substituents was observed. Free energies of activation for internal rotation were obtained from the temperature dependent ^{1}H spectra of three compounds; the rotational barriers are lower than in corresponding thiohydantoins.

Characteristic ^{13}C chemical shift ranges and substituent shifts were established. A linear relation between chemical shifts and electronegativity of the ortho halo aryl substituent was observed. Transmission of substituent effects has been considered in terms of dihedral angles between rings.

Proton spin-lattice relaxation rates in these compounds have been measured in order to establish the relative rates of protons in different environments and the influences on the rates. Evidence for anisotropic motion of the molecules, and inter-ring relaxation mechanisms has been considered.

CURRICULUM VITAE

The author was born in Egypt in 1941. In 1956, he took up residence in France and completed his high school studies at Nice.

He graduated with a B.Sc. in Chemistry from Grenoble and Nice Universities.

In 1969 he immigrated to Canada and joined the Research Department of F. W. Horner Inc. where he is currently employed in the Quality Control Department.

ACKNOWLEDGMENTS

It is a great pleasure to express my thanks to my learned professor, Dr. Lawrence David Colebrook, of the Department of Chemistry, Concordia University, Montréal, under whose direction this work has been accomplished; for his active participation in the experimental part of this thesis, and his patience and kindness.

I am thankful also:

- to Dr. Yoon C. Kim (F. W. Horner Inc.) and Dr. M. A. Khadim (Concordia University) for helpful discussions.

- to Sriyawathie Lokuge (Concordia University) for temperature dependent n.m.r. spectra

- and to my wife for her patience during all evenings passed in studying.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Nuclear magnetic resonance (n.m.r.) spectroscopy has become one of the most powerful techniques available to the chemist for the investigation of the structure and stereochemistry of organic molecules.

The technique can be applied both to conformationally rigid and to conformationally mobile molecules. In the latter case, dynamic nuclear magnetic resonance (DNMR) studies can provide quantitative data on the rates of conformational exchange processes, and on the activation parameters[1]. In many respects, n.m.r. methods can provide information on molecular structure which is not available from other spectroscopic techniques (e.g. infrared, Raman, etc.)[2].

The introduction of ^{13}C n.m.r. spectroscopy provided a number of advances over the older established ^{1}H n.m.r. methods for the investigation of the structures of complex organic or biological molecules. Because of the much greater chemical shifts of ^{13}C than ^{1}H spectra (typically 200 ppm versus 10 ppm), and the fact that ^{13}C spectra are normally recorded with proton decoupling, most carbon signals in complex molecules may be differentiated. However, ^{13}C n.m.r. spectroscopy has its own limitations as a result of lack of sensitivity due to the relatively small magnetogyric ratio and the low natural abundance (1.1%) of the ^{13}C nuclei. These inconvenient properties of the ^{13}C

nucleus have been practically overcome by taking advantage of the increase in sensitivity provided by the nuclear Overhauser effect (NOE)[3] and the utilization of efficient signal enhancement techniques available through the use of the pulse Fourier transform method [4]. Advances in electronics (which have improved the sensitivity of n.m.r. spectrometers) and the widespread use of dedicated mini-computers have made ^{13}C n.m.r. spectroscopy a routine tool for structure determination.

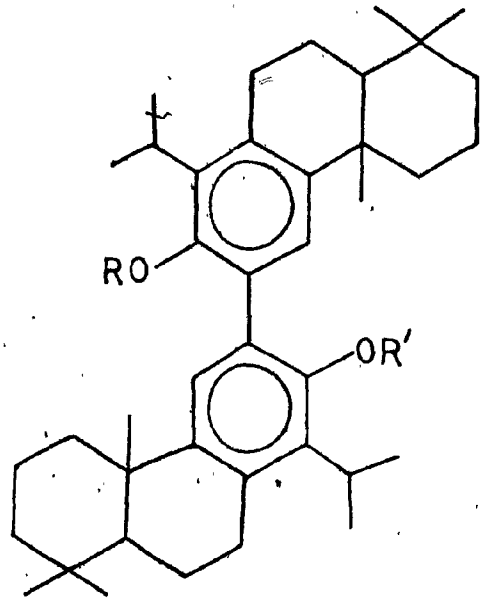
The recent availability of high-field (superconducting magnet) n.m.r. spectrometers has provided a further impetus for ^{1}H n.m.r. studies. The much greater chemical shift dispersion at the higher fields and frequencies now available has reduced a number of the difficulties associated with ^{1}H n.m.r. spectra, e.g. spectra which are second-order (and difficult to interpret) at low fields may become essentially first-order at high fields, and the problems of overlapping signals may be dramatically reduced. A further benefit of high field/frequency operation is an increase of sensitivity, so that smaller samples are required. The introduction of pulse Fourier transform high-field spectrometers has been accompanied by improvements in the instrument computers and their associated hardware, and in computer software, so that very sophisticated experiments can now be carried out on a routine basis.

The work reported in this thesis represents several aspects of the application of n.m.r. techniques to problems in organic chemistry.

BACKGROUND OF THIS THESIS

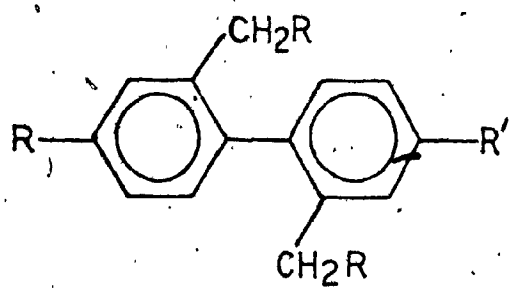
For a number of years, there has been considerable interest in conformational interchange processes involving restricted internal rotation about single bonds[1]. An aspect which has been investigated in the laboratory of Professor L.D. Colebrook has been biphenyl-like isomerism in compounds in which there is steric restriction to internal rotation between two ring systems linked by a C-C or a C-N bond.

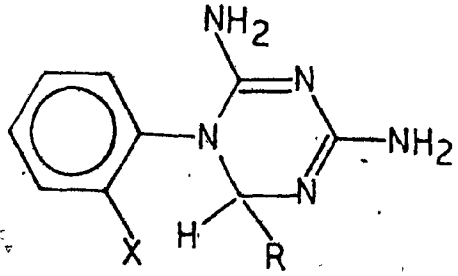
(I)



The study was initiated by Jahnke[5] and Bentz[6,9] who determined barriers to internal rotation in some naturally occurring (I) and synthetic biphenyls (II) and triazines (III), using complete ^1H n.m.r. line shape analysis.

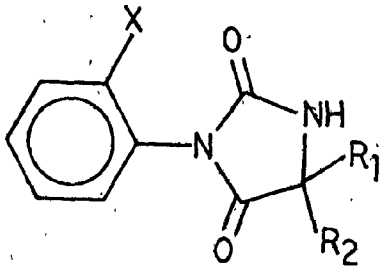
(II)





(III)

Investigation of restricted internal rotation in 3-aryl hydantoins (IV) was initiated by Fehlner [7] and continued by Granata [8] using the same techniques.

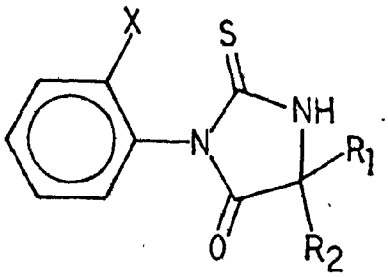


(IV)

Kinetic and thermodynamic data for 3-aryl hydantoins with

a variety of substituents on the heterocyclic and aryl moieties were obtained; so that the effects of substituents on the conformational stability of the molecules could be established.

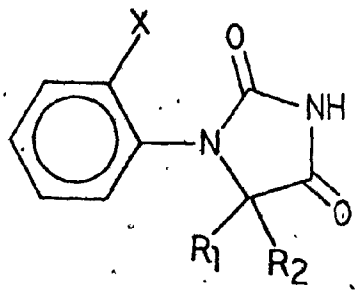
Later, Giles [10] introduced studies of 3-aryl-2-thiohydantoins (V),



(V)

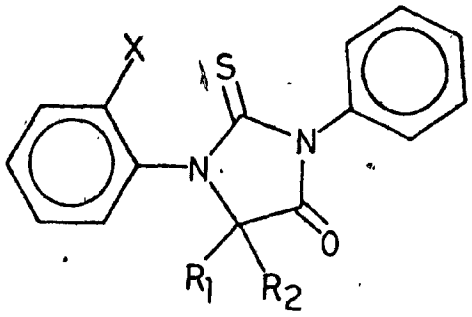
demonstrating that conformational stability is higher than in the hydantoin series. In certain cases one diastereomeric rotational isomer could be isolated, and the rotational barrier evaluated by measuring the rate of return to equilibrium.

1-aryl substituted hydantoins (VI) were investigated by Icli [11] with special attention being given to solvent effects and the thermodynamic parameters associated with restricted internal rotation.



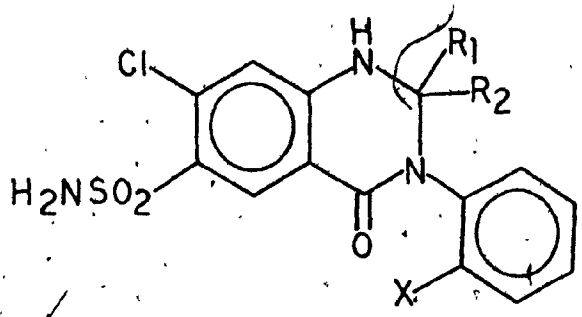
(VI)

Corresponding 1-aryl-2-thiohydantoins (VII) were studied by Khadim [12] using complete line shape analysis; substantially higher barriers to internal rotation are observed when a 2-thio rather than a 2-oxo group is present.



(VII)

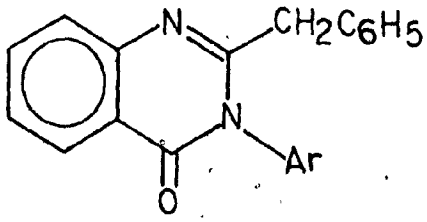
In related investigations, Fehlner [6] measured the rotational barriers in a series of 3-aryl quinazolinones (VIII) using



(VIII)

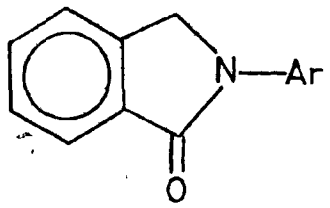
complete line shape analysis, while Giles [13] found high barriers to

internal rotation about aryl C-N bonds in 2-benzyl-3-aryl-4 (3H)-quinazolinones (IX).



(IX)

Carbon-13 n.m.r. studies on compounds from these series were initiated by Williams[14] who examined the spectra of a number of 3-aryl hydantoins (IV) using the continuous wave (C.W.) method, and by Icli[11], who investigated 1-aryl hydantoins (VI). Later ^{13}C n.m.r. studies utilized the pulse Fourier transform technique; Khadim[12,15] investigated 3-aryl-2-thiohydantoins (V), N-aryl isoindolinones (X), and 1-aryl-2-thiohydantoins (VII),



(X)

while Musty[16] measured the ^{13}C spectra of 3-aryl 2,3-dihydro-4(1H)-quinazolinones (VIII) and 3-aryl 4(3H)-quinazolinones (IX).

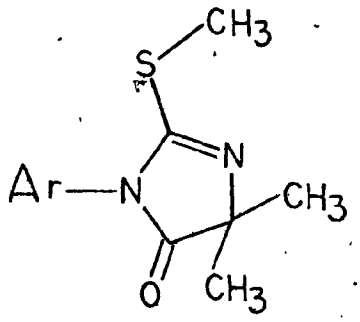
These carbon-13 n.m.r. studies had two major aims:

a) to use ^{13}C spectra as a source of stereochemical information, by investigating the circumstances under which diastereotopically related carbon atoms in enantiomeric rotational isomers, and corresponding carbon atoms in diastereomerically related rotational isomers, may be distinguished;

b) to provide information on the effects of substituents on heterocyclic system carbon chemical shifts, and to identify characteristic chemical shift regions.

OBJECTIVES

The present work was intended to provide information on a stereochemically similar group of compounds; 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolinones (XI),



(XI)

most closely related to the 3-aryl-2-thiohydantoins (V) which had previously been investigated. The investigation was divided into three sections:

a) A ^1H n.m.r. study was aimed at investigating restricted internal rotation about the aryl C-N_1 bond, with the possibility that barriers to internal rotation could be measured by ^1H line shape analysis. It was hoped that this study would provide qualitative information on the steric contribution of the -S-CH3 group relative to that of the =S group (in 3-aryl-2-thiohydantoins).

b) A carbon-13 n.m.r. study of these compounds was undertaken in order to provide chemical shift and substituent effect information on a class of heterocyclic compounds for which no ^{13}C data have appeared in the literature.

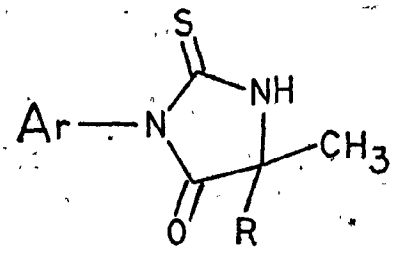
c) A proton spin-lattice relaxation study was undertaken (using a super-conducting magnet spectrometer operating at 270 MHz) to evaluate the potential of ^{1}H relaxation to provide information on the structure, stereochemistry and (possibly) anisotropic motion of a class of heterocyclic compounds.

CHAPTER I

^1H n.m.r. spectra of 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones

Introduction

Studies of conformational isomerism in a number of types of N-aryl substituted heterocyclic compounds, using proton nuclear magnetic resonance spectroscopy, have previously been reported [7,8,9,10,11]. In particular, restricted internal rotation about the aryl C-N bond in 3-aryl-5,5-dimethyl-2-thiohydantoins, and their 5-monomethyl analogues, has been investigated, and barriers to rotation have been measured [7,8,10].



R = H, CH_3

The barrier to internal rotation in ortho aryl-substituted compounds is consistent with the relative sizes of these groups, i.e. the barrier is largely steric in character. Further, comparisons of the rotational barrier in the thiohydantoins and corresponding hydantoins show that replacement of a 2-C=O by a 2-C=S group causes a large increase (@ $\simeq$ 7 Kcal/mole)[7] in the barrier to internal rotation. The rotational barriers are sufficiently high in some of the thiohydantoins that conformational isomers may be isolated at normal temperatures[7, 10].

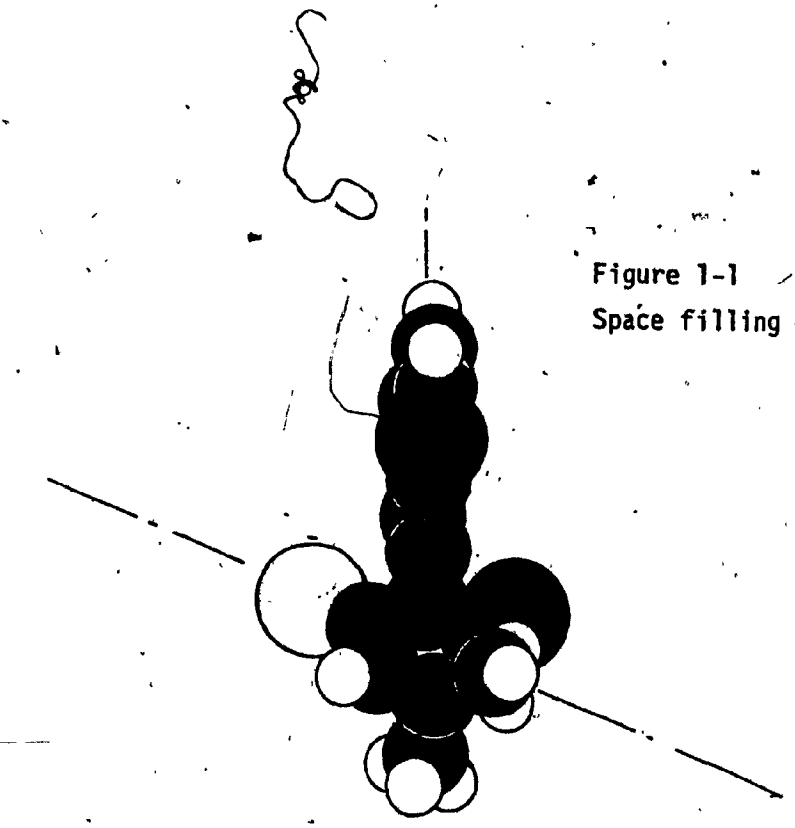
In view of the substantial influence of the thiocarbonyl group on the barrier to rotation, a study of the effect of conversion of the >C=S to a >C-S-CH3 group was undertaken, in the expectation that the new series of compounds, the 2-methylthio imidazolinones, would also exhibit high barriers to internal rotation. Corresponding views of space-filling models of a 3-aryl-5,5-dimethyl-2-thiohydantoin and the equivalent 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-one are depicted in Figure 1-1.

In the hydantoin and thiohydantoin series investigated previously, compounds unsubstituted in position 5 (corresponding to position 4 in the imidazolinones), or with mono or dimethyl substituents in this position were prepared. For reasons associated with the synthetic procedures used, only the 4-dimethyl compounds were prepared in the imidazolinone series.

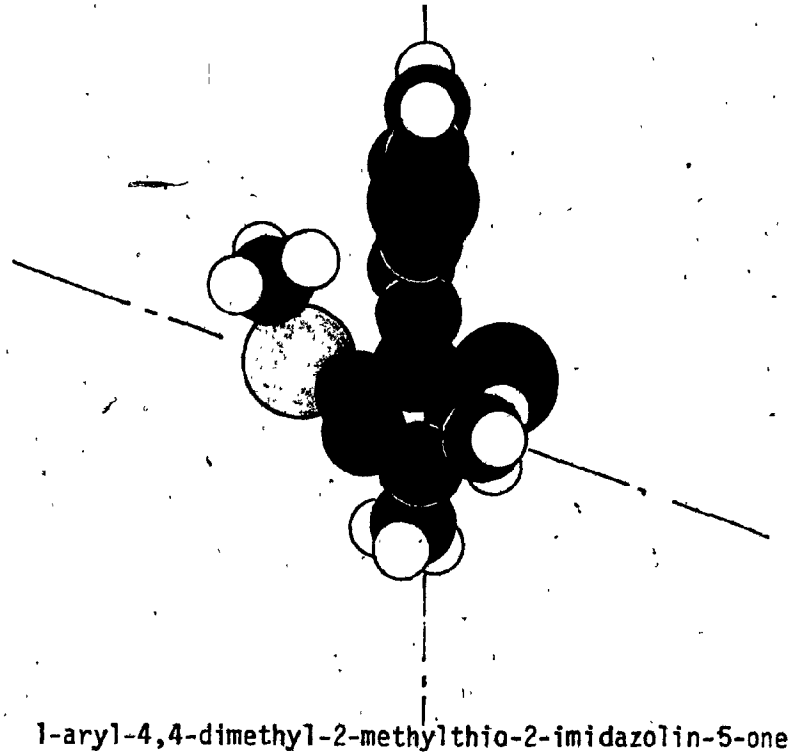
High barriers to internal rotation in this series were expected to be detectable through the appearance of signals arising from the diastereotopically related gem-dimethyl groups, assuming that chemical shift differences would be adequate and that internal rotation would be slow on the n.m.r. time scale at the temperature employed.

