PART I. SYNTHESES AND CARBON-13 SPIN-LATTICE RELAXATION MEASUREMENTS (T_1 VALUES) OF CERTAIN SELECTED ALKYL ω-(2-ANTHRYL)ALKANOATES

PART II. SYNTHESES AND A CONFORMATIONAL STUDY OF CERTAIN SELECTED 3-OXA-7-AZABICYCLO-[3.3.1]NONAN-9-ONES (OR 3-OXA-7-AZABISPIDINONES)

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I thank my parents, Mr. and Mrs. Palanisamy, for the love and devotion given so generously to me during these many years. Finally, I wish to dedicate the whole of this work to my wife, Leelavathi, and our son, Arunkumar, for the little things that mean so much to me.

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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. SYNTHESES AND CARBON-13 SPIN-LATTICE RELAXATION MEASUREMENTS (T_1 VALUES) OF CERTAIN SELECTED ALKYL ω-(2-ANTHRYL)ALKANOATES

CHAPTER I

HISTORICAL

Fluorescent Probes

Optical methods, other than crystallography, still occupy a central position in the study of macromolecular chemistry. Even where X-ray analysis is feasible, methods such as absorption spectroscopy, optical rotary dispersion (ORD), light scattering, nuclear magnetic resonance (NMR) spectroscopy and relaxation spectroscopy are useful in analyzing the subtle conformational changes which macromolecules undergo in solution. Fluorescence spectroscopy is among the most sensitive and one of the most versatile of the many techniques available for studying structure and dynamics of macromolecules.[86]

Before discussing fluorescent probes, a brief introduction to the basic concepts of fluorescence spectroscopy is in order. The important processes for fluorescence spectroscopy are for the most those involving the lowest excited state S_1, as shown in the diagram that follows (page 4). For a given chromophore the above processes are characterized experimentally by the fluorescence spectrum, quantum yield, lifetime and polarization of fluorescence. The fluorescence spectrum represents the intensity of fluoresence at different wavelengths. The fluorescence quantum yield is the fraction of excited molecules which emit light and is related to kinetic parameters by the equation (1)[86] where k_e repre-

$$\phi_f = k_e/(k_e + k_i) \quad (1)$$

sents the specific rate of emission of light from S_1, and k_i is the sum of the rates of all nonradiative processes (wavy line in the diagram) which depopulate S_1. The fluorescence lifetime τ is defined by equation (2)[86] where τ is the time required for the fluorescence intensity, F(t),

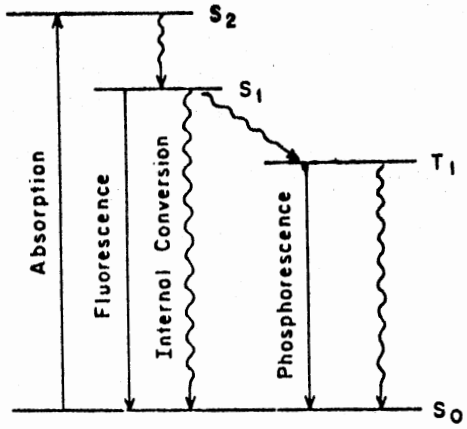
$$F(t) = F_o e^{-t/\tau} \quad (2)$$

to drop to e^{-1} of its initial value F_o. The τ is related to k_e, k_i and ϕ_f by the equations (3)[86] and (4)[86]:

$$1/\tau = k_e + k_i \quad (3)$$

$$\phi_f = k_e\tau \quad (4)$$

One can calculate k_e and k_i from τ and ϕ_f which are measurable. The fluorescence spectrum, ϕ_f and τ are dependent upon the molecular structure of the chromophore and are also sensitive to the environment. Moreover, the spatial and polarization properties of emitted light are controlled by the size, shape, and rigidity of the chromophore to a certain extent.[86]



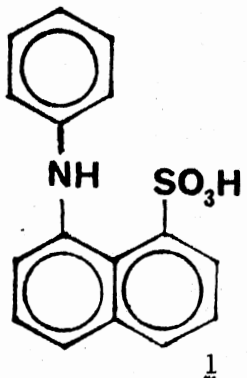
Weber[81] introduced the concept of fluorescent probes not only to reap the potential benefits of fluorescence spectroscopy but also to circumvent the inherent limitations of intrinsic fluorescence in the study of macromolecules. According to his theory, fluorescent compounds of known properties could be used as indicators of probes of macromolecular structure. Edelman and co-workers[28] defined fluorescent probes as small molecules which undergo changes in one or more of their fluorescent properties as a result of noncovalent interaction with a macromolecule. By analyzing the fluorescence of suitably chosen probes, one can derive certain information about macromolecular structure and dynamics in solution.

To serve as a fluorescent probe, an extrinsic chromophore needs to meet certain requirements such as:[75] (1) the chromophore should be bound to the macromolecule at a unique location; (2) fluorescent properties of the probe should be sensitive to the structure and dynamics of its environment <u>in vivo</u> that are amenable for definitive interpretation; (3) insertion of the probe should not appreciably disturb those features of probes which are being investigated.

Depending upon the fluorescence properties of the probe, some or all of the following information about the microenvironment around the probe can often be determined:[79] the polarity, rigidity, pH and pION of the microenvironment of the probe, and the orientation and proximity of the probe to molecules which can act as excited-state energy acceptors or donors.

The dynamic polarity of the local solvent environment can be understood by measuring spectral parameters like the quantum yield (ϕ_f), the excited state lifetime(τ), and the wavelength of maximum emission (λ_F).[79]

Membrane probes like 1-anilino-8-naphthalene sulfone, ANS (1),[74] showed large solvent dependent changes in the spectral parameters, λ_F, ϕ_f and τ.



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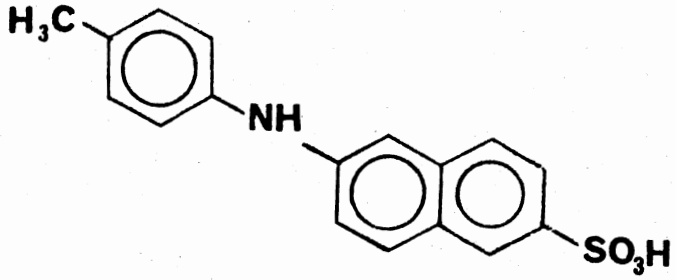

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The λ_F of 1 varied from 454 nm in nonpolar solvents like hexane to 515 nm in water.[74] The red shift of 2-p-toluidinyl-6-naphthalene sulfonate, TNS (2),[13] in viscous polar solvents was found to be time dependent. The time-dependent red shift of 2, which was adsorbed to egg phosphatidylcholine bilayer vesicles, was observed and was interpreted in terms of an excited state interaction of 2 and a polar moiety of restricted mobility.[27] Since ϕ_f and τ depend upon the rate constants k_e and k_i (equations 3 and 4), ϕ_f and τ of certain fluorescent probes were found to be extremely sensitive to solvent polarity.[74]

Rigidity or microviscosity of the local environment of a fluorescent probe can be estimated by measuring the rate of depolarization of the fluorescence of molecules excited with linearly polarized light.[82] The degree of depolarization of a fluorescent probe (spherical) is related to the viscosity of the medium by the equation (5)[82]

$$r_o/r = 1 + kT\tau/\eta v \qquad (5)$$

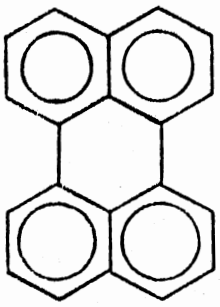
where r_o/r = degree of depolarization, T = absolute temperature,

η = viscosity of the medium, v = effective volume of the fluorescent sphere, τ = average lifetime of excited state of fluorescent probe, and k = Boltzmann constant. Equation (5) is modified for fluorescent probes with planar structure (nonspherical) which is equation (6),[66] where

$$r_o/r = 1 + kT\tau/\bar{\eta}v_o \qquad (6)$$

$\bar{\eta}$ = microviscosity of the system, v_o = effective volume of the rotating sphere. In the above equations (5 and 6) the parameters r_o/r, T, v or v_o, and τ are experimentally measurable; k is known.

Thus, from the depolarization characteristics of a fluorescent probe in a medium of interest, the microviscosity $\bar{\eta}$ can be evaluated. Microviscosity $\bar{\eta}$ was derived from an adequate comparison of the degree of fluorescence depolarization of perylene (3)[66] or 2-methylanthracene (4)[66] dissolved in tested micelles and a reference system of known vis-



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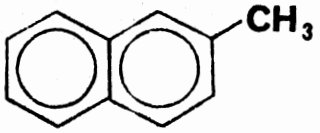

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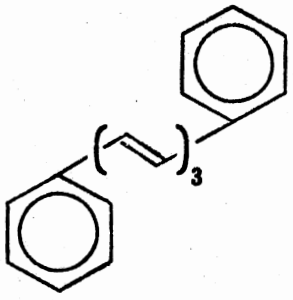


5

cosity. Also fluorescence polarization properties of 1,6-diphenyl-1,3,5-hexatriene (5)[83] were used in evaluating the $\bar{\eta}$ in the surface membrane lipid layer of normal lymphocytes and malignant lymphoma calls.

Rather than fluoresce a chromophore may transfer its excited state energy as far as 80 Å to an acceptor molecule with suitable absorption properties.[85,36] The quantum yield and lifetime of donor fluorescence

drop as energy-transfer efficiency increases in a manner predicted by Forster.[32] In Forster's theory of dipole-dipole energy transfer,[32] the transfer efficiency E is related to distance r between the donor and acceptor by equation (7) where R_o = the distance (in Å) at which the

$$E = r^{-6}/r^{-6} + R_o^{-6} \tag{7}$$

transfer efficiency is 50%. The latter is given in equation (8) where

$$R_o = (JK^2Q_on^{-4})^{1/6}(9.79\ 10^3) \tag{8}$$

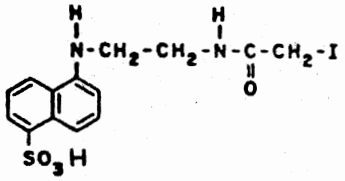
K^2 = orientation factor for dipole-dipole transfer, Q_o = quantum yield of donor in the absence of transfer, and n = refractive index of medium. J, the spectral overlap integral (in $cm^3\ M^{-1}$), is given by equation (9)

$$J = \int F(\lambda)\ e(\lambda)\ \lambda^4\ d\lambda\ /\ \int F(\lambda)\ d\lambda \tag{9}$$

where $F(\lambda)$ = the fluoresence intensity of the donor at wavelength λ and $e(\lambda)$ = the extinction co-efficient of the energy acceptor at that wavelength. Forster's theory has been tested in well-defined model systems.[47] Singlet-singlet energy transfer <u>(spectroscopic ruler)</u> has been recently used to deduce distances on various biological macromolecules.[53]

Wu and co-workers[85] specifically labelled rhodopsin with fluorescent energy donors at three different sites. Three kinds of fluorescent probes were used: iodoacetamide derivatives (<u>6</u>, <u>7</u>, and <u>8</u>), disulfides (<u>9</u> and <u>10</u>) and acridine derivatives (<u>11</u> and <u>12</u>). The 11-<u>cis</u>-retinal (whose absorption band overlapped with emission spectra of donors <u>6</u>-<u>12</u>) was used as energy acceptor. The distances obtained from the transfer efficiencies revealed that the rhodopsin molecule had an elongated shape and suggested that it might traverse the disc membrane

and act as a light controlled gate.



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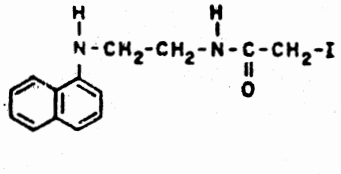

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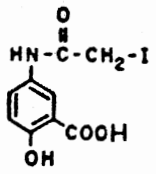

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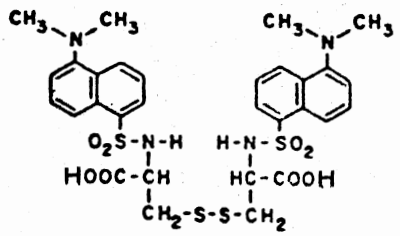

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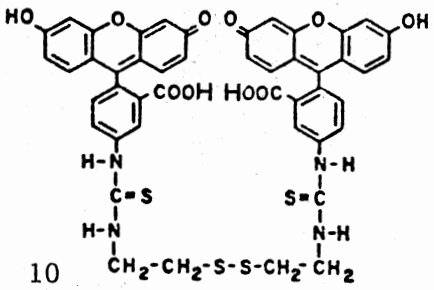

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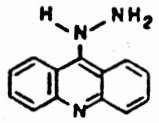

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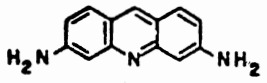

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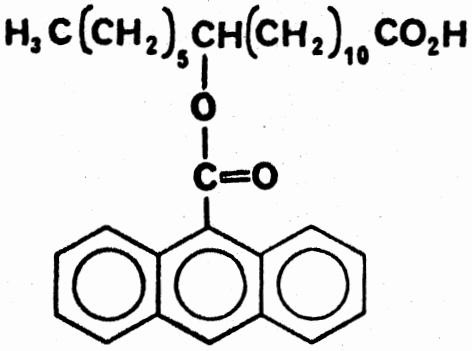
The potential benefits of fluorescence spectroscopy and the vital role of molecular probes are realized in understanding the structure and dynamics of biological membranes.[17,55,59,68,71,80,87] In a recent review, Mantulin and Pownall[55] covered selected developments in the application of fluorescent probe methods to the study of real and model membranes. Waggoner and co-workers[80] synthesized novel fluorescent probes 13 and 14 which were readily incorporated into bilayer vesicles composed of phosphatidyl choline. They concluded that fluorescent chromophores could be selectively placed in different transverse regions of a special membrane system. Yguerabide and Stryer[87] obtained fluorescene excita-

tion, emission and polarization spectra from a single spherical bilayer membrane consisting of oxidized cholesterol and a fluorescent probe.



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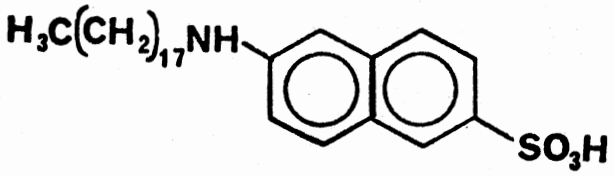

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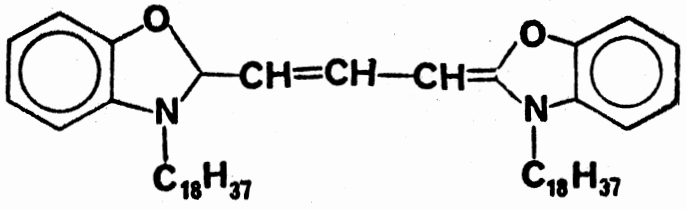
The emission transition moments of N, N'-di(octadecyl)oxacarbocyanine (15) and 13 were found to be aligned parallel to the plane of the bilayer whereas that of p-bis-[2-(4-methyl-5-phenyloxazolyl)]benzene (16) was aligned in a perpendicular direction. All three probes exhibited



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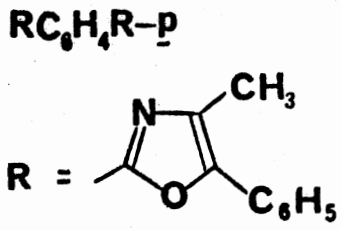

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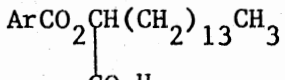
appreciable rotational mobility parallel to the plane of the bilayer in durations of nanoseconds. Cadenhead and co-workers[17] studied three anthroyl probes 13, 17, and 18 using pure and mixed monomolecular films with dipalmitoylphosphatidyl choline. All three probes were found to perturb both the monolayer and the bilayer packing, but the extent of f perturbation decreased as the anthroyl moiety was moved from the 2- to the

16-position. Synthesis and properties of four fluorescent probes, n-(9-anthroyloxy)stearic (or palmitic) acids (19) and their use as fluidity sensors in lipid bilayers were reported recently.[77] Sklar and

Ar = 9-Anthryl



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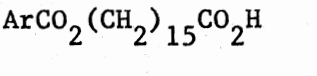

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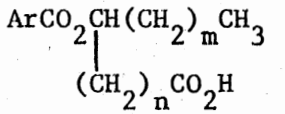

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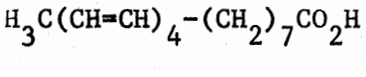

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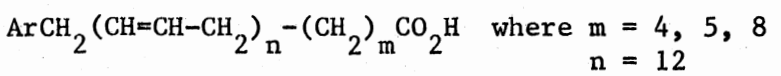


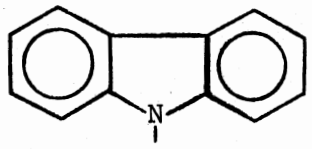
21

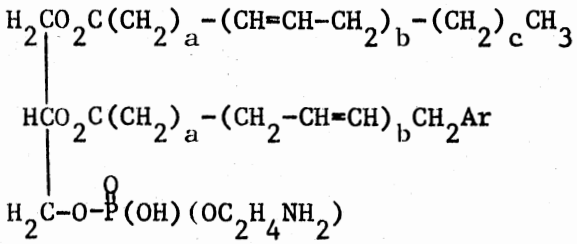
co-workers used the fluorescent parinaric acid (20) as a probe for studying lipid-lipid and lipid-protein interactions.[68] Stoffel and co-workers[71] developed the syntheses of a novel class of fluorescent fatty acids 21, phospholipids 22 and cholesterol esters 23. The above probes were used to determine phase transition in liposomes by fluorescence intensity and polarization measurements. Omann and co-workers[59] discovered that fluorescence of carbazole labelled phospholipid 24 was quenched efficiently by a number of chlorinated hydrocarbons which had markedly different chemical structures. Using carbazole-labelled model membrane systems and the fluorescence quenching technique, they were able to determine both diffusion rates and partition coefficients for

chlorinated hydrocarbons.

Ar = 9-Anthryl

R = 2-Cholesteryl

Ar' = 



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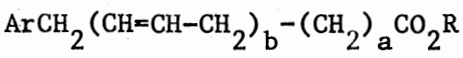

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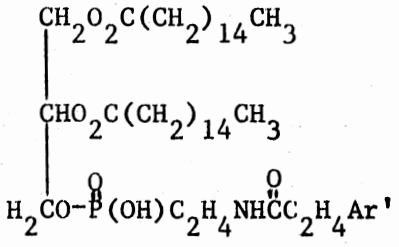

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Some fluroscent probes are available commercially.[63] A few are: cis- and trans-parinaric acids, 12-(9-anthroyloxy)stearic acid, 2-(9-

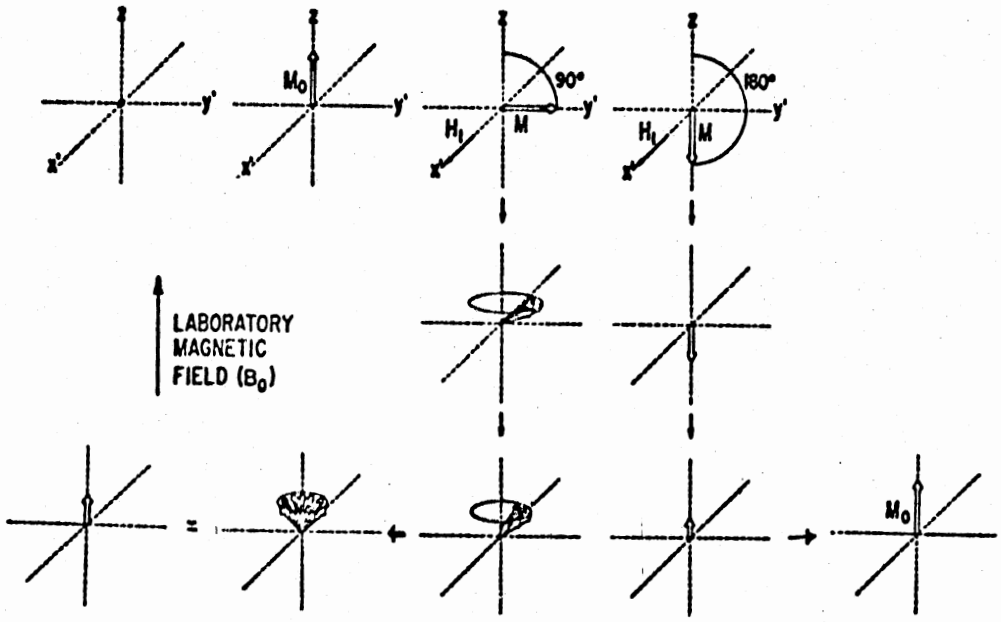
anthroyloxy)stearic acid, 2-(9-anthroyloxy)palmitic acid, 16-(9-anthroyloxy)palmitic acid, 12-(9-anthroyloxy)oleic acid, 9-anthroyl choline bromide, cholesteryl anthracene-9-carboxylate, anthracene-9-carboxaldehyde carbohydrazone, succinimidyloxy anthracene-9-carboxylate, ethoxycarbonyl anthracene-9-carboxylic anhydride, and 2-bromoethylanthracene-9-carboxylate. Undoubtedly other examples will be forthcoming as this research area emerges into a mature field.

Carbon-13 Spin-Lattice Relaxation Times(T_1) and the Mobility of Organic Molecules in Solution

Carbon-13 spin-lattice relaxation measurements obtained from specialized pulsed Fourier transform NMR experiments have shown great promise in structural and dynamic studies of organic molecules.[14,50,54] The information derivable from ^{13}C spin-lattice relaxation measurements is generally unobtainable from the common NMR chemical shift, spin-spin coupling and peak area (integration) parameters. The T_1 values of ^{13}C nuclei in a molecule not only provide information regarding the relaxation mechanisms and molecular dynamics in solution but also provide a reliable aid in the assigment of ^{13}C NMR spectra.[14]

A brief introduction to the phenomenon of spin-lattice relaxation is in order before relating the above to molecular dynamics in solution. Relaxation mechanisms can be better understood by considering the NMR experiment in the so called rotating frame of reference.[60] In the rotating frame, the entire coordinate system rotates at the Larmor, or resonance frequency,[29] corresponding to the experimental laboratory magnetic field, H_o (or B_o), as shown in the diagram that follows (page 14). A unique property of the nuclear spins (here ^{13}C nuclei) is M, the net

magnetization of the entire ensemble of nuclear spins. This M corresponds to the sum of all the individual nuclear magnetic moments.



When a sample is placed in the magnetic field H_0 (or B_0) there is initially no polarization of the nuclear spins. The population of the two quantized ^{13}C energy levels aligned with and against H_0 are equal and therefore M = 0. Due to interactions between the individual ^{13}C nuclei and their surroundings (the lattice), an equilibrium is established with an excess of ^{13}C nuclei in the lower energy level (Boltzmann distribution law). As a result there is a small equilibrium magnetization, M_0, aligned with the direction of the magnetic field. The net magnetization remains equal to M_0 only until rf excitation of the sample is initiated.

When the sample is irradiated, the radiofrequency field H_1 at the ^{13}C frequency is applied along the x-axis, fixed in the rotating frame.

The magnetic component of the rf field rotates M about the x-axis out of alignment with H_o (the z-axis) and toward the y-axis. In pulsed NMR, this process is very rapid. The pulse can be applied for an experimentally determined time (usually 1 to 100 sec) to nutate M by 90^o (page 14) or the pulse width may be twice as long, causing M to completely invert.

The process of spin-lattice relaxation begins immediately following every excitation pulse. In the rotating frame of reference, spin-lattice relaxation is relaxation along the z-axis whereas spin-spin relaxation corresponds to relaxation in the x-y plane. In the return of M to M_o following a single 180^o pulse (page 14), only spin-lattice relaxation is visible since there is no net x-y magnetization. Thus, M returns to M_o according to first order kinetics with a rate constant $1/T_1$ where T_1 is defined as the spin-lattice relaxation time. No free induction decay (FID)[50] is observed following an isolated 180^o pulse. The signal detected in NMR spectrometers is the net magnetization in the x-y plane, which is zero in this case. An isolated 90^o pulse, on the other hand, causes M to coincide with y-axis, in the x-y plane (page 14). The decay of the x-y magnetization as a function of time forms a FID. Following the 90^o pulse, both spin-lattice and spin-spin relaxation processes begin (page 14). The x-y magnetization "dephases" as a function of the spin-spin relaxation time, T_2, as M simultaneously returns vertically toward M_o (T_1 process). No signal is observed after the x-y magnetization is completely dephased, even if z-axis relaxation is incomplete (page 14). This corresponds to a T_2 being smaller than T_1.

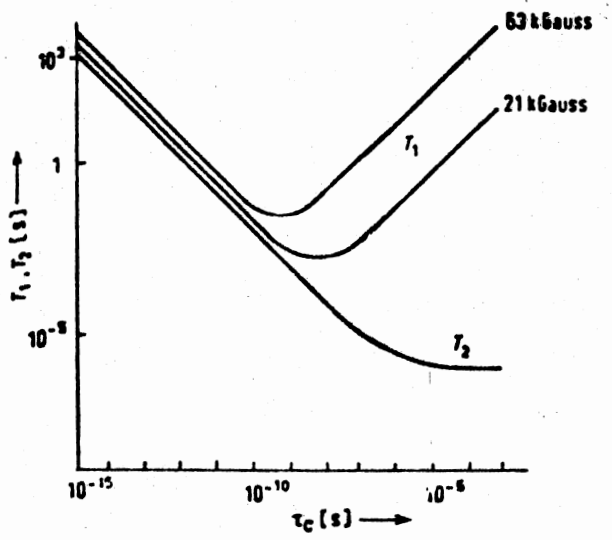
The above process of spin-lattice relaxation allows the lattice

to act as a heat sink for energy absorbed by nuclei when they are irradiated. A mechanism coupling the nuclear spins and the lattice is required for an efficient energy transfer.[50] All of the mechanisms possible for ^{13}C nuclei depend on the presence of fluctuating localized magnetic fields at or near the nucleus being relaxed. The four relaxation mechanisms that are generally considered arise from dipole-dipole (DD) interactions, the spin-rotation (SR) interaction, chemical shift anisotrophy (CSA), and scalar interactions.[50] All of these mechanisms can be operative to various extents for individual carbons in different molecules. However, the first two are the most commonly observed. Detailed mathematical and conceptual descriptions of ^{13}C relaxation mechanisms are provided elsewhere.[50,54]

A spin-lattice relaxation time (T_1) measurement is possible by using both swept continuous wave (CW) NMR and pulse excitation methods. One of the common pulse sequences for T_1 measurements is the inversion-recovery sequence.[50] A variation of the inversion-recovery pulse sequence is developed by Freeman and Hill.[34] Another scheme for measuring T_1 values for ^{13}C is the method of progressive saturation.[35] IRFT, PSFT, and PRFT are used to designate, respectively, inversion-recovery, progressive saturation and partially relaxed FT experiments.[12] Each method has its own merits and limitations.[54]

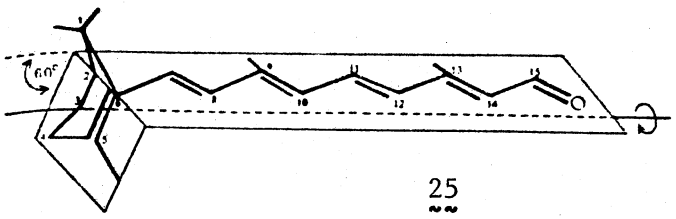
Measurements of spin-lattice relaxation times (T_1) of individual carbon nuclei provide information about intermolecular motions as well as the correlation times for over-all tumbling of molecules in solution. The majority of ^{13}C NMR measurements are performed with solutions or liquid samples with proton decoupling. Under these conditions, T_1 values of carbon depend mainly upon the speed of molecular motion

relative to the ^{13}C Larmor precision frequently. The average time required by a molecule between two reorientations is taken as a measure of molecular motion and is referred at the <u>effective molecular correlation time</u>, τ_c.[29,54] The τ_c is related to T_1 as shown in the following diagram.[14] Very slow molecular motion (10^{-9} s at H_o = 21 KG) leads to an



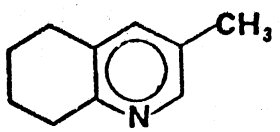
increase in T_1 which is typical of macromolecules.[14] If the viscosity is sufficiently low, small and medium-sized molecules tumble very rapidly. The correlation time becomes smaller and falls to the left of the minima in the above diagram.

Many small molecules tumble anisotrophically in solution. Preferential tumbling modes occur, resulting from inertial, frictional, and electrostatic effects as well as from intramolecular and intermolecular interactions with solvent or solute.[50] The relation between anisotropic molecular motion and nuclear relaxation was derived by Woessner[84] which was applied successfully in determining conformation of all-<u>trans</u>-retinal (25) from T_1 values.[8]



25

While the skeleton of large molecules is often relatively rigid, methyl groups bonded to the backbone are frequently very mobile. The rotation of a CH_3 group is thus much faster than the overall motion of the molecule, $\tau_{c(CH_3)} << \tau_{c(skeleton)}$. T_1 values for all the methyl carbons in 3-methyl-5,6,7,8-tetrahydroquinoline (26),[3] 8,9,9-trimethyl-5,8-methano-5,6,7,8-tetrahydroquinazoline (27),[69] and cholesteryl chloride (28)[3] may be cited as examples. Steric interactions can hinder rotation of methyl groups and thus accelerate methyl relaxation. T_1 values of methyl carbons in 2-butanone oximes (29),[51] 1-methyl naphthalene (30) and 9-methyl anthracene (31),[50] 6,7-dihydrolinalool (32), linalool (33), 6,7-dehydrolinalool (34),[50] and methylated phosphetanes 35[40] illustrate the above observations.



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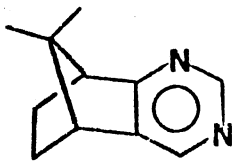

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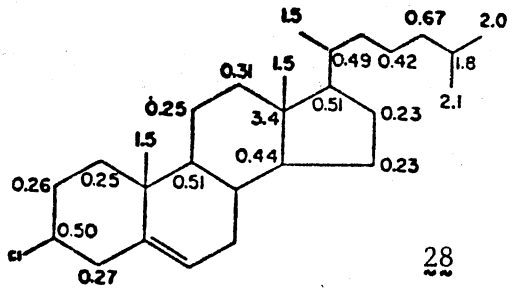

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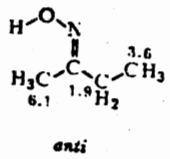

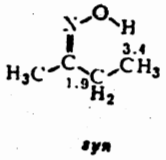

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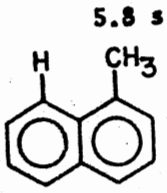

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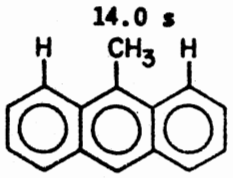

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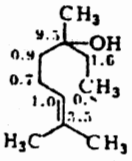

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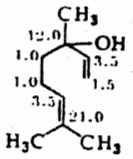

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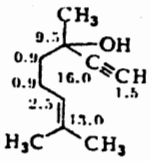

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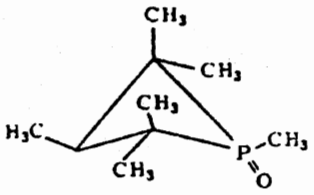


35

Localized motion along an aliphatic chain (or along another molecular substructure) is called segmental motion. Such flexible molecules have different τ_c values for each carbon atom, and this is reflected in the T_1 values. Thus the T_1 values of methylene carbon atoms in long alkane chains pass through a minimum often at the middle of the chain. Segmental motion has been monitored in long alkyl chains by T_1 measurements of carbon atoms in 1-decanol[25] and related compounds 35a (Table I).[20]

$$\overset{12}{R}\overset{3}{C}H_2\overset{4}{C}H_2\overset{5}{C}H_2\overset{6}{C}H_2\overset{7}{C}H_2\overset{8}{C}H_2\overset{9}{C}H_2\overset{10}{C}H_3$$

35a

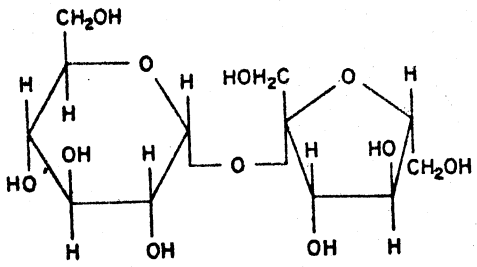
TABLE I

^{13}C SPIN-LATTICE RELAXATION TIMES (T_1) FOR SUBSTITUTED DECANES 35a

Terminal group R	T_1 Values in sec									
	R	2	3	4	5	6	7	8	9	10
CH_2OH	0.6	0.7	0.7	0.8	0.8	0.8	1.1	1.2	1.6	3.0
CO_2H	---	0.4	0.6	0.8	0.8	0.8	1.2	1.4	1.9	3.0
CO_2H	---	1.6	1.8	2.3	2.3	2.3	2.6	3.6	3.9	4.5
CO_2CH_3	5.3	2.6	2.5	2.2	2.2	2.2	2.2	3.6	3.9	4.5
CH_2NH_2	2.8	2.8	2.5	2.2	2.2	2.2	2.4	3.1	3.7	4.0
CH_2SH	3.0	2.6	2.6	2.4	2.1	2.1	2.4	3.1	3.4	3.8
CH_2Ph	1.4	1.2	1.1	1.1	1.1	1.3	1.3	1.8	2.8	3.0
CH_2Br	2.8	2.7	1.9	2.0	2.1	2.1	2.2	3.1	3.9	5.3
CH_2I	2.4	2.2	1.9	1.9	2.0	2.0	2.1	2.7	3.6	3.9
CH_2	5.6	6.0	5.2	4.8	4.3	4.3	4.8	5.2	6.0	5.6

It appears that segmental motion will have a large effect on T_1 values for carbon in alkyl chains only when the overall reorientation of the molecule is restricted. In the case of 1-decanol and 1-decanoic acid this restriction was caused by intermolecular hydrogen bonding. When diluted in a nonpolar solvent (CCl_4), 1-decanoic acid[20] showed a large increase in T_1, a fact probably related to a greater mobility of the molecule due to dissociation of aggregates. In the absence of intermolecular hydrogen bonding, various 1-decane derivatives exhibited a characteristic T_1 minimum near the middle of the chain. A progressive

increase in T_1 values along the side chain of cholesteryl chloride (28)[3,49] was observed and was related to increasing segmental mobility. Similar effects were observed in 1-bromo- and 1-iododecanes.[20] Segmental motion was monitored using T_1 measurements (for ^{13}C) in a number of systems of biological interest such as sucrose (36),[3] adenosine 5'-monophosphate (37),[3] lecithin,[49] ribonuclease,[2] thyrotropin-releasing hormone,[22] the peptide Pro-Leu-GLy-NH_2 (MSH-R-IF, 38),[23] prostaglandin $PGF_{2\alpha}$ (39),[20] oxytocin (40),[24] and lysine vasopressin (41).[24] These studies have been greatly aided by recent theoretical investigations[3,26] as well as data on small organic molecules.[50,51]



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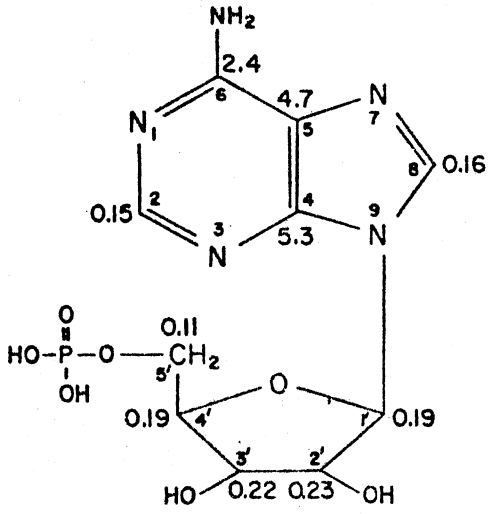

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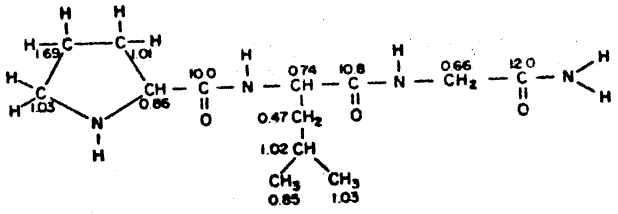

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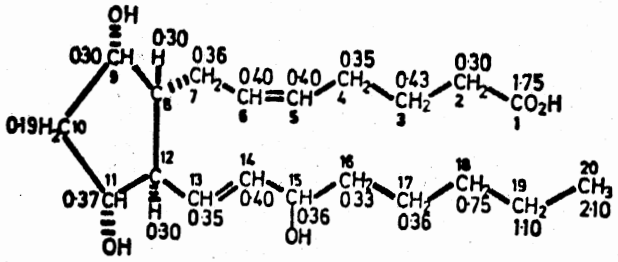

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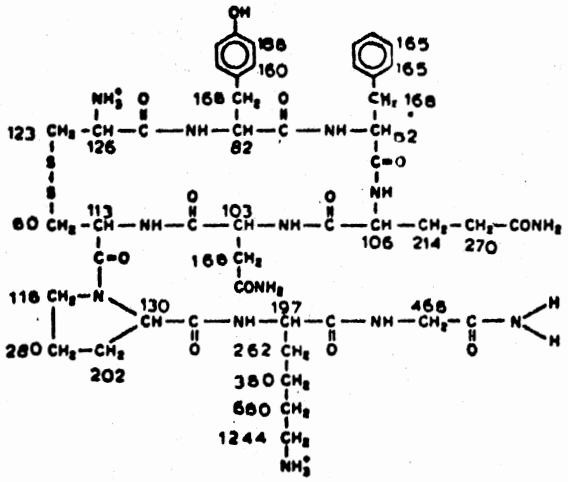

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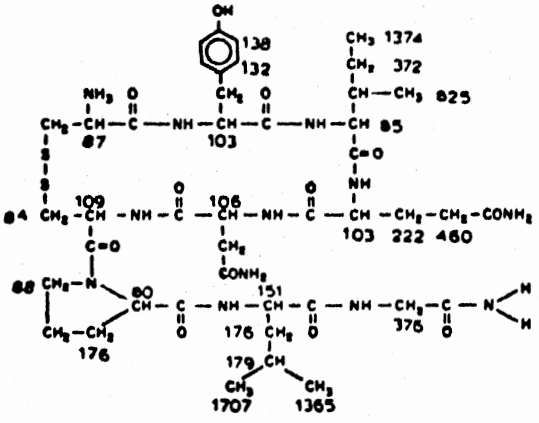

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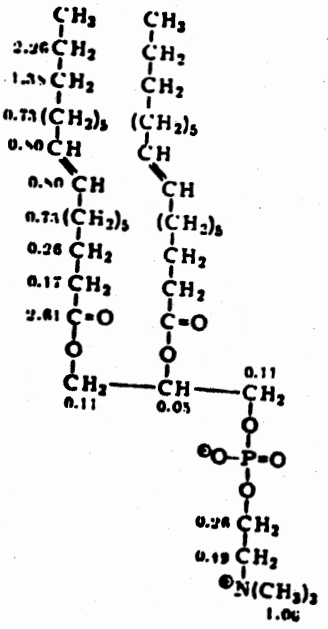


42

In dipalmitoyllecithin (42),[56] the carbon nuclei relax increasingly slowly going from the central glycerol group to the ends of the two fatty acids and then to the tetraalkylammonium end of the choline group. Thus, the mobility increases starting from the glycerol skeleton and proceeding along the fatty acid and choline chains to the molecular periphery. The terminal propyl groups of the fatty acid chains appear to undergo particularly rapid motion.[56] Since mobility of the lipid segments favors molecular transport through a membrane and thereby increases its permeability, a marked increase in T_1 along a lipid fatty acid chain also reflects a more efficient molecular diffusion through the lipid layer of membrane.[48]

In ribonuclease A, T_1 of the carbonyl carbon and the α and β carbon atoms was larger (0.12, 0.099 sec., respectively) in the denatured protein than in the native sample (0.042, 0.04 sec., respectively).[2] This was attributed to the increased flexibility of the macromolecular skeleton perhaps, resulting from conformational changes on denaturation. Considerable segmental mobility of the lysine side chain might be the reason for small change in its T_1 value on denaturation.[2] Conformational changes accompanied by flexibility of molecular skeleton were observed from T_1 measurements on carbons in proteins using models of aminoacids.[4]

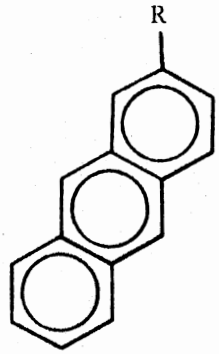
A certain segmental mobility of the chain was deduced from T_1 measurements of carbons in synthetic polymers.[65] The T_1 values of protonated carbons were used to investigate the molecular motion of free and potassium-ion complexed cyclic antibiotics and polyethers.[30] The relationship of lipid structure in membranes with T_1 values (of ^{13}C) was also investigated.[64] A FT ^{13}C and ^{14}N NMR study of the behavior

of acetyl choline was performed to determine local molecular motions and the corresponding activation parameters at each carbon.[9] Johns and co-workers[45] obtained T_1 and τ_c values of the individual carbon atoms in 12-hydroxy- and 6- and 12-(9 anthroyloxy)stearic acids (19) and related the intrinsic segmental motions to fluorescence depolarization of the above fatty acids which were used as fluidity probes in biomembranes. Other ^{13}C relaxation studies of important organic systems will undoubtedly emerge soon.

CHAPTER II

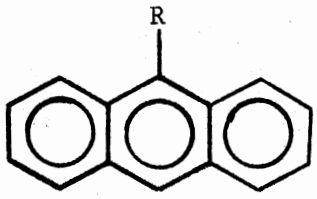
RESULTS AND DISCUSSION

One of the many advantages of the versatile fluorescence spectroscopy is that fluorescence energy transfer can be used as a spectroscopic ruler to deduce proximity relationships between specific sites on a macromolecule.[85] Model donor-acceptor probes for use in energy transfer studies have a number of critical requirement both from the point of view of chemical and physical properties.[55,79] For incorporation into the lipid bilayer, the model donor must be an adequate mimic of the normal lipid components of the layer.[58] One likely candidate which can meet the stringent requirements for certain donor molecules is 43 or possibly the isomeric analog 44. Members of 43 and 44 are expected to



4 R = CH_3

43 R = $(CH_2)_nCO_2H$ (PO_4H, PO_3H_2)

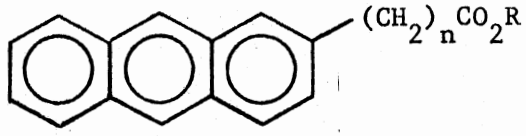


31 R = CH_3

44 R = $(CH_2)_nCO_2H$ (PO_4H, PO_3H_2)

show absorption maxima from 320-380 nm as judged from the spectra of

2- and 9-methylanthracenes (4 and 31, respectively) as model systems which display maxima in this range. The model compounds (4 and 31) have emission (and therefore 43 and 44 are predicted to do likewise) from 380-480 nm. Since the aromatic portion of the molecule is more nearly aligned with the long portion of alkyl chain in 43 than in 44, it may disrupt the lipid bilayer to a smaller extent than 44. Consequently, we undertook the syntheses of selected ω-(2-anthryl)alkanoic acids/esters which have a general structure 45. Surprisingly no examples of members of the above system be found in literature. Presented

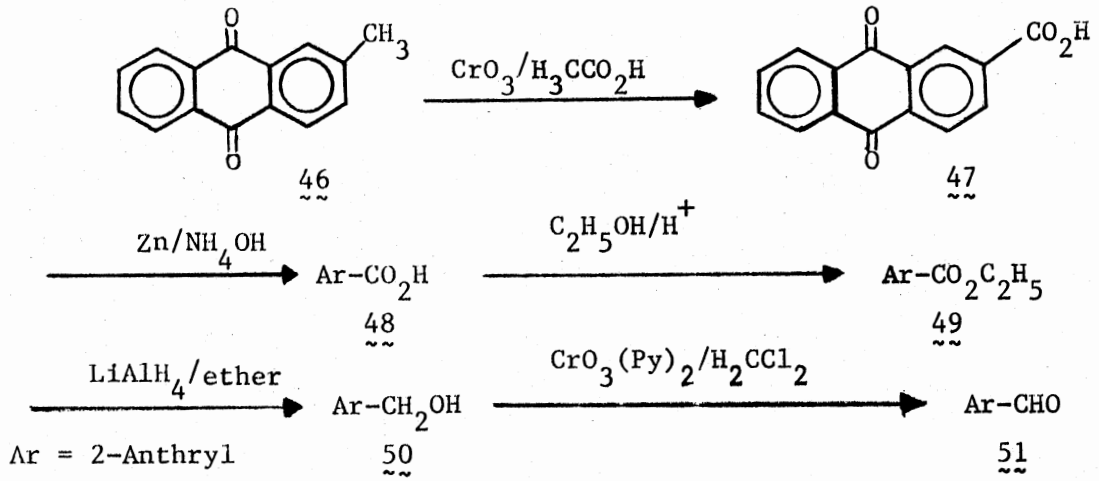


45 n = 2, 4, 6; R = H, CH_3, C_2H_5

herein are the syntheses, physical and spectral characteristics of the above compounds as well as ^{13}C spin-lattice relaxation time (T_1) measurements for two (n = 4,6; R = CH_3) of the above compounds.

2-Anthraldehyde (51) was found to be a valuable synthon in the present work. Preparation and spectroscopic as well as physical properties of 51 were already reported.[31,37] Recorded syntheses of 51 have involved lengthy procedures, produced undesirable side-products, and given poor yields. An alternate route route was, therefore, employed in the sequence 46→47→48→49→50→51 as outlined on page 27. The starting material 2-methylanthraquinone (46) was fairly cheap and was readily available (Aldrich). Conversion of 2-methylanthraquinone (46) to 2-hydroxymethylanthracene (50) was accomplished following literature

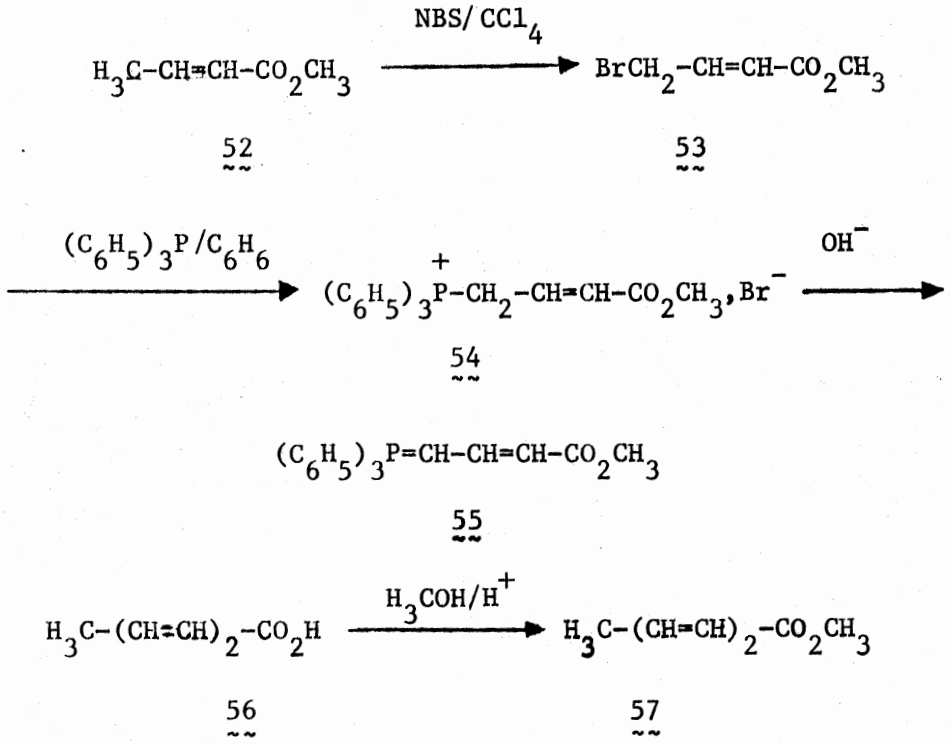
procedures but with certain modifications that were critical for enhanced yields.[11,19,44,52,70,72] Oxidation of 46[44] using CrO_3/H_3CCO_2H gave



anthraquinone-2-carboxylic acid (47) in good yield (83.3%). Zinc-ammonia reduction[11,72] of 47 produced 2-anthroic acid (48, 72%)[52] which was esterified to give ethyl 2-anthroate (49)[19] in a yield of 80%. Careful reduction of 49 using $LiAlH_4$ in dry ether gave 2-hydroxymethylanthracene (50)[70] in excellent yield (95%). As the product 50 was sparingly soluble in ether, the yield was maximized by soxhlet extraction of the insoluble residues using ethanol (95%). Oxidation of 50 to 2-anthraldehyde (51) was accomplished using Collin's reagent, $CrO_3(Py)_2$.[62] The above reagent was prepared *in situ* by mixing anhydrous pyridine and CrO_3 (molar ratio 2:1) in H_2CCl_2 and stirring (magnetic) for 15 min at room temperature. Workup of the reaction mixture gave 51 in good yield (80%). Unlike the reported procedures,[31,37] the present method gave very pure 51. The physical and spectroscopic data (provided in xperimental section) were found to be in good agreement with that expected for 51. Since the aldehyde 51 was found to be light sensitive, it was stored in dark containers. The above procedure gave 51 starting from 46 in an

overall yield of 37.4%. The present method is a superior one to any of the literature methods for 51.

Syntheses of esters 62, 63, and 64 involved a Wittig reaction (outlined below). Phosphoranes 55,[16] 60,[6] and 61[1] were made following literature procedures. Bromination of methyl crotonate (52)[78] using N-bromosuccinimide (NBS) in CCl_4 gave the bromo ester 53 in modest yield (40%) and a small amount of unreacted starting material (8.8%). Acid-catalyzed esterification of sorbic acid (56) using CH_3OH/conc. H_2SO_4 produced methyl sorbate (57)[43] in good yield (82%). Bromination of 57 was effected using NBS without any solvent at fairly high temperature (oil-bath 130°C) in a short reaction time (30 min).[43] The yield in the above reaction was somewhat low (20%), but the procedure was simplistic.



$$\xrightarrow{NBS} BrCH_2\text{-}(CH{=}CH)_2\text{-}CO_2CH_3 \xrightarrow{(C_6H_5)_3P/C_6H_6}$$

58

$$(C_6H_5)_3P^+\text{-}CH_2\text{-}(CH{=}CH)_2\text{-}CO_2CH_3,\ Br^- \xrightarrow{OH^-}$$

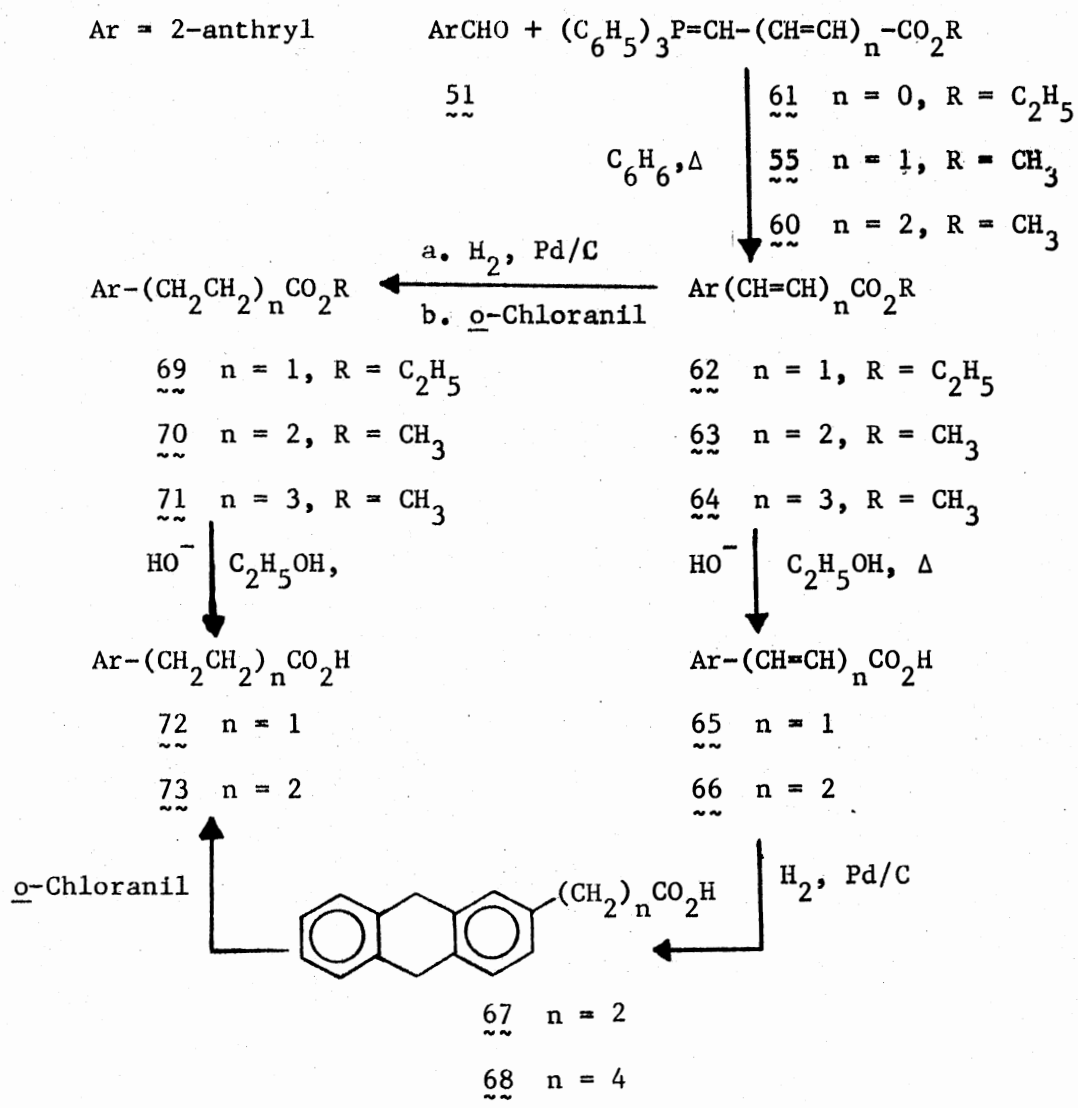
59

$$(C_6H_5)_3P{=}CH\text{-}(CH{=}CH)_2\text{-}CO_2CH_3$$

60

Phosphonium bromides 54[15] and 59[6] were obtained from the corresponding bromo compounds 53 and 58 following the reported procedures. To a stirred solution of $(C_6H_5)_3P$ in benzene (dry) was added the appropriate bromo compound, and the solution was stirred for 24 h under N_2 atmosphere at room temperature. Phosphonium bromide 54 was obtained in excellent yield (92%) with high purity (mp 181-182°C dec; lit[15] mp 179-180°C dec). Phosphonium bromide 59 was also obtained in good yield (64%) by a similar procedure. The above salt 59 was hygroscopic and was found to decompose on long standing, even at room temperature, and had to be stored under vacuum. Therefore, salt 59 was prepared in moderate purity (mp 173-175°C dec; lit[6] mp 188°C dec) and was used immediately. Basification (blue to litmus paper) of 54 with aq. NaOH solution (50%) gave phosphorane 55[16] as a beautiful yellow solid which was used without further purification. Phosphorane 60[6] was obtained as a dark red liquid by treating 59 in water with aq. NaOH solution (50%). It was then extracted with benzene and was used immediately as a concentrate in benzene. The Wittig reaction[6,38,46] of 51 with ylides 55 and 60 gave the expected unsaturated esters 63 and 64. A solution of 51 and the appro-

priate ylides (in excess) in benzene was boiled under N_2 atmosphere for 24 h and gave esters 63 and 64 in modest yield (36%, 19.7%, respectively). Both the esters 63 and 64 were shining yellow flakes, with similar spectral (IR, UV, ^{1}H NMR) characteristics. IR spectra (KBr pellet) of 63 and 64 showed a strong C=O absorption band at ν = 1700-1720 cm^{-1} which is typical for an α,β-unsaturated ester group. UV absorption spectra taken in ethanol had two characteristic λ_{max} at 300-400



nm and 200-220 nm. This is expected for molecules having an anthracene ring moiety (λ_{max} in cyclohexane 220-380 nm) and an α,β-unsaturated

ester group (λ_{max} in ethanol 200-225 nm). Thus, the spectra were comparable with the UV spectra of model compounds like 2-methylanthracene.[39] Analysis of the ^{1}H NMR spectra of 63 and 64 showed a singlet (3.8 ppm) for methyl protons and a multiplet (6-8 ppm) for aromatic and vinylic protons. The above apectral data were aided by elemental analysis in elucidating the structures of esters 63 and 64. All spectroscopic and physical data for 63 and 64 are provided in experimental section.

