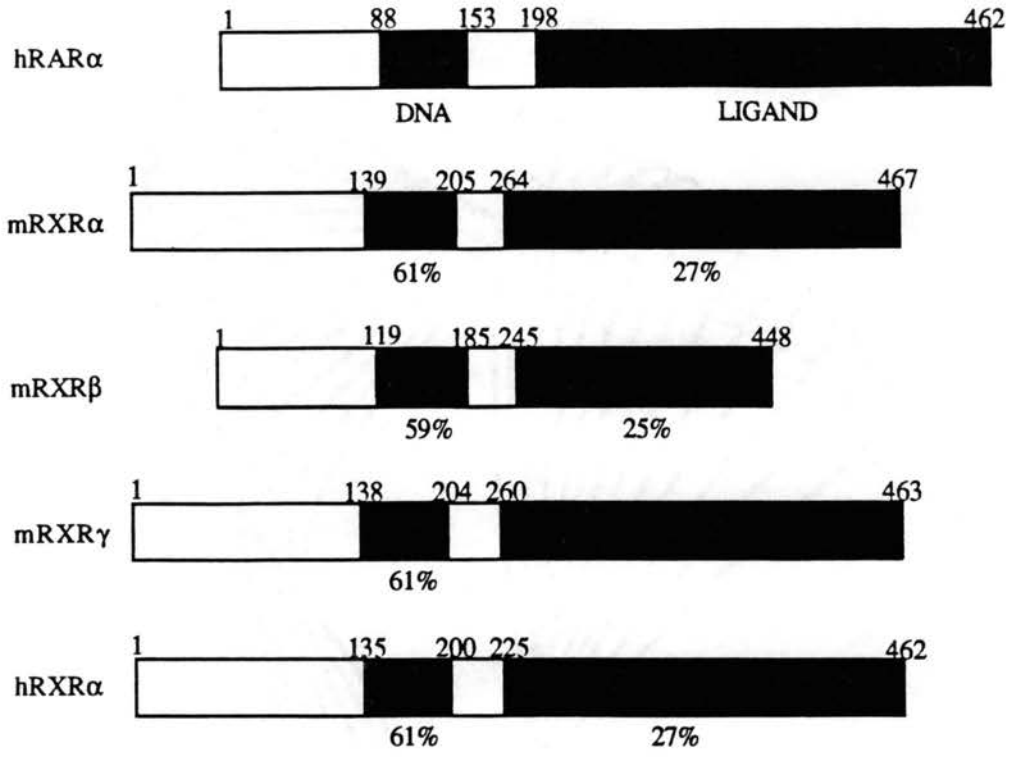


Figure 3. The Retinoid X Receptor (RXR) Family.[42]

Comparison of the amino acid sequence homology in the DNA binding region and ligand binding region between human RARα and mouse RXRα, –β, and –γ and human RXRα. Sequence comparison between the RXRs indicated almost complete conservation of DNA- and ligand-binding regions.[35, 42]

former might recognize common regulatory sequences (Figure 3).[42, 47] It has already been proven that both RXR and RAR activate transcription through the pallindromic thyroid hormone response element.[32] Hence, it was suggested that RXR was likely to regulate a partially overlapping set of RAR responsive genes, and RXR was assumed capable to mediate some of the developmental effects of retinoic acid (**3**).[35] Transcriptional activation by hRXRα was found to be less sensitive to retinoic acid (**3**) and TTNPB (**8**) than hRARα for retinoic acid (**3**) and **8**, suggesting that although RXRα is also activated by **3**, it might be specific for a species (a closely related metabolite or a structural analog of retinoic acid)

other than retinoic acid.[42, 47] Interestingly, 9-*cis*-retinoic acid [**6**, a metabolite of all *trans*-retinoic acid (**3**)] was found to bind RXR with a higher affinity than all-*trans* retinoic acid (**3**).[4,42]

At least two responsive elements that confer different regulation by RARs and RXRs have been identified.[32, 42] One is located in the CRBP-II gene which transcripts the protein required in the movement of vitamin A across the intestine wall. It was also found that although both RAR and RXR can bind to this responsive element, only RXR can activate receptor gene expression.[35b] Another is apolipoprotein A1, a gene which encodes a plasma protein involved in lipid tranfer.[42] Again the promoter, while binding strongly to RXRα, can only bind weakly to both RARα and RARβ.[42]

Retinoic Acid Responsive Elements (RAREs) and Retinoid X Responsive Elements (RXREs)

All the nuclear RARs are ligand-dependent transfer factors, that is they (the retinoic acid-RAR complex) regulate gene expression by interaction with RAREs in the vicinity of the target gene.[14,32] Responsive elements are short DNA sequences (hormone receptor elements or enhancers) which are required for the action of a given class of nuclear receptors.[42] The minor changes in receptor subtypes are postulated to target subtle changes in responsive elements with specific functions. All the responsive elements responding to receptors of the steroid/thyroid super family consist of the repetition of a core motif, AGGTCA (or a related motif), in different configurations with respect to both the orientation (direct or inverse repetition) and the spacing of the two motifs. The specific recognition of response elements by a given receptor is dependent on the actual sequence, orientation, and the spacing (the number and identity of the nucleotides) of the two motifs.[14,32] As can be seen from Figure 4, RAREs have a direct repeat motif separated by five nucleotides. The spacing base pairs between the repeating core motifs are in italics. The same direct arrangement, when separated by three nucleotides, was specific

Type	Nucleotide Configurations
1. RARE (mouse RARβ E)	GGTTCA *CCGAA* AGGACA
2. RARE (human RARβ E)	GGTTCA *CCGAA* AGTTCA
3. RXRE (rat CRBP-II E)	GCTGTCA *C* AGGACA *C* AGGACA
4. VDRE (rat osteocalcin E)	GGGTGA *ATG* AGGACA
5. TRE (rat malic enzyme E)	GGGTCA *GGGG* AGGGACA

Figure 4. Comparison of DNA-binding response elements in steroid/-thyroid hormone receptor superfamily.[32]

for the vitamin D response element (VDRE) and, when separated by four nucleotides, became a thyroid response element (TRE).[32] Similarity in RAREs of human and mouse RARβs should be noted. RXRE (retinoid X responsive element) in the promoter region of the CRBP-II gene has been shown to be made up of five direct repeats of the sequence AGGTCA separated by one nucleotide.[32]

Cellular Retinol- and Retinoic Acid-Binding Proteins (CRBPs and CRABPs)

CRBPs and CRABPs are, respectively, small intracellular retinol and retinoic acid binding proteins which are found to bind retinol (**1**) or retinoic acid (**3**) selectively with high affinity.[2,19] The two proteins are concentrated in a tissue specific manner.[2] Although retinoid-binding proteins were first postulated to represent specific intracellular receptor systems for retinoids,[19] it has now been shown that they do not show any similarity to RAR identity.[19] The exact function of these proteins is not known, but lack of these

proteins in certain tissues suggests that they are not directly involved in retinoic acid activated gene transcription.[19] Regions of high CRBP expression have been found to be distinct from regions of high CRABP expresion.[14] It has also been observed that CRABP attenuates the retinoic acid effect on gene transcription.[14] This is supported by the fact CRABPs are mostly found in sites which are targets for retinol teratogenecity.[14] Conversely, CRBPs are found in sites where retinoic acid is required in high concentration for developmental processes.[14]

Homo- and Heterodimerization of RAR and RXR

Characterization of response elements for thyroid hormone receptors (TRs), RARs RXRs, vitamin D receptors (VDRs), glucocorticoid receptors (GRs), and estrogen receptors (ERs), which belong to the same steroid/thyroid hormone receptor superfamily, has revealed that all consist of two or more repetitions of the same core motif AGGTCA (or a related sequence) (Figure 4). The presence of these repeated motifs in the response elements and the fact that GRs and ERs bind as dimers to pallindromic response elements, suggested that RARs, TRs and RXRs may also bind as dimers to response elements.[32] This was later supported by *in vitro* binding studies of RARs and ERs.[19,32] It has since been found that although at first both RARs and RXRs were thought to function as homodimers (as GRs and ERs),[14] RARs require heterodimerization with RXR or other nuclear factors referred to as RAR coregulators for effective binding to response elements.[19,32] RXR, specifically RXRβ, was also found to bind and enhance binding affinity of several other ligand regulated response elements including TRs and VDRs.[19] Both functional DNA domains and intact ligand binding domains are required for complexation and subsequent retinoic acid coregulator action (Figure 5).[19]

Interaction of RAR-RXR heterodimer formation was characterized by Mangelsdorf and co-workers by mutational analysis in a study using DNA binding of hRARγ mutants and mRXRα mutants to βRARE.[35] As can be seen from Figure 5, the importance of ligand

binding capabilities of the DNA binding (C) region varied. Cyc→Ala mutation is seen to be more detrimental to the DNA binding of hRARγ than to that of mRXRα. Amino acid sequences located within the ligand binding (E) regions of both RAR and RXR are needed for binding to βRARE while deletion of hRARγ N-terminal (A and B) had no significant effect on binding.[32]

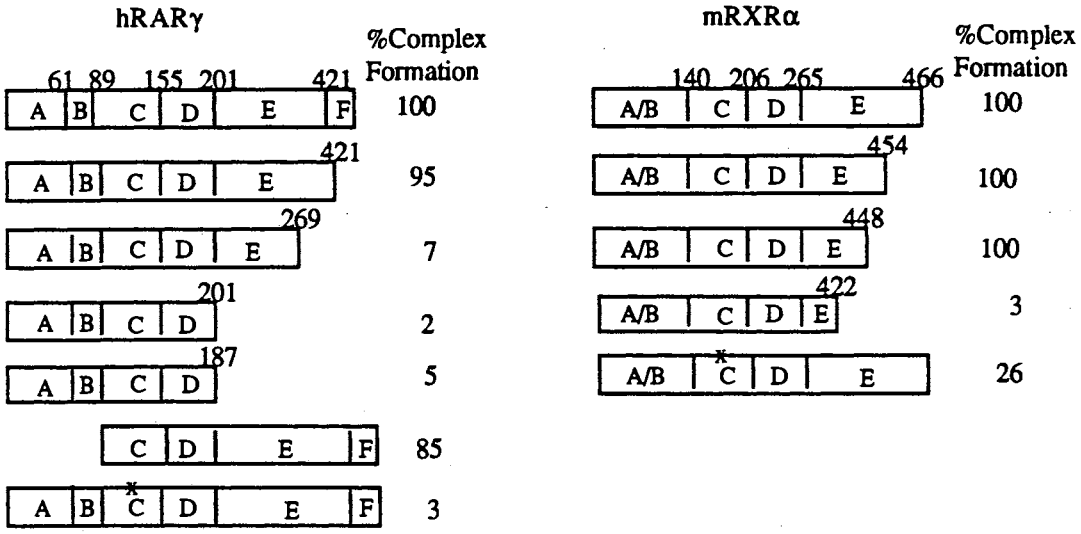


Figure 5 Characterization of RAR-RXR Interaction by Deletion and Mutational Analysis of Each Protein.[32] The X denotes replacement of fourth cysteine in the zinc finger in DNA binding domain to alanine.

An analysis of coregulators is expected to provide insight into the molecular mechanism by which the orientation and spacing of individual core binding motif can confer selectivity to specific nuclear receptors. It is also speculated that since RXR is evolutionarily conserved in Drosophila,[19] preceding the appearance of RAR, the major function of the C-terminus of RXR and other coregulators is to serve as dimerization interfaces in order to permit high affinity binding of nuclear receptors to specific DNA respnose elements.[19] While RARβ enhances binding capacity and specifc transcription action of RAR, TR and VDR RAR inhibits RXRα dependent transactivation of CRBP-II response element.[35] This suggests that while RXRβ-RAR heterodimer functions as a positive transactivator for one

class of DNA sites, the dimer may serve as an inhibitor on a second class of response elements. [19,32]

Although RARs seem to operate effectively as heterodimers, RXRs were found to form and function more effectivly as homodimers in the presence of 9-*cis* retinoic acid (**6**).[31, 65] RXR homodimers have distinct response elements from those of RAR-RXR heterodimers, implying that the two retinoic acid response pathways activate distinct sets of genes.[32, 35] For example, while CRBP I response element did not interact with RXRα, homodimer CRBP II response element bound effectively to 9-*cis*-retinoic acid induced RXRα homodimer. Moreover, CRBP II response element bound RAR-RXR heterodimer and appeared also to have repressor function.[35] Hence, the equilibrium between homodimers and heterodimers may be a means to control two distinct pathways. Therefore, the use of RXR-selective ligands may be a basis for a new therapeutic approach to diseases known to respond to retinoic acid therapy whereby undesireable side effects might be avoided as only RXR-response pathways could be affected.[64,65]

Structure Activity Relationship of Retinoids in Ligand Binding Studies

With the search for retinoids that would activate either RAR or RXR selectively, several synthetic retinoids have been assayed for their ability to induce gene activation using retinoid receptors (RARs and RXRs). Recent studies have focused upon developing retinoid acid analogs which bind RXR selectively (Table V). Conclusions from several such studies are summarized below.[4,24,31]

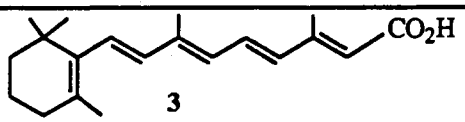
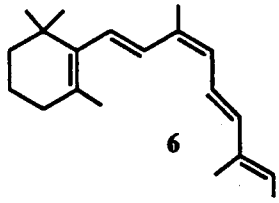
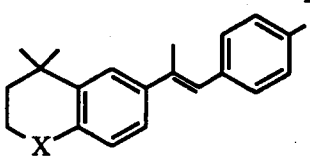
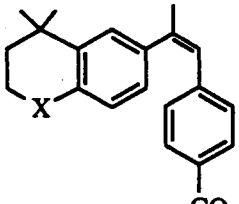
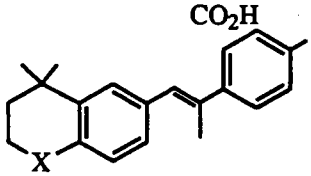
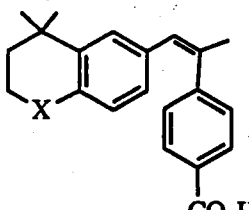
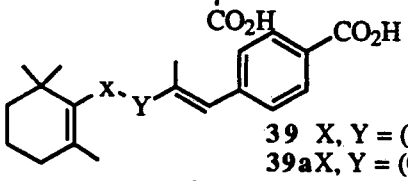
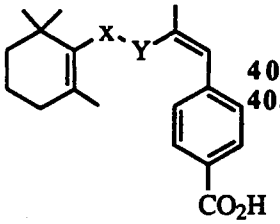
1) All *trans*-retinoic acid (**3**) binds preferentially to RAR, while 9-*cis*-retinoic acid (**6**) binds preferentially to RXR.[4,42]

2) TTNPB (**8**) binds RAR preferentially to 3'-alkylated TTNPB (**31**) which shows a more balanced activation profile.[4]

3) A group of compounds **32** with similar spacial orientation of the lipophilic head and carboxyl terminus to that of 9-*cis*-retinoic acid (**6**) showed the highest activation for

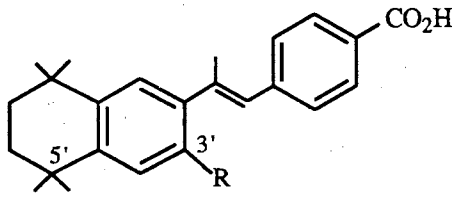
TABLE V

Retinoid-Receptor Selectivity[a]

Retinoid	Retinoid Activity (%) RARα	RARβ	RARγ	RXRα
 **3**	100	97	98	86
 **6**	110	86	127	100
 **8** X = CMe_2	80	69	112	13
22 X = S	56	29	76	6
 **33** X = CMe_2	14	53	76	24
34 X = S	12	11	38	5
 **35** X = CMe_2	63	51	74	6
36 X = S	53	79	96	6
 **37** X = CMe_2	6	66	18	89
38 X = S	45	56	68	71
 **39** X, Y = (*E*)-HC=CH	64	55	107	8
39a X, Y = $(CH_2)_2$	52	31	87	15
 **40** X, Y = (*E*)-HC=CH	10	52	57	4
40a X, Y = $(CH_2)_2$	5	25	27	4

[a]Reference 24

examples **32a** [R, R' = CH_3] and **32b** [R, R' = OCH_2CH_2O].[31] The study also revealed that while lengthy substitution groups reduced activity, smaller groups reduced receptor selectivity.[31] Acid **32a** is the most active and specific ligand reported for any RXR (specifically RXRα).



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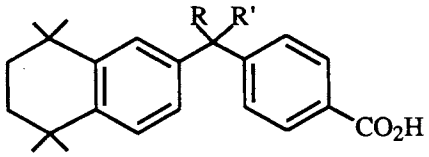


32a R = R' = CH_3
32b R, R' = OCH_2CH_2O

4) Aliphatic interaction between the receptor and retinoid is considered to play an important role in retinoid activation of RXR.[31] Retinoids **37** and **38** (showing high activity for RXRα, Table V) have partially saturated aliphatic rings that occupy spatial volume similar to that in 9-*cis* retinoic acid (**6**) and **32**. Perhaps equally important is the general shape of the side chain/aromatic ring combination.

5) A distance of 9.6-10Å is required between the C-5' in **31** of the tetrahydronaphthyl ring and the carboxyl carbon atom for optimal activation of RXRα.

6) Changing the position of the methyl in the propenyl bridging group and isomerizing the double bond (as in **8**,**22** and **37**,**38**-Table V) altered the conformational relationship between the aryl ring and the tetrahydronaphthyl ring. This led to a reversal of the activation profile from RAR (**8, 22**) to that found with RXR (**37, 38**).[24]

Heteroarotinods as Potential Liquid Crystals

There is reason to believe that certain heteroarotinoids may also be liquid crystalline. Some have molecular structures characteristic of stilbene-like compounds that exhibit liquid crystal (LC) phases.[5,6]

An LC solid is characterized by both orientational and positional order. When a solid melts to a liquid, both orientational and positional order are lost. However, when a

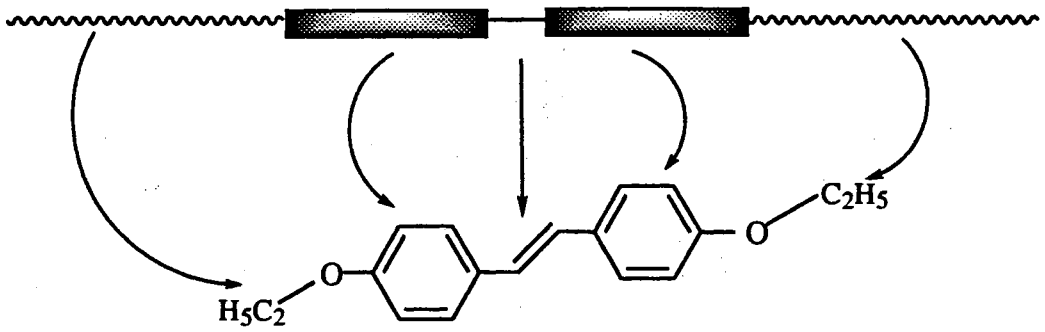
solid melts to a liquid crystal phase, it loses all its positional order as in a liquid but retains some of its orientational order. Therefore, every point in a LC molecules defines a special direction by spending more time along this direction than another. Hence, a given property measured along one direction would give a different value when measured along another. This property is called anisotropy. To maintain this anisotropy, compounds that are liquid crystalline should have the following molecular geometric characteristics:[6]

1) the molecule must be rod-like in shape, *i.e.* it must be significantly longer than it is wide,

2) the molecule must have some rigidity in its central region. (e.g. *trans*-stilbene structure), and

3) the ends of the molecules must be somewhat elongated (e.g. such as alkyl chains).

A basic LC structure is illustrated below with a stilbene derivative **41** (arrows indicate the required structural features as seen in a liquid crystalline stilbene).[9]



41

In short, any structural feature that would give rise to anisotropic, intermolecular attractive forces, with lateral associations being much greater than attraction between the ends of the molecules, would favor a liquid crystal phase.[21] Additionally, to be of any practical use, LCs must be chemically and photochemicly stable, exhibit a wide temperature range encompassing room temperature, have good dielectric anisotropy, very low viscosity and low elastic constants and function at low voltage and power levels.[59] It is the changes in

the optic states caused by the reorientation of the director by an electric field that is utilized in most LC applications.[6,21] The "director" means the direction of preferred orientation of the molecules in a LC.

Nearly 99% of the LCs used in industry are used in electrooptic devices.[1,8] The first generation of LCs used the dynamic scattering effect discovered in the late 1960's.[1,59] With the dicovery of the twisted nematic effect (TNE) in the early 1970's, which proved to be less power consuming (1-2 v as opposed to 10-20 v) and showed greater contrast than the dynamic scattering effect by the mid 1970's, LC have captured a greater share of the electrooptic market.[1,59] The third generation LCs arrived in the early 1980's with the discovery of the ferroelectric LCs.[20,48] These have the added advantage of faster switching times and even greater contrast than TNE LCs.[48] As the name implies, ferroelectric liquid crystals (FLCs) contain a permanent dipole, the orientation of which can be changed by the application of an electric field. In addition, FLCs also contain at least two aromatic rings and a chiral center.

The synthesis and use of FLCs is still a developing field. One ultimate goal in LC research is to facilitate the development of the "flat screen, on the wall" TV. The two main difficulties of using TNE in this field is the slow switching times and poor contrast. FLCs, as mentioned earlier, show faster switching times since both ON and OFF modes are controlled by an electric field (as opposed to only the ON mode in TNE LCs). FLCs also have better contrast since the inherent chirality in the material improves selectivity in refraction of light.[20]

One of the biggest challenges in developing FLC material is the synthesis of compounds where the chiral center will minimize the distortion of the linear alignment of the molecule.[30] This requirement has eliminated the use of most easily available chiral molecules. Hence, the objective of our project was to develop a LC with a large permanent dipole combined with a chiral center which would *not* distort the linearity of the molecule.

CHAPTER II

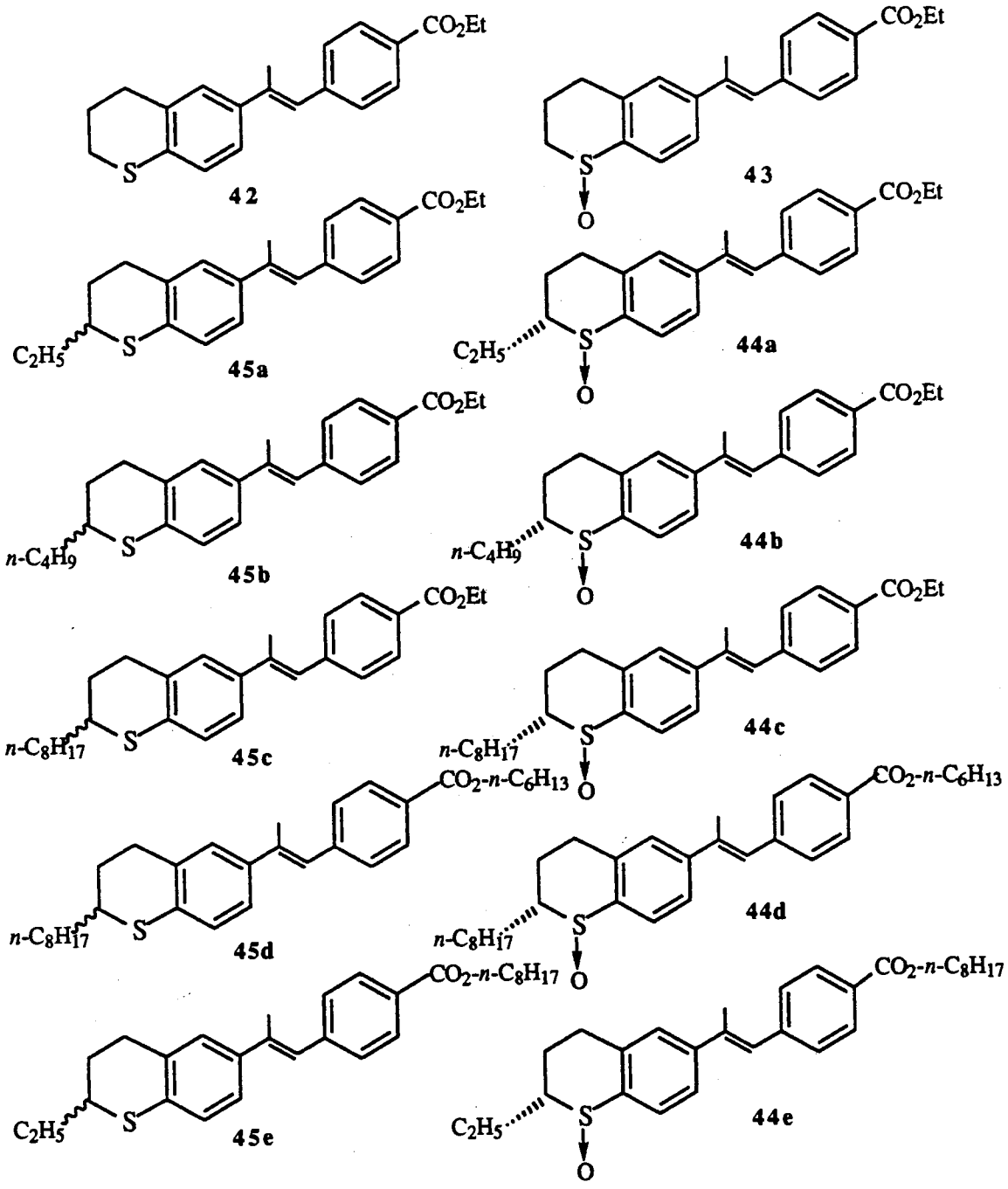
RESULTS AND DISCUSSION

Modified Heteroarotinoids

The twelve new heteroarotinoids **42-45** have been synthesised from our work. Approp-riately substituted 2-alkylsulfoxide-containing heteroarotinoids were targeted for synthesis as potential liquid crystals which would also exhibit anticancer properties. Large alkyl groups at position-2 (alpha to the S→O group) in the heteroarotinoids were expected to screen the S→O group to some degree but yet display a relatively nonpolar center for biological activity while still retaining specificity of action induced by the overall structure. Introduction of the highly polar and chiral S→O group was likewise anticipated to confer ferroelectric liquid crystal properties to 2-alkylated heteroarotinoids.

Preliminary investigations are now underway to determine receptor binding capabilities and activities of newly prepared heteroarotinoids **42**, **43**, **44a**, **44c**, **45a**, and **45c**. Conceivably the alkyl chains could improve the binding capabilites of the retinoid to the receptor through aliphatic, nonbonded interactions.

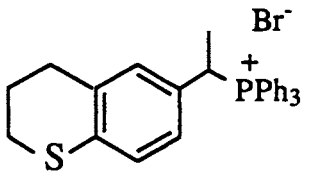
Preliminary characterization of the same retinoids for liquid crystal properties has revealed that both the the sulfoxide **44c** and the sulfide **45c** exhibit a liquid crystal phase. Neither the simple sulfide **42** nor the simple sulfoxide **43** showed any mesophases. This observation is somewhat expected since two flexible ends are normally required for the molecules to align themselves parallel to each other. As expected



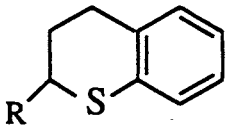
New Heteroarotinoids

both the 2-ethylsulfoxide **44a** and the 2-ethylsulfide **45a** also did not exhibit any mesophases. Possibly these two compounds could still be used as components which confer a permanent dipole moment and/or chirality to liquid crystal mixtures used in electrooptic devices.

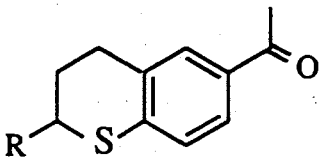
Intermediates **46-50** were also prepared for the first time in our laboratory. All such intermediates were previously unknown except **47**.[56]



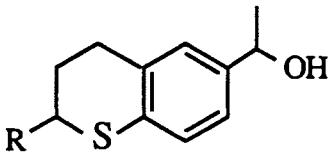
46



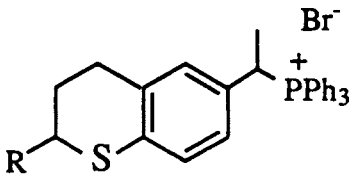
47a R = Et
47b R = *n*-C_4H_9
47c R = *n*-C_8H_{17}



48a R = Et
48b R = *n*-C_4H_9
48c R = *n*-C_8H_{17}



49a R = Et
49b R = *n*-C_4H_9
49c R = *n*-C_8H_{17}



50a R = Et
50b R = *n*-C_4H_9
50c R = *n*-C_8H_{17}

Novel Heteroarotinoid Intermediates

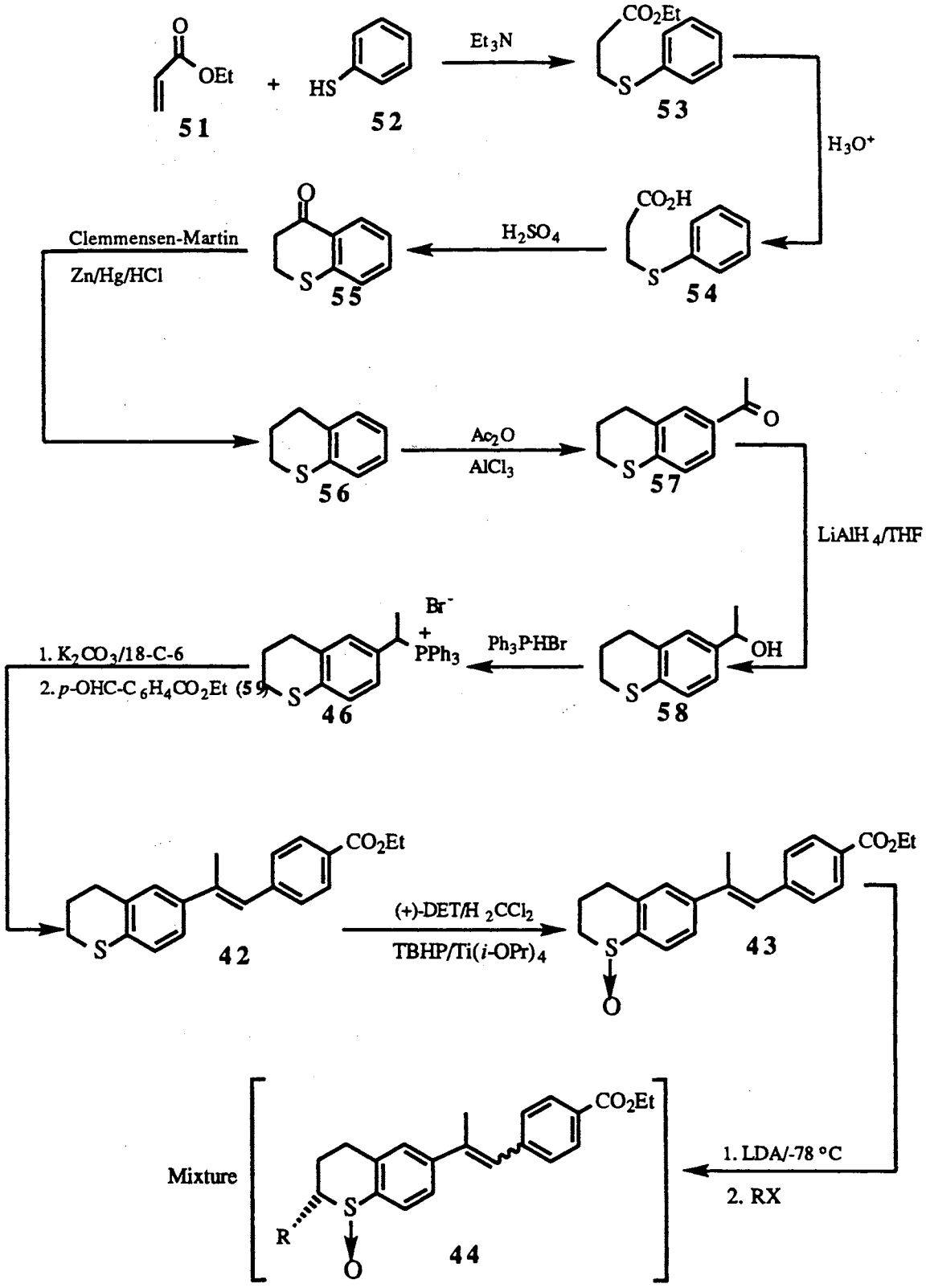
Synthetic Methodology

Phosphonium salt **46** was synthesized according to Scheme I (**51** + **52**→**53**→**54**→**55**→**56**→**57**→**58**→**46**). A few techniques were applied from the chemistry of peripherally-related examples from the literature.[23,36,40,43] In Scheme I, ethyl acrylate (**51**) was treated with thiophenol (**52**) in the presence of triethylamine in a Michael additon to yield ester **53** (quantitative). Hydrolysis of the ester **53** was performed by heating with 2*N* HCl for 15 h. Acid **54** was obtained in a yield of 52%. Although 45% of the starting material (ester **53**) could be recovered, increasing the reaction time did not improve the yield. It was also found that NaOH could *not* be used to saponify ester **53** to acid **54**. The ester underwent a reverse Michael reaction to give **51** and **52**.

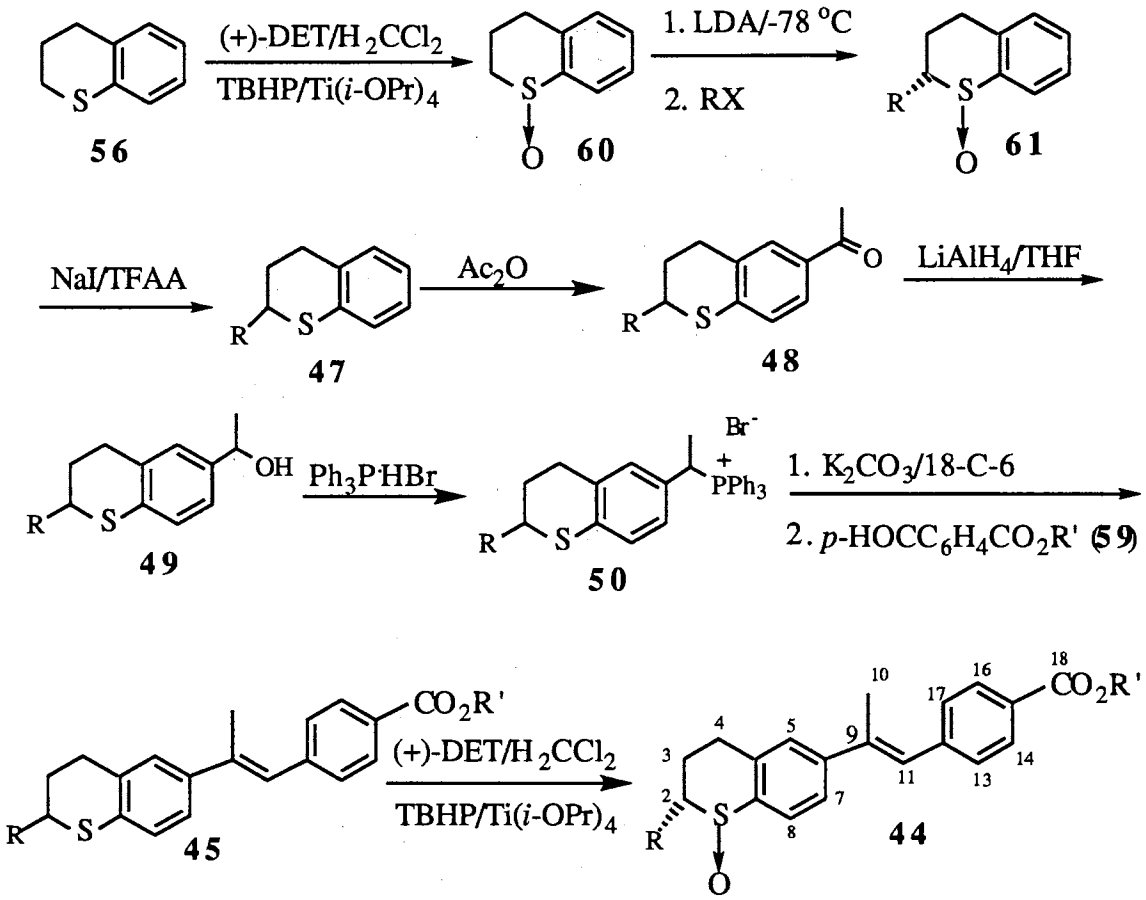
Acid **54** was cyclized to **55** with concentrated sulfuric acid in a intramolecular acylation. The reaction went to near completion (88%) in 45 min at room temperature. Resulting ketone **55** was reduced to sulfide **56** (quantitative) in a modified Clemmensen reduction using a boiling toluene-water mixture with Zn/Hg in the presence of concentrated hydrochloric acid. The long reaction time (72 h) prompted an attempted reduction of **55** via Wolf-Kishner conditions. However, the attempt failed as ^{1}H NMR analysis of the reaction mixture revealed that neither the starting ketone **55** nor the expected product was present in an uncontaminated form. A reverse Michael type reaction was suspected.

Acetic anhydride was found superior to acetyl chloride in the acetylation of **56** to give **57**. The reaction was carried out at room temperature in nitromethane with aluminum trichloride to give **57** (98%) in 48 h. Interestingly, the same reaction conditions could not be applied to the acylation of **47** (Scheme II). The presence of an alkyl chain at C-2 seemed to reduce the solubility of **47** in nitromethane, and a mixture of CS_2 and nitromethane was required as a reaction medium. These conditions lowered the yield (72%) of **48a** but **48b** and **48c** were obtained in high yield (quantitative).

SCHEME I


OEt
51
HS
52
Et3N
CO2Et
53
H3O+
CO2H
54
H2SO4
O
55
Clemmensen-Martin
Zn/Hg/HCl
56
Ac2O
AlCl3
57
LiAlH4/THF
OH
58
Ph3P-HBr
Br-
+
PPh3
46
1. K2CO3/18-C-6
2. p-OHC-C6H4CO2Et (59)
42
(+)-DET/H2CCl2
TBHP/Ti(i-OPr)4
43
Mixture
R
44
1. LDA/-78 °C
2. RX

SCHEME II



56 **60** **61** **47** **48** **49** **50** **45** **44**

45a, R = ethyl, R' = ethyl
45b, R = *n*-butyl, R' = ethyl
45c, R = *n*-octyl, R' = ethyl
45d, R = *n*-octyl, R' = *n*-hexyl
45e, R = ethyl, R' = *n*-octyl

Yields from **56**

44a, R = ethyl, R' = ethyl (23%)
44b, R = *n*-butyl, R' = ethyl (10%)*
44c, R = *n*-octyl, R' = ethyl (6%)
44d, R = *n*-octyl, R' = *n*-hexyl (5%)**
44e, R = ethyl, R' = *n*-octyl (8%)***

*Z:E = 3:1
**Z:E = 3:1
***Z:E = 2:1

47 50 61
a, R = ethyl
b, R = *n*-butyl
c, R = *n*-octyl

Alcohol **58** (Scheme I) was obtained (80%) by reducing ketone **57** with lithium aluminium hydride in THF. Anhydrous ether was preferred to THF in the reduction of **48** to **49** (Scheme II). The change of solvent resulted in a high yield of **49** (80-86%). Ketone **57** was a thick red oil (Scheme I) which was found insoluble in ether. This is may be due to the presence of an aluminum compound still complexed to the S atom. Members of **49** gave yellow oils even after chromatography and were used directly to make **50** (Scheme II). Although **58** could be obtained as a colorless oil by careful vaccum distillation, only about 50% of the purified alcohol could be recovered (Scheme I). Treatment of **58** with triphenylphosphonium hydrobromide in methylene chloride gave phosphonium salt **46** (quantitative).

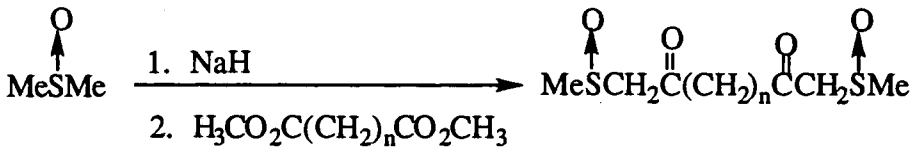
Previous studies in our laboratory had shown that relatively low yields of heteroarotinoids were formed in the last step of the synthesis when classic Wittig conditions were used. Using *n*-BuLi as the base in the synthesis of sulfur-containing retinoids where C-2 was not alkylated (as in **46,** Scheme I) gave similar results. A literature[3] search suggested a novel method using the milder base K_2CO_3 in the presence of catalytic amount of 18-C-6 might give the corresponding ester **42** (Scheme I) in high stereoselectivity and yield (**46** was boiled with K_2CO_3, 18-C-6, and **59** in dry THF for 48 h to obtain **42** - 40%). Phosphonium salt **50** (Scheme II) reacted similarly but methylene chloride was used as a solvent with **59a** (R' = C_2H_5) and resulted in improved yields of 55-91%.

Aldehyde **59a** (R' = C_2H_5) was prepared using a procedure previously developed in our laboratory where *p*-toluic acid was esterified with ethyl alcohol to give ethyl *p*-toluate which was then oxidized with chromium anhydride in acetic anhydride/acetic acid to give an intermediate diacetate. The diacetate was hydrolyzed to a highly unstable aldehyde-ester by boiling with a acidified water-ethanol mixture. Aldehydes **59b** (R' = *n*-C_6H_{13}) and **59c** (R' = *n*-C_8H_{17}), prepared for the first time in our laboratory, however, presented a difficult problem in the final step since both underwent a certain amount of

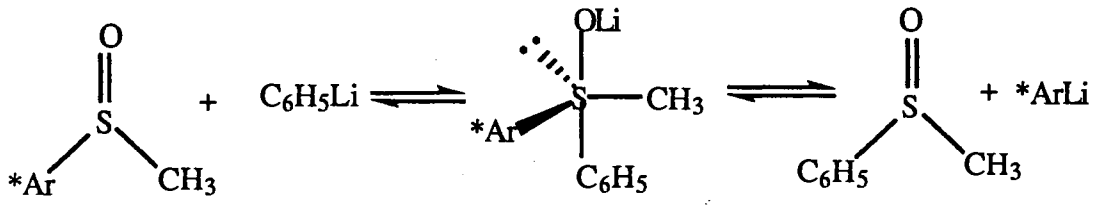
transesterification with ethanol. Attempted separation of **59b** and **59c** on silica gel using hexane:ether 95:5 still resulted in the presence of trace amounts of transesterified products. Thus **59b** and **59c** were used without further purification. The importance of carrying out the Wittig reaction in the dark was quickly recognized. The *Z:E* ratios of retinoids were found to decrease when the reaction was run in the dark. Low *Z:E* ratios produced viscous liquids, and it was not possible to separate the *Z*-isomer from the isomeric mixture if the original reaction was performed without the absence of light.

Oxidation of sulfide **42** to sulfoxide **43** (Scheme I) was carried out in a highly stereospecific manner using modified Sharpless conditions.[44] These milder conditions were employed for asymmetric induction as well as to prevent epoxidation of the C-9=C-11 double bond and oxidation at allylic and benzylic positions. The yields were found to be slightly lower in the oxidation of C-2 alkylated sulfide **45** compared to the corresponding sulfoxide **44** (Scheme II). This could be due to steric hindrance of the alkyl group in **45** to the initial attack by the titanium-water-diethyl tartrate complex. All attempts to separate *Z:E* sulfoxide mixtures of **44** as inclusion complexes with β-cyclodextrin[37] and by using cellulose tribenzoate (prepared by reaction of crystalline cellulose with benzoyl chloride) as the stationary phase in chiral column chromatography[39] failed. This is likely due to the more polar S→O end (even when screened by large 2-alkyl groups) interacting with the stationary phases of β-cyclodextrin and cellulose tribenzoate instead of the aromatic ring system.

Attempted alkylation of the sulfoxide **43** to obtain 2-alkylsulfoxide **44** (Scheme I) using LDA was not successful. A literature survey reported the following reaction where the



carbanion of DMSO reacted with an ester to give a β-keto sulfoxide.[63] Several condensations involving carbonyl groups (aldehydes, ketones, and esters) with carbanions alpha to a chiral sulfoxide have been reported as the example illustrates.[49] The loss of signals for starting material and the absence of signals for protons in the OCH_2CH_3 group in the ^1H NMR spectrum was noted in our work with **43**, suggesting a similar reaction had occurred at the ester carbonyl carbon of sulfoxide **43**. The reaction mixture appeared to be complex, however, and **44** may have been formed as well as its olefinic isomer. Milder bases, such as KH, K_2CO_3, DBU, and potassium *t* -butoxide, resulted in only the recovery of starting material. Alkyllithium reagents are sometimes unsatisfactory bases for the effective generation of a lithio-sulfoxide anion due to a resulting ligand exchange by a simple S_N2 displacement at sulfur as in the following reaction.[61] Since LDA has been used



successfully in alkylation of thiochroman-1-oxide, we initiated a new route (Scheme II) where the α-alkylation of an $-CH_2S(O)-$ system was carried out with simple sulfoxide **60**.[56]

Sulfide **56** was oxidized to the sulfoxide **60** (Scheme II) as previously described with a modified Sharpless reagent.[44] Our isolated sulfoxide **60** possessed the highest ee reported for this compound (the value of the specific rotation for the pure **60** had not been reported). Sulfoxide **60** reacted with LDA at -78 °C in THF and gave a carbanion, the solution of which was allowed to warm to -30 °C and was then again cooled to -78 °C. Finally, the solution was treated with a corresponding alkyl halide to produce **61**. Predominant alkylation to give the *trans* isomer was expected[49] and was presumed realized. Reduction of the sulfoxide **61** to sulfide **47** proceeded smoothly and rapidly under mild

conditions using trifluoroacetic anhydride and NaI.[15] The remainder of the steps to **44** paralleled to some degree that in Scheme I except the final oxidation of tthe S atom. The overall yields of **44** from **56** were considered modest.

Rationale for Predominant *trans* Alkylation.

The stereochemistry of the reaction products depends upon formation of an α-sulfinyl carbanion via two factors, namely (i) kinetic acidity (controls the stereochemistry of the carbanion initially formed) and (ii) thermodynamic acidity (defines the stereochemistry of the intermediate carbanion).[49] With the above reaction conditions (using THF and warming to -30 °C), the contribution of kinetic acidity can be neglected.[49] The carbanion generated apparently has enough time to form its most stable configuration before reacting with an electrophile.[49,61] However, in THF the counter cation of the base employed to extract a proton from the sulfoxide is initially trapped by the sulfinyl oxygen.[38,49,61] Therefore, abstraction of a proton would likely be easier on the H_B side (Figure 6) since electrostatic repulsion between the developing negative charge on the H_B side and the S lone pair is nonexistent. However, as seen in Figure 6, the thermodynamic stability of the

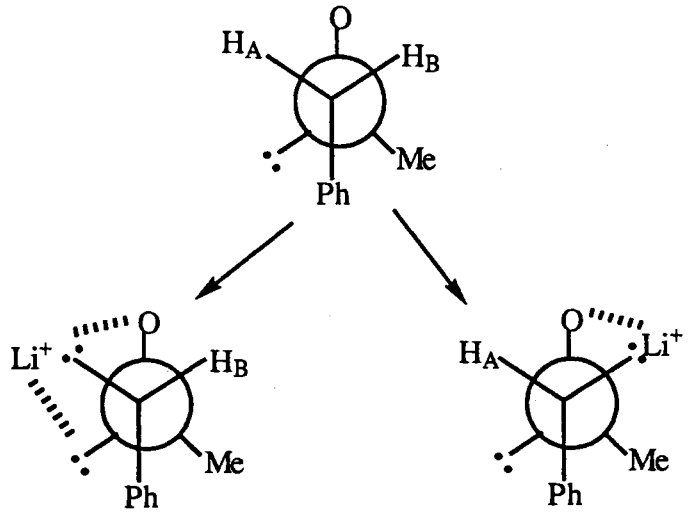


Figure 6. Stereoselectivity of α-Carbanion Formation Next to a S→O Group.

system produced is probably greater when H_A abstraction occurs since the Li cation can coordinate with both oxygen and sulfur lone pairs. Stereoselectivity of the alkylated product is thought to depend upon the electron-donating ability of the electrophile.[61] Electrophiles with the ability to coordinate to the metal counter ion, for example D_2O and CO_2, tend to react with retention of configuration and from the same side as the cation.[61] While many electrophiles, such as alkyl halides, do not coordinate to the cation, approach from the less

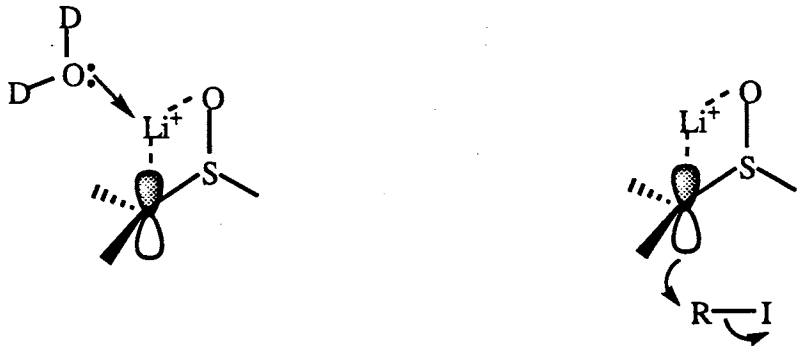


Figure 7. Stereoselectivity of Electrophilic Attack on an α-Carbanion Next to a S→O Group.

hindered face of the anion can occur with inversion of configuration as shown in Figure 7.

Compounds **44b**, **44d**, **44e** and **45b**, **45d**, **45e** (Scheme II) were obtained as *Z:E* isomeric mixtures and could not be separated. The target alkylated esters **44** were obtained in variable yields with the highest yield being realized for R, R' = Et (23% from **56**). The lower yield of **44b** and **44c** when compared to that of **44a**, could be due to the fact that in the final oxidation step from **45c**→**44c** there may be increased steric hindrance to the oxidation by the longer alkyl chain in **45c**. This is supported by the ee% data reported for various alkyl-aryl and alkyl-alkyl sulfoxides, indicating changes in ee with varying alkyl groups as illustrated in Table VI.[25]

The absolute configuration of the sulfoxide **44** produced via asymmetric induction by (+)-diethyl tartrate [(R,R)-DET] in the modified Sharpless oxidation was predicted to be as

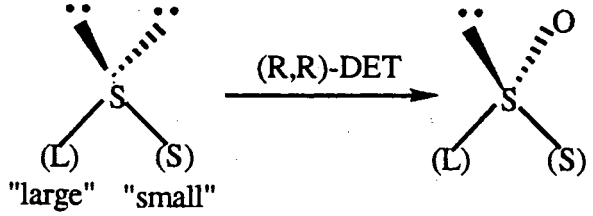
TABLE VI[a]

Asymmetric Oxidation of Aryl Alkyl Sulfides

Ar	Alkyl	Isolated yield (%)	Enantiomeric Excess (%)
p-tolyl	Me	90	88
p-tolyl	Et	71	74
p-tolyl	*n*-Bu	75	20

[a]Reference 25.

illustrated below.[26] This suggests that the titanium complex formed attacks the sulfur atom from the least hindered side, supporting our hypothesis of a trans alkylated sulfoxide **44**.



The ^1H NMR spectral analysis of the sulfoxide **61** (Scheme II) using the chiral shift reagent $Eu(dpm)_3$ revealed that cis:trans ratios could be calculated using signals for H-8.[56] A larger downfield shift was observed for the trans isomer than for the cis isomer. The highest cis:trans ratio reported for **61** was 9:91.[56]

Biological Activity and Receptor Binding

Viability of retinoids as possible anticancer agents can be measured various ways. The activity of retinoids have been assessed by examining their ability in cell differentiation as stated previously.[7] As also cited earlier, the ODC[60] and the TOC[16] assays can be utilized

as well although they are expensive and time consuming. A possible specificity of action can be measured by determining receptor binding of a test retinoid to the receptor subtypes RARα, -β, and -γ. Although specific action of receptor subtypes are not known in a definitive manner, the fact that they are expressed in a tissue specific manner implies specificity of action.[57]

Biological Activity. Biological activity of several heteroarotinoids synthesized in our laboratory has been measured in a different assay, namely the TGase (transglutaminase) assay[53,54] It has been found that the enzyme transglutaminase plays a role in cell differentiation.[54] Differentiation of HEL (human leukemia cell line) cells by retinoic acid (**3**) was accompanied by an increase in tissue transglutaminase.[54] Transglutaminase catalyzes an acyl transfer reaction between the γ-carboxamide group of a glutamine residue and a primary amino group of a lysine or a polyamine.[54] In the TGase assay transglutaminase, activity is measured by the incorporation of radioactive putrescine into *N,N*-dimethyl casein. Activities are reported with reference to the activity of *trans*-retinoic acid (**3**).

From Table VII it can be seen that the simple ester-sulfide **42** and ester-sulfoxide **43** tested in TGase assay showed 42% and 30% activity, respectively. All data were compared to that obtained from **3** as a standard. In the same study, the highest activity was shown by a heteroarotinoid **63** containing an amide function, a carboxylic acid group, and dimethyl groups at C-2 and C-4. The results suggested that retinoids containing an S atom were more active than those with an O atom. A previous study on chalcone derivatives (similar to **65**) reported a decrease in activity with the introduction of a heteroatom into the system.[29] Studies conducted in our laboratory recorded good activity (60%) for the C-2 alkylated chalcone type retinoid **65** containing an S atom. It is hypothesized that this actively may be due to the increased hydrophobicity and improved steric interaction at the binding site. Based, in part, on the above observations and on the fact that the sulfide is

TABLE VII

EFFECT OF HETEROAROTINOIDS ON TGase ACTIVITY[a]

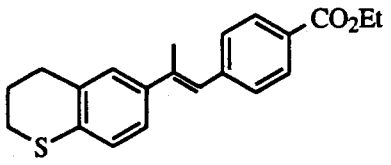
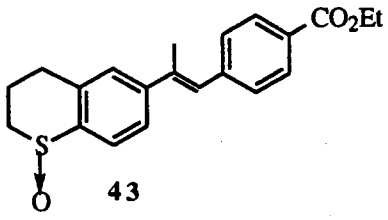
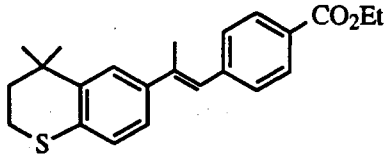
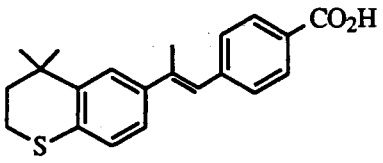
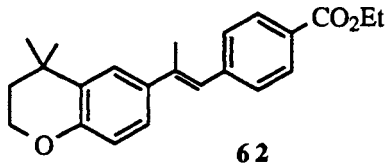
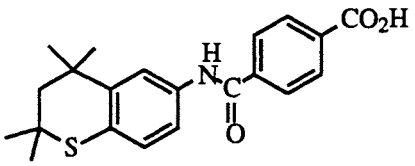
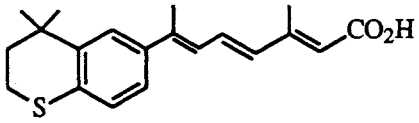
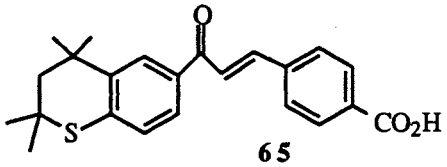
Heteroarotinoids	Ratio Sp. Activity[b]	R[c]
3 [RA]	3.3	1.0
 **42**	1.4	0.42
3 [RA]	3.3	1.0
 **43**	1.0	0.30
3 [RA]	5.1	1.0
 **27**	3.4	0.67
3 [RA]	3.2	1.0
 **22**	1.9	0.59

TABLE VII (Continued)

Heteroarotinoids	Ratio Sp. Activity[b]	R[c]
3 [RA]	5.1	1.0
 **62**	2.6	0.51
3 [RA]	3.3	1.0
 **63**	2.3	0.76
3 [RA]	4.9	1.0
 **64**	3.1	0.63
3 [RA]	3.0	1.0
 **65**	1.8	0.60

[a]Reference 53.

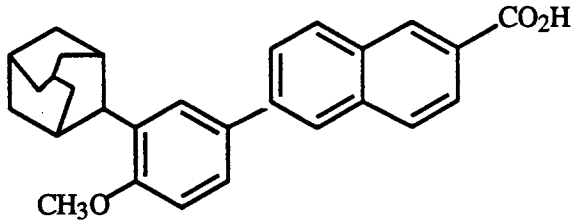
[b]Activity ratio = Specific activity (dpm/mg/hr) of test compound/specific activity (dpm/mg/hr) of control RA (**3**). [Dpm = Decomposition/min].

[c]Activity ratio of test heteroarotinoid/activity ratio of *t*-RA (**3**).

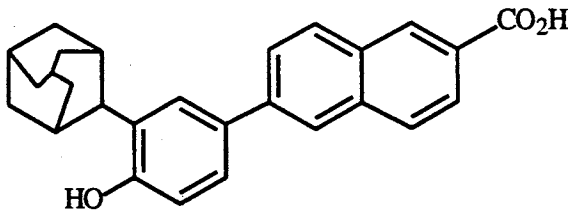
more active than the corresponding sulfoxide, hopefully, our novel C-2 alkylated sulfides (and possibly some of the sulfoxides) may show improved activity in the common retinol assays.

Receptor Binding. With the recent discovery of human retinoic acid and retinoid X receptors (RARs and RXRs) several studies have been carried out to identify retinoids which would selectively bind one RAR (or RXR) subtype.[42] It is hoped, that since the receptor subtypes are distributed in a tissue specific (while RARα is ubiquitous, RARβ is expressed highly in heart, lung and spleen and RARγ in lung and skin)[42] manner, retinoids that specifically target a given RAR could minimize undesirable side affects with improved activity. Several heteroarotinoids synthesized in our laboratory have been tested for human receptor binding capabilities by the Ligand Pharmaceuticals Inc., San Diego, California. From the binding activity studies (Table VIII) it is seen that the most active heteroarotinoids contain a carboxyl group and S as the heteroatom. High specificity for RARα was shown by retinoids with flexible amide spacers (like in **63**) in place of the rigid propenyl bridge and with increased lipophilicity like retinoid **66**. A majority of the retinoids tested did exhibit high RARβ, specificity but many also showed affinity for RARα. Only the two retinoids (**64**, **68**) containing unsaturated side chains disclosed high specificity for RARγ.

RARγ is the most widely expressed receptor subtype in adult human skin.[42] Attempts to synthesize retinoids specific for RARγ revealed that the introduction of an OH group in place of an OMe group (as in **69**→**70**) shifted receptor selectivity from RARβ to RARγ.[42]



69



70

TABLE VIII

HETERAROTINOIDS: DECREASING BINDING POTENCY WITH SPECIFIC HUMAN RETINOIC ACID RECEPTORS[a]

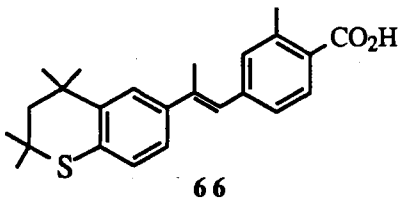
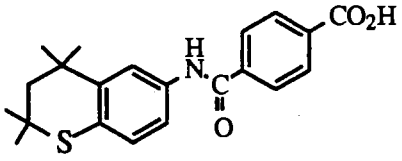
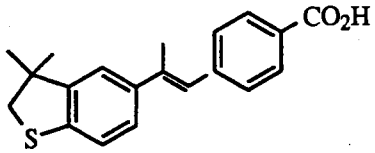
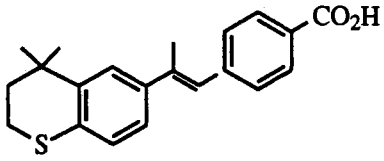
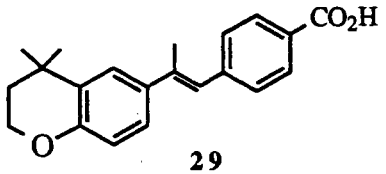
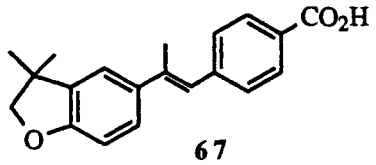
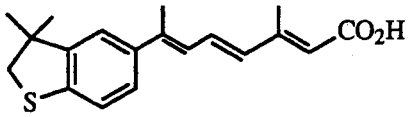
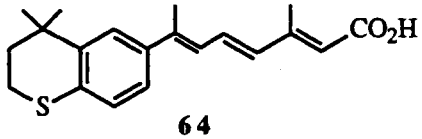
Heteroarotinoid	Potency[b]	Receptor[c]
 **66**	33 43 640	α β γ
 **63**	400 870 960	α β γ
 **26**	18 30 420	β γ α
 **22**	21 57 220	β γ α

TABLE VIII (Continued)

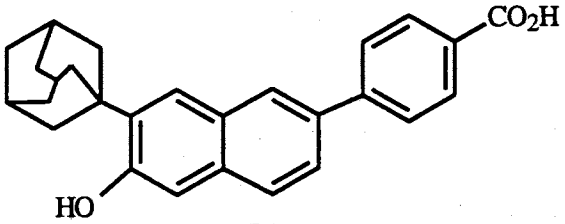
Heteroarotinoid	Potency[b]	Receptor[c]
 **29**	190 200 1100	β γ α
 **67**	320 460 2300	β γ α
 **68**	7.5 1200 1000	γ β α
 **64**	12 43 1400	γ β α

[a]Reference 53.

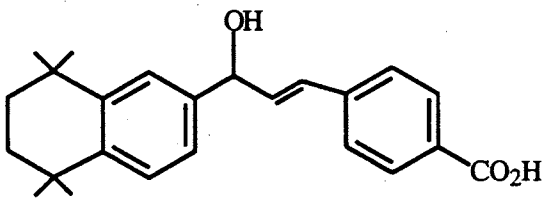
[b]Potency [EC_{50} = Concentration of heteroarotinoid to produce 50% of the maximal observed response of *t*-RA (3)].

[c]Human retinoic acid receptors that is, RARα, RARβ, and RARγ.

Further investigations by the same group on the effect of an OH group introduced in the lipophilic (left) part of the molecule (**71** and **72**) resulted in high selectivity for RARγ.



71



72

These studies suggest that while greater flexibility is required for RARα selectivity, RARγ seemed to require more hydrophilic interactions for greater selectivity. The novel sulfoxides with their highly polar S→O group next to a long α-chain may well fit the latter category of RARγ subtype specific retinoids. The novel sulfides show similarity in structure to RARβ selective retinoids.[53] We are currently awaiting data on receptor specificity of **42**, **43**, **44a**, **44c**, **45a**, and **45c** as indicated previously.

Liquid Crystal Properties of Novel Heteroarotinoids

Synthesis of ferroelectric liquid crystals (FLCs)[20,59] has been of interest since the discovery of bistable, fast-switching, electrooptic light valve. The basic structural features required for a compound to exhibit FLC phases are:

1) an-alkyl-aryl-alkyl system,

2) strong terminal lateral dipoles,

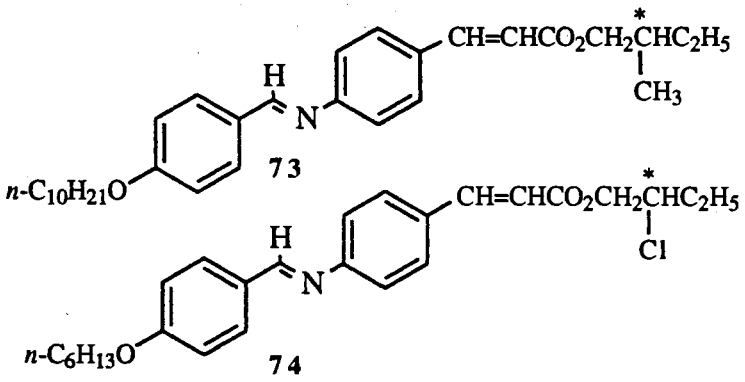
3) at least two aromatic rings, and

4) a chiral center which reduces the symmetry of the phase and produces the ferroeletric properties.

Both the shape of the molecule and its dipolar character can affect the formation of FLC phase.

Structural Features. Structural features which increase the length of the molecule without increasing the width of the system are requirements for formation of any LC phase.[59] Lateral substituents disrupt the formation of a LC phase by increasing the polarizability across the molecule and by increasing the molecular separation.[20] The lengths of the terminal chains are also important factors in LC formation.[9,21] In FLCs with an central ester linkage, it has been found that one of the alkyl chains must be at least eight carbon atoms long while the other must be at least four units long before tilted phases can be observed.[20] However, in the case of certain Schiffs bases these numbers were found to be considerably lower.[20]

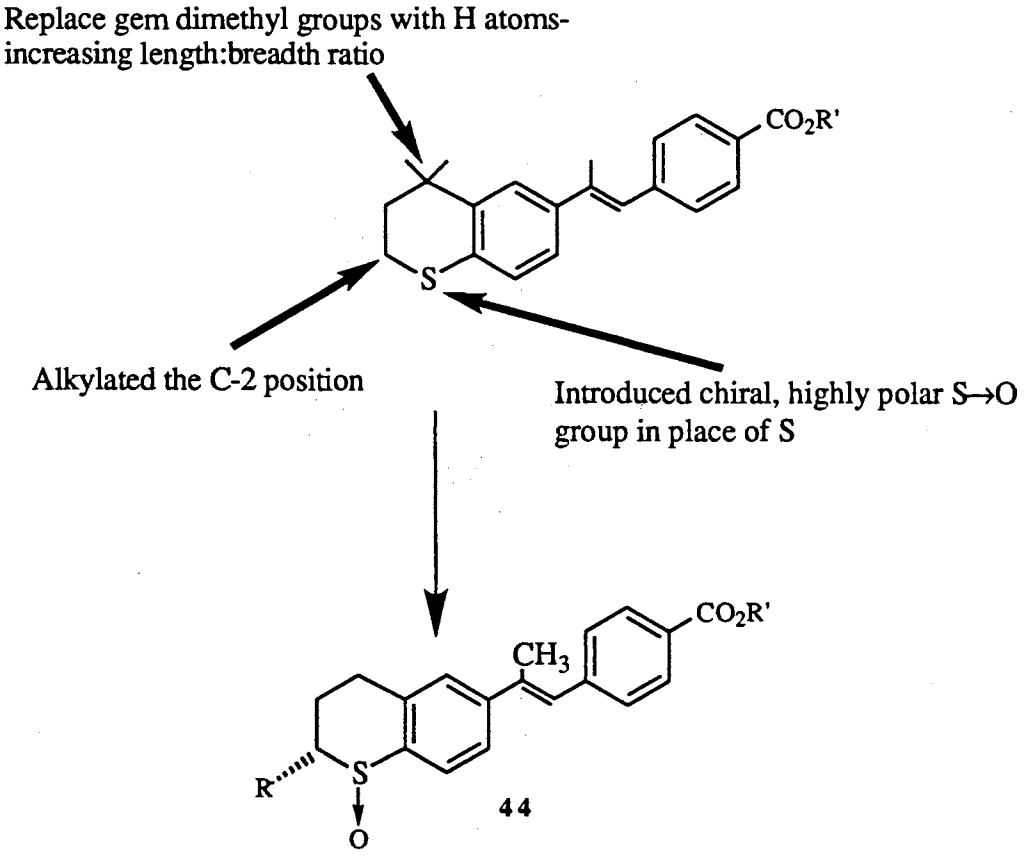
Dipolar Character. The overall net polarization of a molecule is strongly influenced by the strength of the lateral dipoles associated with an optically active center.[30,59] For example spontaneous polarization for **73** was found to be an order of a magnitude lower than that of **74**.[20] This observation may be linked to the lower strength of the dipole of the C-CH_3 bond at the chiral center of **73** compared to the dipole of C-Cl bond at the chiral centrer of **74**. It should be mentioned that the influence of lateral dipoles, other than those of the chiral center, on the magnitude of the net polarization is not clear. Most FLCs



available contain the chiral center at the end of the molecule (mostly due to ease of synthesis). However, this is not recommended[20,59] since at this position the chiral center is free to rotate independent of the highly polarizable central core with the delocalized π

electrons, thereby reducing the contribution of the core to the dipole associated with the chiral center.[20] Restriction of the freedom of rotation of the asymmetric center with respect to the rest of the molecule as a whole was expected to increase the strength of the spontaneous polarization.[20] This is usually achieved by moving the chiral center closer to the core. Linking the center via a dipolar coupling would further increase the interactions between the core and the chiral center.

We modified certain heteroarotinoids with the above structural and electronic requirements for FLCs in mind. Note the basic changes in the structures as drawn below.

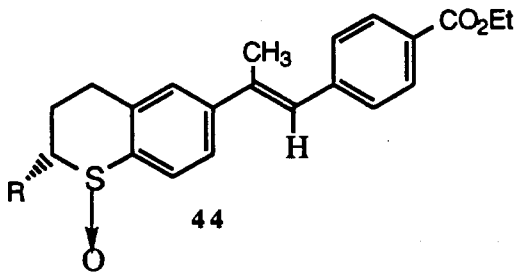


44

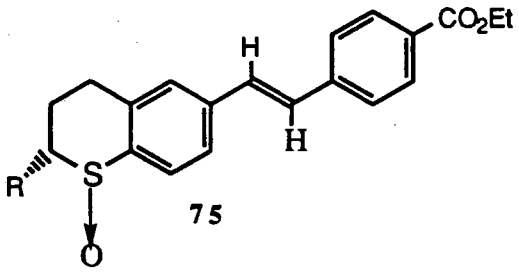
The novel heteroarotinoids were investigated for liquid crystal properties using differential scanning calorimetry (DSC) and optical microscopy with polarized light. DSC involves a comparison of a test sample with an inert reference. Heat is added via a current to filaments

to keep the sample and reference in balance. Since LCs transmit light waves at different velocities, a polarizing microscope was used to characterize mesophases.[9,21]

Both **44c** and **45c** exhibited the focal conic structure typical of the smectic/cholesteric mesophase. The absence of any mesophases in **44a** and **45a** may be due to the presence of a propenyl bridging group which would decrease the length to breadth ratio. This could also decrease the strength of the van der Waals forces required for existence of a mesophase. Substituting the methyl group in the propenyl function (as in **44**) with a hydrogen atom (as in **75**), might be more ideal. Indeed, previous studies on similar systems in our laboratory have shown that the presence of a methyl group prevents total



44



75

planarity of such systems.[42b,62c] Loss of total planarity could disrupt π-electron delocalization and limit polarizability of the molecule. More planar heteroarotinoid **75** might well be a useful LC.

Phase Behavior

Transition temperatures and heats of enthalpy of **43**

First heating:	C 89 °C (1.6 cal/g) C 94 °C (4.3 cal/g) C 100 °C(0.2 cal/g) I
First cooling:	No peaks were observed
Second heating:	No peaks were observed

Transition temperatures and heats of enthalpy of **44a**

First heating: C 92 °C (16.0 cal/g) I

First cooling: No peaks were observed

Second heating: C 87 °C (7.7 cal/g) I

Second cooling: No peaks were observed

Third heating: C 86 °C (9.7 cal/g) I

Third cooling: No peaks were observed

Transition temperatures and heats of enthalpy of **44c**

First heating: C 96 °C (0.5 cal/g) C/M 114 °C (6.5 cal/g) I

First cooling: C 55 °C (-0.6cal/g) M 64 °C (-0.4 cal/g) M 90 °C (-3.1 cal/g) I

Second heating: C 67 °C (0.7 cal.g) C/M 111 °C (6.5 cal/g) I

Second cooling: C 55 °C (-0.7 cal/g) M 64 °C (-0.3 cal/g) M 101 °C (0.8 cal/g) I 111 °C (2.0 cal/g) I 117 °C (0.1 cal/g) I

Transition temperatures and heats of enthalpy of **45a**

First heating: C 66 °C (11.3 cal/g) I

First cooling: No peaks were observed

Transition temperatures and heats of enthalpy of **45c**

First heating: C 63 C (0.3 cal/g) C/M 73 (0.1 cal/g) 84 ° C C/M (10.8 cal/g) I

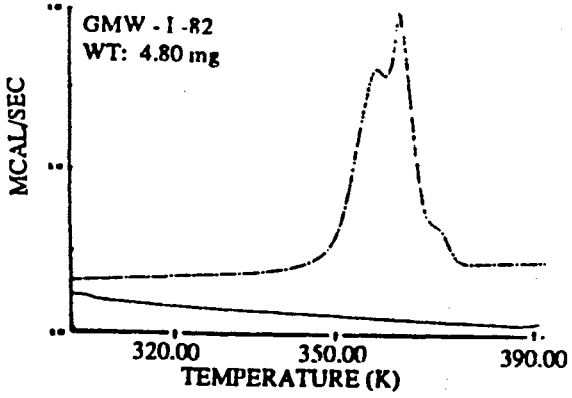
First cooling: C 72 °C(-0.4 cal/g) I

Second heating: C 66 °C (0.2 cal.g) M 84 °C (10.8 cal/g) I

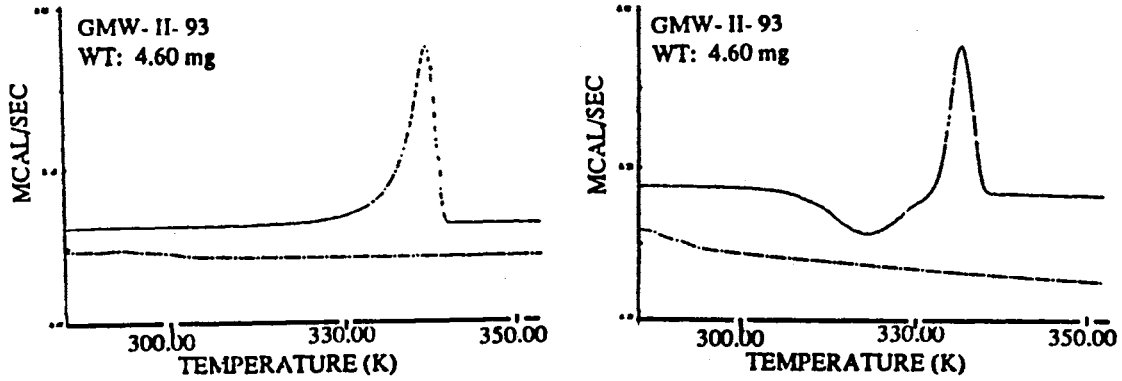
Second cooling: C 72 °C (-0.5 cal/g) I

LC phase transitions were observed for sulfoxide **44c** and sulfide **45c** under a polarizing microscope. The enthalpy changes observed in DSC for the same compounds also were consistent with latent heats for LC transitions (typically between 0.1-3 kcal/mol).[5] Different heating curves were observed for the first and second heating curves

(1).



(2).



(3).