Splitting of the gem-dimethyl signals at normal probe temperatures had previously been observed in the thiohydantoin series.

Figure 1-1
Space filling models of:



3-aryl-5,5-dimethyl-2-thiohydantoin



1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-one

RESULTS AND DISCUSSION

Proton n.m.r. spectra of the 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones were measured at 60 MHz on DMSO-d_6 solutions at a probe temperature of about 36°C using a Varian A-60A spectrometer, and also at 270 MHz on 0.01 M solutions in $CDCl_3$ using a "home-built" superconducting magnet spectrometer located at the University of British Columbia, at a probe temperature of 23°C. Peak positions were measured directly from the A-60A charts for the 60 MHz spectra, but from computer print-outs of position and intensity for the 270 MHz spectra, with respect to internal tetramethylsilane in each case.

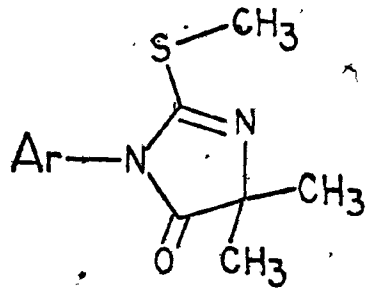
With the exception of compound 2, which has a symmetrically substituted aryl group, all the imidazolinones are potentially capable of exhibiting doublets for the 4-methyl groups.

At 60 MHz, using DMSO-d_6 solutions, only compounds 5, 6 and 7, showed doublets (see Table 1-1). The chemical shifts and geminal dimethyl group peak separations for the corresponding thiohydantoins, measured under similar conditions, are reported in Table 1-2. With the higher dispersion (and lower probe temperature) available with the 270 MHz instrument,

using $CDCl_3$ solutions, all compounds but the 2'-tolyl, 1, exhibited two gem-dimethyl signals (see Table 1-3), thus demonstrating slow internal rotation.

The separation between the geminal methyl signals ranges up to 0.076 ppm, and roughly parallels the size of the ortho subsituent, suggesting that the degree of separation is associated with the effect of the magnetic anisotropy of the aryl ring, which is a function of the dihedral angle between the two rings, as well as with the effect of the substituent itself. The separation is greatest for the 1'-naphthyl compound, 7, for which a large anisotropy effect is expected. The failure to observe separate 4,4-dimethyl group signals in, 1, at 270 MHz, may result from inadequate chemical shift differences rather than from the effects of fast internal rotation. Similar small chemical shift differences have been observed in related O-tolyl-substituted hydantoins and thiohydantoins [7,10].

Table 1-1 - Proton chemical shifts [a] of 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones

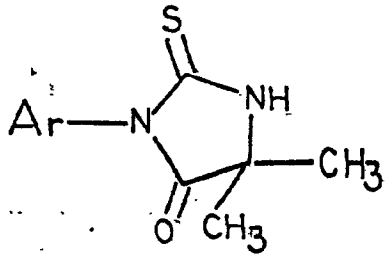


	Ar	4-CH_3		Δ(Hz)	Δ (ppm)	-S-CH_3	-CH_3 (Aryl)
1	2'-Tolyl	1.33	-	-	-	2.37	2.07
2	2',6'-Dimethylphenyl	1.33	-	-	-	2.37	2.03
3	2'-Chlorophenyl	1.37	-	-	-	2.40	-
4	2'-Bromophenyl	1.30	-	-	-	2.37	-
5	2'-Iodophenyl	1.33	1.39	3.6	0.06	2.39	-
6	2'-Nitrophenyl	1.30 b)	1.39	5.4	0.09	2.40	-
7	1'-Naphthyl	1.43	1.53	6.0	0.10	2.40	-

a) ppm from TMS, determined at 60 MHz, DMSO-d_6 solutions

b) shoulder

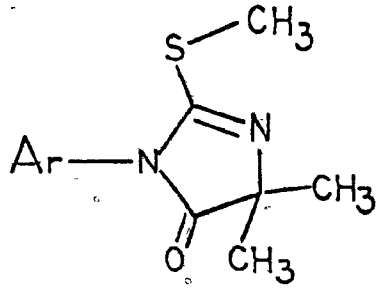
Table 1-2 - Proton chemical shifts [a] of 3-aryl-5,5-dimethyl-2-thiohydantoins



Ar	5-CH_3		Δ(Hz)	Δ(ppm)	Aryl-CH_3
2'-Tolyl	1.45	-	-	-	2.07
2',6'-Dimethylphenyl	1.45	-	-	-	2.07
2'-Chlorophenyl	1.47	-	-	-	-
2'-Bromophenyl	1.46	-	-	-	-
2'-Iodophenyl	1.48	1.51	1.8	0.03	-
2'-Nitrophenyl	1.48	1.52	2.4	0.04	-
1'-Naphthyl	1.54	1.59	3.0	0.05	-

a) ppm from TMS, determined at 60 MHz, DMSO-d_6 solutions.

Table 1-3 - Proton chemical shifts [a] of 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones

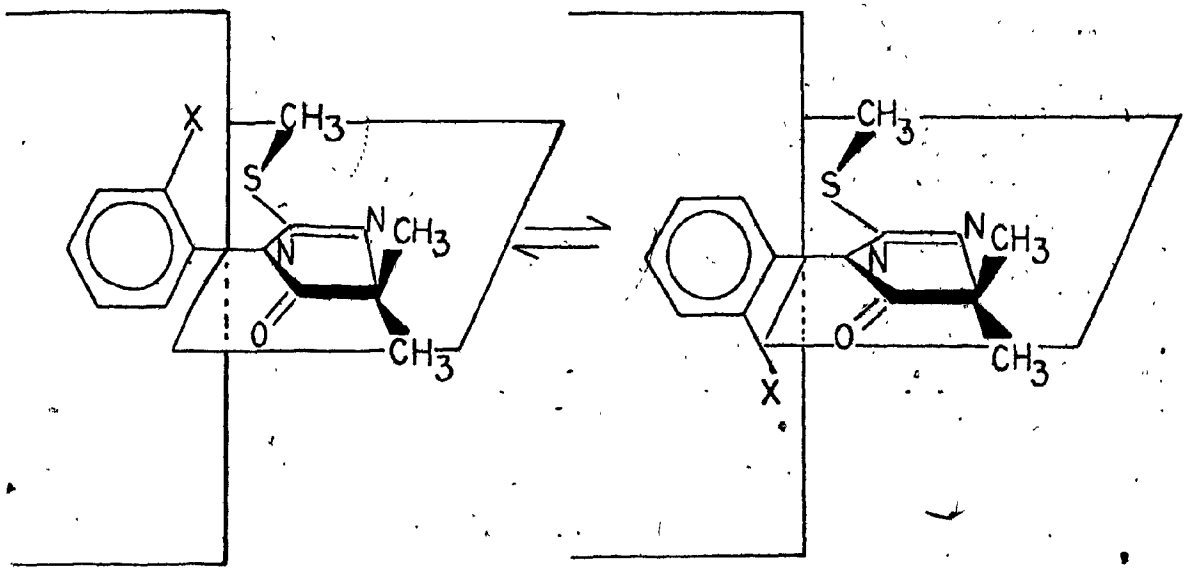


	Ar	Aryl Protons 3'	4'	5'	6'	CH_3	-S-CH_3	4-CH_3	Δ(ppm)
1	2'-Tolyl					2.190	2.488	1.477, 1.477	0.00
2	2',6'-Dimethylphenyl					2.163	2.488	1.485	
3	2'-Chlorophenyl	7.540	7.428	7.382	7.302		2.511	1.483, 1.497	0.014
4	2'-Bromophenyl	7.712	7.351	7.430	7.302		2.513	1.483, 1.511	0.028
5	2'-Iodophenyl	7.949	7.182	7.462	7.281		2.517	1.481, 1.542	0.061
6	2'-Nitrophenyl	8.217	7.652	7.761	7.439		2.529	1.475, 1.500	0.025
7	1'-Naphthyl						2.466	1.550, 1.626	0.076

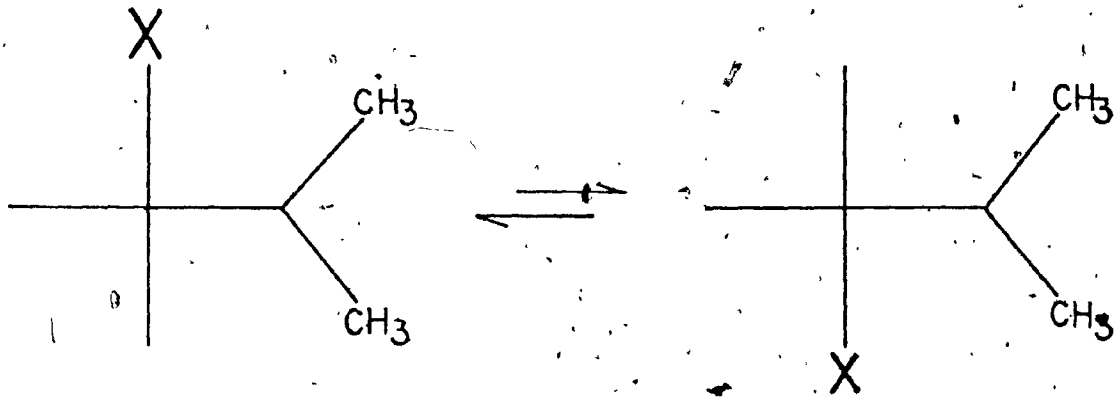
a) ppm from internal TMS, determined at 270 MHz, 0.01 M solutions in 99.8% $CDCl_3$.

ORIGIN OF METHYL GROUP NON EQUIVALENCE

Those imidazolinones with unsymmetrically substituted aryl groups (i.e. all compounds except 2), can exist as two major enantiomeric rotational isomers.



These can be represented in Newman projection as:



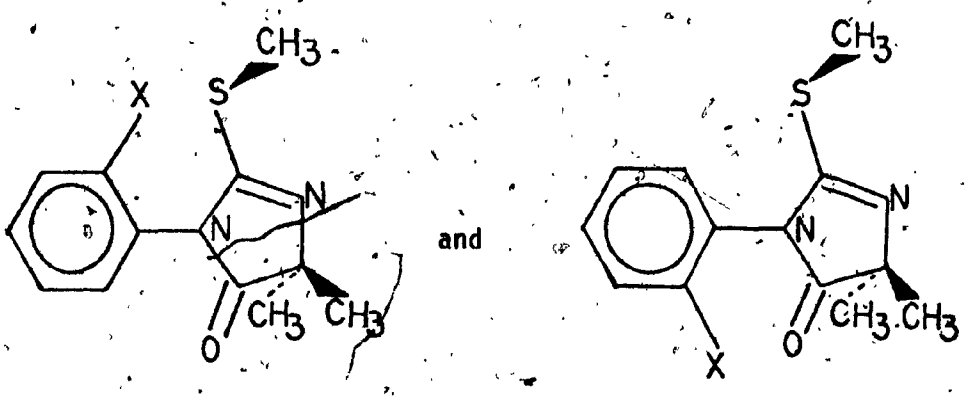
The two ring systems are depicted here as being at right angles for convenience; the actual angles are unlikely to be 90° (see later).

In each of these rotational isomers, the geminal methyl groups are diastereotopic (i.e. have different environments) and should have different chemical shifts, so that the spectrum would consist of a doublet. The two enantiomeric forms would be indistinguishable in achiral media. If rotation about the aryl C-N bond were rapid on the n.m.r. time scale, i.e. the rotational isomers were undergoing rapid interconversion, the doublet would collapse to a singlet.

For intermediate rates of interconversion, partially collapsed spectra would be observed. No such partially collapsed sepctra or significantly broadened lines, were observable at normal temperatures at 270 MHz, in the present case.

There exist two possible transition states for interconversion of the rotamers, namely the states in which the two rings are co-planar.

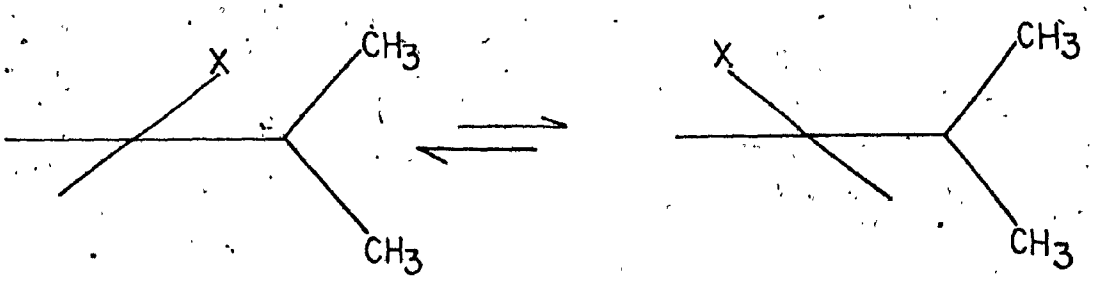
i.e.



No information on the relative importance (i.e. the relative energies) of these two states is obtainable from the present study.

In both forms, severe steric interaction between the aryl ortho substituents and the carbonyl oxygen atom and the methylthio substituents of the hetero-ring is expected. The relative severity of these interactions is expected to be the major factor which determines the relative importance of the two possible interconversion pathways.

In the conformational ground states of the molecules, two conformations of the two rings, separated by a low energy barrier, can be envisaged. In these, the driving force towards coplanarity of the rings, namely conjugation, is balanced by repulsive steric interaction which is a maximum when the rings are coplanar. These two sub-conformations can be represented as:



The existence of such conformational isomers can be presumed, but experimental evidence for their existence is difficult to obtain.

Interconversion of these sub-conformations (i.e. rotation about the aryl C-N bond) must be fast on the n.m.r. time scale so that only the spectrum of the time-averaged conformation can be observed.

The averaged conformation is unlikely to involve a 90^{o} dihedral angle in compounds, such as in the present series, unsymmetrically substituted on both rings; the aryl ortho substituent (X) is likely to lie toward the less hindered transition (co-planar) state. Since the degree of steric repulsion between the two ring systems must depend on the steric bulk of the ortho substituent, the "averaged" dihedral angle must also be dependent on the steric bulk of the substituent.

While a chemical shift difference between the geminal methyl groups can be predicted as a matter of stereochemical principle, its physical origin is of interest. There must be a direct contribution from the ortho substituents themselves, associated with the electrons

in the C-X bond (vs the electrons on the C-H bond in the other ortho position). Differential influences at the two geminal methyl sites are expected because of the "cisoid" and "transoid" relationships to the X-groups. However, this influence might be expected to be small at the relatively remote methyl group sites.

The major contribution to the chemical shift difference probably arises from the magnetic anisotropy associated with the aromatic ring currents of the aryl groups. Unless the "averaged" dihedral angle between the ring is 90^{o} (which is unlikely for reasons given above), the two methyl groups will lie in different "shielding - deshielding" regions of the aryl group (Figure 1-3). Such ring current effects produce some of the largest influences on chemical shifts observable in proton n.m.r. spectra and are thoroughly documented [11, 17].

Another possible contribution to the chemical shift differences between geminal methyl group is the differential effects of specific solvation of the solute molecules. Although the spectra of the imidazolinones were taken in two solvents, $CDCl_3$ and DMSO-d_6, no such solvent effects on the chemical shift differences can be clearly established, in part because of the lower chemical shift dispersion and the lower measurement accuracy of the 60 MHz DMSO-d_6 spectra.

The influence of the ortho substituent on the chemical shift difference between the geminal methyl groups is best seen in the halo-series. Thus, the Δ values parallel the increase in the steric bulk of the ortho halo substituent in the series chloro, bromo, iodo - (3, 4 and 5 respectively, see Table 1-3), increasing from 0.014 to 0.061 ppm. This shift may be interpreted as being predominantly due to a change in the mean dihedral angle between the rings as the steric bulk of the substituent increases.

Interpretation of the chemical shift differences in the other compounds is more difficult because of the different nature of the substituents. However, the largest difference, 0.076 ppm. is associated with the 1'-naphthyl compound, 7, which is expected to show a large aromatic ring current effect.

CONFORMATIONS OF THE -S-CH_3 GROUP

Although, in principle, specific conformational preferences of the -S-CH_3 group could lead to differential shielding or deshielding of the 4,4-dimethyl groups (and to influences on the chemical shifts of protons elsewhere in the molecules), such effects are unlikely to be observed under the conditions of the present study. Rotation about the C_2-S bond should be fast at the temperatures of the measurements. It is probable that the -S-CH_3 has a preferred conformation with respect to the unsymmetrically substituted aryl group, so that the enantiomeric relationship between the aryl group rotational isomers is not affected by the conformational preferences of the -S-CH_3 group.

4-METHYL GROUP CHEMICAL SHIFTS

The chemical shifts of the 4-methyl groups range from 1.475 to 1.626 ppm, the substituent with the greatest influence being the 1'-naphthyl group, 7. The shift induced by the 1'-naphthyl group is in the deshielding direction. This shift is consistent with the location of the 4-CH_3 group in the deshielding zone of the naphthyl group; the deshielding effect should be maximized for dihedral angles near 90^0. The chemical shift of the -S-CH_3 group in the 1'-naphthyl compound, 7, is also consistent with a large dihedral angle between the rings (see later).