Hydrogenation (over 10% Pd-C) was found to reduce the 9- and 10-positions of the anthracene ring in addition to reducing the alkenyl side-chain in certain ω-(2-anthryl)alkenoic acids 65 and 66.[5] In fact, 9,10-dihydro derivatives 67 and 68 were isolated and characterized fully.[5] Formation of the above 9,10-dihydro derivatives was not unreasonable since the 9- and 10-positions in anthracene ring are highly reactive.[21] Aromatization of acids 67 and 68 using o-chloranil gave acids 72 and 73, respectively.[5] Conversion of unsaturated esters 62, 63, and 64 into saturated esters 69, 70, and 71 was accomplished by hydrogenation (Pd-C) and aromatization with o-chloranil without extensive purification of the expected 9,10-dihydro derivatives.

Esters 69, 70, and 71 were white solids and exhibited similar spectral properties. Analysis of the IR(KBr) spectra of the above esters showed a characteristic C=O absorption band at ν = 1725 cm^{-1}. UV absorption bands at $\lambda_{max}^{ethanol}$ 245-255, 300-380 nm were reasonable since the esters 69, 70, and 71 have an anthracene ring ($\lambda_{max}^{cyclohexane}$ 220-380 nm)[67] and an ester group ($\lambda_{max}^{ethanol}$ 210-220 nm).[67] To be sure, the absorptions were comparable with those of model compounds like 2-methylanthracene.[39] Analysis of the ^{1}H NMR spectra of esters 70, and 71 showed a singlet (3.8 ppm) for methyl protons, [for 69, a triplet (1.1-1.3 ppm) for methyl

protons] and a triplet as well as multiplets (1.5-2.8 ppm) for the side-chain methylene protons [for 69, two triplets (2.6-3.2 ppm) for the side-chain methylene protons and a quartet (4-4.2 ppm) for the -O-$\underline{CH}_2$- protons]. ^{13}C NMR chemical shifts (Table II) for esters 69, 70, and 71 were assigned with the aid of model compounds such as 2-methylanthracene[41] and appropriate ethyl/methyl n-alkanoates.[73] The above spectral data were supported by elemental analyses in confirming the structures of 69, 70, and 71.

Spin-lattice relaxation times (T_1) on ^{13}C in esters 70 and 71 were measured to determine segmental motion[50] of the carbons in the alkyl side chains of the above compounds. Segmental motion has been detected by measuring T_1 values (on ^{13}C) of many long-chain compounds.[20,76] The Inversion Recovery FT (IRFT) method[18,61] was employed in measuring T_1 values of esters 70 and 71. ^{13}C chemical shifts and T_1 values are listed in Table II. The T_1 values dropped to a minimum for carbons in the middle of the side-chain. This trend in T_1 values is not unusual and, in fact, has been noted in certain long chain compounds.[20,76] For example, T_1 values (in seconds) of various carbon atoms of methyl 1-decanoate (74)[20] exhibited such a minimum in the middle of the chain.

$$\overset{5.3}{H_3C}-\overset{3.9}{CH_2}-\overset{3.6}{CH_2}-\overset{2.2}{CH_2}-\overset{2.2}{CH_2}-\overset{2.2}{CH_2}-\overset{2.2}{CH_2}-\overset{2.5}{CH_2}-\overset{2.6}{CH_2}-CO_2CH_3$$

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Difference in T_1 values of individual carbon nuclei in the side-chain of 70 and 71 are perhaps due to a motional gradient (segmental motion) of the alkyl chains. Decreased T_1 values of carbon nuclei that are attached directly to an anthracene ring can probably hinder the independent

TABLE II

^{13}C NMR CHEMICAL SHIFTS[a] (^{13}C T_1 VALUES)[b] FOR ANTHRACENE CARBOXYLIC ACID ESTERS 69, 70, and 71

Carbon	69	70	71
C-1	125.9	125.5(1.5)	125.5(1.6)
C-2	137.2	138.7(15.2)	139.2(14.6)
C-3	128.0	127.8(1.5)	127.8(1.5)
C-4	126.7	125.7(15)	125.6(1.4)
C-5	127.9	127.2(1.3)	127.1(1.1)
C-6[c]	124.9	124.7(0.9)	124.9(1.0)
C-7[c]	125.1	124.9(0.9)	124.6(1.0)
C-8	128.2	127.9(1.5)	127.9(1.5)
C-9	125.4	125.0(1.1)	125.1(1.2)
C-10	125.8	125.3(1.1)	125.1(1.2)
C-4a	130.4	130.3(25.1)	130.3(25.1)
C-8a	131.6	131.6(22.7)	131.6(23.0)
C-9a	131.7	131.7(22.6)	131.7(22.4)
C-10a	131.3	131.1(23.3)	131.0(22.6)
C-1' (C=O)	172.6	173.6(37.2)	173.8(38.5)
C-2'	35.5	35.8(1.1)	36.0(1.0)
C-3'	31.3	24.6(1.4)	24.8(1.4)
C-4'	---	33.8(1.7)	28.8(1.1)
C-5'	---	30.2(1.1)	28.8(1.1)
C-6'	---	---	33.9(1.9)
C-7'	---	---	30.6(1.0)

TABLE II (Continued)

Carbon	69	70	71
C-α	60.3	51.3(6.1)	51.2(6.2)
C-β	14.2	---	---

a. Chemical shifts in ppm downfield from internal tetramethylsilane (TMS) in $DCCl_3$.

b. ^{13}C spin lattice relaxation time in seconds.

c. May be interchanged; see structures on page 35.

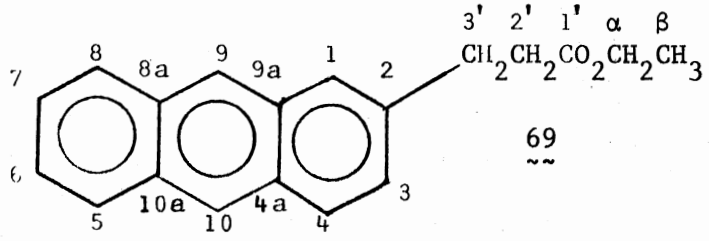
motion of the ω-carbon in the side chain of 70 and 71. This type of steric interaction is not unusual as exemplified in a recent study of T_1 measurements on carbon in some 9-anthroyloxyalkylcarboxylic acids[76] which supports our observations and tentative conclusions.

A study of fluorescent properties of ester 70 is underway.[57] For any fluorophore, the quantum yield, the fluorescence lifetime and the wavelength of the emission maxima depend upon solvent polarity.[79] Therefore, an experimental determination of the quantum yield and fluorescence lifetime of fluorophore 70 can reveal the polarity of a membrane bilayer at the location of the fluorophore. Moreover, by calibrating the response of the λ_{max} of fluorophore 70 in solvents of known polarity and viscosity, the λ_{max} of the fluorophore bound to the bilayer can be used as a measure of bilayer polarity and viscosity at the site of fluorophore.[76]

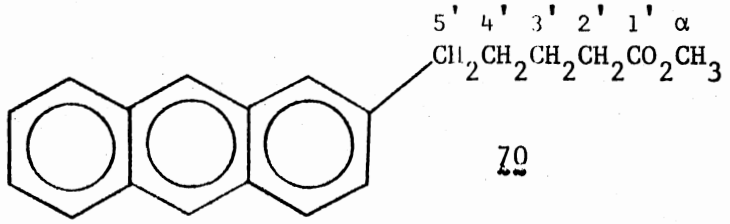
Fluorescence polarization of esters 69-71 may also provide

potential information about the microviscosity of the environment.[76] The polarization of a membrane bound fluorophore has been interpreted in terms of molecular motion within the bilayer. Smaller polarization values apparently imply a more fluid bilayer.[76]

Esters 69-71 are suitable candidates for donor molecules in energy-transfer studies. Different lengths of the alkyl side chains in esters 69-71 can provide information about the distribution of a donor mimic as a function of the distance between a head group (CO_2R) and the anthracene unit.[7,42] For example, one can envision reduced distribution of 69 in the lipid layer (reflected by reduced energy-transfer) when n = 2 as compared to 71 when n = 6 since in the former the anthracene ring is closer to the head and could disrupt the "ordering" of the heads in the bilayer.[7,42]



69



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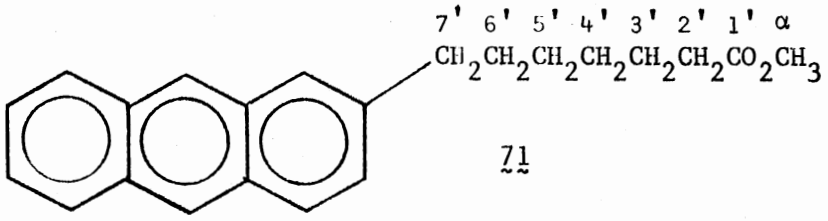

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CHAPTER III

EXPERIMENTAL

General Information

Reactions were carried out under an atmosphere of N_2 where necessary. 2-Methylanthraquinone (Aldrich, mp 170-173°C), CrO_3 (Baker-analyzed, reagent), zinc metal dust (90%, Baker and Adamson), $CuSO_4$ (Baker-analyzed, reagent), C_2H_5OH (U.S.P., anhydrous, 200 proof), $LiAlH_4$ (Ventron), sorbic acid (Aldrich, mp 134.5-137°C), $(C_6H_5)_3P$ (Eastman), 10% palladium on carbon (99.5%, Research Organic/Inorganic Chemical Corporation), o-chloranil (Aldrich), and sodium dithionite (J. T. Baker) were used as purchased without further purification. Anhydrous ether (Mallinckrodt) was dried over sodium before used. Anhydrous pyridine obtained by distillation of reagent-grade material (Baker) from BaO and was stored over Linde 4A molecular sieve. Methylene chloride (Eastman) was purified by shaking with conc. H_2SO_4, then by washing with saturated aq. $NaHCO_3$ and water, then by drying ($CaCl_2$), and finally by distillation. The purified solvent was stored in an amber-color bottle over Linde 4A molecular sieve and kept in the dark. Chromium trioxide (analytical reagent, Mallinckrodt) was stored in a vacuum desiccator over P_2O_5 prior to use. Dry C_6H_6 was obtained by drying ($CaCl_2$) the technical grade material distilling and storing over sodium. Methyl crotonate (Aldrich) was distilled prior to use, bp 118-120°C.

N-Bromosuccinimide (Matheson Coleman and Bell) was recrystallized from water before use, mp 182-183°C. Carbon tetrachloride (Baker, analyzed reagent grade) was distilled and kept over Linde 3A (pellet type) molecular sieve before use. Melting points were determined with a Thomas Hoover capillary apparatus and were uncorrected. IR spectral data were collected on a Beckman IR-5A Unit. NMR spectral signals were recorded in parts per million (ppm) downfield from Me_4Si (TMS) on a Varian XL-100(15) NMR spectrometer equipped with a Nicolet TT-100 PFT accessory operating at 100.1 MHz for ^1H NMR and at 25.2 MHz for ^{13}C NMR. UV spectral data were recorded on a Cary Model-14 recording spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. All organic extracts were dried over Na_2SO_4 and a roto-evaporator was used to remove the organic solvents in the usual workup.

Preparation of Anthraquinone-2-Carboxylic Acid (47)[44]

2-Methylanthraquinone (20 g, 90 mmol) was placed in a 3-L, three-necked, round-bottom flask fitted with a condenser, a thermometer, and a mechanical stirrer, and glacial H_3CCO_2H (1000 ml) was added to the flask which was warmed gently to dissolve the 2-methylanthraquinone with stirring. Subsequently, anhydrous CrO_3 (70 g, 70 mmol) were gradually added under vigorous stirring. The reaction mixture was warmed to 70-80°C (oil-bath) and kept at that temperature with vigorous stirring for 8 h. The reaction mixture was then cooled and diluted with water (8 L). The resulting precipitate was filtered off and washed with water until the disappearance of chromium salts was observed from the

washings. The solid was then treated with a dilute ammonia (1:1) solution at the boiling point until the filtrate ceased to form a precipitate by acidification. The filtrate was then cooled and acidified with conc. HCl. The deposited anthraquinone-2-carboxylic acid was filtered off, was washed with water, and was dried (aspirator). Recrystallization (gl. H_3CCO_2H) gave 18.9 g (83.3%) of 47 as a yellow powder: mp 291-292°C dec (lit[44] mp 291-292°C); IR (KBr) ν_{max} 3000-3050 (O-H), 1700 (C=O, ketone), 1600 cm^{-1} (C=O, acid); ^1H NMR (DMSO-d_6) δ 7.84-8.52 (m, Ar-H).

Preparation of 2-Anthroic Acid (48)[11,72]

A suspension of the acid 47 (10 g, 40 mmol), zinc dust (40 g, 600 mg atom), and $CuSO_4$ catalyst (ca. 0.5 g) in aq. ammonia (20%, 450 mL) was stirred at reflux until the temperature reached 70°C. After 3 h at 70°C, the reaction mixture changed from dark red to amber, and the hot aqueous solution was filtered from insoluble residues, was cooled, and was acidified with dilute HCl (1:1, 400 mL). The resulting yellow solid was filtered off and dried (aspirator). Recrystallization (gl. H_3CCO_2H) gave 6.4 g (73%) of 48 as a yellow powder: mp 283-285°C dec (lit[52] 274°C); IR (KBr) ν_{max} 3000 (O-H), 1670-1680 cm^{-1} (C=O); ^1H NMR (DMS) d_6) δ 7.52-8.80 (m, Ar-H).

Preparation of Ethyl 2-Anthroate (49)[19]

A mixture of the acid 48 (4.9 g, 22 mmol), anhydrous C_2H_5OH (150 mL) and conc. H_2SO_4 (7 mL) was boiled (24 h) and then was allowed to cool. The ethanol was then evaporated. The resulting solid was washed with water and then with saturated Na_2CO_3 solution. Recrystalli-

zation (95% C_2H_5OH) gave 4.4 g (80%) of 49 as white flakes: mp 141-142°C (lit[19] 137.5-139°C); IR (KBr) ν_{max} 1700 (C=O), 2950-2975, 1000-1300 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) δ 1.38-1.54 (3 H, t, CH_3), 4.34-4.56 (2 H, q, CH_2), 7.42-8.56 (9 H, m, Ar-H)

Preparation of 2-Hydroxymethyl-anthracene (50)[70]

A solution of $LiAlH_4$ (3 g, 79 mmol) in dry ether (600 mL) was placed in a 1-L, round-bottom flask equipped with a soxhlet extractor and a condenser with a N_2 inlet. Then ester 49 (12.1 g, 48 mmol) was placed in a sintered crucible and kept inside the soxhlet extractor. The solution was warmed with stirring (magnetic) until all of the ester had been transferred to the reaction flask. The resulting solution was then cooled, and ethyl acetate was added in drops to destroy the unreacted $LiAlH_4$. Water was added to obtain a clear mixture composed of two layers. The ether layer was separated, was washed with water, was dried ($MgSO_4$), and was evaporated to give a yellow solid. The aqueous layer was filtered (suction) and a pale yellow solid was obtained. This, upon soxhlet extraction using 95% ethanol, gave a yellow solid. Recrystallization (C_6H_6) gave 9.6 g (95%) of 50: mp 223-225°C dec (lit[70] mp 223-224°C dec); IR (KBr) ν_{max} 3300 (O-H), 1040-1050 cm^{-1} (C-O-); ^1H NMR ($DCCl_3$) δ 1.57 (1 H, s, O-H), 4.93 (2 H, s, CH), 7.40-8.46 (9 H, m, Ar-H).

Preparation of 2-Anthraldehyde (51)[62]

A 250-mL, three-necked, round-bottom flask equipped with a mechanical stirrer, a thermometer, and a drying tube was charged with C_5H_5N

(5 g, 60 mmol) and H_2CCl_2 (75 mL). The solution was stirred at room temperature and anhydrous CrO_3 (3 g, 30 mmol) was added in one portion. The deep burgandy-colored solution was stirred at room temperature for 15 min. At the end of this period, a suspension of alcohol 50 (1 g, 5 mmol) in H_2CCl_2 (25 mL) was added to the flask. A tarry, black residue separated immediately. Stirring was continued for 15 min. at room temperature, and the solution was decanted from the residue. The black residue was washed with ether (200 mL). The combined organic solutions were washed successively with 5% aq. NaOH solution (3 × 100 mL), 5% HCl (3 × 100 mL), 5% $NaHCO_3$ solution (3 × 100 mL), and finally with saturated aq. NaCl solution (100 mL). The resulting solution was dried ($MgSO_4$) and evaporated to give a yellow solid which turned brick red in light. Consequently, the product was kept in the dark and recrystallized (C_6H_6) to give 0.8 g (81%) of 51 as an yellow powder: mp 202-203° C dec (lit[37] mp 202-203°C dec); IR (KBr) ν_{max} 2675 (C=O), 2800, 2950-3000 cm^{-1} ($-\overset{H}{\underset{|}{C}}=O$); ^1H NMR ($DCCl_3$) δ 7.46-8.58 (9 H, m, Ar-H), 10.16 (1 H, s, HC=O)

Preparation of Methyl 4-Bromocrotonate (53)[78]

Methyl crotonate (76 g, 760 mmol) was dissolved in dry CCl_4 (120 mL) in a 250 mL, round-bottom flask fitted with a condenser and a N_2 inlet. Then N-bromosuccinimide (68 g, 380 mmol) was added to the flask. The reaction mixture was heated (oil-bath, 90-95°C) for 12 h and was then allowed to cool. The solid succinimide formed and was filtered(suction). The filtrate was concentrated and was then distilled under vacuum. The first fraction collected at 30-40°C/2.5 mm (6.7 g) was methyl crotonate. The second fraction collected at 76-77°C/7-8 mm was 53: yield 49.7 g

(40%); IR (neat liquid) ν_{max} 1700 (C=O), 1000-1300 (C-O-C), 1630 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 3.72 (3 H, s, $C\underline{H}_3$), 3.97-4.04 (2 H, d, $C\underline{H}_2$), 5.9-6.06 (1 H, d, $\underline{H}C{=}C\underline{H}$), 6.8-7.1 (1 H, m, $\underline{H}_2C$-CH).

Preparation of (3-Carbomethoxypropen-2-yl-1-)-triphenylphosphonium Bromide (54)[15]

Triphenylphosphine (5.56 g, 21 mmol) was placed in a 100 mL, three-necked, round-bottom flask fitted with an N_2 inlet, an addition funnel, and a glass stopper. Then 20 mL of dry C_6H_6 was added to dissolve the $(C_6H_5)_3P$, and the solution was stirred (magnetic) under N_2. Methyl 4-bromocrotonate (3.5 g, 20 mmol) was added dropwise. The solution became turbid immediately and a white solid separated out as the reaction proceeded. After the addition was complete, the reaction mixture was stirred under N_2 at room temperature for 24 h. After this period, the mixture was washed with dry C_6H_6 (3 × 15 mL) and was filtered (suction). The white powder was again washed with petroleum ether (2 × 15 mL)and was then dried (vacuum) overnight. Some additional product precipitated from the mother liquor upon standing for 24 h. Recrystallization (H_3CCN-$H_3CCO_2C_2H_5$, 1:1) gave 8.1 g (92%) of 54 as white needles: mp 181-182°C dec (lit[15] mp 179-180°C dec). IR (KBr) ν_{max} 2750-2800 ($-\overset{+}{P}-CH_2-$), 1700-1710 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 3.7 (3 H, s, $C\underline{H}_3$), 5.08-5.3 (2 H, dd, $-C\underline{H}_2-$), 6.44-6.70 (2 H, m, $-C\underline{H}{=}C\underline{H}-$), 7.60-7.96 (15 H, m, Ar-$\underline{H}$).

Preparation of Methyl Sorbate (57)[43]

A mixture of sorbic acid (200 g, 1.784 mmol), H_3COH (700 mL); and conc. H_2SO_4 (40 mL) was boiled (overnight) and was cooled. The alcohol was evaporated to obtain a pleasant-smelling liquid which was dissolved

in ether (300 mL). This solution was washed successively with water (300 mL), saturated aq. Na_2CO_3 solution (3 × 200 mL), water (300 mL), and finally with saturated aq. NaCl solution (300 mL). Evaporation of dried ($MgSO_4$) ether layer gave a pleasant smelling liquid which distilled under vacuum: bp 52-55°C/1.75 mm, (lit[43] bp 90°C/3.5 mm); yield 184.4 g (82%); IR (neat) ν_{max} 1720 (C=O), 1680-1600 (C=C), 1000-1300 cm^{-1} (-C-O); ^1H NMR ($DCCl_3$) δ 1.84-1.86 (3 H, d, C-C<u>H</u>$_3$), 3.72 (3 H, s, O-C<u>H</u>$_3$), 5.66-5.83, 6.06-6.2, 7.10-7.38 [4 H, m, (<u>H</u>C=C<u>H</u>)$_2$].

Preparation of Methyl 6-Bromosorbate (58)[43]

The ester 57 (240 g, 1.9 mol), N-bromosuccinimide (84.7 g, 476 mmol), benzoyl peroxide (0.4 g) were placed in a 500 mL, round-bottom flask fitted with a condenser and a N_2 inlet. The mixture was heated (oil bath, 120°C) with stirring (magnetic) until all of the N-bromosuccinimide had dissolved. This reaction mixture was kept at that temperature (15 min) and was allowed to cool. A solid separated which was filtered off and washed (CCl_4). The filtrate was washed with aq. K_2CO_3 solution (2 × 100 mL) and then with water (2 × 100 mL). Evaporation of the dried ($MgSO_4$) organic layer gave a light, brown liquid which gave the following fractions under vacuum distillation: 78-80°C/3.25 mm, (methyl sorbate) 162.4 g, (lit[43] bp 90°C/3.5 mm) 90-130°C/3.25 mm, 13.95 g; and 130-133°C/3.25 mm (methyl 6-bromosorbate) 25.85 g (25%) (lit[43] bp 75°C/1 mm). Spectral analysis of the latter gave: IR (neat) ν_{max} 1725 (C=O), 1600-1650 (C=C), 1030-1150 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) δ 3.74 (3H, s, C<u>H</u>$_3$), 4.00-4.08 (2 H, d, C<u>H</u>$_2$), and 5.86-7.39 [4 H, m, (<u>H</u>C=C<u>H</u>)$_2$].

Preparation of (6-Methoxycarbonylpenta-2,4-dienyl--1-)triphenylphosphonium Bromide (59)[6]

Triphenylphosphine (29 g, 111 mmol) was placed in a 250 mL, three-necked, round-bottom flask equipped with a N_2 inlet, an addition funnel, and a glass stopper. Dry C_6H_6 (100 mL) was added and the solution was stirred (magnetic). The ester 58 (21.5 g, 105 mmol) was added dropwise. The solution became cloudy immediately and a gummy solid began to separate out. The reaction mixture was stirred under N_2 for 24 h at room temperature. At the end of this period, a white solid separated, was filtered, was washed with dry ether (3 × 50 mL) and was dried (vacuum); yield 31.3 g (64%): mp 173-175°C dec (lit[6] mp 188°C dec); IR (KBr) ν_{max} 2700-2800 ($\geq\overset{+}{P}-CH_2-$), 1700 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 3.67 (3 H, s, O-CH_3), 4.97-5.19 (2 H, dd, -CH_2), 5.7-6.00, 6.52-7.1 [4 H, m, (HC=CH)$_2$], 7.32-7.96 (15 H, m, Ar-H).

Preparation of Methyl 5-(2-Anthryl)penta-2,4-dienoate (63)[38]

The phosphonium salt 54 (6 g, 14 mmol) was dissolved in distilled water (200 mL) and aq. NaOH solution (50%) was added until the solution became alkaline to litmus paper. A red-orange solid separated immediately, and the suspension was stirred (magnetic) for 30 min. The solid was filtered (suction) and was dried (vacuum). The yield was quantitative, mp 174-175°C dec (lit[38] mp 180-180.5°C). The phosphorane 55 (2.4 g, 7 mmol) and the aldehyde 51 (1 g, 5 mmol) were dissolved in C_6H_6 (50 mL), and the solution was placed in a round-bottom flask fitted with a condenser and N_2 inlet. The solution was boiled (24 h) and was

filtered while hot. Evaporation of benzene produced a dark brown semi-solid which, upon trituration (anhydrous C_2H_5OH), gave a dull, yellow solid. Recrystallization (C_6H_6) gave 0.5 g (36%) of 63 as a shining, yellow flakes, mp 231-233°C dec. An analytical sample of 63 was obtained by one more recrystallization (benzene), mp 233-234°C dec. IR (KBr) ν_{max} 1700 (C=O), 1625 (C=C); 1010-1040 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) δ 3.78 (3 H, s, $C\underline{H}_3$), 5.96-6.01 (1 H, d, $H_3CO_2C-C\underline{H}=C$), 6.80-8.38 (12 H, m, Ar-$\underline{H}$ and $\underline{H}C=C\underline{H}$); UV (anhydrous C_2H_5OH) λ_{max} in nm 412 (ε 5856), 385 (ε 17117), 367 (ε 19820), 354 (ε 16667), 326 (ε 76577), 314 (ε 64865), 246 (ε 40991), 2228 (ε 27928).

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59.
Found: C, 83.5; H, 5.70.

Preparation of Methyl 7-(2-Anthryl)hepta-2,4,6-trienoate (64)[6]

Phosphonium bromide 59 (4.53 g, 10 mmol) was placed in a 1-L, round-bottom flask fitted with N_2 inlet. Distilled water (300 mL) was added to dissolve the salt and the solution was stirred (magnetic) for 30 min. This solution was made alkaline to litmus by adding an aqueous solution of NaOH (50%), and a dark red oily liquid separated out immediately. The new solution was then extracted (C_6H_6, 5 × 100 mL) until the aqueous layer became almost colorless. The combined benzene extracts were washed with water (200 mL) and with aqueous saturated NaCl solution (200 mL). The dried ($MgSO_4$) benzene solution was concentrated (ca. 50 mL). 2-Anthraldehyde (1 g, 5 mmol) was added to the above benzene solution and was boiled under N_2 overnight. Upon cooling, a yellow solid separated which was filtered. Evaporation of the filtrate gave a dark brown semi-solid which, upon trituration (absolute ethanol), gave

a dull yellow solid. Recrystallization (C_6H_6) gave 0.3 g (19.7%) of 64 as shining yellow flakes, mp 233-235°C dec. An analytical sample was obtained after one more recrystallization (benzene), mp 234.5-236°C dec. IR (KBr) ν_{max} 1700-1720 (C=O), 1600-1630 (C=C), 1040, 1010 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) 3.8 (3 H, s, $C\underline{H}_3$), 5.99-6.14 (1 H, d, -C$\underline{H}$-), 7.00-7.12 (1 H, d, -C$\underline{H}$-), 7.44-8.40 [13 H, m, Ar-$\underline{H}$ and (C$\underline{H}$=$\underline{H}$C)$_2$]; UV (anhydrous C_2H_5OH) λ_{max} in nm 415 (ε 30496), 410 (ε 35816), 390 (ε 35106), 354 (ε 63830), 340 (ε 32624), 225 (ε 14184), 220(ε 12766).

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77.

Found: C, 84.04; H, 5.84.

Preparation of Ethyl 3-(2-Anthryl)propanoate (69)

Ethyl 3-(2-anthryl)prop-2-enoate (62)[5] (0.3 g, 1.1 mm l) and 40 mg of 10% Pd/C were placed in a hydrogenation flask and anhydrous C_2H_5OH (60 mL) was added. Hydrogen gas was passed through the mixture (atmospheric pressure), and the mixture was stirred until hydrogen uptake ceased (4.5 h). The solution was filtered and was evaporated. A glassy mass was obtained from which traces of ethanol were removed by repeatedly dissolving the product in a small volume of dry C_6H_6 (ca. 5 mL) and evaporating the latter. After dissolving the above mass in dry C_6H_6 (10 mL), o-chloranil (0.270 g, 1.1 mmol) was added. The dark red solution was boiled for 3 h under N_2, was allowed to cool to room temperature (purple), and was diluted with ether (50 mL). The ether solution was washed repeatedly with freshly prepared aqueous sodium dithionite solution (saturated) to get a clear, pale yellowish organic layer which was washed with water (50 mL), 2% aq. KOH solution (2 × 50 mL), water (50 mL), and then with saturated aq. NaCl solution (50 mL).

Upon evaporation, the dried ($MgSO_4$) organic solution gave a grey solid. Recrystallization (anhydrous C_2H_5OH) gave 69 as a white powder; 0.225 g (75%), mp 121-123°C. Repeated recrystallizations (anhydrous C_2H_5OH) gave an analytical sample, mp 130-131°C. IR (KBr) ν_{max} 1725 (C=O), 1080, 1050, 1000 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) δ 1.1-1.3 (3 H, t, $-CH_3$), 4.02-4.22 (2 H, q, $O-CH_2$), 3.06-3.22 [2 H, t, $-C(O)CH_2$], 2.68-2.82 (2 H, t, $-CH_2-CH_2$), 7.22-8.30 (9 H, m, Ar-H); ^{13}C NMR: see Table II; UV (anhydrous C_2H_5OH) λ_{max} in nm 376 (ε 5568), 367 (ε 2561), 357 (ε 6570), 347(ε 3675), 340 (ε 4844), 329 (ε 2895), 324 (ε 3007), 316 (ε 2394), 307 (ε 3452), 255 (ε 248148), 247 (ε 103704).

Anal. Calcd. for $C_{19}H_{18}O$: C, 81.99; H, 6.52.

Found: C, 81.80; H, 6.77.

Preparation of Methyl 5-(2-Anthryl)pentanoate (70)

Ester 63 (0.4 g, 1.4 mmol) and 60 mg of 10% Pd/C were placed in a hydrogenation flask and anhydrous C_2H_5OH (75 mL) was added. Hydrogen was passed through the suspension (atmospheric pressure) which was stirred continuously until hydrogen uptake ceased (4.5 h). The solution was filtered and C_2H_5OH was removed to obtain a glassy mass. Traces of C_2H_5OH in the glassy mass were removed by repeatedly dissolving it in C_6H_6 (5 mL) and evaporating the latter. The glassy mass obtained was dissolved in 10 mL of dry C_6H_6, and o-chloranil (0.35 g, 1.4 mmol) was added. The reaction mixture (dark red) was boiled for 3 h under N_2, was cooled (purple) and was diluted with ether (50 mL). This solution was washed repeatedly with freshly prepared saturated aqueous sodium dithionite solution to obtain a clear pale yellow organic layer. This organic layer was washed with water (50 mL), 2% aq. KOH solution (2 × 50

mL), water (50 mL), and then with saturated aq. NaCL solution (50 mL). Evaporation of the dried ($MgSO_4$) organic solution gave an yellowish semi-solid which, upon trituration (petroleum ether), gave a white powder. Recrystallization (anhydrous C_2H_5OH) gave 0.182 g (45%) of 70 as a white powder: mp 105-106°C; IR (KBr) ν_{max} 1725 (C=O), 1170-1000 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) δ 1.68-1.78 (4 H, m, $C\underline{H}_2$-$C\underline{H}_2$), 2.3-2.46 (2 H, m, Ar-$C\underline{H}_2$), 2.72-2.88 (2 H, m, H_3CO_2C-$C\underline{H}_2$), 3.64 (3 H, s, CH_3), 7.32-8.34 (9 H, m, Ar-$\underline{H}$); ^{13}C NMR: see Table II; UV (anhydrous C_2H_5OH) λ_{max} in nm 377 (ε 5343), 368 (ε 2306), 357 (ε 6153), 348 (ε 3431), 339 (ε 4499), 325 (ε 2778), 313 (ε 1462), 255 (ε 251852), 247 (ε 107407).

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90.

Found: C, 81.78, H, 7.10.

Preparation of Methyl 7-(2-Anthryl)heptanoate (71)

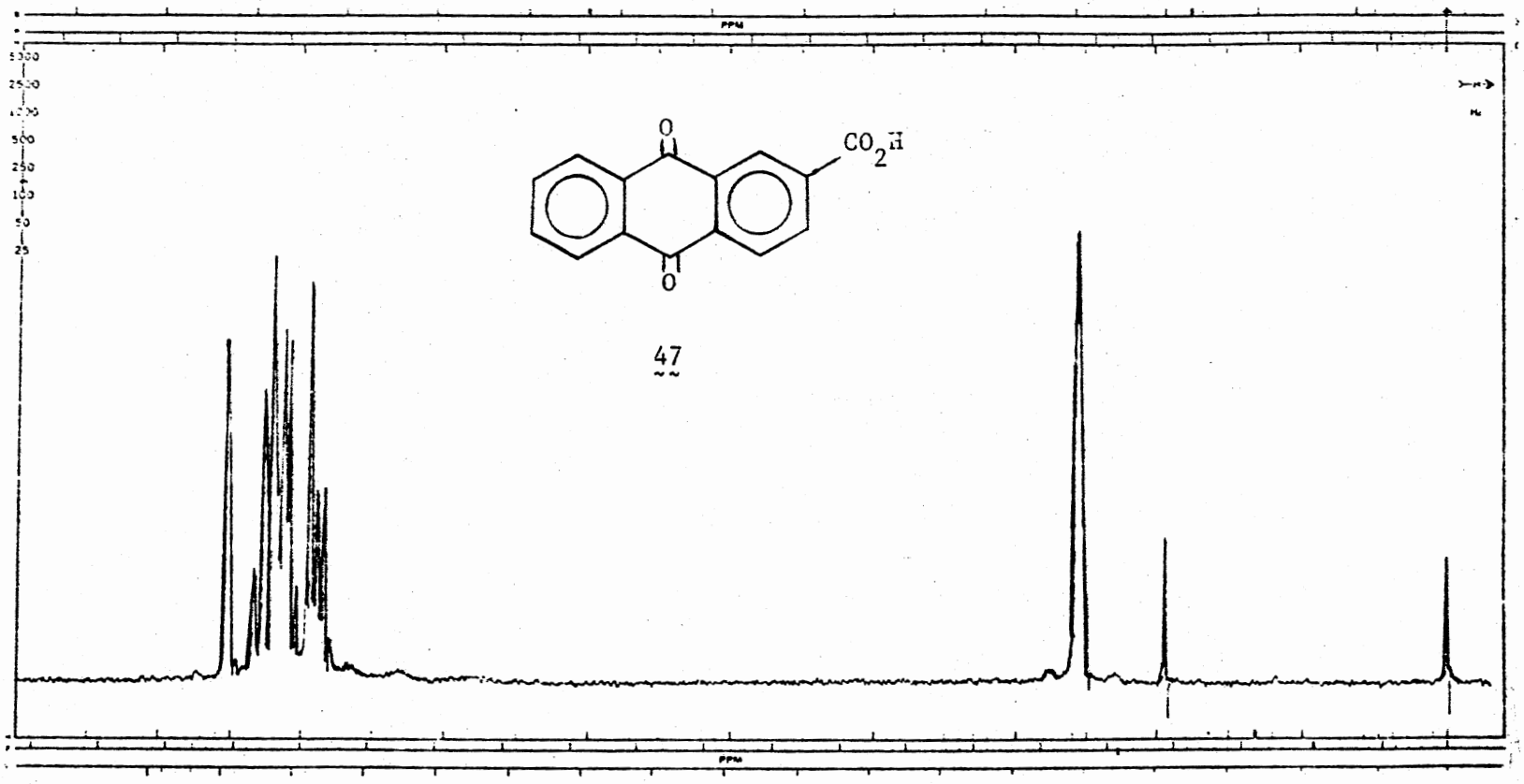
Ester 64 (0.44 g, 1.4 mmol) and 60 mg of 10% Pd/C were placed in a hydrogenation flask and anhydrous C_2H_5OH (75 mL) was added. Hydrogen was passed through the mixture (atmosphere pressure), and the mixture was stirred continuously until no more hydrogen was consumed (4.5 h). The solution was filtered and ethanol was removed to obtain a glassy mass. Traces of ethanol were removed from the glassy mass by repeatedly dissolving it in benzene (5 mL) and evaporating the latter. The hydrogenation product was then dissolved in dry C_6H_6 (15 mL) and o-chloranil (0.350 g, 1.4 mmol) was added. The solution (dark red) was boiled for 3 h under N_2, was cooled (purple) and was diluted with ether (50 mL). This solution was washed repeatedly with freshly prepared aq. sodium dithionite solution (saturated) to obtain a clear, pale yellow organic layer. The ether solution was washed with water (50 mL), 2% aq. KOH

(2 × 50 mL), water (50 mL), and saturated aq. NaCl solution (50 mL). Upon evaporation of the dried ($MgSO_4$) organic solution a yellowish semi-solid formed. This, on trituration (petroleum ether), gave a dull white powder. Recrystallization (anhydrous C_2H_5OH) gave 71 (0.24 g, 54%) as a white powder, mp 93-95°C. An analytical sample was obtained by repeated recrystallizations (anhydrous C_2H_5OH), mp 98-99°C. IR (KBr) ν_{max} 1725 (C=O), 1000-1300 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) δ 3.64 (3 H, s, $C\underline{H}_3$), 2.7-2.86 (2 H, t, $C\underline{H}_2$), 2.12-2.37 (2 H, t, $C\underline{H}_2$), 1.38-1.7 [8 H, m, $(C\underline{H}_2)_4$], 7.32-8.34 (9 H, m, Ar-$\underline{H}$); ^{13}C NMR: see Table II; UV (anhydrous C_2H_5OH) λ_{max} in nm 377 (ε 5031), 368 (ε 2201), 357 (ε 5786), 348 (ε 3459), 339 (ε 4402), 325 (ε 2956), 313 (ε 2201), 255 (ε 265000), 247 (ε 128750).

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55.

Found: C, 82.57; H, 7.62.

PLATE I



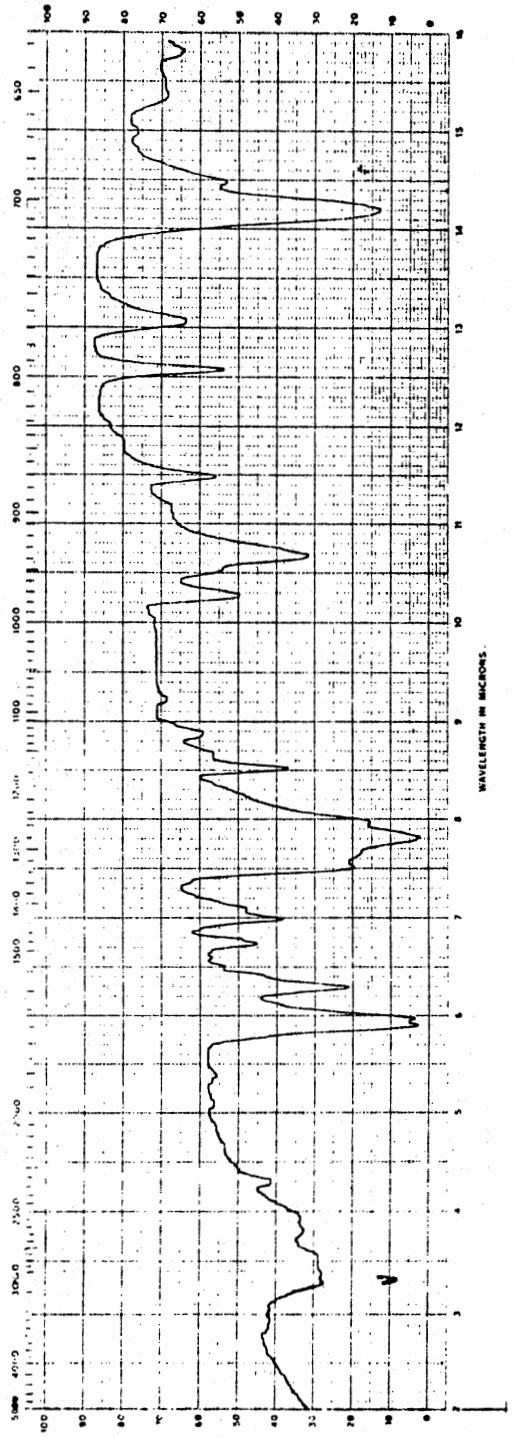
47

^{1}H NMR Spectrum of 47

CW X ; Solvent DMSO-d_6; SO. 86241 Hz; PW. 1000 Hz; T. 30°C; SA. 1.6;

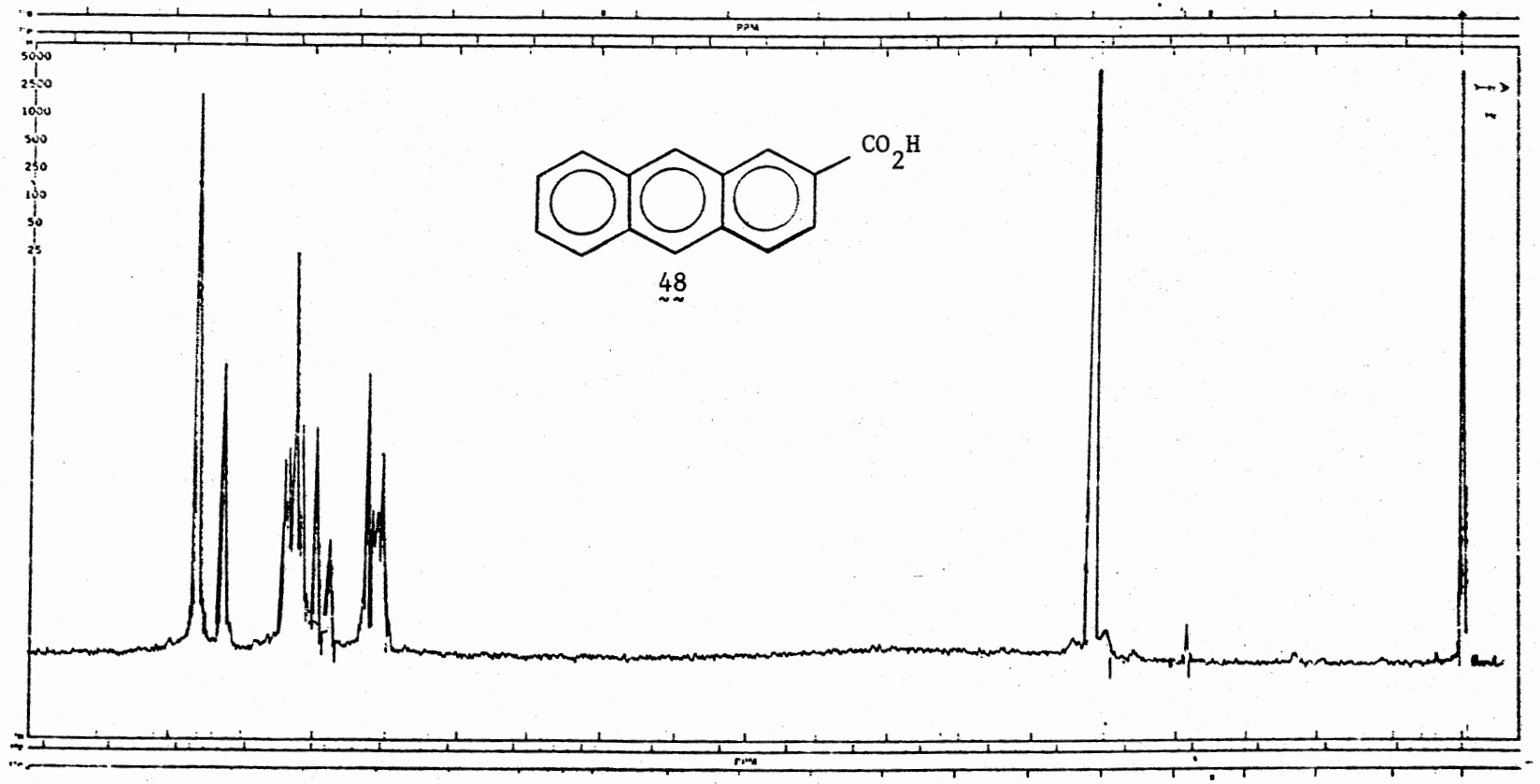
P2/RF. 69 µs/dB; SF. 100.1 MHz; FB. 2 Hz; Lock. ^{2}H ; ST. 250 s.

PLATE II



IR Spectrum of 47, KBr Pellet

PLATE III

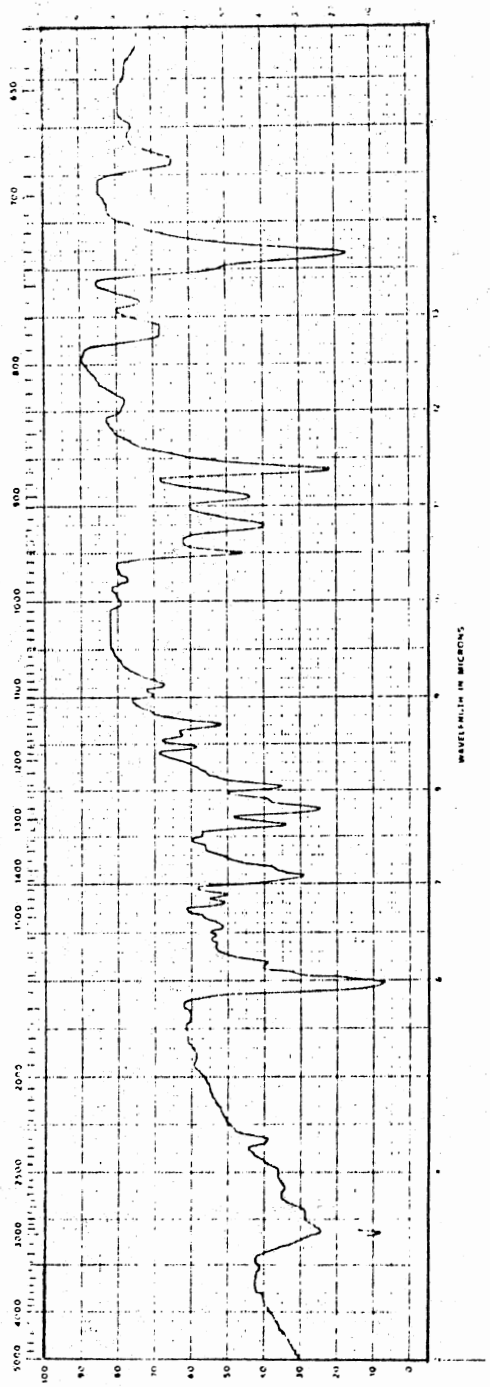


48

^1H NMR Spectrum of 48

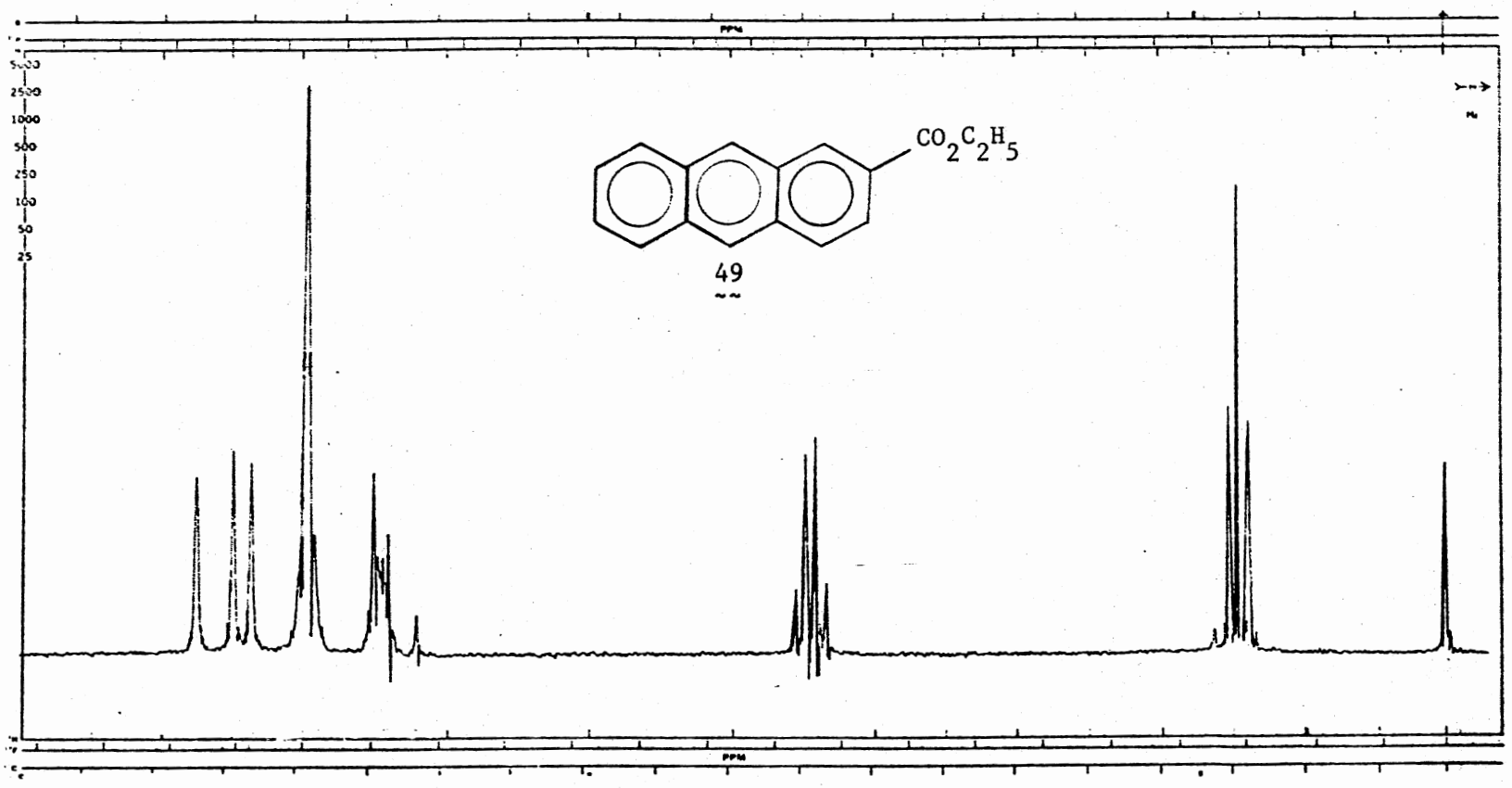
CW X ; Solvent DMSO-d_6 ; SO. 86244 Hz; PW. 1000 Hz; T 30°C; SA. 2.0;
P2/RF. 70 µs/dB ; SF. 100.1 MHz; FB. 2 Hz; Lock. ^2H; ST. 250 s.