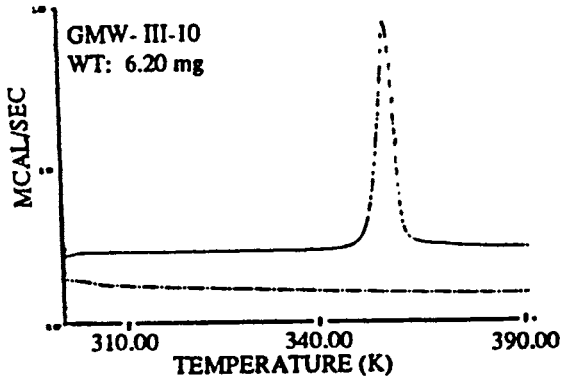


Figure 8. DSC Thermograms: (1) First heating and cooling curves of **43**. (2) First, second and third heating and cooling curves of **44a**. 3) First heating and cooling curves of **45a**

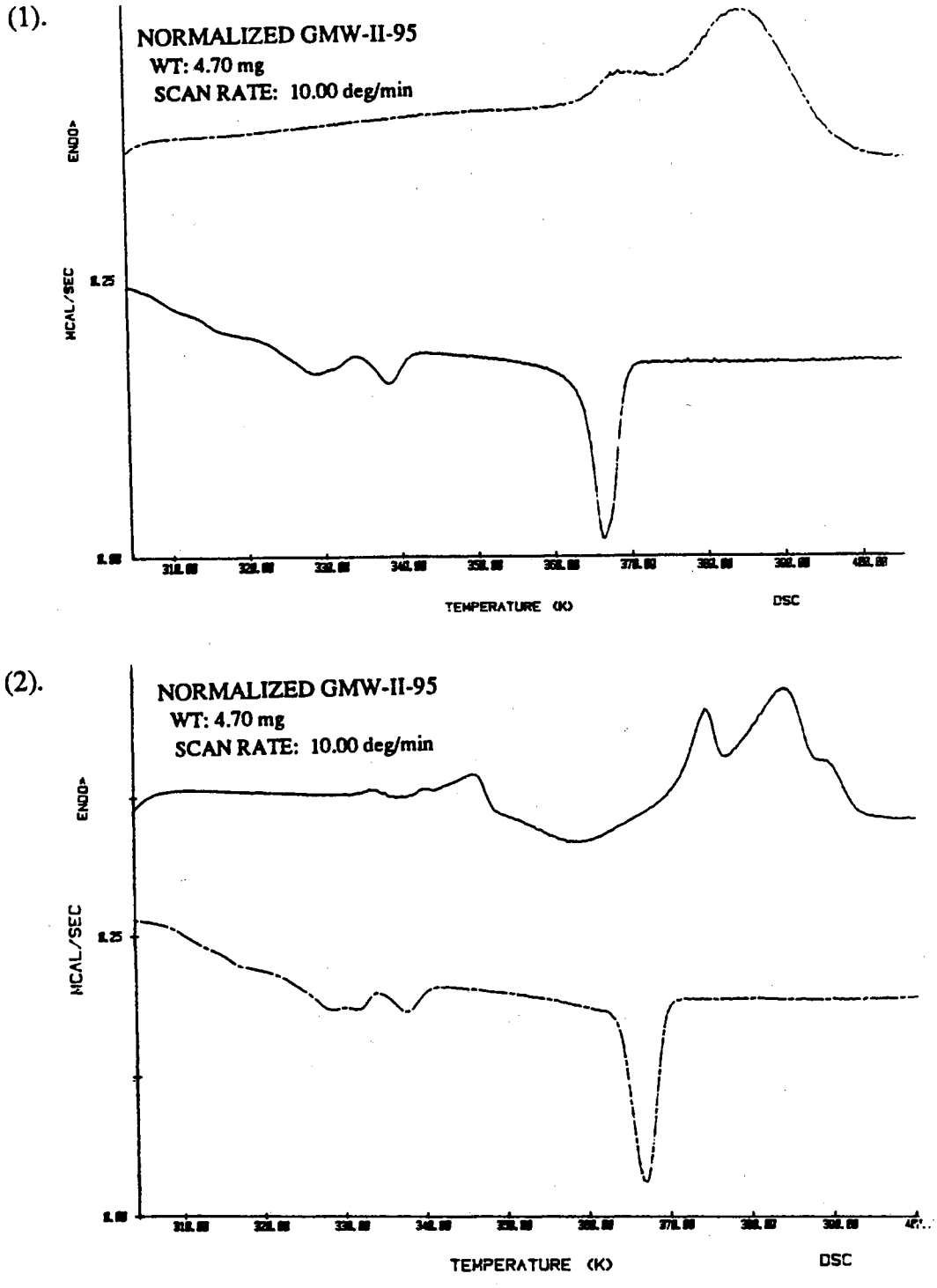


Figure 9. DSC Thermograms of **44c:** (1) First heating and cooling curves of the sample.

(2) Second heating and cooling curves of the sample.

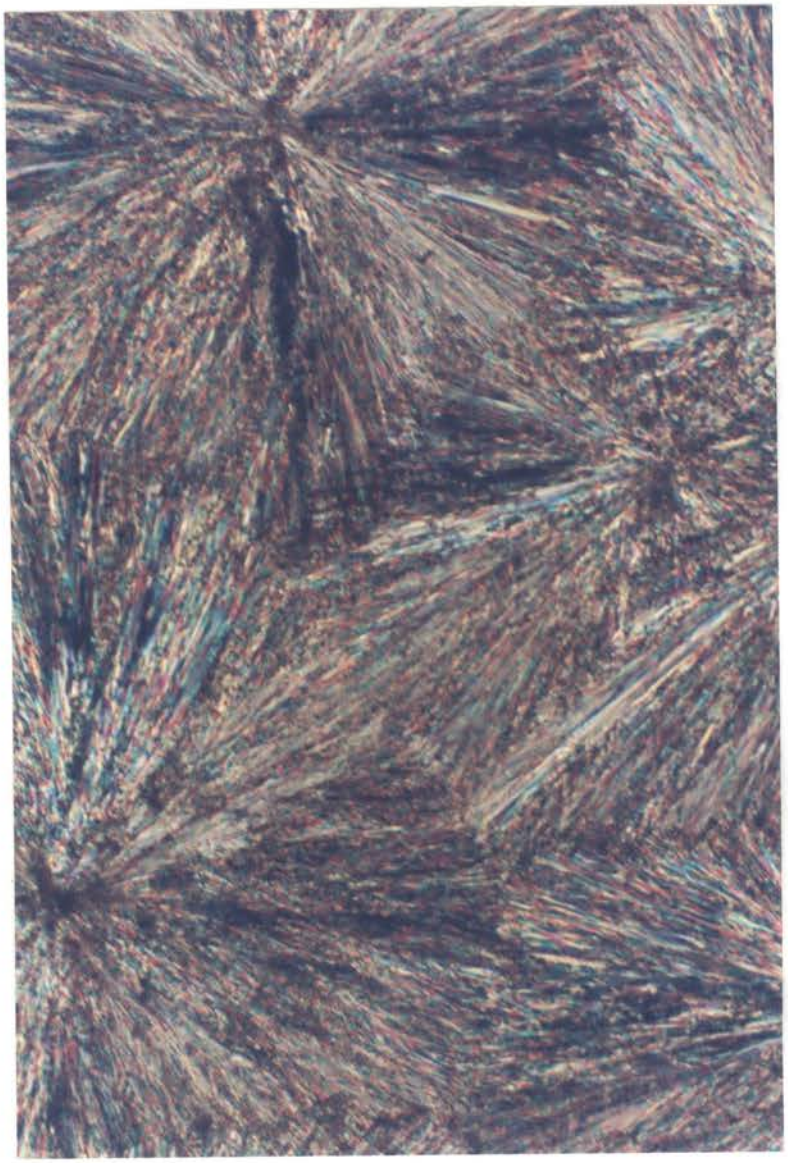
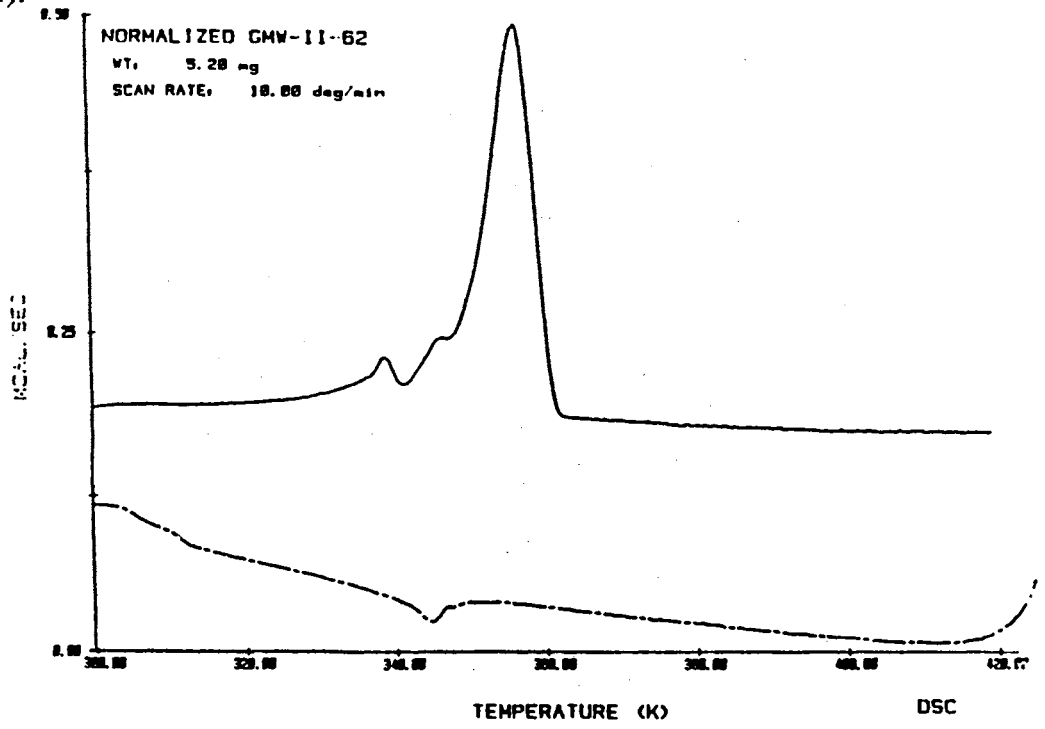


Figure 10. Polarizing Micrograph of **44c** at 66° C, Cooled From the Isotropic Liquid at 2 °C/min.

(1).



(2).

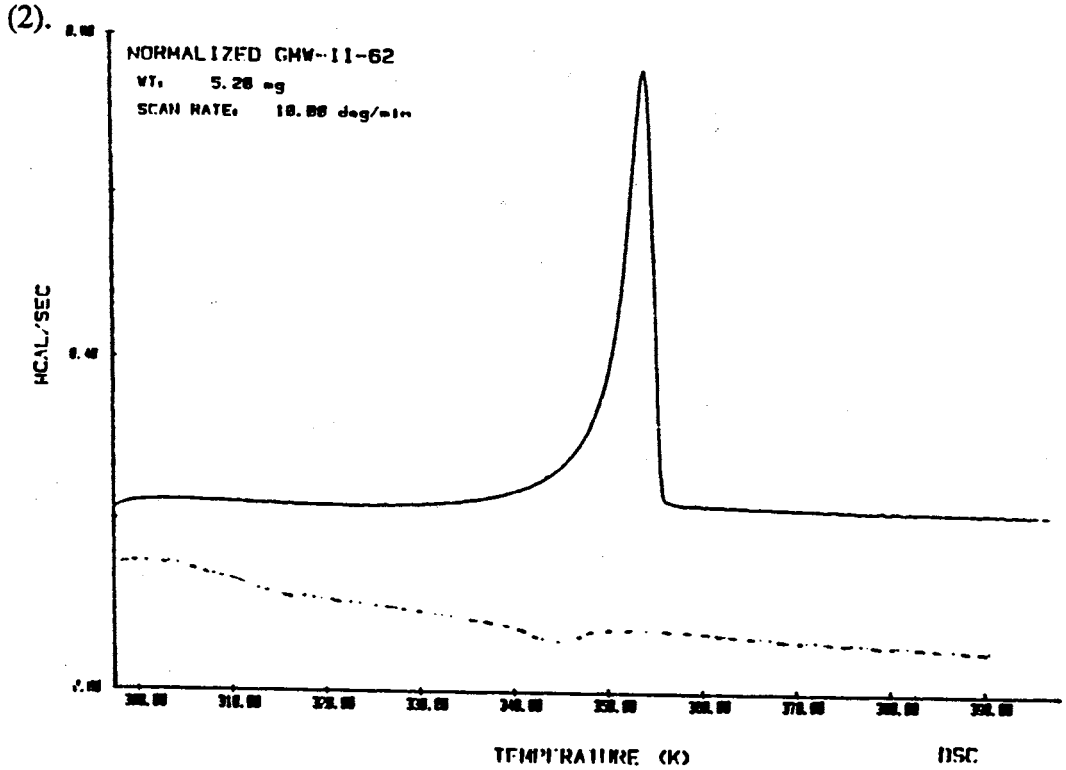


Figure 11. DSC Thermograms of **45c**: (1) First heating and cooling curves of the sample. (2) Second heating and cooling curves of the sample.

Figure 12. Polarizing Micrograph of **45c** at 63 °C, Cooled From the Isotropic Liquid at 2 °C/min.

for sulfoxides **43**, **44a**, and **44c**. Neither sulfoxides **43** (Figure 8) and **44a** nor the sufide **45a** showed mesophases under the polarizing microscope. These observations are consistent with the large enthalpy changes observed in the heating curves of these compounds. None of the three exhibited any peaks in the cooling curves.

The first and second cooling curves of both sulfoxide **44a** and **44c** showed considerable differences. The two *cooling* curves (Figures 8 and 9) of both compounds remained unchanged. No mesophase was observed during the first heating for **44c**. The LC phase observed on cooling **44c** (Figure 10) did exhibit the typical focal conic structure of the smectic/cholesteric mesophases. Both compounds exhibited an broad endothermic (broad endotherms are usually associated with dehydration, temperature dependent phase behavior or melting of polymers) peak in their second heating curves. Since the cooling curves of both sulfoxides are identical for both first and second cooling processes, it is not probable that a loss of water occurred, but rather a temperature dependent phase transition likely has taken place. However, no obvious change was observed under the polarizing microscope.

Sulfide **45c** (Figures 11) showed similarity in first and second heating and cooling curves Under the polarizing microscope there was observed for **45c**, on cooling, a mesophase (Figure 12) which was typical of smectic/cholesteric phases.

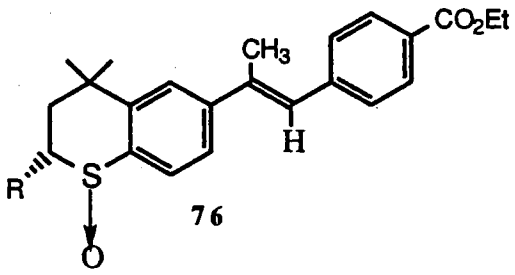
Summary

Several types of sulfur containing, C-2 alkylated heteroarotinoids were synthesized. Asymmetric oxidation at the sulfur to obtain a bifunctionalized (sulfoxide-ester) heteroarotinoid was expected to confer FLC properties to the compounds. Two compounds, sulfoxide **44c** and sulfide **45c**, containing octyl-ethyl chains showed good LC properties. Non-alkylated sulfide **42** and sulfoxide **43** were tested for biological activity in a TGase assay and showed modest activity. Compounds **42**, **43**, **44a**, **44c**,

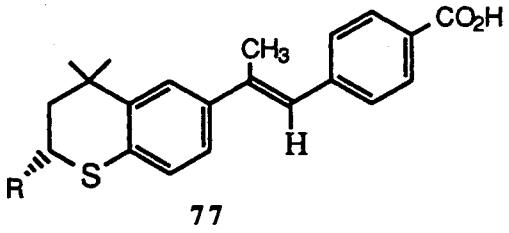
45a and **45c** are currently been screened for retinoid receptor specific activity at Ligand Pharmaceuticals, Incorporated, in San Diego, California.

Suggested Future Work

The modest TGase activity shown (Table VII) by novel retinoids **42** and **43**, coupled with the fact that retinoids can undergo undesirable oxidative degradation at benzylic and allylic positions, suggests that the heteroarotinoids could be further modified for improved biological activity by dimethylation (at C-2 and C-4), α-alkylation, or using a S(O) group as in **76**. Since carboxyl groups are found to be the most efficient polar end groups, an acid-sulfide (as **77**) could be highly active and also possibly RARγ receptor specific (compare with Table VIII).

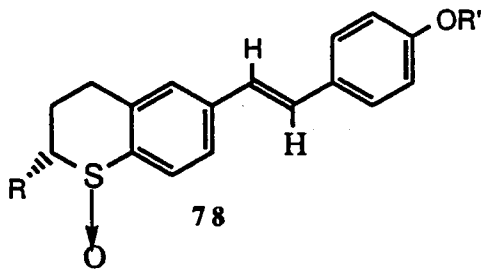


76

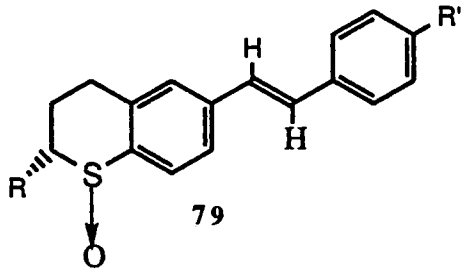


77

Enhanced LC properties could be expected by replacement of the methyl group on the propenyl bridge by an hydrogen atom (as in **78** and **79**). Ferroelectric LC properties could possibly be improved by replacing the ester function with an long chain ether group (**77**) or an alkyl group (**78**) for enhanced polarizabilty of the molecule.



78



79

CHAPTER III

EXPERIMENTAL

General information: All reactions were performed under N_2 with magnetic stirring unless otherwise specified. Evaporation of all solvents was effected with a rotary evaporator (Yamato; model RE-46) unless otherwise stated. IR spectra were recorded on a Perkin-Elmer 681 spectrophotometer as films or from KBr pellets. NMR spectral data were obtained on solutions ($DCCl_3$) using a Varian XL-300 spectrometer with ^1H and ^{13}C data being taken at 299.99 MHz and 75.4 MHz, respectively, and on a Varian XL-400 NMR BB spectrometer with ^1H and ^{13}C data being taken at 399.99 MHz and 100.5 MHz, respectively. References were to TMS in δ values or ppm, respectively. For saving space, the NMR frequencies in the experimental have been rounded to whole numbers. Data are reported as follows: chemical shifts (in δ value or ppm), multiplicity (s = singlet, d = doblet, t = triplet, q = quartet, m = multiplet, and bs = broad singlet), coupling constants (in Hz), and assignments. Mass spectral data were recorded on a VG analytical instrument, model ZAB-2SE. Melting points were determined on a Fischer-Johns melting point apparatus and a Thomas-Hoover melting point apparatus and were uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. A standard check was made with a glucose solution which had α = 2.582° [l = 10 dm, c = 4.92 g/100 mL, H_2O] and [α] = +52.5° {lit[1] [α] = +52.5°}. Differential Scanning Calorimetry (DSC) measurements were performed with a Perkin-Elmer DSC-2 instrument equipped with a TADs 3600 data station. The phase transition behavior and

mesomorph texture were observed with a Nikon OPTIPHOT-POL microscope with crossed polarizer and equipped with a Mettler FP 82 hot stage controlled by a Mettler FP 80 thermoregulator. RT = room temperature.

Reagent grade solvents were used without further purification. Chromatography was performed using the Chromatotron (Harrison Research, model 7924) with silica gel (pF 254 containing gypsum, EM Science) plates (2 mm and 4 mm thick). All elemental analyses were performed by Galbraith Laboratories, Knoxville, TN 37921. The following reagents were obtained commercially: ethyl acrylate (bp 99 °C, Aldrich), thiophenol (bp 169 °C, Aldrich), triethylamine (bp 88.8 °C, Aldrich), thiochroman-4-one (bp 154 °C/12 mm, Aldrich), mossy zinc (Aldrich), mercuric chloride (Aldrich), titanium (IV) isopropoxide (bp 232 °C, Aldrich), diethyl *L*-tartrate {bp 280 °C, $[\alpha]_D$ = +8.5 (neat), Aldrich}, trifluorocetic anhydride (bp 39.5-40 °C, Aldrich), *tert*-butyl hydroperoxide (TBHP, 70% solution in water, Aldrich), *n*-butylithium (1.6 *M* in hexanes, Aldrich), iodoethane (bp 71.6-72 °C, Baker), 1-bromobutane (bp 100.8-101.9 °C, Fisher), 1-bromooctane (bp 201 °C, Aldrich), sodium iodide (Aldrich), acetic anhydride (bp 138-140 °C, Aldrich), acetic acid (glacial, Aldrich), lithium aluminum hydride [mp 125 °C (dec), 95%+, Aldrich], triphenylphosphine (mp 79-81 °C, Aldrich), diisopropylamine (bp 84 °C, Aldrich), 18-crown-6 (99.5+%, Aldrich), potassium carbonate (Baker), *p*-toluic acid (mp 180-182 °C, Aldrich), aluminum chloride (Fisher), chromium (VI) oxide [mp 196 °C (dec), 99%+, Aldrich], ethyl alcohol (bp 78 °C, Aldrich), *n*-hexyl alcohol (bp 137-138 °C, Eastman), and *n*-octyl alcohol (bp 196 °C, Eastman). Ethyl 4-formylbenzoate was synthesized[55] from *p*-toluic acid.

Ethyl (*E*)-4-[2-(3,4-Dihydro-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate (42). A 100-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser, and a N_2 inlet. To a solution of phosphonium salt **46** (16.769 g, 32 mmol) in dry THF (50 mL) was added K_2CO_3 (4.47g, 32 mmol), 18-C-6 (80 mg), and ethyl 4-

formylbenzoate (**59a**, 4.8 g, 30 mmol). The mixture was boiled for 48 h. Water (10 mL) and glacial acetic acid (15 mL) were added successively to the solution which was allowed to cool to RT (1 h). The suspension formed was filtered (gravity), and the filtrate was washed with saturated NaCl (50 mL), dried (Na_2SO_4, overnight), and concentrated (rotovap) to a brown oil which was triturated (RT) with ether to yield sulfide **42** (4.3 g, 40%, white solid); mp 78-79 °C. IR (KBr) 1710 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$, 300 MHz) δ 1.4 [t, $^3J_{HCCH}$ = 7.4 Hz, 3 H, H(20)], 2.15 [quintet, $^3J_{HCCH}$ = 6.4 Hz, 2 H, H(3)], 2.25 [s, 3 H, H(10)], 2.85 [t, $^3J_{HCCH}$ = 6.4 Hz, 2 H, H(4)], 3.05 [t ,$^3J_{HCCH}$ = 6.4 Hz, 2 H, H(2)], 4.4 [q, $^3J_{HCCH}$ = 7.4 Hz, 2 H, H(19)], 6.8 [s, 1 H, H(11)], 7.05-8.05 [m, 7 H, ArH]. ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 14.3 [C(19)], 18.0 [C(10)], 22.9 [C(2)], 27.7 [C(3)], 29.9[C(1)], 60.8 [C(19)]; ArC and vinylic C: 124.13, 125.84, 126.52, 127.56, 128.19, 128.99, 129.43, 132.56, 133.62, 138.97, 139.24, 143.06; 167.0 [C(18)]. Mass spectral (EI) data Calcd for $C_{21}H_{22}O_2S$ *m/z* ($M^{+\cdot}$): 338.1337; Found: 338.1339. Anal. calcd for $C_{21}H_{22}O_2S$: C, 74.52; H, 6.55; S, 9.45. Found: C, 74.29; H, 6.51; S, 9.57.

Ethyl (*E*)-4-[2-(3,4-Dihydro-1-oxy-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate (43).[44] A 15-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, condenser and a rubber septum (N_2). To a stirred mixture of Ti(O-*i*-Pr)4 (14.9 mL, 5 mmol) and (+)-diethyl *L*-tartrate (17.1 mL, 10 mmol) in H_2CCl_2 (50 mL) was introduced water (0.9 mL, syringe) The mixture was stirred to a homogeneous solution. To this was added (syringe) the sulfide **42** (0.02 g, 5 mmol) in H_2CCl_2 (5 mL). The mixture was cooled (-20° C-dry ice-CCl_4), and TBHP (0.5 g, 5.5 mmol) in H_2CCl_2 (1.6 mL) was introduced (dropwise-syringe). Stirring was continued at -20 °C (4 h), and 50 mL of water was then added dropwise (10 min). Stirring was continued at -20 °C (1 h) and then at RT (1 h). A white gel was filtered off (filter aid was used), and the filtrate was evaporated (rotovap) and dried (Na_2SO_4, overnight) to give sulfoxide **43** as a light yellow solid. Crude sulfoxide was recrystallized ($HCCl_3$ and then ethanol) to obtain

white solid **43** (0.01g, 50%); mp 90-92 °C. ^{1}H NMR ($DCCl_3$, 300 MHz) δ 1.3 [t, $^3J_{HCCH}$ = 7.4 Hz, 3 H, H(20)], 1.9-2.05 (m, 1 H, H(3), 2.2 (s, 3 H, H(10)], 2.3-2.5 [m, 2 H, H(3)], 2.7-3.25 [m, 4 H, H(2) and H(4)], 4.3 [q, $^3J_{HCCH}$ = 7.4 Hz, 2 H, H(19)], 6.8 [s, 1 H, H(11)], 7.25-8.05 [m, 7 H, Ar-H]. ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 14.3 [C(2) and C(20)], 18.0 [C(10)], 28.0 [C(3)], 46.0 [C(3)], 61.4 [C(19)]; ArC and vinylic C: 124.31, 125.43, 126.23, 127.59, 128.09, 128.71, 129.42, 129.91, 130.09, 133.42, 139.31, 143.06; 165.02 [C(18)]. Mass spectral (EI) data Calcd for $C_{21}H_{22}O_3S$ *m/z* ($M^{+\cdot}$): 354.1289; Found: 354.1289. Anal. calcd for $C_{21}H_{22}O_3S$: C, 71.76; H, 6.26; S, 9.02. Anal. calcd for $C_{21}H_{22}O_3S{\cdot}0.5\ H_2O$: C, 69.39; H, 6.38. Found: C, 69.24; H, 6.16. ·

Ethyl (*E*)-4-[2-(3,4-Dihydro-2-ethyl-1-oxy-2*H*-1-benzothiopyran-6-yl)-1-propenyl] benzoate (44a).[44] To a stirred mixture of Ti(O-*i*-Pr)$_4$ (1.44 mL, 5 mmol) and (+)-diethyl *L*-tartrate (2.0 g, 10 mmol) in H_2CCl_2 (50 mL) in a 100-mL, two-necked, round-bottomed flask equipped with a magnetic stirrer, an addition funnel, condenser and rubber septum (N_2) was introduced water (88 μL-syringe) in a single portion. The mixture was stirred to a homogeneous solution. To this solution was added sulfide **45a** (R = ethyl, 1.78 g, 5 mmol) in H_2CCl_2 (15 mL, dropwise-addition funnel). To the cooled (-20 °C, dry ice-CCl_4) mixture was added TBHP (0.5 g, 5.5 mmol) in H_2CCl_2 (1.6 mL, dropwise-syringe). Stirring was continued (4 h) at -20 °C, and water (50 mL) was then added (10 min). Stirring was continued at -20 °C (1 h) and at RT (1 h). A white gel was filtered off (filter aid was used), and the filtrate was dried (Na_2SO_4, overnight) and evaporated (roto-vap) to give sulfoxide **44a** (light yellow solid). Crude sulfoxide was then recrystallized ($HCCl_3$ and then ethanol) to yield white **44a** (1.2 g, 64%); mp 88-89 °C. ^{1}H NMR ($DCCl_3$, 300 MHz) δ 0.85 [t, $^3J_{HCCH}$ = 7.3 Hz, 3 H, CH_2CH_3], 1.05 [t, $^3J_{HCCH}$ = 7.4 Hz, 3 H, H(20)], 1.2-1.4 (m, 1 H, H(3), 1.5-1.7 (m, 2 H, CH_2CH_3], 1.8-1.9 [s, 3 H, H(10)], 2.2- 2.3 [m, 1 H, H(3)], 2.5-2.8 [m, 4 H, H(2) and H(4)], 4.1 [q, $^3J_{HCCH}$ = 7.4 Hz, 2 H, H(19)], 6.8 [s, 1 H, H(11)], 7.25-8.05 [m, 7 H, Ar-H]. ^{13}C NMR ($DCCl_3$, 75 MHz) ppm

10.8 [CH_2CH_3]; aliphatic-C: 14.14, 17.39, 20.51, 21.48, 26.57, 59.53, 60.70; ArC and vinylic C: 124.76, 126.89, 128.01, 128.40, 128.80, 129.06, 129.25, 135.43, 138.08, 138.35, 142.09, 145.83, 166.11 [C(18)]. At 26 °C $[\alpha]_D$ = +39.60° (acetone). Mass spectral (EI) data Calcd for $C_{23}H_{26}O_3S$ *m/z* ($M^{+\cdot}$): 382.1602; Found: 382.1600. Anal. calcd for $C_{23}H_{26}O_3S$: C, 72.22; H, 6.86; S, 8.37. Found: C, 72.07; H, 6.92; S, 8.42.

Ethyl (*E*)-4-[2-(3,4-Dihydro-2-*n*-butyl-1-oxy-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate (44b).[44] To a stirred mixture of Ti(O-*i*-Pr)$_4$ (0.7 mL, 2.3 mmol) and (+)-diethyl *L*-tartrate (0.94 g, 4.6 mmol) in H_2CCl_2 (50 mL) in a 100-mL, two-necked, round-bottomed flask equipped with a magnetic stirrer, an addition funnel, condenser and a rubber septum (N_2) was introduced water (41 μL-syringe) in a single portion. The mixture was stirred to a homogeneous solution. To this solution was added sulfide **45b** (R = butyl, 0.9 g, 2.3 mmol) in H_2CCl_2 (15 mL, dropwise-addition funnel). To the cooled (-20 °C, dry ice-CCl_4) mixture was introduced TBHP (0.21 g, 2.3 mmol) in H_2CCl_2 (0.65 mL, dropwise-syringe). Stirring was continued at -20 °C (4 h), and 50 mL of water was then added dropwise (10 min). Stirring was continued at -20 °C (1 h) and then at RT (1 h). A white gel was filtered off (filter aid was used), and the filtrate was evaporated (rotovap) and dried (Na_2SO_4, overnight) to an orange oil which could be partially purified on a silica gel column (eluent-hexane:ethylacetate = 1:2) to give sulfoxide **44b** [light yellow oil; cis-trans mixture (1:3), 0.4 g, 45%]. ^{1}H NMR ($DCCl_3$, 400 MHz) δ 0.65-0.8 [t, $^3J_{HCCH}$ = 7.2 Hz, 3 H, $(CH_2)_3CH_3$], 0.95-1.3 [m, 9 H, $(CH_2)_3CH_3$ and OCH_2CH_3], 2.0-2.2 [s, 4 H, H(10) and H(3)], 2.3- 2.6 [m, 1 H, H(3)], 2.8-2.9 [m, 1 H, H(4), 3.0-3.3 [m, 2 H, H(2) and H(4)], 4.1 [q, $^3J_{HCCH}$ = 7.2 Hz, 2 H, H(19)], 6.4-6.8 [s, 1 H, H(11)], 6.9-8.1-8.05 [m, 7 H, Ar-H]. ^{13}C NMR ($DCCl_3$, 100 MHz) ppm aliphatic-C: 15.11, 15.46, 18.72, 23.74, 25.83, 30.48, 36.44, 38.07, 48.61, 62.08; ArC and vinylic C: 124.98, 126.47, 127.77, 128.69, 129.95, 129.99, 130.11, 130.15, 130.50, 130.63, 138.07, 139.16, 142.22, 143.15, 148.73, 167.44 [C(18)].

Ethyl (*E*)-4-[2-(3,4-Dihydro-2-*n*-octyl-1-oxy-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate (44c).[44] A 100-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, an addition funnel, condenser and a rubber septum. Water (41 μL) was introduced (syringe) in a single portion to a stirred mixture of Ti(O-*i*-Pr)4 (3.7 mL, 2.2 mmol) and (+)-diethyl *L*-tartrate (0.46 g, 4.5 mmol) in H_2CCl_2 (50 mL) (N_2). The mixture was stirred to a homogeneous solution. To this was added sulfide **45c** (R = *n*-octyl, 1.02 g, 2.2 mmol) in H_2CCl_2 (15 mL, dropwise-addition funnel). To the cooled (-20 °C, dry ice-CCl_4) mixture was introduced TBHP (0.19 g, 2.2 mmol) in H_2CCl_2 (0.7 mL, dropwise-syringe). Stirring was continued at -20 °C (4 h), and 4 mL of water was then added dropwise (10 min). Stirring was continued at -20 °C (1 h) and then at RT (1 h). A white gel was filtered off (filter aid was used), and the filtrate was dried (Na_2SO_4, overnight) and evaporated (rotovap) to give sulfoxide **44c** (light yellow solid). Recrystallized (ethanol) product gave a white **44c** (0.2 g, 30%); mp 122-124 °C. ^{1}H NMR ($DCCl_3$, 300 MHz) δ 0.9 [t, $^3J_{HCCH}$ = 7.3 Hz, 3 H, $(CH_2)_7CH_3$], 1.1-2.0 [m, 18 H, $(CH_2)_7CH_3$, OCH_2CH_3 and H(3)], 2.2-2.3 [s, 3 H, H(10)], 2.4- 2.6 [m, 1 H, H(3)], 2.7-3.2, [m, 4 H, H(2) and H(4)], 4.3 [q, $^3J_{HCCH}$ = 7.4 Hz, 2 H, H(19)], 6.8 [s, 1 H, H(11)], 7.25-8.05 [m, 7 H, Ar-H]. ^{13}C NMR ($DCCl_3$, 75 MHz) ppm aliphatic-C: 16.85, 17.11, 20.33, 25.40, 28.57, 28.65, 29.36, 30.50, 31.95, 32.05, 32.17, 34.57, 62.19, 63.75; ArC and vinylic C: 127.12, 128.12, 129.59, 131.61, 131.75, 1131.79, 132.30, 139.30, 140.32, 140.71, 144.83, 150.27; 168.80 [C(18)]. [α] = +29.9° (acetone). Anal. calcd for $C_{29}H_{38}O_3S$: C, 74.64; H, 8.21; S, 6.86. Anal. calcd for $C_{29}H_{38}O_3S{\cdot}0.5\ H_2O$: C, 73.22; H, 8.24. Found: C, 73.09; H, 8.14.

***n*-Hexyl (*E*)-4-[2-(3,4-Dihydro-2-*n*-octyl-1-oxy-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate (44d).**[44] A 100-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, an addition funnel, condenser and a rubber septum. Water (29 μL) was introduced (syringe) in a single portion to a stirred mixture of Ti(O-*i*-Pr)4 (0.47

mL, 1.6 mmol) and (+)-diethyl *L*-tartrate (0.65 g, 3.2 mmol) in H_2CCl_2 (50 mL) (N_2). The mixture was stirred to a homogeneous solution. To this was added sulfide **45d** (R = *n*-octyl, 0.8 g, 1.6 mmol) in H_2CCl_2 (15 mL, dropwise-addition funnel). To the cooled (-20 °C, dry ice-CCl_4) mixture was introduced TBHP (0.14 g mL, 1.6 mmol) in H_2CCl_2 (0.5 mL, dropwise-syringe). Stirring was continued at -20 °C (4 h), and 2 mL of water was then added dropwise (10 min). Stirring was continued at -20 °C (1 h) and then at RT (1 h). A white gel was filtered off (filter aid was used), and the filtrate was dried (Na_2SO_4, overnight) and evaporated (rotovap) to an dark orange oil which could be partially purified on a silica gel column (eluent-hexane:ethylacetate = 1:2) to give sulfoxide **44d** [thick, light yellow oil; cis-trans mixture (1:3), 0.2 g, 25%]. ^1H NMR ($DCCl_3$, 300 MHz) δ 0.9-1.2 [m, 6 H, $(CH_2)_7CH_3$ and $(CH_2)_5CH_3$], 1.15-2.1 [m, 20 H, $(CH_2)_7CH_3$, $(CH_2)_3CH_3$], 1.7-1.85 [m, 3 H, OCH_2CH_2 and H(3)], 2.2-2.3 [s, 4 H, H(10) and H(3)], 2.6- 2.9 [m, 1 H, H(3)], 2.9-3.5 [m, 4 H, H(2) and H(4)], 4.3 [q, $^3J_{HCCH}$ = 7.1 Hz, 2 H, H(19)], 6.4-6.8 [s, 1 H, H(11)], 7.9-8.1, 1 [m, 7 H, Ar-H]. ^{13}C NMR ($DCCl_3$, 75 MHz) ppm aliphatic-C: 13.99, 14.06, 17.60, 22.53, 22.61,25.69, 27.20, 28.68, 29.21, 29.45, 29.51, 31.44, 31.79, 35.62, 36.98, 47.48, 65.17; ArC and vinylic C: 123.91, 125.37, 126.63, 128.84, 128.89, 129.02, 129.39, 129.49, 129.52, 136.94, 138.03, 141.07, 142.00, 147.63; 166.40 [C(18)].

Ethyl (*E*)-4-[2-(3,4-Dihydro-2-ethyl-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate (45a). A mixture of the phosphonium salt **50a** (R = ethyl, 3.9 g, 11 mmol), K_2CO_3 (1.5 g, 11 mmol) and 18-C-6 (30 mg), in H_2CCl_2 (25 mL) was boiled for 2 h in a 100-mL, two-necked, round-bottomed flask equipped with a magnetic stirrer, a condenser, and a N_2 inlet. To the above boiling mixture was added ethyl 4-formylbenzoate **59a** (1.7 g, 10 mmol) in H_2CCl_2 (10 mL) via an addition funnel in single portion.[3] The resulting mixture was boiled for 12 h and then concentrated (rotovap) to obtain an orange oil which was then treated with hexane (150 mL). A suspension formed and was filtered. The

filtrate was washed with brine (50 mL), dried (Na_2SO_4), and concentrated (rotovap) to give a yellow oil which was separated on a silica gel column (eluent-hexane:ethylacetate = 1:1) to give the sulfide **45a** (R = ethyl, not a reported compound) as a yellow solid. Recrystallization (ether) gave sulfide **45a** (R = ethyl, 2.3 g, 91%) as a white solid; mp 63-64 °C. IR (neat) 1750 cm^{-1} (C=O); ^1H NMR ($DCCl_3$, 400 MHz) δ 1.05 [t, J = 7.4 Hz, 3 H, CH_2CH_3], 1.4 [t, J = 7.3 Hz, 3 H, OCH_2CH_3], 1.6-1.85 [m, 3 H, CH_2CH_3 and H(3)], 2.25-2.35 [m, 4 H, H(3) and H(10)], 2.8-2.9 [m, 2 H, H(4)], 3.2-3.3 [m, 1 H, H(2)], 4.4 [q, J = 7.3 Hz, 2 H, OCH_2CH_3], 6.8 [s, 1 H, H(11)], 7.05-8.15[m, 7 H, ArH]; ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 11.49 [CH_2CH_3]; aliphatic-C: 14.39,17.54, 29.43, 29.47, 29.66, 43.98, 60.90 [C(19)]; ArC and vinylic C: 124.11, 125.80, 126.38, 127.16, 127.33, 127.72, 129.09, 129.46, 133.18, 133.65, 139.02, 143.10; 166.14 [C(18)]. Mass spectral (EI) data Calcd for $C_{23}H_{26}O_2S$ *m/z* ($M^{+\cdot}$): 366.1653; Found: 366.1650. Anal. calcd for $C_{23}H_{26}O_2S$: C, 75.38; H, 7.16; S, 8.73. Anal. calcd for $C_{23}H_{26}O_2S \cdot 0.2\ H_2O$: C, 74.64; H, 7.19. Found: C, 74.68; H, 7.30.

Ethyl (*E*)-4-[2-(3,4-Dihydro-2-*n*-butyl-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate (45b). To a boiling mixture of the phosphonium salt **50b** (R = *n*-butyl, 2.7 g, 4.7 mmol), K_2CO_3 (0.65 g, 4.7 mmol) and 18-C-6 (30 mg), in H_2CCl_2 (15 mL) in a 50-mL, two-necked, round-bottomed flask equipped with a magnetic stirrer, a condenser, and a N_2 inlet was added ethyl 4-formylbenzoate (**59a**, 0.76 g, 4.2 mmol) in H_2CCl_2 (10 mL) via an addition funnel in single portion.[5] The resulting mixture was boiled for 12 h and then concentrated (rotovap) to obtain an orange oil which was then treated with hexane (150 mL). A suspension formed and was filtered. The filtrate was washed with brine (50 mL), dried (Na_2SO_4), and concentrated (rotovap) to give a yellow oil which was separated on a silica gel column (eluent-hexane:ethylacetate = 1:1) to give the sulfide **45b** (R = *n*-butyl, 1.0 g, 55%, not a reported compound) as a yellow oil and which was used directly to prepare **44b**. IR (neat) 1750 cm^{-1} (C=O); ^1H NMR ($DCCl_3$, 400 MHz) δ 0.95

[t, J = 7.5 Hz, 3 H, $(CH_2)_7CH_3$], 1.3-1.5 [m, 5 H, $(CH_2)_2CH_3$ and OCH_2CH_3], 1.6-1.85 [m, 3 H, $CH_2(CH_2)_2$ and H(3)], 2.15-2.3 [m, 4 H, H(3) and H(10)], 2.8-2.9 [m, 2 H, H(4)], 3.25-3.35 [m, 1 H, H(2)], 4.35 [q, J = 7.5 Hz, 2 H, OCH_2CH_3], 6.8 [s, 1 H, H(11)], 7.05-8.15[m, 7 H, ArH]; ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 13.96 [$(CH_2)_3CH_3$]; aliphatic-C: 14.22, 17.36, 22.45, 22.62, 25.56, 29.19, 33.91, 37.74, 60.67 [C(19)]; ArC and vinylic C: 123.94, 125.51, 126.25, 127.27, 127.96, 128.65, 128.83, 129.01, 129.26, 137.05, 138.84, 142.91, 168.95 [C(18)].

Ethyl (*E*)-4-[2-(3,4-Dihydro-2-*n*-octyl-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate (45c). A 50-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser, and a N_2 inlet. To a boiling mixture of the phosphonium salt **50c** (R = *n*-octyl, 2.0 g, 3 mmol), K_2CO_3 (0.4 g, 3 mmol) and 18-C-6 (30 mg), in H_2CCl_2 (15 mL) was added ethyl 4-formylbenzoate (**59a**, 0.5 g, 3 mmol) in H_2CCl_2 (10 mL) via an addition funnel in a single portion.[3] The mixture was boiled for 12 h and was then concentrated (rotovap) to obtain an orange oil which was treated with hexane (150 mL). A suspension formed and was filtered. The filtrate was washed with saturated NaCl (50 mL), dried (Na_2SO_4, 2 h), and concentrated (rotovap) to give a yellow oil which was separated on a silica gel column (eluent-hexane:ethylacetate = 1:1) to give the sulfide **45c** (R = *n*-octyl, 1.1 g, 79%, not a reported compound) as a white solid; mp 72-73 °C. IR (neat) 1750 cm^{-1} (C=O); ^1H NMR ($DCCl_3$, 400 MHz) δ 0.95 [t, J = 7.5 Hz, 3 H, $(CH_2)_7CH_3$], 1.1-1.7 [m, 17 H, $(CH_2)_7CH_3$ and OCH_2CH_3], 2.8-2.95 [m, 1 H, H(3)], 2.15-2.3 [m, 4 H, H(3) and H(10)], 2.8-2.9 [m, 2 H, H(4)], 3.1-3.2 [m, 1 H, H(2)], 4.3 [q, J = 7.5 Hz, 2 H, OCH_2CH_3], 6.8 [s, 1 H, H(11)], 7.0-8.1[m, 7 H, ArH]; ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 14.05 [$(CH_2)_3CH_3$]; aliphatic-C: 14.31, 17.46, 22.61, 25.55, 27.08, 29.26, 29.54, 29.63, 31.87, 36.83, 37.83, 42.31; 60.79 [C(19)]; ArC and vinylic C: 124.03, 125.63, 126.34, 127.39, 128.93, 129.36, 132.08, 148.01, 149.10, 149.32, 143.8; 168.82 [C(18)]. Mass spectral (EI) data Calcd for $C_{29}H_{38}O_2S$ *m/z* ($M^{+\cdot}$): 450.2593;

Found: 450.2595. Anal. Calcd for $C_{29}H_{38}O_2S$: C, 77.29; H, 8.51; Found: C, 77.61; H, 8.31.

***n*-Hexyl (*E*)-4-[2-(3,4-Dihydro-2-*n*-octyl-2*H*-1-benzothiopyran-6-yl)-1-propenyl] benzoate (45d).** A 50-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser, and a N_2 inlet. To a boiling mixture of the phosphonium salt **50c** (R = *n*-octyl, 1.5 g, 2.3 mmol), K_2CO_3 (0.33 g, 2.3 mmol) and 18-C-6 (30 mg), in H_2CCl_2 (15 mL) was added *n*-hexyl 4-formylbenzoate (**59b**, 0.55 g, 2.3 mmol) in H_2CCl_2 (10 mL) via an addition funnel in a single portion.[3] The mixture was boiled for 12 h and was then concentrated (rotovap) to obtain an orange oil which was then treated with hexane (150 mL). A suspension formed and was filtered. The filtrate was washed with saturated NaCl (50 mL), dried (Na_2SO_4, 2 h), and concentrated (rotovap) to give a yellow oil which was separated on a silica gel column (eluent-hexane:ethylacetate = 1:1) to give the sulfide **45d** (R = *n*-octyl, 1.2 g, 83%, not a reported compound) as an orange oil containing cis:trans isomers (1:3). It was not possible to separate the desireable trans isomer via column chromatography (silica gel, eluent-hexane:ethylacetate = 1:1). The estimated ratio of isomers based on ^{1}H NMR analysis of signals at δ 6.4 and 6.8 was 1:3. IR (neat) 1750 cm^{-1} (C=O); ^{1}H NMR ($DCCl_3$) δ 0.8-1.8 [29 H, $(CH_2)_7CH_3$, $(CH_2)_5CH_3$, $(CH_2)_7CH_3$, $(CH_2)_4CH_3$, and H(3)], 2.0-2.05 [m, 4 H, H(3) and H(10)], 2.5-2.9 [m, 3 H, H(4)], 3.1-3.4 [m, 1 H, H(2)], 4.3 [q, J = 7.2 Hz, 2 H, $OCH_2(CH_3)_5$, 6.4-8.1 [m, 8 H, H(11) and ArH]; ^{13}C NMR ppm 14.05 [$(CH_2)_3CH_3$]; aliphatic-C: 14.31, 17.46, 22.61, 25.55, 27.08, 29.26, 29.54, 29.63, 31.87, 36.83, 37.83, 42.31; 60.79 [C(19)]; ArC and vinylic C: 124.03, 125.63, 126.34, 127.39, 128.93, 129.36, 132.08, 148.01, 149.10, 149.32, 143.8; 168.82 [C(18)].

1-[(Thiochroman-6-yl)ethyl]triphenylphosphonium Bromide (46). A solution of

the alcohol **58** (4.4 g, 23 mmol) and triphenylphosphine hydrobromide (7.8 g, 23 mmol) in H_2CCl_2 was stirred at RT for 24 h in a 50-mL, single-necked, round-bottomed flask (N_2). The resulting mixture was concentrated (rotovap) to a foam which was dried under vaccum (80 °C/0.25 mm Hg; 1 h) to give **46** as a yellow solid(11.5 g, 97%; mp 68-70°C) which was used directly to prepare **42**. ^{1}H NMR ($DCCl_3$, 300 MHz) δ 1.6 [dd, $^3J_{HCCH}$ = 7.0 Hz, 3 H, C*H*$_3$], 1.8 [quintet, $^3J_{HCCH}$ = 5.7 Hz, 2 H, H(3)], 2.4 [t, $^3J_{HCCH}$ = 5.7 Hz, 2 H, H(4)], 2.8 [t, $^3J_{HCCH}$ = 5.7 Hz, 2 H, H(2)], 6.4-6.5 (m, $^3J_{HCCH}$ = 7.0 Hz, 1 H, CH_3CH), 6.65-7.9 (m, 18 H, ArH). ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 16.92 [CH_3CH], 22.39 [C(3)], 27.54 [C(4)], 29.47 [C(2)], 34.5 [CH_3CH]; ArC: 117.39, 118.21, 126.62, 126.64, 128.00, 128.06, 128.34, 128.39, 128.48, 128.57, 128.60, 128.64, 130.06, 130.18, 132.02, 132.14, 132.16, 132.22, 133.82, 134.06, 134.63, 134.72, 134.77, 134.80.

3,4-Dihydro-2-ethyl-2*H*-1-benzothiopyran (47a).[15] To a stirred mixture of the sulfoxide **61a** (R = ethyl, 2.0 g, 10 mmol) and NaI (3.7 g, 25 mmol) in acetone (20 mL) at 0 °C (ice-water bath) in a 100-mL, 2-necked, round-bottomed flask equipped with a magnetic stirrer, and a condenser was added (addition funnel) slowly (30 min) trifluoroacetic anhydride (4.2 mL, 30 mmol) in acetone (25 mL) under N_2. The reaction mixture was stirred at 0 °C (1 h) after which time acetone was evaporated (rotovap). Water (50 mL) was added to the resulting mixture which was then extracted with ether (3 x 25 mL). The ether extracts were washed with water (50 mL), saturated $Na_2S_2O_3$ (3 x 50 mL), water (50 mL), and saturated NaCl (50 mL). After drying ($MgSO_4$, overnight), the solvent was evaporated (rotovap), and the dark red oil obtained was subjected to flash chromatography (silica gel, eluent-hexane). Hexane was evaporated (rotovap) to give the sulfide **47a** (R = ethyl, 1.8 g, 98%) as a light yellow oil. ^{1}H NMR ($DCCl_3$, 400 MHz) δ 1.07 [t, $^3J_{HCCH}$ = 7.3 Hz, 3 H, CH_3], 1.65-1.85 [m, 3 H, C*H*$_2$CH$_3$ and H(3)], 2.2-2.3 [m, 1 H, H(3)], 2.75-2.9 5 [m, 2 H, H(4)], 3.2-3.3 [m, 1 H, H(2)], 6.9-7.1 [m, 4 H, ArH]; ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 11.4 [CH_3]; aliphatic-C: 29.36, 29.41, 29.43, 43.79; ArC:

123.74, 126.32, 126.38, 129.51, 133.58, 133.83. Recorded[56] properties: ^{1}H NMR ($DCCl_3$) δ 1.04 [t, 3 H], 1.40-3.45 [m, 7 H], 6.83-7.60 [m, 4 H, ArH]. No other properties of **47a** were reported.

3,4-Dihydro-2-*n*-butyl-2*H*-1-benzothiopyran (47b).[15] In a 100-mL, two-necked, round-bottomed flask was stirred a mixture of the sulfoxide **61b** (R = *n*-butyl, 6.4 g, 29 mmol) and NaI (10.4 g, 69 mmol) in acetone (20 mL) at 0 °C (ice-water bath). To the above stirred mixture was added (addition funnel) slowly trifluoroacetic anhydride (11.8 ml, 84 mmol) in acetone (25 mL) under N_2. The reaction mixture was stirred for 1 h. Acetone was evaporated (rotovap), water (50 mL) was added, and the mixture was extracted with ether (3 x 25 mL). The ether extracts were washed with water (50 mL), saturated $Na_2S_2O_3$ (3 x 50 mL), water (50 mL), and saturated NaCl (50 mL). After drying ($MgSO_4$, overnight), the solvent was evaporated (rotovap), and the red oil obtained was passed through a short silica gel column with hexane as eluent. Hexane was evaporated (rotovap) to obtain the sulfide **47b** (R = *n*-butyl, 5.3 g, 90%) as a yellow oil. The oil was used directly to prepare ketone **48b**. ^{1}H NMR ($DCCl_3$, 300 MHz) δ 0.95 [t, $^3J_{HCCH}$ = 0.7 Hz, 3 H, CH_3], 1.2-1.5 [bs, 6 H, $(CH_2)_3CH_3$], 1.95-2.05 [m, 1 H, H(3)], 2.2-2.3 [m, 1 H, H(3)], 2.8-2.95 [m, 2 H, H(4)], 3.15-3.25 [m, 1 H, H(2)], 6.9-7.1 [m, 4 H, ArH]; ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 14.4 [CH_3]; aliphatic-C: 22.9, 29.4, 29.8, 30.2, 36.7, 42.5; ArC: 123.14, 123,31, 125.89, 125.92, 126.05, 129.44. Reported[56] properties: ^{1}H NMR ($DCCl_3$) δ 0.90 [t, 3], 1.35-2.48 [m, 8 H], 2.78 [m, 2 H], 2.90 [m, 1 H], 6.80-7.35 [m, 4 H, ArH]. No other properties of **47b** have been recorded.

3,4-Dihydro-2-*n*-octyl-2*H*-1-benzothiopyran (47c).[15] A 100-mL, two-necked, round-bottomed flask was equipped wirh a magnetic stirrer, and a condenser (N_2). To a stirred mixture of the sulfoxide **61c** (R = *n*-octyl, 1.7 g, 6 mmol) and NaI (2.2 g, 15 mmol) in acetone (20 mL) at 0 °C (ice-water bath) was added (addition funnel) slowly

trifluoroacetic anhydride (2.5 ml, 18 mmol) in acetone (25 mL) under N_2. The reaction mixture was stirred (1 h) at 0 °C. Acetone was evaporated (rotovap), water (50 mL) was added, and the mixture was extracted with ether (3 x 25 mL). The ether extracts were washed with water (50 mL), saturated $Na_2S_2O_3$ (3 x 50 mL), water (50 mL) and saturated NaCl (50 mL). After drying ($MgSO_4$, overnight), the solvent was evaporated (rotovap), and the red oil obtained was passed through a short silica gel column with hexane as eluent. Hexane was evaporated (rotovap) to give sulfide **47c** (R = *n*-octyl, 1.5 g, 95%) as a light yellow oil which was used directly to make **48c**. ^{1}H NMR ($DCCl_3$, 300 MHz) δ 0.88 [t, $^3J_{HCCH}$ = 0.7 Hz, 3 H, CH_3], 1.2-1.5 [bs, 12 H, $(CH_2)_6CH_3$], 1.6-1.8 [m, 3 H, $CH_2(CH_2)_6$ and H(3)], 2.2-2.3 [m, 1 H, H(3)], 2.75-2.9 [m, 2 H, H(4)], 3.25-3.57 [m, 1 H, H(2)], 6.9-7.1 [m, 4 H, ArH]; ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 13.67 [CH_3]; aliphatic-C: 22.22, 22.37, 25.40, 26.70, 28.88, 29.13, 29.27, 31.43, 33.92, 37.21; ArC: 123.14, 123,31, 125.89, 125.92, 126.05, 129.44. Recorded[56] properties: ^{1}H NMR ($DCCl_3$) δ 1.03 [t, 3 H, CH_3], 1.43 [m, 12 H, $(CH_2)_6CH_3$], 1.8-2.62 [m, 4 H, $CH_2(CH_2)_6$ and H(4)], 2.80-3.10 [dd, 2 H, H(3)], 3.15-3.57 [bs, 1H, H(2)] , 6.97-7.31 [m, 4 H, ArH]. No other properties of **47c** have been reported.

6-Acetyl-2-ethylthiochroman (48a). To a stirred suspension of $AlCl_3$ (2.9 g, 22 mmol) in nitromethane (50 mL, magnetic stirrer, N_2) at 0 °C (ice-water bath),in a 200-mL, three-necked, round-bottomed flask equipped with a condenser and an addition funnel was added (via syringe) acetic anhydride (0.9 mL, 10 mmol). To the mixture was added (addition funnel, 5 min) a solution of thiochroman **47a** (R = ethyl, 1.8 g, 10 mmol) in CS_2:nitromethane (1:5, 25 mL). The solution was stirred at 0 °C for 1 h and then allowed to warm to RT. Stirring was continued for 48 h after which time the solution was cooled to 0 °C (ice-water bath) and then quenched with water (75 mL, 30 min). The aqueous layer was extracted with $HCCl_3$ (4 x 50 mL). Combined organic extracts were washed with saturated $NaHCO_3$ (3 x 50mL), water (2 x 50 mL) and saturated NaCl (1 x

50 mL). After drying (Na_2SO_4, overnight), the solution was evaporated (rotovap) to a red oil which was separated on a silica gel column (hexane:ether = 20:80) to give the ketone **48a** (R = ethyl, 1.5 g, 72%, not a reported compound) as an orange oil. The ketone **48a** was used directly to prepare **49a**. IR (neat) 1680 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$, 400 MHz) δ 1.05 [t, $^3J_{HCCH}$ = 7.4 Hz, 3 H, CH_3], 1.6-1.8 [m, 3 H, H(3) and CH_2CH_3] , 2.2-2.3 [m, 1 H, H(3)], 2.3 [m, 1 H, H(3)], 2.5-2.6 [s, 3 H, $CH_3C(O)$], 2.65-3.0 [m, 2 H, H(4)], 3.2-3.3 [m, 1 H, H(2)], 7.2-7.7 [m, 3 H, ArH]; ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 11.25 [CH_3]; aliphatic-C: 26.26, 28.75, 29.24, 29.82, 44.0; ArC: 126.01, 126.22, 129.23, 132.70, 133.41, 141.27; 197.25 [C(O)].

6-Acetyl-2-*n*-butylthiochroman (48b). A 200-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, condenser, and a N_2 inlet. Acetic anhydride (1.7 mL, 18 mmol) was added to a stirred suspension of $AlCl_3$ (5.2 g, 39 mmol) in nitromethane (50 mL) at 0 °C (ice-water bath) under N_2. To the above stirred mixture was added (addition funnel, 25 min) a solution of thiochroman **47b** (R = *n*-butyl, 3.6 g, 18 mmol) in CS_2:nitromethane (1:5, 25 mL). The solution was stirred at 0 °C for 1 h and then allowed to warm to RT; stirring was continued for 48 h. The solution was cooled (ice-water bath) to 0 °C and then quenched with water (150 mL). The aqueous layer was extracted with $HCCl_3$ (4 x 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (3 x 50 mL), water (2 x 50 mL) and saturated NaCl (1 x 50 mL). After drying (Na_2SO_4, overnight), the solution was evaporated (rotovap) to give ketone **48b** (R = *n*-butyl, 4.3 g, quantitative) as a red oil which was used directly to prepare alcohol **49b**. IR (neat) 1680 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$, 300 MHz) δ 0.85 [t, $^3J_{HCCH}$ = 0.7 Hz, 3 H, CH_3], 1.2-1.6 [m , 6 H, $(CH_2)_3CH_3$], 1.85 [m, 1 H, H(3)], 2.15 [m, 1 H, H(3)], 2.5 [s, 3 H, $CH_3C(O)$], 2.7-2.9 [m, 2 H, H(4)], 3.05-3.15 [m, 1 H,H(2)], 7.1-7.7 [m, 3 H, ArH]; ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 13.99 [CH_3]; aliphatic-C: 22.64, 22.84,

25.12, 26.29, 29.08, 33.84, 37.61; ArC: 126.23, 126.03, 129.49, 132.61, 137.66, 139.84, 197.32 [C(O)].

6-Acetyl-2-*n*-octylthiochroman (48c). Acetic anhydride (0.5 mL, 6 mmol) was added to a stirred suspension of $AlCl_3$ (1.4 g, 9 mmol) in nitromethane [50 mL, 0 °C (ice-water bath) magnetic stirrer, N_2] in a 200-mL, three-necked, round-bottomed flask equipped with a condenser/addition funnel (N_2). To the above stirred mixture was added (addition funnel, 5 min) a solution of 2-octylthiochroman **47c** (R = *n*-octyl, 1.5 g, 6 mmol) in CS_2:nitromethane (1:5, 25 mL). The solution was stirred at 0 °C for 1 h and then allowed to warm to RT; stirring was continued for 48 h. The solution was cooled to 0° C (ice-water bath) and then quenched with water (50 mL, 15 min). The aqueous layer was extracted with $HCCl_3$ (4 x 50 mL). Combined organic extracts were washed with saturated $NaHCO_3$ (3 x 50mL), water (2 x 50 mL) and saturated NaCl (1 x 50 mL). After drying (Na_2SO_4, overnight), the solution was evaporated (rotovap) to a red oil which was separated on a silica gel column (hexane:ether = 20:80) to give the ketone **48c** (R = *n*-octyl, quantitative yield, not a reported compound) as an orange oil. The ketone **48c** was used directly to make **49c**. IR (neat) 1680 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$, 300 MHz) δ 0.9 [t, $^3J_{HCCH}$ = 0.7 Hz, 3 H, CH_3], 1.35-1.45 [m 14 H, $(CH_2)_7CH_3$], 2.0 [m, 1 H, H(3)], 2.3 [m, 1 H, H(3)], 2.7 [s, 3 H, $CH_3C(O)$], 2.9-3.3 [m, 3 H, H(2) and H(4)], 7.2-7.7 [m, 3 H, ArH]; ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 14.07 [CH_3]; aliphatic-C: 22.62, 22.90, 25.11, 27.99, 29.37, 29.42, 29.51, 29.62, 31.82, 34.19, 37.67; ArC: 126.29, 126.34, 129.56, 132.67, 137.75, 139.89; 197.42 [C(O)].

2-Ethylthiochroman-6-ethanol (49a). To a stirred suspension of $LiAlH_4$ (0.39 g, 10 mmol) in dry ether (10 mL) under N_2 in a 50-mL, two-necked, round-bottomed flask equipped with a magnetic stirrer, condenser, and a addition funnel was added (addition funnel, 10 min) a solution of the ketone **48a** (R = ethyl, 1.5 g, 7 mmol) in dry ether (15

mL). The resulting mixture was boiled for 6 h. It was then cooled (0 °C; ice-water bath), and ethyl acetate (25 mL) was slowly added via an addition funnel (~0.5 h) followed by 5% HCl (10 mL, 10 min). The new mixture was stirred for 5 min. The aqueous layer was extracted with ether (3 x 25 mL). Combined organic layers were washed with saturated $NaHCO_3$ (2 x 25 mL), water (25 mL) and saturated NaCl (25 mL). After drying ($MgSO_4$, overnight), the solvent was evaporated (rotovap) to give an orange oil which was separated on a silica gel column (hexane:ether = 1:1) to give alcohol **49a** (R = ethyl, 1.3 g, 86%, not a reported compound) as a yellow oil. Alcohol **49a** was used directly to prepare **50a.** IR (neat) 3350 (O-H) cm^{-1}; ^1H NMR ($DCCl_3$, 400 MHz) δ 1.05 [t, $^3J_{HCCH}$ = 7.4 Hz, 3 H, CH_3], 1.4-1.5 [d, $^3J_{HCCH}$ = 6.4 Hz, 3 H, $CH_3C(OH)$], 1.6-1.8 [m, 3 H, H(3) and CH_3CH_2], 1.9-2.05[s, 1 H, OH], 2.2-2.3 [m, 1 H, H(3)], 2.8-2.9 [m, 2 H, H(4)], 3.15-3.25 [m, 1 H, H(2)], 4.75-4.85 [m, $^3J_{HCCH}$ = 6.4 Hz, 1 H, $CH_3CH(OH)$], 6.9-7.1 [m, 3 H, ArH]; ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 11.39 [CH_3]; aliphatic-C: 24.92, 29.32, 29.36, 29.46, 43.76; 69.97 [$CH_3C(OH)$]; ArC: 123.51, 123.59, 126.42, 126.61, 133.82, 141.72.

2-*n*-Butylthiochroman-6-ethanol (49b). A 100-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, condenser, and a N_2 inlet. To a stirred suspension of $LiAlH_4$ (0.82 g, 38 mmol) in dry ether (25 mL) under N_2 was added (addition funnel, 10 min) the ketone **48b** (R = *n*-butyl, 3.6 g, 25 mmol) in dry ether (25 mL). This mixture was boiled for 6 h. It was then cooled to 0 °C, and ethyl acetate (25 mL) was slowly added via an addition funnel (30 min) followed by 5% HCl (10 mL, 10 min). The resulting mixture was stirred for 5 min. The aqueous layer was extracted with ether (3 x 25 mL). Combined organic layers were washed with saturated $NaHCO_3$ (2 x 25 mL), water (25 mL), and saturated NaCl (25 mL). After drying ($MgSO_4$, overnight), the solvent was evaporated (rotovap) to give the alcohol **49b** (R = *n*-butyl, 3.0 g, 85%) as a yellow oil. This oil was used directly to prepare salt **50b**. IR (neat) 3350 (O-H) cm^{-1};

^{1}H NMR ($DCCl_3$, 300 MHz) δ 0.9 [t, $^3J_{HCCH}$ = 7.1 Hz, 3 H, CH_3], 1.1-1.85 [m 9 H, $(CH_2)_3CH_3$, H(3) and $CH_3C(OH)$], 2.05-2.2 [m, 1 H, H(3)], 2.8 [m, 2 H, H(4)], 3.2-3.45 [m, 1 H, H(2)], 4.8 [m, 1 H, $CH_3CH(OH$], 7.0-7.1 [m, 3 H, ArH]; ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 14.03 [CH_3]; aliphatic-C: 22.61, 22.71, 22.74, 24.99, 29.06, 29.09, 36.27, 42.15; 70.11 [$CH_3C(OH)$]; ArC: 123.63 123.67, 126.51, 126.72, 133.87, 141.43.

2-*n*-Octylthiochroman-6-ethanol (49c). A solution of the ketone **48c** (R = *n*-octyl, 1.5 g, 6 mmol) in dry ether (15 mL) was added (addition funnel, 10 min) to a stirred suspension of $LiAlH_4$ (0.38 g, 9 mmol) in dry ether (10 mL) under N_2 in a 50-mL, two-necked, round-bottomed flask equipped with a magnetic stirrer, condenser, and a addition funnel. This mixture was heated at reflux for 6 h. It was then cooled to 0 °C (ice-water bath), and ethyl acetate (25 mL) was slowly added via an addition funnel (~0.5 h) followed by 5% HCl (10 mL, 10 min). The mixture was stirred for 5 min. The aqueous layer was extracted with ether (3 x 25 mL). Combined organic layers were washed with saturated $NaHCO_3$ (2 x 25 mL), water (25 mL) and saturated NaCl (25 mL). After drying ($MgSO_4$, overnight), the solvent was evaporated (rotovap) to give an orange oil which was separated on a silica gel column (hexane:ether = 1:1) to give alcohol **49c** (R = *n*-octyl, 1.2 g, 80%, not a reported compound) as a yellow oil and which was used directly to make **50c**. IR (neat) 3350 (O-H) cm^{-1}; ^{1}H NMR ($DCCl_3$, 300 MHz) δ 0.9 [t, $^3J_{HCCH}$ = 0.7 Hz, 3 H, CH_3], 1.1-1.6 [m 17 H, $(CH_2)_7CH_3$ and $CH_3C(OH)$], 1.75-1.95 [m, 2 H, OH and H(3)], 2.0-2.2 [m, 1 H, H(3)], 2.8 [m, 2 H, H(4)], 3.1-3.15 [m, 1 H, H(2)], 4.65-4.8 [m, 1 H, $CH_3CH(OH$], 6.9-7.1 [m, 3 H, ArH]; ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 14.07 [CH_3]; aliphatic-C: 22.62, 22.70, 25.68, 25.70, 27.11, 29.27, 29.55, 29.64, 31.83, 34.34, 37.75; 70.05 [$CH_3C(OH)$]; ArC: 123.540, 123.62, 126.50, 126.92, 126.98, 139.08, 141.01.

1-[(2-Ethylthiochroman-6-yl)ethyl]triphenylphosphonium Bromide (50a). A

solution of alcohol **49a** (1.3g, 6 mmol) and triphenylphosphine hydrobromide (2.0 g, 6 mmol) in H_2CCl_2 (50 mL) was stirred at RT (24 h, N_2) in a 100-mL, single-necked, round-bottomed flask equipped with a magnetic stirrer and a condenser. After concentrating (rotovap) the mixture, the resulting orange oil was triturated with dry ether (50 mL) to obtain phosphonium salt **50a** (R = ethyl, 3.0 g, 96%) as a white solid. IR ($HCCl_3$) 3043 cm^{-1} (Ar C-H). Salt **50a** has not been reported previously.

1-[(2-*n*-Butylthiochroman-6-yl)ethyl]triphenylphosphonium Bromide (50b). In a 100-mL, single-necked, round-bottomed flask equipped with a condenser, magnetic stirrer, and a N_2 inlet was stirred (RT) a solution of alcohol **49b** (3.0 g, 12 mmol) and triphenylphosphine hydrobromide (4.1 g, 12 mmol) in H_2CCl_2 (25 mL). Stirring continued for 24 h, and the solvent was evaporated (rotovap). The resulting yellow oil was triturated (dry ether-50 mL, RT) to give phosphonium salt **50b** as a yellow solid (6.5 g, 90%). IR ($HCCl_3$) 3043 cm^{-1} (Ar C-H). Salt **50b** has not been reported previously.

1-[(2-*n*-Octylthiochroman-6-yl)ethyl]triphenylphosphonium Bromide (50c). A solution of alcohol **49c** (R = *n*-octyl, 4.4 g, 14 mmol) and triphenylphosphonium hydrobromide (5.0 g, 14 mmol) in H_2CCl_2 (50 mL) was stirred at RT (N_2, 24 h) in 100-mL, single-necked, round-bottomed flask eqiupped with a magnetic stirrer and a condenser. The solvent was then evaporated (rotovap), and the oil obtained was triturated (RT) with dry ether (50 mL) to obtain **50c** as a white solid (9.0 g, 98 %); mp 67-68 °C. Salt **50c** was used directly to prepare **45c**. ^1H NMR ($DCCl_3$, 400 MHz) δ 0.9 [t, $^3J_{HCCH}$ = 6.6 Hz, 3 H, CH_3], 1.1-1.6 [m 14 H, $(CH_2)_7CH_3$], 1.7-1.95 [m, 4 H, CH_3CH and H(3)], 2.0-2.2 [m, 1 H, H(3)], 2.5-2.7 [m, 1 H, H(4)], 2.8 [m, 1 H, H(4)], 3.0-3.1 [m, 1 H, H(2)], 6.55 [m, 1 H, CH_3CH], 6.9-7.1 [m, 3 H, ArH]; ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 14.15 [CH_3]; aliphatic-C: 16.89, 17.29, 22.68, 26.74, 26.95, 29.36, 29.44, 29.50, 29.74, 31.9, 34.12; 37.55 [$CH_3C(H)$]; ArC: 117.42, 117.52, 118.24, 118.33, 126.88, 128.55, 128.67,

129.26, 129.36, 130.04, 130.08, 130.12, 130.16, 130.21, 130.24, 132.11, 132.21, 133.82, 133.97, 134.64, 134.67, 134.73, 134.76, 134.82. Salt **50c** has not been reported previously.

Ethyl 3-(phenylthio)propionate (53).[43] In a 150-ml, three-necked, round-bottomed flask equipped with a magnetic stirrer and N_2 inlet was placed ethyl acrylate (**51**, 15.0 g, 0.15 mol) and thiophenol (**52**, 16.5 g, 0.15 mol). To this system, cooled in an ice-water bath, was added $HCCl_3$ (30 mL). The mixture was stirred for 10 min, and triethylamine (0.75 mL) was added (syringe through a septum). The ice-water bath was removed after the addition. The reaction mixture was then stirred at RT for 6.5 h. This mixture was allowed to cool to RT and diluted with ether (10 mL). The organic layer was washed with 10% NaOH (3 x 10 mL), water (1 x 25 mL) and saturated NaCl (1 x 20 mL). After drying (Na_2SO_4, overnight), the solvent was evaporated (rotovap) to give **53** as a light yellow oil (31.5 g, 100%). This oil was used directly to prepare **54**. IR (neat) 1740 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$, 400 MHz) δ 1.34 [t, $^3J_{HCCH}$ = 7.2 Hz, 3 H, CH_3], 2.5 [t, $^3J_{HCCH}$ = 7.3 Hz, 2 H, H(3)] , 3.05 [t, $^3J_{HCCH}$ = 7.3 Hz, 2 H, H(2)], 4.14 [q, $^3J_{HCCH}$ = 7.2 Hz, 2 H, CH_2CH_3], 7.1-7.3 [m, 5 H, ArH]; ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 16.33 [CH_3], 31.21 C(3), 36.61 C(2), 62.87 [OCH_2], ArC: 128.69, 131.16, 132.24, 137.42; 173.90 [C(O)].

3-(Phenylthio)propionic Acid (54).[43] In a 150-mL, single-necked, round-bottomed flask equipped with a magnetic stirrer, a N_2 inlet, and a condenser was placed ester **3** (20 g, 0.095 mol), acetone (60 mL), and 2 *N* HCl (30 mL). This mixture was boiled for 15 h and was then was then diluted with ether (4 x 25 mL). Combined ether extracts were washed with saturated $NaHCO_3$ (4 x 25 mL). Acidification of the solution in an ice bath to pH 1 with conc HCl and refrigeration overnight of the resulting solution produced white crystals of acid **54** (52%) which were filtered and dried (vaccum); mp 58.5-59 °C

(lit.[43] mp 59 °C). This solid was used without further purification to prepare **55**. ^{1}H NMR ($DCCl_3$, 400 MHz) δ 2.69 [t, $^3J_{HCCH}$ = 7.3 Hz, 2 H, H(3)], 3.17 [t, $^3J_{HCCH}$ = 7.3 Hz, 2 H, H(2)], 7.2-7.4 [m, 5 H, ArH]; ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 28.41 C(3), 33.84 C(2), ArC: 126.41, 128.74, 129.97, 134.52; 177.78 [C(O)].

3,4-Dihydro-2*H*-1-benzothiopyran-4-one (55).[23] Acid **54** (2 g, 16 mmol) was dissolved in conc H_2SO_4 (15 mL) at RT in a 100-mL volumetric flask to form a dark red solution. After 45 min at RT, the solution was poured onto crushed ice (150 g). The mixture was extracted (ethyl acetate-4 x 25 mL), and the organic phase was washed with water (2 x 50 mL), saturated $NaHCO_3$ (2 x 50 mL), water (1 x 50 mL), and saturated NaCl (50 mL). After drying ($MgSO_4$, overnight), the solution was evaporated (rotovap) to ketone **55** as a yellow oil (2.65 g, 88%). This oil was used directly to prepare **56**. IR (neat) 1680 (C=O) cm^{-1}; ^{1}H NMR ($DCCl_3$, 400 MHz) δ 2.99 [t, $^3J_{HCCH}$ = 6.6 Hz, 2 H, H(3)], 3.26 [t, $^3J_{HCCH}$ = 6.6 Hz, 2 H, H(2)], 7.1-8.2 [m, 5 H, ArH]; ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 26.93 C(3), 39.89 C(2), ArC: 125.33, 127.92, 129.52, 131.23, 133.58, 142,49; 194.34 [C(O)]. Reported properties:[43] bp 112-114 °C/1.5mm).

3,4-Dihydro-2*H*-1-benzothiopyran (56). In a 1-L, two-necked, round-bottomed flask equipped with a magnetic stirrer, N_2 inlet and a condenser was placed in the following order thiochroman-4-one **55** (3 g, 18 mmol), toluene (75 ml), water (120 mL), conc HCl (60 mL), and the Clemmenson-Martin[36] amalgam [50 g, prepared by shaking for 5 min a mixture of mossy Zn (50 g, 765 g atom), mercuric chloride (5 g, 18 mmol), conc HCl (2.5 mL), and water (75 mL)]. The heterogeneous mixture was boiled and stirred for 72 h, adding 20-mL portions of conc HCl at intervals of about 6 h to maintain a total volume of 500 mL. The mixture was allowed to cool to RT (1 h) and was then gravity filtered. The aqueous layer was extracted with toluene (2 x 50 mL). Combined organic layers were separated and washed with saturated $NaHCO_3$ (2 x 50 mL), water (2 x 50 mL), and

saturated NaCl (50 mL). Then the solution was dried ($MgSO_4$) overnight. Evaporation (rotovap) of the solvent gave **56** as a yellow oil (2.7 g, 98%) which was used directly to prepare ketone **57**. IR (neat) 1680 (C=O, weak) cm^{-1}; ^1H NMR ($DCCl_3$, 400 MHz) δ 2.1 [quintet, $^3J_{HCCH}$ = 6.1 Hz, 2 H, H(3)], 2.8 [t, $^3J_{HCCH}$ = 6.2 Hz, 2 H, H(4)], 3.0 [t, $^3J_{HCCH}$ = 6.0 Hz, 2 H, H(2)], 7.05-7.2 [m, 4 H, ArH]; ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 22.75 [C(3)], 27.46 [C(4)], 29.56 [C(2)]; ArC: 123.79, 126.28, 126.45, 129.87, 132.77, 133.73. Reported properties:[56] bp 81.5-82.5 °C/1.2 mm; ^1H NMR ($DCCl_3$) ppm 1.90 [m, 2 H, H(3)], 2.92 [quintet, 4 H, H(2) and H(4)], 6.90 [s, 4 H, ArH].

