PART I. SYNTHESIS AND NMR ANALYSIS OF SELECTED 2-AMINO-4,5-DISUBSTITUTED THIAZOLES

PART II. NUCLEAR OVERHAUSER ENHANCEMENT MEASUREMENTS FOR CERTAIN ORGANOPHOSPHORUS COMPOUNDS. EVALUATION OF RELAXATION MECHANISMS FOR ^{31}P

By

MELVIN DALE HERD

Bachelor of Science

Central State University

Edmond, Oklahoma

1977

Submitted to the Faculty of the Graduate College
of the Oklahoma State University
in partial fulfillment of the requirements
for the Degree of
DOCTOR OF PHILOSOPHY
December, 1981

DEDICATION

I wish to dedicate the whole of this work to the memory of my mother,

DORIS ANN HERD

"She lives on, both in her deeds and our memories"

Thank you for being there.

PART I. SYNTHESIS AND NMR ANALYSIS OF SELECTED 2-AMINO-4,5-DISUBSTITUTED THIAZOLES

PART II. NUCLEAR OVERHAUSER ENHANCEMENT MEASUREMENTS FOR CERTAIN ORGANOPHOSPHORUS COMPOUNDS. EVALUATION OF RELAXATION MECHANISMS FOR ^{31}P

Thesis Approved:

K D Berlin

Thesis Adviser

Ernest M. Hodnett

Doc Purdie

Franklin R. Teady

Norman N Durham

Dean of the Graduate College

ACKNOWLEDGMENTS

I would like to thank Dr. K. Darrell Berlin for his support during the extent of this project. I would also like to extend my thanks to the members of Dr. Berlin's research group for their suggestions and and enjoyable discussions over every facet of this work.

I would like to acknowledge the financial teaching assistantships granted to me by the Chemistry Department at Oklahoma State University, and the fellowships awarded me by the Phillips Petroleum Company, Dow, and Conoco, as well as the National Institute of Health during my stay at Oklahoma State University.

I wish to thank Mr. Wayne Adkins and Mr. Stan Sigle for their help in obtaining apparatus and data needed for completion of this work. I also give a special note of thanks to Ms. Sue Heil for typing this manuscript.

Finally, I wish to thank my father, Mr. Melvin C. Herd for his love and devotion given so generously to me during these very difficult years.

TABLE OF CONTENTS

Chapter

Page

LIST OF TABLES

Table — Page

LIST OF FIGURES

Figure Page

PART II. NUCLEAR OVERHAUSER ENHANCEMENT MEASUREMENTS FOR CERTAIN ORGANOPHOSPHORUS COMPOUNDS. EVALUATION OF RELAXATION MECHANISMS FOR ^{31}P

LIST OF PLATES

INTRODUCTION

Owing to the difference in the primary objective of the two investigations recorded herein, this dissertation has been divided into two parts. Each is complete and independent of the other, containing its own Historical section, Results and Discussion, Experimental section and Bibliography.

PART I

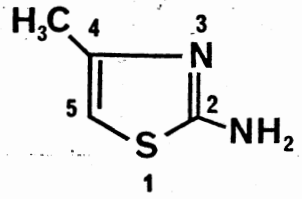
SYNTHESIS AND NMR ANALYSIS OF SELECTED 2-AMINO-4,5-DISUBSTITUTED THIAZOLES

CHAPTER I

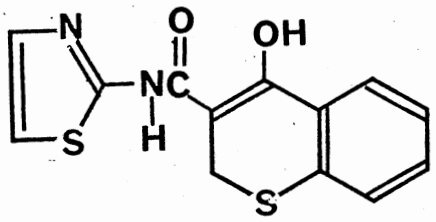
HISTORICAL

Medicinal Properties of 2-Aminothiazoles

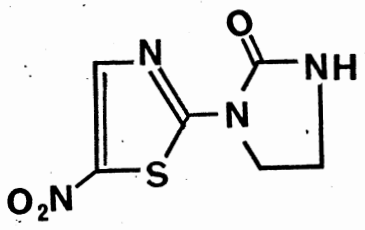
In 1887 Hantzsch and Weber published a paper describing 4-methyl-2-aminothiazole.[51] This was the first reference to a class of com-



pounds which have broad biological activity and occupy a major position in the pharmaceutical industry. Various substituted 2-aminothiazoles have been used in agriculture and medicine (primarily as antifungicidal and microbic agents). The most widely studied property has been the antiinflammatory activity of the 2-aminothiazoles. Sudoxican (1)[76,77,78,87,121] and Ambilhar (2)[2,53,75,88,100,103,118]

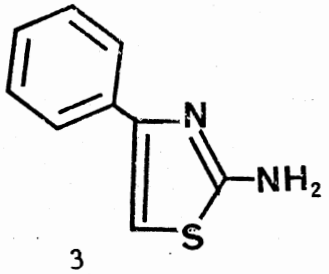


1

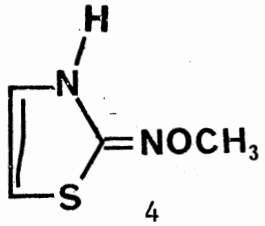


2

possess this activity and have found some clinical use. Other important medicinal properties exhibited by aminothiazoles involve some central nervous system activity by 3 and inhibition of morphine tolerance by 4.[50]

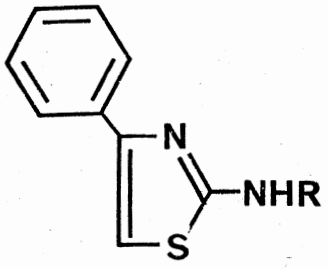


3

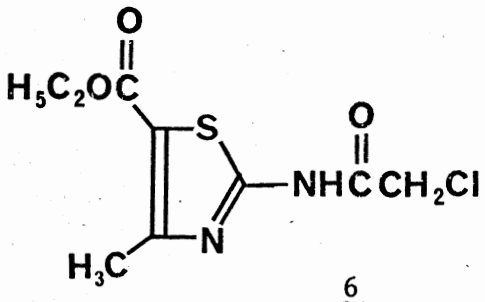


4

In spite of the wide applicability of 2-aminothiazoles in medicine, their use in cancer chemotherapy has been very limited. Thiazole 5 has



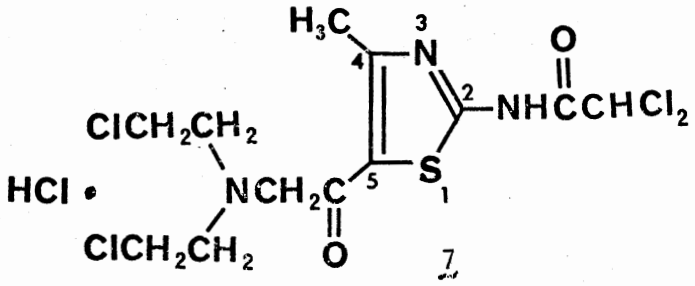
5



6

R = H, CH_3, CO_2CH_3, $CONHCH_2CHCH_2$

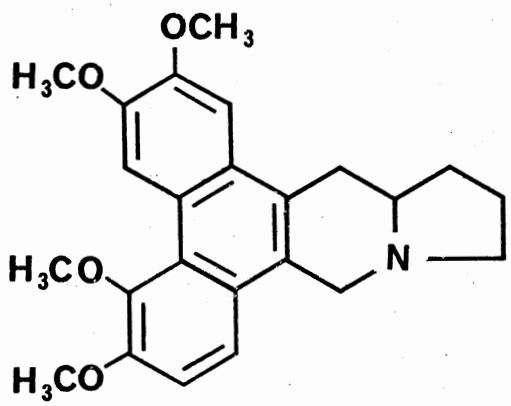
been used in antiviral chemotherapy,[38,39,40,73,74] while 6 has shown activity against Walker carcinoma.[111] Compound 7 also possesses anti-



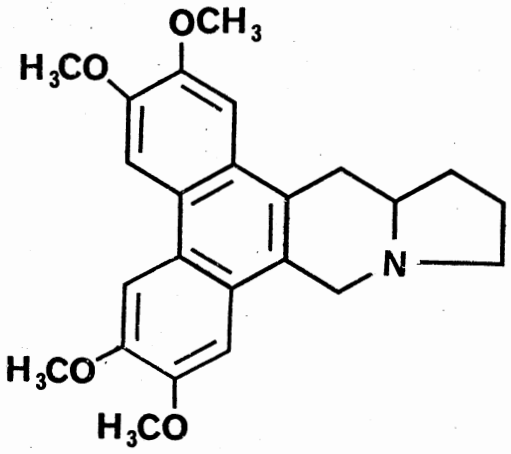
7

neoplastic activity as well as being an antimitotic.[66] From these examples, it was concluded that for antineoplastic activity to be present, an alkyl or aromatic substituent had to occupy position 4, and the thiazole ring should also bear a 2-acetoamido group.[10] It may be noted that the acetate group [or a -C(O)R group] is present at the 2-position in a wide variety of 2-aminothiazoles which possess antiviral (or antibacterial) activity.[113] Mono- or poly-substituted phenyl groups in the 4-position also exhibit the same properties.[40,74] Substituents on the phenyl groups included halogen, alkyl, methoxyl and hydroxyl.[29,68,91,112]

However, the above are not the only common structural features found in nonalkylating carcinostatic compounds! Cheng and co-workers[65,66] noted that two oxygen atoms along with a nitrogen atom formed a triangular arrangement in certain systems. Tylophora alkaloids tylocrebrine (8) and tylophorine (9) possessed activity against L-1210 leukemia



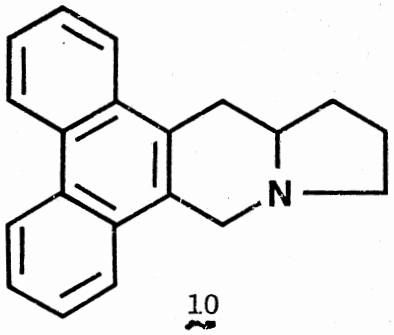
8



9

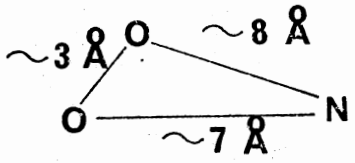
cancer in mice.[35,41] Surprisingly, the parent nucleus of these alkaloids, like phenanthro[9,10:6',7']indolizidine (10), was devoid of

activity.[42] This demonstrated that the methoxy groups were clearly needed for activity, and implied that the methoxyl groups were perhaps more important than the nitrogen atom.[23] C. C. Cheng postulated

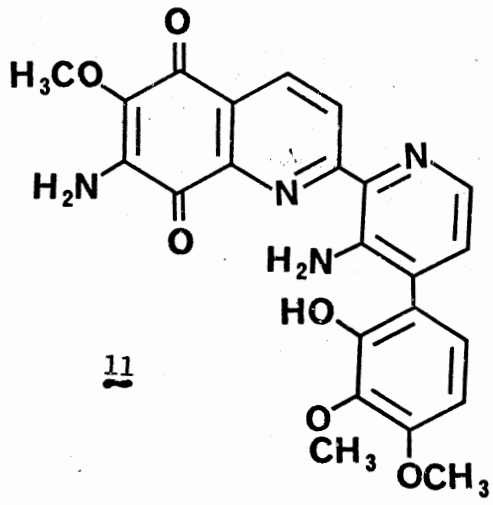


10

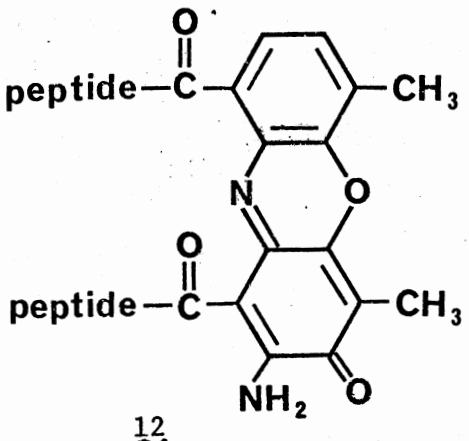
that a triangular arrangement between the two oxygen atoms and the nitrogen atom were required for activity. The illustration gives proposed optimum distances for the O-O-N triangle. In streptonigrin



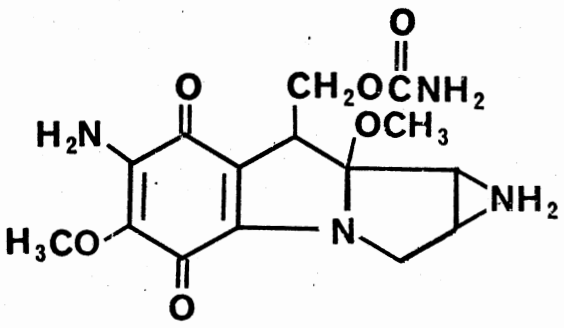
(11), actinomycin D (12) and mitomycin C (13) an aminoquinone nucleus



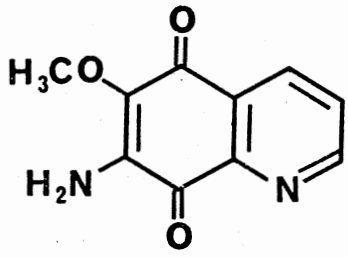
11



12

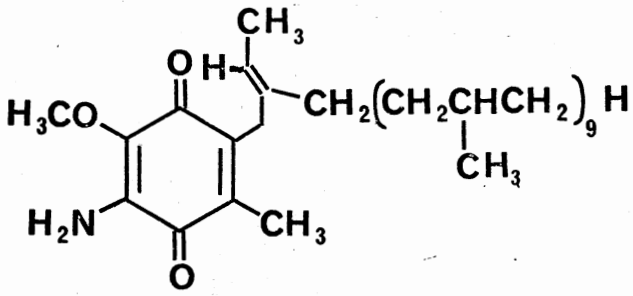


13



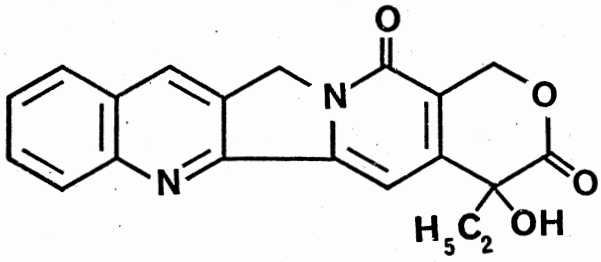
14

is present, and all three antibiotics have antitumor properties. In contrast, quinone 14 failed to retain the activity.[72,98] Rhodoquinone (15), however, did possess anticancer properties and clearly demon-



15

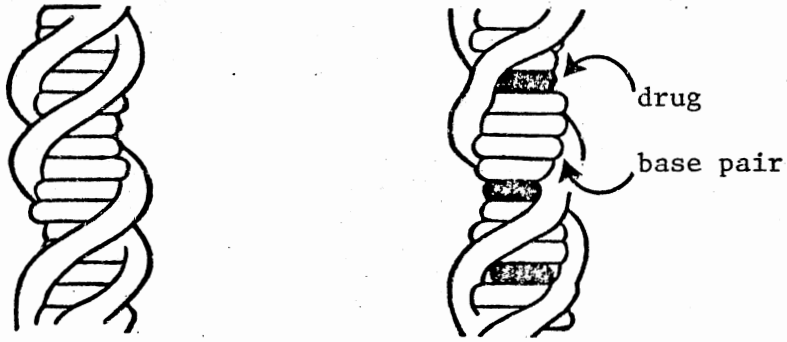
strated that a nitrogen nucleus need not always be present for activity.[21,85] The alkaloid camptothecin (16) possesses antileukemic



16

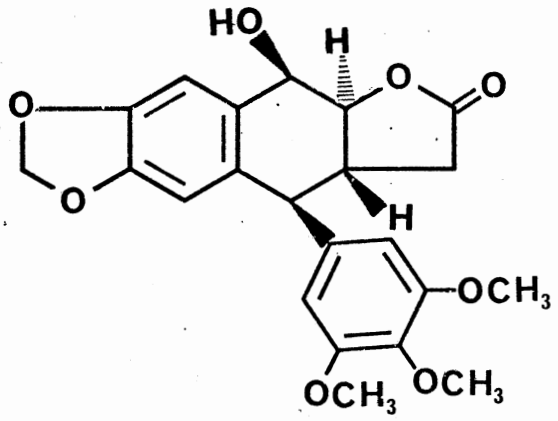
activity, and it was postulated that the hydroxyl and carbonyl groups in the lactone ring were responsible for the activity.[45,95,116] If the hydroxyl group was replaced with hydrogen, the activity was lost as was observed also if the pentacyclic moiety was modified.[25]

A molecule bearing the O-O-N arrangement was originally thought to intercalate (or "fit in") between base pairs on DNA.[20] It has since

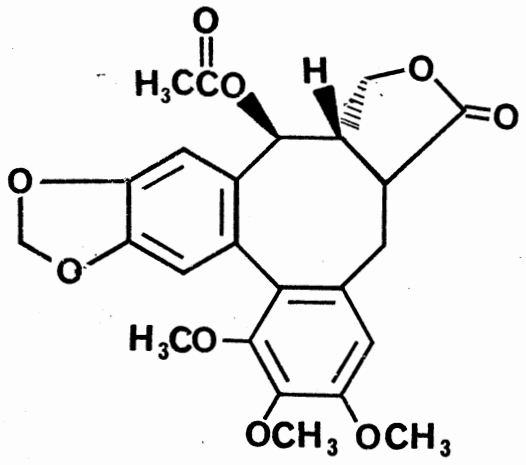


been postulated that the oxygen atoms were necessary for the inhibition of transfer RNA O-methylases[37] which were found at very high levels in a variety of neoplastic tissues.[44,109] Thus the triangulation pattern may be a common feature among those anticancer drugs which share a common transport system into leukemic cells.[1] If this is true, then a planar structure with adjacent alkoxy groups would likely show at least some activity against tumors. The literature reveals that this is indeed true. Podophyllotoxin (17) inhibits sarcoma 37,[46] while steganacin (18) is active against Steganotaenia aruliacea.[64] Demecolcine (19) is active against leukemias,[69] and the analog 20 is active against sarcoma 37[45] in mice (both compounds not found in nature) and strongly suggests that the arrangement of methoxyl groups is crucial for activity.

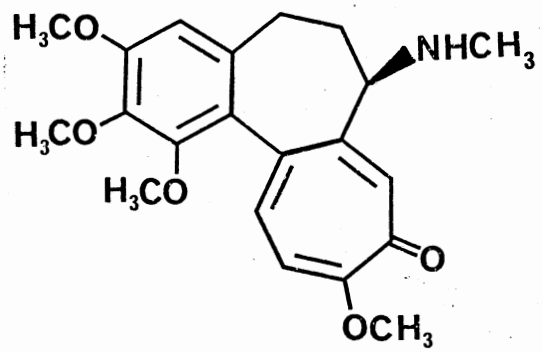
Consequently, it is conceivable that certain heterocycles properly



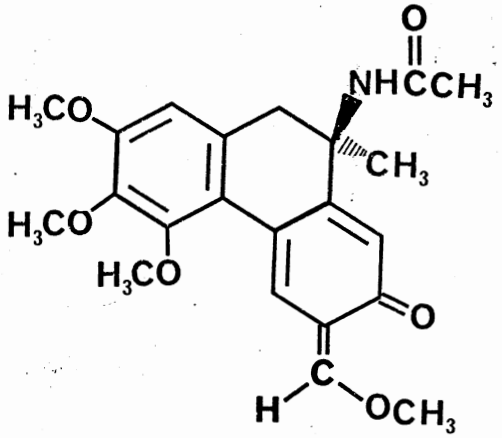
17



18

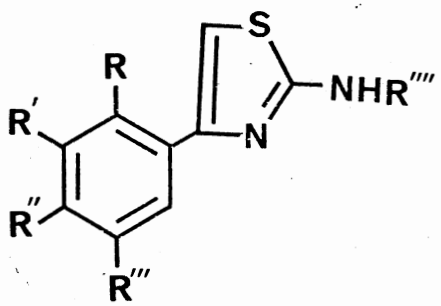


19

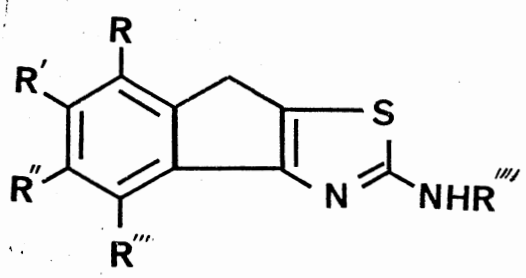


20

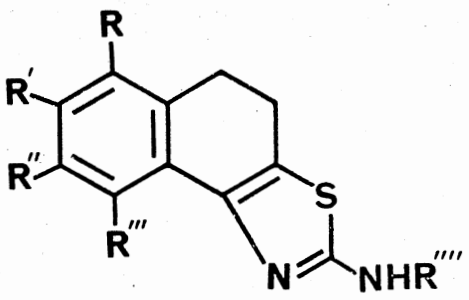
substituted, such as aminothiazole structures 21-24, might possess antitumor activity as well as the ability to penetrate cell



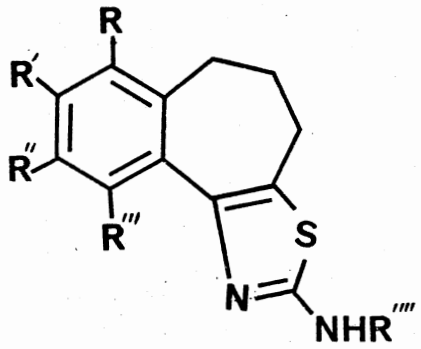
21



22



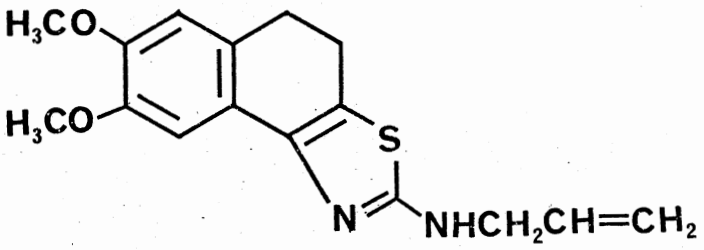
23



24

a. R = R'''' = H; R' = R'' = OCH_3
b. R = R''' = OCH_3; R' = R'' = H
c. R = H; R' = R'' = R''' = OCH_3
d. R = R' = R'' = OCH_3; R''' = H
(R'''' = H, allyl, acetate)

membranes. One member of this family was prepared in our laboratory and screened for antineoplastic activity. 2-Allylamino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-d]thiazole (25) showed good activity against $CD8F_1$ mammary tumor and colon 38 tumors.[97]



25

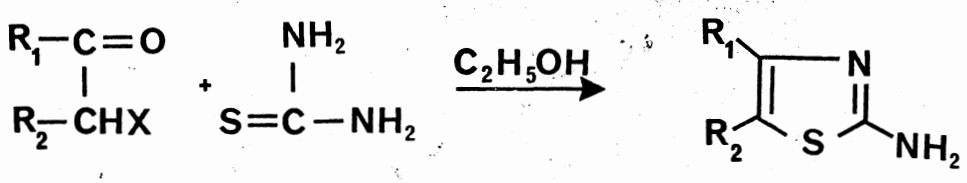
Tumor	Dose	T/C ratio
B 1b	25 mg/kg	116
CD8F	100 mg/kg	122
colon 38	100 mg/kg	196

The relative positions of the methoxyl groups on the aromatic ring could be important. Mitscher[82] noted that for certain methylenedioxyl analogs of quinolone antimicrobial agents, the oxygen atoms had to be in the 6,7-positions for the compound to show activity. When the oxygen atoms were in other positions (5,6 or 7,8), activity was lost.

In addition to the above features, the aminothiazoles proposed are somewhat similar to steroids in structure. Steroidal aminothiazoles are known[19] but no data is available on any antineoplastic activity.

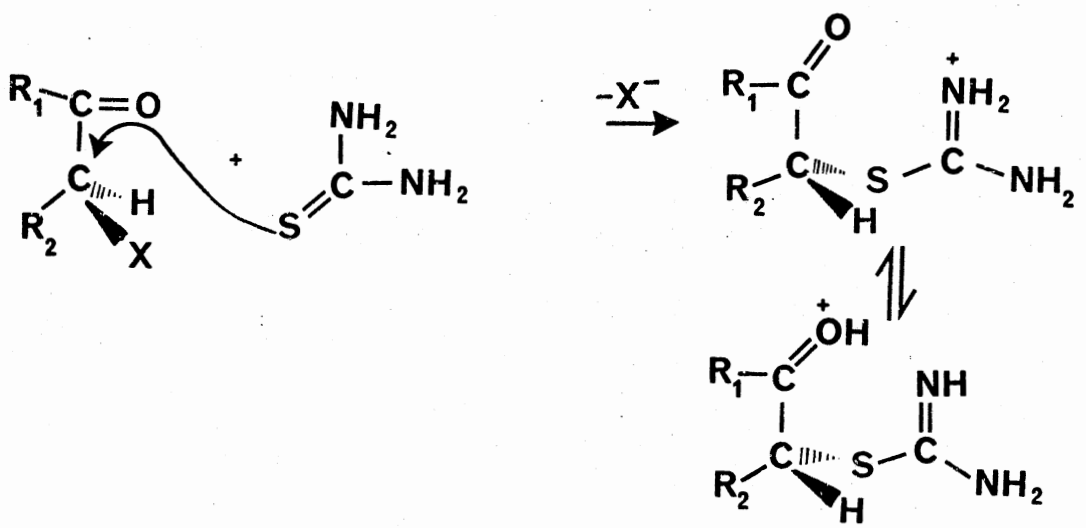
Formation of the 2-Aminothiazole Nucleus and Synthetic Route

Condensation of an α-haloketone with an equimolar amount of thiourea has been reported to generate the corresponding 2-aminothiazole.[114] The product (usually obtained as the HX salt) could

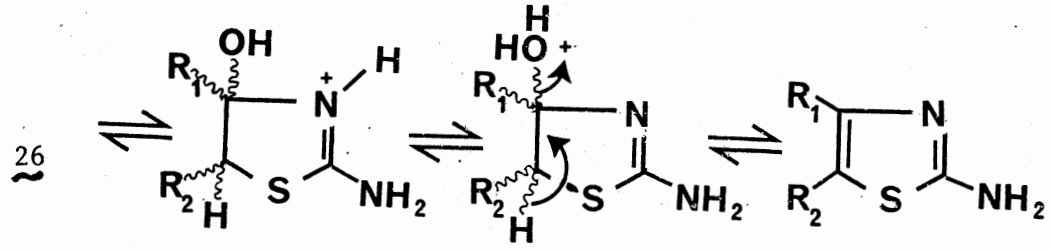


be neutralized with NaOH or NH_4OH to yield the free base. One mechanism for the formation of the thiazole involves a two-step process. Initially, a displacement of the halide ion X^- by the sulfur atom in the thiocarbonyl group on 26[7,8,90] was postulated as shown. The second step was an elimination of H_3O^+ to generate the cyclic structure;[7,8] illus-

trated below.



26



27

A different method has appeared in the literature[6,27,28,57,59,104] and involves the use of I_2, thiourea and a ketone having the general structure $ArC(O)CH_2R'$. A ketone (one equivalent) is mixed with two equivalents of thiourea and one equivalent of I_2, and the mixture is heated on a steam bath overnight to give the corresponding 2-amino-thiazole.

Reagents other than I_2 may be used; for instance, Cl_2, Br_2, $ClSO_3H$, S_2Cl_2, SO_3, 60% HNO_4, H_2SO_4 or SO_2Cl_2. The mechanism for reactions involving the above reagents are uncertain. However, the intermediates may be formamidine disulfide $[-S-C=NH_2]_2$, an

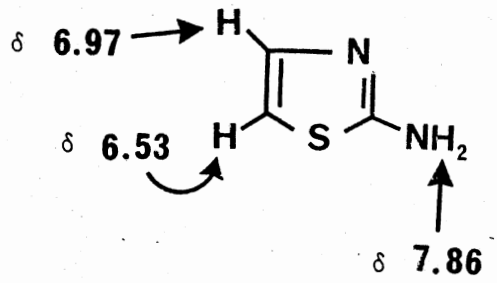
oxidized form of thiourea,[14] and not the α-haloketone (of course, it is not possible to form the α-haloketone with SO_3, HNO_4, etc.).

Iodomercuriketones[86] and the reaction of such ketones with cyanamide and sulfur[36] have also been used to synthesize 2-aminothiazoles. The yields for various 2-aminothiazoles ranged from 50-100%, depending on the starting material used. N-Monosubstituted thioureas have also been employed instead of thiourea with α-haloketones, to give N-substituted-2-aminothiazoles.[114] Substituents could be alkyl,[125] acetyl,[110] aryl,[101] naphthyl,[120] allyl,[5] heteroaryl[17] or benzyl[15] with yields approximating those found using thiourea.

Synthesis of cyclic ketones by Koo[61] and co-workers in the production of deaminocolchinic acid anhydride resulted in a general route later utilized by Mawdsley[79] to produce substituted suberones and naphthalones. Anderson and Greef modified Koo's procedure to give a simpler synthetic approach.[3] Starting with the conversion of 3,4,5-trimethoxybenzoic acid to the methyl ketone by action of methyl lithium, followed by condensation of the ketone with diethyl carbonate, it was possible to increase the yield of ethyl 3-oxo-3-(3',4',5'-trimethoxyphenyl)propionate.[3]

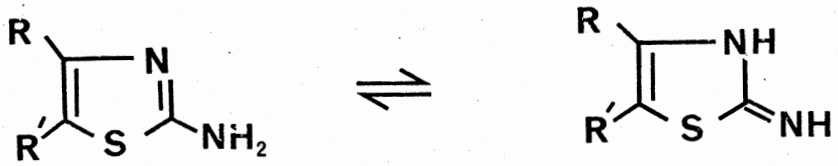
^{1}H and ^{13}C NMR Study of Conformation and Equilibria of 2-Aminothiazoles

Some ^{1}H NMR data is available on aminothiazoles. The chemical shift assignments for 2-aminothiazole have been reported as shown.[32] For



4-phenyl-2-aminothiazole (5, R=H), the signals for NH_2 appeared at δ 7.08, for H(5) at 7.0 and for the aromatic signals between δ 7.4-7.9,[106] all for a specific concentration of solute, of course.

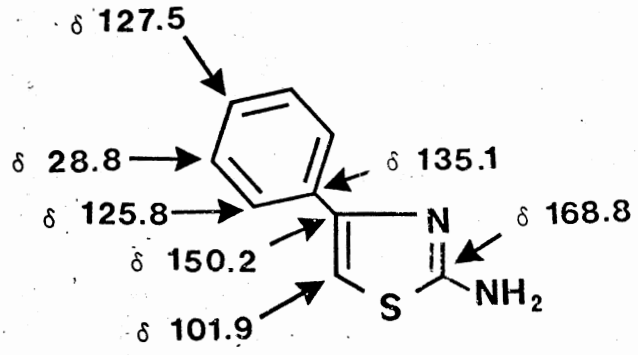
Attempts have been made to measure the ratio of tautomeric forms 28 and 29 by use of ^1H NMR analysis,[22,106] and there appears to be a large excess of 28. This observation and in view of certain inconsis-



28 R = R' = H, alkyl, aryl. 29

tencies in the experimental data[30] requires that the interpretation of ^1H NMR data for determining the (28)/(29) ratio in 28 ⇌ 29 be done with caution!

^{13}C NMR assignments for 4-phenyl-2-aminothiazole (5, R=H) have been recorded as shown.[31,32] The use of model thiazoles 28 (R = C_2H_5)



and 29 indicates from the ^{13}C NMR shifts that 28 is by far the predominate form.[31]

The use of ^{13}C NMR to determine the relative conformation (or the dihedral arrangement) between the thiazole ring and the phenyl ring has been explored.[31] Begtrop conducted studies on various substituted phenylazoles and utilized ^{13}C NMR shifts assigned to the ortho and para carbons in the phenyl ring as indicators of the dihedral angle between the two rings.[12,13] The difference in chemical shifts for the ortho verses the meta carbons in the phenyl ring was taken as a measure of the extent of interannular conjugation between the thiazole and phenyl rings. It was found that $\delta_{meta}-\delta_{ortho} \cong 3.2-3.8$ ppm or use of $\delta_{ortho} \cong 124.5-126.4$ was diagnostic if the conjugation was extensive (the two rings were nearly planar). In contrast, if $\delta_{meta}-\delta_{ortho} \cong 0-0.7$ ppm or $\delta_{ortho} \cong 128-128.5$ ppm conjugation was impeded (rings nearly perpendicular in respect to one another).[12] For 4-phenyl-2-aminothiazole, $\delta_{meta}-\delta_{ortho} = 128.8-125.8$ ppm = 3 ppm. The value of 3 ppm was suggested to indicate that there was extended interannular conjugation. X-ray diffraction data, along with extended Hückel molecular orbital calculations, also indicated that the dihedral angle[33,71] in the solid state was about 19.1° which supported the ^{13}C NMR data. A literature search did not reveal data (X-ray or ^{13}C NMR) on related, fused systems similar to 21 to 24.

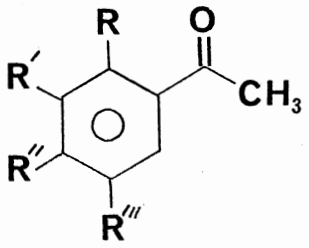
The planarity of the two rings in aryl thiazoles must be important if the molecules intercalate between the base pairs of DNA. The greater is the magnitude of the dihedral angle, the less likely the molecule would intercalate. ^{13}C NMR data could then furnish information concerning the conformation of the molecule in solution.

The nitrogen-14 NMR spectrum of thiazole[122] has been recorded. However, no data could be found for any 2-aminothiazoles. Use of ^{14}N NMR analysis to examine the tautomeric equilibrium 28 ⇌ 29 or to measure the extent of interannular conjugation between the thiazole and phenyl rings might also prove instructive. Nitrogen-15 NMR analysis on thiazole revealed a signal at 323 ppm for the ring nitrogen[70] and could well prove more useful than ^{14}N NMR analysis (despite a lower natural abundance of ^{15}N). Peak line-widths are very small for ^{15}N which allows classification of structural types with small chemical shift differences.[84] These widths are often very large for ^{14}N (frequently 1000 Hz).

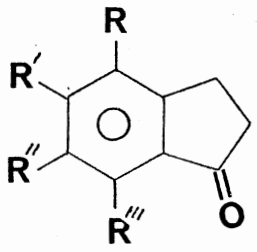
CHAPTER II

RESULTS AND DISCUSSION

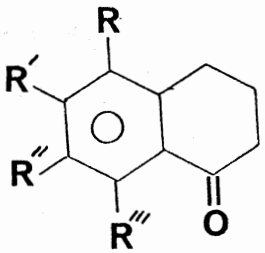
We have discovered that methoxy-substituted, aryl-substituted thiazoles can be prepared in reasonably good yields starting from the ketones shown. These ketones possess at least two methoxy groups



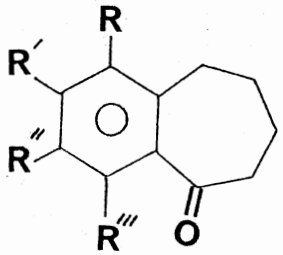
30



31



32



33

a. R = R''' = H; R' = R'' = OCH_3

b. R = R''' = OCH_3; R' = R'' = H

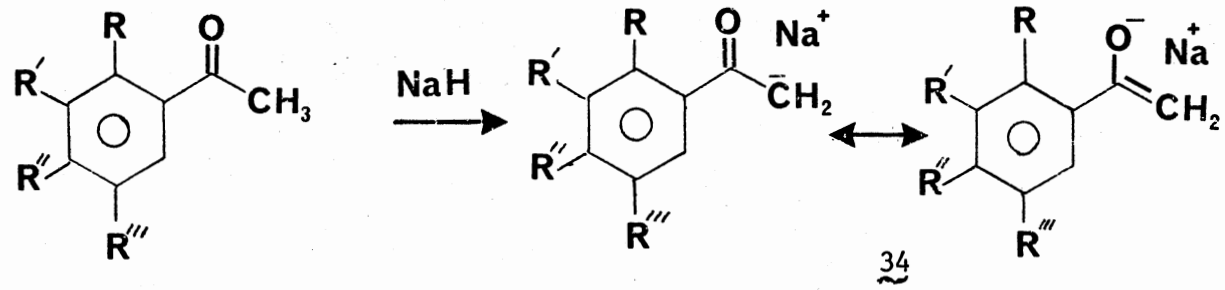
c. R = H; R' = R'' = R''' = OCH_3

d. R = R' = R'' = OCH_3; R''' = H

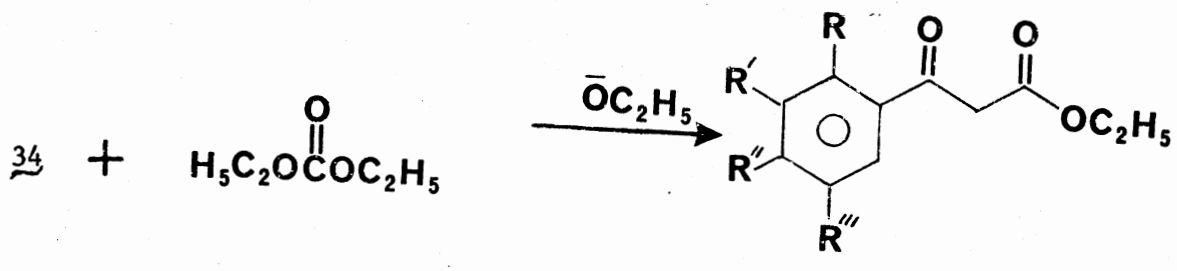
on the phenyl ring and also have a variety of rings attached to the phenyl group. Not all of the ketones were commercially available and several had to be prepared by independent routes or modifications of published procedures. Methyl ketones 30a-30d (commercially available or prepared by Friedel-Crafts acylation) were utilized as precursors for cyclic ketones 31a-31d, 32a-32d, and 33a-33d. To illustrate, acylation of phenolic ethers by acetyl chloride in the presence of 115% polyphosphoric acid (PPA) resulted in good yields of methyl phenyl ketones.

Elaborate purification procedures or unusual conditions were not required in the use of PPA (unlike the $AlCl_3/C_6H_5NO_2$ system).[55,107] Indeed, normal Friedel-Craft conditions resulted in poor yields of the acylation products 30a-30d from phenolic ethers.

Chain lengthening of the methyl ketones 30a-30d by one carbon was accomplished by use of diethyl carbonate. Abstraction of an an acidic proton by sodium hydride gave anion 34. Attack of 34 on diethyl



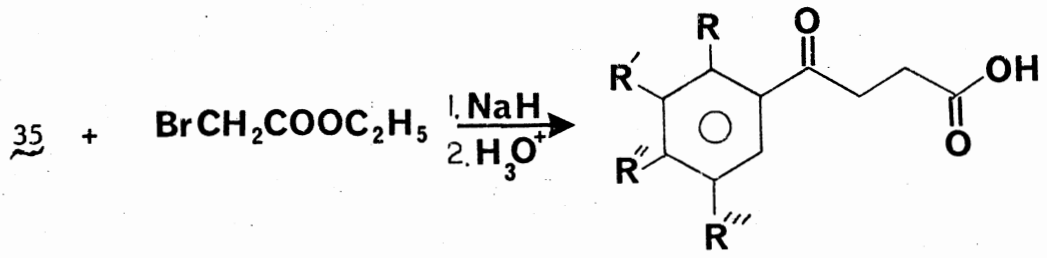
34



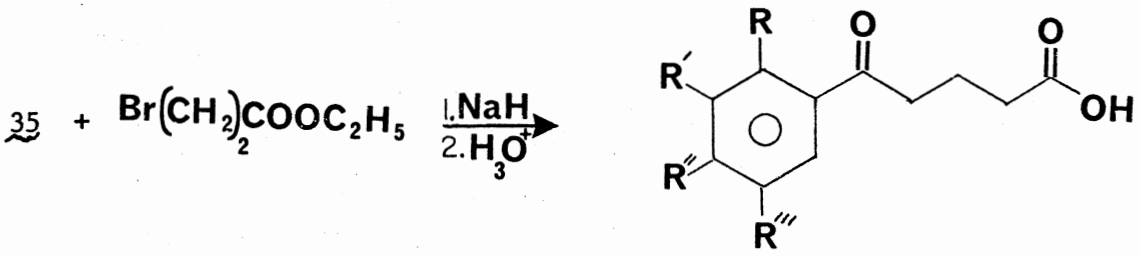
35

carbonate generated the malonate system 35 with yields in the 70-80% range. When diethyl carbonate served as both a reagent and as the solvent, slightly decreased yields (80 %) of 35 were observed. However, the experimental conditions were greatly simplified in both procedures compared to those found in the literature.[11,62]

Addition of one or two more carbons was accomplished by alkylation of 35 with ethyl bromoacetate or ethyl β-bromopropionate. However,

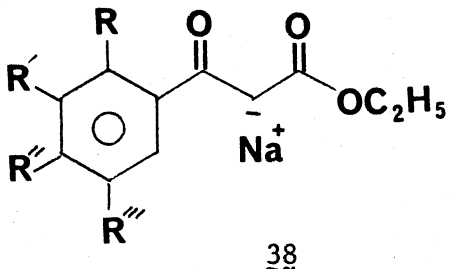


36

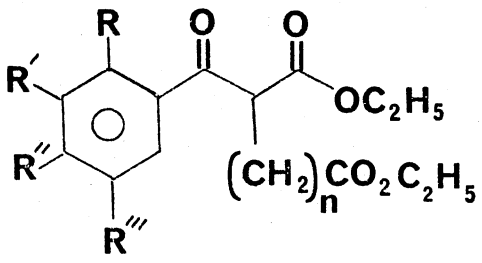


37

a change in experimental conditions from those in the literature[61,79] resulted in lower yields. Standard literature conditions (utilized for 35a and 35c involved the use of $NaOC_2H_5/HOC_2H_5$ to generate the malonate anion 36 which displaced bromide ion to give 39. Destruction of $NaOC_2H_5$ by pouring the reaction mixture onto an ice/HCl mixture was followed by extraction (ether). The dried extracts were combined and evaporated to give 37a(or 37c) as an oil. Acid hydrolysis with



38



39

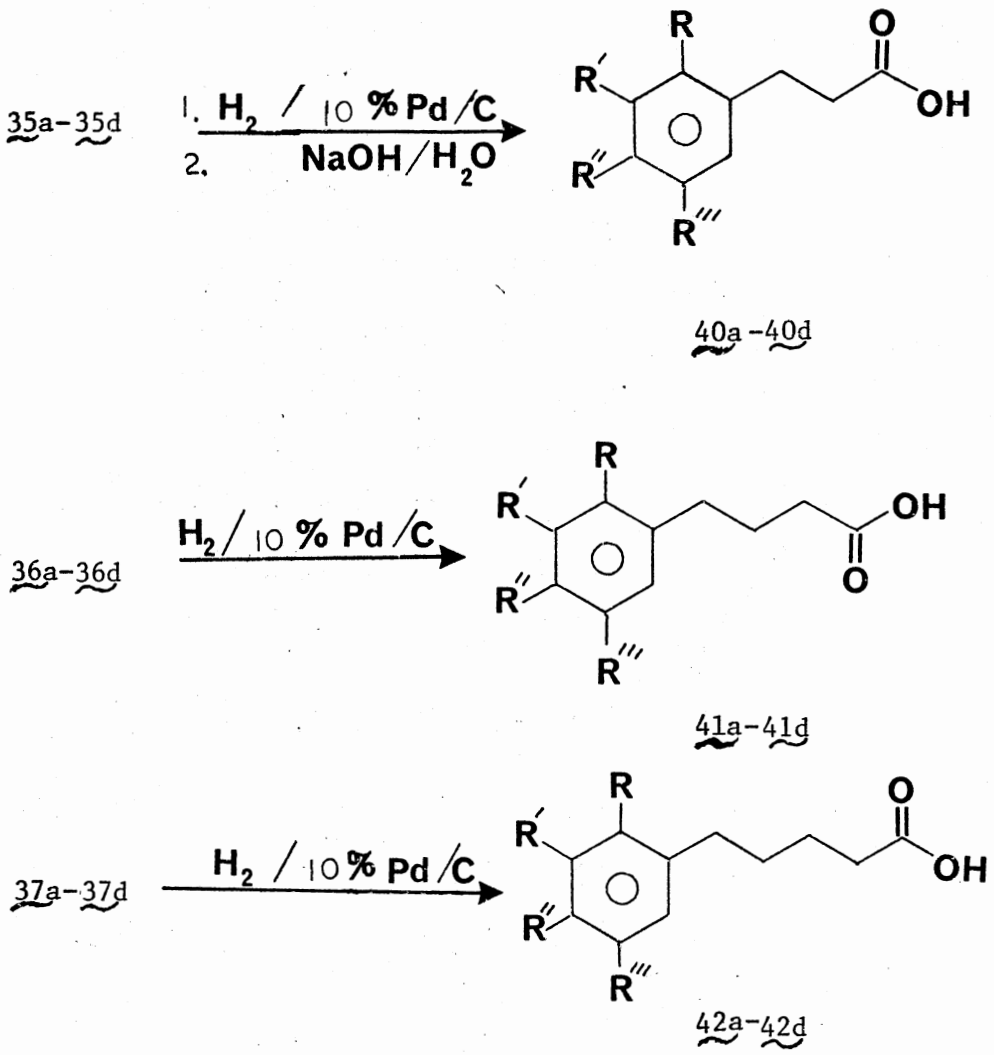
a. n = 1
b. n = 2

decarboxylation (20% H_2SO_4) led to acids 36 and 37. Since C_2H_5OH is present in the hydrolysis of 39a (or 39b), most literature procedures terminate with a saponification of the hydrolysis product to insure the destruction of any residual ester.

Simplification of the procedure (for 35b and 35d) involved the use of the NaH/THF system to produce the salt 38 (it should be noted that salt 38 often precipitated in C_2H_5OH; the use of THF circumvented this problem). Ethyl bromoacetate (or ethyl β-bromopropionate) was added in excess, and the solution was stirred at room temperature for 24 hours after which time 10% H_2SO_4 was added. Distillation of the THF from the mixture resulted in an acidic residual solution which was boiled for 24 hr. Cooling of the aqueous solution resulted in the precipitation of acid 36 (or 37).

Reduction of the carbonyl group in acids 36 and 37 and ester 35 with H_2/10% Pd/C (glacial CH_3CO_2H) proceeded well (90%). Saponification of reduced esters 35a-35d led to hydrocinnamic acids 40a-40d. Cyclization of these acids 40-42 with 115% PPA gave ketones 31-33.

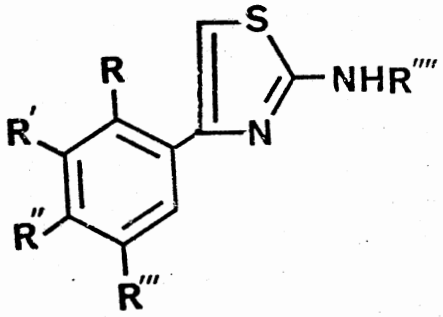
The synthesis of thiazoles 21-24 required specific bromoketones of 30a-33a-33d. Bromination was accomplished by a modification of



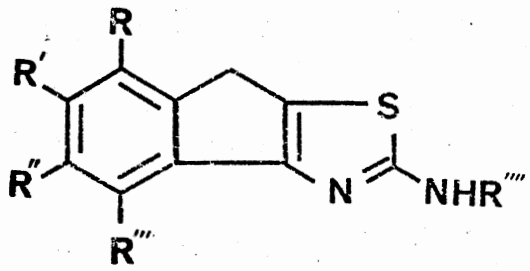
the procedure of Hashem[47] or by the procedure of Gilman and Blatt.[37] Modification of Hashem's procedure involved adding a trace of CH_3CO_2H to a solution of the requisite ketone in C_2H_5OH (95%):$HCCl_3$ (1:1) before adding the Br_2 in $HCCl_3$ at room temperature. Proper adjustment of solvent ratios was found to cause precipitation of the bromoketone in extremely high purity. Although bromination of ketones with $CuBr_2$ has been recorded,[16,54,58] the instability of our bromoketone 31a under the reaction conditions resulted in reduced yields of an impure product. However, it was also found that attempts at purification of

any of the bromoketones produced impurities difficult to remove. Therefore the bromoketones were used in crude form.

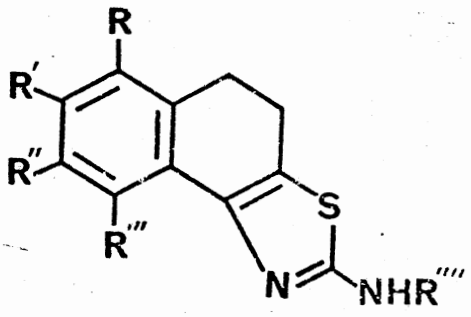
Thiourea reacted with the bromoketones to give thiazoles 21-24. The yields of thiazoles 21-24 were moderate (40-60%). The literature[10]



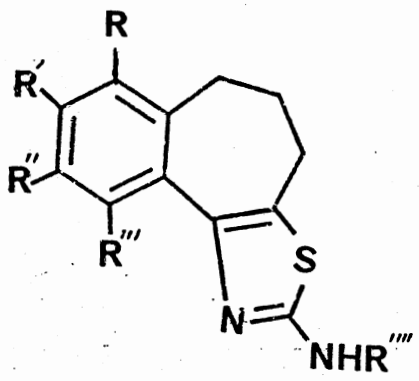
21



22



23



24

a. $R = R''' = H$; $R' = R'' = OCH_3$

b. $R = R''' = OCH_3$; $R' = R'' = H$

c. $R = H$; $R' = R'' = R''' = OCH_3$

d. $R = R' = R'' = OCH_3$; $R''' = H$

(R'''' = H, allyl, acetate)

has frequently indicated that 2-aminothiazoles are produced in excellent yields (80-90%) in a reasonably pure form. However, since HBr is a byproduct during the formation of thiazoles 21-24, cleavage of methoxy groups can be a competitive side reaction. In several cases (notably the 3,4,5-trimethoxy and 2,5-dimethoxy systems 22b and 23c) the products formed were brown-black and proved hard to purify. Possibly, steric crowding around the methoxy groups restricted C-O bond rotation and protonation was facilitated in the initial cleavage of the ether linkage.[48]

Ketones 32c and 33c was brominated under our standardized conditions. That bromination had occurred was deduced from examination of the ^{1}H NMR spectrum of crude bromoketones from 32b-32c and 33c. A triplet for the β-methylene protons was absent in the spectrum of the crude bromoketones, and the signal for the lone α-proton (geminal C-Br bond) was shifted downfield.

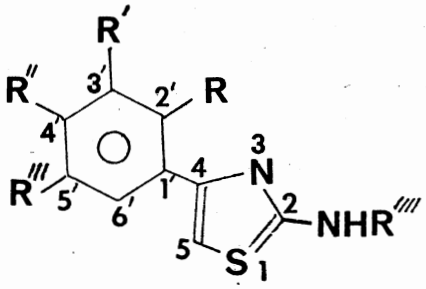
Unfortunately, all attempts to convert the bromoketone from 32b-32c and 33c gave very dark materials. Chromatography of the product on neutral alumina (with C_6H_6, C_6H_6-ether, H_2CCl_2) gave only highly colored solids (pasty like). All attempts at recrystallization did not provide pure materials.

Acylation of 21-24 (R"" = H) with acetic anhydride/gl. CH_3CO_2H (RT, overnight with stirring) gave moderate yields (50-60%) of the corresponding acetate 21-24 (R"" = Ac).[9] The allyl-substituted derivatives of 21-24 were obtained (60-80%) by treatment of the bromoketones of 30-33 with allylthiourea. Either recrystallization or sublimination provided pure 21-24 (R"" = allyl) members.

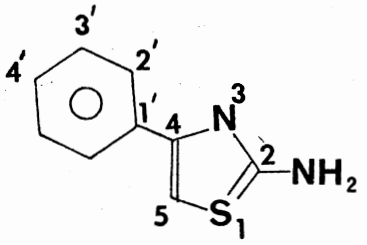
In summary, a literature survey did not reveal any member of

families 21-24. Thus, these first examples open an area in which the biological activity of such fused thiazoles can be examined.

Table I displays ^{1}H NMR data for acyclic 2-aminothiazoles 21a-22c (R"" = H, Ac, allyl). In thiazole systems 21a-21c (R"" = H) the assignment of the NH_2 and H(5) resonances was made by comparison with the ^{1}H NMR signals for the NH_2 protons in 2-amino-4-phenylthiazole (5).[106] In the latter, the resonances for the protons in NH_2 occur at δ 4.7 (highly temperature and concentration dependent) while the H(5) chemical shifts can be found at δ 6.64. In the 2-aminothiazoles 21a-21c (R"" = H), the proton signals for NH_2 fall in the ranges of δ 5.00-5.5 while the H(5) resonances occur at about δ 6.5-6.83; the acetate and allyl derivatives of 21a-21c



21



5 (R = H)

a. R = R"" = H; R' = R" = OCH_3
b. R = R"" = OCH_3; R' = R" = H
c. R = H; R' = R" = R"" = OCH_3
d. R = R' = R" = OCH_3; R"" = H
(R"" = H, allyl, acetate)

did not display a signal for the NH proton. The H(5) resonances were found downfield in each of the acetate derivatives as compared to 5.

TABLE I

PROTON CHEMICAL SHIFTS FOR THIAZOLE 21a-21c

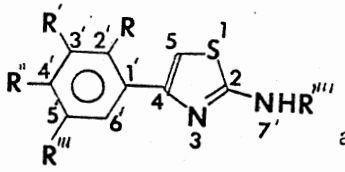
Compound[a,b]	H(5)	H(2')	H(3')	H(4')	H(5')	H(6')	H(7')[c]	OCH_3	H(8')	H(9')	H(10')
21a, R''''=H	6.58	7.29	----	----	6.85	7.29	5.07	3.90;3.94	----	----	----
21b, R''''=H	6.83	----	7.64	6.81	----	6.80	5.24	3.80;3.85	----	----	----
21c, R''''=H	6.64	7.00	----	----	----	7.00	5.50	3.94(bs)	----	----	----
21a, R''''=Ac	7.02	7.34	----	----	6.90	7.30	d	3.91(bs)	----	1.86	----
21b, R''''=Ac	6.89	----	7.60	6.85	----	7.59	d	3.74;3.88	----	1.85	----
21c, R''''=Ac	6.98	7.22	----	----	----	7.22	d	3.80;3.92	----	1.74	----
21c, R''''=allyl	6.56	7.38	----	----	7.26	6.86	d	3.89;3.94	3.94	5.94	5.20 (cis), 5.40 (trans)
21b, R''''=allyl	7.06	----	7.06	7.34	----	7.34	d	3.80;3.85	4.14	5.99	5.20 cis), 5.48 (trans)
21c, R''''=allyl	7.02	6.76	----	----	----	6.76	d	3.82;3.86	3.71	5.75	5.06 (cis), 5.22 (trans)

a. All ^1H NMR shifts are in δ values relative to TMS.

b. Numbering for allyl and acetate begins with 8' (NH is 7').

c. Dependent upon temperature and concentration.

d. Not observed.

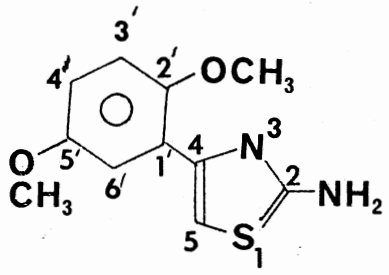


acetate = $C^{8'}(O)C^{9'}H_3$

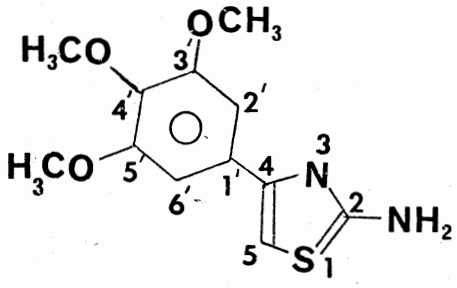
allyl = $CH_2^{8'}CH^{9'}=CH_2^{10'}$

This could be due to the electron-withdrawing effect of the C=O group which could deshield H(5).[9] No similar trend for H(5) was detected in the allyl substituted compounds (21a-21e; R"" = allyl).

The protons of the methoxy groups were found at about δ 3.70-3.95. Unfortunately, no definitive assignments were possible for the CH_3O protons. However, in the case of thiazoles 21c (R"" = H, Ac, allyl) it was found that protons in the most hindered CH_3O-group experienced an upfield shift. In two cases (the 2,5-dimethoxy and 3,4,5-trimethoxy derivatives 21a and 21c), the upfield resonances were assigned to



21a (R"" = H)

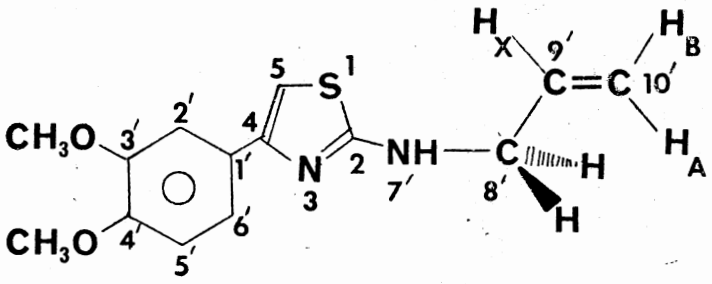


21c

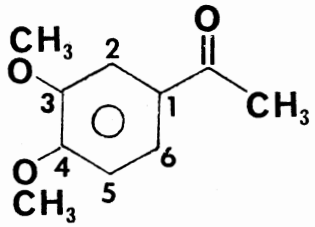
protons in the 2-methoxy and 4-methoxy groups, respectively.

Assignment of proton shifts in the N-substituted compounds (the acetates 21a-21c and allyl compounds 21a-21c) was made by comparison with appropriate analogs [$NH_2CO_2CH_3$ and $NH_2CH_2CH{=}CH_2$ in each instance].[81] The N-allyl protons displayed a characteristic NMR pattern of an ABX system degenerating to an ABC pattern. The arrangement observed was a broad multiplet at about δ 5.9 to be a triplet. However, as the coupling constants were found to be unequal on each side of the triplet, it was deduced that the real pattern was a doublet of doublets [from the cis (H_X and H_B) and trans (H_X and H_A) protons in the ABX systems $H_X{-}C{=}C{<}^{H_B}_{H_A}$] which had overlapped. The broad multiplet was

assigned to the H_X proton split by both the vinylic protons H_A and H_B as well as by H(8') (protons of the CH_2 in the allyl group). No definitive signals for H(8') were observed, and it was assumed that these resonances were obscured by the proton signals in the CH_3O group. This was confirmed via integration of the signal pattern at δ 3.7-3.9. Irradiation of the signal (proton decoupling of the H(9') signal from the H(8') signal) at δ 3.94 (for 21a, R"" = allyl) resulted in the disappearance of the multiplet at δ 5.94 and appearance of a doublet of doublets. This is exactly the pattern to be expected for an ABX system in which H(9') was assigned the H_X signal.



21a (R"" = allyl)

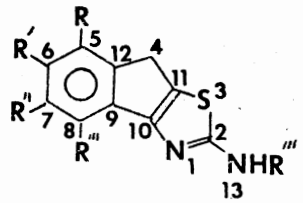


30a

Assignments for aromatic protons in the thiazoles were based on comparisons with spectra of the parent ketones. The spectrum of thiazole 21a (R"" = H) revealed two doublets the downfield one of which was overlapped by a singlet. In 3,4-dimethoxyacetophenone (30a), a similar pattern was observed. The upfield doublet was assigned to H(5') (δ 6.85), and the overlapped singlet and doublet were assigned to the H(2') and H(6') protons (δ 7.29), respectively, in 21a (R"" = H). Thiazoles 21b and 21c (R"" = H) were assigned in an analogous manner and the data can be found in Table I.

TABLE II

PROTON CHEMICAL SHIFTS FOR THIAZOLES 22A, 22c and 22d



acetate= $^{14}CH_3\overset{15}{C}(O)$

allyl= $^{14}CH_2\overset{15}{C}H=\overset{16}{C}H_2$

Compound[a,b]	H(4)	H(5)	H(8)	H(13)[c]	H(14)	H(15)	H(16)	OCH_3
22a, R''''=H	3.60	7.02	7.14	d	----	----	----------	3.78;3.82
22c, R''''=H	3.62	6.86	----	5.90	----	----	----------	3.88;3.92;4.04
22a, R''''=Ac	3.74	7.08	7.22	d	----	2.17	----------	3.79;3.82
22c, R''''=Ac	3.78	6.92	----	d	----	2.26	----------	3.90;3.94
22a, R''''=allyl	3.59	7.02	7.16	d	3.99	5.90	5.29 (cis), 5.42 (trans)	3.88;3.91
22c, R''''=allyl	3.58	6.80	----	d	3.96	5.86	5.12 (cis), 5.36 (trans)	3.82;3.86;4.02
22d, R''''=allyl	3.59	----	6.90	d	3.84	5.84	5.12 (cis), 5.36 (trans)	3.80;3.89

a. All ^1H NMR shifts are in δ values relative to TMS.

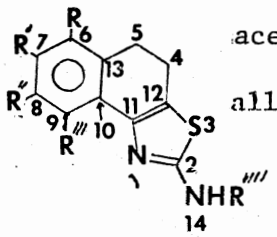
b. Numbering for allyl and acetate begins with 14 (NH is 13).

c. Dependent upon temperature and concentration.

d. Not observed.

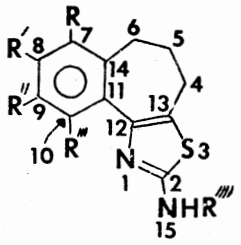
TABLE III

PROTON CHEMICAL SHIFTS FOR THIAZOLES 23 and 24



acetate= $^{15}CH_3\overset{16}{C}(O)$

allyl= $^{15}CH_2\overset{16}{C}H=\overset{17}{C}H_2$



acetate= $^{16}CH_3\overset{17}{C}(O)$

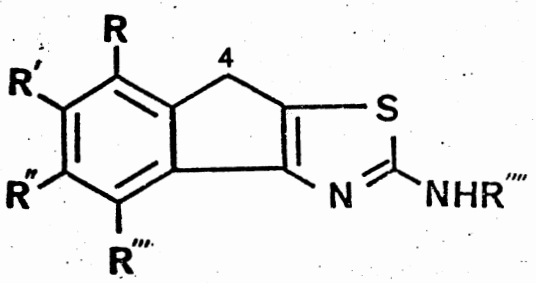
allyl= $^{16}CH_2\overset{17}{C}H=\overset{18}{C}H_2$

Compound[a,b]	H(4)	H(5)	H(6)	H(7)	H(8)	H(9)	H(10)	H(14)	H(15)	H(16)	H(17)	H(18)	OCH_3
23d, $R'''=H$	2.79	2.79	----	----	----	6.80	-----	b	----	----	----	----	3.77; 3.86
23d, $R'''=Ac$	2.98	2.98	----	----	----	7.28	-----	b	----	2.01	----	----	3.90; 3.96
23a, $R'''=allyl$	2.64	2.64	6.58	----	----	7.80	-----	b	3.70	5.46	4.92 5.14	----	3.50; 3.58
23c, $R'''=allyl$	2.71	2.85	6.75	----	----	----	-----	b	3.89	5.91	5.15 5.41	----	3.89; 3.95
23d, $R'''=allyl$	2.70	2.88	----	----	----	7.24	-----	b	3.98	5.96	5.14 5.36	----	3.80; 3.86; 3.91
24a, $R'''=allyl$	2.10	2.80	2.80	6.66	----	----	7.38	----	b	3.96	5.82	5.38 5.50	3.88; 4.06

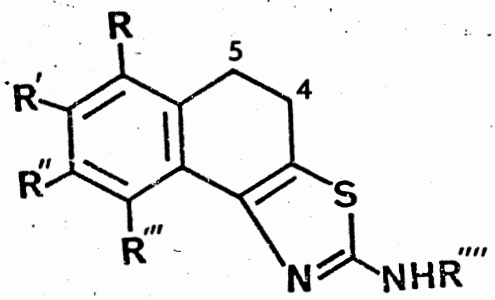
a. All ^1H NMR shifts in δ values relative to TMS.

b. Not observed.

The proton chemical shifts for systems 22, 23 and 24 are given in Tables II and III. In almost every case, the signal patterns were found to be either similar to the acyclic system 21 or simplified when compared to those found in analogous thiazoles 21. The differences in the spectra of 21, 22, 23 and 24 arose from the bridging CH_2 groups. For example, in members of 22 the H(4) resonances occur as singlets at

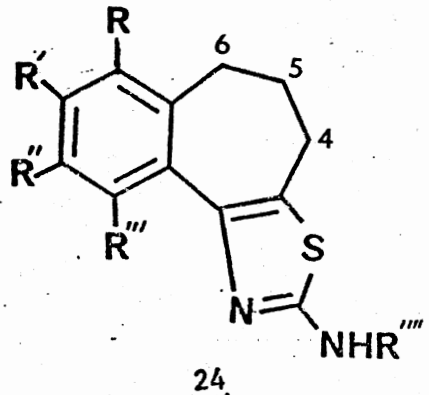


22



23

about δ 3.59-3.78 while in thiazoles 24 the H(4) and H(5) protons result in an AA'BB' pattern at about δ 2.80. Thiazole 24 displayed a broad multiplet at δ 2.80 for the protons in the three CH_2 groups.

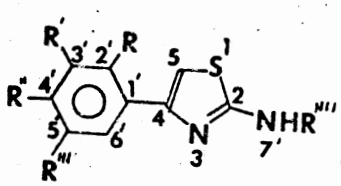


24

Aromatic proton signals were singlets in all systems, and assignments were based on comparison of shifts with those of similar protons in the acyclic systems.

TABLE IV

CARBON CHEMICAL SHIFTS OF THIAZOLES 21a-21c



acetate = $C(O)CH_3$

allyl = $CH_2CH=CH_2$

Carbon[a,b]	21a	21b	21c	21a[c]	21b[c]	21c[c]	21a	21b	21c
		R''''=H			R''''=Ac			R''''=allyl	
C(2)	166.9	165.5	167.2	168.2	168.3	168.3	169.5	168.6	168.9
C(4)	150.8	151.0	150.9	150.1	150.7	150.4	150.8	150.3	150.8
C(5)	101.1	107.7	102.0	106.1	106.4	106.4	99.0	105.1	104.8
C(1')	127.8	123.9	130.3	127.3	123.1	131.0	128.0	136.2	131.7
C(2')	109.3	153.4	109.6	109.3	156.1	107.8	109.4	152.9	108.8
C(3')	148.6	113.8	153.1	148.6	113.8	146.8	148.6	113.7	148.7
C(4')	148.5	114.6	153.1	148.8	114.0	152.0	148.4	114.0	152.1
C(5')	111.6	146.4	153.1	110.0	152.8	142.2	110.9	152.2	142.5
C(6')	118.2	117.0	137.8	118.1	144.2	156.7	118.3	117.6	110.2
C(8')	-----	-----	-----	d	183.9	d	48.1	47.9	48.2
C(9')	-----	-----	-----	22.4	22.4	22.4	133.4	131.8	133.3
C(10')	-----	-----	-----	-----	-----	-----	116.6	115.9	116.6
OCH_3	55.7	55.9 55.7	56.1 60.8	55.6 55.4	55.7 55.3	55.8 60.6	55.7	55.8 56.1	56.0 60.8

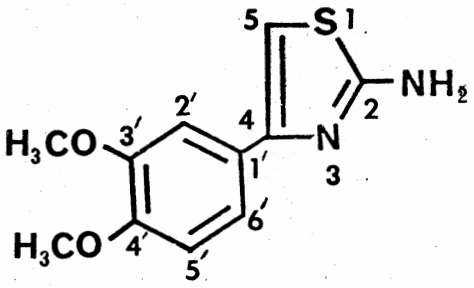
a. All ^{13}C NMR shifts in ppm relative to TMS.

b. Tenatitive assignments. See text.

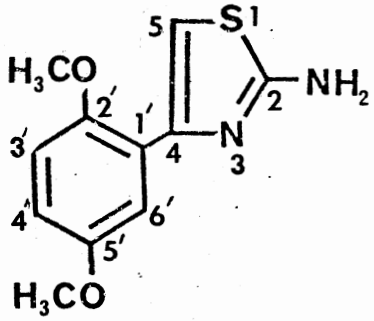
c. Spectrum obtained with DMSO-d_6 as solvent.

d. Carbonyl resonance not observed.

Values for the ^{13}C NMR shifts for various carbons in the acyclic thiazoles 21a-21c (R"" = H, Ac, allyl) have been placed in Table IV. Assignments for the thiazole ring systems were made by comparison with data for 2-amino-4-phenyl thiazole (5).[31,32,105] The C(2) carbons all exhibit resonances in the range of about 165-169 ppm, while the C(4)



21a



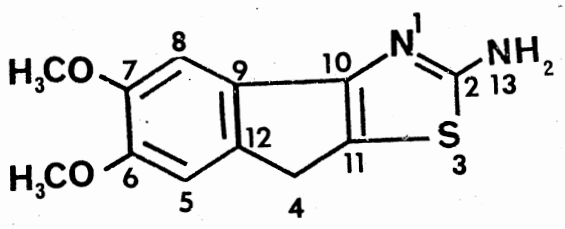
21b

shifts are fairly constant near 150 ppm. In contrast, signals for C(5) cover a large range from 99-107 ppm and give little or no indication of any possible trends due to substituent effects.

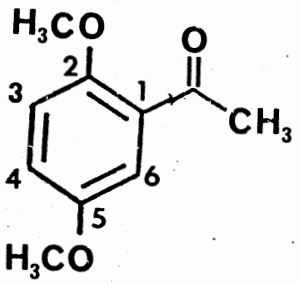
Assignment of carbon shifts in the phenyl group is difficult. The signals are easily divided into two groups, those aromatic carbons that bear CH_3O groups and those aromatic carbons that possess directly bonded protons. It is apparent from Table IV that the methoxy bearing carbons have resonances that range from 146.8-156.1 ppm. Since the signal for the C(5) carbon of the thiazole ring falls into this range, assignment of chemical shifts for this carbon becomes dubious.

Proton-bearing carbons possess shifts of about 109-120 ppm. In the case of 21a and 21b, there are three aromatic carbons that possess protons (2',5' and 6' in 21a; 3',4', and 6' in 21b). Literature assignment[26] of ^{13}C resonances for ketone 30b (starting material for 21b) reveals shifts of 113.8, 113.8 and 119.6 ppm for carbons C(3), C(4)

and C(6), respectively. Similar resonances were found in the ^{13}C NMR spectrum of 21b, and so assignment of the resonances [113.8, 114.6 and 118.0 ppm for C(3'), C(4') and C(6') respectively] could be made based on a comparison with the spectrum of starting material 30b. The signal



22a



30b

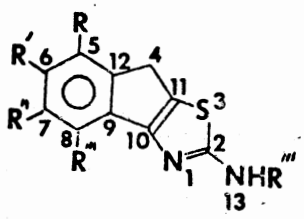
for C(6') in 21a would be expected to be similar to the resonance for C(6') in 21b. A shift of 118.2 ppm was found and was assigned to C(6') in 21a. The similarity of the shifts for C(6') in 21a and 21b was probably due, in part, to an ortho steric effect from the thiazole system and was not greatly affected by the presence of an adjacent CH_3O-group.

Such an ortho steric effect could then influence the ^{13}C NMR signal of C(2') in 21a if the thiazole ring displayed a symmetric environment in regards to both C(2') and C(6') (in 21a). If the thiazole ring was nearly planar with respect to the phenyl ring, ortho steric effects would be different for C(2') and C(6') in 21a due to the dissymmetry of the environments.