An interesting observation, for which no satisfactory explanation is obvious, is illustrated in Figure 1-2, which is a plot of the proton chemical shifts versus the Pauling electronegativities[18] of the halo substituents (compounds 3, 4 and 5). The chemical shift of the high field signal is almost independent of the halo substituent, whereas the low field signal shows an apparently linear dependence on the electronegativity, the methyl signal of the iodo compound, 5, appearing at lowest field. Since it is

difficult to see how a through-bond electronic effect of sufficient magnitude could be operative, it is probable that through-space effects, possibly coupled with the influence on dihedral angles of changes in the steric bulk of the substituents, are largely responsible.

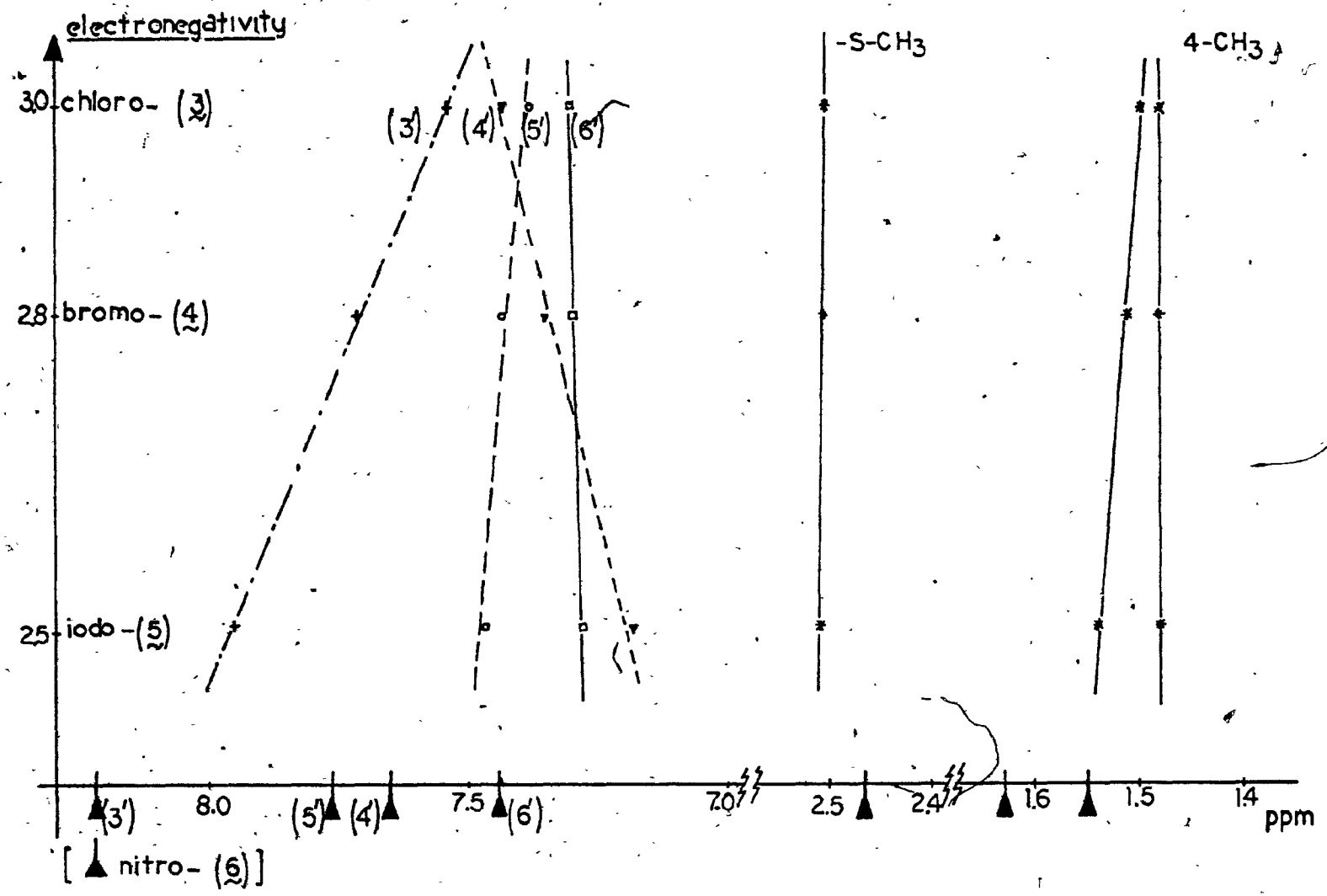


Figure 1-2 Plot of the proton chemical shifts (ppm) versus the Pauling electronegativities of the halo substituents.

S-CH_3 CHEMICAL SHIFTS

The chemical shifts of the -S-CH_3 protons range from 2.466 to 2.529 ppm, the highest field signal appearing in the spectrum of the 1'-naphthyl compound, 7. This upfield shift is consistent with the large magnetic anisotropy of the naphthyl group, provided that the dihedral angle between the rings is large enough that the -S-CH_3 group lies in the shielding region (see Figure 1-3). Thus, the -S-CH_3 shift data provide further evidence for a large dihedral angle.

The lowest field -S-CH_3 signal is shown by the nitro compound, 6. An adequate explanation is not obvious.

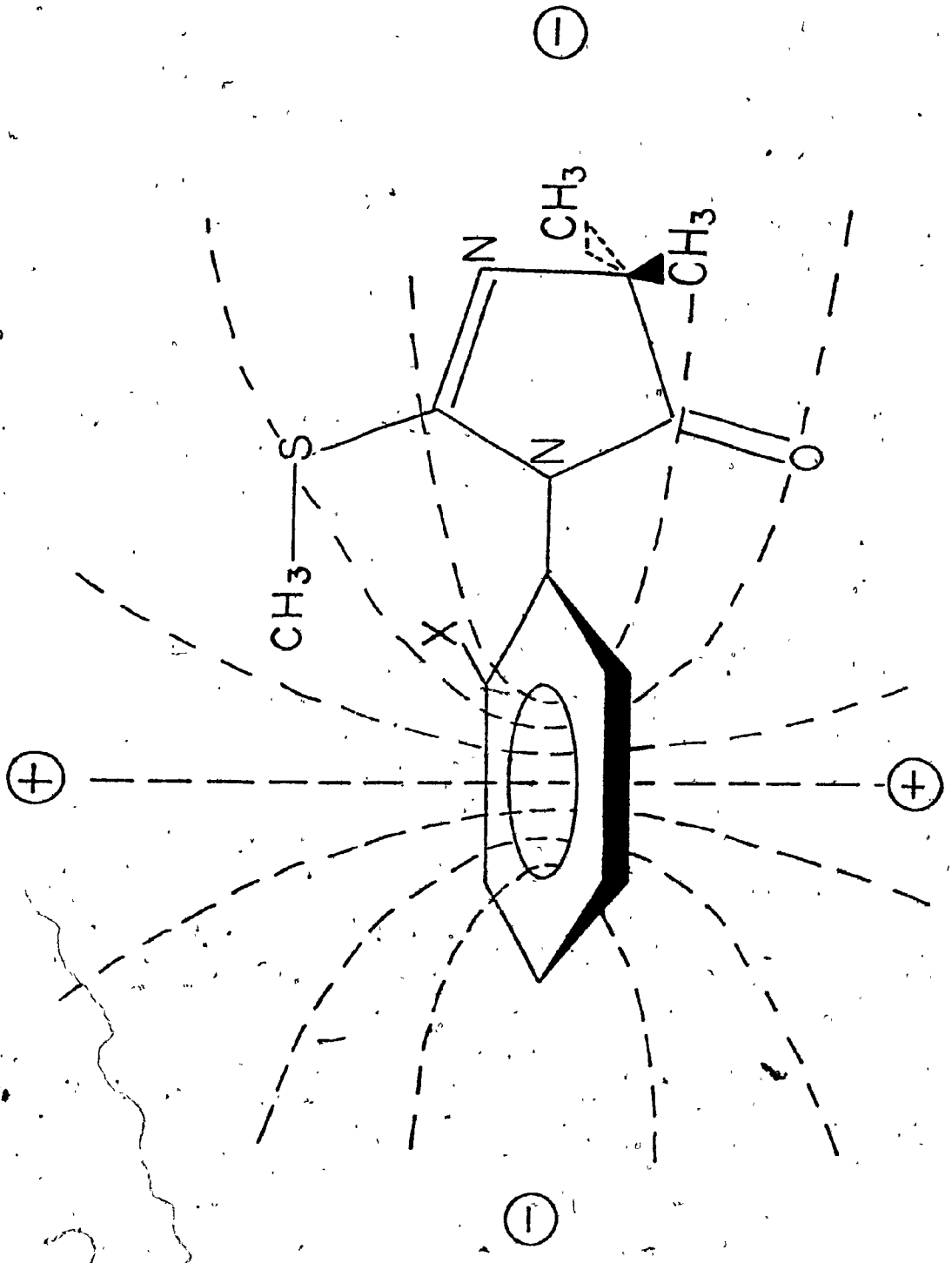


Figure 1-3 Shielding (+) effect of an aromatic group on the -S-CH_3 group.

AROMATIC PROTONS

The high dispersion at 270 MHz of the spectra of the aromatic ring protons 3, 4, 5 and 6 permitted complete analysis of the spectra of these four spin systems for all chemical shifts and coupling constants. The iodo-compound, 5, and the nitro-compound, 6, produced particularly well dispersed spectra (see Figures 1-4 and 1-5, respectively). One doublet of 5 was masked by the signal from the residual $CHCl_3$ in the 99.8% $CDCl_3$ solvent, but this did not seriously interfere with analysis of the spectrum. Although dispersion was not as high in the cases of the chloro-(3) and the bromo-(4) compounds, all transitions were resolved, and analysis was reasonably straightforward.

Line positions of the multiplets were taken directly from the print-outs of line positions and intensities made by the system computer in the "peak picking" routine. Initial values of the chemical shifts and coupling constants, required for the start of the iterative analysis procedure, were obtained by approximate

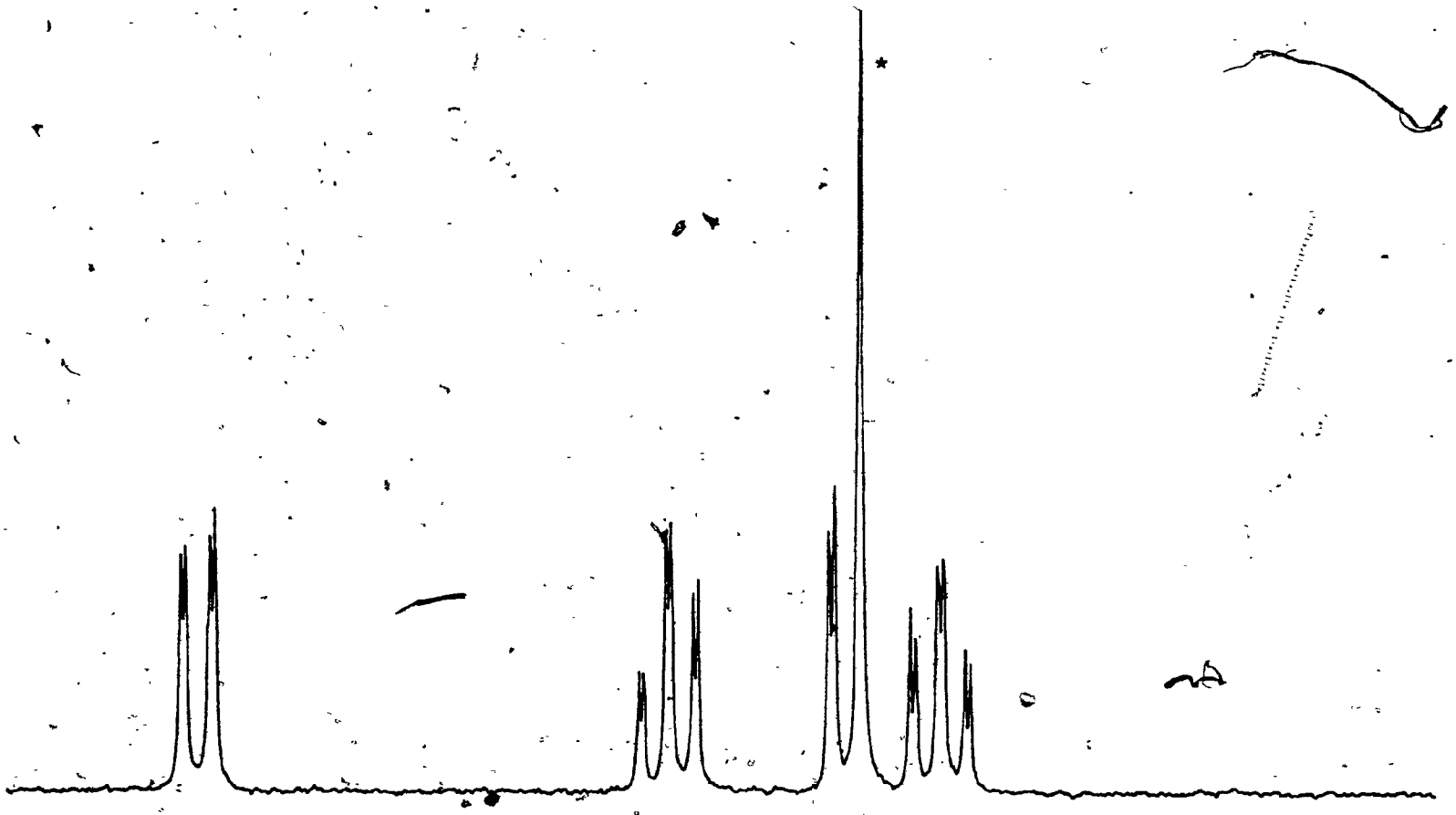


Figure 1-4 270 MHz proton n.m.r. spectrum of the aromatic protons of 1-(2'-iodophenyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one(5). *Residual $CHCl_3$.

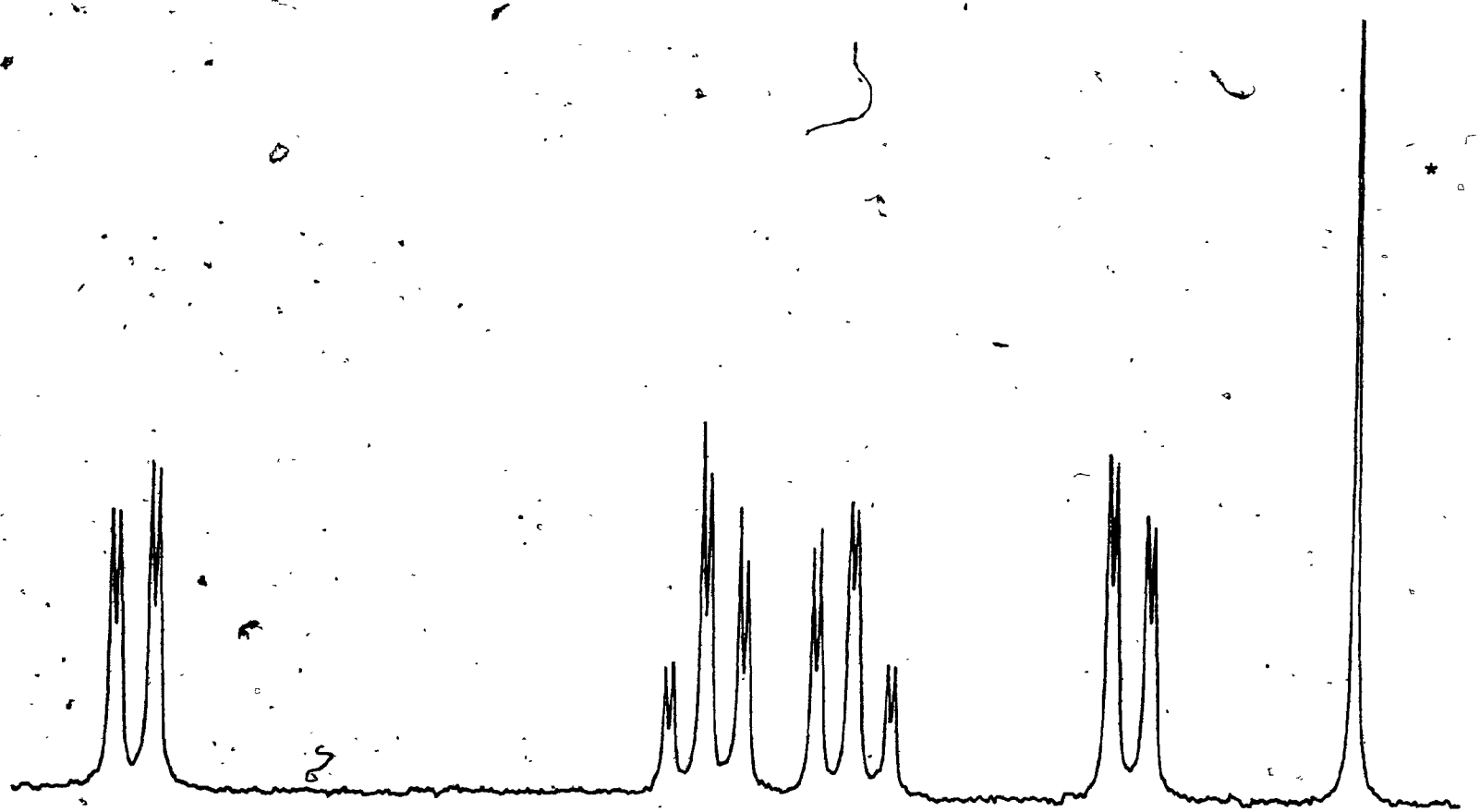


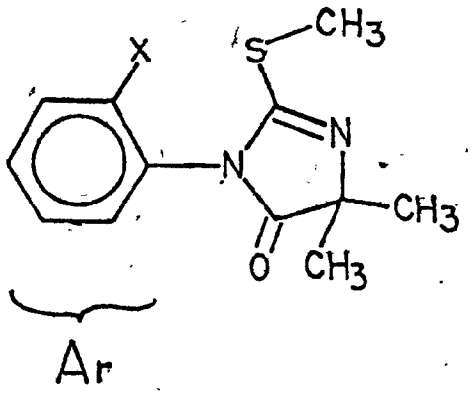
Figure 1-5 270 MHz proton n.m.r. spectrum of the aromatic protons of 1-(2'-nitrophenyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (6). *Residual $CHCl_3$.

first order analysis. The multiplets arising from the 3' and 6' protons were easily recognized as quartets with one large and one small coupling constant (corresponding to three-and four-bond couplings, respectively). The chemical shifts of these protons were assigned with reference to values reported in the literature for similarly constituted compounds.