6-Acetylthiochroman (57). Acetic anhydride (4.1 g, 40 mmol) was added (syringe) to a stirred suspension of $AlCl_3$ (11.6 g, 88 mmol) in nitromethane (50 mL, magnetic stirrer) at 0 °C (ice-water bath) under N_2 to a 200-mL, three-necked flask, round-bottomed flask equipped with a condenser and an addition funnel. To the above stirred mixture was added (addition funnel, 15 min) a solution of thiochroman **56** (6.0 g, 40 mmol) in nitromethane (25 mL). The solution was stirred at 0 °C for 1 h and was then allowed to warm to RT; stirring was continued for 48 h. The solution was cooled (ice bath) to 0 °C and then quenched (water-150 mL). The aqueous layer was extracted with $HCCl_3$ (4 x 50 mL). Combined organic extracts were washed with 5% $NaHCO_3$ (3 x 50mL), water (2 x 50 mL) and saturated NaCl (1 x 50 mL). After drying (Na_2SO_4, overnight), the solution was evaporated (rotovap) to give ketone **57** as a red oil (7.6 g, 98%) which was used directly to prepare **58**. IR (neat) 1680 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$, 400 MHz) δ 1.9 [quintet, $^3J_{HCCH}$ = 6.0 Hz, 2 H, H(3)] , 2.35 [s, 3 H, $CH_3C(O)$], 2.65 [t, $^3J_{HCCH}$ = 6.0 Hz, 2 H, H(4)], 2.85 [t, $^3J_{HCCH}$ = 6.0 Hz, 2 H, H(2)], 6.9-7.5 [m, 3 H, ArH]; ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 22.87 [C(3)], 27.55 [C(4)], 29.77 [C(2)]; ArC: 126.01, 126.22, 129.23, 132.70, 133.41, 141.27; 197.25 [C(O)]. The mp of the 2,4-DNP of **57** (prepared in standard fashion) was 243-245 °C (lit.[23] mp 245 °C).

Thiochroman-6-ethanol (58). To a stirred suspension of $LiAlH_4$ (2.1 g, 55 mmol) in dry THF (140 mL) in a 250-mL, two-necked, round-bottomed flask equipped with a condenser and a magnetic stirrer was added (addition funnel, 30 min) under N_2 ketone **57** (7.0 g, 37 mmol) in dry THF (35 mL). This mixture was boiled for 6 h. It was then cooled to 0 °C, and ethyl acetate (75 mL) was slowly added (45 min) followed by 5% HCl (100 mL, 30 min). The resulting mixture was stirred for 5 min. The aqueous layer was extracted with $HCCl_3$ (3 x 50 mL). Combined organic layers were washed with saturated $NaHCO_3$ (2 x 50 mL), water (2 x 50 mL), and saturated NaCl (1 x 50 mL). After drying ($MgSO_4$, overnight), the solvent was evaporated (rotovap) to give crude alcohol **58** (5.6 g, 80%). Separation on silica gel [gradient elution, ethyl acetate:hexane (4:1) followed by MeOH] gave alcohol **58** as a red oil (5.05 g, 72%) which was used without further purification to prepare **46**. IR (neat) 3650-3100 (O-H) cm^{-1}; ^1H NMR ($DCCl_3$, 300 MHz) δ 1.64 [d, $^3J_{HCCH}$ = 6.4 Hz, 3 H, $CH_3C(OH)$], 1.9-2.05 [s, 1 H, OH], 2.3 [quintet, $^3J_{HCCH}$ = 6.1 Hz, 2 H, H(3)], 3.0 [t, $^3J_{HCCH}$ = 6.1 Hz, 2 H, H(4)], 3.2 [t, $^3J_{HCCH}$ = 6.1 Hz, 2 H, H(2)], 4.9 [q, $^3J_{HCCH}$ = 6.4 Hz, 1 H, $CH_3CH(OH)$], 7.2-7.3 [m, 3 H, ArH]; ^{13}C NMR ($DCCl_3$,, 75 MHz) ppm 22.87 [C(3)], 24.95 [$CH_3C(OH)$], 27.55 [C(4)], 29.77 [C(2)], 70.03 [$CH_3C(OH)$]; ArC: 123.63, 126.63, 127.05, 131.96, 133.86, 141.05.

Ethyl 4-Formylbenzoate (59a). A 250-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer and a condenser. A solution of **80a** (5.8 g, 35 mmol) in freshly distilled acetic anhydride (50 mL) and glacial acetic acid (50 mL) was cooled to 0 °C (ice-salt water bath). To the stirred solution was added conc H_2SO_4 (2.5 mL). To this solution was added slowly (1 h) CrO_3 (10.6 g, 100 mmol). Care was taken to maintain the temperature below 5 °C during the addition. When the addition was complete, a dark green reaction mixture remained which was stirred for 2 h at 0 °C. Decomposition was effected by slowly pouring the mixture onto crushed ice (250 g) and then adding (very slowly) 250 mL of cold water. A green-colored solution formed, and this was extracted

with ether (4 x 50 mL). Combined ether extracts were washed with water (2 x 50 mL), 5% Na_2CO_3 (4 x 50 mL), and brine (50 mL). When dried (Na_2SO_4, 2 h), the solution was evaporated (rotovap) to obtain the diacetate (4.7 g, 48%) as a yellow oil. To the diacetate in a 100-mL, single-necked round bottomed flask was added water (30 mL), 95% ethanol (30 mL), and conc H_2SO_4 (2 mL). The resulting solution was boiled for 6 h. After allowing to cool to RT (30 min), the solution was treated with water (20 mL), and the aqueous phase was extracted with $HCCl_3$ (3 x 50 mL). The combined extracts were washed with water (1 x 50 mL), 10% $NaHCO_3$ (2 x 50 mL), water (1 x 50 mL), and saturated NaCl (50 mL). When dried (Na_2SO_4, overnight), the solution was evaporated (rotovap) to give **59a** (2.3 g, 44%) as a colorless oil which was used immediately in the Wittig reaction with the phosphonium salts. Properties of **59a** are: IR (neat) 1740 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 1.4 (t, J = 7.5 Hz, 3 H, CH_3), 4.4 (q, J = 7.5 Hz, 2 H, CH_2), 7.9-8.2 (m, 4 H, Ar-H), 10.1 (s, 1 H, CHO). ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 14.15 [CH_3], 61.48 [CH_2]; ArC: 129.36, 130.02, 135.33, 138.97, 166.91 [C(O)OEt], 191 .57 [C(O)H]. These data agreed with previously reported properties.[55]

***n*-Hexyl 4-Formylbenzoate (59b).** A solution of **80b** (10.7 g, 49 mmol) in freshly distilled acetic anhydride (60 mL) and glacial acetic acid (60 mL) was cooled to 0 °C (ice-salt water bath) in a 300-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, a condenser, and a N_2 inlet. To the stirred solution was added conc H_2SO_4 (3 mL). Then CrO_3 (14.7 g, 146 mmol) was added slowly (1 h, the temperature was kept below 5 °C during the addition). When the addition was complete, a dark green reaction mixture remained which was stirred for 2 h at 0 °C. Decomposition was effected by slowly pouring the mixture onto crushed ice (250 g) and then adding (very slowly) 250 mL of cold water. A green-colored solution formed, and this was extracted with ether (4 x 50 mL). Combined ether extracts were washed with water (2 x 50 mL), 5% Na_2CO_3 (4 x 50 mL), and brine (50 mL). When dried (Na_2SO_4, 2 h), the solution was

evaporated (rotovap) to obtain the diacetate (5.2 g, 38%) as a yellow oil. To the diacetate (3 g, 11 mmol) in a 100-mL, single-necked round bottomed flask was added water (30 mL), 95% ethanol (30 mL), and H_2SO_4 (1 mL), and the resulting solution was boiled for 6 h. After allowing to cool to RT (30 min), water (20 mL) was added, and the aqueous phase was extracted with $HCCl_3$ (3 x 50 mL). Combined extracts were washed with water (1 x 50 mL), 10% $NaHCO_3$ (2 x 50 mL), water (1 x 50 mL), and saturated NaCl (50 mL). When dried (Na_2SO_4, overnight), the solvent was evaporated (rotovap) to give **59b** (1.4 g, 56%) as a colorless oil which was used immediately in the Wittig reaction with the phosphonium salts. Properties of **59b** are: IR (neat) 1740 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$, 300 MHz), δ 0.9 (t, J = 7.5 Hz, 3 H, CH_3), 1.2-1.55 [m, 6 H, $(CH_2)_3CH_3$], 1.75-1.8 [quintet, J = 7.5 Hz, 2 H, OCH_2CH_2], 4.4 (q, J = 7.5 Hz, 2 H, OCH_2), 7.9-8.2 (m, 4 H, Ar-H), 10.1 (s, 1 H, CHO). ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 14.21 [CH_3], aliphatic-C: 22.48, 25.61, 28.55, 31.37, 61.55 [OCH_2]; ArC: 129.43, 130.09, 135.13, 139.02, 165.36 [C(O)O], 191.63 [C(O)H].

***n*-Octyl 4-Formylbenzoate (59c).** In a 250-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer and a condenser was stirred a solution of **80c** (6.7 g, 27 mmol) in freshly distilled acetic anhydride (30 mL) and glacial acetic acid (30 mL). To the cooled 0 °C (ice-salt water bath) solution was added conc H_2SO_4 (2.5 mL). To this solution was added slowly (1 h) CrO_3 (8.1 g, 81 mmol), taking care to maintain the temperature below 5 °C during the addition. When the addition was complete, a dark green reaction mixture remained which was stirred for 2 h at 0 °C. Decomposition was effected by slowly pouring the mixture onto crushed ice (250 g) and then adding (very slowly) 250 mL of cold water. A green-colored solution formed, and this was extracted with ether (4 x 50 mL). Combined ether extracts were washed with water (2 x 50 mL), 5% Na_2CO_3 (4 x 50 mL), and brine (50 mL). When dried (Na_2SO_4, 2 h), the solvent was evaporated (rotovap) to obtain the diacetate (2.8 g, 37 %) as a yellow oil. To the

diacetate in a 100-mL, single-necked, round-bottomed flask was added water (25 mL), 95% ethanol (25 mL), and H_2SO_4 (0.5 mL). The resulting solution was boiled for 6 h. After allowing to cool to RT (30 min), water (20 mL) was added, and the aqueous phase was extracted with $HCCl_3$ (3 x 50 mL). Combined extracts were washed with water (1 x 50 mL), 10% $NaHCO_3$ (2 x 50 mL), water (1 x 50 mL), and saturated NaCl (50 mL). When dried (Na_2SO_4, overnight), the solvent was evaporated (rotovap) to give **59c** (1.2 g, 50%) as a colorless oil which was used immediately in the Wittig reaction with the phosphonium salts to prepare **45e**. Properties of **59c** are: IR (neat) IR (neat) 1740 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$, 400 MHz), δ 0.9 (t, J = 7.5 Hz, 3 H, CH_3), 1.2-1.55 [m, 10 H, $(CH_2)_5CH_3$], 1.75-1.8 [quintet, J = 7.5 Hz, 2 H, OCH_2CH_2], 4.4 (q, J = 7.5 Hz, 2 H, OCH_2), 7.9-8.2 (m, 4 H, Ar-H), 10.1 (s, 1 H, CHO). ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 13.60 [CH_3], Aliphatic-C: 13.76, 22.16, 25.29, 28.80, 28.93, 31.33, 32.26, 62.40[OCH_2]; ArC: 129.00, 129.65, 134.92, 138.59, 165.10 [C(O)O], 191.25 [C(O)H].

3,4-Dihydro-2*H*-1-benzothiopyran-1-oxide (60).[44] In a 300-mL, three-necked, round-bottomed flask (N_2), fitted with a condenser/addition funnel, septum, and a magnetic stirrer was dissolved Ti(O-*i*-Pr)$_4$ (43 mL, 40.6 g, 143 mmol) and (+)-diethyl *L*-tartrate (49 mL, 58.9 g, 286 mmol) in H_2CCl_2 (250 mL). Water (2.6 mL) was introduced (syringe). The resulting mixture was stirred (20 min) to a homogeneous solution. To this solution was added (addition funnel) in a single portion sulfide **56** (21.45 g, 143 mmol). The mixture was cooled to -20 °C (dry ice, CCl_4), and a 3.1 *M* solution of TBHP (180 mmol) in H_2CCl_2 (51 mL) was introduced dropwise (addition funnel, 5 min). Stirring was continued for 4 h at -20 °C, and 25 mL of water was then added dropwise (10 min). Stirring was continued at -20 °C for another hour and then for 1 h at RT. A white gel formed and was filtered off (filter aid was used), and the filtrate was evaporated (rotovap) and dried (Na_2SO_4, overnight). The resulting mixture was separated on silica gel (column chromatography; gradient elution with ethyl acetate:hexane = 85:15, 100%

MeOH). The fraction from methanol was evaporated (rotovap) to yield thiochroman-S-oxide **60** (19 g, 82%) as a yellow oil. ^{1}H NMR ($DCCl_3$, 300 MHz) δ 2.0-2.2 [m, 1 H, H(3)], 2.4-2.7 [m, 1 H, H(3)], 2.8-3.3 [m, 4 H, H(2) and H(4)], 7.2-7.9 [m, 4 H, ArH]; ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 14.12 [C(3)], 28.43 [C(4)], 46.37 [C(2)]; ArC: 127.42, 130.51, 130.81, 131.65, 136.01, 138.04. The optical rotation of **60** was taken in cells (1 cm x 10 cm) on a Perkin-Elmer 241 polarimeter. At 26 °C $[\alpha]_D$ = -114.15° (acetone). Reported[56] properties: bp 117-120 °C/0.04 mm, ^{1}H NMR δ 1.09-3.50 [m, 6 H], 7.20-7.90 [m, 4 H]. The reported[7] specific rotation is $[\alpha]_D$ = -21.8° (acetone) at 25 °C.

3,4-Dihydro-2-ethyl-2*H*-1-benzothiopyran-1-oxide (61a).[44] In to 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, condenser, a rubber septum, and a N_2 inlet was placed a solution of diisopropylamine (6.0 mL, 43 mmol) in THF (50 mL). To the above cooled (-78 °C, dry ice-acetone) solution was added (syringe) *n*-butyllithium (26 mL, 1.6 *M* in hexanes). The reaction mixture was stirred at RT for 1 h and again cooled to -78 °C. The sulfoxide **60** (6.5 g, 39 mmol) in THF (50 mL) was then added (addition funnel) to this solution. The reaction mixture was allowed to warm to -30 °C (1 h) and was again cooled to -78 °C after which ethyl iodide (3.1 mL, 43 mmol) was added (syringe). Stirring continued for 12 h after which time 5% hydrochloric acid (50 mL) was added (addition funnel), and the resulting solution was then extracted with $HCCl_3$ (3 x 50 mL). Combined extracts were washed with water (1 x 50 mL), $NaHCO_3$ (2 x 50 mL), water (50 mL), and brine (50 mL). When dried (Na_2SO_4, overnight), the solution was concentrated (rotovap) to give a brown oil which was separated on a silica gel column (eluent-hexane:$HCCl_3$:ethyl acetate = 4:1:1). The second fraction gave the alkylated product **61a** (R = ethyl, 4.2 g, 80%) as a light yellow oil. ^{1}H NMR ($DCCl_3$, 400 MHz) δ 1.13 [t, $^3J_{HCCH}$ = 7.5 Hz, 3 H, CH_3], 1.47 [m, 1 H, H(3)], 1.94 [m, 2 H, CH_2CH_3], 2.5 [m, 1 H, H(3)], 2.92-3.25 [m, 3 H, H(2) and H(4)], 7.21-7.85 [m, 4 H, ArH]. ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 10.97 [C(3)], 20.67 [-

CH_2CH_3], 21.27 [-CH_2CH_3], 26.6 [C(4)], 59.7 [C(2)]; ArC: 127.2,129.1, 129.6, 130.9, 136.6, 138.1. Recorded[56] properties: ^{1}H NMR ($DCCl_3$) δ 1.09 [t, 3 H, CH_3], 1.40-3.45 [m, 7 H], 6.83-7.08 [m, 4 H]. No other properties of **61a** have been reported.

3,4-Dihydro-2-*n*-butyl-2*H*-1-benzothiopyran-1-oxide (61b).[44] To a cooled (-78 °C, dry ice-acetone) solution of diisopropylamine (6.7 mL, 48 mmol), in THF (50 mL) in a 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, condenser, and a rubber septum was added (via syringe, under N_2) *n*-butyllithium (30 mL, 1.6 *M* in hexanes). The resulting solution was stirred at RT for 1 h and was again cooled to -78 °C. The sulfoxide **60** (7.2 g, 44 mmol) in THF (50 mL) was added (15 min, addition funnel). The reaction mixture was allowed to cool to -30 °C (1 h), then again cooled to -78 °C, and *n*-butyl bromide (3.7 mL, 34 mmol) was added (syringe). Stirring was continued for another 12 h, after which time 5% hydrochloric acid (50 mL) was added (addition funnel). The resulting solution was extracted with $HCCl_3$ (3 x 50 mL). Combined extracts were washed with water (1 x 50 mL), $NaHCO_3$ (2 x 50 mL), water (50 mL), and brine (50 mL). When dried (Na_2SO_4, overnight), the solution was concentrated (rotovap) to give a brown oil which was separated on a silica gel column (eluent-hexane:$HCCl_3$:ethyl acetate = 4:1:1). The second fraction gave the alkylated product as a yellow oil **61b** (R = *n*-butyl, 6.4 g, 65%). ^{1}H NMR ($DCCl_3$, 300 MHz) d 0.95 [t, $^3J_{HCCH}$ = 7.4 Hz, 3 H, CH_3], 1.2-1.5 [m, 5 H, (CH_2)$_2CH_3$] and H(3)], 1.7-1.85 [m, 2 H, $CH_2(CH_2)_2$], 2.2-2.4[m, 1 H, H(3)], 2.8-3.0 [m, 3 H, H(2) and H(4)], 7.1-7.7 [m, 4 H, ArH]; ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 14.21 [C(3)]; aliphatic-C: 21.21, 22.93, 26.76, 28.47, 29.09, 58.03 [C(2)]; ArC: 127.59, 129.56, 129.87, 131.07, 135.88, 140.00. Recorded[56] properties: ^{1}H NMR ($DCCl_3$) δ 0.94 [t, 3 H, CH_3], 1.18-3.13 [m, 10 H], 7.20-7.80 [m, 4 H]. No other properties **61b** have been reported.

3,4-Dihydro-2-*n*-octyl-2*H*-1-benzothiopyran-1-oxide (61c).[44] A 250-mL, three-

necked, round-bottomed flask was equipped with a magnetic stirrer, condenser, and a rubber septum (N_2). To a cooled (-78 °C, dry ice-acetone) solution of diisopropylamine (4.8 mL, 34 mmol) in THF (50 mL) in the above system was added dropwise *n*-butyllithium (22 mL, 1.6 *M* in hexanes) over a period of 1 h (via syringe, under N_2). The resulting solution was stirred at RT for 1 h. After the solution was again cooled to -78 °C, the sulfoxide **60** (5.72 g, 30 mmol) in THF (50 mL) was added (15 min, addition funnel). The solution was then allowed to warm to -30 °C (1 h) and then again cooled to -78 °C. Then *n*-octyl bromide (5.4 mL, 34 mmol) was added via syringe in a single portion. Stirring was continued for another 12 h after which 5% hydrochloric acid (50 mL) was added (addition funnel), and the solution was extracted with $HCCl_3$ (3 x 50 mL). Combined extracts were washed with water (1 x 50 mL), $NaHCO_3$ (2 x 50 mL), water (50 mL), and brine (50 mL). When dried (Na_2SO_4, overnight), the solution was concentrated (rotovap) to give a brown oil which was separated on a silica gel column (hexane:$HCCl_3$:ethyl acetate = 4:1:1). The second fraction gave the alkylated product **61c** (R = *n*-octyl, 3.2 g, 40%) as a light yellow oil. ^{1}H NMR ($DCCl_3$, 300 MHz) δ 0.9 [t, $^3J_{HCCH}$ = 0.7 Hz, 3 H, CH_3], 1.2-1.4 [bs, 12 H, $(CH_2)_6CH_3$], 1.4-1.7 [m, 2 H, $CH_2(CH_2)_6$], 1.85 [m, 1 H, H(3)], 2.45 [m, 1 H, H(3)], 2.8-3.1 [m, 3 H, H(2) and H(4)], 7.1-7.8 [m, 4 H, ArH]; ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 14.06 [C(3)]; aliphatic-C: 20.75, 22.54, 26.32, 26.53, 28.31, 29.08, 29.25, 29.40, 31.71; 57.99 [C(2)]; ArC: 127.2, 129.18, 129.46, 130.67, 135.47, 140.0. Recorded[56] properties: ^{1}H NMR ($DCCl_3$) δ 0.88 [t, 3 H], 1.1-3.10 [m, 22 H], 7.24-8.10 [m, 4 H]. No other properties of **61c** are been reported.

Ethyl *p*-Toluate (80a). In a 100-mL, single-necked, round-bottomed flask, equipped with a magnetic stirrer, N_2 inlet, a condenser, and a Dean-Stark trap was dissolved *p*-toluic acid (5.5 g, 40 mmol) in dry benzene. To the stirred solution was added absolute alcohol (7.5 mL) and conc sulfuric acid (1 mL). After boiling the solution for 24 h, the near theoretical amount of water was collected in a Dean-Stark trap. Water (40 mL) was

added to the solution which was allowed to cool to RT (30 min), and the aqueous layer was extracted with ether (2 x 25 mL). The combined organic layers were washed with water (1 x 25 mL), saturated $NaHCO_3$ (2 x 25 mL), water (1x 25 ml),and saturated NaCl (25 mL). After drying (Na_2SO_4, overnight), the solvent was evaporated (rotovap) to obtain ethyl *p*-toluate **59a** (5.8 g, quantitative)as a light yellow oil. This oil was used without further purification to prepare ethyl 4-formylbenzoate (**59a**). Properties of **80a** are: IR (neat) 1750 cm^{-1} (C=O); ^1H NMR ($DCCl_3$, 300 MHz) δ 1.3 [t, J = 7.5 Hz, 3 H, OCH_2CH_3], 2.3 [s, 3 H, $ArCH_3$), 4.2 [q, J = 7.5 Hz, 2 H, OCH_2CH_3], 7.05-7.9[m, 4 H, ArH]. ^{13}C NMR ($DCCl_3$, 75 MHz) ppm 14.57 [OCH_2CH_3], 21.84 [$ArCH_3$], 60.95 [CH_2]; ArC: 128.00, 129.42, 129.78, 143.62, 166.91 [C(O)]. These data agreed with previously reported properties.[55]

***n*-Hexyl *p*-Toluate (80b).** In a 100-mL, single-necked, round-bottomed flask, equipped with a magnetic stirrer, N_2 inlet, a condenser, and a Dean-Stark trap was stirred a solution of of *p*-toluic acid (10.0 g, 74 mmol), *n*-hexanol (9.2 mL, 74 mmol)) in dry benzene (80 mL). To the above stirred mxture was added conc sulfuric acid(1.5 mL). The resulting solution was stirred for 24 h at which time the near theoretical amount of water was collected via a Dean-Stark trap. Water (40 mL) was added to the solution which was allowed to cool to RT (30 min), and the aqueous layer was extracted with ether (2 x 25 mL). Combined organic layers were washed with water (1 x 25 mL), saturated $NaHCO_3$ (2 x 25 mL), water (1x 25 ml),and saturated NaCl (25 mL). After drying (Na_2SO_4, overnight), the solvent was evaporated (rotovap) to obtain *n*-hexyl *p*-toluate **80b** (10.8 g, 62 %) as a light yellow oil. This oil was used without further purification to prepare *n*-hexyl 4-formylbenzoate (**59b**). Properties of **80b** are: IR (neat) 1750 cm^{-1} (C=O); ^1H NMR ($DCCl_3$, 400 MHz) δ 0.9 [t, J = 7.5 Hz, 3 H, $O(CH_2)_5CH_3$], 1.25-1.5 [m, 6 H, $(CH_2)_3CH_3$], 1.7-1.8 [quintet, 2 H, OCH_2CH_2], 2.4[s, 3 H, $ArCH_3$), 4.3 [q, J = 7.5 Hz, 2 H, OCH_2CH_2], 7.05-7.9[m, 4 H, ArH]. ^{13}C NMR ($DCCl_3$, 100

MHz) ppm 13.91 [$(CH_2)_5CH_3$], aliphatic-C; 22.48, 25.64, 28.64, 31.40, 64.83 [OCH_2]; ArC: 127.76, 128.92, 129.47, 143.27, 166.91 [C(O)].

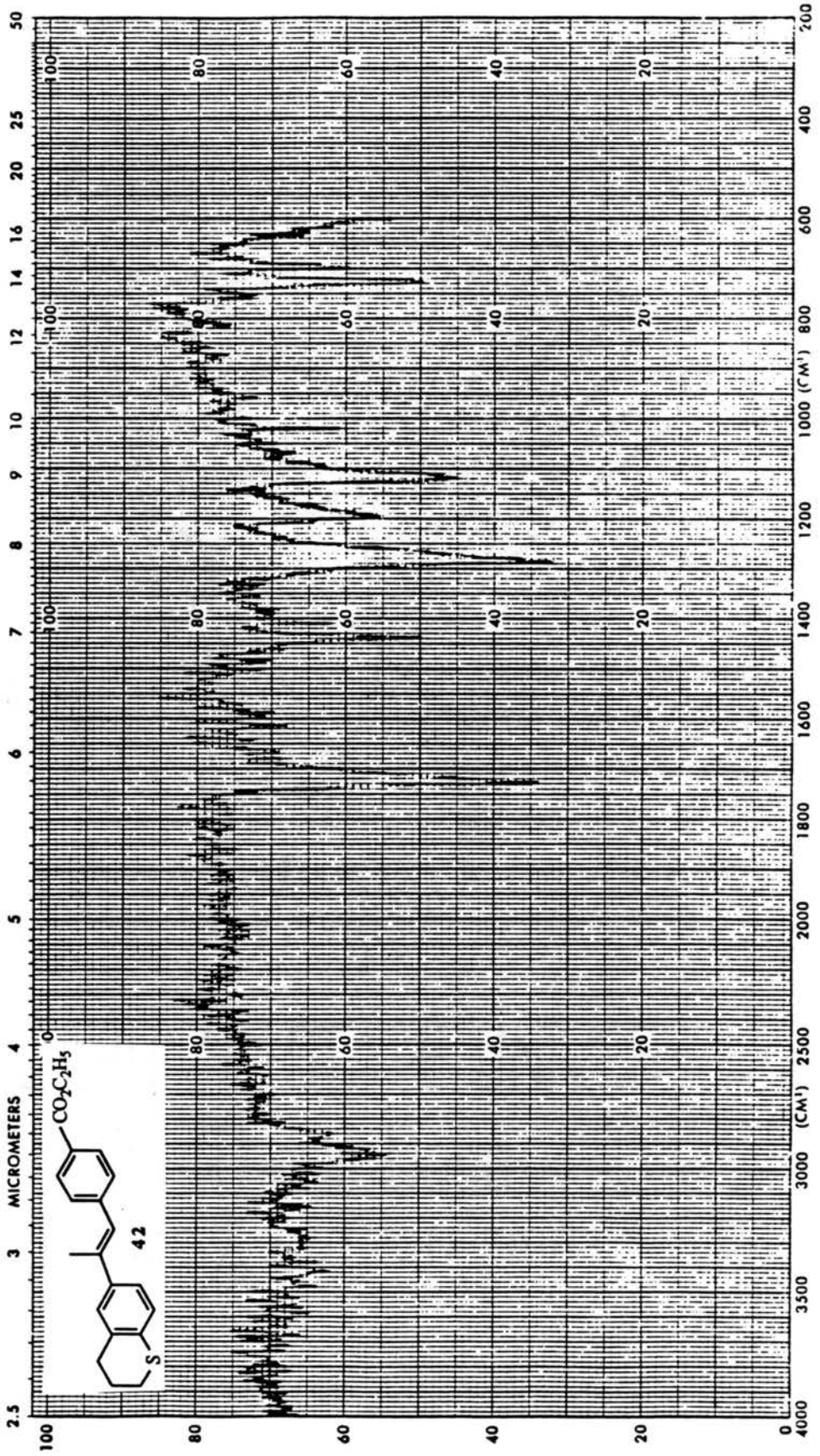
***n*-Octyl *p*-Toluate (80c).** To *p*-toluic acid (5.0 g, 37 mmol) in dry benzene (40 mL) in a 100-mL, single-necked, round-bottomed flask, equipped with a magnetic stirrer, N_2 inlet, a condenser, and a Dean-Stark trap was added *n*-octanol (5.8 mL, 37 mmol) and conc sulfuric acid (1 mL). After boiling the solution for 24 h (when the near theoretical amount of water was collected via a Dean-Stark trap), the solution was allowed to cool to RT (30 min). Water (40 mL) was added, and the aqueous layer was extracted with ether (2 x 25 mL). Combined organic layers were washed with water (1 x 25 mL), saturated $NaHCO_3$ (2 x 25 mL), water (1x 25 ml), and saturated NaCl (25 mL). After drying (Na_2SO_4, overnight), the solvent was evaporated (rotovap) to obtain *n*-octyl *p*-toluate **80c** (6.7 g, 73 %) as a light yellow oil. This oil was used directly to prepare *n*-octyl 4-formylbenzoate (**59c**). IR (neat) 1750 cm^{-1} (C=O); ^1H NMR ($DCCl_3$, 400 MHz) δ 0.9 [t, J = 7.5 Hz, 3 H, $O(CH_2)_5CH_3$], 1.2-1.55 [m, 10 H, $(CH_2)_5CH_3$], 1.7-1.8 [quintet, 2 H, OCH_2CH_2], 2.4 [s, 3 H, $ArCH_3$), 4.3 [q, J = 7.5 Hz, 2 H, OCH_2CH_2], 7.05-7.9 [m, 4 H, ArH]. ^{13}C NMR ($DCCl_3$, 100 MHz) ppm 13.64 [$(CH_2)_5CH_3$], aliphatic-C; 21.19, 22.20, 25.60, 28.29, 28.75, 28.81, 31.35 64.83 [OCH_2]; ArC: 127.76, 128.55, 129.10, 143.27, 166.91 [C(O)].

Attempted Preparation of Ethyl (*E*)-4-[2-(3,4-Dihydro-2-ethyl-1-oxy-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate (44a) Via Alkylation of Ethyl (*E*)-4-[2-(3,4-Dihydro-1-oxy-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate (43). A 50-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, condenser and a rubber septum (N_2). To a cooled (-78 °C, dry ice-acetone) solution of diisopropylamine (44 μL, 0.3 mmol) in THF (10 mL) was added dropwise *n*-butyllithium (31 μL, 1.6 *M* in hexane). The resulting solution was stirred at RT for 1 h. After it was

again cooled to -78 °C, the solution was treated (syringe) with sulfoxide **43** (0.1 g, 0.3 mmol) in THF (5 mL). The reaction mixture was allowed to warm to -30 °C (1 h), and then again it was cooled to -78 °C. Iodoethane (23 μL, 0.3 mmol) was then added in a single portion (syringe). Stirring was continued for another 12 h after which time 5% HCl (5 mL) was added (addition funnel), and the resulting solution was extracted with $HCCl_3$ (2 x 10 mL). Combined organic extracts were washed with water (1 x 10 mL), saturated $NaHCO_3$ (2 x 10 mL), water (1 x 10 mL), and saturated NaCl (1 x 10 mL). When dried (Na_2SO_4, overnight), the solution was concentrated (rotovap) to give a thick brown oil. The ^1H NMR analysis of the brown oil did not show the presence of OCH_2CH_3 group. The desired **44a** was apparently not formed in a useful quantity.

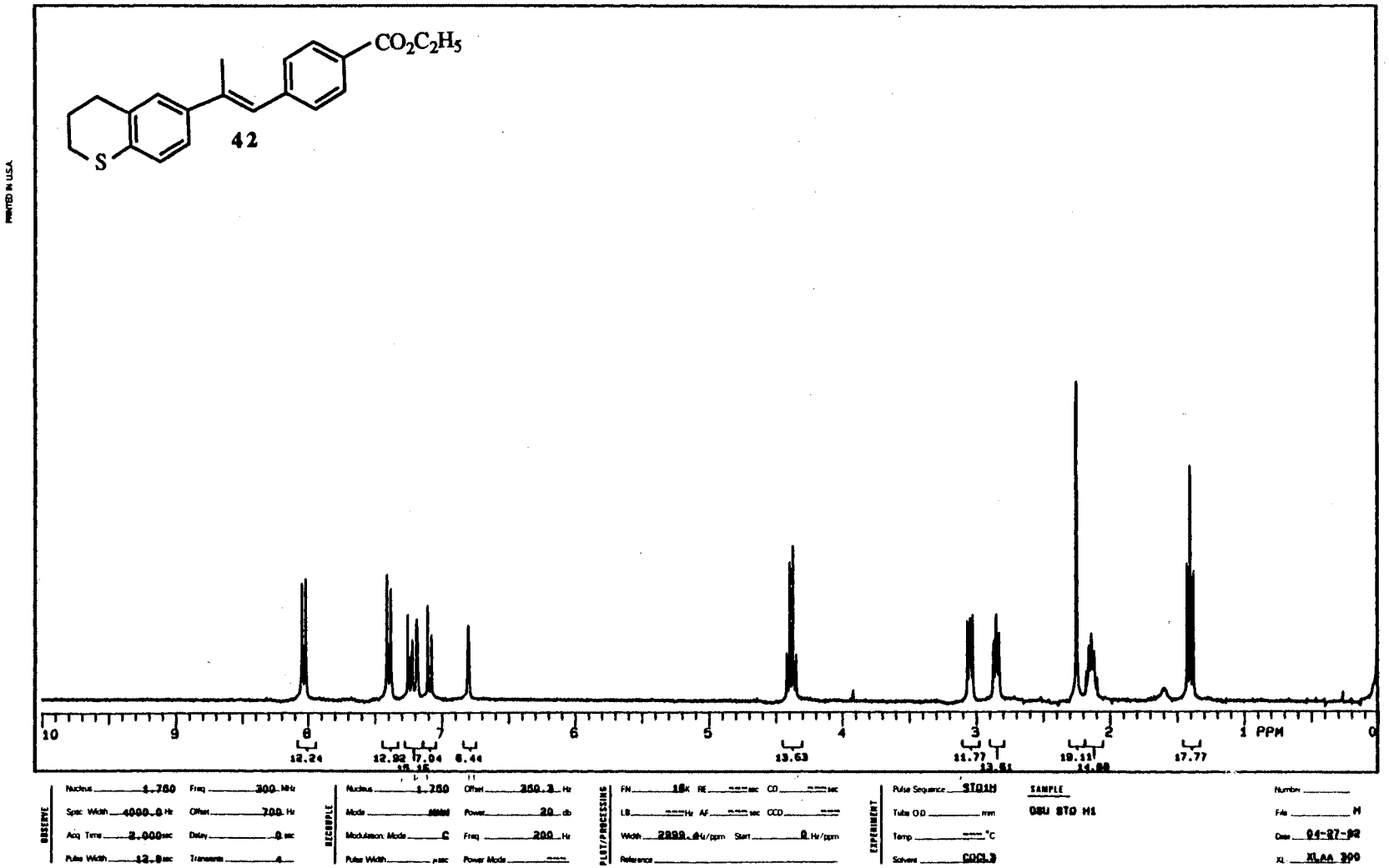
Attempted Preparation of Ethyl (*E*)-4-[2-(3,4-Dihydro-2-ethyl-1-oxy-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate (44a) Via Alkylation of Ethyl (*E*)-4-[2-(3,4-Dihydro-1-oxy-2*H*-1-benzothiopyran-6-yl)-1-propenyl]benzoate (43). In a 50-mL, two-necked, round-bottomed flask equipped with a condenser, magnetic stirrer and a N_2 inlet was stirred a mixture of the sulfoxide **43** (0.5 g, 1.4 mmol), potassium hydride (0.06 g, 1.4 mmol) and 18-C-6 (20 mg) in dimethoxyethane (25 mL, RT, 6 h). To this stirred solution was added *n*-bromooctane (0.3 mL, 1.4 mmol), and the resulting solution was stirred for 24 h. It was then cooled to 0 °C (ice-water bath) and 4 *N* HCl (5 mL) was added. The aqueous layer was extracted with $HCCl_3$ (2 x 10 mL). The combined organic extracts were washed with water (1 x 10 mL), saturated $NaHCO_3$ (2 x 10 mL), water (1 x 10 ml), and saturated NaCl (1 x 10 mL). After drying (Na_2SO_4, overnight), the solvent was evaporated (rotovap) to give an orange oil. The ^1H NMR analysis revealed it to be only starting material. Similar results were obtained with the use of potassium *t*-butoxide, CaH_2 and K_2CO_3 as bases.