Examination of the next higher homolog 22a revealed that the C(8) positions in 22a could be analogous to the C(2') carbon in 21a, if the

TABLE V

CARBON CHEMICAL SHIFTS TO THIAZOLES 22a-22d



acetate= $^{14}CH_3\overset{15}{C}(O)$

allyl= $^{14}CH_2\overset{15}{C}H=\overset{16}{C}H_2$

Carbon[a,b]	22a	22c	22a	22c	22a	22c	22d
	R''''=H		R''''=Ac		R''''=allyl		
C(2)	172.7	172.1	167.9	167.9	173.8	173.9	174.1
C(4)	31.9	32.2	31.8	32.1	32.3	32.7	29.9
C(5)	104.5	120.1	102.2	122.8	102.1	120.1	149.7
C(6)	147.9	150.6	148.1	151.3	148.2	151.2	146.9
C(7)	146.2	145.3	146.9	145.7	146.6	145.9	127.4
C(8)	116.8	141.4	110.0	141.8	109.0	141.4	110.4
C(9)	130.5	140.3	129.6	140.4	130.8	140.9	133.5
C(10)	155.5	153.8	154.7	152.9	156.6	154.8	154.9
C(11)	120.6	126.9	127.7	126.3	120.9	105.4	107.5
C(12)	137.4	123.7	137.9	127.4	137.4	124.2	122.0
C(14)	-----	-----	171.7	c	48.0	48.0	48.0
C(15)	-----	-----	22.4	22.4	133.4	133.7	133.7
C(16)	-----	-----	-----	-----	116.9	116.8	116.7
OCH_3	55.6 55.7	56.0 60.5 61.5	55.8 55.6	55.9 60.5 61.3	56.2 56.1	61.9 61.3 56.4	55.4 56.3

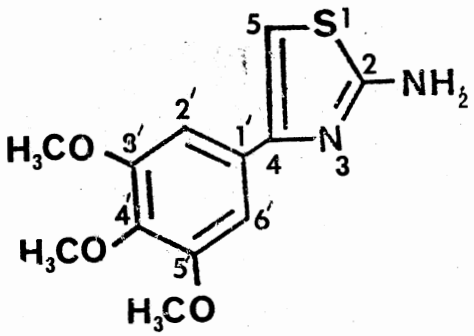
a. All ^{13}C NMR shifts in ppm relative to TMS. DMSO-d_6 is solvent

b. Tenative assignments. See text.

c. Not observed.

thiazole and phenyl rings were planar and oriented as shown in 21a (p. 32). Carbon-8 in 22a was assigned a resonance of 109.1 ppm (Table V) as a result of off-resonance decoupling experiments. The off-resonance spectrum for 22a displayed a doublet for the 109.1 resonance, indicative of a carbon directly bound to one proton, possibly C(5).

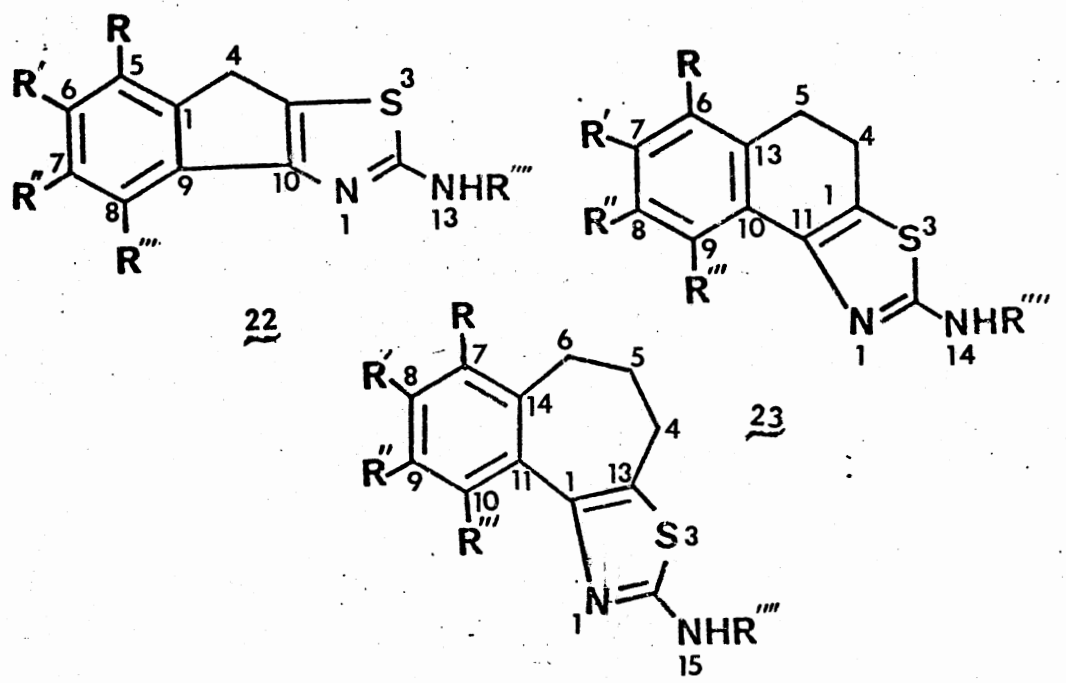
Additional evidence for a near planar arrangement between the thiazole and phenyl rings can be found from examination of the ^{13}C chemical shifts for thiazole 21c. Only one signal at 153.1 ppm was discovered



21c

for carbons in the CH_3O group, which suggested little steric interaction between the three adjacent CH_3O groups. However, two signals (109.6 and 137.8 ppm) were visible for the two ring carbons possessing protons [C(2') and C(6')]. If the thiazole ring was perpendicular with respect to the phenyl ring, the C(2') and C(6') carbons should experience a similar ortho effect from the thiazole ring, and the shifts would be closer in magnitude then observed.

^{13}C NMR analysis of the fused systems 22, 23 and 24 revealed (excluding CH_3O and the various R"" groups) five major patterns for the ^{13}C resonances. These patterns correspond to the five major types of carbon nuclei which are:



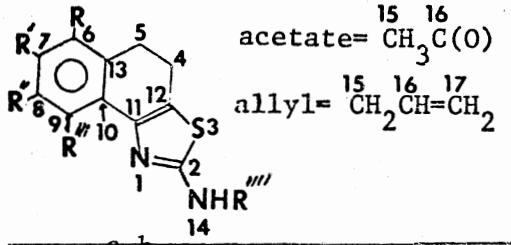
22 23 24

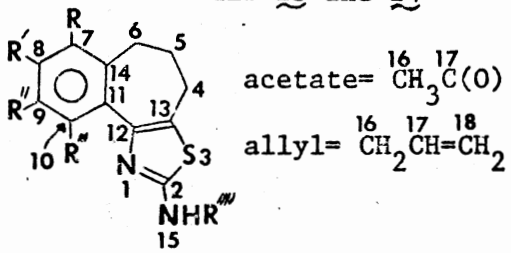
1. thiazole ring carbons
2. bridging CH_2 groups (between phenyl and thiazole rings)
3. aromatic (phenyl) carbons bearing protons
4. aromatic (phenyl) carbons bearing CH_3O groups
5. aromatic (phenyl) carbons fused to thiazole ring

Tables V and VI contain the tentative assignments for the ^{13}C chemical shifts for thiazole systems 22, 23 and 24. The ^{13}C resonance for C(2) in 22, 23 or 24 occurred at about 164-174 ppm. The other thiazole ring carbons gave rise to shifts of about 144-156 ppm for the carbon alpha to the ring nitrogen and 102-127 ppm for the carbon alpha to the thiazole sulfur atom. Since methoxy-bearing carbons gave rise to resonances in the range of 140-155 ppm, signals in this region could not be assigned definitively [such as signals for the C(10) or C(11) alpha to the ring

TABLE VI

CARBON CHEMICAL SHIFTS OF THIAZOLES 23 and 24





Carbon[a,b]	23d	23d	23a	23c	23d	24a
	R''''=H	R''''=Ac	R''''=allyl			
C(2)	167.9	167.9	167.8	166.9	164.5	168.3
C(4)	28.2	22.3	28.7	28.6	23.1	33.9
C(5)	21.1	20.9	21.9	19.6	20.9	26.8
C(6)	149.4	150.5	115.5	120.9	149.9	27.9
C(7)	149.2	155.6	147.5	148.4	149.6	112.8
C(8)	142.2	142.7	147.3	146.5	143.1	147.4
C(9)	120.9	119.8	111.6	151.6	121.3	149.0
C(10)	126.9	126.9	126.8	128.3	127.1	110.5
C(11)	145.6	151.5	144.8	147.1	145.6	134.3
C(12)	110.7	102.2	106.8	111.9	109.7	118.8
C(13)	127.3	122.4	124.7	129.3	127.5	119.4
C(14)	-----	-----	-----	-----	-----	129.7
C(15)	-----	c	48.1	48.2	48.1	-----
C(16)	-----	20.3	133.7	133.7	133.9	49.1
C(17)	-----	-----	116.6	116.7	116.7	133.6
C(18)	-----	-----	-----	-----	-----	117.2
OCH_3	55.5 60.3 60.4	55.5 60.3 60.5	55.9	55.8 60.2 61.3	60.9 60.8 60.7	56.8 55.9

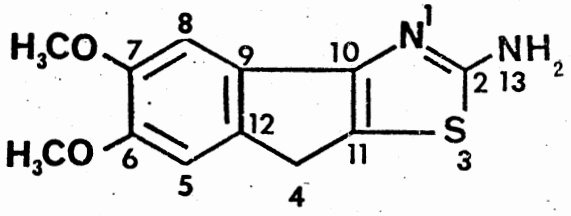
a. All shifts in ppm relative to TMS. DMSO-d_6 is solvent.

b. Assignments tenative. See text.

c. Not observed.

nitrogen). Off-resonance decoupling experiments permitted assignment of the aromatic carbons bearing protons but offered no insight for assignments in the region of 144-150 ppm signals in this region are attributed to carbons C(6) and C(7) denuded of protons. As a result, assignments for this region which are displayed in Tables V and VI are tentative.

Aromatic carbons fused to the thiazole ring exhibited shifts in the range of 125-140 ppm. However, as in the case of 22a (R"" = H),



22a

C(11) (alpha to the thiazole sulfur atom) also gave rise to a resonance in this region.

Thiazole 22a (R"" = H) displayed carbon resonances for two aromatic, proton-bearing carbons (in the analogous aminothiazoles 22a and 22d, only one aromatic C-H bond exists and the signal for the carbon can be assigned by offpresonance decoupling experiments). Off-resonance decoupling experiments on 22a indicated that signals at 104.5 ppm and 116.8 ppm were assignable to C(5) or C(8). Due to the splitting patterns evolved, absolute assignments were not possible.

The bridging carbons C(4) in 22a, C(4), (5) in 23a had signals at 19-35 ppm. In the thiazole system 22, the signals for the carbon in the

bridging CH_2 groups were found at about 30 ppm, while there was an upfield shift for the same carbons in the bridging CH_2 groups in systems 23 and 24.

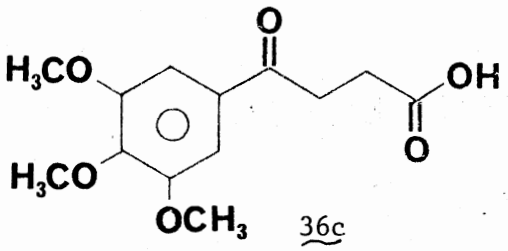
In summary, we have observed four regions of ^{13}C chemical shifts in the thiazoles with resonances in each region arising from five major types of carbons present. The regions were: 19-35 ppm (assignable to carbons in bridging CH_2 groups: 102-116 ppm (for aromatic carbons bearing thiazole ring, and to the thiazole carbon alpha to sulfur); and 140-156 ppm (assignable to aromatic carbons bearing OCH_3 groups, and to the thiazole carbon alpha to the ring nitrogen). More specific assignments within each region were not possible without labeling studies. The C(2) carbon of thiazole 21, the protons of the methyl groups (CH_3O), and substituent groups ($CH_2CH=CH_2$ and $CH_3C(O)$) possess signals easily assigned by comparison with the acyclic thiazoles 21a-21c.

Initial biological screening of 21a (R""=H, Ac) indicated that these systems possessed little or no anticancer activity. T/C ratios were found to be only slightly over 100; T/C ratios of about 150 or larger are needed for good activity. No other screening data has been received to date.

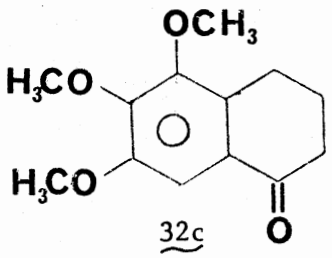
Suggestion for Future Work

A simplification of the synthetic route to the various cyclic ketones is potentially possible by performing a Freidel-Crafts acylation using various cyclic acid anhydrides[89] (i.e. succinic, glutaric, etc.) in PPA. Although the advantages of using PPA versus $AlCl_3$ have been noted, a search of the literature revealed no such use of PPA.

It would be advantagous to be able to protect the C=O group of the keto-acid formed. In the case of 1,2,3-trimethoxybenzene, acylation would yield 36c. Protection of the C=O, followed by cyclization and

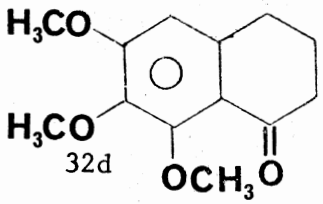


36c



32c

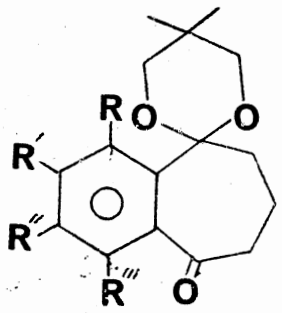
reduction (acidic media in both reactions) results in ketone 32c. Without protection of the C=O, reduction then cyclization would give ketone 32d. Thus the major product of the acylation reaction could



32d

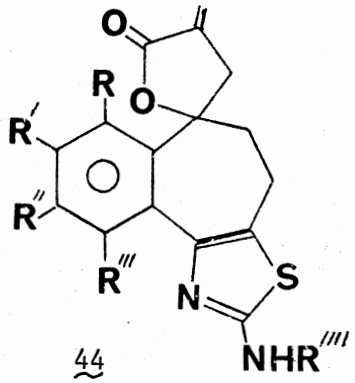
give two ketones. Use of 2,2-dimethylpropane-1,3-diol to form the corresponding 1,3-dioxan should result in a protecting group that offers fair stability in weakly acidic media and ease in formation.[81] A search of the literature indicates that both the cyclization and reduction steps would be feasible with the 1,3-dioxan system.[4,81]

The use of 1,3-dioxans as protecting groups leads to another interesting synthetic aspect. It could be possible to generate the system 43[4,81]



43

Two different cytotoxic groups could be formed, for example the material 44 could be synthesized. This would involve reaction at one ketonic



44

site (to form the spiro lactone group), followed by regeneration of the second C=O group, and then reaction at the second ketonic site to form the aminothiazole ring.

CHAPTER III

EXPERIMENTAL

General Information

All NMR spectra were obtained on a Varian XL-100(15) NMR spectrometer (with a Nicolet TT-100 PFT accessory) using tetramethylsilane (TMS) as an internal reference. A Perkin-Elmer 681 or a Beckman 5A infrared spectrophotometer was utilized to obtain IR spectra which were calibrated using the 1602 cm^{-1} band of polystyrene. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected as are all boiling points.

The mass spectral data were obtained on a CEC Model 21-110B HR mass spectrometer and are presented as per cent of (and normalized to) the most intense ion. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. The polyphosphoric acid (PPA) used was obtained from FMC.

Preparation of 3,4-Dimethoxyacetophenone (30a)

Polyphosphoric acid (115%, 920 g) in a three-necked round bottom flask was heated to 40-50°C under N_2 (stirring), and a mixture of veratrole (50.4 mL, 54.6 g, 0.395 mole) and acetyl chloride (56.8 mL, 62.7 g, 0.799 mole) was added slowly (∿ 1 hour). The reaction mixture turned deep violet and a gas (HCl) was given off. The mixture was heated for 1.5 hours after the addition was completed. It was then cooled

to r.t., was then allowed to stir overnight, and then was poured into 500 mL of ice/H_2O slurry. Extraction with benzene (6 x 75 mL) gave a yellow-brown organic phase which was washed with 50 mL of H_2O, 50 mL of sat. aqueous Na_2CO_3 and 50 mL of H_2O. The resulting organic phase was dried ($CaCl_2$) and evaporated to a yellow oil which solidified upon standing. Sublimation of this yellow solid at 0.01 mm/100°C gave white cubes (74%) of 3,4-dimethoxyacetophenone (30a):m.p. 48-50°C; ^1H NMR ($DCCl_3$) δ 2.52 (s, 3 H, CH_3), 3.89 (bs, 6 H, OCH_3), 6.84 (d, 1 H, J = 8 Hz), 7.54 (bm, 2 H, Ar-H); IR (KBr) 2990 (Ar), 2980, 2940, 1670 (C=O), 1590, 1510, 1420, 1270, 1020, 805, 640 cm^{-1}.

Preparation of 2-Amino-4-(3',4'-dimethoxyphenyl)-thiazole (21a)

3,4-Dimethoxyacetophenone (30a), (4.9 g, 0.027 mole), 1.54 mL (0.093 mole) of Br_2 and thiourea (5 g, 0.0658 mole) were used in the general procedure. Filtration of the crude solid and recrystallization ($HCCl_3$) gave 2.7 g (42%) of product 21a: mp 193-194°C; ^1H NMR ($DCCl_3$) δ 3.90 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 5.07 (bs, 2 H, NH_2), 6.58 (s, 1 H, C=CH), 6.85 (d, 1 H, J = 8 Hz, ArH), 7.29 (bm, 3 H, ArH); IR (KBr) 3400 (NH_2), 3300, 3145, 3000 (Ar), 2960, 1640, 1540, 1490, 1250, 1235, 1025, 850, 805, 765, 700, 620 cm^{-1}; ^{13}C NMR ($DCCl_3$) ppm ; 67.1 [C(2)], 150.8 [C(4)], 144.8 [C(3') or C(4')], 148.6 [C(4') or C(3')], 127.9 [C(1')], 118.3 [C(6')], 111.1 [C(5')], 109.4 [C(2')], 101.1 [C(5)], 55.9 (OCH_3). Anal. Calcd. for $C_{11}H_{12}O_2N_2S$:C, 55.93; H, 5.08; N, 11.86; S, 13.56. Found: C, 55.66; H, 5.06; N, 11.83; S, 13.52.

Preparation of 2-Allylamino-4-(3',4'-dimethoxyphenyl)thiazole (21a, R""=allyl)

The synthesis of 4-(3',4'-dimethoxyphenyl)-2-allylaminothiazole (21a R""=allyl) is used as an example. 3,4-Dimethoxyacetophenone (30a) (1.5 g, 0.0083 mole) was dissolved in 50 mL of $HCCl_3$:Abs. C_2H_5OH (1:1, v:v) and 2 drops of glacial CH_3CO_2H was added. Bromine (1.53 g, 0.01 mole) in 10 mL of $HCCl_3$ was added dropwise to the ketone over the course of about 2 hours, after which time the solution acquired a light red-brown color. If the solution was not a light red-brown, additional Br_2 (ca. a 10% excess of the molar amount of ketone used) in 5 mL of $HCCl_3$ was added slowly to the solution. In either case, the solution was stirred overnight (O.N.) (N_2) and then washed with 25 mL of aqueous sat. NaCl solutions. The organic layer left from the washing procedure was evaporated to give a yellow-brown oil. Scratching the oil in the cold ($\sim 5^oC$) gave a pale yellow solid. This solid, the α-bromoketone, without further purification was dissolved in 25 mL of $HCCl_3$:Abs. C_2H_5OH (1:1, v:v) along with 2 g (0.017 mole) of allylthiourea and was boiled with stirring (N_2). After 24 hours, the solution was cooled and evaporated to give a solid which was dissolved in 5 mL of C_2H_5OH (95%)/H_2O (5 mL:100 mole). The pH of this aqueous solution was adjusted to 10 (or slightly greater) by addition of conc. NH_4OH and was then chilled ($\sim 5^oC$) O.N. This gave a yellow solid which could be filtered, dried, and sublimed (ca. 0.1 mm/150°C) to give white solid 21a (R""=allyl). (2.0 g, 87.3%):mp 98-99°C; ^1H NMR ($DCCl_3$) δ 3.91 (bm, 8 H, $OC\underline{H}_3$, $C\underline{H}_2CH=CH_2$), 5.18 (bd, 2 H, J = 9 Hz; $CH=C\underline{H}_2$), 5.40 (bs, 1 H, $N\underline{H}$), 5.94 (bm, 1 H, $C\underline{H}=CH_2$), 6.54 (s, 1 H, S-$C\underline{H}$=C), 6.94 (d, 1 H, J = 8 Hz,

Ar-H), 7.29 (bm, 2 H, Ar-H); IR (KBr) 3110 (NH), 3050, 2980, 1560, 1410, 1319, 1225, 1165, 1122, 1025, 935, 850, 823, 765, 700 cm^{-1}. ^{13}C NMR ($DCCl_3$) ppm 169.5, 150.8 [C(4)], 148.6 [C(3') or C(4')], 148.4 [C(3') or C(4')], 133.4 [C(8)], 128.0 [C(1')], 118.3 [C(6')], 116.6 [C(9)], 110.9 [C(5')], 109.4 [C(2')], 99.0 [C(5)], 55.7 (OCH_3), 48.1 C(7) . Anal. (Calcd. for $C_{14}H_{16}O_2N_2S$:C, 60.87; H, 5.79, N, 10.14; S, 11.59. Found: C, 60.72; H, 5.87; N, 10.08; S, 11.44.

Preparation of 2-Acetoamino-4-(3',4'-dimethoxy-phenyl)thiazole (21a, R""=acetate)

The synthesis of 2-acetamido-4-(3'-4'-dimethoxyphenyl)thiazole (21a, R""=Ac) is used as an illustration of the procedure. 2-Amino-4-(3',4'-dimethoxyphenyl)thiazole (21a) (1 g, 3.6 mole) was dissolved in 10 mL of CH_3CO_2H (glacial). The mixture was heated to dissolve the aminothiazole, and the solution was cooled to room temperature (r.t.) and 5 mL (0.05 mole) of $[CH_3C(O)]_2O$ was added. This solution was stirred at r.t. for 24 hours (N_2) and then diluted with 10 mL of H_2O. The resulting aqueous mixture (a small amount of precipitate was present) was then neutralized with Na_2CO_3 (sat. solution) and allowed to stand O.N. in the cold ($\sim 5^oC$). A white solid precipitated and was filtered and washed with cold H_2O. This solid sublimed at 0.1 mm/100°C to give 0.56 g (56%) of white solid 21a: m.p. 97-98°C; ^1H NMR ($DCCl_3$) δ 1.86 (s, 3 H, CH_3), 3.91 (s, 6 H, two OCH_3), 6.90 (d, 1 H, J = 8 Hz, Ar-H), 7.03 (s, 1 H, SCH=C), 7.36 (m, 2 H, Ar-H); IR (KBr) 3380 (NH), 3180, 3000, 1630 (O=C), 1590, 1510, 1420, 1350, 1270, 1220, 1140, 1080, 1010, 870, 810, 770, 610 cm^{-1}; ^{13}C NMR ($DCCl_3$)

ppm 168.2 [C(2)], 150.1 [C(4)], 148.6, 148.4, 127.3 [C(1')], 118.1 [C(6')], 110.6 [C(5')], 109.3 [C(2')], 106.1 [C(5)], 55.6, 55.4, 22.4 [C(8')]; mass spectrum m/e, calcd. for $C_{13}H_{14}O_3N_2S$: M^+ 278.0725; Found: M^+ 278.0723.

Preparation of Ethyl 3-(3',4'-Dimethoxyphenyl)-3-oxopropionate (35a)

To 13.5 gms (281 moles) of NaH (50% oil disp.) in 100 mL of $(EtO)_2C=O$ was added dropwise 50 gms (0.278 mole) of 3,4-dimethoxyacetophenone (30a) in 100 mL of $(EtO)_2C=O$ (N_2 atmo.; stirring). A gas evolved, and the light grey mixture turned tan in color. After all of the acetophenone had been added, the mixture was boiled overnight, cooled, and poured onto an ice HCl (200 mL:20 mL) slurry. The aqueous solution was extracted with $HCCl_3$ (6 x 50 mL), and the organic extracts were dried ($CaCl_2$) and evaporated to give a yellow oil (19.8 g, 28.3%) which was used in crude form for further experiments: ^{1}H NMR ($DCCl_3$) δ 124 (t, 3H, J = 6 Hz, $C\underline{H}_3$), 3.74 (s, 2 H, $C\underline{H}_2$), 3.94 (s, 6 H, two $OC\underline{H}_3$), 3.20 (q, 3 H, J = 6 Hz, 6 Hz, C$\underline{H}$2), 6.88 (d, 1 H, J = 8 Hz, Ar-$\underline{H}$), 7.64 (M, 2 H, Ar-H); IR (neat) 2990, 2840, 1740 (C=O), 1675 (O=$\underline{C}OC_2H_5$), 1590, 1520, 1460, 1420, 1270, 1150, 1020, 870, 805, 765, 630 cm^{-1}.

Preparation of 2-Amino-6,7-dimethoxyindeno-[1,2-d]thiazole (22a)

5,6-Dimethoxyindanone (31a) (2 g, 0.01 mole), Br_2 (0.56 mL, 0.011 mole) and thiourea (1 gm, 0.013 mole) was used in the general procedure on page 44. The yield of 22a was 1.3 (51%): m.p. 203-204(d); ^{1}H NMR (DMSO-d_6) δ 3.60 (s, 2 H, $C\underline{H}_2$), 3.79 (s, 3 H, $C\underline{H}_3$), 3.82 (s,

3 H, $C\underline{H}_3$), 7.02 (s, 1 H, Ar-H), 7.14 (s, 1 H, Ar-H); IR (KBr) 3620 (N-H), 3510, 3190, 2990, 1620, 1590, 1535, 1460, 1280, 1205, 1150, 1110, 1060, 840, 770 cm^{-1}; ^{13}C NMR (DMSO-d_6) ppm 172.7 [C(2)], 155.5 [C(10)], 147.9 [C(6)], 146.2 [C(8)], 137.4 [C(12)], 130.4 [C(9)], 120.6 [C(11)], 116.8 [C(8)], 104.5 [C(5)], 55.7, 55.6, 31.2 [C(4)]; mass spectrum m/e calcd. for $C_{12}H_{12}O_2N_2S$: M^+ 298.0932; Found: 298.0931.

Preparation of 2-Allylamino-6,7-dimethoxy-indeno[1,2-d]thiazole (22a, R""=allyl)

5,6-Dimethoxyindanone (31a) (2 g, 0.0104 mole), Br_2 (1.83 g, 0.0115 mole), and thiourea (1.58 g, 0.021 mole) were employed in the general procedure described on page 44. The crude solid was sublimed (0.01 mm/120°C) to give white 22a (R"" = allyl), 1.7 g (57%): m.p. 184-185°C: ^1H NMR ($DCCl_3$) δ 3.59 (s, 2 H, $C\underline{H}_2$), 3.88 (s, 3 H, $OC\underline{H}_3$), 3.91 (s, 3 H, $OC\underline{H}_3$), 3.99 (d, 2 H, J = 4 Hz, $C\underline{H}_2$), 5.29 (d, 1 H, J = 9 Hz, $H\diagdown C{=}C\diagup^{H}_{\underline{H}}$), 5.42 (s, 1 H, $H\diagdown C{=}C\diagup^{H}_{\underline{H}}$), 5.90 (m, 1 H, $H\diagdown C{=}C\diagup^{H}_{\underline{H}}$), 7.02 (s, 1 H, Ar-H), 7.16 (s, 1 H, Ar-$\underline{H}$); IR (KBr) 3200 (NH), 3100, 2980, 1600, 1520, 1490, 1455, 1415, 1380, 1280, 1205, 1140, 1070, 990, 915, 840, 770, 700 cm^{-1}; ^{13}C NMR ($DCCl_3$) ppm 173.8 [C(2)], 156.6 [C(10)], 148.2, 146.6, 137.4 [C(12)], 133.4 [C(12)], 130.8 [C(9)], 120.9 [C(11)], 116.9 [C(16)], 109.0 [C(8)], 102.1 [C(5)], 56.2, 56.1, 48.0 [C(14)], 32.3 [C(4)]; mass spectrum m/e calcd. for $C_{14}H_{16}O_2N_2S$: 298.0932; Found: 298.0931.

Preparation of 2-Acetoamino-6,7-dimethoxyindeno-[1,2-d]thiazole (22a, R""=acetate)

2-Amino-6,7-dimethoxyindeno 1,2-d thiazole (22a) (1 g, 0.004 mole) 2 mL of CH_3CO_2H and 2 mL of $(CH_3CO)_2O$ was used in the general proce-

dure. The crude product 22a, R'''' = Ac, was sublimed (0.01 mm/200°C) to give 0.76 g (65%) of 22a, R'''' = Ac: m.p. 278-280(d) °C; ^{1}H NMR (DMSO-d_6) δ 2.17 (s, 3 H, CH_3), 3.74 (s, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 7.08 (s, 1 H, Ar-H), 7.22 (s, 1 H, Ar-H); IR (KBr) 3200 (NH), 3000, 1660 (C=O), 1560, 1390, 1280, 1150, 1000, 845, 770 cm^{-1}; ^{13}C NMR (DMSO-d_6) ppm 171.7 (C=O), 167.9 [C(2)], 154.7, 148.1, 146.9, 137.0, 129.6, 127.7, 110.0, 102.2, 55.8, 55.6, 31.8, 22.4; mass spectrum m/e calcd. for $C_{14}H_{14}O_3N_2S$: M^+ 290.0724; Found: M^+ 290.0729.

Preparation of 5-(3',4'-Dimethoxyphenyl)-5-oxo-pentanoic Acid (37a)

Sodium (3.5 g., 0.15 g. at.) was dissolved in 250 ml of absolute ethanol with stirring. While the solution was yet warm (40°C), 28.2 g. 0.10 mole) of 35a was added. After stirring for 15 min., the solution was cooled in an ice/H_2O bath. Ethyl bromopropionate (6.0 g., 0.038 mole) was added and the solution was stirred for 1 hour. An additional 12.0 g. (0.0755 mole) of ethyl bromopropionate was added and the solution was stirred overnight. The mixture was cooled again, diluted with water, acidified (50% HCl), and extracted with ether. The ethereal extracts were washed twice with 100 ml. of H_2O and dried ($MgSO_4$); the ether was evaporated leaving a pale yellow oil. This oil was boiled in 250 ml. of 20% aqueous sulfuric acid for 45 hours. After cooling, the mixture was extracted with ether, the solvent was removed, and the residue was boiled with 200 ml. of 5% sodium hydroxide solution for 1 hour. Acidification of the aqueous solution, followed by filtration gave 15 g (55%) of 37a: m.p. 145-7 °C; ^{1}H NMR ($DCCl_3$) δ 2.06 (q, 2 H, J = 6 Hz, CH_2), 2.48 (t, 2 H, J = 6 Hz, CH_2), 3.02 (t, 2 H, J = 6 Hz,

CH_2), 3.92 (s, 6 H, two OCH_3), 6.88 (d, 1 H, J = 8 Hz, Ar-H), 7.52 (m, 2 H, Ar-H); IR (KBr) 3400 (OH), 2980, 1760 (C=O), 1590, 1415, 1300, 1130, 610 cm^{-1}.

Preparation of 5-(3',4'-Dimethoxyphenyl)-pentanoic Acid (42a)

5-(3',4'-Dimethoxyphenyl)-5-oxopentanoic acid (37a) (10 g, 0.039 mole) was dissolved in 100 mL of CH_3CO_2H (glacial) and placed in a Parr hydrogenation bottle. Catalyst [Pd/C (10%, 1 g)] was added to the contents of the bottle, and shaking was commenced at 60°C under H_2 (35 psi). After about 1 hour, the shaking was stopped, and the bottle contents were filtered through celite. Evaporation of the filtrate, followed by dilution with 100 mL cold (~5°C) H_2O, gave 8.9 g (95%) of white 42a: m.p. 165-167°C; ^1H NMR ($DCCl_3$) δ 1.65 (m, 4 H, two CH_2), 2.38 (t, 2 H, J=5 Hz, CH_2), 2.58 (t, 2 H, J=5 Hz, CH_2), 3.84 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 6.72 (m, 3 H, Ar-H); IR (KBr) 3100 (OH), 2920, 1700, (C=O), 1590, 1510, 1420, 1320, 1240, 1130, 990, 810, 735, 660 cm^{-1}.

Preparation of 7,8-Dimethoxysuberone (33a)

5-(3',4'-Dimethoxyphenyl)pentanoic acid (42a) (5 g, 0.021 mole) was dissolved in 50 gm of 115% PPA. The thick solution was heated to about 75°C and stirred (N_2) for 2 hours. The resulting dark red syrup was poured onto 200 mL of ice/H_2O slurry and was allowed to stand at ~5°C O.N. A precipitate formed was filtered and sublimed to give 3.9 g (84%) of 33a: m.p. 61-63°C; ^1H NMR ($DCCl_3$) δ 1.82 (m, 4 H, two CH_2), 2.72 (t, 2 H, J=5 Hz, CH_2), 2.90 (t, 2 H, J=5 Hz, CH_2), 3.90 (s, 3 H,

$OC\underline{H}_3$), 3.92 (s, 3 H, $OC\underline{H}_3$), 6.66 (s, 1 H, Ar-$\underline{H}$), 7.38 (s, 1 H, Ar-$\underline{H}$); IR (KBr) 2925, 1760 (C=O), 1600, 1510, 1450, 1400, 1350, 1260, 1050, 880, 775 cm^{-1}.

Attempted Preparation of 2-Amino-8,9-dimethoxy-subero[1,2-d]thiazole (24a)

7,8-Dimethoxysuberone (42a) (2 g, 0.0097 mole), Br_2 (0.56 mL, 0.011 mole) and thiourea (0.912 g, 0.012 mole) were employed in the general procedure (page 44). A dark semisolid material was isolated. Column chromatography on neutral alumina (1 g material:25 g alumina) utilizing benzene-ether mixtures as eluting solvents resulted in highly colored bands. No one produce was isolated.

Preparation of 2-Allylamino-8,9-dimethoxysubero-[1,2-d]thiazole (24a, R""=allyl)

7,8-Dimethoxysuberone (42a) (2 g, 0.0097 mole), Br_2 (0.56 mL, 0.011 mole) and allylthiourea (1.39 g, 0.012 mole) were employed in the general procedure (page 44). A dark oil isolated was acidified with 25 mL of aq. HCl (6 M). A washing of this aqueous acidic solution with ether (3 x 25 mL) was followed by neutralization with 25 mL of aqueous 6 M NH_4OH. A dark solid was isolated which was recryatallized from $C_2H_5OH/(C_2H_5)_2O$ to give 0.61 g (20%) of 24a, R"" = allyl: mp 167-9(d)°C; ^1H NMR ($DCCl_3$) δ 2.10 (m, 2 H, CH_2), 2.80 (m, 4 H, CH_2), 3.88 (s, 3 H, OCH_3), 3.96 (s, 2 H, CH_2), 4.06 (s, 3 H, OCH_3), 5.38 (d, 1 H, J = 6 Hz, cis H), 5.50 (s, 1 H, trans H), 5.82 (m, 1 H, $C\underline{H}=CH_2$), 6.66 (s, 1 H, Ar-H), 7.38 (s, 1 H, Ar-H); IR (KBr) 3100, 2920, 1620, 1540, 1450, 1350,

1260, 1030, 920 cm ^{13}C NMR (DMSO-d_6) ppm 168.3 (C-2), 149.0, 147.4, 134.3, 133.6, [C(17)], 129.7 , 119.4 [C(14)], 118.8, 117.2 [C(18)], 112.8, 110.5, 49.1, 56.8 , 55.9, 33.9, 27.9, 26.8 ; mass spectrum m/e calcd. for $C_{17}H_{20}O_2N_2S$; M^+ 316.1245; Found: M^+ 316.1248.

Preparation of 2-Amino-4-(3',4',5'-trimethoxyphenyl)thiazole (21c)

3,4,5-Trimethoxyacetophenone (30c) (10 g, 0.048 mole), Br_2 (2.97 mL, 0.058 mole) and 12 g (0.158 mole) of thiourea were used. The crude yellow product was collected by filtration and sublimed at 160°C/5 x 10^{-5} mm to give white solid 21c (4.3 g, 34%): m.p. 169-171°C; ^{1}H NMR ($DCCl_3$) δ 3.83 (s, 3 H, OCH_3), 3.86 (s, 6 H, OCH_3), 5.65 (bs, 2 H, N-H_2), 6.64 (s, 1 H, SCH=C), 7.01 (s, 1 H, Ar-H); IR (KBr) 3380 (NH), 3150, 2990, 1640, 1590, 1540, 1495, 1460, 1410, 1350, 1235, 1120, 1000, 845, 710 cm^{-1}; ^{13}C NMR ($DCCl_3$) ppm 167.2 C(2) , 153.1 [C(3'), C(4'), C(5')], 159.0 [C(4)], 137.8 [C(6')], 130.3 [C(1')], 109.6 [C(2')], 102.0 [C(5)], 60.8, 56.1; mass spectrum m/e calcd. for $C_{12}H_{14}O_3N_2S$: M^+ 266.0724; Found: M^+ 266.0720.

Preparation of 2-Allylamino-4-(3',4',5'-trimethoxyphenyl)thiazole (21c, R""=allyl)

3,4,5-Trimethoxyphenylacetophenone (30c) (5 g, 0.024 mole), Br_2 (1.5 mL, 0.028 mole) and 7 g (0.0921 mole) of allylthiourea was employed. The crude product was recrystallized (ether) to give 1.8 g (24.7%) of pale yellow solid 21c, R"" = allyl: m.p. 70-71°C; ^{1}H NMR δ 3.86 (bs, 11 H, OCH_3, CH_2), 5.06 (bd, 2 H, J = 9 Hz, $H\diagup C{=}C\diagdown^{H}_{H}$), 5.25 (bs, 1 H, $H\diagup C{=}C\diagdown^{H}_{H}$), 5.72 (bm, 1 H, $CH{=}CH_2$), 6.74 (s, 1 H, Ar-H), 7.02

(s, 1 H, Ar-H); IR (KBr) 3200 (NH), 2990, 2940, 1560, 1520, 1475, 1430, 1390, 1350, 1280, 1255, 1230, 1190, 1100, 1025, 1005, 930, 850, 720 cm^{-1}; ^{13}C NMR ($DCCl_3$) δ 168.9 [C(2)], 152.1, 150.8 [C(4)], 148.8, 142.5, 133.3 [C(9')], 131.7 [C(1')], 116.6 [C(10')], 110.1, 108.8, 104.8 [C(5)], 60.9 (OCH_3), 60.8 (OCH_3), 56.0 (OCH_3), 48.2 [C(8')]. Mass spectrum m/e: calcd. M^+ 306.1037; Found: M^+ 306.1031.

Preparation of 2-Acetoamido-4-(3',4',5'-trimethoxyphenyl)thiazole (21c, R""=acetate)

2-Amino-4-(3',4',5'-trimethoxyphenyl)thiazole (21c) (0.5 g, 0.0016 mole), 2 mL of CH_3CO_2H, and 2 mL of $(CH_3CO)_2O$ were employed in the general procedure. Recrystallization (C_2H_5OH) of crude amide gave 0.39 g (70%) of white solid 21c (R"" = ac): m.p. 187-188°C; ^1H NMR ($DCCl_3$) δ 1.74 (s, 3 H, CH_3), 3.8 (s, 3 H, OCH_3), 3.92 (s, 6 H, OCH_3), 6.98 (s, 2 H, Ar-H), 7.25 (s, 1 H, SCH=C); IR (KBr) 3190 (NH), 3060, 2990, 2940, 2830, 1650 (C=O), 1580, 1480, 1425, 1385, 1340, 1300, 1240, 1195, 1170, 1120, 1035, 1000, 995, 925, 870, 825, 775, 740, 610 cm^{-1}; ^{13}C NMR (DMSO-d_6) ppm 168.5 [C(8')], 168.3 [C(2)], 156.7, 152.0, 150.4, 146.8, 142.2, 131.0 [C(1')], 107.8, 106.4, 60.6 (OCH_3), 22.4 [C(9')]; mass spectrum m/e calcd. for $C_{14}H_{16}O_4N_2S$: 308.0826; Found: 308.0817.

Preparation of Ethyl 3-Oxo-3-(3',4',5'-trimethoxyphenyl)propionate (35c)

Sodium hydride (6 g of 50% oil disp., 0.125 mole) was placed in a 3-necked, round-bottom flask with 100 mL of dry $(C_2H_5O)_2C=O$ (forms a gray slurry). 3,4,5-Trimethoxyacetophenone (30c) (20 g, 0.0952 mole) was dissolved in 100 mL of $(C_2H_5O)_2C=O$ and added dropwise to the NaH

slurry (N_2). A gas formed and the mixture turned red-brown. This new solution was heated to reflux after all of the ketone had been added and then was boiled for 3 hours followed by cooling with stirring overnight. This mixture was poured onto an ice/conc. HCl (200 mL/20 mL) slurry, and the resulting aqueous mixture was extracted with benzene (3 x 50 mL). The organic extracts were combined, washed with 100 mL of H_2O, dried ($CaCl_2$) and evaporated to give a yellow oil which crystallized upon standing. Recrystallization (CH_3OH) gave 19.0 g (70.77%) of white solid 33c: m.p. 81.5-82.5°C; ^{1}H NMR ($DCCl_3$) δ 1.28 (t, 3 H, J = 7 Hz, $CH_2\underline{CH}_3$), 3.93 (bs, 9 H, $O\underline{CH}_3$), 4.24 (q, 2 H, T = 2 Hz, $\underline{CH}_2CH_3$), 7.23 (s, 2 H, Ar-H); IR (KBr) 3020 (Ar), 2940, 2840, 1740 (C=O), 1670 ($O{=}COC_2H_5$), 1580, 1505, 1410, 1315, 1120, 1000, 895 cm^{-1}.

Preparation of 3-(3',4',5'-Trimethoxyphenyl)-propionic Acid (40c)

The keto ester 35c (5.52 g, 0.0196 mole) was dissolved in 50 mL of glacial CH_3CO_2H and 0.5 g of Pd/C (10%) was added to the solution. The acidic mixture was then heated to ∿ 60°C, and H_2 at a pressure of 25 psi was released into the flask. After about 4 hours, the theoretical uptake of H_2 was observed to be complete (∿ 3 psi drop in pressure was observed). After the hydrogen was removed under aspirator pressure, the hot mixture was filtered through celite to remove Pd/C and then reduced in volume to ∿ 10 mL. Water (∿ 50 mL) was added, and the solution was allowed to stand at ∿ 5°C O.N. Since a solid did not form, the solution was then extracted ($HCCl_3$, 3 x 25 mL). The organic extracts were combined, washed with H_2O, sat. aqueous Na_2CO_3, H_2O (∿ 25 mL each) and dried ($CaCl_2$). Evaporation of solvent yielded

a light yellow oil. This oil was boiled with ∿ 50 mL of H_2O containing 5 g of NaOH for 24 hours. The mixture was neutralized to give a white solid. Recrystallization (C_2H_5OH:H_2O) gave white solid 40c (4.4 g, 93.5%): m.p. 123-124°C; ^{1}H NMR ($DCCl_3$) δ 2.68 (q, 4 H, J = 5 Hz, 3 Hz, CH_2) (AA'BB' pattern), 3.81 (s, 6 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.42 (s, 2 H, Ar-H); IR (KBr) 2940 (b) (Ar), 2840, 1700 (CO_2H), 1590, 1510, 1455, 1420, 1320, 1240, 1130, 1000, 840, 660 cm^{-1}.

Preparation of 5,6,7-Trimethoxyindanone (31c)

3-(3',4',5'-Trimethoxyphenyl)propionic acid (40c) (4.4 g, 0.018 mole) was added all at once to 118.4 g of 115% PPA (the PPA was heated to 70-75°C). Heating of the mixture was continued for 5-10 min. and then poured onto 100 mL of H_2O/ice slurry. The aqueous mixture was extracted ($HCCl_3$, 3 x, 20 mL), and the organic extracts were washed with H_2O, sat. aqueous Na_2CO_3, and then H_2O (10 mL each). The $HCCl_3$ solution was dried ($CaCl_2$) and evaporated to give a brown solid. Sublimation at 0.1 mm/100°C gives 2.6 g (63.9%) of 5,6,7-trimethoxyindanone (31c): m.p. 109-110°C; ^{1}H NMR ($DCCl_3$) δ 2.64 (t, 2 H, J = 6 Hz, CH_2), 3.04 (t, 2 H, J = 6 Hz, CH_2), 3.86 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 4.06 (s, 3 H, OCH_3), 6.7 (s, 1 H, Ar-H); IR (KBr) 2995 (Ar), 2920, 1690 (C=O), 1595, 1480, 1460, 1440, 1415, 1320, 1255, 1235, 1195, 1040, 990, 905, 850, 680 cm^{-1}.

Preparation of 2-Amino-6,7,8-trimethoxyindeno-[1,2-d]thiazole (22c)

5,6,7-Trimethoxyindanone (31c) (2 g, 9.0 mmole), Br_2 (0.51 mL, 10 mmole) and thiourea (0.8 g, 0.01 mole) were employed in the general

procedure on page 44. Sublimnation gave 1.1 g (47%) of 22c: m.p. 279-280°C; ^{1}H NMR ($DCCl_2$) δ 3.62 (s, 2 H, $C\underline{H}_2$), 3.88 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.04 (s, 3 H, $OC\underline{H}_3$), 5.90 (bs, 2 H, $N\underline{H}_2$), 6.86 (s, 1 H, Ar-$\underline{H}$); IR (KBr) 3150 (NH), 2990, 1610, 1510, 1470, 1420, 1385, 1310, 1250, 1110, 1080, 1020, 960, 820, 730, 620 cm^{-1}; ^{13}C NMR (DMSO-$\underline{d}_6$) ppm 172.1 [C(2)], 153.8, 150.6, 145.3, 141.4, 140.3, 126.9, 123.7, 120.1, 61.5, 60.5, 56.0, 32.2 [C(4)]; mass spectrum m/e calcd. for $C_{13}H_{14}O_3N_2S$: M^+ 278.07249; Found: M^+ 278.0728.

Preparation of 2-Allylamino-6,7,8-trimethoxy indeno[1,2-d]thiazole (22c, R""=allyl)

5,6,7-Trimethoxyindanone (31c) (0.83 g, 3.75 mmole), 0.23 mL of Br_2 (4.5 mmole) and 1 g of allylthiourea (8.55 mmole) were employed. The crude product sublimed at 103°C/10^{-4} mm to give 1.19 g (40.3%) of pure 22c, R"" = allyl: m.p. 103-106(d)°C; ^{1}H NMR ($DCCl_3$) δ 3.66 (s, 2 H, $C\underline{H}_2$), 3.82 (s, 3 H, $OC\underline{H}_3$), 3.86 (s, 3 H, $OC\underline{H}_3$), 3.96 (bs, 2 H, $C\underline{H}_2$), 4.02 (s, 3 H, $OC\underline{H}_3$), 5.13 (d, 2 H, J = 10 Hz, $^{H}\!\!\searrow\!C{=}C\!\!\nearrow^{\underline{H}}_{H}$), 5.36 (bs, 1 H, $^{H}\!\!\searrow\!C{=}C\!\!\nearrow^{H}_{\underline{H}}$), 5.84 (bm, 1 H, $^{\underline{H}}\!\!\searrow\!C{=}C\!\!\nearrow^{H}_{H}$), 6.80 (s, 1 H, Ar-$\underline{H}$); IR (KBr) 3210 (N-H), 3065, 2920, 1570, 1510, 1470, 1380, 1315, 1240, 1200, 1170, 1115, 1040, 990, 940, 915, 830, 805, 780, 760, 720, 660 cm^{-1}; ^{13}C NMR ($DCCl_3$) ppm 173.9 [C(2)], 154.8, 151.2, 145.9, 141.4, 140.9, 133.7 [C(15)], 124.2, 120.1, 116.8, [C(16)], 105.4 [C(11)], 61.9, 61.3, 56.4, 48.0 [C(14)], 32.7 [C(4)]; mass spectrum m/e calcd. for $C_{16}H_{18}O_3N_2S$: M^+ 318.1033; Found: M^+ 318.1025.

Preparation of 2-Acetoamido-6,7,8-trimethoxy-indeno[1,2-d]thiazole (22c, R""=acetate)

2-Amino-6,7,8-trimethoxyindano[1,2-d]thiazole (22c) (1 g, 0.0036 mole), 2 mL of CH_3CO_2H and 2 mL of $(CH_3CO)_2O$ was employed (see page 45 for general procedure). The crude solid was recrystallized (acetone) to give 0.79 g (68%) of white solid 22c (R"" = Ac): m.p. 275-276(d)°C; ^{1}H NMR ($DCCl_3$) δ 2.16 (s, 3 H, CH_3), 3.78 (s, 2 H, CH_2), 3.90 (s, 6 H, OCH_3), 3.94 (s, 3 H, OCH_3), 6.91 (s, 1 H, Ar-H); IR (KBr) 3180 (N-H), 3060, 1385, 1310, 1295, 1240, 1110, 1040, 820, 780, 690, 620 cm^{-1}; ^{13}C NMR (DMSO-d_6) ppm 167.9 [C(2)], 152.9, 151.3, 145.7, 141.8, 140.4, 127.4, 126.3, 122.8, 61.3, 60.5, 55.9, 32.1 [C(4)], 22.4 [C(15)]; mass spectrum m/e calcd. for $C_{15}H_{16}O_4N_2S$: M^+ 320.0831; Found: M^+ 320.0840.

Preparation of 4-Oxo-4-(3',4',5'-trimethoxy-phenyl)butyric Acid (36c)

NaH (1.848 g of a 50% oil dispersion) was added to 200 mL dry THF (stirring, N_2). Ethyl 3-oxo-(3',4',5'-trimethoxyphenyl)propionate (10 g, 0.035 mole) was added to the ether suspension, and, after 15 minutes of stirring, ethyl bromoacetate (6.4 g, 0.038 mole) was added dropwise. The addition was complete after one hour and the mixture was then stirred for 48 hours at r.t. Sulfuric acid (15 %, 150 mL) was added to the THF mixture, and the THF was then distilled from the reaction flask. The now acidic solution was boiled for 48 hours and then cooled. A white precipitate formed and was filtered, washed (25 mL, H_2O) and dried to give 6.7 g (71%) of 36c: m.p. 117-119°C; ^{1}H NMR ($DCCl_3$) δ 2.79 (t, 2 H, J = 6 Hz, CH_2), 3.28 (t, 2 H, J = 6 Hz, CH_2), 3.88 (s, 9 H,

three OCH_3), 7.20 (s, 2 H, Ar-H); IR (KBr) 3400 (OH), 2960, 1720 (C=O), 1580, 1420, 1320, 1230, 1220, 990, 870, 770, 620 cm^{-1}.

Preparation of 4-(3',4',5'-trimethoxyphenyl)-butyric Acid (41c)

The keto acid 36c (7 g, 0.026 mole) was dissolved in 100 mL of CH_3CO_2H (glacial) and 0.5 g of Pd/C (10%) added to the solution. The mixture was placed in a Parr hydrogenation apparatus which was heated to 60°C and shaken under H_2 (35 psi). After about one hour, the mixture was filtered through celite, evaporated and diluted with 100 mL of H_2O. A solid formed which was filtered and dried. Recrystallization (C_2H_5OH/H_2O) gave 5.9 g (90%) of 41c: used crude ; ^1H NMR ($DCCl_3$) δ 2.12 (q, 2 H, J = 6 Hz, CH_2), 2.50 (t, 2 H, J = 6 Hz, CH_2), 3.02 (t, 2 H, J = 6 Hz, CH_2), 3.88 (s, 9 H, three OCH_3), 7.21 (s, 1 H, Ar-H); IR (KBr) 3500 (OH), 3000, 2920, 1690, 1590, 1510, 1260, 1140, 1015 cm^{-1}.

Preparation of 3,4-Dihydro-6,7,8-trimethoxy-napthalone (32c)

The crude 4-(3',4',5'-trimethoxyphenyl)butanoic acid (41c) was added to 500 g of 115% PPA, and the resulting mixture was heated (65-70°C) and stirred for 45 min. A dark mixture formed and was cooled to room temperature and poured into 1000 ml of ice/H_2O (5/5). After the mixture was thoroughly hydrolyzed, the product was filtered out, washed (2% aq. $NaHCO_3$) and air dried to give crude 3,4-dihydro-6,7,8-trimethoxy-1(2H)-naphthalenone (32c). Sublimation (110°C/0.01 mm) gave pure 32c [23.7 g (53% from 41c)], m.p. 118-121°C; ^1H NMR ($DCCl_3$) 2.58 (s, 2 H, J = 6 Hz, CH_2), 2.88 (t, 2 H, J = 6 Hz, CH_2), 3.95 (s, 9 H, three OCH_3), 6.98 (s, 1 H, Ar-H); IR (KBr) 3010, 2930, 1725 (C=O),

2590, 1525, 1455, 1230, 1010, 945, 870, 705, 650 cm^{-1}.

Attempted Preparation of 2-Amino-4,5-dihydro-6,7,8-trimethoxynaphthaleno[1,2-d]thiazole (23c)

3,4-Dihydro-6,7,8-trimethoxynaphthalone (32c) (2 g, 0.0098 mole), Br_2 (0.56 mL, 0.011 mole), and thiourea (0.912 g, 0.012 mole) were employed in the procedure (page 44). A dark semisolid material was isolated. Column chromatography on neutral alumina (1 g material: 25 g alumina) utilizing benzene-ether mixtures as eluting solvents resulted in highly colored bands. No product was isolated.

Repeated recrystallizations from various solvents did not improve the purity. The material on contact with certain solvents ($HCCl_3$, C_2H_5OH) appeared to darken after a short (about 5 min.) period.

Preparation of 7,8,9-Trimethoxysuberone (33c)

5-(3',4',5'-Trimethoxyphenyl)pentanoic acid (37c)(3.3 g, 0.012 mole) was mixed with 30 g of 115% polyphorphoric acid (PPA) at a temperature of 65°C for 1 hour (N_2). The resulting, red, viscous solution was poured over 100 mL of ice/H_2O slurry, and the aqueous solution was extracted with ether (3 x 25 mL). The ether extracts were washed with sat. aqueous Na_2CO_3 (5 mL) and dried ($CaCl_2$) to give a yellow oil. Sublimation at 0.1 mm/100°C gave a white solid 33c (1.3 g). Acidification of the Na_2CO_3 extract and filtration gave 0.2 g of recovered acid 37c. The yield of product 33c (minus recovered acid) was 44.9%: m.p. 98-9°C; ^1H NMR ($DCCl_3$) δ 1.78 (m, 4 H, CH_2), 2.60 (m, 4 H, CH_2), 3.82 (s, 3 H, OCH_3), 3.86 (s, 6 H, OCH_3), 6.42 (s, 1 H, Ar-H);

IR (KBr) 2990 (Ar), 2940, 2860, 1675 (C=O), 1590, 1490, 1455, 1400, 1350, 1320, 1260, 1190, 1155, 1140, 1090, 1060, 1010, 990, 920, 860, 820, 670 cm^{-1}.

Attempted Preparation of 2-Amino-8,9,10-trimethoxysubero[1,2-d]thiazole (24c)

7,8,9-Trimethoxysuberone (33c) (2 g, 0.008 mole), Br_2 (0.56 mL, 0.011 mole), and thiourea (0.912 g, 0.012 mole) were employed in the general procedure (pg 44). A dark semisolid material was isolated. Column chromatography on neutral alumina (1 g material: 25 g alumina) utilizing benzene-ether mixtures as eluting solvents resulted in highly colored bands. No product was isolated.

Repeated recrystalizations from various solvents did not improve the purity. The material on contact with certain solvents ($HCCl_3$, C_2H_5OH) appeared to darken after a short (about 5 min.) period.

Attempted Preparation of 2-Allylamino-8,9,10-trimethoxysubero[1,2-d]thiazole (24c, R''''= allyl)

7,8,9-Trimethoxysuberone (33c) (2 g, 8 mmole), Br_2 (0.56 mL, 0.011 mole) and allylthiourea (1.16 g, 0.01 mole) were employed in the general procedure (pg 44). A dark semisolid material was isolated. Column chromatography on neutral alumina (1 g material: 25 g alumina) utilizing benzene-ether mixtures as eluting solvents resulted in highly colored bands. No product was isolated.

Repeated recrystalizations from various solvents did not improve

the purity. The material on contact with certain solvents ($HCCl_3$, C_2H_5OH) appeared to darken after a short (about 5 min.) period.

Preparation of Methyl 3-Oxo-3-(2',3',4'-trimethoxyphenyl)propionate (35d)

2,3,4-Trimethoxyacetophenone (30d) (25 g, 0.0933 mole) in 100 mL of dimethyl carbonate was added dropwise to NaH (4.93 g of a 50% oil dispersion, 0.1026 mole) in 100 mL of $(CH_3O)C=O$ (N_2). A gas was evolved, and the mixture changed color from gray to red-brown. After 1 hour, all of the ketone had been added, and the mixture was heated at reflux O.N. This mixture was then cooled to r.t., poured onto an ice/conc. HCl (200 ml:3 mL) slurry and extracted with $HCCl_3$ (5 x 50 mL). The organic extracts were combined and evaporated to give a yellow oil. Trituration with ether/Skelly B (1:1) in the cold gave yellow crystals. Recrystallization (95% C_2H_5OH) gave white solid 35d (23.7 g, 74.3%):m.p. 44-45°C; ^1H NMR ($DCCl_3$) δ 3.73 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.95 (s, 2 H, CH_2), 3.98 (s, 3 H, OCH_3), 6.72 (d, 1 H, J = 8 Hz, Ar-H), 7.64 (d, 1 H, J = 8 Hz, Ar-H); IR (KBr) 3000 (Ar), 2950, 2840, 1740 (C=O), 1670 (CO_2CH_3), 1585, 1490, 1460, 1410, 1330, 1290, 1100, 1000, 805, 670 cm^{-1}.

Preparation of 3-(2',3',4'-Trimethoxyphenyl)-propionic Acid (40d)

Methyl 3-(2',3',4'-trimthoxyphenyl)-3-oxopropionate (35d) (10 g, 0.0373 mole) was dissolved in 100 mL of glacial CH_3CO_2H, and 1 g of 10% Pd/C was added. The mixture was placed in a Parr hydrogenation apparatus and shaken at 60°C under H_2 (35 psi). After the theoretical uptake of H_2 ceased (∿ 1 hour), the mixture was filtered hot through

celite and then evaporated to give a clear oil. This oil was mixed with 50 mL of H_2O, and the resulting solution was neutralized with NaOH (∿ 0.1 g). An additional 1.64 g of NaOH was dissolved in the mixture which was then boiled O.N. The aqueous solution was poured onto 50 mL ice, and conc. HCl was added until a pH of 2 was attained. A white solid 40d formed and was filtered to give 8.3 g (92.7%); m.p. 95-97°C; ^{1}H NMR ($DCCl_3$) δ 2.75 (q, 4 H, J = 12 Hz, 6 Hz, $C\underline{H}_2$) (AA'BB' pattern), 3.82 (s, 3 H, $OC\underline{H}_3$), 3.84 (s, 3 H, $OC\underline{H}_3$), 3.88 (s, 3 H, $OC\underline{H}_3$), 6.54 (d, 1 H, J = 8 Hz, Ar-$\underline{H}$), 6.84 (d, 1 H, J = 8 Hz, Ar-H); IR (KBr) 3430 (OH), 2940 (b), 1710 (CO_2H), 1600, 1490, 1470, 1420, 1265, 1095, 800, 695 cm^{-1}.

Preparation of 4,5,6-Trimethoxyindanone (31d)

3-(2',3',4'-Trimethoxyphenyl)propionic acid (40d) 8.3 g, 0.0346 mole) was added to 100 g of 115% PPA, and the resulting mixture was heated to 65°C. Stirring was initiated, and the heating with stirring was continued for 0.5 hour. The resulting dark red, vicous mass was poured onto 20 mL of H_2O/ice slurry. The aqueous solution formed was extracted (3 x 25 mL) with $HCCl_3$. The $HCCl_3$ extracts were combined and washed with sat. aqueous NaCl (10 mL), sat. aqueous Na_2CO_3 (10 mL) and sat. aqueous NaCl (10 mL). These extracts were dried ($CaCl_2$) and the $HCCl_3$ was evaporated to give a yellow solid. Sublimation (0.1 mm/100°C) gave 2.2 g (29%) of 31d: m.p. 123-124°C; ^{1}H NMR ($DCCl_3$) δ 2.62 (t, 2 H, J = 6 Hz, $C\underline{H}_2$), 3.04 (t, 2 H, J = 6 Hz, $C\underline{H}_2$), 3.88 (s, 3 H, $OC\underline{H}_3$), 3.94 (s, 3 H, $OC\underline{H}_3$), 3.96 (s, 3 H, $OC\underline{H}_3$), 7.0 (s, 1 H, Ar-$\underline{H}$); IR (KBr) 3000 (Ar), 2940, 2825, 1720 (C=O), 1600, 1475, 1430, 1400, 1260, 1230, 1200, 1070, 1025, 1000, 800, 715, 625 cm^{-1}.

Attempted Preparation of 2-Amino-5,6,7-trimethoxyindeno[1,2-d]thiazole (22d)

4,5,6-Trimethoxyindanone (31d)(2 g, 9 mmole), Br_2 (0.56 mL, 0.011 mole) and thiourea (0.912 g, 0.012 mole) were employed in the general procedure (pg 44). A dark semisolid material was isolated. Column chromatography on neutral alumina (1 g material: 25 g alumina) utilizing benzene-ether mixtures as eluting solvents resulted in highly colored bands. No product was isolated.

Repeated recrystalizations from various solvents did not improve the purity. The material on contact with certain solvents ($HCCl_3$, C_2H_5OH) appeared to darken after a short (about 5 min.) period.

Preparation of 2-Amino-4,5-dihydro-6,7,8-trimethoxynaptheno[1,2-d]thiazole (23d)

3,4-Dihydro-5,6,7-trimethoxynaphthalenone (33d)(1 g, 4,3 mmole), Br_2 (0.24 mL, 4.7 mmole) and thiourea (0.4 g, 5.3 mmole) were employed in the general procedure. Neutralization with NH_4OH gave a dark pasty material, which when recrystallized from $C_6H_5CH_3$ gave a pale grey solid. Recrystallization from CCl_4 gave white needles (0.3g, 33 %) of 23d: m.p. 166-168(d)°C; ^1H NMR (DMSO-d_6) δ 2.79 (m, 4 H, two CH_2), 3.77 (s, 6 H, two OCH_3), 3.86 (s, 3 H, OCH_3), 6.80 (s, 1 H, Ar-H); IR (KBr) 3400, 3120 (N-H), 3000, 2930, 1640, 1530, 1470, 1410, 1390, 1370, 1360, 1230, 1110, 1080, 1025, 960, 775, 745, 710 cm^{-1}; ^{13}C NMR (DMSO-d_6) ppm 167.9 [C(2)], 149.4, 149.2, 145.6, 142.2, 127.3, 126.9, 110.9, 110.7, 60.4, 60.3, 55.5, 28.2, 21.1; mass spectrum m/e calcd. for $C_{14}H_{16}O_3N_2S$: M^+ 292.0881; Found: M^+ 292.0875.

Preparation of 2-Allylamino-4,5-dihydro-6,7,8-trimethoxynaptheno[1,2-d]thiazole (23d, R''''=allyl)

3,4'-Dihydro-5,6,7-1(2H)-naphthalenone (33d)(0.833 g, 3.5 mmole), Br_2 (0.22 mL, 0.0042 mole), and allylthiourea (1 g, 0.0086 mole) were employed in the general procedure. The crude product was recrystallized (abs. C_2H_5OH) to give 0.2 g (17%) of 23d, R''''= allyl :m.p. 136-137°C; ^1H NMR ($DCCl_3$) δ 2.82 (bm, 4 H, $C\underline{H}_2$), 3.8 (s, 3 H, $OC\underline{H}_3$), 3.86 (s, 3 H, $OC\underline{H}_3$), 3.92 (s, 3 H, $OC\underline{H}_3$), 3.96 (bd, 2 H, $C\underline{H}_2$), 5.14 (d, 2 H, J = 8 Hz, $C=C\underline{H}_2$), 3.36 (bs, 1 H, N-H), 5.94 (bm, 1 H, $C\underline{H}=CH_2$), 7.25 (s, 1 H, Ar-H); IR (KBr) 3350 (NH), 2970 (Ar), 2930, 2900, 1540, 1460, 1390, 1360, 1255, 1230, 1200, 1085, 1025, 925, 905, 730 cm^{-1}; ^{13}C NMR ($DCCl_3$) δ 164.5 [C(2)], 149.9, 149.7, 145.5, 143.1, 133.9 [C(16)], 127.5, 127.1, 121.3, 116.7 [C(17)], 109.7 [C(12)], 60.9 (OCH_3), 60.6 (OCH_3), 48.1 [C(15)], 23.1, 20.9; mass spectrum m/e, calcd. for $C_{17}H_{20}O_3N_2S$: M^+ 332.1194; Found: $M^{+\cdot}$ 332.1187.

Preparation of 2-Acetoamido-4,5-dihydro-6,7,8-trimethoxynaptheno[1,2-d]thiazole (23d, R''''=acetate)

2-Amino-4,5-dihydro-6,7,8-trimethoxynaphthaleno[1,2-d]thiazole (23d)(0.5 g, 1.7 mmole), acetic acid (2 mL) and acetic anhydride (1 mL, 10.6 mmole) were employed in the general procedure on page 45. Sublimation at 200°C/0.1 mm gave 0.26 g (57%) of 23d: m.p. 221-222°C; ^1H NMR (DMSO-d_6) δ 201 (s, 3 H, $C\underline{H}_3$), 2.98 (m, 4 H, two $C\underline{H}_2$), 3.90 (s, 3 H, $OC\underline{H}_3$), 3.96 (s, 3 H, OCH_3), 7.28 (s, 1 H, Ar-H); IR (KBr) 3180 (NH), 2940, 1690 (C=O), 1650, 1550, 1460, 1390, 1290, 1110, 1035, 850, 760 cm^{-1}; ^{13}C NMR (DMSO-d_6) ppm 171.7 (C=O), 167.9 [C(2)], 154.7, 148.1,

146.9, 137.9, 129.6, 127.7, 110.0, 102.2, 55.8, 55.6, 31.8, 22.4 [C(15)]; mass spectrum m/e calcd. for $C_{16}H_{17}O_4N_2S$: M^+ 334.0987; Found: M^+ 334.0993.

Preparation of 2,5-Dimethoxyacetophenone (30b)

1,4-Dimethoxybenzene (29b) (110 g, 0.796 mole) was dissolved in $CH_3C(O)Cl$ (68.7 g, 0.876 mole) and added dropwise to 2300 g of 115% PPA at ∿ 40°C (N_2, mechanical stirring). A gas was evolved and the mixture became a violet color. After all of the ketone and acid chloride had been added, the mixture was stirred for 2 hours with heating (no additional gas evolution was detected). This mixture was then poured onto 1500 mL of an ice/H_2O slurry and was allowed to stand for several hours. The aqueous solution was extracted ($HCCl_3$, 6 x 75 mL) and the organic phases were combined and evaporated to give a yellow brown liquid. Distillation of this liquid at 0.1 mm/80°C gave a clear liquid (88.7 g, 61.9%): ^{1}H NMR ($DCCl_3$) δ 2.59 (s, 3 H), 3.74 (s, 3 H), 3.82 (s, 3 H, OCH_3), 6.88 (s, 1 H, ArH), 6.96 (d, 1 H, J = 4 Hz, ArH), 7.25 (d, 1 H, J = 4 Hz, ArH); IR (KBr) 3000, 2950, 2840, 1670 (C=O) 1610, 1590, 1500, 1410, 1355, 1280, 1220, 1180, 1040, 880, 810, 740, 690 cm^{-1}.

Preparation of 2-Amino-4-(2',5'-dimethoxyphenyl)thiazole (21b, R""=H)

2,5-Dimethoxyacetophenone (30b) (5 g, 0.028 mole), 4.9 g of Br_2 (0.031 mole) and thiourea (6 g, 0.079 mole) were employed in the general procedure on page 44. The crude product was sublimed at 0.1mm

100 °C to give 2.64 g (40%) of 21b, R""=H: m.p. 123.5-124.5 °C; ^{1}H NMR ($DCCl_3$) δ 3.80 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 5.23 (bs, 2 H, NH_2), 6.81 (m, 2 H, Ar-H, SCH=C), 7.21 (s, 1 H, Ar-H), 7.64 (d, 1 H, J = 4 Hz, Ar-H); IR (KBr) 3400 (NH), 3300, 3140, 3000, 2940, 2825, 1810, 1790, 1620, 1535, 1500, 1485, 1405, 1340, 1300, 1275, 1240, 1220, 1175, 1160, 1050, 1020, 940, 905, 880, 810, 795, 740, 730, 700, 660 cm^{-1}; ^{13}C NMR ($DMSO-d_6$) ppm 165.5 [C(2)], 153.4 [C(2')], 151.0 [C(4)], 146.4 [C(5')], 123.9 [C(1')], 117.0 [C(6')], 114.6 [C(4')], 113.8 [C(3')], 107.7 [C(5)], 55.9. 55.7; mass spectrum m/e calcd. for $C_{11}H_{12}O_2N_2S$: M^+ 236.0621; Found: M^+ 236.0630.

Preparation of 2-Allylamino-4-(2',5'-dimethoxyphenyl)thiazole (21b, R""=allyl)

2,5-Dimethoxyacetophenone (30b) (1 g, 0.0056 mole), Br_2 (0.986 g, 0.00616 mole) and allylthiourea (1 g, 0.0086 mole) were employed in the general procedure (page 44). Isolation as the HCl salt and recrystallization (C_2H_5OH/H_2O) gave 0.72 g (47%) of 21b: m.p. 138-9 °C; ^{1}H NMR ($DCCl_3$) δ 3.80 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.14 (d, 2 H, J=4 Hz, CH_2), 5.20 (d, 1 H, J=9 Hz, $^{H}\!\!\searrow\!C{=}C\!\!\nearrow^{H}_{H}$), 5.48 (s, 1 H, $^{H}\!\!\searrow\!C{=}C\!\!\nearrow^{H}_{H}$), 5.94 (m, 1 H, $^{H}\!\!\searrow\!C{=}C\!\!\nearrow^{H}_{H}$), 7.06, (m, 2 H, Ar-H, SC=C-H), 7.34 (m, 2 H, Ar-H); IR (KBr) 3100 (NH), 2910, 1650, 1605, 1490, 1425, 1300, 1240, 1210, 1095, 1030, 950, 840, 800, 750 cm^{-1}; ^{13}C NMR ($DMSO-d_6$) ppm 168.6 [C(2)], 152.9 [C(2')], 152.2 [C(5')], 150.3 [C(4)], 136.2 [C(1')], 131.8 [C(9')], 117.6 [C(6')], 115.9 [C(10')], 114.0 [C(3)], 113.7 [C(4')], 105.1 [C(5)], 56.1 (OCH_3), 55.8 (OCH_3), 47.9 [C(8')]; mass spectrum m/e calcd. for $C_{14}H_{14}O_2N_2SCl$: M^+ 309.0458; Found: M^+ 309.0461 .