Attempts were then made to recognize the multiplets in which the large and the small couplings occurred by searching the remaining multiplets for splittings of similar magnitude. Because of the close similarity of the various 3- and 4-bond coupling constants in the series (see Table 1-4), the remaining multiplets could not be assigned unambiguously on this basis. Instead, it was necessary to carry out two parallel sets of calculations to resolve the ambiguity in the assignment of the signals arising from the 4'- and 5'- protons.

Because of the similarity in the magnitudes of the 3- and 4-bond coupling constants, the signals arising from the 4'- and 5'-protons appeared as triplets of doublets, i.e. as triplets further split by a small (4-bond) coupling.

Table 1-4. Coupling constants (Hz) for aryl protons in 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones



	Ar	Aryl protons $J_{3'4'}$	$J_{3'5'}$	$J_{3'6'}$	$J_{4'5'}$	$J_{4'6'}$	$J_{5'6'}$
3	2'-Chlorophenyl	8.1	1.4	<0.5	7.6	1.6	7.8
4	2'-Bromophenyl	8.0	1.3	<0.5	7.7	1.6	7.6
5	2'-Iodophenyl	8.1	1.4	<0.5	7.8	1.3	7.8
6	2'-Nitrophenyl	7.9	1.3	<0.5	7.7	1.5	7.6

The technique of spectral analysis can be illustrated using the example of the 2'-nitrophenyl compound, 6. The spectrum of the aromatic region (Figure I-6) consists of two doublets of doublets at about 7.4 and 8.2 ppm, i.e. the high and the low field limits, respectively, of the region. Because of its low field chemical shift, plus the fact that splitting due to only two coupling constants appears, the 8.2 ppm multiplet can be assigned with complete confidence to the 3'-proton, which is influenced strongly by the adjacent nitro group. Because of its multiplicity, the 7.4 ppm multiplet must arise from H-6'.

The remaining multiplets, at about 7.6 and 7.8 ppm, which must be due to H-4' and H-5', consist of triplets of doublets. It is not clear from a visual inspection of the spectrum which multiplet should be assigned to H-4' and which to H-5'. The multiplets show some second-order skewing of intensities, sufficient to suggest that the larger coupling in the 7.8 ppm multiplet is to H-6', so that this multiplet should be due to H-5', but the appearance of the multiplets does not permit a confident assignment. Since the interpretation of the proton spin-lattice relaxation data requires an accurate assignment of these multiplets, a computer analysis of the spectra was required. The final analysis was based to some extent on the

"goodness of fit" criteria returned by the computer, but mainly on comparison of computed intensities of lines within the multiplets with the experimental spectra. Fortunately, the two modes of comparison agreed in all cases.

The spectra were analysed using the iterative program LAOCN3[19]. This program requires that an initial spectrum be calculated using a first guess as to the values of the chemical shifts and the coupling constants. The chemical shifts were estimated from the centres of the multiplets, allowing for some second-order skewing. Initial estimates of coupling constants were obtained by determining the line separations using the spectral print-out from the Nicolet 1180 computer on the spectrometer. Because of the similar magnitudes of the various large and the various small coupling constants, a clear-cut identification of the coupling pathways, which could have led to assignment of the multiplets, could not be obtained, but the differences in the magnitudes of the first-order coupling constants obtained from each multiplet were large enough that different values could be used in the initial calculation. In some spectra, some lines were masked by the strong signal from

the residual $CHCl_3$ in the 99.8% $CDCl_3$ solvent, but this caused no particular difficulty. All coupling constants were assumed to be positive[20]. As an initial check on the accuracy of the spectral assignments, theoretical spectra were calculated using a Hewlett-Packard 1000 computer, and plotted (using an X-Y recorder) on a scale suitable for visual comparison with the experimental spectra. Reasonable agreement, i.e. close visual correspondence in line position and intensity, was obtained in all cases.

The program LAOCN3 was then used to fit a theoretical spectrum to the experimental line positions (using a CDC Cyber 172 computer). This requires an initial assignment of theoretical transition numbers to lines in the actual spectrum; these were obtained from the print-out of the initial calculation. The iterative fitting procedure converged rapidly in all cases. Use of LAOCN3 requires that any obvious discrepancies in transition assignments be rectified at this stage, and the fitting process be repeated. Some minor adjustments were made in most cases; eventually it was clear that the transitions were correctly assigned.

For each spectrum, two sets of computations were carried out, corresponding to the two possible assignments of $H_{4'}$ and $H_{5'}$. Fairly good fits to the experimental line positions were obtained in all cases, though the error analyses revealed significant differences. It should be noted that LAOCN3 fits only to line positions, not to line intensities. A representative pair of computed data sets (for compound 5) is shown in Figure 1-6.

The best fit spectra of each pair were resimulated (as plots on the X-Y recorder) and compared with the experimental spectra. Differences in the spectral intensities were sufficient to enable an unambiguous assignment of the chemical shifts in all cases. Experimental, and best-fit simulated spectra of 5 and 6 are shown in Figures 1-7 and 1-8.

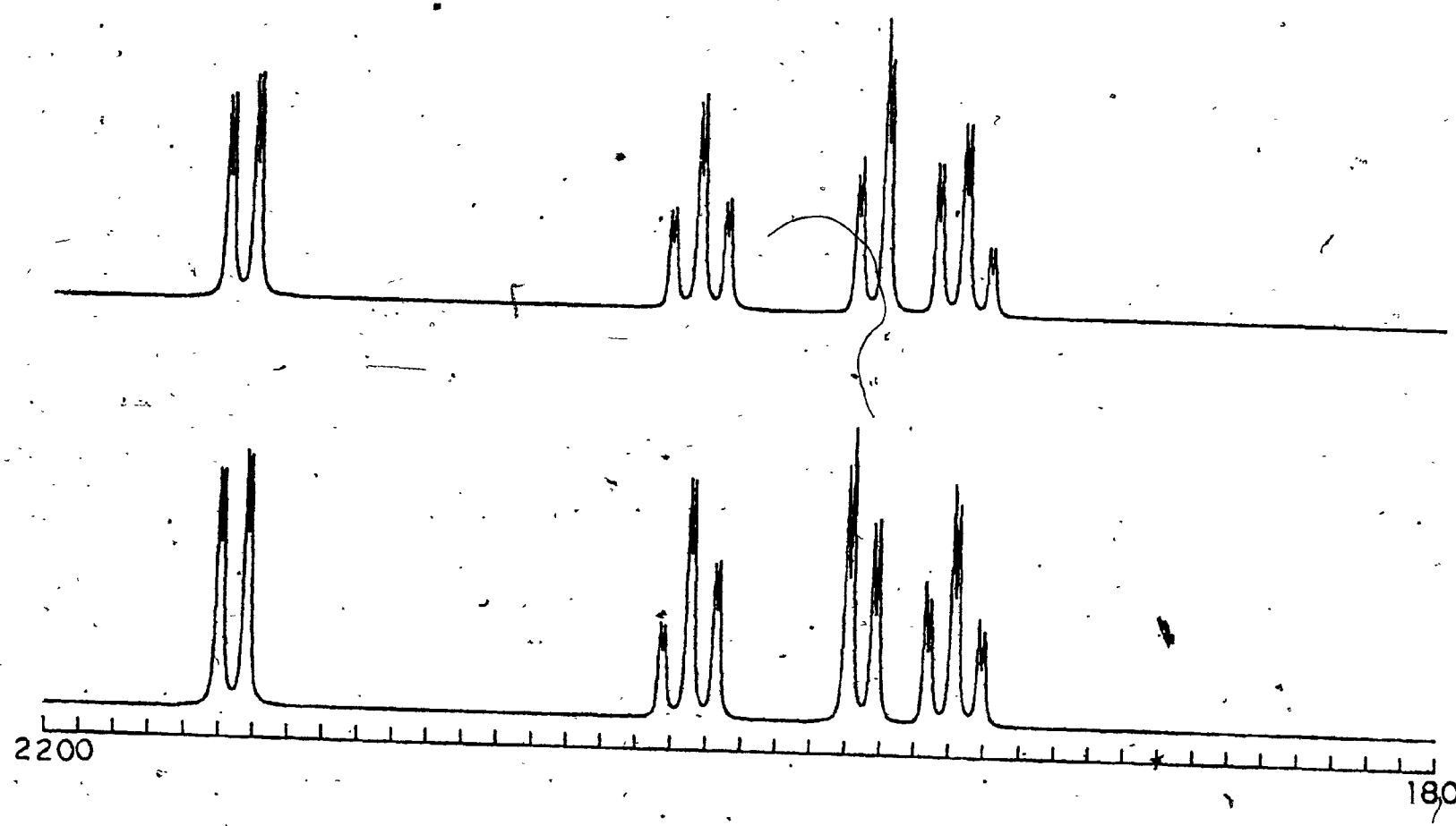
Chemical shift and spin-spin coupling constant data for the four sets of spectra analysed are shown in Tables 1-3 and 1-4, respectively.

A plot of the chemical shifts of the aromatic proton versus the Pauling electronegativities of the halo substituents (Figure 1-2) provides a very satisfactory confirmation of the correctness of the aryl proton chemical shift assignments. These plots are highly linear, and clearly show a crossover of the relative chemical shifts of the 4' and 5', and the 4' and 6' proton chemical shifts as the halo substituent is changed from Cl to Br to I.

Figure 1-2 demonstrates the sensitivity of the aryl proton chemical shifts to the nature of the aryl group substituent. The chemical shifts are all displaced to lower field when a nitro group is introduced (Figure 1-2). The protons ortho to the substituent (i.e. 3') show the greatest substituent dependence; those in the 6'- position the least.

Of the vicinal aromatic coupling constants, $J_{3',4'}$ is the largest at 8.0 $\pm$0.1 Hz. The remaining vicinal coupling constants, $J_{4',5'}$ and $J_{5',6'}$ are identical at 7.7 $\pm$ 0.1 Hz. The 4-bond coupling constants, $J_{3',5'}$ and $J_{4',6'}$ are much smaller, 1.5 $\pm$ 0.2 Hz, as expected.

Figure 1-6 Representative pair of computed data sets for 1-(2'-iodophenyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (5).



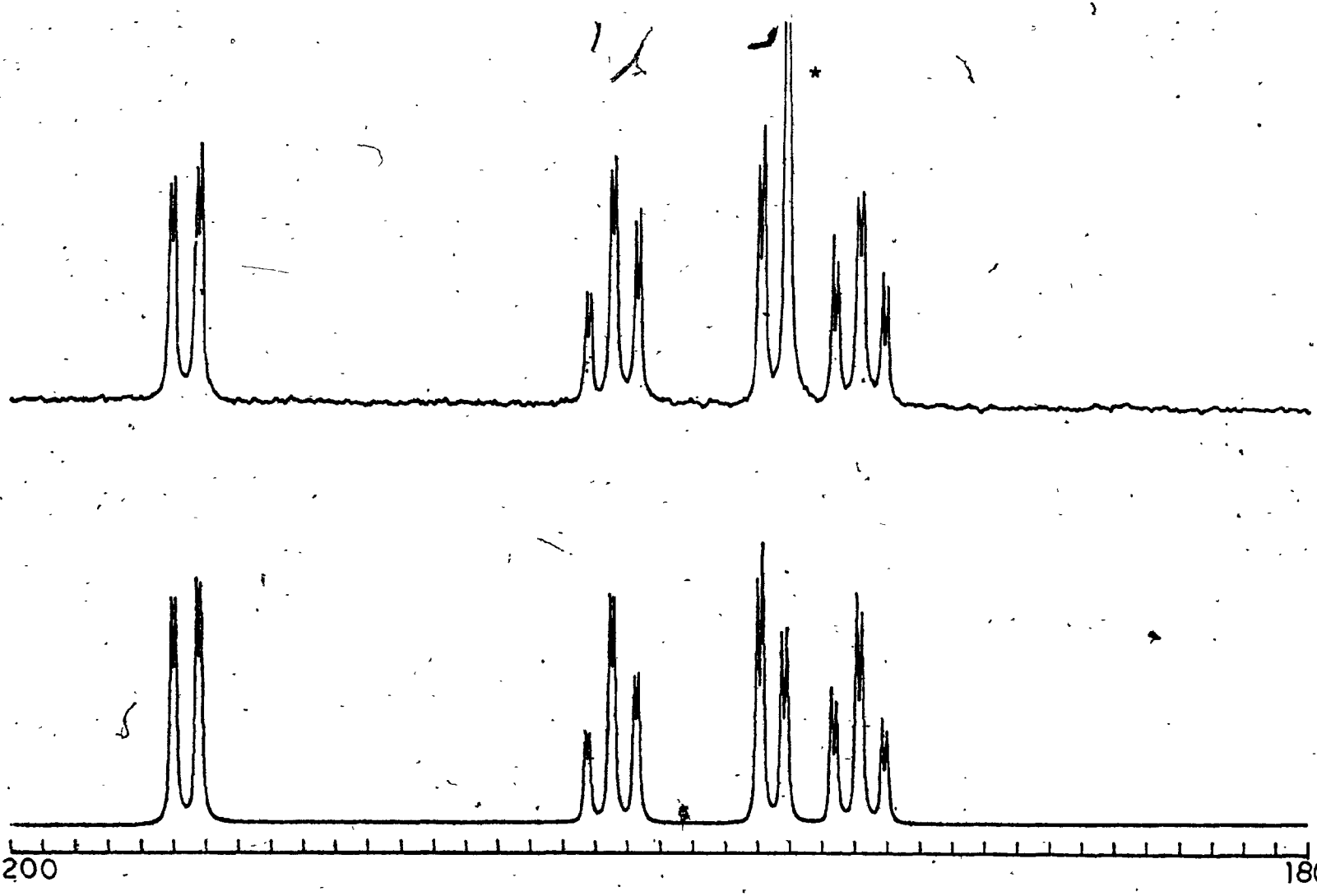


Figure 1-7 Experimental (upper curve) and calculated (lower curve) spectra of the aromatic proton region of 1-(2'-iodophenyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (5). *Residual $CHCl_3$.

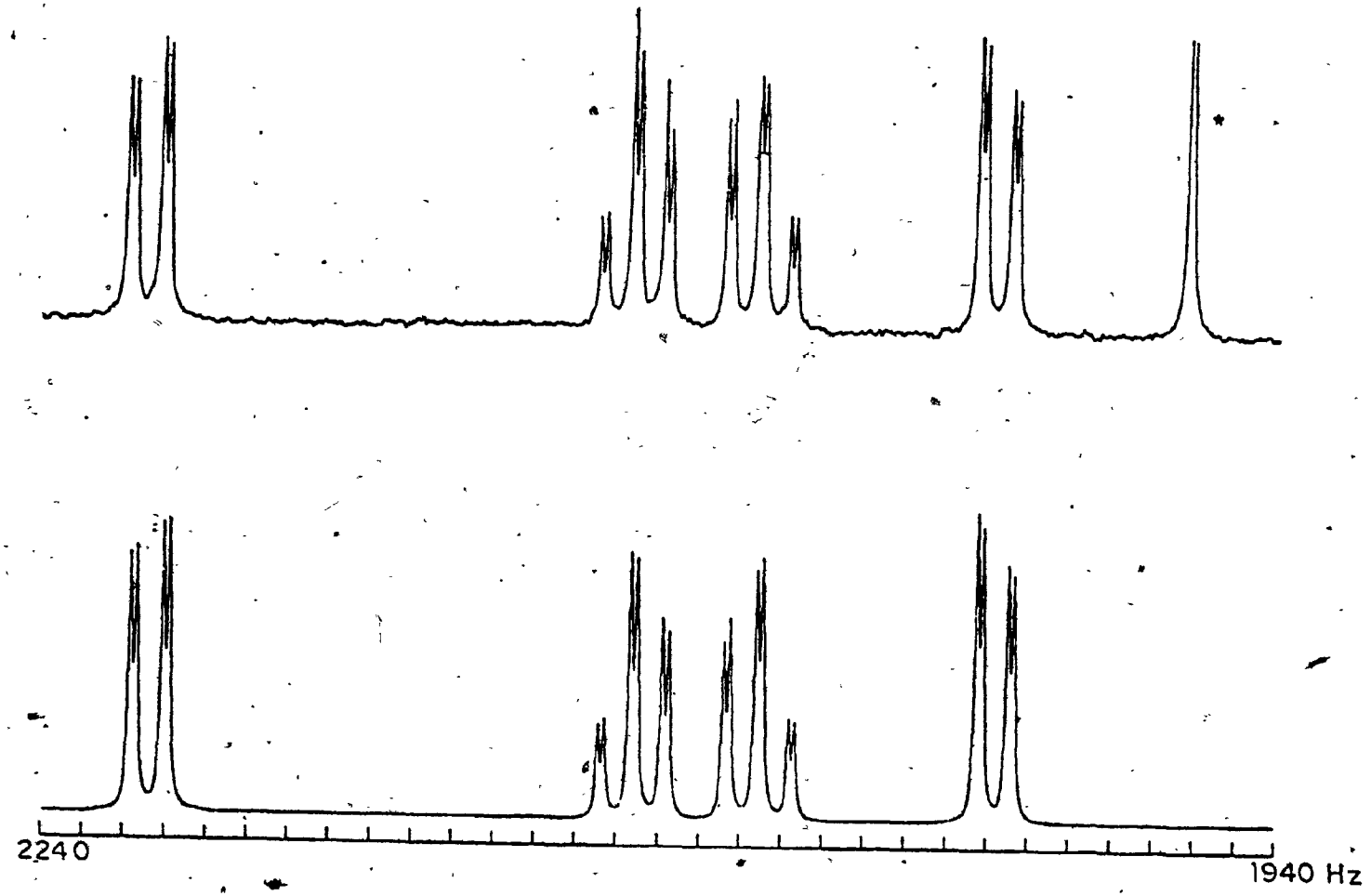


Figure 1-8 Experimental (upper curve) and calculated (lower curve) spectra of the aromatic proton region of 1-(2'-nitrophenyl-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (6).