Plate I



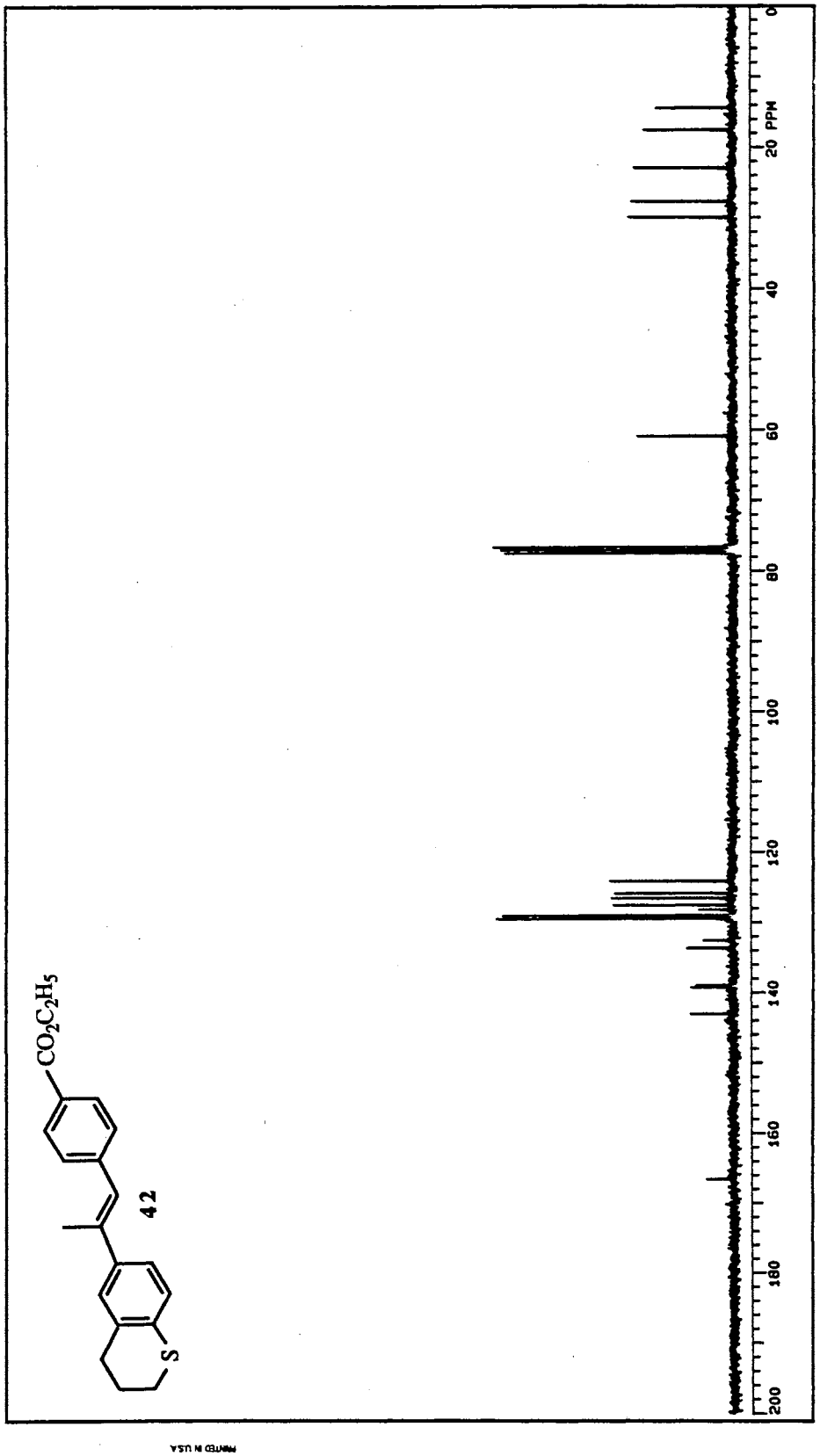
IR Spectrum of **42**

Plate II



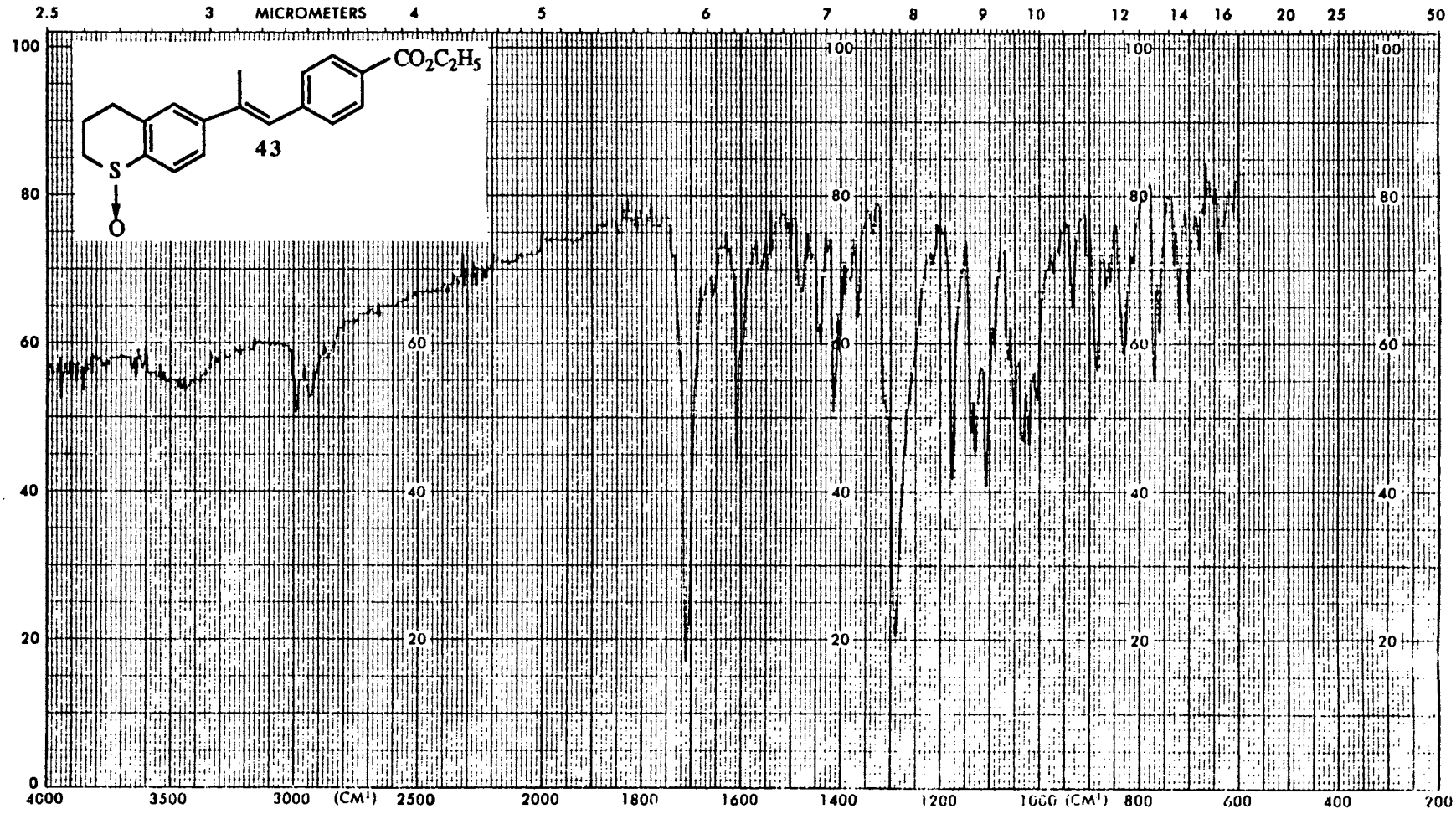
^{1}H NMR Spectrum of 42

Plate III



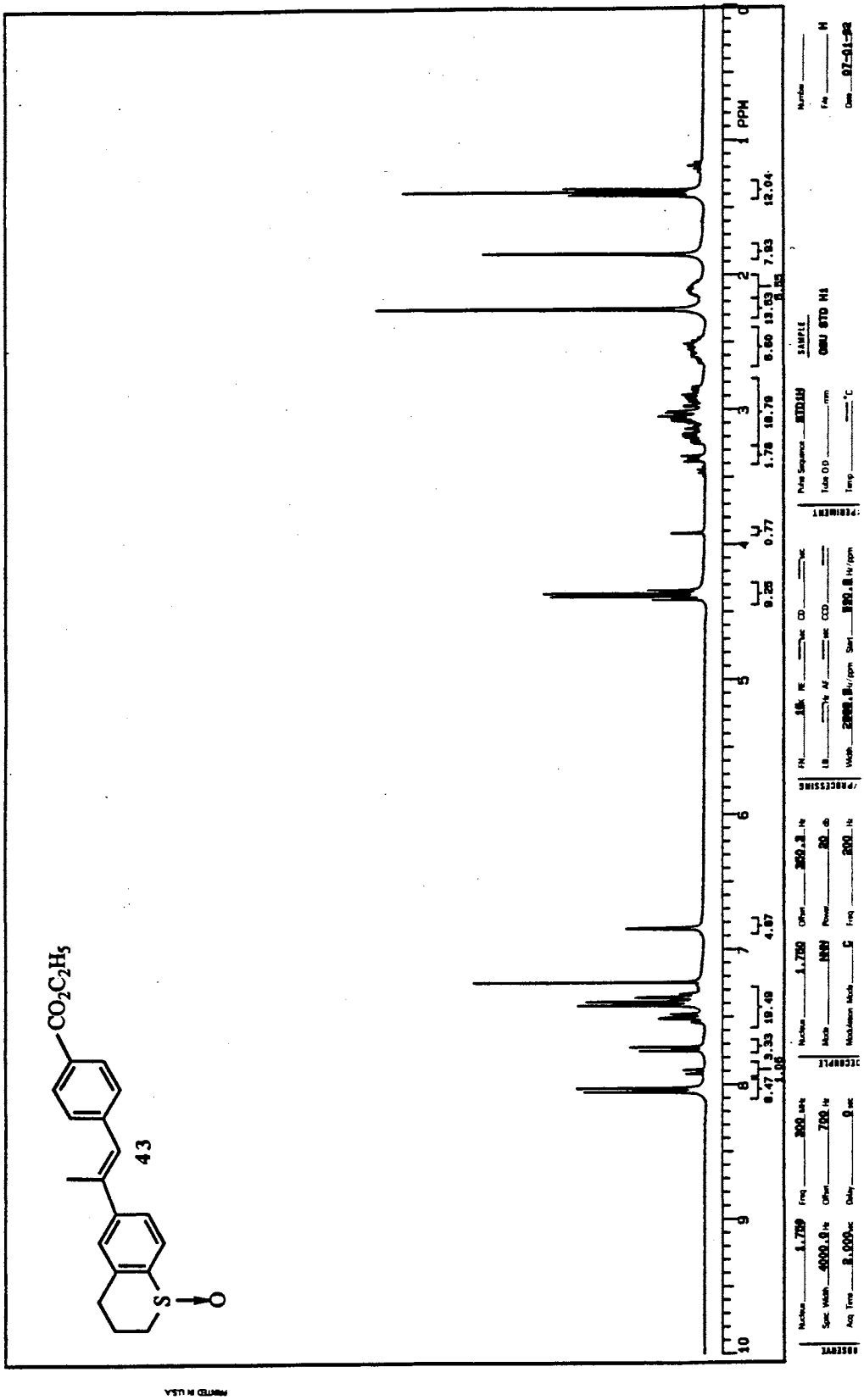
^{13}C NMR Spectrum of **42**

Plate IV



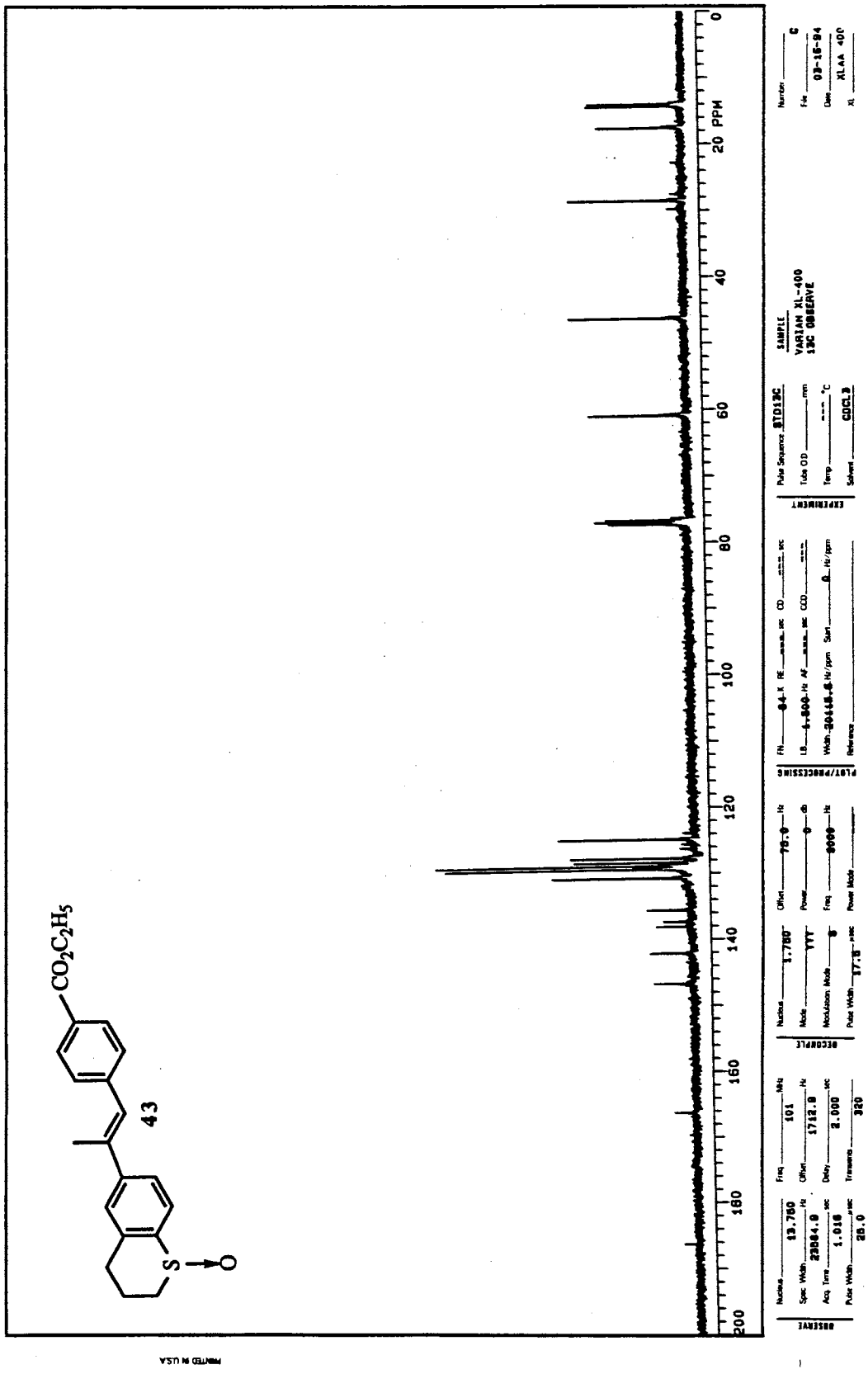
IR Spectrum of **43**

Plate V



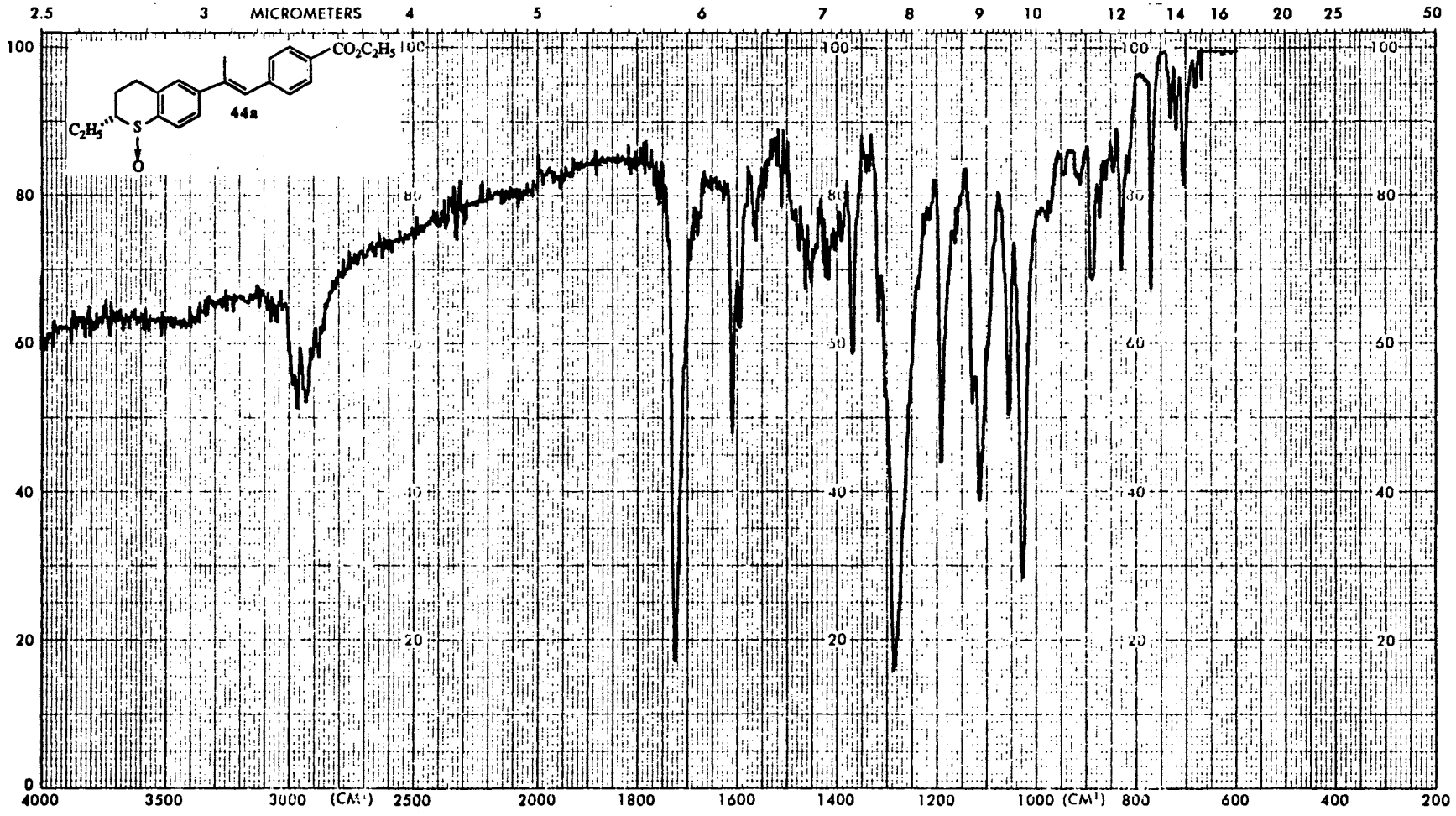
^{1}H NMR Spectrum of 43

Plate VI



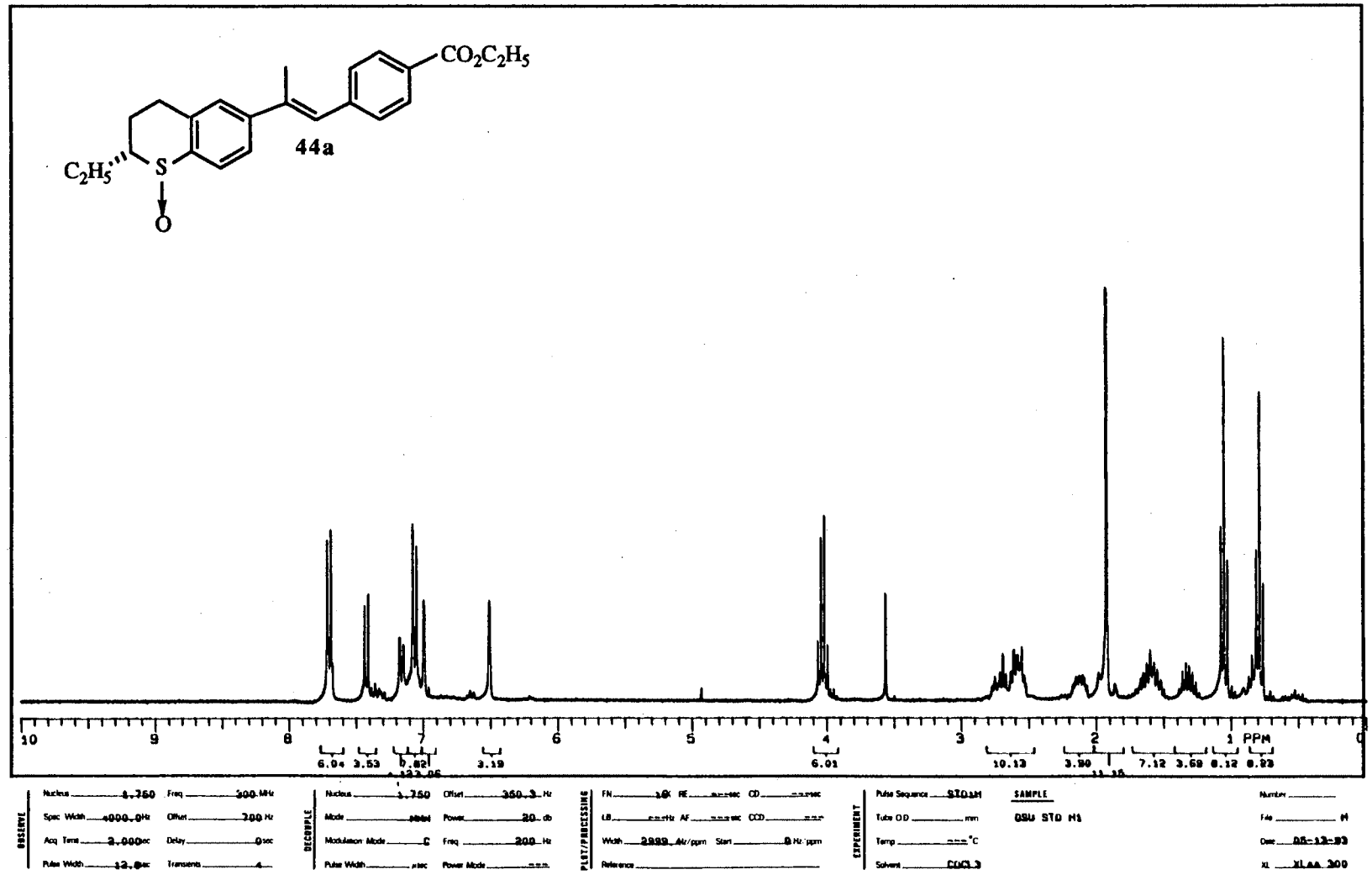
^{13}C NMR Spectrum of 43

Plate VII

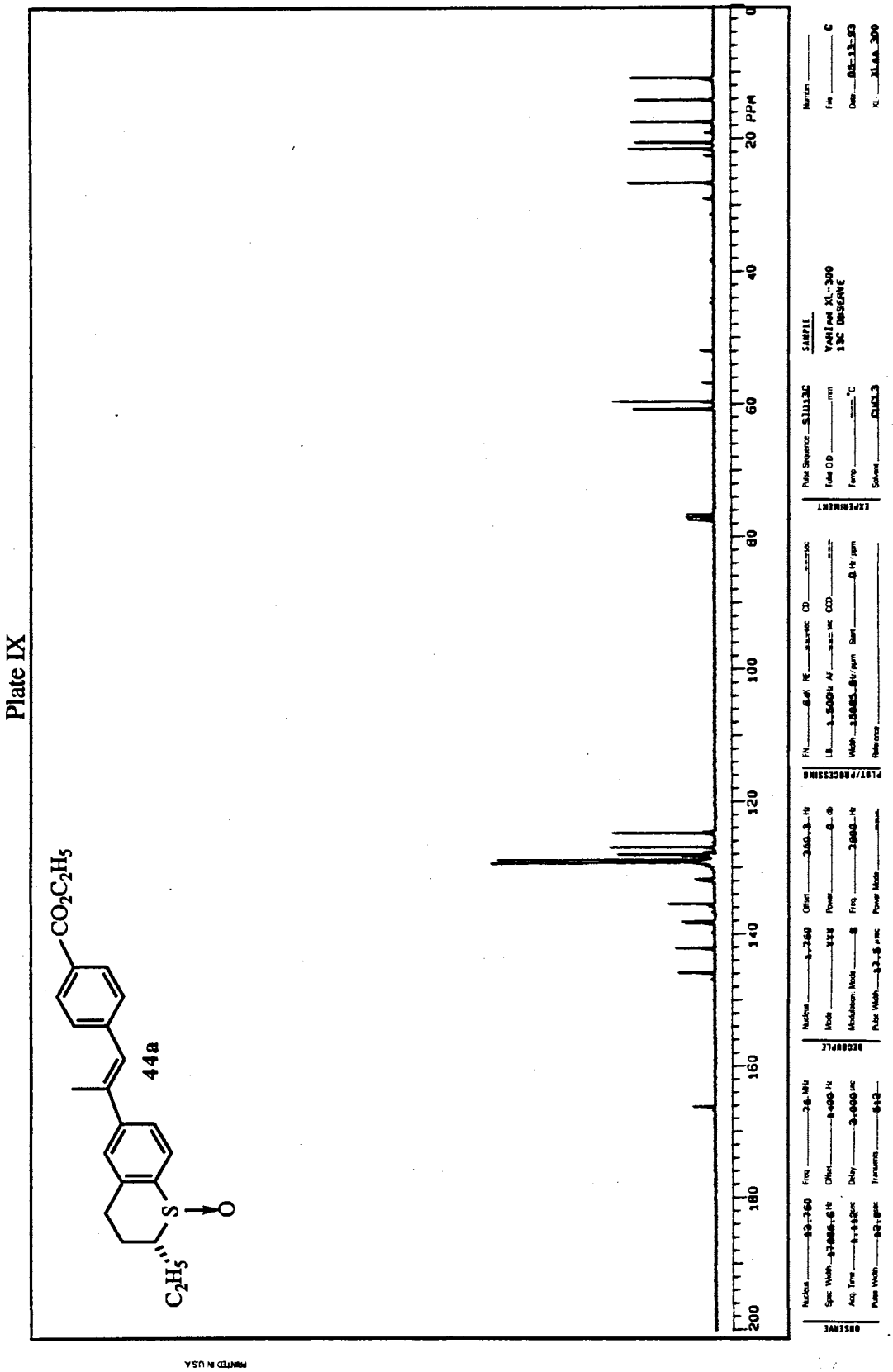


IR Spectrum of **44a**

Plate V111

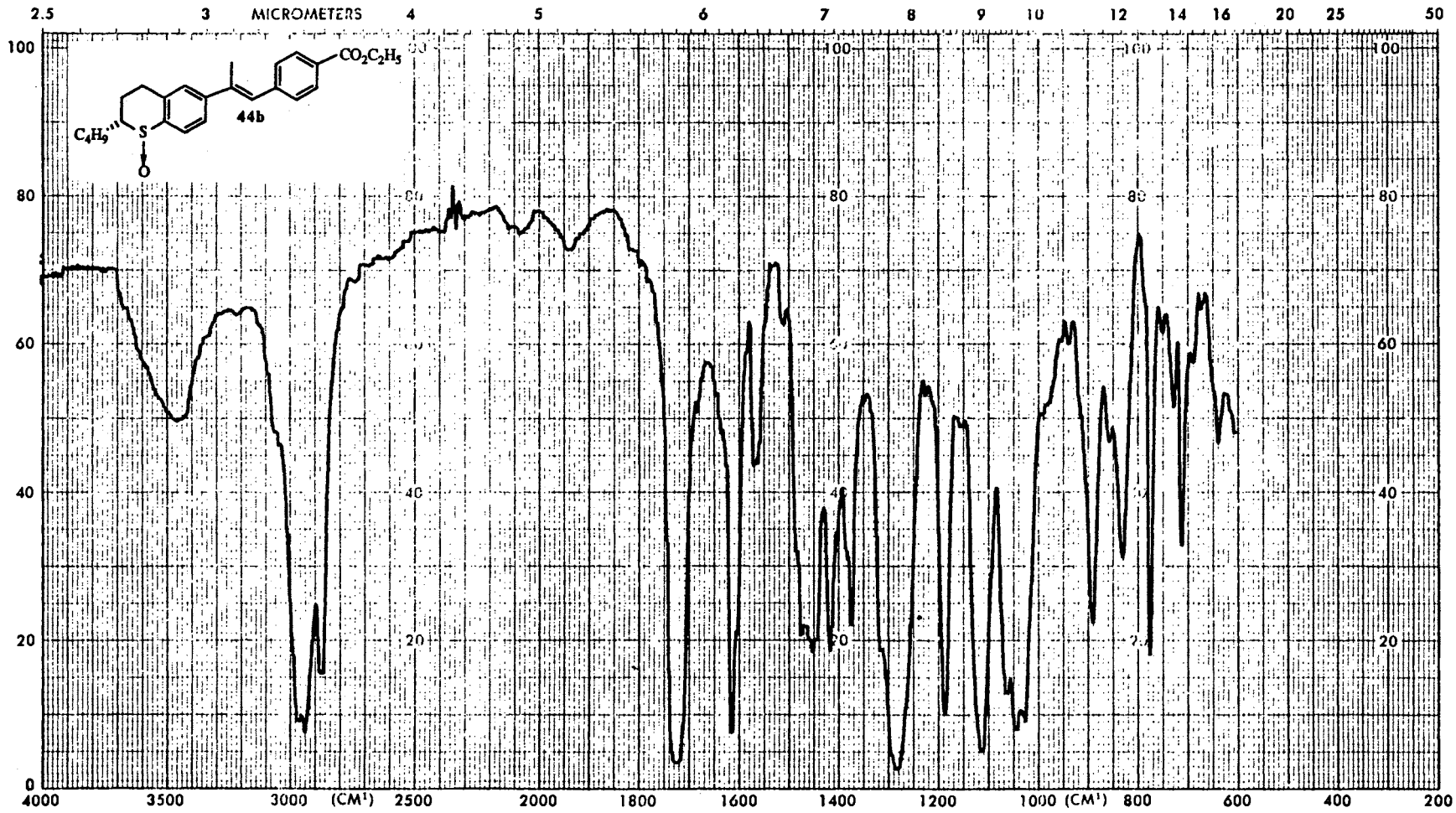


^{1}H NMR Spectrum of **44a**



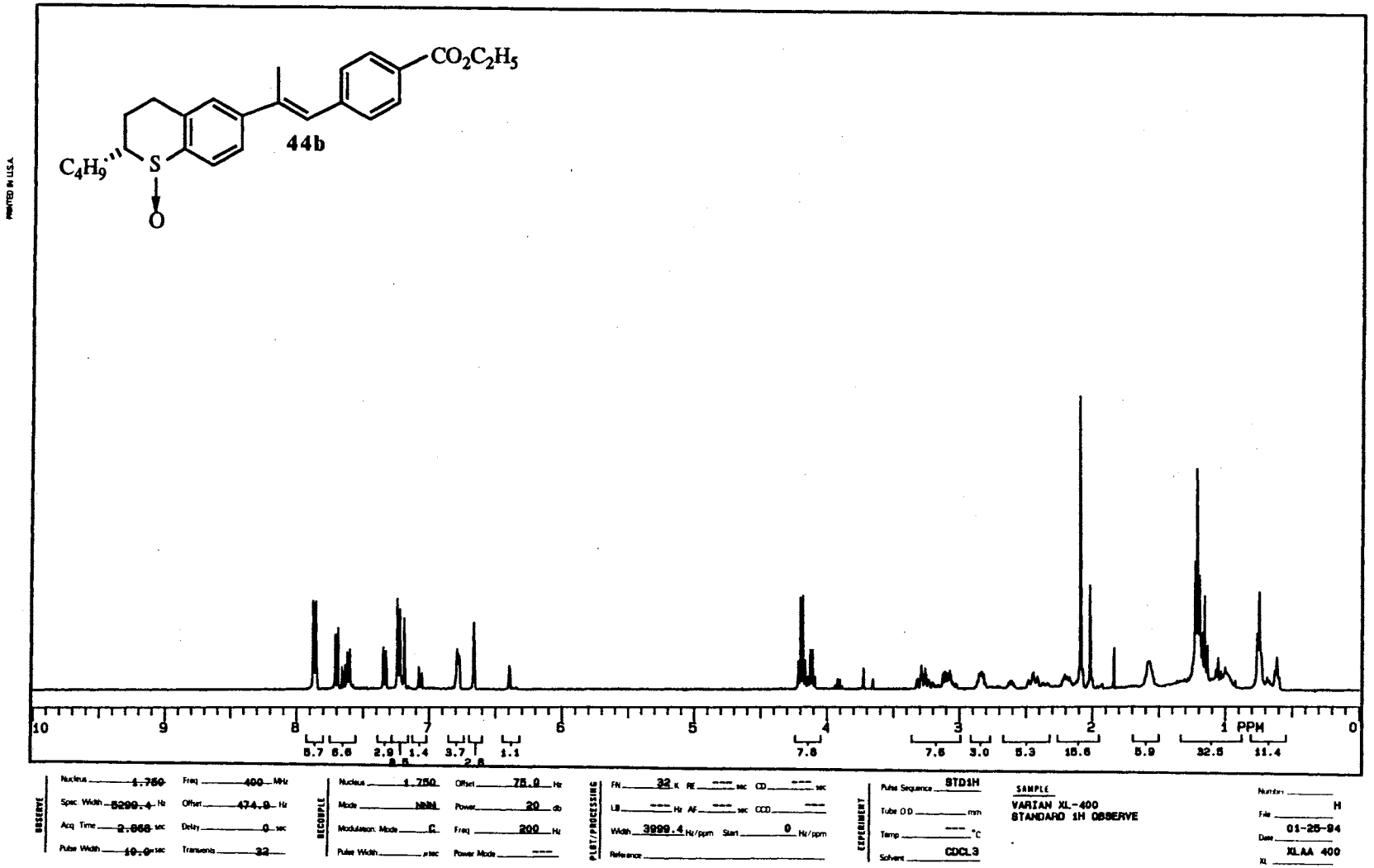
^{13}C NMR Spectrum of **44a**

Plate X



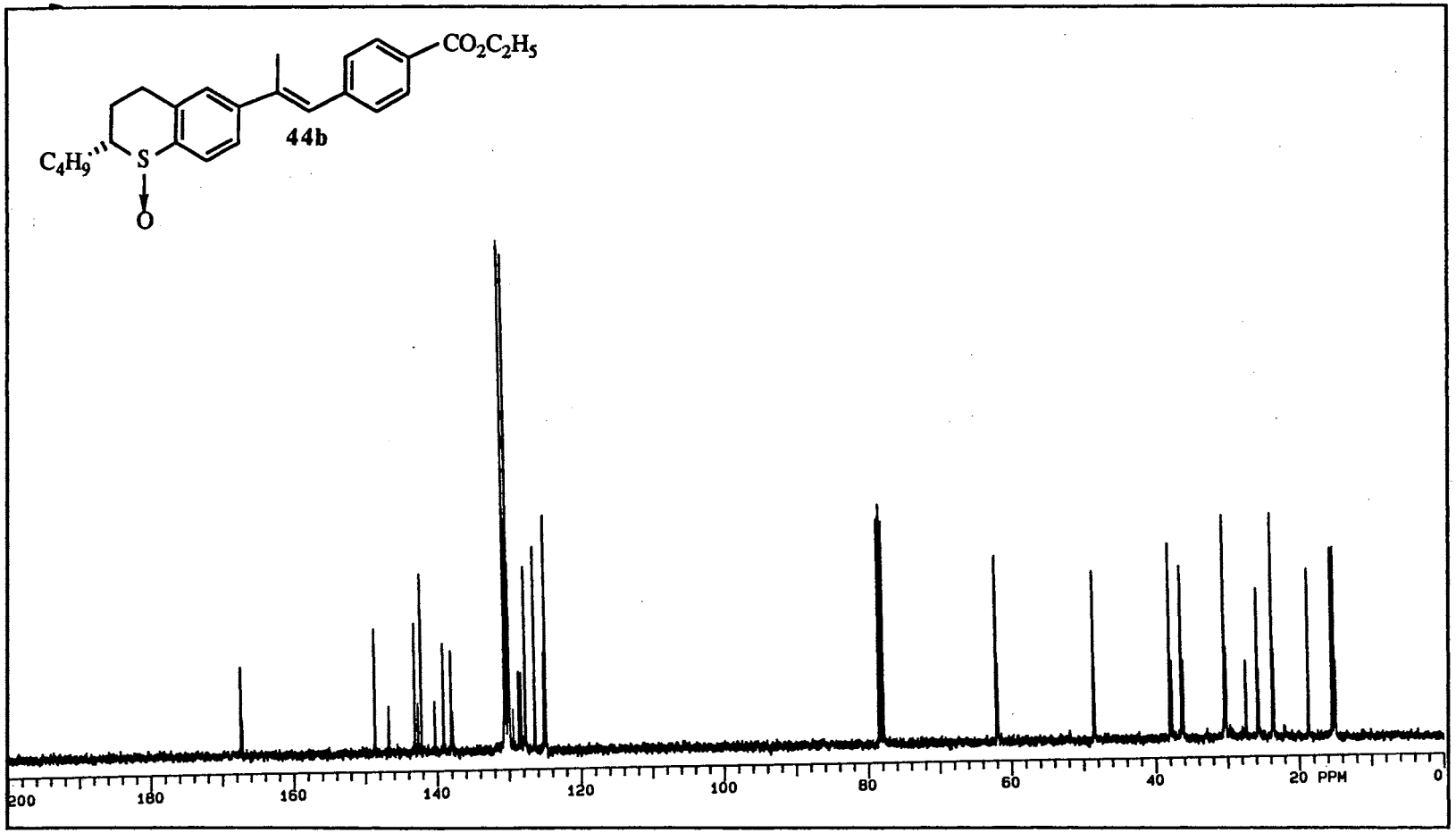
IR Spectrum of **44b**

Plate XI



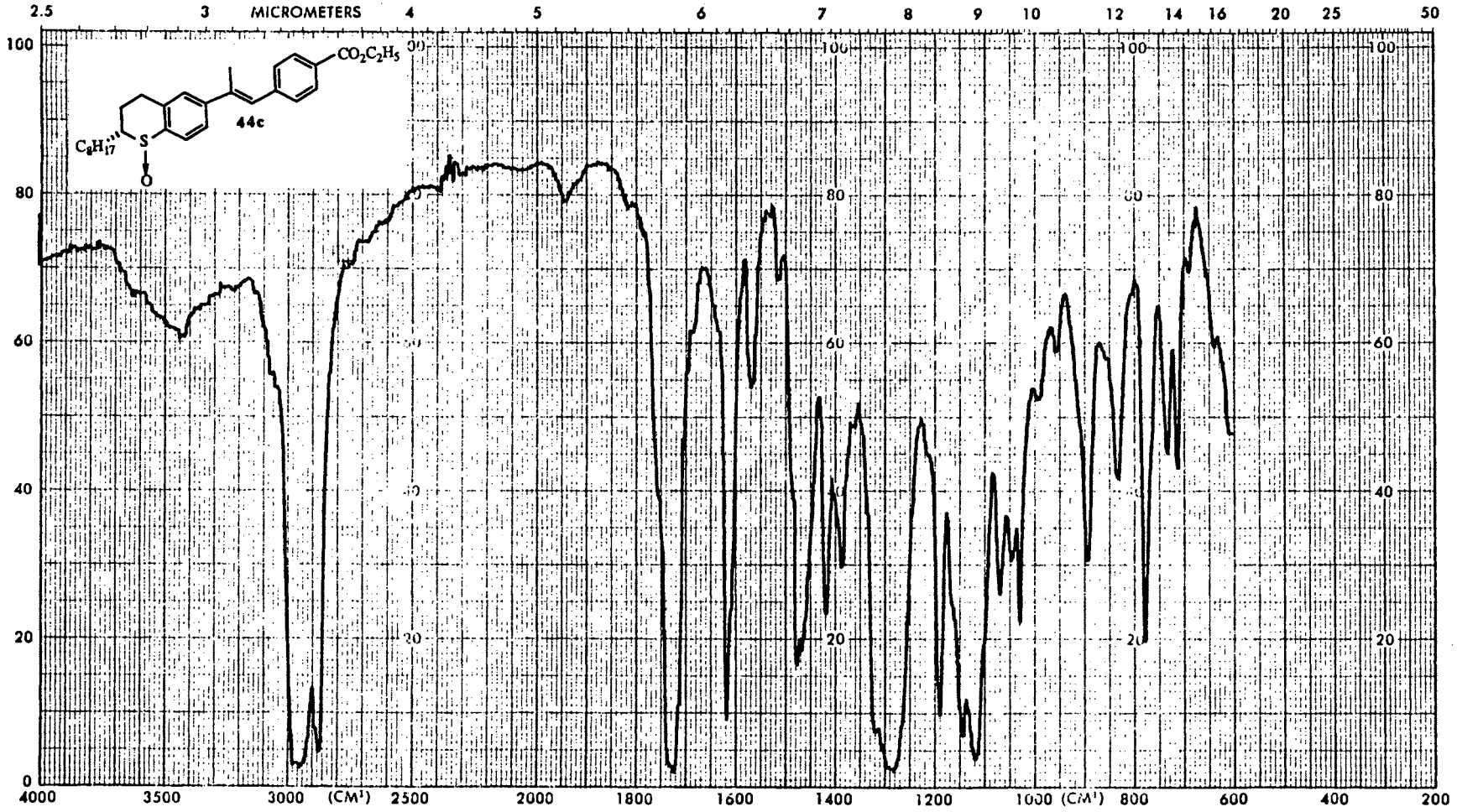
^{1}H NMR Spectrum of **44b**

Plate XII



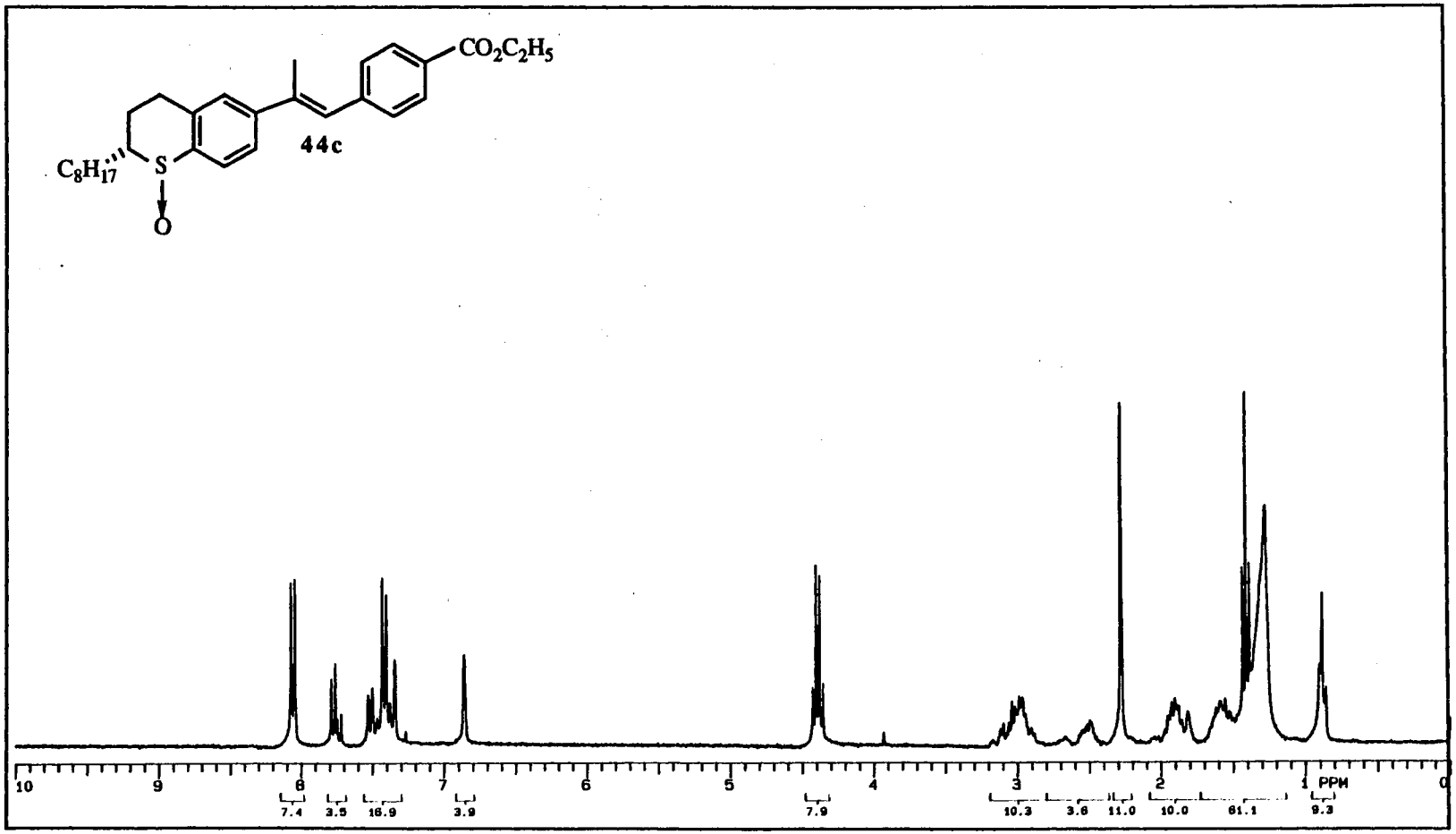
^{13}C NMR Spectrum of **44b**

Plate XIII



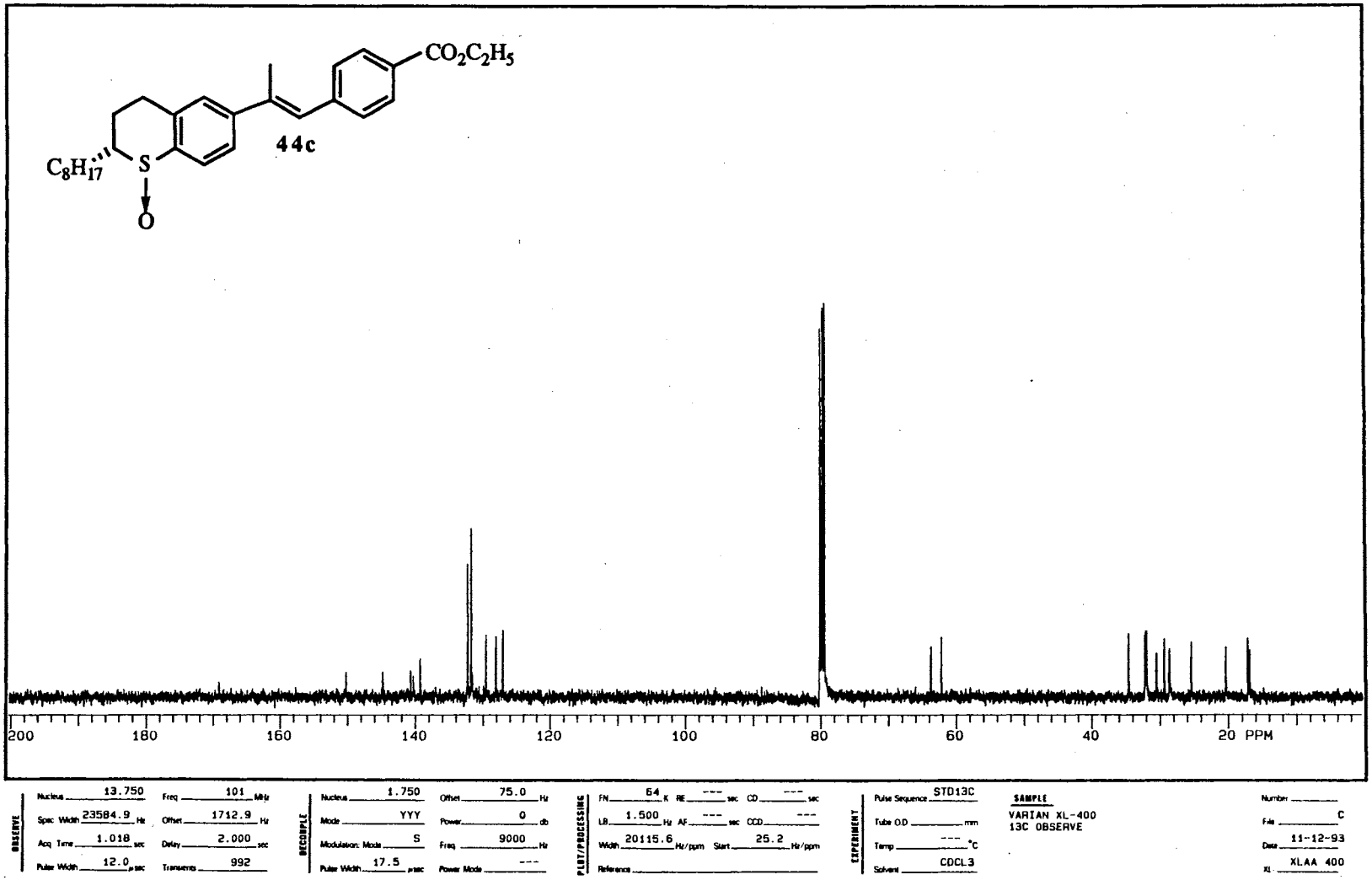
IR Spectrum of **44c**

Plate XIV



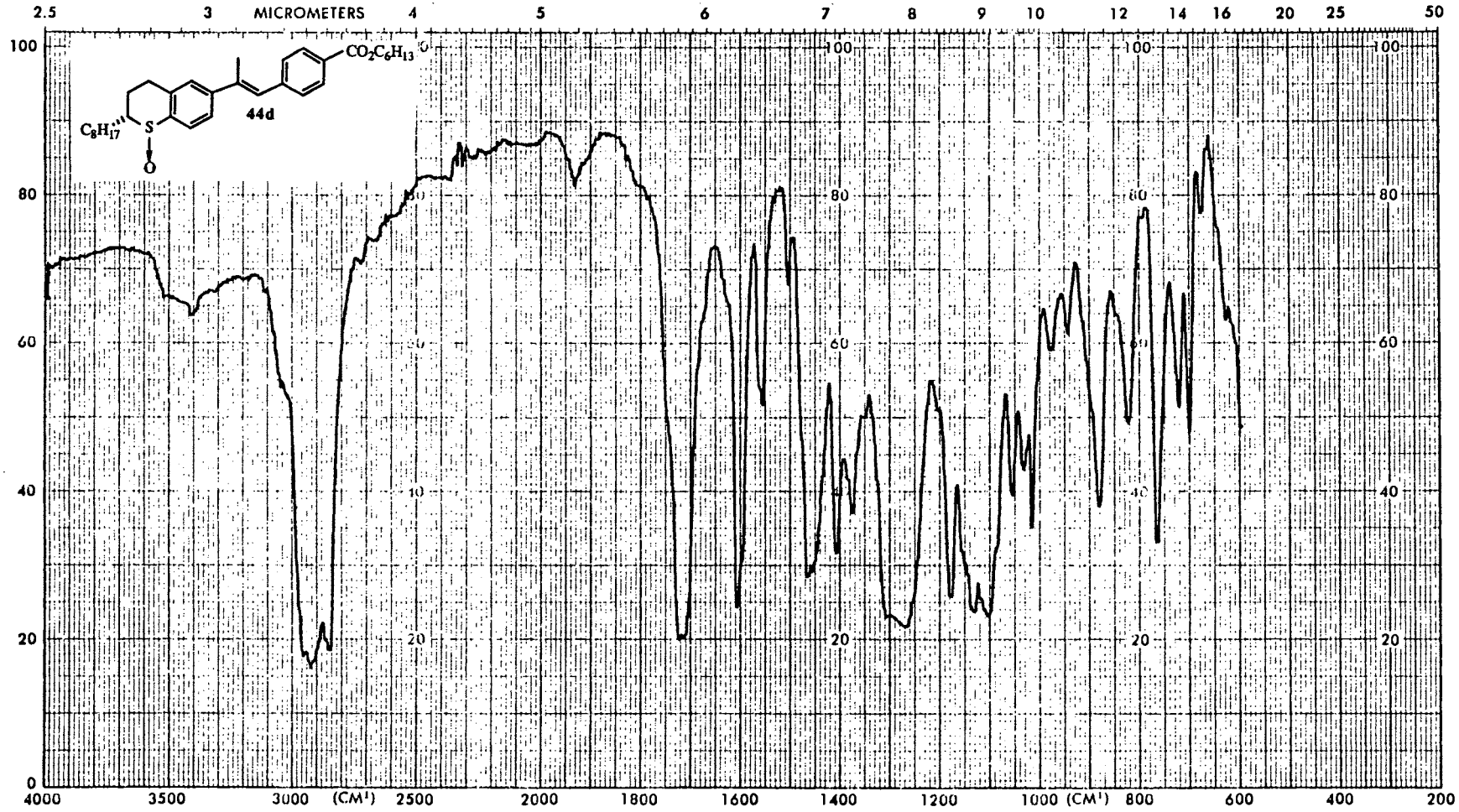
^{1}H NMR Spectrum of **44c**

Plate XV



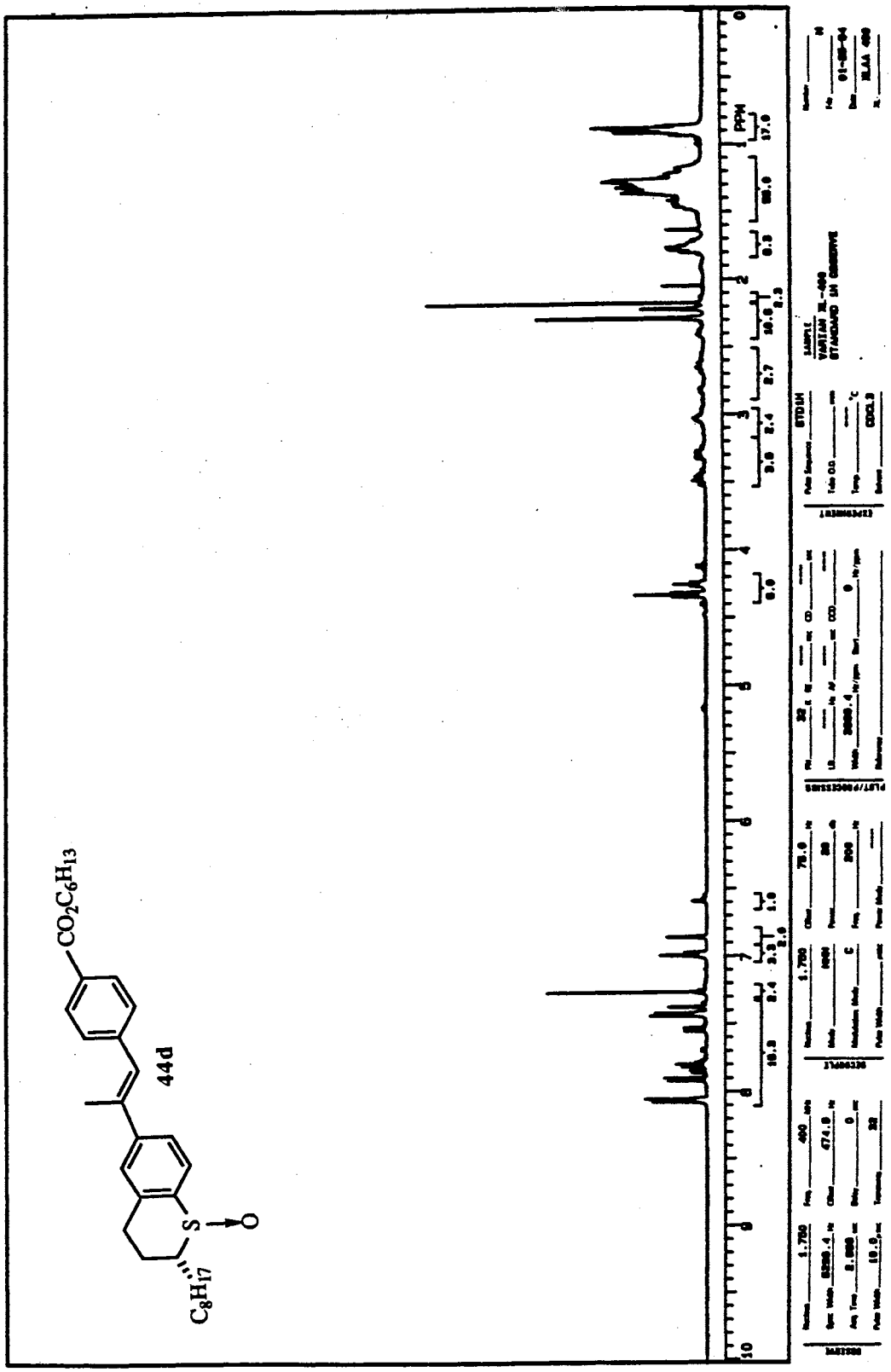
^{13}C NMR Spectrum of **44c**

Plate XVI



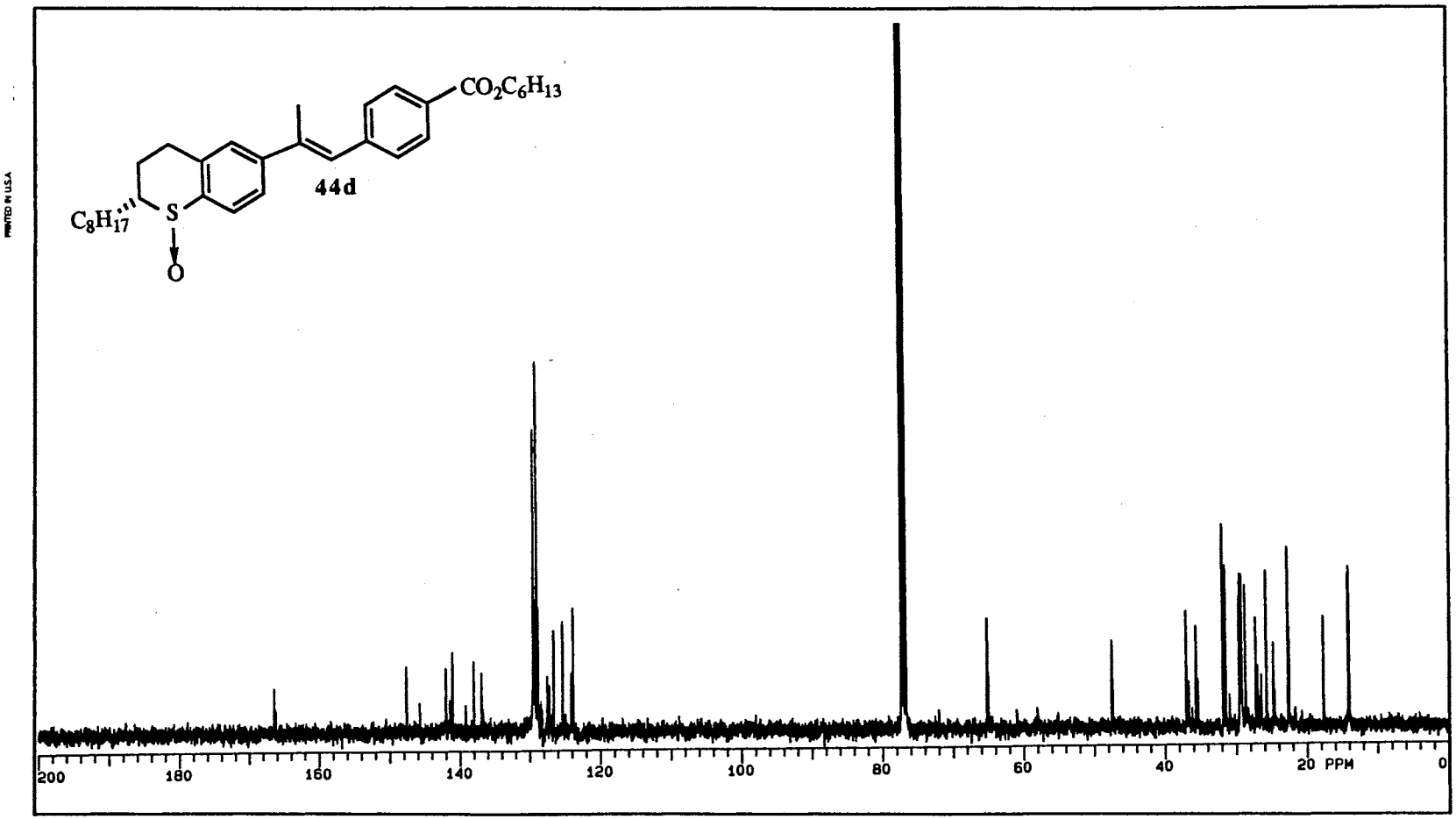
IR Spectrum of **44d**

Plate XVII



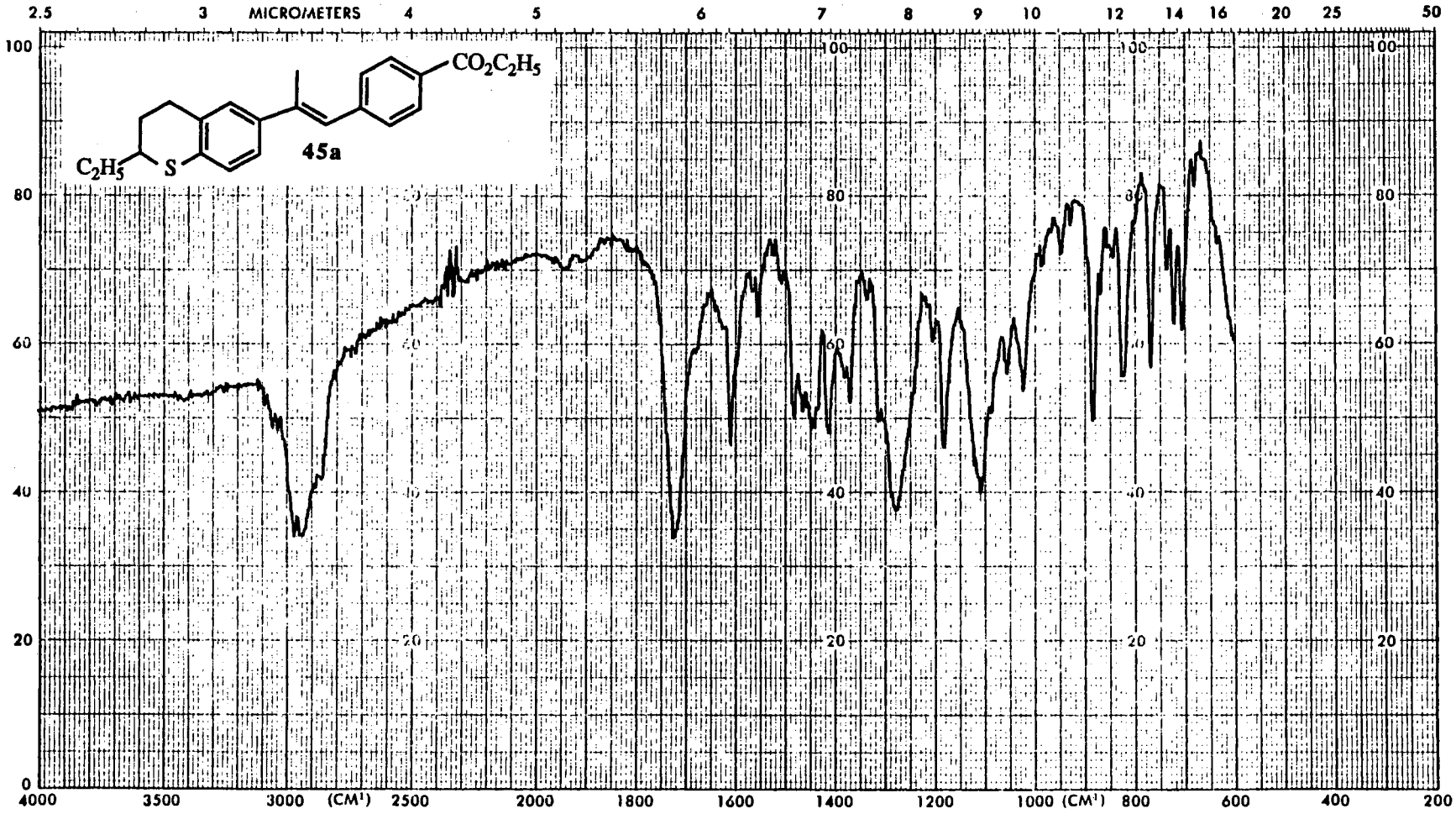
^1H NMR Spectrum of **44d**

Plate XVIII



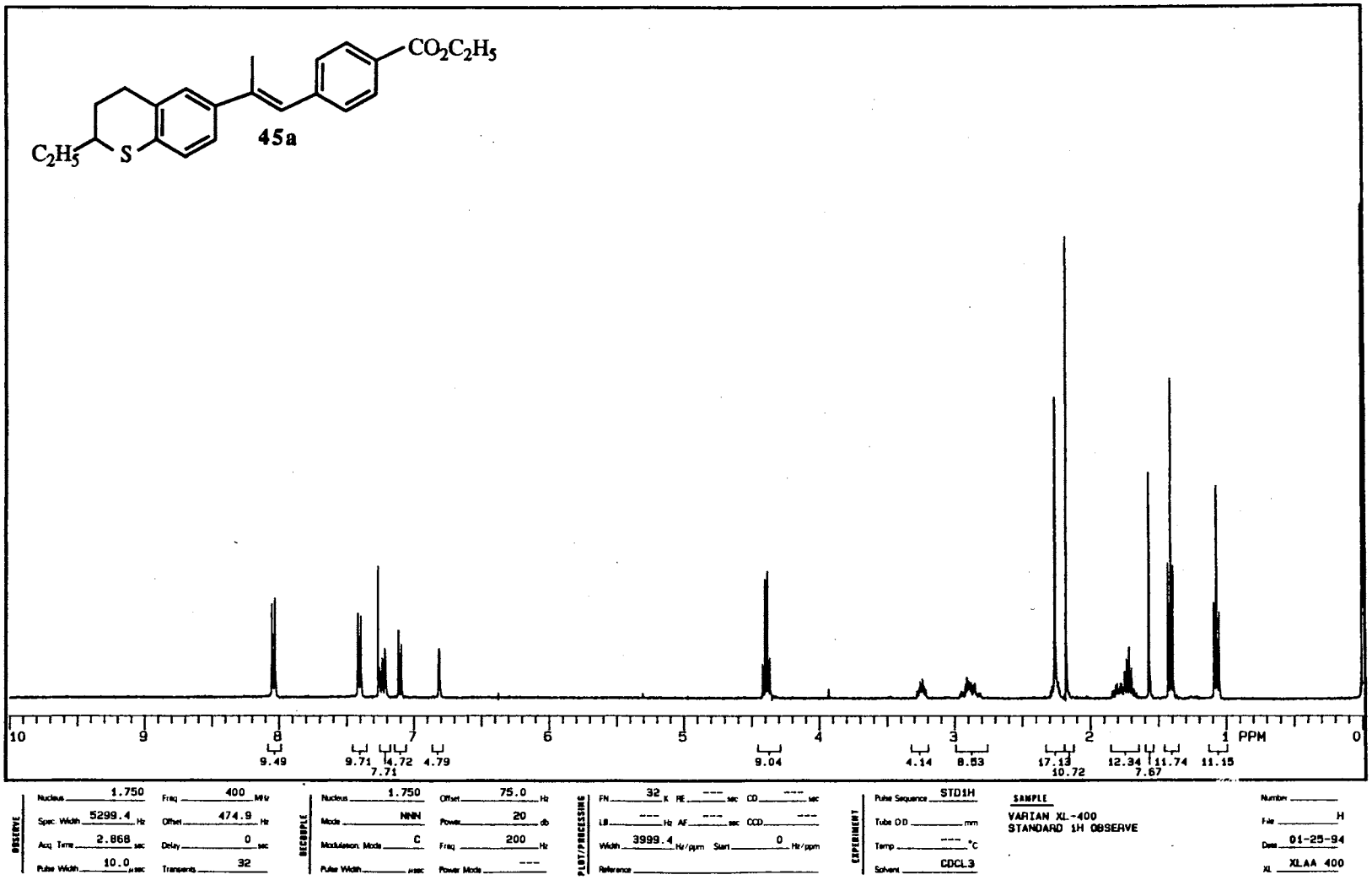
^{13}C NMR Spectrum of **44d**

Plate XIX



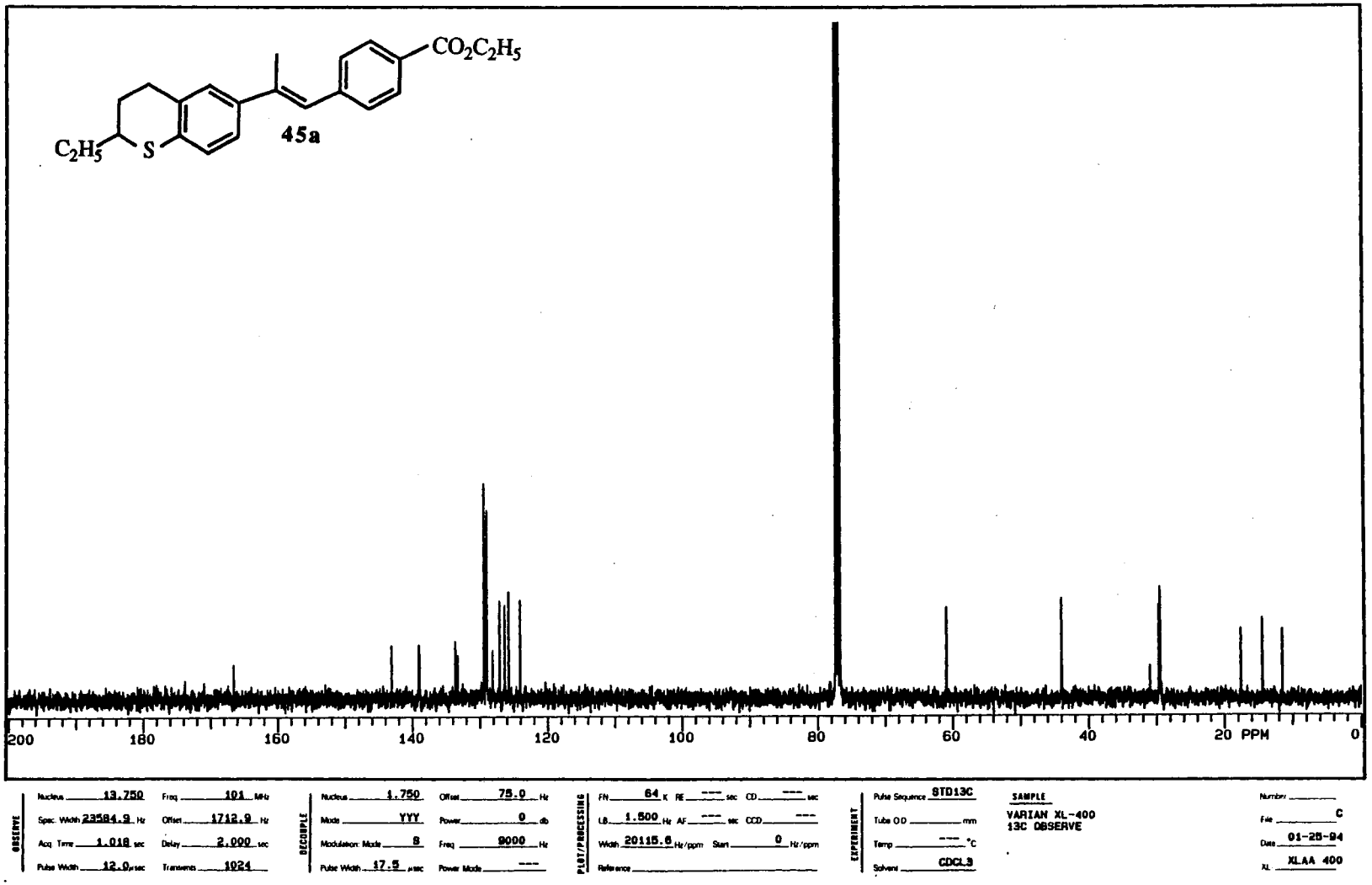
IR Spectrum of **45a**

Plate XX



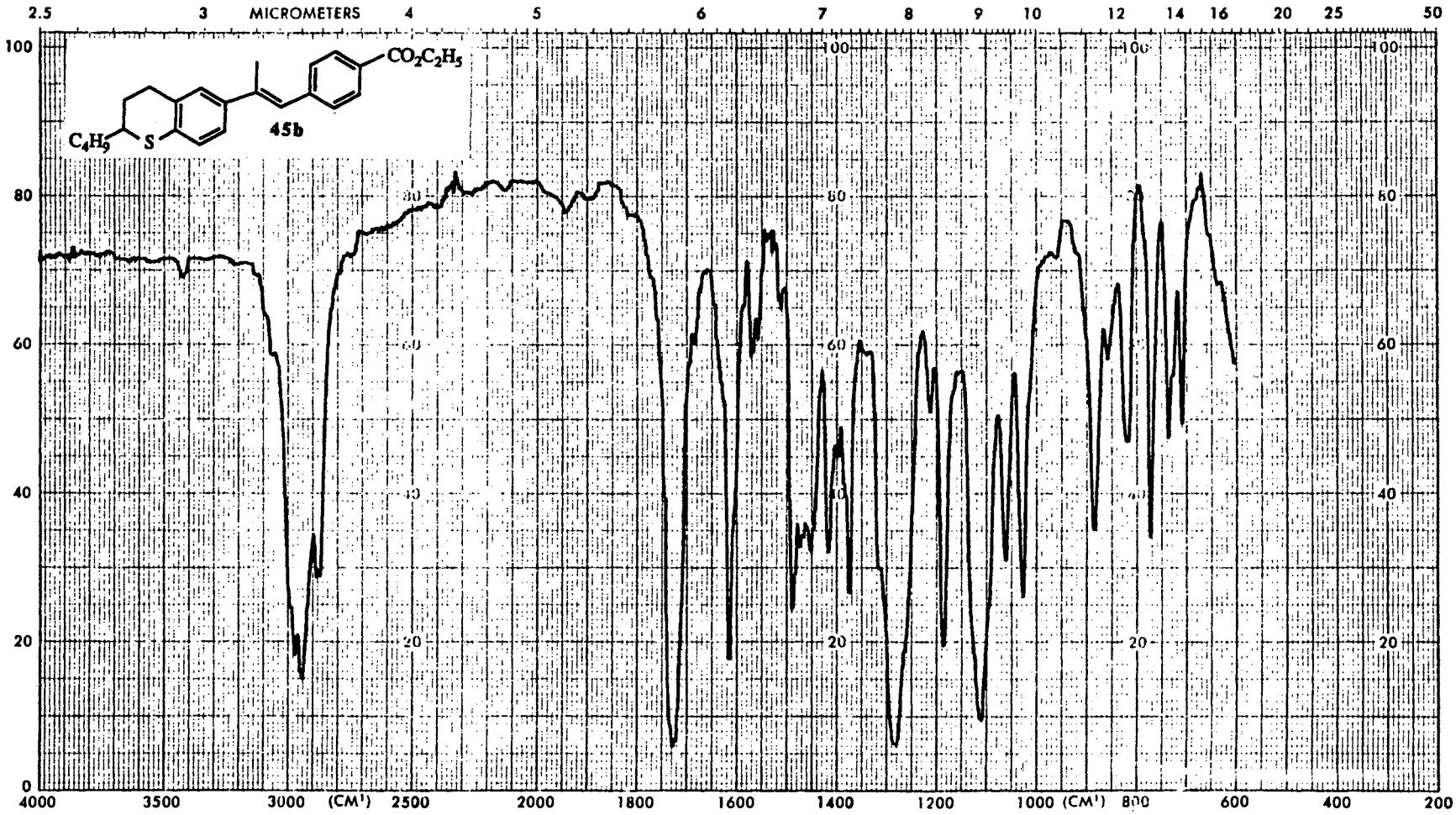
^{1}H NMR Spectrum of **45a**

Plate XXI



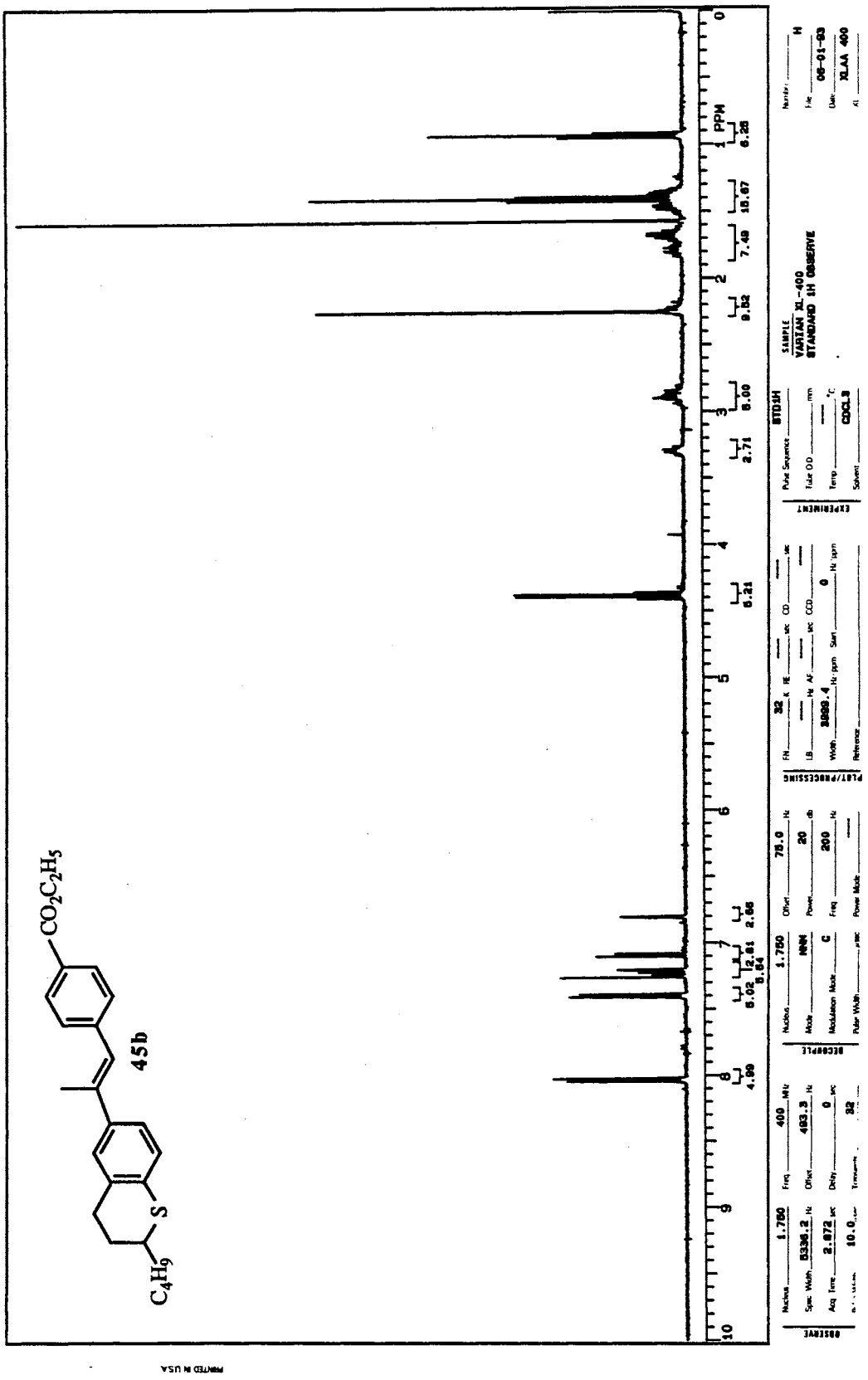
^{13}C NMR Spectrum of **45a**

Plate XXII



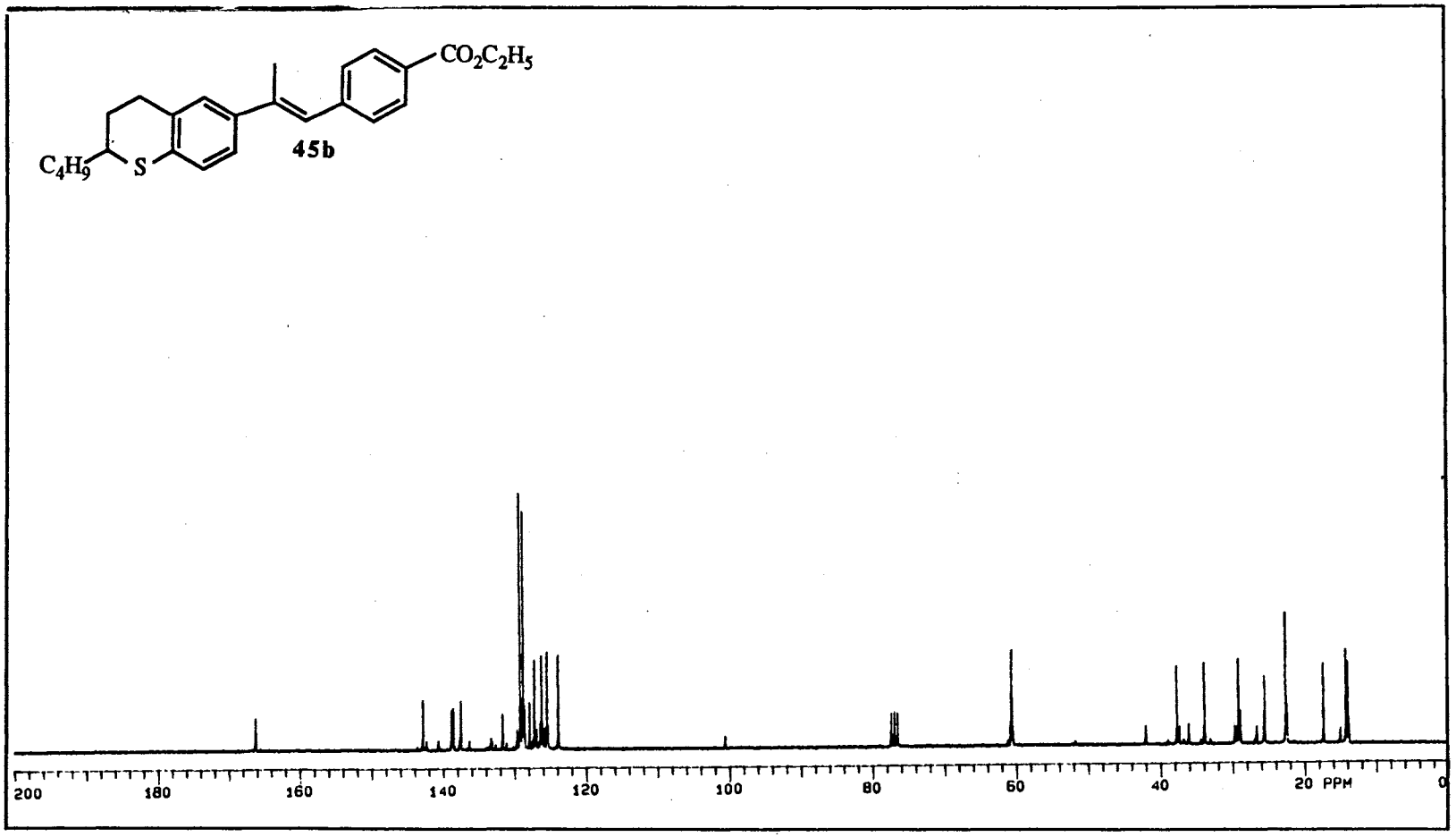
IR Spectrum of **45b**

Plate XXIII



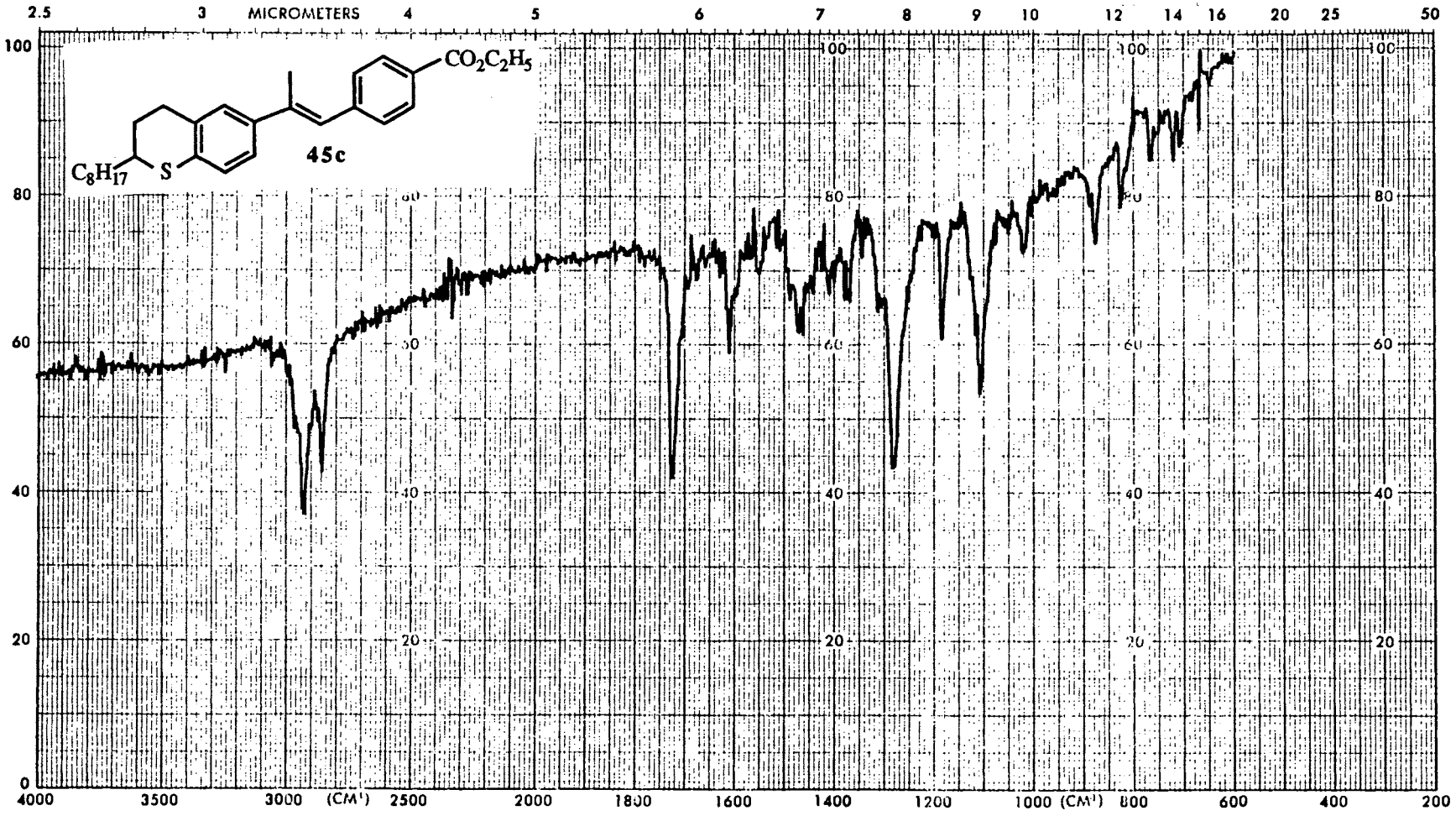
^{1}H NMR Spectrum of **45b**