Preparation of 2-Acetoamido-4-(2',5'-dimethoxyphenyl)thiazole (21b, R""=acetate)

2-Amino-4-(2',5'-dimethoxyphenyl)thiazole (21b)(1 g, 0.0042 mole), 2 mL of CH_3CO_2H, and 2 mL of $(CH_3CO)_2O$ were used in the general procedure. The crude product 21b was recrystallized (C_2H_5OH) and gave 0.83 g (70%) of 21b, R''=acetate: m.p. 196-197°C; ^1H NMR ($DCCl_3$) δ 1.89 (s, 3 H, CH_3), 3.74 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.86 (m, 2 H, SC=CH, Ar-H), 7.58 (m, 2 H, Ar-H); IR (KBr) 3200 (NH), 3000, 3980, 1665, 1550, 1500, 1445, 1380, 1250, 1220, 1050, 800, 740, 610 cm^{-1}; ^{13}C NMR (DMSO-d_6) ppm 183.9 (C=O), 168.3 [C(2)], 156.1, 152.8, 150.7, 144.2, 114.0, 113.8, 106.4, 55.7, 55.3, 22.4 (CH_3); mass spectrum m/e calcd. for $C_{13}H_{14}O_3N_2SO$: M^+ 278.07249; Found: M^+ 278.07.

Preparation of Methyl 3-Oxo-3-(2',5'-dimethoxyphenyl)propionate (35b)

2,5-Dimethoxyacetophenone (30b)(50 g, 0.278 mole) was dissolved in 100 mL of $(CH_3O)_2C=O$ and added dropwise to a mixture of NaH (50% oil disp., 14.8 g, 0.2056 mole) in 200 mL of $(CH_3O)_2C=O$. After all of the ketone had been added (∿ 1 hour), the mixture was boiled for 1 hour. This mixture was allowed to cool to r.t., and was then allowed to stand overnight. The resulting pasty mixture was poured over 250 mL H_2O/HCl (10:1), whereupon two layers separated. The bottom organic layer was drawn off, and the aqueous layer was extracted (ether, 5 x 25 mL). The organic layers were combined and dried ($CaCl_2$) to give a yellow-brown liquid. The ether was evaporated off to an oil, which, when triturated with Skelly B:ether (1:1) in

the cold, gave a yellow-brown solid. Recrystallization (95% C_2H_5OH) gave a white solid (42.8 g, 64.7%):m.p. 79.5-80.5°C; ^1H NMR ($DCCl_3$) δ 3.72 (s, 3 H, $C\underline{H}_3$), 3.80 (s, 3 H, $OC\underline{H}_3$), 3.86 (s, 3 H, $OC\underline{H}_3$), 3.98 (s, 2 H, $C\underline{H}_2$), 6.94 (s, 1 H, ArH), 7.04 (d, 1 H, J = 3 Hz, ArH), 7.41 (d, 1 H, J = 3 Hz, ArH); IR (KBr) 3015 (Ar), 2950, 2840, 2000, 1725 (C=O), 1670 (CO_2CH_3), 1615, 1575, 1490, 1420, 1330, 1220, 1130, 1030, 1010, 1000, 890, 805, 740, 635 cm^{-1}.

Preparation of 3-(2',5'-dimethoxyphenyl)-propionic Acid (40b)

Methyl 3-(2',5'-dimethoxyphenyl)-3-oxopropionic acid (35b)(7 g, 0.03 mole) was dissolved in 100 mL of CH_3CO_2H (glacial) and the solution was placed in a Parr hydrogenation bottle. Pd/C (10%, 1 g) was added to the bottle contents, which was then shaken at 60°C under H_2 (35 psi) for about 1 hour. The mixture was then filtered hot through celite, evaporated, and mixed with 50 mL of H_2O. The resulting mixture was neutralized with solid NaOH (∿ 0.1 g), and an additional 1.29 g (0.032 mole) of NaOH added. The basic mixture was boiled O.N., cooled, and acidified with conc. HCl until a pH of 2 was attained. A white precipitate formed and was filtered to give 5.6 g (93%) of 40b: m.p. 67-68 °C °C; ^1H NMR ($DCCl_3$) δ 2.8 (m, 4 H, two $C\underline{H}_2$), 3.72 (s, 3 H, $OC\underline{H}_3$), 3.74 (s, 3 H, $OC\underline{H}_3$), 6.72 (bs, 3 H, Ar-H); IR (KBr) 3200 (OH), 2940, 1710 (C=O), 1500, 1430, 1220, 1040, 800, 720 cm^{-1}.

Preparation of 4,7-Dimethoxyindanone (31b)

3-(2',5'-Dimethoxyphenyl)propionic acid (40b) (7 g, 0.033 mole) was dissolved in 150 g of 115 % PPA. The thick, viscous solution was

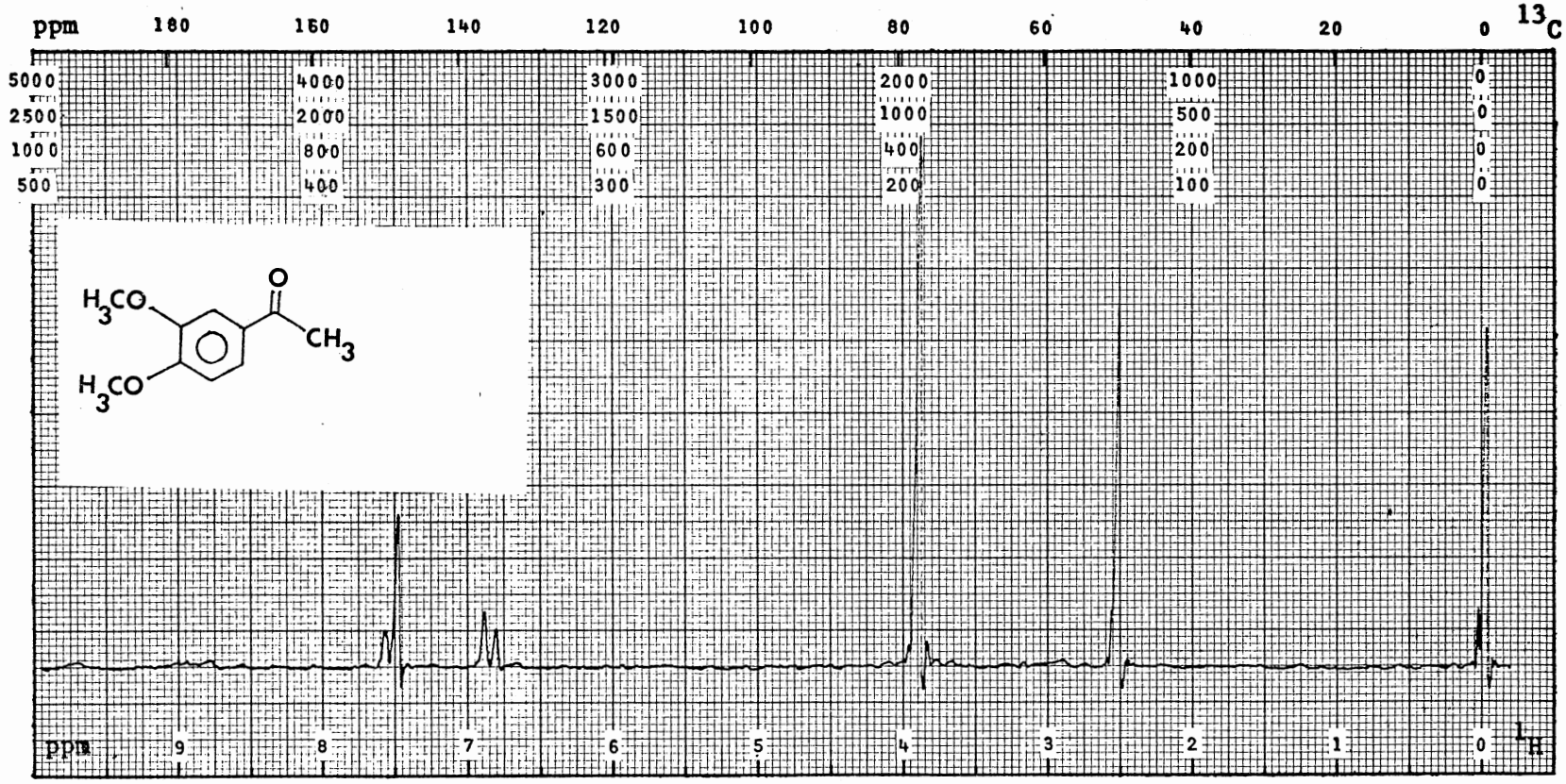
heated (about 65°C) (N_2) and stirred for 1 hour and then poured onto 300 mL of ice/H_2O slurry. This aqueous solution was extracted with ether (6 x 40 mL) and the organic extracts were combined and washed with sat. aq. Na_2CO_3(25 mL) and sat. aq. NaCl (25 mL), dried ($CaCl_2$). Evaporation of the organic solvent gave a crude yellow solid. Sublimation (100 °C/0.1 mm) gave 5.2 g (55 %) of 31b: m.p. 110-111°C; ^1H NMR ($DCCl_3$) δ 2.64 (t, 2 H, J = 6 Hz, CH_2), 3.02 (t, 2 H, J = 6 Hz, CH_2), 3.88 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 7.01 (s, 2 H, Ar-H); IR (KBr) 2940, 1720 (C=O), 1600, 1470, 1425, 1320, 1130, 1090, 1030, 850 cm^{-1}.

Attempted Preparation of 2-Amino-5,8-dimethoxy-indeno [1,2-d] thiazole (21b)

4,7-Dimethoxyindanone (31b)(2 g, 0.01 mole), Br_2 (0.56 mL, 11 mmole and thiourea (0.912 g, 0.012 mole) were employed in the general procedure (pg 44). A dark semisolid material was isolated. Column chromatography on neutral alumina (1 g material: 25 g alumina) utilizing benzene-ether mixtures as eluting solvents resulted in highly colored bands. No product was isolated.

Repeated recrystallization from various solvents did not improve the purity. The material on contact with certain solvents ($HCCl_3$, C_2H_5OH) appeared to darken after a short (about 5 min.) period.

PLATE I



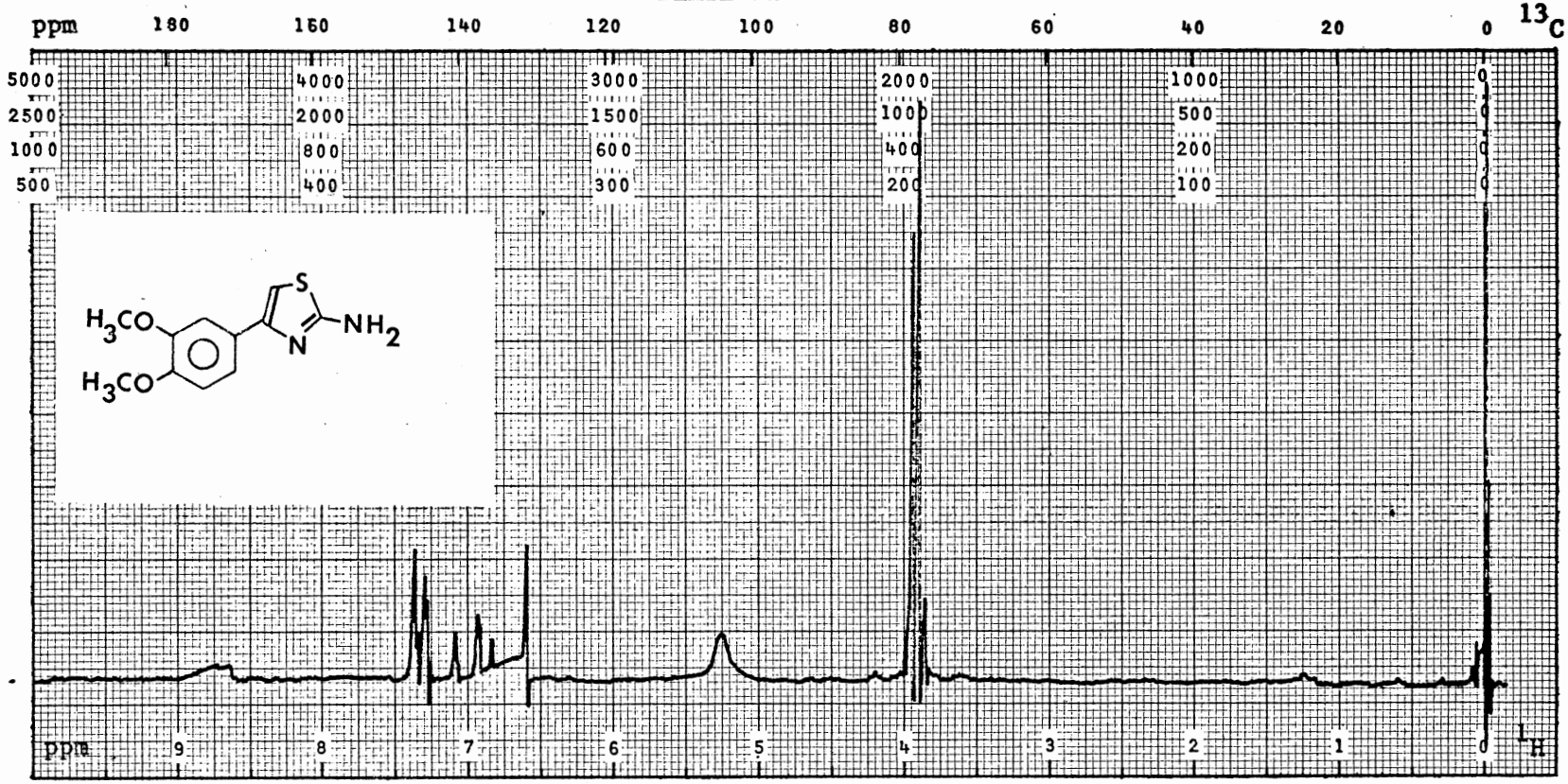
^{1}H NMR Spectrum of 3,4-Dimethoxyacetophenone (30a)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 43 µs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}H; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE II



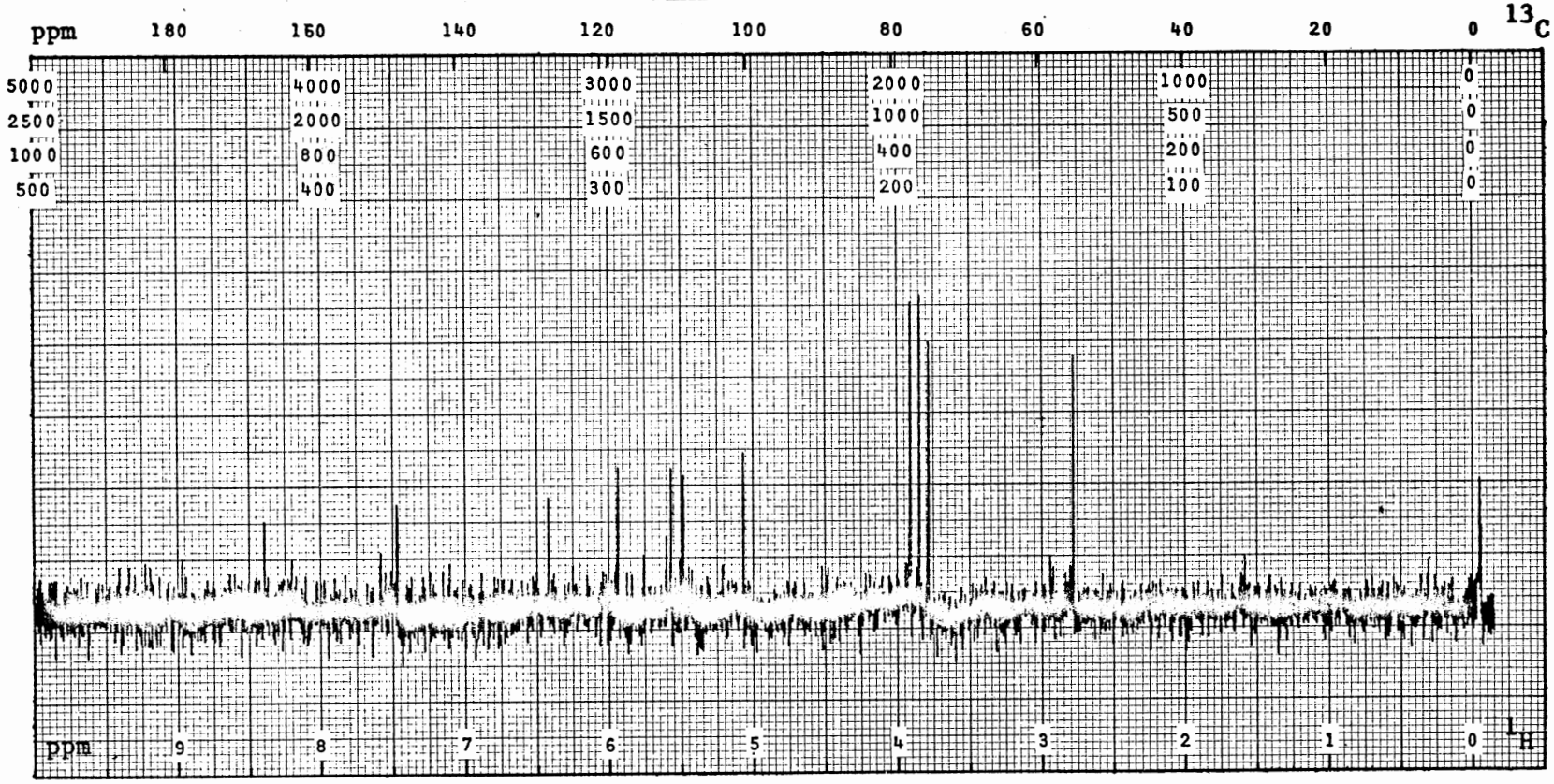
^{1}H NMR Spectrum of 2-Amino-4-(3',4'-dimethoxyphenyl)thiazole (21a)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE III



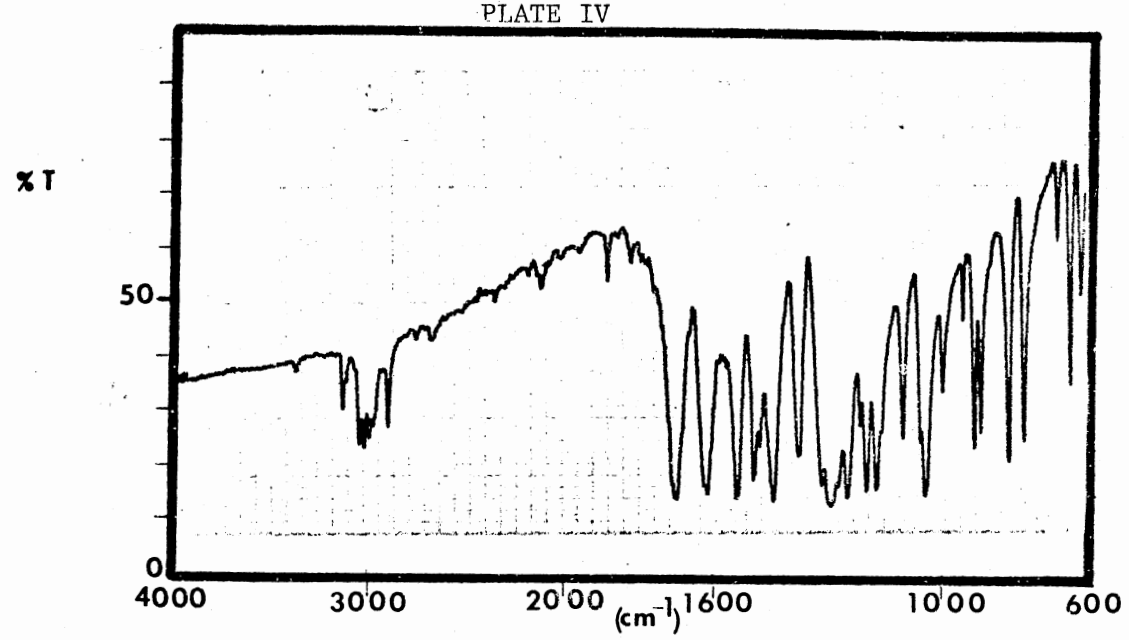
^{13}C NMR Spectrum of 2-Amino-4-(3',4'-dimethoxyphenyl)thiazole (21a, R'''' = H)

PFT ^{13}C CW _ ; Solvent. . $DCCl_3$; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 1000

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 3Hz; Lock. . ^{2}D; D5/ST. . 6s

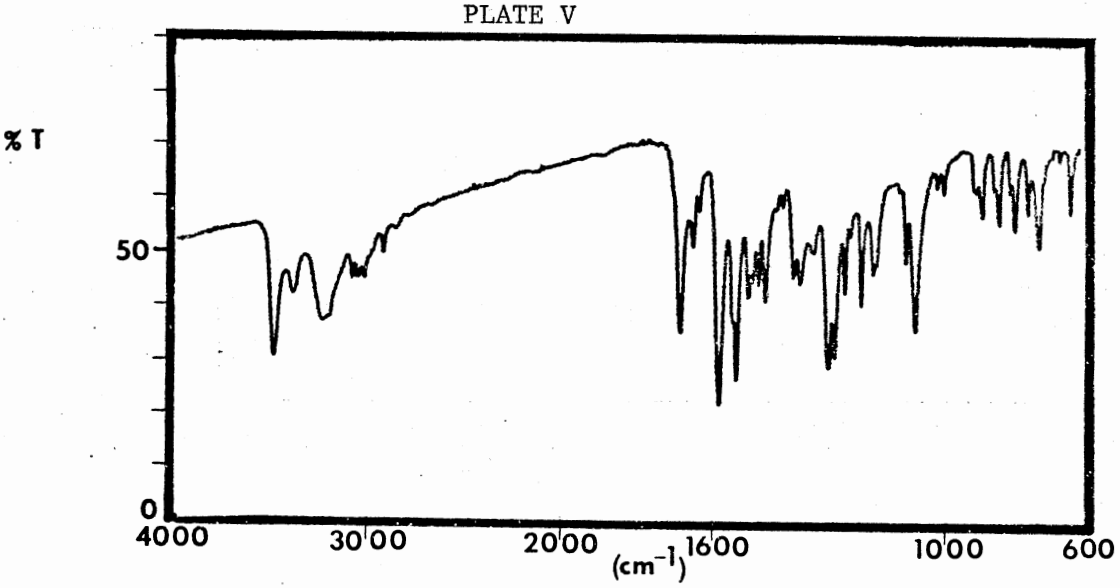
DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 63W/dB; NBW. . 100Hz

PLATE IV



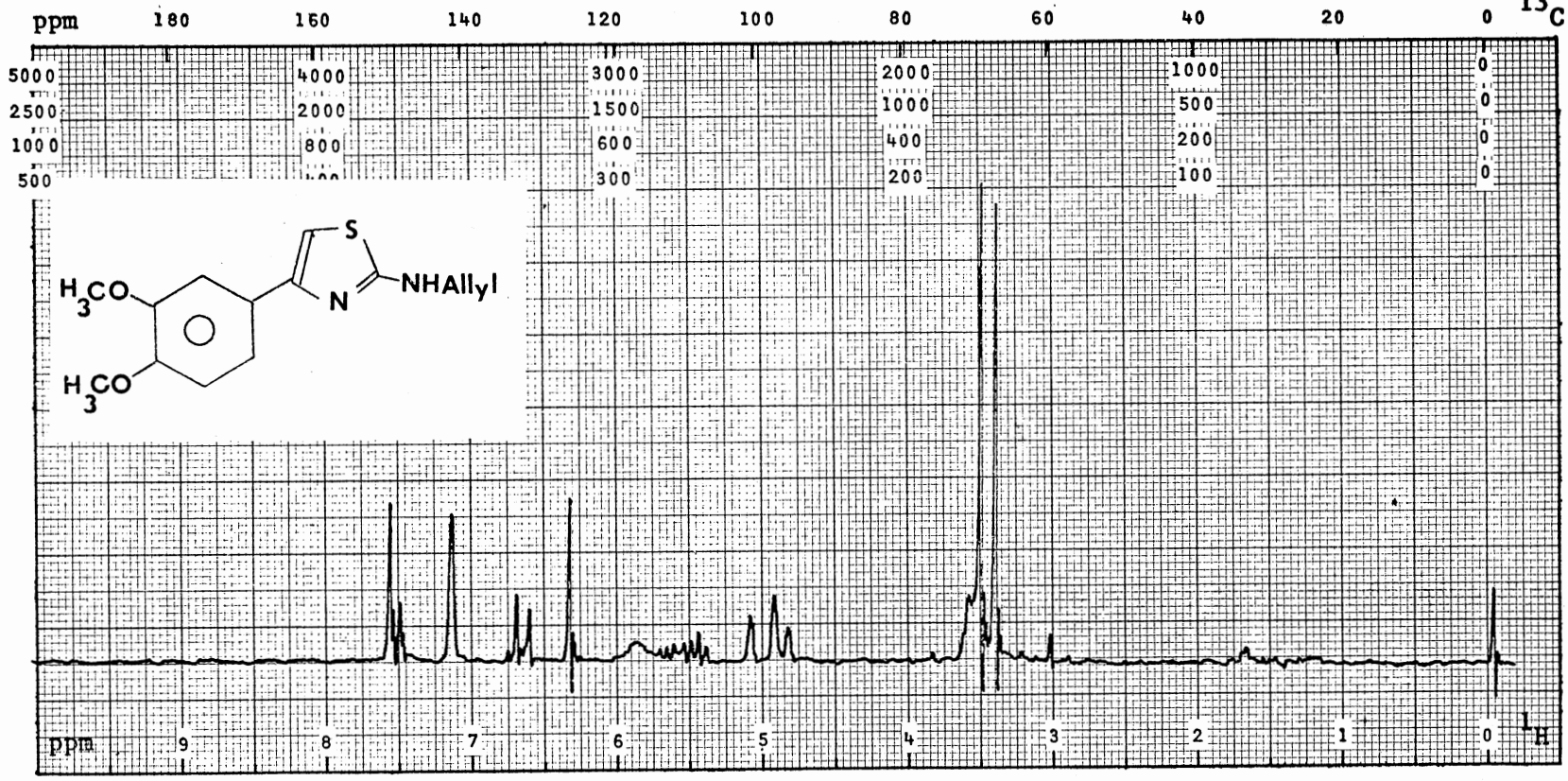
IR Spectrum of 3,4-Dimethoxyacetophenone (30a), KBr Pellet

PLATE V



IR Spectrum of 2-Amino-4-(3',4'-dimethoxyphenyl)thiazole (21a), KBr Pellet

PLATE VI



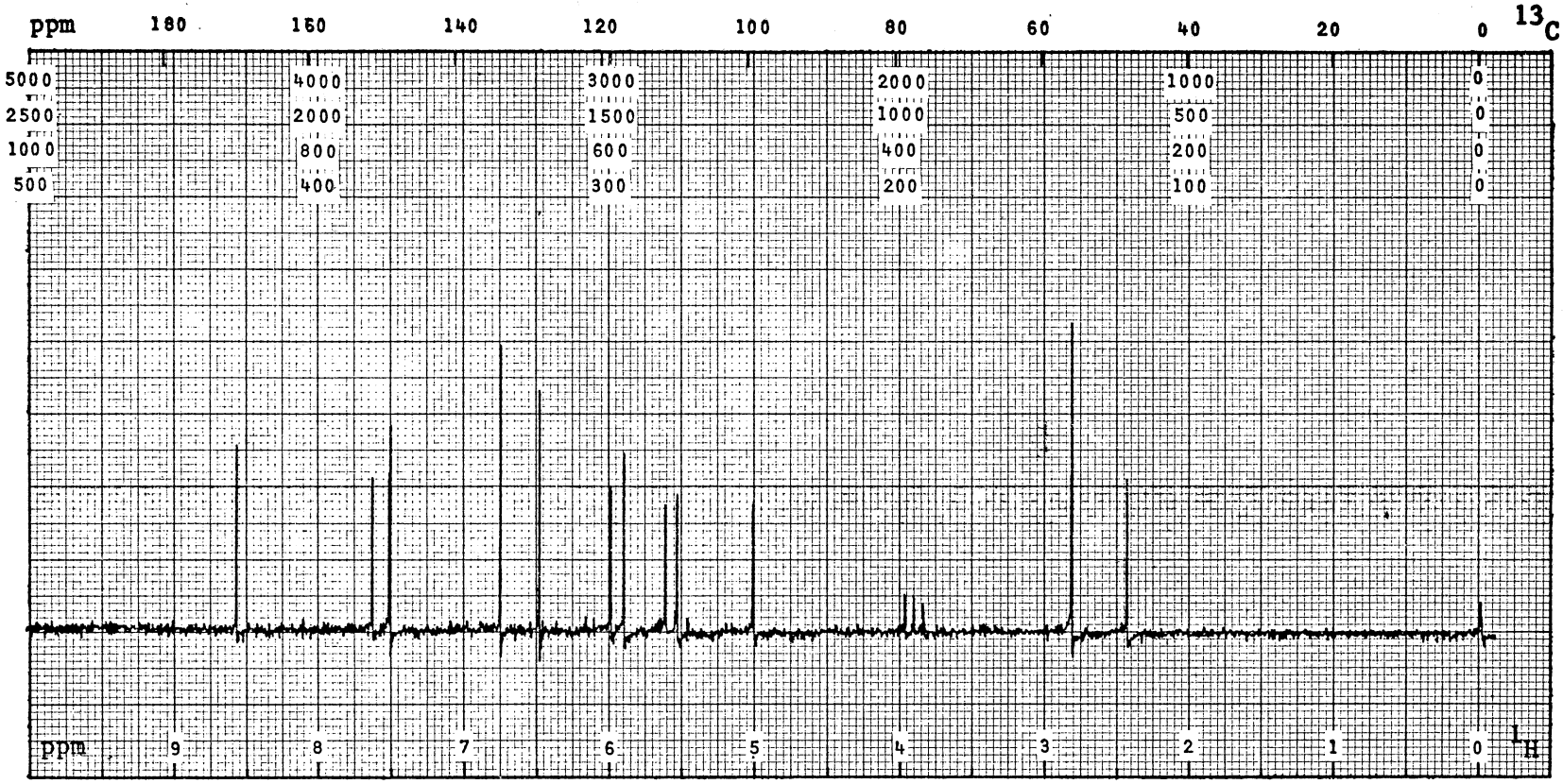
^{1}H NMR Spectrum of 2-Allylamino-4-(3',4'-dimethoxyphenyl)thiazole (21a, R""=allyl)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 88°C; Acq/SA. . 1.0

Size. . K; P2/RF. . µs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE VII



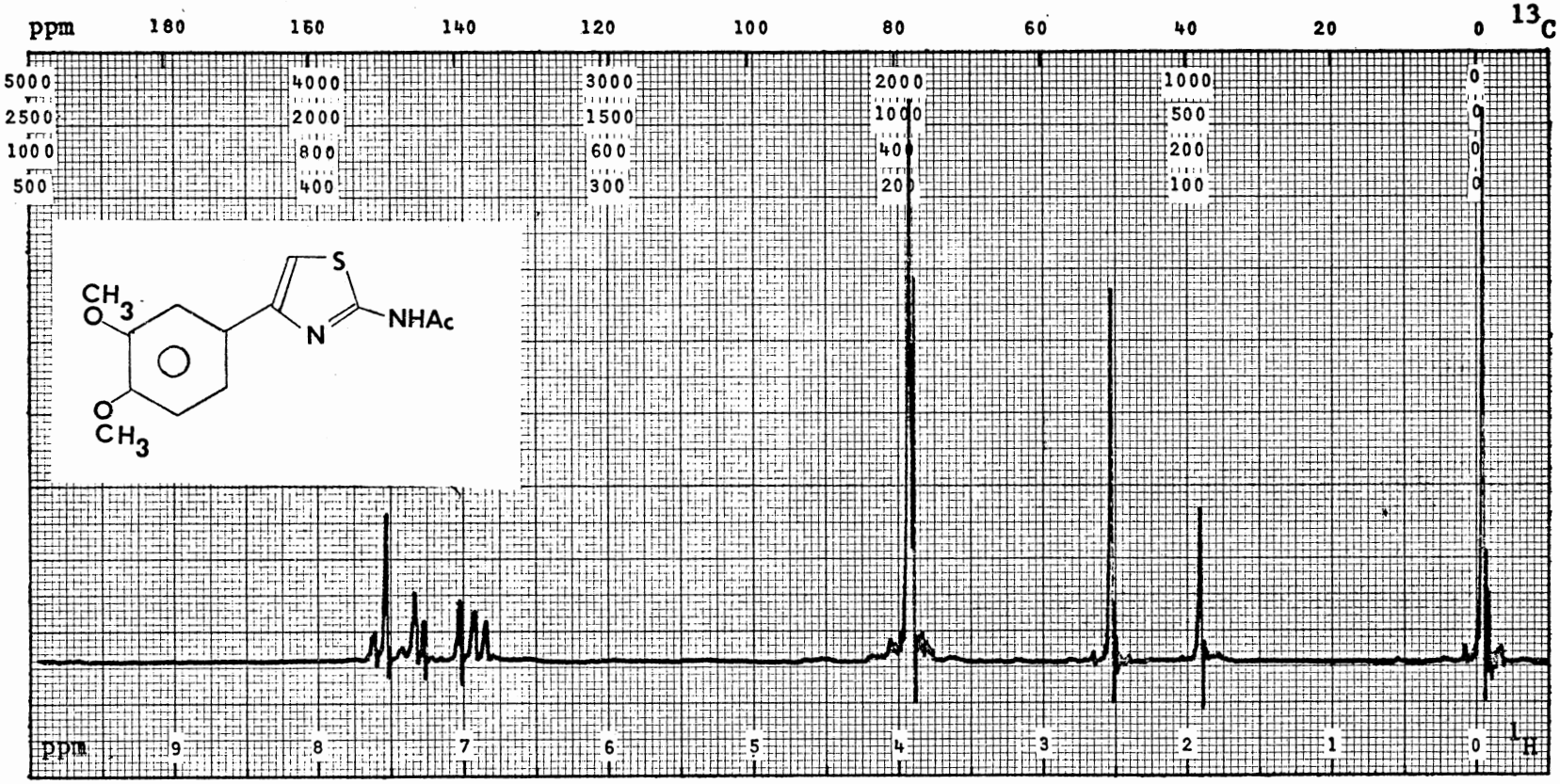
^{13}C NMR Spectrum of 2-Allylamino-4-(3',4'-dimethoxyphenyl)thiazole (21a, R'''' = allyl)

PFT $^{13}\underline{C}$ CW _ ; Solvent. . $DCCl_3$; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 200

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 6s

DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 94W/dB; NBW. . 100Hz

PLATE VIII



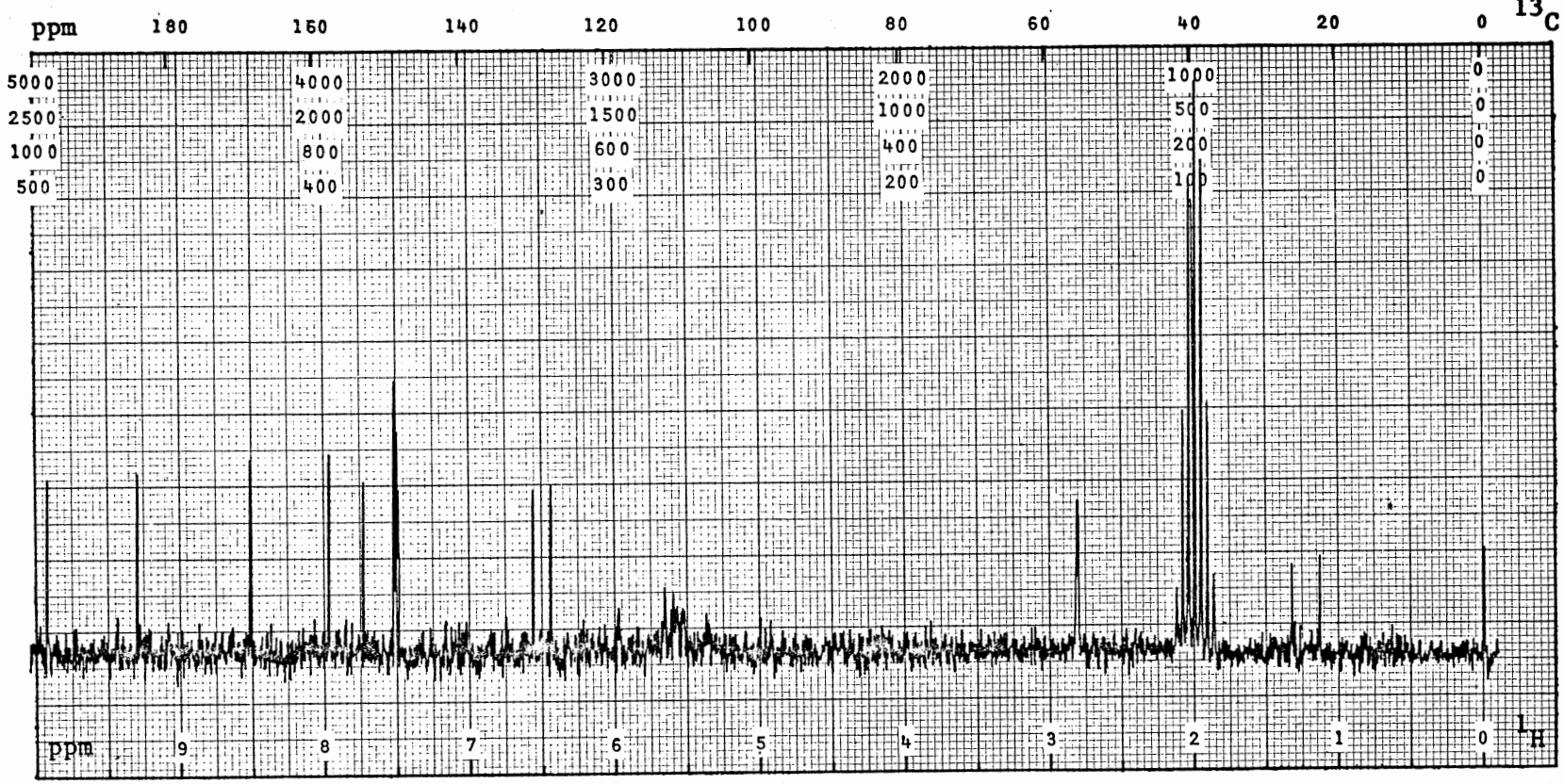
^{1}H NMR Spectrum of 2-Acetoamido-4-(3',4'-dimthoxyphenyl)thiazole (21a, R""=Ac)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69µs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE IX



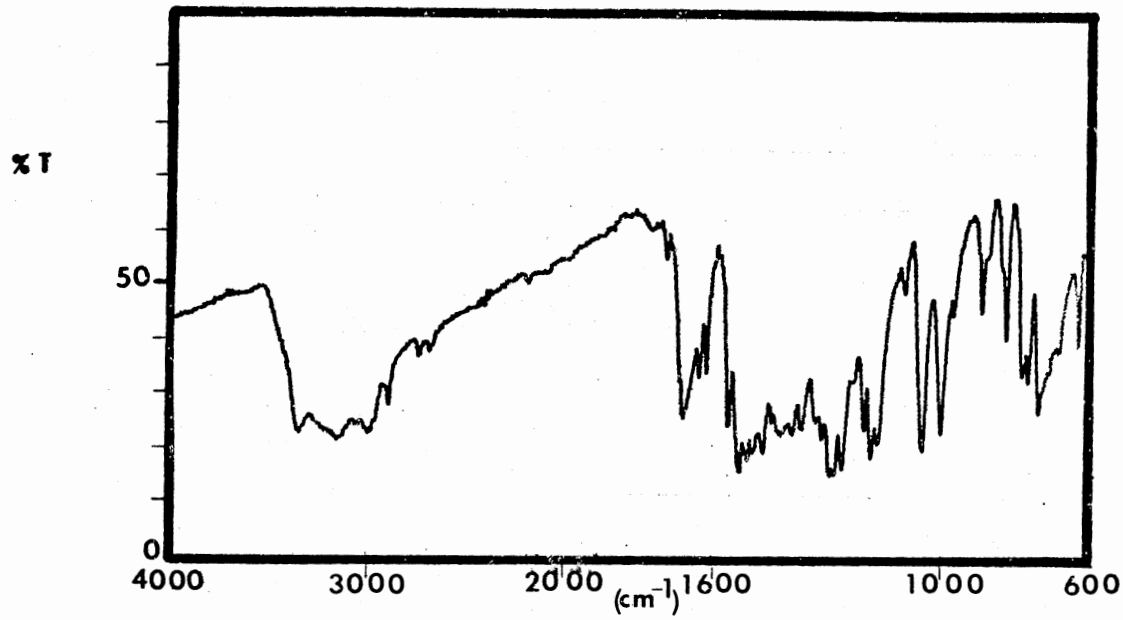
^{13}C NMR Spectrum of 2-Acetoamido-4-(3',4'-dimethoxyphenyl)thiazole (21a, R""=Ac)

PFT ^{13}C CW _ ; Solvent. . DMSO-d_6; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 900

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 2Hz; Lock. . ^{2}D ; D5/ST. . 6s

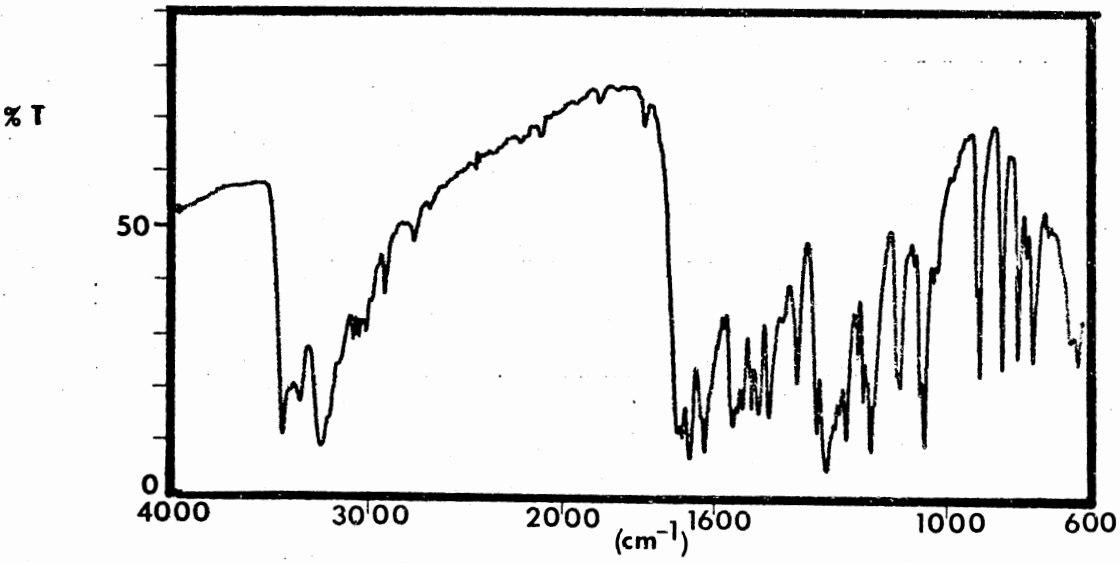
DC. . ^{1}H; Gated Off. . ; Offset. . 45808Hz; RF. . 94 W/dB; NBW. . 100Hz

PLATE X



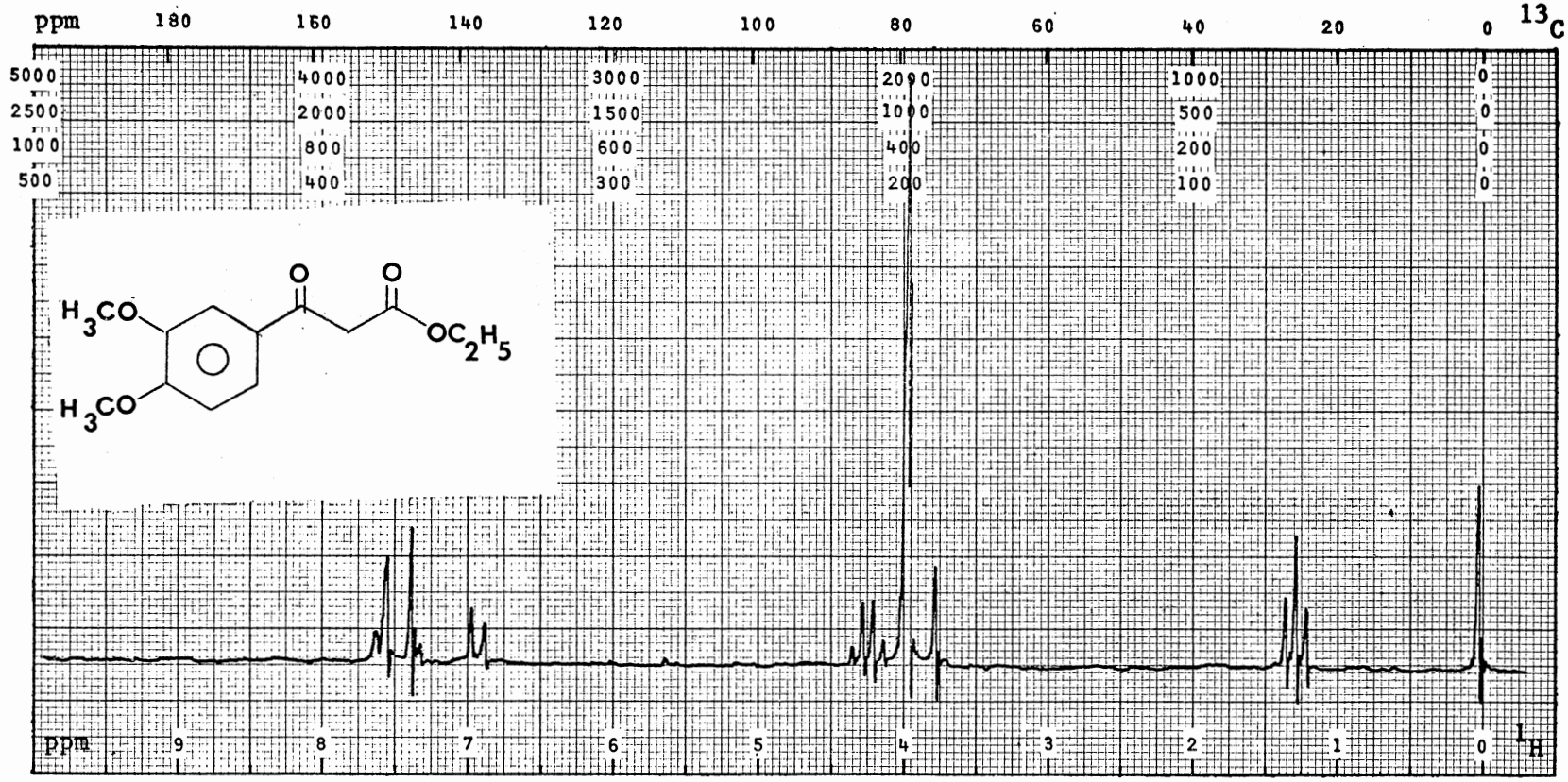
Ir Spectrum of 2-Allylamino-4-(3',4'-dimethoxyphenyl) thiazole (21c, R"" = acetate), KBr Pellet

PLATE XI



IR Spectrum of 2-Acetoamido-4-(3',4'-dimethoxyphenyl) thiazole(21b, R"" = allyl), KBr Pellet

PLATE XII



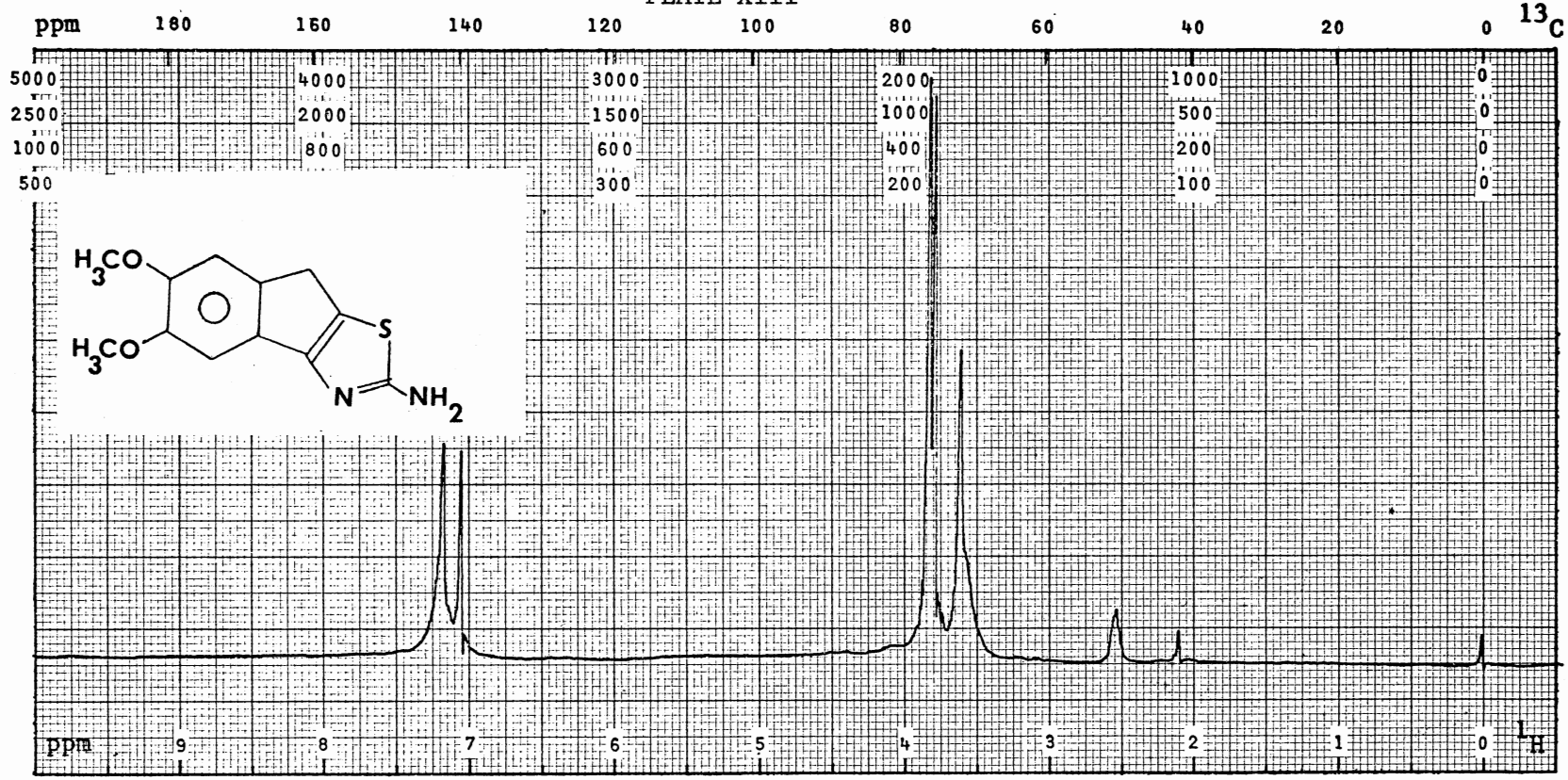
^{1}H NMR Spectrum of Ethyl 3-(3',4'-Dimethoxyphenyl)-3-oxopropionate (35a)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69μs/dB; SF. . 100.1Hz; FB. . Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XIII



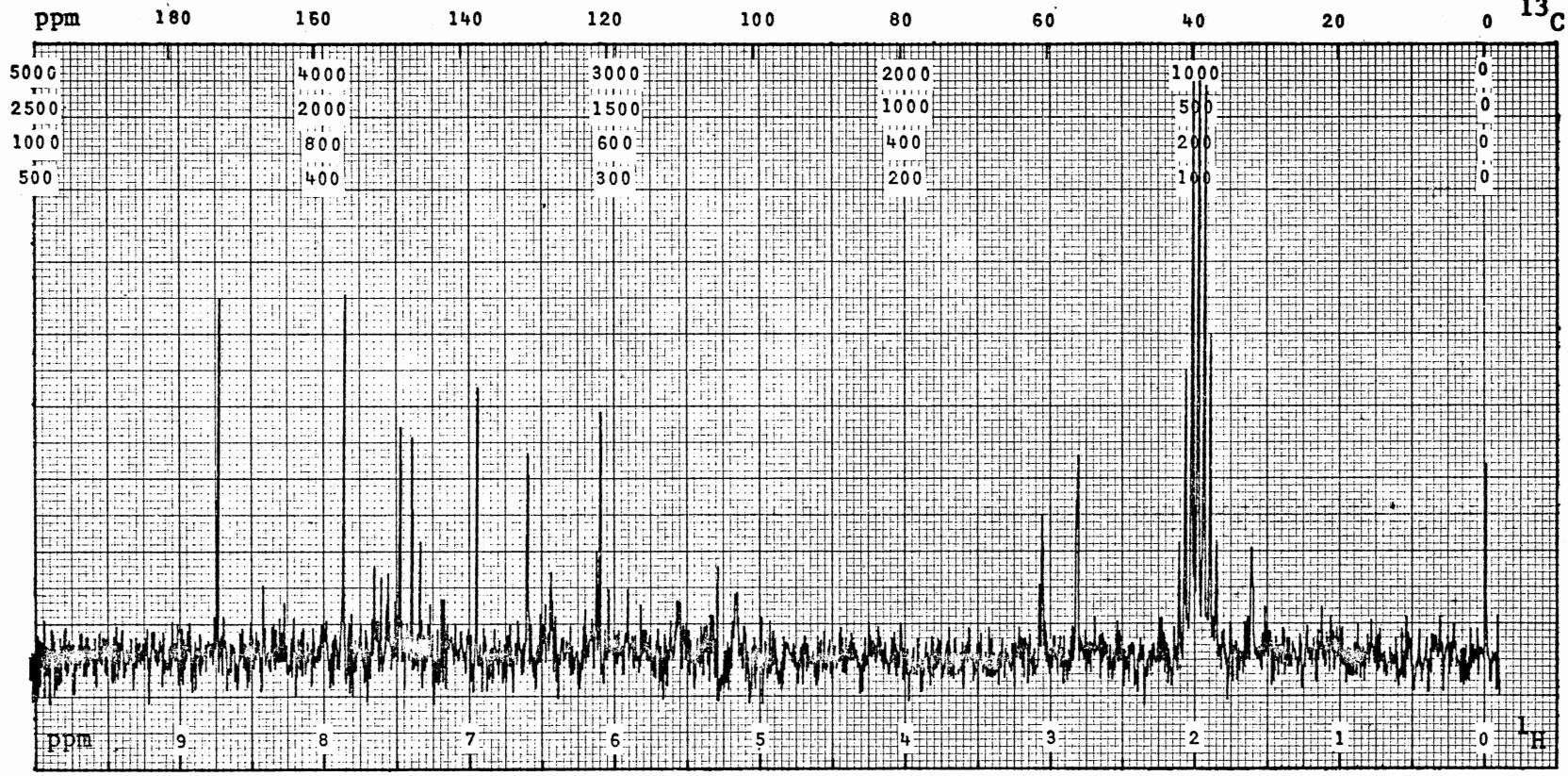
^{1}H NMR Spectrum of 2-Amino-6,7-dimethoxyindeno[1,2-d]thiazole (22a, R""=H)

PFT _ CW X ; Solvent. . DMSO-d_6; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XIV



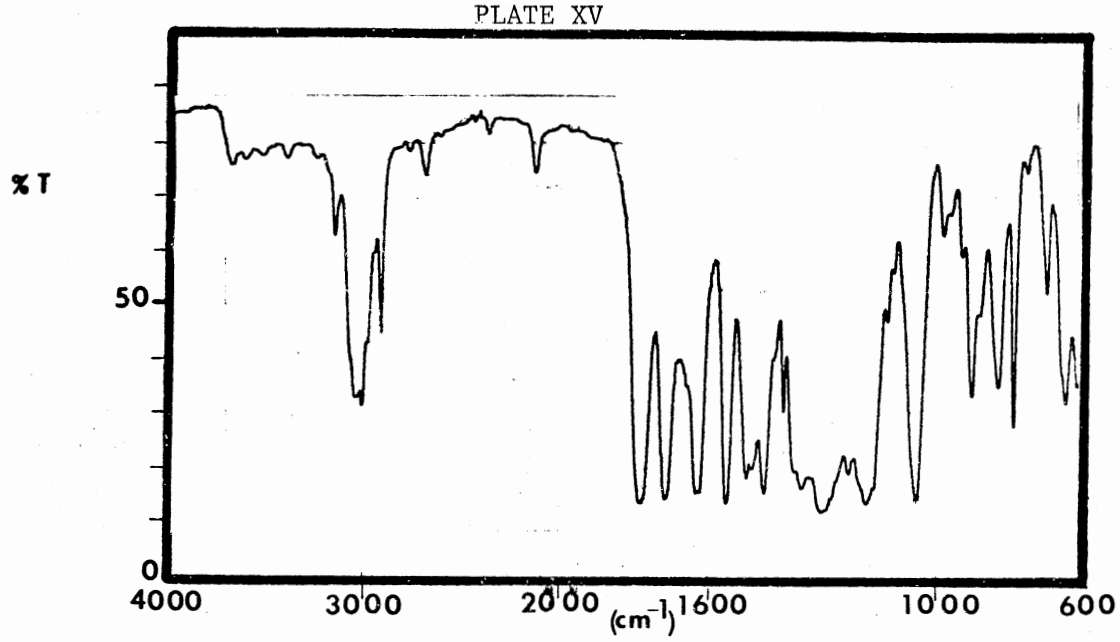
^{13}C NMR Spectrum of 2-Amino-6,7-dimethoxyindeno[1,2-d]thiazole (22a, R''''=H)

PFT ^{13}C CW _ ; Solvent. . DMSO-d_6; SO. . 8510Hz; PW. . 5000Hz; T. . 88°C; Acq/SA. . 900

Size. . 8K; P2/RF. . 10μs/dB; SF. . 252Hz; FB. . 4Hz; Lock. . ^{2} ; D5/ST. . 6s

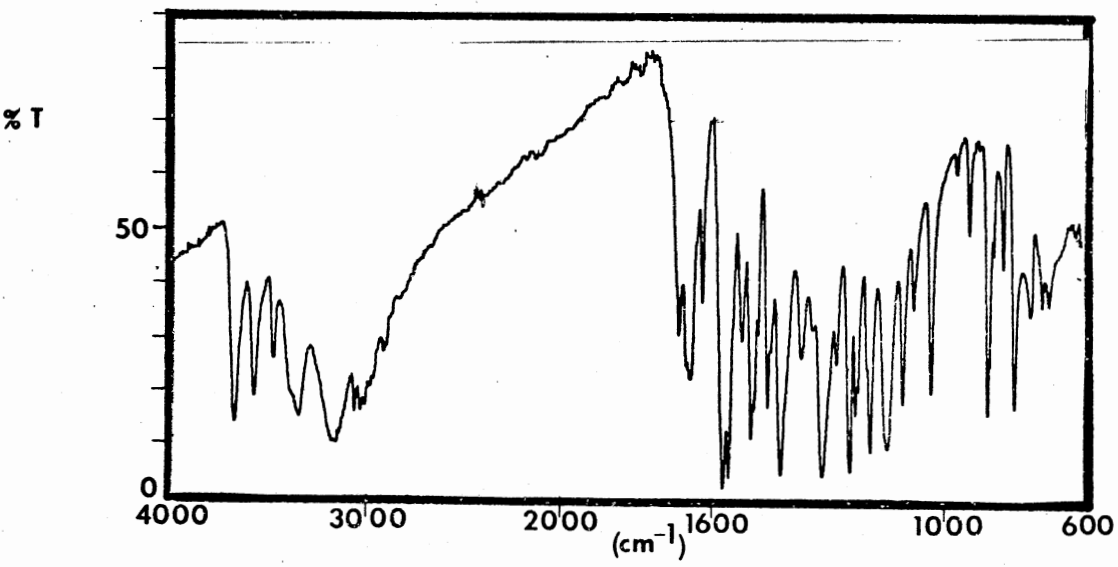
DC. . ^{1}H; Gated Off. . ; Offset. . 4580Hz; RF. . 94 W/dB; NBW. . 100Hz

PLATE XV



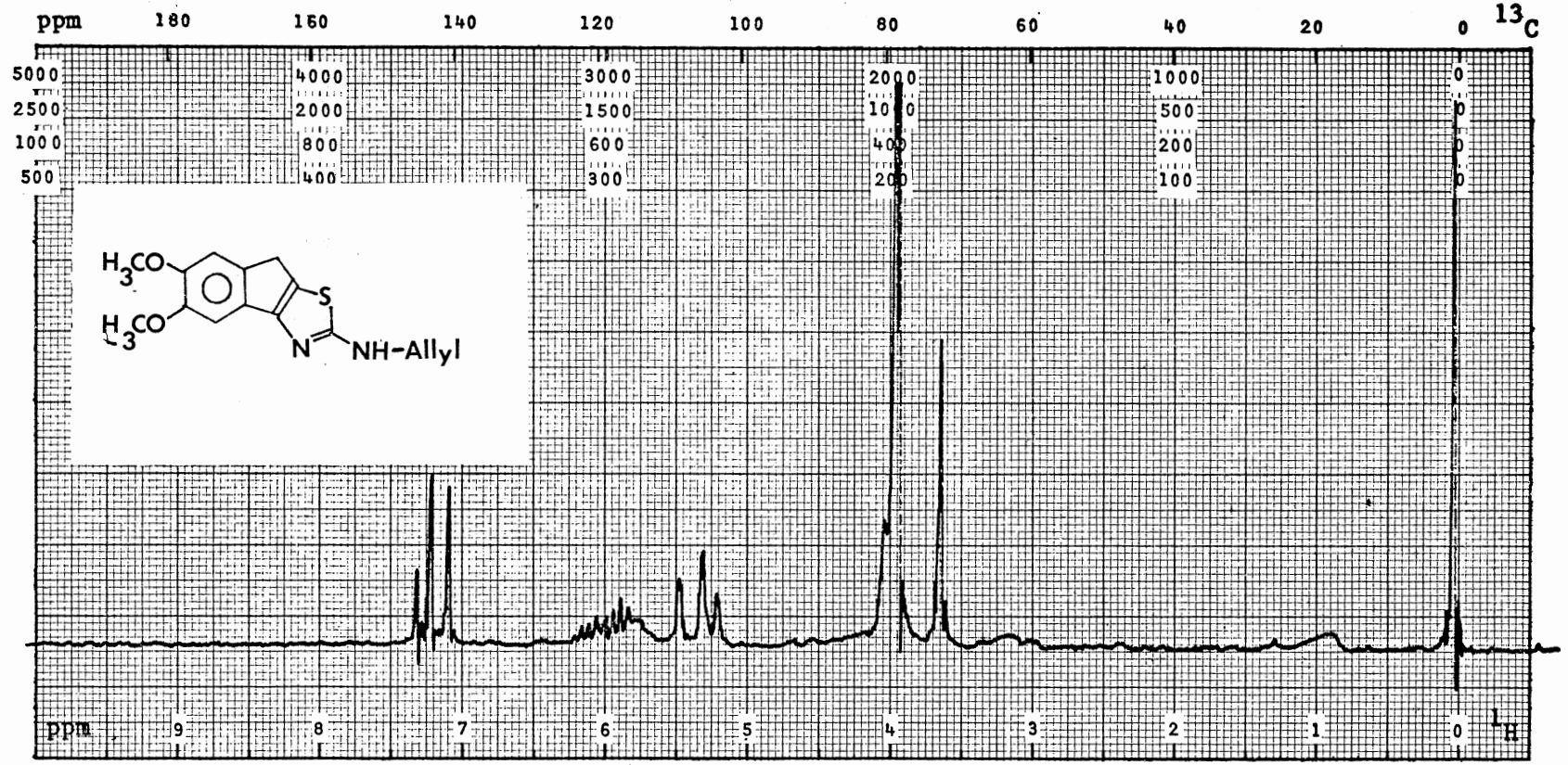
IR Spectrum of Ethyl 3-(3',4'-Dimethoxyphenyl)-3-oxopropionate (35a), KBr Pellet

PLATE XVI



IR Spectrum of 2-Amino-6,7-dimethoxyindeno[1,2-d]thiazole (22a, R"" = H), KBr Pellet

PLATE XVII



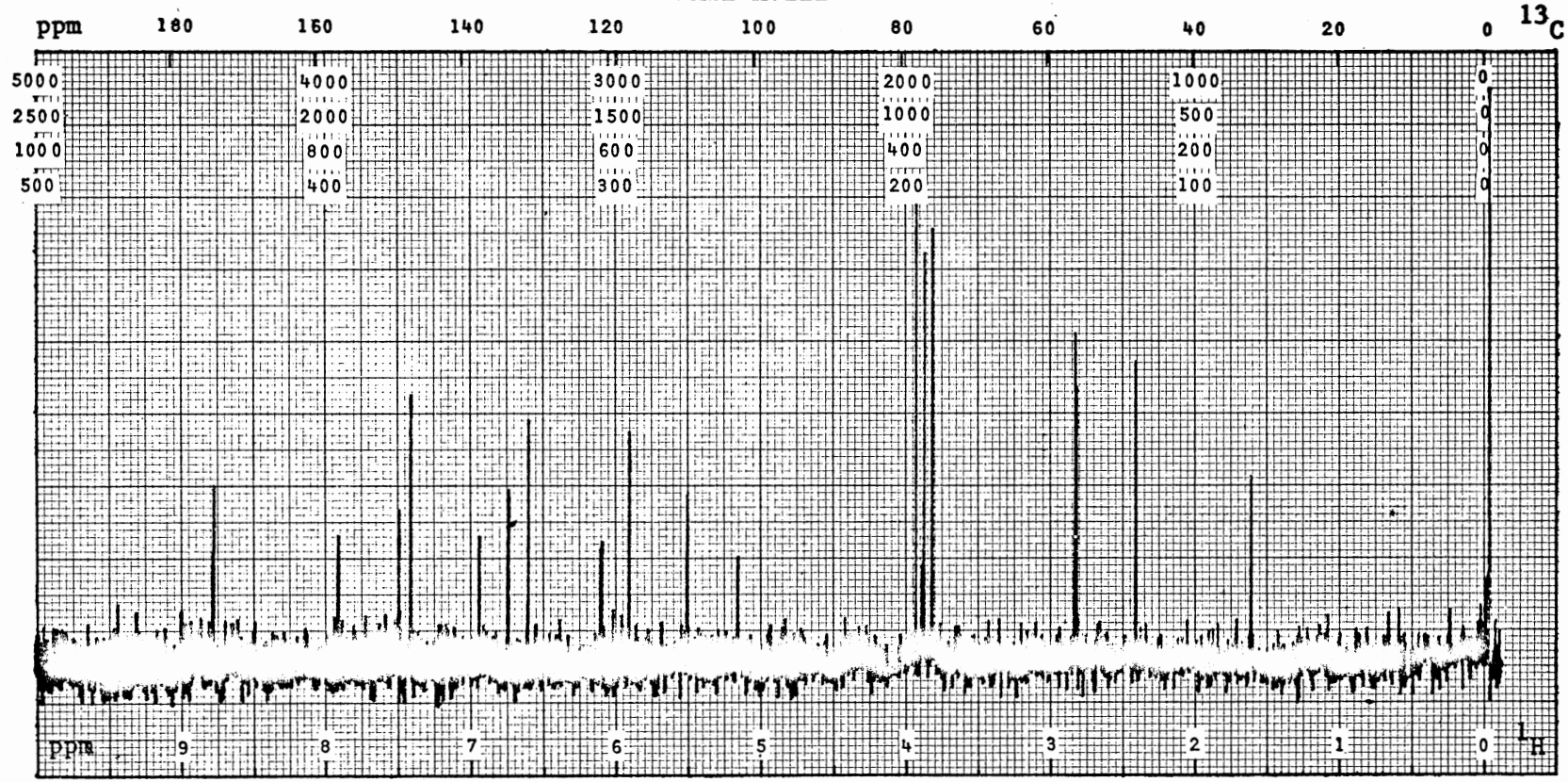
^{1}H NMR Spectrum of 2-Allylamino-6,7-dimethoxyindeno[1,2-d]thiazole (22a, R""=allyl)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 62μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XVIII



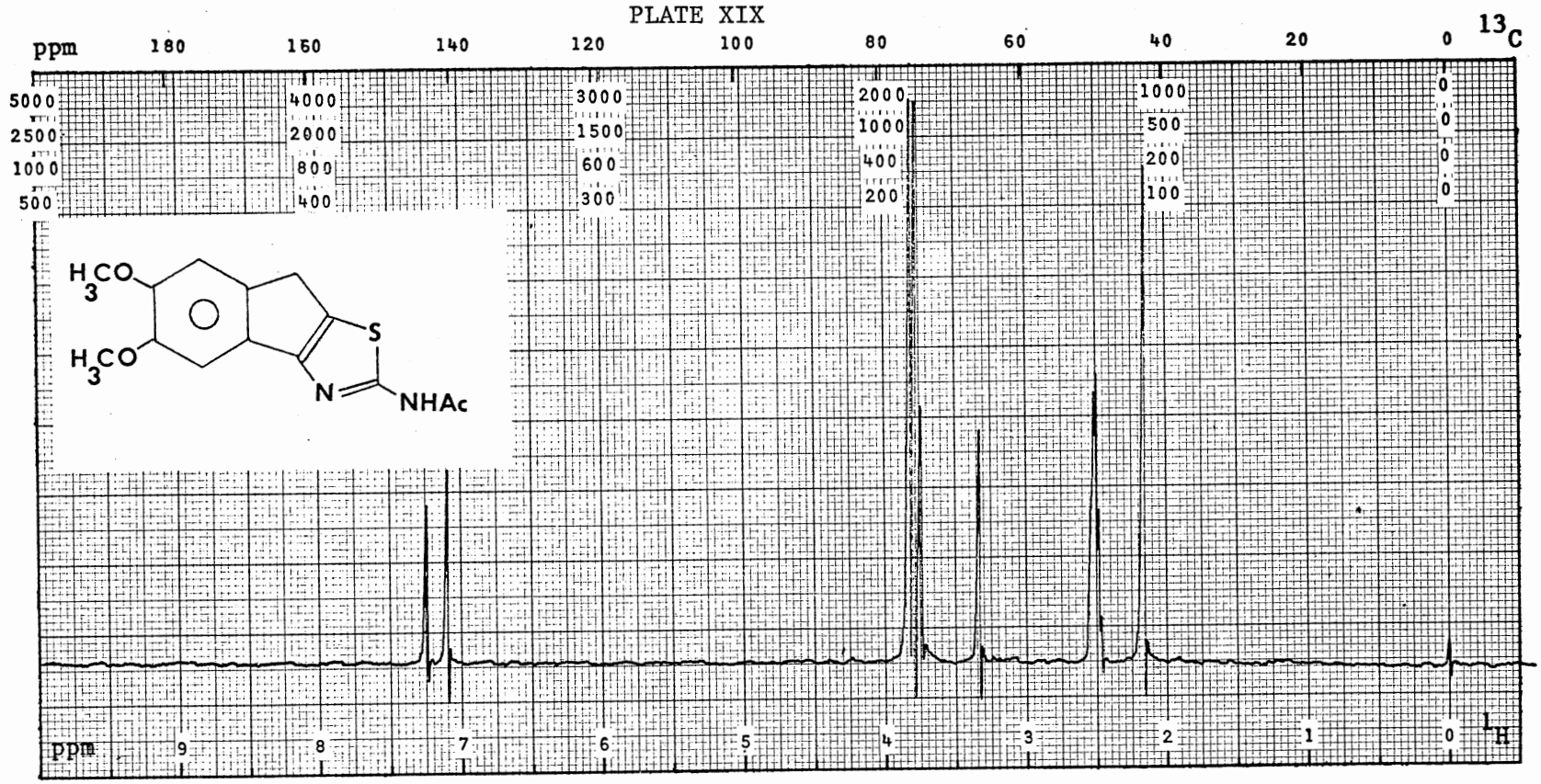
^{13}C NMR Spectrum of 2'-Allylamino-6,7-dimethoxyindeno[1,2-d]thiazole (22a, R"" = allyl)