*Residual $CHCl_3$

MEASUREMENT OF HINDERED ROTATION IN SOME IMIDAZOLINONES

INTRODUCTION

The compounds under investigation are capable of undergoing internal rotation about the aryl C-N bond, a process which can, in principle, be detected in their n.m.r. spectra. Indeed, if the rotation rate is slow, the spectrum of the 4,4-dimethyl groups will consist of two separate signals.. However, if the rate of internal rotation is fast, there will be only one signal, in an averaged position. When two signals are seen (as in 5, 6, and 7) due to steric interference between the aryl and the heterocyclic moieties, the spectrum is expected to be temperature dependent. As the temperature is raised, the resulting increase in the rate of rotation should ultimately result in the collapse of the doublet to a singlet. The rate of rotation may be easily determined for one particular temperature, that temperature at which the two peaks coalesce (the coalescence point). The free energy of activation ($\Delta G^{\ddagger}$) for internal rotation of the two moieties may then be calculated.

THEORY

In compounds 5, 6, and 7, the barrier to internal rotation is high, and the chemical shift difference between the gem dimethyl protons is large enough that two signals are seen at normal probe temperatures. In the following treatment, the two molecular environments are referred to as sites A and B. During rotation, there is interchange of nuclei (i.e. methyl groups) between sites A and B. In this system, spin coupling between the nuclei on the two sites is negligible. We suppose that the nuclei on the two sites have Larmor frequencies ω_A and ω_B, respectively (radian/sec.)

It will be assumed that while a nucleus is in an A position, there is a constant probability, τ_A^{-1}, per unit time, of its making a jump to a B position. τ_A is then the mean lifetime for a stay on an A site. Another corresponding time τ_B can be defined for the lifetime on the B position.

The fractional populations of A and B sites, P_A and P_B ($P_A = 1 - P_B$), are related to τ_A and τ_B by:

$$P_A = \frac{\tau_A}{\tau_A + \tau_B}$$

$$P_B = \frac{\tau_B}{\tau_A + \tau_B}$$

In a slow rotation or exchange

The lifetimes, τ_A and τ_B, are sufficiently large with respect to the inverse of the separation, $(\omega_A - \omega_B)^{-1}$, that the spectrum will consist of distinct signals in the vicinity of the frequencies ω_A and ω_B (because the nucleus enters site A and precesses at $(\omega_A - \omega_0)$ many times before leaving site A and entering into site B).

In a fast rotation or exchange

We have τ_A and τ_B small, so that, when a nucleus enters site A, it begins to precess at $(\omega_A - \omega_0)$ but the lifetime of A expires before the precession is complete, and it enters into site B. The spectrum will consist of a distinct sharp resonance line at the frequency (ω_0) (average of the two Larmor frequencies ω_A and ω_B).

Intermediate rate of rotation or exchange

This is the region of transition between the two lines to one line when the lifetimes τ_A and τ_B are of the order of $(\omega_A - \omega_B)^{-1}$. The equation for a pair of singlets collapsing to a single peak was derived from the Bloch equations[21] by Gutowsky and Holm[22].

The intensity, at any point ω, when the two transverse relaxation times T_{2A} and T_{2B} are equal, is

$$I = -\gamma H_1 M_o \left(\frac{\left(1 + \frac{\tau}{T_2}\right) P + QR}{P^2 + R^2} \right)$$

where

$$\tau = \frac{\tau_A \tau_B}{\tau_A + \tau_B}$$

$$P = \tau \left\{ \left(\frac{1}{T_2}\right)^2 - \left[\frac{1}{2}(\omega_A + \omega_B) - \omega\right]^2 + 1/4(\omega_A - \omega_B)^2 \right\} + \frac{1}{T_2}$$

$$Q = \tau \left[1/2\,(\omega_A + \omega_B) - \omega - 1/2\,(P_A - P_B)(\omega_A - \omega_B) \right]$$

$$R = \left[1/2\,(\omega_A + \omega_B) - \omega \right] \left(1 + \frac{2\tau}{T_2}\right) + \frac{1}{2}(P_A - P_B)(\omega_A - \omega_B)$$

This may be considerably simplified under the following conditions:

- equal populations and lifetimes so that

$$P_A = P_B = 1/2$$
$$\tau_A = \tau_B = 2T$$

- large transverse relaxation times, i.e.

$$T_{2A}^{-1} = T_{2B}^{-1} = 0$$

If the signal width is small compared to the separation of the signals, and as

$$\nu = \frac{\omega}{2\pi} \quad \text{(cycles per second)}$$

the shape function[23] is:

$$g(\nu) = K \frac{\tau(\nu_A - \nu_B)^2}{[1/2(\nu_A+\nu_B) - \nu]^2 + 4\pi^2\tau^2(\nu_A - \nu)^2(\nu_B - \nu)^2}$$

K is a normalizing constant.

This means that the actual shape of this function depends only on the product $\tau(\nu_A - \nu_B)$. The equation predicts that if τ is large, we have two lines, at ν_A and ν_B, while for a small τ, there will be one line halfway between.

Coalescence is obtained for:

$$\tau = \frac{1}{\sqrt{2}\,\pi\,(\nu_A - \nu_B)}$$

so that τ can be calculated if $(\nu_A - \nu_B)$ is known.

Free energy of activation

For calculating the free energy of activation, the Eyring equation[24] is used:

$$k = \kappa \left(\frac{TK_B}{h}\right) \exp\left(\frac{-\Delta G^{\neq}}{RT}\right)$$

when K_B = Boltzmann's constant ($1.38\ 10^{-16}$ erg.deg.$^{-1}$)

h = Planck's constant ($6.625\ 10^{-27}$ erg. deg.$^{-1}$)

κ = transmission coefficient ($\simeq 1$)

k = rate constant

T = absolute temperature

R = gas constant (1.987 cal deg.$^{-1}$ mole.$^{-1}$)

This equation can be transformed as follows;

$$\ln k = \ln \frac{K_B T}{h} - \frac{\Delta G^{\ddagger}}{RT}$$

$$\frac{\Delta G^{\ddagger}}{RT} = \ln \frac{K_B T}{h} - \ln k$$

$$\Delta G^{\ddagger} = RT \left(\ln \frac{K_B}{h} T - \ln k\right)$$

To calculate $\Delta G^{\ddagger}$ the rate constant, k, must be found:

Since $k = \frac{1}{\tau_A}$

and at the coalescence point we have:

$$\tau = \frac{1}{\sqrt{2}\,\pi\,(\nu_A - \nu_B)}$$

and $\tau_A = \tau_B = 2\tau$

so,

$$\tau_A = \frac{2}{\sqrt{2}\,\pi\,(\nu_A - \nu_B)} = \frac{\sqrt{2}}{\pi\,(\nu_A - \nu_B)}$$

and $$k = \frac{\pi\,(\nu_A - \nu_B)}{\sqrt{2}}$$

So that the equation becomes:

$$\Delta G^{\neq} = RT \left(\text{Ln} \frac{K_B}{h} + \text{Ln}\, T + \text{Ln}\, \tau_A\right)$$

$$\Delta G^{\neq} = RT \left(\text{Ln} \frac{K_B}{h} + \text{Ln}\, T + \text{Ln} \frac{\sqrt{2}}{\pi(\nu A - \nu B)}\right)$$

$\nu A - \nu B$ is the separation of peaks in the absence of exchange.

When the values of the constants are included, the equation can be written:

$$\Delta G^{\neq} = 2.303\, RT \left(10.319 + \log_{10} T + \log_{10} \tau_A\right)$$

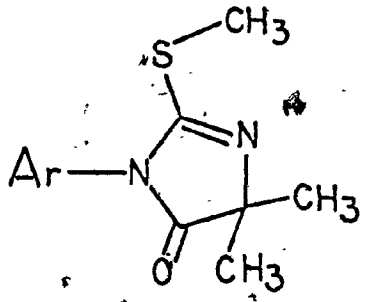
Calculation of the mean lifetime by the coalescence point method gives an approximate value. More precise calculation of τ can be made using complete line shape analysis, without the simplifying assumptions used in the above treatment. However, because of the small chemical shift differences observed in the present study, this procedure was not practicable.

RESULTS AND DISCUSSION

Values for free energies of activation, $\Delta G^{\ddagger}$, for compounds 5, 6, 7, the only compounds which exhibited separate gem dimethyl group signals at 60 MHz, were calculated for the coalescence temperature, and are reported in Table 1-5. The high temperature spectra used in these determinations were obtained by S. Lokuge. The $\Delta G^{\ddagger}$ values range from 19.2 to 24.5 Kcal mol^{-1}, the most highly hindered compound being the 2'-iodophenyl compound, 5.

One aim of this study was to compare barriers to internal rotation in imidazolinones with those of corresponding 2-thiohydantoins. The 2-thiohydantoins are so highly hindered that rotation of the gem dimethyl compounds could not be measured by line shape analysis; instead barriers in the monomethyl compounds were measured by equilibration. Hence, exact comparisons were not possible, but the differences in internal rotational barriers in mono and dimethyl compounds are expected to be negligible.

Table 1-5 Free energies of activation for hindered rotation about the C-N bond of 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones



	Ar	Coalescence Temperature in °C	$\nu_A - \nu_B$ (Hz)	τ(sec)	k(sec^{-1})	$\Delta G^{\neq}$ (Kcal $mole^{-1}$)
5	2'-Iodophenyl	164	2.2	.205	4.888	24.54
6	2'-Nitrophenyl	73	2.5	.180	5.554	19.19
7	1'-Naphthyl	100	4.3	.105	9.554	20.34

Rotational barriers for 3-(α -naphthyl)-5-methyl-2-thiohydantoin, a close analogue of 7, have been reported by Fehlner[7]. For this compound, $\Delta G^{\neq}$ = 25.55 kcal mole^{-1} at 25°C. Fehlner's experimental data were used to calculate $\Delta G^{\neq}$ at a temperature, 100°C, corresponding to the coalescence temperature of 7, since it is necessary to compare $\Delta G^{\neq}$ values at the same temperature. At this temperature, the $\Delta G^{\neq}$ value of the thiohydantoin is 26.81 kcal mole^{-1}, i.e. 5.5 kcal mole^{-1} higher than that of 7.

We see, therefore, that transformation of α -naphthyl-2-thiohydantoin into the corresponding imidazolinone, by methylating the thiocarbonyl sulfur atom, results in a substantial reduction in the barrier to internal rotation. The differences in the rotational barrier probably arise from two major factors:

a) Conversion of a C = S double bond to a C-S- single bond,

b) Introduction of a double bond into the hetero ring.

The latter factor may cause changes in the geometry of the hetero ring sufficient to alter steric interactions between the ring systems. However, the major cause of the difference in rotational barriers is likely to result from a).

Steric strain in the approximately planar transition state for internal rotation must be relieved by bond bending processes, including bending of the C=S or C-S bonds. The greater rigidity of the double bond is probably responsible for a large part of the higher rotational barrier in the thiohydantoin.

In the imidazolinone series, the largest value of $\Delta G^{\neq}$ is observed for the iodo compound, 5, i.e. a compound with a very bulky ortho aryl substituent. The smallest barrier is observed for the nitro compound, 6, i.e. a compound with an ortho substituent which is known to have relatively small steric bulk[25]. Although electronic effects of substituents may influence rotational barriers by favouring conjugation between the rings, the dominant influences on the barriers in these compounds appear to be steric in origin.

CONCLUSIONS

Proton n.m.r. spectroscopy has been found to be a powerful tool for the investigation of restricted internal rotation about the aryl C-N bond in 3-aryl-5,5-dimethyl-2-thiohydantoins and 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones. However, the smaller chemical shift differences between the diastereotopically related gem dimethyl groups of the imidazolinones restricts the use of the technique for these compounds. The high dispersion of a 270 MHz spectrometer is of help overcoming this limitation.

The much lower barriers to internal rotation in the imidazolinones than in the thiohydantoins are an interesting indication of the differing abilities of molecules to relieve steric strain in the rotational transition states as a result of differing arrangements of double and single bonds.

The high dispersion of the aryl proton signals at 270 MHz has permitted much more complete analysis of the spectra than would have been feasible at 60 MHz, with a consequent increase in the information available on substituent effects on chemical shifts.

CHAPTER II

^{13}C n.m.r. spectra of 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones

Introduction

Within the last few years, carbon-13 n.m.r. spectroscopy has become an increasingly important technique for the investigation of organic structure and stereochemistry. Carbon-13 has a spin of 1/2, as does the proton, but occurs in a natural abundance of only 1.1%. Further, the magnetogyric ratio of ^{13}C is only about 1/4 that of ^{1}H. These two factors result in the sensitivity of ^{13}C in natural abundance being very much less than that of ^{1}H, with the consequence that development of ^{13}C n.m.r. spectroscopy lagged considerably behind that of ^{1}H spectroscopy. However, the recent development of pulse and Fourier transform techniques coupled with the use of dedicated minicomputers, has resulted in a rapid development of ^{13}C n.m.r. spectroscopy, so that ^{13}C spectra may now be taken on a routine basis.

The applications of ^{13}C n.m.r. spectroscopy to organic compounds have been extensively reviewed [26, 27]. In general, ^{13}C spectra can provide information on substituent and steric effects, on the inductive and conjugative influences of substituents, and on relaxation processes. An aspect of the sensitivity of ^{13}C spectra to steric influences is the effect on nonequivalent nuclei of conformational exchange processes, e.g. involving restricted internal rotation [14].

The study of the ^{13}C n.m.r. spectra of the 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones reported in this thesis was undertaken to obtain information on the chemical shifts of the carbon nuclei in the conformational ground states, i.e. under conditions in which rotation about the C-N bond is slow., Substituent effects on the resonances of the skeletal carbon atoms, and chemical shift differences between diastereotopically related nuclei were investigated. It was expected that the information obtained would be valuable for structure determination purposes in future studies of compounds of this type, and that insight into the use of ^{13}C spectroscopy for determining stereochemistry would result.

EXPERIMENTAL

The pulse Fourier transform, ^{13}C n.m.r. spectra were determined at a probe temperature of about 35°C using an extensively modified Varian HA-100 spectrometer operating at 25.1 MHz with a homonuclear (^{13}C) lock provided by the solvent. Broadband ^{1}H decoupling was employed. The spectrometer was interfaced to a Hewlett-Packard 2114A computer, using a 4K word data block and a block averaging technique to improve dynamic range. Spectral width was 5000 Hz (i.e. about 200 ppm) in all cases. Concentrations of 2 to 4% (weight/volume) in dimethylsulfoxide (DMSO) were employed, the proton-decoupled solvent providing the lock signal.

Chemical shifts (ppm) are reported relative to tetramethylsilane (TMS) and were measured with respect to the DMSO signal (40.40 ppm). They are estimated to be accurate to 2.0 Hz, equivalent to about 0.05 ppm, unless otherwise indicated.

RESULTS AND DISCUSSION

Stereochemical Considerations

The ^{1}H n.m.r. spectra of these compounds clearly indicate that internal rotation about the aryl C-N bond is slow at normal probe temperatures (about 35°C). In consequence, it was expected that the ^{13}C spectra would be associated with the conformational ground states of the molecules. With one exception (compound 2) all of the compounds can exist as enantiomeric rotational isomers A and B, with identical spectra. However, within each conformer, the 4,4-dimethyl carbons are diastereotopically related and are expected to give rise to separate ^{13}C signals, provided that the chemical shift difference is adequate and that the rate of internal rotation is sufficiently slow. With one exception (compound 6), two such signals were observed.

The 2', 6'-dimethylphenyl compound, 2, contains a symmetrically substituted aryl group, so that the rotational isomers are identical and no carbon atoms are diastereotopically related; no additional signals were expected, or observed.

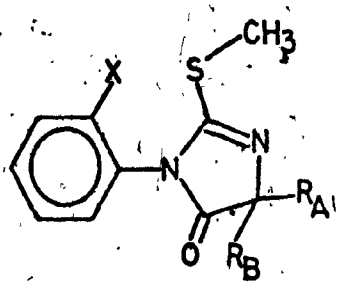
CHEMICAL SHIFT ASSIGNMENTS

The chemical shifts of the carbon atoms in the series of compounds (Table 2-1), were assigned using the values reported in the literature [28, 29, 30, 31] and data obtained in this laboratory for related compounds [11, 14, 15]. Chemical shifts of some related compounds are reported in Tables (2-2, 2-3, 2-4, 2-5, 2-6, 2-7). In order to facilitate investigation of influences on chemical shifts throughout the series, the data are tabulated and discussed according to the carbon position (Table 2-1).

Strong ^{13}C signals in these compounds can be assigned unambiguously by comparison of the chemical shifts with data in the literature. The remaining ambiguities can generally be resolved with reference to the spectra of suitable model compounds.