PLATE IV



IR Spectrum of 48, KBr Pellet

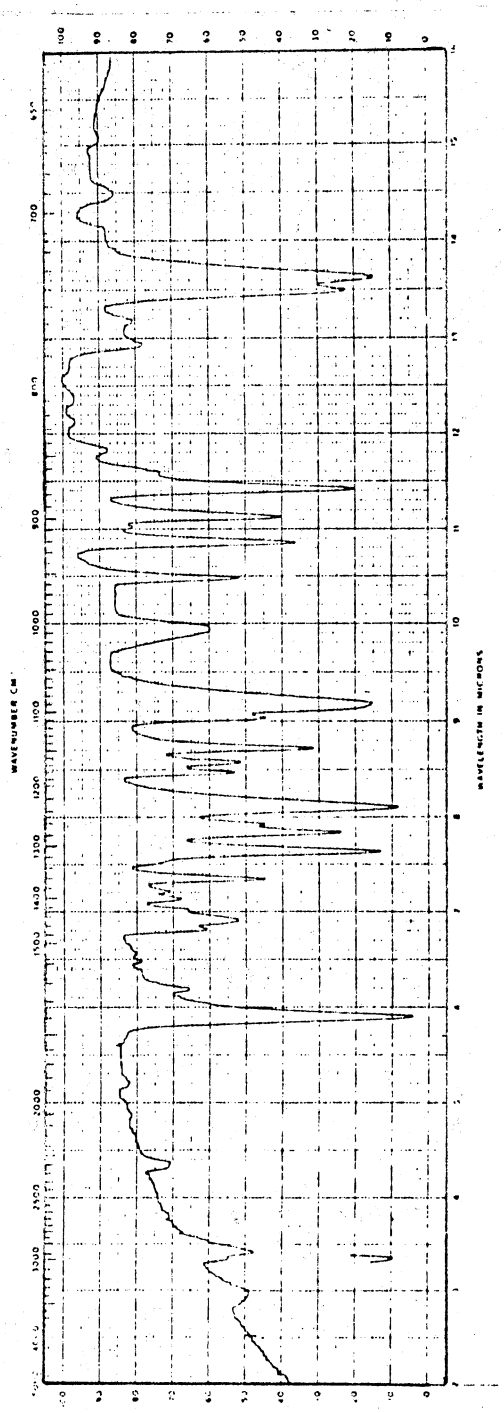
PLATE V



^1H NMR Spectrum of 49

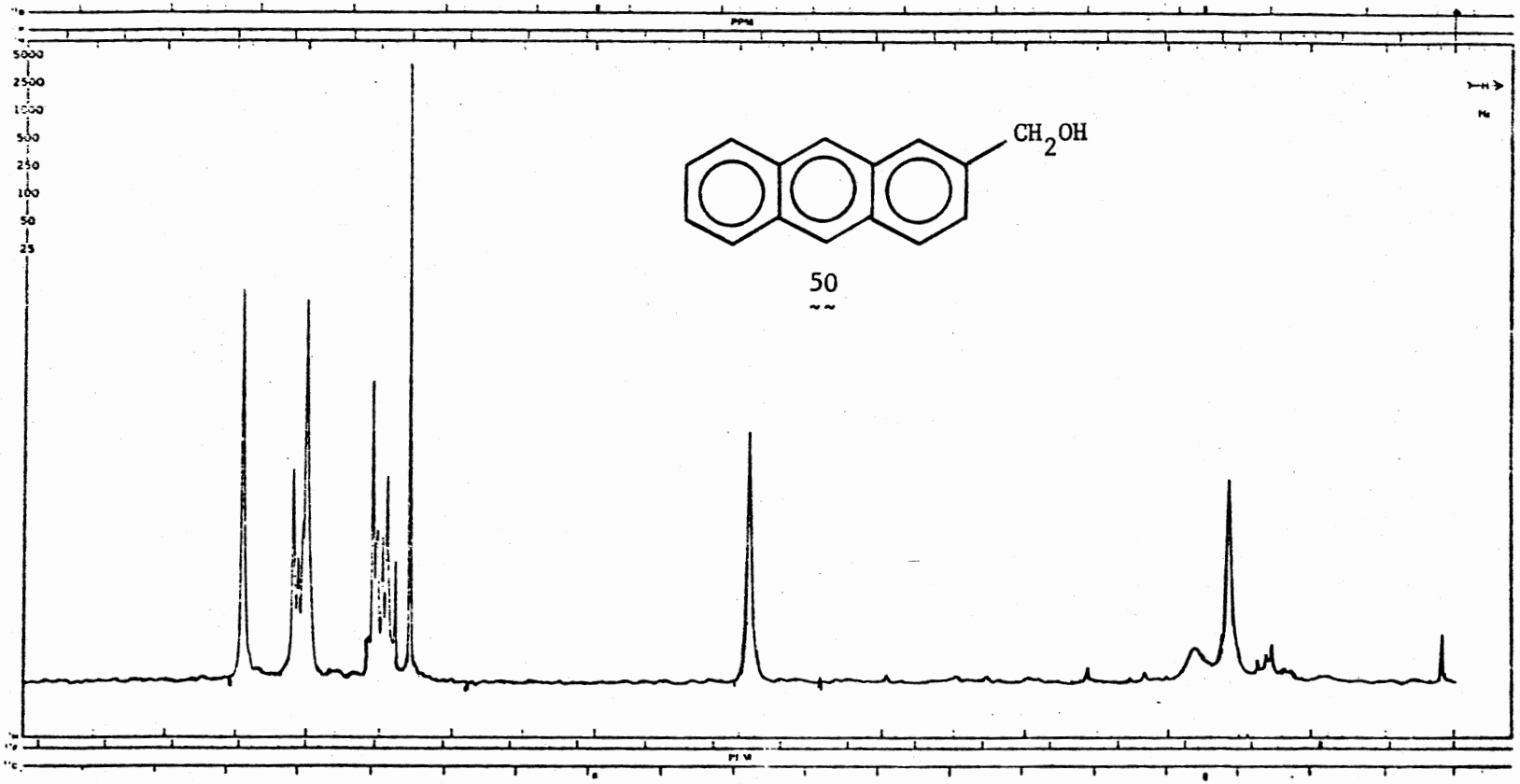
CW X ; Solvent $DCCl_3$; SO. 85771 Hz; PW. 1000 Hz; T. 30°C; SA. 1.0;
P2/RF. 65 µs/dB; SF 100.1 MHz; FB. 2 Hz; Lock. ^2H; ST. 250 s.

PLATE VI



IR Spectrum of 49, KBr pellet

PLATE VII



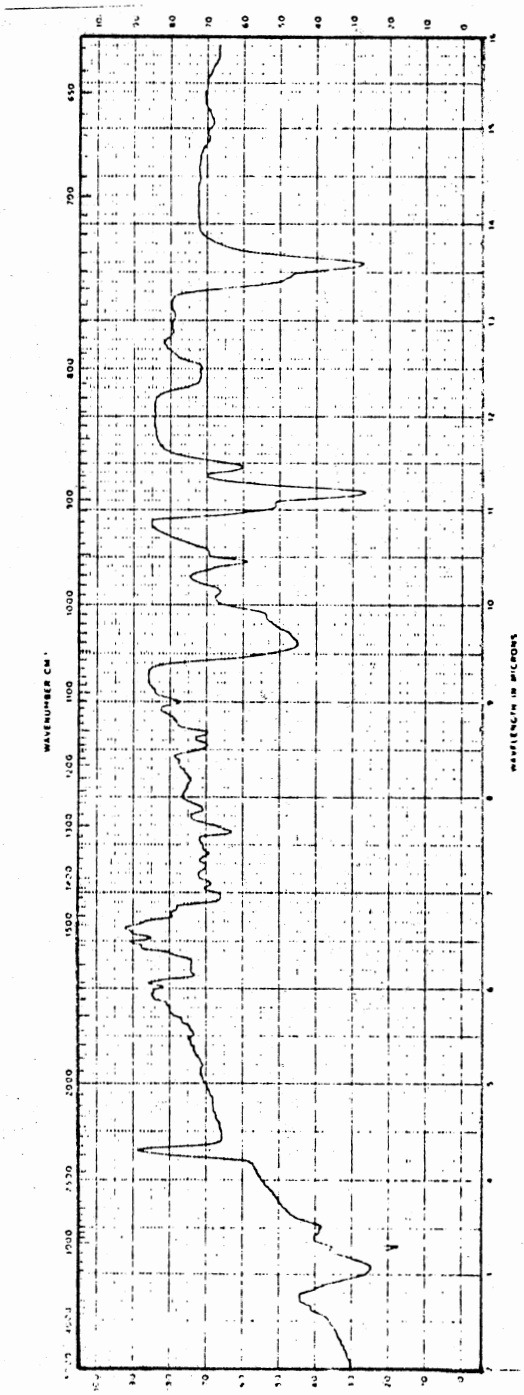
50

^{1}H NMR Spectrum of 50

PFT X ; Solvent $DCCl_3$; SO. 45251 Hz; PW. 1000 Hz; T. 30°C; Acq. 200;

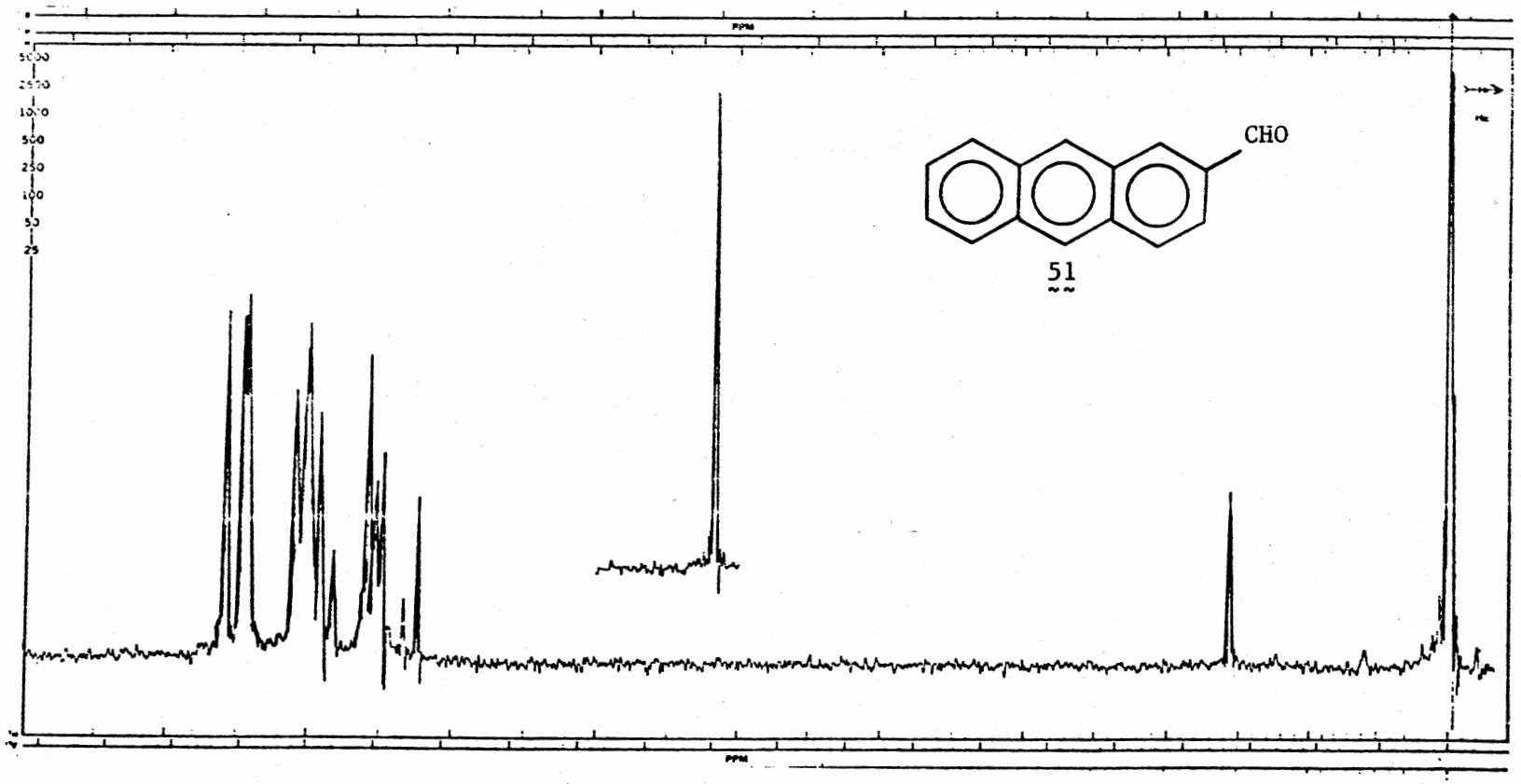
Size 8 K; P2/RF. 5.2 µs/dB; SF. 100.1 MHz; Lock ^{2}H.

PLATE VIII



IR Spectrum of 50, KBr Pellet

PLATE IX



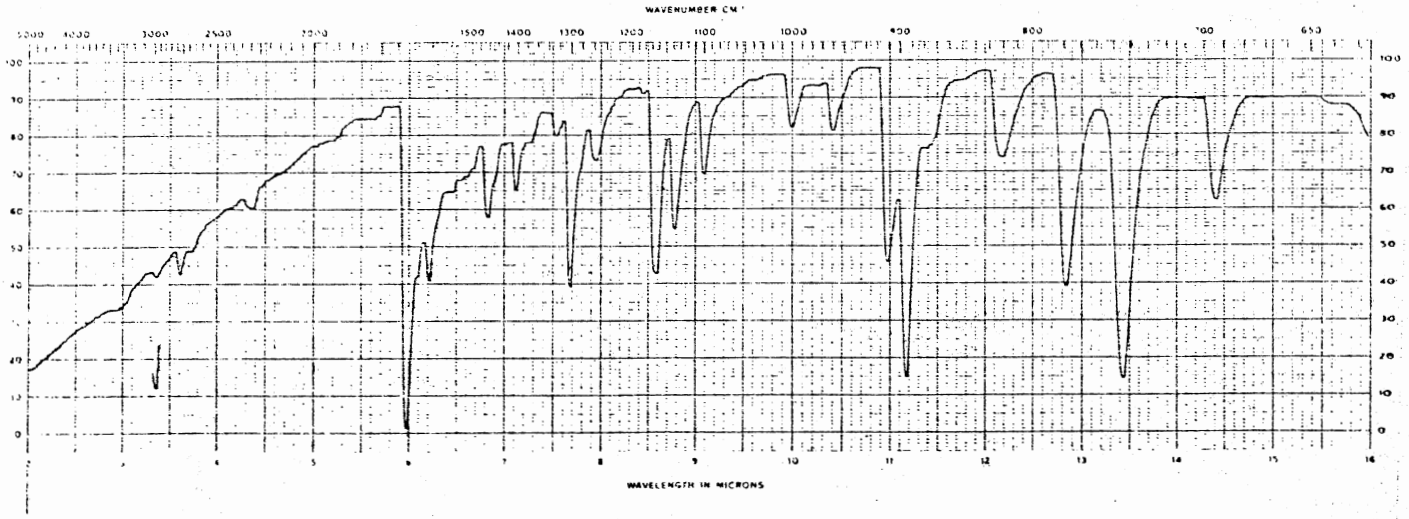
51

^{1}H NMR Spectrum of 51

CW X; Solvent $DCCl_3$; SO 85771 Hz; PW. 1000 Hz: T. 30°C; SA. 4.0;

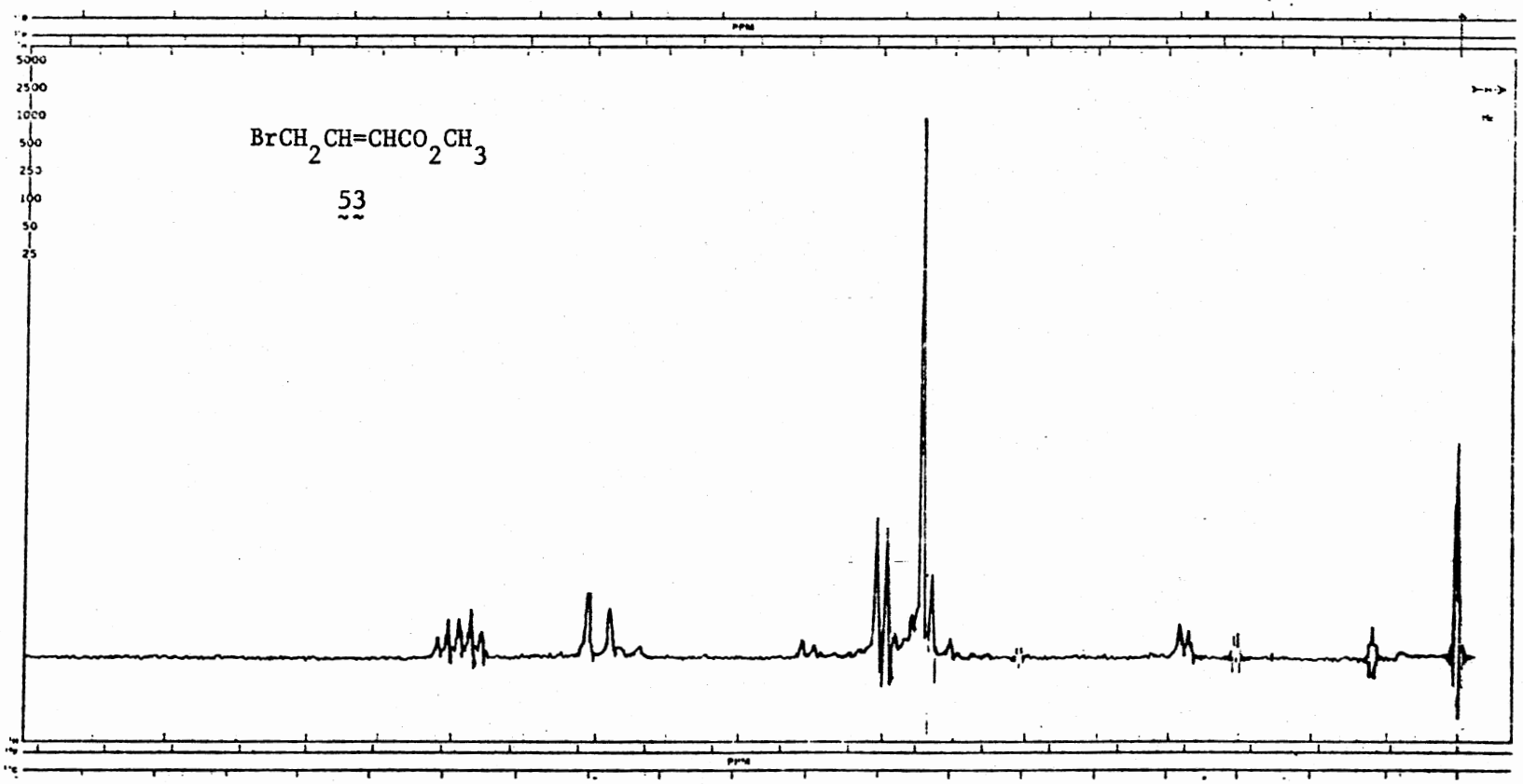
P2/RF 74 µs/dB; SF. 100.1 MHz; FB. 2 Hz; Lock ^{2}H; ST. 250 s.

PLATE X



IR Spectrum of 51, KBr Pellet

PLATE XI

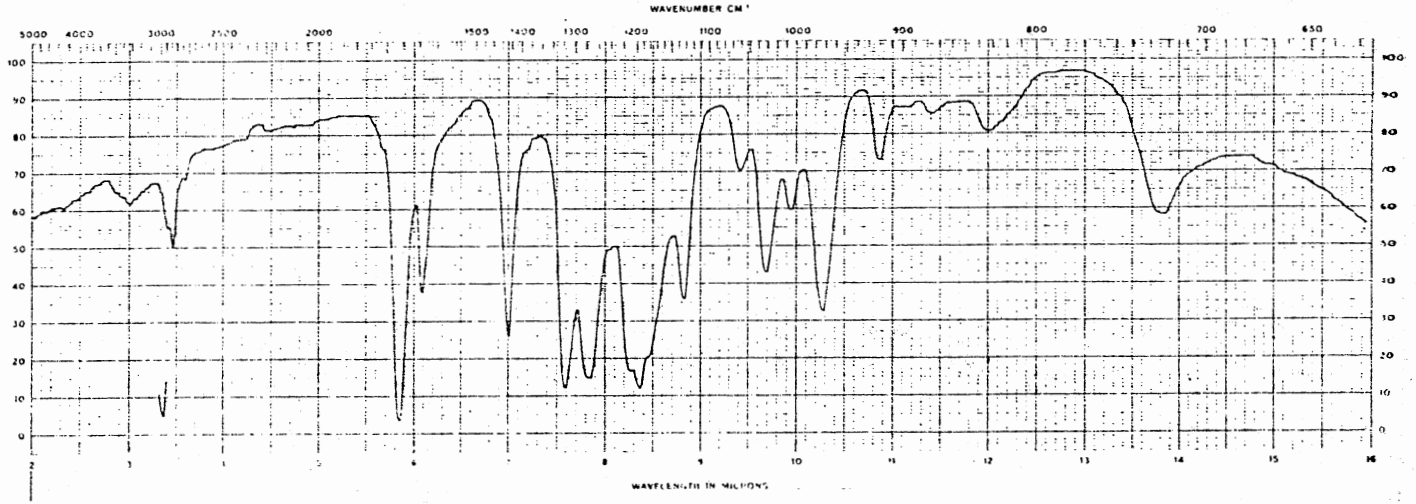


^1H NMR Spectrum of 53 (slightly impure)

CW X; Solvent CCl_4; So. 83701 Hz; PW. 1000 Hz; T. 30°C; SA. 1.25;

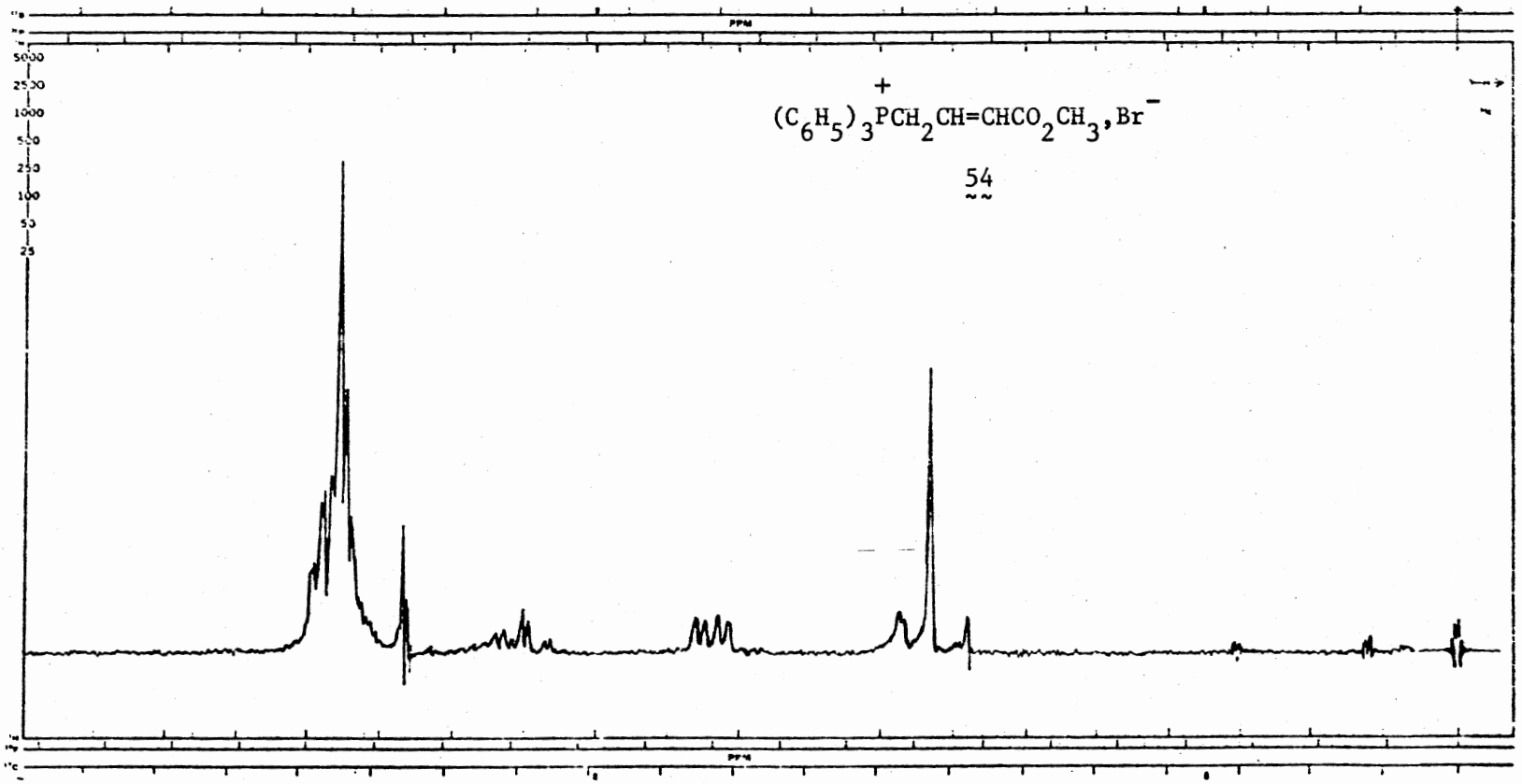
P2/RF 50 µs/dB; SF. 100.1 MHz; FB. 2 Hz; ST. 250 s.

PLATE XII



IR Spectrum of 53, Neat Liquid

PLATE XIII

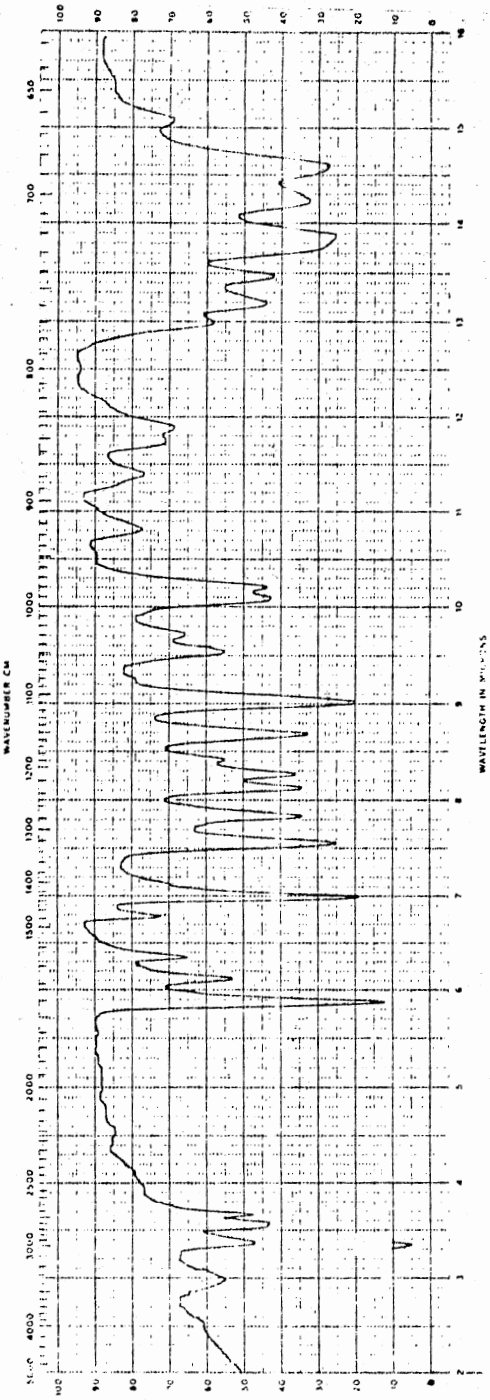


^1H NMR Spectrum of 54

CW X; Solvent $DCCl_3$; So. 83701 Hz; PW. 1000 Hz; T. 30°C; Sa 1.6;

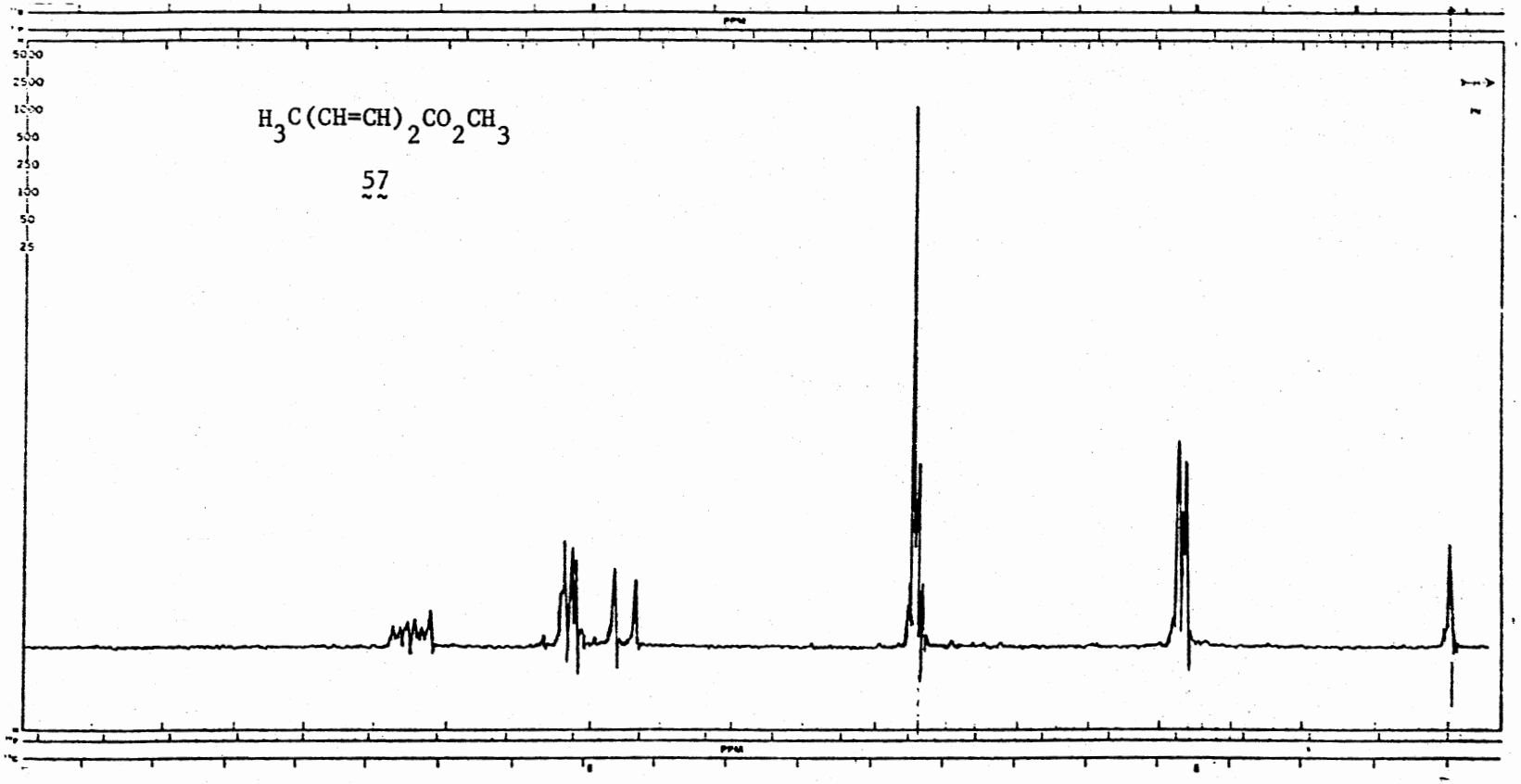
P2/RF 62 µs/dB ; SF 101.1 MHz; FB. 2 Hz; Lock. ^2H; ST. 250 s.

PLATE XIV



IR Spectrum of 54, KBr Pellet

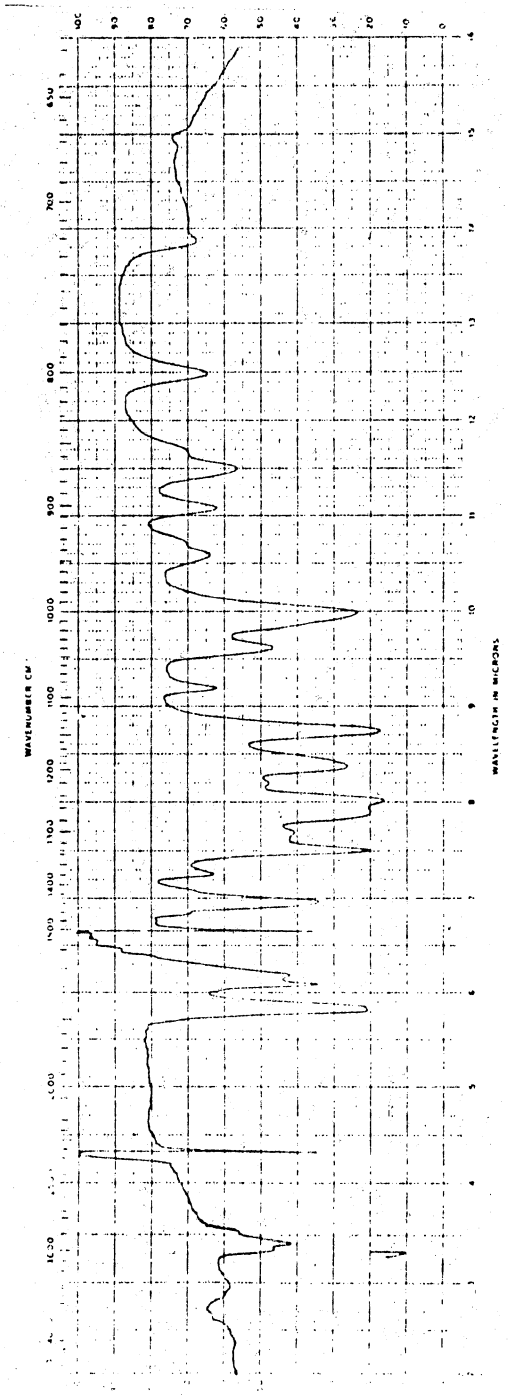
PLATE XV



^1H NMR Spectrum of 57

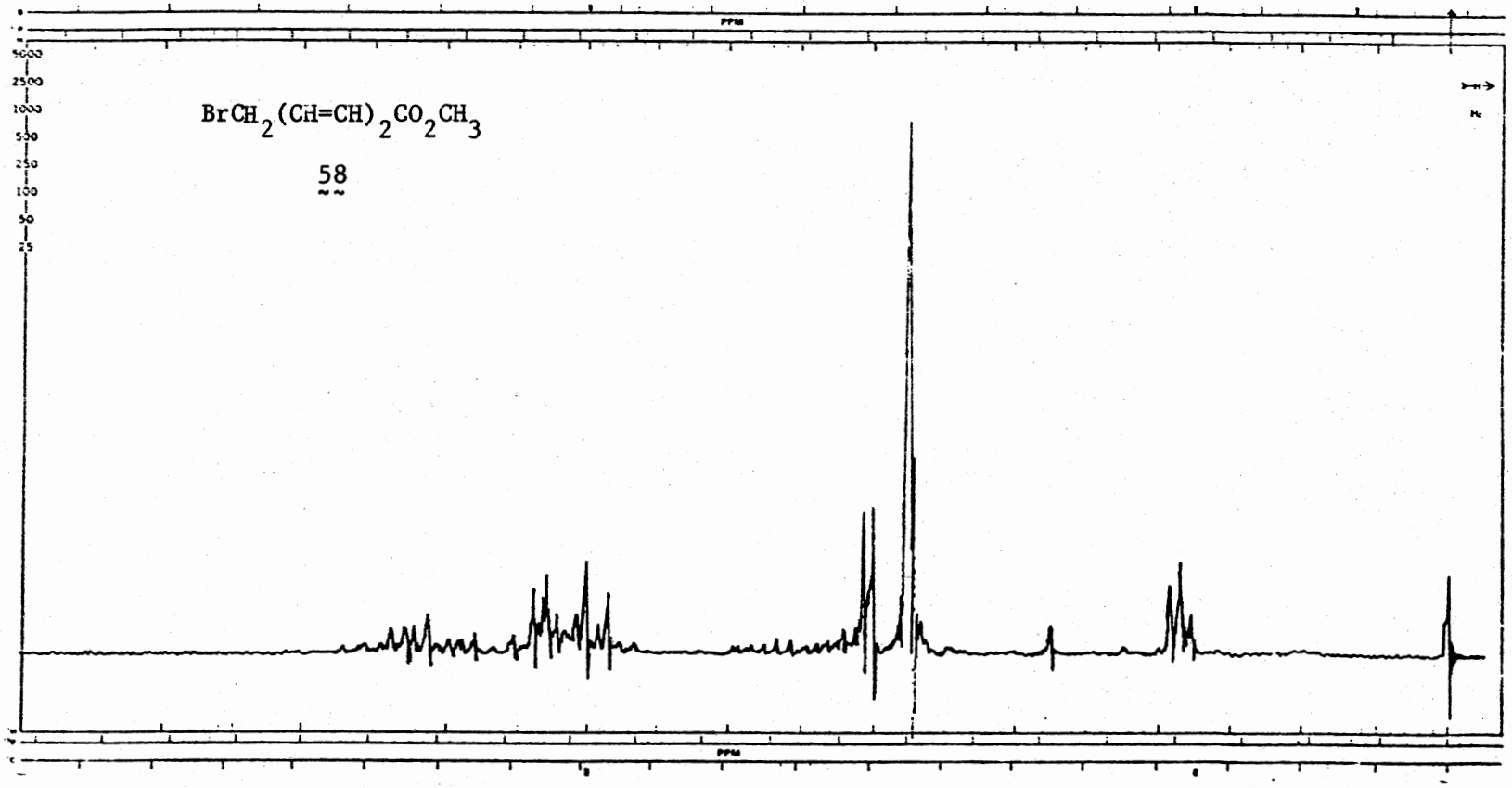
CW X; Solvent $DCCl_3$; SO 85771 Hz; PW. 1000 Hz; T. 30°C; SA 1.0;
P2/RF 51 µs/dB; SF. 100.1 MHz; FB. 2 Hz; Lock ^2H; St. 250 s.

PLATE XVI



IR Spectrum of 57, Neat Liquid

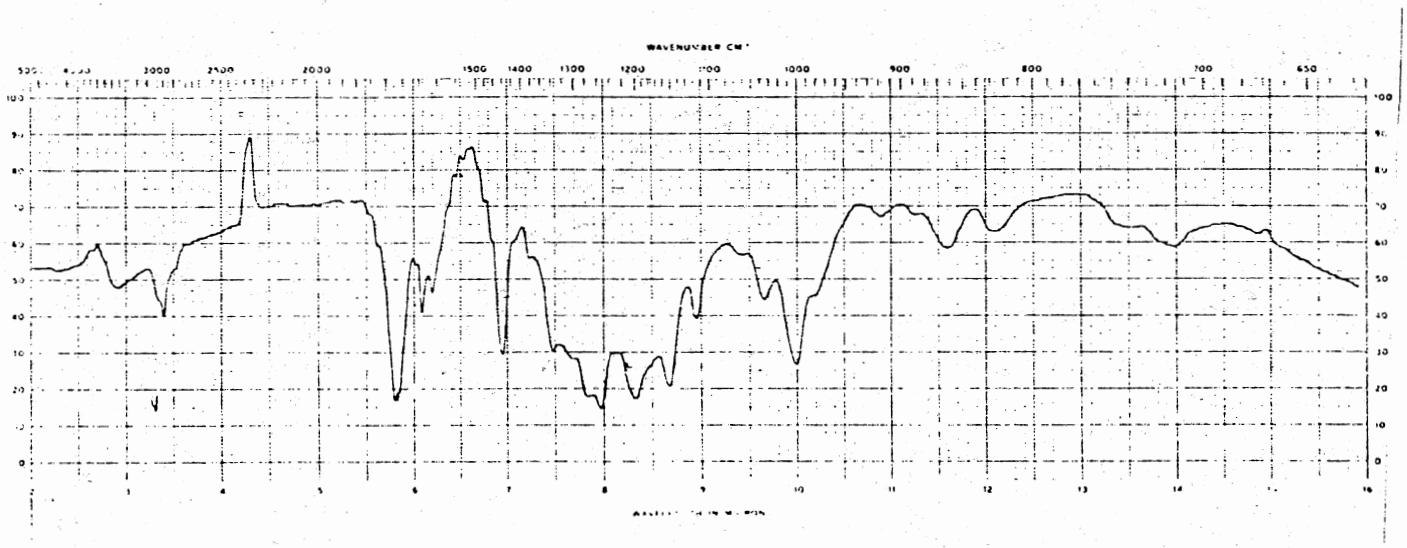
PLATE XVII



^1H NMR Spectrum of 58

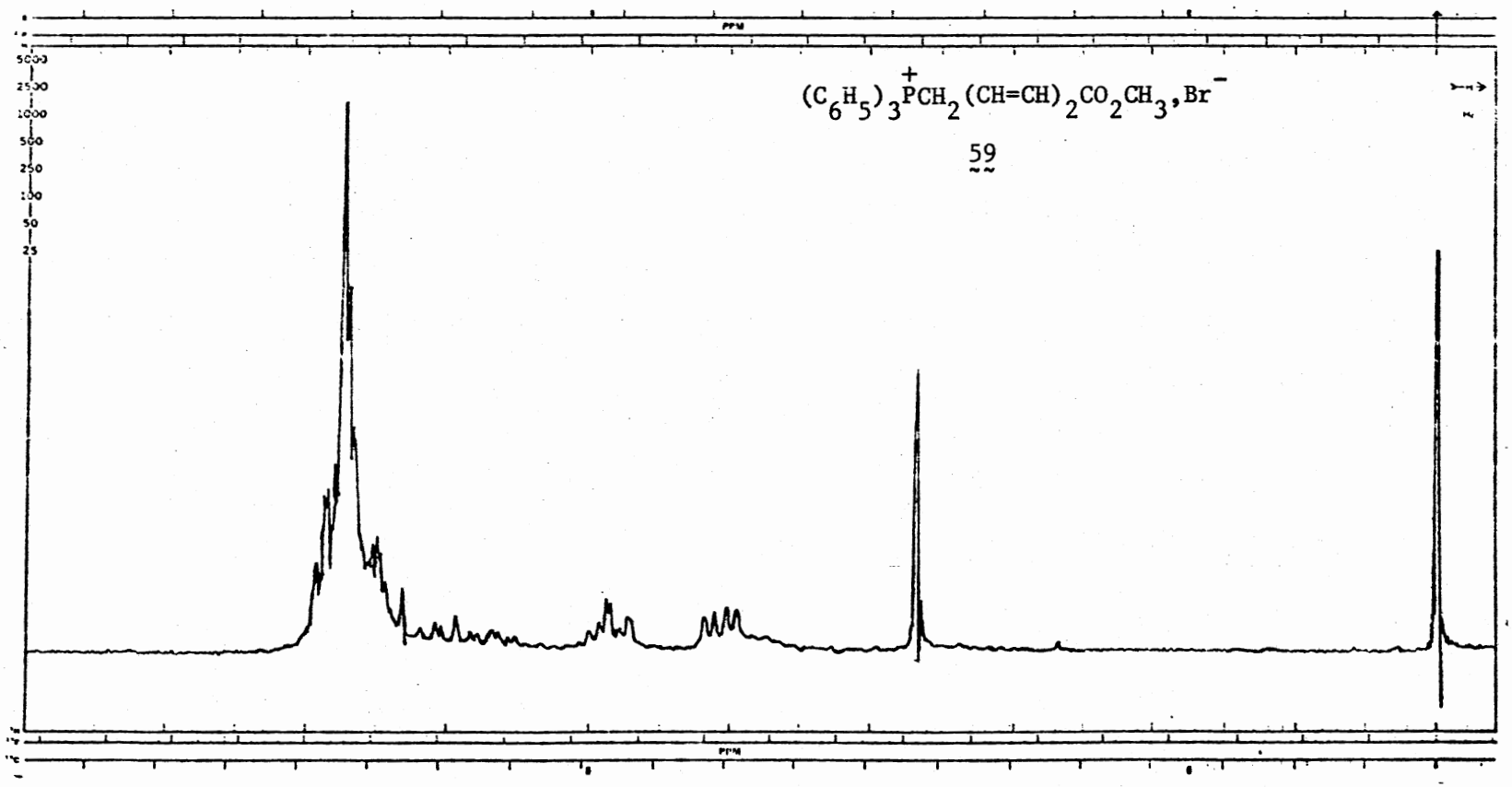
CW X; Solvent $DCCl_3$; SO 85771 Hz; PW. 1000 Hz; T. 30°C; sa 1.0;
P2/RF 52 µs/dB; SF. 100.1 MHz; FB. 2 Hz; Lock ^2H; St. 250 s.

PLATE XVIII



IR Spectrum of 58, Neat Liquid

PLATE XIX

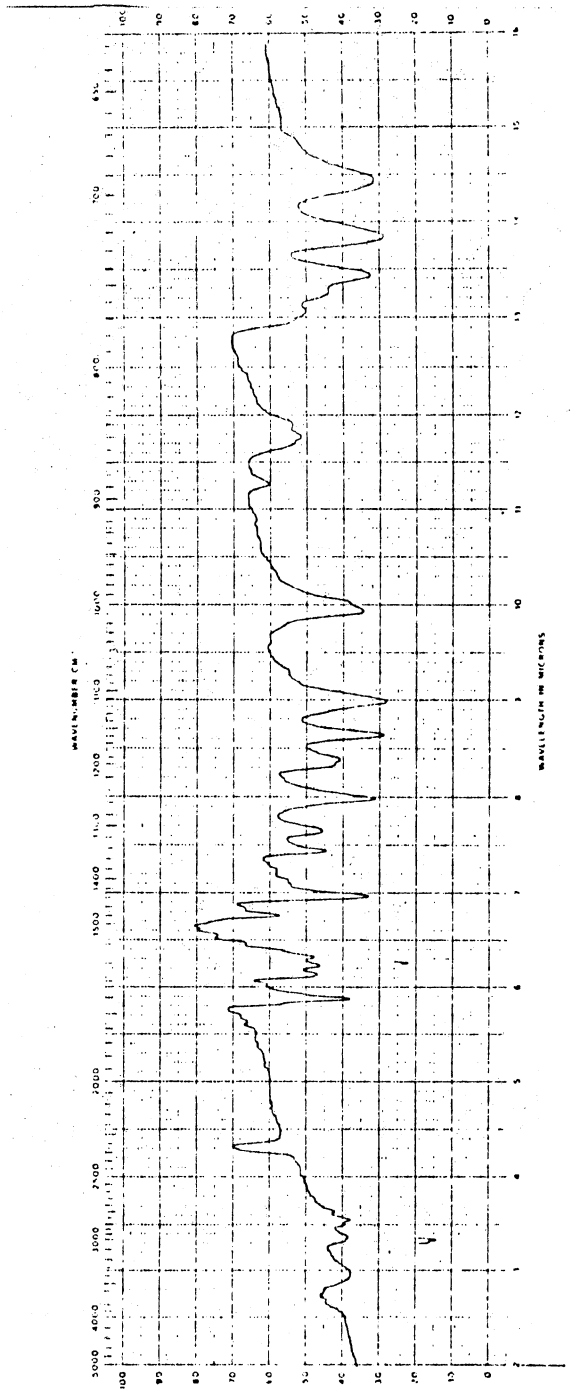


^1H NMR Spectrum of 59

CW X; Solvent $DCCl_3$; SO. 85771 Hz; PW. 1000 Hz; T. 30°C; SA 1.0;

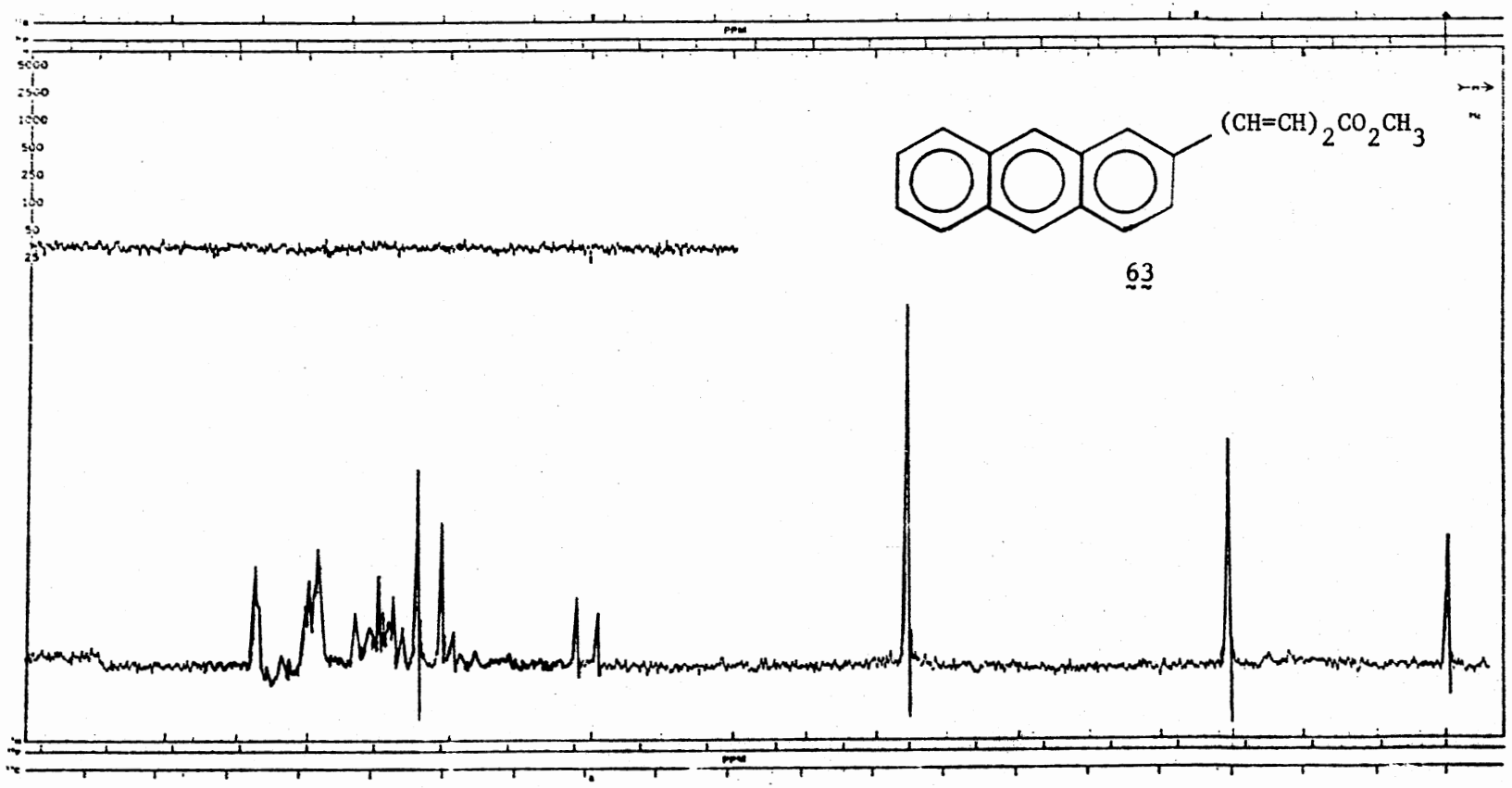
P2/RF 69 µs/dB; Sf. 100.1 Mhz; FB. 2 Hz; Lock ^2H; ST. 250 s.

PLATE XX



IR Spectrum of 59, KBr Pellet

PLATE XXI

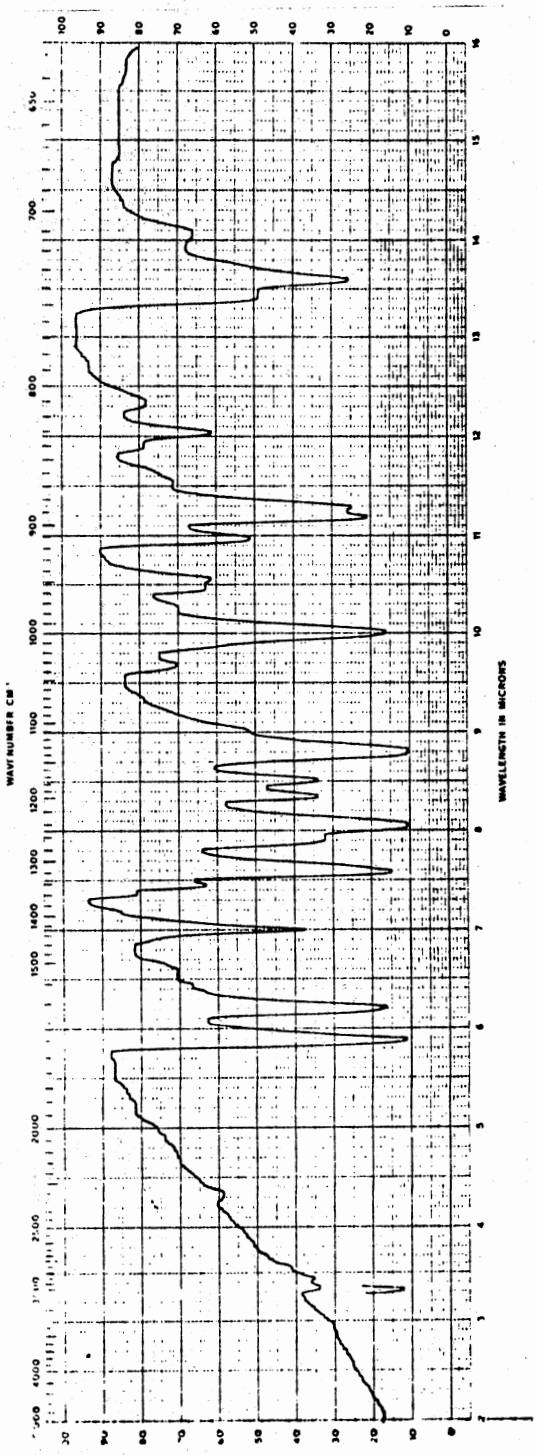


63

^{1}H NMR Spectrum of 63

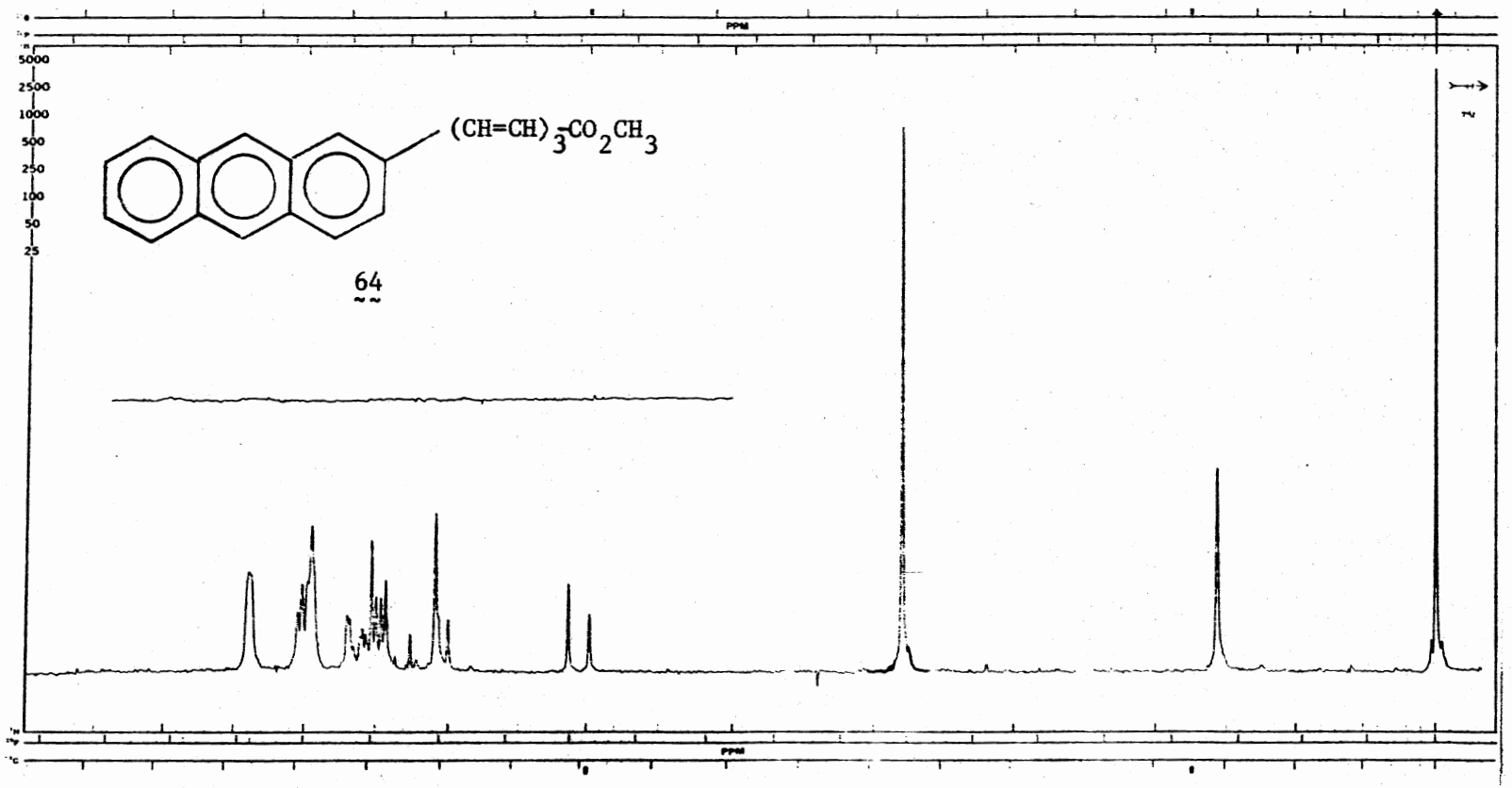
CW X; Solvent $DCCl_3$; SO. 86771 Hz; PW. 1000 Hz; T. 30°C; SA 1.0;
P2/RF 73 µs/dB; SF 100.1 MHz; FB 2 Hz; Lock ^{2}H; ST. 250 s.