PFT ^{13}C CW _ ; Solvent. . $DCCl_3$; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 1400

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 3Hz; Lock. . ^{2}D; D5/ST. . 5s

DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 65W/dB; NBW. . 100Hz

PLATE XIX



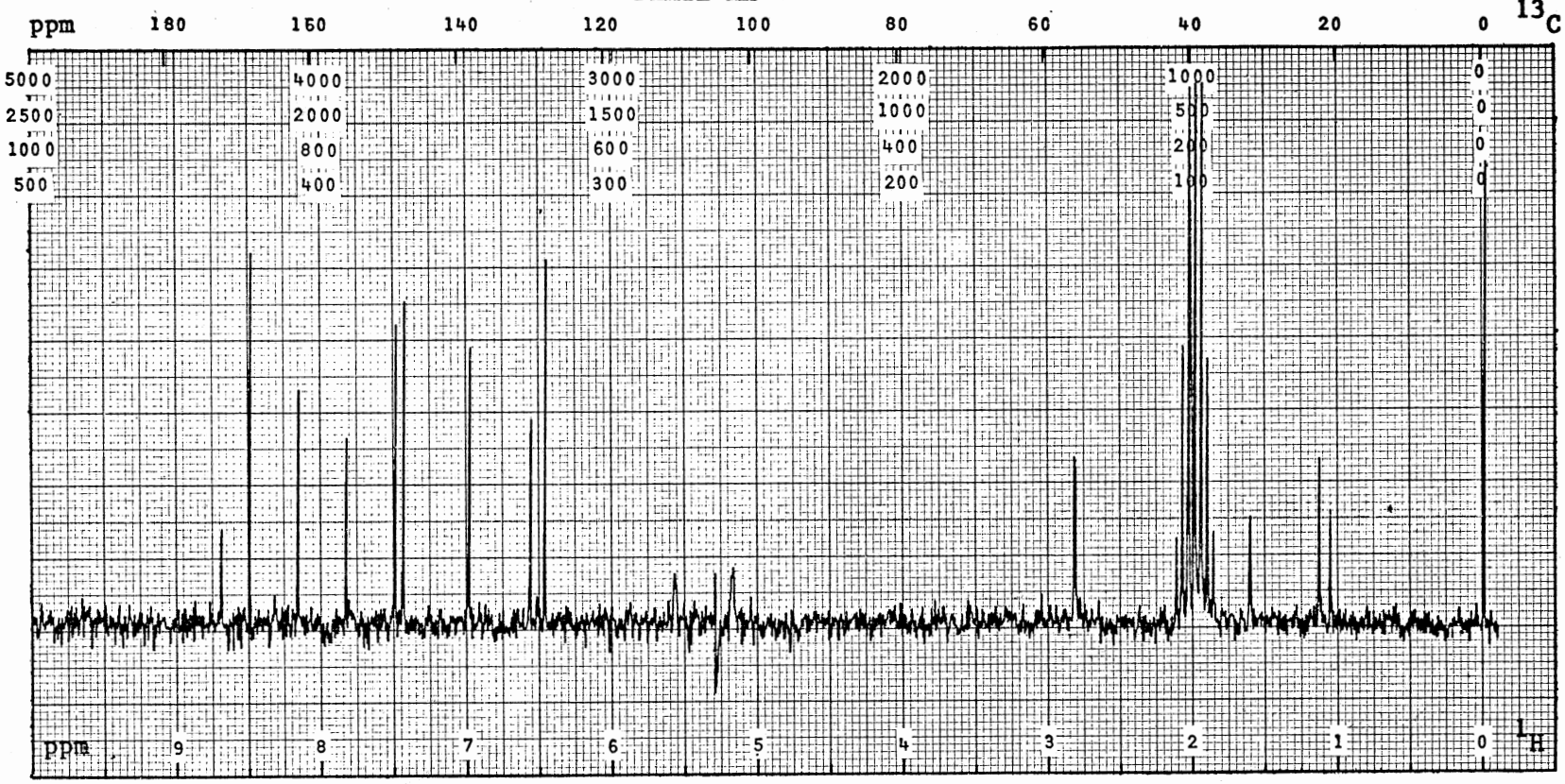
^{1}H NMR Spectrum of 2-Acetoamido-6,7-dimethoxyindeno[1,2-d]thiazole (22a, R""=Ac)

PFT _ CW X ; Solvent. . DMSO-d_6; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 10

Size. . K; P2/RF. . 69μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XX



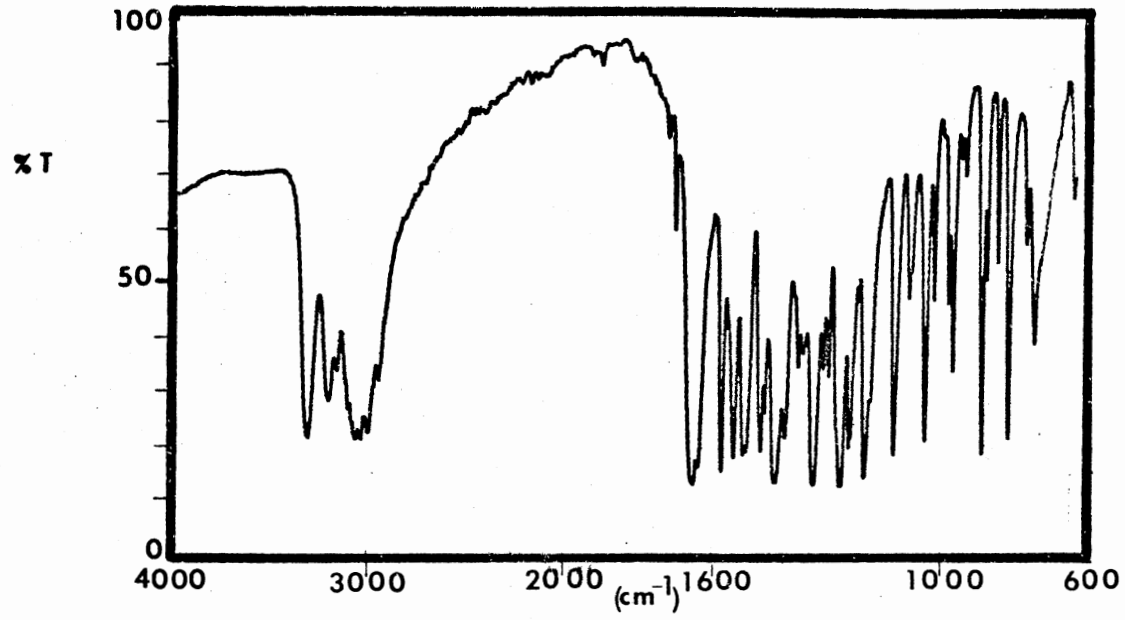
^{13}C NMR Spectrum of 2-Acetoamido-6,7-dimethoxyindeno[1,2-d]thiazole (22a, R""=Ac)

PFT ^{13}C CW _ ; Solvent. . DMSO-d_6; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 900

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 4Hz; Lock. . ^{2}D; D5/ST. . 6s

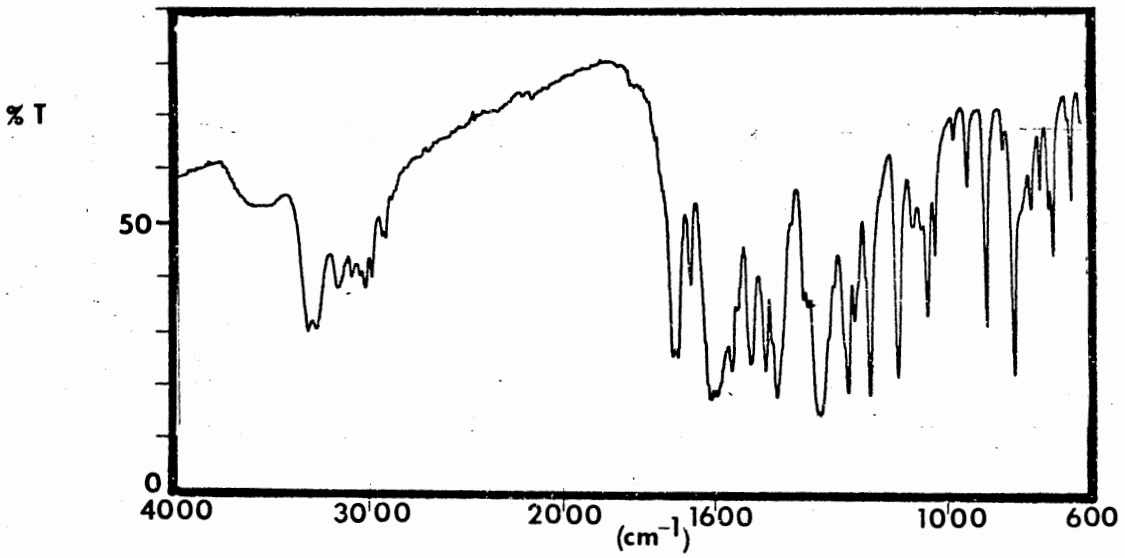
DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 94 W/dB; NBW. . 100Hz

PLATE XXI



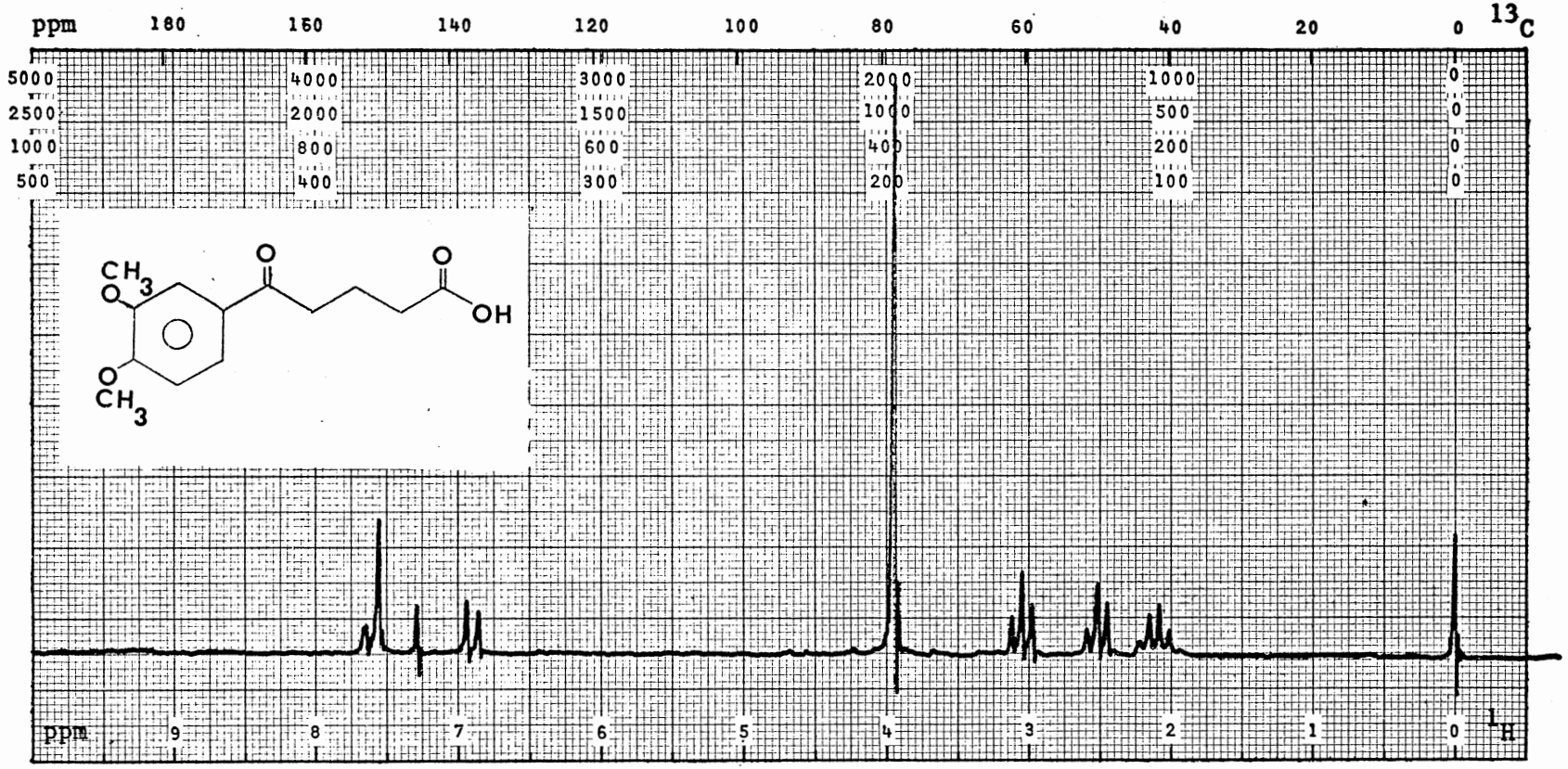
IR Spectrum of 2-Allylamino-6,7-dimethoxyindeno[1,2-d] thiazole (22a, R'''' = allyl), KBr Pellet

PLATE XXII



Ir Spectrum of 2-Acetoamido-6,7-dimethoxyindeno[1,2-d] thiazole (22a, R'''' = acetate), KBr Pellet

PLATE XXIII



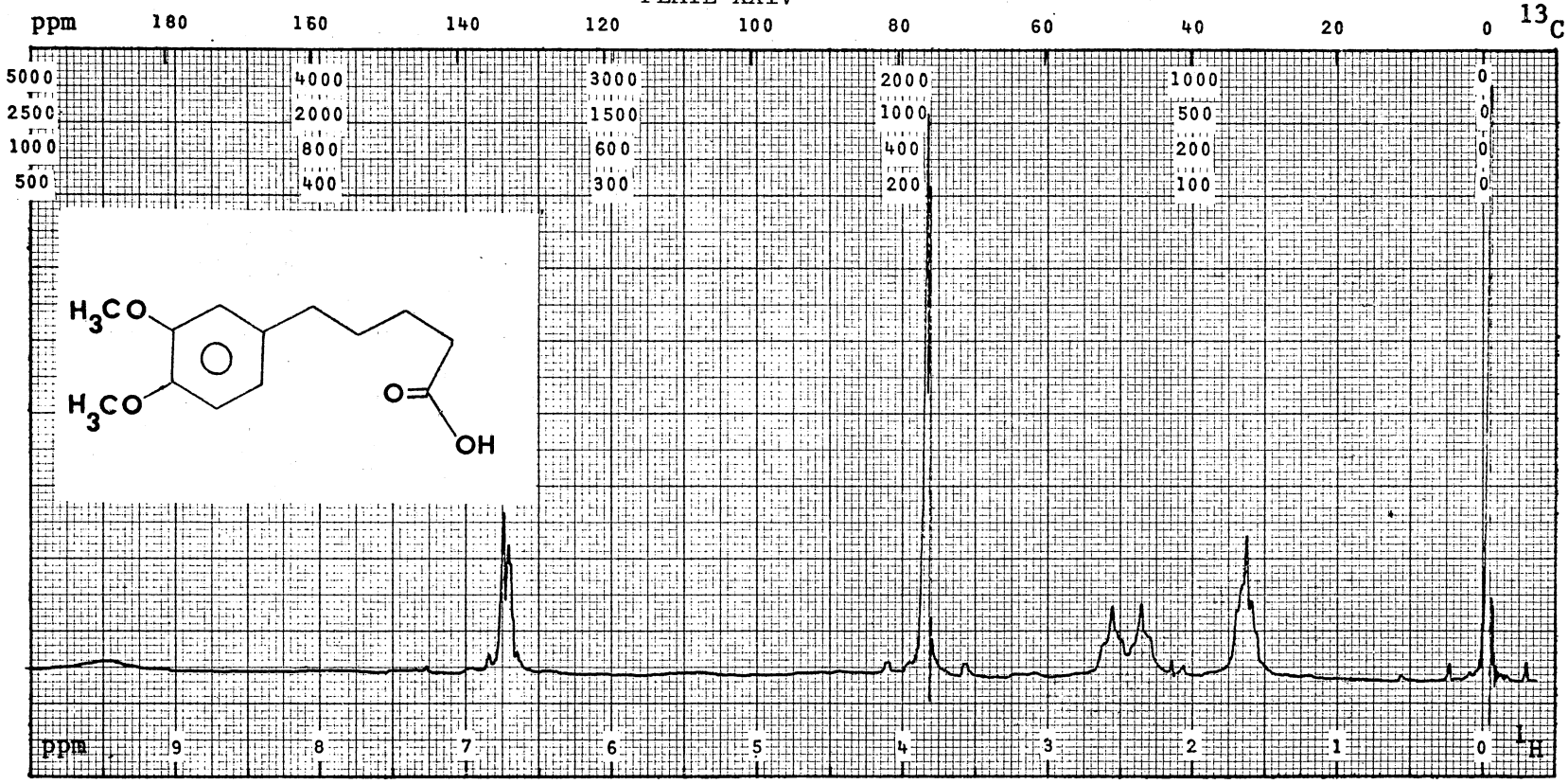
^{1}H NMR Spectrum of 5-(3',4'-Dimethoxyphenyl)-5-oxopentanoic Acid (37a)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 77μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XXIV



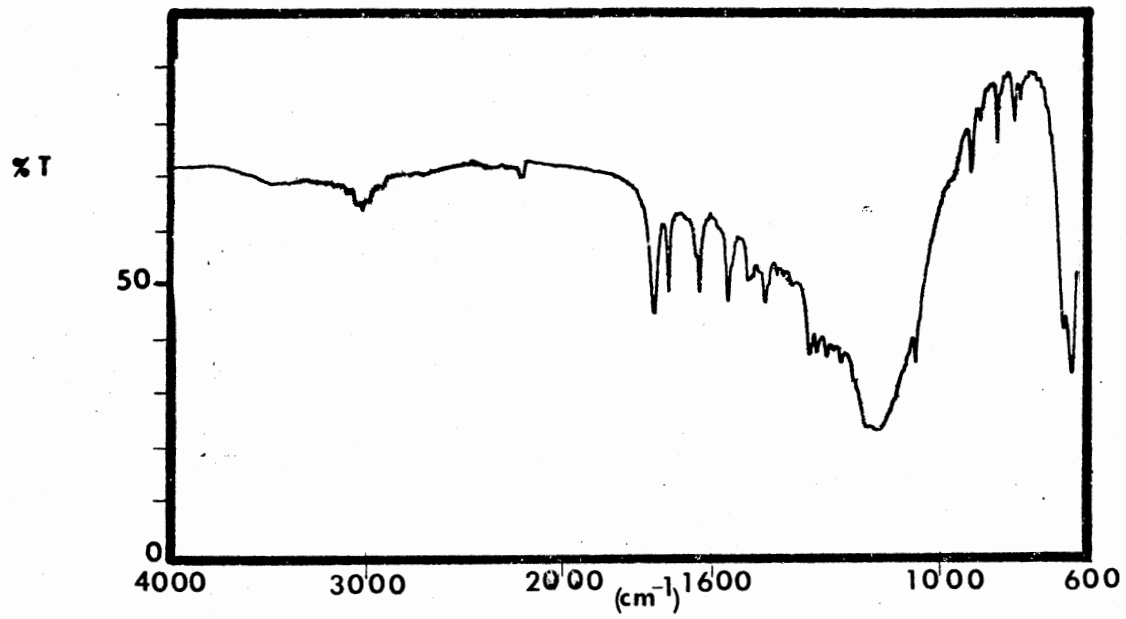
^{1}H NMR Spectrum of 5-(3',4'-Dimethoxyphenyl)pentanoic Acid (42a)

PFT _ CW X ; Solvent. . $DCCl_8$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

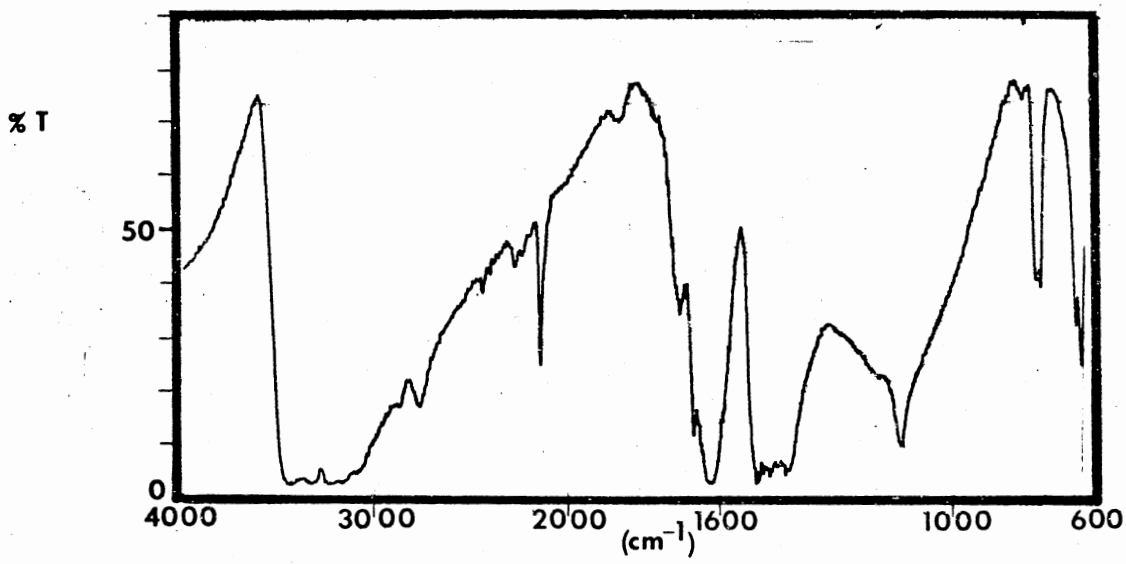
DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XXV



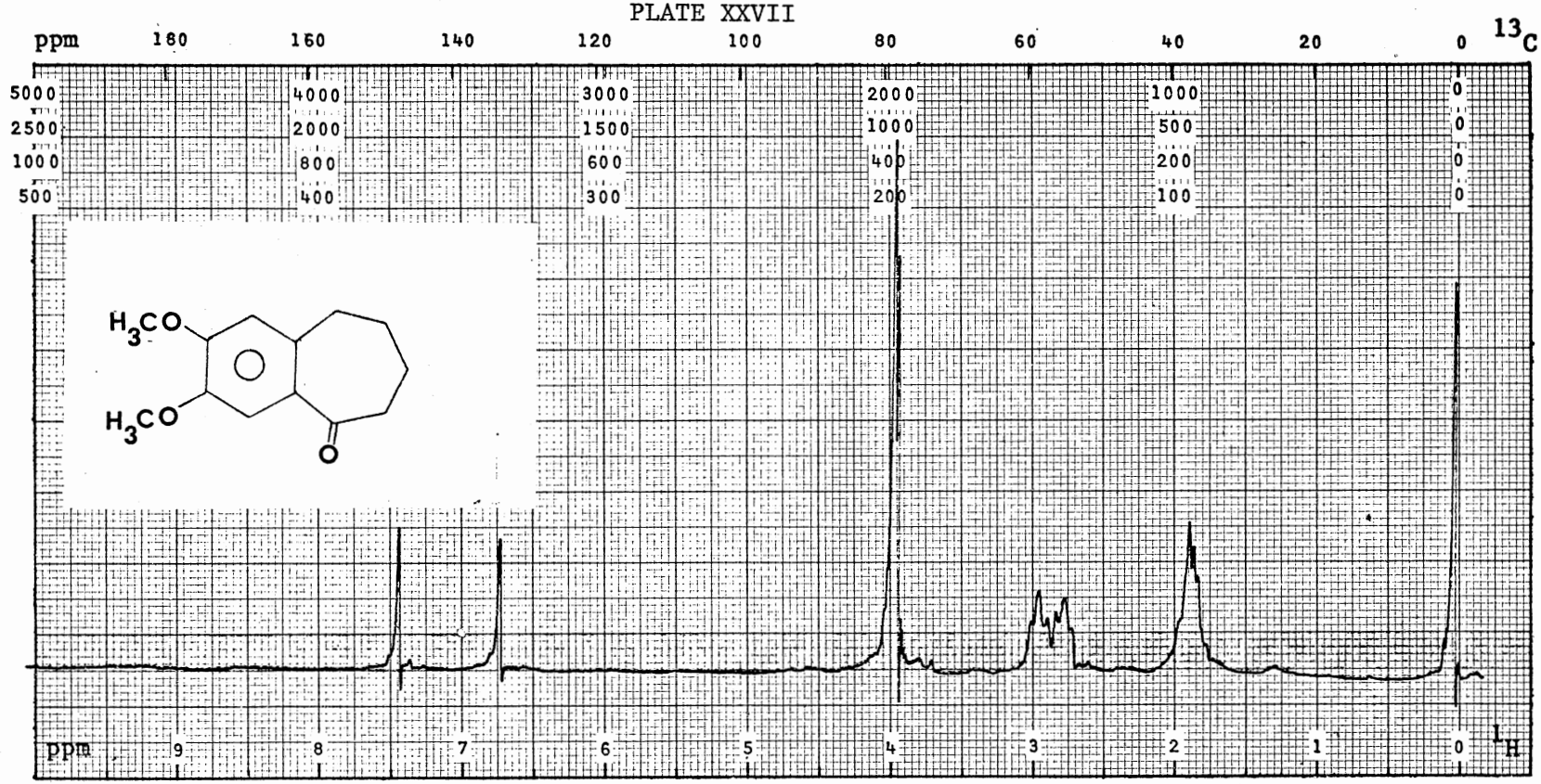
IR Spectrum of 5-(3',4'-Dimethoxyphenyl)-5-oxopentanoic Acid (37a), KBr Pellet

PLATE XXVI



IR Spectrum of 5-(3',4'-Dimethoxyphenyl)pentanoic Acid (42a) KBr Pellet

PLATE XXVII

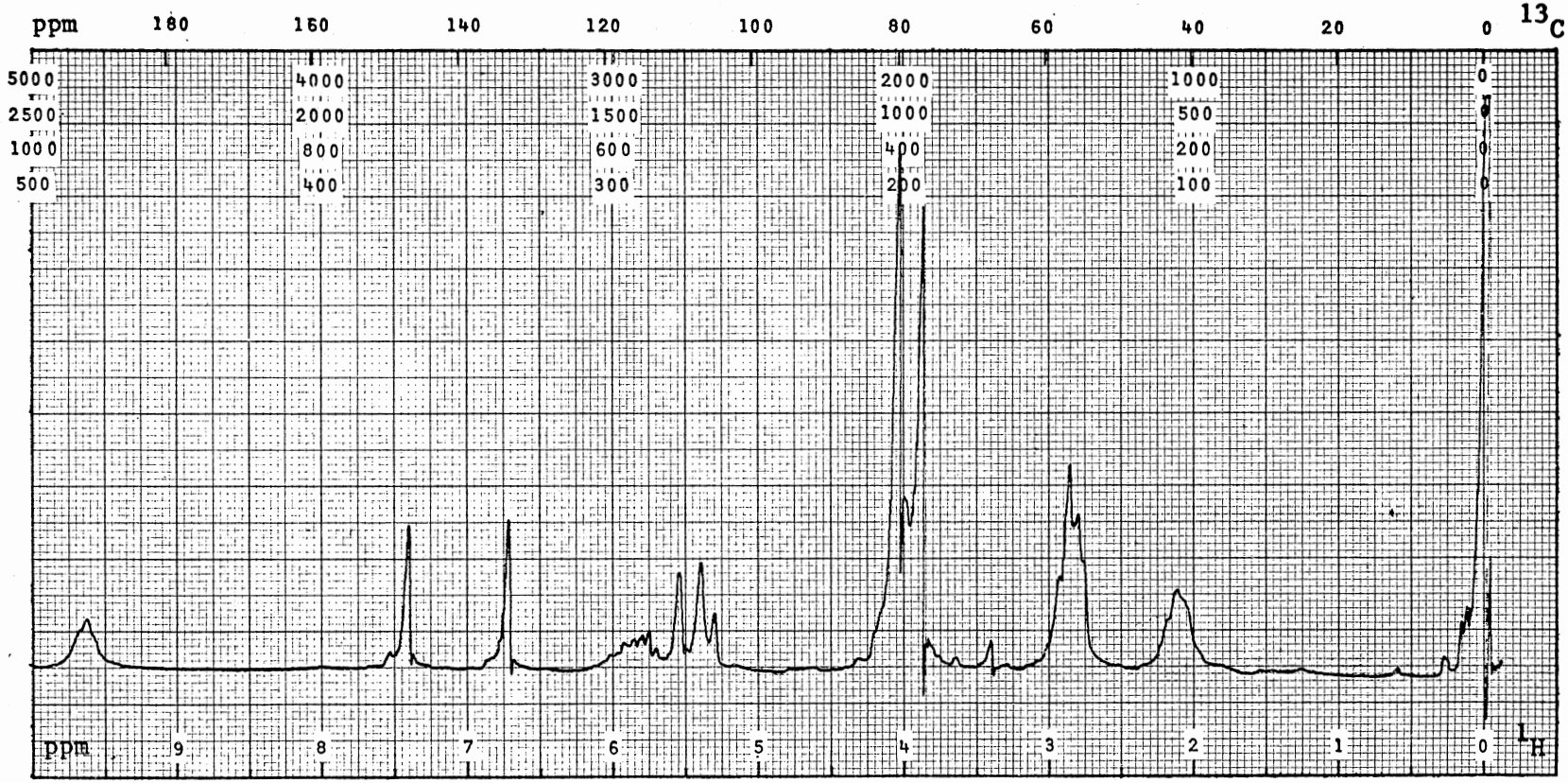


^{1}H NMR Spectrum of 7,8-Dimethoxysuberone (33a)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69µs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

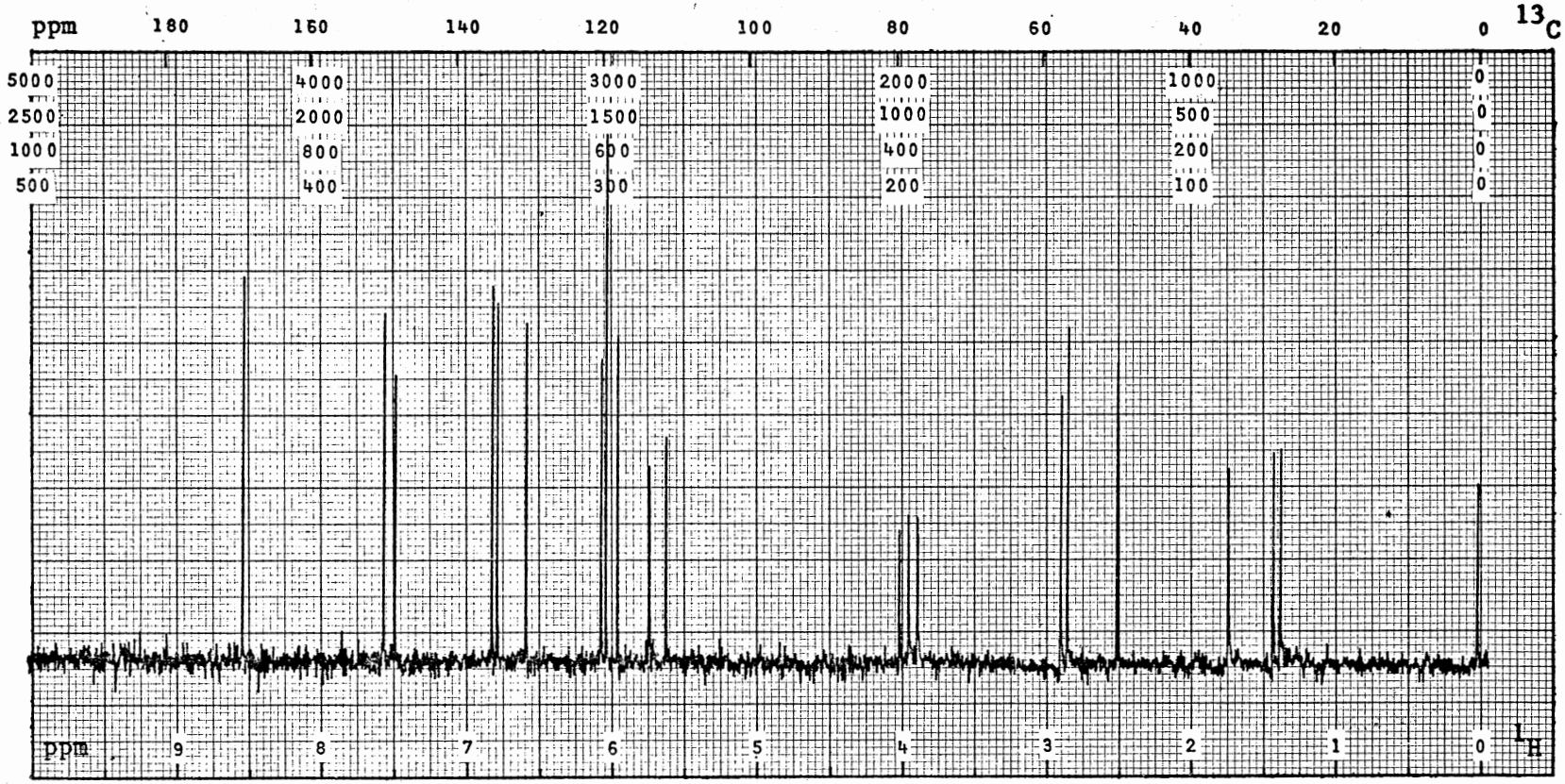


^{1}H NMR Spectrum of 2-Allylamino-8,9-dimethoxysubero[1,2-d]thiazole (24a, R''''=allyl)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69μs/dB; SF. . 100.1Hz; FB. . 4Hz; Lock. . ^{2}D; D5/ST. . 150s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz



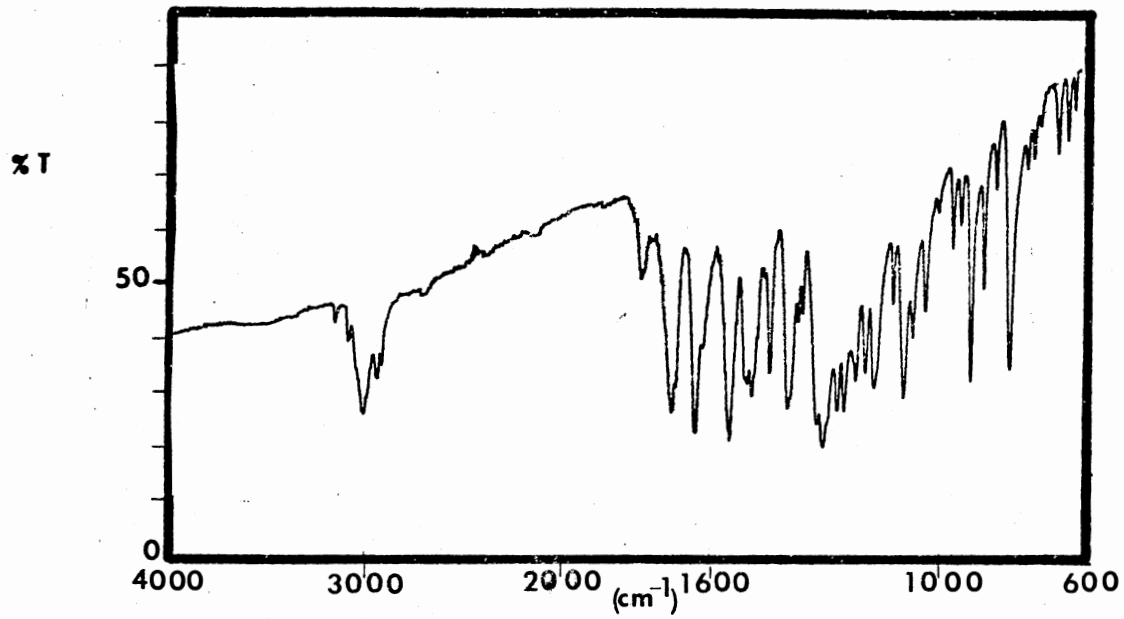
^{13}C NMR Spectrum of 2-Allylamino-8,9-dimethoxysubero[1,2-d]thiazole (24a, R""=allyl)

PFT ^{13}C CW _ ; Solvent. . $DCCl_3$; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 300

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 3Hz; Lock. . ^{2}D; D5/ST. . 5s

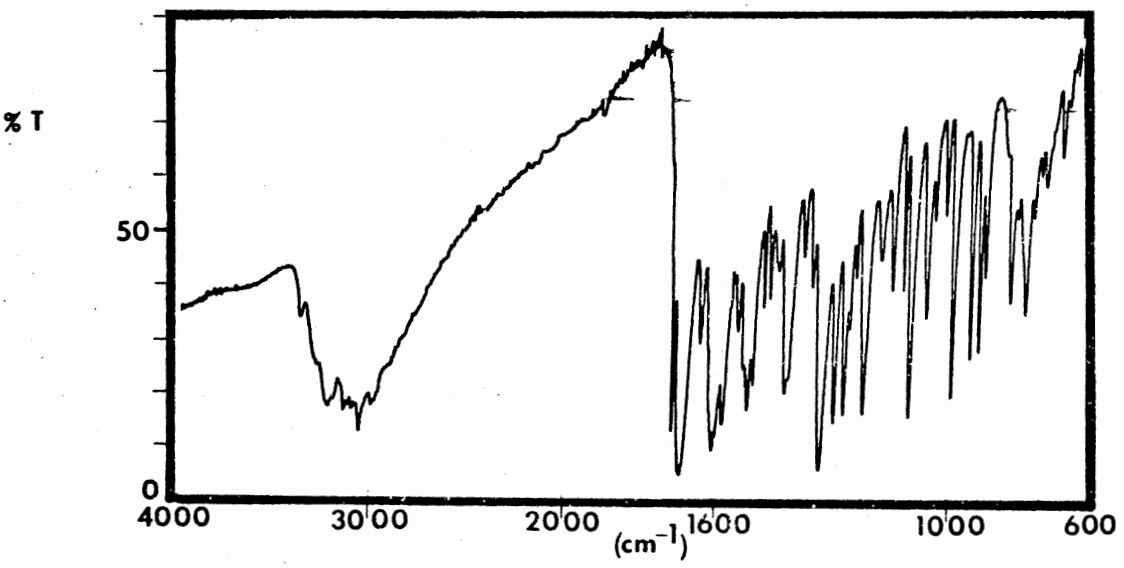
DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE XXX



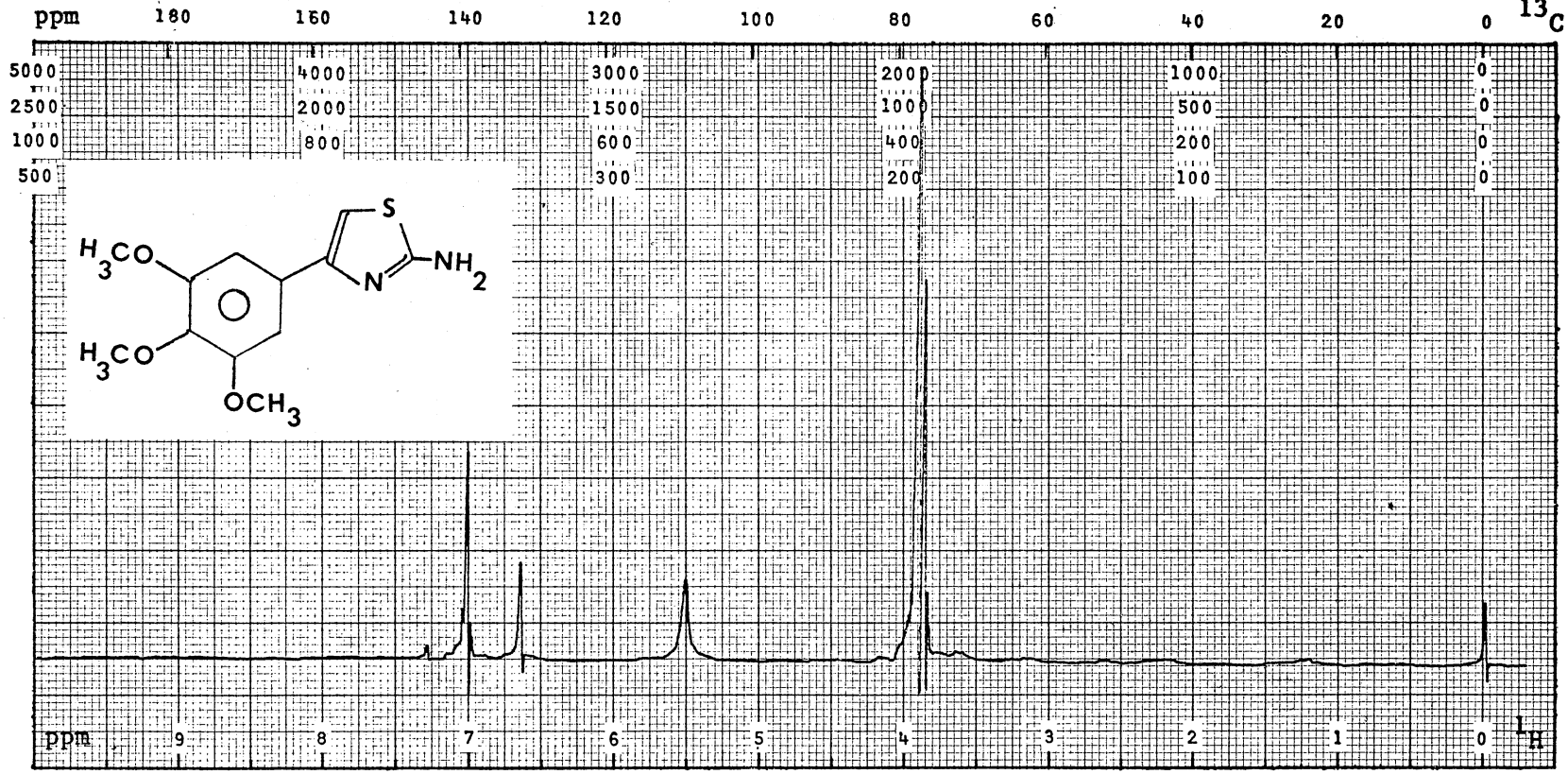
IR Spectrum of 7,8-Dimethoxysuberone (33a), KBr Pellet

PLATE XXXI



IR Spectrum of 2-Amino-8,9-dimethoxysubero[1,2-d]-thiazole (24a), KBr Pellet

PLATE XXXII



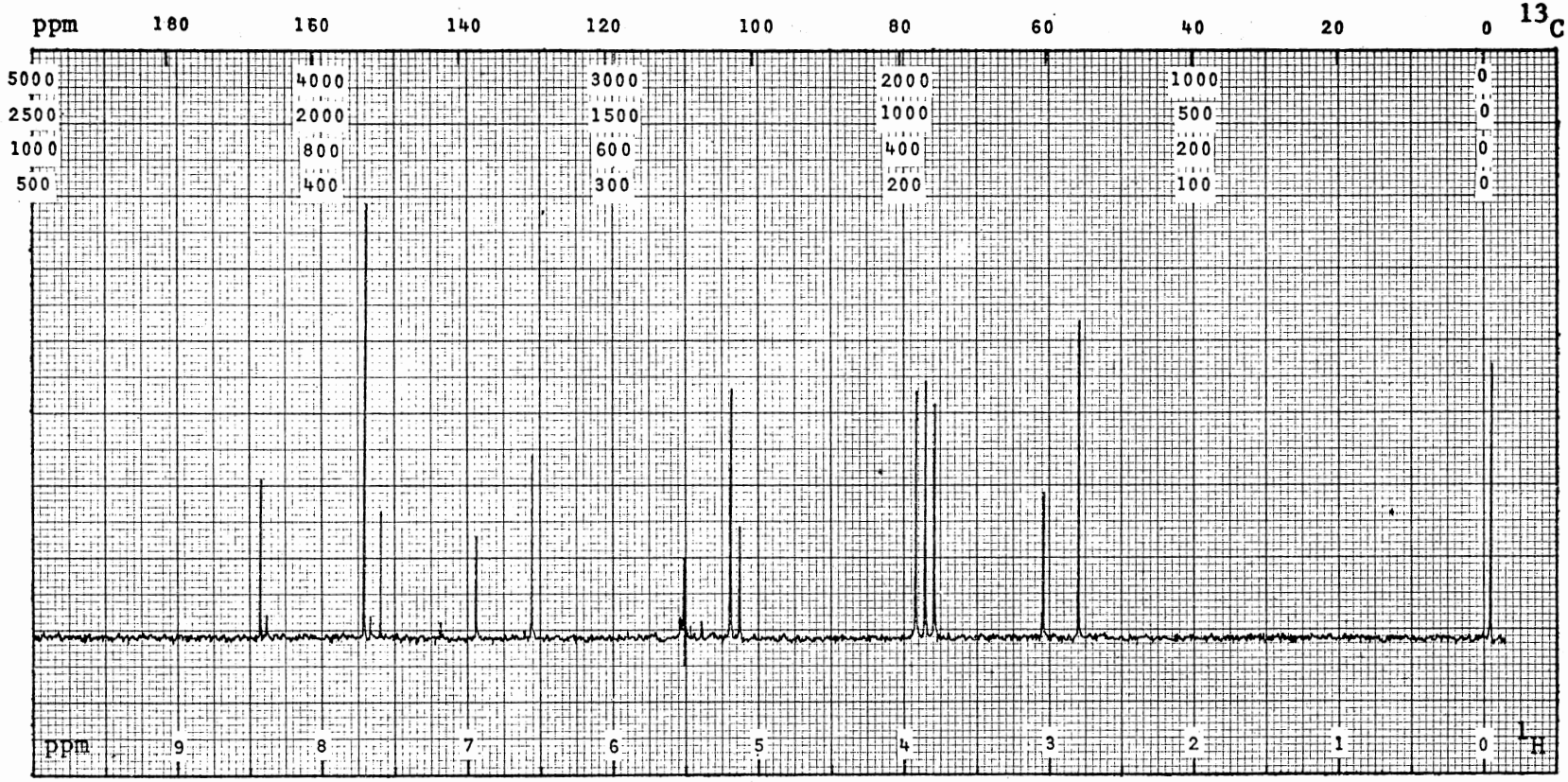
^{1}H NMR Spectrum of 2-Amino-4-(3',4',5'-trimethoxyphenyl)thiazole (21c, R''''=H)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69µs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XXXIII



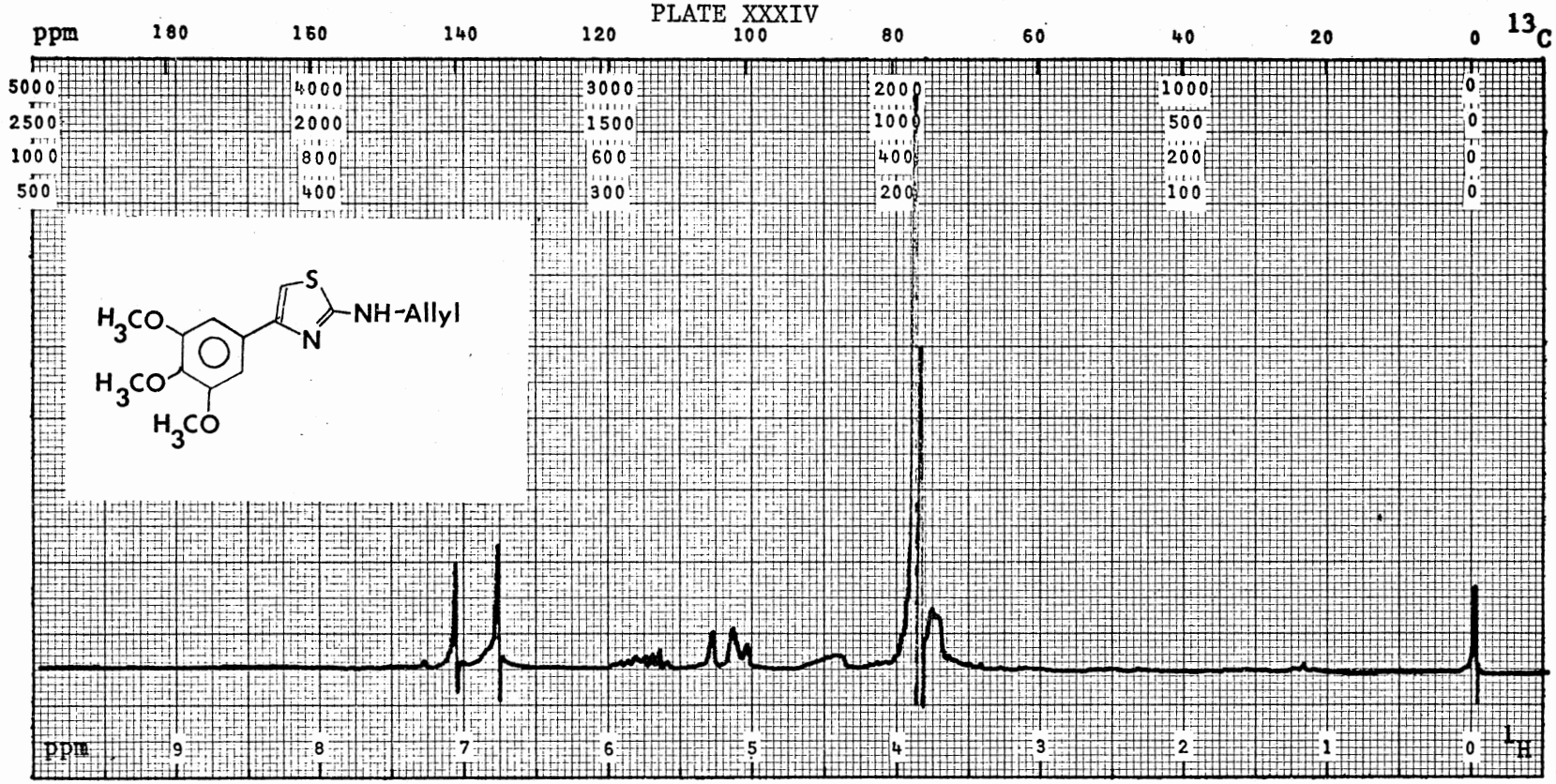
^{13}C NMR Spectrum of 2-Amino-4-(3',4',5'-trimethoxyphenyl)thiazole (21c, R''''=H)

PFT ^{13}C CW _ ; Solvent. . $DCCl_3$; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 8000

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 4Hz; Lock. . ^{2}D; D5/ST. . 5s

DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE XXXIV



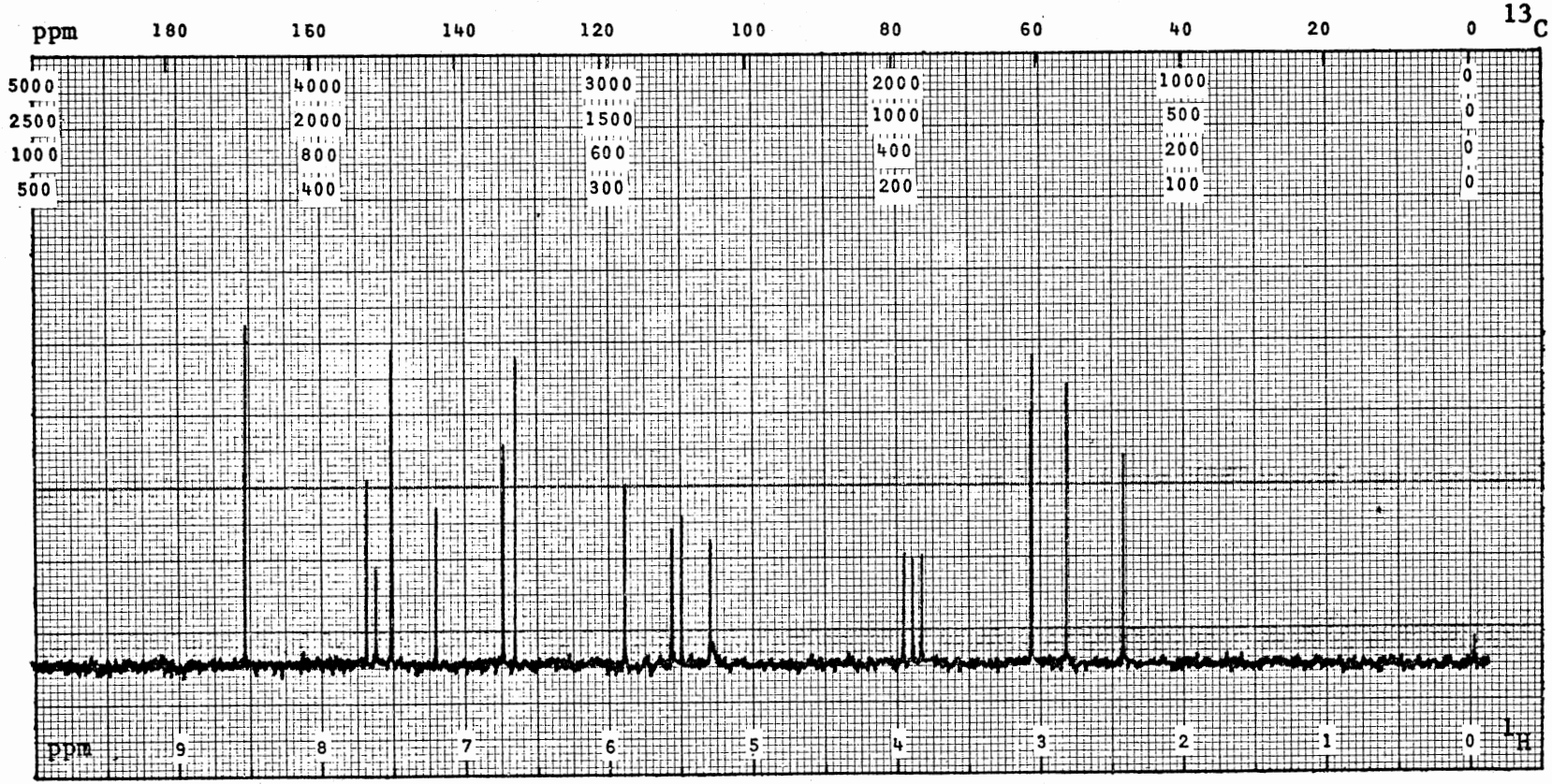
^{1}H NMR Spectrum of 2-Allylamino-4-(3',4',5'-trimethoxyphenyl)thiazole (21c, R''''= allyl)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 8577Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 52μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XXXV



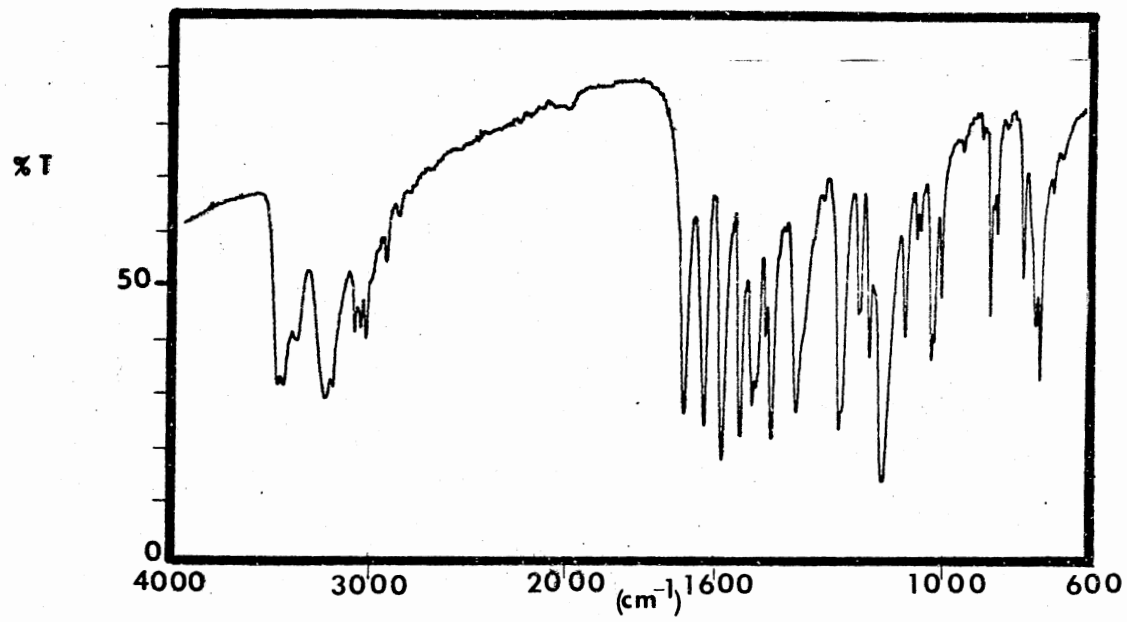
^{13}C NMR Spectrum of 1-Allylamino-4-(3',4',5'-trimethoxyphenyl)thiazole (21c, R'''' = allyl)

PFT ^{13}C CW _ ; Solvent. . $DCCl_3$; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 500

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 3Hz; Lock. . ^{2}D; D5/ST. . 5s

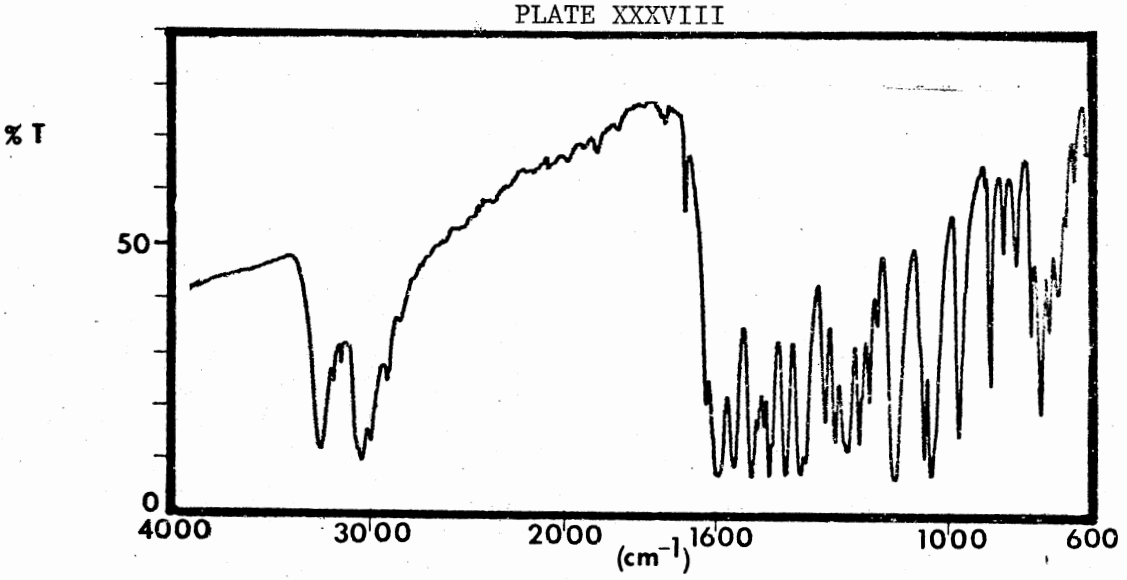
DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE XXXVII



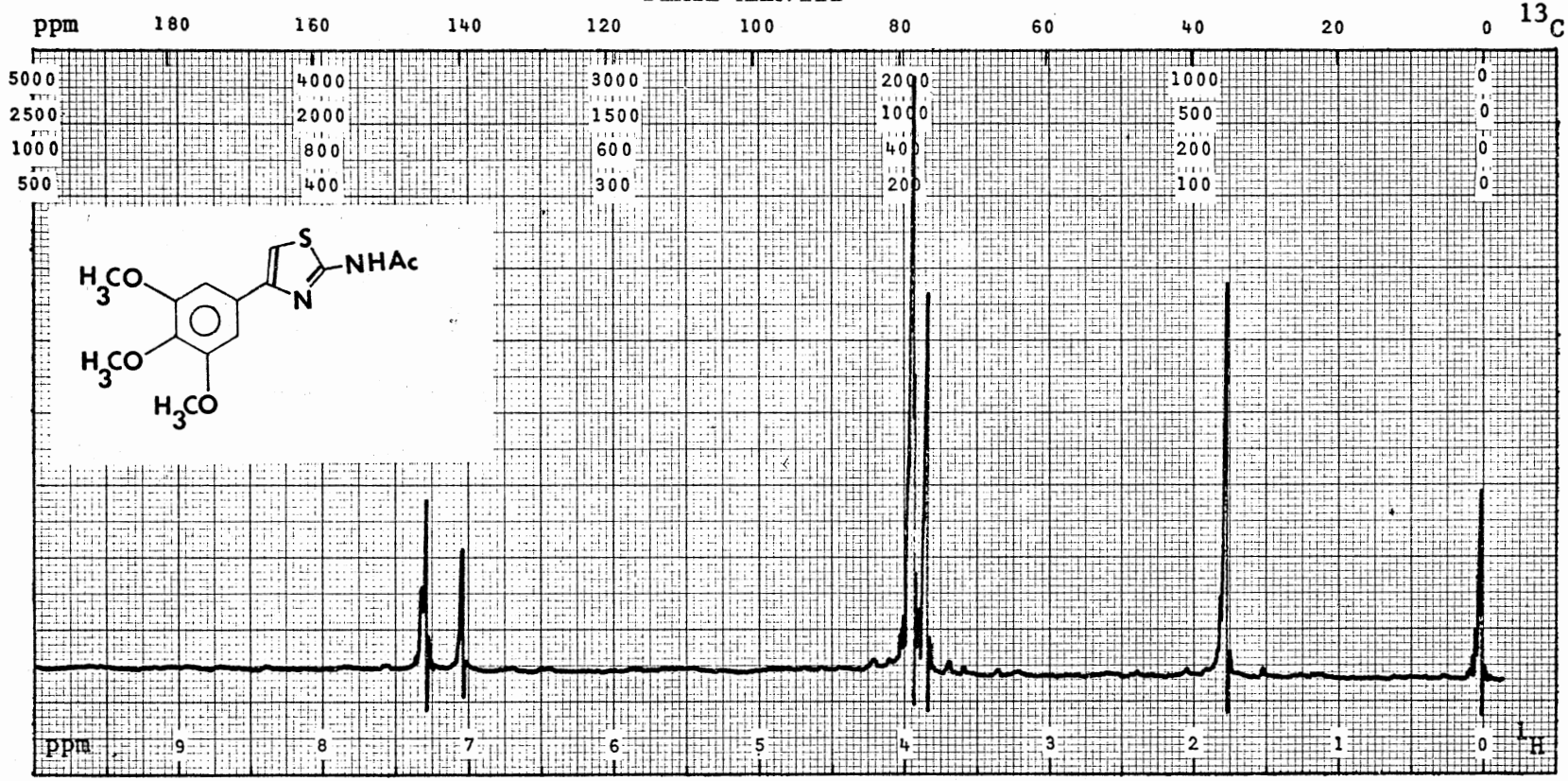
IR Spectrum of 2-Amino-4-(3',4',5'-trimethoxyphenyl)thiazole (21c) KBr Pellet

PLATE XXXVIII



IR Spectrum of 2-Allylamino-4-(3',4',5'-trimethoxyphenyl) thiazole (21c, R"" = allyl), KBr Pellet

PLATE XXXVIII



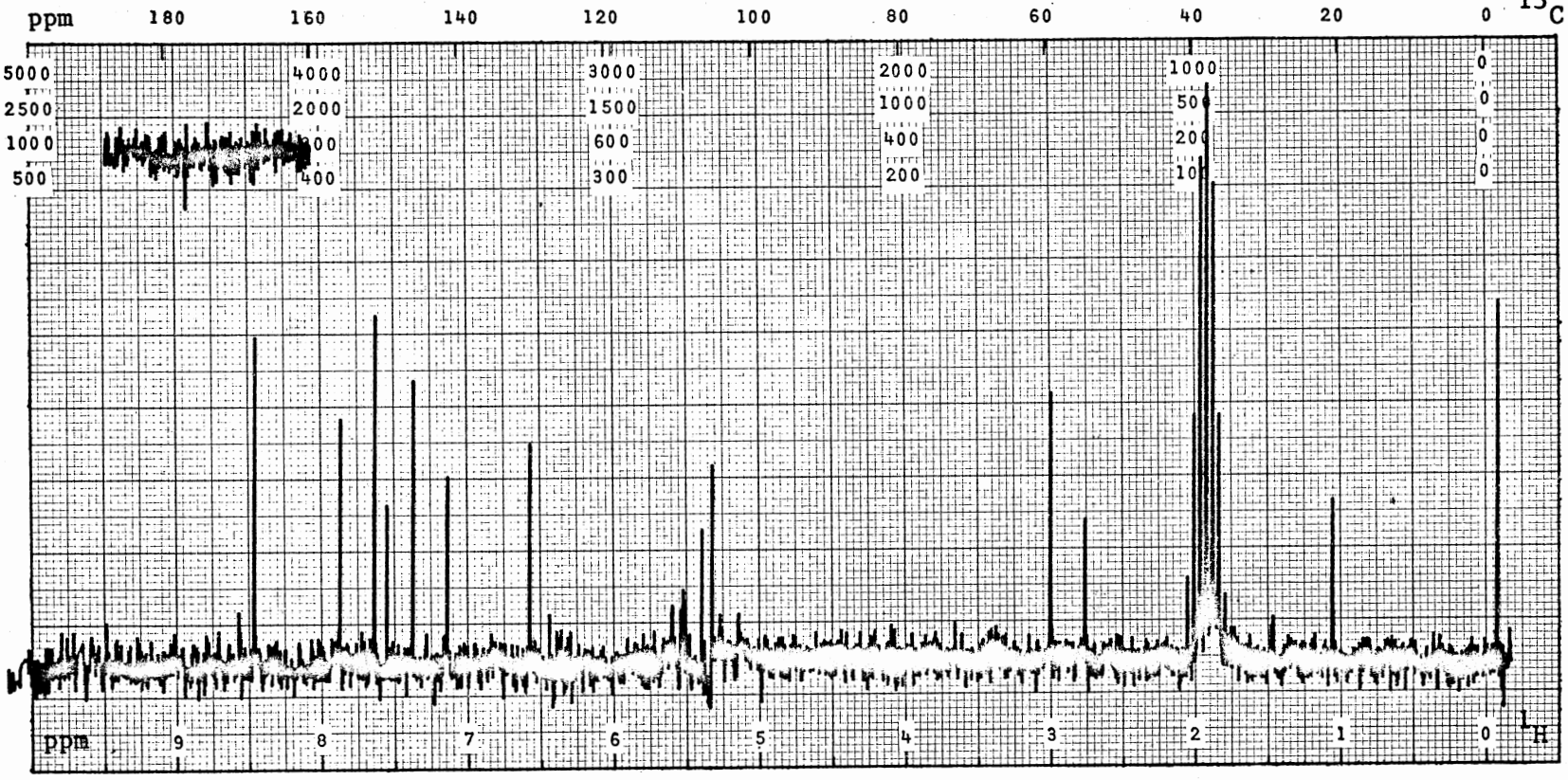
^{1}H NMR Spectrum of 2-Acetoamido-4-(3',4',5'-trimethoxyphenyl)thiazole (21c, R''''=Ac)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XXXIX



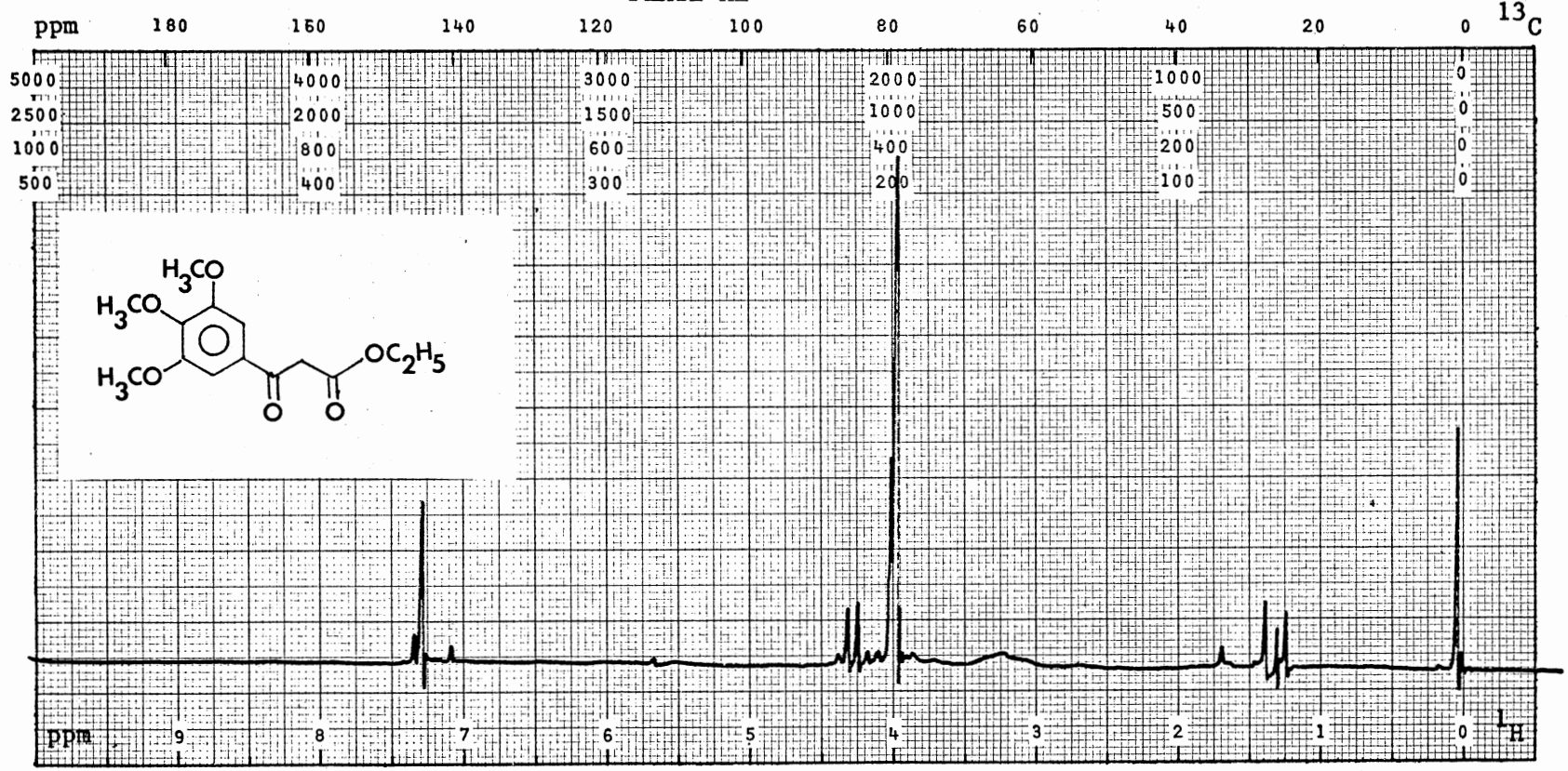
^{13}C NMR Spectrum of 2-Acetoamido-4-(3',4',5'-trimethoxyphenyl)thiazole (21c, R"" = Ac)

PFT ^{13}C CW _ ; Solvent. . DMSO-d_6; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 560

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 3Hz; Lock. . ^{2}D; D5/ST. . 5s

DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE XL



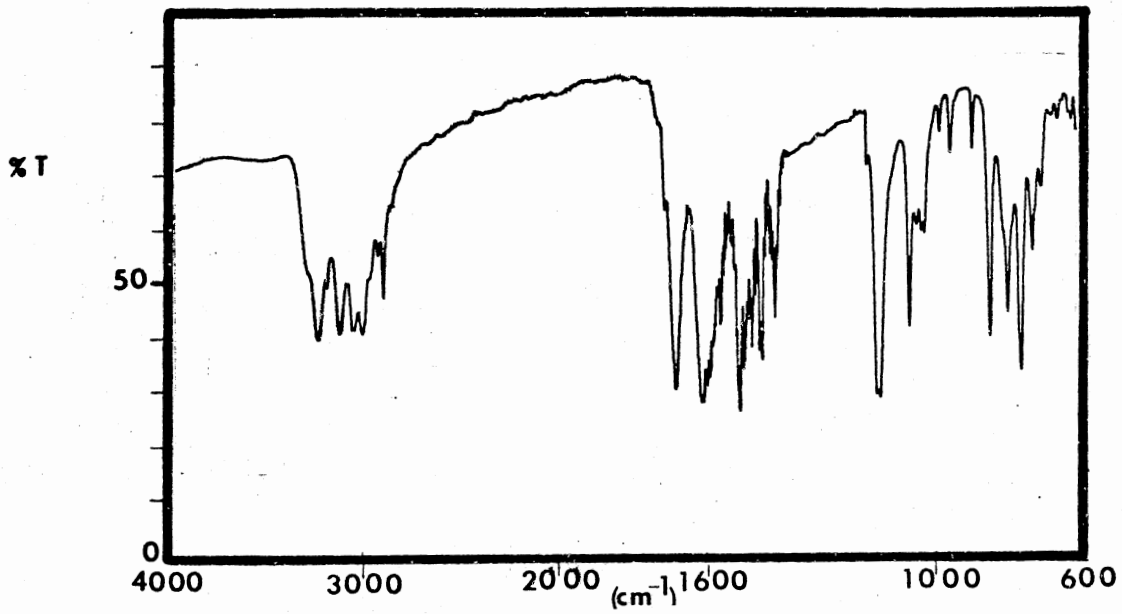
^{1}H NMR Spectrum of Ethyl 3-Oxo-3-(3',4',5'-trimethoxyphenyl)propionate (35c)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 8577Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 60μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

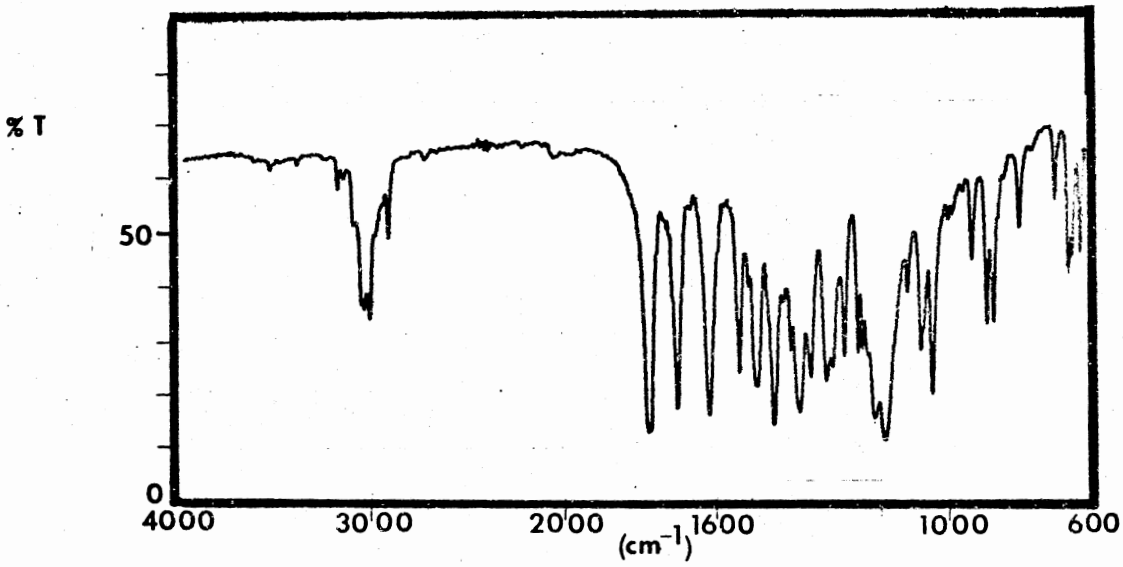
DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XLI



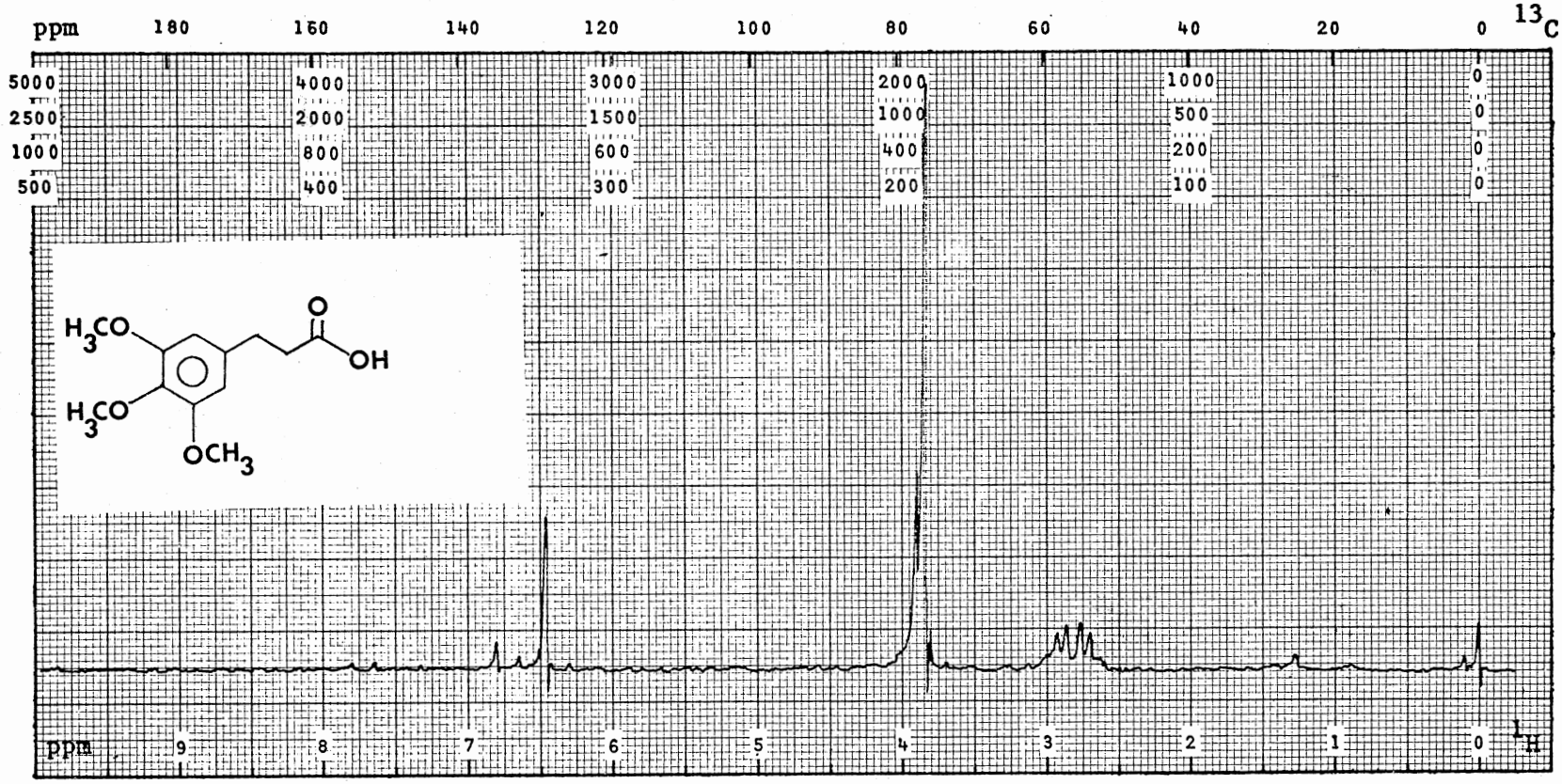
IR Spectrum of 2-Acetoamido-4-(3',4',5'-trimethoxyphenyl)-thiazole (21c, R"" = acetate), KBr Pellet

PLATE XLII



IR Spectrum of Ethyl 3-Oxo-3-(3',4',5'-trimethoxyphenyl)-propionate (35c), KBr Pellet

PLATE XLIII



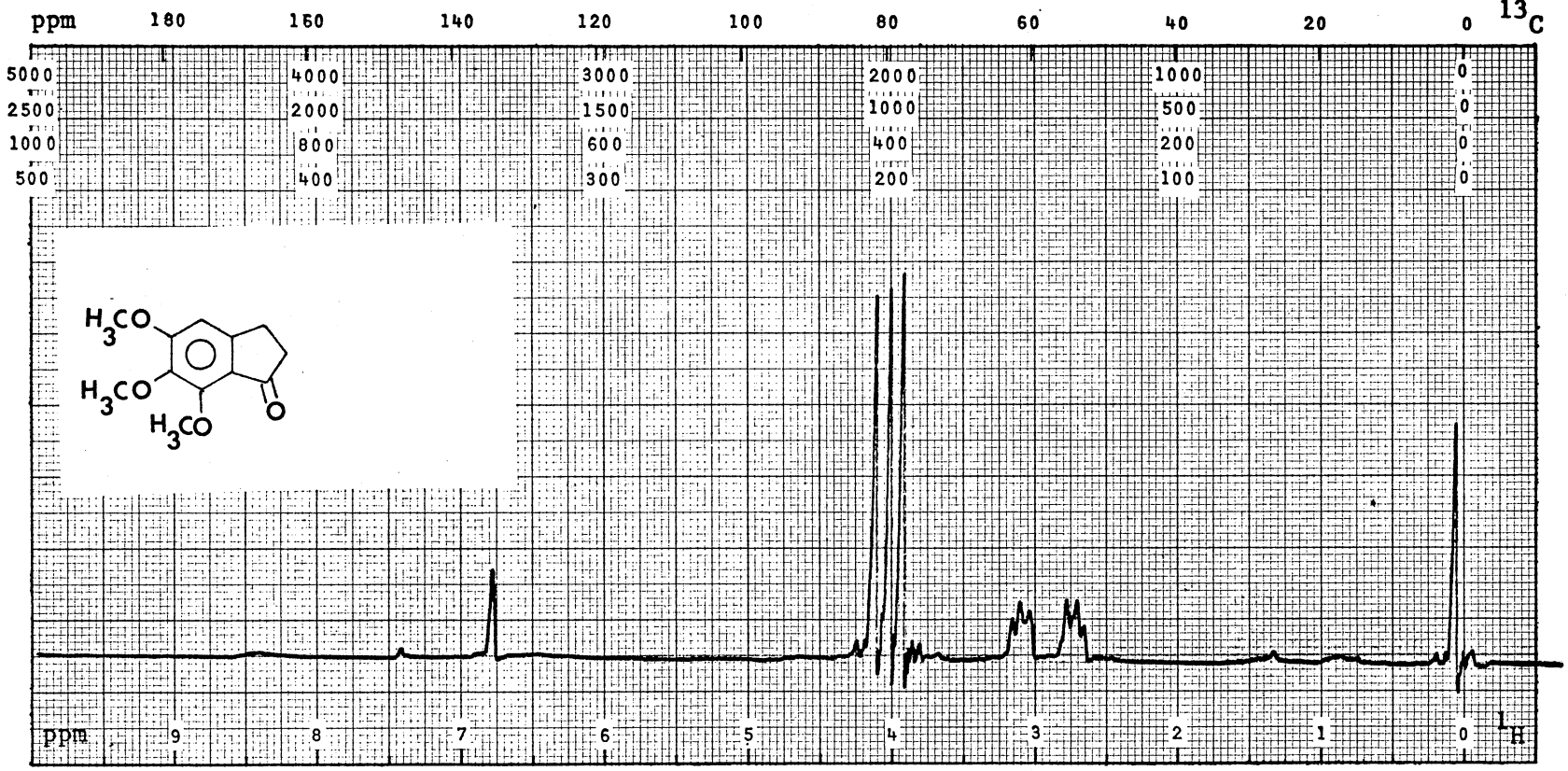
^{1}H NMR Spectrum of 3-(3',4',5'-Trimethoxyphenyl)propionic Acid (40c)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 50µs/dB; SF. . 100.1Hz; FB. . 2 Hz; Lock. . ^{2}H; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XLIV



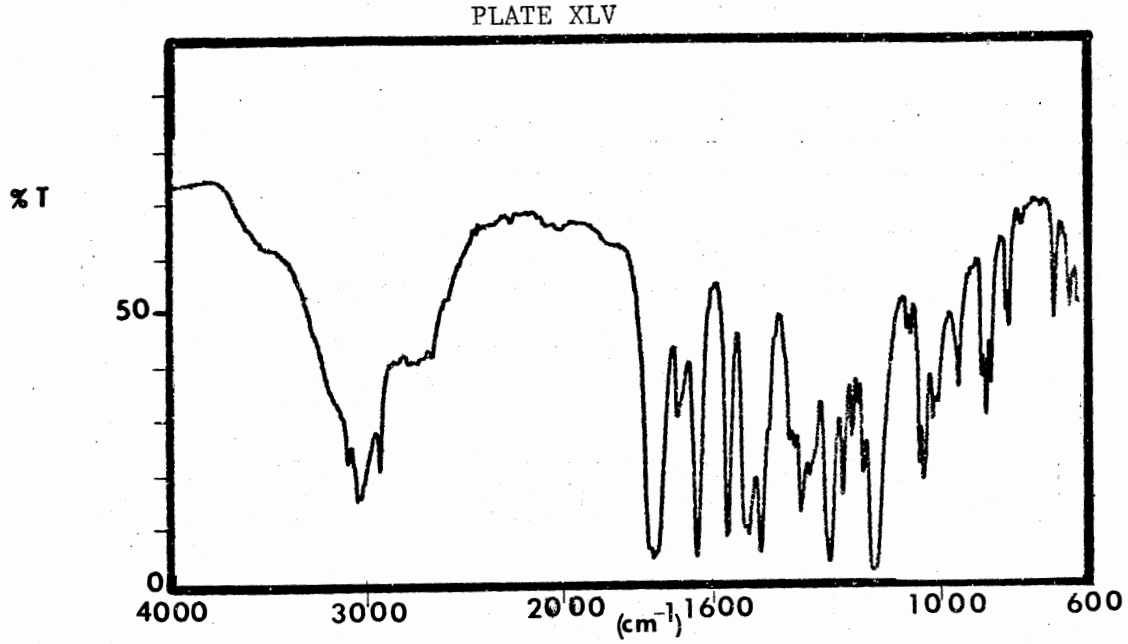
^{1}H NMR Spectrum of 5,6,7-Trimethoxyindanone (31c)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 50μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

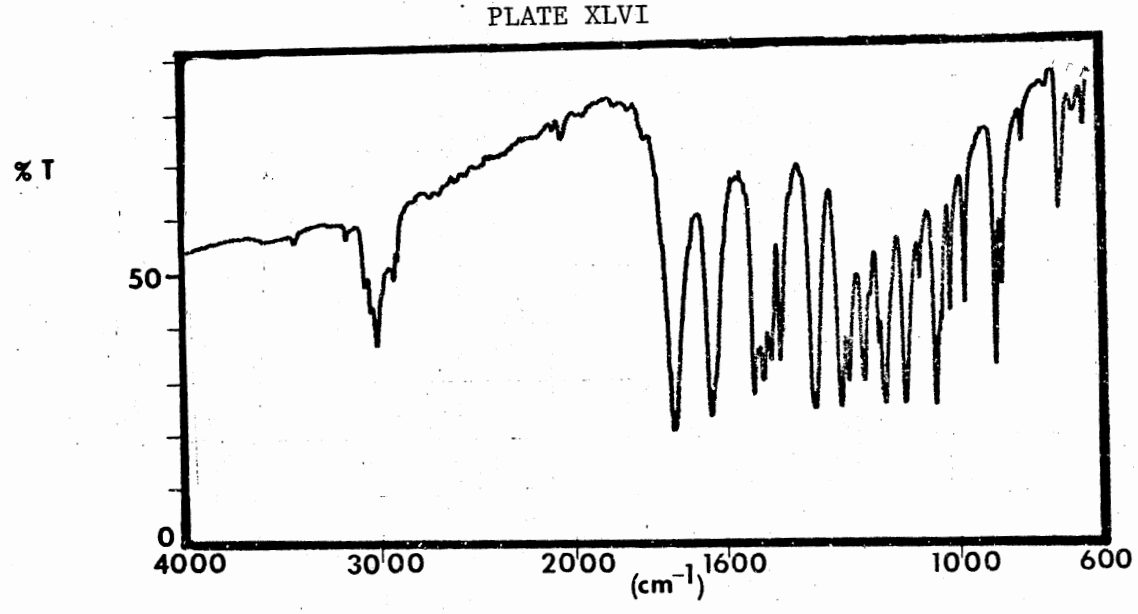
DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XLV



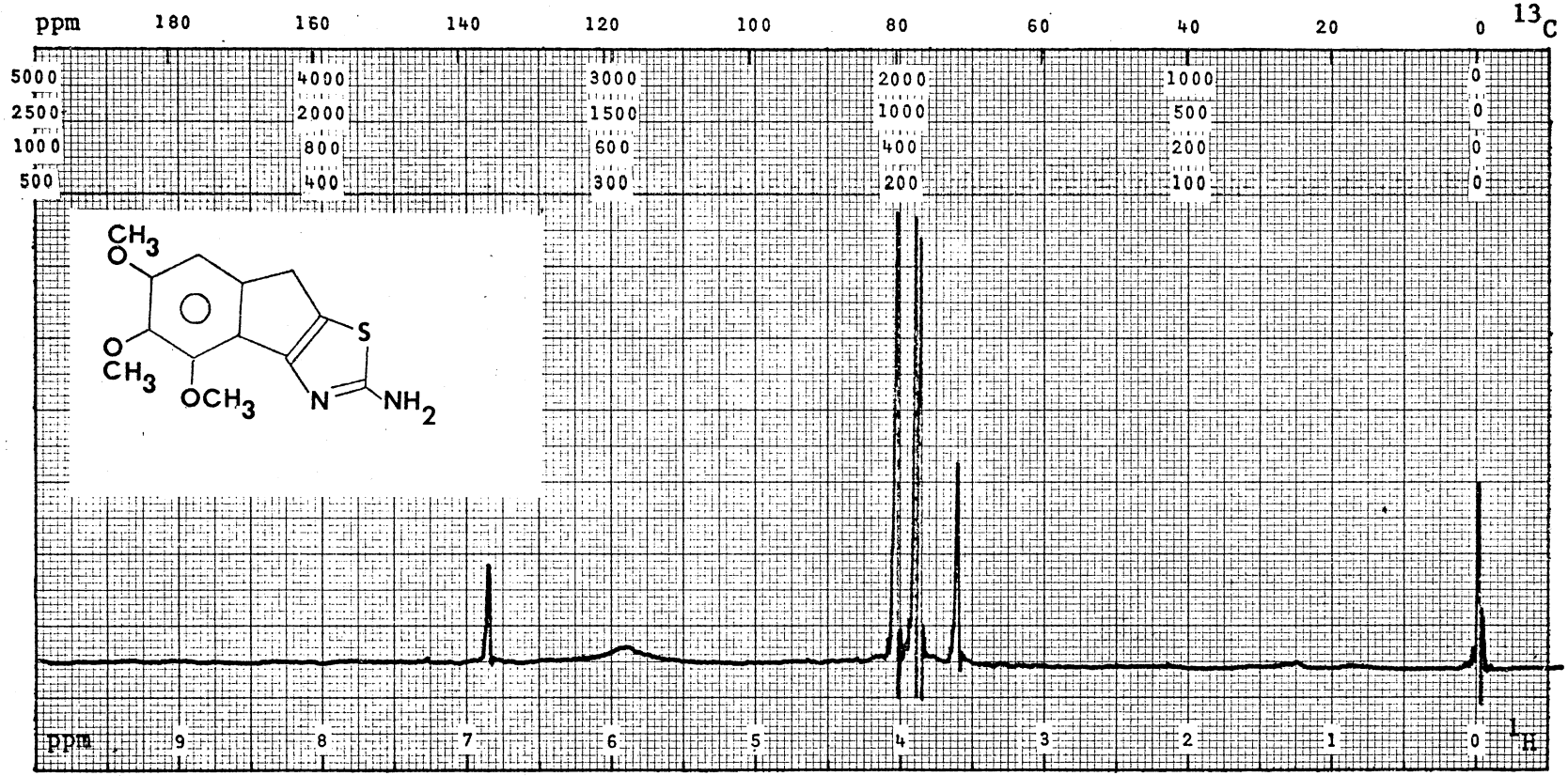
IR Spectrum of 3-(3',4',5'-Trimethoxyphenyl)propionic Acid (40c) KBr Pellet

PLATE XLVI



IR Spectrum of 5,6,7-Trimethoxyindanone (31c), KBr Pellet

PLATE XLVII



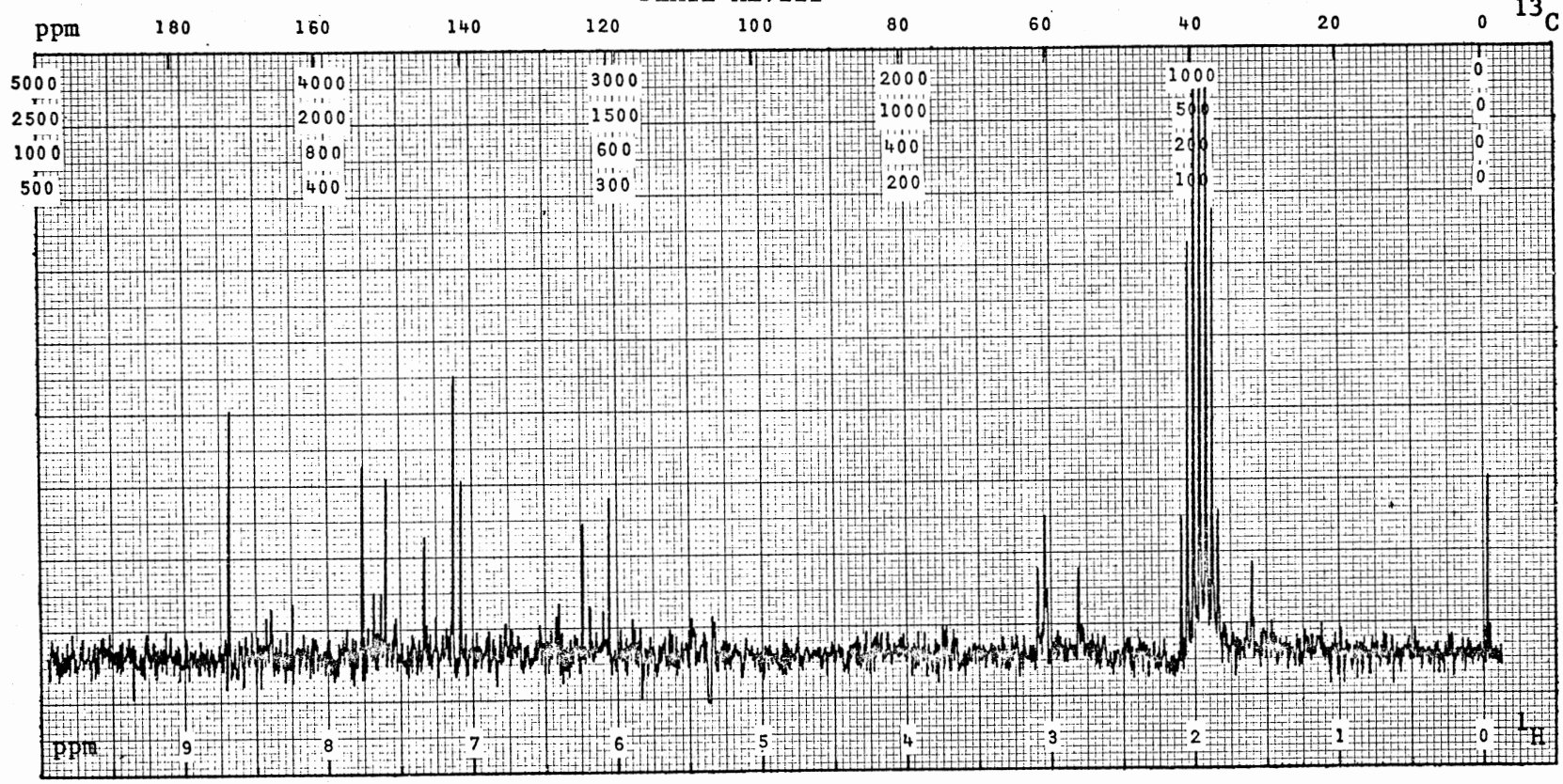
^{1}H NMR Spectrum of 2-Amino-6,7,8-trimethoxyindeno[1,2-d]thiazole (22c, R''''=H)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69µs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XLVIII



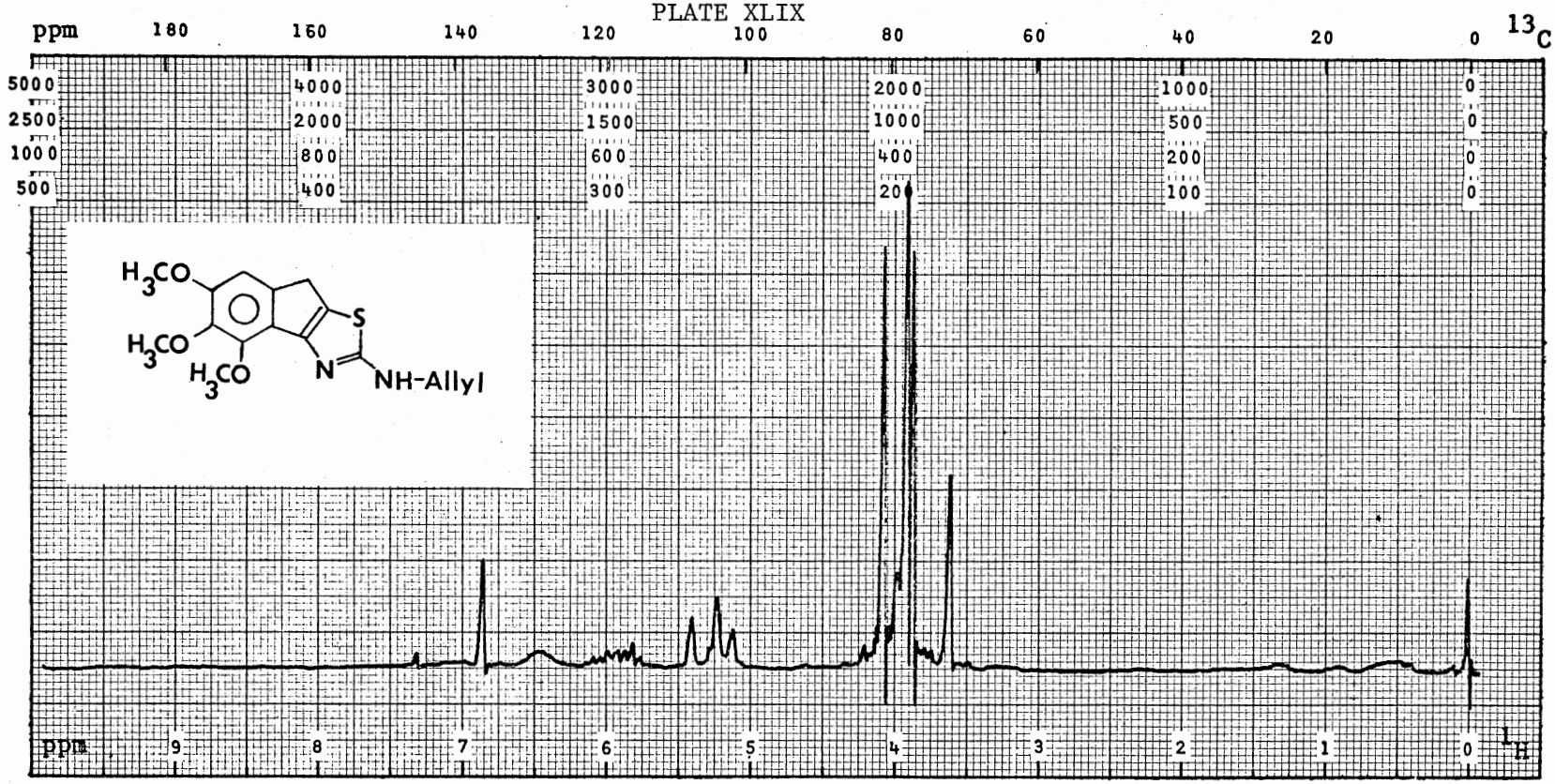
^{13}C NMR Spectrum of 2-Amino-6,7,8-trimethoxyindeno[1,2-d]thiazole (22c, R''''=H)

PFT ^{13}C CW _ ; Solvent. . DMSO-d_6; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 600

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 4Hz; Lock. . ^{2}D; D5/ST. . 5s

DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE XLIX



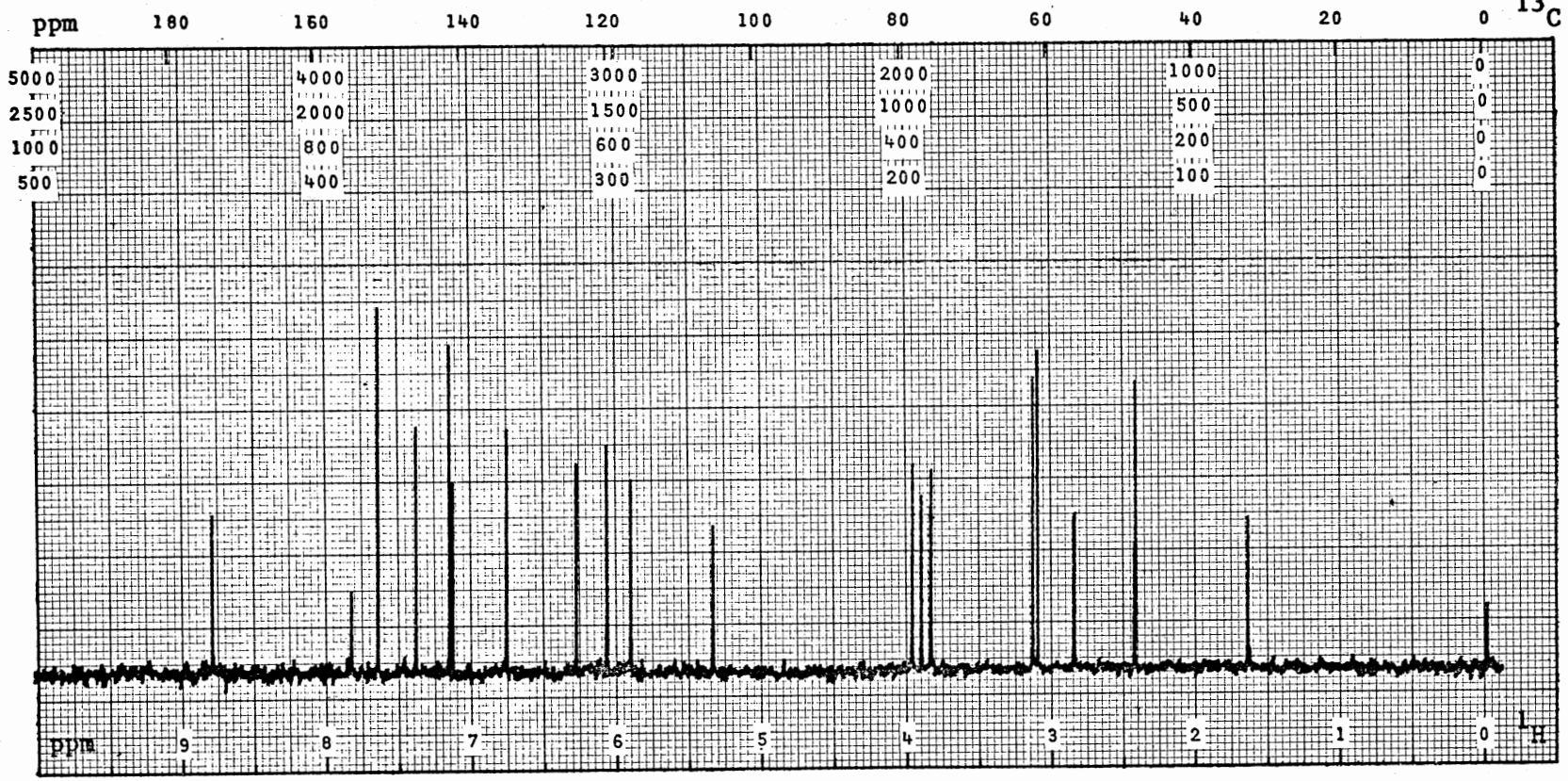
^{1}H NMR Spectrum of 2-Allylamino-6,7,8-trimethoxyindeno[1,2-d]thiazole (22c, R"" = allyl)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 8577 Hz; PW. . Hz; T. . 33 °C; Acq/SA. . 1.0

Size. . K; P2/RF. . 55μs/dB; SF. . 100.1 Hz; FB. . 2 Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE L



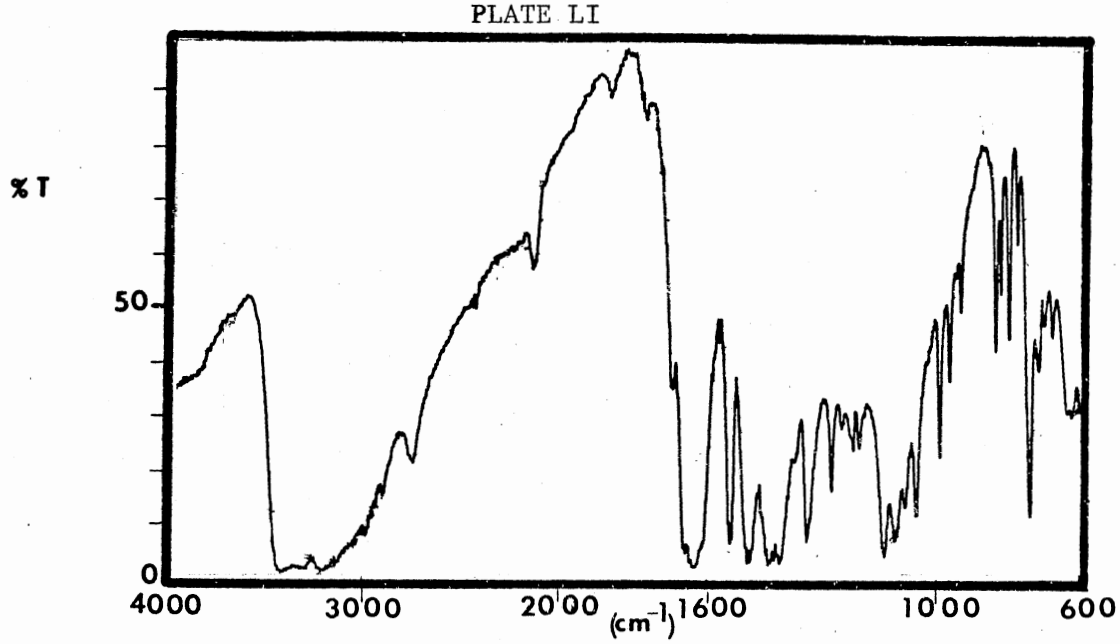
^{13}C NMR Spectrum of 2-Allylamino-6,7,8-trimethoxyindeno[1,2-d]thiazole (22c, R'''' = allyl)

PFT ^{13}C CW _ ; Solvent. . $DCCl_3$; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 2000

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 3Hz; Lock. . ^{2}D; D5/ST. . 5s

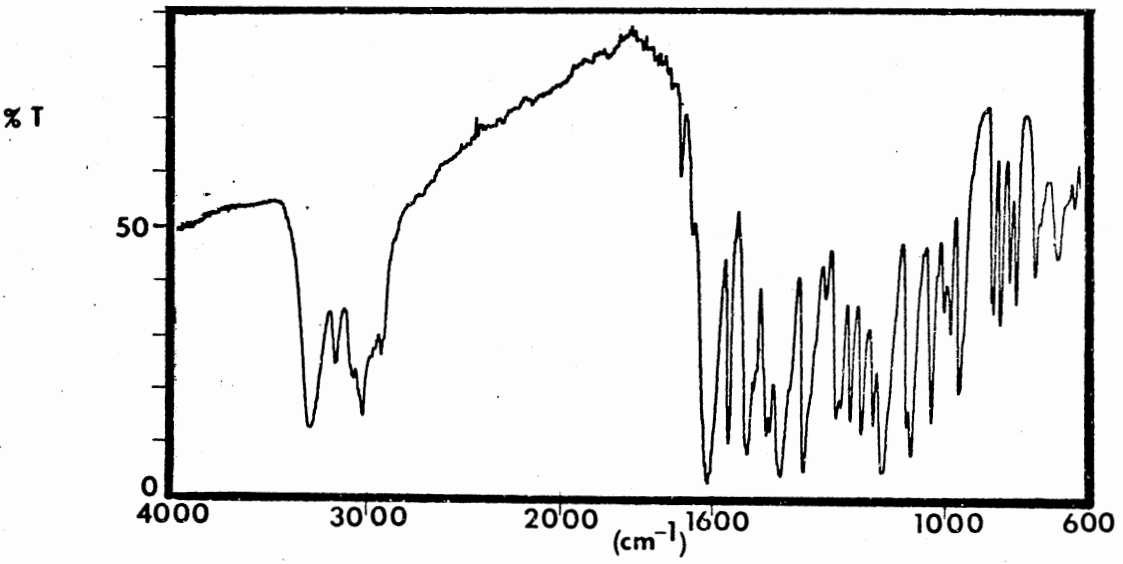
DC. . ^{1}H; Gated Off. . ; Offset. . 5308Hz; RF. . 63W/dB; NBW. . 100Hz

PLATE LI



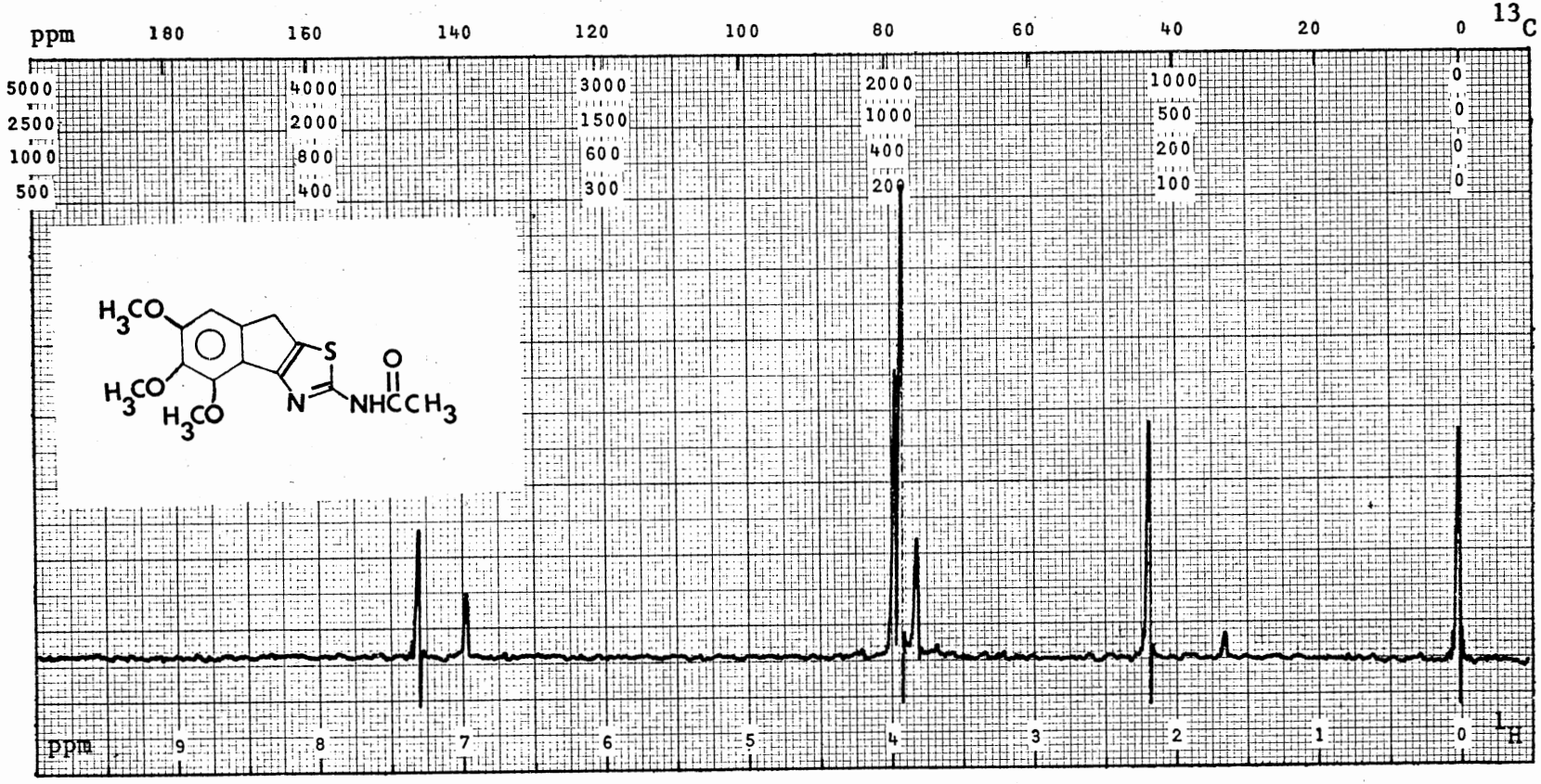
IR Spectrum of 2-Amino-6,7,8-trimethoxyindeno[1,2-d]thiazole (22c, R''''= H) KBr Pellet

PLATE LII



IR Spectrum of 2-Allylamino-6,7,8-trimethoxyindeno[1,2-d]thiazole (22c, R''''= allyl) KBr Pellet

PLATE LIII



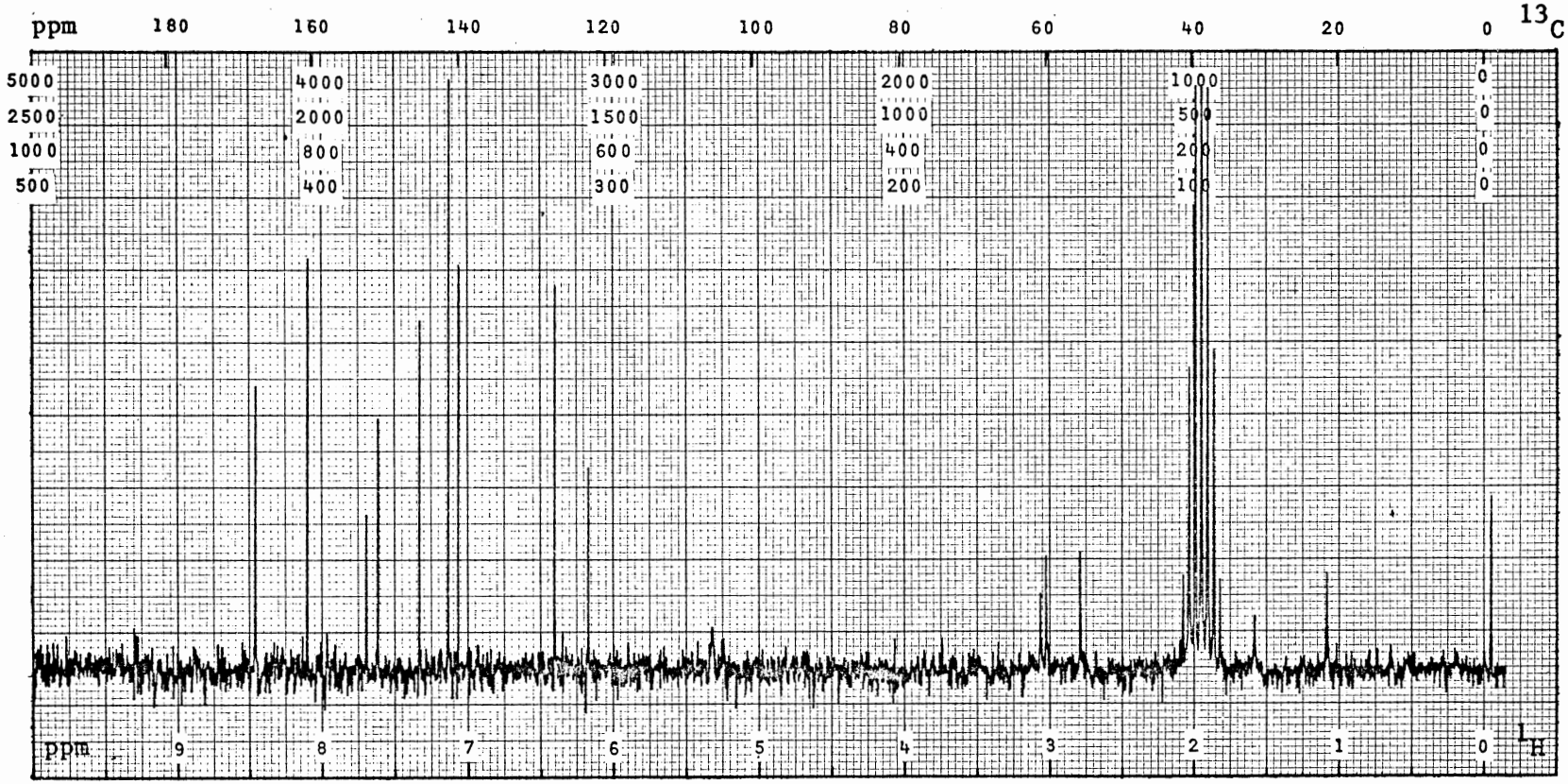
^{1}H NMR Spectrum of 2--Acetoamido-6,7,8-trimethoxyindeno[1,2-d]thiazole (22c, R""= acetate)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69µs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LIV



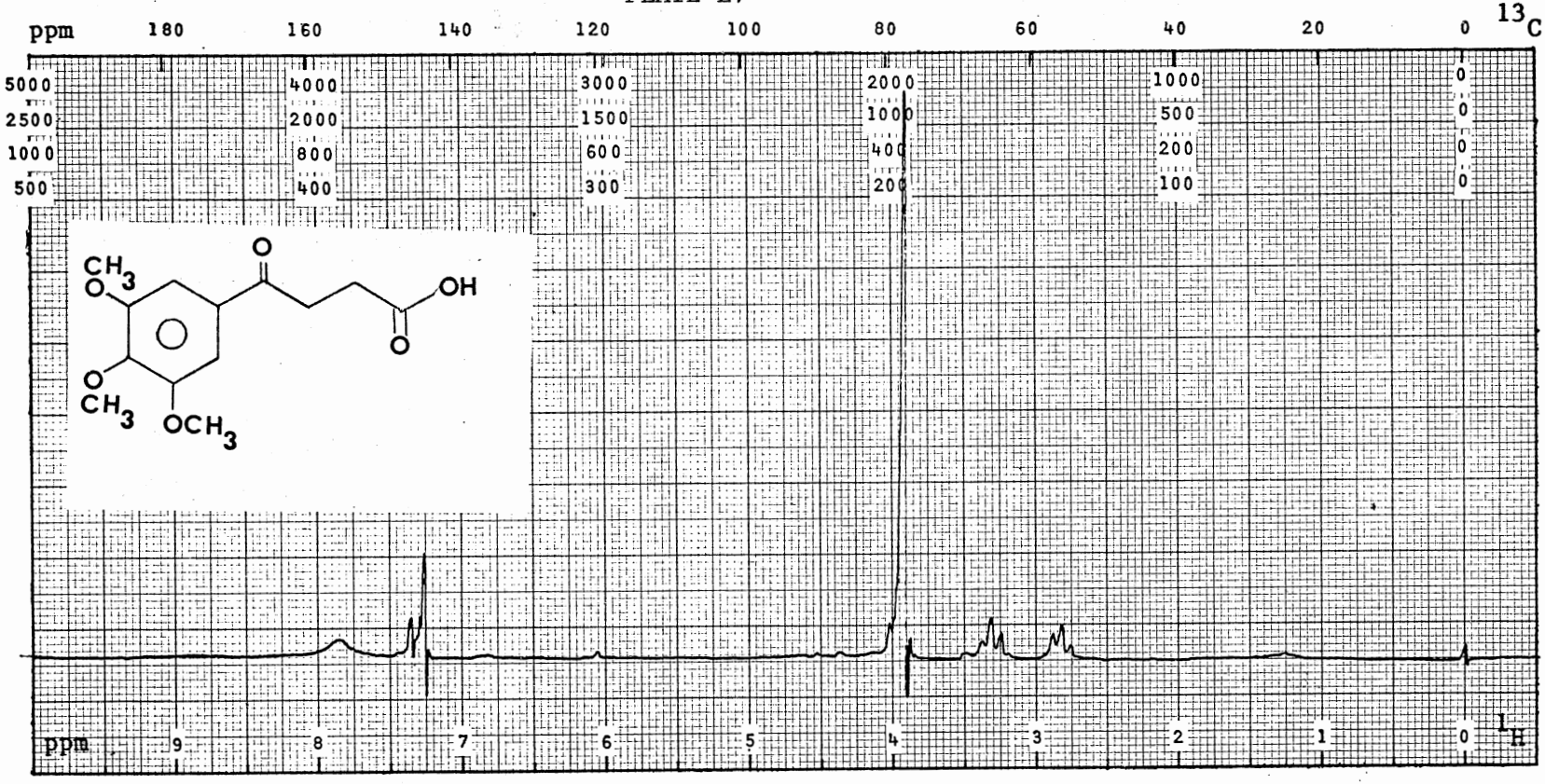
^{13}C NMR Spectrum of 2-Acetoamido-6,7,8-trimethoxyindeno[1,2-d]thiazole (22c, R''''=Ac)

PFT ^{13}C CW _ ; Solvent. . DMSO-d_6; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 600

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 4Hz; Lock. . ^{2}D; D5/ST. . 5s

DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE LV



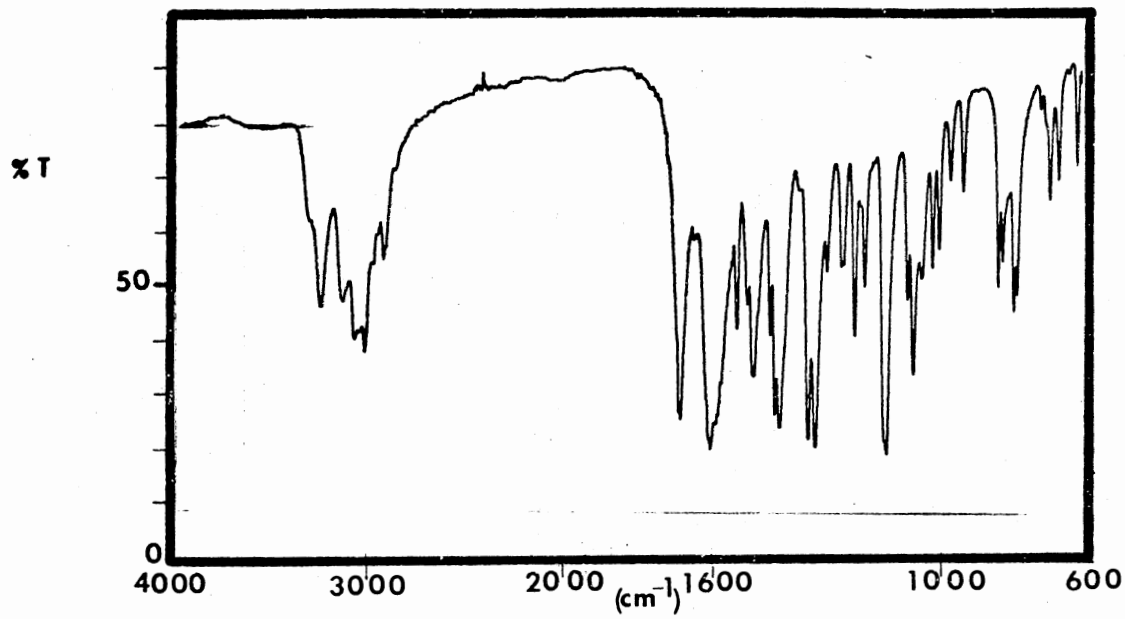
^{1}H NMR Spectrum of 4-Oxo-4-(3',4',5'-trimethoxyphenyl)butyric Acid (36c)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69µs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

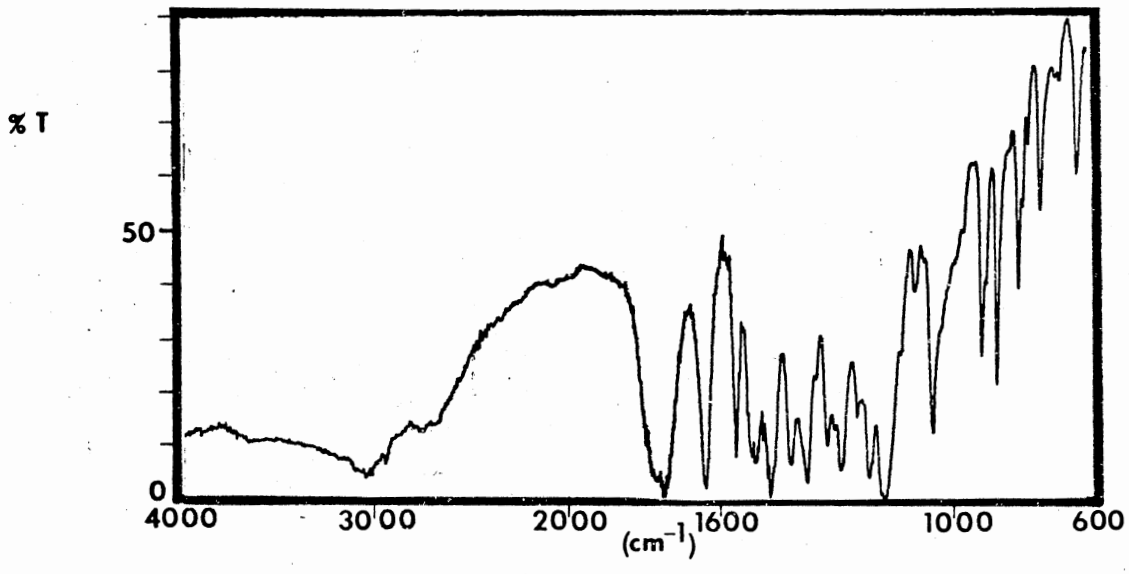
DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LVI



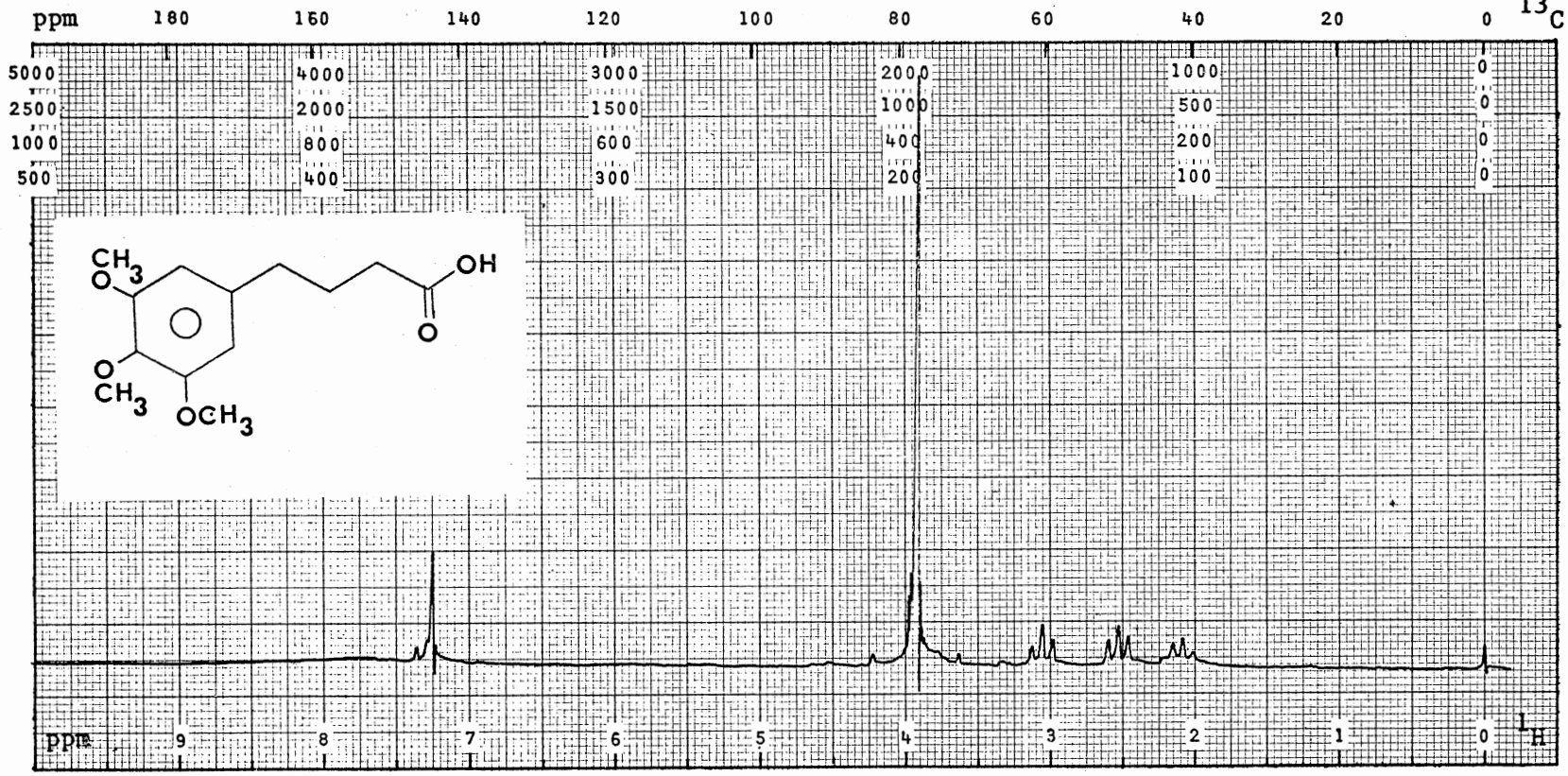
IR Spectrum of 2-Acetoamido-6,7,8-trimethoxyindeno[1,2-d]thiazole (22c) KBr Pellet

PLATE LVII



4-Oxo-IR Spectrum of 4-Oxo-4-(3',4',5'-trimethoxyphenyl)butyric Acid (36c) KBr Pellet

PLATE LVIII



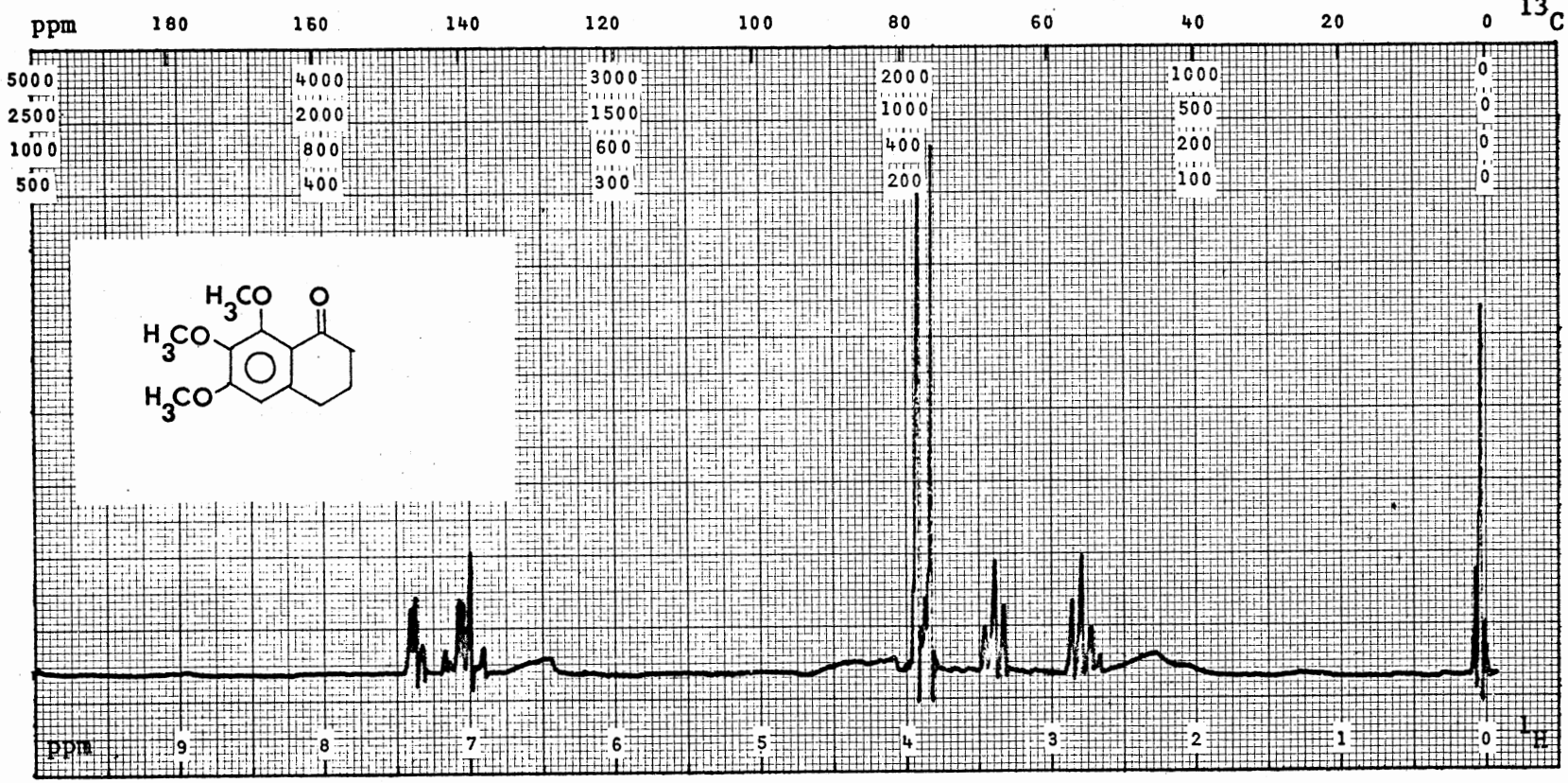
^{1}H NMR Spectrum of 4-(3',4',5'-Trimethoxyphenyl)butyric Acid (41c)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 60μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LIV



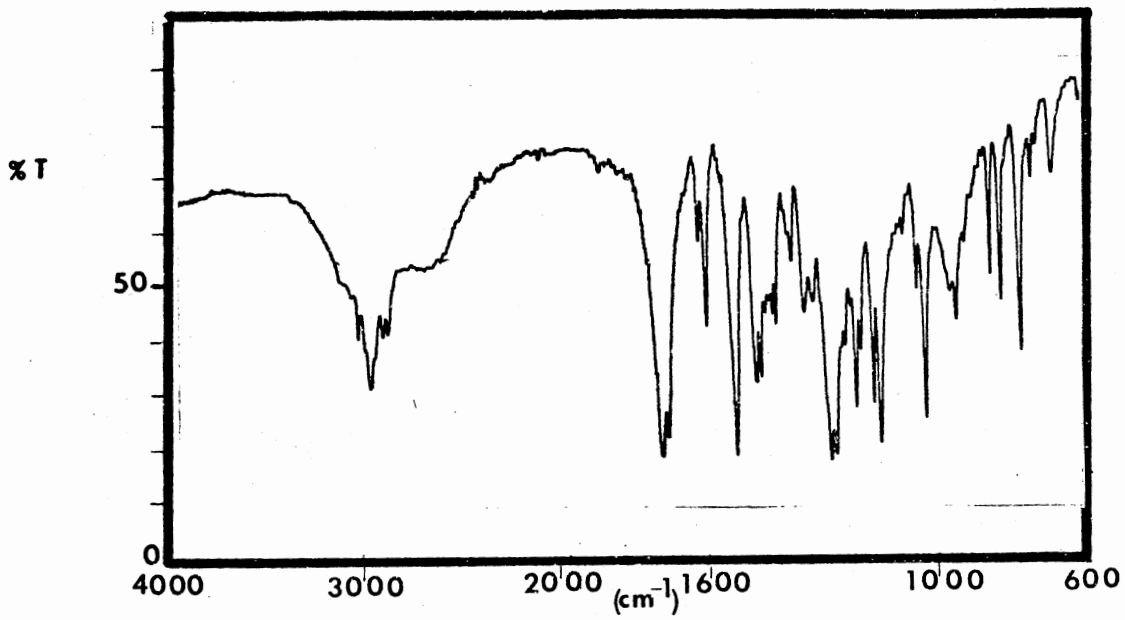
^{1}H NMR Spectrum of 3,4--Dihydro-6,7,8--trimethoxynapthalone (32c)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 60μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

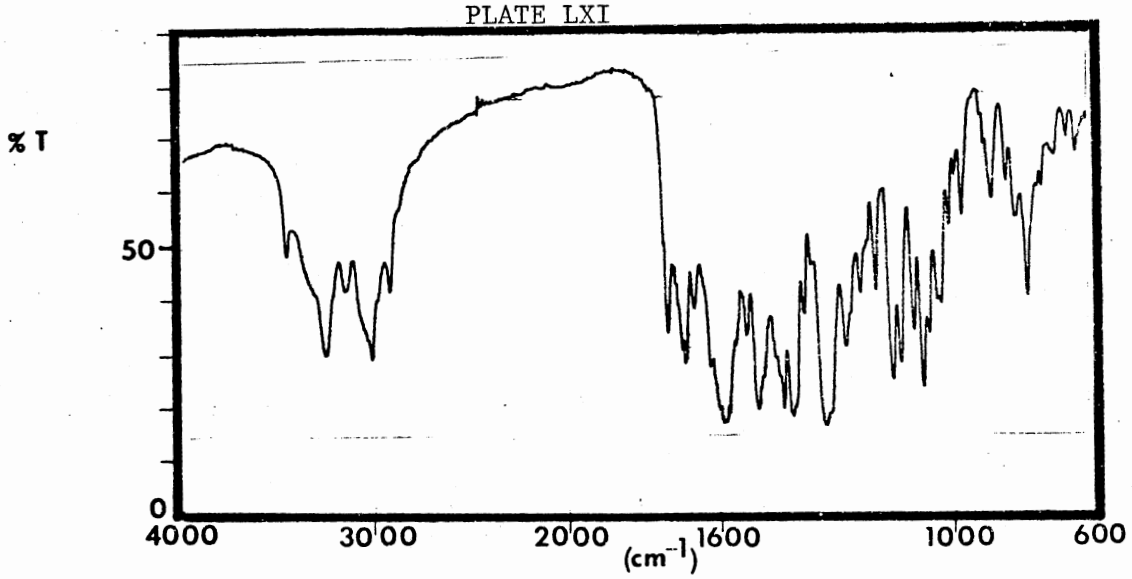
DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LX



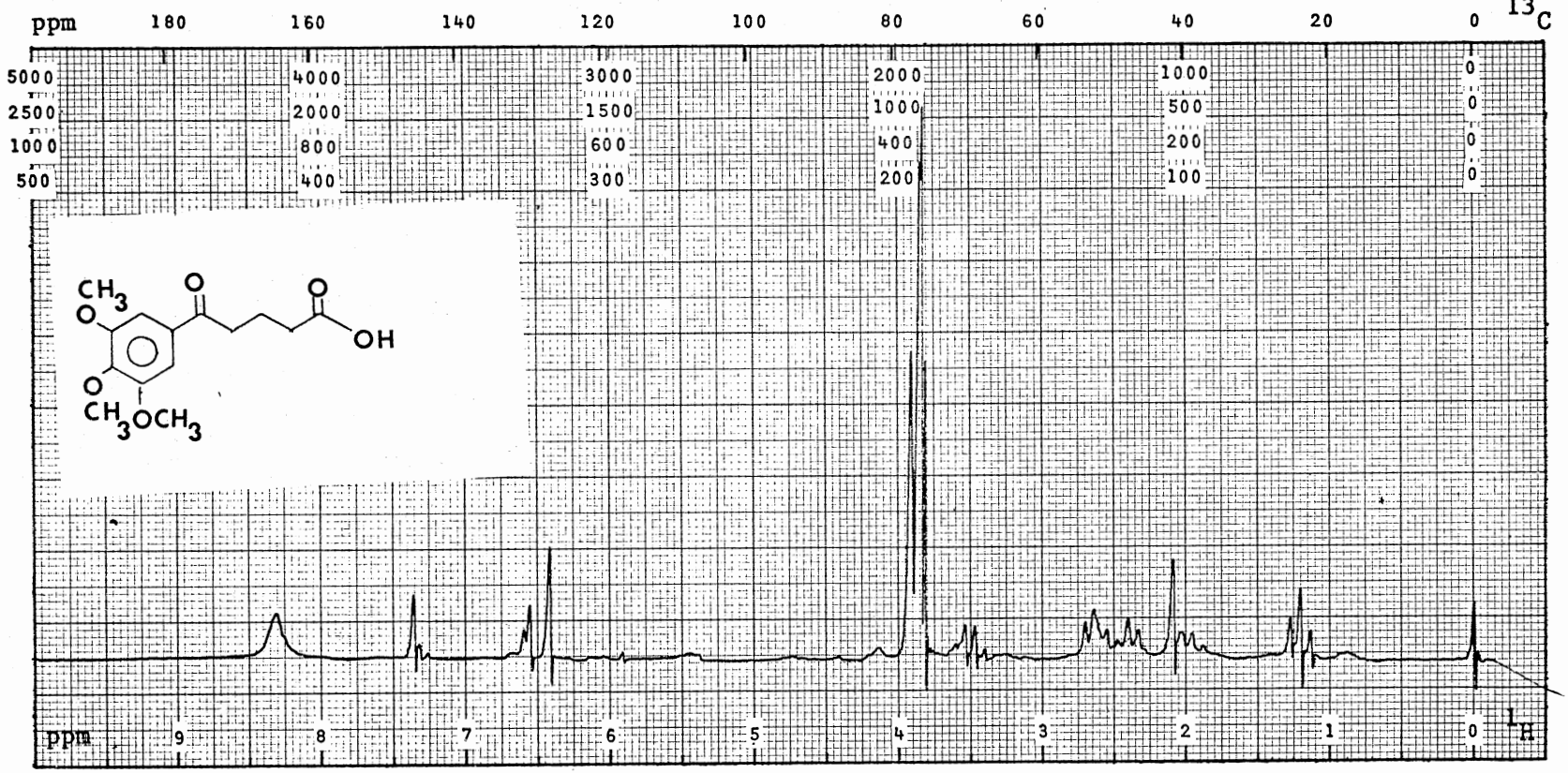
IR Spectrum of 4-(3',4',5'-Trimethoxyphenyl)butyric Acid (41c) KBr Pellet