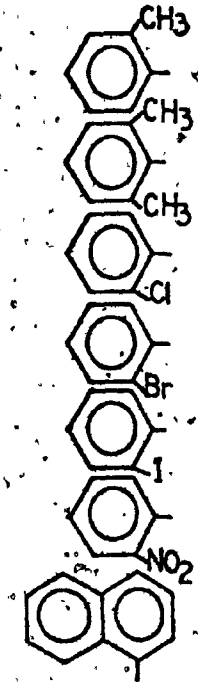
TABLE 2- 1

^{13}C chemical shift values for different carbon atom position in the 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones in ppm from TMS



$R_A = R_B = CH_3$

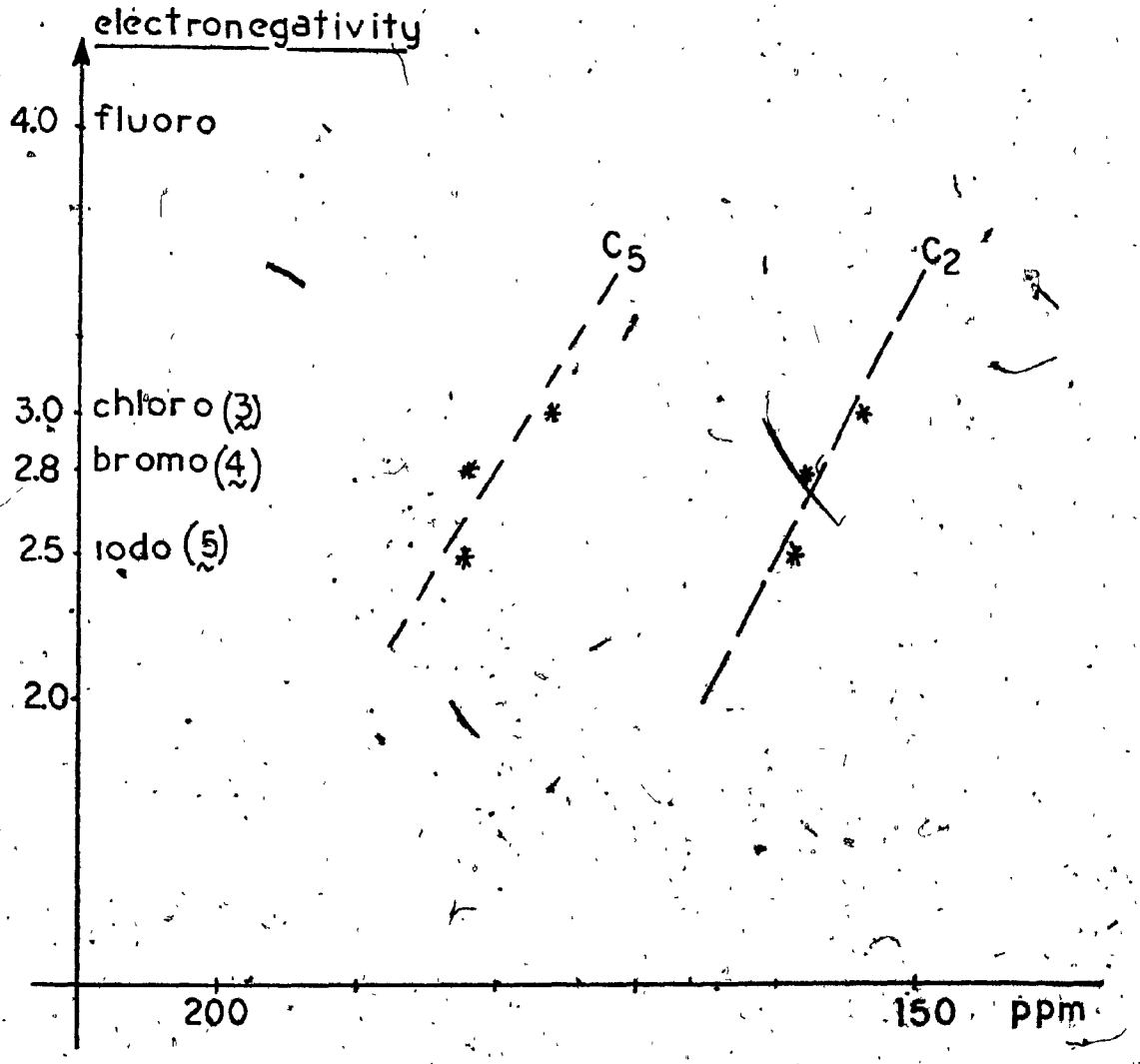
Substituent (name, No., concentration in mole/litre)	Carbon Atoms Positions C_5	C_2	C_4	S-CH_3	$C_{R(A,B)}$	Aryl methyl
1 2'-Tolyl (0.5)	183.01	159.38	68.22	12.09	24.62;23.95	16.82
2 2',6'-Dimethylphenyl (0.7)	182.33	158.47	67.40	11.73	23.66; -	16.90
3 2'-Chlorophenyl (0.9)	175.96	153.38	58.45	12.05	25.25;24.14	-
4 2'-Bromophenyl (0.6)	182.17	158.19	68.04	11.69	24.25;23.62	-
5 2'-Iodophenyl (0.5)	182.14	158.50	68.33	12.11	23.94;23.23	-
6 2'-Nitrophenyl (0.7)	182.33	157.27	68.12	12.09	23.58; -	-
7 1'-Naphthyl (0.7)	183.40	159.66	68.20	11.69	24.37;23.78	-



INFLUENCES ON CHEMICAL SHIFTS

The shielding effects of various substituents have been reported [32]; in general, it is found that, within a series of compounds with different substituents, carbon chemical shifts tend to follow well established trends. For example, the influence of methyl groups in alkanes on carbon atoms located α-, β- and γ- to the substituent (i.e. involving a 1-, 2- and 3- bond separations) has been rationalized. The α-effect (deshielding) is an inductive effect with some steric contribution, the β-effect (deshielding) is not well defined, but the γ-effect (shielding) results from a steric perturbation. It has been found that, in general, steric effects influence carbon chemical shifts. In the present work, steric effects were noted for various substituents (e.g. naphthyl, iodo, etc..), and inductive effects were identified when substituents with different electronegativities (e.g. iodo, chloro, bromo) were present (See Figure 2-1). Such influences are discussed in the section on each carbon site in these molecules.

Figure 2-1 Plot of electronegativities (Pauling number [18]) versus chemical shifts values found in ppm from TMS for two carbon positions in the 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones substituted with a halogen group.



ASSIGNMENT OF CARBON SIGNALS FROM THE HETEROCYCLIC MOIETY

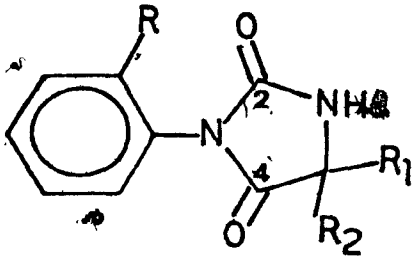
Chemical shift values of the carbonyl group (C_5) are listed in Table 2-1. Assignments are based on data reported by Khadim[15], Williams[14], and Icli[11] from hydantoins and thiohydantoins and Breitmaier[29] et al. for thioketones and carbonyl groups in esters and amides (see Table 2-2). No suitable reference data for the thioether carbon (C_2) were available, but the assignments could be made by comparison with the data reported for the hydantoins and thiohydantoins.

Khadim[15] has reported a carbonyl carbon range of 173.10 - 178.19 ppm in thiohydantoins and 173.70 - 175.41 ppm in hydantoins (Tables 2-3 and 2-4) corresponding to the 160 - 175 ppm range reported by Breitmaier[29] et al. In the present imidazolinone series, the carbonyl (C_5) signals were identified as the lowest field resonances, at 175.96 - 183.40 ppm, in close agreement with the values reported for the related hydantoins and thiohydantoins.

TABLE 2-2

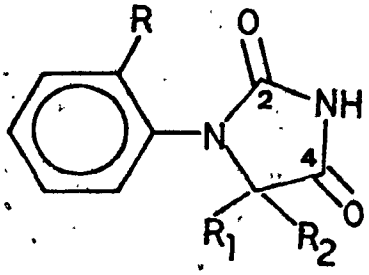
^{13}C chemical shift values for different carbon atoms in ppm from TMS for various compounds

3-aryl hydantoin



C_2	152.8 158.6
C_4	174.0 175.3

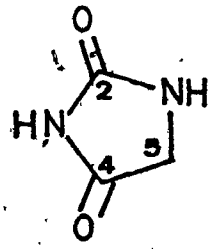
1-aryl hydantoin (a)



C_2	155.4 157.6
C_4	172.8 179.4

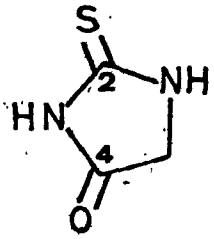
(a) in morpholine

Hydantoin



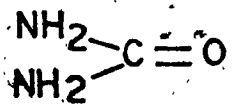
C_2	158.6
C_4	174.0
C_5	47.6

Thiohydantoin



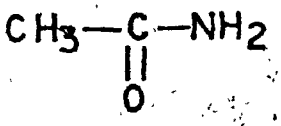
C_2	183.6
C_4	174.3

Urea



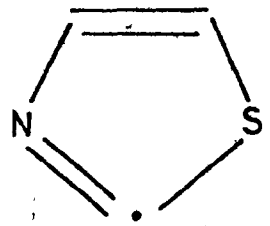
C_2	160.4

Acetamide



C(CO)	172.0
C(Me)	22.2

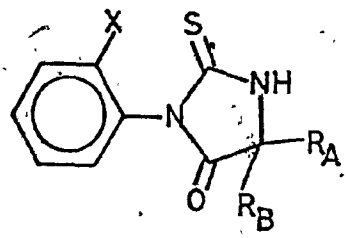
No data on closely analogous compounds were available to aid in the assignment of the thioether carbon (C_2). However, the indicated carbon in



has been reported[31] as absorbing near 158 ppm. Thiocarbonyl carbon atoms in thiohydantoins and thioketones have been reported as absorbing at 179-184 ppm; a greater degree of shielding is expected for the thiovinylether system. Accordingly, the signals at 153.38 - 159.66 ppm have been assigned for C_2; no other signals are expected in this region.

TABLE 2-3

^{13}C chemical shift values for different carbon atom position in the 3-aryl-5,5-dimethyl thiohydantoin series in ppm from TMS[15]



$R_A = R_B = CH_3$

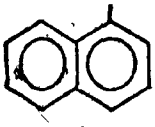
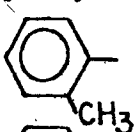
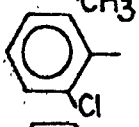
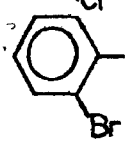
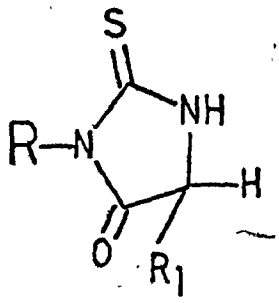
Substituent name	Carbon Atom Positions				
	C_2	C_4	C_5	CR_A	CR_B
 1'-Naphthyl- (enantiomer)	180.38	176.60	60.98	23.44	24.10
 2'-Tolyl- (enantiomer)	178.79	175.60	59.49	24.12	25.32
 2'-Chlorophenyl- (enantiomer)	180.14	176.56	61.24	23.10	24.10
 2'-Bromophenyl- (enantiomer)	181.77	176.80	60.60	23.50	24.57

TABLE 2-4

^{13}C chemical shift values for different carbon atoms in thiohydantoin series in ppm from TMS [15]



R	R_1	C_2	C_4	C_5	CH_3	CH_3 (aryl)
H	H	183.60	-	47.60	-	-
2'-Tolyl	CH_3	182.77	174.41	55.01	16.84;17.04	15.94;1644
2'-Fluorophenyl	CH_3	181.56	174.41 174.01 d)	55.10	15.94;16.34	-
1'-Naphthyl	CH_3	182.52	175.41 175.21 d)	55.51	16.30;16.80	-
2',3'-Dimethylphenyl	CH_3	182.78	174.41 174.73 d)	54.91	16.04;16.44	13.66;13.26 20.02;19.02

d) doublet

In the thiohydantoin series, the carbon atom corresponding to C_4 absorbs at 54.91 - 61.58 ppm and in thiohydantoin itself at 47.60 ppm[15] (Tables 2-3 and 2-4). The C_4 chemical shift in the imidazolinones ranges from 58.45 to 68.33 ppm (Table 2-1), i.e. there is a downfield displacement on methylation of the sulfur atom and introduction of a 2,3 double bond.

ASSIGNMENT OF METHYL SIGNALS

In this series, all compounds have -S- methyl, and geminal methyl groups at C_4. Additional methyl groups may be present on the aryl substituent, e.g. 2'-tolyl or 2', 6'-dimethylphenyl. Assignments of methyl signals are straightforward using Tables 2-4, 2-5 and 2-6. Previous theses from this laboratory, and publications on related compounds have established the range 16.98 - 19.0 ppm in dimethylanilines, and 16.9 - 17.9 ppm in 3-aryl-hydantoins for ortho methyl groups. Aryl methyl carbon chemical shifts tend to be on the high field side of the geminal dimethyl groups.

In the imidazolinone series, two compounds, 1 and 2, have a single aryl methyl substituent, so assignment is straightforward (16.82 ppm for the 2'-tolyl compound, 1, and 16.90 ppm for the two equivalent aryl methyl groups in the 2', 6'-dimethylphenyl compound, 2) (Table 2-1).

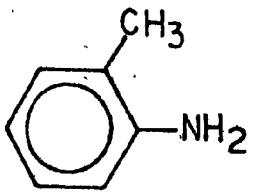
Two signals are expected for the diastereotopic C_4 methyl groups in compounds 1, 3 - 7, and a single signal for the

TABLE 2-5

^{13}C chemical shift values for methyl carbon atoms in various substituted aniline compounds in ppm from TMS [26]

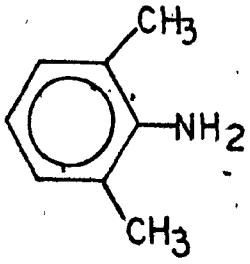
2'-Methylaniline

17.3



2',6'-Dimethylaniline

Position	
17.6	(2)
17.6	(6)



2',3'-Dimethylaniline

Position	
12.6	(2)
20.3	(3)

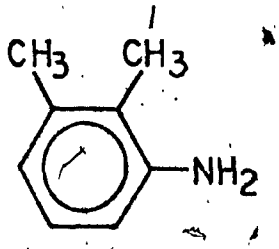
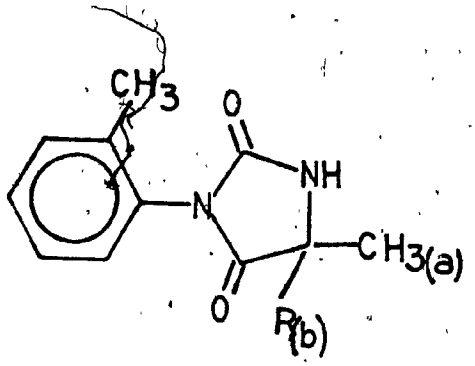


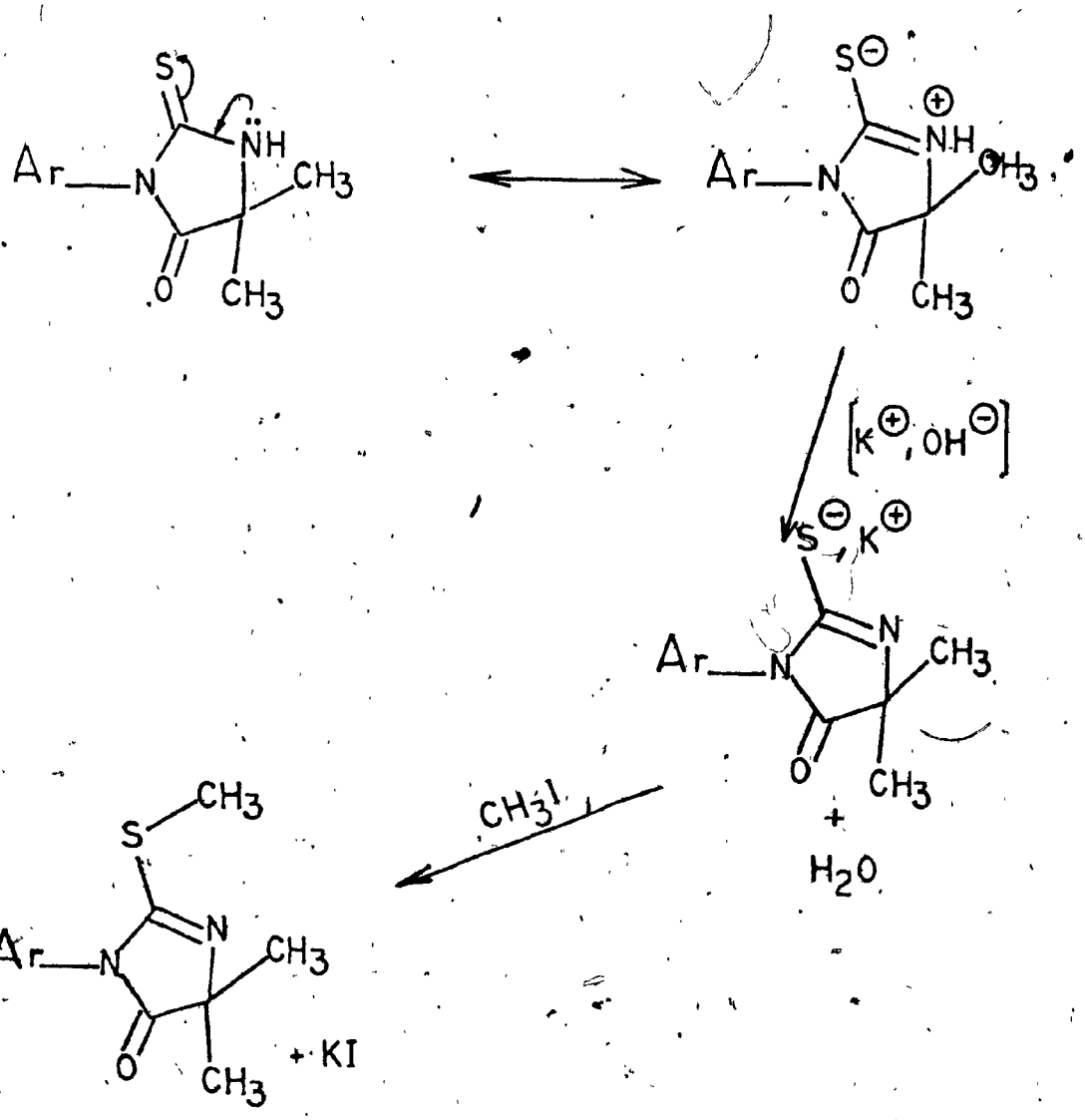
TABLE 2-6

^{13}C chemical shift values for methyl carbon atoms in various 3-aryl-hydantoins series in ppm from TMS