PLATE XXII



IR Spectrum of 63, KBr Pellet

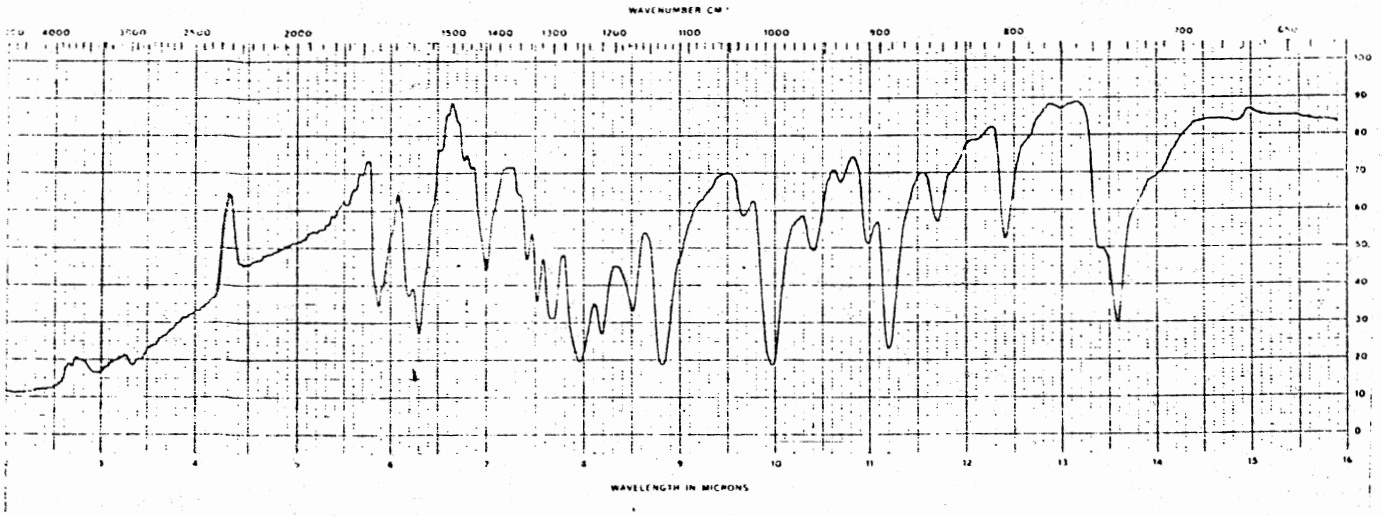
PLATE XXIII



^{1}HNMR Spectrum of 64

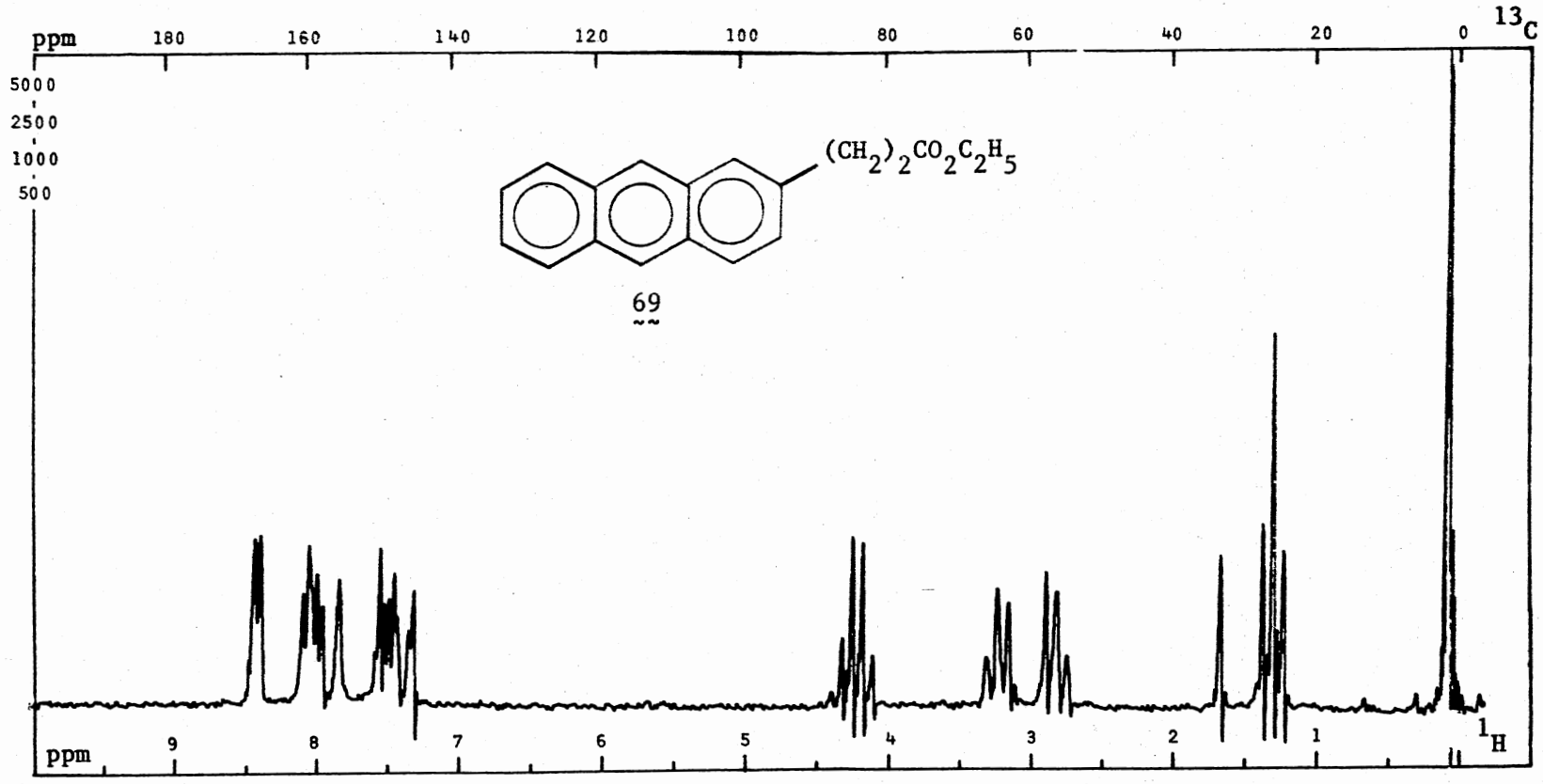
PFT X; Solvent $DCCl_3$; SO. 45251 Hz; PW. 1000 Hz; T. 30°C; SA 100;
P2/RF 5 µs/dB ; SF. 100.1 MHz; FB. 1K Hz; Lock. ^{2}H; ST. 1 s.

PLATE XXIV



IR Spectrum of 64, KBr Pellet

PLATE XXV

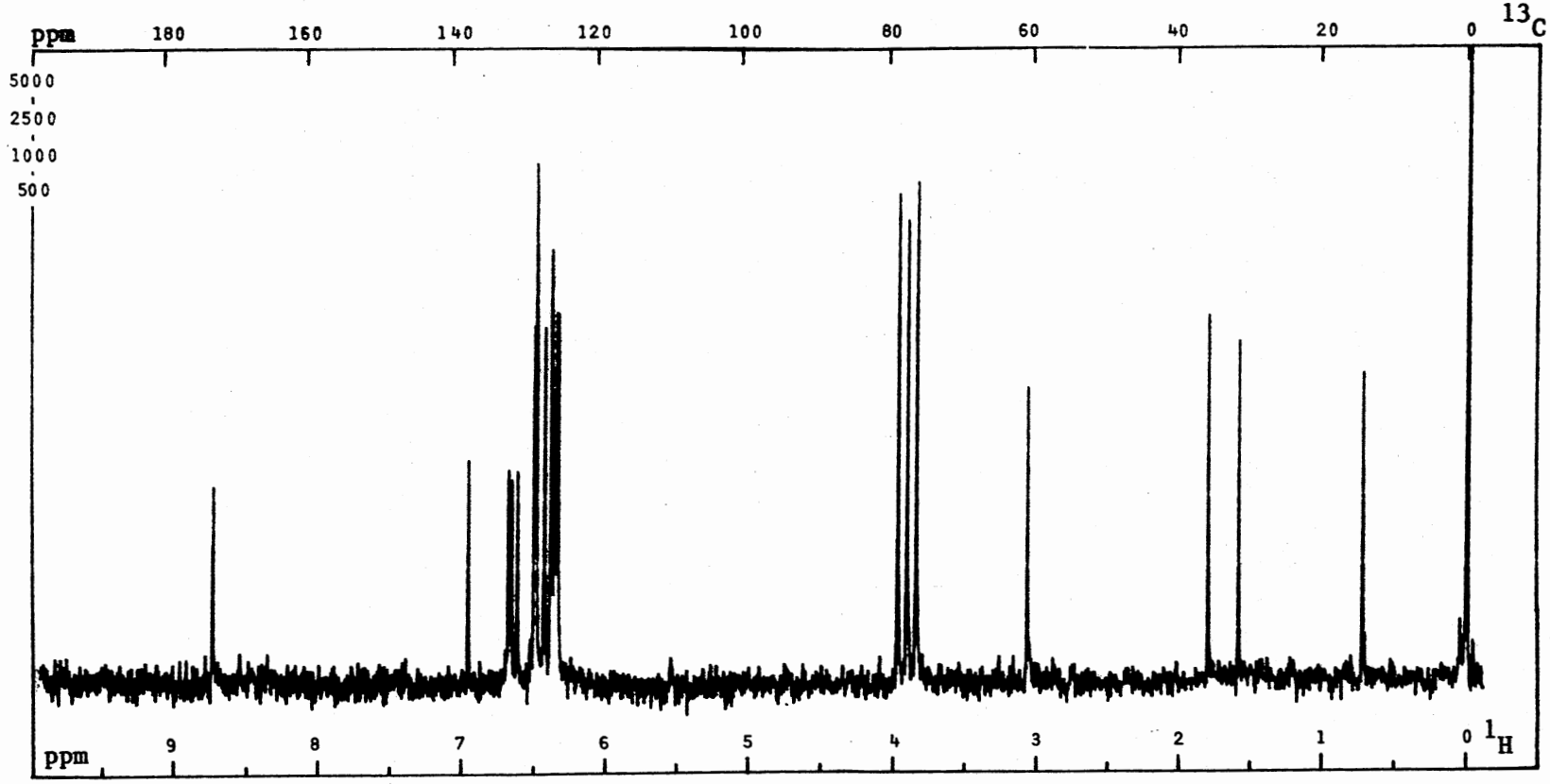


^{1}H NMR Spectrum of 69

CW X; Solvent $DCCl_3$; SO. 85771 Hz; PW. 1000 Hz; T. 30°C; SA. 2.0;

P2/RF 7 µs/dB ; SF 100.1 MHz; FB. 2 Hz; Lock. ^{2}H; ST. 250 s.

PLATE XXVI

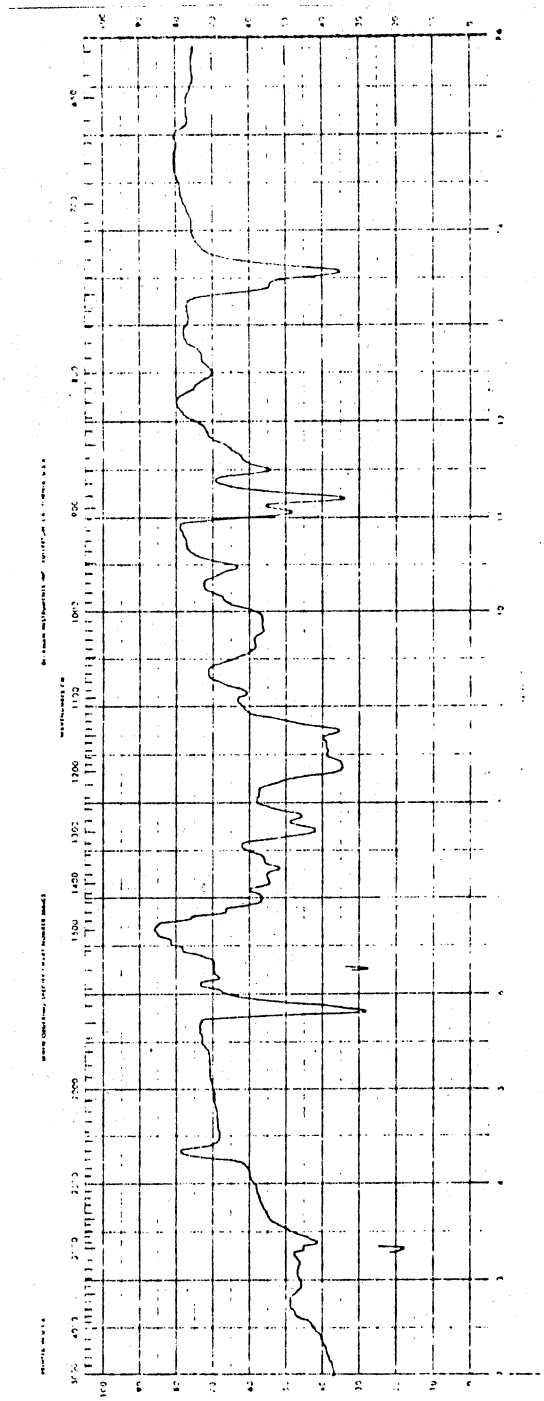


^{13}C NMR Spectrum of 69

PFT X; Solvent $DCCl_3$; SO 35101 Hz; PW. 5000 Hz; T. 30°C; Acq. 8500;

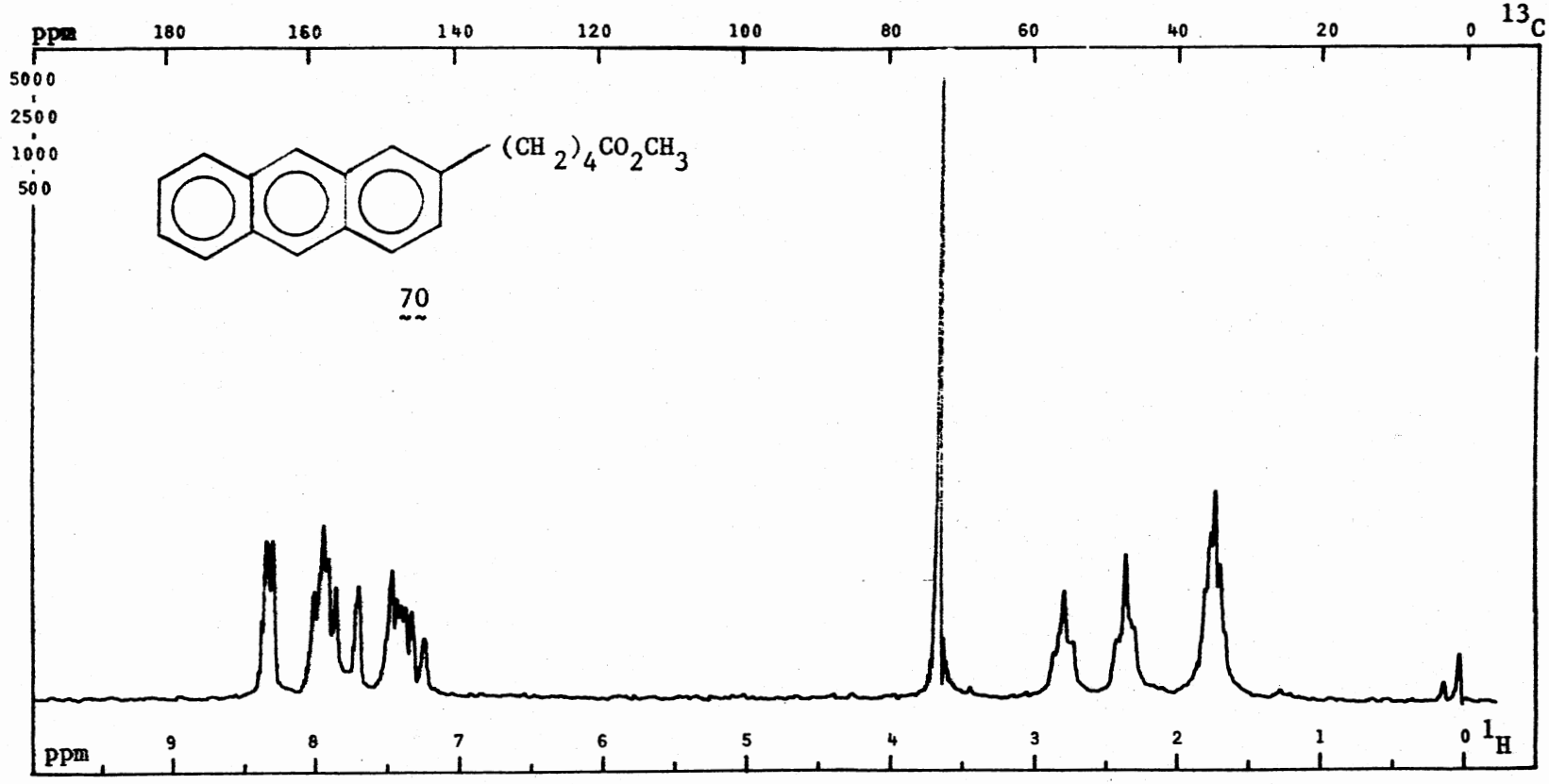
Size 8 K; P2/RF 10 µs/dB; SF 25.0 Mhz; FB 2 Hz; Lock. ^2H; D5 1.3 s.

PLATE XXVII



IR Spectrum of 69, KBr Pellet

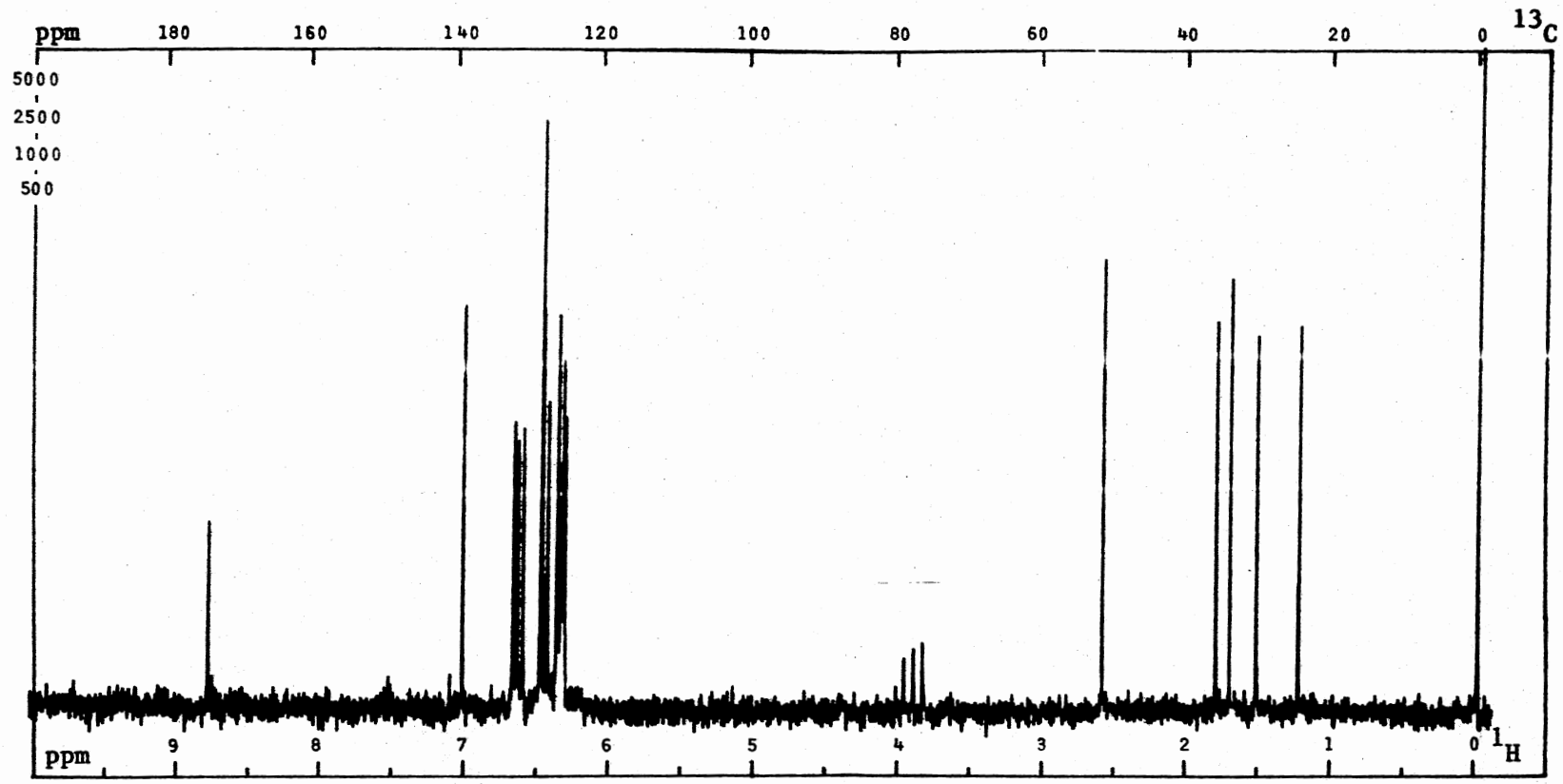
PLATE XXVIII



^{1}H NMR Spectrum of 70

CW X; Solvent $DCCl_3$; SO. 85771 Hz; PW. 1000 Hz; T. 30°C; SA. 1.6;
P2/RF 69 µs/dB ; SF. 100.1 MHz; FB. 2 Hz; Lock. ^{2}H; ST. 250 s.

PLATE XXIX

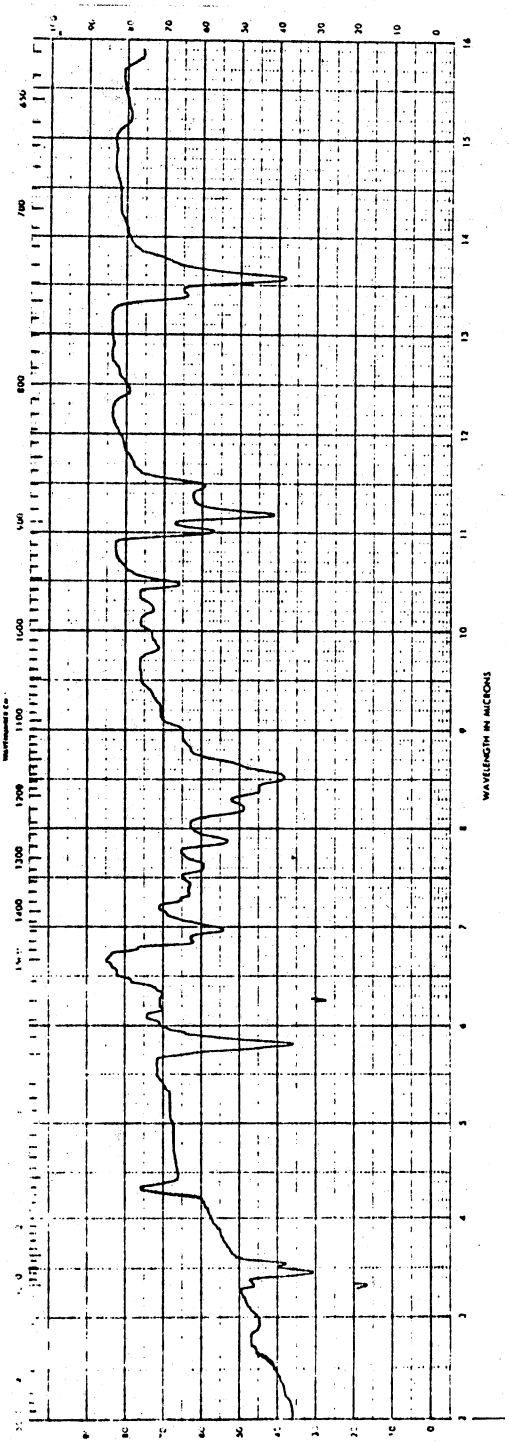


^{13}C NMR Spectrum of 70

PFT X; Solvent $DCCl_3$; SO. 35101 Hz; PW. 5000 Hz; T. 30°C; acq/SA. 700;

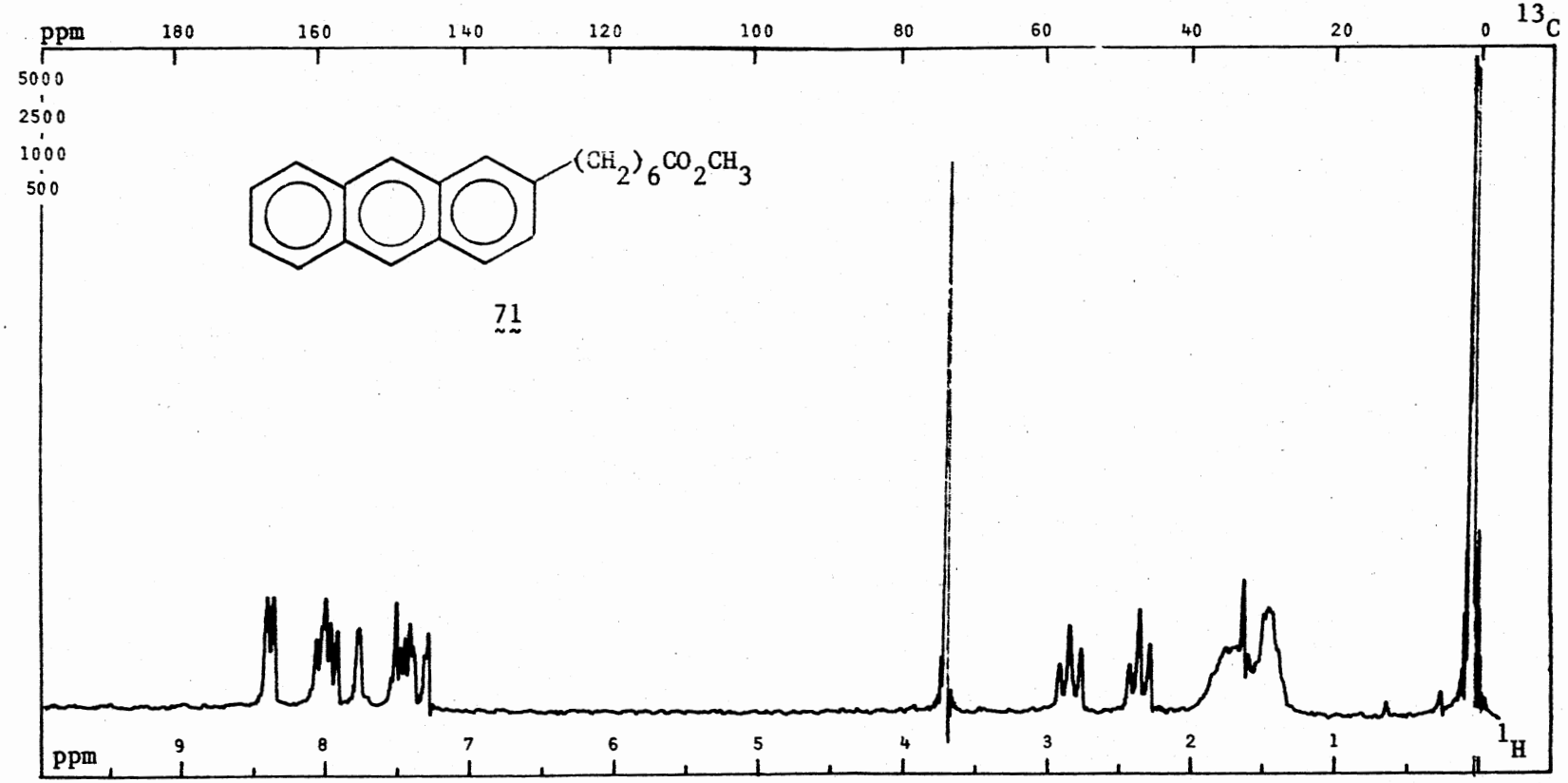
Size 8 K; P2/RF 19 µs/dB; SF. 25.2 MHz; FB. 3K Hz; Lock. ^{2}H; D5 34.5 s.

PLATE XXX



IR Spectrum of 70, KBr Pellet

PLATE XXXI

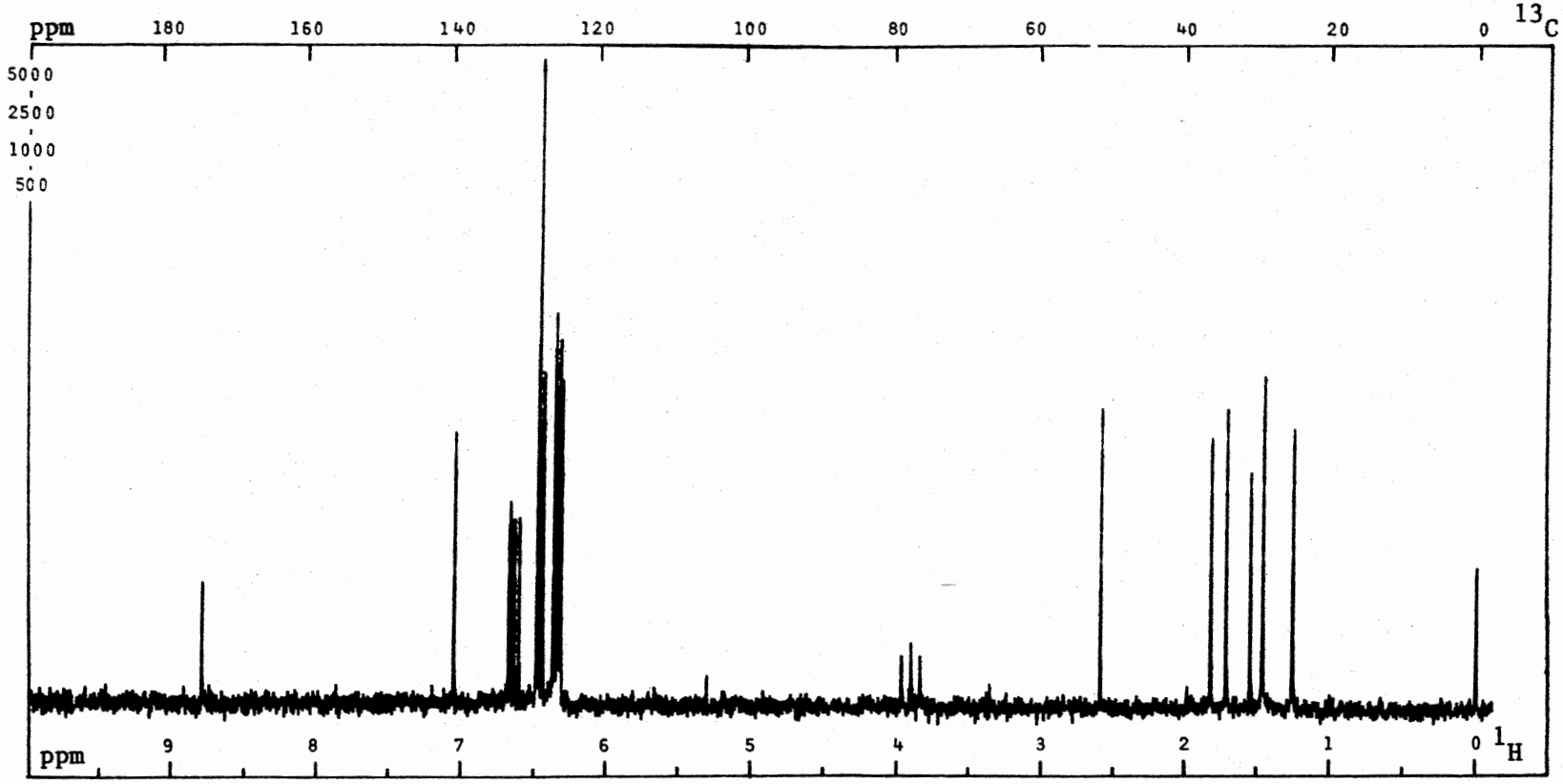


^{1}H NMR Spectrum of 71

CW X; Solvent $DCCl_3$; SO. 85771 Hz; PW. 1000 Hz; T. 30°C; SA. 1.6;

P2/RF. 69 µs/dB ; SF 100.1 MHz; FB. 2 Hz; Lock. ^{2}H; ST. 250 s.

PLATE XXXII

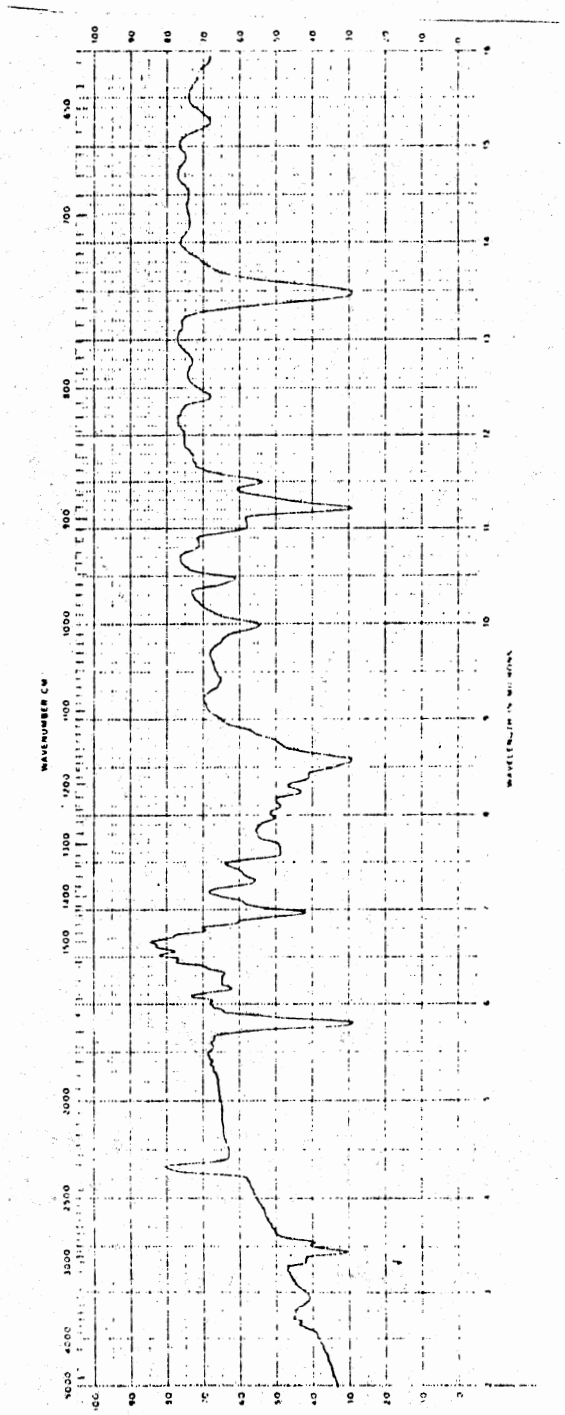


^{13}C NMR Spectrum of 71

PFT X; Solvent $DCCl_3$; SO. 35101 Hz; PW. 5000 Hz; T. 30°C; Acq. 900;

Size 8 K; P2/Rf 10 µs/dB; SF. 25.2 MHz; FB. 3K Hz; Lock. ^{2}H; D5 5 s.

PLATE XXXIII



IR Spectrum of 71, KBr Pellet

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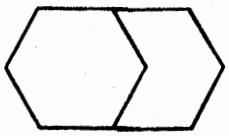
PART II. SYNTHESES AND A CONFORMATIONAL STUDY OF CERTAIN SELECTED 3-OXA-7-AZABICYCLO-[3.3.1]NONAN-9-ONES (OR 3-OXA-7-AZABISPIDINONES)

CHAPTER I

HISTORICAL

The bicyclo[3.3.1]nonane ring system 1 has been known for about



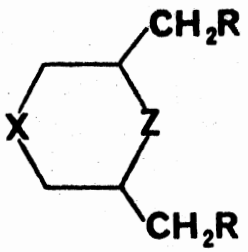
1

seventy years and the chemistry of bicyclo[3.3.1]nonanes has received much attention from synthetic and theoretical points of view.[13,60,88] Heteroanalogs of the above bicyclic system are of novel interest because the heteroatoms not only modify the physical properties or chemical behaviour of the system but also provide some interesting and unique conformational features. Moreover, many heteroanalogs of 1 occur in the skeleton of natural alkaloids and possess potential biological activity.[90]

Various synthetic approaches to bicyclo[3.3.1]nonanes have been discussed in recent reviews.[13,60] Chiavarelly and co-authors[15] published a review on 3,7-diaza-derivatives covering the literature up to 1968. There is also another excellent and general review on the syntheses of heteroanalogs of 1 in 1973.[90]

One of the most common procedures to synthesize heteroanalogs of 1 involves the cyclization of 1,3-disubstituted 4-heteracyclohexanones such as 2-6 to give 7-11. Treatment of the bisiodide 2 with silver

oxide produced the oxabicyclononane 7.[77] Dehydration of the diol 3



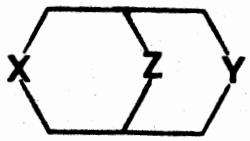
2 X = Z = O; R = I

3 X = Z = CH_2; R = OH

4 X = Z = CH_2; R = $O_3SC_6H_4CH_3$-p

5 X = CH_2; Z = O; R = OH

6 X = Z = O; R = HgCl



7 X = Y = Z = O

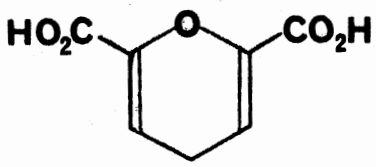
8 X = Z = CH_2; Y = O

9 X = Z = CH_2; Y = NC_2H_4OH

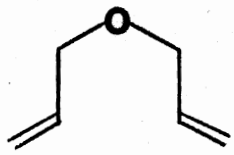
10 X = Y = CH_2; Z = O

11 X = Z = O; Y = S

readily gave the 3-oxabispidine 8.[87] Interaction of the bistosylate 4 with ethanolamine yielded the 3-azabispidine 9.[51] The diol 5 was obtained from the dicarboxylic acid 12 in several steps. Tosylation of 5,



12

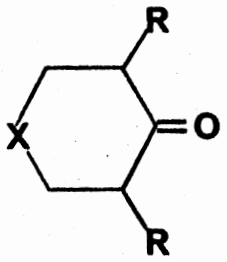


13

followed by treatment with sodiomalonic ester produced the oxabispidine 10.[17] The bisiodide 3 was prepared (via a chloromercury derivative 6) from the bisallyl ether 13 and was then condensed with sodium sulfide to produce the 3,9-dioxa-7-thiabispidine 11.[78,79]

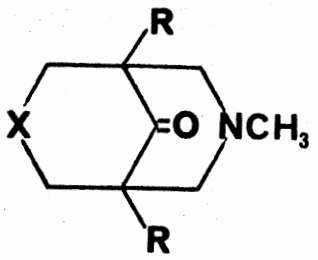
Bicyclo[3.3.1]nonan-9-ones (bispidinones) and various heteroanalogs have been synthesized using Mannich type cyclocondensations starting from ketones like 14 and 15. With cyclohexanone 14, the reaction led to the bicyclic ketone 16.[8,36,37,65,73] The ethoxy carbonyl groups in the amino ketone 16 were readily removed by acid hydrolysis.[8,36] The

precursor diethoxycarbonylcyclohexanones had been obtained from β-dicarbonyl compounds or from diethyl 1,3-acetonedicarboxylate.[72] Inter-



14 X = CH_2; R = $CO_2C_2H_5$

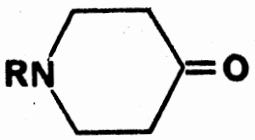
15 X = NH; R = H



16 X = CH_2; R = $CO_2C_2H_5$

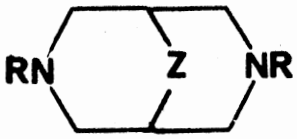
17 X = NH; R = H

action of piperidone 15 with formaldehyde and ammonium acetate resulted in the formation of bispidinones 17.[15,31] Piperidones 18 and 19 also condensed in a Mannich type reaction to give bispidinones 20 (which was



18 R = CH_3

19 R = $CH_2C_6H_5$



20 R = CH_3; Z = C=O

21 R = CH_3; Z = CH_2

22 R = $CH_2C_6H_5$; Z = C=O

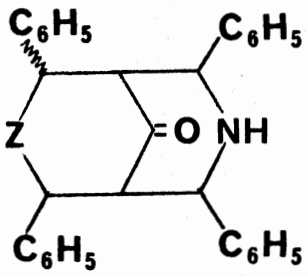
23 R = $CH_2C_6H_5$; Z = CH_2

24 R = H; Z = CH_2

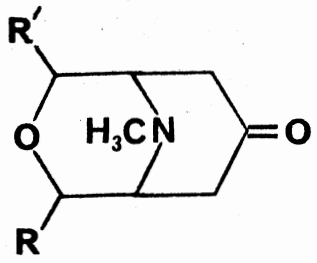
then reduced under modified Wolff-Kishner conditions to obtain the bispidine 21)[22] and 22, respectively. Reduction (Wolff-Kishner) of 22 gave 23 which was then catalytically debenzylated to yield the bispidine 24.[69,74]

Baliah and co-workers[5] pioneered the syntheses of various substituted bicyclic ketones 25 using Mannich type cyclocondensations. Conden-

sation of the appropriate 4-heteracyclohexanones with different aromatic aldehydes and ammonium acetate gave the corresponding bicyclic ketones but conditions were critical for maximum yields. Various substituted 3-oxabispidinones 26 were synthesized from the corresponding 2,4-dialkyl-3-oxaglutaraldehydes.[54]

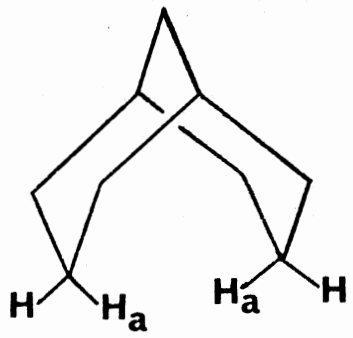


25 Z = CH_2, NH, S, O

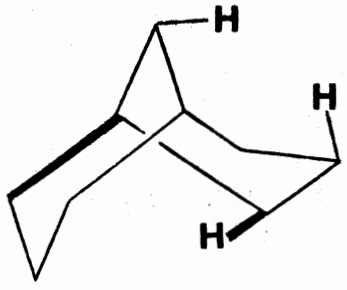


26 R = H, C_2H_5, $CH_2CO_2CH_3$;
R' = H, C_2H_5

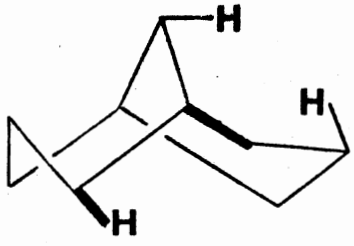
The bicyclo[3.3.1]nonane system is of considerable stereochemical interest. Three conformations relatively free from angular strain can be postulated for bicyclo[3.3.1]nonane itself: chair-chair (CC, 1a), chair-boat (CB, 1b) and boat-boat (BB, 1c). All three conformations have strong destabilizing interactions between nonbonded atoms, how-



1a



1b



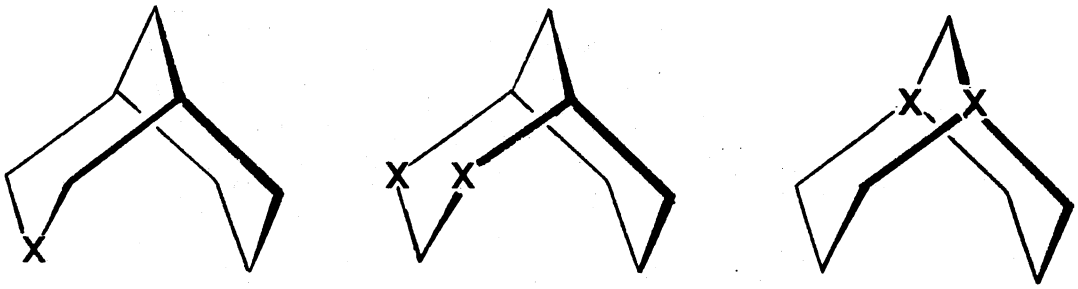
1c

ever. The destabilization of the boat conformations 1b and 1c is due to the bond opposition strain (see the darkened bonds in 1b and 1c) and to the "bowspirit flagpole-flagpole" interactions.[25] These interactions are well known in certain cyclohexanes.[25] Conformation 1a is destabilized by the nonbonded interaction between the $H_a(3)$ and $H_a(7)$. The interatomic distance (ca. 0.81 A^o)[3] between $H_a(3)$ and $H_a(7)$ is less than the van der Walls radius of the hydrogen atom (ca. 1.2 A^o),[32] and hence the above short nonbonded interaction results.

Among the conformations 1a-1c, conformation 1a is more favored on the basis of enthalpy considerations.[89] This is even more pronounced in the case of cyclohexanes wherein the free energy difference between chair and boat conformations has been found to be fairly large (5-7 kcal).[25] However, all three conformations 1a-1c are limiting and in specific instances these ideal forms will suffer distortions (to various degrees) which will decrease the strain. For example, the flattening of the six-membered rings in 1a and bending of the C-H bonds at C(3) and C(7), i.e., the decrease of H-C(3)-H or H-C(7)-H angle, can reduce the internal energy considerably.[11,48] As a result, 1a is the best candidate as the most stable conformation in the ideal situation (i.e., for the parent hydrocarbon).[48]

Conformational analysis of six-membered heterocycles revealed the same fundamental conformational characteristics which were uncovered for cyclohexane derivatives.[24,89] In broad outline, the geometry of bicyclic molecules containing the usual heteroatoms (O, N and even S) simulates fairly satisfactorily the geometry of carbon analogs.[88] Introduction of a heteroatom in the 3-position, as in 27, should stabilize the CC conformation as it is devoid of the so called 3,7-nonbonded inter-

action.



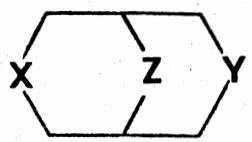
27 28 29

The relative lengths of C-C and C-X (X = heteroatom) bonds are also critical.[88] If the C-X bond is appreciably shorter than the C-C bond, the introduction of a heteroatom in the 2- and 4-positions (28, for example X = O) or in the 1- and 5-positions (29, for example X = N) should destabilize the system because of enhanced 3,7-repulsion characteristics. The converse, namely a decrease in the 3,7-repulsion with an increase in the C-X bond length (28, for example X = S, Se), is also expected. However, exact conformations of individual heteroanalogs of 1 and derivatives thereof is also dependent upon various other factors such as electrostatic interactions of heteroatoms, the interaction of the lone electron pairs, and the size of the heteroatoms.[3,9,40,88]

Various experimental techniques (NMR, IR, X-ray, electron diffraction) have been employed along with considerable theoretical investigations in analyzing the conformations of 1 as well as of some heteroanalogs. A brief discussion of the conformational analysis of 1 (and of the heteroanalogs) by different spectroscopic techniques is deemed appropriate here.

The application of ^{1}H NMR spectroscopy to the study of the bicyclo-[3.3.1]nonane system is based upon two parameters: (1) a difference in

chemical shifts of the axial and equatorial protons,[9,44,54,91] and (2) the relationship between $^3J_{HH}$ and the dihedral angle [the Karplus equation $^3J_{HH} = f(\phi)$].[91] The ^1H NMR chemical shift values have been primarily used to assign the configuration, i.e., to differentiate H_a and

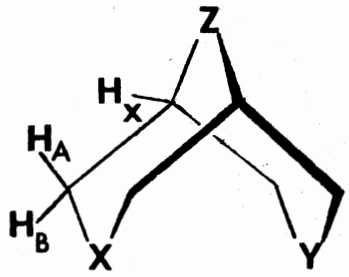


30 X = Y = Z = O

31 X = O; Y = Z = S

32 X = Y = S; Z = O

H_e. Zefirov and co-workers[91] analyzed the conformations of 30-32 with the aid of the $^3J_{HH}$ values. They arrived at certain conclusions by considering both $^3J_{AX}$ and $^3J_{BX}$ for the conformational equilibrium 33 ⇄ 34 ⇄ 35 ⇄ 36. For the conformation 33 both constants J_{AX} and J_{BX} were small (ca. 2-4 Hz). Any ring deformation (flattening) of 33 requires an



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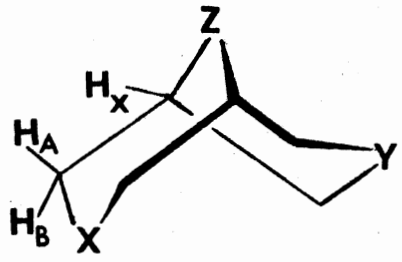

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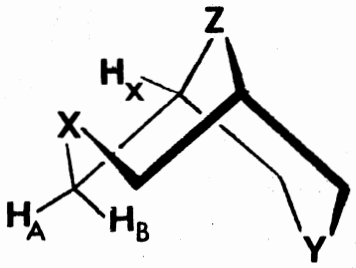

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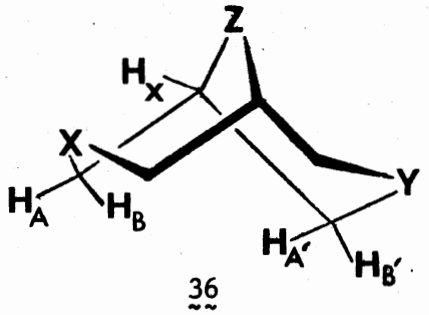


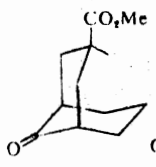
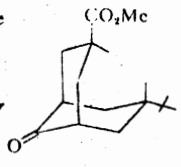
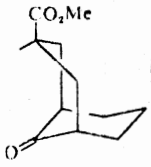
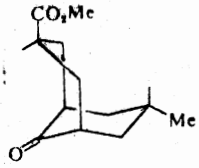
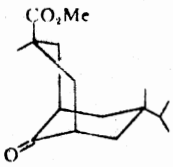
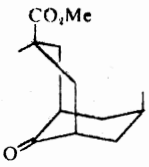
36

increase in J_{AX} and a decrease in J_{BX}. For conformations 34 and 35 a large increase in J_{AX} (ca. 9-11 Hz) would be required. Likewise, a large J_{AX} and $J_{A'X'}$ value can be expected for members of 36. On the

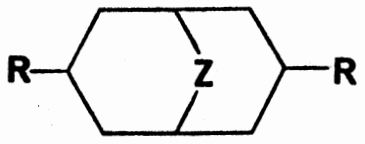
basis of the observed J_{AX} and J_{BX} values, the authors[91] assigned conformation 33 for compounds 30 and 31; perhaps, both the O(3)·····O(7) and O(3)·····S(7) repulsions cause only flattening of the wings of the molecules. In contrast, conformation 34 (or 35) was assigned to 32 (because of large J_{AX} values); probably, the S(3)·····S(7) repulsion was sufficiently great to result in conformation 34 (or 35) to form. Thus, ^{1}H NMR data showed that the 3,7-repulsion rose across the series to be O···O<O···S<<S···S. X-ray data on solid 31 and 32 supported the above conclusions.[92] Peters and co-workers[61] took advantage of the relation between $^3J_{HH}$ values and the dihedral angle (HCCH) in analyzing the conformations of certain 3,7-disubstituted bicyclononan—9-ones 37a-37f, (Table I). However, in the ^{1}H NMR analysis, various amounts of shift reagents were used and a critical assumption was made that the shift reagents had no significant influence on the coupling constants or on the geometry of the substrate. The above assumption was questionable and the authors[61] were forced to conclude that errors were possible in relating $^3J_{HH}$ values and specific conformations because the $^3J_{HH}$ values could be an average of structures in rapid equilibrium.[2,91] Perhaps, more important is that flattening of the rings in 33-35 (due to longer C-X bonds in certain cases where X = S, Se etc) could negate a legitimate comparison of these $^3J_{HH}$ values with those predicted from the (modified) Karplus equation. Surprisingly, this ^{1}H NMR study has been widely quoted by a large number of workers to elucidate the configuration at heteroatoms and to deduce conformations of various heteroanalogs of 1 and derivatives[12,52,71,88] in spite of the above weaknesses.