PLATE LXI



IR Spectrum of 3,4-Dihydro-6,7,8-trimethoxynapthalone (32c) KBr Pellet

PLATE LXII



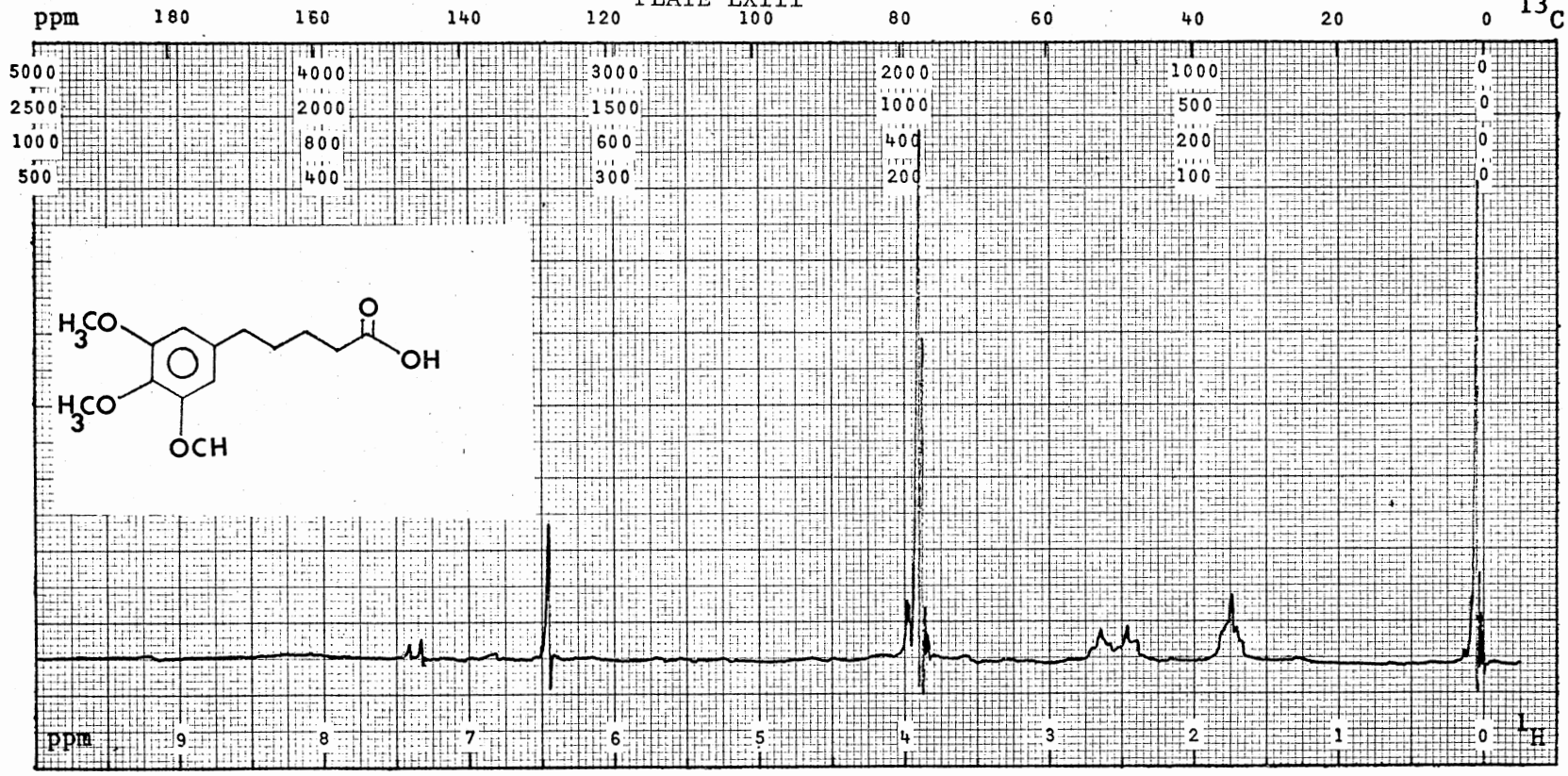
^{1}H NMR Spectrum of 5-Oxo-5-(3',4',5'-trimethoxyphenyl)pentanoic Acid (37c)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 60μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}H; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LXIII



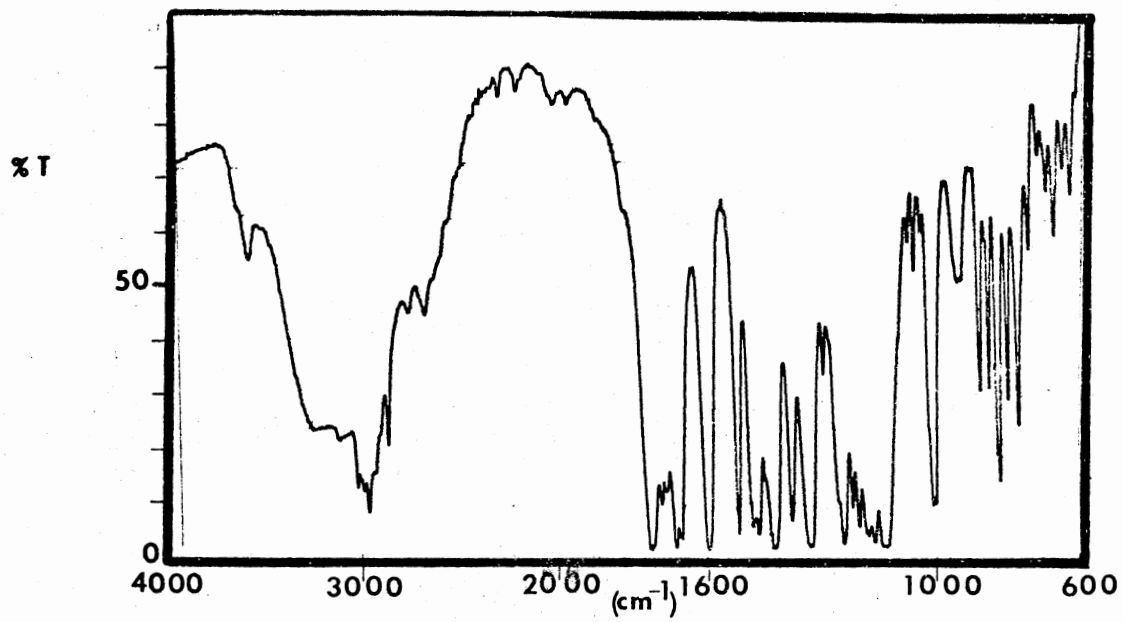
^{1}H NMR Spectrum of 5-(3',4',5'-Trimethoxyphenyl)pentanoic Acid (38c)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 60μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}H; D5/ST. . 250s

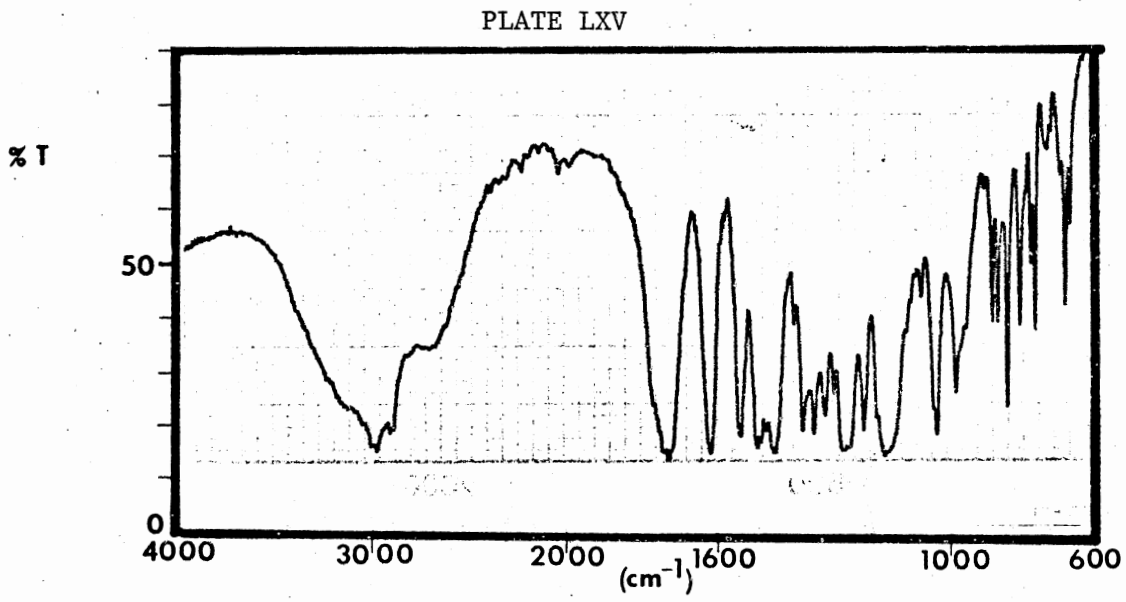
DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LXIV



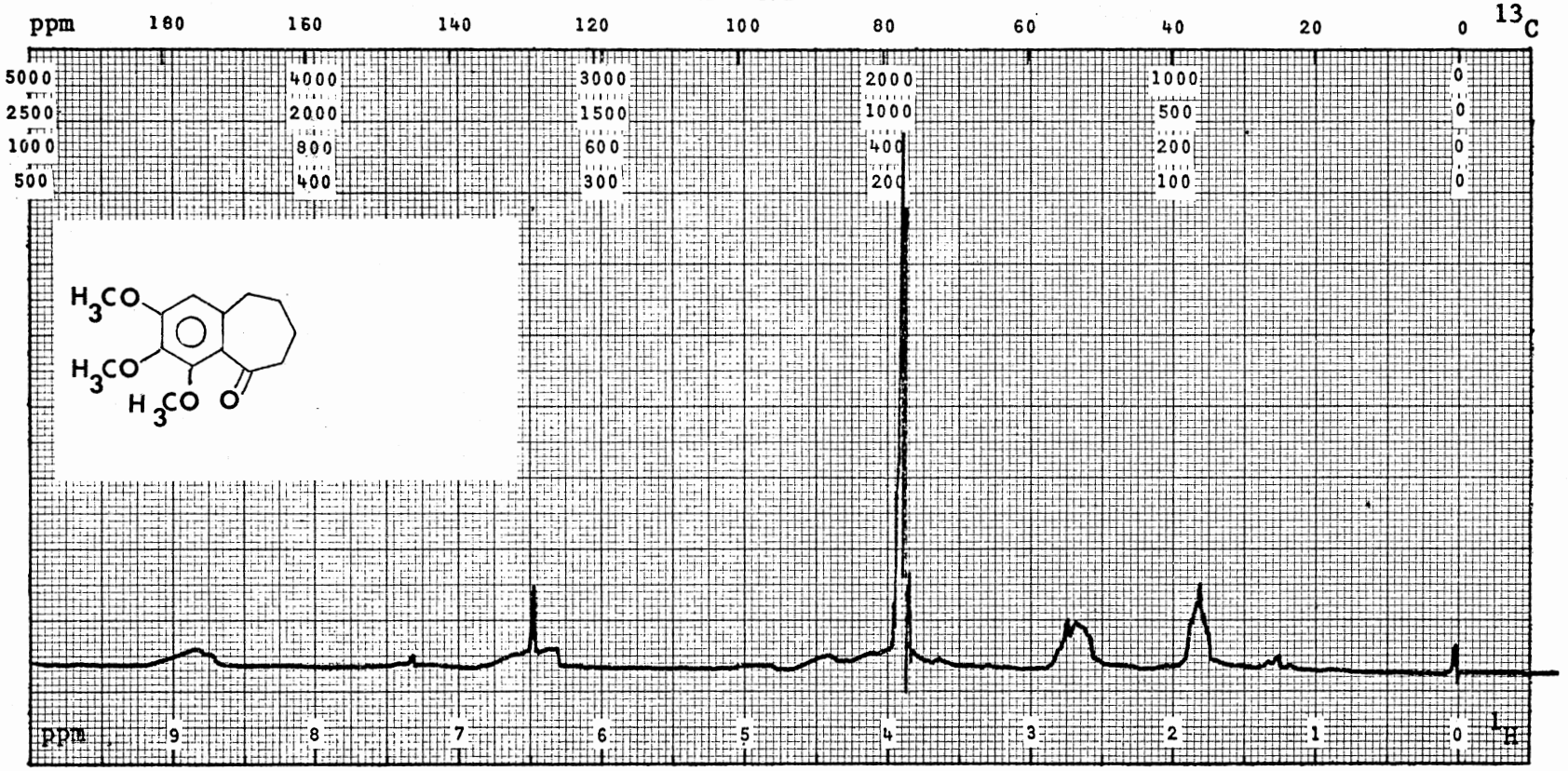
IR Spectrum of 5-Oxo-5-(3',4',5'-trimethoxyphenyl)pentanoic Acid (37c) KBr Pellet

PLATE LXV



IR Spectrum of (5-(3',4',5'-Trimethoxyphenyl)pentanoic Acid (42c) KBr Pellet

PLATE LXVI



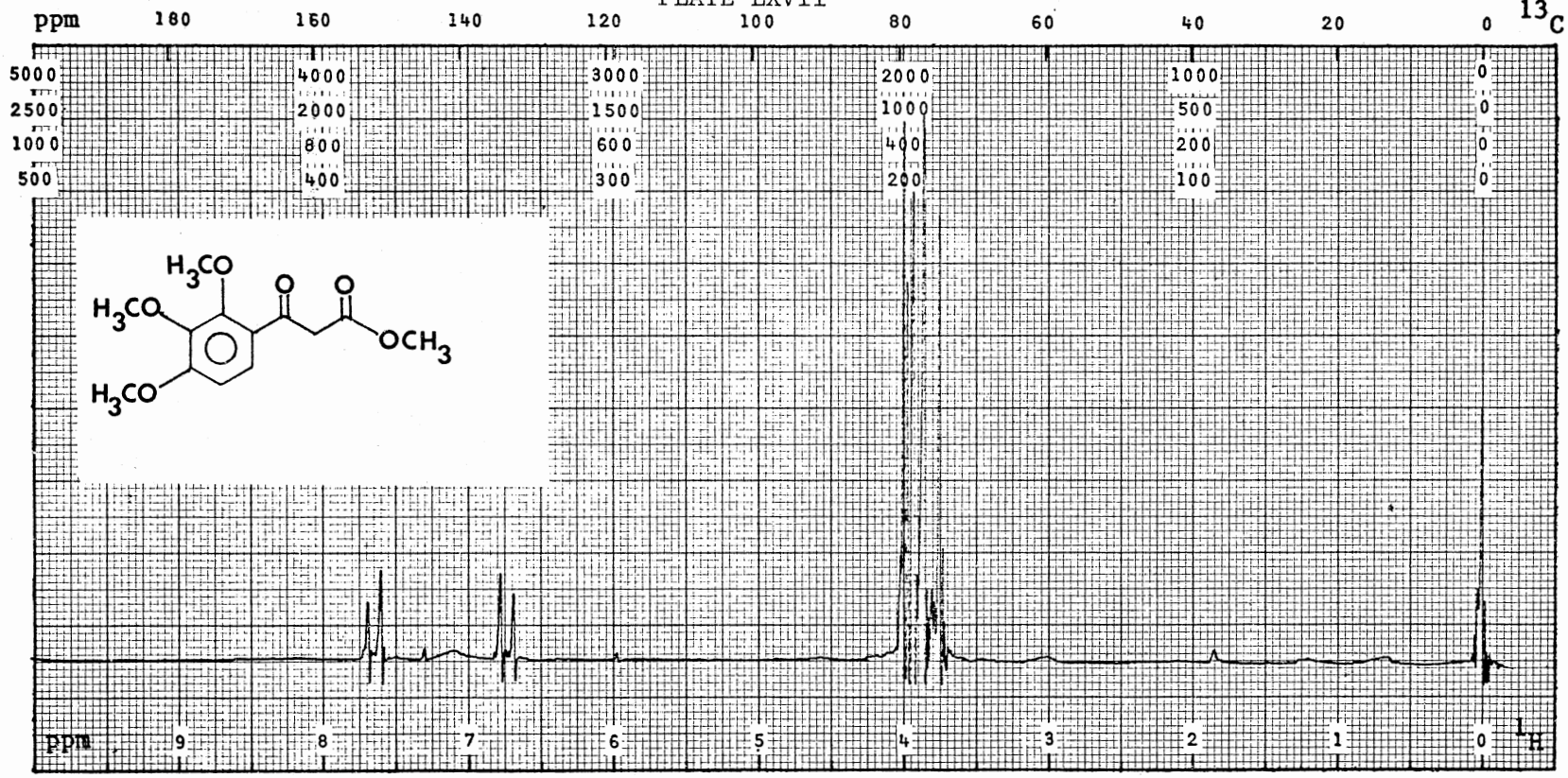
^{1}H NMR Spectrum of 7,8.9-Trimethoxysuberone (33c)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 62μs/dB; SF. . 1001Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LXVII



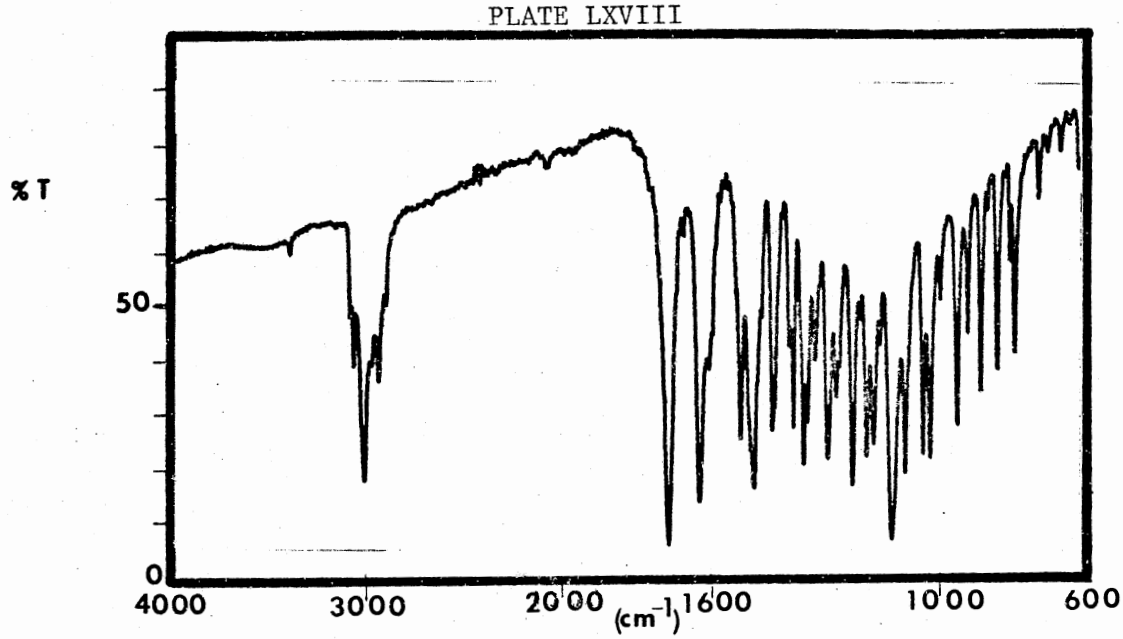
^{1}H NMR Spectrum of Methyl 3-(2',3',4'-trimethylphenyl)-3-oxopropionate (35d)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 59μs/dB; SF. . 100.1Hz; FB. . 2 Hz; Lock. . ^{2}H; D5/ST. . 250s

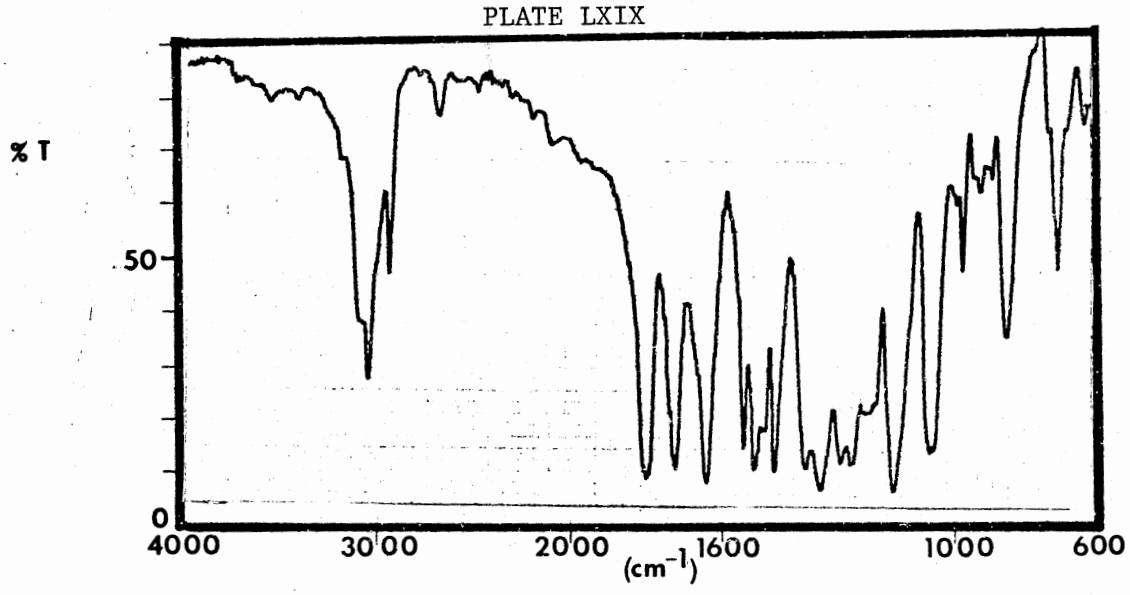
DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LXVIII



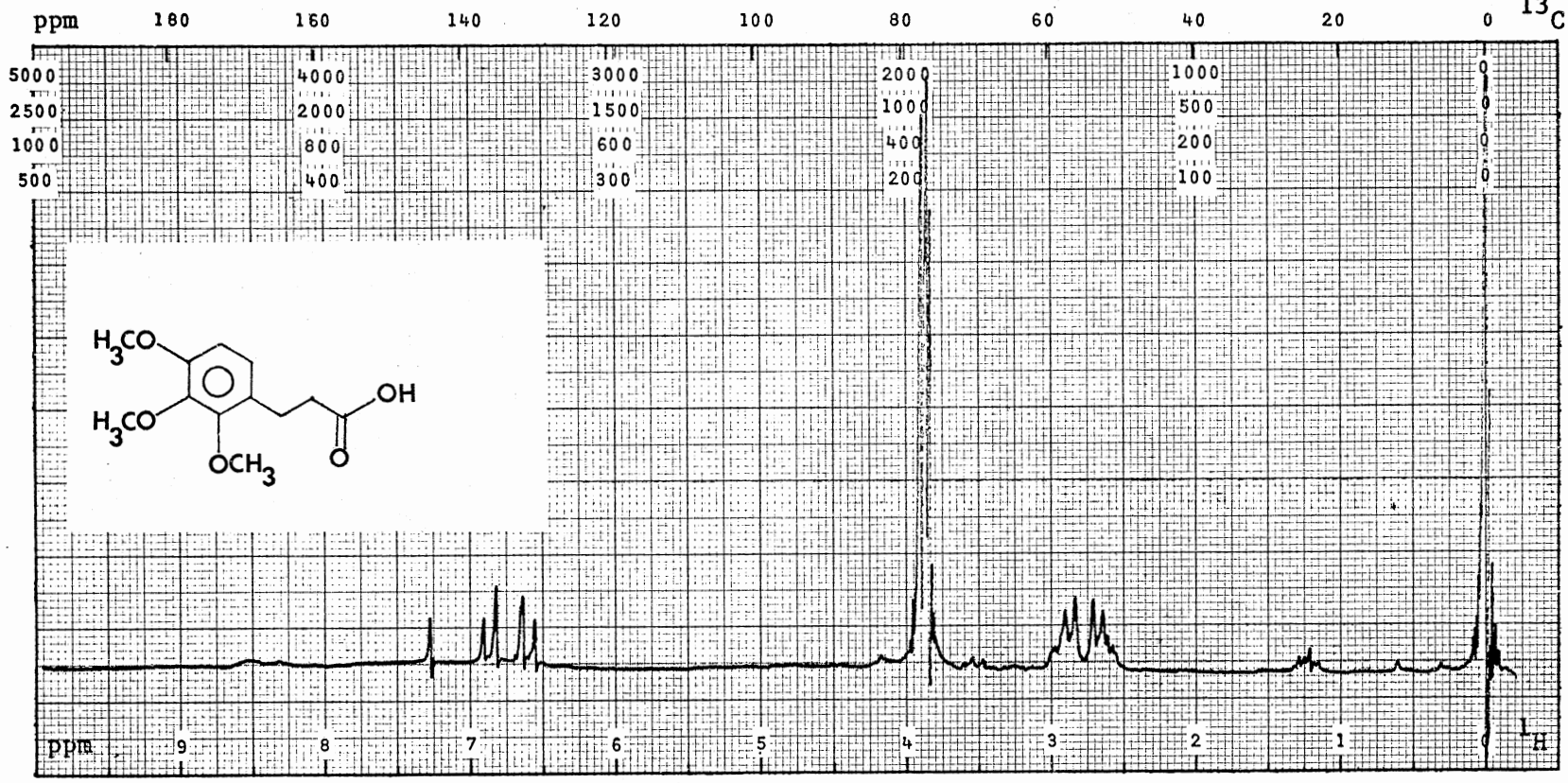
IR Spectrum of 7,8.9-Trimethoxysuberone (33c), KBr Pellet

PLATE LXIX



IR Spectrum of Methyl 3-Oxo-3-(2',3',4'-trimethoxyphenyl)-Propionate (35d), KBr Pellet

PLATE LXX



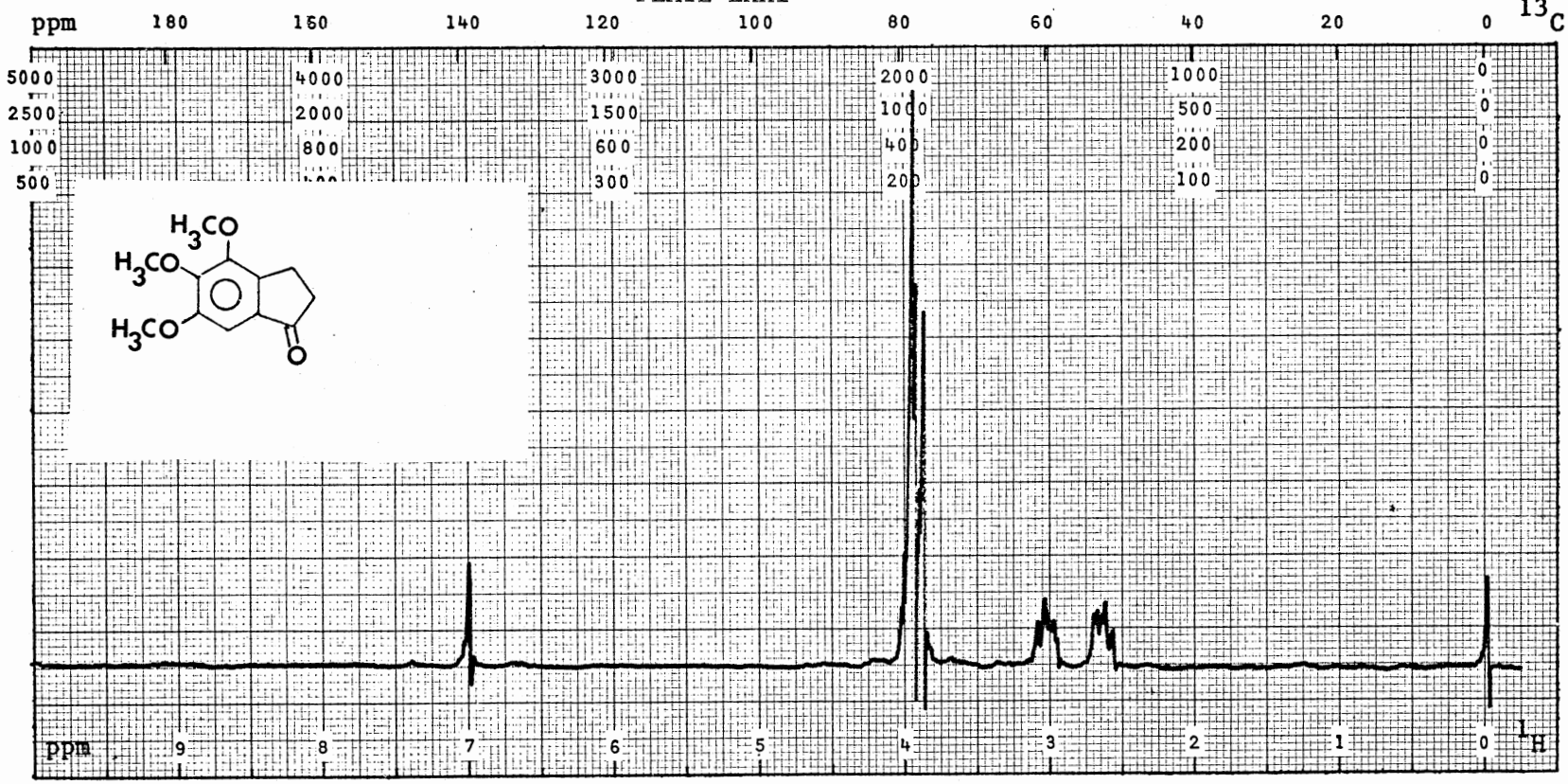
^1H NMR Spectrum of 3-(2',3',4'-Trimethoxyphenyl)propionic Acid (40d)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^2H; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LXXI



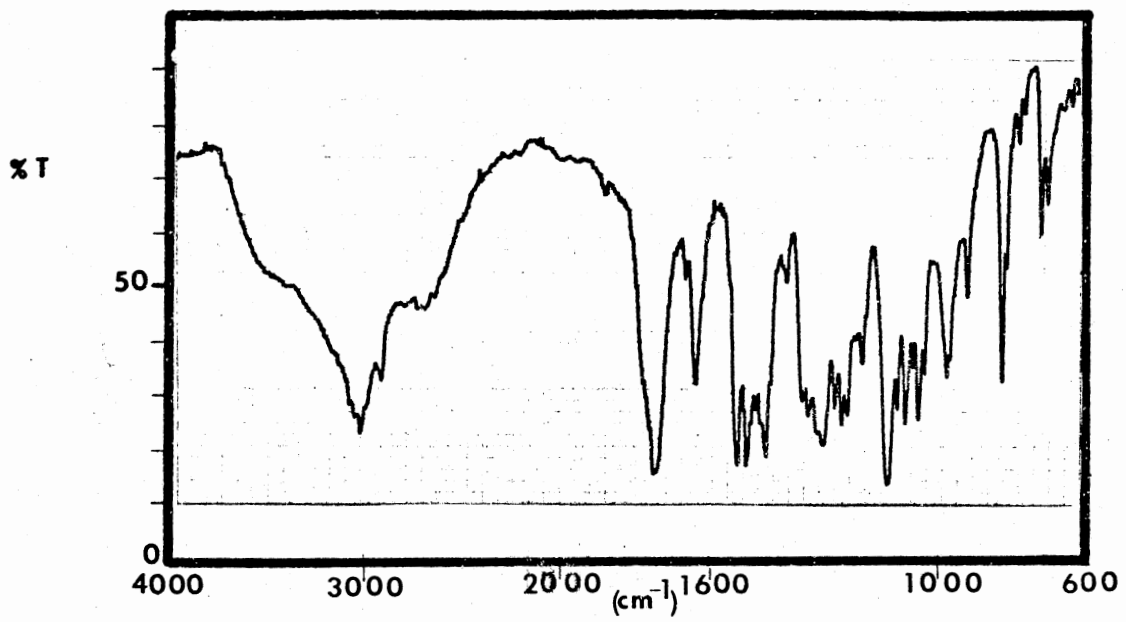
^{1}H NMR Spectrum of 4,5,6-Trimethoxyindanone (31d)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 59μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

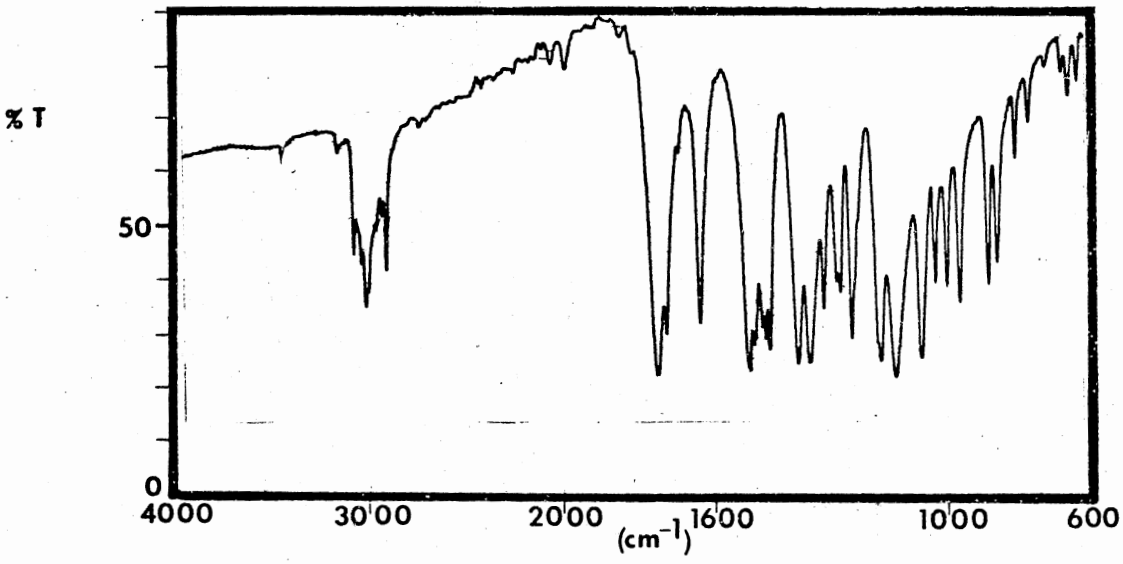
DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LXXII



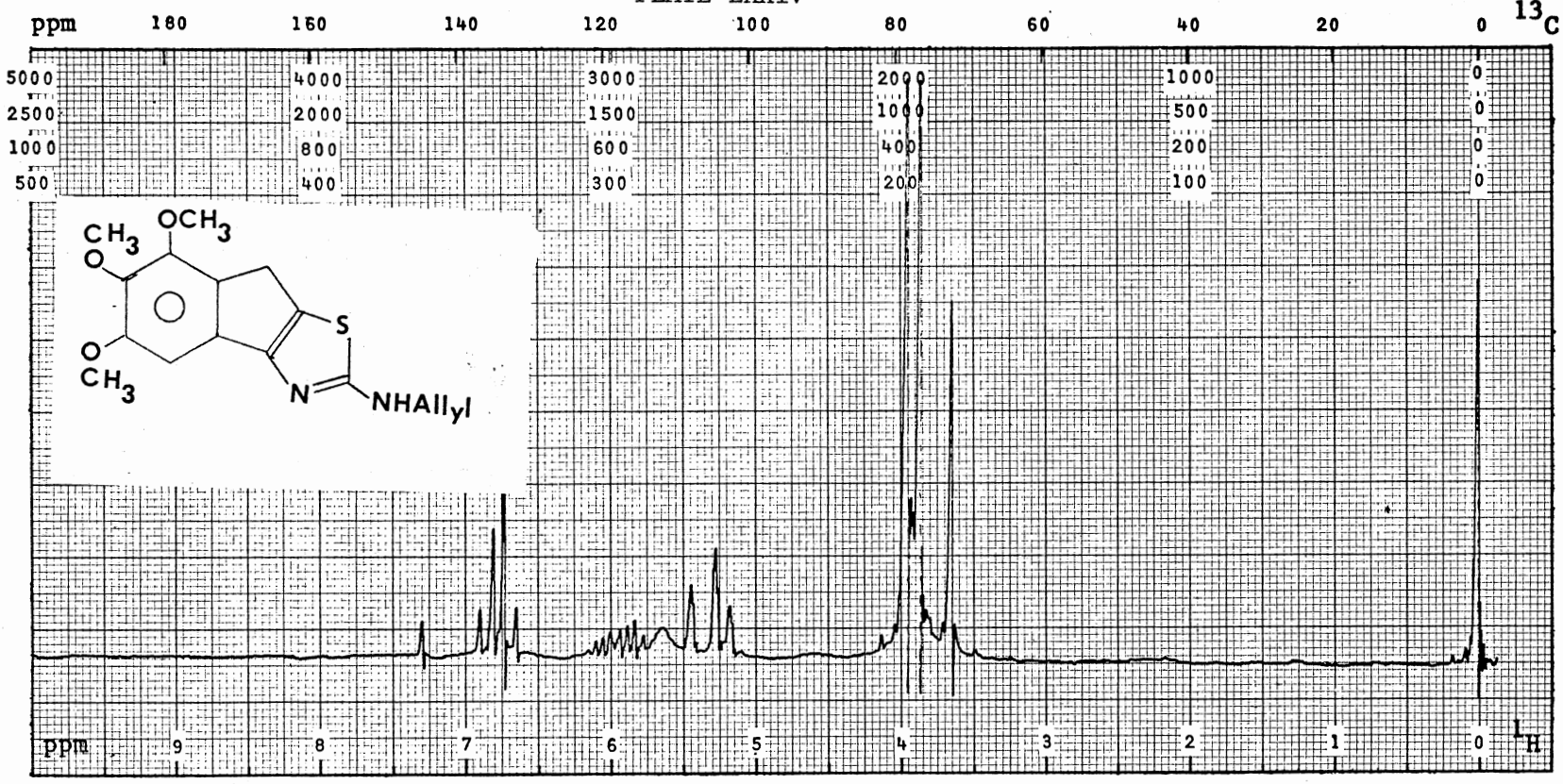
IR Spectrum of 3-(2',3',4'-Trimethoxyphenyl)propionic Acid (40d), KBr Pellet

PLATE LXXIII



IR Spectrum of 4,5,6-Trimethoxyindanone (31d), KBr Pellet

PLATE LXXIV



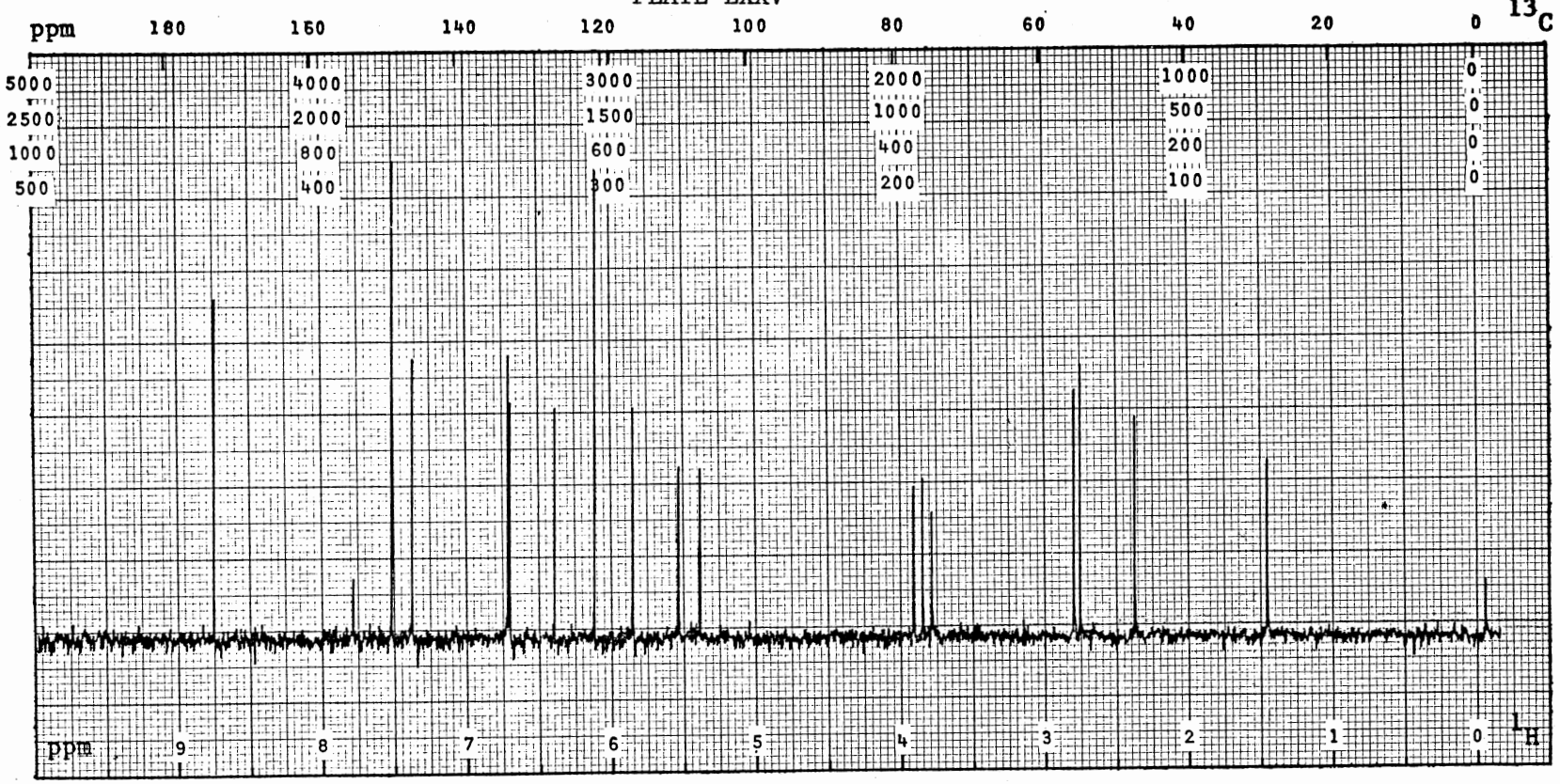
^{1}H NMR Spectrum of 2-Allylamino-5,6,7-trimethoxyindeno [1,2-d] thiazole (22d, R""=allyl)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 8577Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LXXV



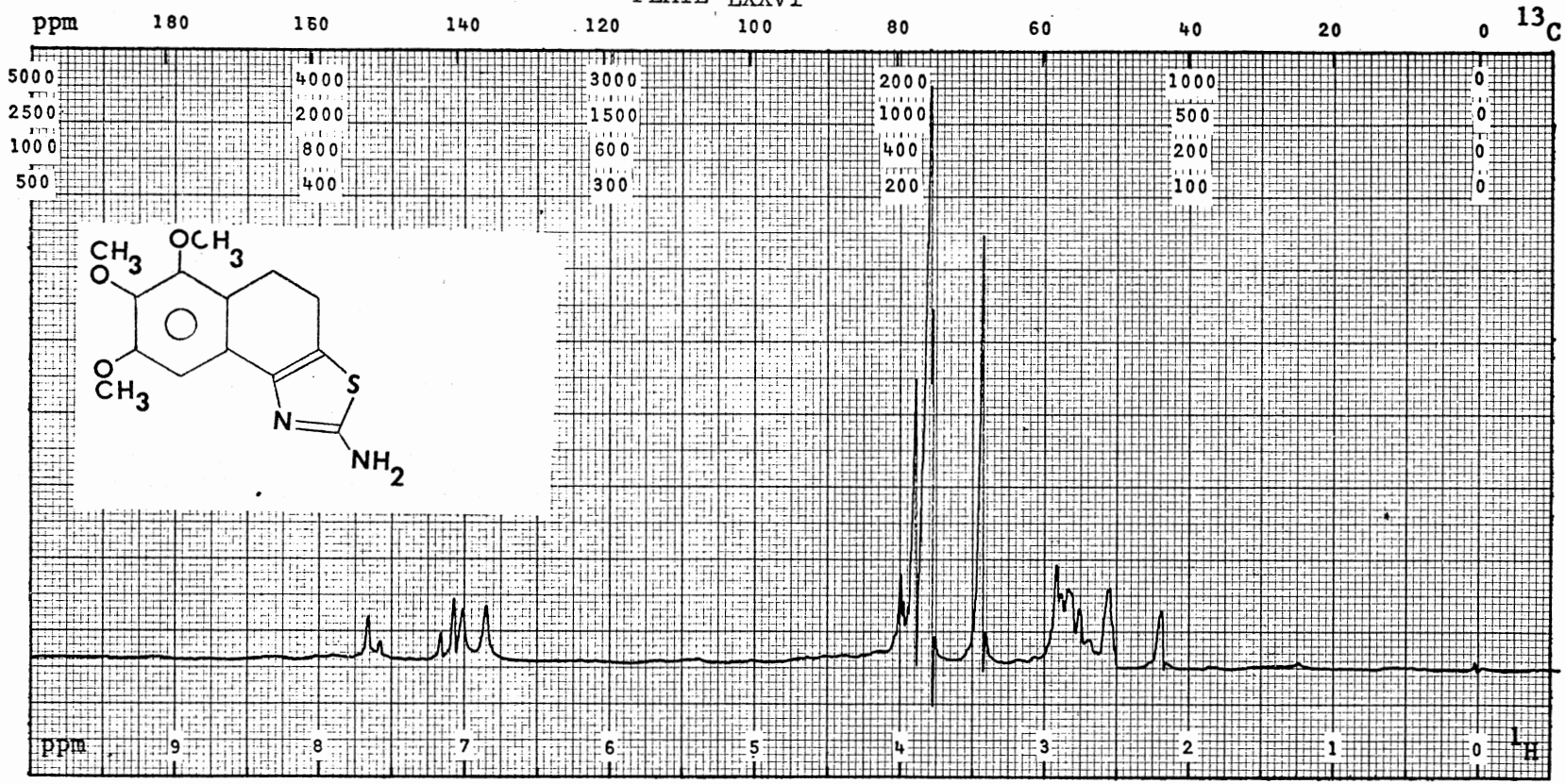
^{13}C NMR Spectrum of 2-Allylamino-5,6,7-trimethoxyindeno[1,2-d]thiazole (22d, R""=allyl)

PFT ^{13}C CW _ ; Solvent. . $DCCl_3$; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 300

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 3Hz; Lock. . ^{2}D; D5/ST. . 5s

DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE LXXVI



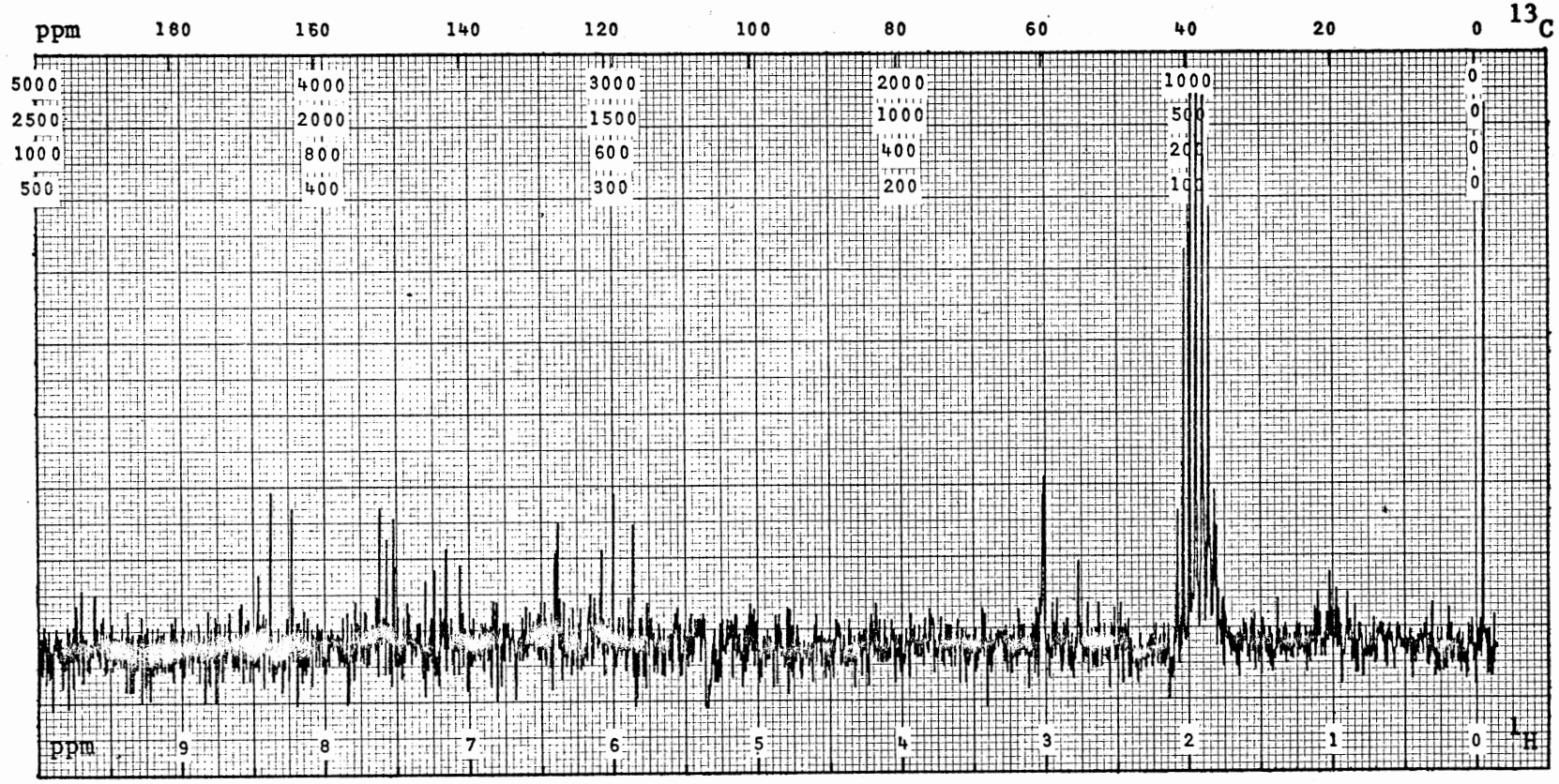
^{1}H NMR Spectrum of 2-Amino-4,5-dihydro-6,7,8-trimethoxynaptheno[1,2-d]thiazole (23c, R''''=H)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LXXVII



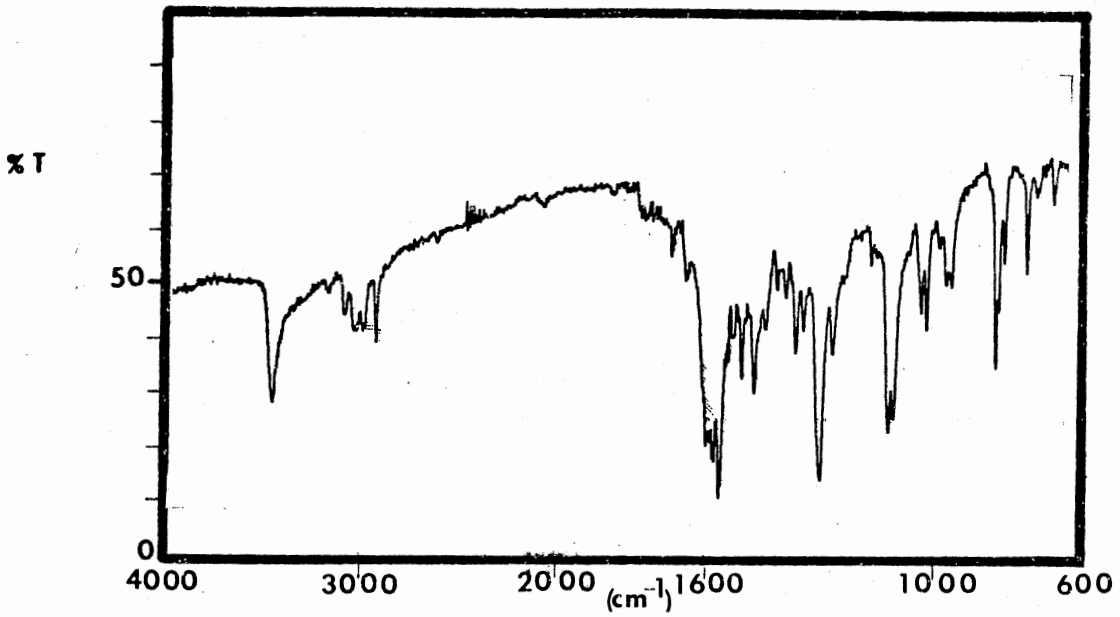
^{13}C NMR Spectrum of 2-Amino-4,5-dihydro-6,7,8-trimethoxynaptheno[1,2-d]thiazole (23c, R""=Ac)

PFT ^{13}C CW _ ; Solvent. . DMSO-d_6; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 600

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 4Hz; Lock. . ^{2}D; D5/ST. . 5s

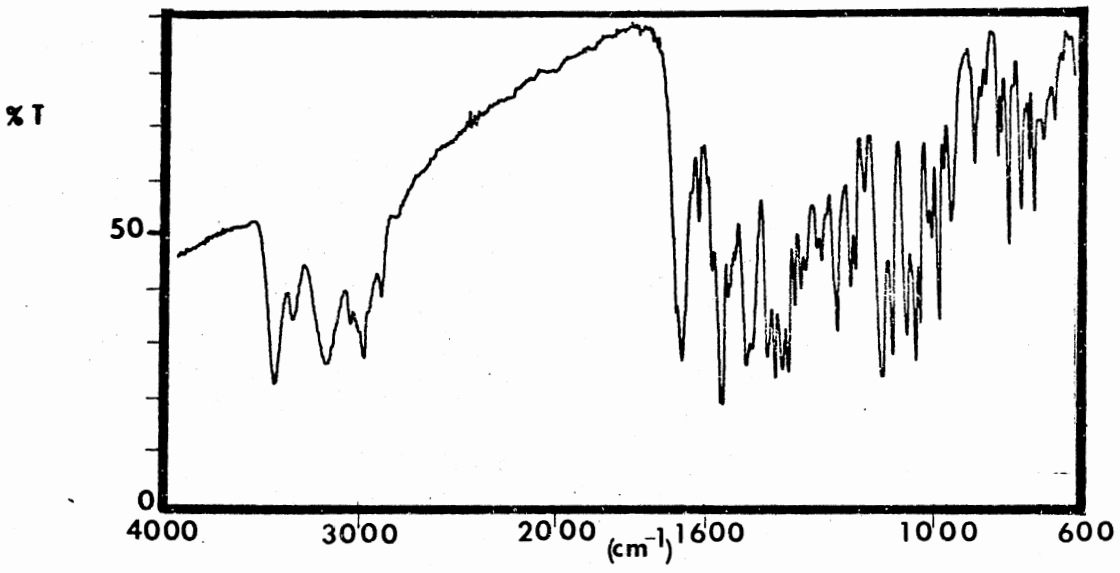
DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE LXXVII



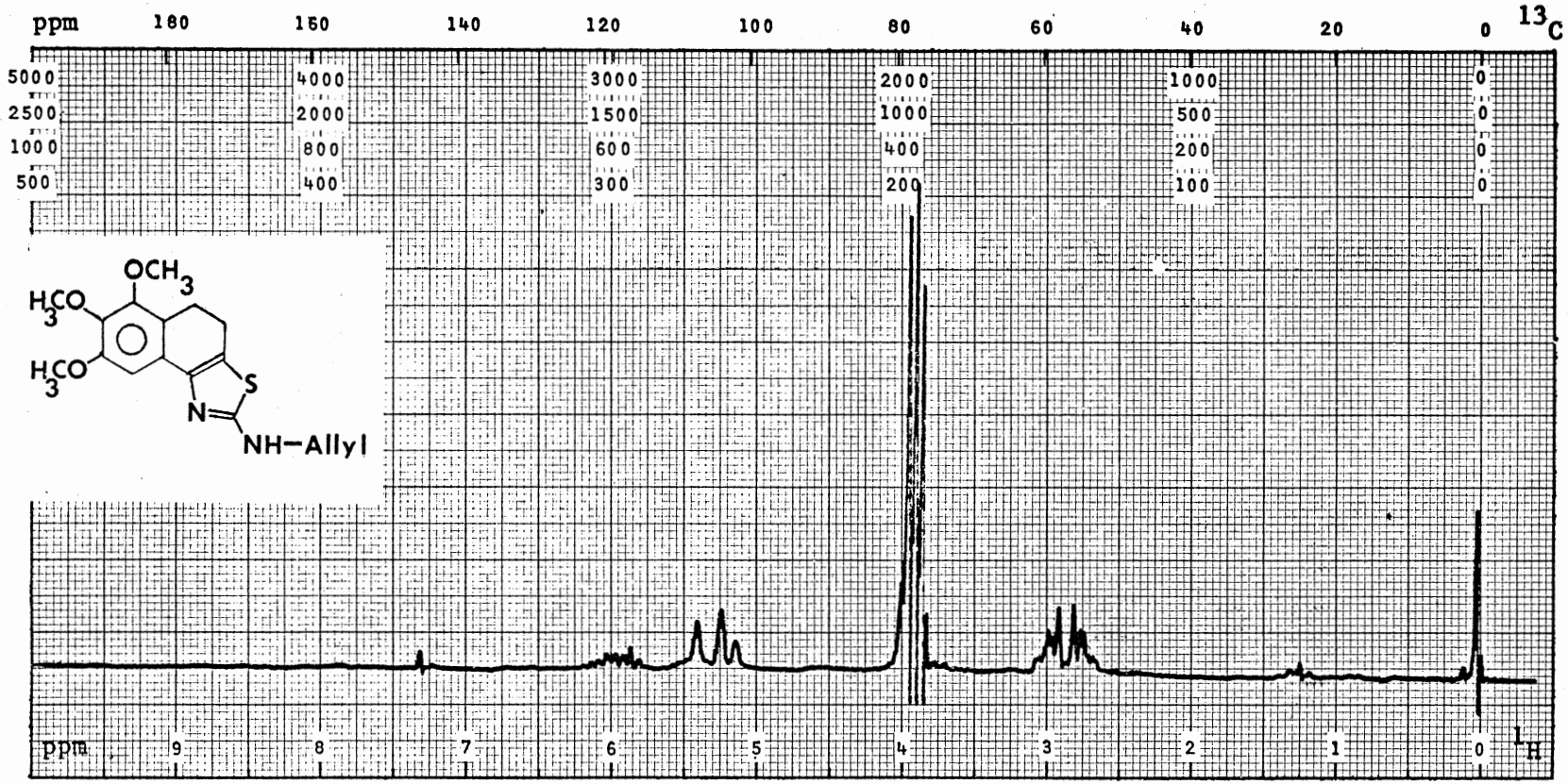
IR Spectrum of 2-Allylamino-5,6,7-trimethoxyindeno [1,2-d] thiazole (22d), KBr Pellet

PLATE LXXIX



IR Spectrum of 2-Amino-4,5-dihydro-6,7,8-trimethoxynaptheno[1,2-d]-thiazole (23d), KBr Pellet

PLATE LXXX



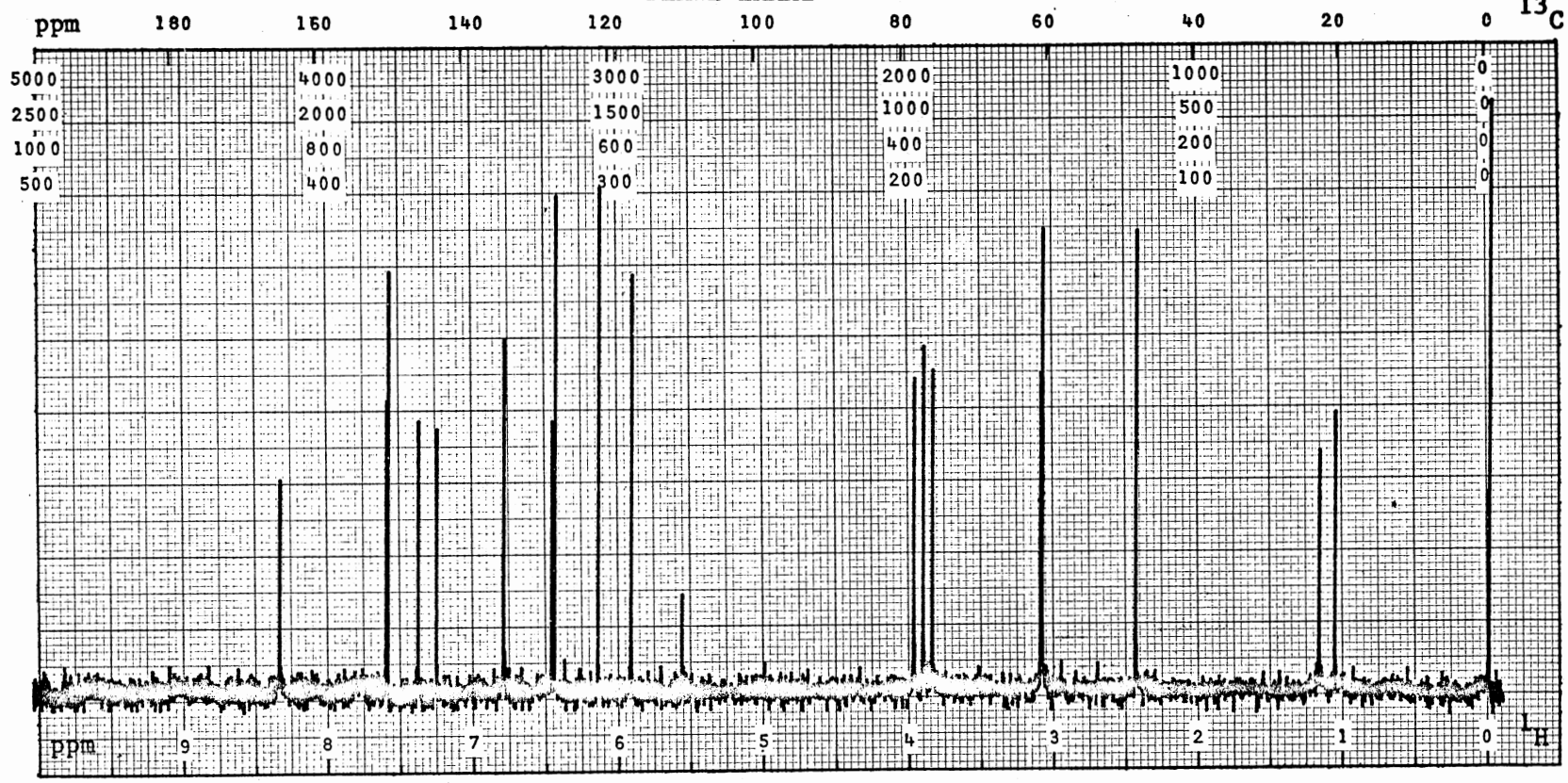
^{1}H NMR Spectrum of 2-Allylamino-4,5dihydro-6,7,8-trimethoxynapthaleno[1,2-d]thiazole (23d, R""=allyl)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69µs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LXXXI



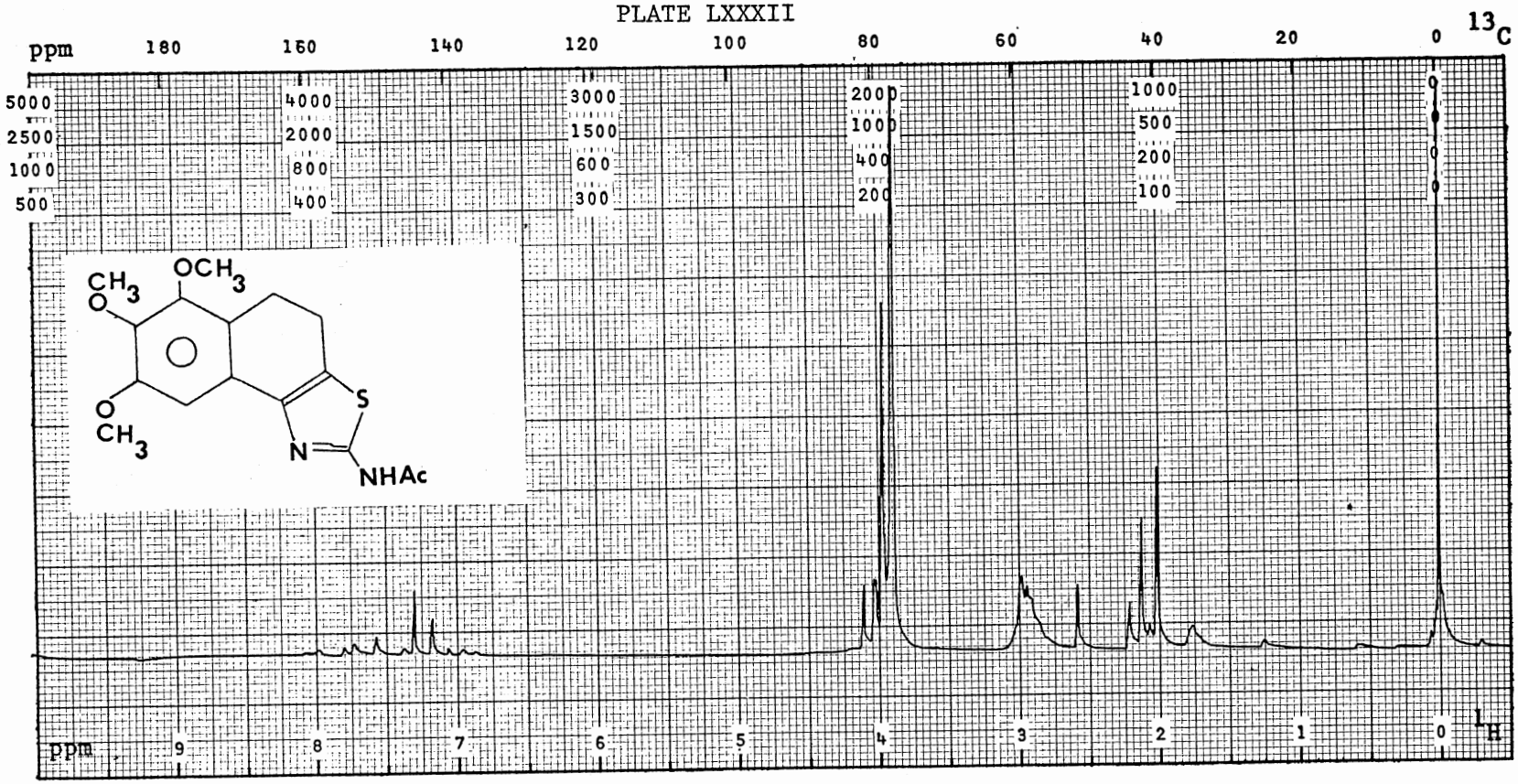
^{13}C NMR Spectrum of 2-Allylamino-4,5-dihydro-6,7,8-trimethoxynaptho[1,2-d]thiazole (23c, R"" = allyl)

PFT ^{13}C CW _ ; Solvent. . $DCCl_3$; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 2500

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 5s

DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE LXXXII



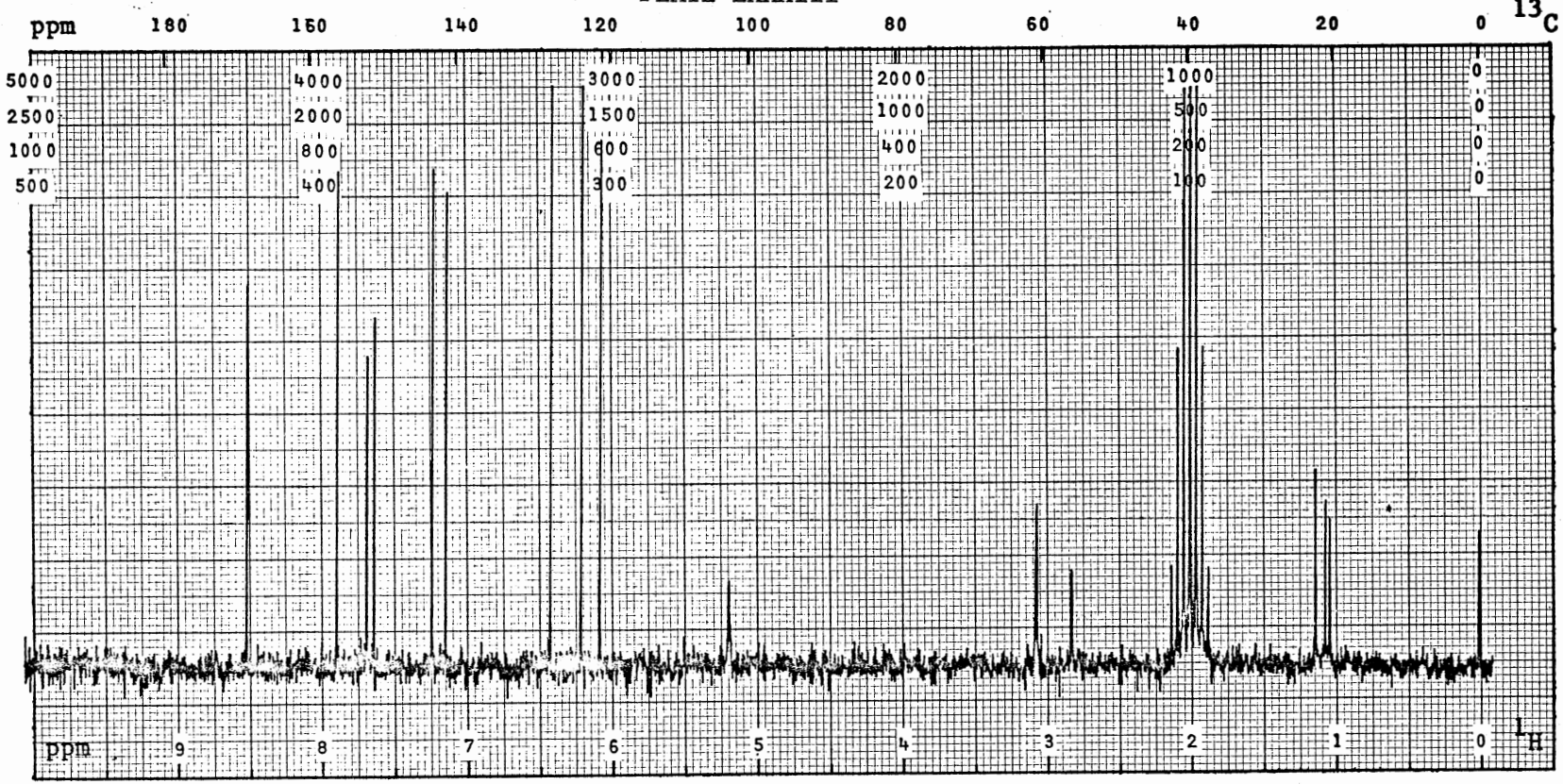
^{1}H NMR Spectrum of 2-Acetoamido-4,5-dihydro-6,7,8-trimethoxynaptheno[1,2-d]thiazole (22c, R""=Ac)

PFT - CW X ; Solvent. . DMSO-d_6; SO. . 4580Hz; PW. . 1000Hz; T. . 88°C; Acq/SA. . 44

Size. . 8K; P2/RF. . 5.7μs/dB; SF. . 100.1Hz; FB. . 4Hz; Lock. . ^{2}D; D5/ST. . 4.0s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE LXXXIII