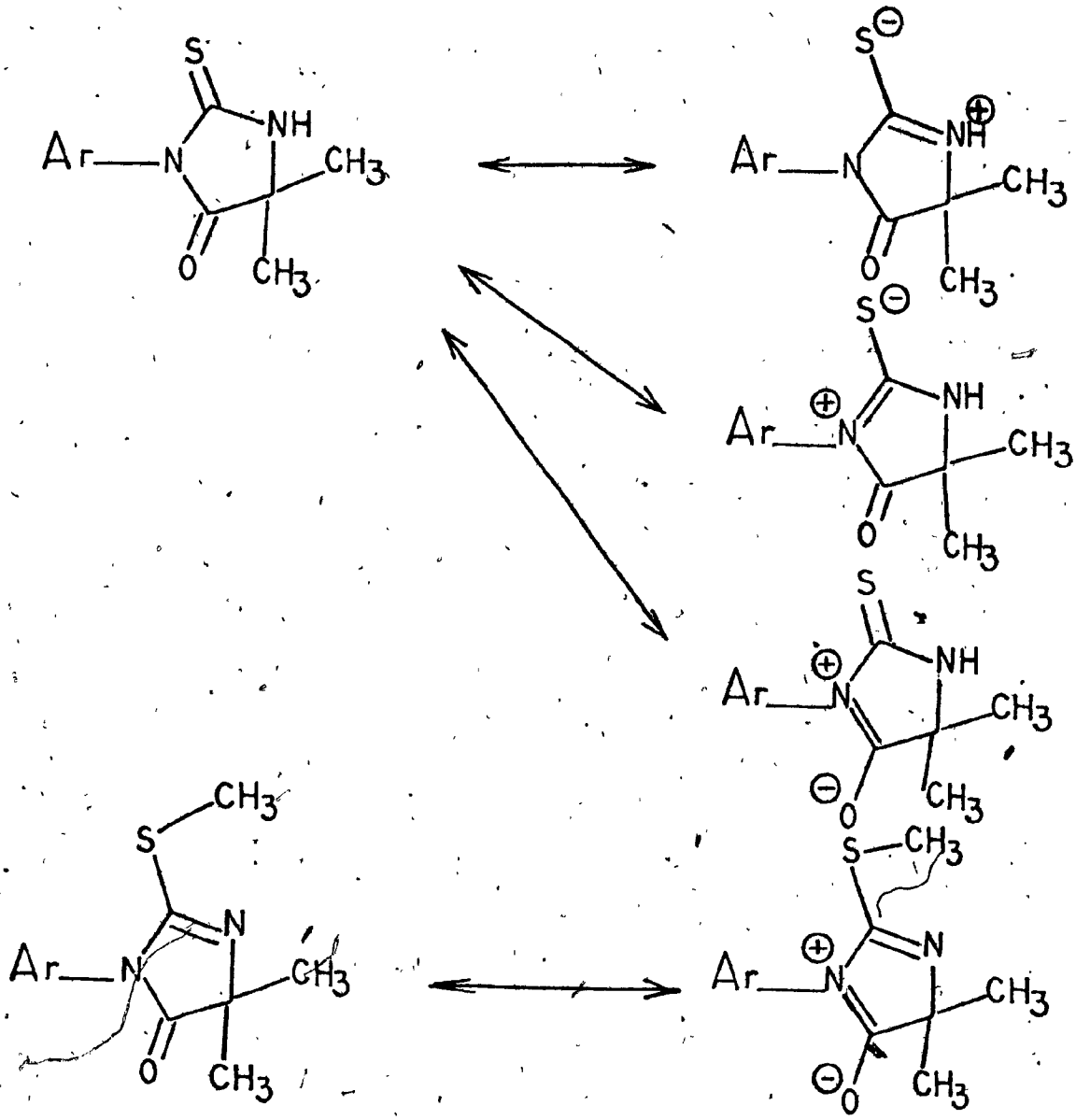
R	Aryl Methyl	Methyl (a)	Methyl (b)	Ref.
H	17.9	18.10 18.61	-	(11)
H	16.9	17.10 17.61	-	(14)
CH_3	17.9	25.42	26.12	(11)
CH_3	16.9	24.12	25.12	(14)

Figure 2-2 Synthesis route for methylation of thiocarbonyl sulfur atom in the thiohydantoins to form the imidazolinones.



RESONANCE INFLUENCES ON CHEMICAL SHIFTS

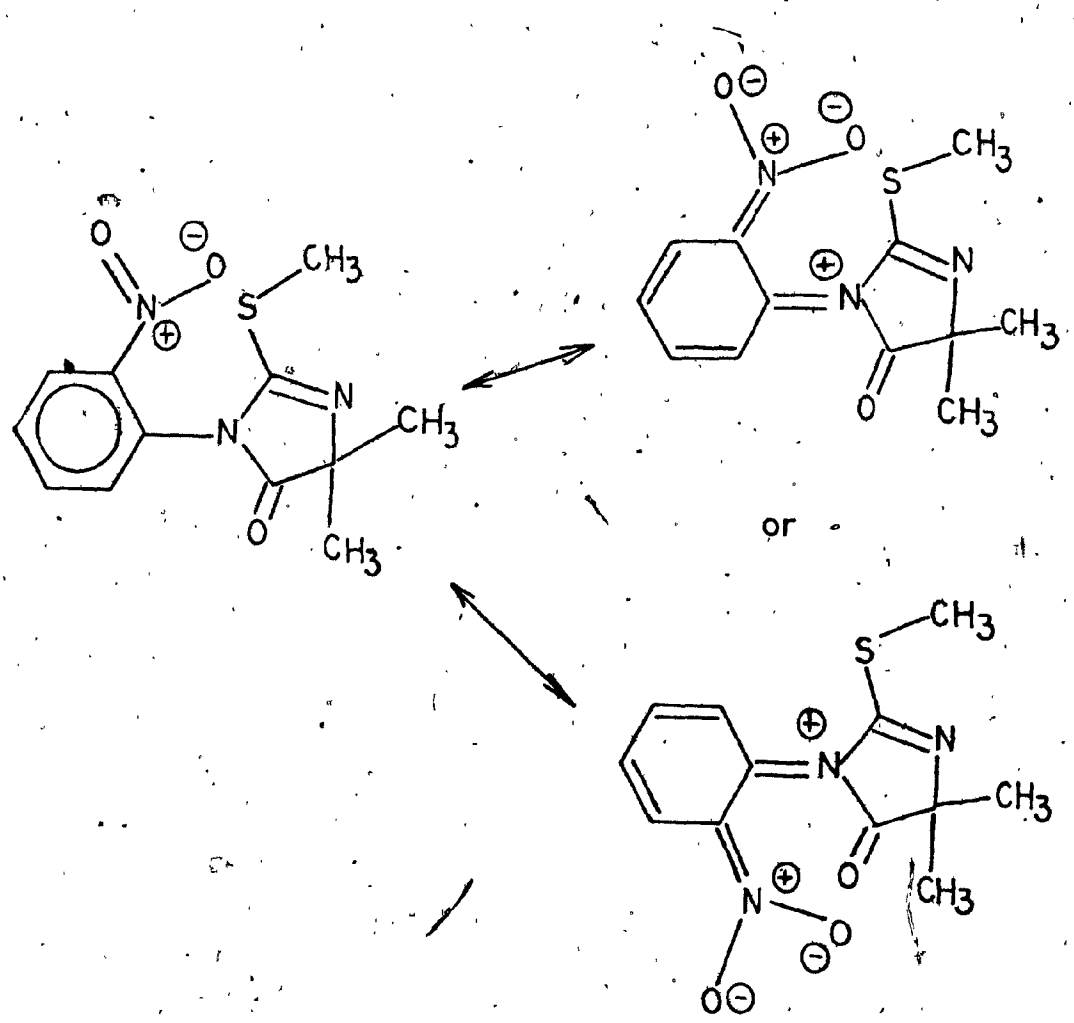
The following resonance forms are likely to make significant contributions to the electronic structures of the hetero rings of the thiohydantoins and the imidazolinones.



Thus, there are fewer amide or thioamide-type resonance contributions in the imidazolinones than in the thiohydantoins. However, since in both series this type of resonance should result in the development of a partial positive change on the nitrogen atom attached to the aryl group, the electronic influences of the aryl group substituents should be similar in both series. In general, electron donation from aryl group subtituents should stabilize those resonance contributors with a positive charge on nitrogen; electron withdrawal should destabilize them. Such electronic influences might be expected to affect the chemical shifts of hetero group carbons.

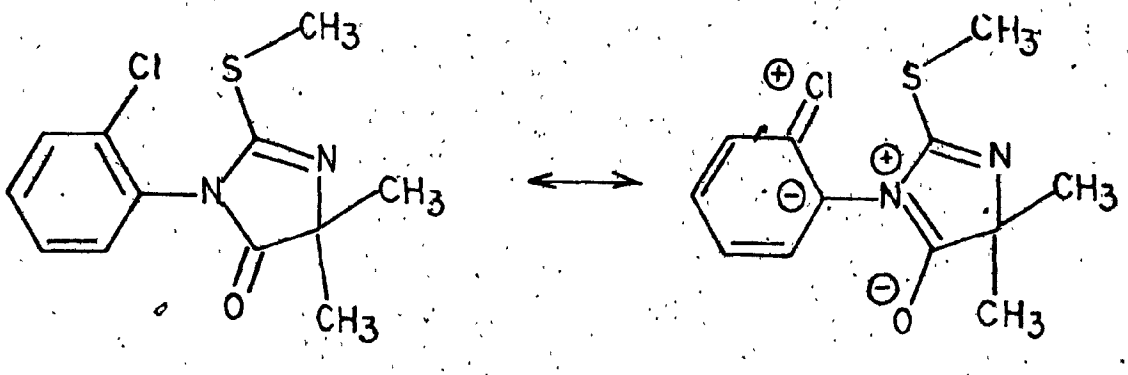
The electronic influences of aryl group substituents are likely to be predominantly inductive, but some resonance effects should be considered.

For example, an O-nitro group could, in principle, be involved in conjugated structures with the hetero ring:



However, steric factors must severely limit the contribution of such structures and, in fact, they determine the energy maxima in the pathways for internal rotation about the C-N bond. To the extent that they do contribute, these structures represent a driving force towards coplanarity and could possibly be, in fact, indirectly responsible for the lack of a chemical shift difference between the diastereotopic methyl groups in the ^{13}C (but not in the ^{1}H) spectrum of 6.

Mesomeric electron donation by O-halo substituents could stabilize the amide type resonance contributions through structures such as:



A careful examination of the experimental data has failed to reveal any clear-cut correlations between the possible contributions of these resonance forms and the chemical shifts of the hetero-ring carbon atoms.

A complicating factor which cannot be evaluated is that electronic contributions of aryl group substituents may influence the solvation patterns between the solute molecules and the highly polar solvent (DMSO) which had to be used (for reasons of solubility). Solvent effects on related compounds have been noted earlier [34]. Such solvent effects could easily obscure the direct electronic influence of the substituents.

CARBONYL AND THIOETHER CARBON ATOMS

The chemical shift ranges of the carbonyl and thioether carbon atoms of the imidazolinones and the carbonyl and thiocarbonyl carbons atoms of the reference compounds, are as follows:

Carbonyl range:

Aryl substituted-5-methyl-thiohydantoins	173.70-175.40[15]
Aryl substituted-5,5-dimethyl-thiohydantoins	173.80-178.20[15]
Aryl substituted-4,4-dimethyl-2-imidazolinones	175.96-183.40

Thiocarbonyl and thioether range:

Aryl substituted-5-methyl-thiohydantoins	180.13-182.77[15]
Aryl substituted-5,5-dimethyl-thiohydantoins	176.80-181.50[15]
Aryl substituted-4,4-dimethyl-2-imidazolinones	153.38-159.66

It should be noted that, since the rotational isomers of the aryl imidazolinones are enantiomeric (or identical), rather than diastereomeric, only a single carbonyl or thioether carbon signal is seen.

In the imidazolinone series, the carbonyl carbon atoms absorb, in most cases, at lower field than the carbonyl carbon atoms of the corresponding thiohydantoins (Table 2-9). The 2'- chlorophenyl compound (3) is an exception, at present unexplained, the carbonyl carbon atom absorbing 2.8 ppm to higher field than in the thiohydantoin. This difference may be associated with the electronegativity and relatively small size of the chloro substituent.

The C_2 carbon atoms in the imidazolinones, which are essentially in a vinyl thioether moiety, are about 20 ppm shielded with respect to the thiocarbonyl carbons atoms of the corresponding thiohydantoins (Table 2-9). The C_2 carbon of the 2'- chlorophenyl-imidazolinone (3) absorbs at highest field in the series, and also shows the greatest displacement (26.8 ppm) from the thiocarbonyl group of the corresponding thiohydantoin (Table 2-9).

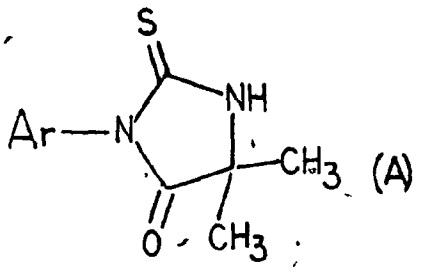
The chemical shifts of C_2 and C_5 are somewhat dependent on the nature of the aryl group substituents. Within the group of three ortho halo-compounds (3, 4, 5), for example, the chemical shifts of both C_2 and C_5 vary in the sequence of $I \geqslant Br > Cl$.

Plots of chemical shift versus the Pauling electronegativity (Figure 2-1) suggest a correlation but, rather surprisingly, the greater the electronegativity of the substituent, the greater the shielding of C_2 and C_5.

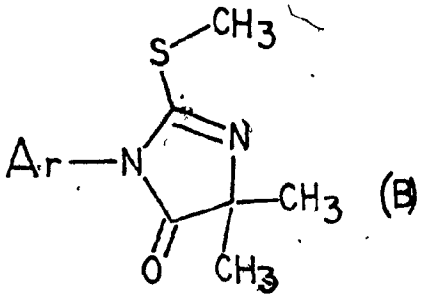
However, the effect of the nitro group does not appear to correlate with that of the halo substituent so it is likely that influences additional to inductive effects are observed.

TABLE 2-9

Comparative ^{13}C chemical shifts for 3-aryl-5,5-dimethyl thiohydantoins (A)[15] and 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones (B) in ppm from TMS



(A)



(B)

Substituents	C=S	C-S-	C = O		C< Me Me	
Ar	(A)	(B)	(A)	(B)	(A)	(B)
1'-Naphthyl	180.38	159.66	176.60	183.40	60.98	68.20
2'-Tolyl	178.79	159.38	176.60	183.01	59.49	68.22
2'-Chlorophenyl	180.19	153.38	176.56	175.96	61.29	58.45
2'-Bromophenyl	181.77	158.19	176.80	182.17	60.60	68.04

THE C_4 CARBON CHEMICAL SHIFTS

In the imidazolinone series, the C_4 carbon absorbs in the range 58.45 - 68.33 ppm, the O-chloro compound (3), having the highest field, and the O-iodo compound (5), having the lowest field signal. Excluding the O-chloro compound, the range is reduced to 67.40 - 68.33 ppm. The corresponding carbon atom absorbs at 59.49 - 61.29 ppm (see Table 2-9) and 59.0 - 59.4 ppm[11] in structurally related thiohydantoins and hydantoins repsectively.

The large deshielding shift in the imidazolinones compared to the thiohydantoins is directly attributable to the presence of the adjacent double bond.

The carbon-4 in the heterocyclic moiety has an δ relationship to the ortho aryl substituent, so the direct substituent effect is expected to be small. Although the electronic influences of the aryl group substituents may be transmitted to carbon-4 via different resonance contributions, a satisfactory correlation cannot be established, particularly in the presence of unknown contributions from solvation effects.

THIOMETHYL CARBON ATOMS

The thiomethyl carbon atoms absorb at 11.69 to 12.11 ppm, i.e. a range of only 0.42 ppm. Since the $-S-CH_3$ group is freely rotating, only a single peak is observed. No correlation between the $-S-CH_3$ chemical shift and the aryl group substituents can be detected, indicating that these chemical shifts are insensitive to inductive, resonance, or steric bulk influences from the aryl group. Thiomethyl chemical shifts in other types of compounds have been reported in the range 10 to 30 ppm [31].

ARYL METHYL CHEMICAL SHIFTS

The chemical shifts of the O-methyl groups of compounds 1 and 2 are 16.82 and 16.90, respectively. The aryl methyl group chemical shifts of thiohydantoins with only ortho methyl substituents are 15.94 - 16.44 ppm, while for similarly constituted hydantoins they are 16.9 - 17.90 ppm. Thus the aryl methyl group appear to be relatively insensitive to changes in the structure of the heterocyclic moiety.

4-METHYL CARBON CHEMICAL SHIFTS

If internal rotation about the aryl C-N bond is slow on the carbon n.m.r. time scale, two peaks might be detected from the diastereotopically related geminal methyl groups in all cases except 2. In 2, the symmetrical substitution pattern of the aryl group causes the environments of the geminal methyl groups to the enantiomeric, so that the chemical shifts must be identical. With one exception, the O-nitro compound, 6, two 4-methyl group signals were observed, the separation ranging up to 1.11 ppm (for the 2'-chloro compound, 3). The magnitude of the separation shows no obvious correlation with the nature of the aryl group substituents. Since the 2'-nitro compound, 6, exhibits two peaks arising from the geminal methyl groups in its proton n.m.r. spectrum (see Chapter I), taken at a similar sample temperature, it is clear that the rate of internal rotation in this compound is slow under the conditions of the experiment. The absence of a second methyl group signal in the ^{13}C n.m.r. spectrum must, therefore, be attributed to a fortuitous coincidence of the chemical shifts.

The range of 4-methyl group chemical shifts in the series is 23.23 - 25.25 ppm (see Table 2-1). In corresponding 5-dimethyl thiohydantoins, the chemical shifts range has been reported[15] as 23.10 - 25.32 ppm (see Table 2-3); i.e. the differences in the heterocyclic ring systems of the imidazolinones and the corresponding thiohydantoins have no detectable effects on the geminal dimethyl chemical shifts.

Some correlations between the nature of the aryl group substituent and the mean value of the geminal dimethyl chemical shifts are suggested by the data. For example, within the group of ortho halo compounds (3 to 5) there is a progressive shift to greater shielding in the sequence $I > Br \gtrsim Cl$.

However, it is difficult to accommodate other substituents in any rationalization of these effects. Chemical shift influences may arise from inductive, mesomeric and steric bulk effects of aryl group substituents, accompanied by differences in the solvation patterns of the highly polar solvent used (DMSO). Since the geminal dimethyl groups are rather remote from the aryl group substituents, and significant solvent effects on the stereochemistry of closely

related thiohydantoins have been identified[34], solvent effects may, in fact, be the dominant source of variations in the 4-methyl carbon chemical shifts.

CONCLUSIONS

The 1-aryl-2-methylthio-4,4-dimethyl-2-imidazolin-5-ones give rise to well resolved ^{13}C nuclear magnetic resonance spectra. In many cases, peak assignments can be made easily with the aid of the literature and previous studies on related compounds carried out in this laboratory. However, the aryl carbon signals are difficult to assign, so that only the 1'- and 2'- carbon signals can be assigned with confidence.

Methylation of the sulfur atom in thiohydantoins to form the imidazolinones creates changes in bond lengths (e.g. the C_2-N double bond), bond angles and hybridization, all of which may influence the chemical shifts of carbons in positions 2,4 and 5 of the hetero-ring. Such chemical shift changes have been identified in comparisons of the ^{13}C spectra of thiohydantoins and corresponding imidazolinones.