TABLE I

$^{3}J_{HH}$ VALUES (Hz) OF BICYCLO[3.3.1]NONAN-9-ONES 37a-37f

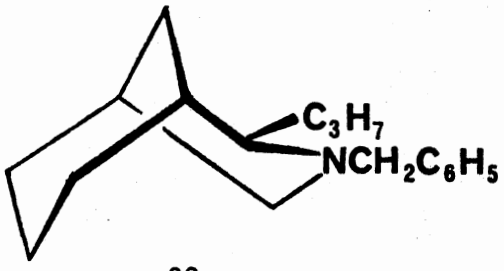
	 37a	 37b	 37c	 37d	 37e	 37f
$J_{12\alpha}$	<3	<3	<3	~2	<3	<3
$J_{12\beta}$	4.3	4.2	9	10	9.5	10
$J_{13\alpha}$	---	<3	<3	<3	2-3	2-3
$J_{13\beta}$	---	3	3	---	3	2.2
$J_{2\alpha2\beta}$	-14.0	-14.0	-14.0	-14.0	-14.0	-14.0
$J_{2\alpha3}$	5.2	5.5	12.5	12.7	13.0	12.5
$J_{2\beta3}$	12.7	12.0	5.5	5.2	5.5	5.5

^{13}C NMR chemical shifts are sensitive to many stereochemical factors.[26,46,62,67,85] Moreover, the effects of substituents of certain ^{13}C shieldings are often additive within a class of compounds.[76] These features make ^{13}C NMR a powerful tool for conformational analysis. Peters and co-workers[62] reported the ^{13}C chemical shift data of certain 3- and 7-substituted bicyclo[3.3.1]nonanes and corresponding 9-oxo derivatives 38. They discovered that the ^{13}C chemical shifts (Table II and III) were diagnostic for the conformation of 38 after correcting for substituent (α, β, γ) effects. The ^{1}H and ^{13}C NMR spectral features of 39 indicated that it probably preferred a chair-boat (CB)



38 R,R' = CH_3, $C_3H_6(OH)$, $C(CH_3)_3$

Z = CH_2, C=O



39

conformation as shown.[67] This was not confirmed, however. Stereodynamics of certain 3,7-diazabicyclo[3.3.1]nonan-9-ones have also been investigated using variable temperature ^{13}C NMR.[80]

TABLE II

AVERAGE ^{13}C CHEMICAL SHIFTS OF BICYCLO[3.3.1]NONANE 38

Conformation	^{13}C Chemical shift (ppm)					
	C_1	C_2	C_3	C_6	C_7	C_9
Double-chair	28.1	31.5	22.3	31.5	22.3	34.4
Chair-boat	25.9	26.7	19.0	33.3	16.4	28.6
Double-boat	26.3	31.4	20.7	31.4	20.7	23.7

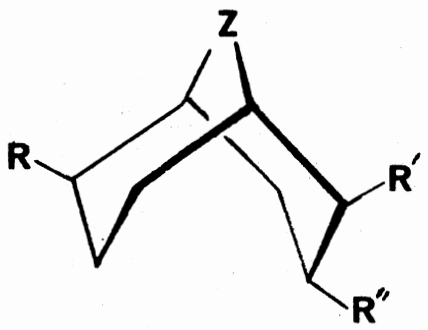
The IR spectra of polycyclic compounds in which two or more methylene groups are in very close proximity are known to contain anomolous IR absorption bands at 1490 cm^{-1} and 2990 cm^{-1}.[88] The IR spectra of

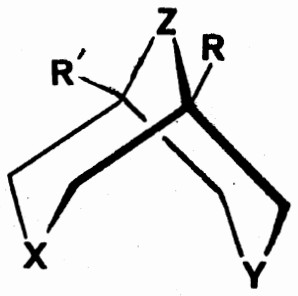
many bicyclononane derivatives also contain these high frequency bands which have been attributed to the $H_a(3)\cdots\cdots H_a(7)$ interaction ("scissoring" vibrational mode) in CC conformation 1a (page 91).[23,82] The conformations shown for ketone 40,[27] for the alcohol 41,[53] and for 9-heteroanalogs 42,[28] 43,[18] and 44[48] were suggested on the basis of IR spectroscopic analysis. However, with 45 it was noted that the above absorption bands were not observed even though the compound was known to exist in a CC conformation in the solid state.[2] In a recent review, conformational analysis of certain heteroanalogs of 1 by IR spectroscopy has been well discussed,[1] but the value of such data in structure diagnosis is not totally established.

TABLE III

AVERAGE ^{13}C CHEMICAL SHIFTS OF 9-OXOBICYCLO-[3.3.1]NONANE 38

Conformation	^{13}C chemical shift (ppm)					
	C_1	C_2	C_3	C_6	C_7	C_9
Double-chair	46.0	34.2	21.0	34.2	21.0	221.4
Chair-boat	44.0	29.9	20.6	35.7	15.7	220.6
Double-boat	43.3	33.5	21.6	33.5	21.6	224.7





40 R = Cl; R' = R'' = H; Z' = C=O

41 R = R' = H; R'' = OH; Z = CH_2

42 R = R' = Br; R'' = H; Z = O

43 R = R' = R'' = H; Z = S

44 R = R' = R'' = H; Z = Se

45 R = R' = H; R' = OH; Z = NCH_3

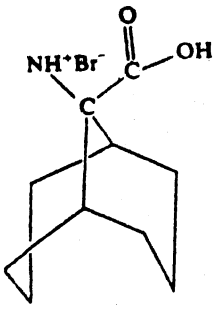
45 X = Z = CH_2; Y = $\overset{+}{N}H_2$,Br^-; R = R' = H

47 X = Y = CH_2; Z = CHOH; R = $CH_2SO_3C_6H_6Br$-p; R' = CH_3

48 X = O; Y = C = O; Z = NCH_3; R = R' = H

The X-ray diffraction study is perhaps the only single technique which provides unequivocal proof of the exact conformation of the bicyclononane system but only in the solid state. Dobler and Dunitz[21] were the first to show that hydrobromide 46 had a flattened CC conformation. The N(3)·····C(7) distance had increased to 3.02 A^o owing to the flattening. X-Ray data on 47 indicated a flattened CC conformation.[11] The bicyclononane skeleton in 48 adopted the CC conformation with an O(3)·····C=O distance of 2.75 A^o.[42]

X-Ray data of certain bicyclononanes 49-59 were analyzed recently.[7] From available data, interesting conformational features of the above compounds were discussed in terms of the bond lengths, bond angles and torsional angles. Compounds 49-56 preferred the CC conformations whereas the compounds 52b and 57-59 (with bulky substituents at positions 3



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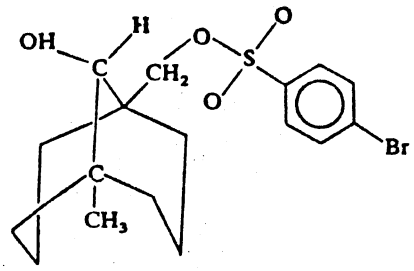

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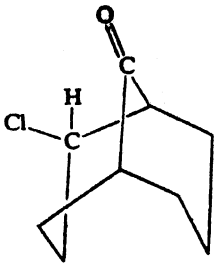

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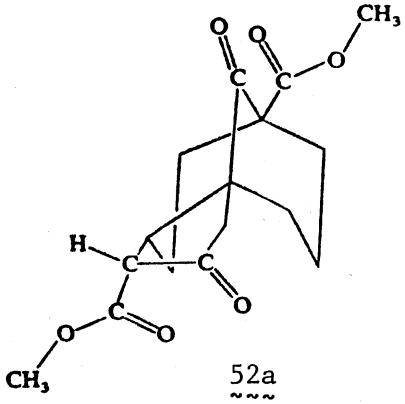
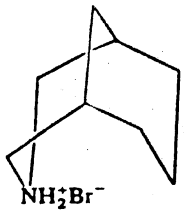


52a



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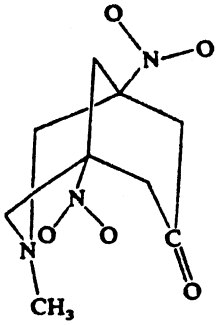

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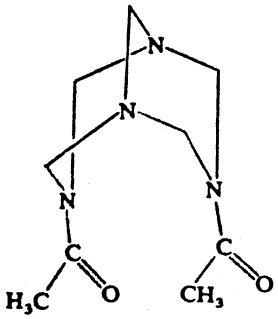

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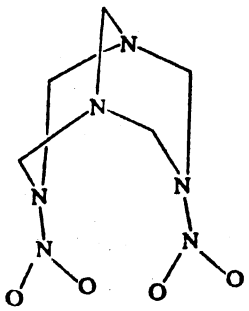

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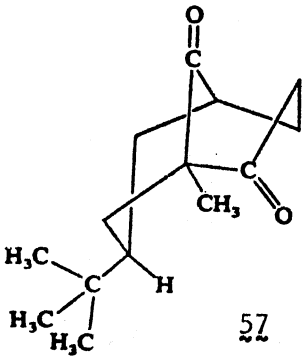

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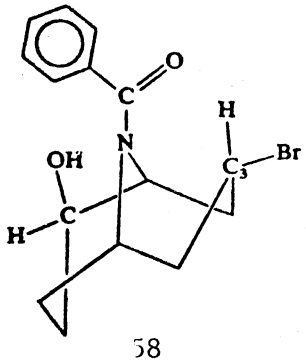

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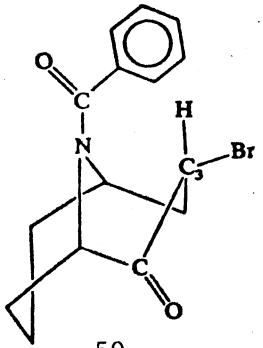

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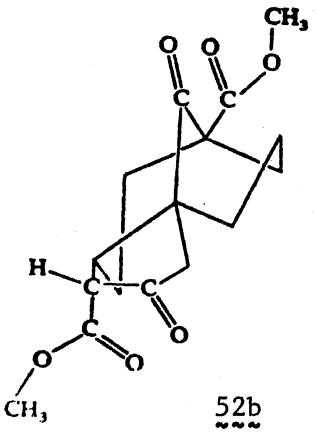
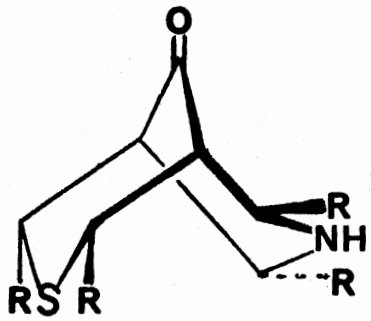
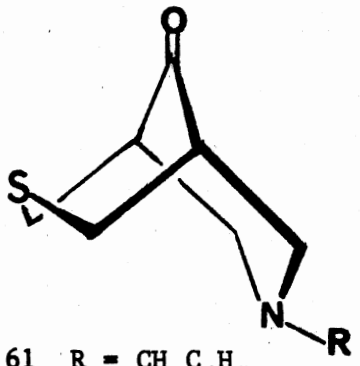


52b

and 7) adopted CB conformations. It is interesting that ketone 60[33] has been found to exist in a CB conformation while the related 61[4] adopted



60 R = C_6H_5



61 R = $CH_2C_6H_5$

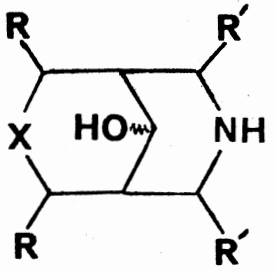
a BC conformation. Hence, steric effects as well as the nature of heteroatom are important and probably govern which conformer is preferred.

The amount of CC conformation in bicyclo[3.3.1]nonane (1a on page 91, 95-75%) in equilibrium with the BC conformation (1b on page 91, 5-25%) has been measured using electron diffraction at different temperature, and this was supported by calculations employing molecular mechanics.[55] Semi-empirical quantum-mechanical techniques and extended Huckel and CNDO/2 methods have also been used in the calculations to deduce the conformer of lowest energy in the bicyclo[3.3.1]nonane system and certain nitrogen analogs.[14,29]

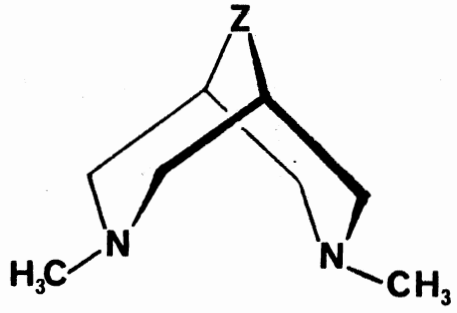
Literature citations to nucleophilic additions to heterabicyclo-[3.3.1]nonan-9-ones are quite limited and there is almost no information on the stereochemistry of the addition products. Nucleophilic additions are expected to give epimeric products since the nucleophile can approach the C=O group from either side. However, the ratio and the stereochemistry of the addition products depend upon the stereochemistry of the substrate as well as the nature of the nucleophile.[84] Moreover,

two factors namely the steric approach control and the product development control should also be considered important in determining the stereochemical course of the bicyclic ketones.[20]

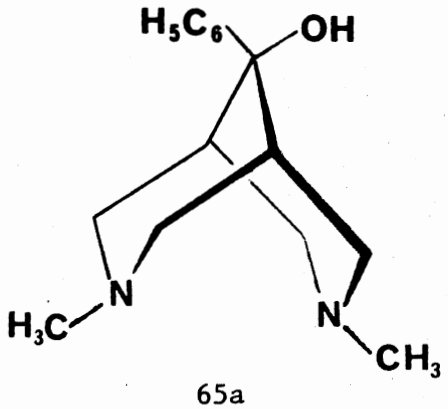
Baliah and co-workers[5] prepared the epimeric alcohols 62 by reducing [$NaBH_4$, $LiAlH_4$, $Al(OC_3H_7\text{-}\underline{2})_3$] the corresponding ketones. They tentatively assigned the stereochemistry of some isolated epimeric alcohols from IR spectroscopic data, but the exact configuration at C(9) and the conformations of the overall systems have not been confirmed. Nucleophilic attack at the C=O group in 63 with $NaBD_4$ and C_6H_5Li gave 64 and 65, respectively.[70,75] Analysis of the IR spectrum of solid 65 showed strong intramolecular H-bonding, supportive of conformer 65b in the solid state. Speculation that an equilibrium between 65a and 65b could exist in solution could not be eliminated from consideration, however. Reduc-



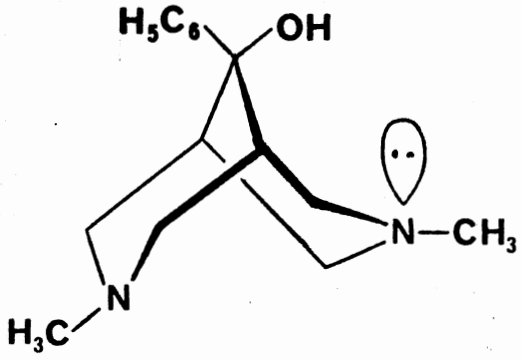
62 X = CH_2, S, NH;
R = H, C_6H_5; R' = C_6H_5



63 Z = C=O; 64 Z = C(D)OH

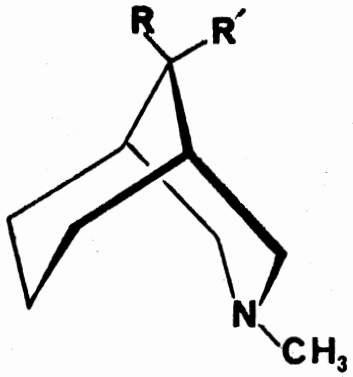


65a



65b

tion ($NaBH_4$) of the amino ketone 66 produced isomeric alcohols 67 and 68 (1:2) which were separated by treatment with p-nitrobenzoyl chloride.[36] The aminoalcohol 67 afforded the p-nitrobenzoate ester, and the unreacted isomer 68 was converted to a hydrochloride. The marked difference in esterification rate of 67 and 68 (which permitted not only the separation of the esters but also a tentative assignment for the configuration at C(9) in 67 and 68) was attributed to the reversible formation of a certain intermediate.[36]

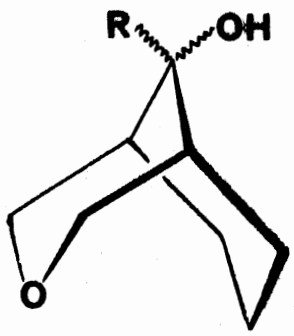


66 R,R' = C=O

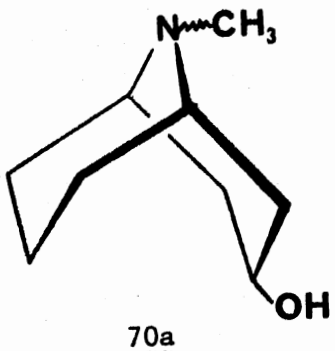
67 R = H; R' = OH

68 R = OH; R' = H

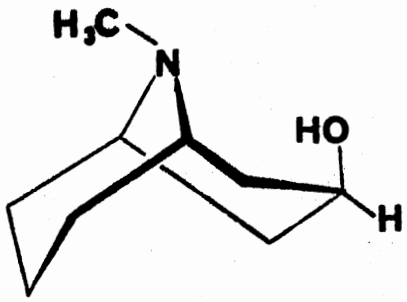
The configuration of OH group at C(9) in a series of 3-oxabicyclo-[3.3.1]nonan-9-ols 69 has been evaluated in terms of ^1H NMR analysis.[12]



69 R = H, C_6H_5;



70a

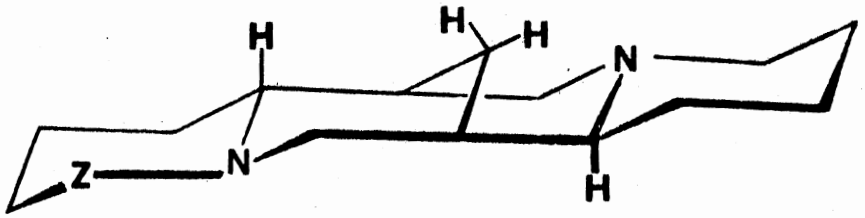


70b

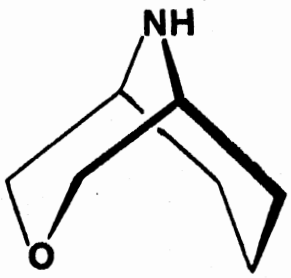
Chemical evidence strongly supported the configuration at C(3) and C(9) in grantanol to be best represented by 70a in the solid state.[2] However, ^1H NMR and IR spectral data of grantanol in solution suggested an equilibrium between 70a and 70b,[2] and thus the status of the major conformer

is not settled.

The 3,7(9)-azabicyclo[3.3.1]nonane fragment occurs in the structures of many natural alkaloids. For example, 3,7-diazabicyclononane occurs in the skeleton of alkaloids in the plant family Papilionaceae: lupanine (71) and sparteine (72).[90] The general 3-azabicyclononane fragment has also been found in the structure of certain diterpene alkaloids.[83] Another series of alkaloids are also based on 9-azabicyclononane fragment.[32] The 3-oxa-9-azabicyclo[3.3.1]nonane (73) and many of its derivatives have a marked effect on cholinergic systems in certain



71 Z = C=O; 72 Z = CH_2



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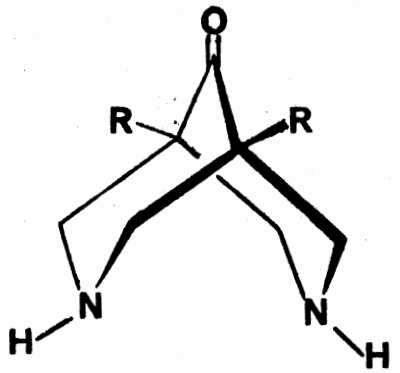
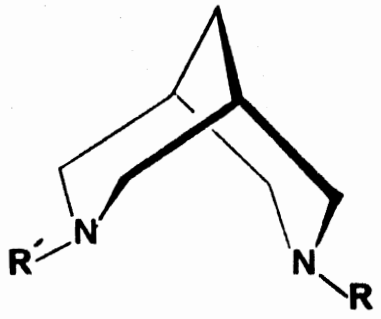
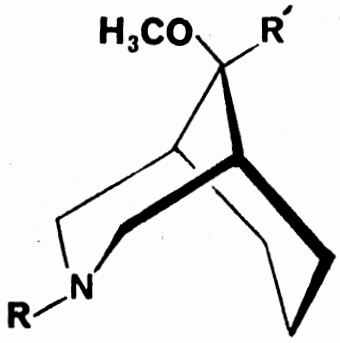


74 R = C_6H_5

organisms.[90] A number of derivatives of 3-azabicyclononanes have ganglion-blocking and hypotensive activities.[64,65] Derivatives of 1,5-diphenyl-3,7-diazabicyclononan-9-one (74) have been used as local anes-

thetics.[43] Ruenitz and co-workers[68] reported the antiarrhythmic activity of the bispidine 75 and the bispidinebenzamide 76. Bispidine 77 exhibited potential analgesic and antitussive activities, and the N-carbamate 78 demonstrated appreciable antiinflammatory effects with analgesic activity.[59] It appears this family of heterocycles is potentially fruitful in terms of having good candidates as medicinal agents.





75 R = R' = $CH(C_6H_5)_2$

76 R = CH_3; R' = $C(O)OC_6H_4Cl$-p

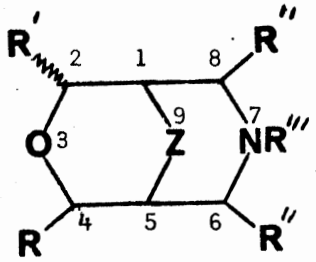
77 R = CH_3; R' = C_6H_4OH-m

79 R = $C(O)OC_2H_5$; R' = C_6H_5

CHAPTER II

RESULTS AND DISCUSSION

Heterocyclic bicyclo[3.3.1]nonanes (bispidines) are of considerable interest both from a theoretical point of view, as well as, potential biological activity.[13,15,60,88,90] Nitrogen analogs of bicyclo[3.3.1]-nonan-9-ones (bispidinones)[5,8,22,31,37,38,65,69,72-74] have been studied but work on other hetero (O, S, P, etc) analogs is quite limited. To date, only a few 3-oxa-7-azabicyclo[3.3.1]nonan-9-ones[5] have been reported. The objectives of the present work were to develop reliable synthetic methods for and to perform conformational analyses of certain substituted 3-oxa-7-azabicyclo[3.3.1]nonan-9-ones with the general structure 79.



79 a. R = R'' = C_6H_5; R' = cis C_6H_5; R''' = H; Z = C=O

b. R = R'' = C_6H_5; R' = trans C_6H_5; R''' = H; Z = C=O

c. R = R' = R''' = H; R'' = o-C_6H_4Cl; Z = C=O

d. R = R' = R''' = H; R'' = o-C_6H_4Cl; Z = CH(OH)

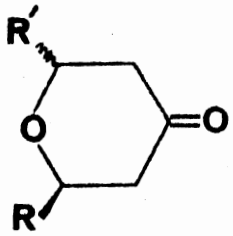
e. R = R' = R'' = H; R''' = $CH_2C_6H_5$; Z = C=O

f. R = R' = R'' = H; R''' = $CH_2C_6H_5$; Z = CH(OH)

g. R = R' = R'' = H; R''' = $CH_2C_6H_5$; Z = $CC_6H_5(OH)$

h. R = R' = R'' = H; R''' = $CH_2C_6H_5$; Z = CH_2

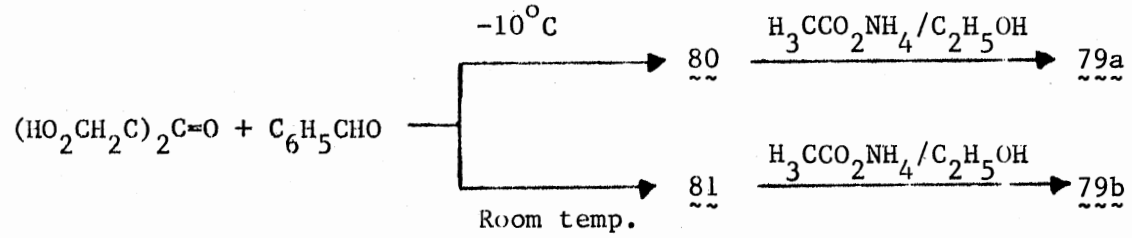
Syntheses of members of 79 were approached via two routes: (1) a Mannich condensation of selected tetrahydro-4H-pyran-4-one with appropriate aldehydes and amines and (2) the addition of amines ($R'''-NH_2$, R''' = H, CH_3, $CH_2C_6H_5$) to certain 3,5-dibenzylidenetetrahydro-4H-pyran-4-one. The first route was productive while the second route failed to give the expected products and usually starting material was recovered. Both cis- and trans-2,6-diphenyltetrahydro-4H-pyran-4-ones (80 and 81,



80 R = C_6H_5; R' = cis-C_6H_5

81 R = C_6H_5; R' = trans-C_6H_5

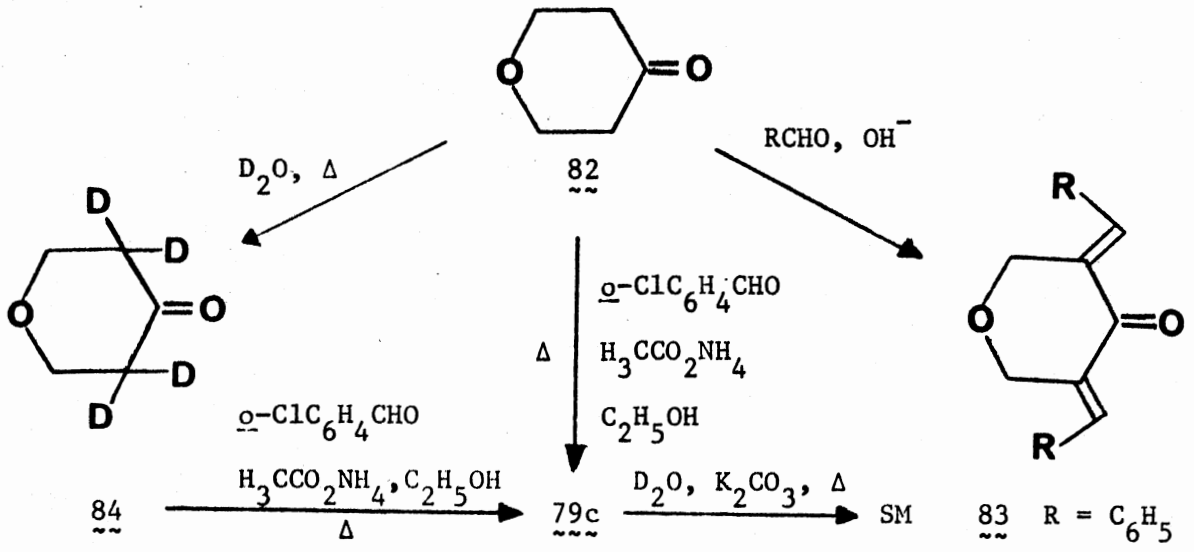
respectively)[6] were prepared by an acid-catalyzed condensation of acetonedicarboxylic acid with excess benzaldehyde at -10°C and at 25°C (room temperature), respectively. Baliah and co-workers have reported the syntheses of the bispidinones 79a and 79b. We were unable to reproduce their data under the conditions given. However, ketones 79a and 79b were obtained via a modified procedure as outlined below. Reaction time



(ca. 4 h) and temperature (oil bath, 55-60°C) were critical in the syntheses of 79a and 79b and excess ammonium acetate [3 equivalents for each equivalent of the ketones (80 or 81) used] was employed to maximize the yield under the conditions utilized.

A Mannich type cyclocondensation of the ketone 82 with o-chloro-

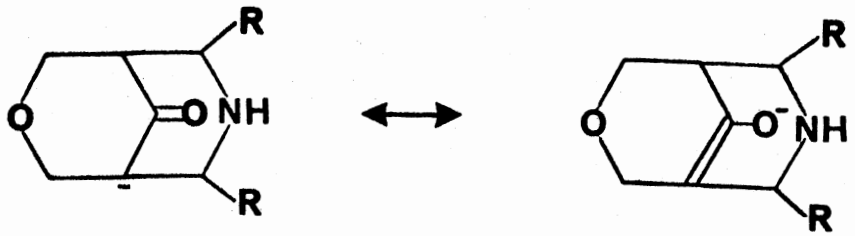
benzaldehyde and ammonium acetate produced the bispidinone 79c as outlined below. Reaction time (30 min), reaction temperature (hot plate, ca.



60°C), and the ratio of the reactants (for 1 equivalent of 82, 2 equivalents of o-ClC_6H_4CHO and 1 equivalent of $H_3CCO_2NH_4$) were crucial to obtain bispidinone 79c. o-Chlorobenzaldehyde was used instead of benzaldehyde as the latter gave a mixture of the starting material and the dibenzylidene compound 83. Surprisingly, attempts to prepare bispidinones failed from the condenzation of benzaldehyde and benzylamine with only the dibenzylidene compound 83[19] being obtained quantitatively.

A preliminary attempt was made to prepare a deuterium analog of 79c [D(1,5)] in an effort to facilitate the NMR analysis. Ketone 84 was obtained successfully and was condensed with o-ClC_6H_4CHO in the presence of $H_3CCO_2NH_4$. However, the product was identified (via an analysis of the ^1H NMR and mass spectral data) as 79c. Apparently all of the deuterium in 84 was lost [undoubtedly the deuterium was exchanged with protons either from the solvent (C_2H_5OH) or from the salt ($H_3CCO_2NH_4$)] under the reaction conditions employed. Deuteration of

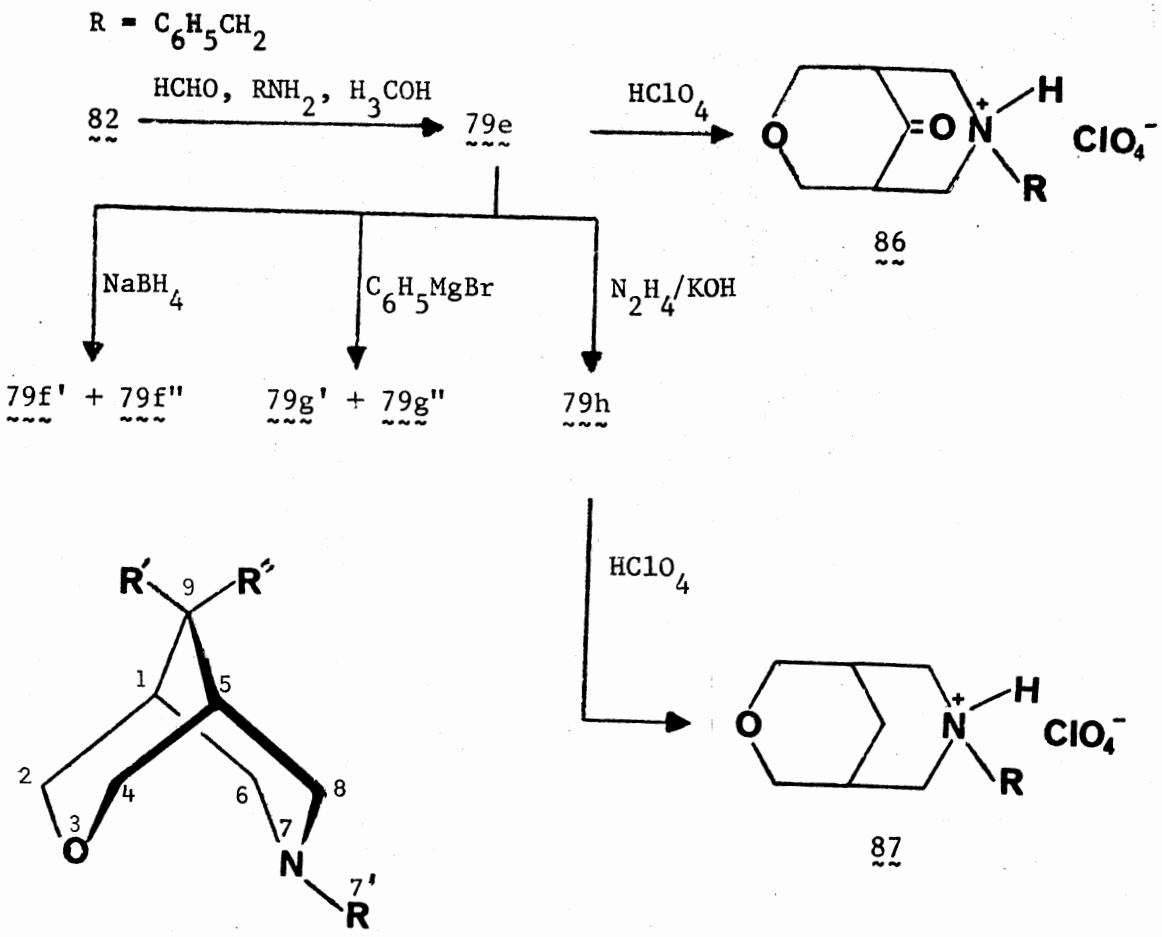
ketone 79c also failed and the starting material was recovered quantitatively. This result was not entirely surprising since deuterium exchange could involve the enolate 85b as an intermediate, the



85a R = C_6H_4Cl-o 85b

structure of which violates the so called Bredt's rule. Similar attempts at deuteration of the bridgehead carbon of bicyclic compounds (all appeared to have failed) can be found in a recent review.[13] However, structures which violate the Bredt's rule are not known[13,35] and perhaps deuteration (at the bridgehead positions) of 79c requires a more powerful base such as LDA for removal of H(1,5) as well as an aprotic solvent such as HMPA.

The bispidinone 79e was prepared by a double Mannich condensation of ketone 82 with formaldehyde and benzylamine. Certain 3-nitrogen analogs of 79e have been recorded via a Mannich condensation of the appropriate 4-heteracyclohexanone and formaldehyde and benzylamine.[22,69,74] However, the methods involved long reaction time (30 days), and the products were invariably used in crude form. We have developed a facile procedure (outlined below) to obtain bispidinone 79e in a short reaction time (6 h) and in good yield. Since the bispidinone 79e decomposed during distillation (vacuum), it was characterized as the perchlorate 86. Interestingly, the perchlorate formed a monohydrate in good yield (83%). Formation of such hydrates in 1-hetera-4-cyclohexa-



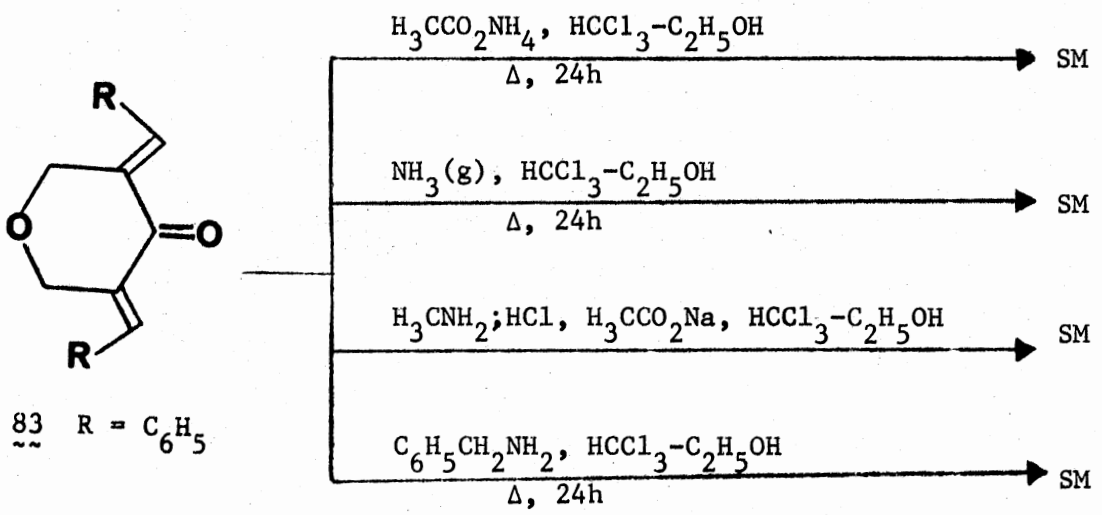
79f' R' = OH; R" = H; 79f" R' = H; R" = OH;

79g' R' = C_6H_5; R" = OH; 79g" R' = OH; R" = C_6H_5;

nones is known.[10,41] Amine 79h was obtained (quantitative) by reducing the amino ketone 79e under modified Wolff-Kishner conditions and was characterized via its perchlorate 87. X-Ray analysis of perchlorates 86 and 87 are in progress under the direction of Dr. Van der Helm at OU.

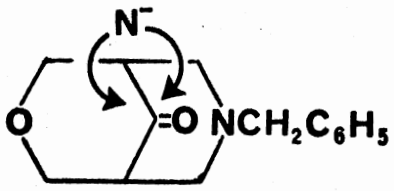
Surprisingly, treatment of the pure dibenzylidene derivatives 83[19] under a variety of conditions (as outlined below) did not produce any expected products. Thus, it is suggested that free dienones like 83 may not be intermediates in the formation of the bispidinones discussed

previously.



83 R = C_6H_5

Conformational analysis was performed on several of the bispidinones obtained from this study. Assuming a chair chair (CC) form for 79e, one might expect a 1:1 ratio of products from nucleophilic additions to C=O group. However, if a chair-boat (CB) form existed in solu-

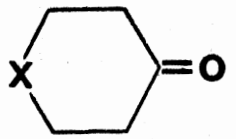


79e

tion, the ratio would probably differ significantly from 1:1 because of a preferred orientation of the attacking reagent (steric approach control).[20,84] Reduction of 79e with $NaBH_4$ in 2-propanol (room temp) gave what appears to be two isomers (ca. 1:1) of 79f. Also, addition of C_6H_5MgBr in ether (room temp) gave two isomers (ca. 1:1.2) of 79g.

Separation of the two isomers of 79f was accomplished via chromatography on a florisil column but only one isomer of 79g could be obtained pure via the same technique because of decomposition of the other isomer on the column. However, on the basis of TLC and NMR analysis and the near unity product ratios from the above nucleophilic ($NaBH_4$, C_6H_5MgBr) additions to the amino ketone 79e there is suggested that a CC conformation is highly probable for this bispidinone in the solvents employed.

Analysis of the ^1H NMR spectra of the compounds 79a-79h, 86 and 87 proved interesting and instructive to a degree. Chemical shifts for H(1,5), H(2,4), and H(6,8) were assigned partially on the basis of electronegativity effects of the heteroatoms on α-protons and from extensive proton decoupling studies. Also, the NMR spectra of ketones 19[50] and 82



19 X = $NCH_2C_6H_5$

82 X = O

were used for comparison purposes. Chemical shifts for 79e-79h were found to be in the order: $\delta_{H(1,5)} < \delta_{H(6,8)} < \delta_{H(C\underline{H}_2C_6H_5)} < \delta_{H(2,4)} < \delta_{Ar-\underline{H}}$. However, for the perchlorates 86 and 87, the chemical shifts were found to be in the order: $\delta_{H(1,5)} < \delta_{H(2,4)} < \delta_{H(6,8)} < H(\underline{H}_2CC_6H_5) < \delta_{Ar-\underline{H}}$. This was expected because of the protonation of N(7). The protonated form of the latter atom is known to exert a large deshielding effect on the α-protons H(6,8) and $H(C\underline{H}_2C_6H_5)$.[50] Also chemical shifts of $H_a(2,4)$ and $H_a(6,8)$ appeared at higher field than

those of $H_e(2,4)$ and $H_e(6,8)$, respectively. Such a chemical shift difference between the axial and equatorial protons has been observed in the spectra of simple pentamethylene heterocycles and was explained in terms of diamagnetic anisotropic effects.[45] Several recent studies on 3,7-diazabispidinones support this assignment.[22,54,69,74]

Multiplets observed for the signals for H(2,4) and H(6,8) in 79e-79h constituted the AB part of an ABX pattern except with that for H(6,8) in 79e which was found to be the AM part of an AMX pattern. A second order analysis yielded the $\delta_{H_a(2,4)}$, $\delta_{H_e(2,4)}$, $\delta_{H_a(6,8)}$, and $\delta_{H_e(6,8)}$ in 79e-79h except for H(6,8) in 79e where a first order analysis (i.e., the midpoint of each doublet) was found to be sufficient to obtain $\delta_{H_a(6,8)}$ and $\delta_{H_e(6,8)}$.[39,47] The geminal coupling constants for H(2,4) and H(6,8) in 79e-79h occurred in the range of 10-12 Hz which is what one would expect for a methylene group having tetrahedral geometry.[30] The vicinal coupling constants in 79e and 79h [$^3J_{H(1,5)H_a(2,4)}$, $^3J_{H(1,5)H_e(2,4)}$, $^3J_{H(1,5)H(6,8)}$, and $^3J_{H(1,5)H(6,8)}$] were small (ca. 2-4 Hz). This was informative because of the known relationship between the dihedral angle (HCCH) and $^3J_{HH}$ in simple carbon cyclic systems.[91] It has been shown that $^3J_{HH}$ for a BC (or CB) conformation (i.e., $^3J_{HH}$ is expected to be ca. 10-12 Hz) is greater than for CC conformation ($^3J_{HH} \simeq$ 2-4 Hz).[91] In compounds 79e and 79h, $^3J_{HH}$ was small (ca. 2-4 Hz) while in compounds 79a-79d, 79f, and 79g it was apparently unresolvable at 100 MHz (below 0.5 Hz) or absent entirely.

^{13}C NMR chemical shifts for compounds 79c-79h are listed in Table IV. These shifts for 79c-79h were assigned with the aid of model compounds 19 and 82.[34] Off-resonance ^{13}C spectra were recorded (for 79c,

TABLE IV

^{13}C NMR CHEMICAL SHIFTS[a] FOR COMPOUNDS 79c, 79e-79h, 86, and 87

Compound	Carbon					
	C(1,5)	C(2,4)	C(6,8)	C(9)	Ar-CH_2	Aromatic Ring
79c[b]	52.5	69.9	60.3	209.7		137.0, 132.4 129.8, 128.9 128.7, 126.8
79e	49.5	73.3	57.5	211.5	61.1	137.7, 128.4 128.0, 126.9
79f"[c]	37.9	72.1	52.2	67.0	63.3	131.2, 130.9 130.3, 129.7 129.3, 129.1
79g'	39.2	70.6	54.4	70.6	63.2	142.8, 130.8 130.7, 129.8 129.6, 129.5 126.7, 126.9
79h[d]	30.2	70.6	57.6	30.2	63.1	131.8, 131.1 130.3, 130.1
86	39.0	55.5	61.8	92.9	70.2	131.8, 131.1 130.8, 130.2
87[e]	29.9	58.1	62.5	30.4	72.9	131.8, 131.1 130.3, 130.1

a. Chemical shifts are in ppm downfield from internal tetramethylsilane (TMS); solvent: $DCCl_3$ for 79c, 79e, and 79h; H_3COD for 86 and 87; D_3COD for 79f" and 79g'.

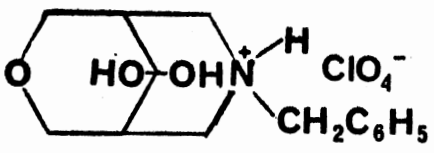
b. Off-resonance spectrum showed a doublet for signal at 60.3 ppm and a triplet for signal at 69.9 ppm.

c. Off-resonance spectrum showed a doublet for signal at 67.0 and a triplet for signal at 72.1.

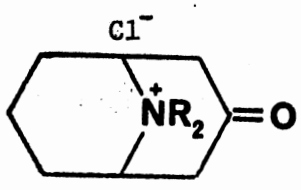
d. Off-resonance spectrum showed a multiplet for signal at 30.2 ppm.

e. Off-resonance spectrum showed a doublet for signal at 29.9 ppm and a triplet for signal at 30.4 ppm.

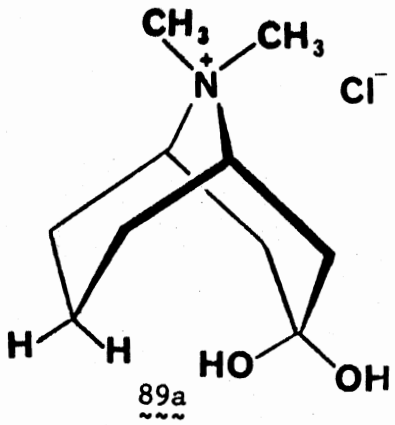
79f' (page 110), 79h, and 87) in order to distinguish between ^{13}C signals for a methine carbon and that for a methylene carbon. As expected,ddd ^{13}C chemical shifts were dependent upon steric effects (particularly by very large substituents) as well as upon the electron-density changes imposed by substituents.[62,67,76,85] The ^{13}C NMR spectrum of perchlorate 86 was somewhat novel and did not show the expected signal for a C=O group (a signal at 211 ppm was observed for the C=O group in 79e), but a ^{13}C signal appeared at 92.9 ppm (Table IV). This shift is reminiscent of that for a carbon holding gem-dioxy groups.[41] Analysis of the IR spectrum of 86 also did not reveal a C=O absorption band (ν_{max} 1730 cm^{-1} was observed for 79e) but rather a broad, intense absorption occurred at 3300-3500 cm^{-1}. Elemental analysis of 86 indicated a molecular formula $C_{14}H_{20}ClNO_7$ which corresponded to a monohydrate of 86. This suggested that perchlorate 86 existed as a hydrate such as 88. Similar carbonyl hydration effects in quaternary salts of certain 4-piperidones[41] and 4-phosphorinanones[10] have been reported where the hydrated carbon has a ^{13}C NMR signal at 101.7 and 94.4 ppm, respectively. In contrast, the carbonyl carbon in 89 resonated at 201.7 ppm in water.[86] Perhaps, hydrate formation (in 89) was insignificant because of steric interactions of the endo hydroxyl group in either conformation 89a or 89b.



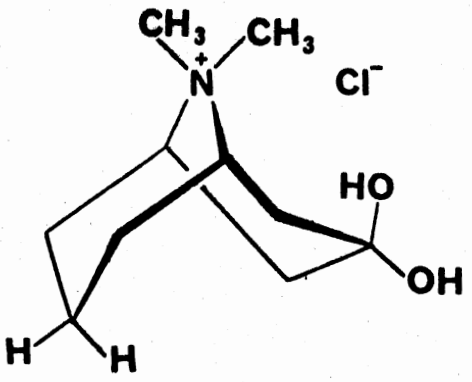
88



89 R = CH_3

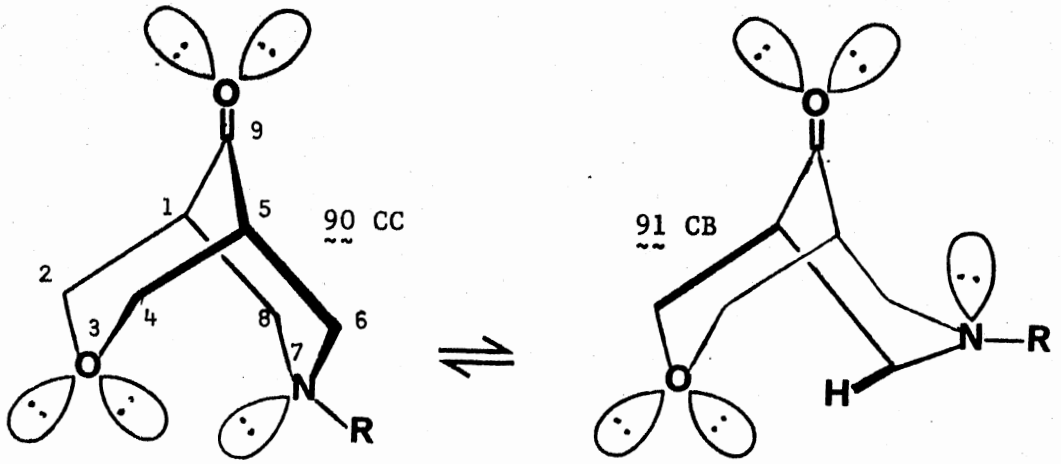


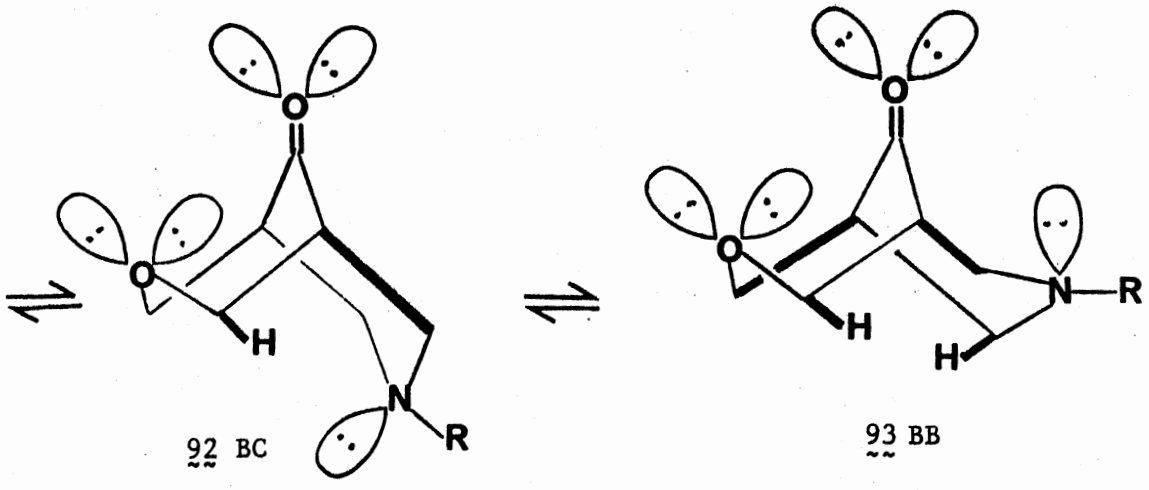
89a



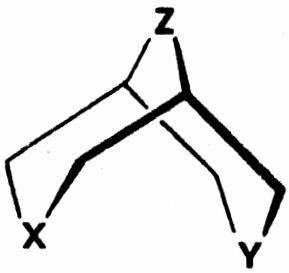
89b

Certain tentative conclusions about the conformation of the bispidinones 79a-79h described herein can be deduced from the spectral data gathered. Before proceeding, a brief discussion on general conformational features of the 3-oxa-7-azabispidinone system is in order. Members of 79 can exist in four resonable conformations 90-93. All four conformers have strong destabilizing interactions between certain nonbonded atoms, however. The destabilization in 91-93 is due to the bond opposition strain (see the darkened bonds in 91-93) and "bowsprit flagpole-flagpole" interactions (see the lone pair orbitals in 91-93).[25] This is demonstrated in the parent carbocyclic compound-bicyclo[3.3.1]-nonane (1) as well as in simple cyclohexane systems.[25,88] Conformation





90 might be more favored from enthalpy considerations which has been demonstrated for 1 by theoretical as well as experimental investigations.[88] However, there is a destabilizing factor for 90, namely the nonbonded interactions between O(3) and N(7) which may be due to one or all of the following factors:[3,9,40,88] (1) steric repulsion of the heteroatoms, (2) dipole-dipole repulsion, and (3) lone pair orbital repulsion. Because of such factors, both rings in 90 can be distorted substantially. Distortion has been found in certain related compounds 31, 46, and 48 which have CC conformations in the solid state via X-ray analysis.[21,42,92] Analysis of ^{1}H NMR spectral data and the dipole moment



21 X = Y = NCH_3; Z = CH_2

31 X = O; Y = Z = S

46 X = Z = CH_2; Y = $\overset{+}{N}H_2$, Br^-

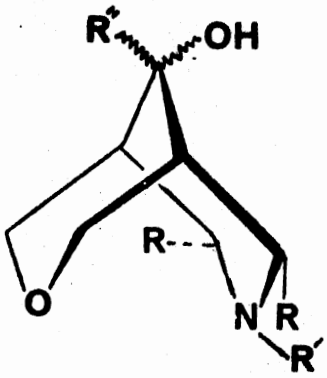
48 X = O; Y = C=O; Z = NCH_3

(2.02 ± 0.02 D) of 21 favored a CC conformation which was also supported by a LACO-MO calculations.[14,21]

Analysis of the ^{1}H NMR spectra of compounds 79a-79h showed that the vicinal coupling constants [$^3J_{H(1,5)H_a(2,4)}$, $^3J_{H(1,5)H_e(2,4)}$, $^3J_{H(1,5)H_a(6,8)}$, and $^3J_{H(1,5)H_e(6,8)}$] were small (ca. 2-4 Hz). These data can be explained only by the CC conformation 90.[91] For conformations 91-93, at least one of the coupling values above [i.e., $^3J_{H(1,5)H_e(6,8)}$ in 89; $^3J_{H(1,5)H_e(2,4)}$ in 90; $^3J_{H(1,5)H_e(2,4)}$ and $^3J_{H(1,5)H_e(6,8)}$ in 91] should be fairly large (ca. 10-12 Hz),[91] and this was not observed for any member of 79. Consequently, on the basis of our ^{1}H NMR spectral data ($^3J_{HH}$ values) for 79a-79h and when compared to certain related compounds 21, 31, 46, and 48 of known configuration, conformation 90 (possibly with ring flattening) is tentatively assigned as the probable conformer for the 3-oxa-7-azabispidinones in this study.

Two isomers of alcohols 79f were obtained by reduction ($NaBH_4$) of the amino ketone 79e. Since the $^3J_{HH}$ values were quite small [ca. 2-4 Hz, obtained by measuring the width at half height ($w_{1/2}$) of the multiplet signals obtained for H(2,4) and H(6,8)],[13] the isomeric alcohols probably have a CC conformation. Moreover, the IR spectrum (CCl_4) of alcohol 79d (mixture of isomers) was taken at three different concentrations (1.2×10^{-2} M, 6.0×10^{-3} M and 3.0×10^{-2} M), and only a sharp, narrow absorption band with a ν_{max} 3614 cm^{-1} was found at all three concentrations. This indicates a free OH group. From these observations, it is concluded that a solution of alcohol 79f can exhibit only an intermolecular hydrogen bonded OH group at high concentrations. Since the solution was fairly dilute, the alcohol (mixture of isomers) 79d existed as a monomer (without any significant intermolecular association

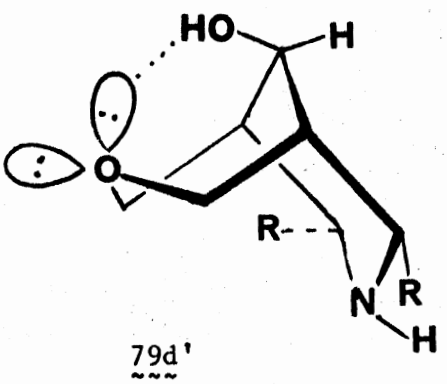
via H-bonding of the OH group), and the free OH group absorbed (sharply) at 3614 cm^{-1}. If an intramolecular hydrogen bonded OH group existed in 79d [which is possible only in 79d' (BC conformer), or in 79d" (CB conformer)], the ν_{OH} should be below 3500 cm^{-1} as a broadened signal (regardless of the concentration) which should approach a constant frequency but remain broad. This was not observed.[1,71] These spectral observations, therefore, favor a CC conformation for the alcohols 79d, 79f, and 79h.