Plate XXIV



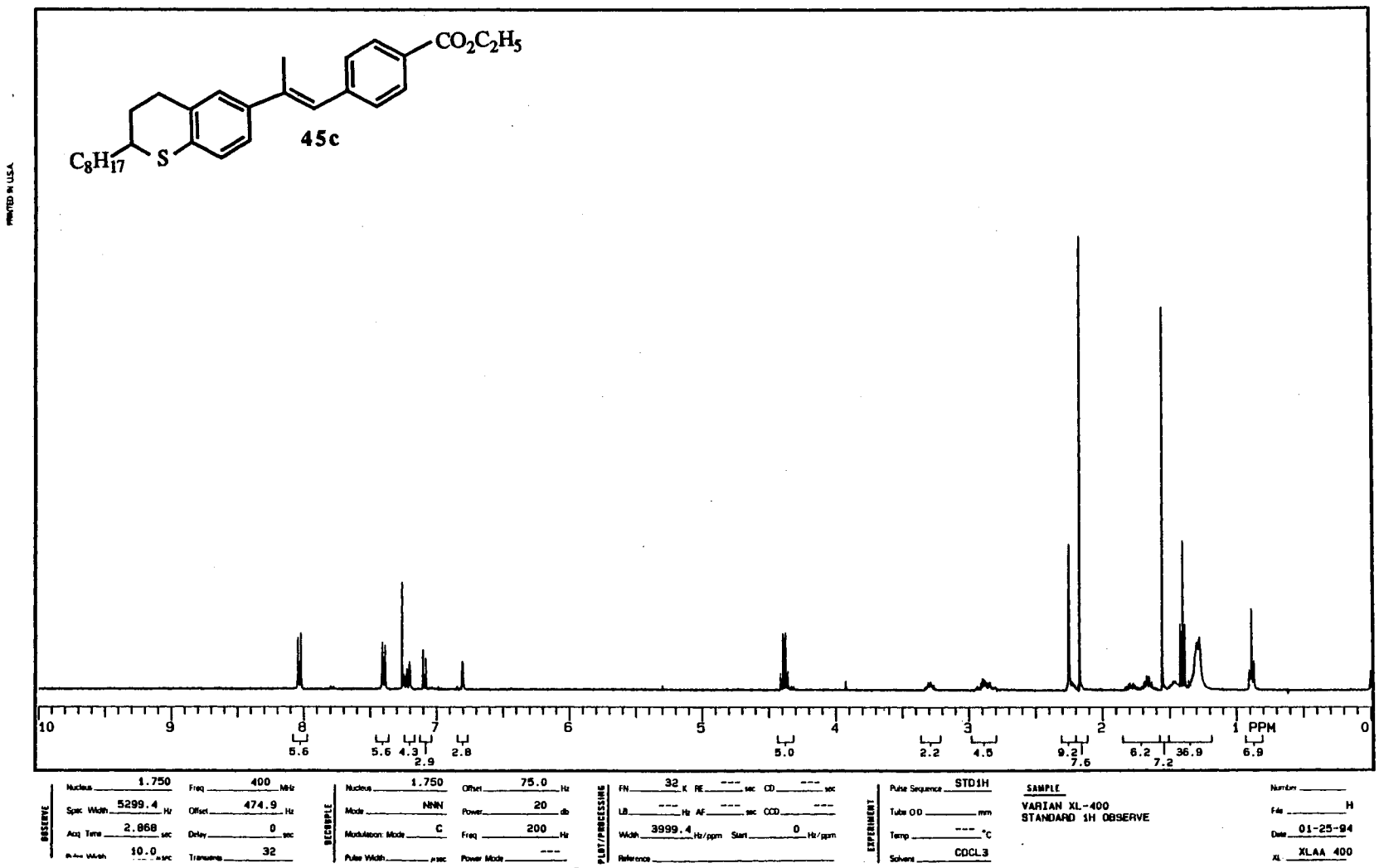
^{13}C NMR Spectrum of **45b**

Plate XXV



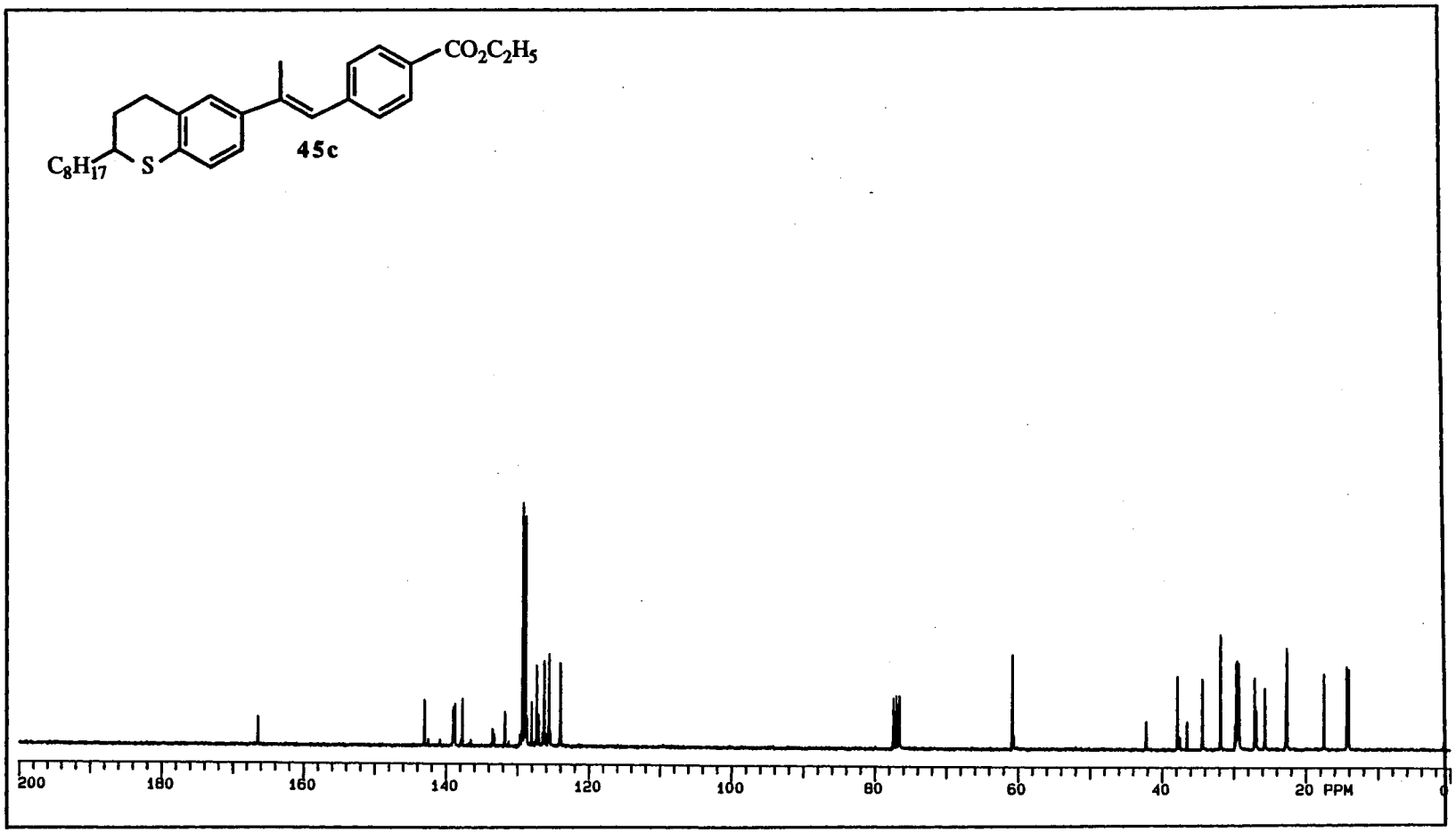
IR Spectrum of **45c**

Plate XXVI



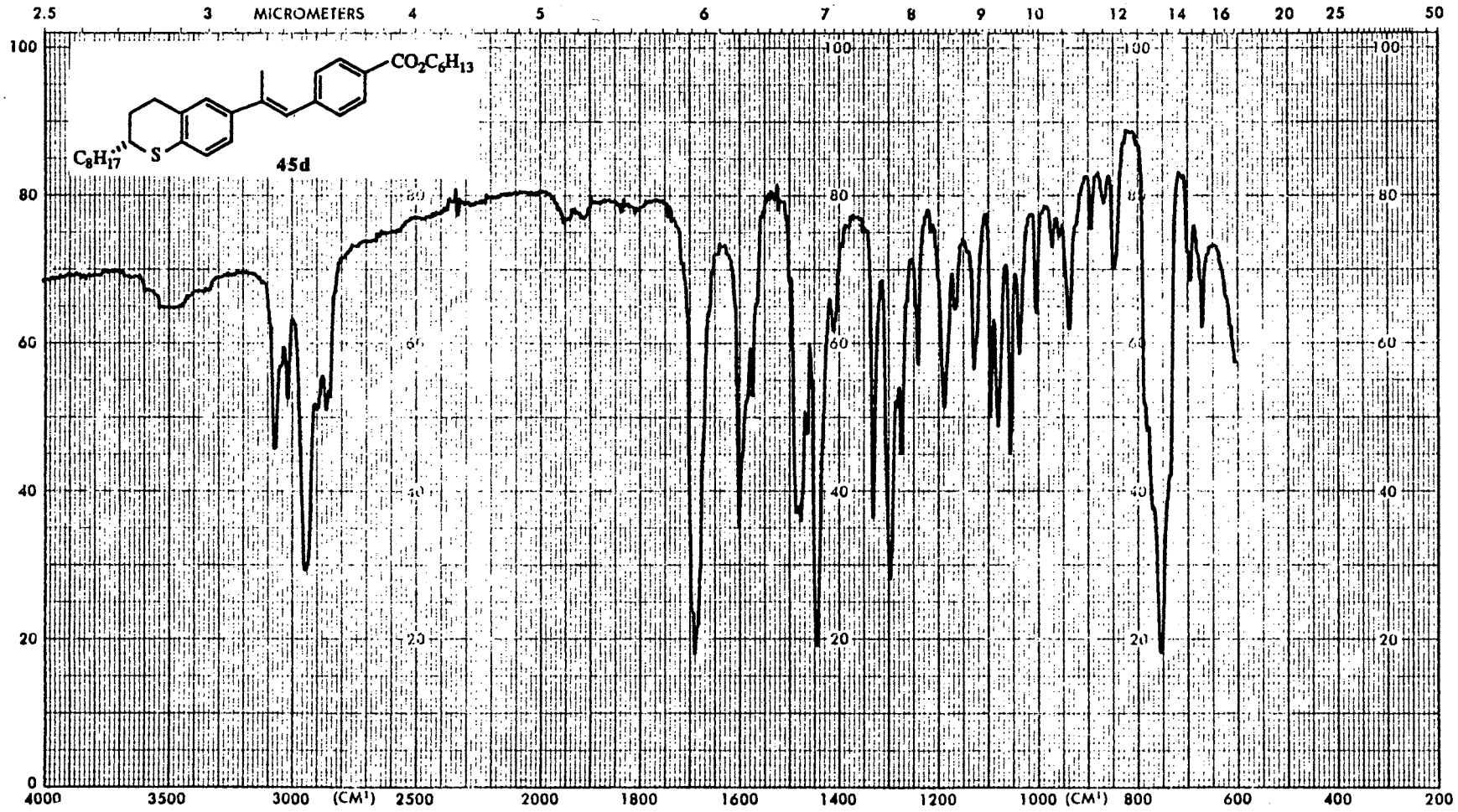
^{1}H NMR Spectrum of **45c**

Plate XXVII



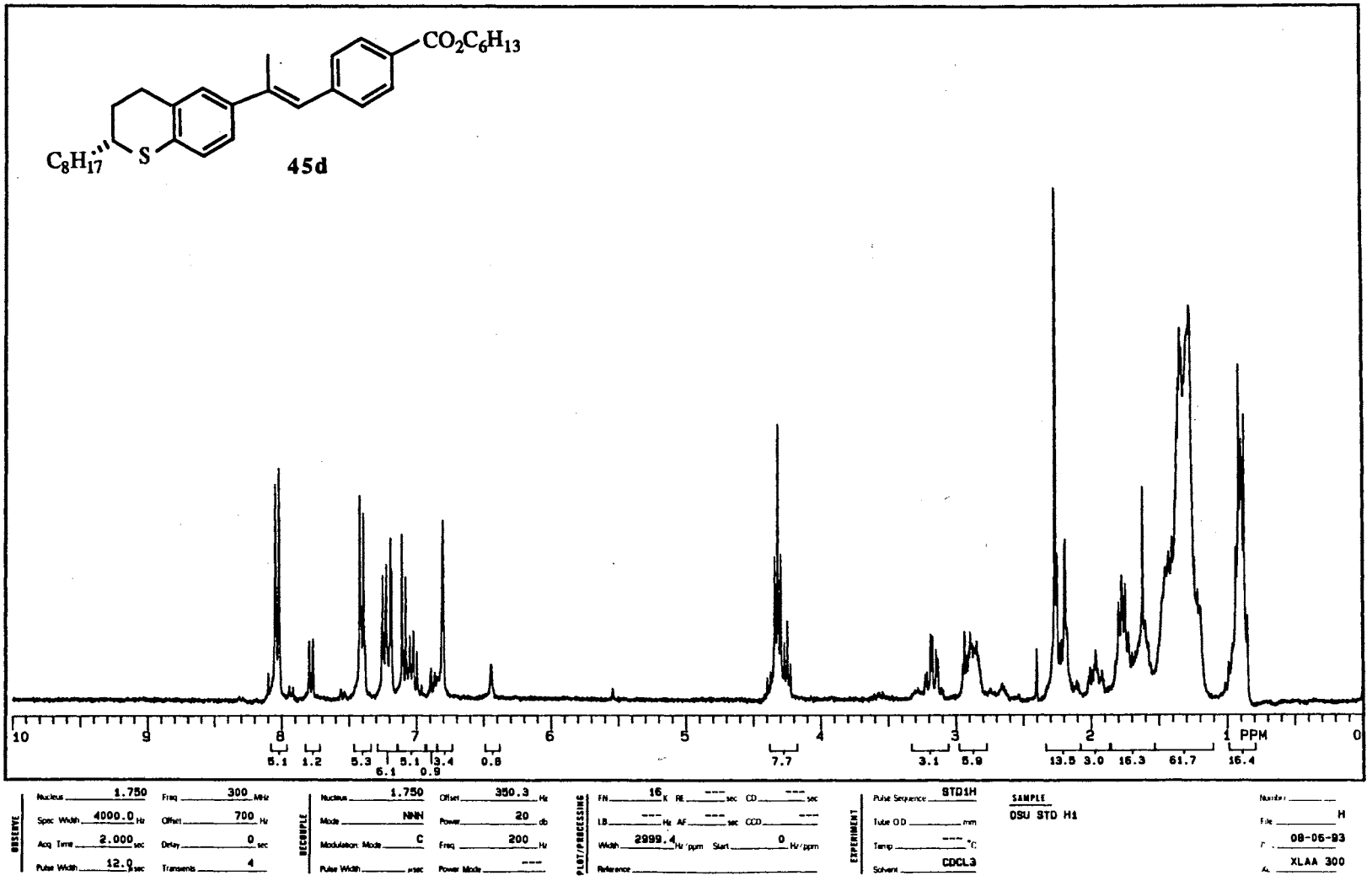
^{13}C NMR Spectrum of **45c**

Plate XXVIII



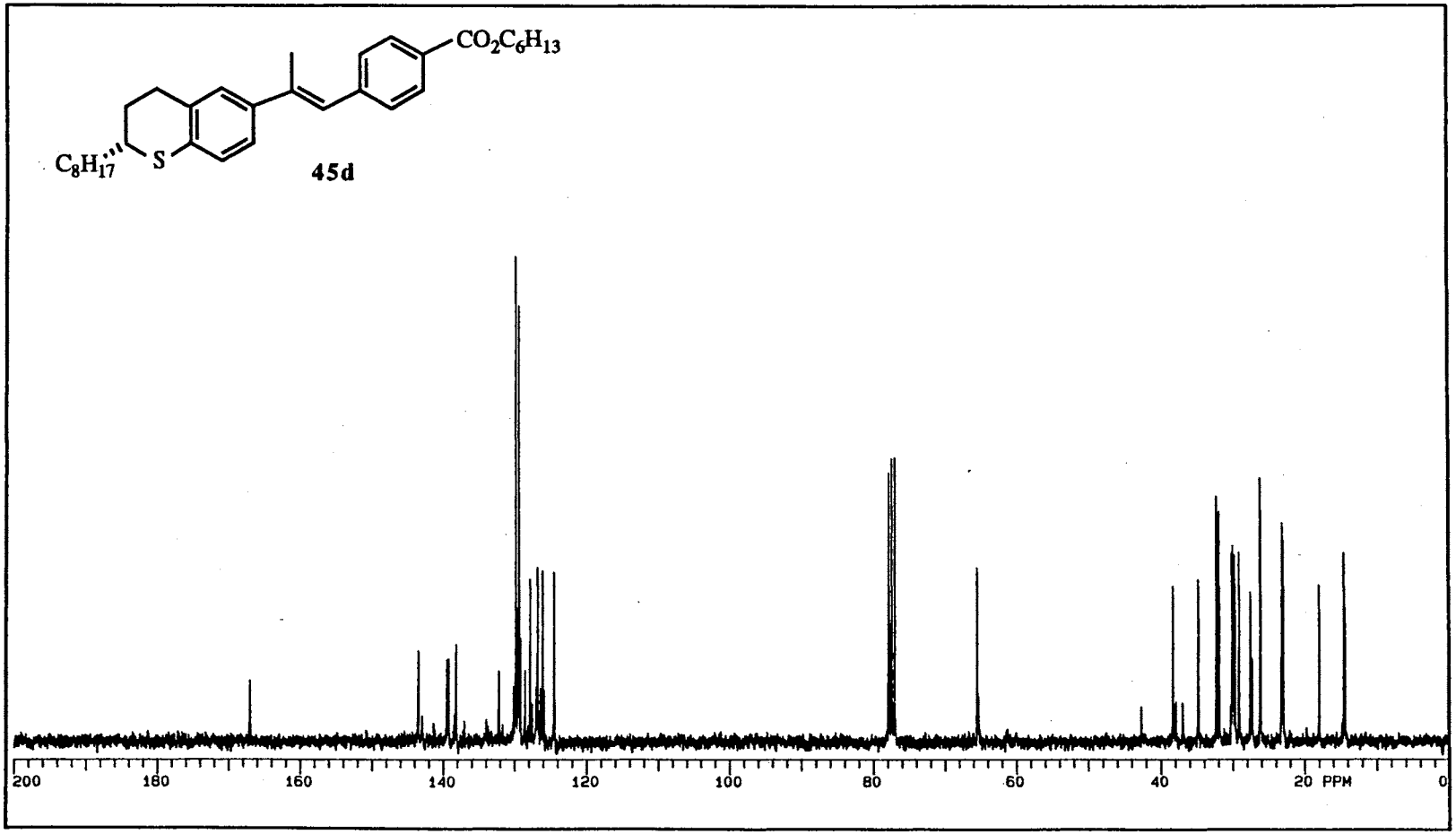
IR Spectrum of **45d**

Plate XXIX



^{1}H NMR Spectrum of **45d**

Plate XXX

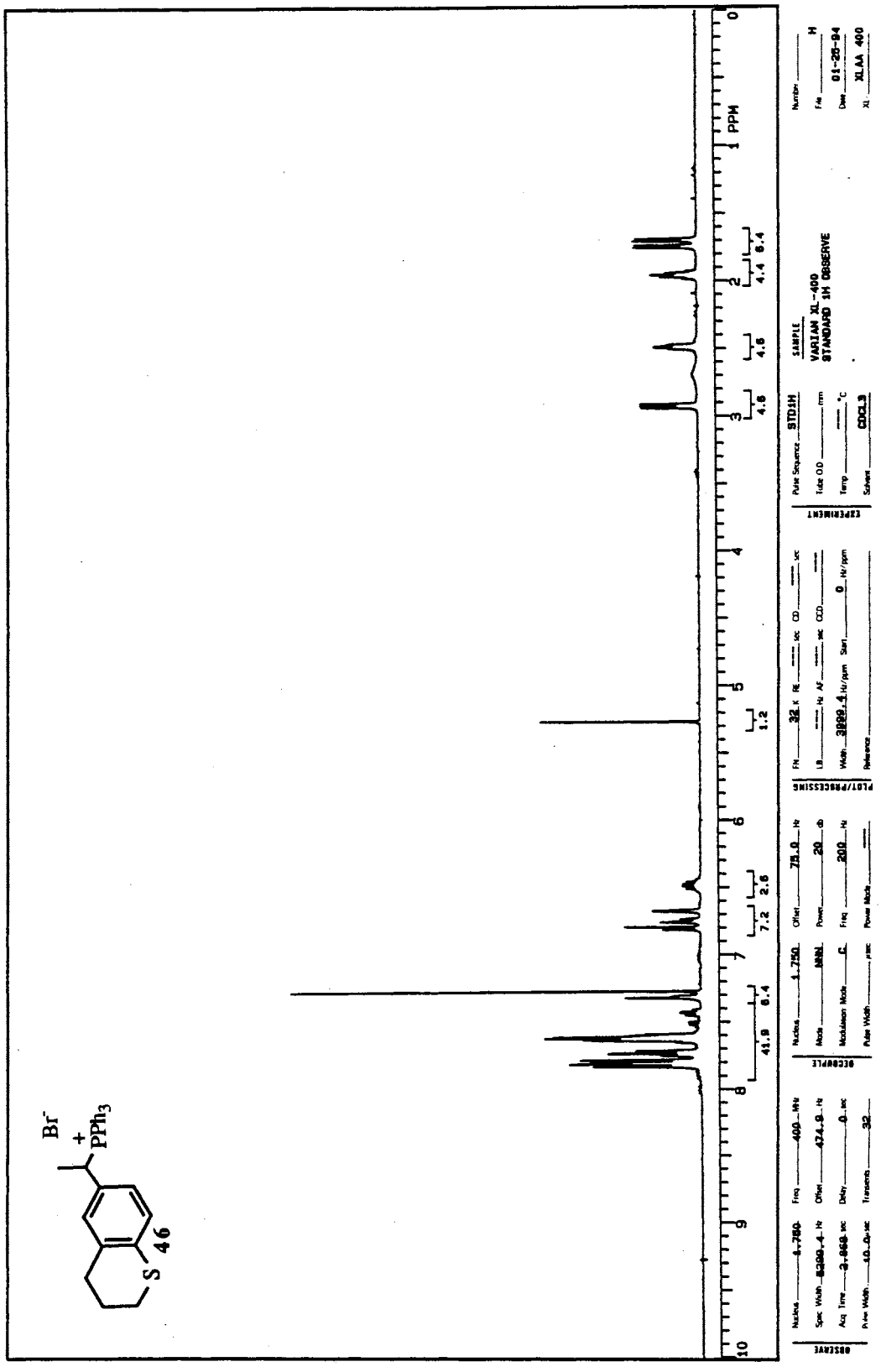


^{13}C NMR Spectrum of **45d**

Plate XXXI

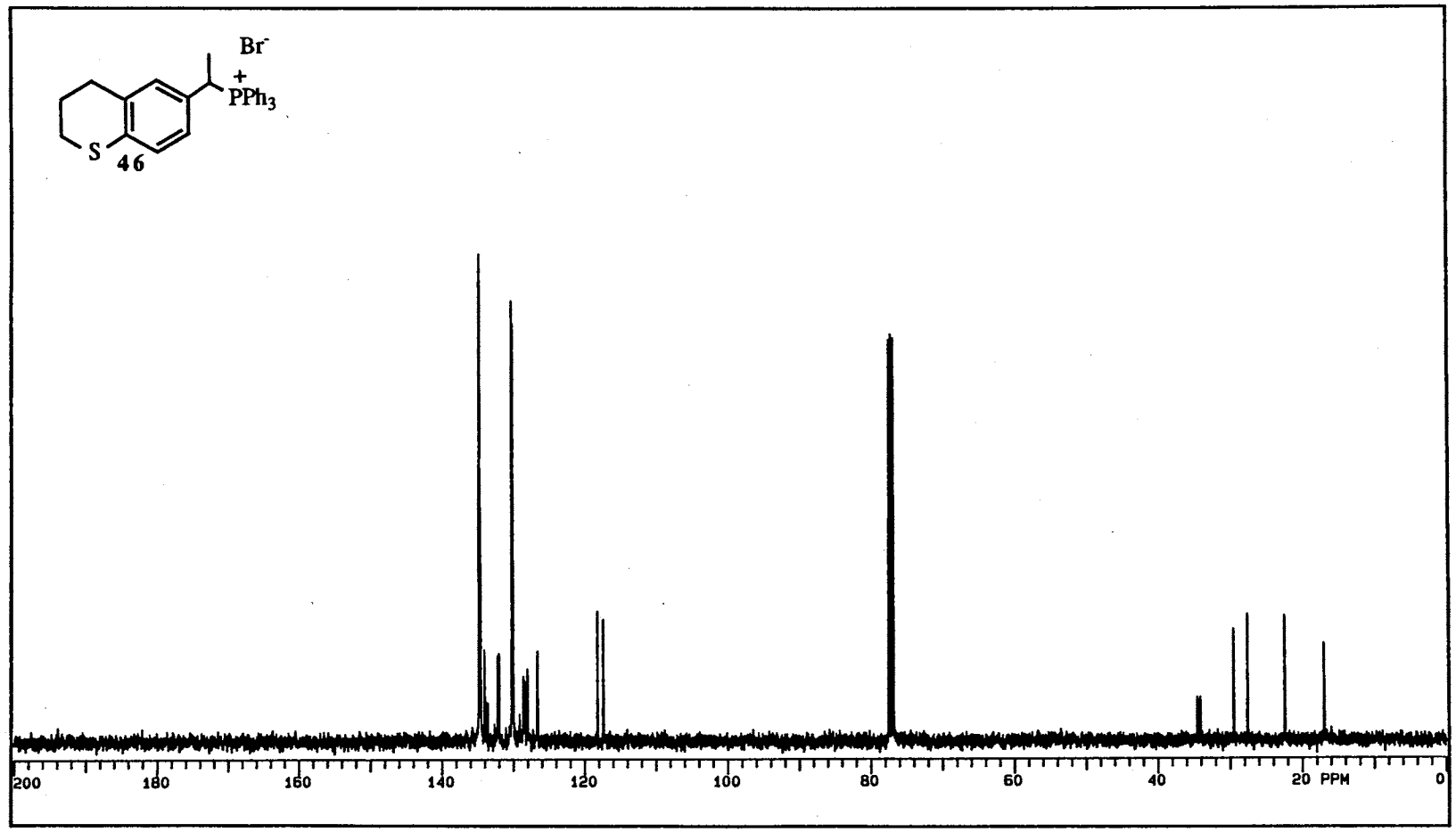
IR Spectrum of **46**

Plate XXXII



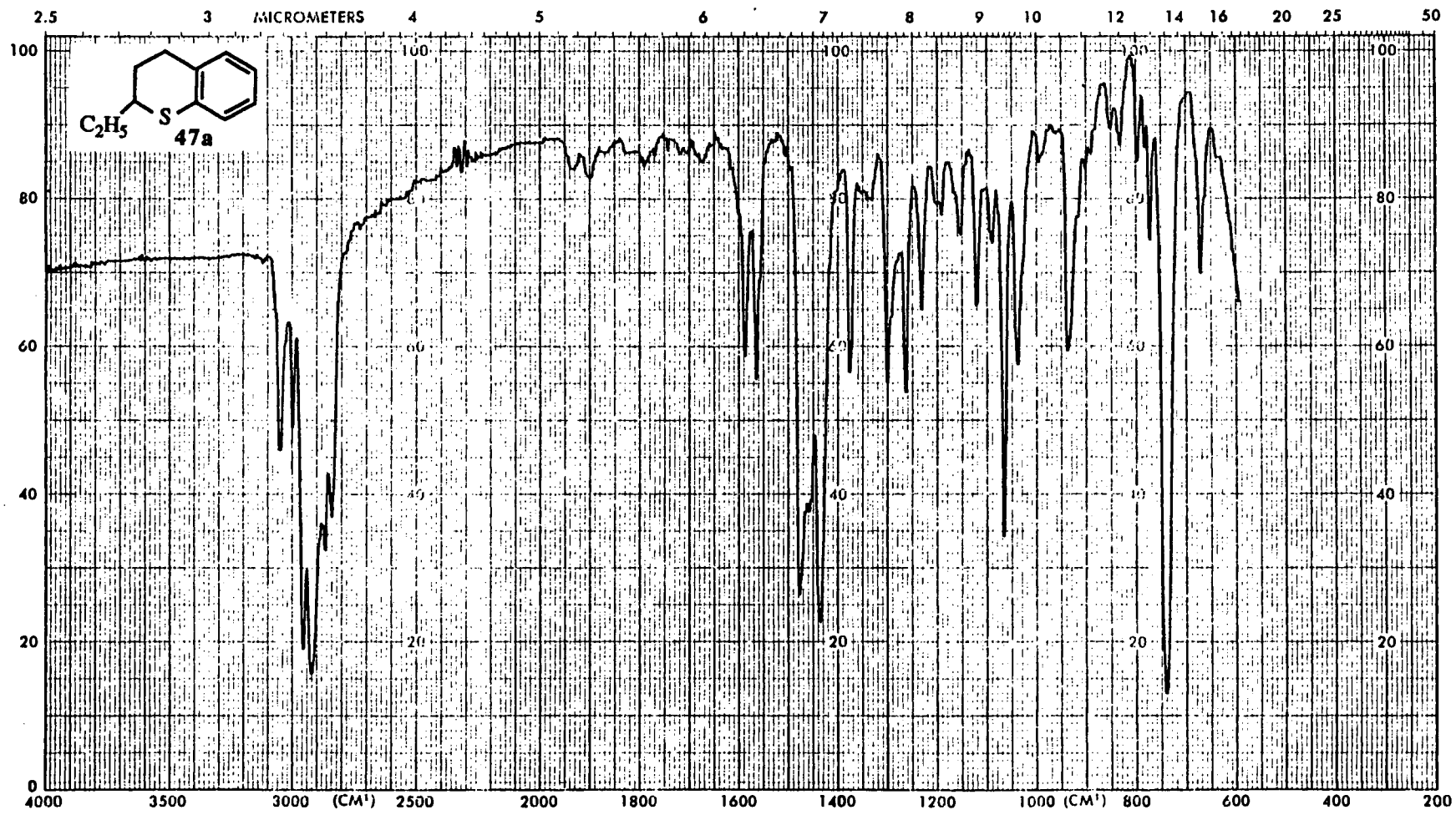
^{1}H NMR Spectrum of **46**

Plate XXXIII



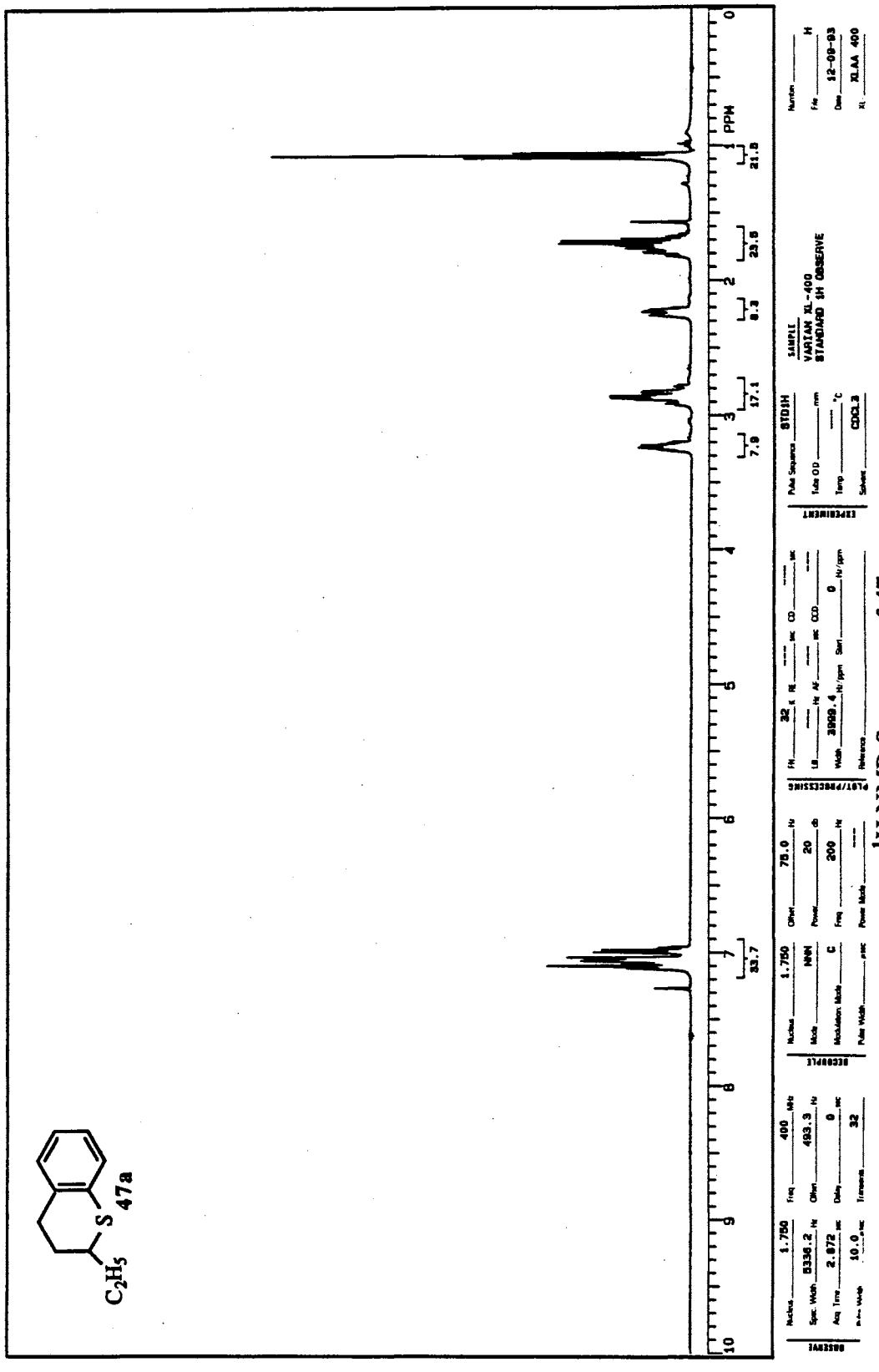
^{13}C NMR Spectrum of **46**

Plate XXXIV



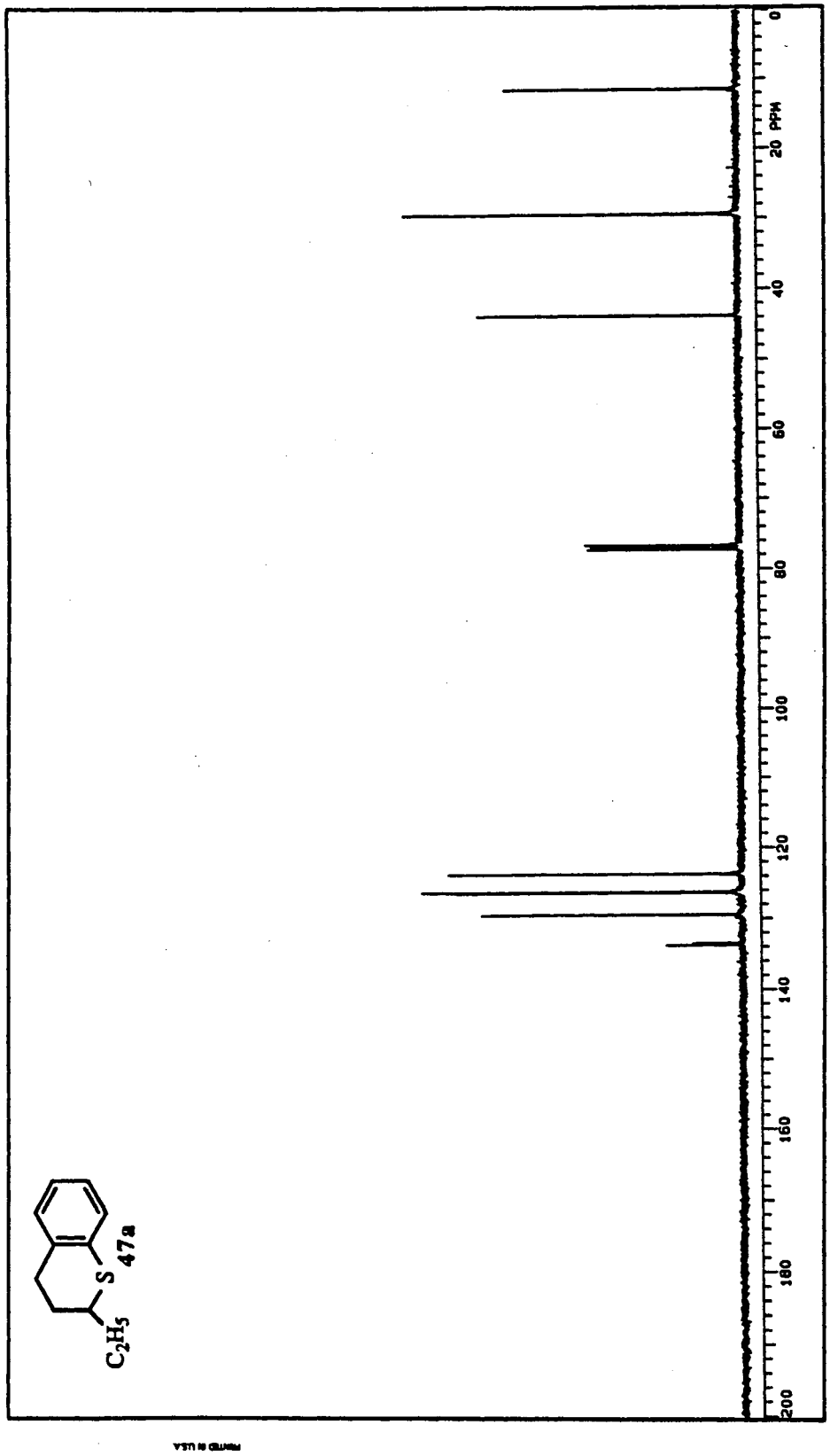
IR Spectrum of **47a**

Plate XXXV



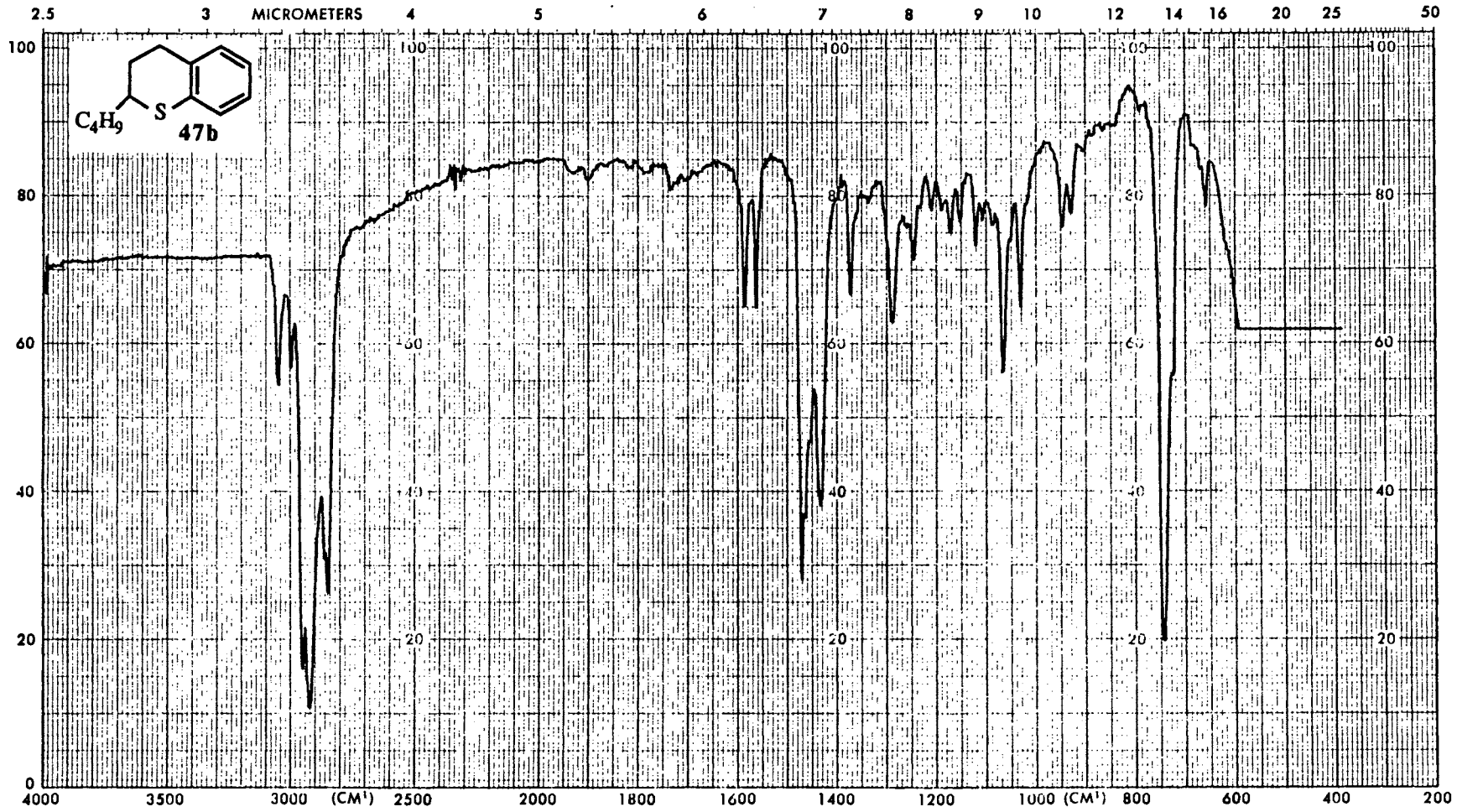
^{1}H NMR Spectrum of **47a**

Plate XXXVI



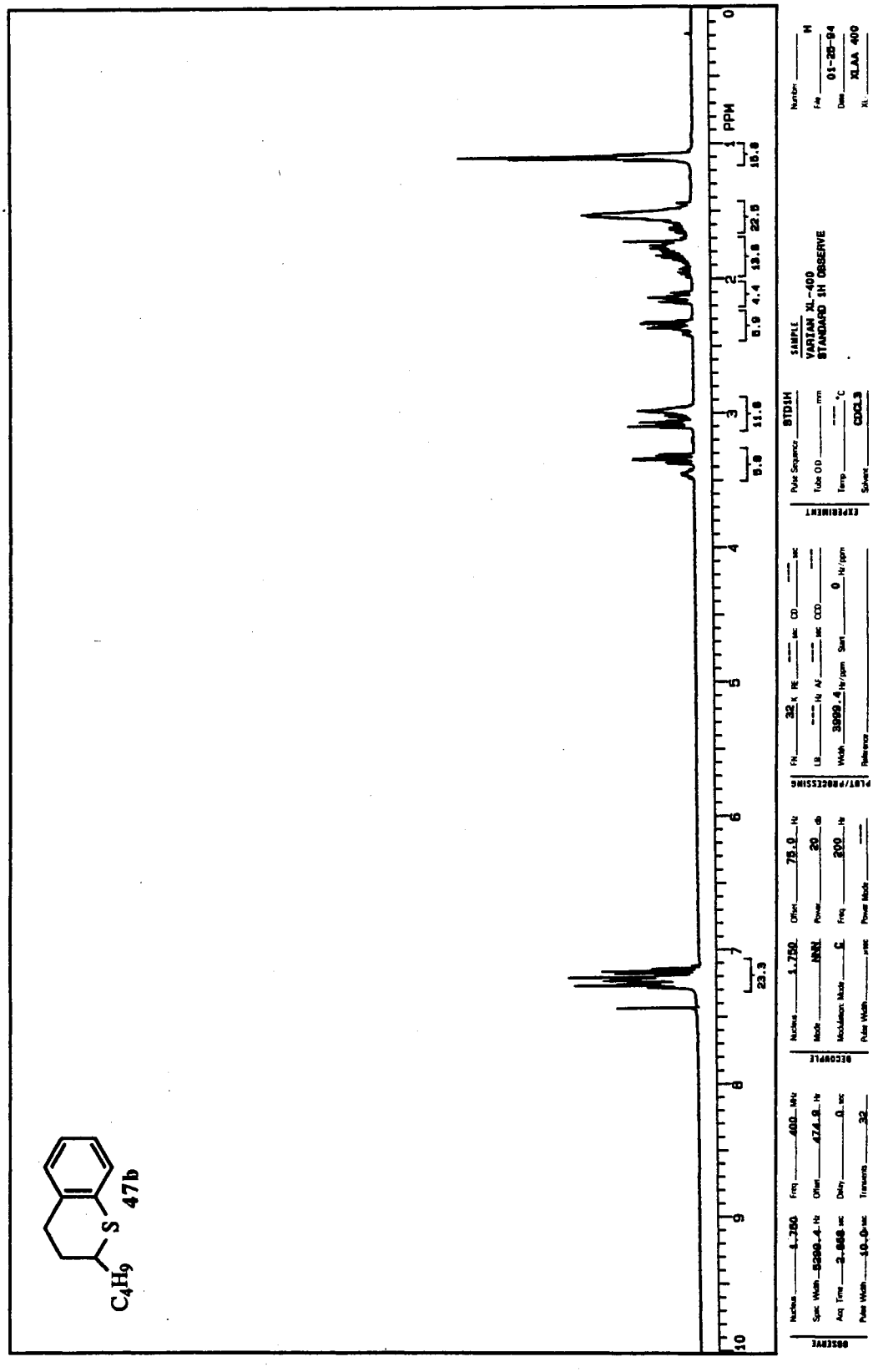
^{13}C NMR Spectrum of 47a

Plate XXXVII



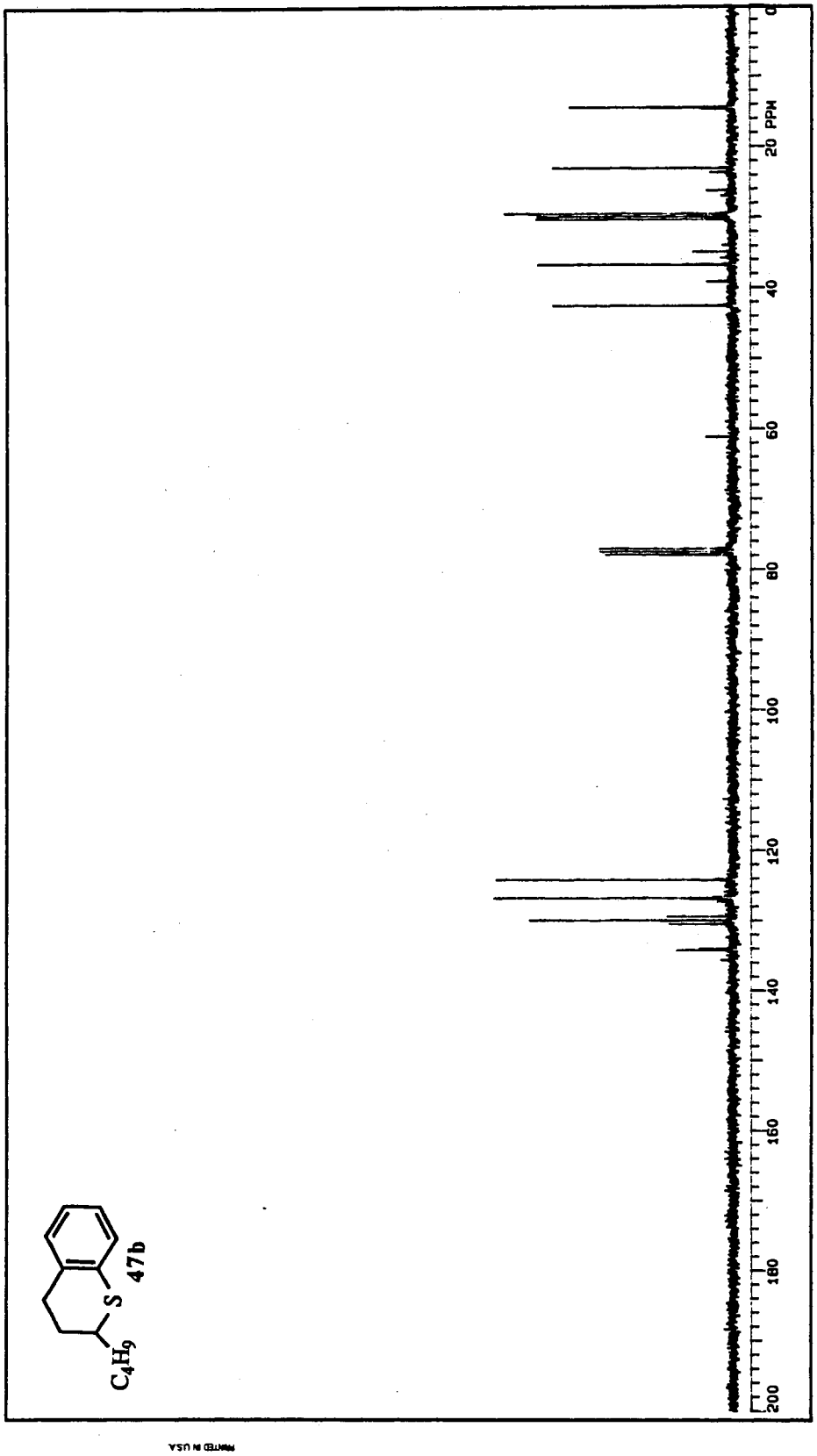
IR Spectrum of **47b**

Plate XXXVIII



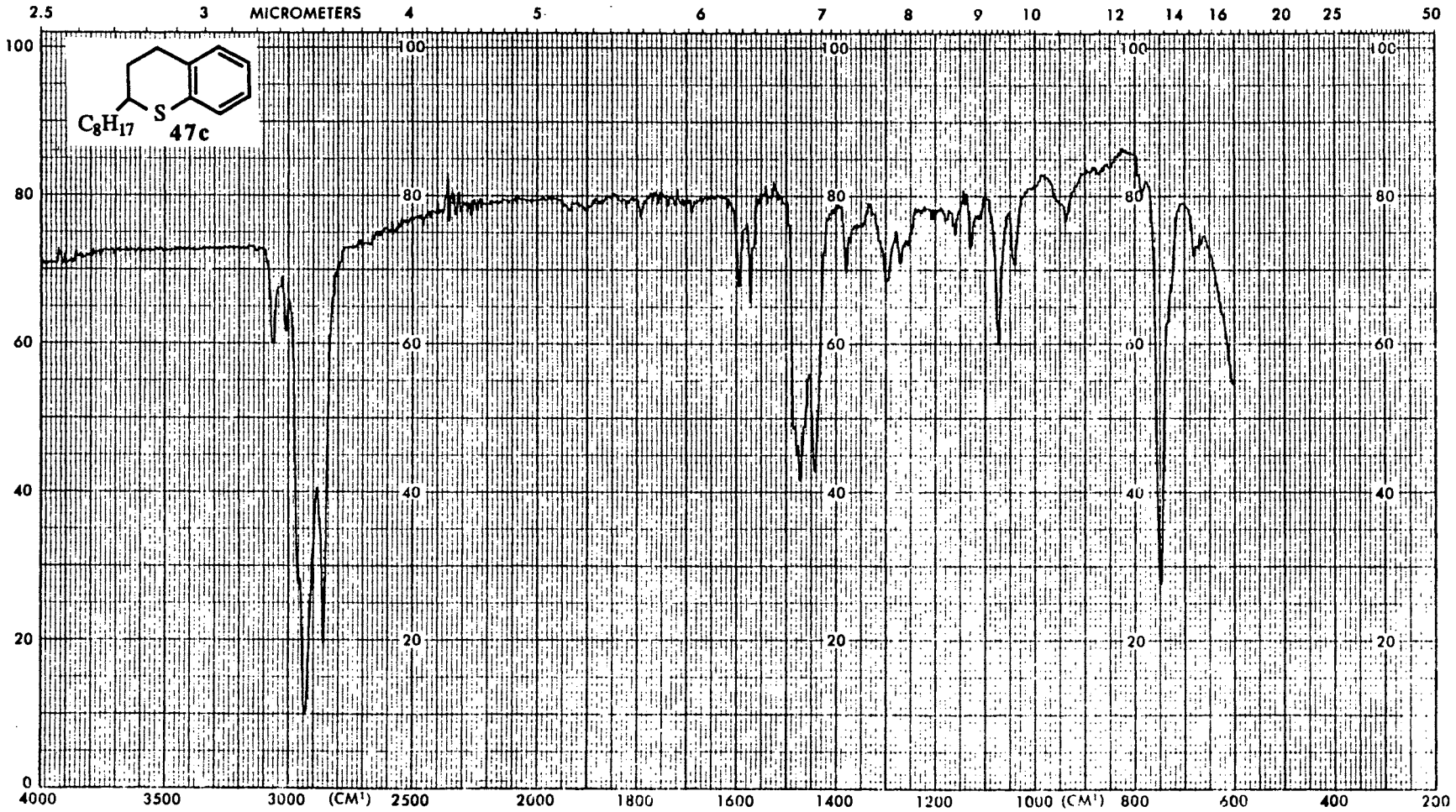
^{1}H NMR Spectrum of **47b**

Plate XXXIX



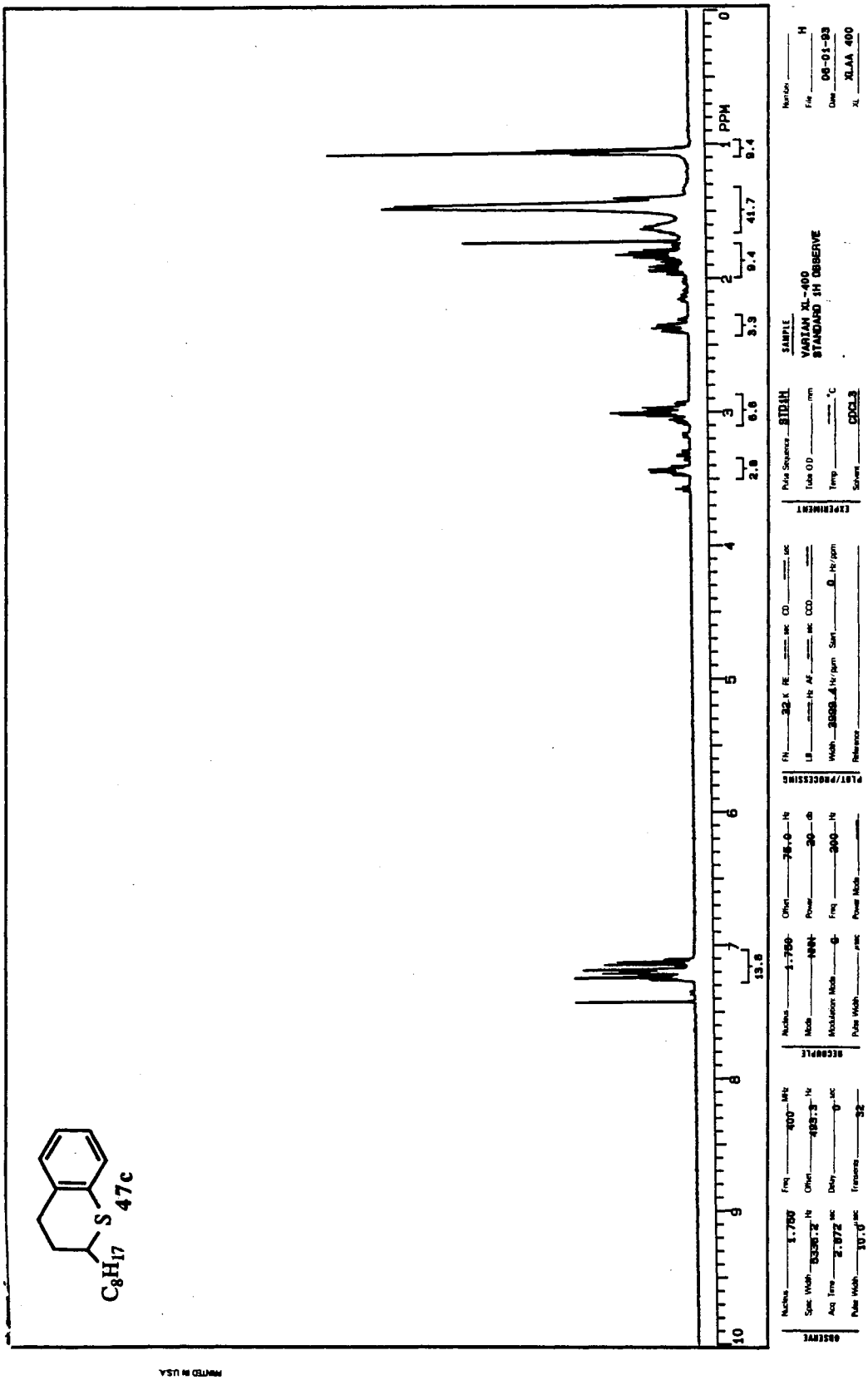
^{13}C NMR Spectrum of **47b**

Plate XL



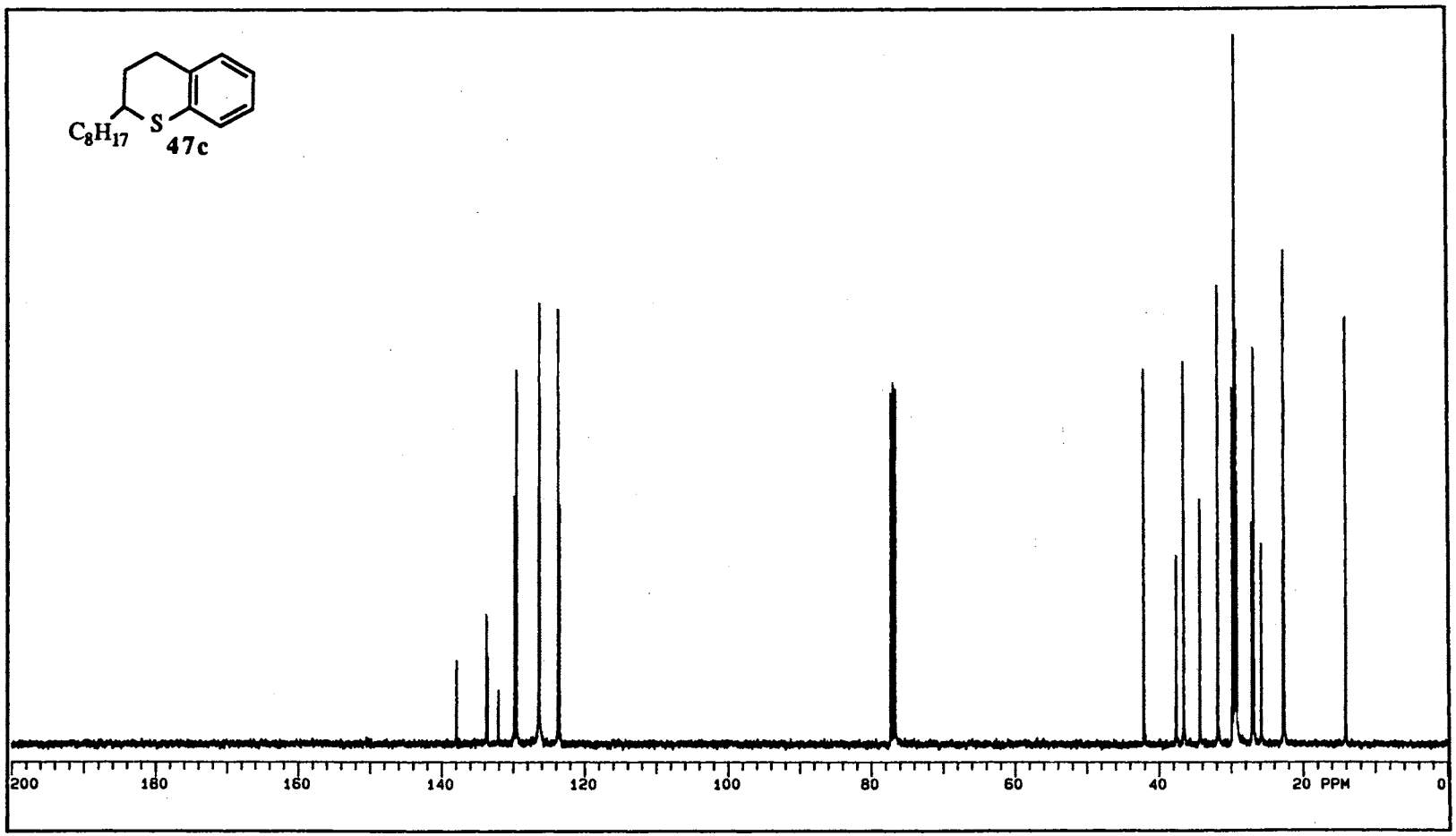
IR Spectrum of **47c**

Plate XLI



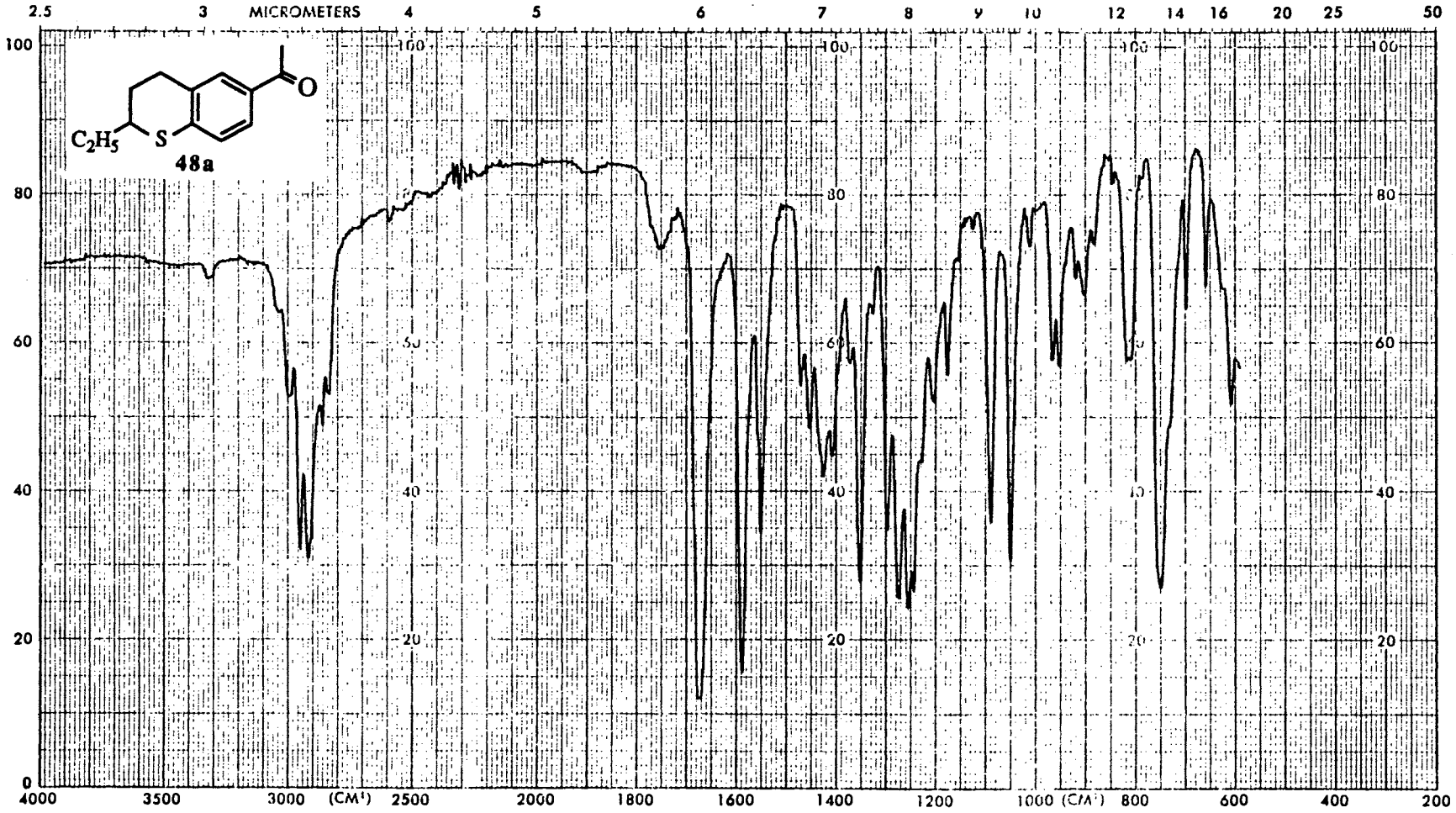
^{1}H NMR Spectrum of **47c**

Plate XLII



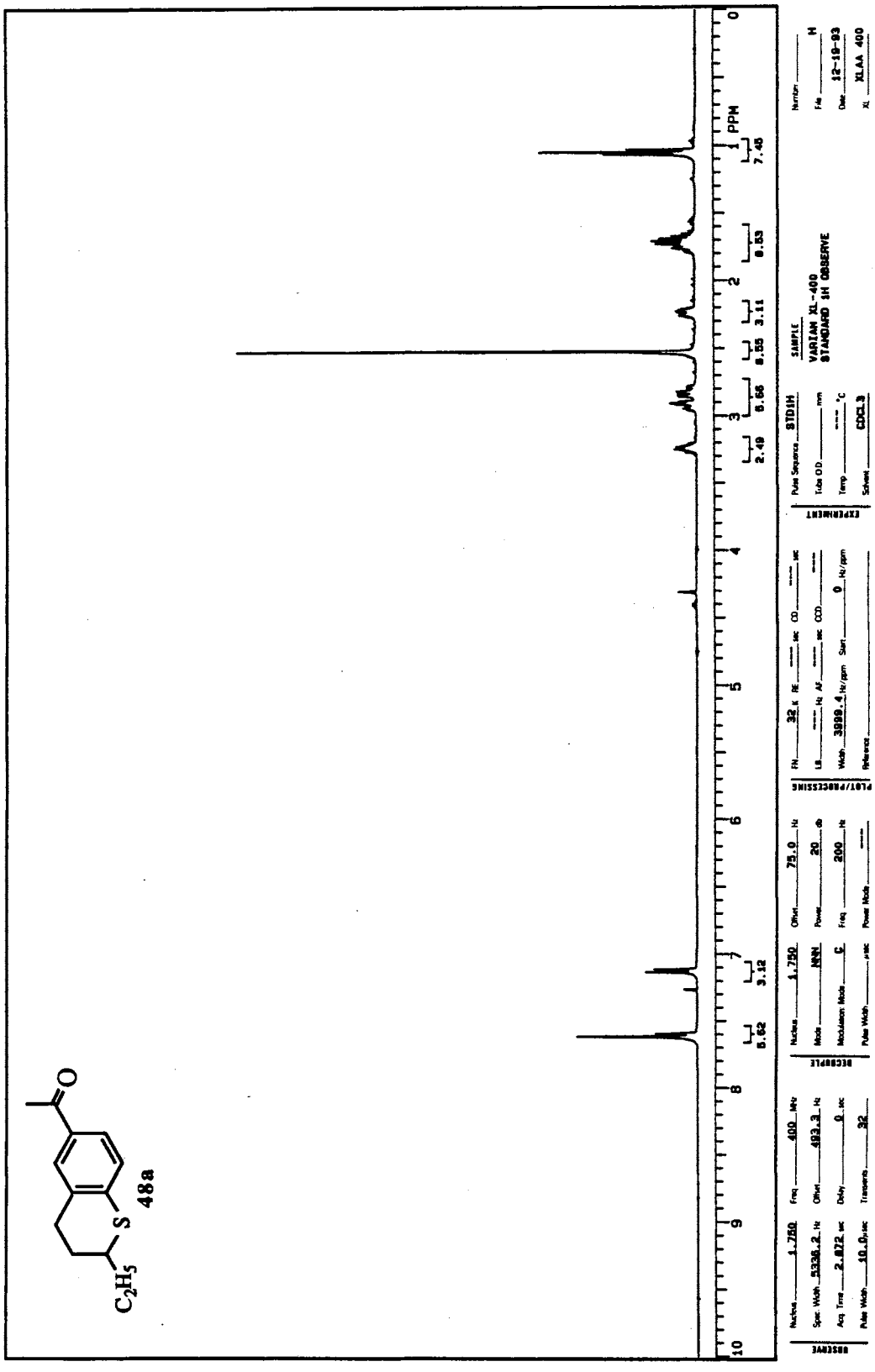
^{13}C NMR Spectrum of **47c**

Plate XLIII



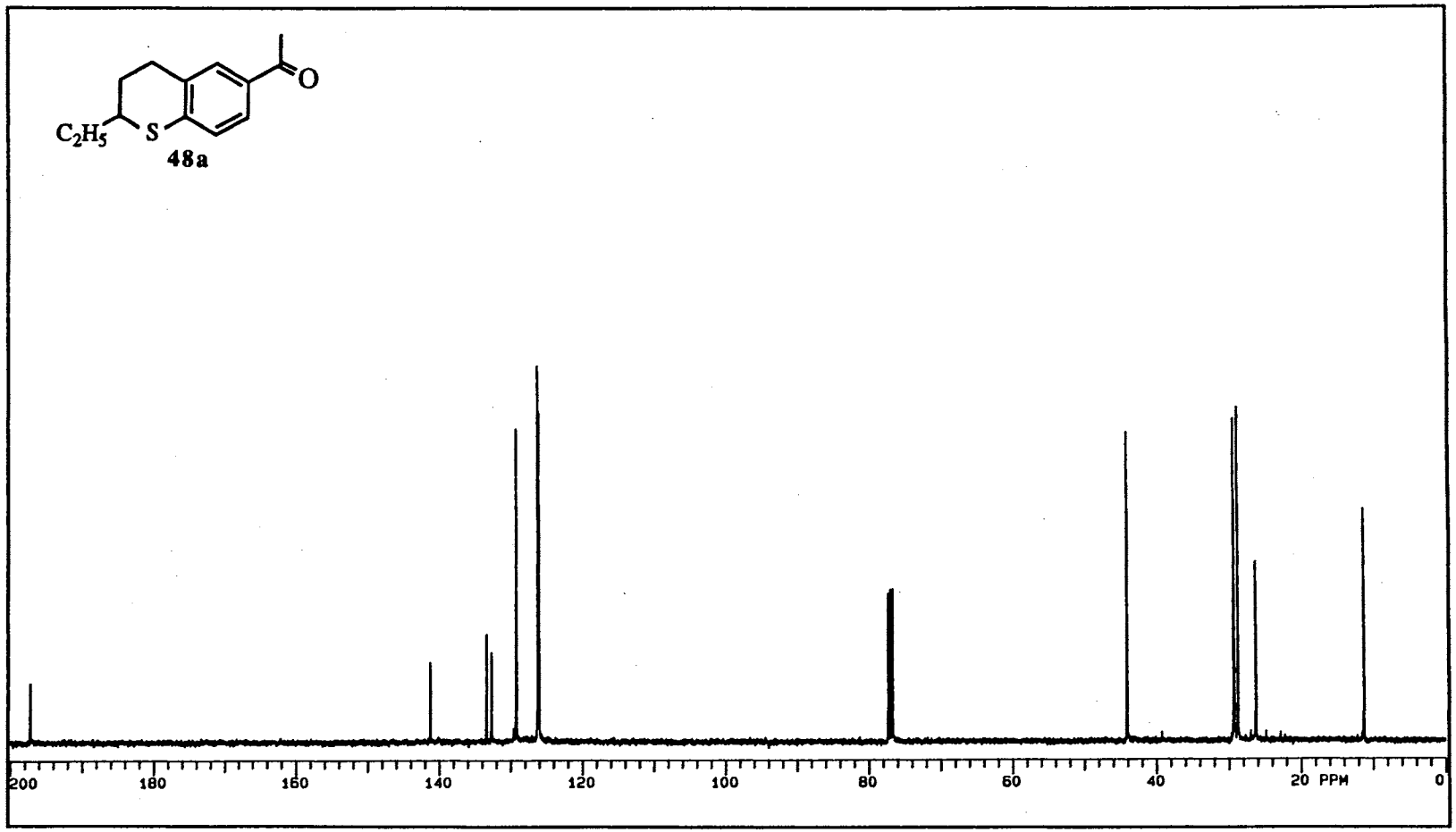
IR Spectrum of **48a**

Plate XLIV



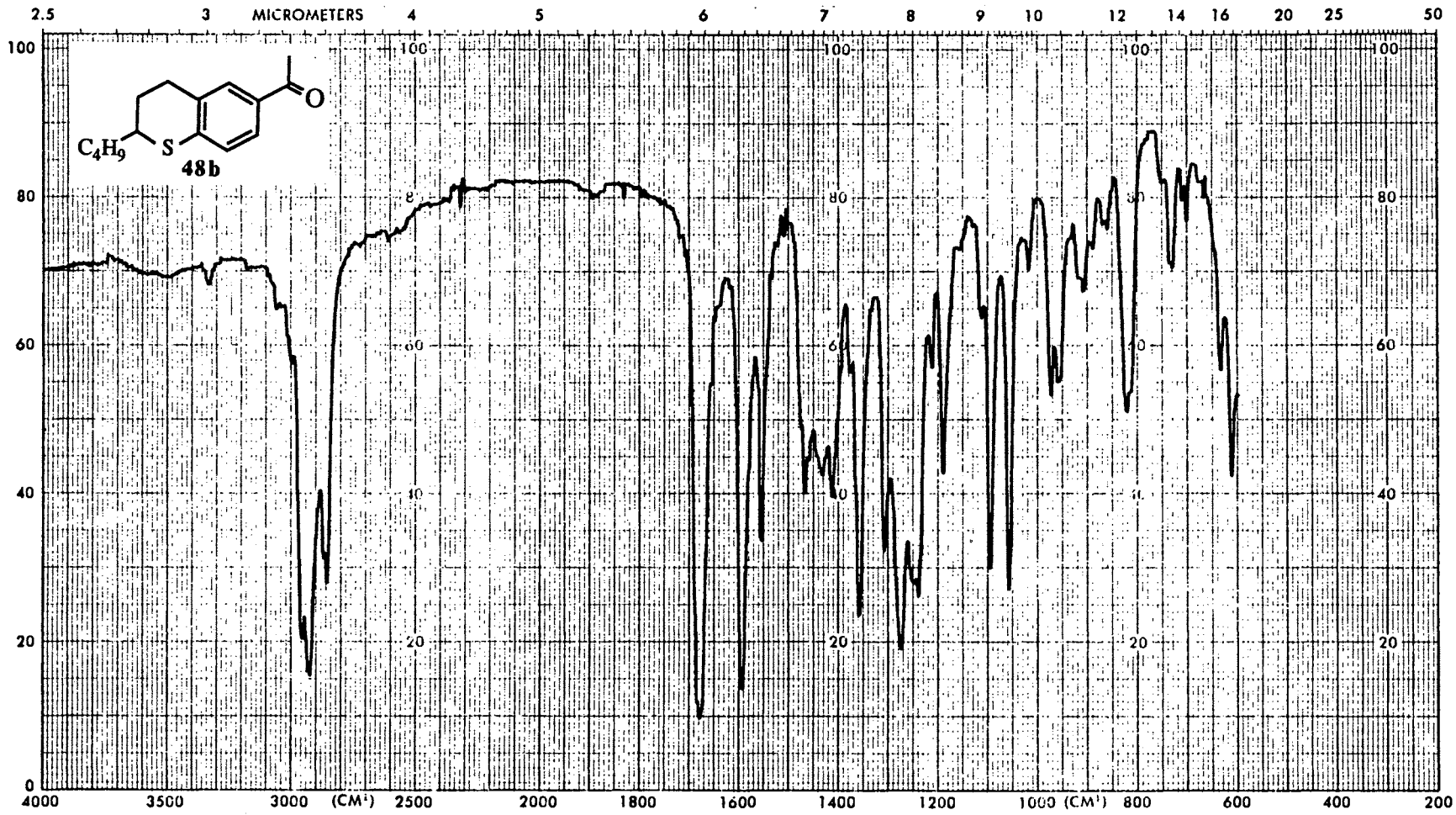
^{1}H NMR Spectrum of **48a**

Plate XLV



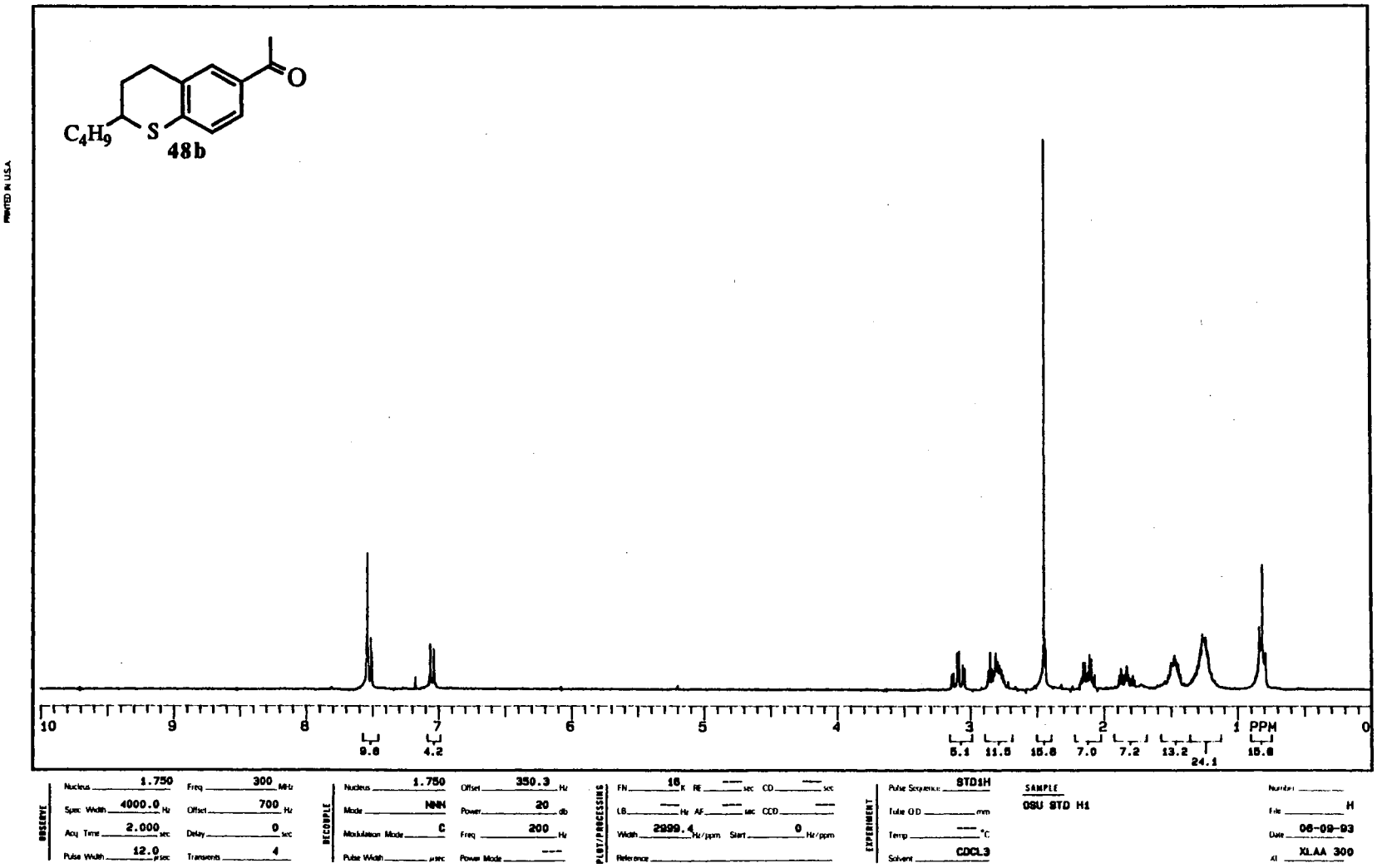
^{13}C NMR Spectrum of **48a**

Plate XLVI



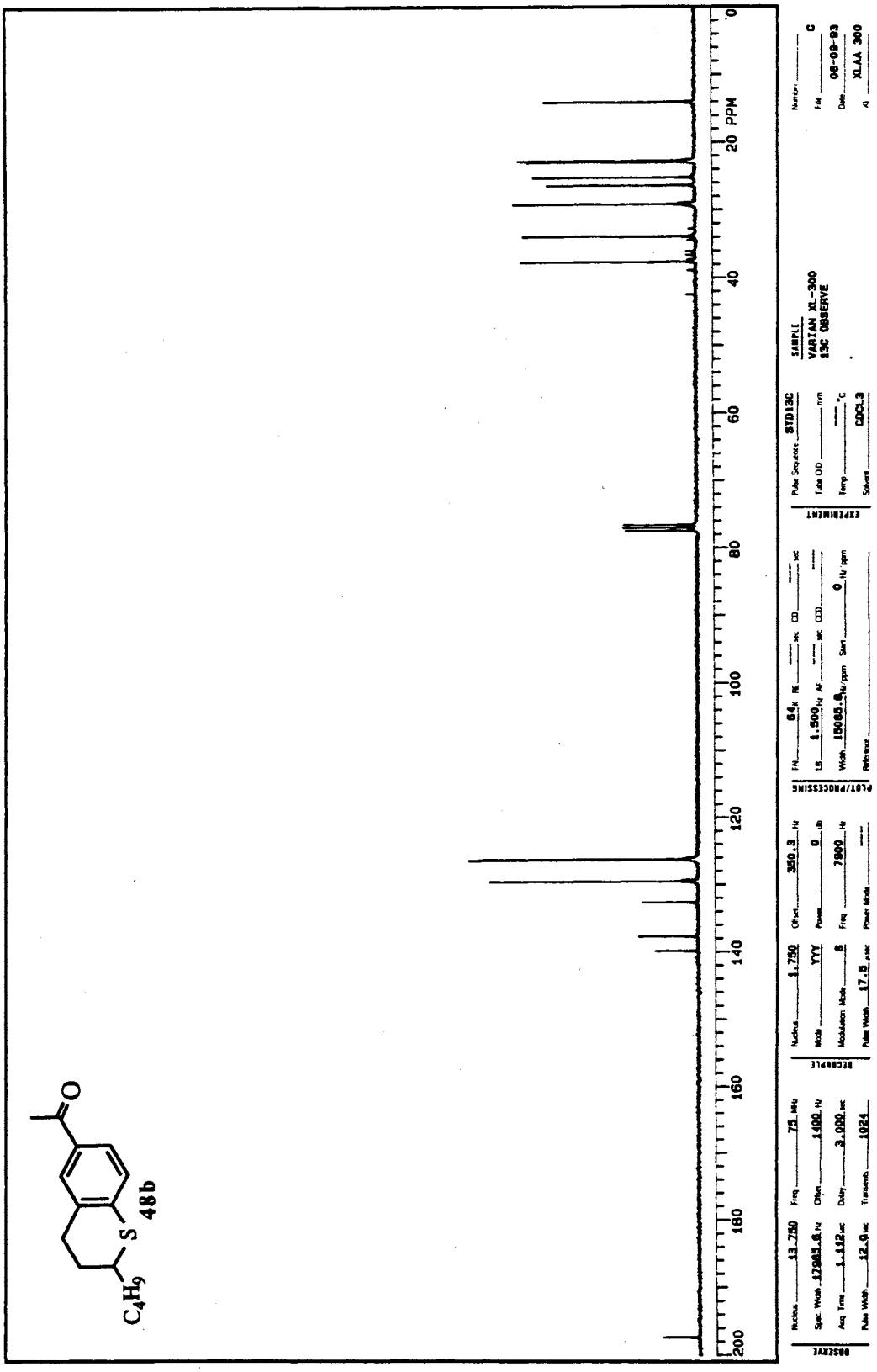
IR Spectrum of **48b**