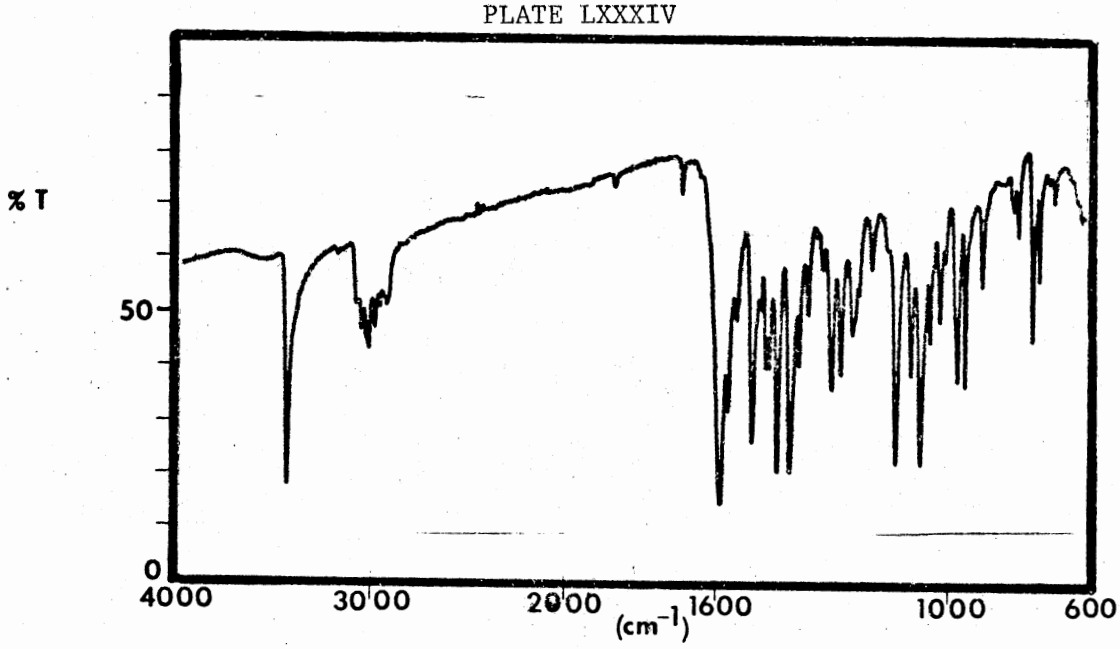
^{13}C NMR Spectrum of 2-Acetoamido-4,5-dihydro-6,7,8-trimethoxynaptheno[1,2-d]thiazole (22c, R""=Ac)

PFT ^{13}C CW _ ; Solvent. . DMSO-d_6; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 600

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 4Hz; Lock. . ^{2}D; D5/ST. . 5s

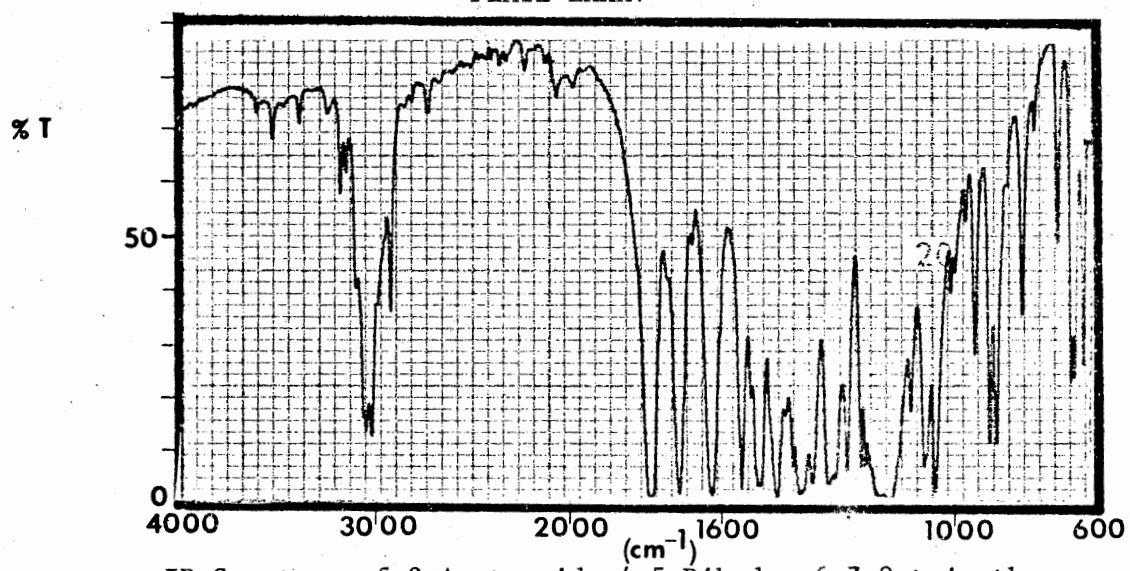
DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE LXXXIV



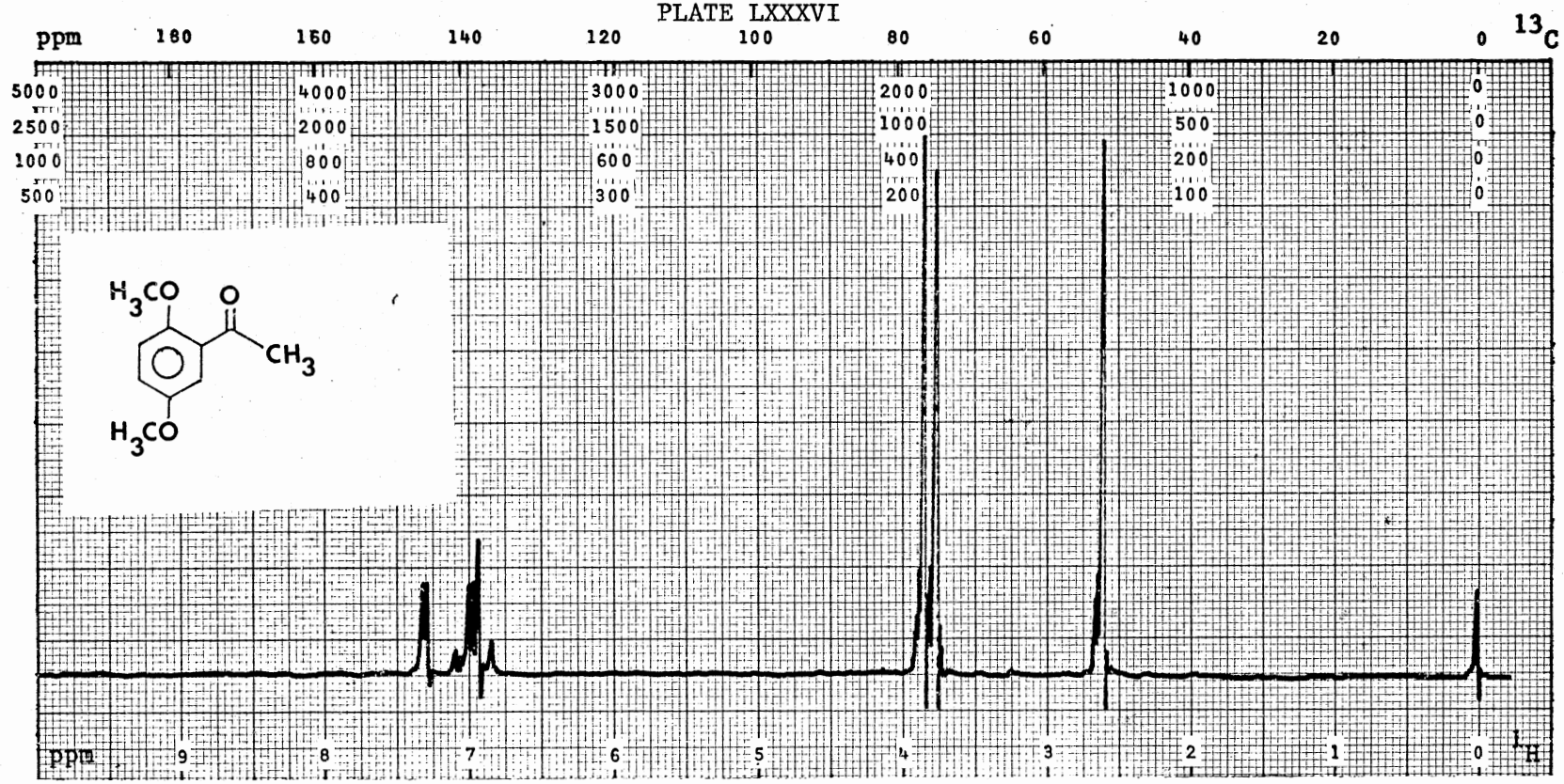
IR Spectrum of 2-Allylamino-4,5-dihydro-6,7,8-trimethoxynaptheno-[1,2-d]thiazole (~~23d~~, R""=allyl) KBr Pellet

PLATE LXXXV



IR Spectrum of 2-Acetoamido-4,5-Dihydro-6,7,8-trimethoxy-naptheno [1,2-d] thiazole (~~23d~~, R""= acetate) KBr Pellet

PLATE LXXXVI



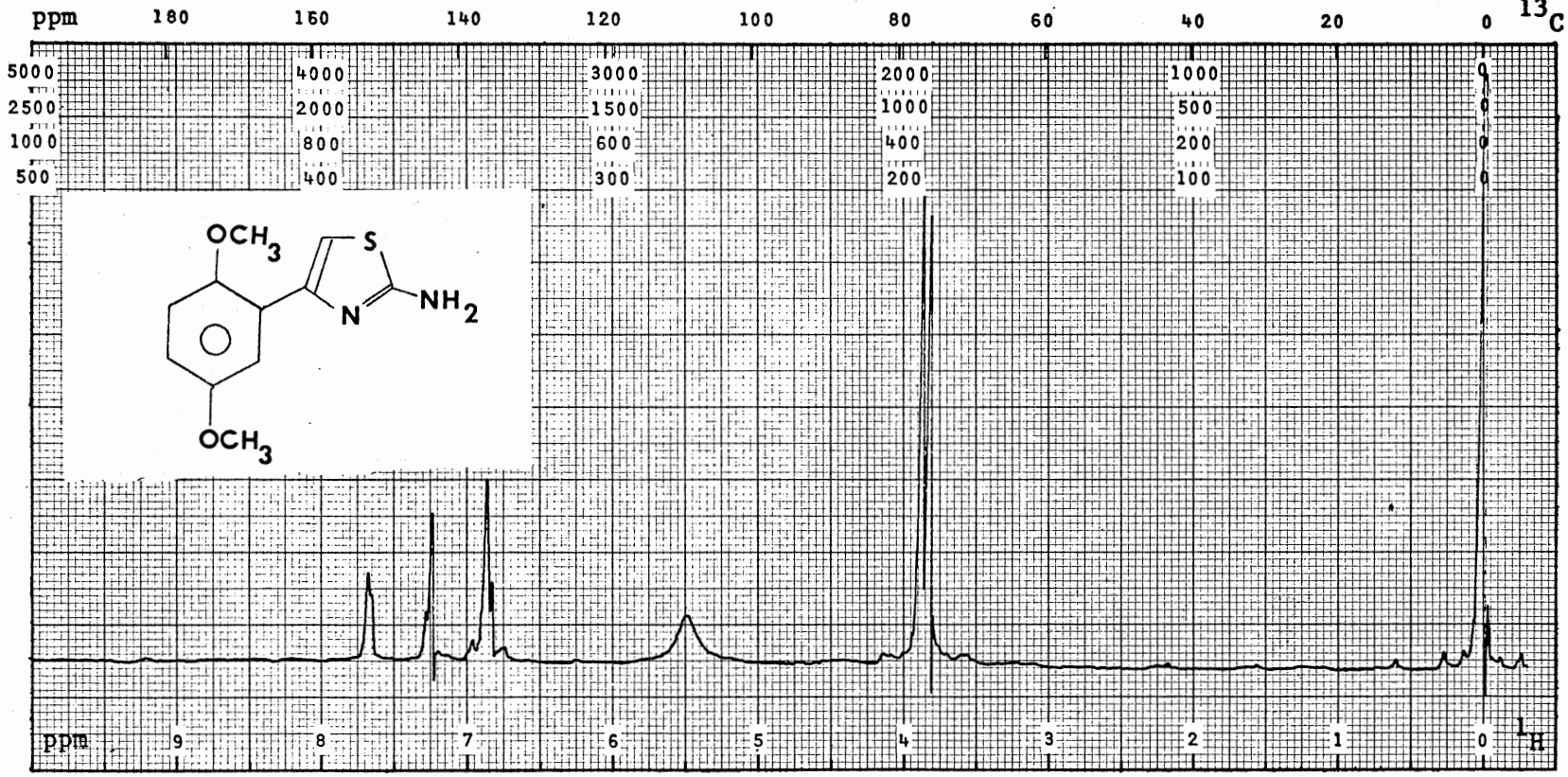
^{1}H NMR Spectrum of 2,5-Dimethoxyacetophenone (30b)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 59µs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LXXXVII



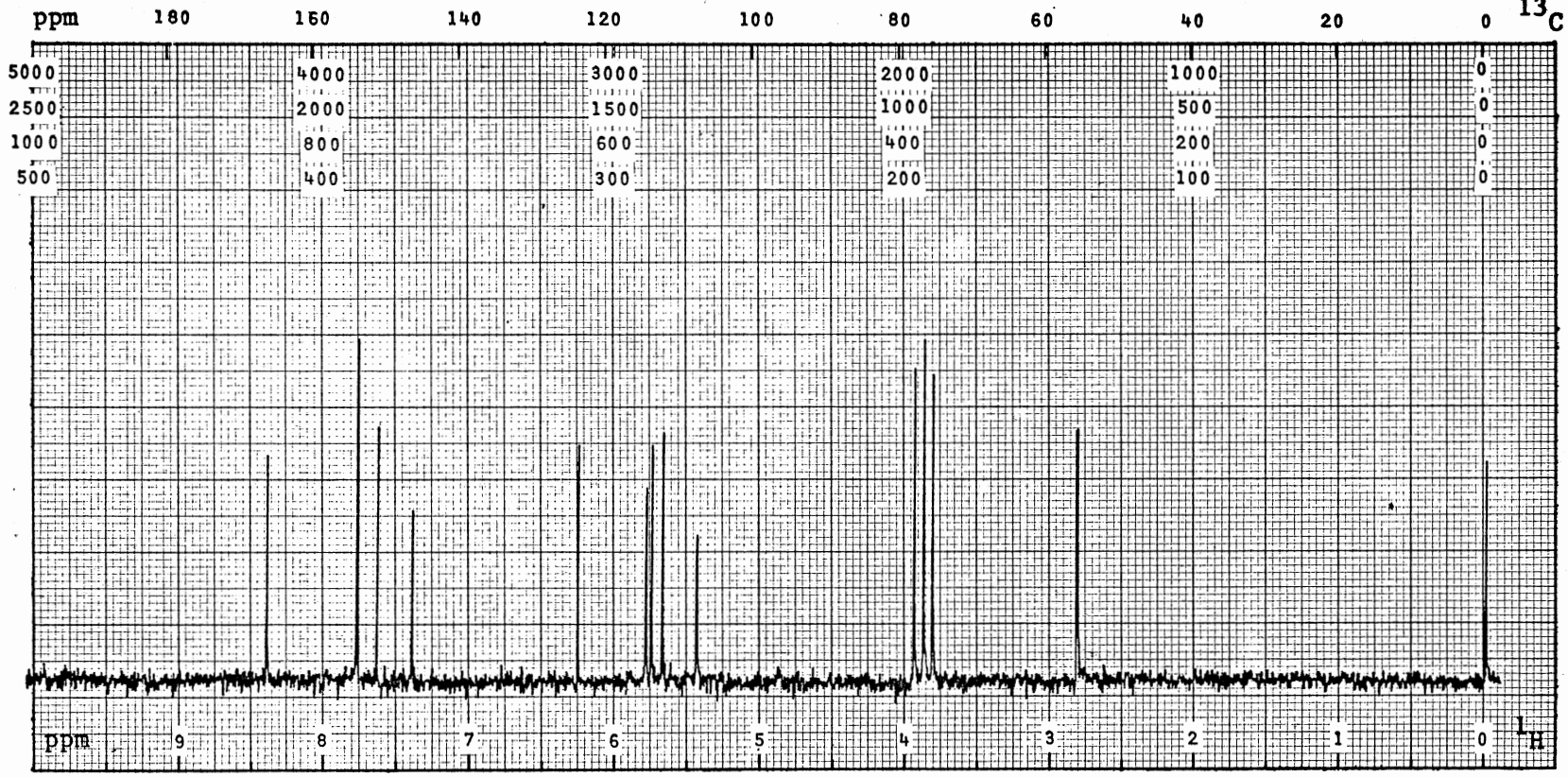
^{1}H NMR Spectrum of 2-Amino-4-(2',5'-dimethoxyphenyl)thiazole (21b, R''''=H)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69µs/dB; SF. . 100.1Hz; FB. . 2 Hz; Lock. . ^{2}D; D5/ST. . 250 s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE LXXXVII



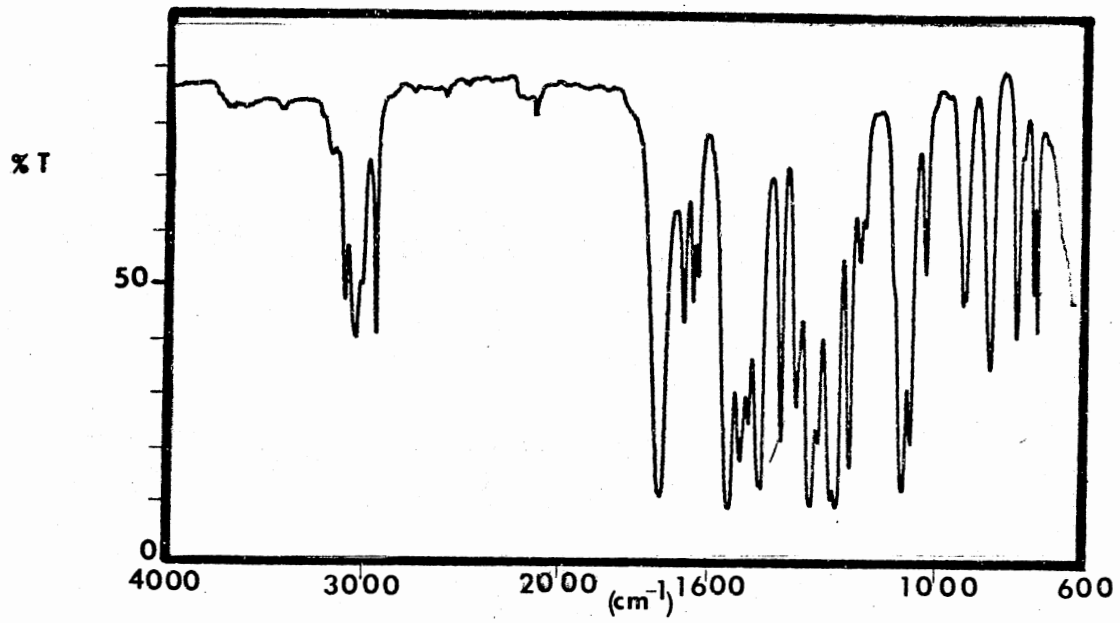
^{13}C NMR Spectrum of 2-Amino-4-(2',5'-dimethoxyphenyl)thiazole (21b)

PFT ^{13}C CW _ ; Solvent. . $DCCl_3$; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 300

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 3Hz; Lock. . ^{2}D; D5/ST. . 5s

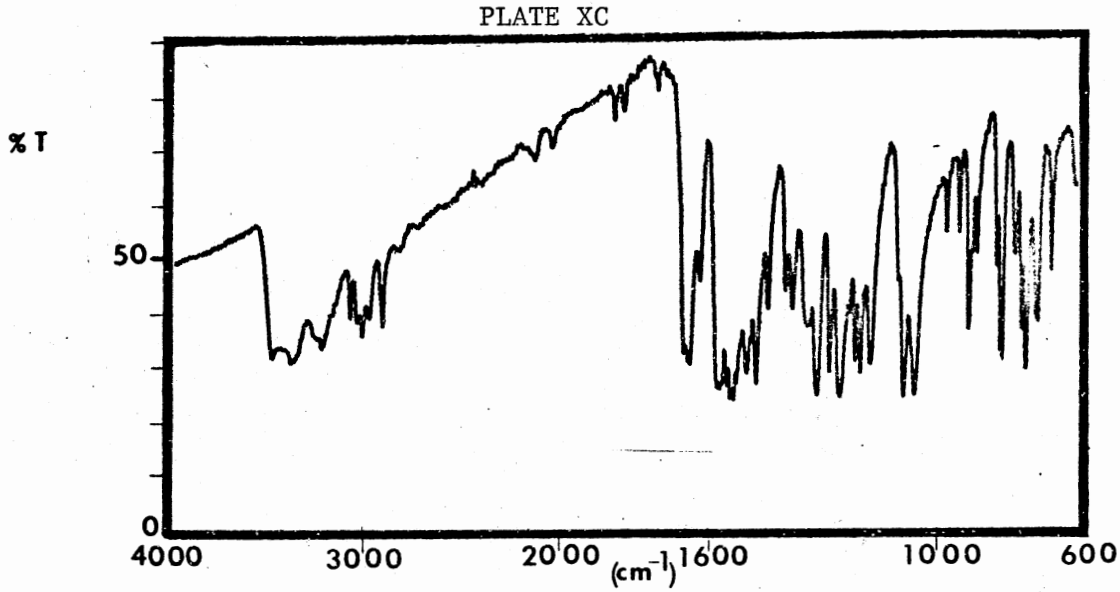
DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE LXXXIX

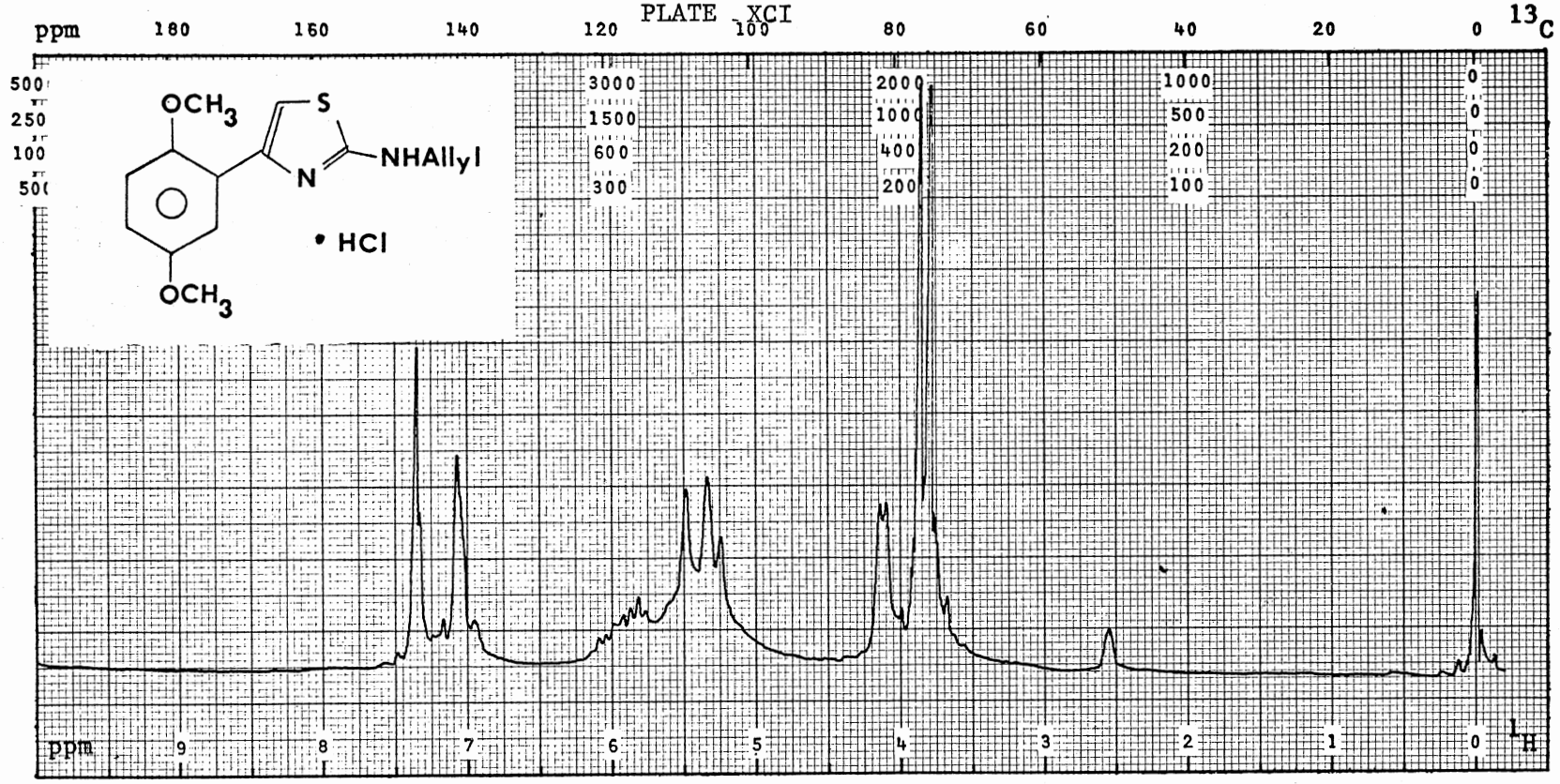


IR Spectrum of 2,5-Dimethoxyacetophenone (30b) KBr Pellet

PLATE XC



IR Spectrum of 2-Amino-4-(2',5'-dimethoxyphenyl)thiazole (21b)
KBr Pellet



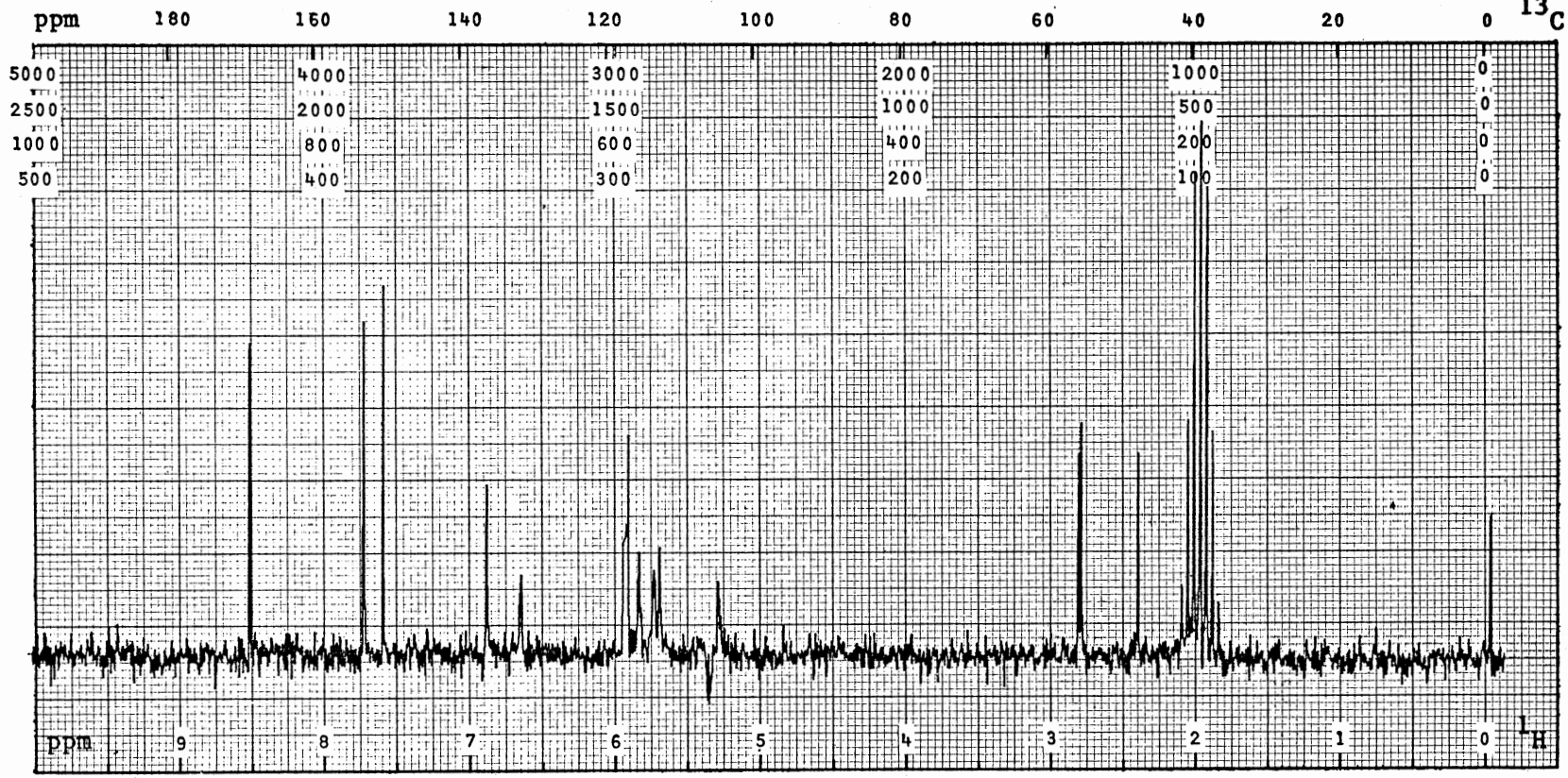
^{1}H NMR Spectrum of 2-Allylamino-4-(2',5'-dimethoxyphenyl)thiazole (21b, R""=allyl)

PFT _ CW X ; Solvent. . DMSO-d_6; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69µs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XCII



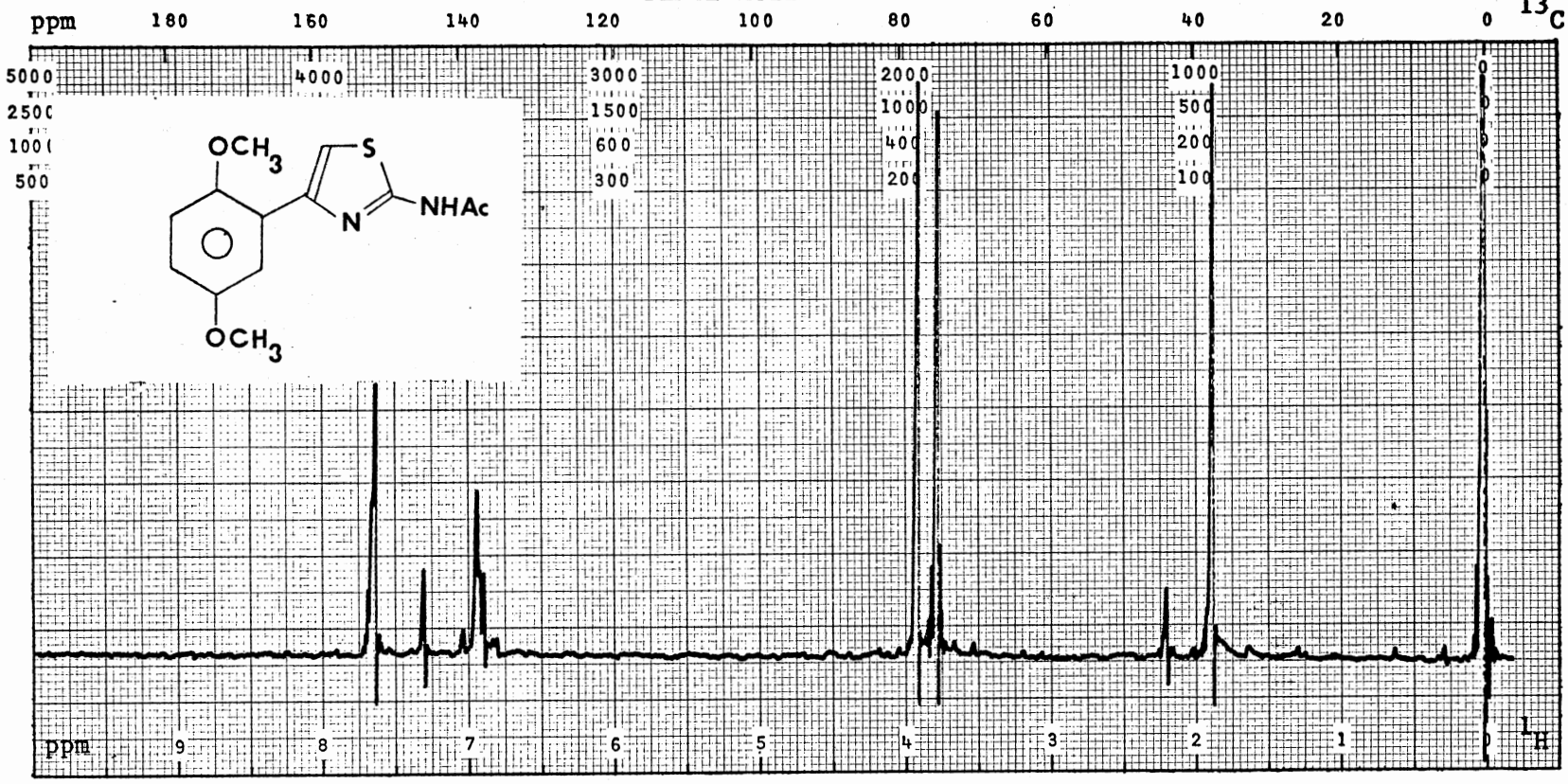
^{13}C NMR Spectrum of 2-Allylamino-4-(2',5'-dimethoxyphenyl)thiazole (21b, R''''= allyl)

PFT ^{13}C CW _ ; Solvent. . DMSO-d_6; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 600

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 4Hz; Lock. . ^{2}D; D5/ST. . 5s

DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE XCIII



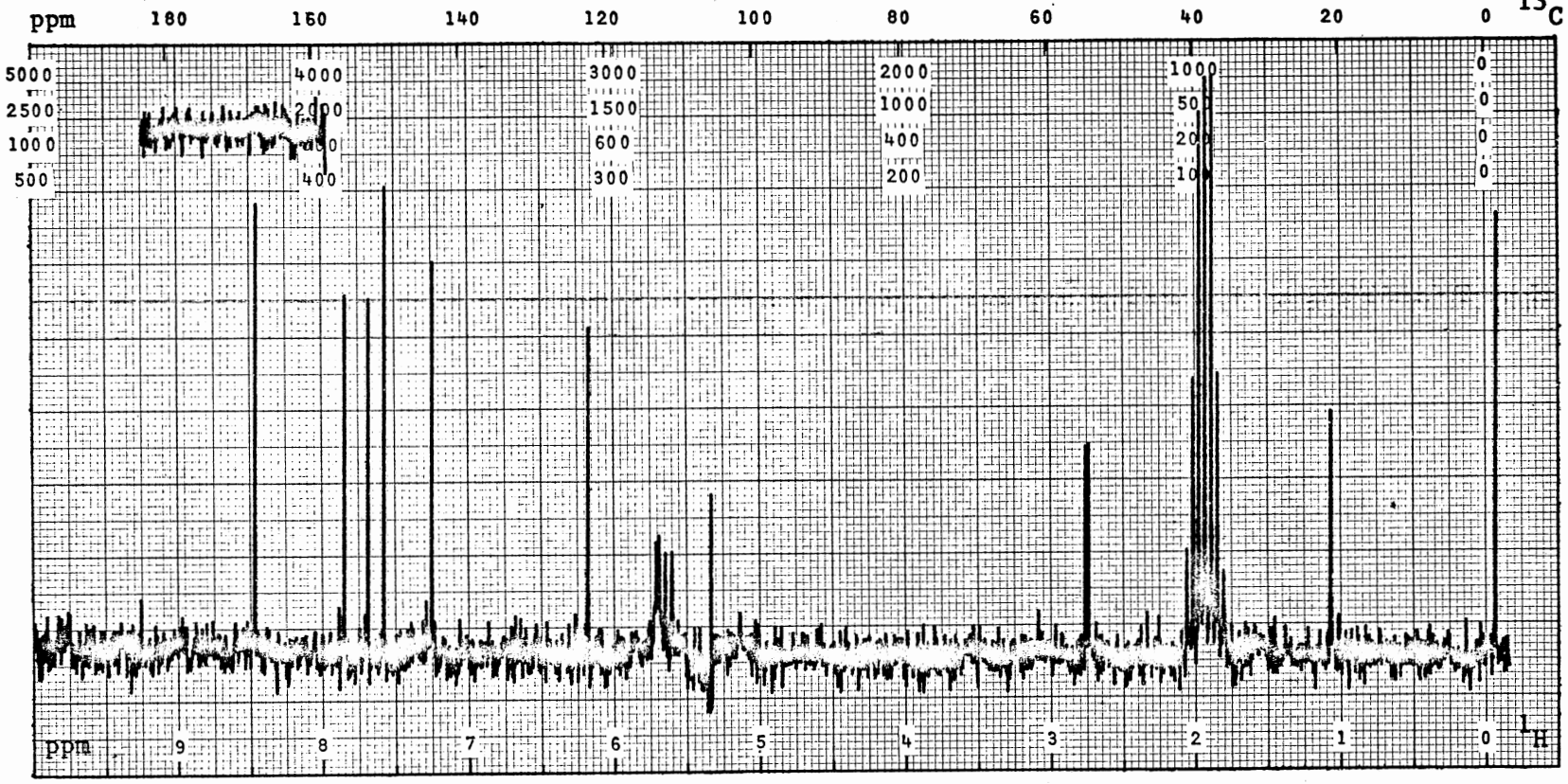
^{1}H NMR Spectrum of 2-Acetoamido-4-(2',5'-dimethoxyphenyl)thiazole (21b, R''''=Ac)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 69μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XCIV



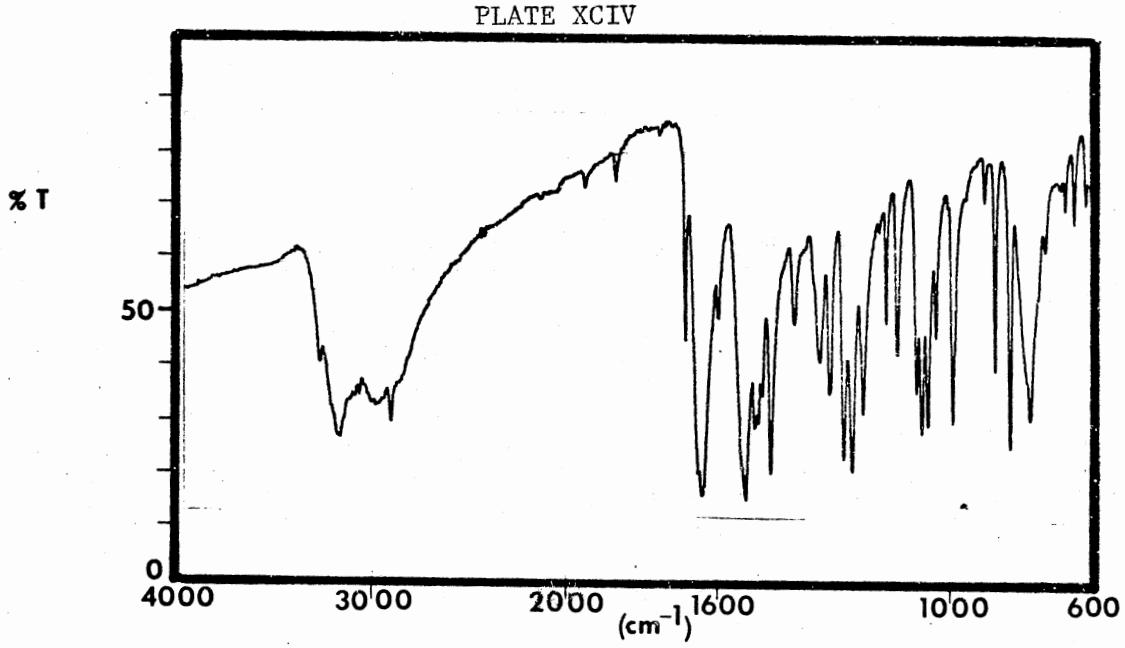
^{13}C NMR Spectrum of 2-Acetoamido-4-(2',5'-dimethoxyphenyl)thiazole (21b, R"" = acetate)

PFT ^{13}C CW _ ; Solvent. . DMSO-d_6; SO. . 35101Hz; PW. . 5000Hz; T. . 33°C; Acq/SA. . 600

Size. . 8K; P2/RF. . 10μs/dB; SF. . 25.2Hz; FB. . 4Hz; Lock. . ^{2}D; D5/ST. . 5s

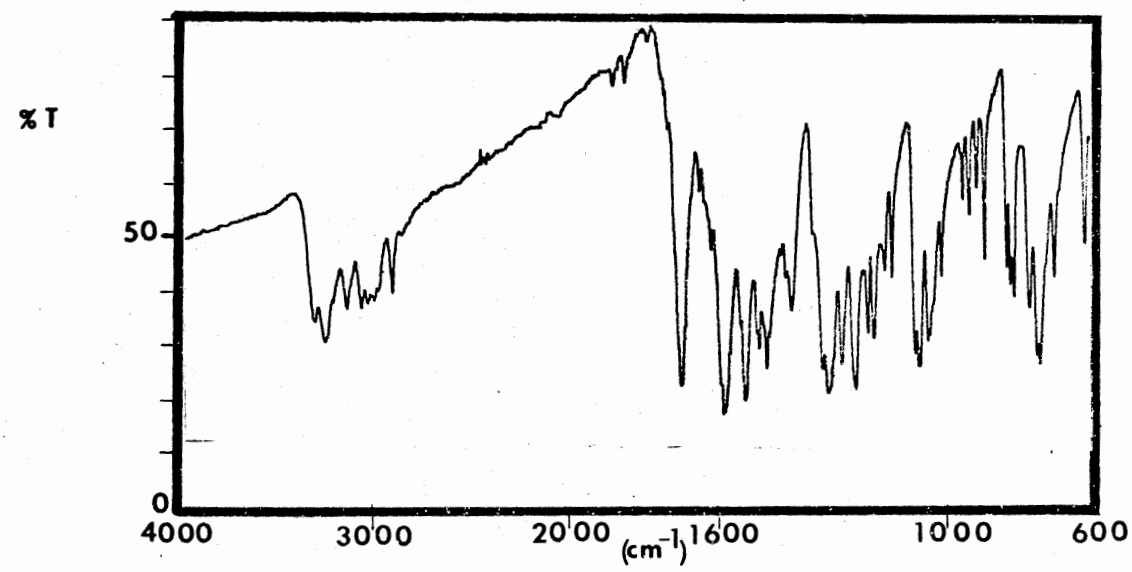
DC. . ^{1}H; Gated Off. . ; Offset. . 45308Hz; RF. . 69W/dB; NBW. . 100Hz

PLATE XCIV



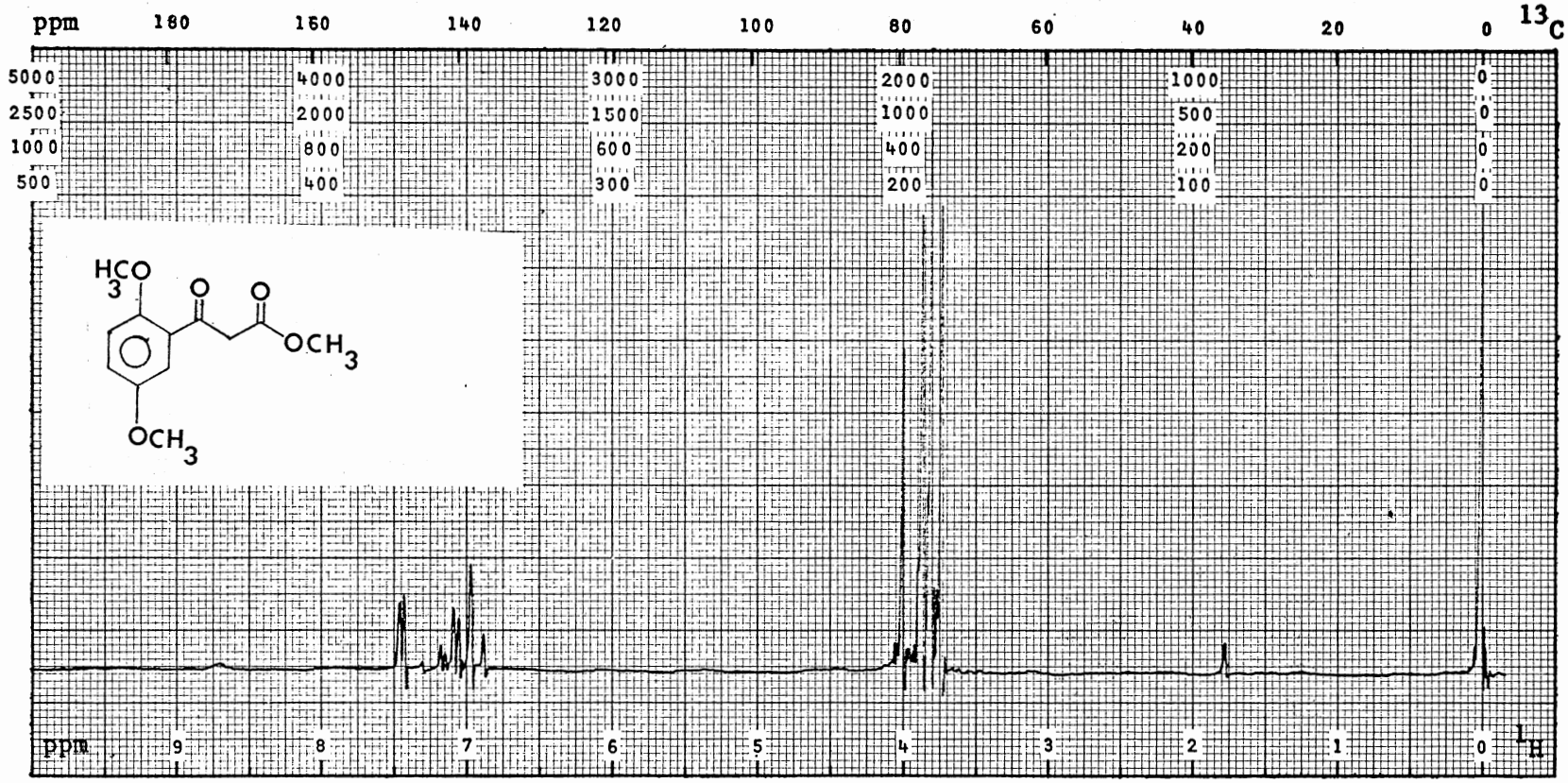
IR Spectrum of 2-Allylamino-4-(2',5'-dimethoxyphenyl)thiazole (21b, R''''= acetate), KBr Pellet

PLATE XCV



IR Spectrum of 2-Acetoamido-4-(2',5'-dimethoxyphenyl)thiazole (21b, R''' = acetate), KBr Pellet

PLATE XCVI



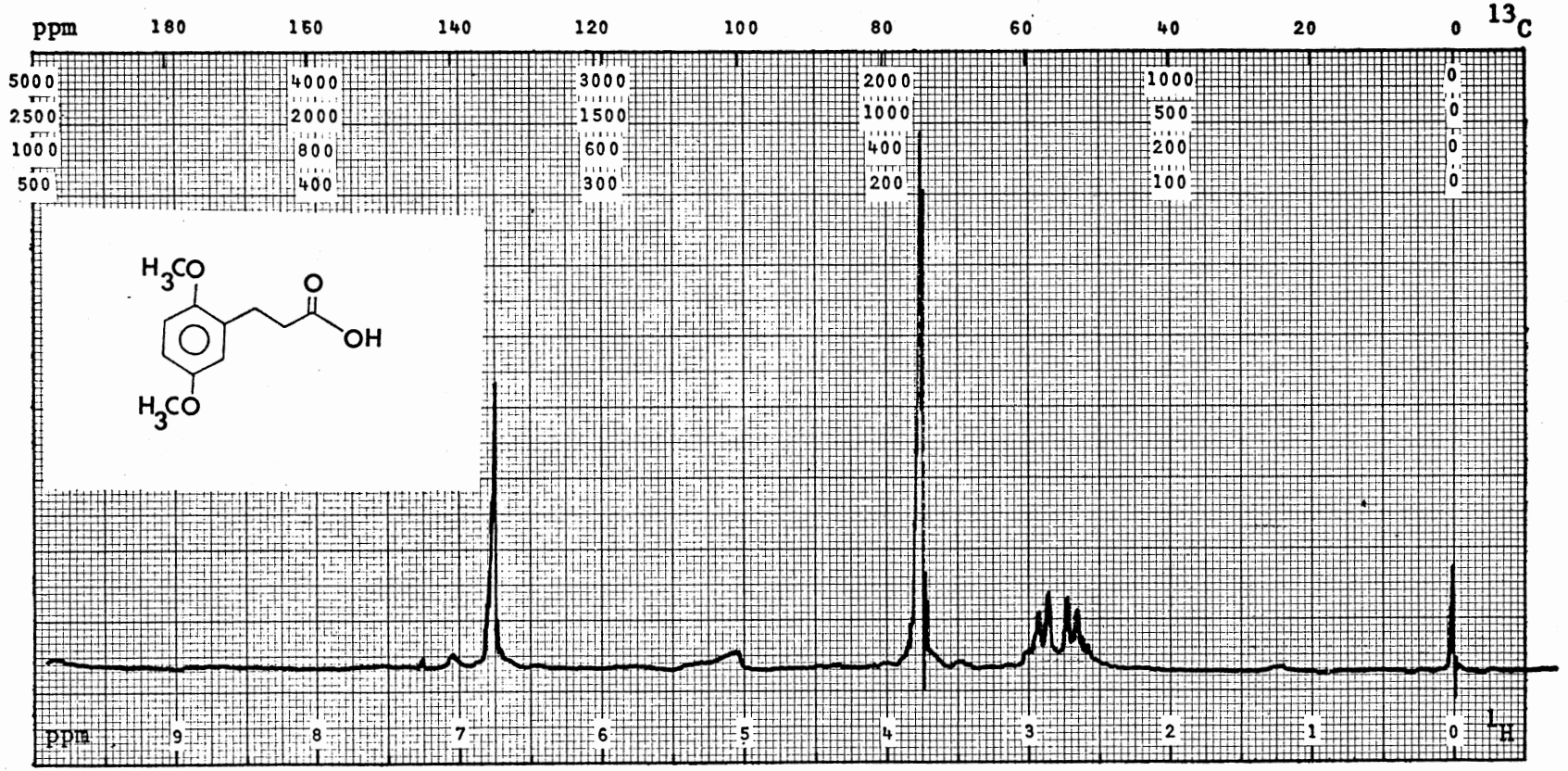
^{1}H NMR Spectrum of Methyl 3-(2',5'-dimethoxyphenyl)-3-oxopropionate (32b)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 59μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}H; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XCVII



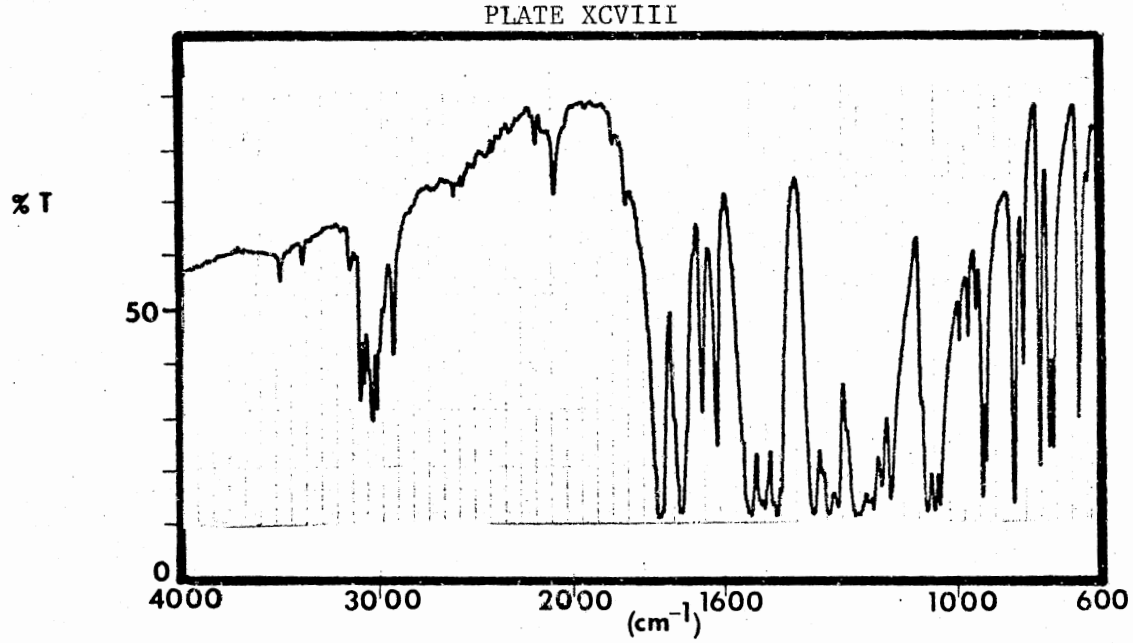
^{1}H NMR Spectrum of 3-(2',5'-Dimethoxyphenyl)propionic Acid (40b)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 1.0

Size. . K; P2/RF. . 52µs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

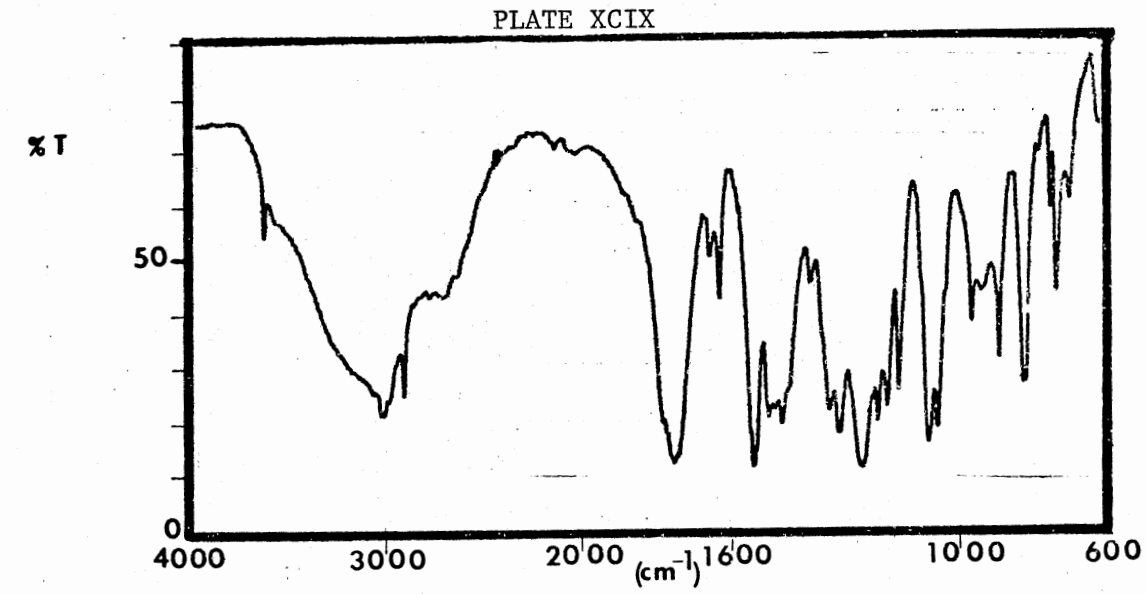
DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE XCVIII



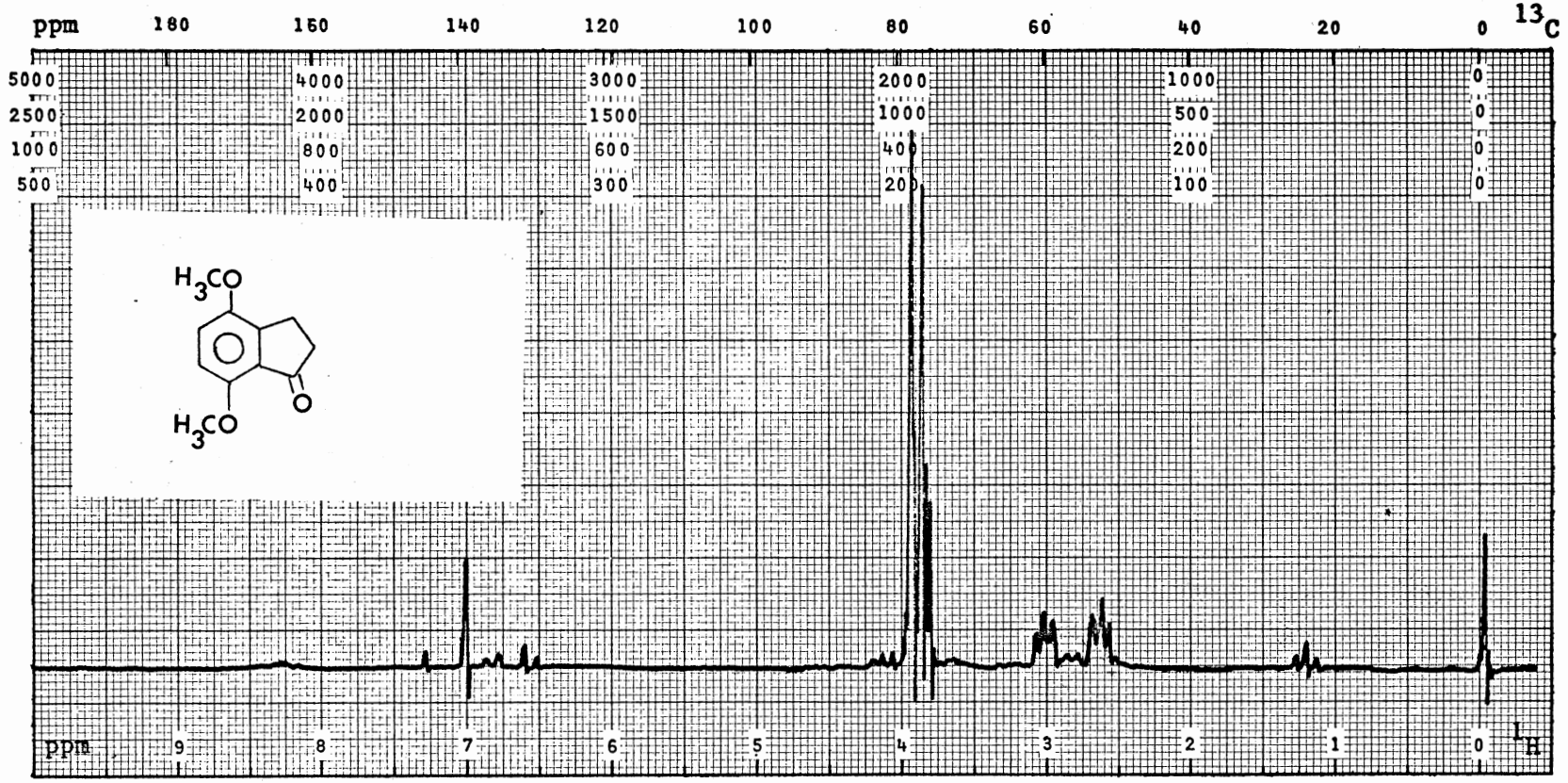
IR Spectrum of Methyl 3-(2',5'-Dimethoxyphenyl)-3-oxopropionic Acid (35b), KBr Pellet

PLATE XCIX



IR Spectrum of 3-(2',5'-Dimethoxyphenyl)propionic Acid (40b) KBr Pellet

PLATE C



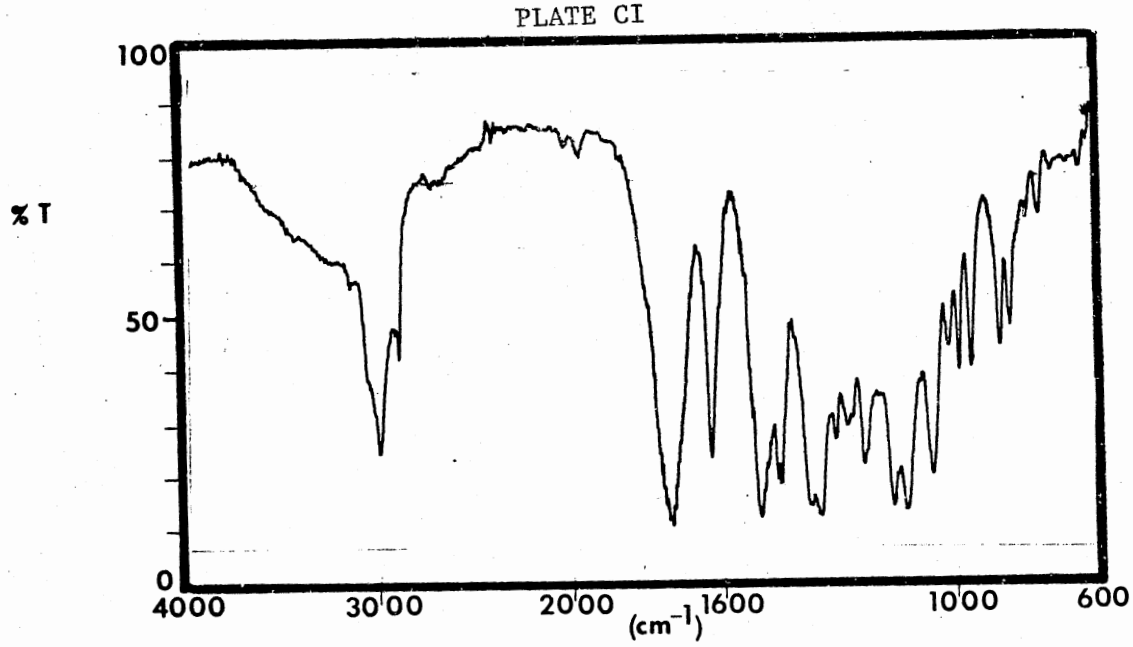
^{1}H NMR Spectrum of 4,7-Dimethoxyindanone (31b)

PFT _ CW X ; Solvent. . $DCCl_3$; SO. . 85771Hz; PW. . Hz; T. . 33°C; Acq/SA. . 10

Size. . K; P2/RF. . 56μs/dB; SF. . 100.1Hz; FB. . 2Hz; Lock. . ^{2}D; D5/ST. . 250s

DC. . ; Gated Off. . ; Offset. . Hz; RF. . W/dB; NBW. . Hz

PLATE CI



IR Spectrum of 4,7-Dimethoxyindanone (31b)
KBr Pellet

BIBLIOGRAPHY

1. Adamson, R. H., "Rational Development of Antitumor Agents", Pharmacology and the Future of Man (Proceedings of the 5th International Congress of Pharmacology (1973), San Francisco, California) Basel, Switzerland: Kanger, v. 3, p. 402.

2. Ahluwalia, S. S., Indian J. Anim. Sci., 43, 428 (1973); Chem. Abstr., 81, 860065 (1978).

3. Anderson, A. G. and Greef, H. F., J Amer. Chem. Soc., 74, 2923 (1952).

4. Anliker, A. S., Lindsay, A. R., Nettleton, D. E. and Turner, R. B., J. Amer. Chem. Soc., 79, 220 (1957).

5. Arena, B., Gulbe, R. and Arens, A., Latv. Psr Zinat. Akad., Vestis, Kim. Ser., 5, 600 (1975); Chem. Abstr., 84, 87735 (1976).

6. Azawa, S. A. and Bakir, M. A., Bull. Coll. Sci. Univ. Baghdad, 12-13, 91 (1973); Chem. Abstr., 82, 34567 (1974).

7. Babadjamian, A., Thesis, University of Marseille, France, 1972.

8. Babadjamian, A., Gallo, R., Metzger, J. and Chanon, M., J. Heterocyclic Chem., 13, 1205 (1976).

9. Bambas, L. L., J. Amer. Chem. Soc., 67, 671 (1945).

10. Barone, R., Chanon, M. and Gallo, R., "Aminothiazoles and Their Derivatives," in The Chemistry of Heterocyclic Compounds, Metzger, J. V., ed., v. 34, pt. 2, Wiley and Sons, New York, N. Y., 1979, p. 9.

11. Becher, P., J. Amer. Chem. Soc., 74, 2823 (1952).

12. Begtrup, M., Acta Chim. Scand., 27, 3101 (1973).

13. Begtrup, M., Acta Chim. Scand., B28, 61 (1974).

14. Bhattacharya, A. K., Indian J. Chem., 5, 62 (1967).

15. Bhattacharya, A. K., J. Indian Chem. Soc., 44, 57 (1967).

16. Bose, N. K. and Chaudhury, D. N., J. Indian Chem. Soc., 42, 211 (1965).

17. Buttery, R. G., Guadagni, D. G. and Lundin, R. E., J. Agric. Food Chem., 24, 1 (1976).

18. Campbell, K. N., Schrage, A. and Campbell, B. K., J. Org. Chem., 15, 1135 (1950).

19. Catsoulacos, P. and Kallias, D., J. Heterocyclic Chem., 16, 763 (1979).

20. Cheng, C. C., J. Pharm. Sci., 64, 645 (1972).

21. Cheng, C. C., in "Pharmacological Basis of Cancer Chemotherapy," Williams and Wilkins Co., Baltimore, Md., 1975, p. 165.

22. Clarke, G. M. and Williams, D. H., J. Chem. Soc., 4597 (1965).

23. Cline, M. J. and Haskell, C. M., "Cancer Chemotherapy," W. B. Saunders Co., Philadelphia, 1975.

24. Dahlbom, R., Ekstrand, T., Gronowitz, S. and Mathiasson, B., Acta Chem. Scand., 17, 2518 (1963).

25. Danishefsky, S. and Quick, J., Tetrahedron Letters, 2525 (1973).

26. Dhami, K. S. and Stothers, J. B., Can. J. Chem., 43, 479 (1965).

27. Dodson, R. M. and King, L. C., J. Amer. Chem. Soc., 67, 2242 (1945).

28. Dodson, R. M. and King, L. C., J. Amer. Chem. Soc., 68, 871 (1946).

29. Driscoll, P. R., Mobil Oil Corp., U. S. Patent No. 3531572, 1969; Chem. Abstr., 74, 87962q (1971).

30. Elguero, J., Marzin, C., Katritzky, A. T. and Linda, P., "The Tautomerism of Heterocycles," ed., Academic, New York, 1975, p. 18.

31. Faure, R., Assaf, A., Vincent, E-J. and Aune, J-P., J. Phys. Chem., 75, 727 (1978).

32. Faure, R., Galy, J-P., Vincent, E-J. and Elguero, J., Can. J. Chem., 56, 46 (1978).

33. Form, G. R., and Raper, E. S., Acta Cryst., B30, 342 (1974).

34. Galasso, V. and Trinajstić, N., Tetrahedron, 28, 2799 (1972).

35. Gellert, E. and Rudzats, R., J. Med Chem., 7, 361 (1964).

36. Gewald, K., Boettcher, H., and Mayer, R., J. Prakt. Chem., 23, 298 (1964).

37. Gilman, H. and Blatt, A. H., Org. Synth., 1, 127 (1950).

38. Grafe, A., Liebig, H. and Pfetzing, H., Riedelde Haen A. G., German Patent No. 2144683, 1971; Chem. Abstr., 78, 159585b (1973).

39. Grafe, A., Liebig, H., and Pfetzing, H., Riedelde Haen A. G., German Patent No. 2132431, 1971; Chem. Abstr., 78, 84394c (1973).).

40. Grafe, A., Liebig, H., and Pfetzing, H., Arzn. Forsch., 24, 153 (1974); Chem. Abstr., 81, 85952.

41. Govindachari, T. R., in "Tylophora Alkaloids," in The Alkaloids, v. 9, Manske, R, H. F., ed., Academic, New York, N. Y., 1967, p. 517.

42. Govindachari, T. R., Lakshmikantham, Nagarajan, K. and Pai, B. R., Tetrahedron, 4, 311 (1958).

43. Hall, S. S., Lipsky, S. D. McEnroe, F. J., and Bartels, A. P., J. Org. Chem., 36, 2588 (1971)..

44. Hancock, R. L. and Abbott, B. J., Cancer Research, 33, 1747 (1972).

45. Hartwell, J. L. and Abbott, B. J., Ad. in Pharm. and Chemotherapy, 7, 117 (1969).

46. Hartwell, J. L. and Schrecker, A. W., Fortschr. Chem. Org. Naturst., Zechmeister, L., ed., v. 15, Springer-Verlag, Vienna, 1958, p. 83.

47. Hashem, M. M., Ph.D. Thesis, Oklahoma State University, 1975.

48. Horton, W. J. and Spence, J. T., J. Amer. Chem. Soc., 80, 2453 (1953).

49. Huang-Minlon, J. Amer. Chem. Soc., 68, 2487 (1946).

50. Hui, K. S., Experientia, 32, 1313 (1976).

51. Huntzsch, A. and Weber, Ber., 20, 3118 (1887).

52. Itoh, N. and Sugasawa, S., Tetrahedron, 6, 16 (1959).

53. Jackson, H. Jones, P., and Whiting, IRCS Libre Compend., 2, 1331, (1974); Chem Abstr., 82, 11207(1976).

54. Jemison, R. W., Aust. J. Chem., 21, 217 (1968).

55. Johnson, W. S., and Glenn, H. J., J. Amer. Chem. Soc., 71, 1092 (1949).

56. Kabalka, G. W., Yang, D. T. C. and Baker, J. D., J. Org. Chem., 41, 574 (1976).

57. King, L., and Hlavack. J. Amer. Chem. Soc., 72, 3722 (1950).

58. King, L., and Ostrum, G. K., J. Org. Chem., 29, 3459 (1964).

59. King, L. C., and Ryden, I., J. Amer. Chem. Soc., 69, 1813 (1947).

60. Knock, F. E., "Anticancer Agents," Charles C. Thomas, Springfield, 1967.

61. Koo, J., J. Amer. Chem. Soc., 75, 720 (1953).

62. Koo, J., J. Amer. Chem. Soc., 75, 1891 (1953).

63. Korolkovas, A. and Burckhalter, J. H., "Essentials of Medicinal Chemistry," Wiley and Sons, New York, 1976.

64. Kupchan, S. M., Britton, R. W., Ziegler, M. F., Gilmore, C. J., Restivo, R. J., and Bryan, R. F., J. Amer. Chem. Soc., 95, 1335 (1973).

65. Kwang-Yuen Zee Cheng and Cheng, C. C., J. Pharm. Sci., 59, 1631 (1970).

66. Kwang-Yuen Zee Cheng and Cheng, C. C., and Paull, K. D., J. Med. Chem., 17, 347 (1974).

67. Lane, C. F., Syn., 135 (1975).

68. Lednecer, D., Upjohn Co., U. S. Patent No. 345826, 1969; Chem. Abstr., 72, 31777 (1970).

69. Lessman, E. M., and Sonal, J. E., J. Amer. Med. Ass., 175, 741 (1961).

70. Levy, G. C. and Lichter, R. L., "Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy," Wiley and Sons, New York, 1979, p. 84.

71. Levy, G. C., Lichter, R. L., and Nelson, G. L., "Carbon-13 Nuclear Magnetic Resonance Spectroscopy," 2nd ed., Wiley and Sons, New York, 1980, p. 109.

72. Liao, T. K., Nyberg, W. H. and Cheng, C. C., Angew. Chem., 79, 100 (1967).

73. Liebig, H. and Pfetzing, H., Arzn. Forsch., 25, 1716 (1975); Chem. Abstr., 84, 53779 (1976).

74. Liebig, H., Pfetzing, H. and Grafe, A., Arzn. Forsch., 24, 887 (1974); Chem. Abstr., 82, 38452 (1974).

75. Lin, Y. Hulbert, P., Bueding, E. and Robinson, C., J. Med. Chem., 17, 835 (1974).

76. Lombardino, J. G., Wiseman, E. H., and Chiaini, J., J. Med. Chem., 16, 493 (1973).

77. Lombardino, J. G., and Wiseman, J. Med. Chem., 16, 512 (1973).

78. Lombardino, J. G., Pfizer Inc., U. S. Patent No. 3927002, 1973; Chem. Abstr., 84, 135693 (1976).

79. Mawdsley, E. A., Ph.D. Thesis, Oklahoma State University, 1975.

80. Mahajanshetti, C. S. and Nargund, K. S., J. Indian Chem. Soc., 39, 420 (1962).

81. McOmie, J. F. W., "Protective Groups in Organic Chemistry," Plenum Press, New York, 1973.

82. Mitscher, L. A., Flynn, D. L. Gracey, H. E. and Drake, S. D., J. Med. Chem., 22, 1354 (1979).

83. Mathur, K. B. L., Sharma, J. N., Vendataramanon, K., and Krishnamurty, H. G., J. Amer. Chem. Soc., 84, 566783d (1976).