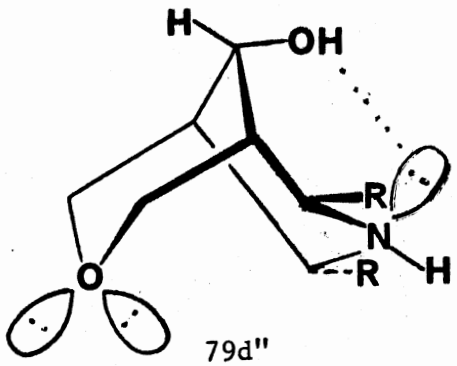
79d R = C_6H_4Cl-o; R' = R" = H

79f R = R" = H; R' = $CH_2C_6H_5$

79g R = H; R' = $CH_2C_6H_5$; R" = C_6H_5

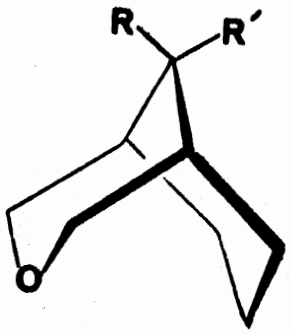


79d'



79d"

The configuration at C(9) for isomers of alcohols 79f and 79g was tentatively assigned via analysis of the ^1H NMR spectral data. For comparison purposes, the ^1H NMR spectral data of a series of alcohols 69a-69d,[12] were examined. Comparison of ^1H NMR spectral data (Table V) of the alcohols 79f' (isomer with R_F = 0.35) and 79f" (isomer with



69a R = OH; R' = H

69b R = H; R' = OH

69c R = OH; R' = C_6H_5

69d R = C_6H_5; R' = OH

R_F = 0.65) with that of 79h showed that $H_a(2,4)$ in 79f' experienced a deshielding (ca. 0.04 ppm) effect imposed by the OH group while $H_a(2,4)$ in 79f" was shielded (ca. 0.06 ppm) compared to $H_a(2,4)$ in 79h. If the shielding effect of the OH group is the same as in model compounds 69a and 69b,[12] then the OH group should be in the β-arrangement (i.e., OH is *syn* to the pyran ring) in 79f' and in the α-arrangement (i.e., OH is *anti* to the pyran ring) in 79f". In the case of alcohol 79g, only one isomer 79g' (R_F = 0.84) could be separated by column chromatography

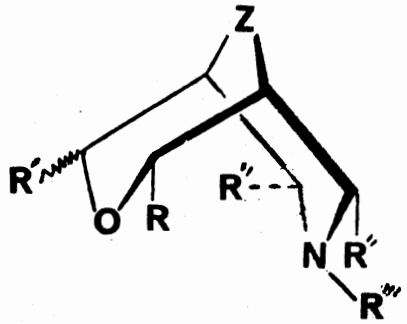
TABLE V

^1H NMR CHEMICAL SHIFTS OF $H_a(2,4)$ AND $H_e(2,4)$ IN 79f-79h

H	Compound (shift in δ values)			
	79f'	79f"	79g'	79h
$H_a(2,4)$	3.80	3.70	3.72	3.76
$H_e(2,4)$	4.16	3.80	3.94	3.92

as the second isomer 79g" degraded during the repeated attempts at separation by column chromatography. Analysis of the ^{1}H NMR spectrum of 79g' showed that H_a(2,4) experienced a small shielding effect compared to H_a(2,4) in 79h. Using the model compound 69d,[12] we tentatively conclude that the OH group in 79g' should be in an α-arrangement. It then follows that in the much less stable isomer 79g" the OH group should have the β-configuration.

To summarize, the syntheses of amino ketones 79a-79c and 79e were possible via a Mannich type cyclocondensations of the appropriate tetrahydropyran-4-ones. Certain chemical data (pages 137-139) suggested that free dienones like 83 may not be intermediates in the formation of the bicyclic compounds. Nucleophilic additions ($NaBH_4$, C_6H_5MgBr) to the amino ketone 79e gave alcohols 79f and 79g as isomeric (ca. 1:1)



79 a. R = R" = C_6H_5; R' = cis C_6H_5; R''' = H; Z = C=O

b. R = R" = C_6H_5; R' = trans C_6H_5; R''' = H; Z = C=O

c. R = R' = R''' = H; R" = o-C_6H_4Cl; Z = C=O

d. R = R' = R''' = H; R" = o-C_6H_4Cl; Z = CH(OH)

e. R = R' = R" = H; R''' = $CH_2C_6H_5$; Z = C=O

f. R = R' = R" = H; R''' = $CH_2C_6H_5$; Z = CH(OH)

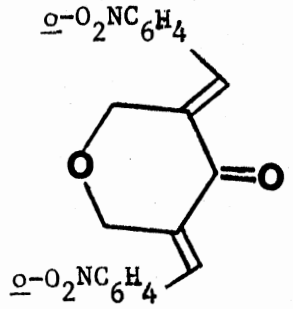
g. R = R' = R" = H; R''' = $CH_2C_6H_5$; Z = CC_6H_5(OH)

h. R = R' = R" = H; R''' = $CH_2C_6H_5$ Z = CH_2

mixtures which were separated by column chromatography. The small $^3J_{HH}$ values (ca. 2-4 Hz) for the ketones 79a-79c, and 79e indicated 90 as the major conformer (at least in solution), and this conformational preponderance was further reflected in the product ratios (ca. 1:1) from the nucleophilic ($NaBH_4$, C_6H_5MgBr) additions to the ketone 79e. The absence of an intramolecular, hydrogen-bonded OH group (detected by an IR spectroscopic study) in 79d and the small $^3J_{HH}$ values for the alcohols 79d, 79f, and 79g support a CC conformation for the above alcohols. The configuration of OH group in alcohols 79f', 79f", 79g', and 79g" were tentatively deduced via analysis of the ^1H NMR spectral data.

Suggestions for Future Work

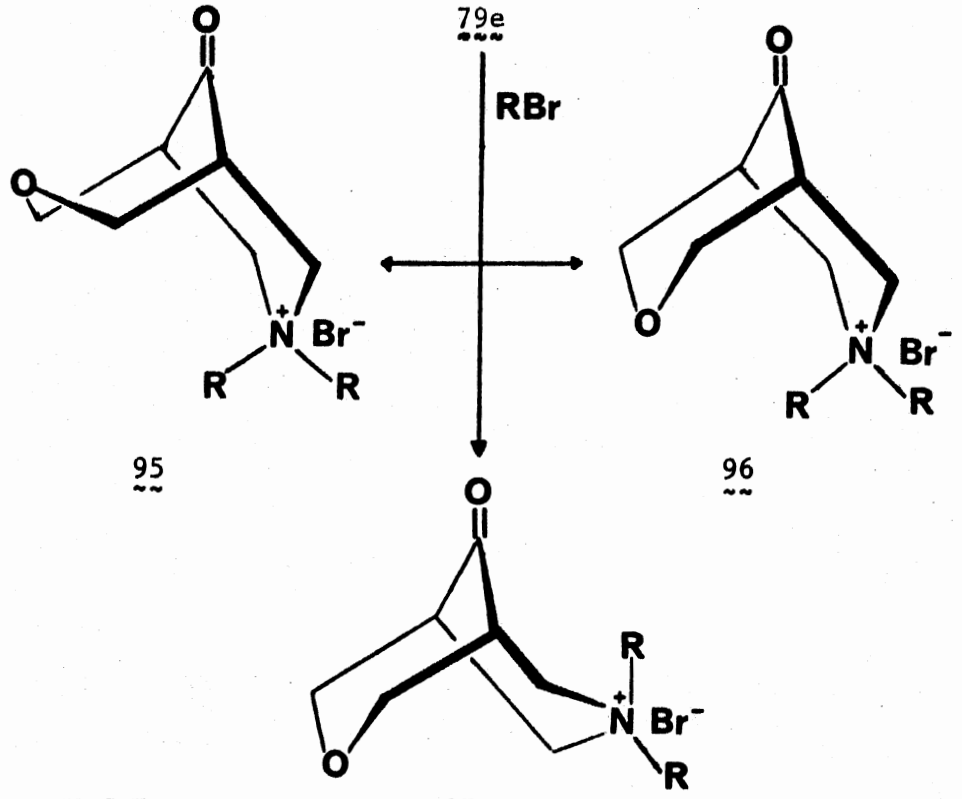
Free dienones like 94 (or the *para* isomer) can be condensed with



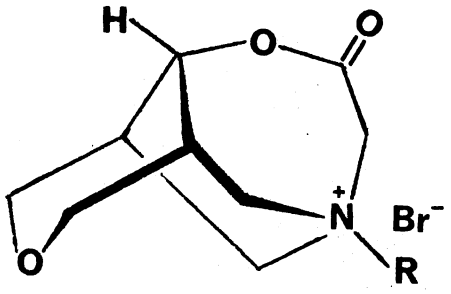
94

various amines [eg. RNH_2 where R = $CH_2C_6H_5$, C_2H_5, C_6H_{11}, $CH_2C_6H\ OCH_3$-*o*(or *p*)] in order to assess the influence of electronic factors in the nucleophilic cycloadditions to 94. Probably vigorous reactions (like a sealed-tube, pressure method) may be required to force stable dienones like 94 to undergo nucleophilic cycloadditions. In addition to the available spectroscopic techniques (IR, ^1H NMR and X-ray), certain chemical methods can be tried to elucidate the conformational preference of

the bispidinones reported herein. For instance, introducing a bulky group at N(7) in 79e may favor only 95 because of the severe nonbonded interactions involved in 96 or 97.[52,71] In the case of amino alcohols 79f and 79g, separation of isomers 79f', 79f", 79g', and 79g" can be facilitated via the esterification (p-nitrobenzoates) method which can also be informative with regard to the configuration of the OH groups in these isomers.[36] In all of the reported alcohols 79d, 79f, and 79g, one ppppossible avenue to capture the boat form (as with 79f", if such exists)

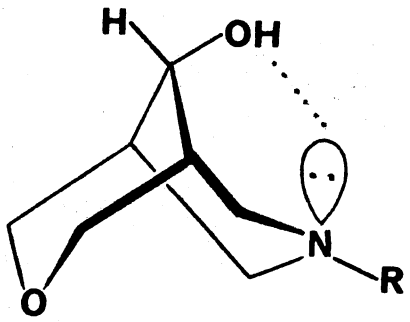


could involve alkylation of the N(7) with an alkyl bromoacetate. Lactonization could be effected to yield 98.[16] This would not be an absolute confirmation of a precursor CB 99 but it would be evidence that at least a psuedo boat could be tolerated in the 3-oxa-7-aza-bispidine system.



98

R = $CH_2C_5H_5$



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CHAPTER III

EXPERIMENTAL

General Information

Melting points were obtained on a Thomas-Hoover melting point apparatus and were uncorrected. The ^{1}H and ^{13}C NMR data were obtained on a Varian XL-100(15) NMR spectrometer equipped with a Nicolet TT-100 PFT accessory operating at 100.1 MHz for ^{1}H and 25.2 MHz for ^{13}C NMR with Me_4Si as internal standard in both cases. Infrared spectral data were obtained on a Beckman IR-5A Unit. Mass spectral data were collected on a CEC Model 21-110B HR mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennesse.

Starting Materials

1,3-Acetonedicarboxylic acid (Aldrich, mp 133°C dec), benzaldehyde (analytical reagent, Mallinckrodt), tetrahydro-4H-pyran-4-one (Aldrich, 99%, bp 166-165.5°C), ammonium acetate (analytical reagent, Mallinckrodt), D_2O (Aldrich, 99.8% D), triethylene glycol (Aldrich), hydrazine hydrate (Fisher Scientific Company), $NaBH_4$ (Ventron), and Mg (Mallinckrodt, analytical reagent) were purchased and used as such. o-Chlorobenzaldehyde (Eastman, bp 86-90°C/10 mm) and bromobenzene (Aldrich, bp 40°C/ > 5 mm) were distilled prior to use. Neutral Al_2O_3 (Brinkman activity stage I), and florisil (Research Specialties Company) were used

as packing material for the chromatographic separations and plastic sheets precoated with neutral Al_2O_3 (Brinkmann F-254, type E) were used in TLC experiments. Organic solvents were distilled before use. All organic extracts were dried (Na_2SO_4) and a roto-evaporator was used to evaporate the organic solvents in the usual workup. The ketones 80 [mp 70-72°C (lit[6] 69-70°C), 25 g (35%)] and 81 [mp 133-135°C (lit[6] 131°C), 16 g (21%)] were prepared by acid-catalyzed condensation of 1,3-acetonedicarboxylic acid (42 g, 287 mmol) with benzaldehyde (125 g, 1178 mmol) at -10°C and at room temperature, respectively.[6] The dibenzylidene compound 83 [mp 186-187°C (lit[19] 185°C), 1.5 g (53%)] was obtained by a base-catalyzed condensation of ketone 82 (1 g, 10 mmol) and benzaldehyde (2.1 g, 20 mmol).[19]

Preparation of 6,8-Diphenyl-*cis*-2,4-diphenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (79a)

A mixture of ketone 80 (1.26 g, 5 mmol), benzaldehyde (1.1 g, 10 mmol), ammonium acetate (1.2 g, 15 mmol), and anhydrous ethanol (10 mL) was placed in a 50 mL, round-bottom flask and was heated (oil bath, 55-60°C) with stirring (magnetic) under N_2. After 30 min, a clear yellow solution was obtained. A white solid began to form after 1.5 h. This reaction mixture was heated under the same conditions (2 h) and was allowed to cool to room temperature. After standing in a refrigerator overnight, a white solid was filtered off (suction), was washed well with ether (4 × 10 mL), and was dried (suction). Recrystallization (C_6H_6) gave 0.4 g (18%) of 79a as a white powder: mp 254-256°C dec (lit[5] 242-244°C dec); IR (KBr) ν_{max} 1715 (C=O), 1000-1100 (C-O-C), 3278 cm^{-1} (-NH); ^1H NMR ($DCCl_3$) δ 1.55 (1 H, bs, NH), 3.06 [2 H, bs, H(1,5),

$w_{1/2}$ = 4 Hz] , 4.52 [2 H, bs, H(6,8), $w_{1/2}$ = 4 Hz], 5.06 [2 H, bs, H(2,4), $w_{1/2}$ = 4 Hz], 6.64-6.8 (5 H, m, Ar-H), 7.0-7.8 (5 H, m, Ar-H), 7.37-7.7 (10 H, m, Ar-H); mass spectrum m/e, calcd. for $C_{31}H_{27}NO_2$: M^+ 445.2042; Found: M^+ 445.2042.

Preparation of 6,8-Diphenyl-*trans*-2,4-diphenyl-3-oxa-7-azabicyclo[3.3.1]nonane-9-one (79b)

This condensation was carried out as in the preparation of 79a using ketone 81 (1.26 g, 5 mmol), benzaldehyde (1.1 g, 10 mmol), ammonium acetate (1.2 g, 15 mmol), and anhydrous ethanol (15 mL). Recrystallization (C_6H_6) of the product gave 0.37 g (16%) of 79b as a white powder: mp 266-268°C dec (lit[5] 245-247°C dec); IR (KBr) ν_{max} 1715 (C=O), 1000-1100 cm^{-1} (C-O-C), 3279 (-NH); ^1H NMR ($DCCl_3$) δ 2.14 (1 H, bs, NH), 2.88 [2 H, bs, H(1,5), $w_{1/2}$ = 4 Hz], 4.36 [2 H, bs, H(6,8), $w_{1/2}$ = 4 Hz], 4.7 [2 H, bs, H(2,4), $w_{1/2}$ = 4 Hz], 6.62-6.8 (5 H, m, Ar-H), 6.96-7.06 (5 H, m, Ar-H), 7.34-7.64 (10 H, m, Ar-H); mass spectrum m/e, calcd. for $C_{31}H_{27}NO_2$: M^+ 445.2042; Found: M^+ 445.2035.

Preparation of 6,8-Di(*o*-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (79c)

A mixture of the ketone 82 (0.5 g, 5 mmol), *o*-chlorobenzaldehyde (1.4 g, 10 mmol), ammonium acetate (0.4 g, 5 mmol), and anhydrous ethanol (10 mL) was placed in a 50 mL Erlenmeyer flask and was heated *slowly* (hot plate, 60°C) with constant stirring (magnetic). A clear pale yellow solution was obtained (15 min) and heating was continued (30 min). The reaction mixture was allowed to cool to room temperature. Removal of the solvent resulted in a brown syrup which, upon trituration (ether),

gave a white solid. Recrystallization (2-propanol) gave 0.140 g (8%) of 79c as white flakes: mp 212-214°C dec; IR (KBr) ν_{max} 1715 (C=O), 1000-1100 (C-O-C), 3278 cm^{-1} (-NH); ^1H NMR ($DCCl_3$) δ 2.31 (1 H, bs, NH), 2.71 [2 H, bs, H(1,5), $w_{1/2}$ = 5 Hz], 3.73 [2 H, d, H_a(2,4), J = 12 Hz], 4.11 [2 H, d, H_e(2,4), J = 12 Hz], 4.96 [2 H, bs, H(6,8), $w_{1/2}$ = 10 Hz], 7.22-7.5 (6H, m, Ar-H), 8.02 (2 H, d, Ar-H, $^3J_{HH}$ = 8 Hz); ^{13}C NMR: see Table IV; mass spectrum m/e, calcd. for $C_{19}H_{17}Cl_2NO_2$: M^+ 361.0636; Found: M^+ 361.0628.

Anal. Calcd. for $C_{19}H_{17}Cl_2NO_2$: C, 63.00; H, 4.73; Cl, 19.57; N, 3.87

Found: C, 62.95; H, 4.73; Cl, 19.55; N, 3.78.

Preparation of 6,8-Di(o-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-ols (79d)

The ketone 79c (0.100 g, 0.3 mmol) was suspended in anhydrous methanol (10 mL) and $NaBH_4$ powder (0.060 g, 1.6 mmol) was added in one portion. This reaction mixture was stirred (magnetic) overnight. A clear solution was obtained which, upon acidification with aq. HCl (10%, 20 mL) followed by basification with aq. NaOH (10%, 30 mL), gave a white solid. The white solid was filtered (suction), was washed with ice-cold water (5 × 20 mL), and was dried (aspirator). This mixture of isomers (0.097 g, 97%) was evaluated as such: mp 130-140°C; IR (KBr) ν_{max} 3500 (OH), 1000-1200 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) δ 2.0 [2 H, bs, H(1,5), $w_{1/2}$ = 8 Hz], 1.6-2.2 [2 H bs, NH, exchanged with D_2O], 3.5 [2 H, bt, H(9)], 3.8 [2 H, bt, H_a(2,4)], 4.4 [2 H, bm, H_e(2,4)], 5.3 [2 H, bs, H_a(6,8), $w_{1/2}$ = 6 Hz], 7.3 (6 H, m, Ar-H), 7.9 (2 H, bd, Ar-H); mass spectrum m/e, calcd. for $C_{19}H_{19}Cl_2NO_2$: M^+ 363.0793; Found: M^+ 363.0790; TLC [neutral alumina,

$HCCl_3$-H_3COH (40:1)], R_F = 0.85 and 0.70.

IR (CCl_4) spectral analysis [0.05 mm calibrated, sealed, liquid cell (NaCl), Beckmann] were recorded for this isomeric mixture on three different (1.2×10^{-2} M; 6.0×10^{-3} M and 3.0×10^{-3} M) concentrations to differentiate between an intra- and an intermolecular hydrogen-bonded OH group. Only a sharp absorption band at 3614 cm^{-1} was detected at all three concentrations.

Preparation of 7-N-Benzyl-3-oxa-7-azabicyclo-[3.3.1]nonan-9-one (79e)

Benzylamine (1.1 g, 10 mmol) was neutralized carefully with glacial H_3CCO_2H (0.6 g, 10 mmol) and the resulting white solid was dissolved in anhydrous H_3COH (40 mL) with stirring (magnetic) under N_2. Paraformaldehyde (2.4 g, 80 mmol) was suspended in the above solution. Heating (oil bath) and stirring (magnetic) were begun with the simultaneous addition of the ketone 82 (1.0 g, 10 mmol) in small portions. The reaction mixture (brown) was then boiled under reflux (6 h), was allowed to cool (room temperature), and was stirred (magnetic) overnight at room temperature. Evaporation of methanol gave a brown oil which was shaken with ether (50 mL) and water (50 mL). The ether layer was discarded. After washing with ether (2 × 50 mL), the aq. layer was cooled (ice) and was made strongly basic (pH ≃ 10) by adding NaOH pellets. The resulting suspension was extracted with $HCCl_3$ (3 × 25 mL). Evaporation of the dried organic extracts gave a brown oil, which upon distillation (vacuum), yielded 79e (0.9g, 39%) as a clear liquid: bp 118-120°C/1 mm (oil bath, 200-210°C); IR (neat liquid) ν_{max} 1730 (C=O), 1000-1100 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) δ 2.5 [2 H, bs, H(1,5), $w_{1/2}$ = 10 Hz], 2.9 [2 H,

dd, $\underline{H}_a$(6,8), $^2J_{HH}$ = 11 Hz, $^3J_{HH}$ = 6 Hz], 3.1 [2 H, dd, $\underline{H}_e$(6,8), $^2J_{HH}$ = 11 Hz, $^3J_{HH}$ = 4 Hz], 3.52 [2 H, s, $\underline{H}_2$CAr], 3.82 [2 H, dd, $\underline{H}_a$(2,4), $^2J_{HH}$ = 11 Hz, $^3J_{HH}$ = 3 Hz], 4.16 [2 H, bd, $\underline{H}_e$(2,4), $^2J_{HH}$ = 11 Hz, $w_{\frac{1}{2}}$ = 4 Hz], 7.28 (5 H, bs, Ar-$\underline{H}$); ^{13}C NMR: see Table IV; mass spectrum m/e, calcd. for $C_{14}H_{17}NO_2$: M^+ 231.1259; Found: M^+ 231.1263.

Amino ketone 79e was prepared as before using benzylamine (5.5 g, 50 mmol), H_3CCO_2H (3.0 g, 50 mmol), paraformaldehyde (12.0 g, 400 mmol), ketone 82 (5.0 g, 50 mmol), and H_3COH (200 mL). The crude ketone 79e (11.1 g, 48 mmol, 95.99%) was dissolved in dry ether (20 mL) and was cooled (ice). A solution of 60% aq. $HClO_4$ (8.4 g, 48 mmol) in ether (10 mL) was added dropwise. A pale yellow precipitate was obtained, was washed with ether (3 × 20 mL), was filtered and was dried (suction). The crude perchlorate 86 (15.35 g, 96.4%) was suspended in water (100 mL), and C_2H_5OH (95%, 50 mL) was added to increase the solubility of 86 in water. The above suspension was made strongly alkaline (to litmus) by adding aq. NaOH solution (15%). A pale yellow oil separated and was extracted with $HCCl_3$ (4 × 30 mL). Evaporation of the dried $HCCl_3$ solution gave 79e (8.3 g, 72%) as a brown oil. IR and ^{1}H NMR spectral data confirmed the identity of the product as 79e obtained previously.

Preparation of 7-N-Benzyl-3-oxa-7-azabicyclo-[3.3.1]nonan-9-ols (79f' and 79f")

To a solution of the amino ketone 79e (0.6 g, 2.6 mmol) in 2-propanol (10 mL), were added $NaBH_4$ powder (0.6 g, 16 mmol) and water (5 mL), and the reaction mixture was stirred overnight. A clear solution was obtained which, upon acidification with aq. HCl (10%, 25 mL) followed by

basification with aq. NaOH (10%, 15 mL), gave a suspension. The suspension was extracted with $HCCl_3$ (3 × 50 mL), and the extracts were dried. Upon evaporation, the dried organic extract yielded 0.6 g of crude 79f as a brown oil which was found to be a mixture of two compounds from TLC experiment [neutral alumina; $HCCl_3$-H_3COH, (40:1); R_F = 0.65 and 0.35]. This brown oil was chromatographed on a column (neutral alumina, ca. 60 g) with 100 mL total portion of each of the following solvent systems as eluants in order: Petroleum ether (bp 37-60°C); petroleum ether-C_6H_6 (3:1, 1:1 and 1:3); C_6H_6; C_6H_6-ether (3:1, 1:1, and 1:3); ether; ether-$H_3CCO_2C_2H_5$ (3:1, 1:1, and 1:3); $H_3CCO_2C_2H_5$; ether-$HCCl_3$ (3:1, 1:1, and 1:3); $HCCl_3$, and $HCCl_3$-H_3COH (40:1). However, only mixtures of isomers of 79f (0.4 g) were obtained using $HCCl_3$-H_3COH (1:40, 100 mL). A portion of the isomeric mixture (0.250 g) was rechromatographed on a florisil (4 g) column using n-C_6H_{14} (100 mL), $HCCl_3$ (100 mL) and $HCCl_3$-H_3COH (40:1, 100 mL) as eluants in the order given. Two isomers (79f' with R_F = 0.65, 0.100 g; 79f" with R_F = 0.35, 0.100 g; mixture of 79f' and 79f", 0.050 g) were separated using $HCCl_3$-H_3COH (40:1, 100 mL) as eluant. The isomer 79f" (R_F = 0.35) (page 110) was found to have the following characteristics: mp 200-201°C dec; IR (KBr) ν_{max} 3350-3450 (OH), 1000-1200 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) δ 2.2 [2 H, dd, H_a(6,8), $^2J_{HH}$ = 11 Hz, $^3J_{HH}$ = 4 Hz], 3.15 [2 H, bt, H_e(6,8), $^2J_{HH}$ = 11 Hz], 3.4 [1 H, bs, OH, D_2O exchanged], 3.48 [2 H, s, H(7')], 3.70 [2 H, bdd, H_1(2,4), $^2J_{HH}$ = 11 Hz], 3.74 [1 H, bs, H(9)], 3.80 [2 H, bdd, H_e(2,4), $^2J_{HH}$ = 11 Hz], 7.25 [5 H, m, Ar-H]; ^{13}C NMR: see Table IV; mass spectrum m/e, calcd. for $C_{14}H_{17}NO_2$; M^+ 233.1416; Found: M^+ 233.1416.

Analysis of the ^1H NMR spectrum of the other isomer 79f' (R_F = 0.65) (page 110) indicated the presence of ^1H NMR signals at δ 1.5 which were

not expected for 79f' (and might be due to some impurity). Therefore, the isomer 79f' was rechromatographed on a florisil column (4 g) using $n\text{-}C_6H_{14}$ (100 mL), $HCCl_3$ (100 mL) and $HCCl_3\text{-}H_3COH$ (40:1, 100 mL) in order. The isomer 79f' (50 mg) was separated using $HCCl_3\text{-}H_3COH$ (40:1, 100 mL) and was analyzed: mp 150-155°C dec; IR (KBr) ν_{max} 3350-3450 (OH), 1000-1200 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) δ 1.9 [2H, bd, H(1,5)], 2.5 [2 H, bdd, H_a(6,8), $^3J_{HH}$ = 10 Hz], 3.1 [2 H, bdd, H_e(6,8), $^2J_{HH}$ = 10 Hz], 3.42 [1 H, bs, OH, exchanged with D_2O], 3.6 [2 H, bs, H(7')], 3.8 [3 H, bdd, H_a(2,4) and H(9)], 4.16 [2 H, bdd, H_e(2,4)], 7.3 [5 H, bs, Ar-H]; mass spectrum m/e, calcd. for $C_{14}H_{17}NO_2$: M^+ 233.1416; Found: M^+ 233.1425. TLC analysis neutral alumina, $HCCl_3\text{-}H_3COH$ (40:1) of 79f' showed only one spot but the ^1H NMR analysis indicated trace amounts of an impurity.

Preparation of 7-N-Benzyl-9-phenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ols (79g' and 79g")

A 100-mL, 3-necked round-bottom flask (fitted with an addition funnel, stopper and a condenser) was heated (heat-gun) and was flushed with N_2 (30 min). Pure magnesium turnings (90 mg, 3.6 mg atom) were placed in the flask and flushing (with N_2 while heating) was continued. The magnesium turnings were covered with a small volume (2 mL) of dry ether. A solution of bromobenzene (freshly distilled, 0.57 g, 3.6 mmol) in dry ether (10 mL) was added dropwise, and the reaction mixture was heated (hot plate) gently with stirring (magnetic) to dissolve the entire magnesium (4 h). The reaction mixture (turbid) was allowed to cool (room temperature), and then a solution of the ketone 79e (0.56 g, 2.4 mmol) in dry ether (20 mL) was added dropwise. A white solid formed immediately, and the mixure was stirred (magnetic) overnight under N_2

atmosphere. The addition complex was decomposed by adding ice-cold, satd. aq. NH_4Cl (100 mL) to obtain a clear aqueous and ether layers. The ether layer was separated and the aq. layer was extracted with ether (2 x 50 mL). These ether extracts were combined and were dried; evaporation of the solvent gave a semisolid. Upon trituration of the semisolid (Skelly B, 5 mL), a white solid (0.415 g) was obtained. Recrystallization (Skelly B) gave 0.271 g (36.2%) of alcohol 79g as a white powder, mp 91-95°C. TLC neutral alumina, $HCCl_3$-H_3COH (40:1) analysis indicated the presence of two components (R_F = 0.84 and 0.51). This isomeric mixture (0.200 g) was chromatographed on a florisil (20 g) column using n-C_6H_{14} (100 mL), $HCCl_3$ (100 mL), and $HCCl_3$-H_3COH (100 mL of each 40:1, 20:1, 10:1 mixtures). Unfortunately, only a mixture of compounds was obtained with all of the above eluants. The column was then stripped with H_3COH (200 mL), and the original mixture (0.150 g) was recovered after evaporation of the solvent. This mixture was rechromatographed on a florisil (15 g) column using n-C_6H_{14} (100 mL), $HCCl_3$ (100 mL) and $HCCl_3$-H_3COH (40:1, 200 mL). One isomer 79g' (R_F = 0.84, 0.020 g) (page 110) was separated using $HCCl_3$-H_3COH (40:1, 200 mL) and was found to possess the following physical and spectral characteristics: mp 157-159°C dec; IR (KBr) ν_{max} 3300-3350 (OH), 1000-1200 cm^{-1} (C-O-C); ^1H NMR (D_3COD) δ 2.62 [2 H, bs, H(1,5)], 3.20 [2 H, bdd, H_a(6,8), $^2J_{HH}$ = 11 Hz], 3.4 [2 H, bdd, H_e(6,8), $^3J_{HH}$ = 11 Hz], 3.6 [2 H, bs, H(7')], 3.72 [2 H, bdd, H_a(2,4), $^3J_{HH}$ = 11 Hz], 3.84 [1 H, bs, H(9)], 3.94 [2 H, bdd, H_e(2,4), $^3J_{HH}$ = 11 Hz], 7.88 [10 H, m, Ar-H]; ^{13}C NMR: see Table; mass spectrum m/e calcd. for $C_{20}H_{23}NO_2$: M^+ 309.1739; Found: M^+ 309.1741.

The chromatographic eluation was continued using $HCCl_3$-H_3COH

(100 mL of each 40:1, 20:1, and 10:1) as eluant, but only a mixture was obtained. The column was stripped with H_3COH (200 mL), and the mixture (0.100 g) was recovered by evaporation of the solvent. This new mixture was rechromatographed on a florisil (10 g) column using n-C_6H_{14} (100 mL), $HCCl_3$ (100 mL of each 40:1, 20:1, 10:1, 3:1, 1:1, and 1:3) as eluants. Again only a mixture (TLC, R_F = 0.84 and 0.50) was obtained initially, but in the last stage using $HCCl_3$-H_3COH (1:3, 200 mL), a single component (R_F = 0,52, 0.015 g) was separated and was found to possess the following characteristics: mp 270-275°C dec; IR (KBr) ν_{max} 2960, 2920, 1730, 1450, 1260, 1100 1100-1200 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.9 (6 H, bt), 1.42 (10 H, bm), 4.2 (2 H, bd), 7.2-7.7 (2 H, bm, Ar-H). The above data did not correspond to the expected second isomer 79g" which might have been altered or degraded on the column during the repeated eluation.

Preparation of 7-N-Benzyl-3-oxa-7-aza-bicyclo[3.3.1]nonane (79h)

A magnetically stirred solution of amino ketone 79e (2.3 g, 9.9 mmol), hydrazine hydrate (85% solution, 2.93 g, 49.7 mmol), and triethylene glycol (30 mL) maintained under N_2 was heated to 60°C and 85% KOH (pellets, 3.69 g, 55.9 mmol) was added. The yellow solution was boiled under reflux (internal solution temperature 145°C; oil bath, 150-155°C) for 4 h; then a Dean-Stark trap was inserted and the distillate was removed until the temperature of the reaction solution reached 200°C. The cooled contents of reaction flask were poured into water (30 mL), and the suspension was extracted with ether (4 × 25 mL). The ether extract was washed with aq. NaOH (0.1 N, 2 × 25 mL). Evaporation of the

dried ether layer gave 79h (2.2 g, 100%) as a clear liquid. IR (neat) ν_{max} 3000-3010 (aromatic) 2750-3000 (Bohlmann bands), 1000-1100 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) δ 1.48-1.84 [4 H, m, H(1,5,9)], 2.3 [2 H, bd, H_a(6,8), $^2J_{HH}$ = 11 Hz], 2.92 [2 H, bd, H_e(6,8), $^2J_{HH}$ = 11 Hz], 3.48 [2 H, s, H(7')], 3.76 [2 H, bd, H_a(2,4), $^2J_{HH}$ = 10 Hz], 3.92 [2 H, bd, H_e(2,4), $^2J_{HH}$ = 10 Hz], 7.2-7.4 (5 H, m, Ar-H); ^{13}C NMR: see Table IV; mass spectrum m/e, calcd. for $C_{14}H_{19}NO$: M^+ 217.1467; Found: M^+ 217.1466.

This sample of 79h was converted to the perchlorate 87 for final characterization.

Preparation of Tetrahydro-4H-pyran-4-one-d_4-(3,3,5,5) (84)

A mixture of the ketone 82 (0.5 g, 5 mmol), anhydrous K_2CO_3 (0.9 g, 7 mmol) and D_2O (22 g, 1100 mmol) was stirred (magnetic) under N_2 at room temperature for 72 h. The solution was then extracted with $HCCl_3$ (3 × 15 mL). Evaporation of the dried organic phase resulted in a clear liquid (0.5 g, 96%). Incorporation of deuterium was essentially quantitative. IR (KBr) ν_{max} 1706 (C=O), 1000-1100 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$) δ 3.96 (s, O-CH); mass spectrum m/e, calcd. for $C_5H_4D_4O_2$: M^+ 104.0775; Found: M^+ 104.0772

Preparation of the Perchlorate of 7-N-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (86)

Amino ketone 79e (0.400 g, 1.7 mmol) was dissolved in anhydrous ether (ca. 20 mL), and the solution was cooled (ice). To the cold solution was added aq. $HClO_4$ (60%, 0.290 g, 1.7 mmol) and a white solid

separated out which was filtered, was washed with anhydrous ether (4 × 25 mL) and was dried (aspirator). Recrystallization (H_3CCN-$H_3CCO_2C_2H_5$, 1:2) gave 86 (0.460 g, 82.6%) as a pure white solid: mp 182-185°C (softening), 201-202°C dec; IR (KBr) ν_{max} 3350 (OH), 1070-1120 (ClO_4), 1000-1200 cm^{-1} (C-O-C); ^1H NMR (D_2O, TSP) δ 2.1 [2 H, bs, H(1,5)], 3.66 [6 H, bs, H(2,4)], 4.08 [4 H, bs, H(6,8)], 4.36 (2 H, bs, Ar-CH_2), 7.56 (5 H, s, Ar-H); ^{13}C NMR: see Table IV.

Anal. calcd. for $C_{14}H_{18}ClNO_6.H_2O$: C, 48.8; H, 5.76 N, 4.01

Found: C, 48.14; H, 5.90; N, 4.01

Preparation of the Perchlorate of 7-N-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonane (87)

Crude amine 79h (1.0 g, 4.6 mmol) was dissolved in dry ether (20 mL) and the solution was cooled (ice). A solution of 60% aq. $HClO_4$ (0.8 g, 4.6 mmol) in dry ether (5 mL) was added dropwise. The white precipitate, which separated out immediately, was washed with dry ether (3 × 10 mL), was filtered and was dried (aspirator). Recrystallization (H_3CCN-ether, 1.5) gave 1.45 g (99.2%) of 87 as a pure white solid: mp 191-192.5°C dec; IR (KBr) ν_{max} 1070-1120 (ClO_4), 1000-1120 cm^{-1} (C-O-C); ^1H NMR (D_2O, TSP) δ 1.9-2.20 [4 H, bm, H(1,5,9)], 3.20-4.20 [8 H, m, H(2,4,6,8)], 4.34 [2 H, s, H(7')], 7.54 (5 H, s, Ar-H); ^{13}C NMR: see Table IV. [TSP = $(CH_3)_3SiCD_2CD_2CO_2Na$]

Anal. calcd. for $C_{14}H_{20}ClNO_5$: C, 52.92; H, 6.43; N, 4.41.

Found: C, 53.01; H, 6.40; N, 4.46.

Attempted Preparation of 6,8-Di(o-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one-d_2-(1,5)

Method I. The reaction was performed as in the preparation of 79c but using ketone 84 (0.5 g, 5 mmol), o-chlorobenzaldehyde (1.4 g, 10 mmol), ammonium acetate (0.4 g, 5 mmol), and anhydrous ethanol (10 mL). Recrystallization (2-propanol) gave 0.050 g (3%) of white flakes (mp 212-213°C dec) which was identified as 79c from IR (KBr) and ^{1}H NMR spectral data; mass spectrum m/e calcd. for $C_{19}H_{15}Cl_2NO_2D_2$: M^+ 363.07618; Found: M^+ 361.0624. This corresponds to m/e calcd. for $C_{19}H_{17}Cl_2NO_2$: M^+ 361.0636. Thus, deuteration did not occur.

Method II. A mixture of ketone 79c (0.05 g, 0.2 mmol), anhydrous K_2CO_3 (0.205 g, 0.2 mmol) and D_2O (11 g, 500 mmol) was boiled (oil bath, 110°C) with stirring under N_2 for 24 h. The reaction mixture was cooled and filtered. Recrystallization (2-propanol) gave 0.030 g (60%) of shining white flakes; mp 212-214°C dec; IR and ^{1}H NMR data are found to be identical with those of ketone 79c.

Attempted Preparation of 6,8-Diphenyl-3-oxa-7-aza-bicyclo[3.3.1]nonan-9-one

Method I. A mixture of ketone 83 (0.1 g, 0.4 mmol), ammonium acetate (0.03 g, 0.4 mmol) and anhydrous ethanol (20 mL) was boiled (oil bath, 85°C) with stirring (magnetic) under N_2 for 24 h. Upon cooling (overnight, refrigirator), the reaction mixture yielded an yellow solid (0.08 g, 180-183°C dec) which was identified as 83.

Method II. Into a solution of ketone 83 (0.100 g, 0.4 mmol) in anhydrous ethanol (20 mL) was passed ammonia (gas), and the solution

was heated (oil bath, 60°C) with stirring (magnetic) under N_2 for 10 h. Upon cooling the reaction mixture, the starting material 83 (0.09 g, mp 183-186°C dec) precipitated. Changing the solvent [95% C_2H_5OH, $(CH_3)_2CHOH$, $HCCl_3$-C_2H_5OH, 1:1] and reaction time (12 h, 24 h) did not result in much conversion of the starting material 83.

Attempted Preparation of 6,8-Diphenyl-7-N-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one

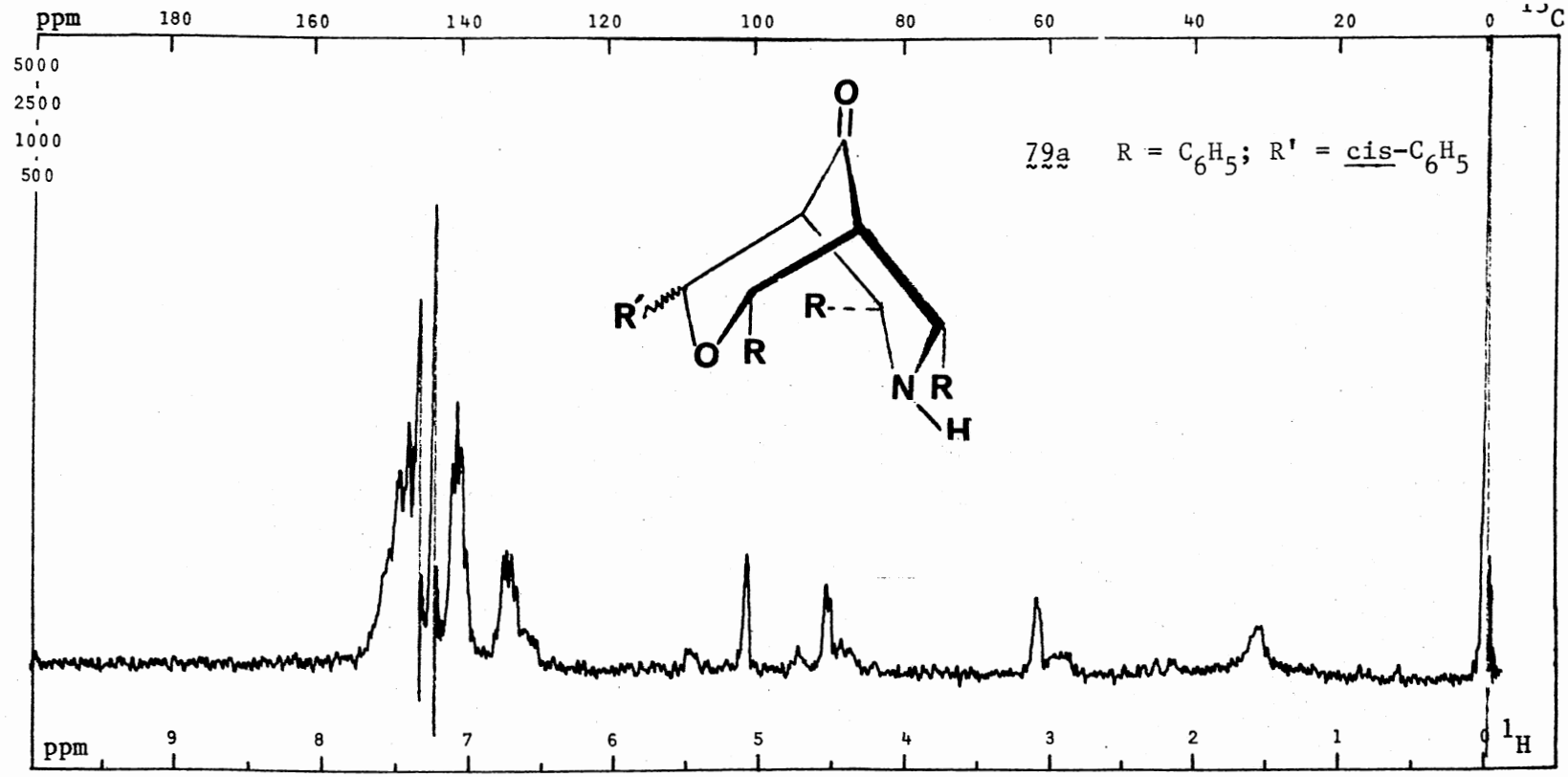
A mixture of ketone 83 (0.1 g, 0.4 mmol) methylamine hydrochloride (0.05 g, 0.7 mmol), sodium acetate (0.1 g, 0.7 mmol), and C_2H_5OH-$HCCl_3$ (1:1), 10 mL) was heated (oil bath, 60°C) with stirring (magnetic) under N_2 for 12 h. Upon cooling the reaction mixture, the starting material 83 (0.085 g, mp 183-185°C dec) precipitated.

Attempted Preparation of 6,8-Diphenyl-7-N-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one

Freshly distilled benzylamine (1.1 g, 10 mmol) and glacial H_3CCO_2H (0.6 g, 10 mmol) were mixed to form a white solid which was dissolved in ethanol (20 mL) by stirring (magnetic). Benzaldehyde (2.2 g, 20 mmol) and the ketone 82 (1 g, 10 mmol) were added to the above solution, and the resulting solution was heated (oil bath, 60°C) under N_2. The solution became yellow (0.5 h), and a solid began to separate out (1.5 h). Upon continued heating, a large amount of solid separated out, and the reaction mixture was allowed to cool (room temperature) and was filtered (suction) to obtain an yellow solid (1.2 g), mp 185-187°C. The ^1H NMR and IR spectra were found to be identical with that of 83. A mixture of 83 (0.1 g, 0.4 mmol) and benzylamine (0.05 g, 0.4 mmol) in

C_2H_5OH-$HCCl_3$ (1:1, 10 mL) was boiled for 24 h and then was allowed to cool. An yellow solid (0.07 g, 180-183°C dec) precipitated and was identified as the starting material 83.

PLATE I

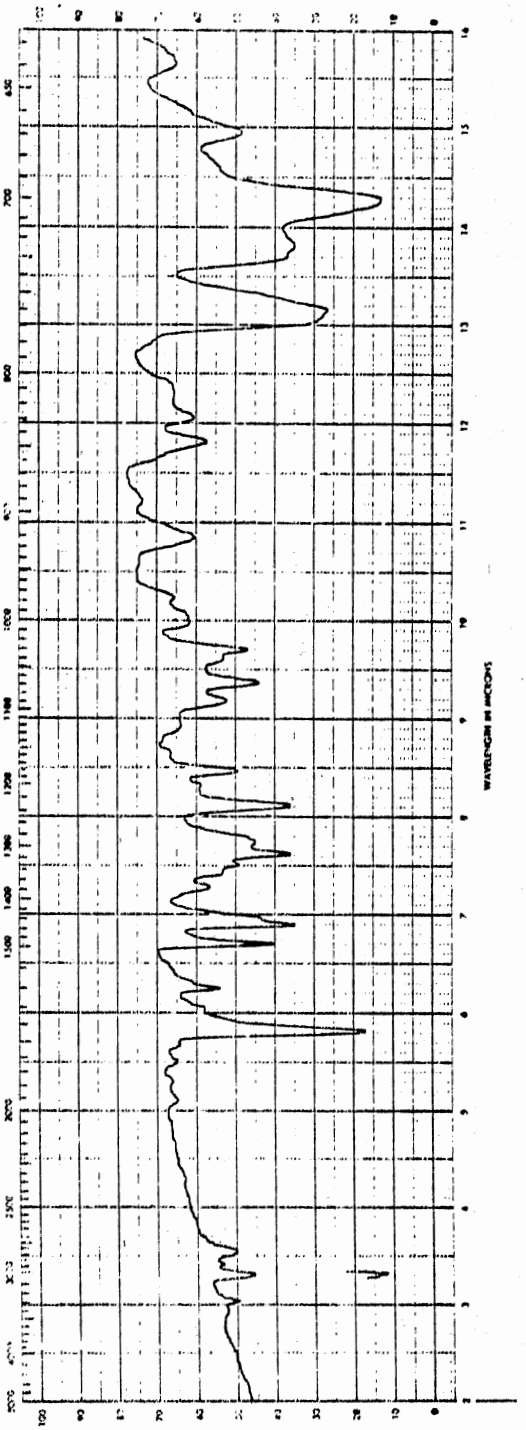


^1H NMR Spectrum of 6,8-Diphenyl-cis-2,4-diphenyl-3-oxa-7-azabicyclo[3.3.1] nonan-9-one (79a)

CW X; Solvent $DCCl_3$; SO. 85771 Hz; PW. 1000 Hz; T. 30°C; SA. 4;

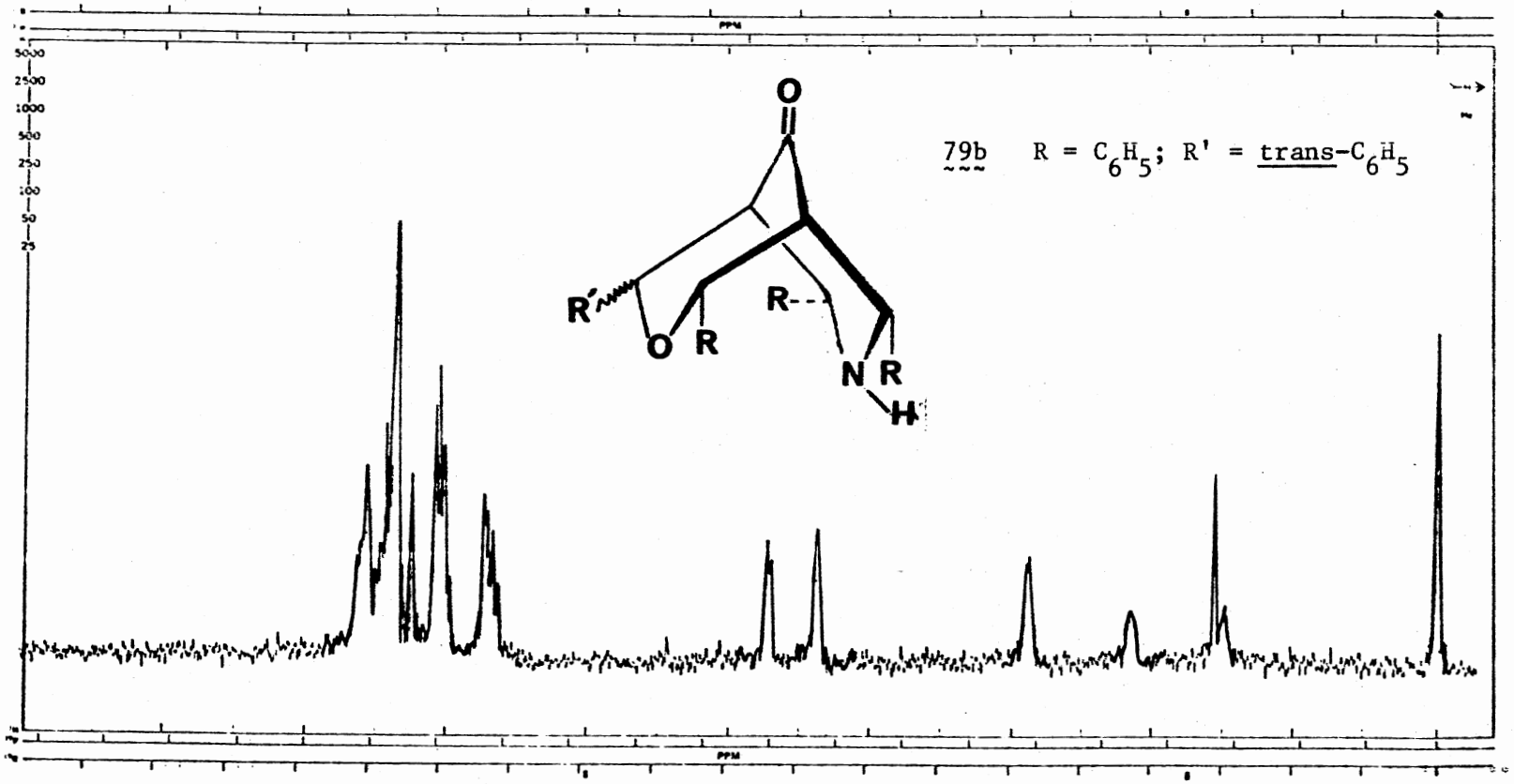
SF. 100.1 MHz; FB. 2 Hz; Lock ^2H; ST. 250 s.