Plate XLVII



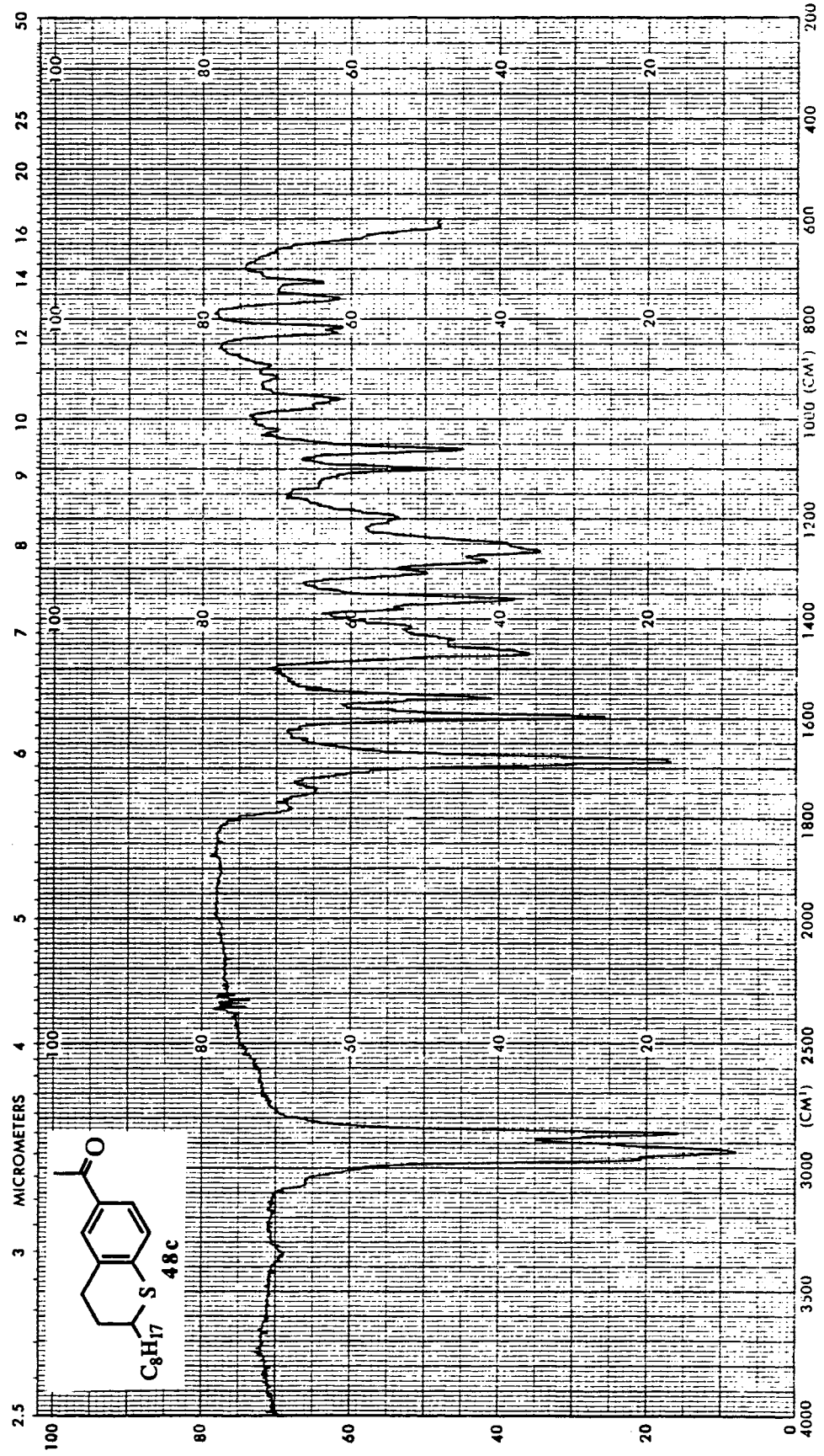
^{1}H NMR Spectrum of **48b**

Plate XLVIII



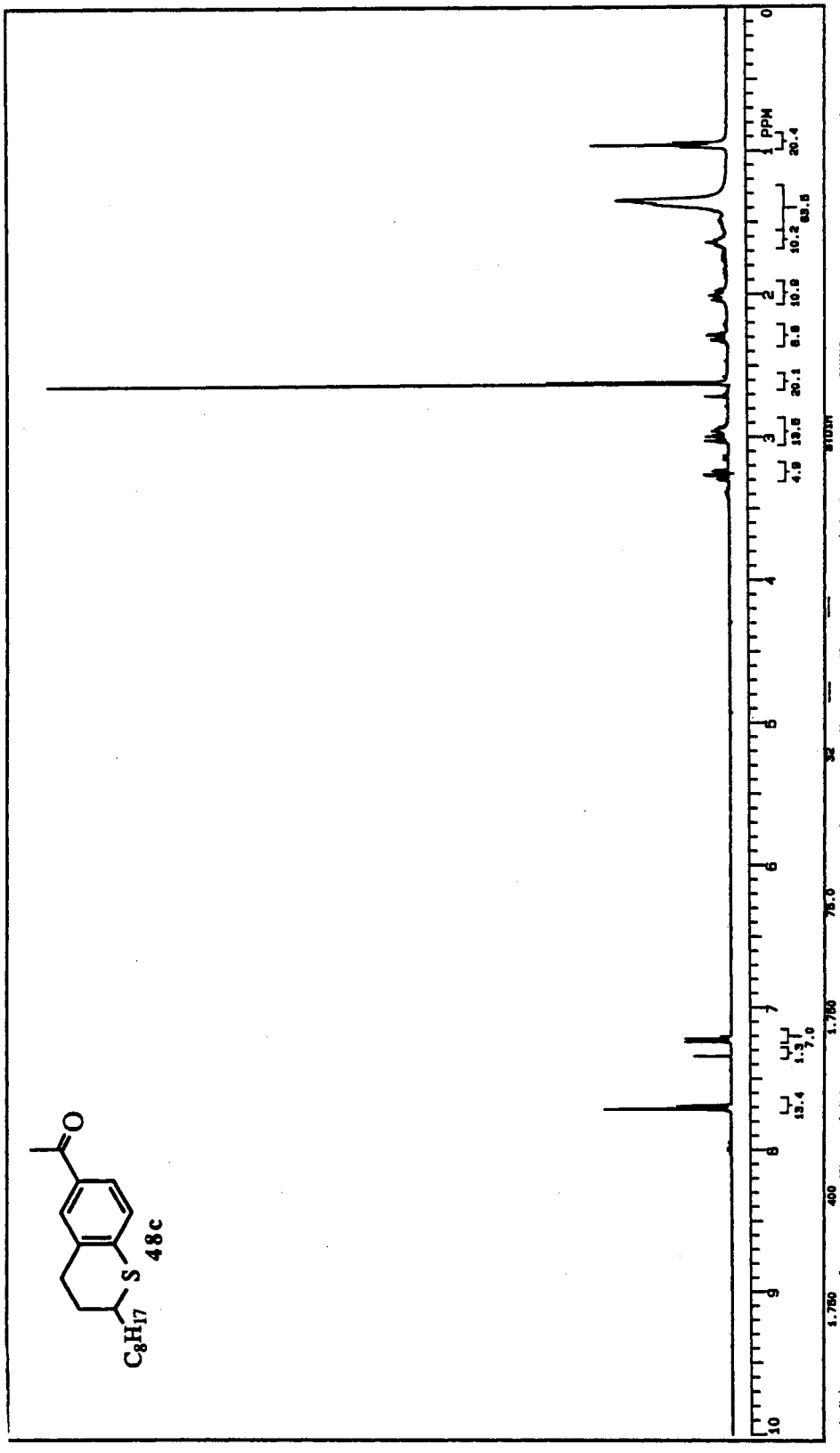
^{13}C NMR Spectrum of **48b**

Plate XLIX



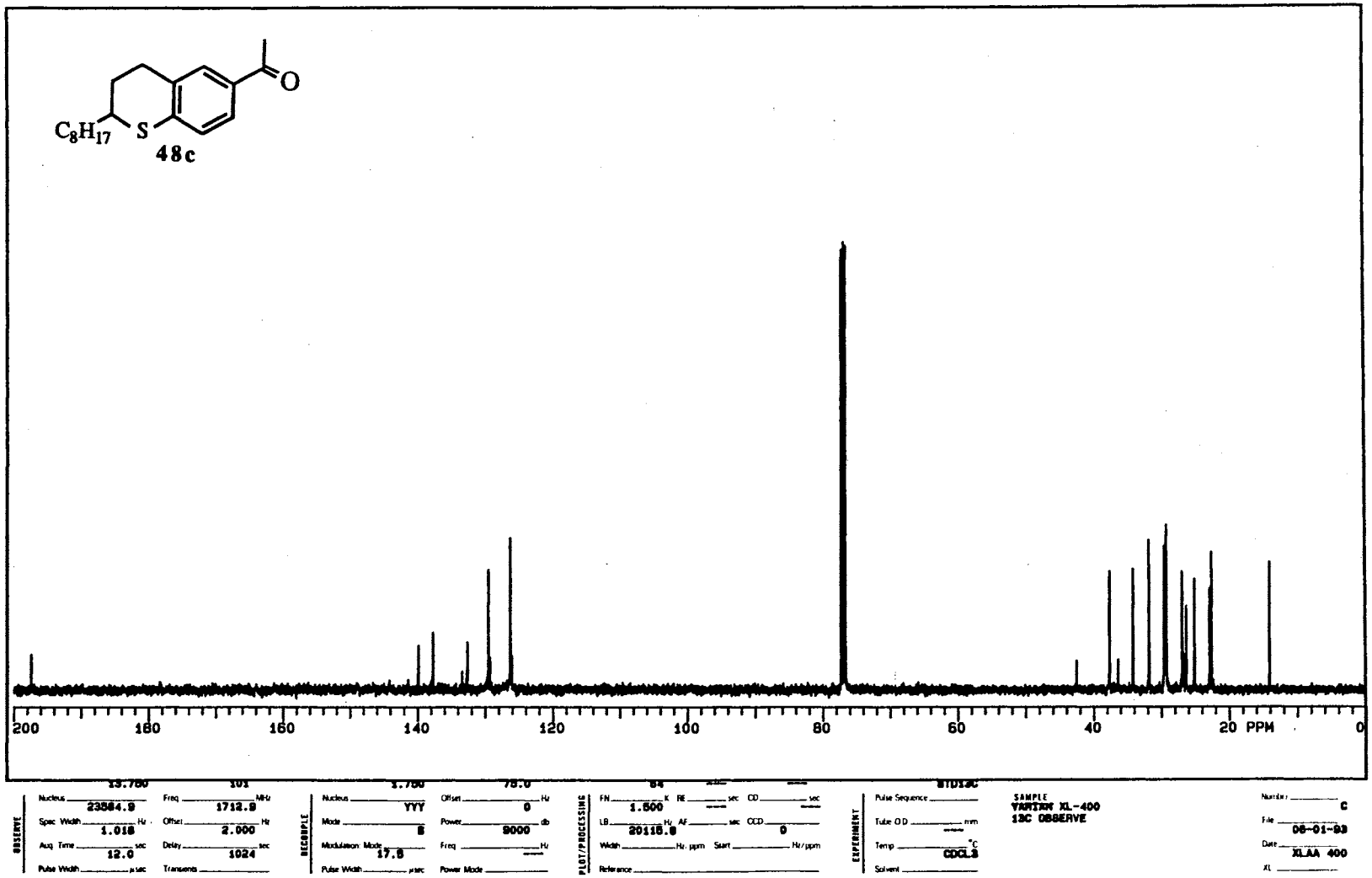
IR Spectrum of **48c**

Plate L



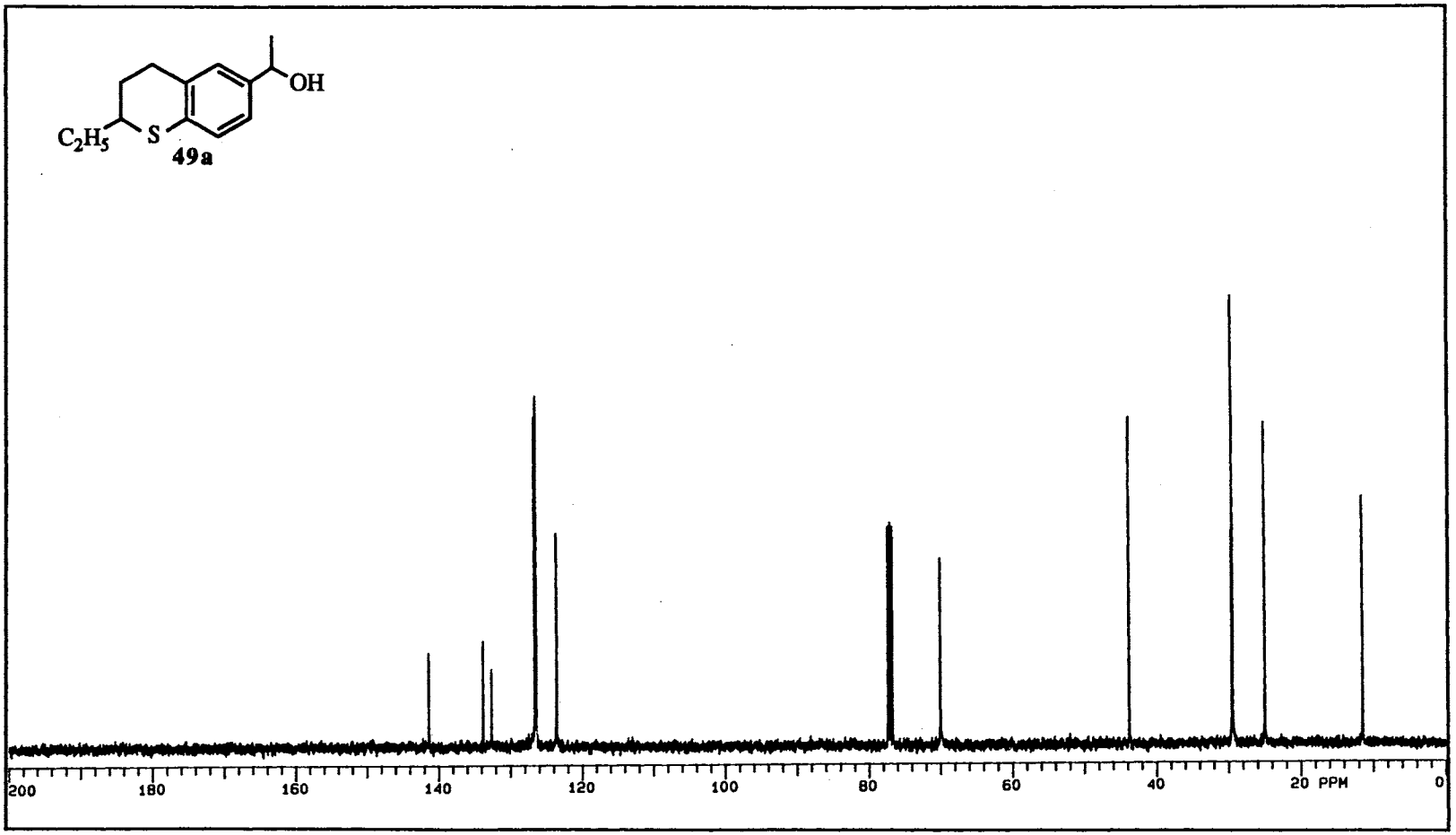
^{1}H NMR Spectrum of 48c

Plate LI



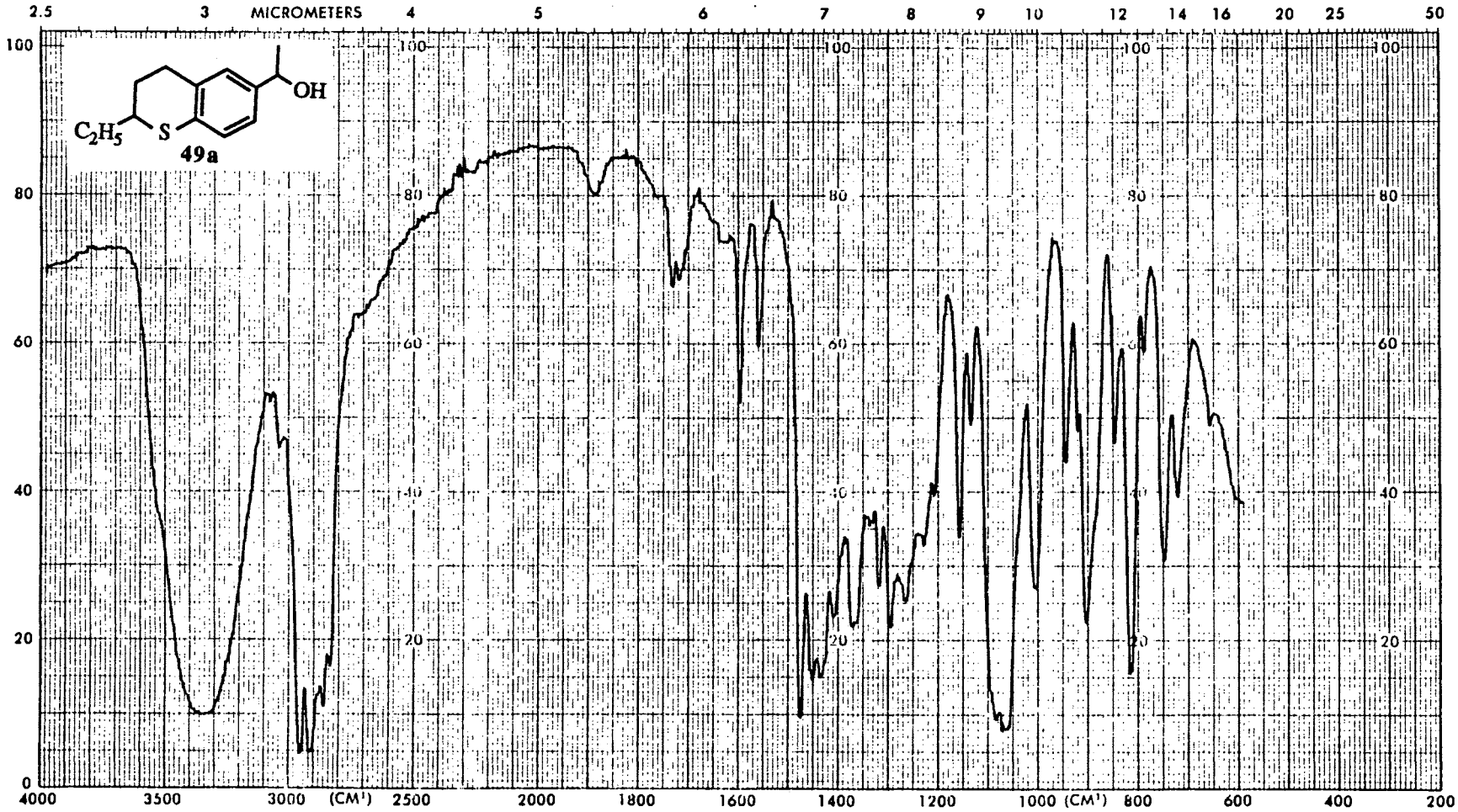
^{13}C NMR Spectrum of **48c**

Plate LIV



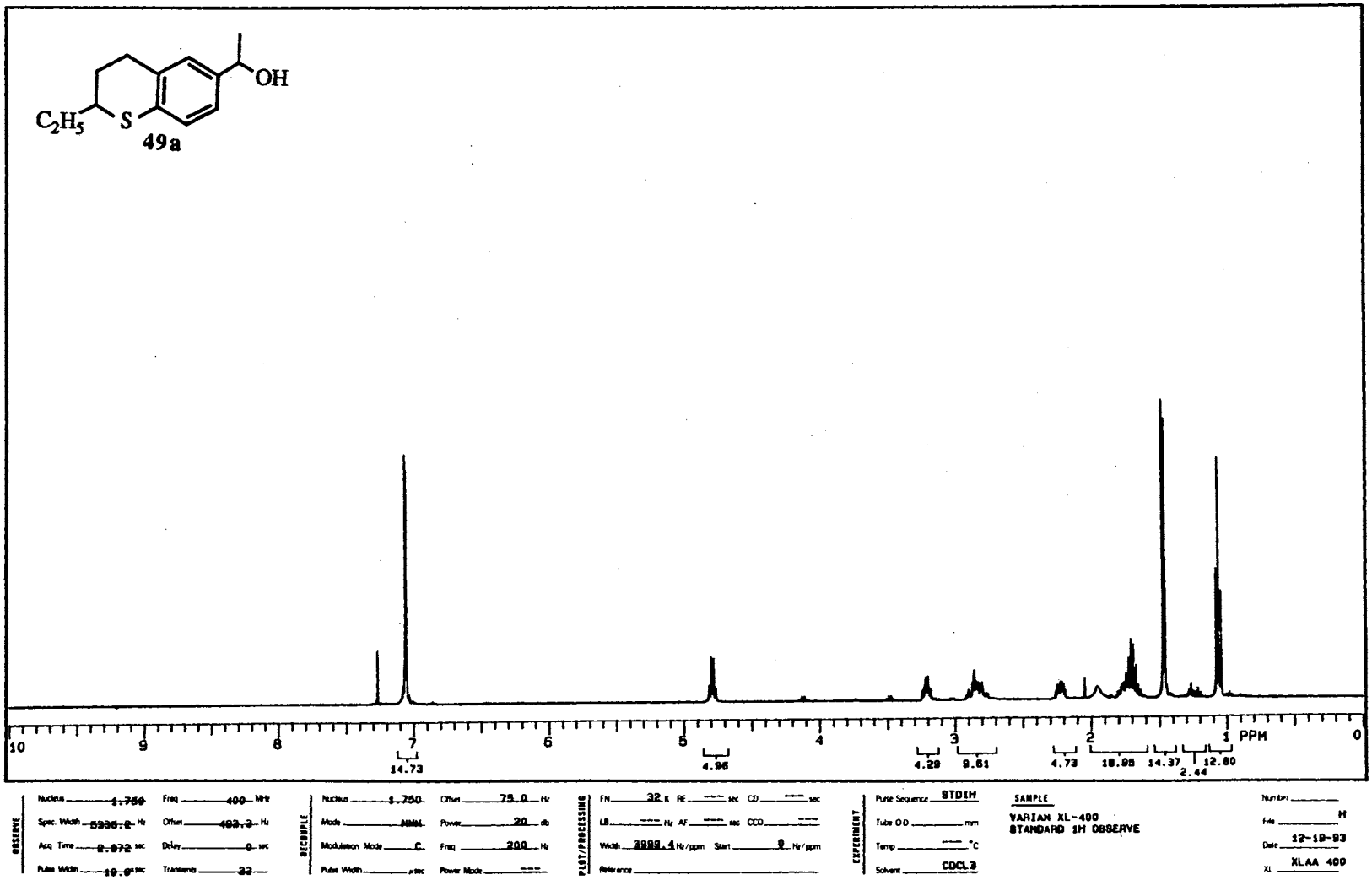
^{13}C NMR Spectrum of **49a**

Plate LII



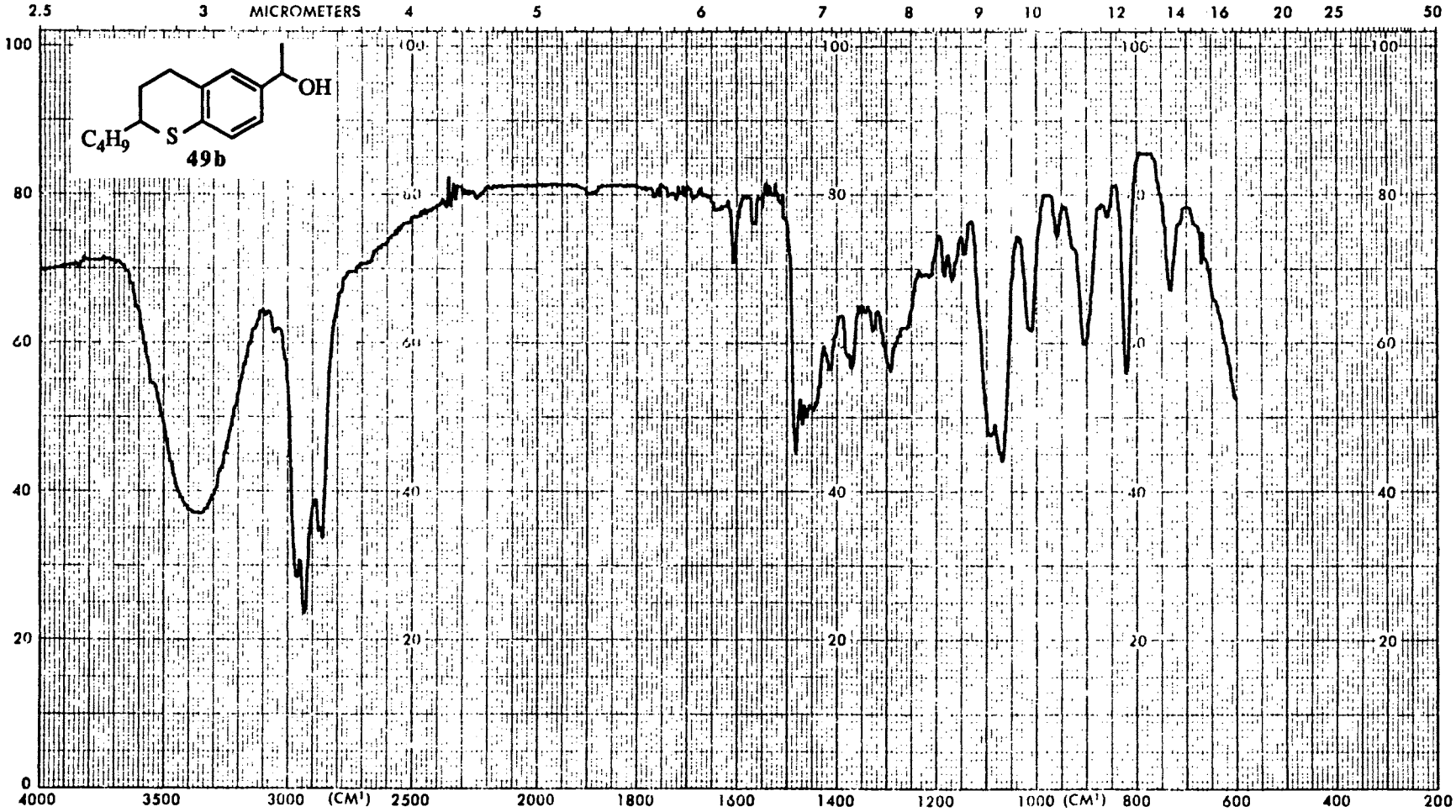
IR Spectrum of **49a**

Plate LIII



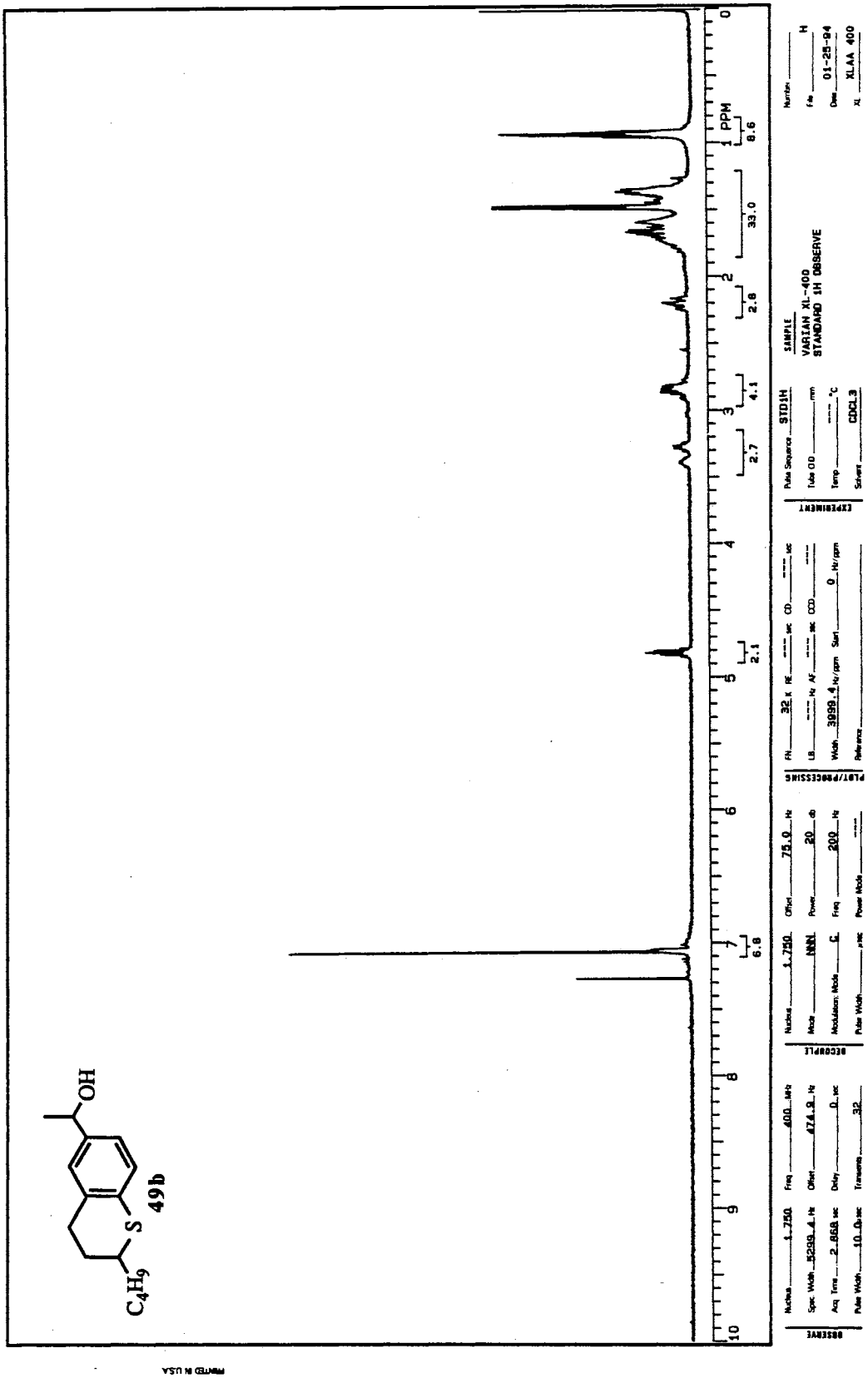
^{1}H NMR Spectrum of **49a**

Plate LV



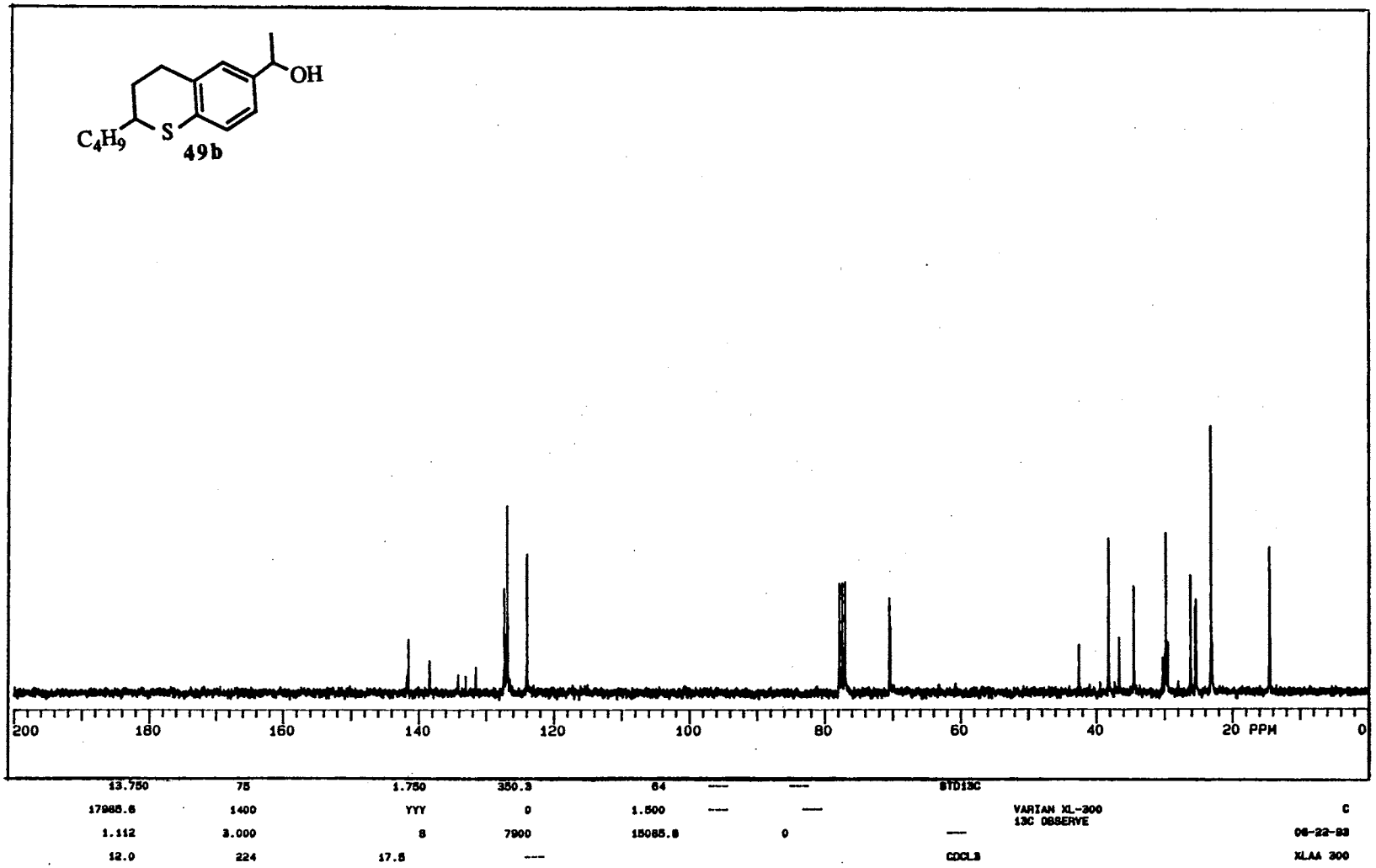
IR Spectrum of **49b**

Plate LVI



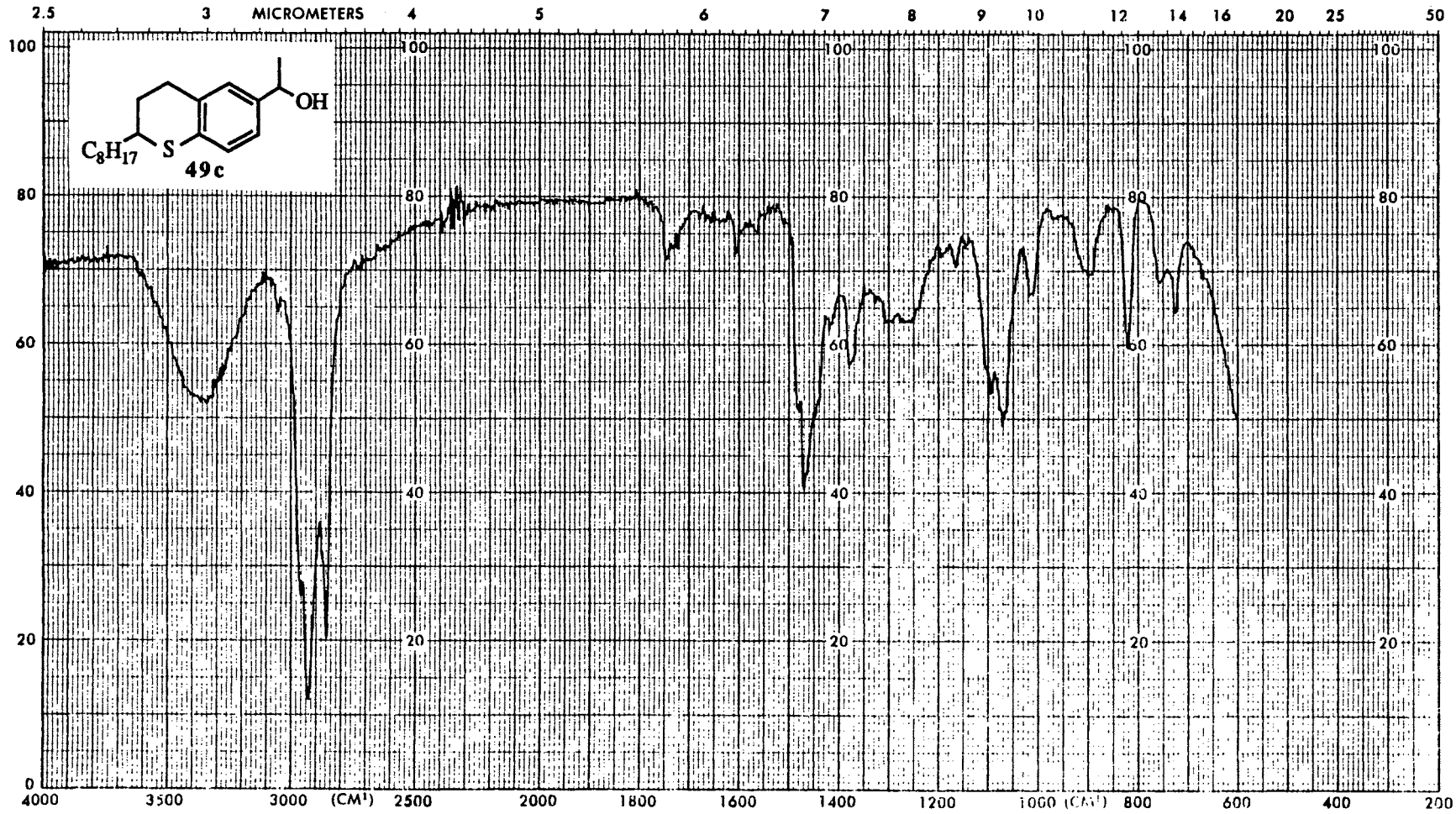
^{1}H NMR Spectrum of **49b**

Plate LVII



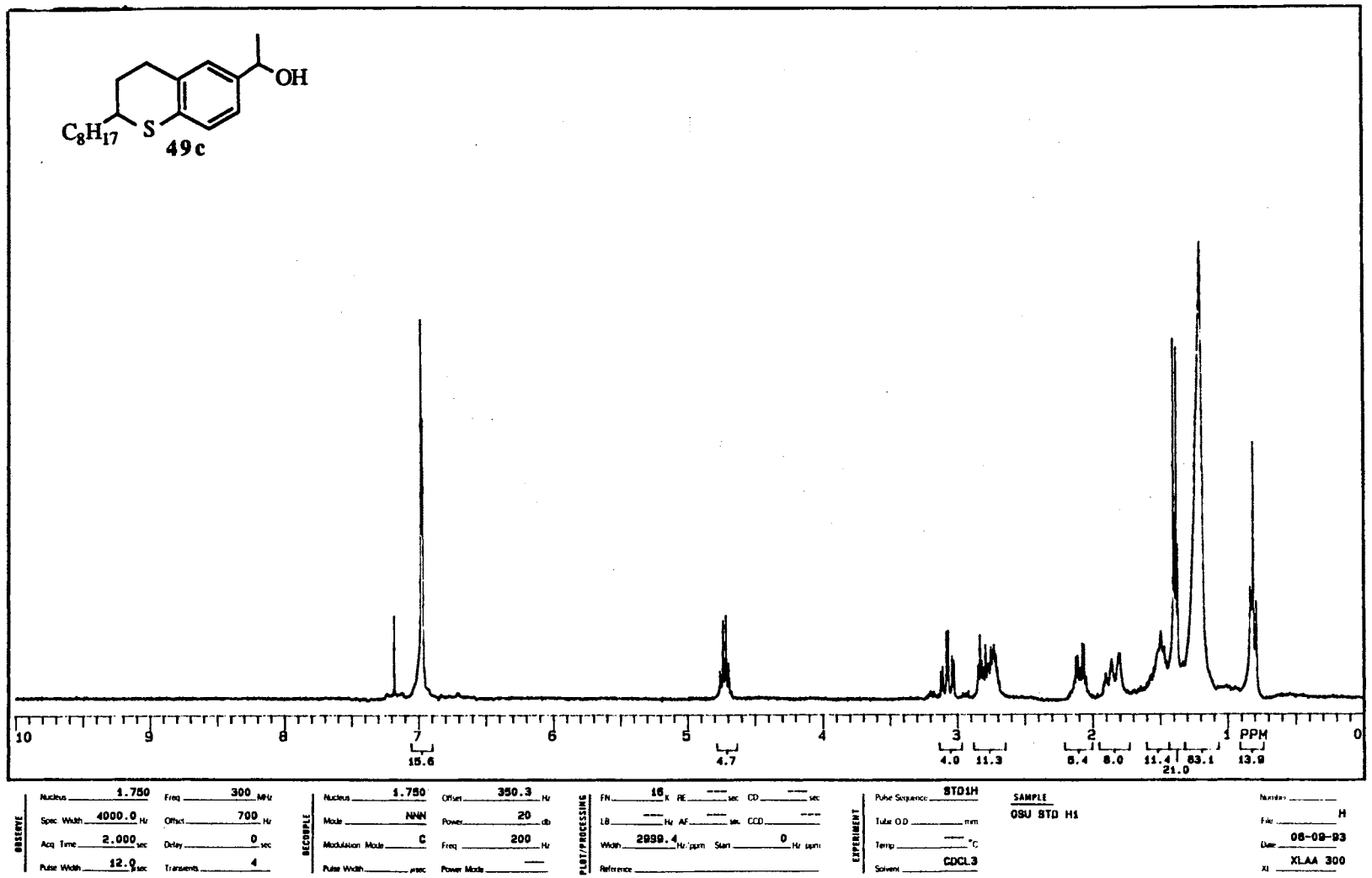
^{13}C NMR Spectrum of **49b**

Plate LVIII



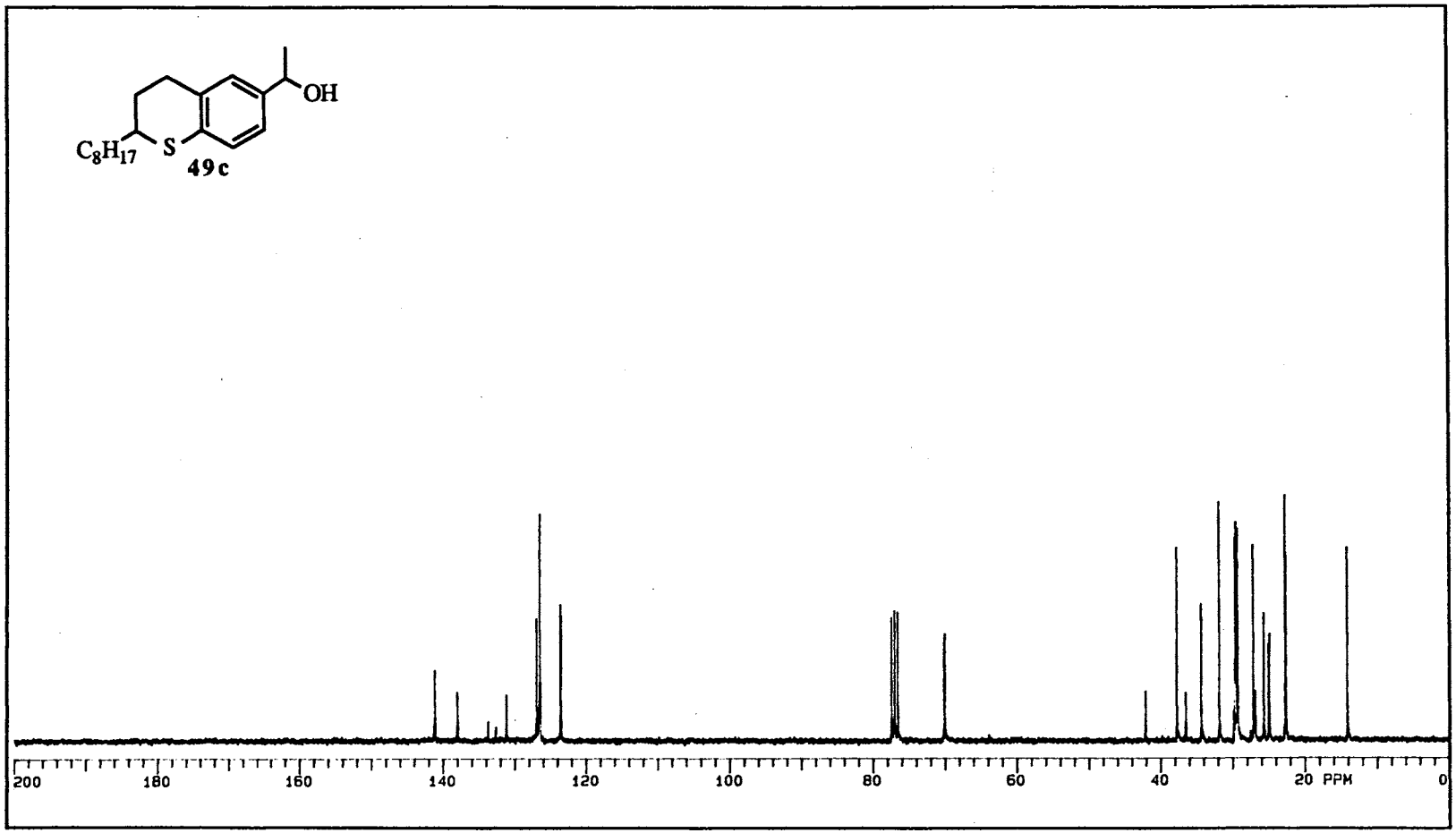
IR Spectrum of **49c**

Plate LIX



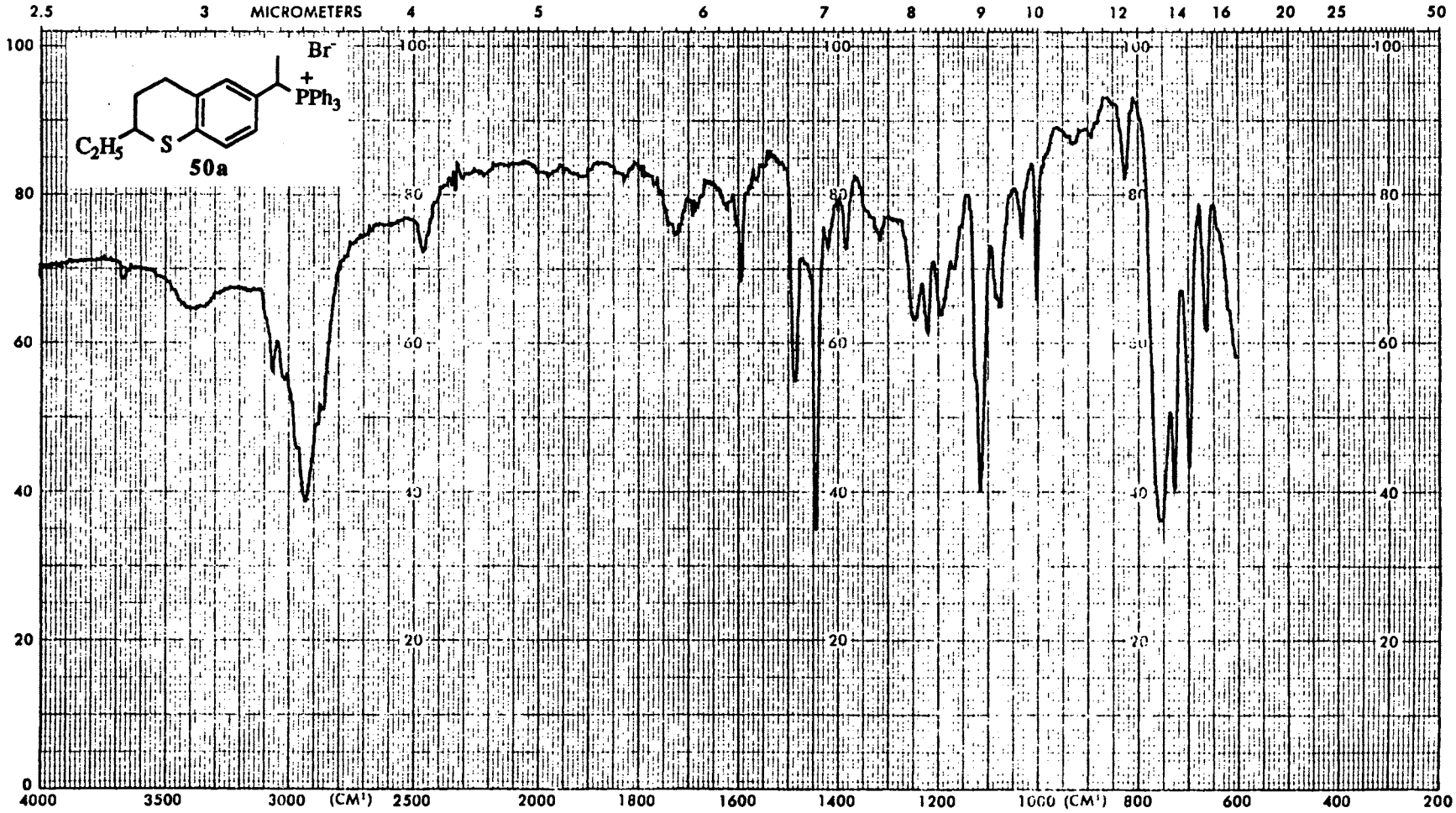
^{1}H NMR Spectrum of **49c**

Plate LX



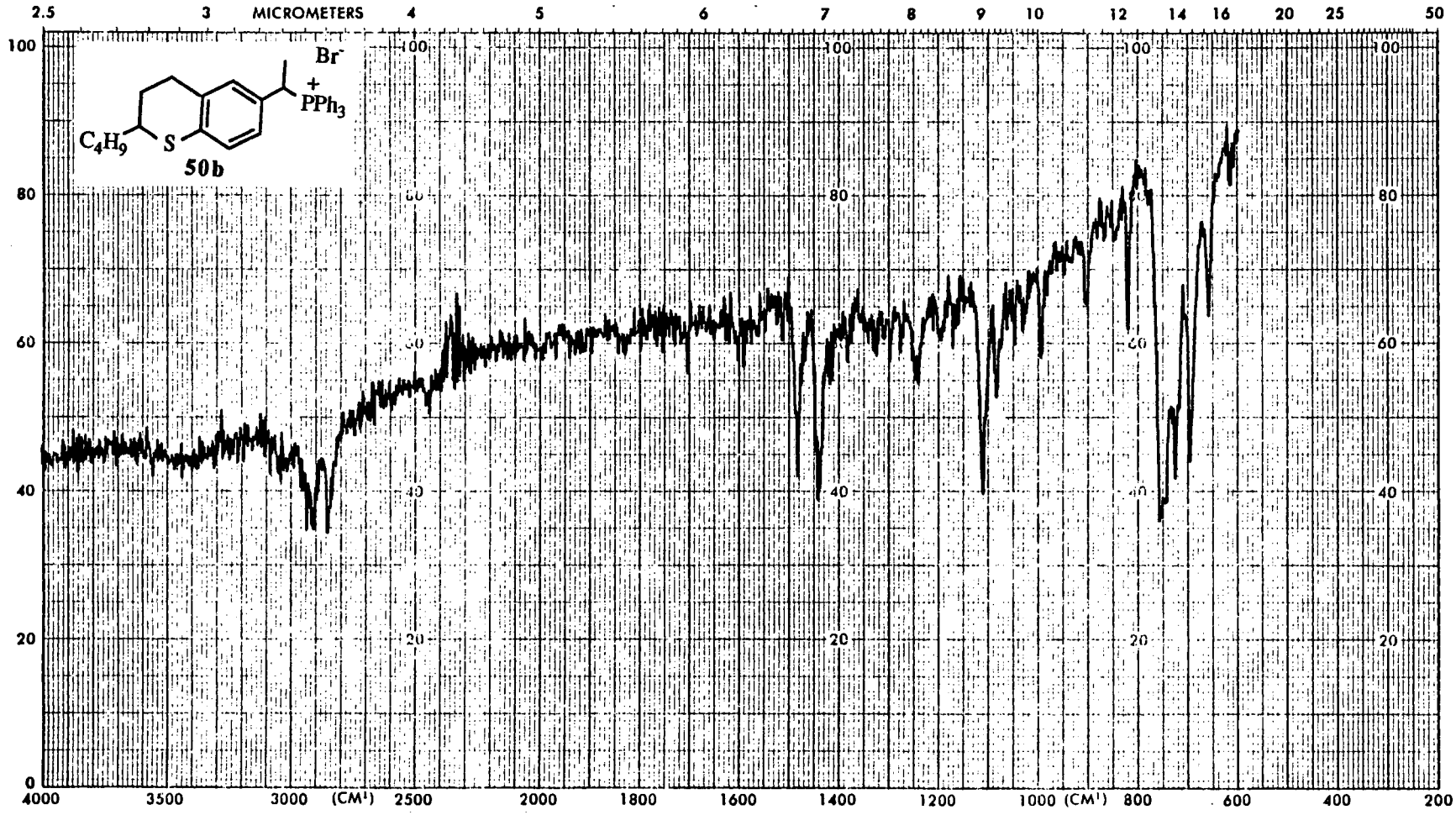
^{13}C NMR Spectrum of **49c**

Plate LXI



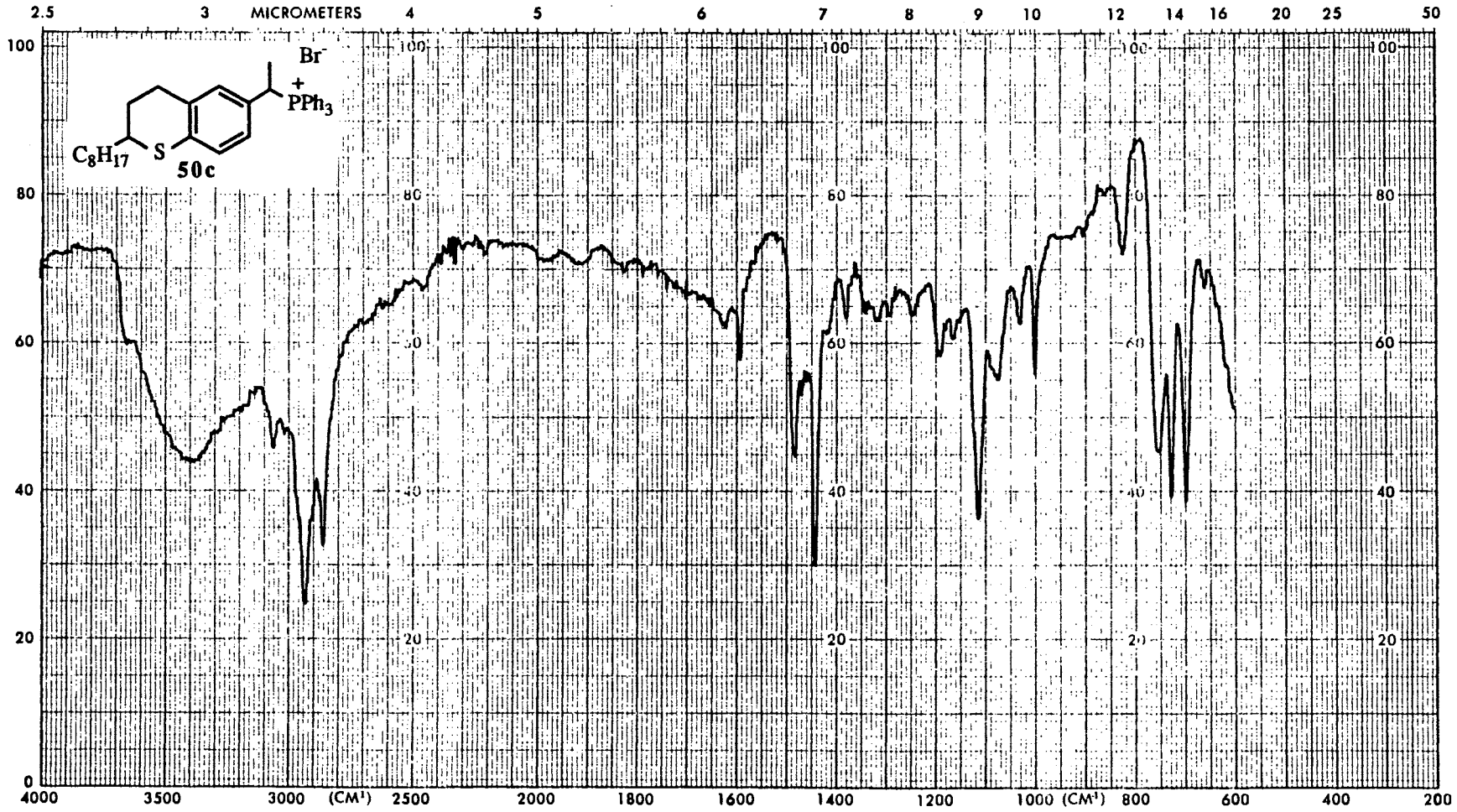
IR Spectrum of **50a**

Plate LXII



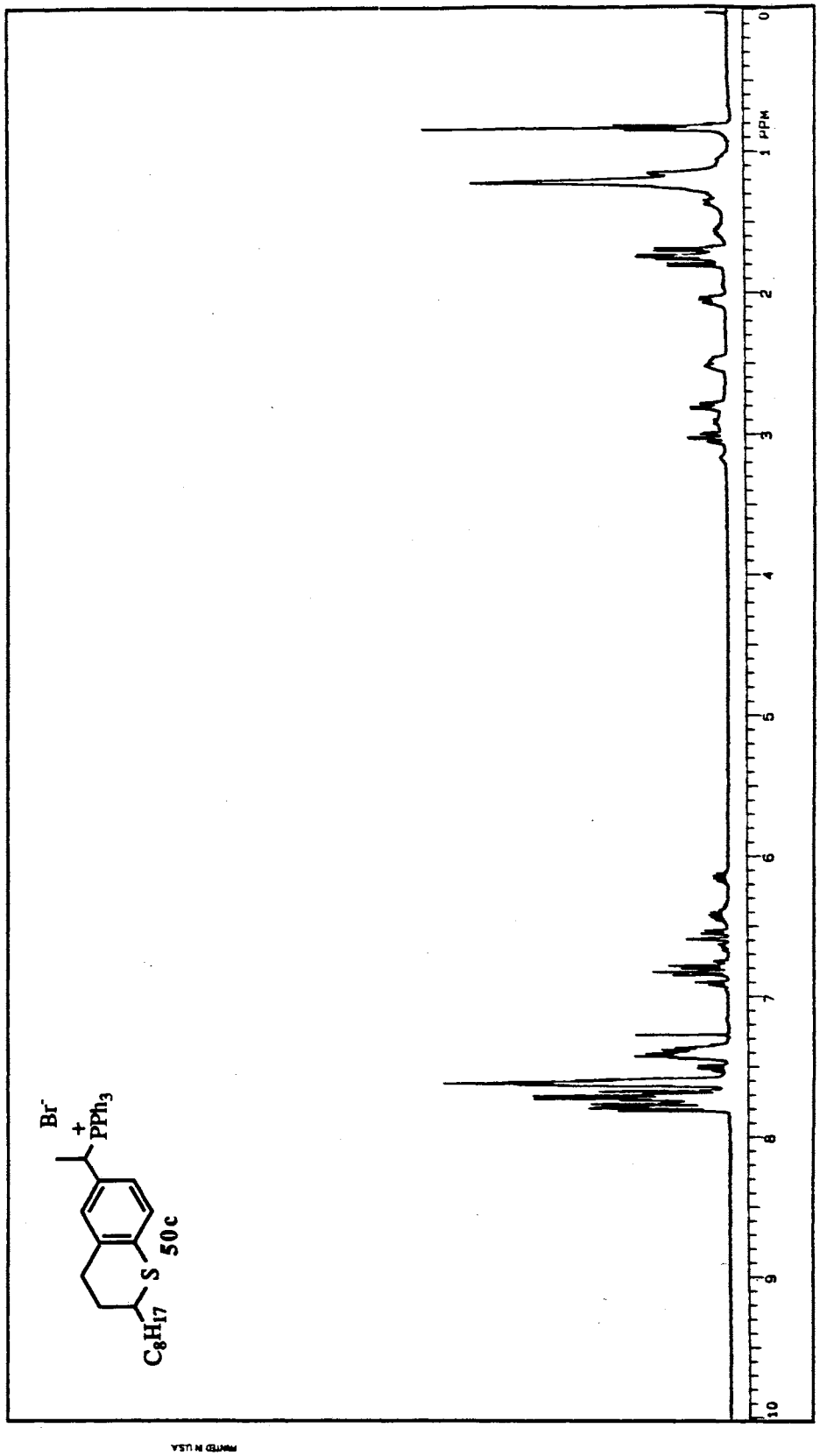
IR Spectrum of **50b**

Plate LXIII



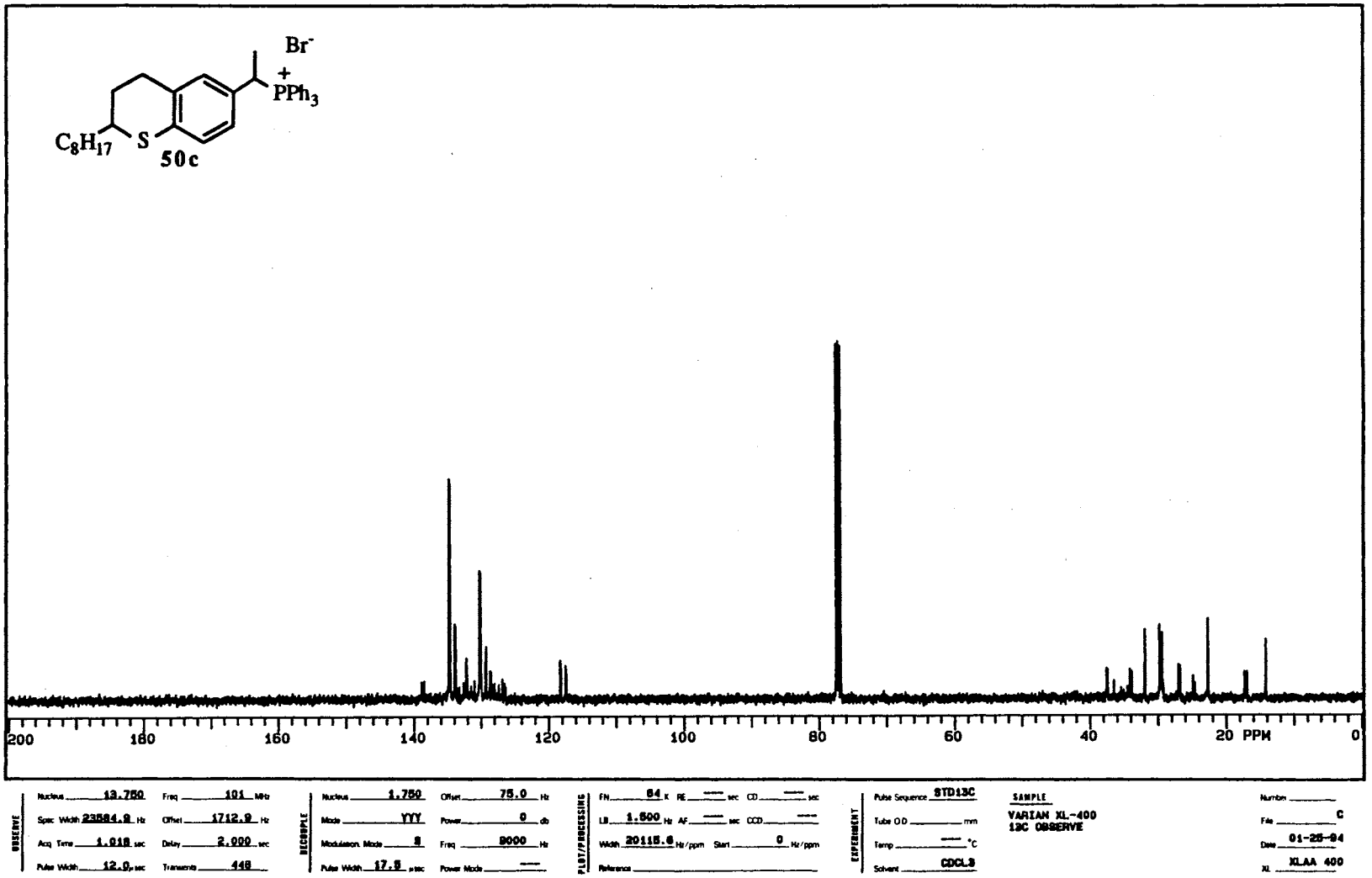
IR Spectrum of **50c**

Plate LXIV



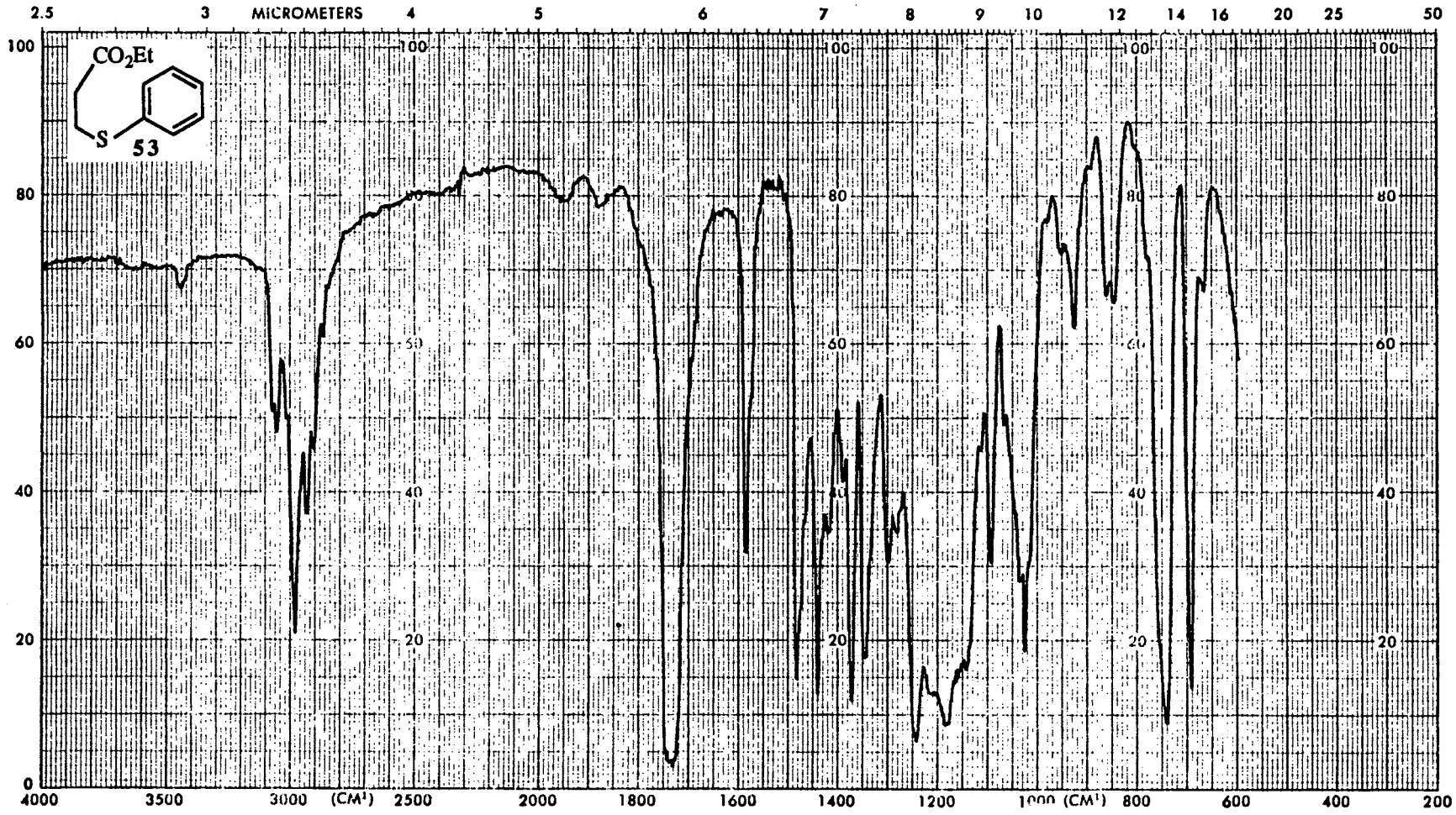
^{1}H NMR Spectrum of 50c

Plate LXV



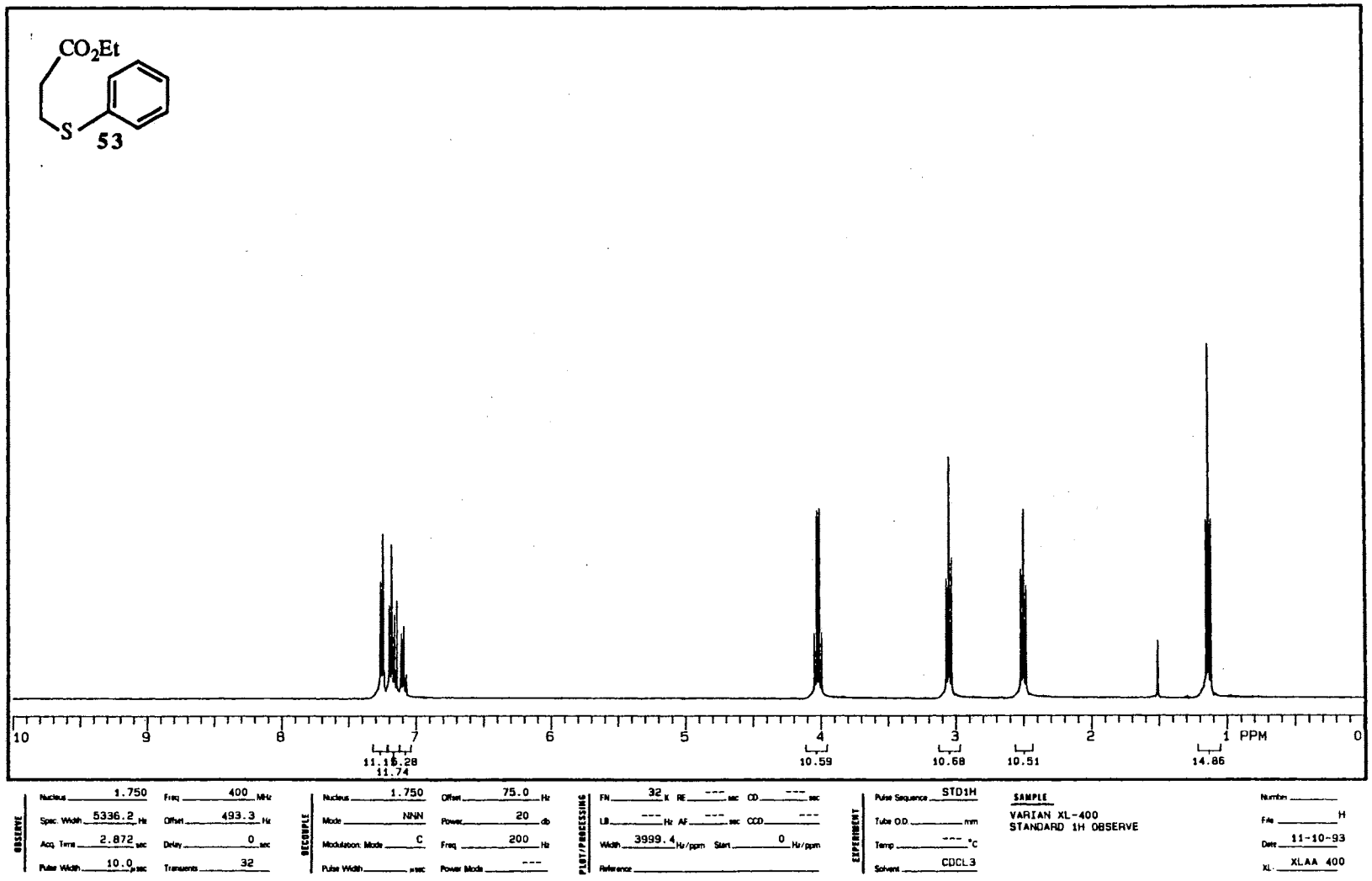
^{13}C NMR Spectrum of **50c**

Plate LXVI



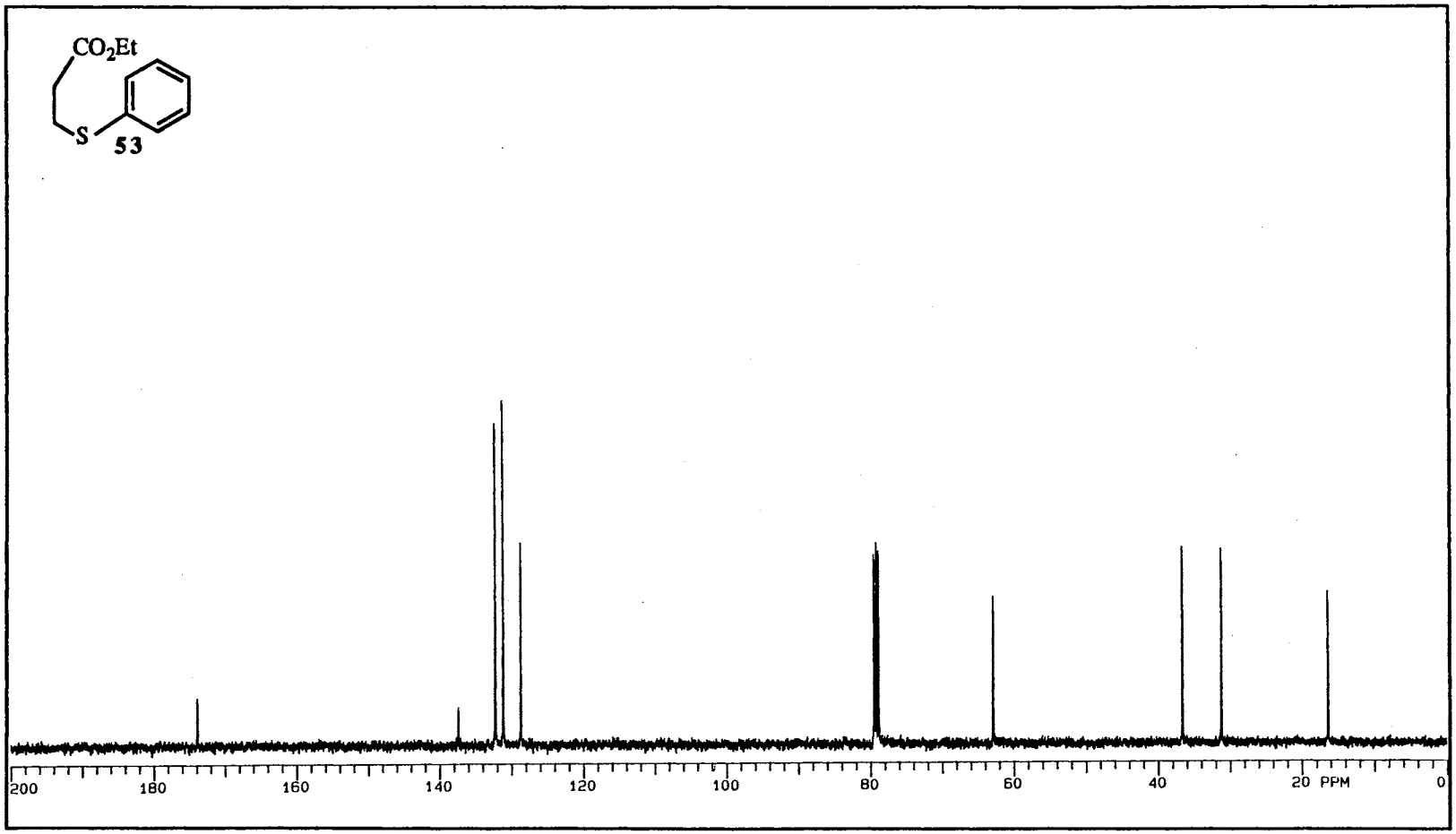
IR Spectrum of **53**

Plate LXVII



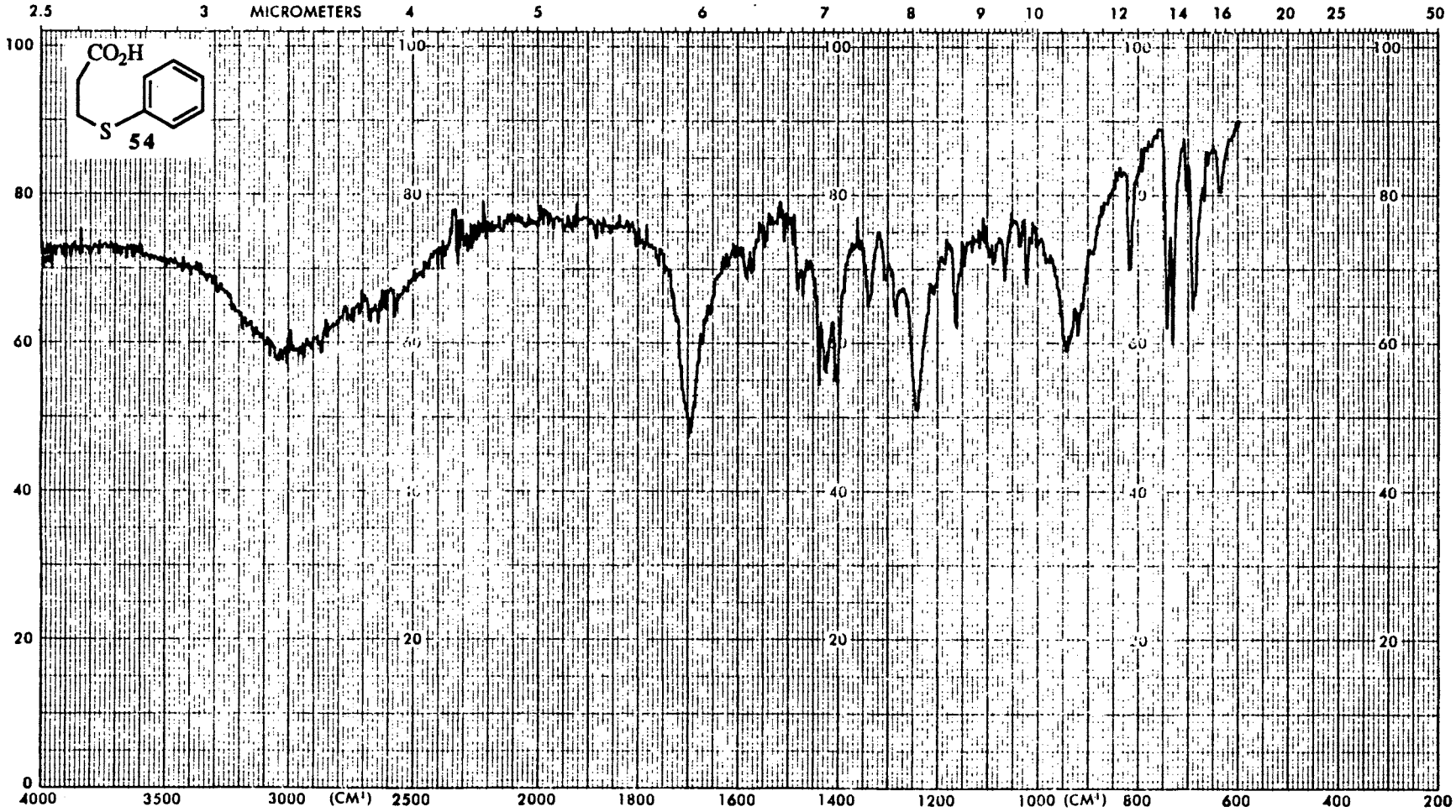
^{1}H NMR Spectrum of **53**

Plate LXVIIf



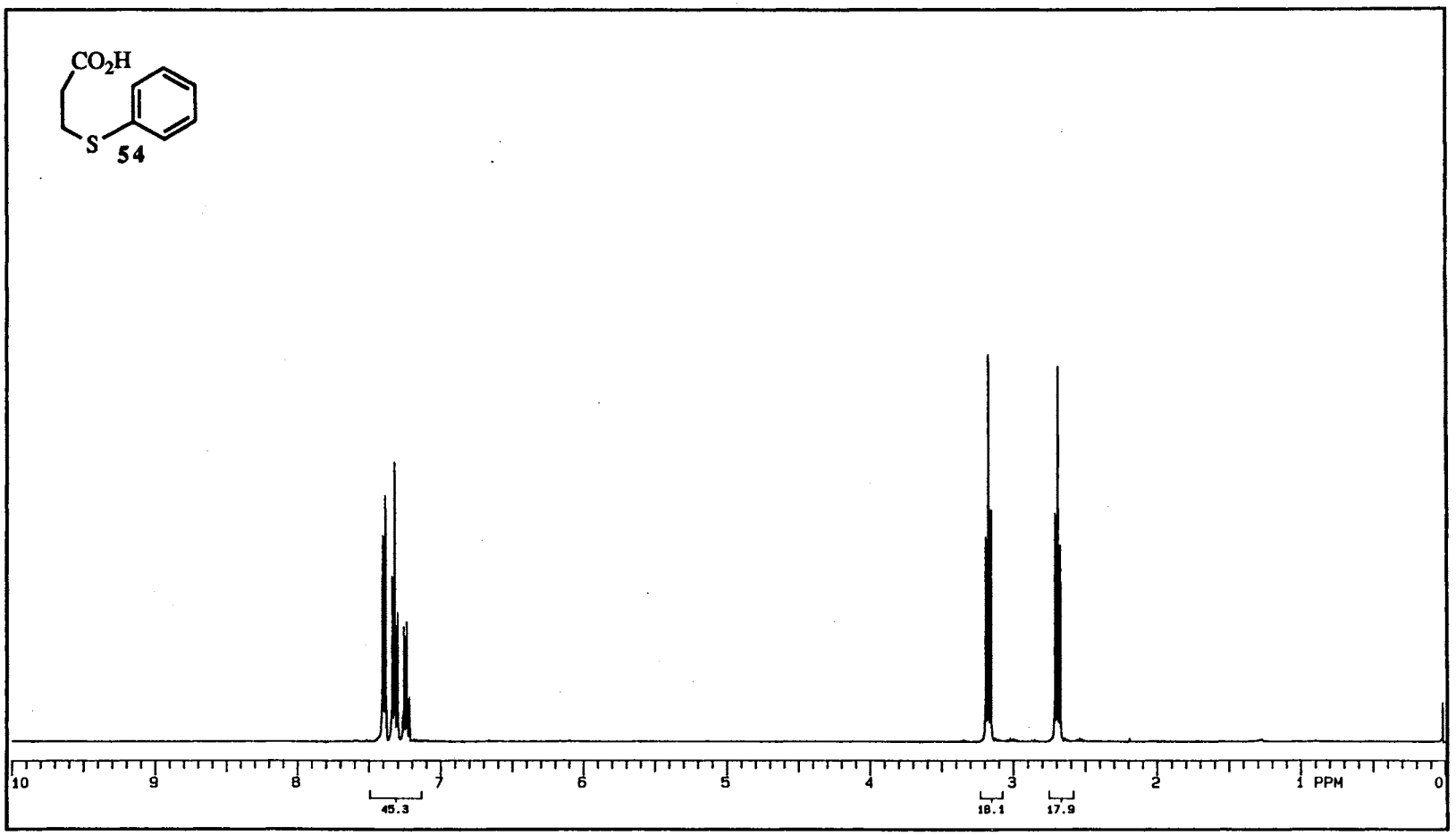
^{13}C NMR Spectrum of **53**

Plate LXIX



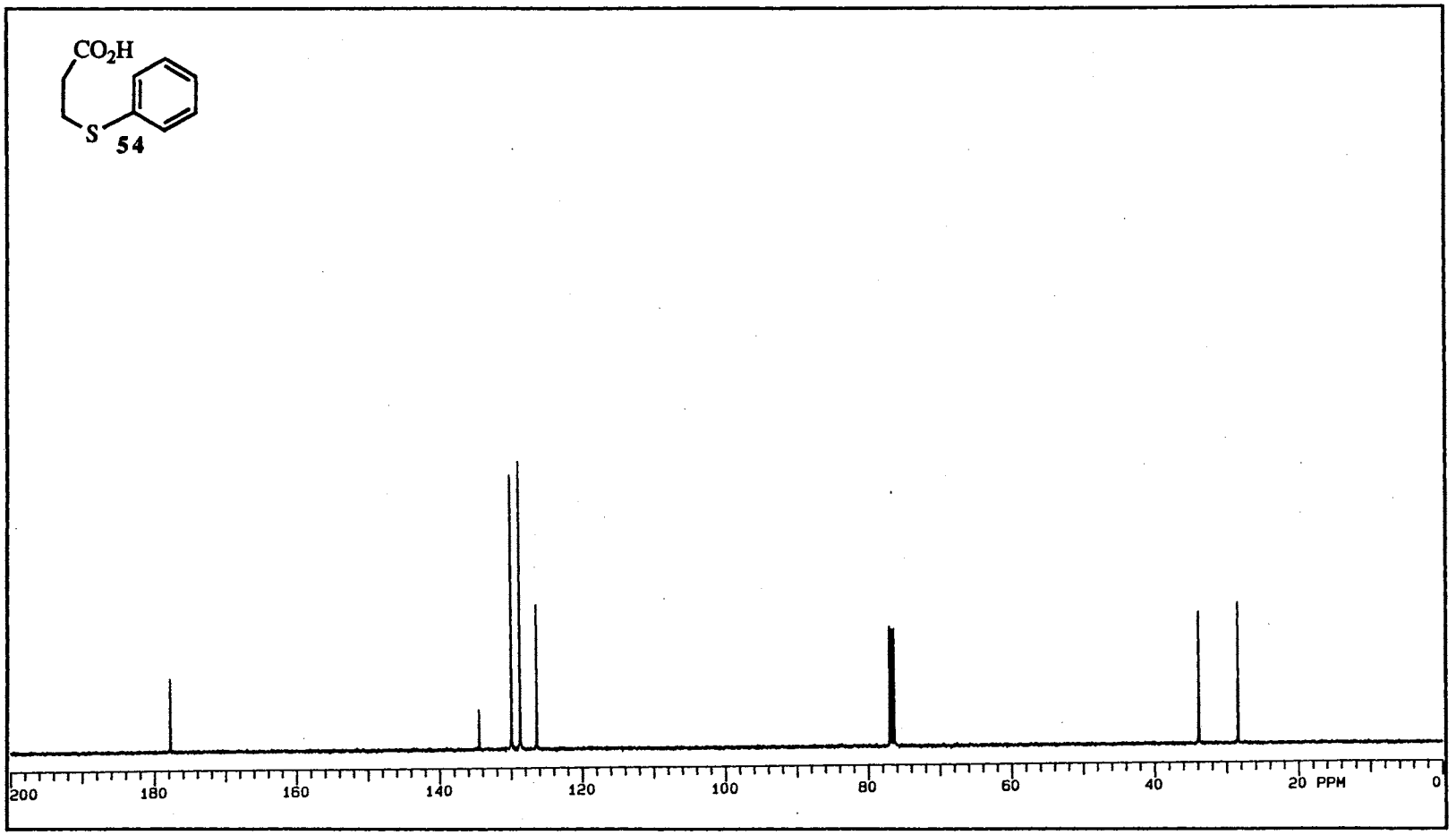