84. Mndzhoyan, A. L. and Afrikyan, V. G., Izvest. Akad. Nauk Armyam., S. S. R., Khim. Nauki, 10, 143 (1957); Chem. Abstr., 52, 4641.

85. Moore, H. W. and Folkers, K., J. Amer. Chem. Soc., 88, 567 (1966).

86. Morton, A. and Penner, H., J. Amer. Chem. Soc., 73, 3300 (1951).

87. Nakao, H., Yanagisawa, H., Shimizu, B., Kaneko, M., Nagano, M. and Sugawara, S., Sankyo Co. Ltd. U. S. Patent No. 3971802, 1976; Chem. Abstr., 86, 5478 (1977).

88. Naito, S., Japanese Patent No. 7230665, 1972; Chem. Abstr., 78, 29761 (1973).

89. Noller, C. R. and Adams, R., J. Amer. Chem. Soc., 46, 1889 (1924).

90. Okamiya, J., Nippon Kagaku Zasshi, 82, 87 (1961); Chem. Abstr., 56, 10122 (1962).

91. Ornellas, M. R., Thuret, F., and Laborit, H., Agressologie, 10, 265 (1969).

92. Papa, D., Schwenk, E. and Whitman, B., J. Org. Chem., 7, 587 (1942).

93. Paul, J. H., Silverman, R. and Schwartz, L. H., Org. Prep. Proceed. Int., 7, 149 (1975).

94. Perdue, R. E., Wall, M. E., Hartwell, J. L. and Abbott, B. J., Lloydia, 31, 229 (1968).

95. Pettit, G. R., "Biosynthetic Products for Cancer Chemotherapy," v. 1, Plenum Press, New York, 1977.

96. Plattner, P. A., ed., "Chemotherapy of Cancer," Elsevier, New York, 1964.

97. Rahman, A., van der Helm, D., Herd, M. D., Hashem, M. M., and Berlin, K. D., J. Heterocyclic Chem., 17, 1549 (1980).

98. Rao, K. V., Biemann, K. and Woodward, R. B., J. Amer. Chem. Soc., 85, 2532 (1963).

99. Riddick, J. A., and Bunger, W. B., "Organic Solvents," Techniques of Chemistry, v. II, Weissberger, A., ed., Wiley and Sons, New York, 1978.

100. Salah, M. K., and Abdel Aziz, F. T., Zentralbl. Veterinaermed. Reihe A, 21, 344 1974); Chem. Abstr., 81, 86150 (1976).

101. Sawhney, S. N., Singh, J., and Bansal, O. P., J. Indian Chem. Soc., 52, 561 (1975).

102. Schmidt, P., Eichenberger, K., Ilvespaa, A. O. and Wilhelm, M., Ann. N. Y. Acad. Sci., 160, 530 (1969).

103. Schmidt, P. and Wilhelm, Chimia, 20, 253 (1966).

104. Schroetter, E., Raddatz, A., and Oettel, M., J. Prakt. Chem., 31, 520 (1975).

105. Selim, M., Martin, G. and Selim, M., Bull. Soc. Chim. France, 8, 3268 (1968).

106. Shah, G. D. and Nargund, K. S., J. Univ. Bombay, 15A, 19 (1947); Chem. Abstr., 42, 1999f (1948).

107. Sheid, B., Lu, T., and Nelson, J. H., Cancer Research, 33, 2518 (1973).

108. Silberg, A., and Frenkel, Z., Bull. Soc. Chim. France, 6, 2235 (1967).

109. Silberg, A., Frenkel, Z., Szotyori, L., and Axente, V., Farm. Bucharest., 15, 275 (1967); Chem. Abstr., 68, 49498 (1977).

110. Takeo, U., Sadatake, K., Shigeshi, T., and Fumio, U., Dai-Nippon Drug Manufacturing Co., Japanese Patent No. 3531572, 1960; Chem. Abstr., 55, 6499 (1961).

111. Taniyama, H., Yasui, B. and Inoue, F., J. Pharm. Soc Japan, 73, 276 (1953).

112. Vernin, G., "General Synthetic Methods for Thiazole and Thiazolium Salts," in the Chemistry of Heterocyclic Compounds, Metzger, J. V., ed., v. 34, pt. 1, Wiley and Sons, New York, N. Y., 1979.

113. Walker, E. R. H., Chem. Soc. Rev., 5, 23 (1976).

114. Wall, M. E. Wani, M. C., Cook, C. E., Palmer, K. H., McPhail, and Sims, G. A., J. Amer. Chem. Soc., 88, 3888 (1966).

115. Wallingford, V. H., Homeyer, A. H. and Jones, D. M., J. Amer. Chem. Soc., 63, 2056 (1941).

116. Werbel, L. M., and Battaglia, J. R., J. Med. Chem., 14, 10 (1971).

117. West, C. T., Donnelly, S. J., Kooistra, D. A. and Doyle, M. P., J. Org. Chem., 38, 2675 (1973).

118. Westphal, G. and Wasicki, H., Z. Chem., 8, 337 (1968).

119. Wise, E. H. and Chiaini, J., Biochem. Pharmacol., 21, 2323 (1972).
120

120. Witanowski, M., Stefaniak, L., Januszewski, H., and Grabowski, Z., Tetrahedron, 28, 637 (1972).

121. Wright, S. E., Gallagher, R. E., Ting, R. C. and Gallo, R. C., Cancer Research, 33, 2513 (1973).

122. Zeitoun, R., Ghazal, A. and Bakry, N., Egyt. J. Pharm. Sci., 13, 273 (1972); Chem. Abstr., 81, 163441 (1973).

123. Ziemelis, K., Gudriniece, E. and Matseevskaya, E. K., Latv. Psr Zinat. Akad. Vestis, Kim. Ser., 4, 445 (1967); Chem. Abstr., 68, 12889 (1960).

PART II

NUCLEAR OVERHAUSER ENHANCEMENT MEASUREMENTS FOR CERTAIN ORGANOPHOSPHORUS COMPOUNDS. EVALUATION OF RELAXATION MECHANISMS FOR ^{31}P

CHAPTER I

HISTORICAL

Nuclear magnetic resonance spectroscopy involving the phosphorus atom has been well documented.[5,20] However, only recently has there appeared in the literature reports of relaxation phenomena (T_1 and NOE values) for the phosphorus nucleus.[3,6,8,12,13,18,19,22,23] Dale and Hobbs determined T_1 and NOE values for ^{31}P nuclei in several phosphites and phosphates[6] and related the relaxation time to a viscosity/temperature ratio. Wilkie observed ^{13}C relaxation parameters in triphenylphosphine, triphenylarsine, and triphenylstibine.[22] Later work by Wilkie recorded the T_1 and NOE values for the ^{31}P nucleus in triphenylphosphine as well as for the corresponding oxide and sulfide.[23]

^{13}C and ^{31}P NMR spin-lattice relaxation times have been related to molecular motions in macromolecules[18] such as RNA and DNA.[3] Use of T_1 and NOE values to gain insight into molecular properties of a few phosphines and certain corresponding phosphonium salts have also been reported.[8] A knowledge of the different relaxation mechanisms for the transfer of energy between the various nuclei and the environment can provide important structural information.[14] Relaxation studies of ^{31}P in orthophosphate solutions[12] and in adenosine monophosphate (important in biological systems)[13] indicate that spin-rotation (SR) interactions predominate with dipole-dipole (DD) interactions contributing perhaps 5-10 %. Other workers[19,23] have recorded similar results

for (DD) interactions in phosphines, the corresponding P-oxides and P-sulfides with the exception that the chemical shift anisotropy (CSA) mechanism can participate to a small extent in aryl-substituted phosphorous-containing compounds.

The maximum NOE that can be observed for a phosphorus nucleus may be calculated from the ratios fo the gyromagnetic constants of hydrogen and phosphorus.[14] In a few systems such as $(C_2H_5)_3Pm$ $(CH_3)_3P$, $O{=}P(OCH_3)_3$ and $P[N(CH_3)_2]_3$, the NOE values found were 0.4, 0.07, 0.38 and 0.26, respectively.[8,19]

$$\eta_{max} = \frac{\gamma_H}{2\gamma_P} = \frac{26{,}752}{21{,}658} = 1.235$$

The Relaxation Mechanisms

Phosphorus possesses a spin number of 1/2 and is an NMR active nucleus.[13-15] NMR active nuclei may be placed in a strong magnetic field (H_o or B_o), and those active nuclei will then have induced a precessing magnetic moment (μ), the frequency and magnitude of which depends upon H_o (or B_o).[2,4] If a second magnetic field H_1 is now applied to the nucleus under observation, such that $H_1 << H_o$ and $H_1 \perp H_o$, then that nucleus can be made to align against the direction of H_o.[11] Realignment (also known as "spin flipping") occurs only when the energy of H_1 is applied at the same frequency at which μ is quantitized and will be available only when H_1 is of the proper frequency (known as the Larmor precessional frequency).[11] A typical NMR experiment consists of placing a sample in H_o (or B_o), irradiating with different frequencies of H_1, and observing the

absorption of energy. A plot of energy absorbed versus frequency (in ppm) yields an NMR spectrum.

In an experiment in which a sample is exposed to H_o (or B_o), but not to H_1, a certain Boltzmann distribution of nuclei arises.[14] There exists an excess of nuclei in a lower energy spin state in equilibrum with a lesser populated excited state.[14] When H_1 is applied, the equilibrium ratio of nuclei in the ground spin state to that in the excited spin state is inverted, and a new equilibrium is established. Removal of H_1 will allow a return to the ratio of excited nuclei/ground state nuclei in the original Boltzmann distribution.[11] In order for this phenomenon to occur, nuclei in the excited spin state must release energy to the environment (lattice) by some mechanism.[4] Loss of energy by a mechanism occurs exponentially with time and can be described by first order kinetics:[14]

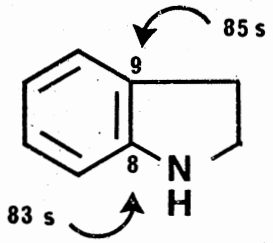
$$(N - N_{eq}) = (N - N_{eq})_{t=0} \exp(-\frac{t}{T_1}).$$

N is the numerical difference in excited and ground states at any time, t; N_{eq} is the numerical difference in excited and ground status in the Boltzmann distribution; and T_1 is the first order rate constant. T_1 is defined as the spin-lattice relaxation time[14] and is characteristic for a particular nucleus in a unique electronic and magnetic environment.

The magnetic environment in which a nucleus resides determines the mechanism(s) by which it relaxes (or transfers energy). There are believed to exist four major processes of relaxation: scalar coupling (SC), chemical shift anisotropy (CSA), spin rotation (SR), and dipole-dipole (DD) coupling.[2,4,14]

Chemical Shift Anisotropy (CSA)

Anisotropic distribution of electrons around a nucleus [such as around C(8) and C(9) in indole][14] can cause relaxation of that nucleus.



As the molecule tumbles through the solution, reorientation of the anisotropically distributed electrons with respect to H_o (or B_o) generates locally fluctuating magnetic fields which can cause relaxation of an NMR active nucleus.[3] The (CSA) mechanism is field dependent; thus the measured T_1 values are inversely proportional to the square of the magnetic field H_o (or B_o) applied.[14] Thus for the best evaluation of a possible (CSA) mechanism operating, the T_1 values should be obtained on a particular nucleus at two different field strengths.

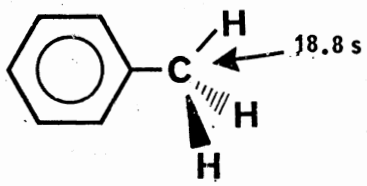
$$\frac{1}{T_{1(CSA)}} \propto H_o^2$$

Scalar Coupling (SC)

Quadupolar nuclei with $I \geq 1$ ($I = 3/2$) relax very fast. If such a nucleus (for example, ^{79}Br) is adjacent to another NMR active nucleus (such as ^{13}C), then the quadrupolar nucleus (^{79}Br) can accelerate the relaxation of the adjacent nucleus.[10] If the Larmor precessional frequencies are very similar for two nuclei (as in ^{13}C-^{79}Br where the values are 10.705 MHz for ^{13}C and 10.667 MHz for ^{79}Br), then the contribution by (SC) to the overall relaxation will be large.

Spin Rotation (SR)

If a molecule or molecular segment rotates, the magnetic moments due to bonding electrons will also rotate and generate fluctuating magnetic fields which can effect relaxation of adjacent nuclei.[10] The

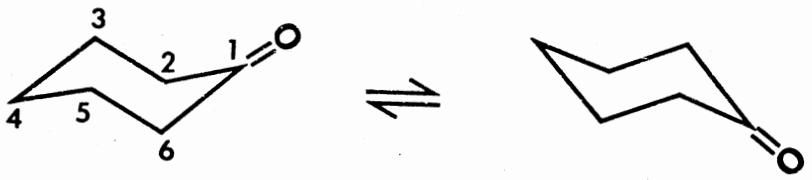


methyl group of toluene relaxes by an (SR) process, for example.[17] As the temperature increases, the distribution of types of rotations increases, and the distribution of fluctuating magnetic fields increases. More fields exist which have a frequency close to the Larmor frequency of the adjacent nuclei; therefore, very efficient relaxation can occur.[4] The (SR) mechanism has been found to be most efficient at room temperature and above.[14]

$$\frac{1}{T_{1(SR)}} \propto \text{Temp.}$$

Dipole-Dipole (DD)

While tumbling in solution, the magnetic moment μ of a nucieus reorients with respect to H_o (or B_o) and leads to the production of local magnetic fields. These generated magnetic fields influence the magnetic moments of adjacent (directly bonded or close) nuclei and results in dipole-dipole (DD) relaxation. In cyclohexanone, (a dynamic system), C(2)-C(6) relax by the (DD) mechanism. A temperature increase



results in decreased coupling between nuclei, in general, and so relaxation by the (DD) mechanism is less efficient[10] (despite an increased tumbling rate). This temperature dependency phenomenon for the (DD) mechanism (T_1 increasing with increasing temperature) is in contrast to that of (SR) mechanism and so (DD) operates most efficiently at low temperatures.[3]

$$T_{1(DD)} \propto \text{Temp.}$$

Proton decoupling (^1H) is usually performed in ^{13}C and ^{31}P NMR experiments in order to collapse complex multiplets (caused by long and short range spin-spin coupling of ^1H to ^{13}C or ^{31}P) to singlets (or a simple pattern). Irradiation of protons in decoupling experiments requires an energy input. Since protons bonded to carbon usually relax by (DD) mechanisms predominately, energy is transferred to attached nuclei (usually carbon) thereby causing an increase in the number of such carbon nuclei in an excited state. This increased population of carbon atoms in the excited state yields a signal enhancement termed the Nuclear Overhauser Enhancement (NOE) effect.[10,14]

NOE's can be determined by comparison of peak areas in a fully decoupled spectra (full NOE) to those areas in a gated[22,23] decoupled spectra (no NOE). Evaluation of NOE effects can lead to structural assignments for NMR signals and an estimation of the amount of (DD)

mechanism operating.[14] Separation of the contribution of the (DD) relaxation term from the overall relaxation process ia accomplished by use of equations (1), (2) and (3).[10,14]

$$\text{NOE factor } (\eta) = \frac{\text{area of fully decoupled peak}}{\text{area of gated decoupled peak}} - 1 \qquad (1)$$

$$\%(\underline{DD}) = \eta \times \frac{100}{1.235} \qquad (2)$$

$$T_{1(\underline{DD})} = T_{1(\text{experimental})} \times \frac{1.235}{\eta} \qquad (3)$$

where 1.235 is the calculated theoretical maximum NOE for ^{31}P-^{1}H (DD) relaxation.[14]

Mathematical treatment[10,14] of the problem of (DD) relaxation (developed primarily for relaxation of ^{13}C nuclei) shows that for S

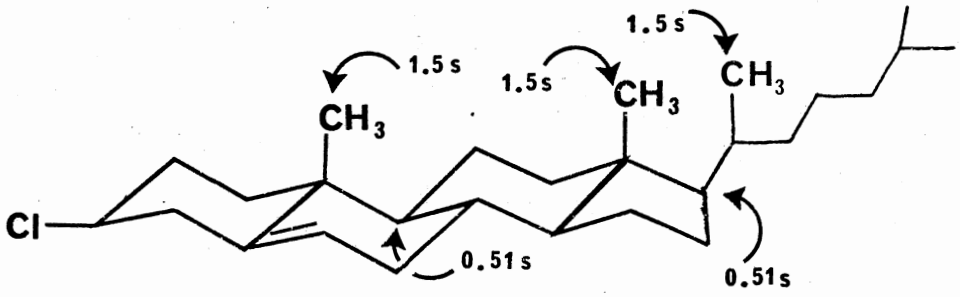
$$\frac{1}{T_{1(\underline{DD})}} = \sum_{S} \frac{\hbar^2 \nu_Z^2 \nu_S^2}{r_{SZ}^6} \tau_{eff} \qquad (4)$$

nuclei interacting with Z nucleus (where $\hbar$ is Plank's constant ($6.626 \cdot 10^{-34}$ Js) divided by 2π, γ is the gyromagnetic constant for S and Z nuclei, respectively, and r is the internuclear distance) can be described by Eq. (4). An effective isotropic correlation time (τ_{eff}) is employed and can be utilized as a qualitative estimate of correlated motion. The τ_{eff} term is assumed to be constant for all (DD) interactions in an isotropically tumbling molecule.[10] Very low frequency vibrations and some internal rotations can invalidate this assumption.[10]

For anisotropically tumbling molecules (such as an asymmetric rotating top like C_2H_5OH), Eq. (4) becomes more sophisticated [Eq. (5)]

$$\frac{1}{T_{1(\underline{DD})}} = n_S h^2 \nu_Z^2 \nu_S^2 \left[C_+\tau_+ + C_-\tau_- + C_1\tau_1 + C_2\tau_2 + C_3\tau_3\right] \qquad (5)$$

where the various τ values are correlation times for certain motional reorientations about the principal axes and the C values are geometrical constants.[24] As more complex motions are considered, more τ values are required to describe the reorientation of the molecule with respect to those motions that are effective in causing relaxation [all angular displacements are not equally effective in relaxing nuclear spins in those systems governed by τ (or τ_{eff})].[10] Information contained in $T_{1(\underline{DD})}$ values pertains to <u>only</u> those motions that are effective in relaxation by the (<u>DD</u>) mechanism and <u>not</u> the overall motion of a molecule. This can be demonstrated in the case of cholesteryl chloride[1] as shown. Relaxation times of the methyl groups are 3



times <u>longer</u> than the T_1 values for the methine carbons in the ring systems. Thus, there exists two τ values, one for the methyl carbons and one for the methine carbons (which is 9 times as effective as

τ_{CH_3}).[10]

The temperature dependency of τ often appears in an Arrhenius type relationship Eq. (6) in carbon systems

$$\tau = \tau^{o} \exp^{(\frac{\Delta E}{RT})} \qquad (6)$$

where

ΔE = energy of activation for molecular reorientation [for motions effective in (DD) relaxations].

R = ideal gas law constant.

T = temperature in Kelvin.

By plotting $T_{1(DD)}$ versus the reciprocal temperature, ΔE for molecular rotation may be calculated.[14] The viscosity of the solution affects τ_c, and it has been found that $\Delta E \cong$ viscosity (for nonassociated liquids).[14] Typical τ_c values for molecules such as CH_3I, are close to 10^{-13} seconds with $\Delta E \simeq$ 1-2 kcal/mole.[14]

CHAPTER II

DISCUSSION OF RESULTS

Because of the known potential of relaxation data, along with NOE values, to be of diagnostic value in the interpretation of molecular motion and the motion of individual groups in ^{13}C NMR spectroscopy, the lack of such data for the ^{31}P nucleus leaves a large gap in ^{31}P NMR analysis. Therefore, we elected to determine the NOE values for the ^{31}P nucleus in a number of phosphorus-containing systems shown below. Since T_1 values had been determined previously for these molecules in our laboratory by Dr. Ramarajan,[15] it was reasoned that the acquisition of the NOE values would permit an evaluation of the relaxation mechanisms operating in these systems. Three different temperatures were selected and two different concentrations of the compounds would also be examined. Selection of these materials was also done with the intention to have systems which would allow the role of protons on adjacent carbons to be assessed in terms of influence on the relaxation process. In addition, a cyclic molecule was also investigated and compared with an open-chain counterpart.

NOE values (as a function of temperature and concentration) are reported in Tables I and II for compounds 1-5. It can be seen that (DD) interactions in 1-5 are a minor part of the overall relaxation mechanism. In systems 1-4 where an increasing number of protons are found adjacent to the ^{31}P nucleus, no tendency for an increase in (DD)

$(C_6H_5)_3X$

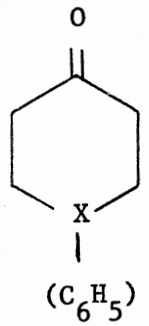
1

$(C_6H_5)_2XCH_2X(C_6H_5)_2$

2

$(C_6H_5)_2XCH_2CH_2X(C_6H_5)_2$

3



$(C_6H_5)_3\overset{+}{P}CH_3\ I^-$

5

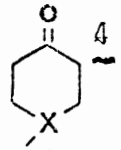
a. X = P:; b. X = P=O; c. X = P=S

contribution can be observed. In comparing phosphines 1a, 2a, and 4a to the corresponding P-sulfides 1b, 2b, and 4b, it is evident that more (DD) relaxation is present in the P-sulfides. Phosphine 3a, P-oxide 3b and P-sulfide 3c appear to have roughly the same amount of (DD) interaction operating. This is in contrast to observations of the relaxation of ^{31}P in systems 1, 2, and 4.

It must be remembered that the motion characteristics of a molecule affect the relaxation of the molecule. The "shape" of a molecule also determines to some extent what motions predominate. Courtauld models of systems 1-4 imply that the phosphine 1a, P-oxide 1b and P-sulfide 1c have a "propeller" shape. Phosphine 4a has a "flat rectangular" shape (with ring reversal possible to allow some flexibility) while phosphine oxide 4b and phosphine sulfide 4c are "rigid flat rectangles" (with some rotation of phenyl ring possible).

TABLE I

NOE VALUES EXPRESSED AS η AND % DD AS A FUNCTION OF T AND CONCENTRATION FOR SYSTEMS 1-4.

		X = phosphine						X = P-oxide						X = P-sulfide					
	conc.†	15°		25°		35°		15°		25°		35°		15°		25°		35°	
		η	%DD	η	%DD	η	%DD	η	%DD	η	%DD	η	%DD	η	%DD	η	%DD	η	%DD
1 $(C_6H_5)_3X$	a	0.09	7.3	0.10	8.1	0.14	11.3	0.09	7.3	0.07	5.7	0.11	8.9	0.23	18.6	0.20	16.2	0.18	14.6
	b	0.11	8.9	0.10	8.1	0.12	9.7	0.09	7.3	0.13	10.5	0.09	7.3	0.25	20.2	0.27	21.9	0.22	17.8
2 $[(C_6H_5)_2X]_2CH_2$	a	0.08	6.5	0.13	10.5	0.09	7.3	0.09	7.3	0.07	5.7	0.04	3.2	0.19	15.4	0.25	20.2	0.27	21.9
	b	0.08	6.5	0.06	4.9	0.06	4.9	0.10	8.1	0.06	4.9	0.05	4.2	0.26	21.0	0.28	22.7	0.22	17.8
3 $[(C_6H_5)_2XCH_2]_2$	a	0.10	8.1	0.10	8.1	0.09	7.3	0.07	5.7	0.04	3.2	0.07	5.7	0.09	7.3	0.09	7.3	0.07	5.7
	b	0.10	8.1	0.12	9.7	0.19	15.4	0.08	6.5	0.05	4.0	0.09	7.3	0.06	4.9	0.05	4.0	0.04	3.6
 4	a	0.15	12.1	0.19	15.4	0.26	21.1	0.06	4.9	0.05	4.0	0.04	3.2	0.23	18.6	0.18	14.6	0.15	12.2
	b	0.17	13.8	0.20	16.2	0.24	19.4	0.04	3.2	0.09	7.3	0.07	5.7	0.27	21.9	0.25	20.2	0.24	19.2

† a=0.05 M, b=0.03 M for phosphines; a=0.2 M, b=0.1 M for oxide and sulfides.

TABLE II

NOE VALUES EXPRESSED AS η AND % DD AS A FUNCTION OF T AND CONCENTRATION FOR 5.

5 $(C_6H_5)_3\overset{+}{P}CH_3$ I^-		15°		25°		35°	
	conc	η	%DD	η	%DD	η	%DD
	0.2	0.14	11.3	0.14	11.3	0.17	13.8

The phosphine 2a, P-oxide 2b and P-sulfide 2c appear to be "rigid cubes" (with the phosphine 2a somewhat less rigid than the P-oxide 2b or P-sulfide 2c). In comparison, 3a, 3b and 3c probably have less restricted rotation about the methylene groups.

Inspection of the T_1 values[15] in Tables III and IV indicate that in the P-oxides and P-sulfides 1-4 tumbling slows and (DD) interactions are more efficient as the molecules increase in size in each family. The NOE data support this (Tables I and II) since there is a higher percentage of (DD) contribution in the heavier sulfides than in the oxides (the sulfides would be expected to tumble slower as they are bulkier). The P-sulfide 2c (a very bulky and rigid structure) shows the greatest percentage of (DD) relaxation. In systems 3a, 3b and 3c relaxation of the ^{31}P nucleus appears to have little contribution from the (DD) mechanism. This may be due to the fact that rapid rotation about the P-C-C-P axis may take place and will reduce the efficiency of that motion in the (DD) relaxation process.[16] Phosphine 4a is more rigid than the other phosphines and contains more C-H bonds in close proximity to the ^{31}P nucleus. However, some of these (DD) interactions take place at longer ranges than others. The NOE values (Tables I and II) are greater in phosphine 4a than in the phosphines 1a, 2a and 3a. In phosphines 2a and 3a (which are larger than phosphines 1a and 4a), less motion can occur (due to the larger size).

The T_1 values as a fuction of temperature for phosphines 2a andd 3a indicate relaxation predominately by (CSA) [the (DD) contribution is low as estimated from the NOE values]. Phosphine 3a (which is bulkier than phosphine 1a) is less rigid than phosphine 2a, and the ^{31}P nucleus should relax faster in this molecule. This was found to be true for

TABLE III

RELAXATION DATA FOR SYSTEMS 1-5

Cpd.	Conc. (mole/liter)	T_1 (sec)		
		15°C	25°C	35°C
1a	0.05	23.2 ±.4	20.2 ±.3	17.3 ±.2
2a	0.05	20.6 ±.7	21.3 ±.3	22.7 ±.2
3a	0.05	16.5 ±.4	19.1 ±.1	21.1 ±.2
4a	0.05	16.0 ±.2	16.0 ±.2	14.9 ±.1
1b	0.2	14.4 ±.2	15.6 ±.6	18.7 ±1.2
2b	0.2	6.4 ±.07	7.07 ±.23	8.37 ±.14
3b	0.2	3.78 ±.02		6.28 ±.47
4b	0.2	8.79 ±.04	9.85 ±.07	11.3 ±.3
1c	0.2	27.5 ±.3	29.7 ±.2	32.5 ±.1
2c	0.2	8.60 ±.1	9.90 ±.2	11.9 ±.1
3c	0.2	6.61 ±.07	7.98 ±.16	9.14 ±.1
4c	0.2	13.2 ±.0	14.7 ±.3	16.0 ±.1
5	0.2	9.78 ±.05	10.8 ±.2	12.6 ±.2

TABLE IV

RELATION RELAXATION DATA FOR SYSTEMS 1-4

Cpd.	Conc. (mole/liter)	T_1 (sec)		
		15°C	25°C	35°C
1a	0.03	27.8 ±.7	23.1 ±.3	21.1 ±.5
2a	0.03	20.2 ±.7	23.3 ±.2	25.2 ±.7
3a	0.03	17.5 ±.5	18.8 ±.3	20.1 ±.4
4a	0.03	15.4 ±.2	14.4 ±.1	14.0 ±.2
1b	0.1	18.9 ±.2	19.9 ±.6	24.3 ±1.2
2b	0.1	6.45 ±.1	7.45 ±.14	9.94 ±.45
3b	0.1	5.42 ±.05	6.25 ±.11	7.03 ±.25
4b	0.1	10.4 ±.3	11.1 ±.3	12.1 ±.3
1c	0.1	27.4 ±.2	29.7 ±.3	32.9 ±.2
2c	0.1	9.48 ±.06	10.7 ±.1	12.2 ±.2
3c	0.1	7.15 ±.04	8.30 ±.08	9.75 ±.12
4c	0.1	13.3 ±.1	15.7 ±.5	16.6 ±.3

phosphine 3a. In the phosphines, the size of the lone pair is probably smaller than the =O or =S group (in 3b and 3c, respectively) and thus greater motion should occur in phosphine 3a. Therefore the correlation times should be smaller in value in all phosphine systems 1a-4a, and the T_1 values should be then closer in magnitude as compared to the corresponding phosphine-oxides and sulfides, as was observed.

The (SR) mechanism is suggested to be dominant in phosphines 1a[10] and 4a in view of the observed temperature dependency of the T_1 values. However, in phosphine 4a the effect is small, and so the (SR) mechanism is probably only slightly more dominate than in 1a (phosphine).

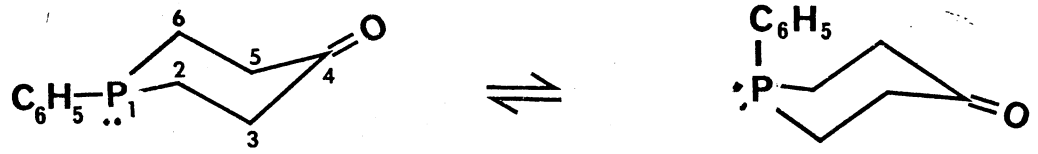
It has been noted that if (SR) and (CSA) mechanisms are both operating, T_1 values may pass through a maximum with respect to temperature.[10] Wilke recently published T_1 and NOE values for 1a, 1b, and 1c and observed a temperature maxima (from -70 to 40° C) for oxide 1b and sulfide 1c at 30°C.[23] This would imply that the (CSA) mechanism is competing with the (SR) mechanism at room temperature and that the (CSA) mechanism dominates at lower temperatures. Dale and Hobbs found that the ^{31}P nucleus relaxes by the (CSA) mechanism when a P=O bond is present [as in $O{=}P(OCH_3)_3$].[6] Indeed, it would be expected that the (CSA) mechanism would be present in systems 1-4 as all compounds investigated contain unsymmetrical charge distributions about the phosphorus nucleus.

It should be noted at this point that the (CSA) mechanism possesses a temperature dependency which is the same as that of the (DD) mechanism[10] where σ^2 is the chemical shielding tensor. Investigations of carbon systems have ignored this fact since evaluations of T_1 values at different magnetic field strengths provide conclusive

$$T_{1(\underline{CSA})} = \frac{\gamma_I^2 H_o^2}{5} \sigma^2 \tau$$

evidence on the contribution of (CSA) to the relaxation process. It seems clear that the temperature dependency of the T_1 values is real for the majority of systems examined. If the (CSA) pathway was the predominate one for relaxation, T_1 values would increase with increasing temperature as noted when the (DD) mechanism predominates. However, the NOE measurements (Tables I and II) indicate that (DD) is not a major contributor for any system (based on the low NOE values).

Dynamic systems, such as phosphine 4a, can undergo conformational



4a

exchange processes (known as ring reversal)(it should be noted that the P=O and P=S bonds are axial in 4a oxide and sulfide).[21] Ring reversal occurs in six-membered rings such as cyclohexanone.[9] Spin-lattice times have been reported for ^{13}C in cyclohexanone[9] and it appears that the effect of the process on the relaxation values is unknown. Apparently, the ring reversal process [on the NMR time scale] may be comparable to (or faster than) the correlation time (angular displacement time for one radian of rotation of the molecule) and of sufficient magnitude in some cases to contribute to the observed T_1.[9] However, in cyclohexanone, the T_1 value for C(4), (7.6 s) is similar to the values measured for C(2) and C(3) (ca. 8.0 s). If

the exchange process was contributing significantly to the relaxation of C(2), C(3) and C(4), C(4) might be expected to have a considerably different T_1 value since it is on the end of the molecule which undergoes the most rapid motion in a ring reversal process. Since the values are of similar size for all three carbons, ring reversal is assumed to possess a time scale slower than that of molecular reorientation although no data is available to explain this hypothesis.

Earlier discussion indicated that the temperature dependency of the (DD) mechanism followed an Arrhenius relationship. A plot of log $T_{1(DD)}$ versus 1/Temperature should therefore be linear and yield an activation energy (from the slope) for reorientation. Figures 1-6 display the temperature dependence of the (DD) spin-lattice relaxation time. Systems 1c, 2a, 3a, 3c, 4b, and 4c appear to possess a linear dependence of T_1 with temperature and a negative slope (some slopes are positive, indicating negative ΔE's for the (DD) process; however, the overall ΔE is still positive. Since most of the systems examined do not follow an Arrhenius relationship, it appears that a different temperature dependency may be operative. SR relaxation is known to possess a linear temperature term in addition to the Arrhenius terms.[10] It is conceivable that in the ^{31}P systems under observation, the (DD) temperature relationship may include different temperature terms. This would require additional theorical considerations.

Carbons not directly bonded to protons (but in close proximity to protons on adjacent carbons) have not been examined for (DD) temperature dependency to the best of our knowledge. Due to the rapid decline of the (DD) interaction with distance, investigations have

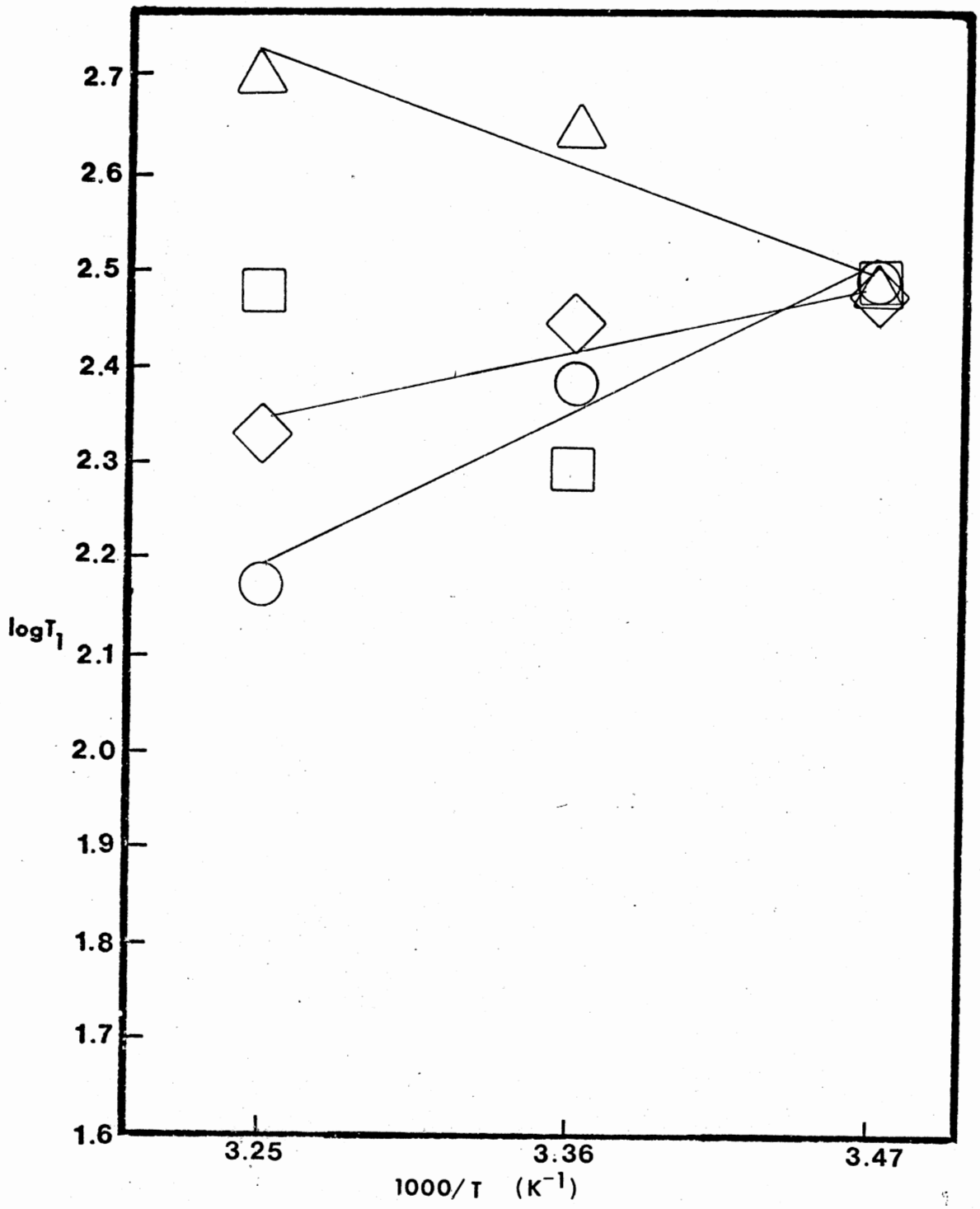


Figure 1. Temperature Dependence of Spin-lattice Relaxation Times in 1a and 2a.

○ represents 0.05 M 1a;
□ represents 0.05 M 2a;
◇ represents 0.03 M 1a;
△ represents 0.03 M 2a.

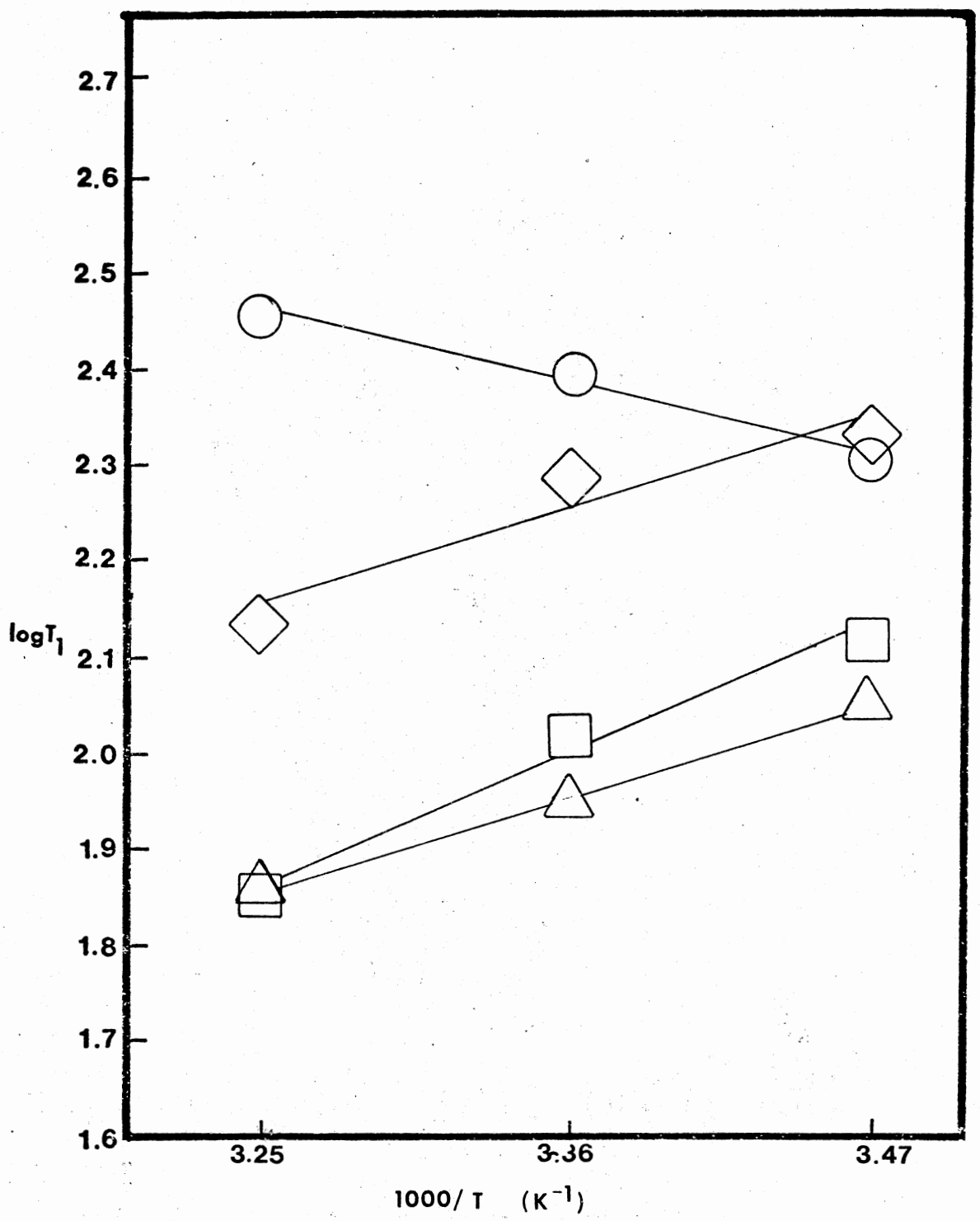


Figure 2. Temperature Dependence of Spin-lattice Relaxation Times in 3a and 4a.

○ represents 0.05 M 3a;
□ represents 0.05 M 4a;
◇ represents 0.03 M 3a;
△ represents 0.03 M 4a.

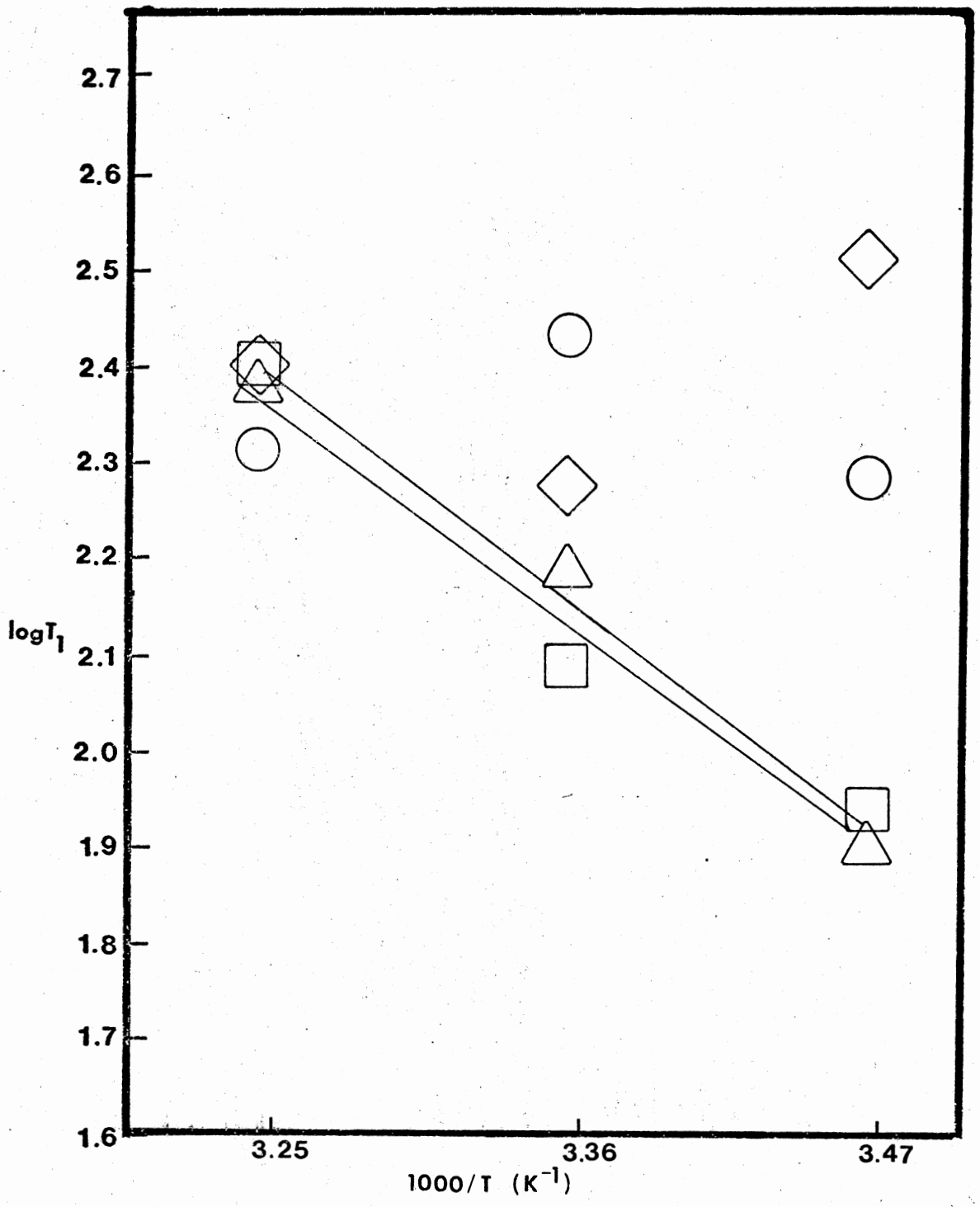


Figure 3. Temperature Dependence of Spin-lattice Relaxation Times in 1b and 2b.

○ represents 0.2 M 1b;
□ represents 0.2 M 2b;
◇ represents 0.1 M 1b;
△ represents 0.1 M 2b.

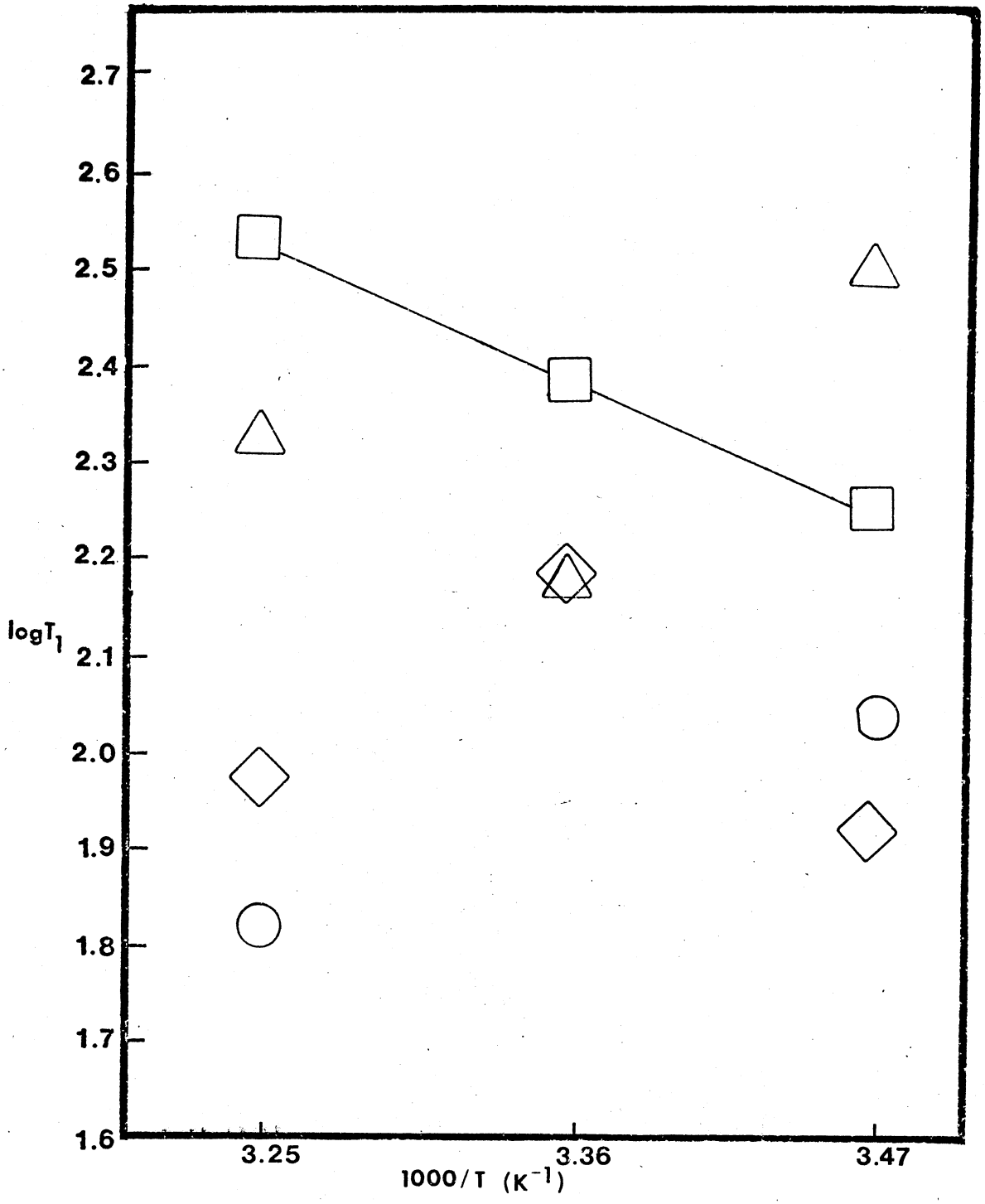


Figure 4. Temperature Dependence of Spin-lattice Relaxation Times in 3b and 4b.

○ represents 0.2 M 3b;
□ represents 0.2 M 4b;
◇ represents 0.1 M 3b;
△ represents 0.1 M 4b.

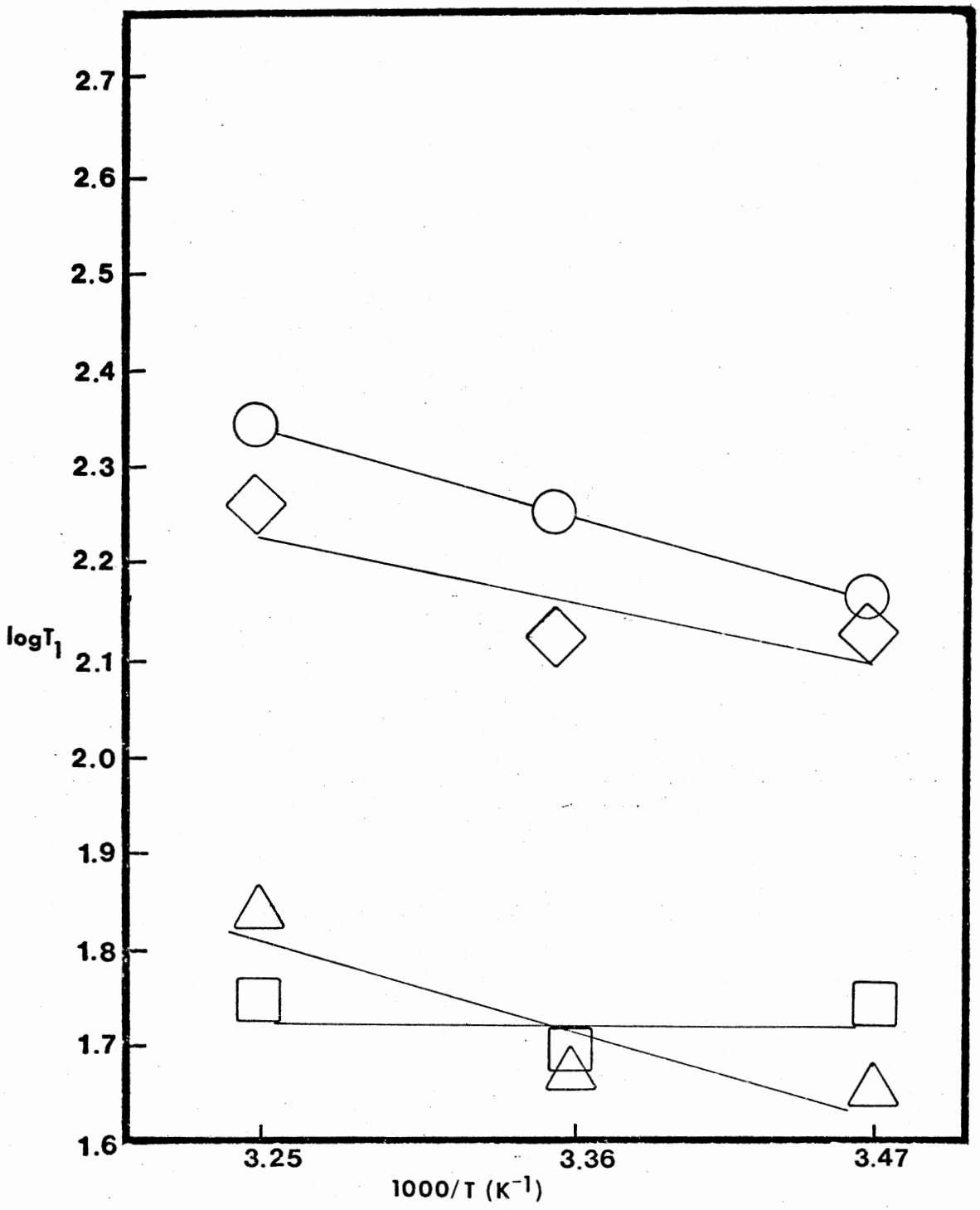


Figure 5. Temperature Dependence of Spin-lattice Relaxation Times in 1c and 2c.

○ represents 0.2 M 1c;
□ represents 0.2 M 2c;
◇ represents 0.1 M 1c;
△ represents 0.1 M 2c.

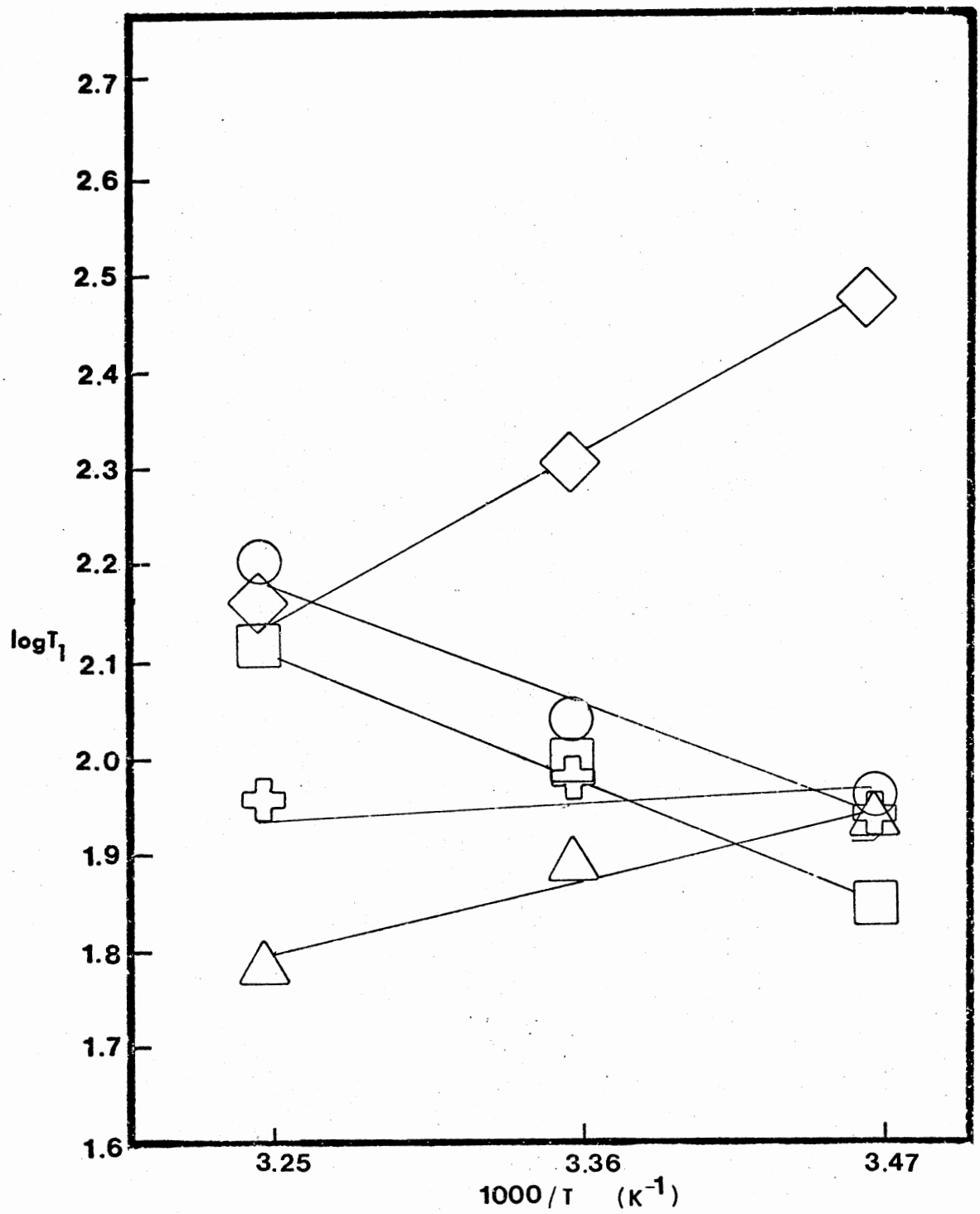


Figure 6. Temperature Dependence of Spin-lattice Relaxation Times in 3c, 4c, and 5.

○ represents 0.2 M 3c;
□ represents 0.2 M 4c;
◇ represents 0.1 M 3c;
△ represents 0.1 M 4c;
✣ represents 0.2 M 5.

assumed that there does not exist an appreciable (DD) relaxation process for carbons denuded of bonded protons.[10] Consequently, measurements of (DD) contributions (and to measure the temperature process for carbons denuded of bonded protons or from C-H geminal carbons.[14] Consequently, measurements of (DD) contributions (and to measure the temperature dependency) of these non-bonded (DD) interactions (from C-H bonds at large distances) have not been made. In our phosphorus systems, activation energies (ΔE_{DD}) of reorientation of the dipole-dipole vector varied in the systems which appeared to have a significant (DD) relaxation mechanism operating for ^{31}P. For example, P-sulfide 1c (0.1 M) had ΔE_{DD} = 0.47 kcal/mole, phosphine sulfide 2c (0.1 M) had ΔE_{DD} = 0.07 kcal/mole, phosphine 4a (0.03 M) had ΔE_{DD} = 0.53 kcal/mole and phosphine sulfide 4c (0.1 M) had ΔE_{DD} = 1.4 kcal/mole.

The relatively small and symmetrical molecule triphenylphosphine sulfide (1c) had a low activation energy, implying that the molecule tumbled easily in solution. Indeed the less symmetrical and relatively large molecule, such as 2c $(C_2H_5)_2P(S)CH_2P(S)(C_2H_5)_2$, had a lower activation energy for this process. Intuitively, the data for the latter two compounds seems to be in reverse order. However, the rotational reorientation of these molecules in solution is undoubtedly different due to their different sizes and shapes. Each molecule has dissimilar motional characteristics. Since all angular displacements are not equally effective in causing relaxation via one particular mechanism,[14] the activation energies reflect the reorientation of the molecule with respect to the motions that cause relaxation by a particular process.[14] This is demonstrated for 4a (cyclic phosphine) and 4c

(cyclic P-sulfide). The activation energy for 4a is 2.3 kcal/mole while the value is 1.4 kcal/mole for 4c. These data would seem to be in reverse order again since 4a is a small molecule and less rigid than 4c. Examination of the T_1 values for 4a with respect to temperature revealed that the (SR) mechanism was probably operative (T_1 decreased as temperature increased) while for 4c the (CSA) mechanism likely dominated (T_1 increased as temperature increased). In view of the observed NOE values for 4a and 4c, we assume that the (DD) mechanism also participated to relax ^{31}P in these molecules. Consequently, different motions occur in each system and therefore the ΔE values [which are a measure of the rotational reorientation of a molecule with respect to those motions causing relaxation by a (DD) process] cannot be legitimately compared.[14] Activation energies reported herein are for the dipole-dipole rotational reorientation process only.

It is clear from these studies that ^{31}P nuclei are subject to similar parameters as ^{13}C nuclei in terms of effects[5] on the relaxation processes. NOE values appear to demonstrate that the (SR) mechanism and the (CSA) mechanisms are operative in the systems examined along with some (DD) contribution. The (DD) contribution seems to be much less in the phosphines, phosphine oxides and phosphine sulfides compared to any carbon systems which might be considered as models. This is not unreasonable since none of the phosphorus systems have a P-H bond which could be considered the counterpart of C-H bonds in the carbon-containing analogues.

The question remains as to whether the technique of substituting for the gated decoupled experiment the use of an off-resonance and

low power (5 W) to obtain a fully coupled spectrum is reliable. It is known that the newer and larger NMR units with computer programs permit the altermative concurrent acquisition of a fully decoupled and gated decoupled spectral data in two separate memory banks for subsequent manipulation (which is a more reliable method to obtain T_1 values). It was observed that the NOE data (room temperature) for triphenylphosphine (1a), triphenylphosphine oxide (1b) and triphenylphosphine sulfide (1c) was similar in magnitude to that very recently published.[23] These other workers apparently performed the decoupled and gated decoupled experiments in sequence which, of course, is subject to abberrations from the spectrometer. In our work, the samples were degassed and several separate samples (on separate days) were evaluated at three different temperatures which we feel enhances the value of the conclusions.

Suggestions for Future Work

Separation of several relaxation mechanisms is often difficult. Hubbard[14] derived the relationship

$$\tau \, \tau_{SR} = I/6KT \qquad (7)$$

where

I = moment of inertia

$K = 1.38 \cdot 10^{-16}$ erg/^{o}K molecule

T = temperature in Kelvin

τ = rotational correlation time

The correlation times τ and τ_{SR} can be related to $T_{1(\underline{SR})}$, $T_{1(\underline{DD})}$ and $T_{1(\underline{CSA})}$[14] as follows

$$1/T_{1(\underline{SR})} = \left(\frac{2IkT}{3\hbar^2}\right)C^2 \tau_{SR} \tag{8}$$

$$1/T_{1(\underline{DD})} = \left(\frac{3/2\ \gamma^4\hbar^2}{r^6}\right)\tau \tag{9}$$

$$1/T_{1(\underline{CSA})} = \frac{\gamma^2 H_o^2}{5}\delta^2\tau \tag{10}$$

where

δ = chemical shielding tensor

I = moment of inertia

$k = 1.38 \cdot 10^{-16}$ erg/^oK molecule

T = temperature

$\hbar = 1.054 \cdot 10^{-27}$ erg s

γ = gyromagnetic constant

r = internuclear distance

H_o = intensity of the dc magnetic field

C = spin-rotation interaction tensor.

Substitution of eq. (8) and (9) into eq. (7) gives

$$T_{1(\underline{DD})}\ T_{1(\underline{SR})} = \frac{6r^6}{I^2\gamma^4\hbar} \tag{11}$$

$$T_{1(\underline{SR})}\ T_{1(\underline{CSA})} = \frac{45\ \hbar}{\gamma^2 H_o^2 I C^2 \delta^2} \tag{12}$$

Since

$$\frac{1}{T_1} = \frac{1}{T_{1(\underline{DD})}} + \frac{1}{T_{1(\underline{SR})}} + \frac{1}{T_{1(\underline{CSA})}}$$

is true, and if the NOE factors are known, then separating the (DD) contribution from the overall T_1 values leaves only (SR) and (CSA) contribution. Separation of (SR) and (CSA) mechanisms conceivably could be performed by plotting log T_1 verses 1/T to obtain the maximum T_1 value.[14] At the maximum,

$$T_{1(\underline{SR})} = T_{1(\underline{CSA})}$$

for Brownian isotropic rotational diffusion.[10] No maximum was observed in the temperature ranges examined, and so further measurements at higher and lower temperatures would be required for systems 1-5.

Other systems should be examined to note trends in relaxation of the ^{31}P nucleus as a function of molecular shape. Families (consisting of the phosphine, phosphine-oxide and phosphine-sulfide) of $(C_6H_5)_2PCH_3$, $(C_6H_5)_2PCH_2CH_3$ and $(C_6H_5)_2PH$ should possess rotational properties similar to the $(C_6H_5)_3P$ system and yield interesting relaxation data.

Error Analysis

Peak reproduciblity is often found to be the primary measurement of errors in carbon and phosphorus NOE experiments.[11,14,23] Typical NOE values have been found to be accurate to $\pm$ 0.1 in the triphenylphosphine oxide and triphenylphosphine sulfide systems.[23] The variances for phosphorus containing systems 1-5 at selected temper-

atures are displayed in Table V along with the % difference of the (DD) contribution from the average. The calculations are performed utilizing Eq. (13) and (14),

$$\text{variance} = \frac{\text{highest NOE value - lowest NOE value}}{2}$$

$$\%\ \text{difference of (DD) contribution} = \frac{\text{Average \% (DD) contribution - V}}{\text{Average \% (DD) contribution}}$$

TABLE V

ERRORS ASSOCIATED WITH NOE MEASUREMENTS

Compound	conc. (M)	temp. (^{o} C)	NOE variance	% Deviation of (DD)
1a	0.05	15	± 0.033	37
1a	0.05	25	± 0.038	38
1a	0.05	35	± 0.07	49
2a	0.05	25	± 0.041	31
3a	0.05	25	± 0.011	11
4a	0.05	25	± 0.062	32
1b	0.1	25	± 0.025	36
2b	0.1	25	± 0.031	45
3b	0.1	25	± 0.010	26
4b	0.1	25	± 0.004	7.8
1c	0.1	25	± 0.07	35
2c	0.1	25	± 0.026	10
3c	0.1	25	± 0.009	11
4c	0.1	25	± 0.069	39

CHAPTER III

EXPERIMENTAL

NOE values (η) were obtained by performing coupling and decoupling experiments alternatively, with a delay times of $\geq 5T_1$. Decoupler power was set at 5 watts. Samples were weighed and dissolved in $DCCl_3$ (except for the phosphines in which acetone-$\underline{d}_6$ was used). The samples were frozen (liq. N_2) and evacuated under a pressure of $< 10^{-4}$torr. After 5-10 min. under vacuum, the sample was disconnected from the vacuum system and allowed to liquify. The cycle was repeated $\sim$ 4-5 times and the sample was sealed at $< 10^{-4}$torr. A typical NOE experiment can be described as follows: A degassed sample was placed in the sample probe, and the instrument was locked onto the deuterium signal in the solvent. To compensate for local fluctuations in the magnetic field, alternate pulses were applied, one with decoupler frequency set at 45,000 Hz (decoupler on) and one with decoupler frequency set at 65,000 Hz (decoupler off). At the power setting (5 W), this results in a fully coupled spectra. These alternate pulses were stored in two separate files, and yielded two spectra, one coupled and one fully decoupled. Identical acquisitions of data in each file (A and B) coupled with the technique of alternatively performing the two experiments were done so that any variations in experimental conditions (magnetic fluctuation, etc.) affected both measurements presumably in

an equivalent manner. Peak areas for the ^{31}P NMR signals were evaluated by cutting and weighing the actual area and by use of a planimeter.

Most workers[3,18] have utilized experimental procedures in which a fully decoupled experiment was performed and then a gated decoupled experiment was performed on the same sample. The areas of the peaks from the two spectra were compared in order to obtain the NOE factor.[13] However, such a technique almost surely results in greater differences in instrument variations between the two experiments leading to possible larger errors in the NOE value.

A Varian temperature regulator was used for temperature control during the T_1 measurements. A sealed capillary filled with methanol and a trace of HCl placed in 5 mm NMR tube containing 0.5 ml acetone-$\underline{d}_6$ was used as a check to measure the temperature according to the method of van Geet.[16] The T_1 values were previously recorded[15] and included the use of a three-parameter fit equation.[7]

Activation energies for those systems having a significant (DD) contribution to the ^{31}P relaxation process were calculated.[14] For phosphine-sulfide 1c (10.1 M), ΔE_{DD} = 0.47 kcal/mole; phosphine-sulfide 4c (0.1 M), $\Delta E_{(DD)}$ = 1.4 kcal/mole; phosphine 2c (0.1 M), $\Delta E_{(DD)}$ = 0.07 kcal/mole; and phosphine 4a (0.003 M), $\Delta E_{(DD)}$ = 0.53 kcal/mole. A plot of log $T_{1(DD)}$ versus temperature gave a straight line with negative slope for these systems. The slope multiplied by -1.98 cal/mole yielded the activation energy for reorientation of the dipole-dipole vector.

BIBLIOGRAPHY

1. Allerhand, A., Doddrell, D. and Komoroski, R., J. Chem. Phys., 55, 189 (1971).

2. Becker, E. D., "High Resolution NMR," Academic, New York (1969).

3. Bolton, P. H. and James, T. L., J. Phys. Chem., 83, 3359 (1979).

4. Bovey, F. A., "Nuclear Magnetic Resonance Spectroscopy," Academic, New York (1969).

5. Crutchfield, M. M., Dungan, C. H., Letcher, J. H., Mark, V., Van Wazer, J. R., "^{31}P Nuclear Magnetic Resonance, "Topics in Phosphorus Chemistry, v. 5, Wiley and Sons, New York (1968).

6. Dale, S. W. and Hobbs, M. E., J. Phys. Chem., 75, 3537 (1971).

7. Hubbard, P. S., Phys. Rev., 131, 1155 (1963).

8. Koale, N. J., De Koning, A. J. and De Bie, M. T. A., J. Mag. Res., 25, 375 (1975).

9. Komorski, R. A. and Levy, G. C., J. Phys. Chem., 80, 2410 (1976).

10. Lyerla, J.R. and Grant, D. M., "Carbon-13 Nuclear Spin Relaxation," MTP International Review of Science, s.1, v.4, University Park Press, Baltimore (1972).

11. Martin, M. L., Delpuech, J-J., and Martin, G. J., "Practical NMR Spectroscopy," Heyden, Philadelphia, 1980.

12. McCain, D. C. and Markley, J. L., J. Amer. Chem. Soc., 102, 5559 (1980).

13. Nanda, R. K., Ribeiro, A., Jardetzky, T. S. and Jardetzky, O., J. Mag. Res., 39, 119 (1980).

14. Noggle, J. H. and Schirmer, "The Nuclear Overhauser Effect," Academic, New York (1971).

15. Ramarajan, K., Ph.D. Thesis, Oklahoma State University (1980).

16. Sass, M. and Ziessow, D., J. Mag. Res., 25, 263 (1977).

17. Schmidt, C. F. and Chan, S. I., J. Mag. Res., 5, 151 (1970).

18. Shindo, H., Biopolymers, 19, 509 (1980).

19. Tabony, J., Spectrachima Acta, 35A, 217 (1979).

20. Van Wazer, J. R. and Glonek, T., Analytical Chemistry in Phosphorus Compounds., Halmann, M., ed., v. 37, Wiley and Sons, New York (1972).

21. Venkataramu, S. D., Berlin, K. D., Ealick, S. E., Baker, J. R., Nichols, S., and van der Helm, D., Phosphorus & Sulfur, 7, 133 (1980).

22. Wilkie, C. A. J. Mag. Res., 33, 127 (1979).

23. Wilkie, C. A., J. Amer. Chem. Soc., 100, 2288 (1978).

24. Woessner, D. E., J. Chem. Phys., 37, 647, 1962.

VITA

Melvin Dale Herd

Candidate for the Degree of

Doctor of Philosophy

Thesis: PART I. SYNTHESIS AND NMR ANALYSIS OF SELECTED 2-AMINO-4,5-DISUBSTITUTED THIAZOLES

PART II. NUCLEAR OVERHAUSER ENHANCEMENT MEASUREMENTS FOR CERTAIN ORGANOPHOSPHORUS COMPOUNDS. EVALUATION OF RELAXATION MECHANISMS FOR ^{31}P

Major Field: Chemistry

Biographical:

Personal Data: Born in Chandler, Oklahoma, April 1, 1954, to Melvin C. and Doris Ann Herd.

Education: Graduated from Chandler High School, Chandler, Oklahoma, in May 1972; recieved Bachelor of Science degree in Chemistry from Central State University in 1977; completed requirements for the Doctor of Philosophy degree at Oklahoma State University in December, 1981.