PLATE II



IR Spectrum of 79a, KBr Pellet

PLATE III

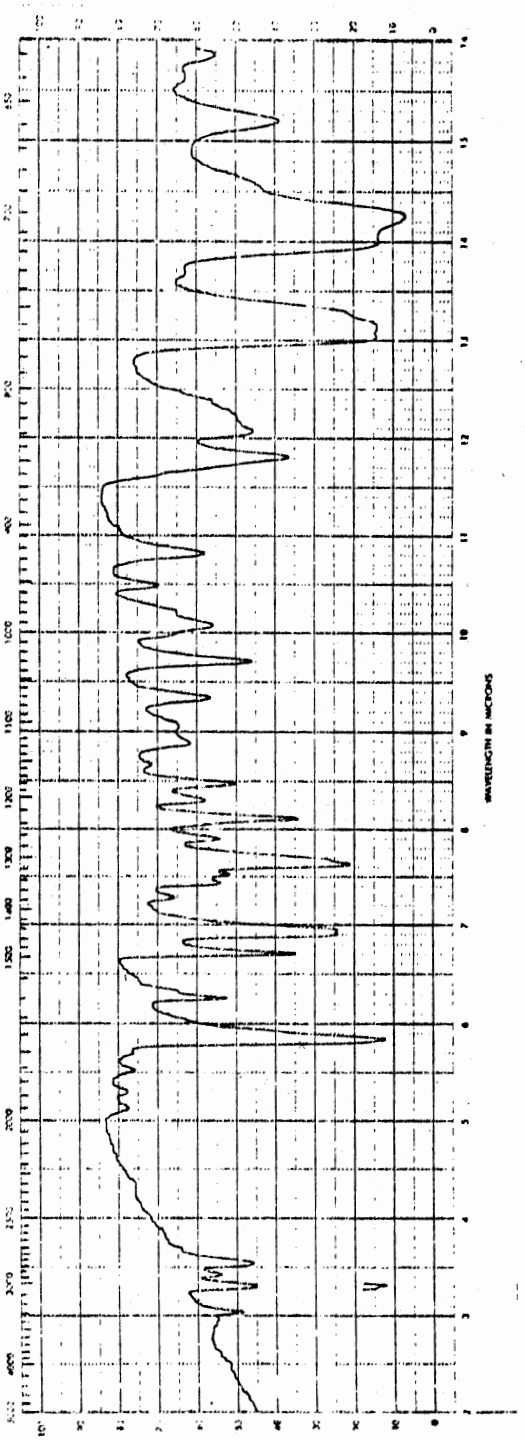


^{1}H NMR Spectrum of 6,8-Diphenyl-trans-2,4-diphenyl-3-oxa-7-azabicyclo[3.3.1]nonane-9-one (79b)

CW X; Solvent $DCCl_3$; So. 85771 Hz; PW. 1000 Hz; T. 30°C; SA. 3.2;

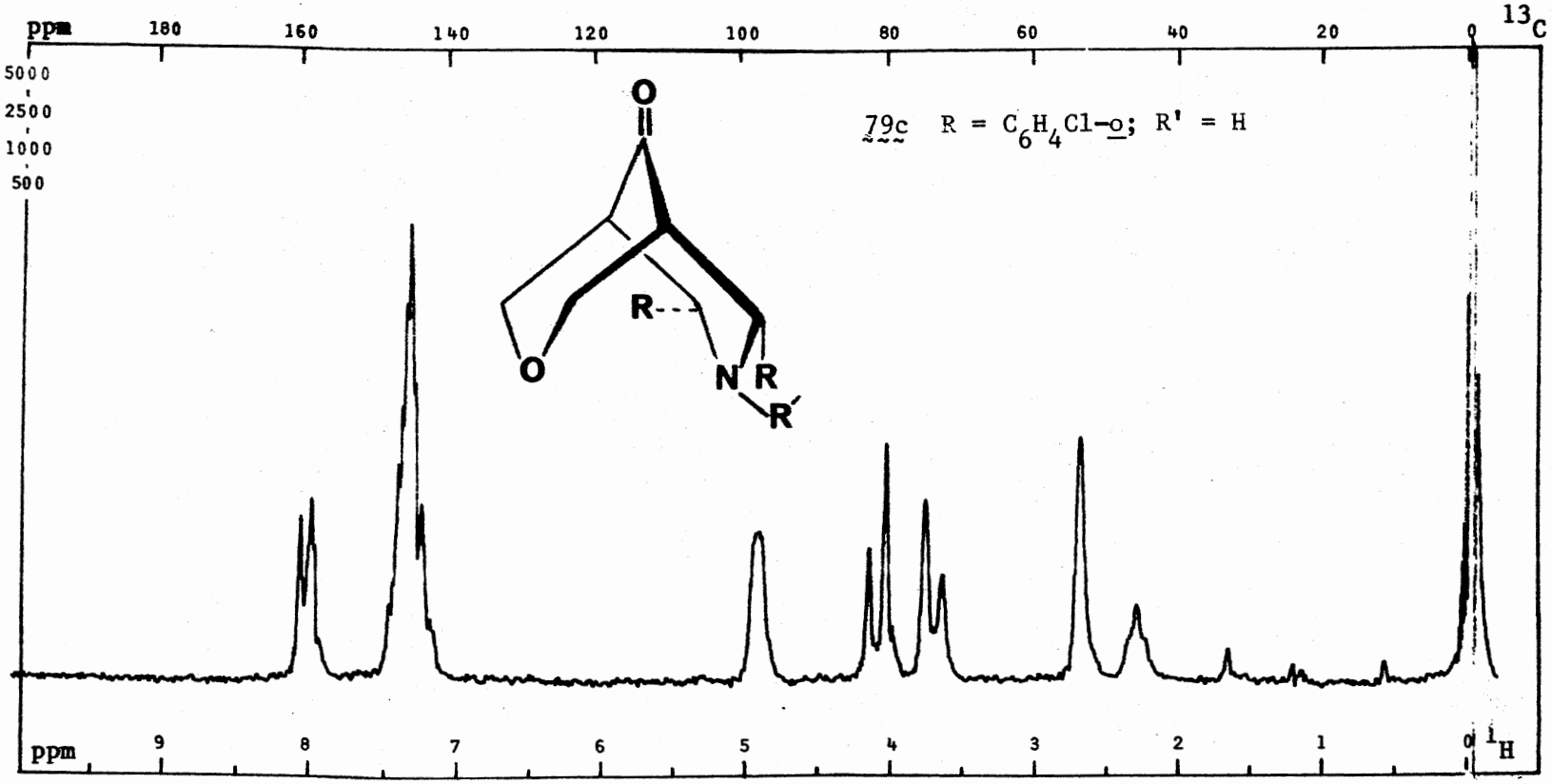
SF. 100.1 MHz; FB. 2 Hz; Lock ^{2}H ; St. 250 s.

PLATE IV



IR Spectrum of 79b, KBr Pellet

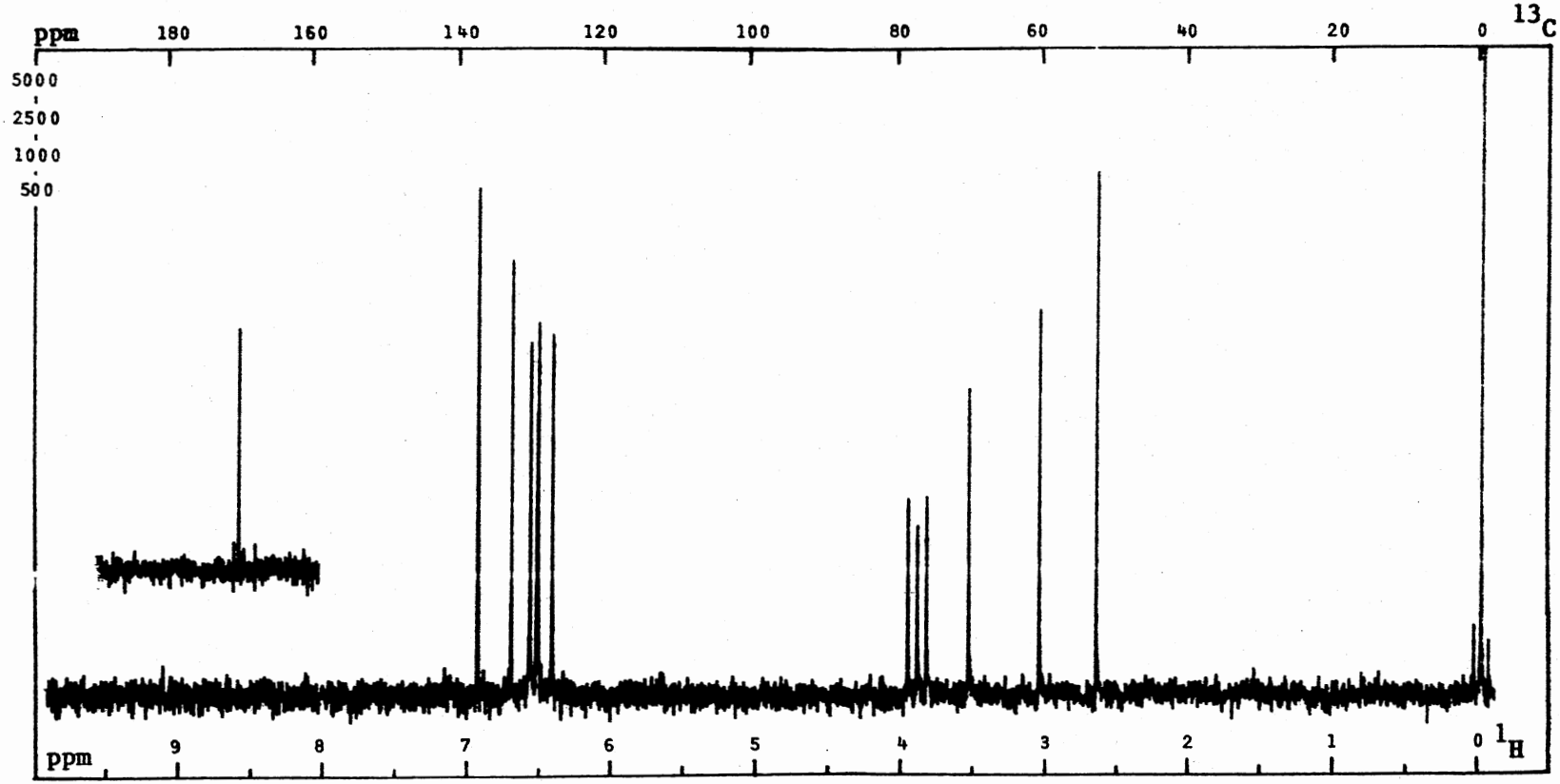
PLATE V



^{1}H NMR Spectrum of 6,8-Di(o-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (79c)

CW X; Solvent $DCCl_3$; So. 85771 Hz; PW. 1000 Hz; T. 30°C; SA. 1.6;
SF. 100.1 MHz; FB. 2 Hz; Lock. ^{2}H; ST. 250 s.

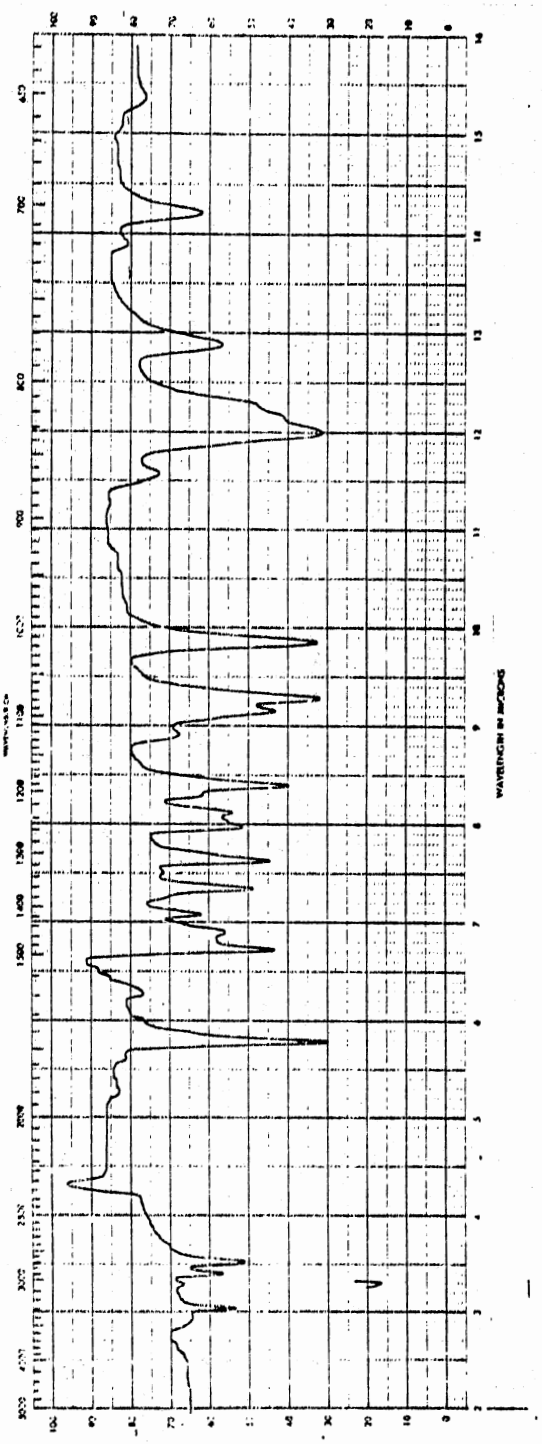
PLATE VI



^{13}C NMR Spectrum of 79c

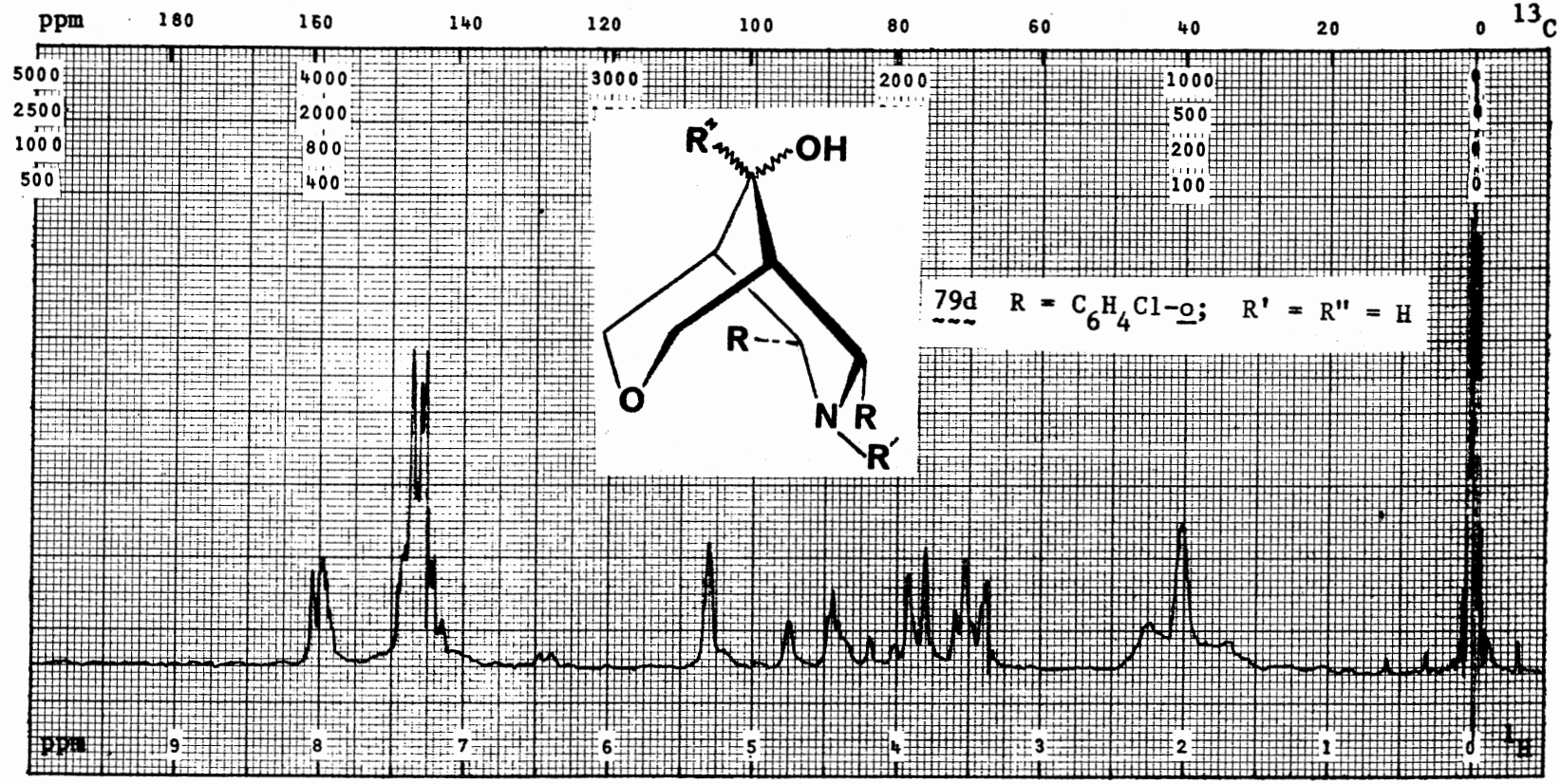
PFT X; Solvent $DCCl_3$; SO. 35101 Hz; PW. 5000 Hz; T. 30°C; Acq. 1200;
Size 8 K; SF 25.2 MHz; FB. K; Lock ^2H; D5 5 s; DC. ^1H;
Offset 45051 Hz; RF. 910 W/dB; NBW 100 Hz.

PLATE VII



IR Spectrum of 79c

PLATE VIII

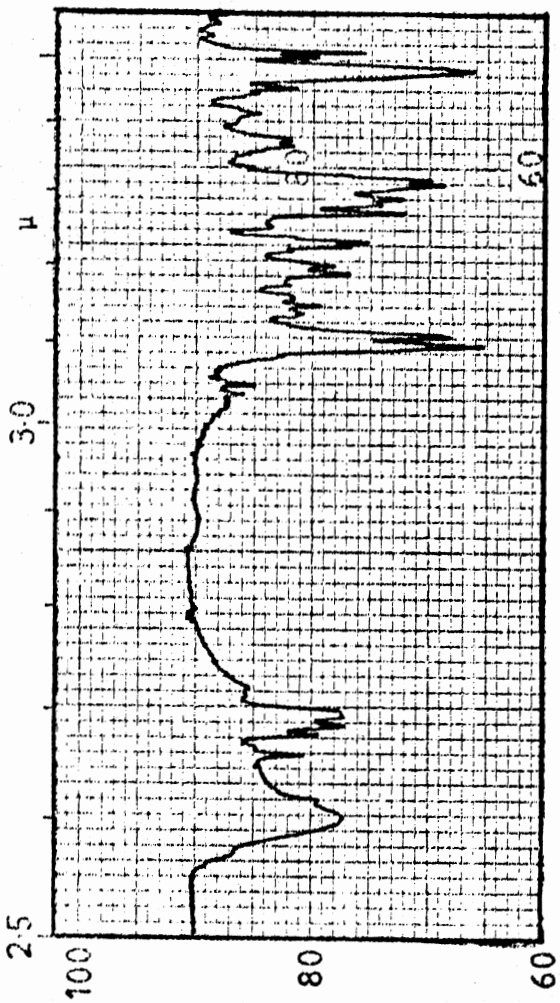


^{1}H NMR Spectrum of 6,8-Di(o-chlorophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-ols (79d)

CW X; Solvent $DCCl_3$; So. 85771 Hz; PW. 1000 Hz; T. 30°C; SA 1.0;

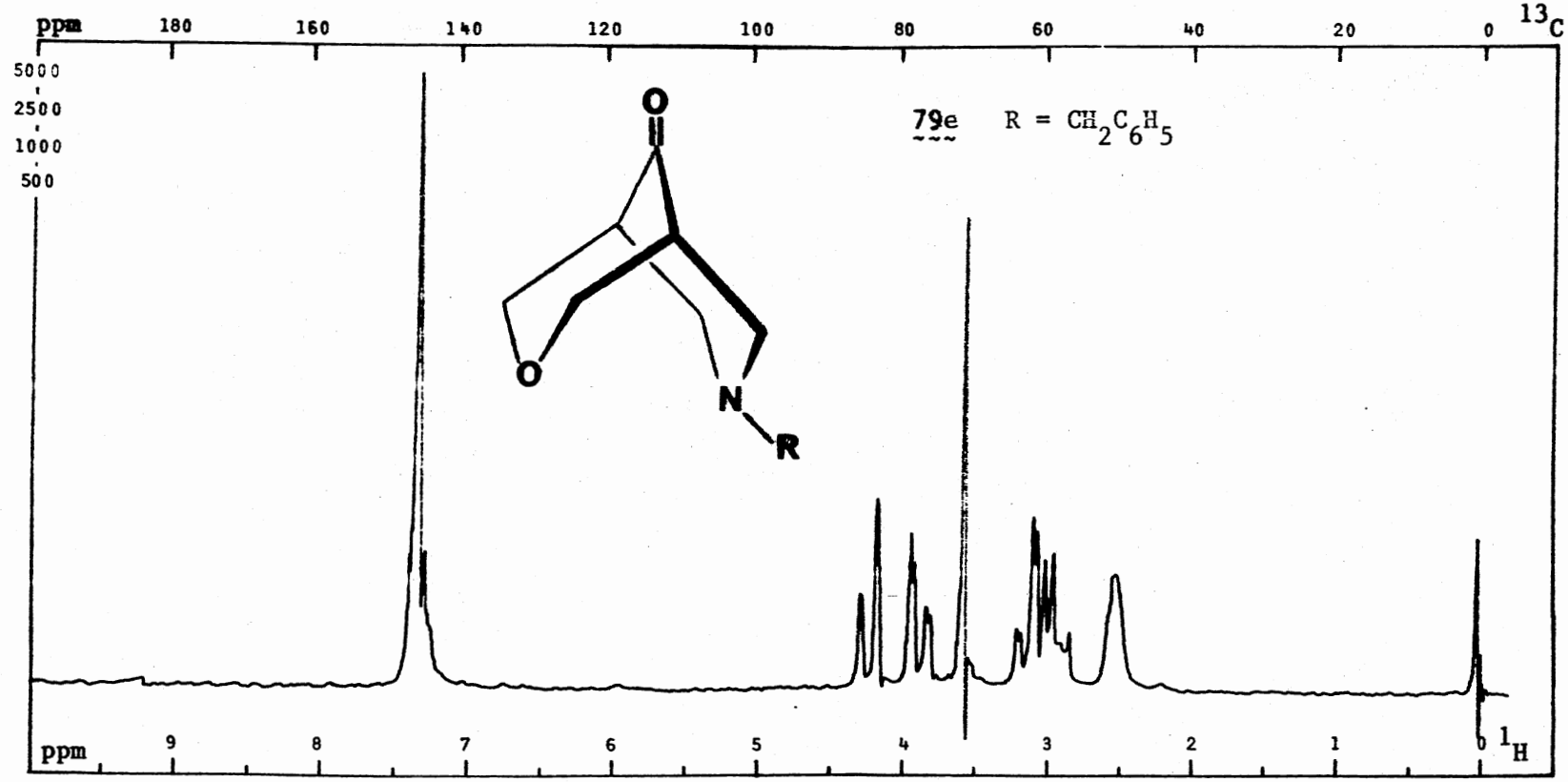
P2/RF 69 µs/dB; SF. 100.1 MHz; FB. 2 Hz; Lock ^{2}H; ST 250s.

PLATE IX



IR Spectrum of 79d, KBr Pellet

PLATE X

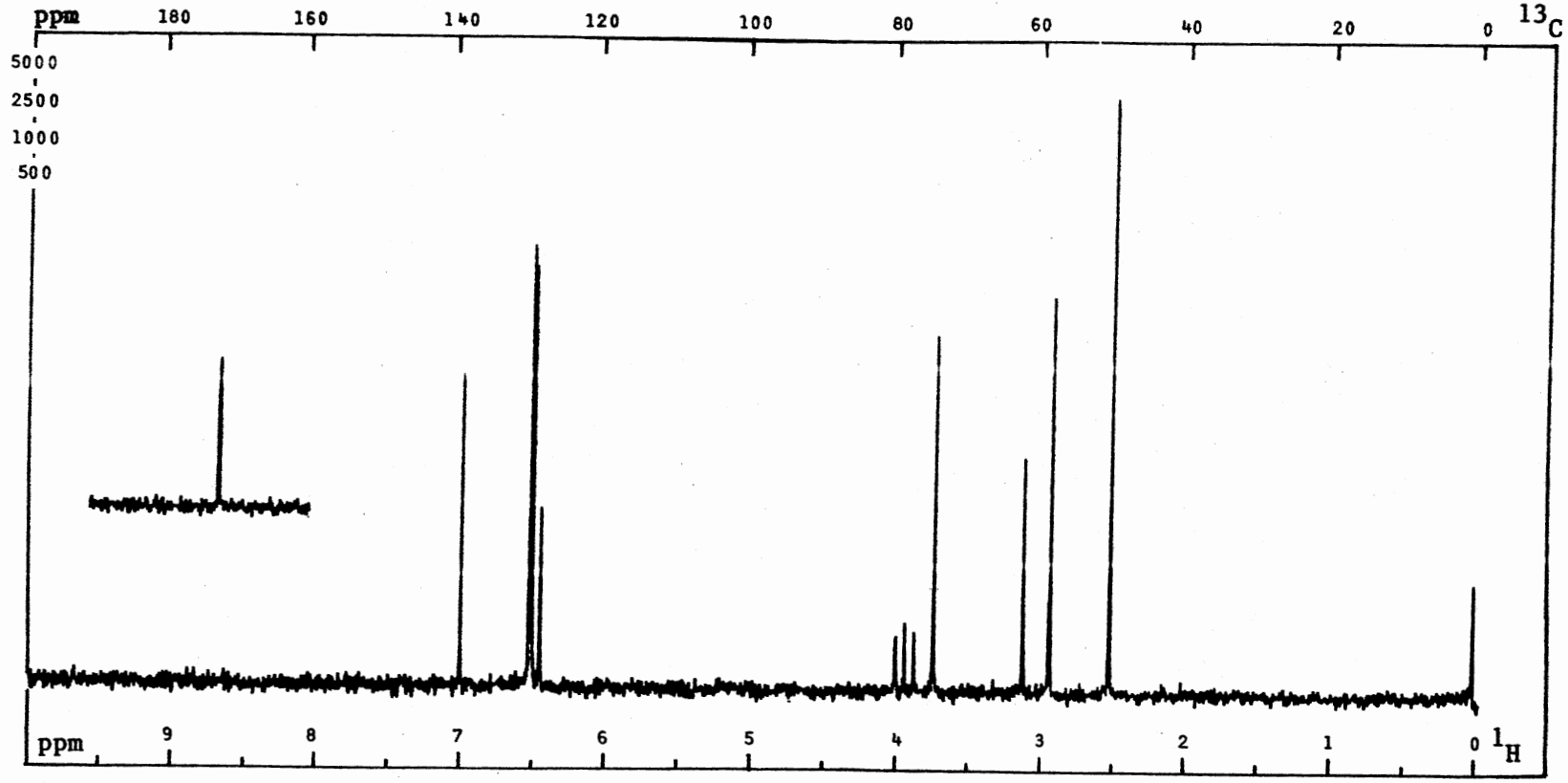


^{1}H NMR Spectrum of 7-N-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (79e)

CW X; Solvent $DCCl_3$; SO. 85771 Hz; PW. 1000 Hz; T. 30°C; SA. 1;

P2/RF 53 µs/dB; SF. 100.1 MHz; FB. 2 Hz; Lock. ^{2}H; ST. 250 s.

PLATE XI



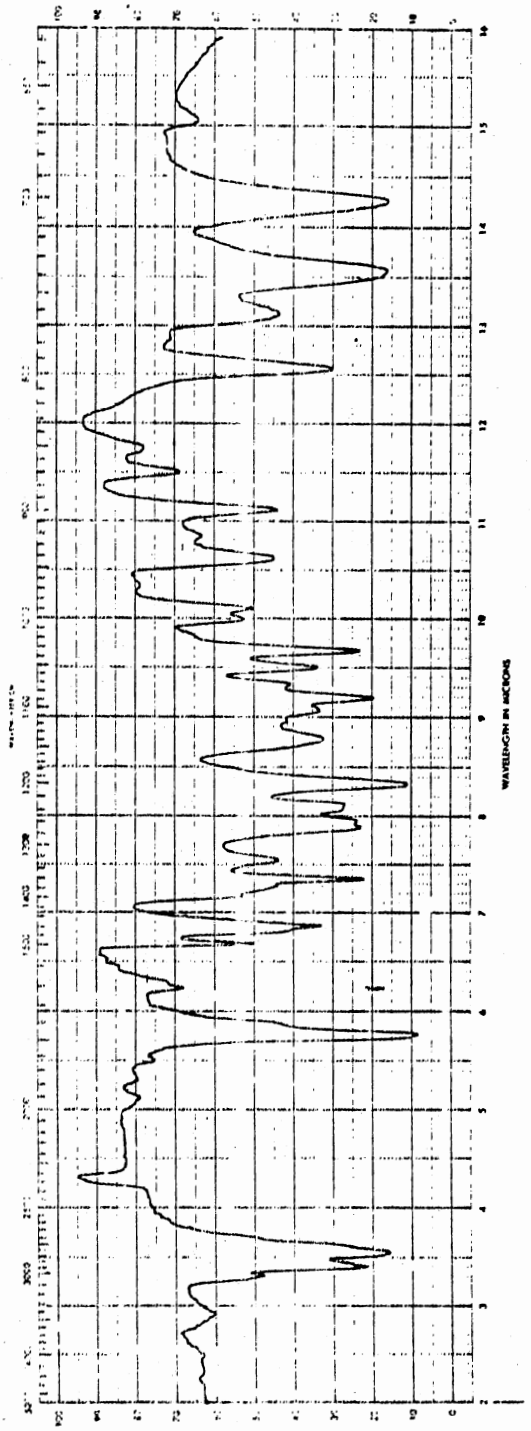
^{13}C NMR Spectrum of 79e

PFT. X; Solvent $DCCl_3$; SO. 35101 Hz; PW. 5000 Hz; T. 30°C; Acq. 800;

Size 8 K; P2/RF 10 µs/dB; SF. 25.2 MHz; Lock ^{2}H; D5 5 s; DC ^{1}H;

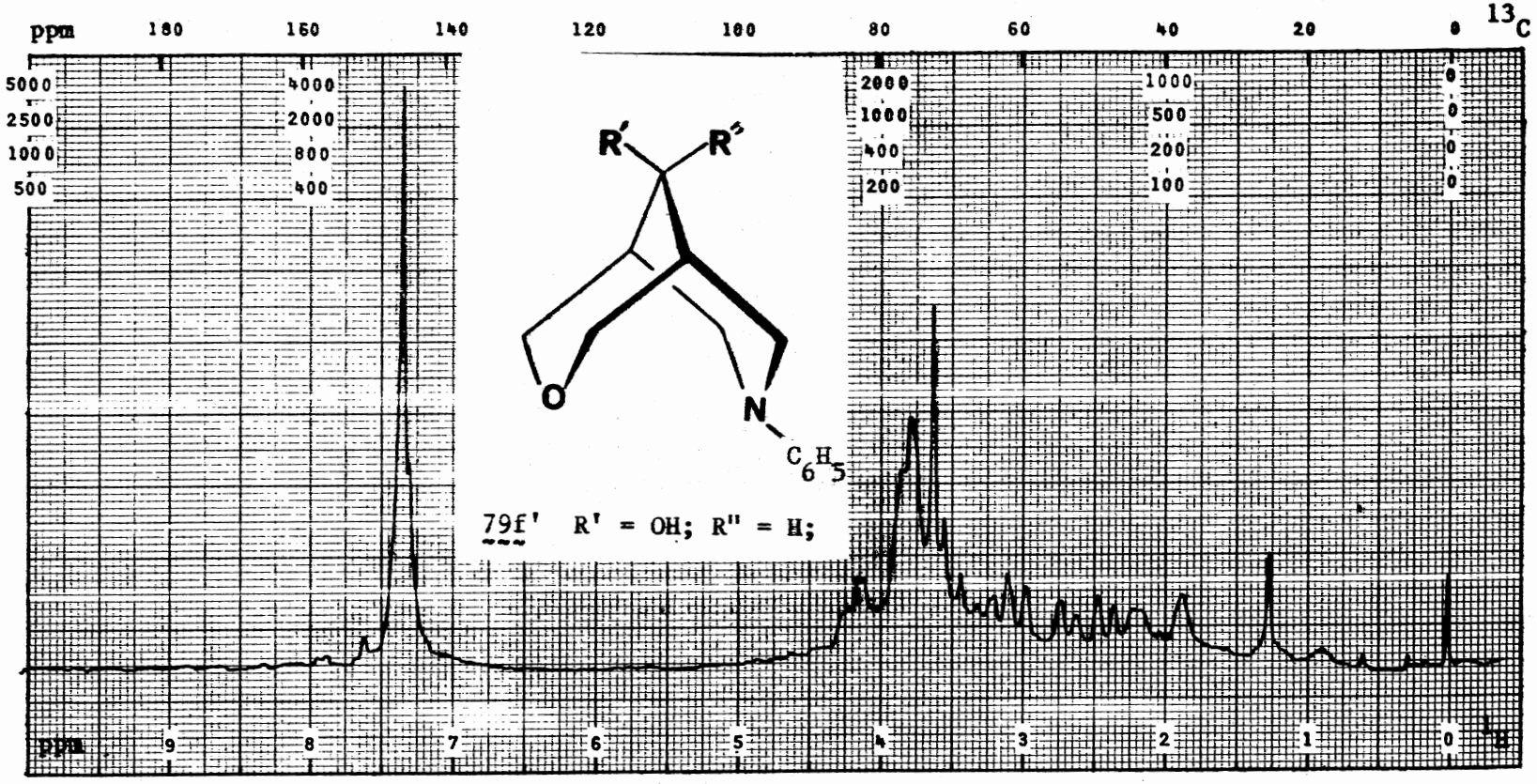
Offset 45051 Hz, RF 910 W/dB; NBW 100 Hz.

PLATE XII



IR Spectrum of 79e, Neat Liquid

PLATE XIII

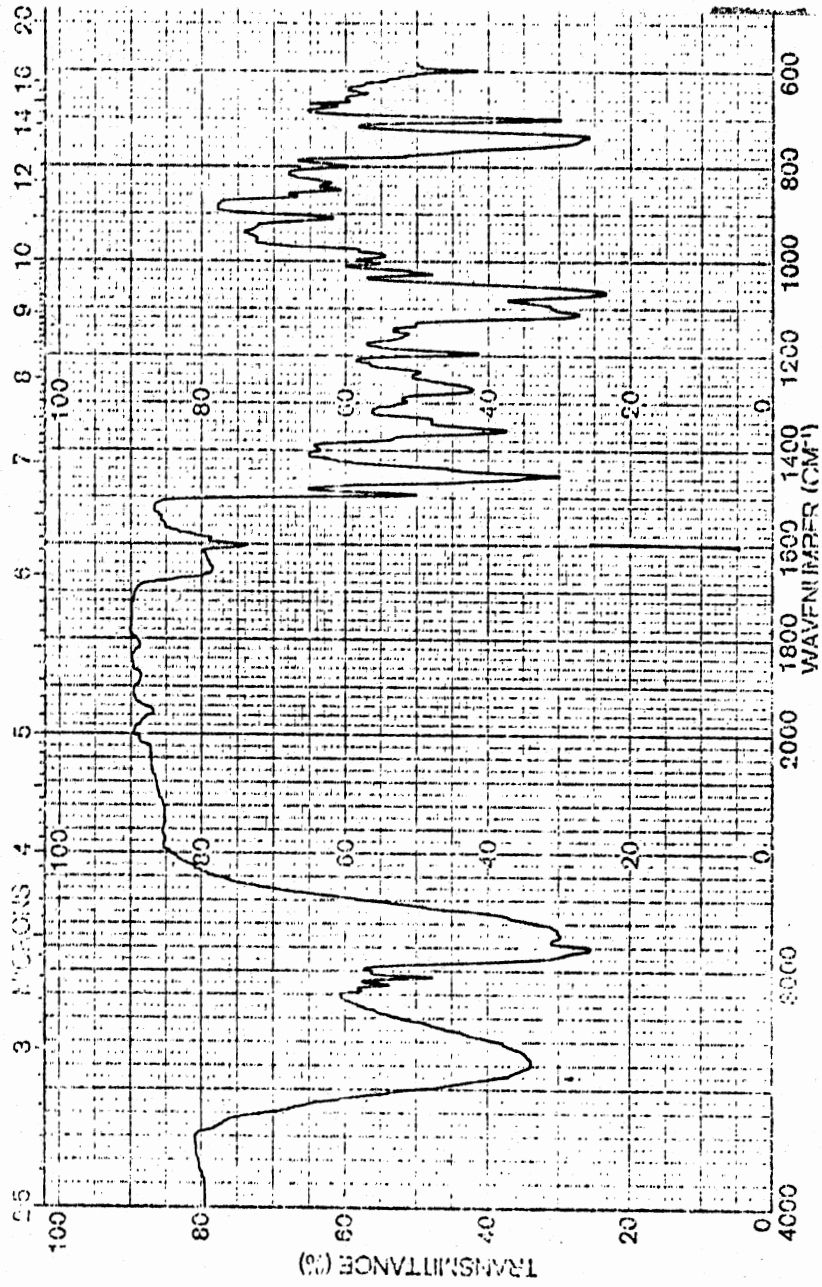


^{1}H NMR Spectrum of 7-N-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (79f')

CW X; Solvent $DCCl_3$; SO. 85771 Hz; PW. 1000 Hz; T. 30°C; SA. 1.0;

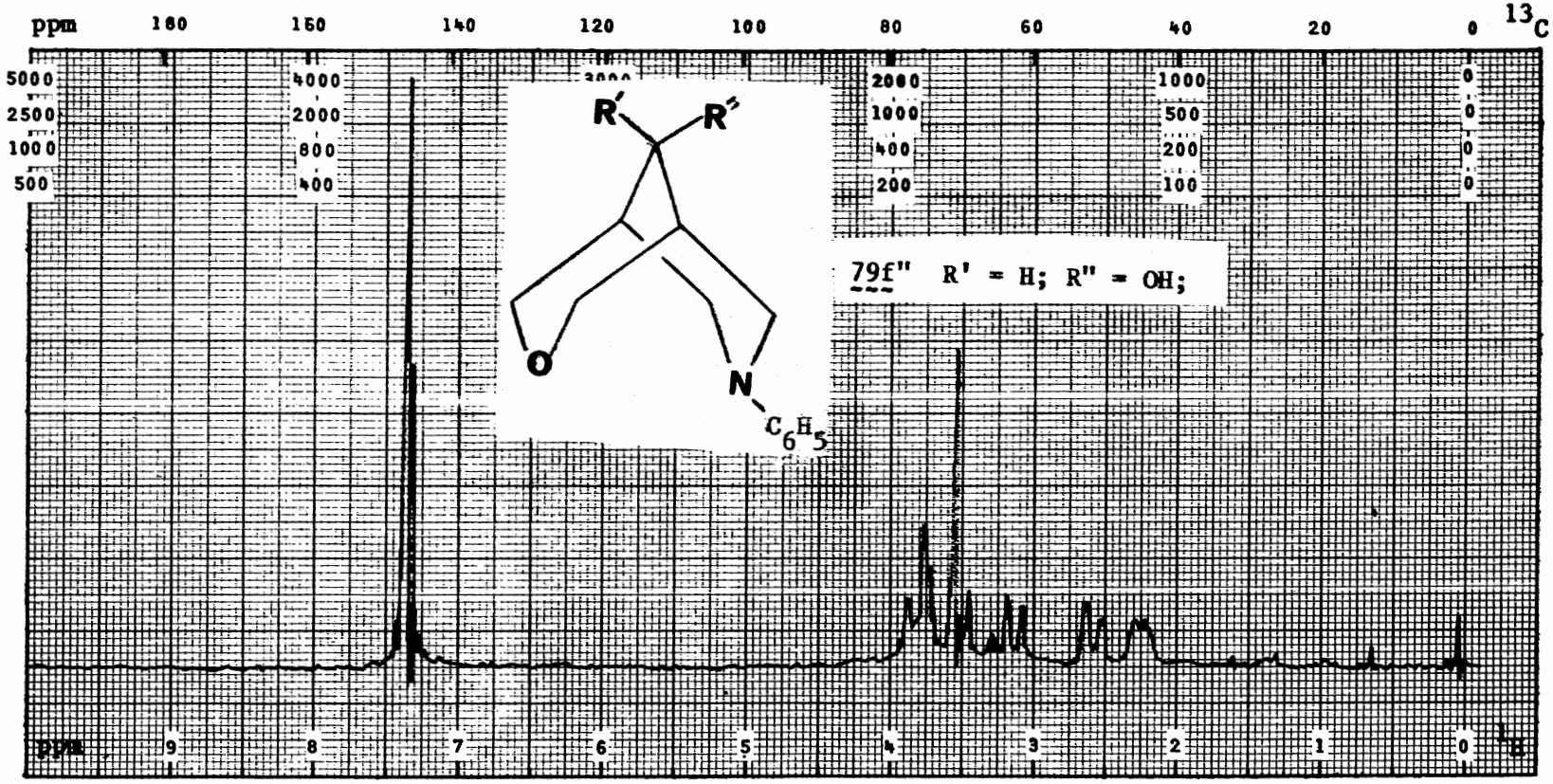
P2/RF 69 µs/dB; Sf. 100.1 MHz; FB. 2 Hz; Lock ^{2}H; ST. 250 s.

PLATE XIV



IR Spectrum of 79f', KBr Pellet

PLATE XV

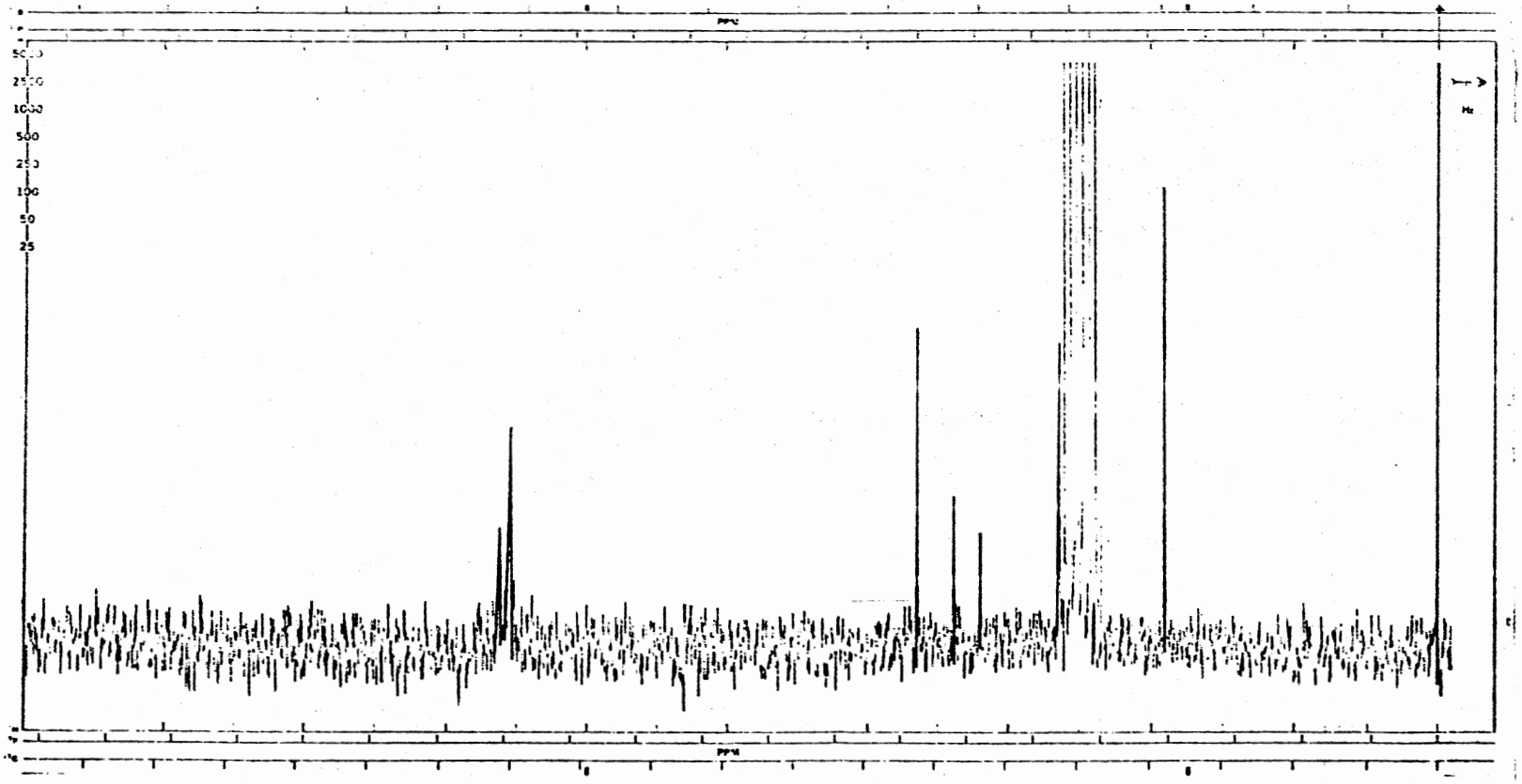


^{1}H NMR Spectrum of 7-N-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (79f")

CW X; Solvent $DCCl_3$; SO. 85771 Hz; PW. 1000 Hz; T. 30°C; SA. 1.25;

P2/RF 18 µs/dB; SF. 100.1 MHz; FB. 1 Hz; Lock ^{2}H; ST. 250 s;

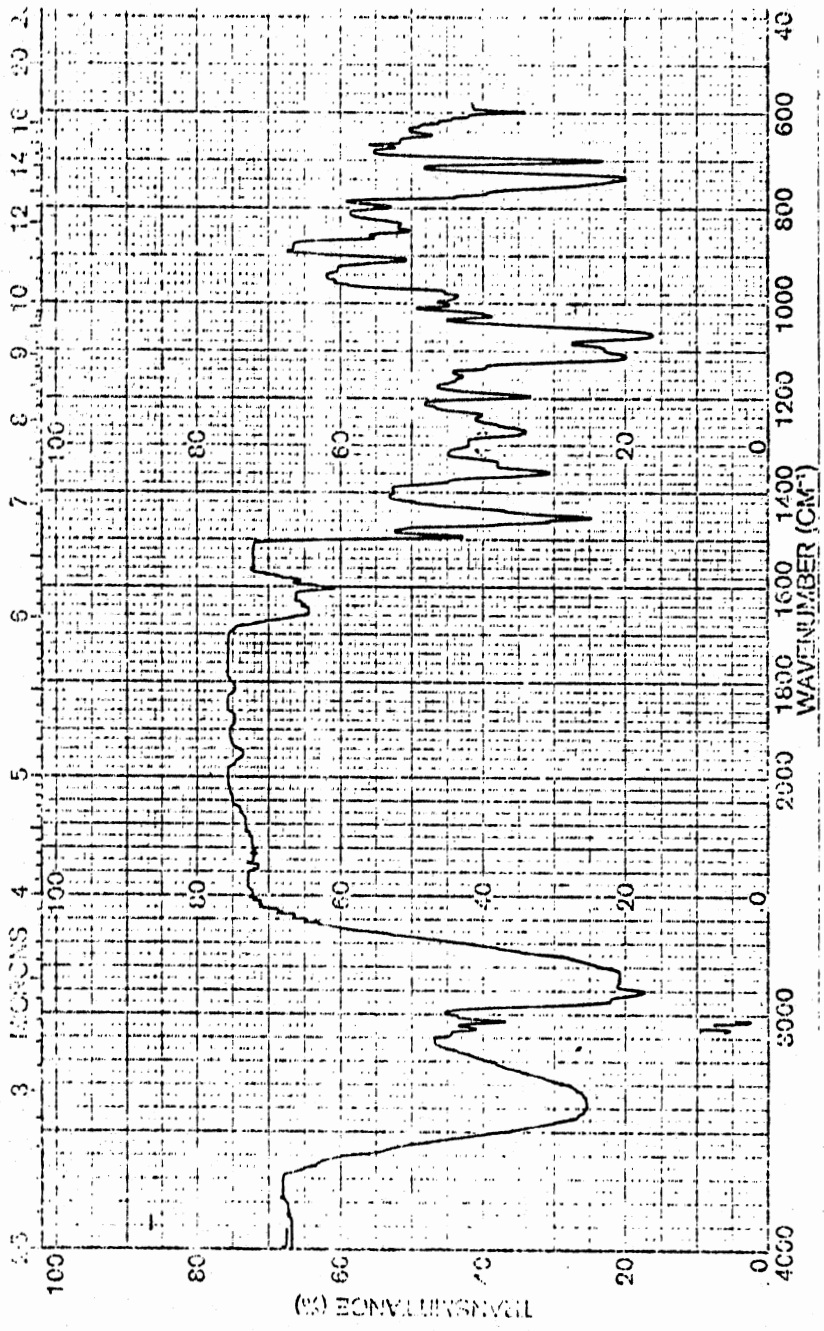
PLATE XVI



^{13}C NMR Spectrum of 79f"

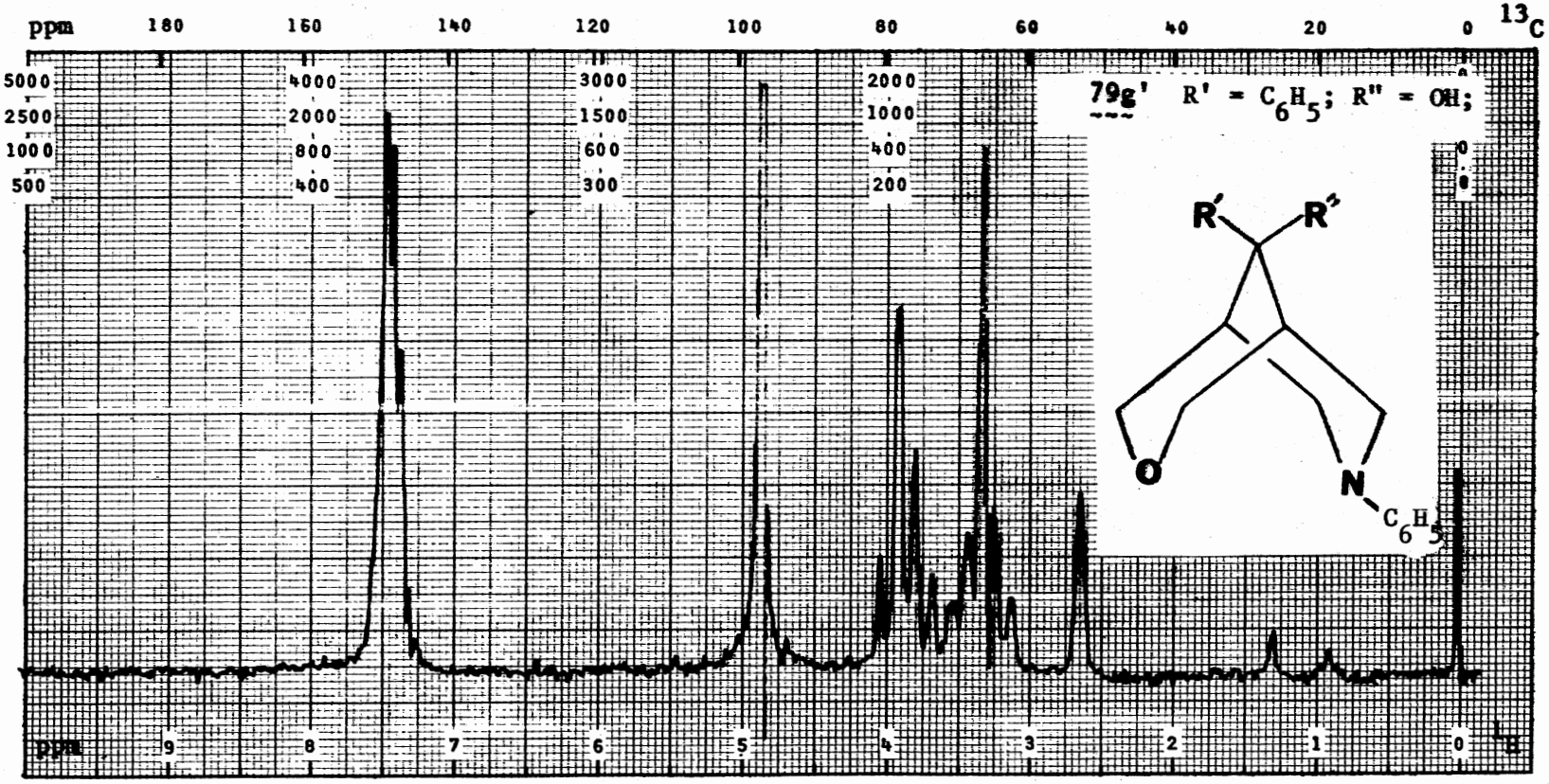
PFT. X; Solvent D_3COD; SO. 35051 Hz; PW. 5000 Hz; T. 30°C; Acq. 8500;
Size K; P2/RF 10 µs/dB; SF. 25.2 MHz; FB. 315 Hz; Lock ^2H; D5 5 s;
DC. ^1H; Offset 45051 Hz; Rf. 910 W/dB; NBW. 100 Hz.

PLATE XVII



IR Spectrum of 79f", KBr Pellet

PLATE XVIII

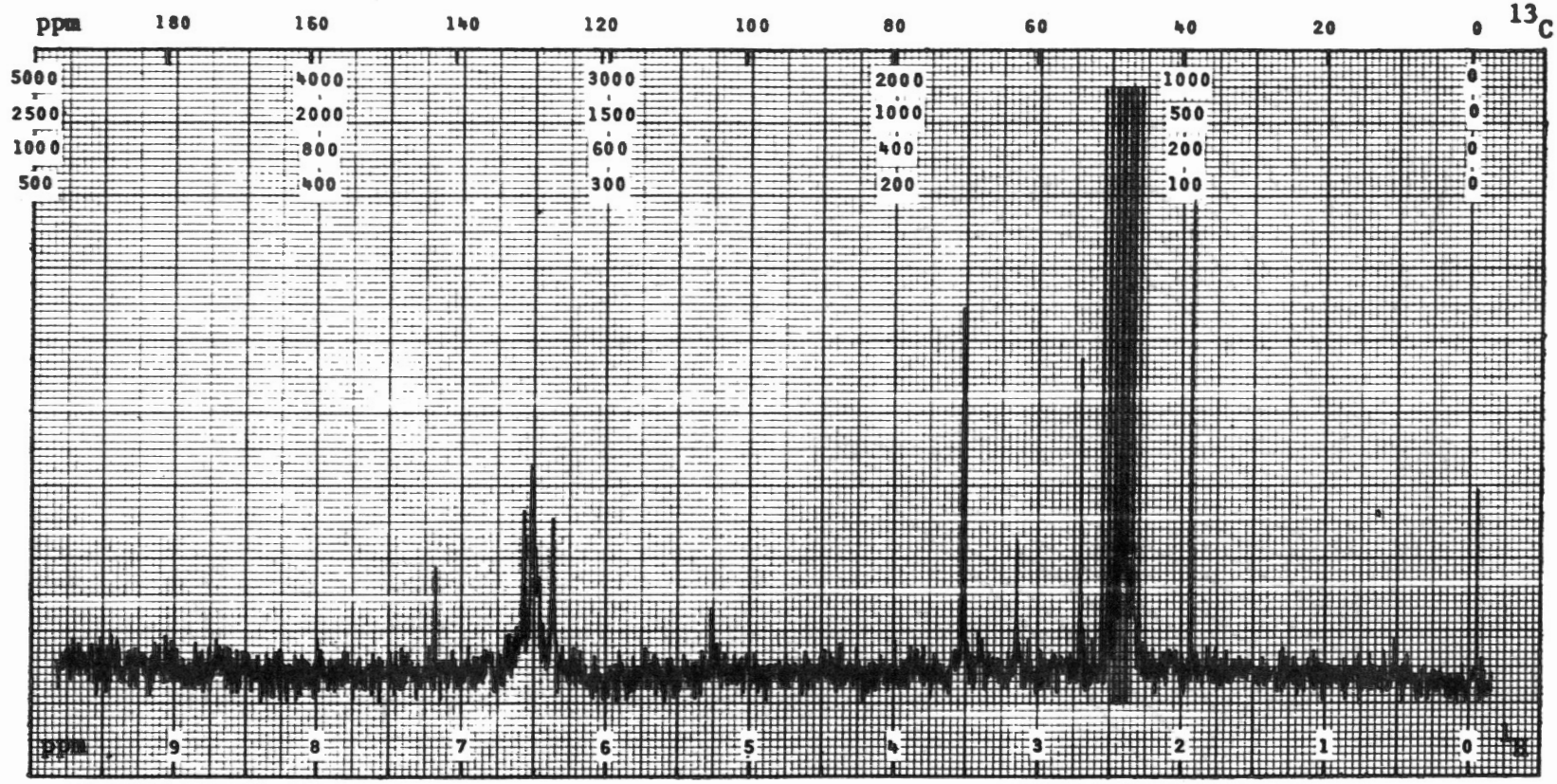


^{1}H NMR Spectrum of 7-N-Benzyl-9-phenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (79g')

CW X; Solvent D_3COD; SO. 86165 Hz; PW. 1000 Hz; T. 30°C; SA. 5.0;

P2/RF 70 µs/dB; SF. 100.1 Hz; FB. 2 Hz; Lock ^{2}H; ST 250 s.