IR Spectrum of **54**

Plate LXX



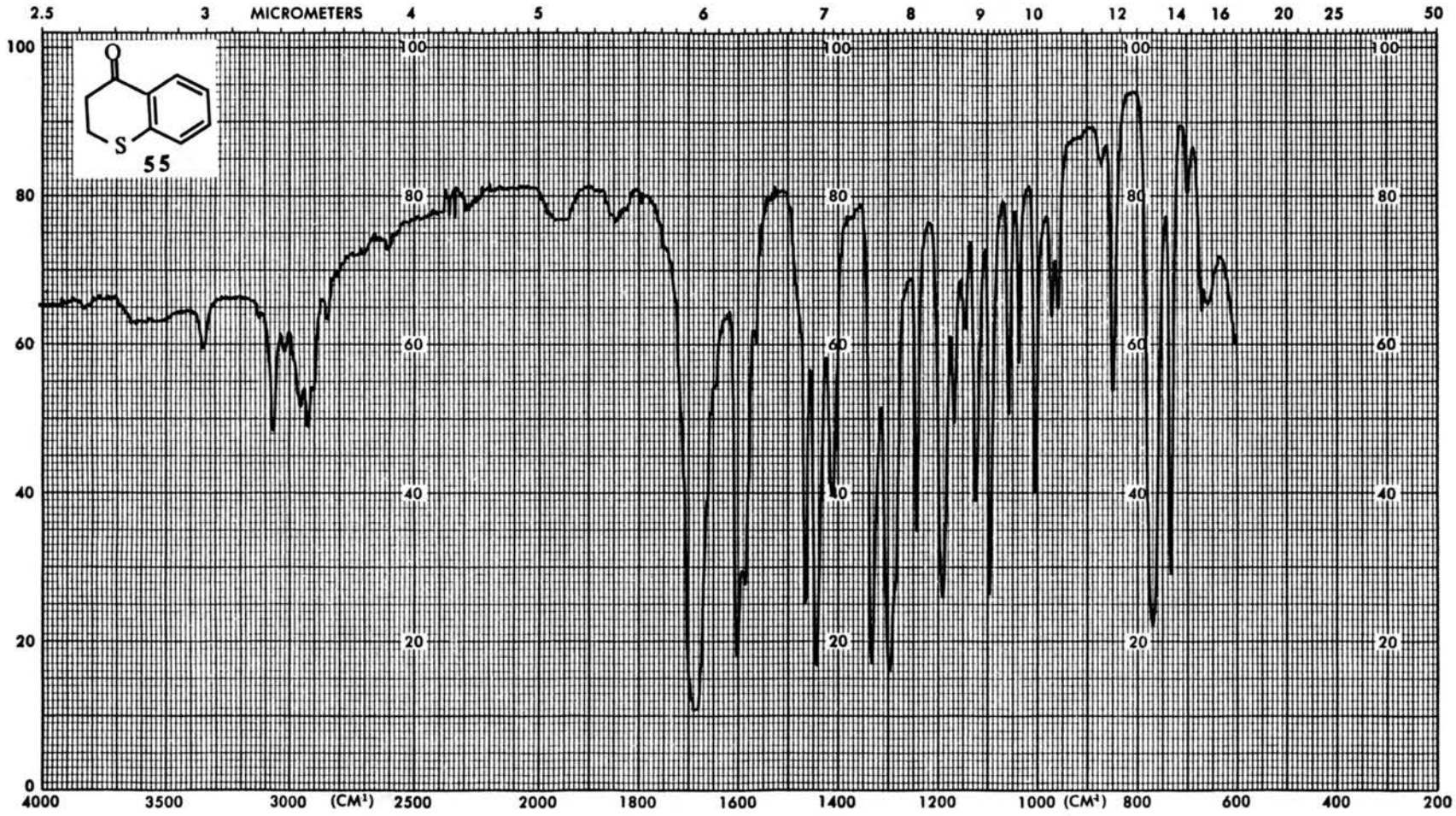
^{1}H NMR Spectrum of **54**

Plate LXXI



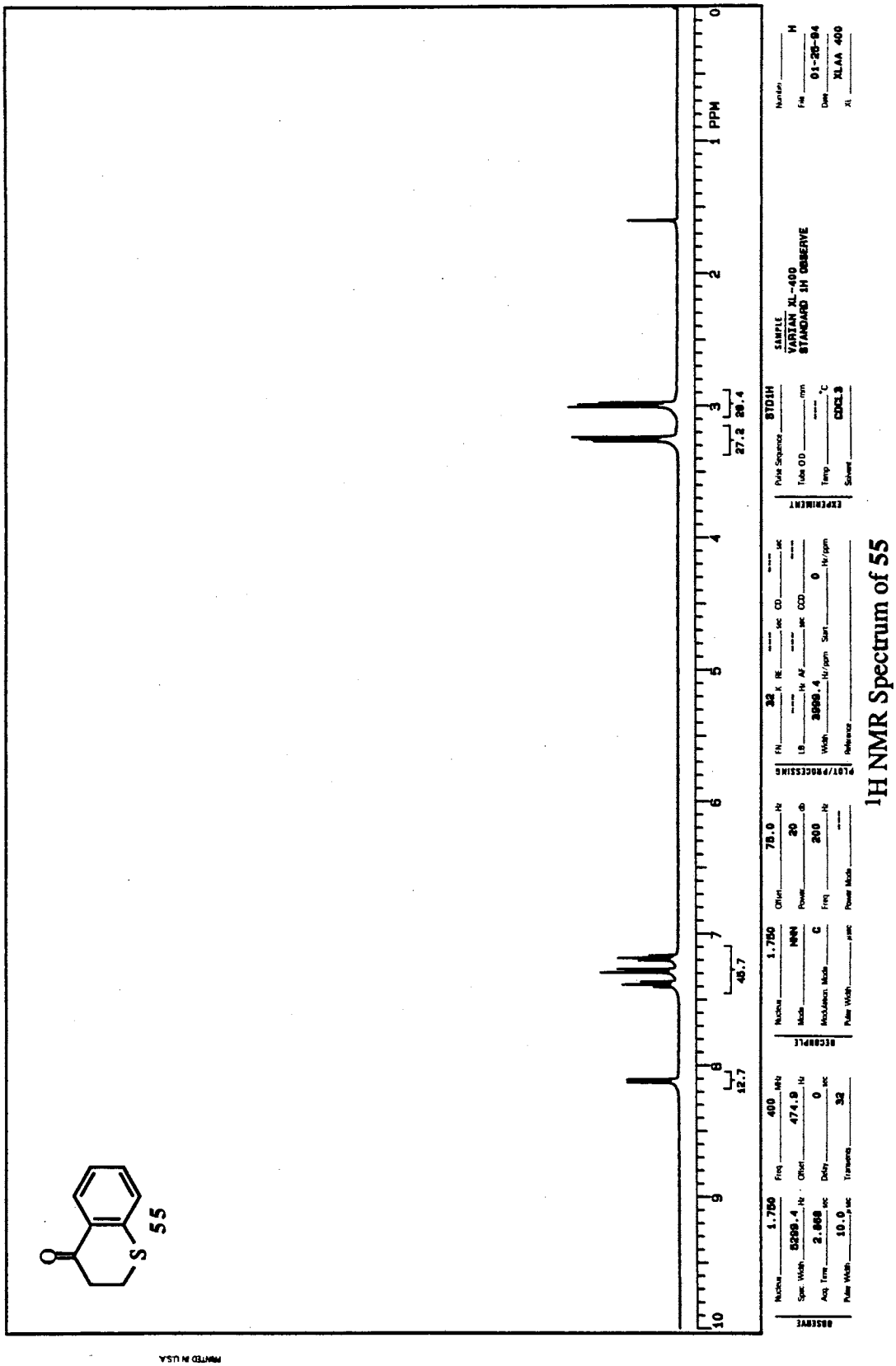
^{13}C NMR Spectrum of **54**

Plate LXXII



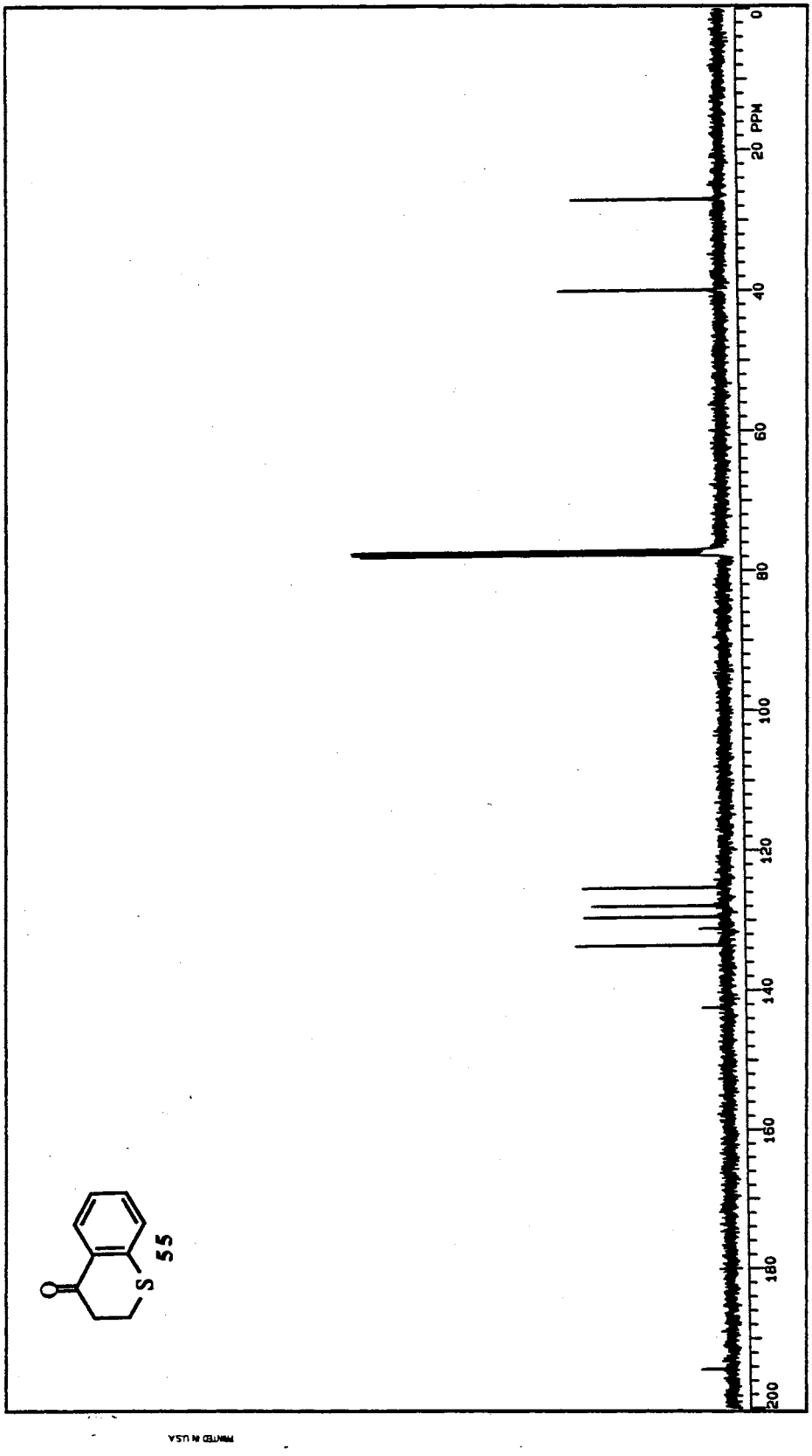
IR Spectrum of **55**

Plate LXXIII



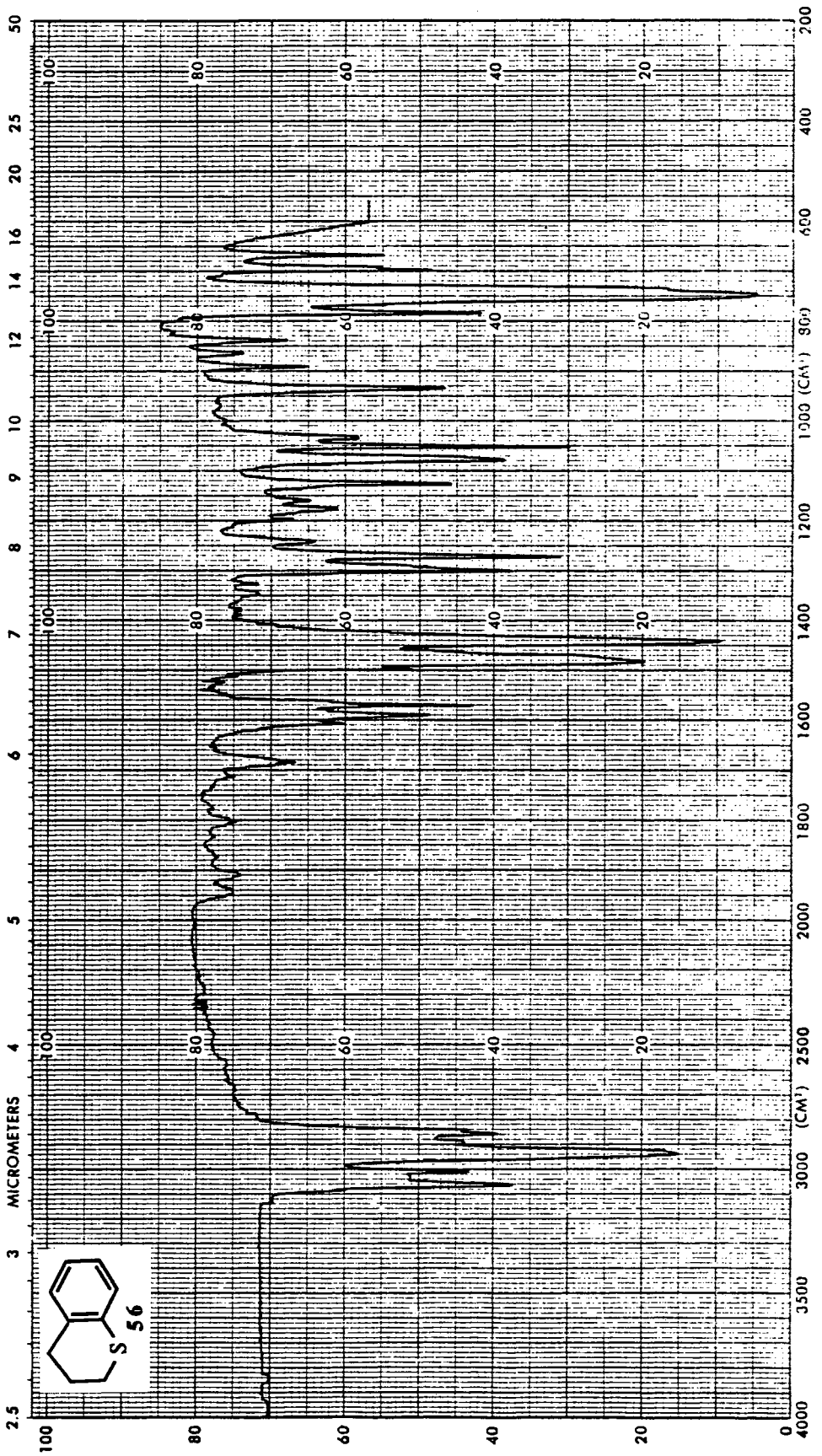
^{1}H NMR Spectrum of **55**

Plate LXXIV



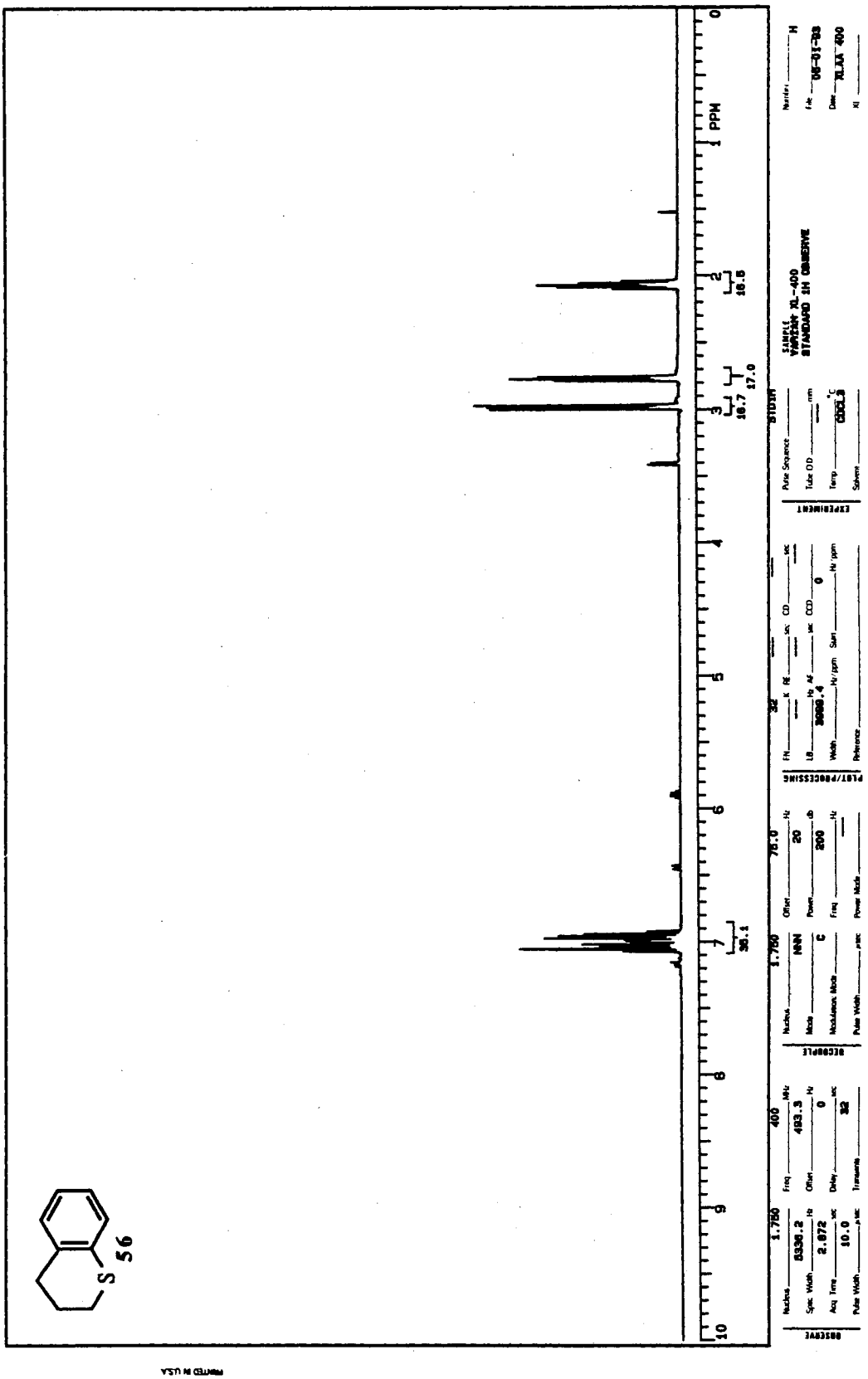
^{13}C NMR Spectrum of **55**

Plate LXXV



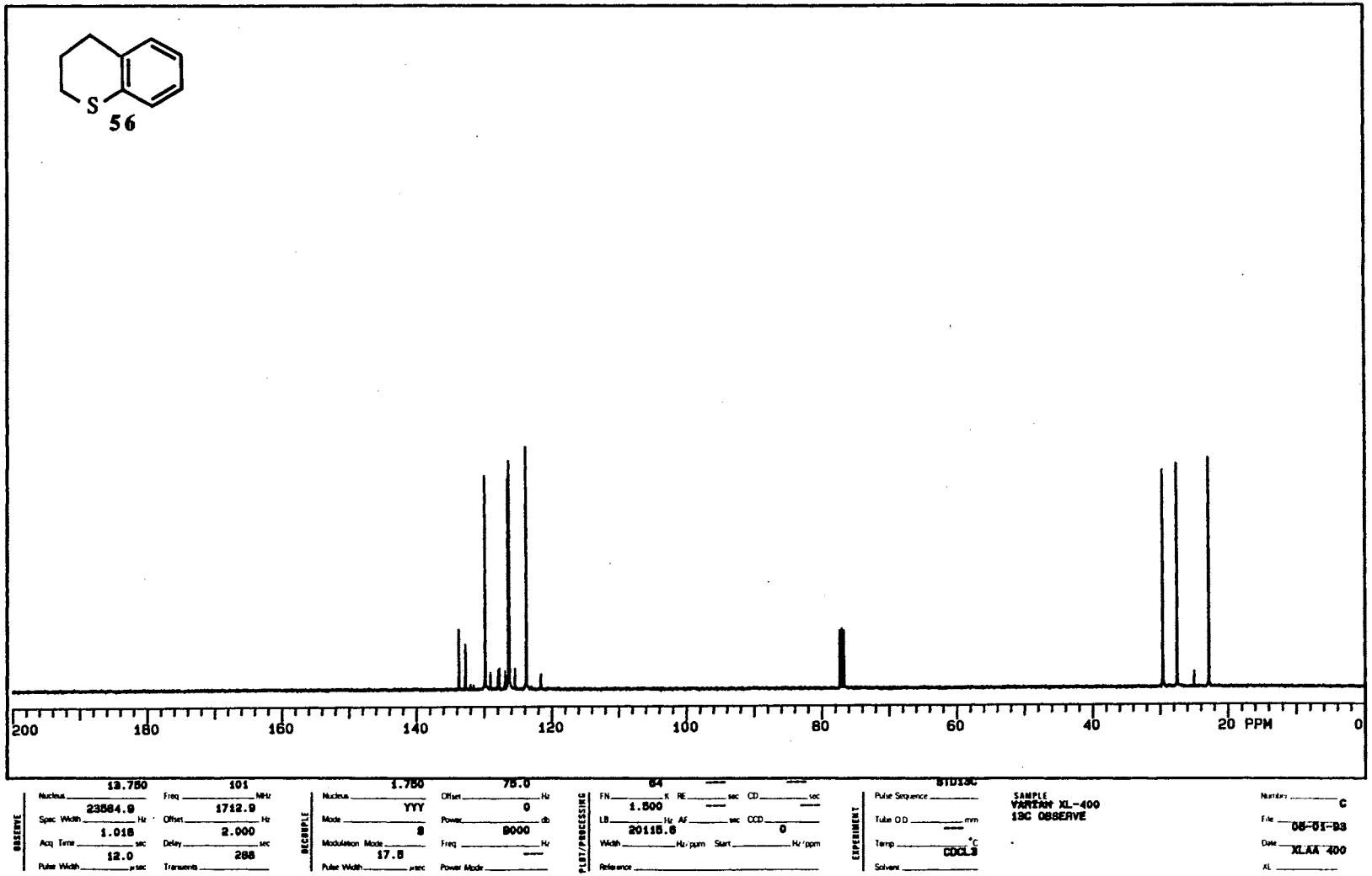
IR Spectrum of **56**

Plate LXXVI



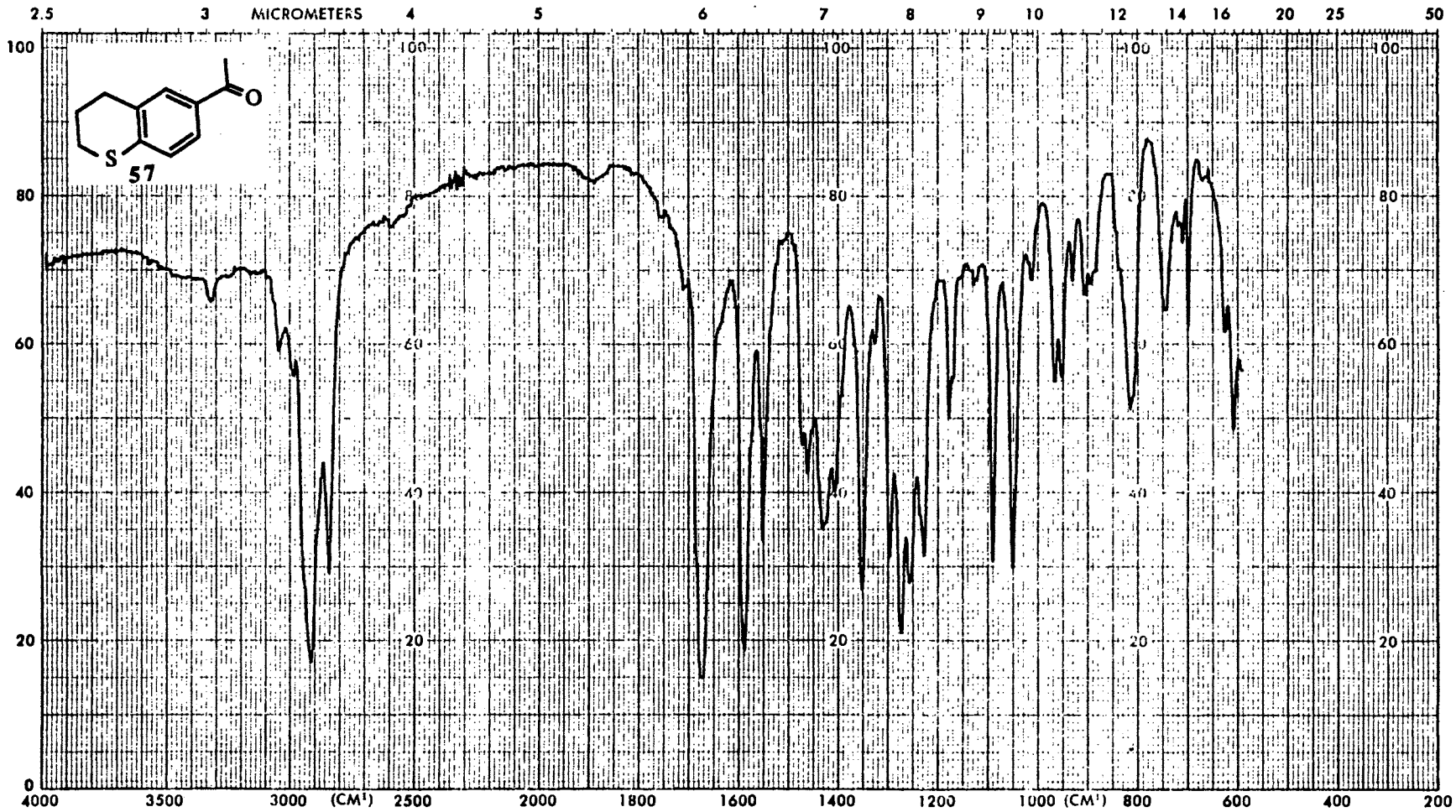
^{1}H NMR Spectrum of **56**

Plate LXXVII



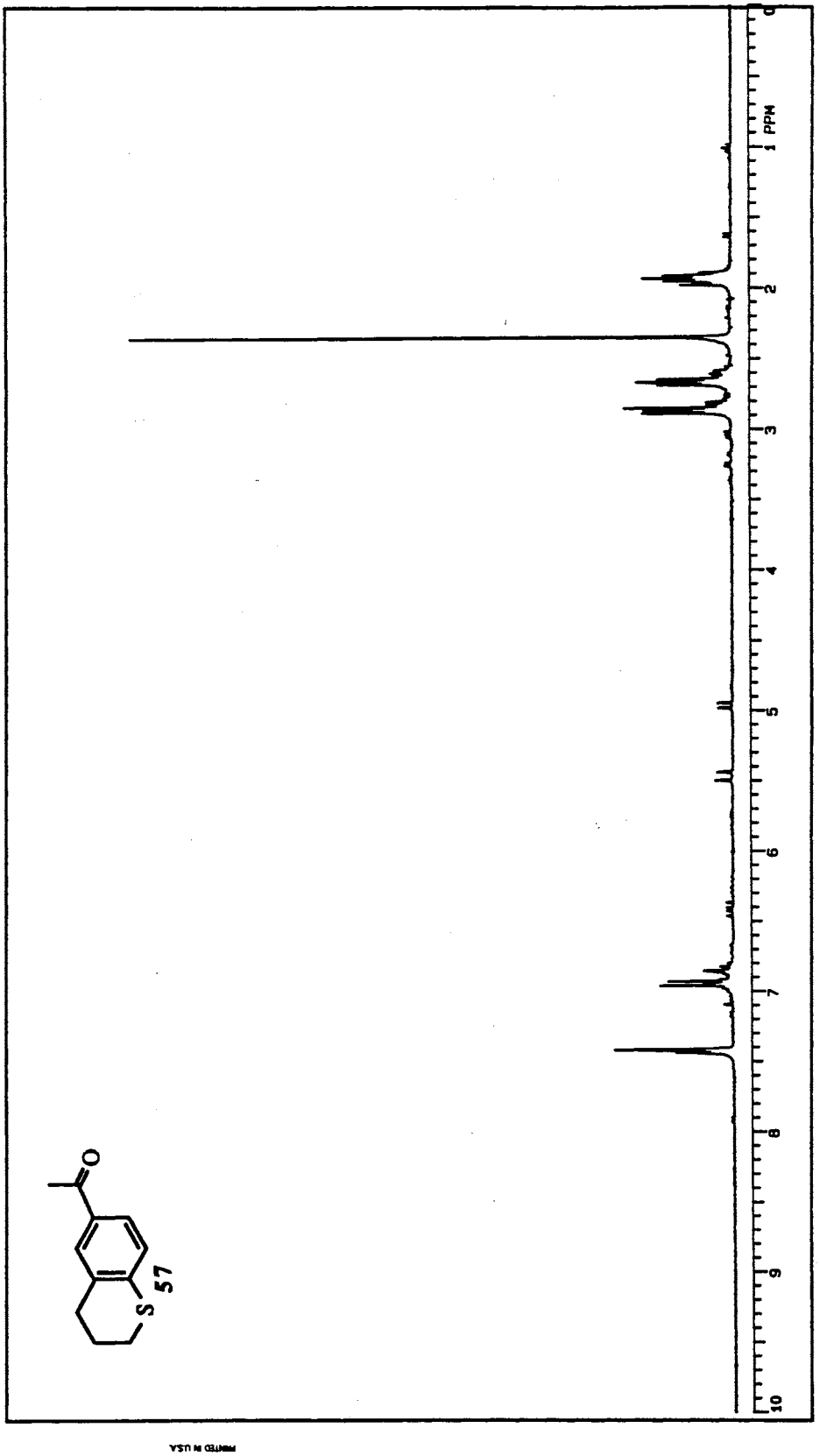
^{13}C NMR Spectrum of **56**

Plate LXXVIII



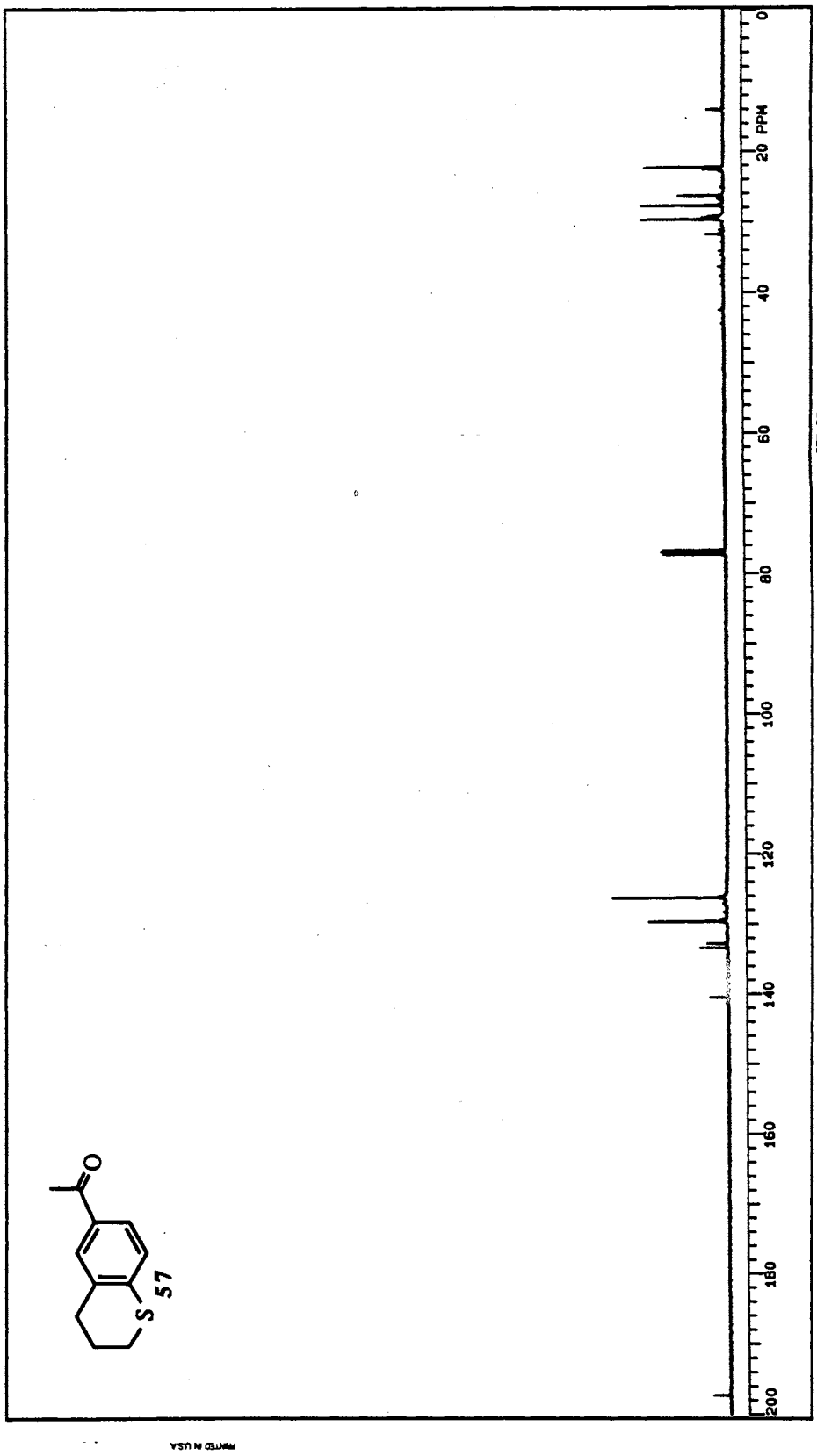
IR Spectrum of **57**

Plate LXXIX



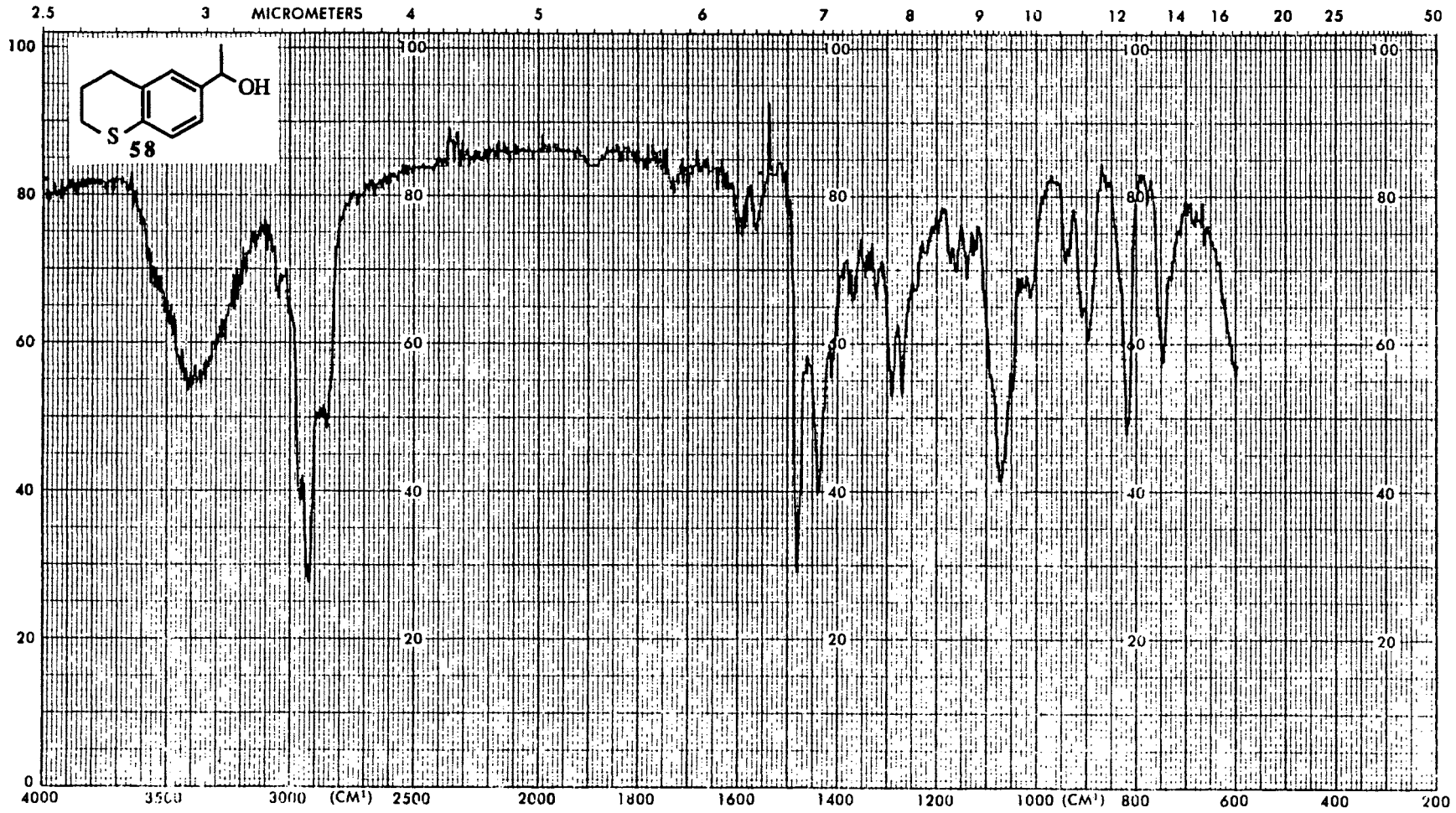
^{1}H NMR Spectrum of **57**

Plate LXXX



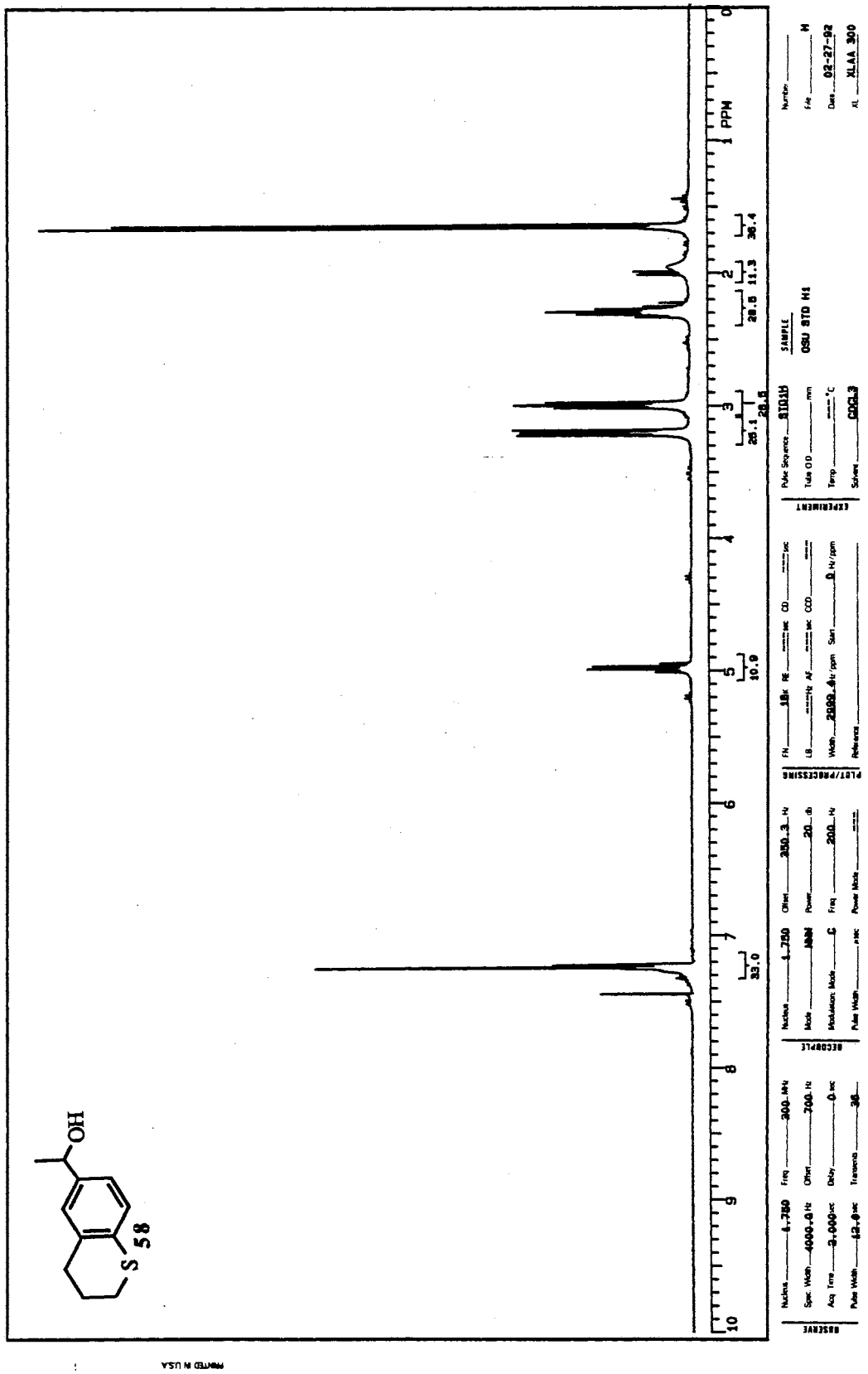
^{13}C NMR Spectrum of **57**

Plate LXXXI



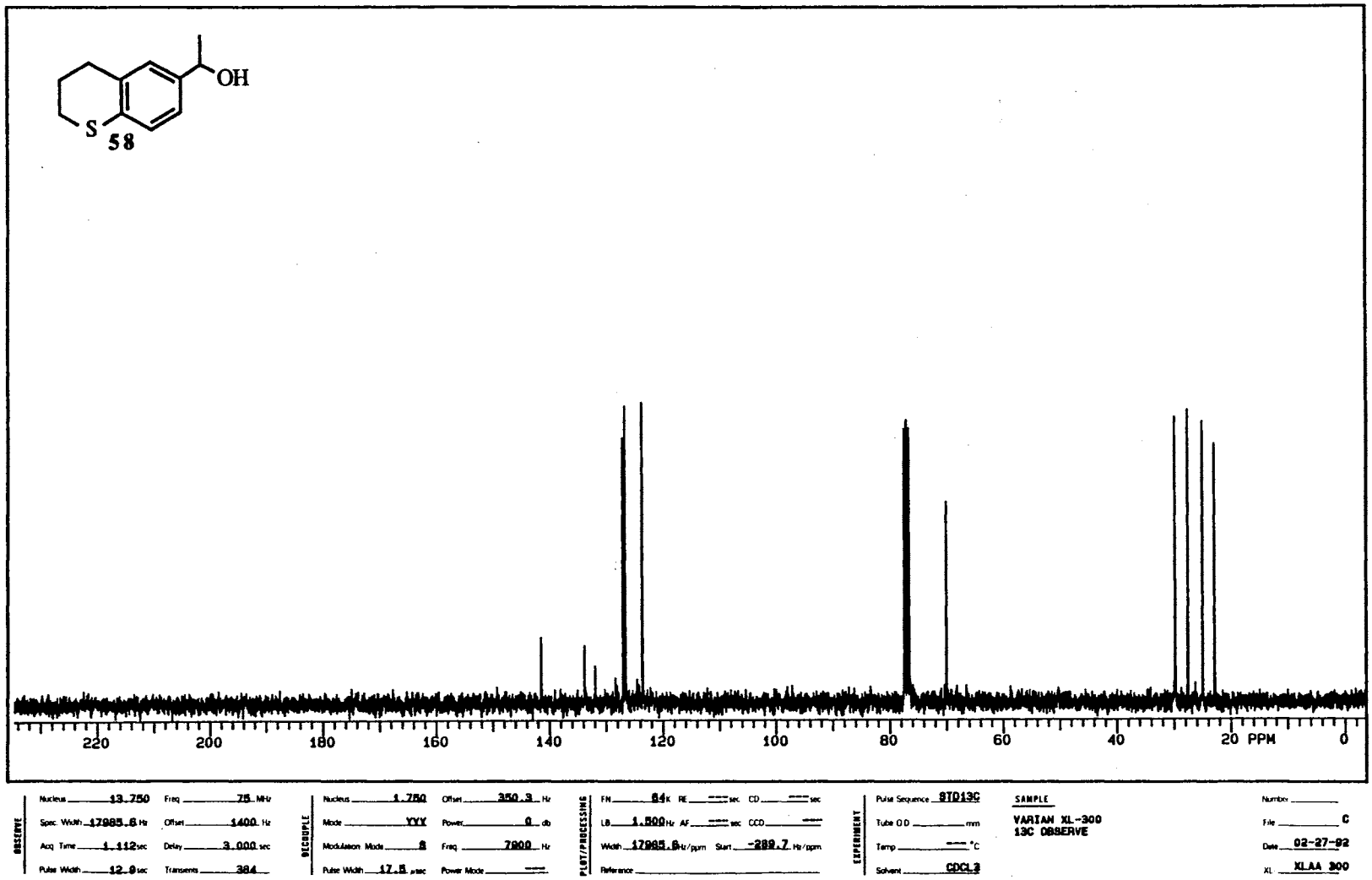
IR Spectrum of **58**

Plate LXXXII



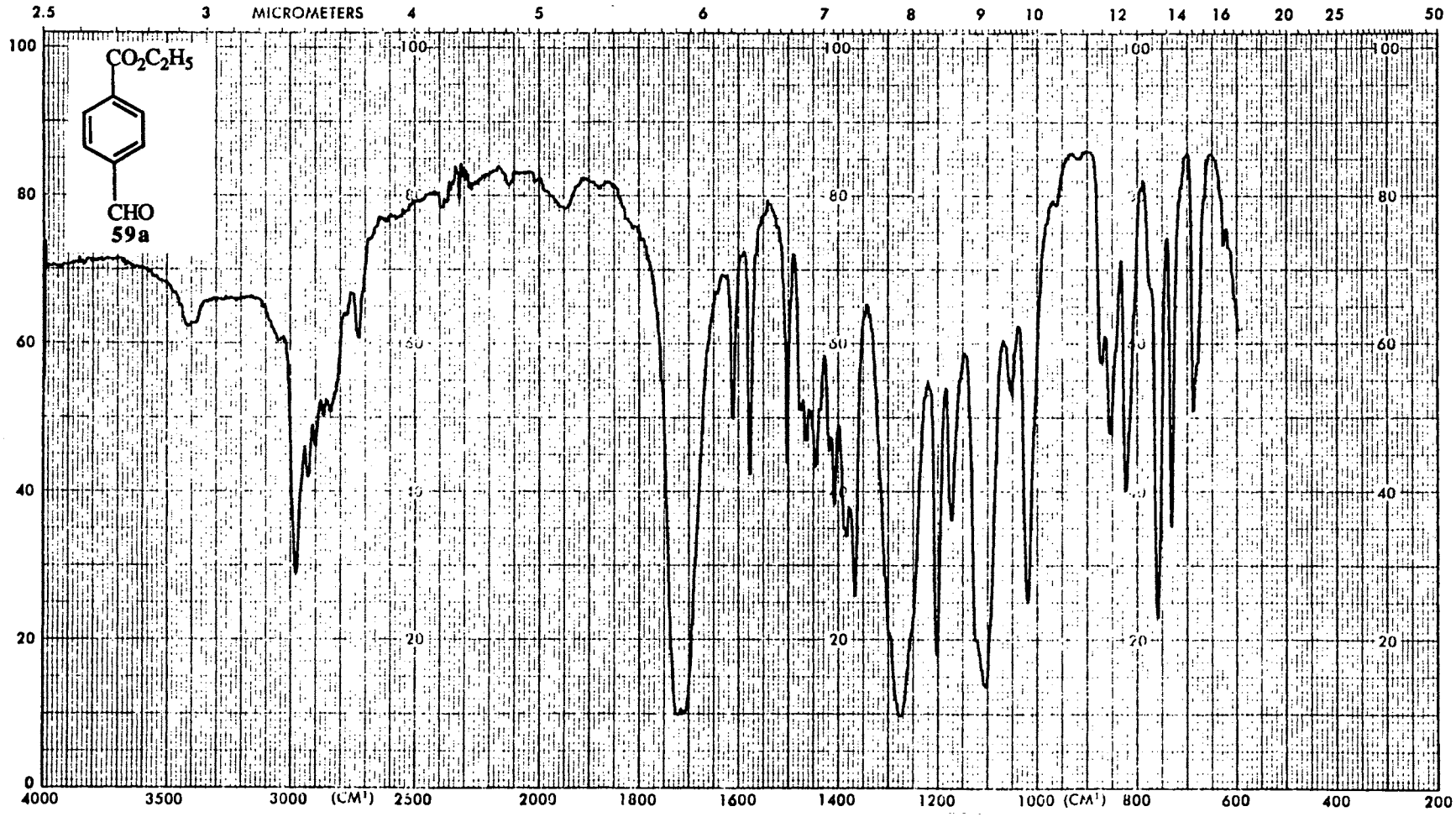
^{1}H NMR Spectrum of **58**

Plate LXXXIII



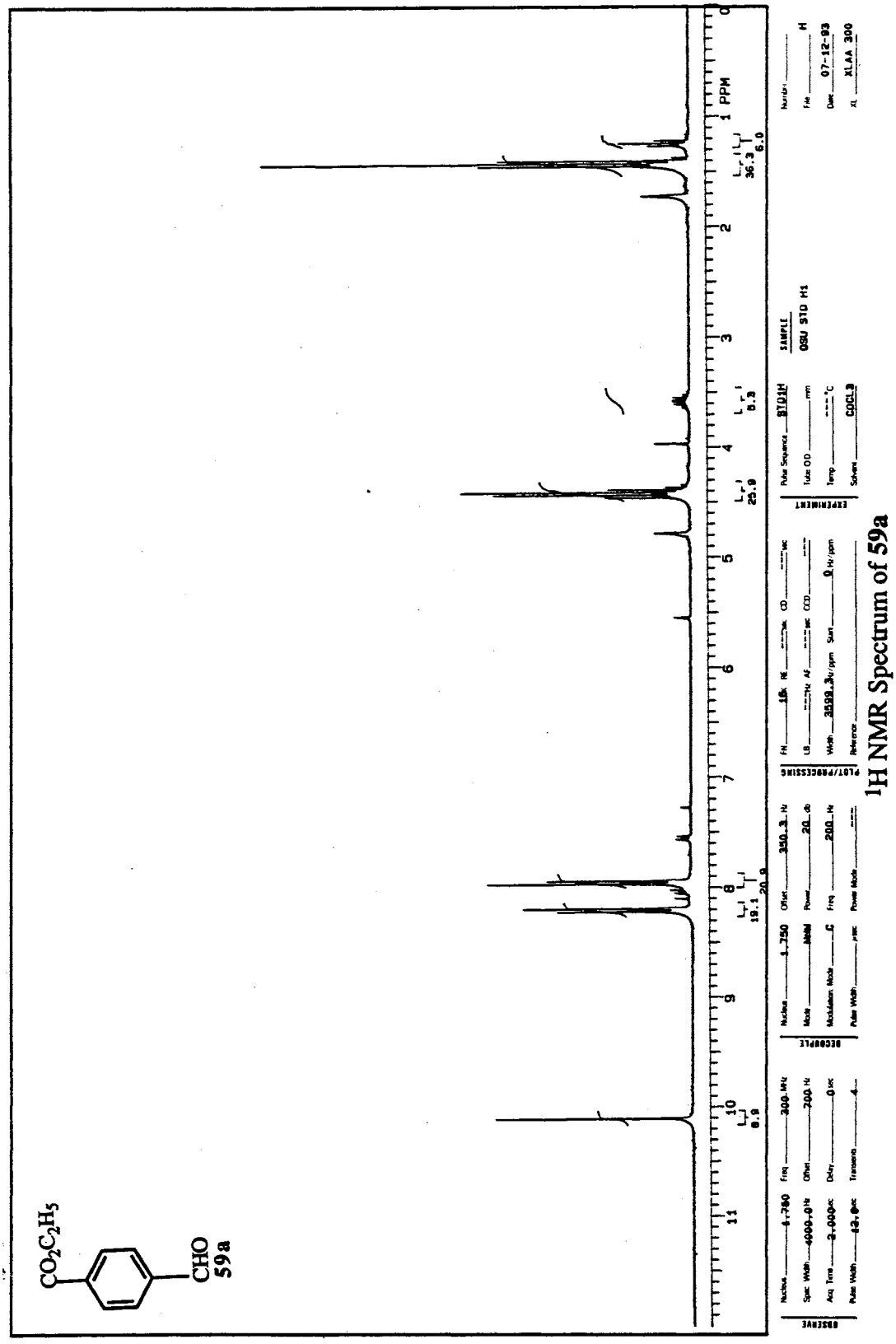
^{13}C NMR Spectrum of **58**

Plate LXXXIV



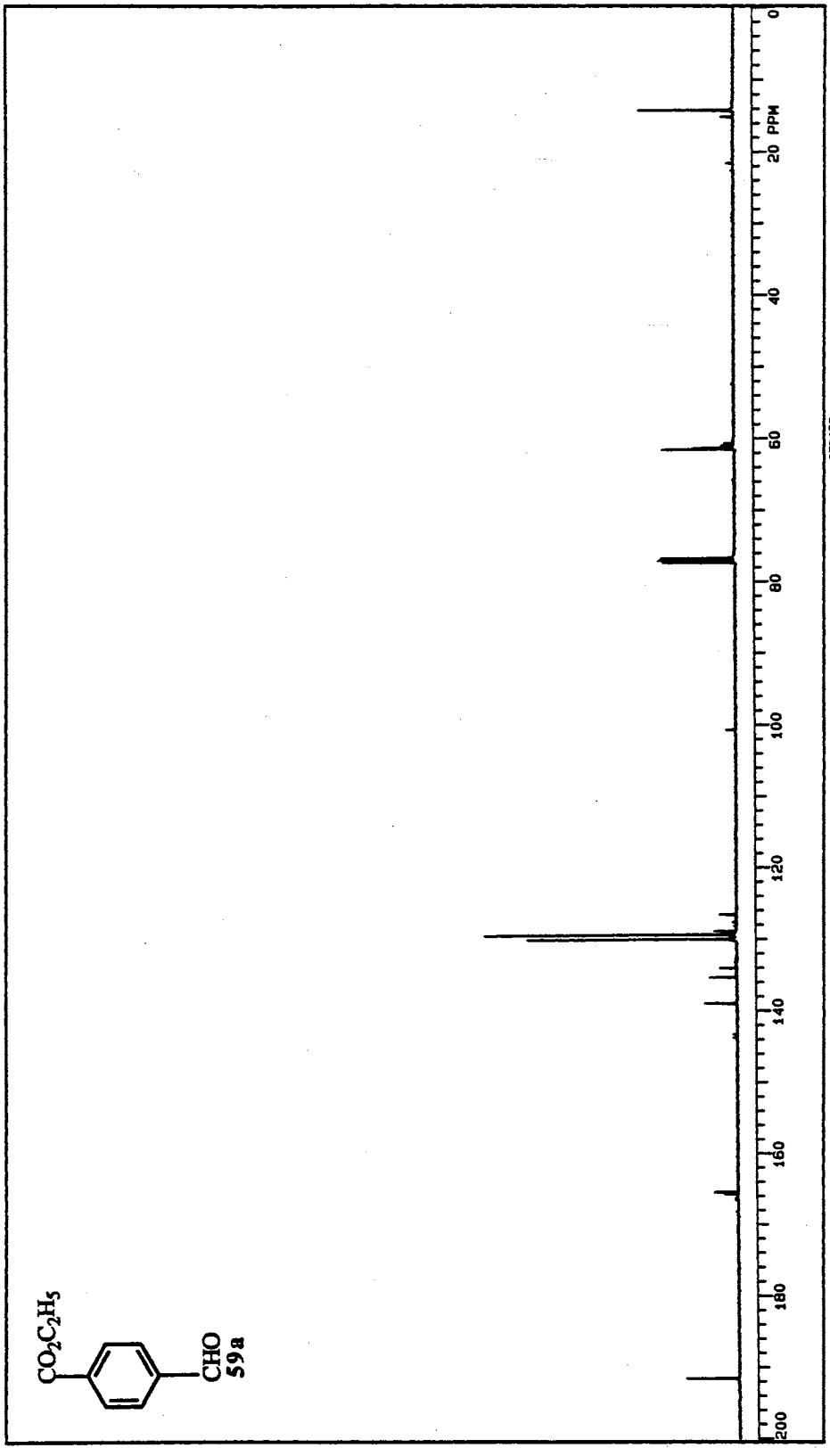
IR Spectrum of **59a**

Plate LXXXV



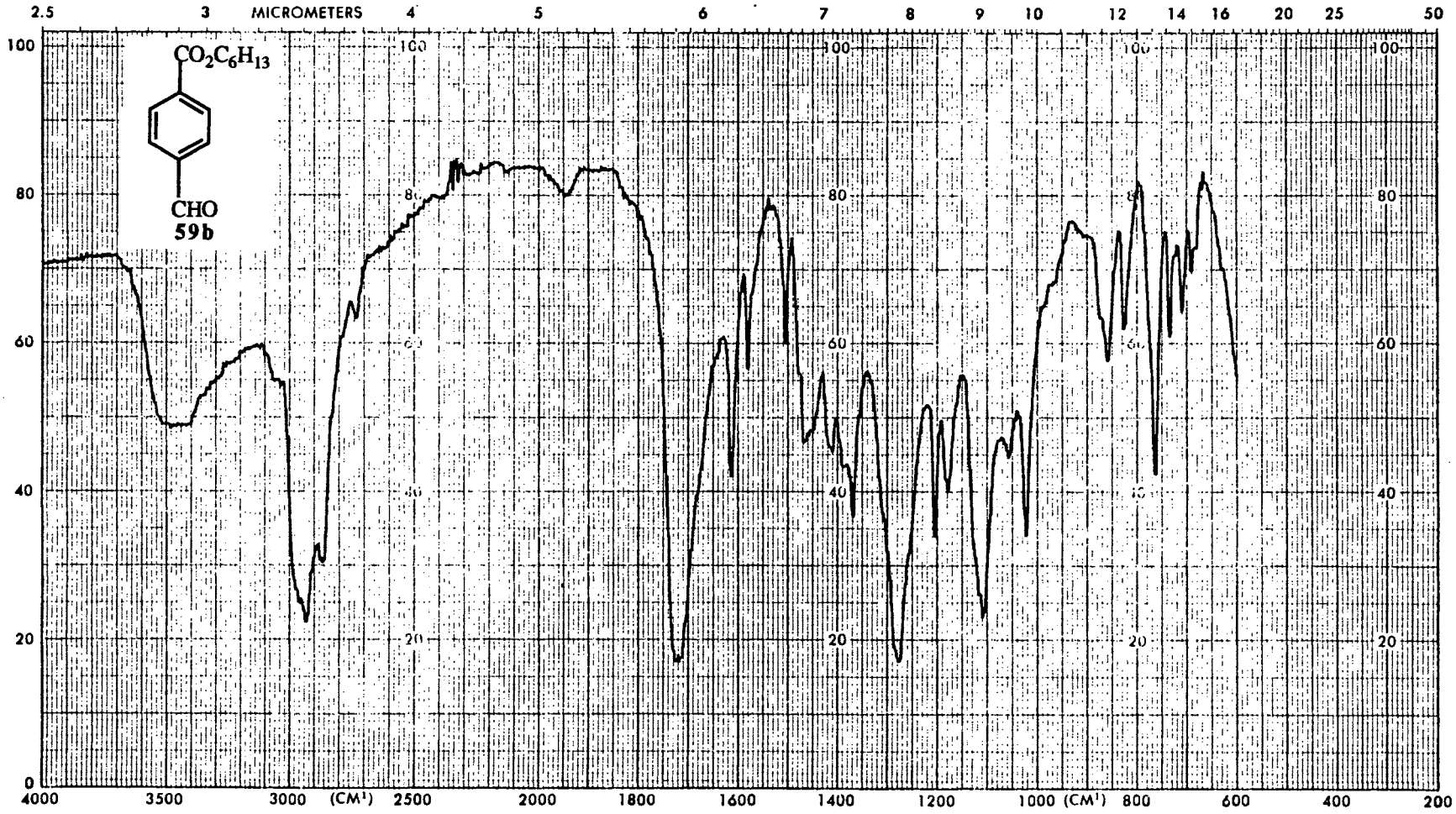
^{1}H NMR Spectrum of **59a**

Plate LXXXVI



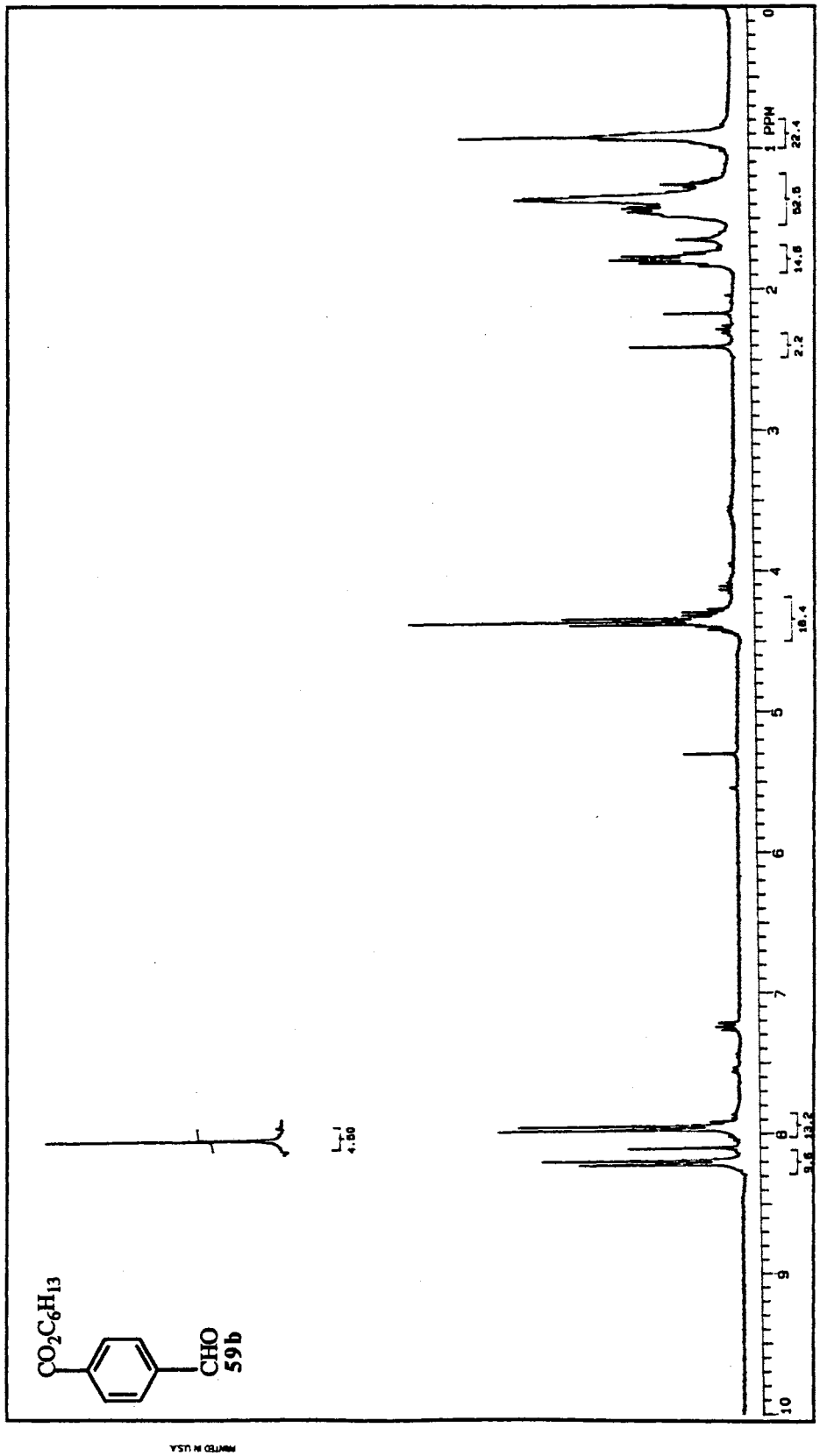
^{13}C NMR Spectrum of **59a**

Plate LXXXVII



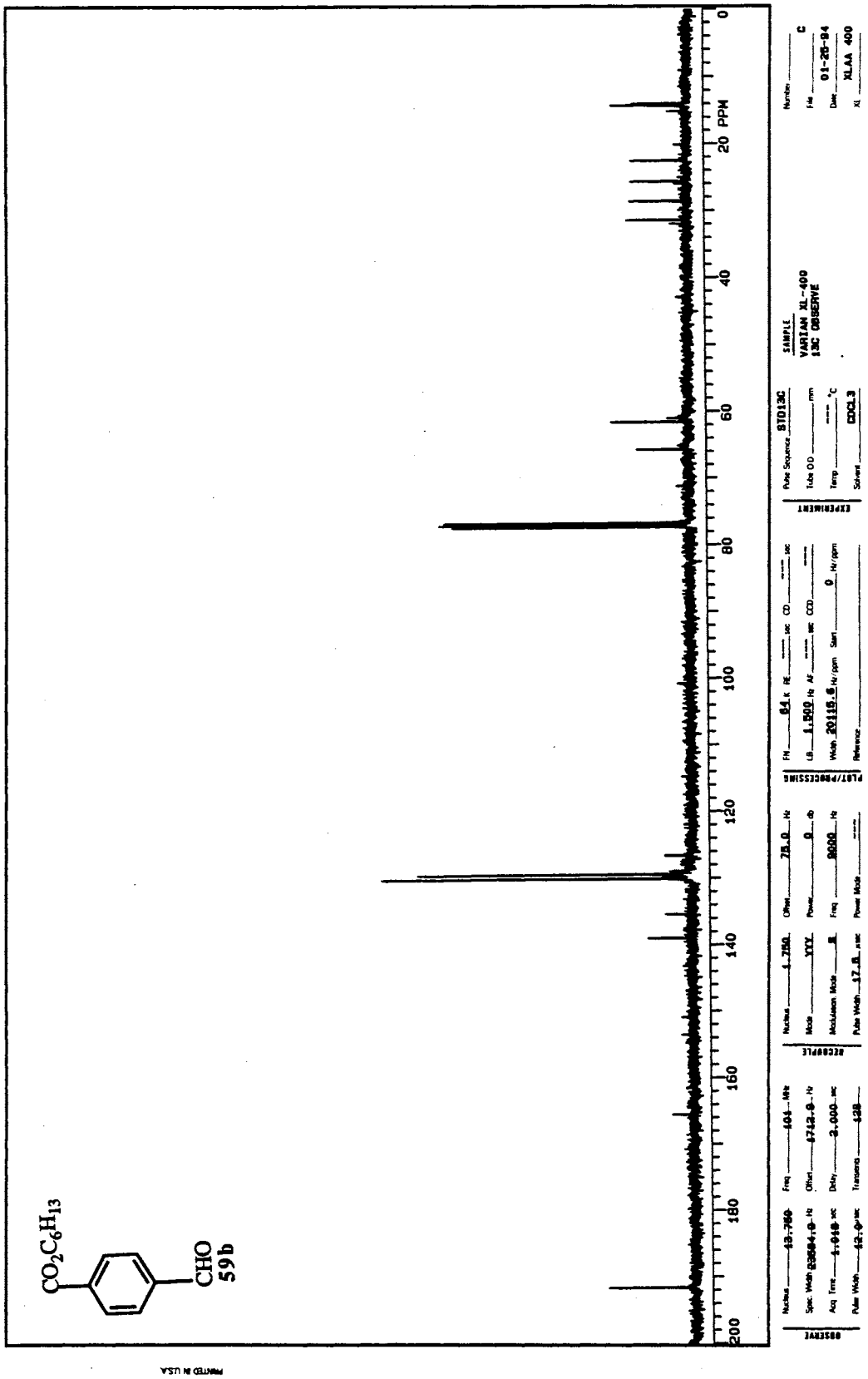
IR Spectrum of **59b**

Plate LXXXVIII



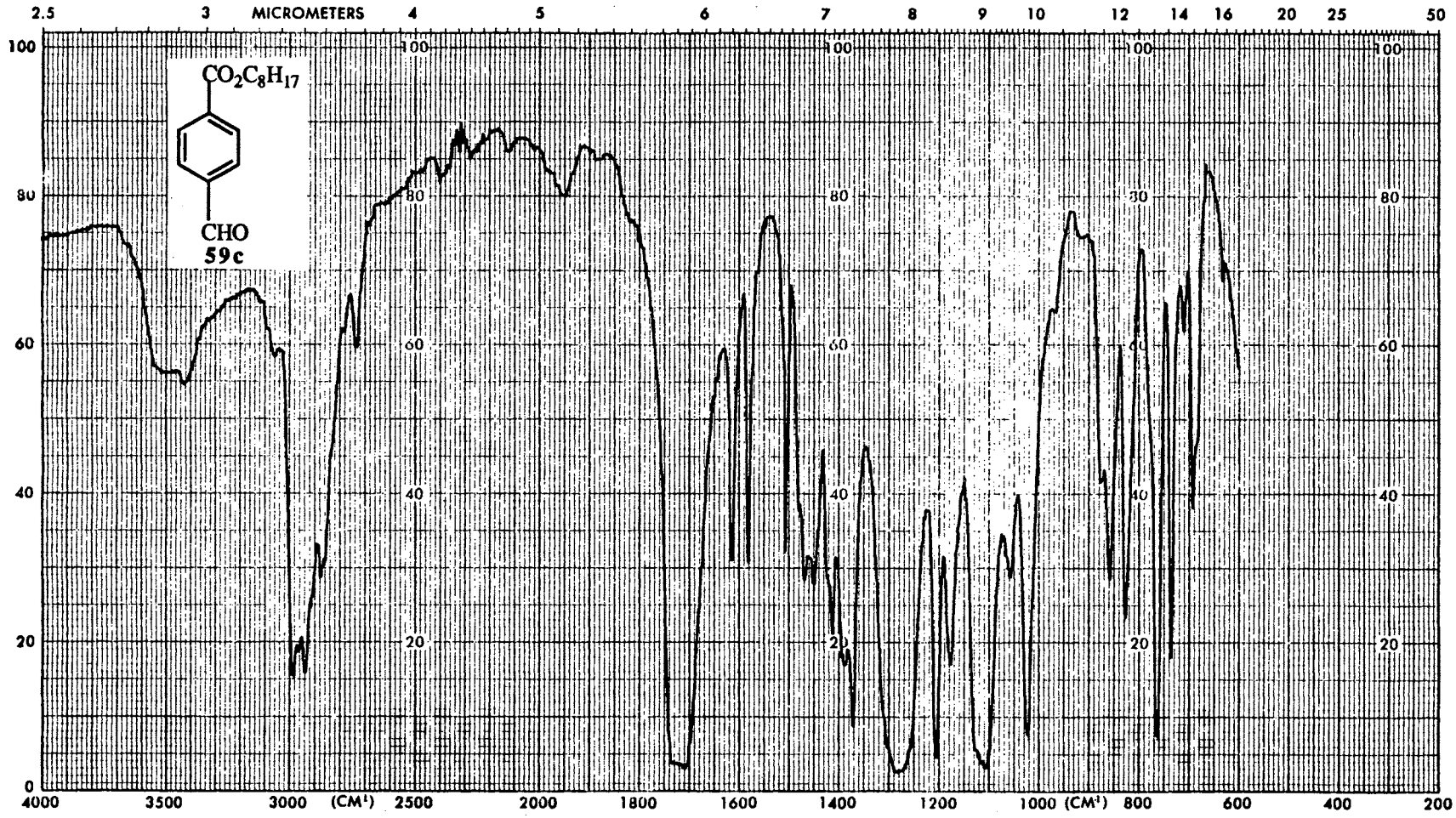
^{1}H NMR Spectrum of **59b**

Plate LXXXIX

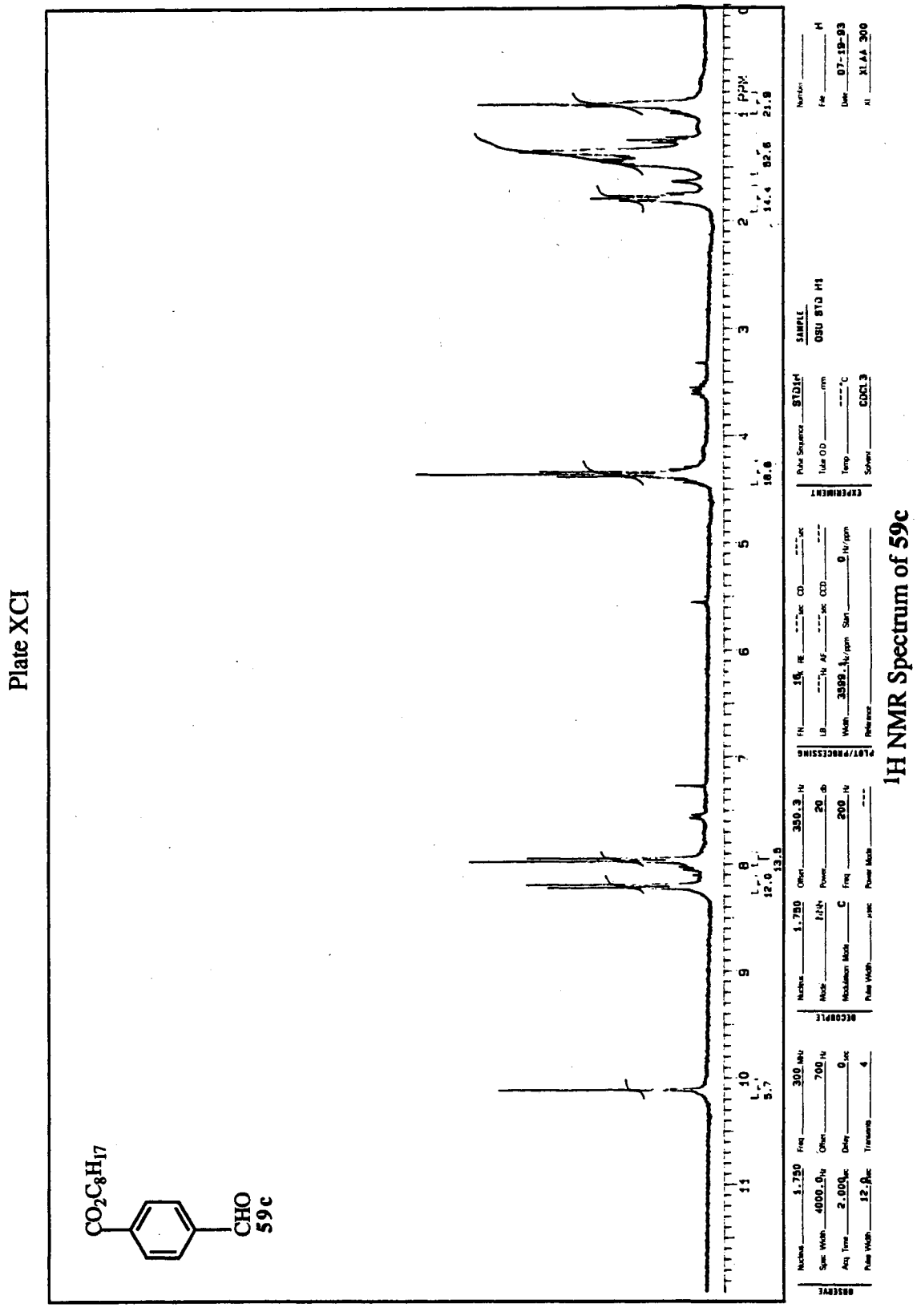


^{13}C NMR Spectrum of 59b

Plate XC

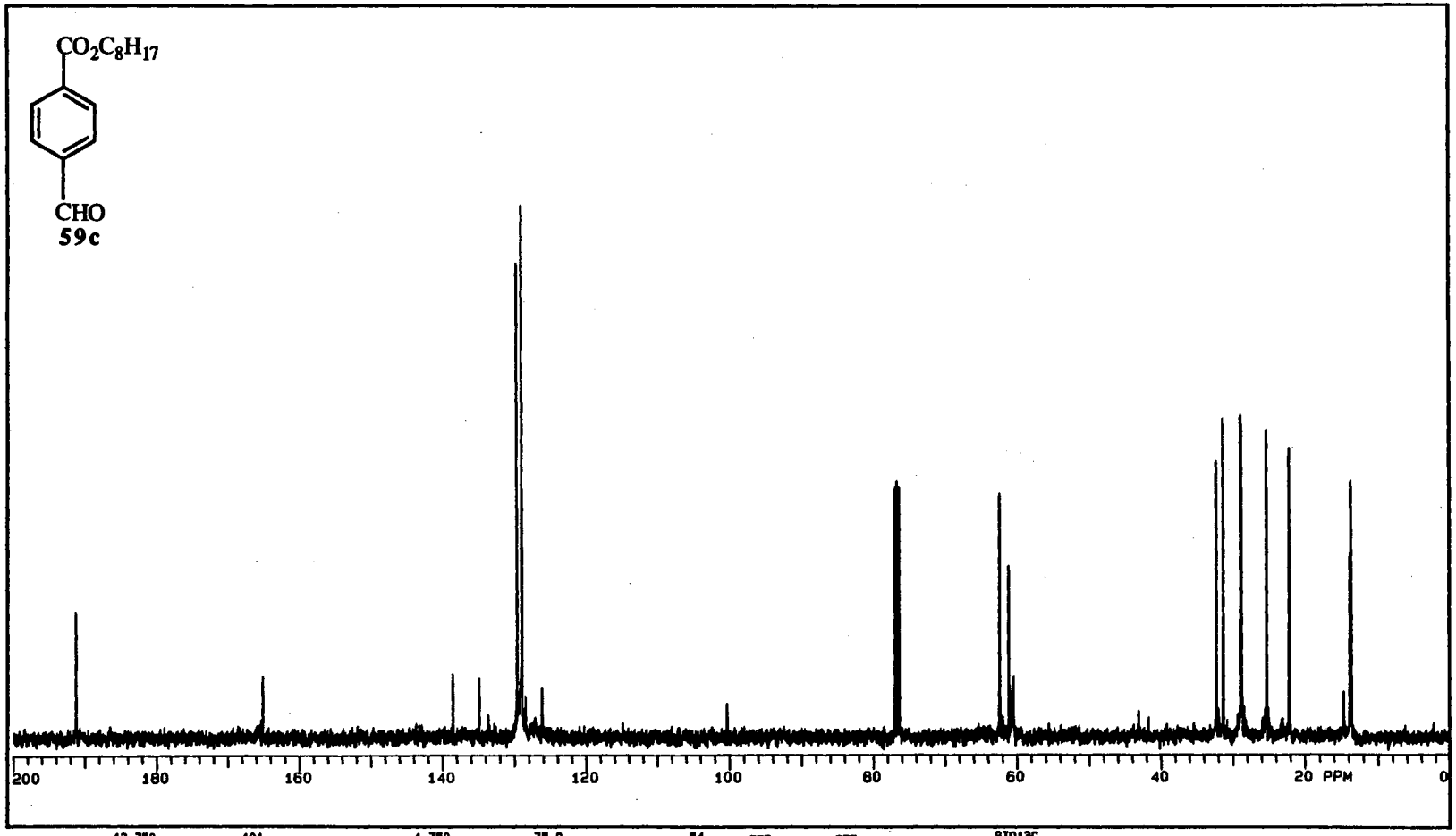


IR Spectrum of **59c**



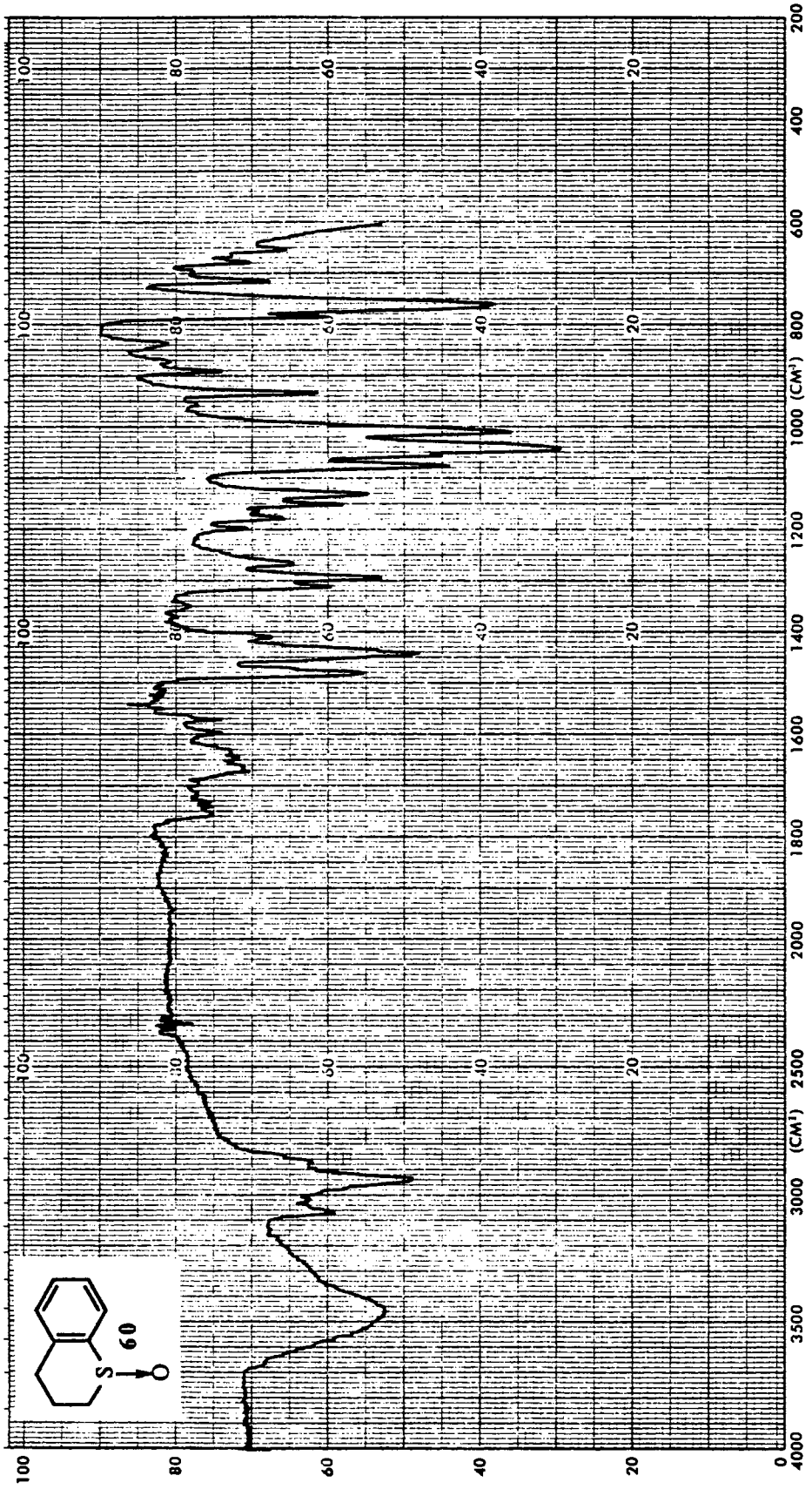
^{1}H NMR Spectrum of **59c**

Plate XCII



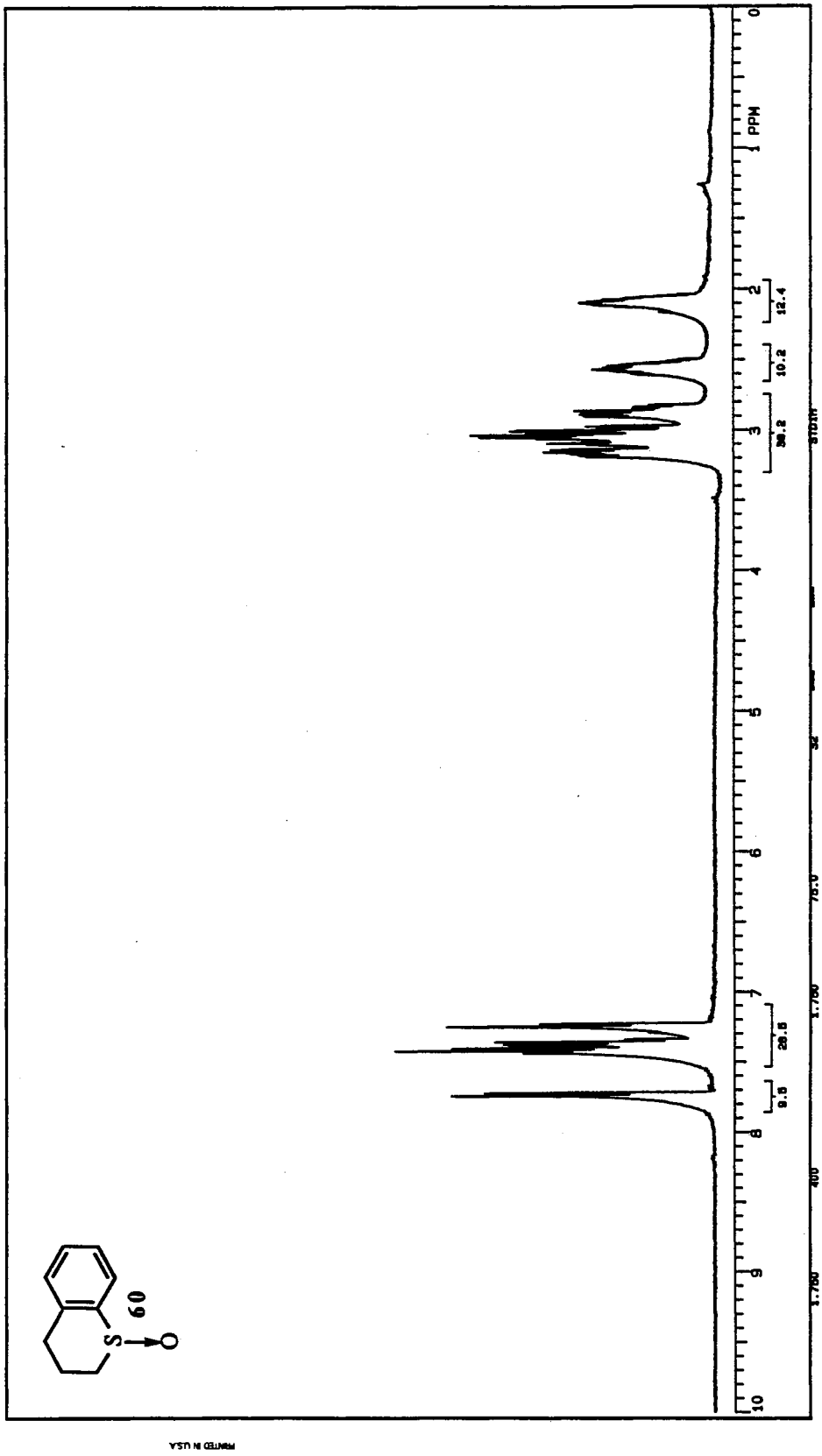
^{13}C NMR Spectrum of **59c**

Plate XCIII



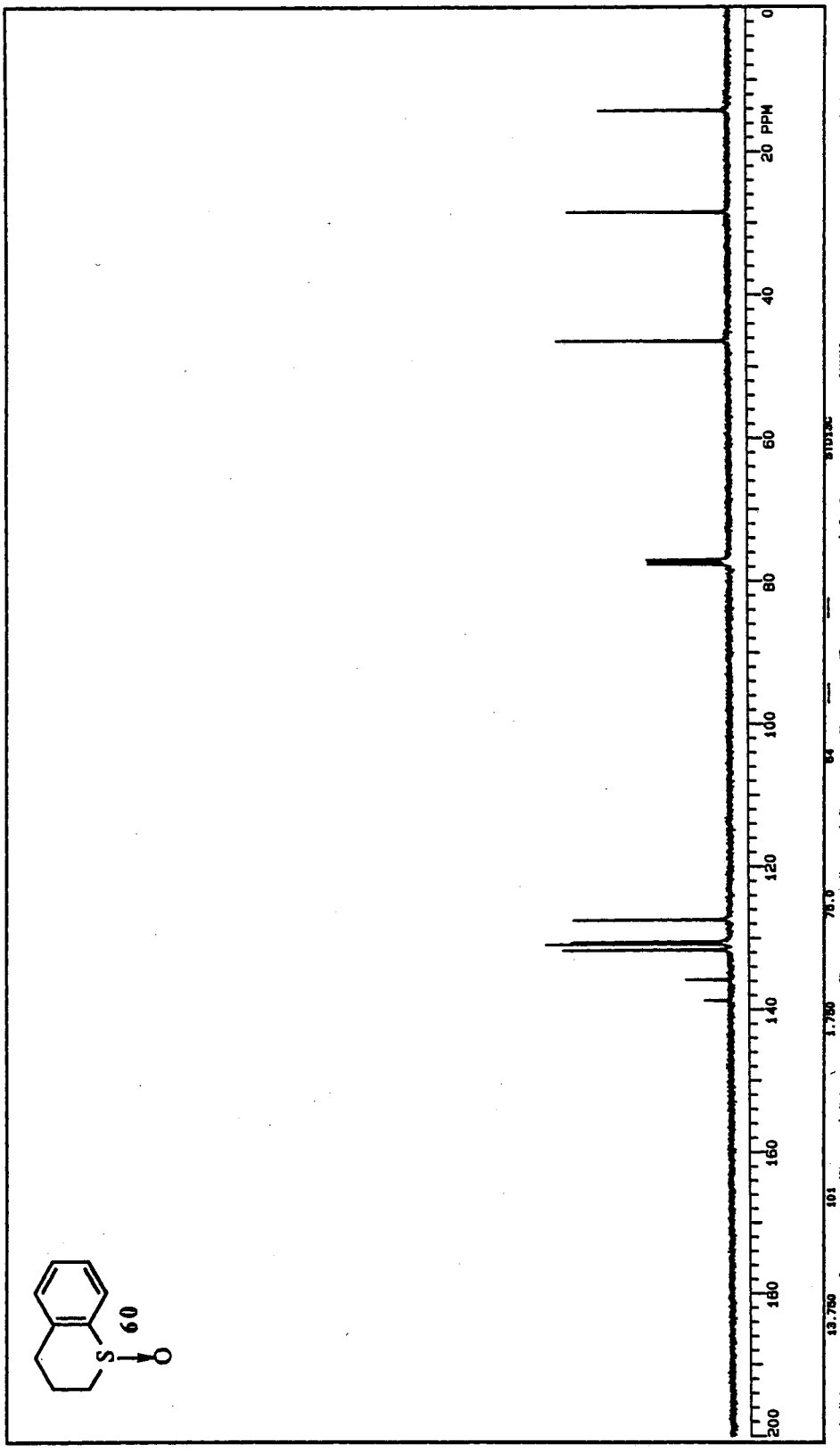
IR Spectrum of **60**

Plate XCIV



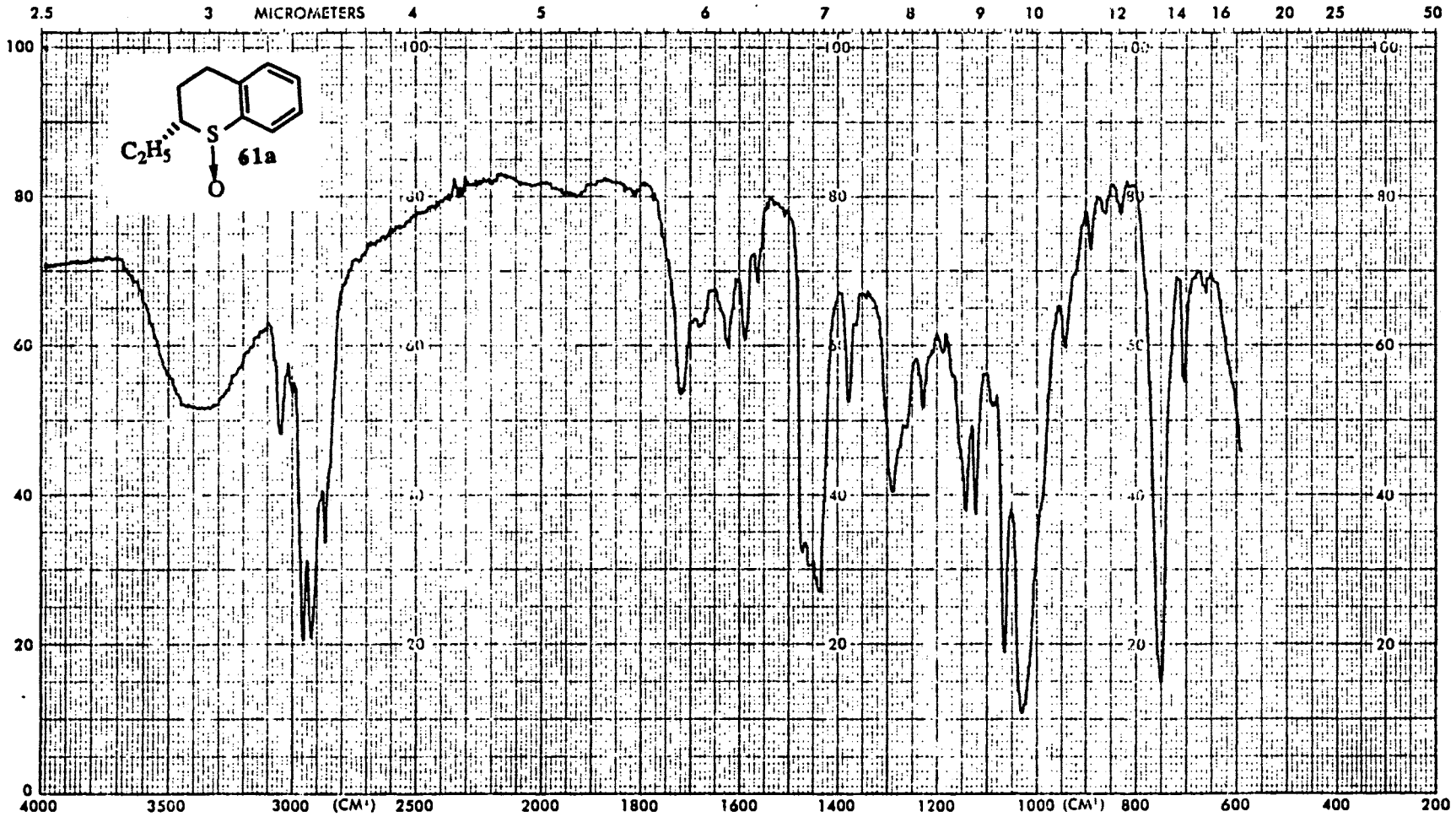
^{1}H NMR Spectrum of **60**

Plate XCV



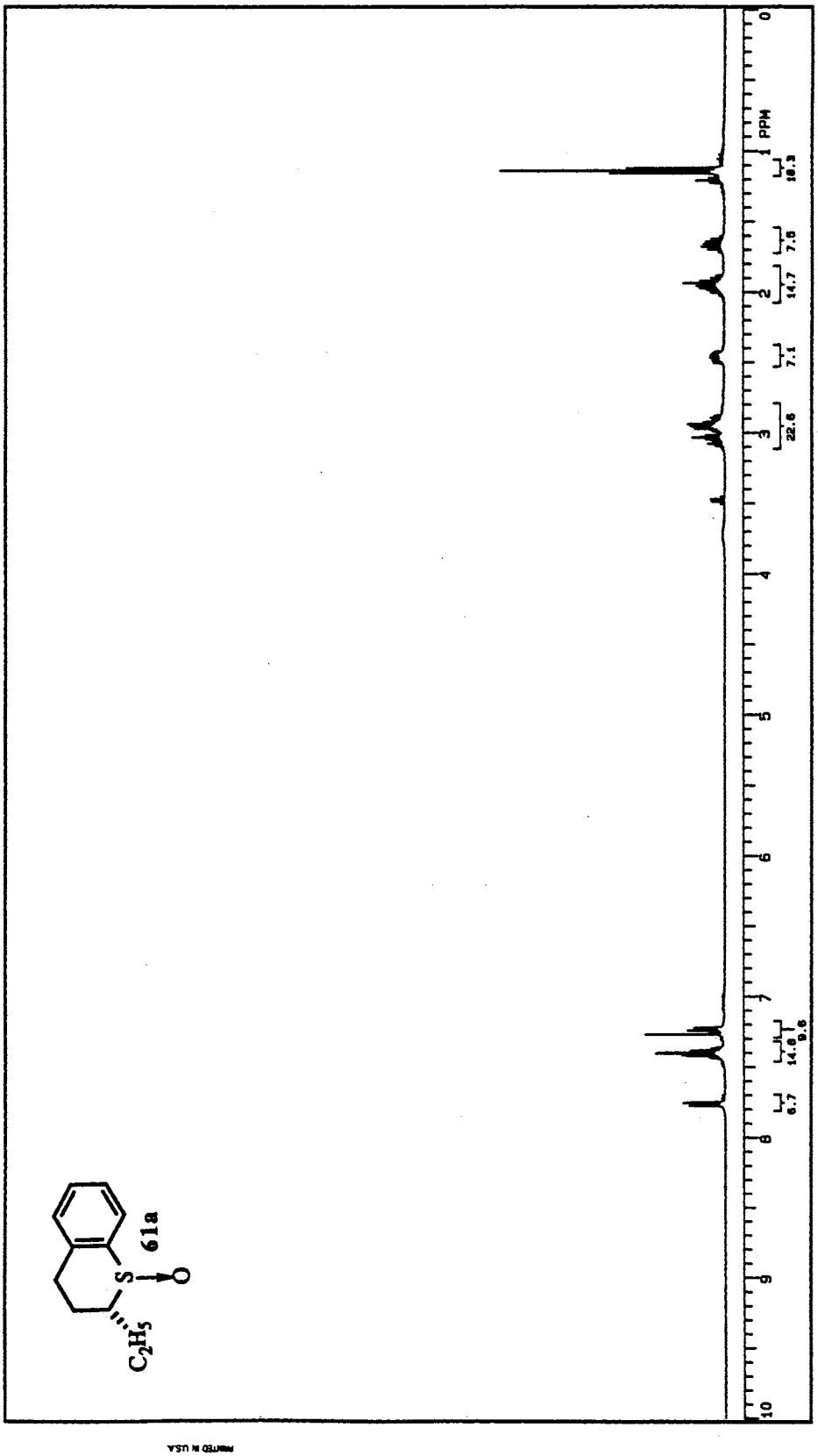
^{13}C NMR Spectrum of **60**

Plate XCVI



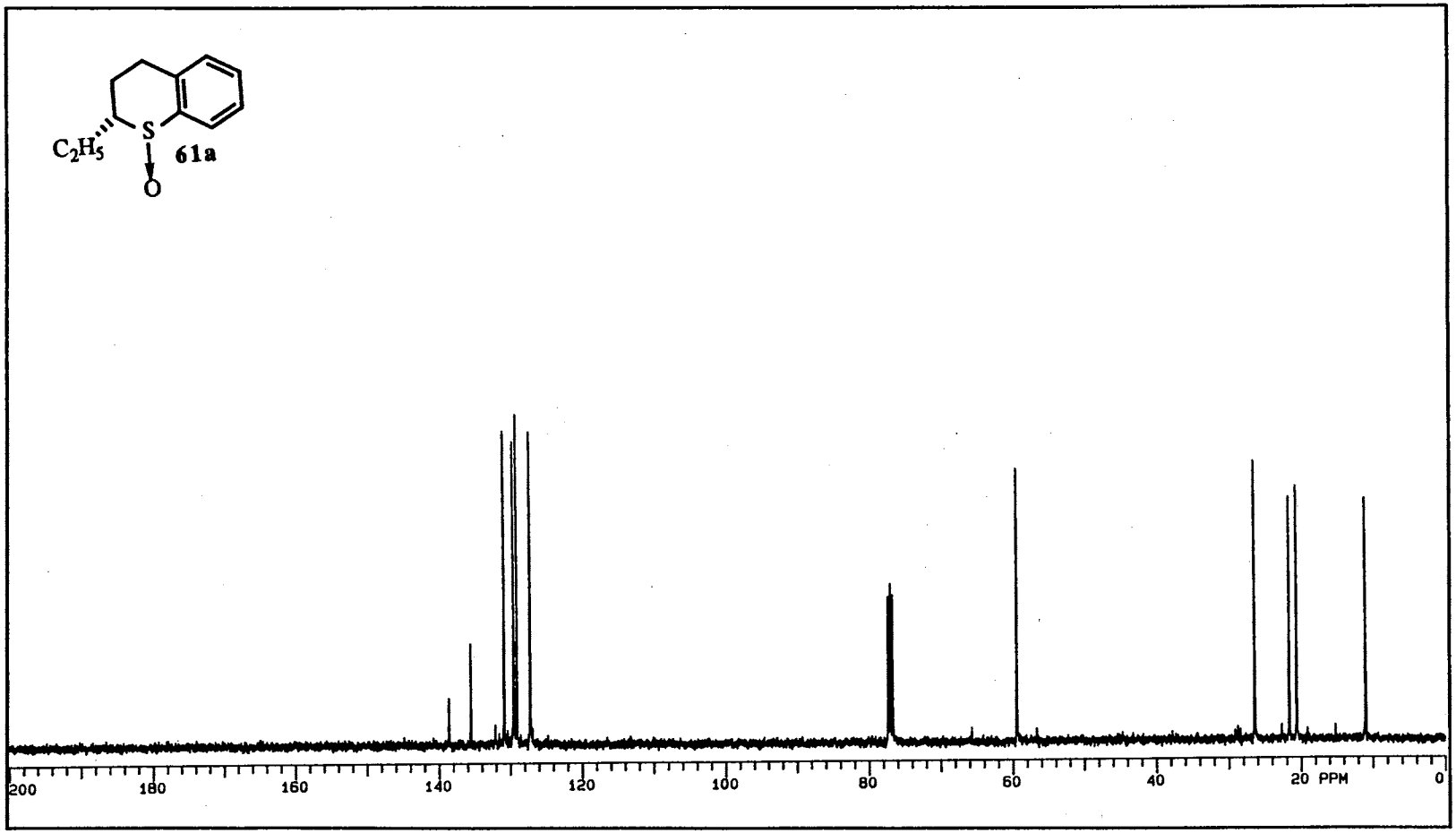
IR Spectrum of **61a**

Plate XCVII



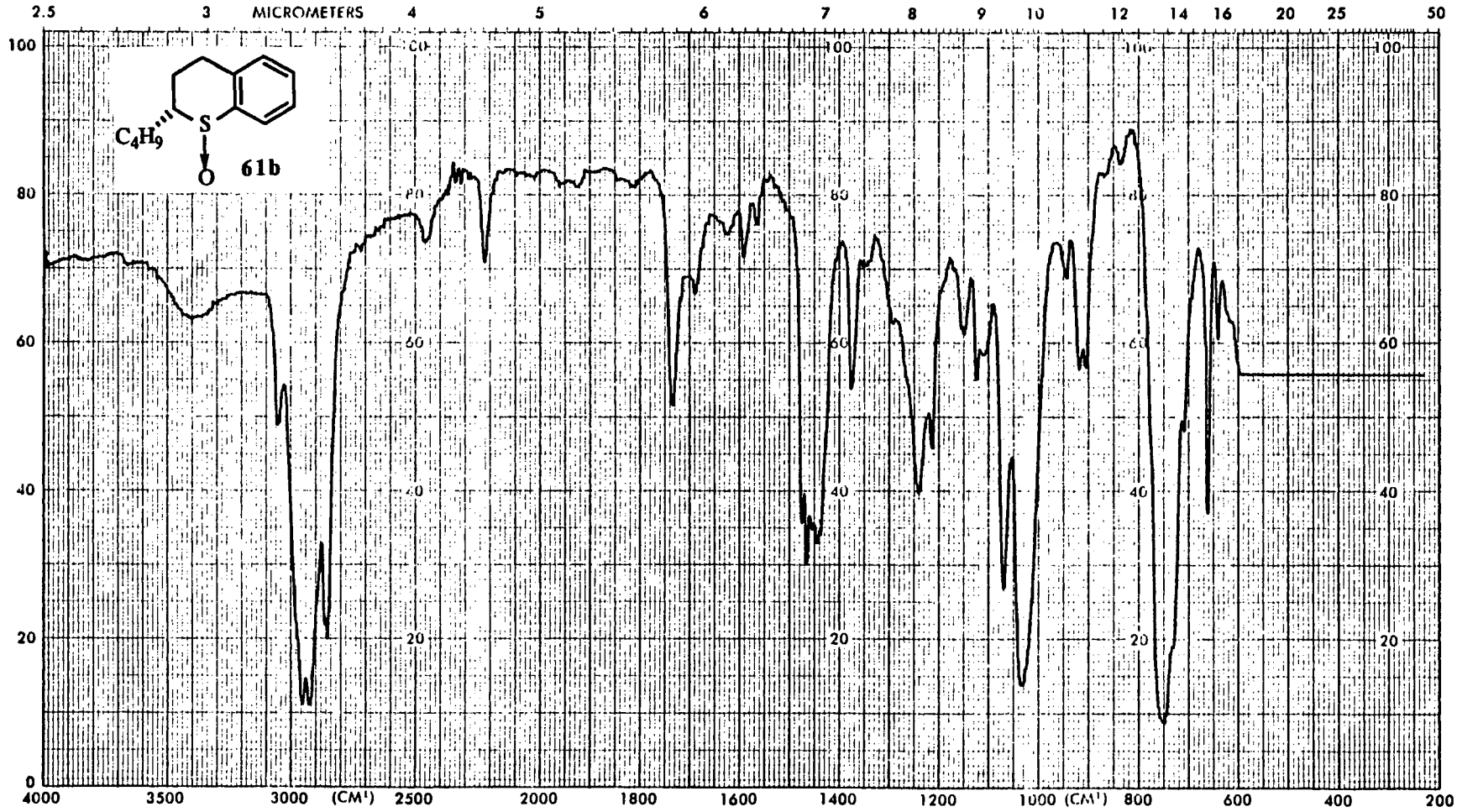
^{1}H NMR Spectrum of **61a**

Plate XCVIII



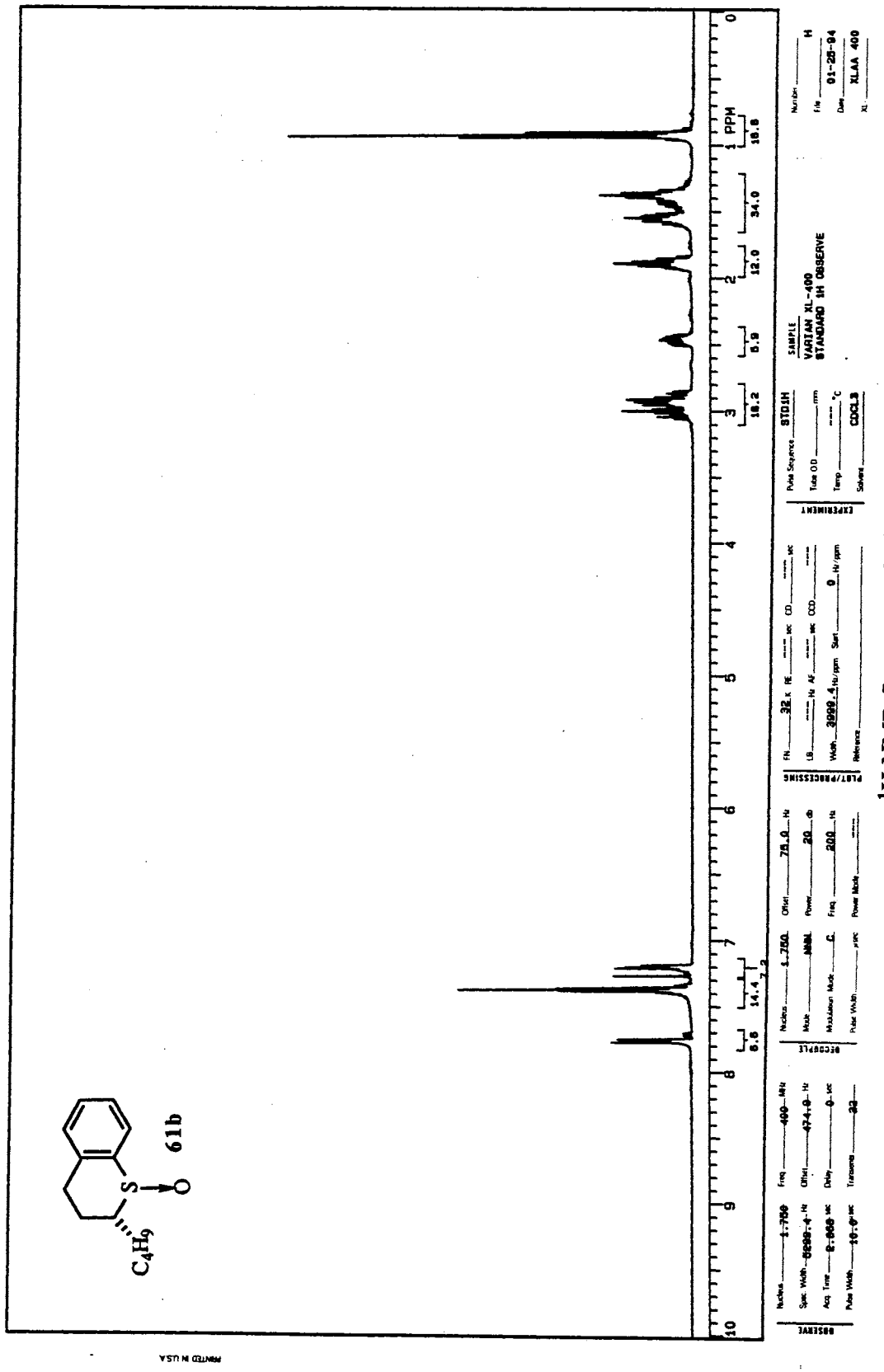
^{13}C NMR Spectrum of **61a**

Plate XCIX



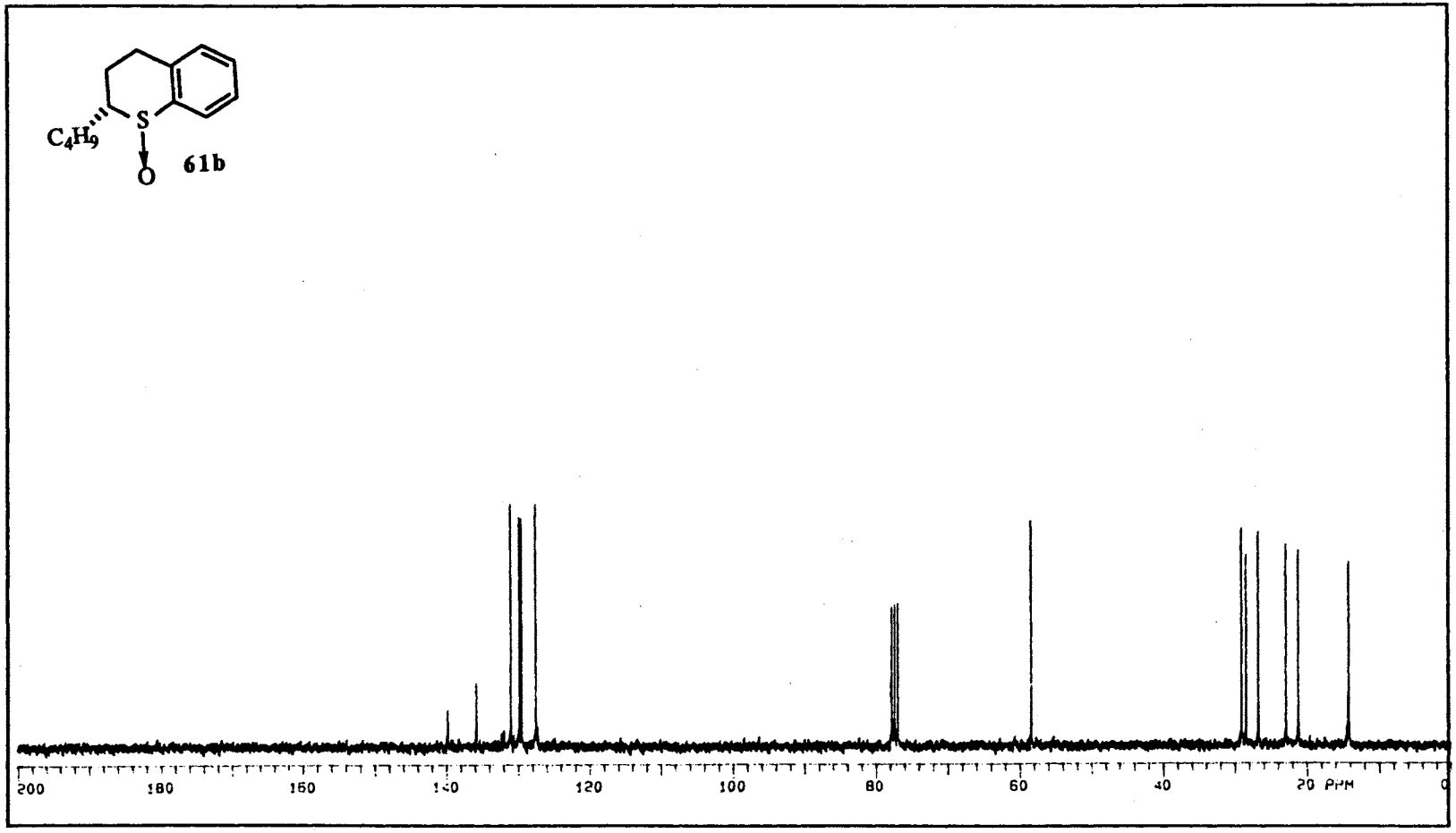
IR Spectrum of **61b**

Plate C



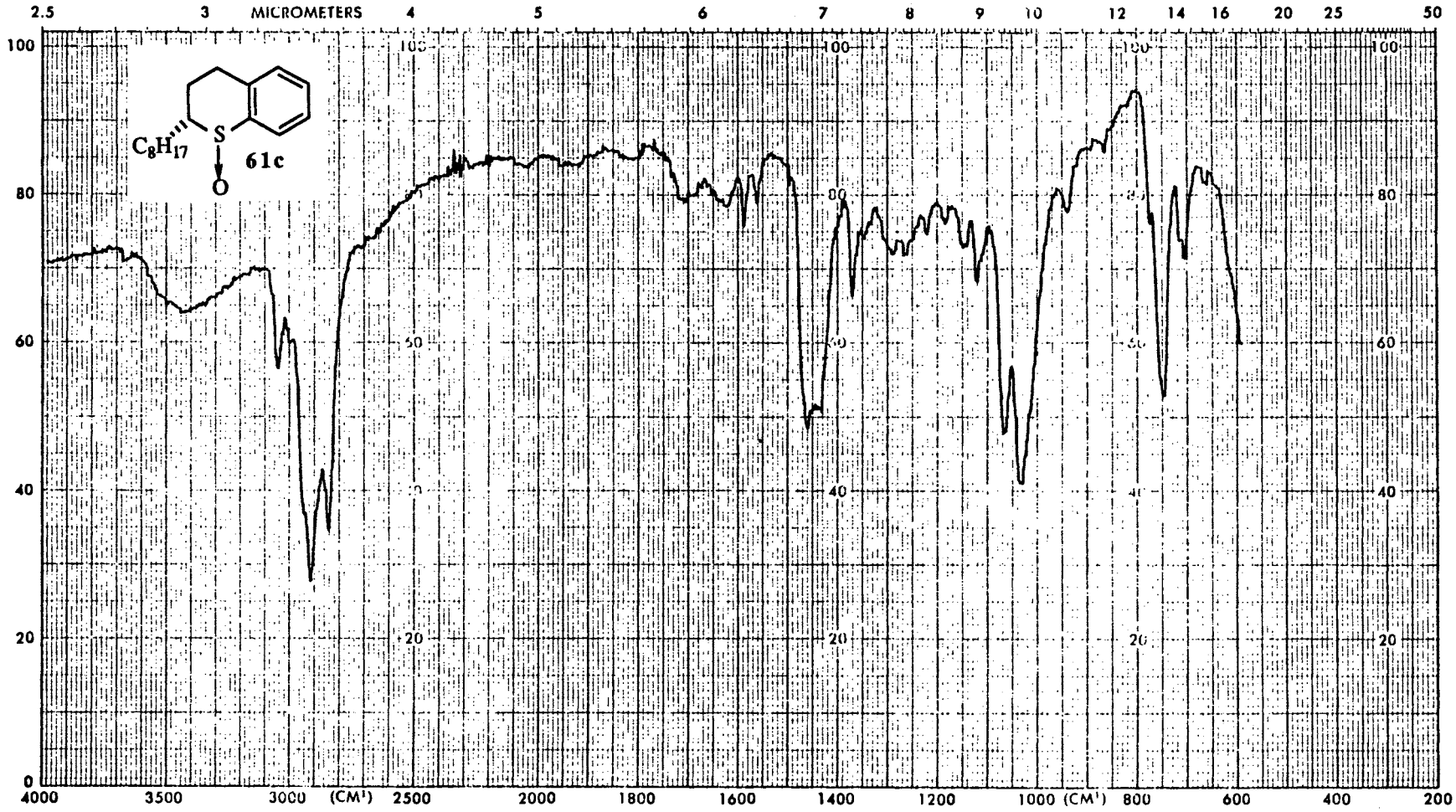
^{1}H NMR Spectrum of **61b**

Plate CI



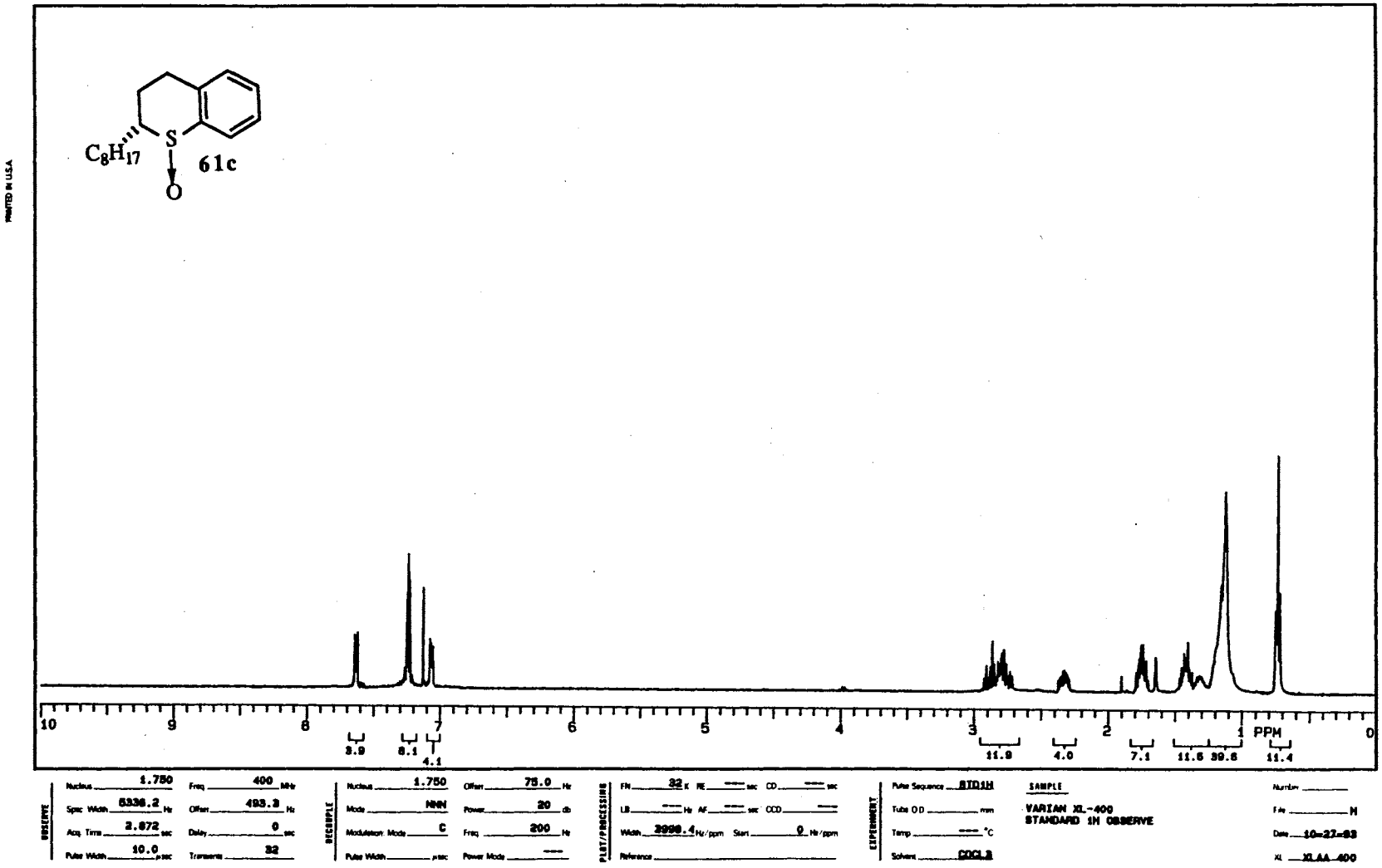
^{13}C NMR Spectrum of **61b**

Plate CII



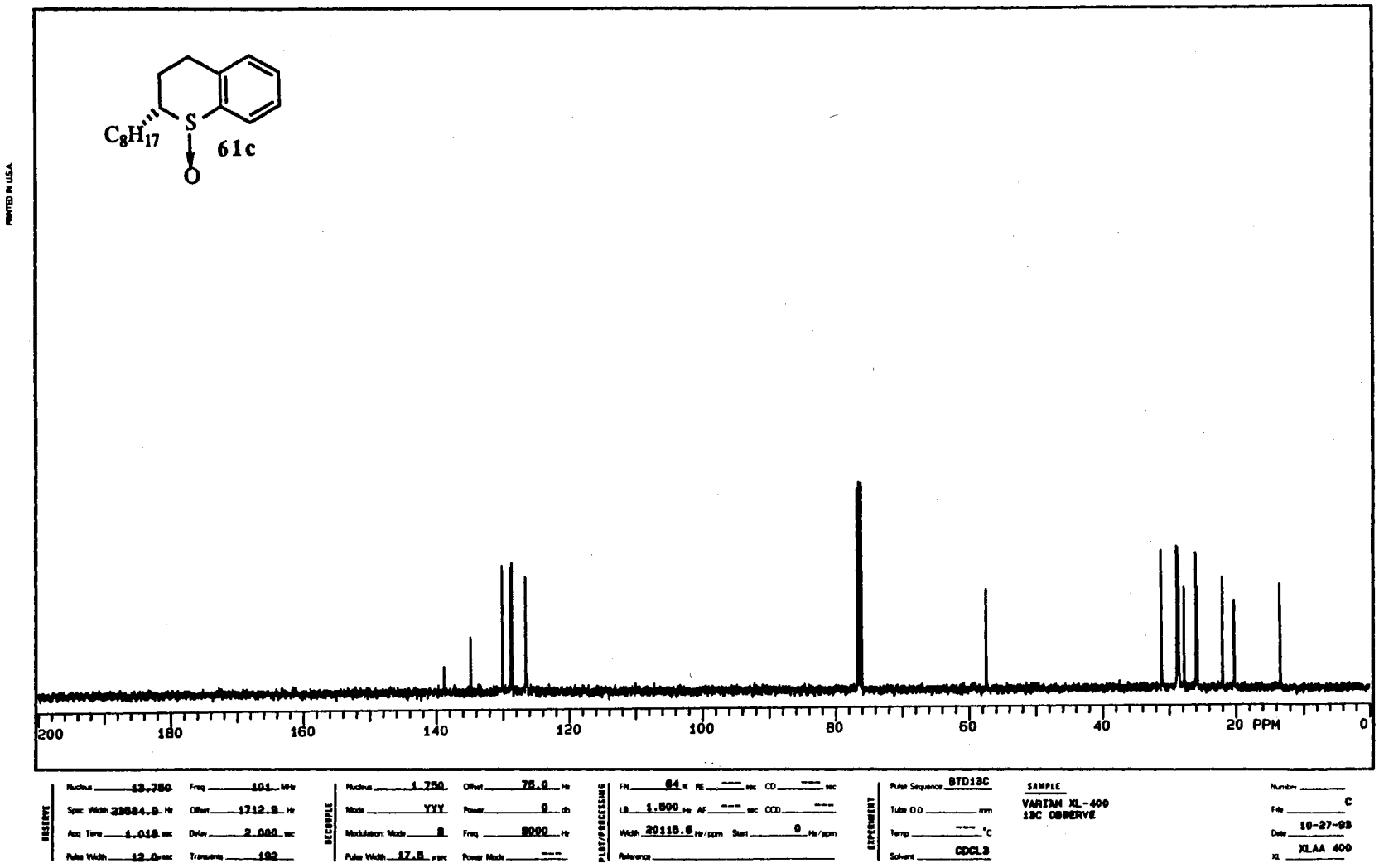
IR Spectrum of **61c**

Plate CIII



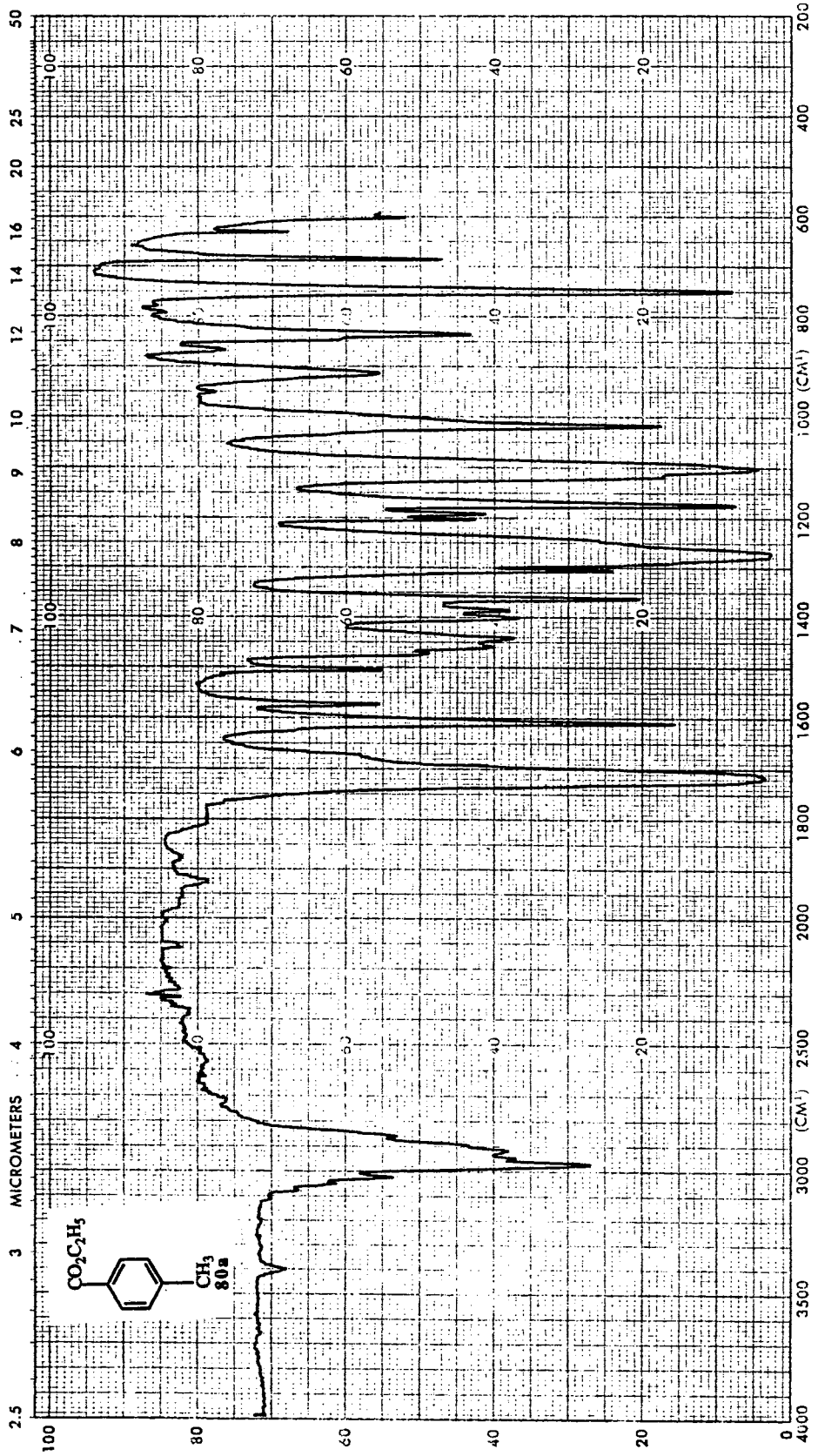
^{1}H NMR Spectrum of **61c**

Plate CIV



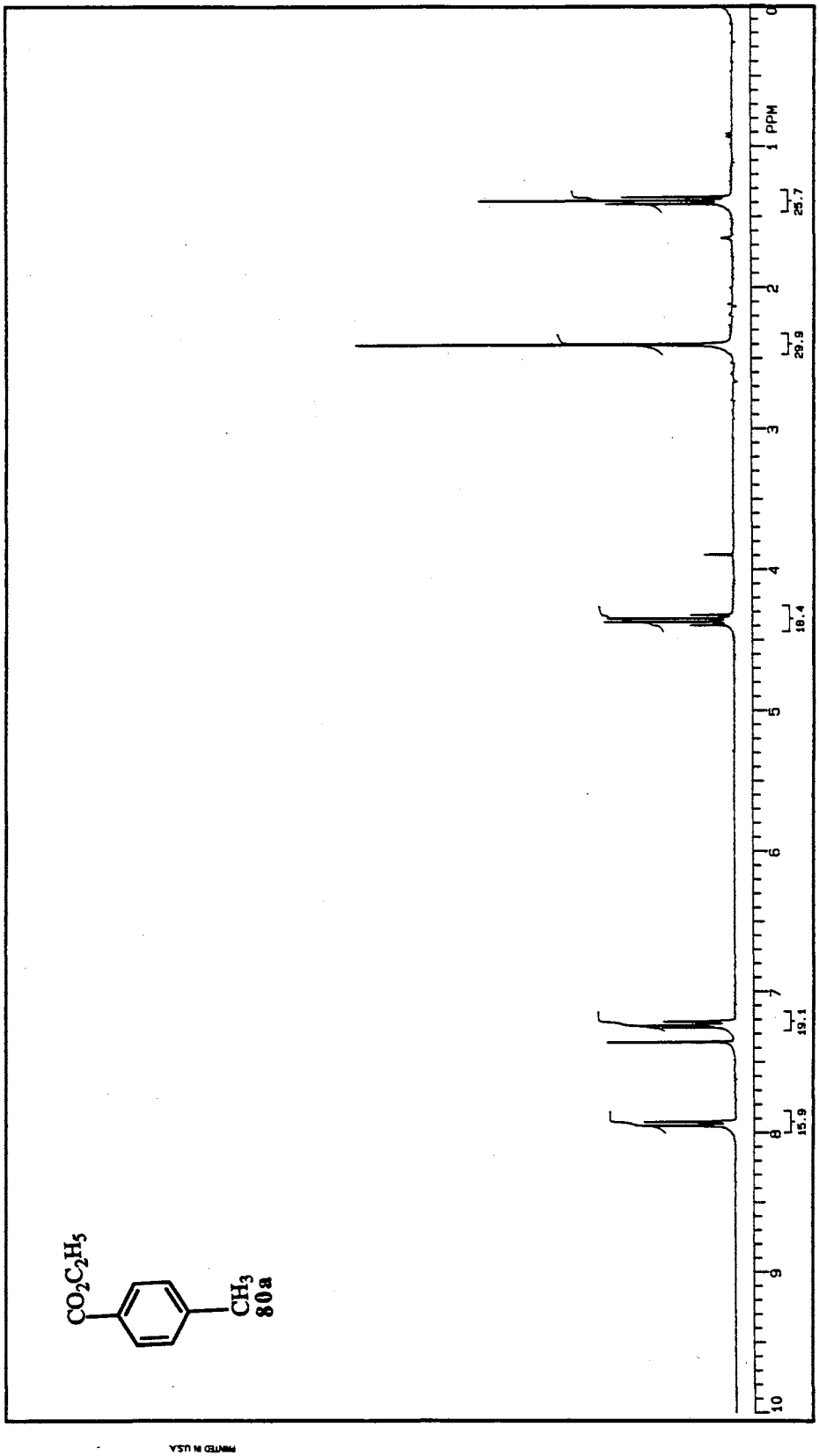
^{13}C NMR Spectrum of **61c**

Plate CV



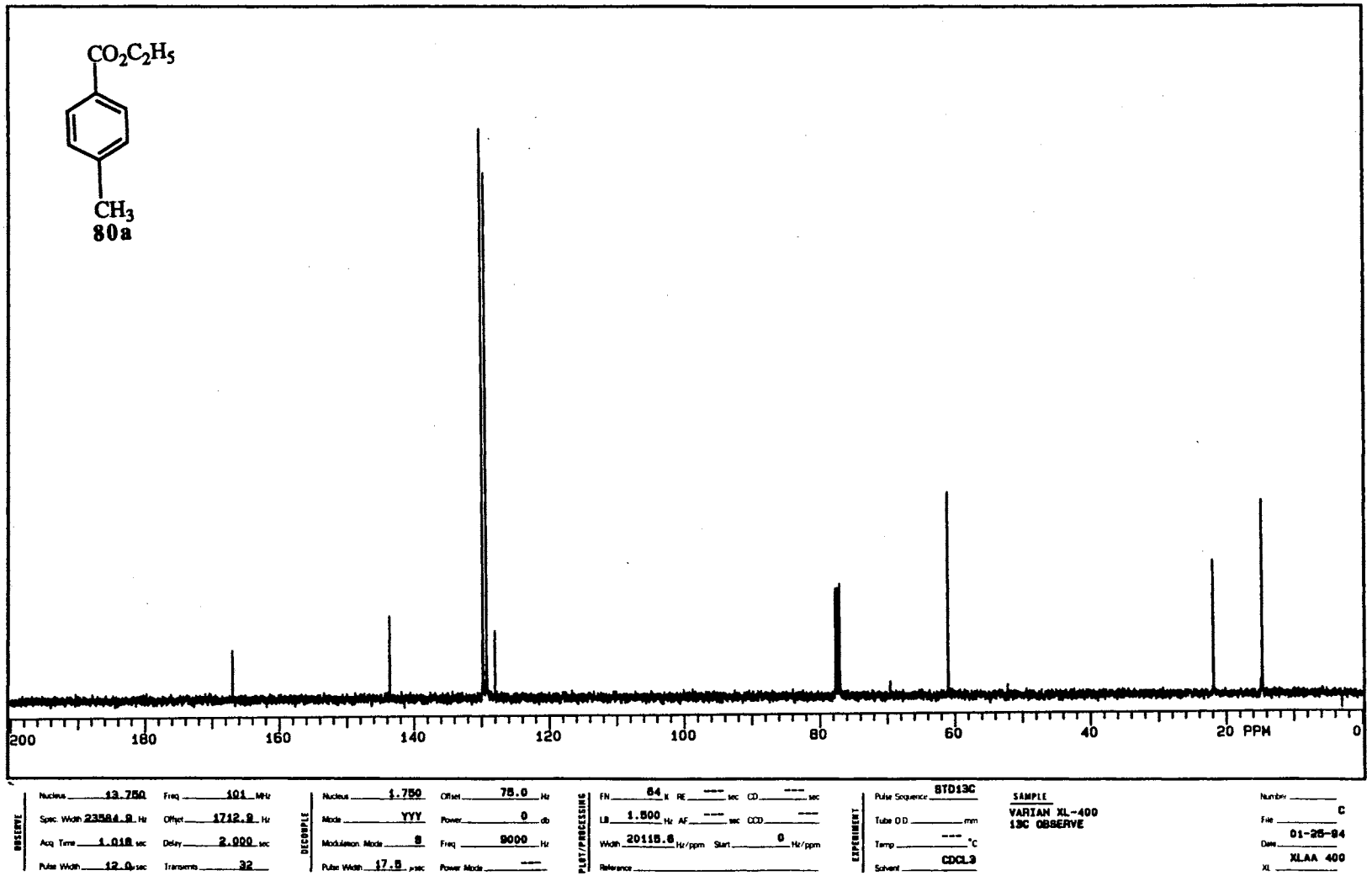
IR Spectrum of **80a**

Plate CVI



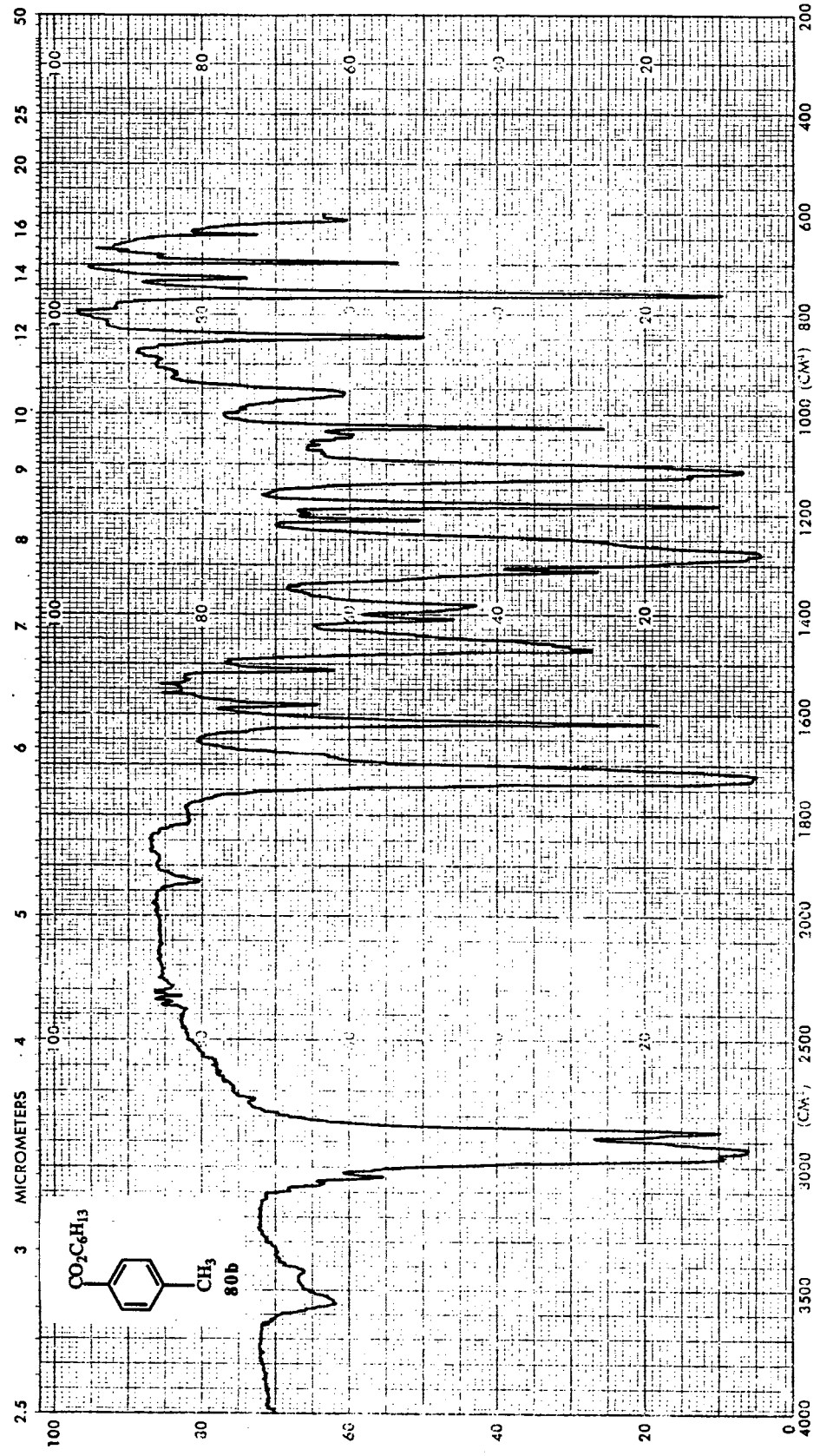
^1H NMR Spectrum of **80a**

Plate CVII



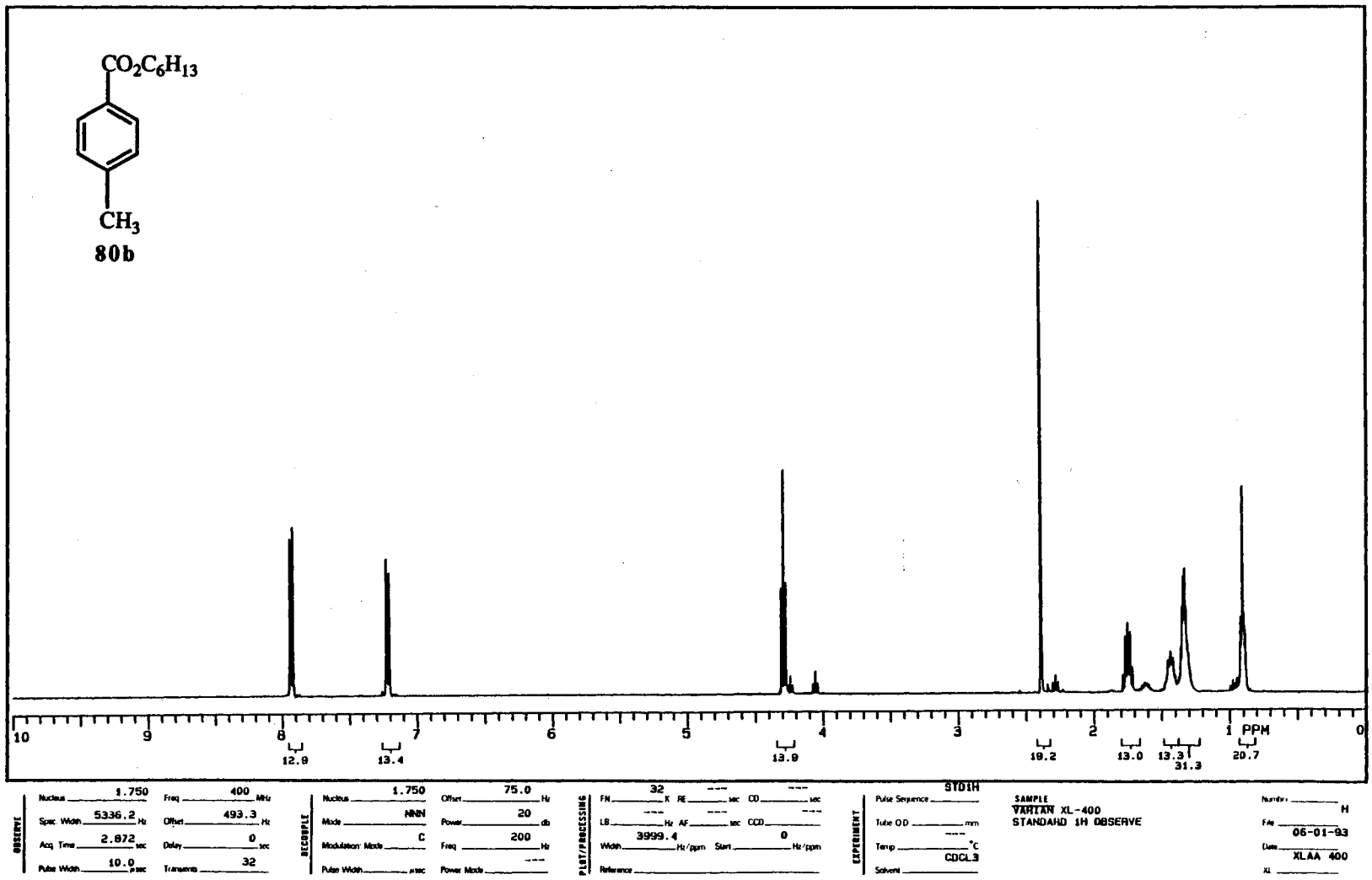
^{13}C NMR Spectrum of **80a**

Plate CVIII



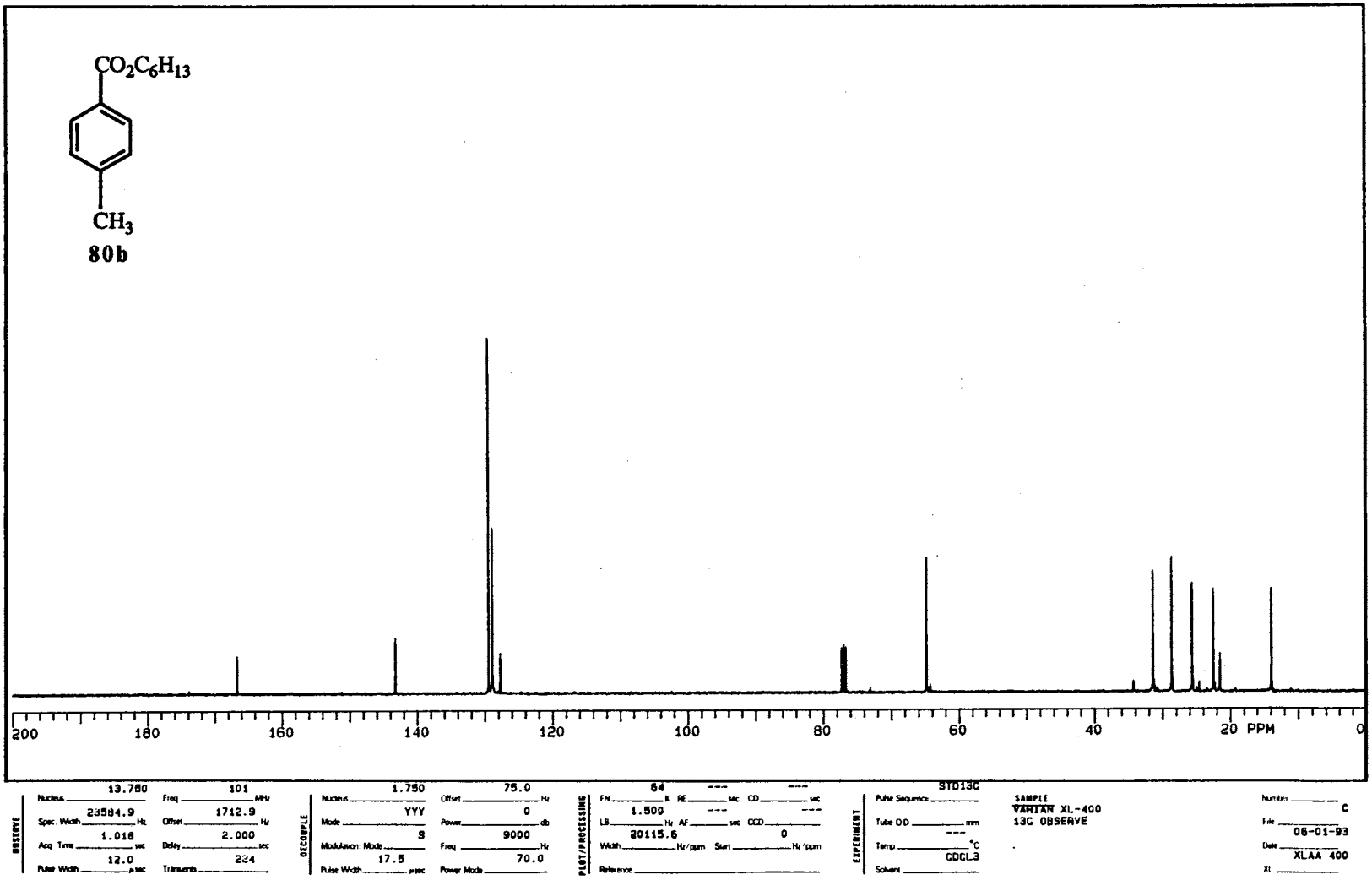
IR Spectrum of **80b**

Plate CIX



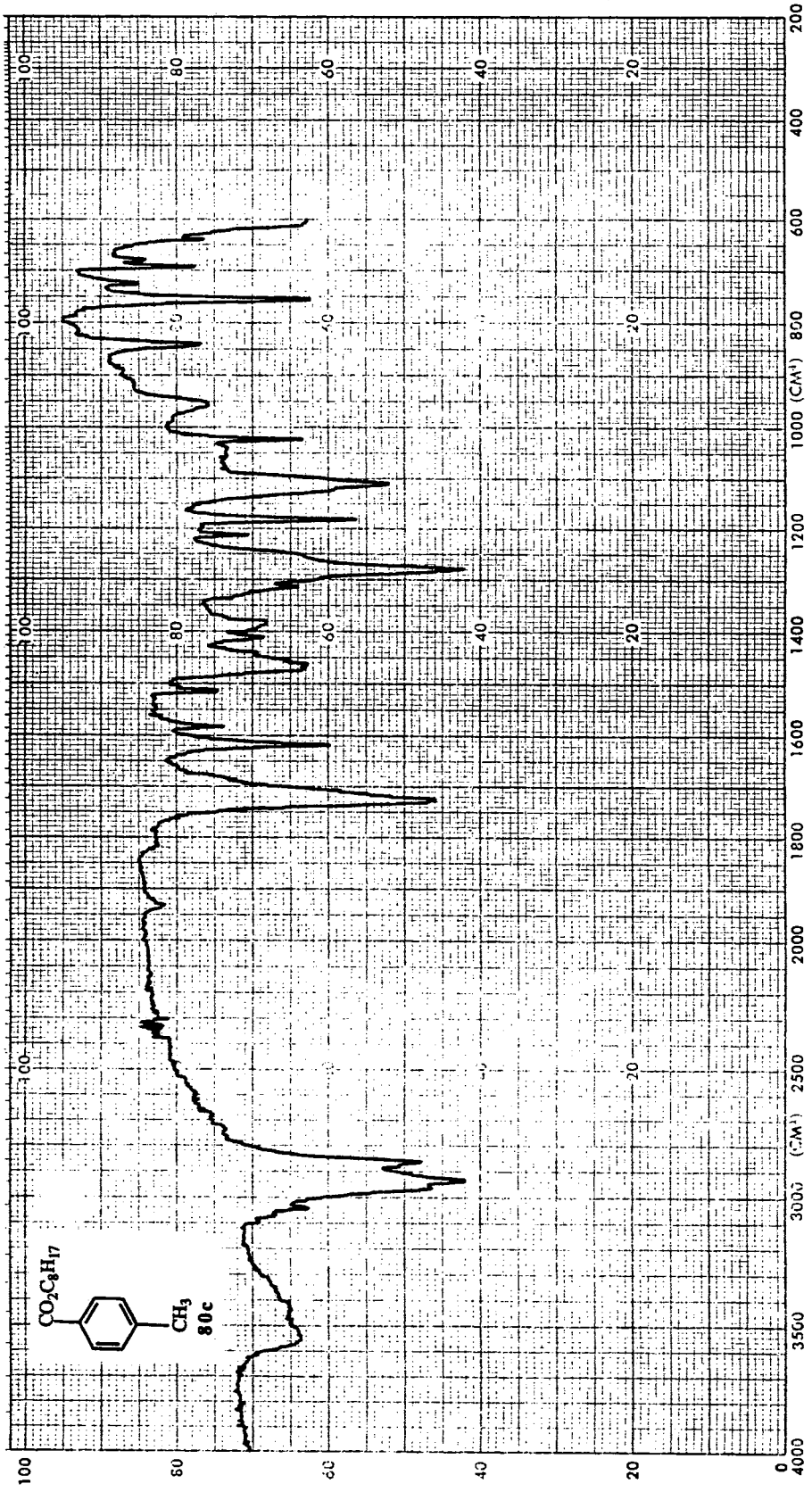
^{1}H NMR Spectrum of **80b**

Plate CX



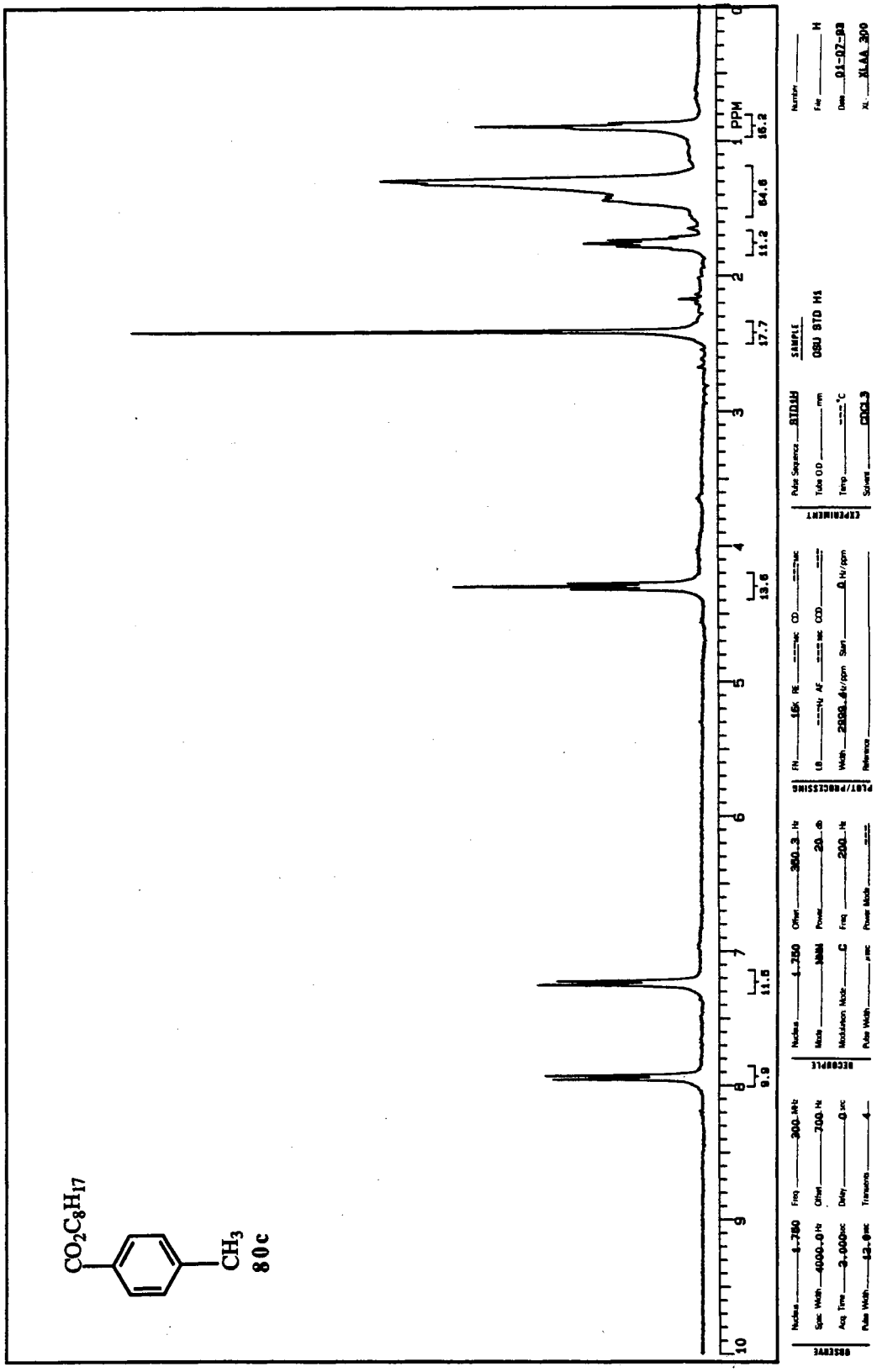
^{13}C NMR Spectrum of **80b**

Plate CXII



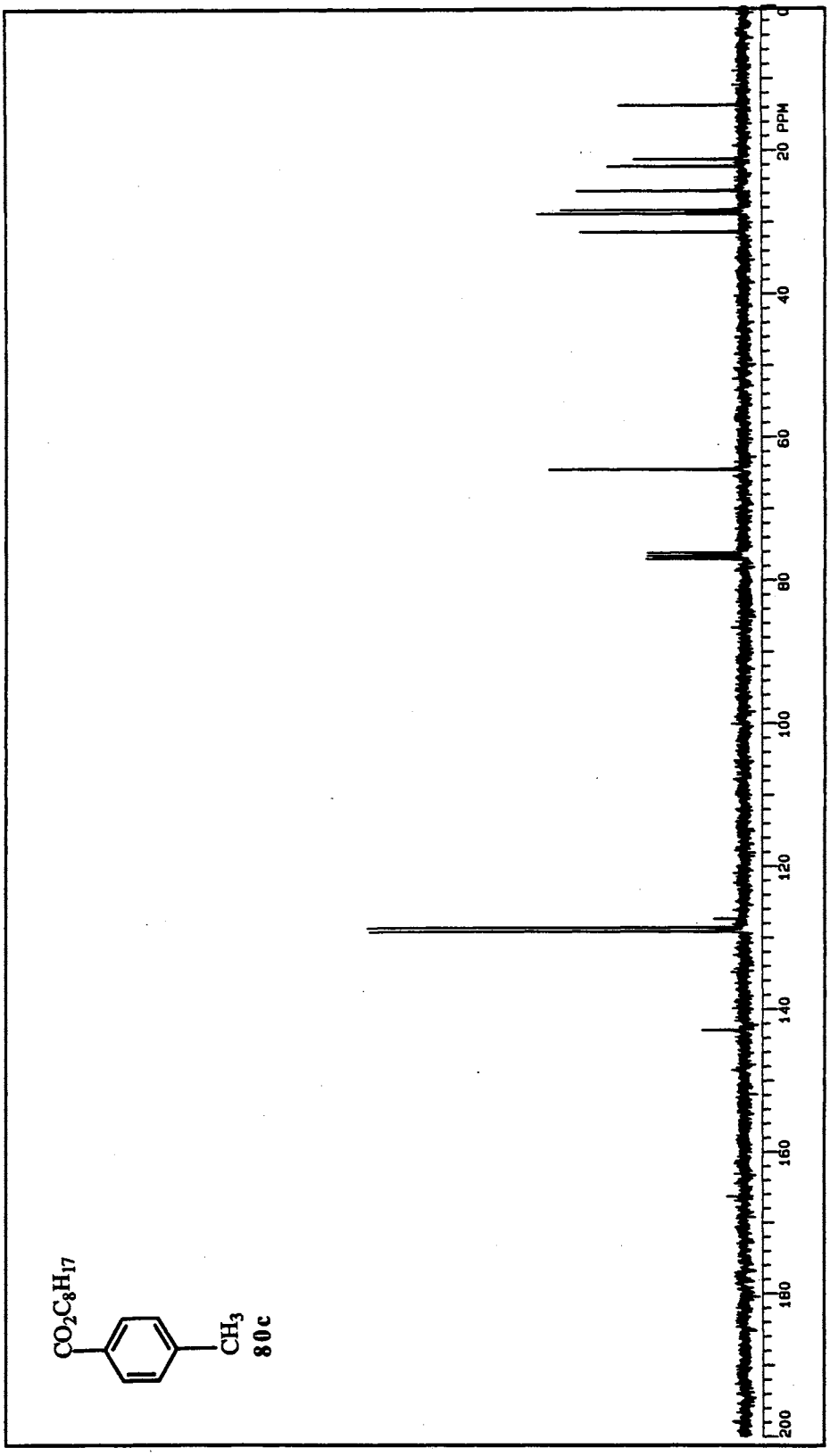
IR Spectrum of **80c**

Plate CXII



^{1}H NMR Spectrum of **80c**

Plate CXIII



^{13}C NMR Spectrum of 80c

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VITA 2

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