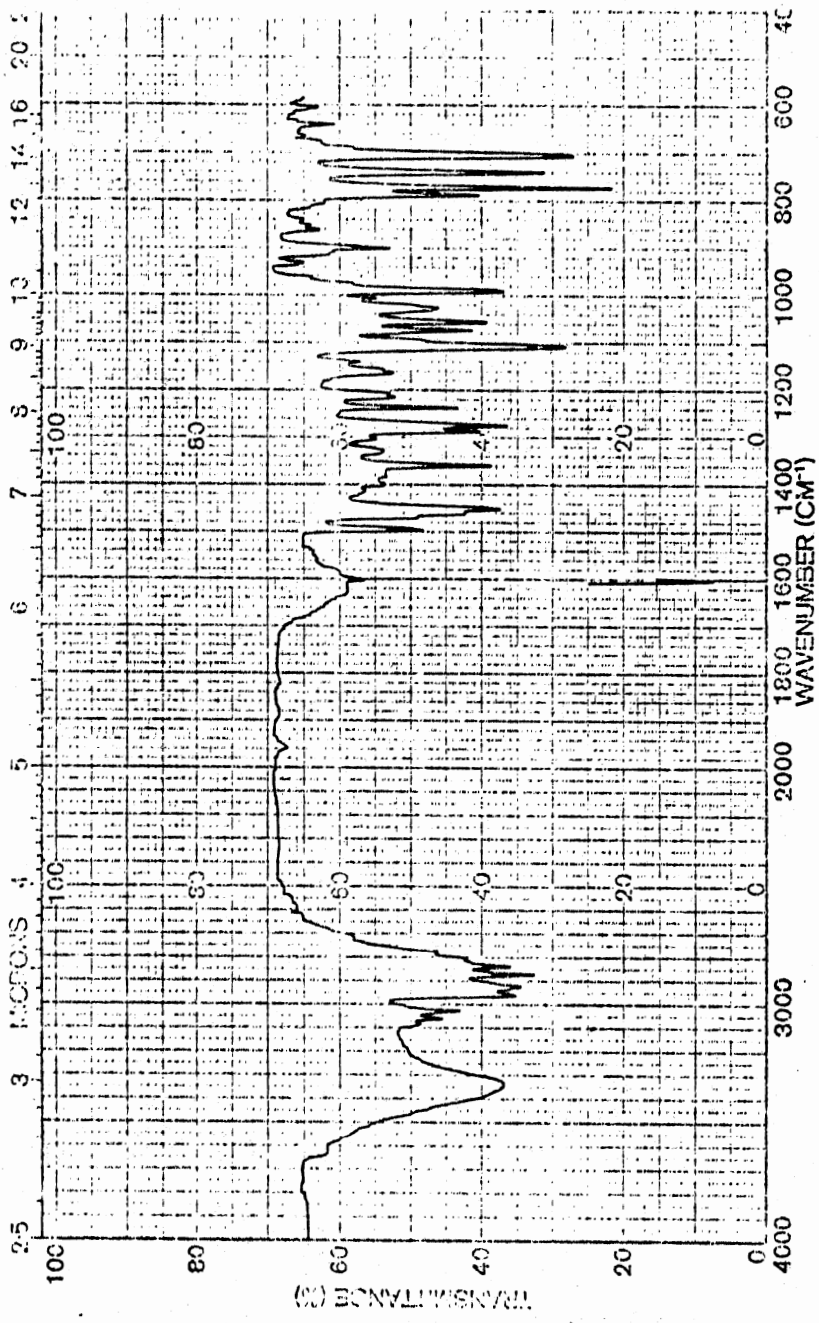
PLATE XIX



^{13}C NMR Spectrum of 79g'

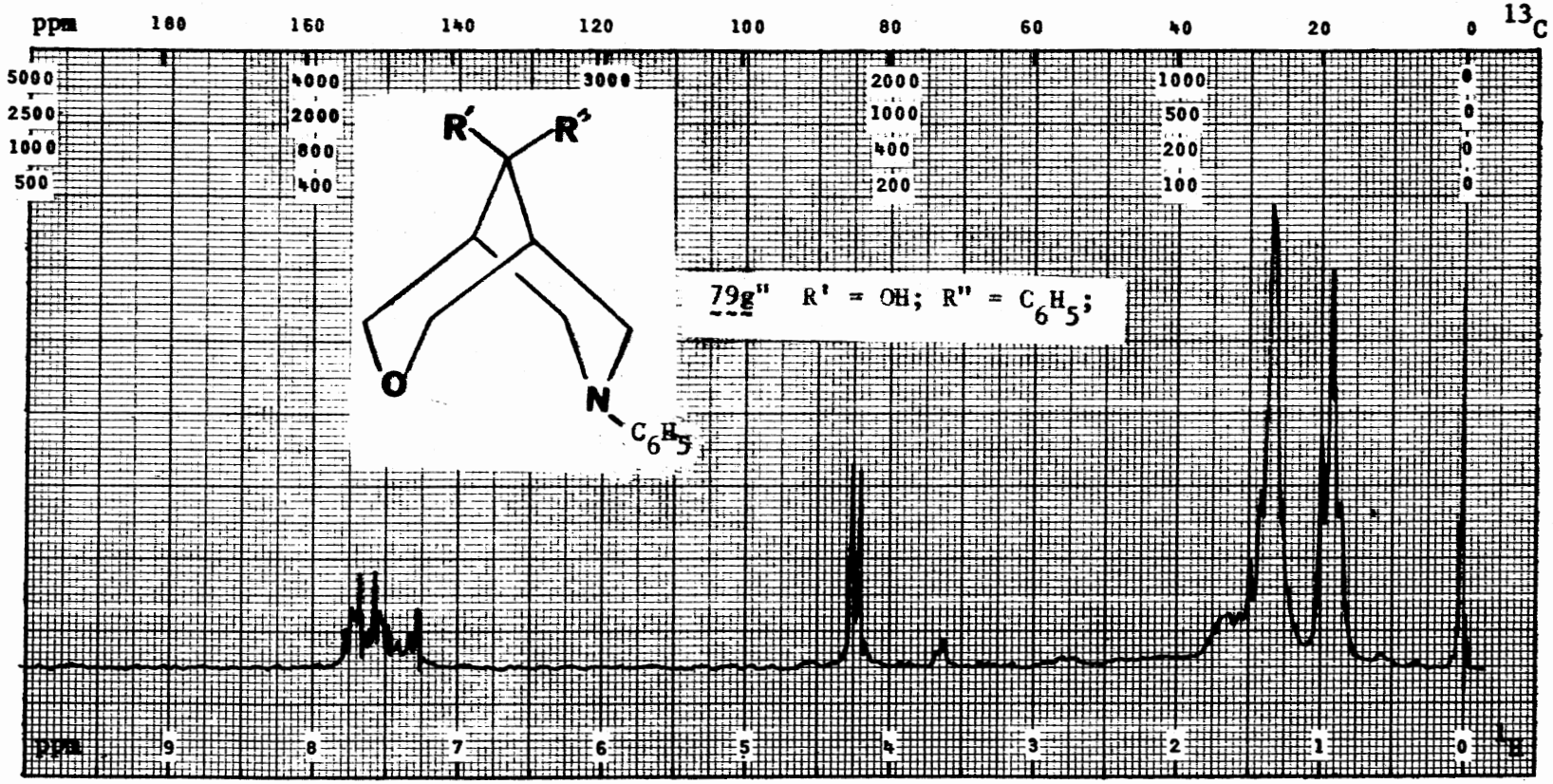
PFT. X; Solvent D_3COD; SO. 35051 Hz; PW. 5000 Hz; T. 30°C; Acq. 22000;
Size. 8K; P2/RF 10 µs/dB; SF. 25.2 MHz; Lock ^{2}H; D5 5 s; DC ^{1}H;
Offset 45051 Hz; RF 910 W/dB; NBW 100 Hz.

PLATE XX



IR Spectrum of 79g'

PLATE XXI

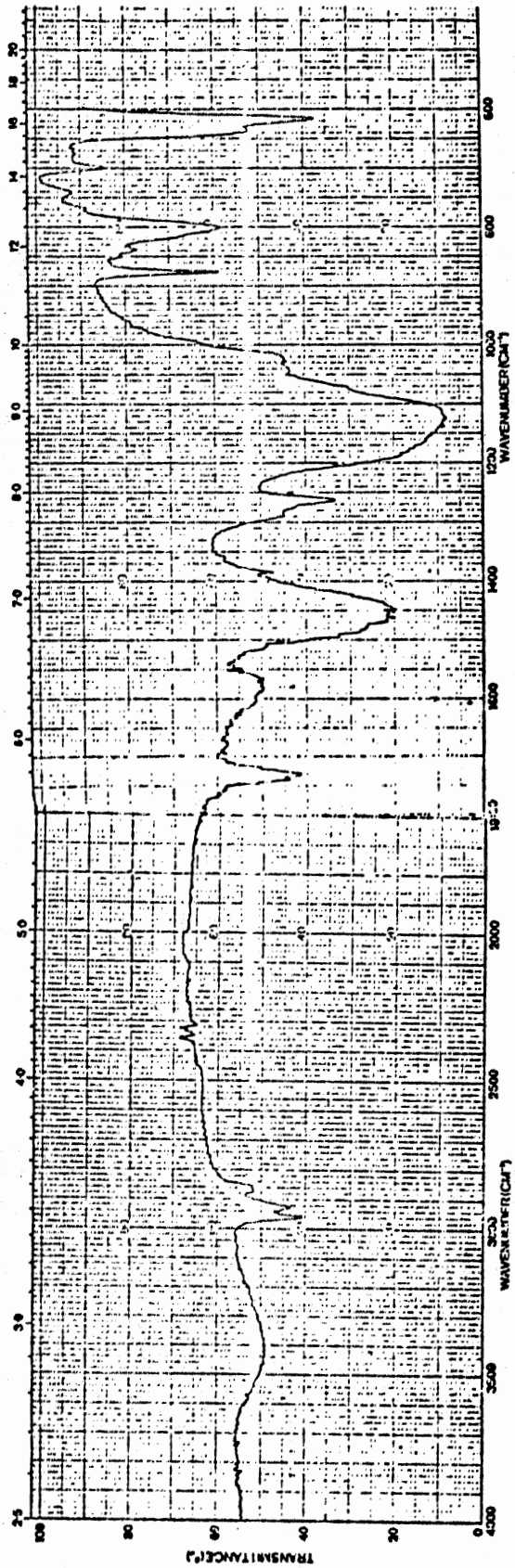


^{1}H NMR Spectrum of 7-N-Benzyl-9-phenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (79g")

CW X; Solvent $DCCl_3$; SO. 85771 Hz; PW. 1000 Hz; T. 30°C; SA. 1.0;

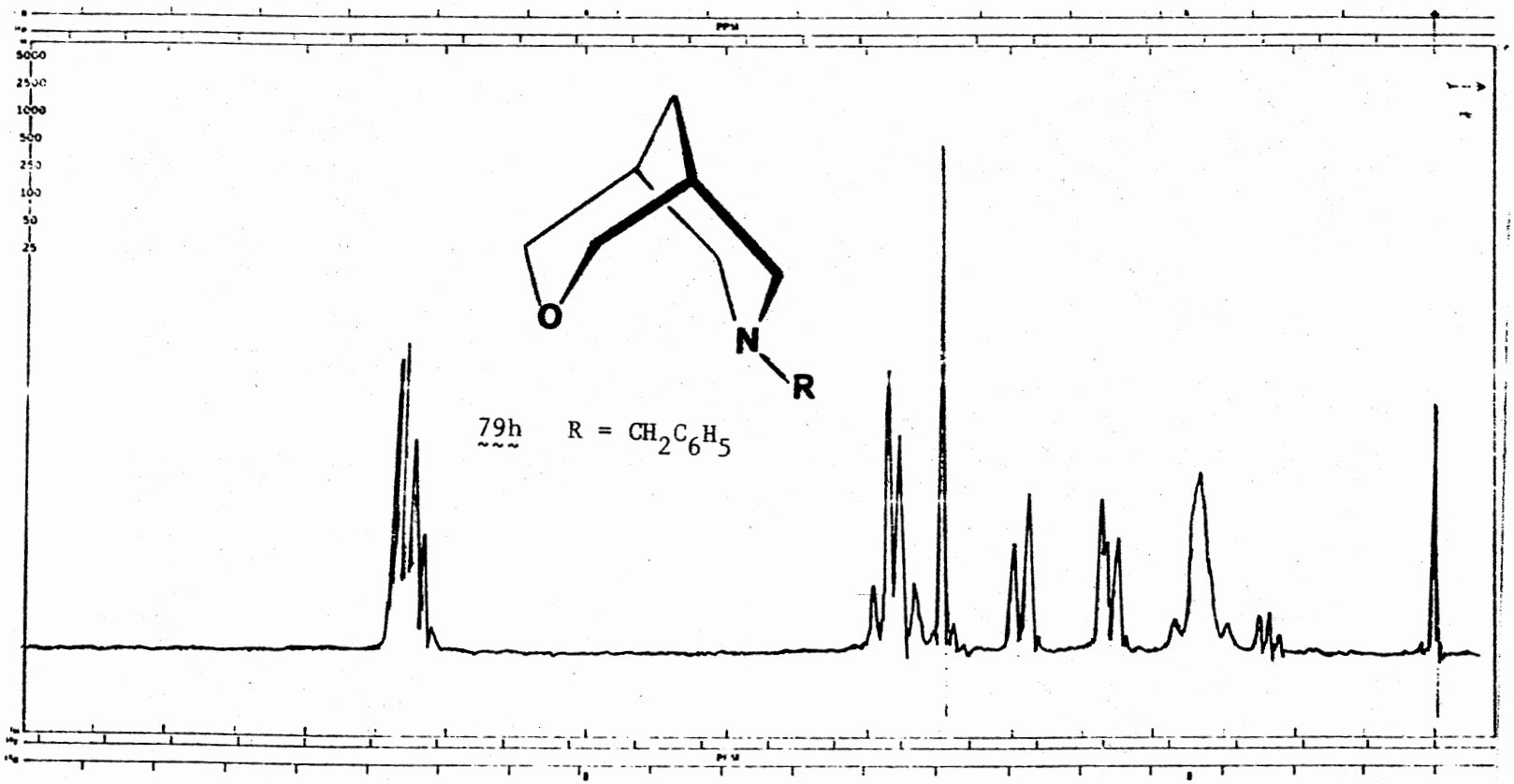
P2/RF 69 µs/dB; SF. 100.1 MHz; FB. 2 Hz; Lock ^{2}H; ST. 250 s.

PLATE XXII



IR Spectrum of 79g", KBr Pellet

PLATE XXIII



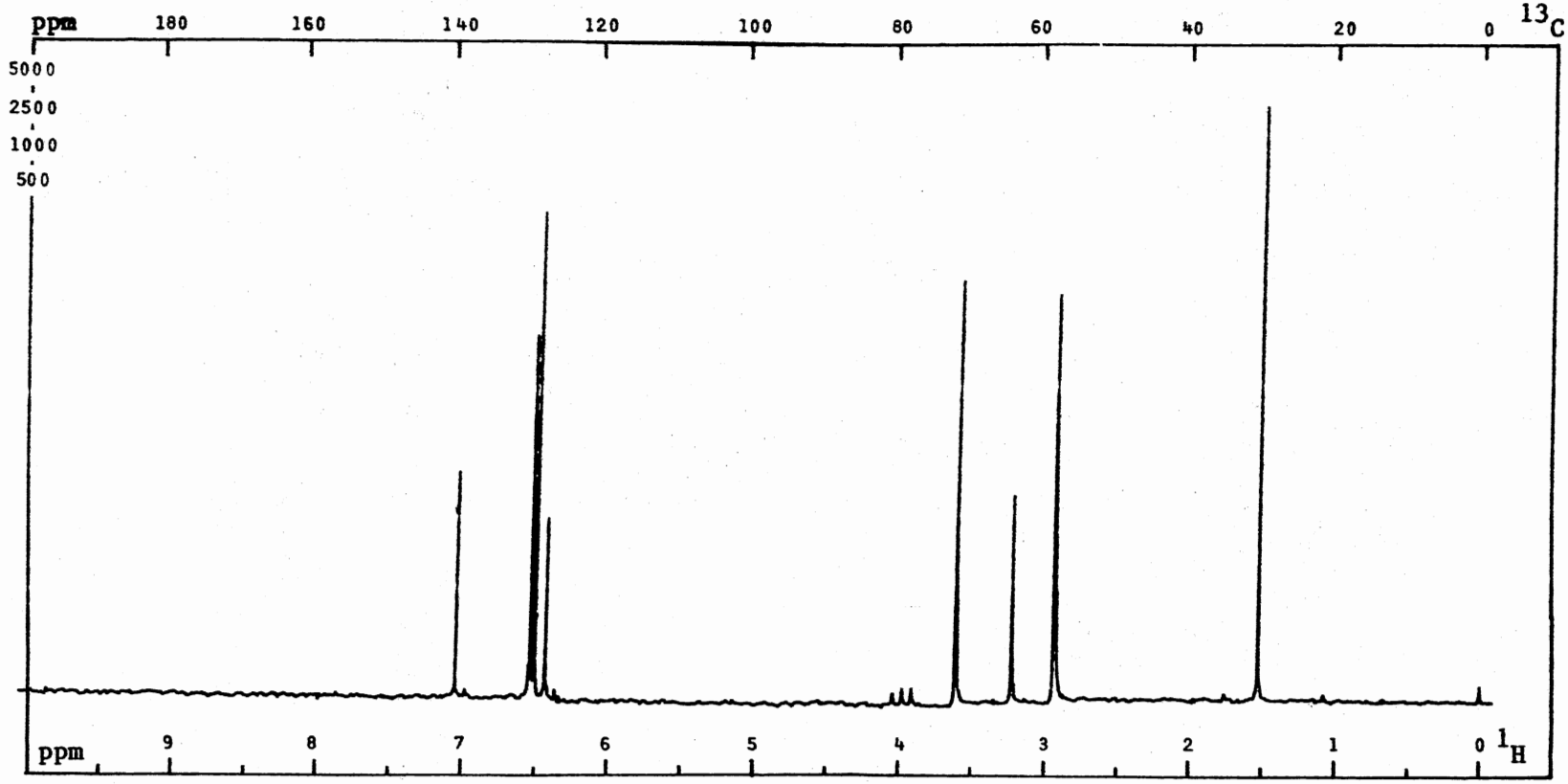
79h R = $CH_2C_6H_5$

^1H NMR Spectrum of 7-N-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan (79h)

CW X; Solvent $DCCl_3$; SO. 85771 Hz; PW. 1000 Hz; T. 30°C; SA. 1.0;

P2/RF 54 µs/dB; SF. 100.1 MHz; FB. 1 Hz; Lock ^2H; ST. 250 s.

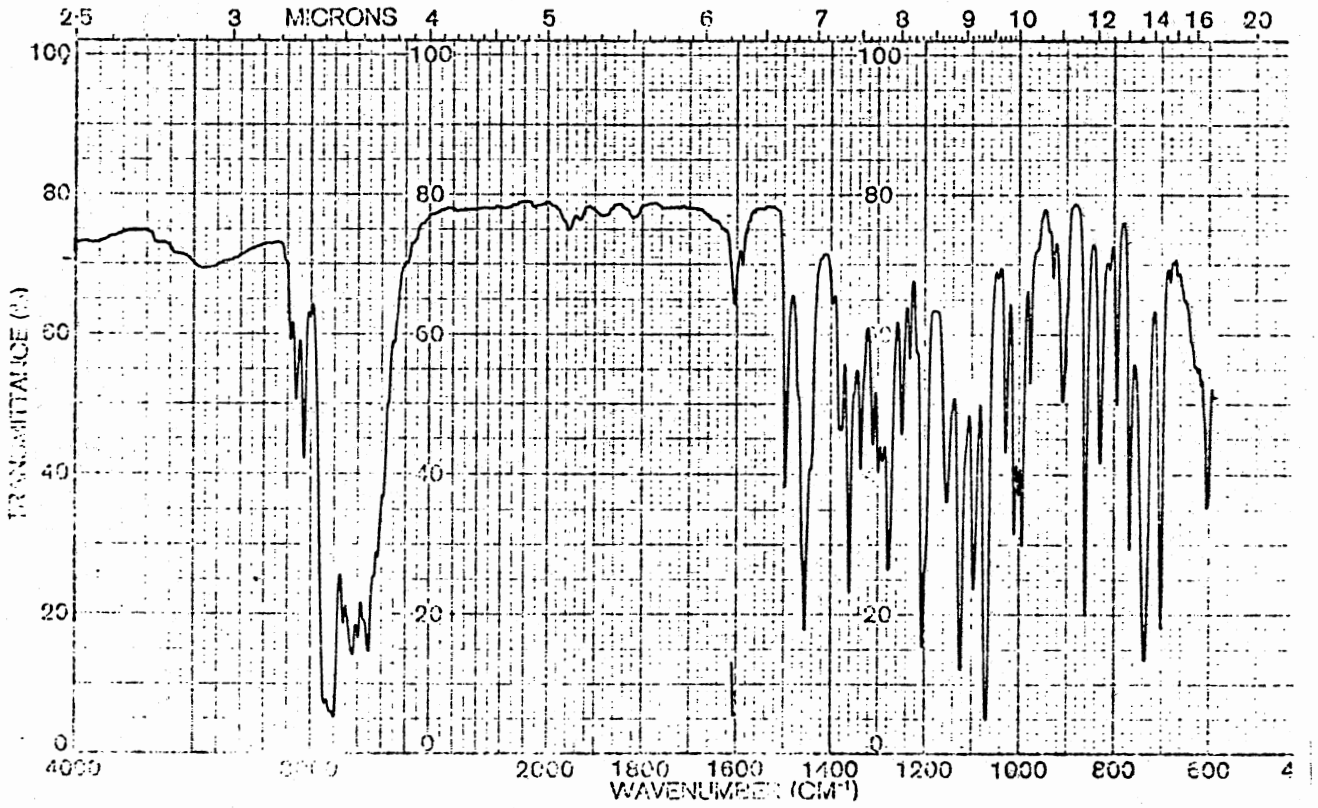
PLATE XXIV



^{13}C NMR Spectrum of 79h

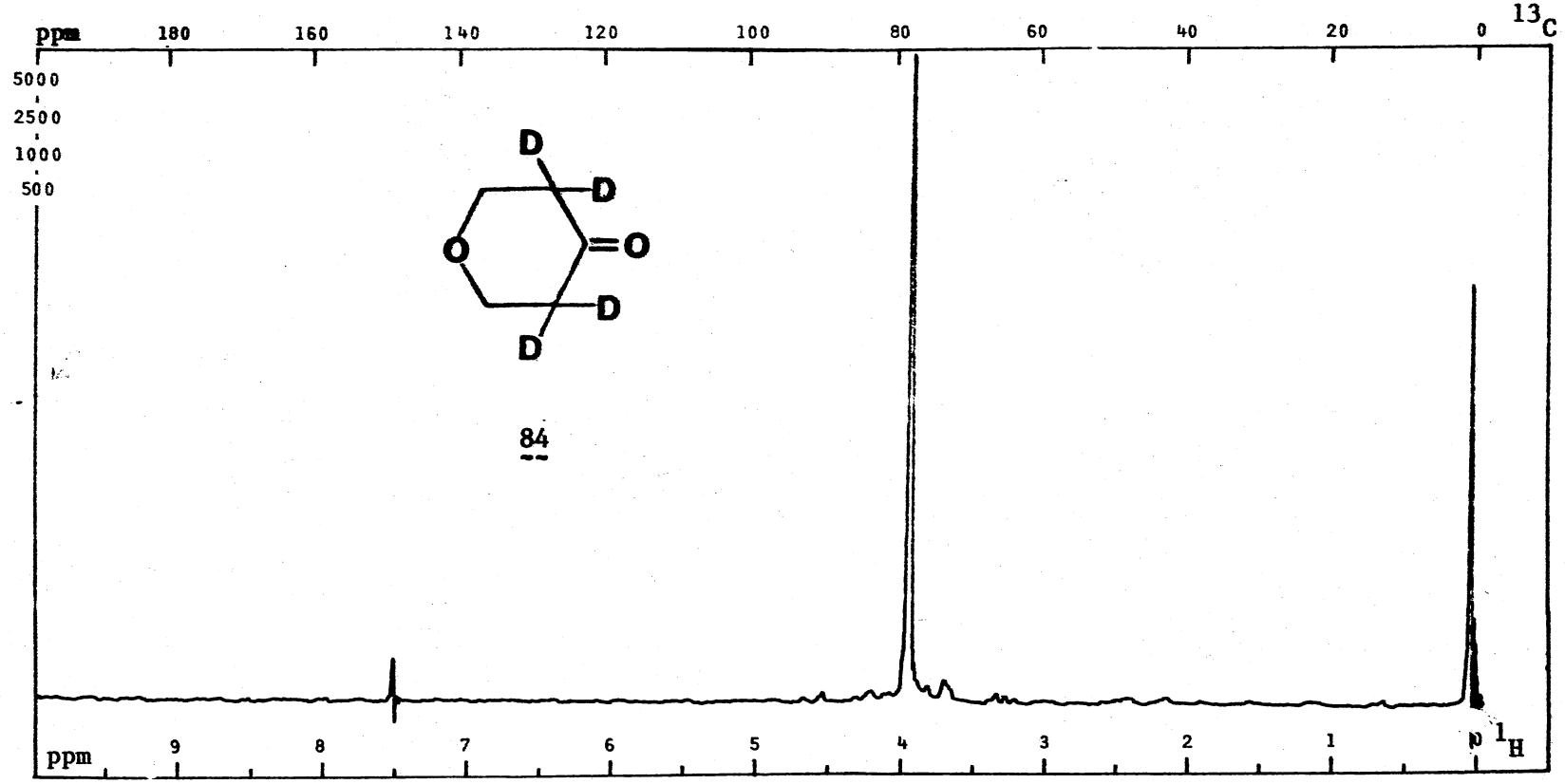
PFT. X; Solvent $DCCl_3$; SO. 35101 Hz; PW. 5000 Hz; T. 30°C; Acq. 360;
Size 16K; P2/RF 10 µs/dB; SF. 25.2 Mhz; FB. 360 Hz; Lock ^{2}H; D5 5 s;
DC. ^{1}H; Offset 45051 Hz; RF. 910 W/dB; NBW. 100 Hz.

PLATE XXV



IR Spectrum of 79h, Neat Liquid

PLATE XXVI

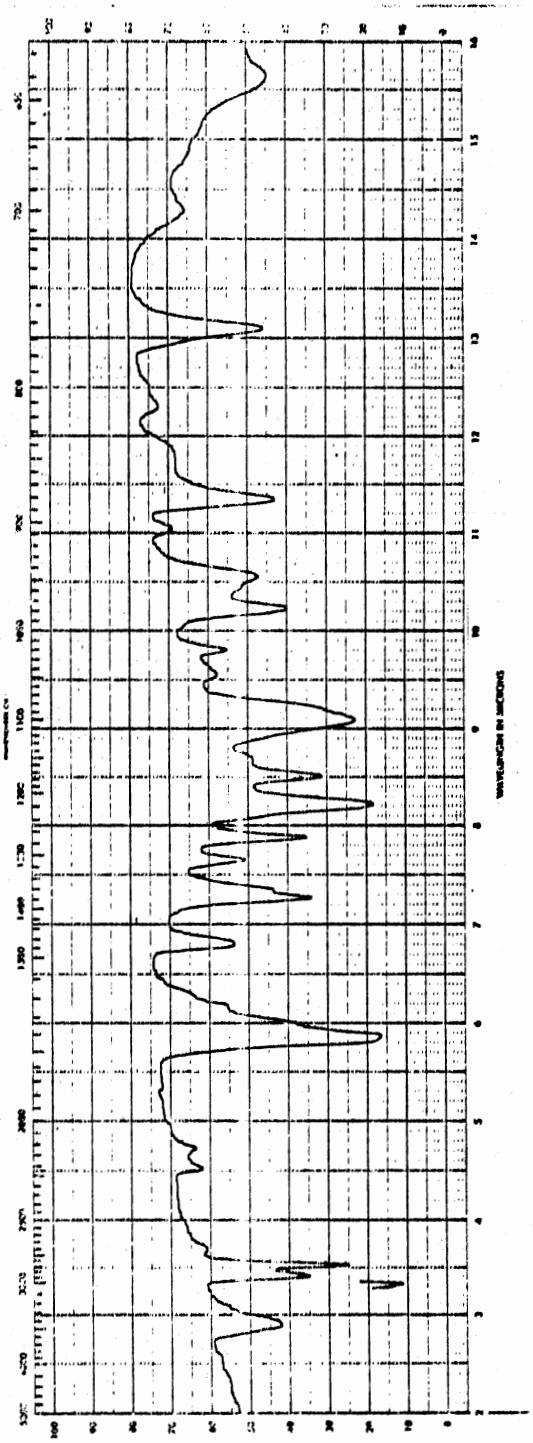


^{1}H NMR Spectrum of Tetrahydro-4H-pyran-4-one-d_4-(3,3,5,5) (84)

CW X; Solvent CCl_4; SO. 83857 Hz; PW. 1000 Hz; T. 30°C; SA. 1.0;

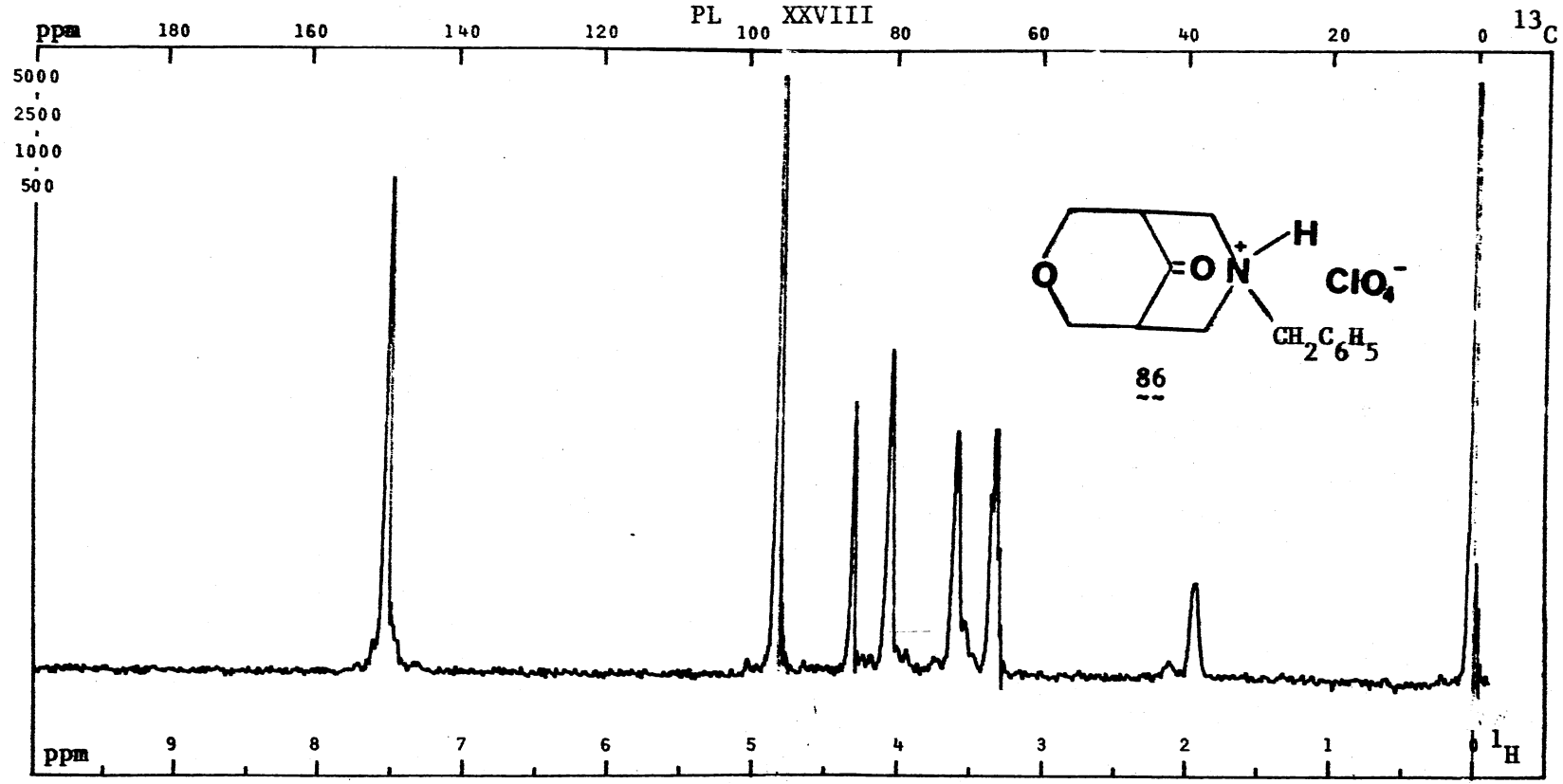
RF. 69 dB; SF. 100.1 MHz; Lock ^{2}H; ST. 250 s.

PLATE XXVII



IR Spectrum of 84, Neat Liquid

PLATE XXVIII

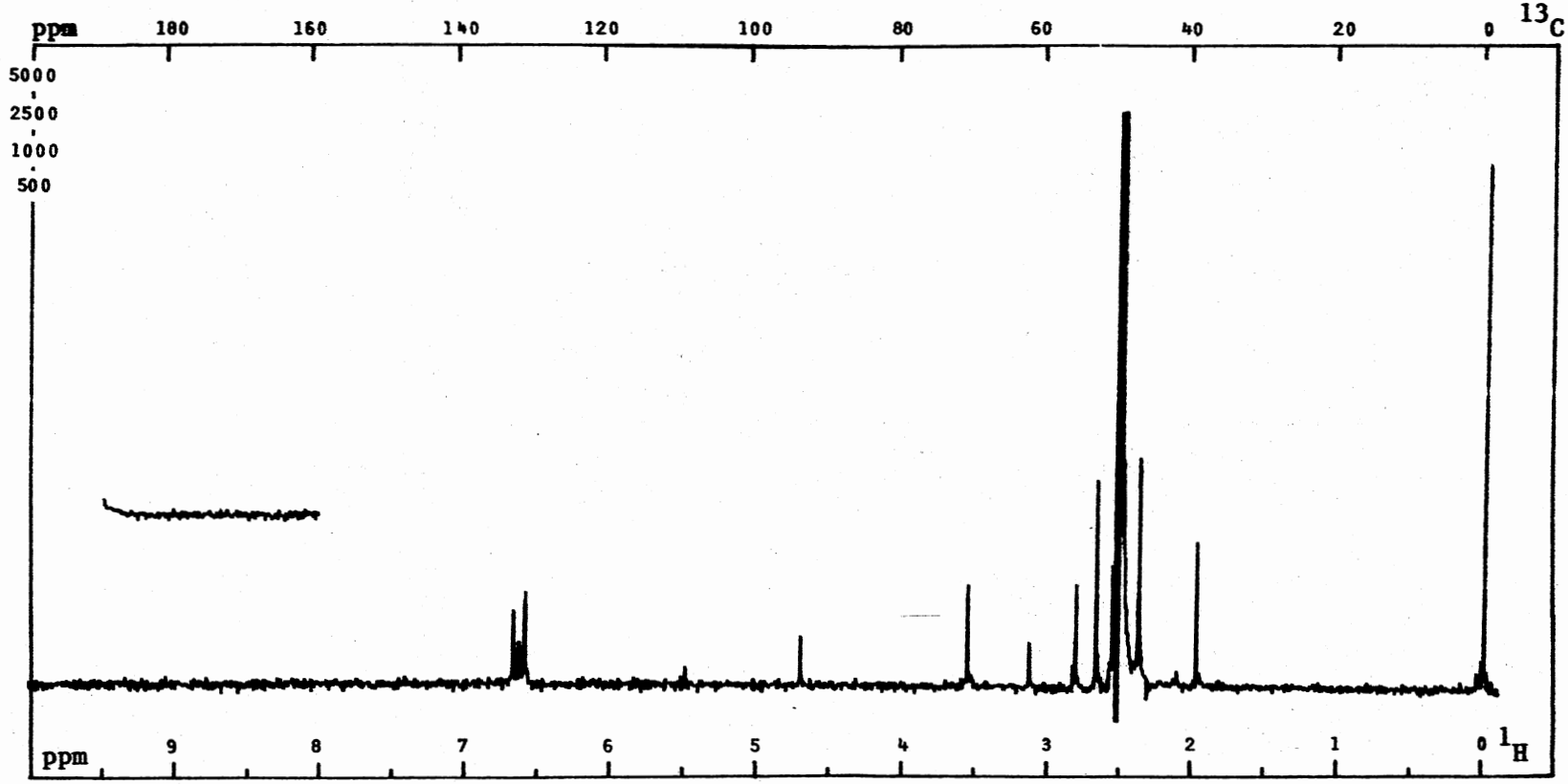


^{1}H NMR Spectrum of Perchlorate of 7-N-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (86)

CW X; Solvent D_2O; SO. 86015 Hz; PW. 10000 Hz; T. 30°C; SA. 2.5;

P2/RF. 100 µs/dB; SF. 100 MHz; FB. 2 Hz; Lock ^{2}H; ST. 250 s.

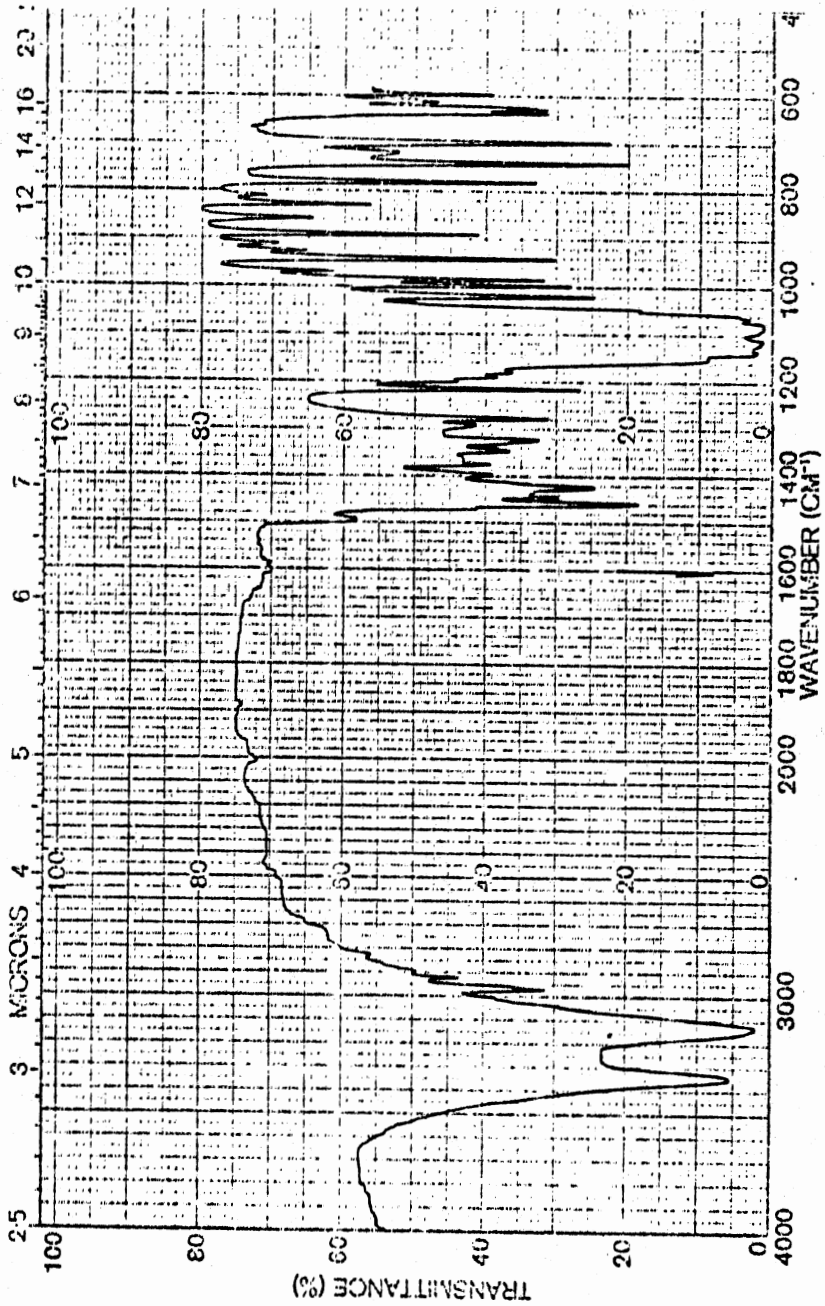
PLATE XXIX



^{13}C NMR Spectrum of 86

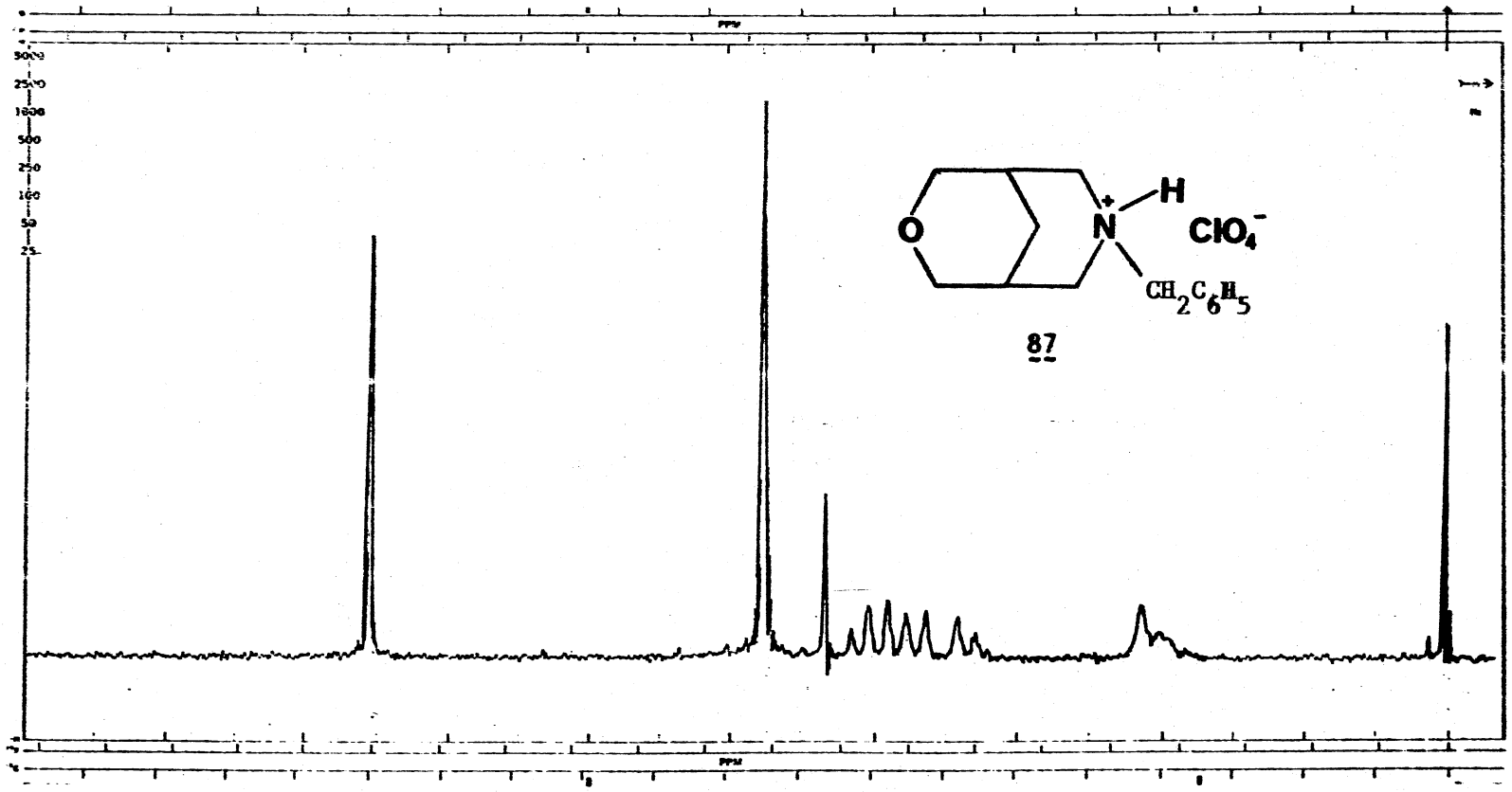
PFT. X; Solvent H_3COD; SO. 35101 Hz; PW. 5000 Hz; T. 30°C; Acq. 16500;
Size 8 K; P2/RF. 10 µs/dB; SF. 25.2 MHz; Lock ^{2}H; D5 5 s; DC. ^{1}H;
Offset 45051 Hz; RF. 910 W/dB; NBW 100 Hz.

PLATE XXX



IR Spectrum of 86, KBr Pellet

PLATE XXXI



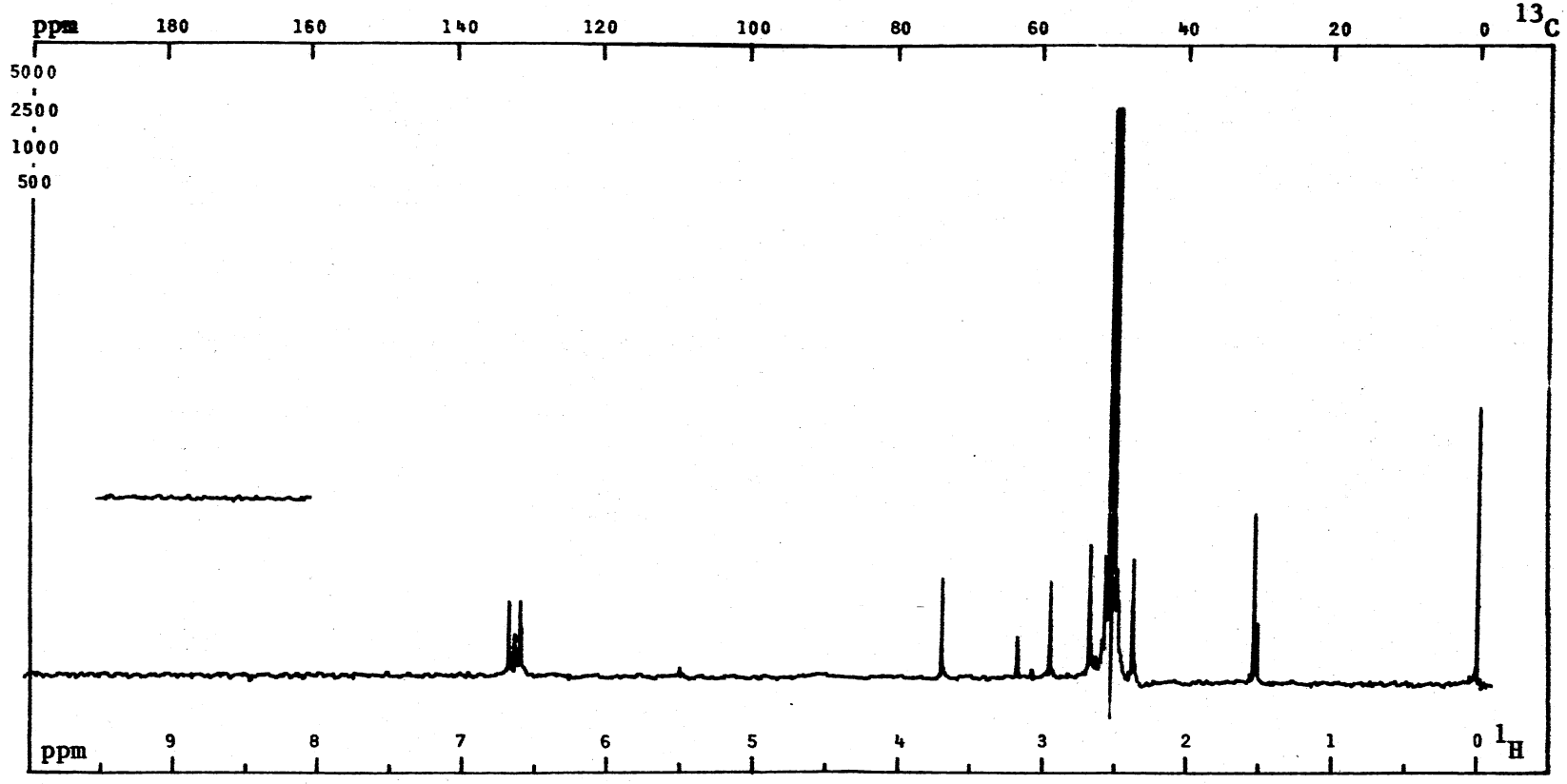
87

^1H NMR Spectrum of Perchlorate of 7-N-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonane (87)

CW X; Solvent D_2O; SO. 86014 Hz; PW. 1000 Hz; T. 30°C; SA. 2.5;

P2/RF 70 µs/dB; SF. 100.1 MHz; FB. 2 Hz; Lock ^2H; ST. 250s.

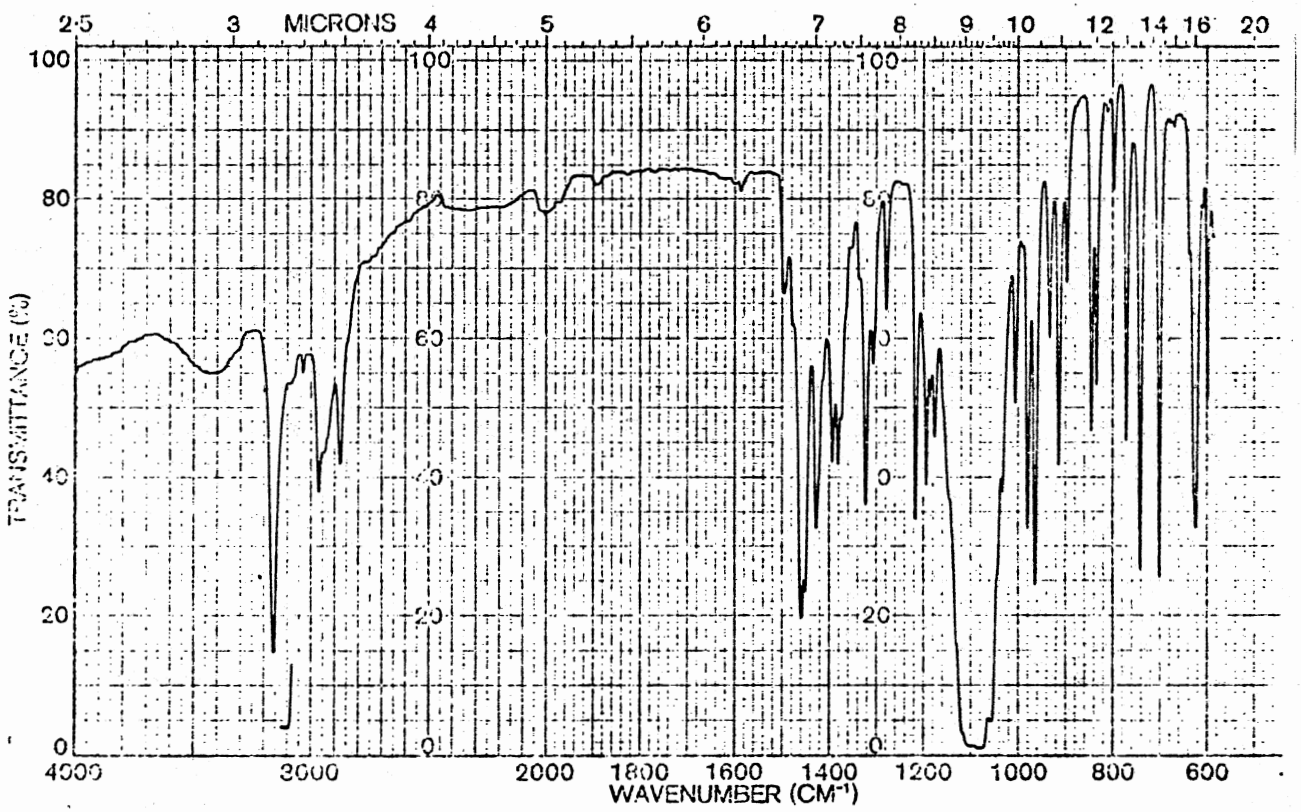
PLATE XXXII



^{13}C NMR Spectrum of 87

PFT. X; Solvent H_3COD; SO. 35101 Hz; PW. 5000 Hz; T. 30°C; Acq. 25500;
Size 8 K; P2/RF 10 µs/dB; SF. 25.2 MHz; Lock ^{2}H; D5 4 s; DC. ^{1}H;
Offset 45051 Hz; RF. 910 W/dB; NBW. 100 Hz.

PLATE XXXIII



IR Spectrum of 87, KBr Pellet

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VITA

Palanisamy Arjunan

Candidate for the Degree of

Doctor of Philosophy

Thesis: Part I. SYNTHESES AND CARBON-13 SPIN-LATTICE RELAXATION MEASUREMENTS (T_1 VALUES) OF CERTAIN SELECTED ALKYL ω-(2-ANTHRYL)ALKANOATES

Part II. SYNTHESES AND A CONFORMATIONAL STUDY OF CERTAIN SELECTED 3-OXA-7-AZABICYCLO[3.3.1]NONAN-9-ONES (OR 3-OXA-7-AZABISPIDINONES)

Major Field: Chemistry

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