The influences of substituents on the aryl moiety on the chemical shifts of hetero-ring carbons in the imidazolinones are relatively small. No significant correlation between the steric effects of aryl substituents could be established, but a correlation between chemical shifts and electronegativity of the aryl substituent (evidently associated with inductive effects)has

been observed.

In comparison with the thiohydantoins, the imidazolinones have limited possibilities for resonance contributions with the hetero-ring which might be influenced by the inductive or mesomeric effects of aryl group substituents. However, electron donation via resonance of a substituent such as chlorine may tend to stabilize polar forms of the two ring systems, with consequent influences on chemical shifts.

The hetero-ring chemical shifts of the O-chloro compound are somewhat anomalous; this may possibly be associated with the relatively small steric bulk and the large electronic influence of the chloro substituent.

Aryl substituent influences on the methyl carbon chemical shifts are small, and correlations with the nature of the substituent cannot be established.

The effects of varying patterns of solvation in the very polar solvent used for this study cannot be evaluated; such solvation effects may have a significant influence on chemical shifts.

In general, the ^{13}C magnetic resonance spectra of the imidazolinones are well resolved, and show chemical shifts which are characteristic for this group of compounds. Thus, the data obtained in this study will be useful for characterization purposes.

CHAPTER III

Proton spin-lattice relaxation rates of 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones

INTRODUCTION

Routinely, high resolution nuclear magnetic resonance spectroscopy has been utilized for studying the structure and the stereochemistry of organic compounds. To the usual parameters measured from these spectra, namely the chemical shifts, the coupling constants and the integrated areas, further magnetic resonance information can be added. This includes the spin-lattice relaxation times (T_1 values) and the spin-spin relaxation times (T_2 values).

With the development of new instrumental technigues (especially Fourier transform (FT) spectroscopy), it has become possible to measure, on a routine basis, the T_1 values of any resonance that can be clearly resolved in a nuclear magnetic resonance spectrum, even in systems which are chemically complex. Spin-lattice

relaxation times can be measured for proton or ^{13}C nuclear magnetic resonance spectroscopy.

In the literature, we can find reports of various investigations on the potential of proton spin-lattice relaxation rates (R_1 values) for providing diagnostic information on the molecular structures of a variety of compounds such as carbohydrate[35] and nucleoside [36] derivatives, the alkaloid vindoline[37] and recently, complex natural products such as terpenoids, steroids and alkaloids[38].

In this part of the thesis, we are reporting the proton relaxation rate measurements (R_1 values) for a series of 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones. In these compounds, which exhibit very high barriers to internal rotation about the aryl C-N bond, effects of internal rotation are undetectable in the proton nuclear magnetic resonance spectra at normal probe temperatures.

The relaxation rates (R_1 values) in this series of compounds were determined with a view to ascertaining their sensitivity to structural and stereochemical features, with a particular interest in detecting possible inter-ring relaxation pathways and evidence for anisotropic motion.

In studying spin-lattice relaxation phenomena, we are interested in the way in which, and the rate at which the magnetic energy is transferred between the magnetic nuclei under study (the spins) and their surrounding environment (the lattice). The rate at which this transfer occurs is the relaxation rate (R_1 value , sec.$^{-1}$) and the reciprocal of that rate is the spin-lattice relaxation time (T_1 value, sec.).

Consider a sample containing nuclei with spin ½ placed in the magnetic field Ho. The nuclei will precess around the direction of the field with a frequency known as the Larmor frequency (ωo). The nuclei are either aligned with or opposed to the direction of Ho as shown in Figure 3-1. Since there is a slight Boltzman excess of nuclei aligned with the magnetic field, these will give rise to a resultant magnetization vector Mo, which also lies in the same direction as Ho.

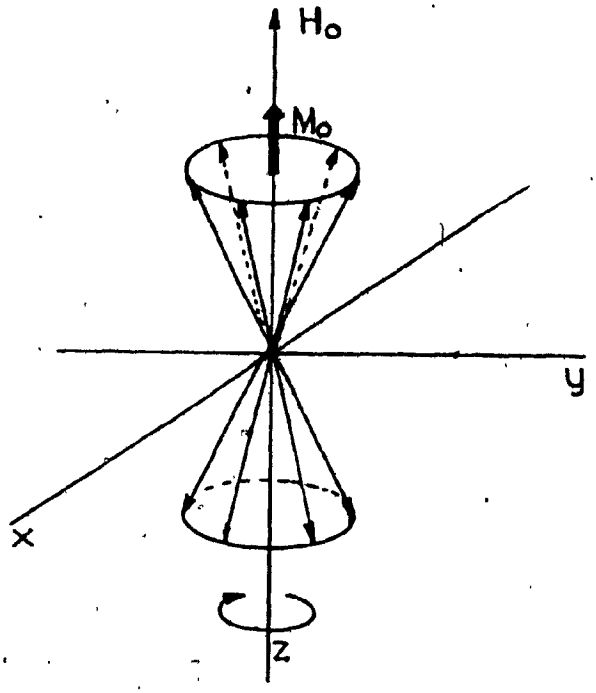


Figure 3-1 Motion of nuclei vectors in magnetic field.

If the frame rotates at the Larmor frequency, it can be represented as described in the Figure 3-2.

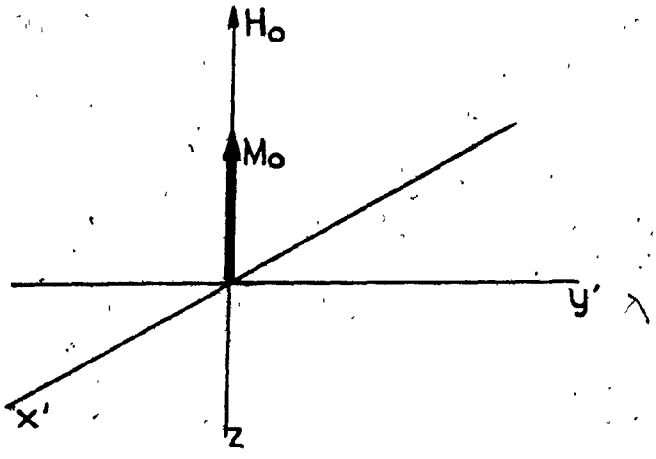


Figure 3-2 Orientation of bulk magnetization in a frame rotating at the Larmor frequency.

We now apply a pulse of radio frequency radiation for a time t also at the resonant frenquency ω_o, along the -x-axis to the frame (which is rotating at the same frequency, ω_o). This is equivalent to applying a static field H_1 along the -x'-axis of the rotating frame. Consequently, as Mo is stationary in the rotating frame, the effect of applying a constant field would be to cause Mo to rotate as shown in Figure 3-3. The angle θ is known as the pulse or tip angle.

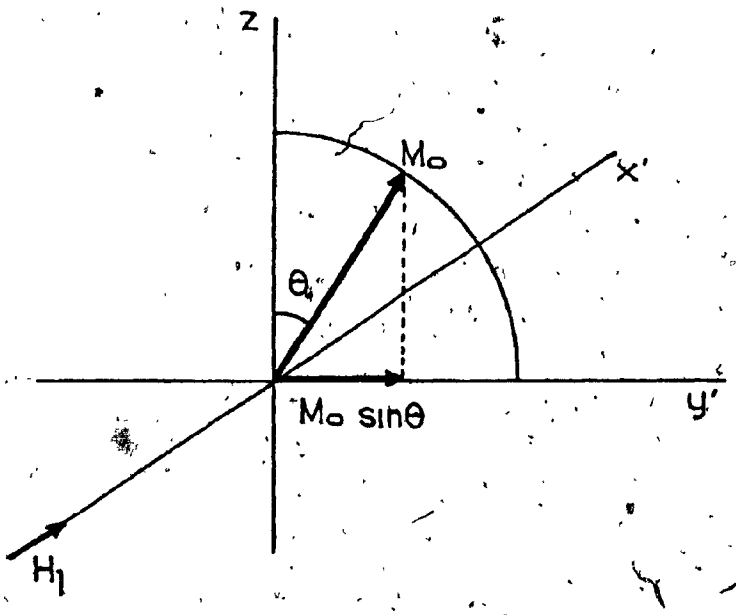


Figure 3-3 The behaviour of the bulk magnetization vector M after a pulse tipping it through an angle θ has been applied.

Once the radiofrequency pulse has been removed, the perturbed spin system will begin to relax back toward its equilibrium condition by means of two separate processes.

In the first of these, the component of the magnetization remaining along the -z-axis relaxes back along the -z-axis to its original value Mo by an exponential decay process characterized by a relaxation time T_1. This process is known as spin-lattice relaxation, since relaxation occurs by the loss of energy from the excited nuclear spins to the surrounding molecular lattice.

In the second process, the nuclear spins interchange with one another so that some now precess faster than ωo while other go slower, with the result that the spins begin to lose phase coherence. This process is known as the spin-spin relaxation process.

In the spin-lattice relaxation process, if the initial magnetization along the -z-axis is Mo and the component at a time t (sec.) after a pulse has been applied is M_z, the M_z returns to Mo as shown in the Figure 3-4.

Mathematically, we can express this process as:

$$Mo - M_z = Mo\,(1 - \cos\theta\,)\exp(^{-t}/T_1)$$

When M_z returns to Mo along the-y'-axis, the component $M_{y'}$ decays, so that :

we have $M_z = Mo$

$M_{y'} = 0$

If after a pulse $M_{y'}(o)$ is the component of M [41]

$$M_{y'}(o) = Mo \sin\theta$$

and

$$M_{y'}(t) = M'_y(o)\exp(^{-t}/T_1)$$

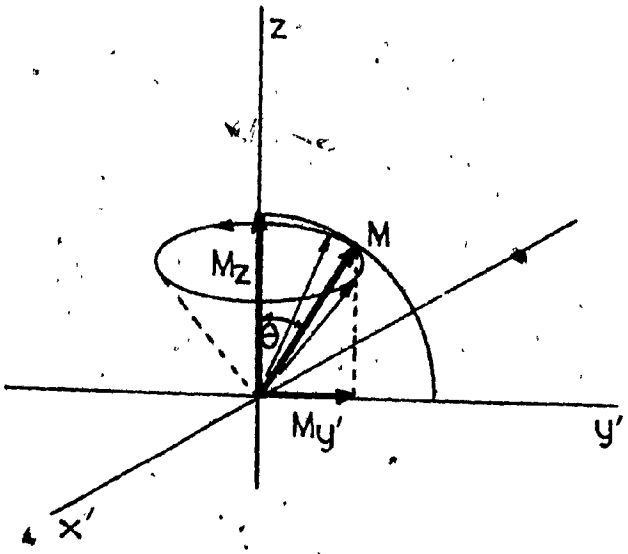


Figure 3-4 Relaxation mechanisms.

Component of M in x'y' plane

$M_{x'} = 0$

$M_{y'} = Mo \sin\theta$

$M_z = Mo \cos\theta$

There are a number of mechanisms which can contribute to spin-lattice relaxation in a molecule. The most common of these along with their associated relaxation times are:

dipole-dipole	T_1 DD
spin-rotation	T_1 SR
quadrupolar	T_1 Q
scalar	T_1 SC
chemical shift anisotropy	T_1 CSA

Each of these combines to produce an overall spin-lattice relaxation time T_1 given by:

$$\frac{1}{T_1} = \frac{1}{T_1\ DD} + \frac{1}{T_1\ SR} + \frac{1}{T_1 Q} + \frac{1}{T_1\ SC} + \frac{1}{T_1\ CSA}$$

For convenience, we consider the relaxation rates (R_1 in sec^{-1}), with the relation.

$$R_1 = \frac{1}{T_1}$$

Hence,

$$R_1 = R_1\ DD + R_1\ SR + R_1\ Q + R_1\ SC + R_1\ CSA$$

For all these mechanisms, the contributions to the spin-lattice relaxation rates are included in the experimental value, and it is very often difficult to derive from the experimental value the individual contribution from a specific relaxation mechanism. Fortunately, we can conduct experiments in which of one of these mechanisms, the intra-molecular dipole-dipole mechanism, dominates the relaxation, and under optimum conditions is the only operative mechanism. In practice, the molecule studied must move more or less isotropically in solution. These molecules should be studied in dilute magnetically inert solvents which minimize the contributions from intermolecular effects. For this requirement deuterated solvents without fluorine have been used.

In a system where the dipole-dipole mechanism is predominant[39], the contribution can be expressed as:

$$R_1{}^R = \frac{1}{T_{1R}} \propto \frac{\gamma_D{}^2 \gamma_R{}^2}{(r_{D,R})^6} \tau_c (D,R)$$

This equation is valid provided that the molecule is tumbling rapidly enough that the extreme narrowing condition ($\omega_0{}^2 \tau_c{}^2 \ll 1$) is met.

In this equation, D refers to the donor nucleus and R to the receptor nucleus. τ_c is the motional correlation time for the D,R vector, the γ's are the magnetogyric ratios and r is the internuclear distance.

The efficiency with which any receptor nucleus, R, is relaxed by a donor nucleus, D, is proportional to the square of the magnetogyric ratio (γ) of each nucleus and to the correlation time of the motion of the vector D→R with respect to the field. It falls off as the inverse sixth power of the distance (r D→R) between the two nuclei. This means that contributions to the relaxation of a nucleus are attenuated very rapidly when the distance between the two nuclei increases, i.e. the R_1 value of a proton is largely dependent on the number and the proximity of its immediate neighbours.

Since only protons have a high value of γ, intramolecular relaxation will be dominated by interproton interactions, with the nearest protons making the largest contributions. Hence one can anticipate the possibility that the proton spin-lattice relaxation times will show pronounced configurational dependencies. In most

organic molecules, each individual proton will be relaxed by interactions with several other protons. (D_1, D_2...) in the same molecule and hence its total relaxation rate will have the form given by the equation: -

$$R_1^R = R_1^{D1} + R_1^{D2} + R_1^{D3} + \cdots\cdots\cdots$$

and the magnitude of each of these contributions will depend on the relative magnitudes of the individual internuclear distances.

In summary, under suitable conditions, proton spin-lattice relaxation involves through-space interactions between individual protons in the same molecule. Since the efficiency of these interactions decreases with the distance, each proton receives most of its relaxation from its nearer neighbour protons. This property can be used as a possible way to determine the conformation of the molecule. It can frequently be assumed that the molecule rotates or tumbles isotropically in solution (with equal facility in all directions)[40]. However, many molecules are not spherical and so have particular axes of rotation preferred, in general, coincident with the axes of inertia of the molecule (Figure 3-5).

For example, the molecule shown is likely to tumble anisotropically in solution about the long molecular axis.

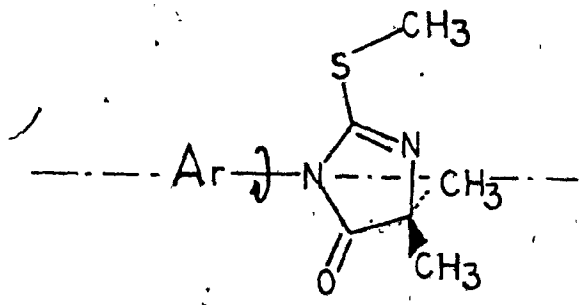


Figure 3-5 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-one

Since the relaxation rate is dependent on the angle between the relaxation vector (D,R) and the preferred axis of rotation, R_1 measurements may provide information on the anisotropic motion of the molecule as a whole or on segmental motion within the molecule (e.g. biphenyl[41]). In view of the shapes of the molecules studied

in this thesis, it was considered that anisotropic motion was likely to be a factor influencing the relaxation rates.

The dominance of the intramolecular dipole-dipole relaxation mechanism may be assured if dilute solutions in solvents which do not themselves provide relaxation pathways are employed. It is sufficient to use perdeuterated solvents for proton relaxation measurements, since the small magnetogyric ratio of deuterium makes this nucleus very inefficient for relaxation (6.3% that of an equivalent proton). Dissolved oxygen in the solution is usually the most important source of paramagnetic (dipole-dipole) relaxation. If required, oxygen may be removed by standard techniques, but it has been shown that this is unnecessary for most qualitative studies, such as the present one[38]. The rate constant for relaxation to oxygen is very similar for all protons in a molecule, so that all of the R_1 values determined for protons in a molecule will be increased by an essentially constant amount.

Since relaxation rates are dependent on rates of molecular tumbling, a change in the mass or geometry of a substituent in a molecule may affect the R_1 values of all the nuclei, not only those

in the immediate vicinity of the substitution site. Thus, if the R_1 values of molecules with different substituents or geometries are to be compared, it is advisable to normalize the relaxation rates with respect to the rate of the nucleus remote from the site of substitution, on the assumption that changes in the R_1 values of this nucleus will reflect changes in the tumbling rates rather than the direct effect of the substituent.

MEASUREMENTS OF PROTON SPIN-LATTICE RELAXATION TIMES

In recent years, several semi-automated systems have become available for routinely determining spin-lattice relaxation times. As we have seen before, the magnetization vector normally lies along the z direction at equilibrium while the spectrometer detects signals in the x'y' plane (Figures 3-1 and 3-2). When this vector lies along the-z-axis, no signal is detected by the spectrometer which is designed to respond only to that component of the magnetization which lies in the x'y' plane. Thus, to assay the amount of magnetization, it is necessary to tip the magnetization vector through 90^0 into the x'y' plane. This is accomplished by applying a suitable amount of radiofrequency in the form of short pulse of 90^0. In general, a pulse which is able to tip the magnetization through 90^0 from the z to the-y'-axis is known as a 90^0 or $(\pi/2)$ pulse and the time for which the pulse is applied as the 90^0 pulse time. The time for which the pulse is applied must be short when compared to the rate of change of magnetization along the-z-axis.

If twice that amount of power is applied by doubling the length of the pulse, then the original magnetization vector will be tipped through 180^0 and will lie along the -z-axis (Figures 3-6 and 3-7). This pulse is known as a 180^0 or (π) pulse.

The relaxation rates of the 1-aryl-2-methylthio-4,4-dimethyl-2-imidazolin-5-ones were determined by the conventional "inversion recovery" two pulse sequence. In this method, a 180^0 pulse is applied to invert the magnetization to the -z-axis (Figure 3-6). Hence, immediately after the pulse, the magnetization vector Mz equals $-Mo_z$ and will now begin to relax back along the -z-axis towards its equilibrium value, Mo_z, via the spin-lattice relaxation process.

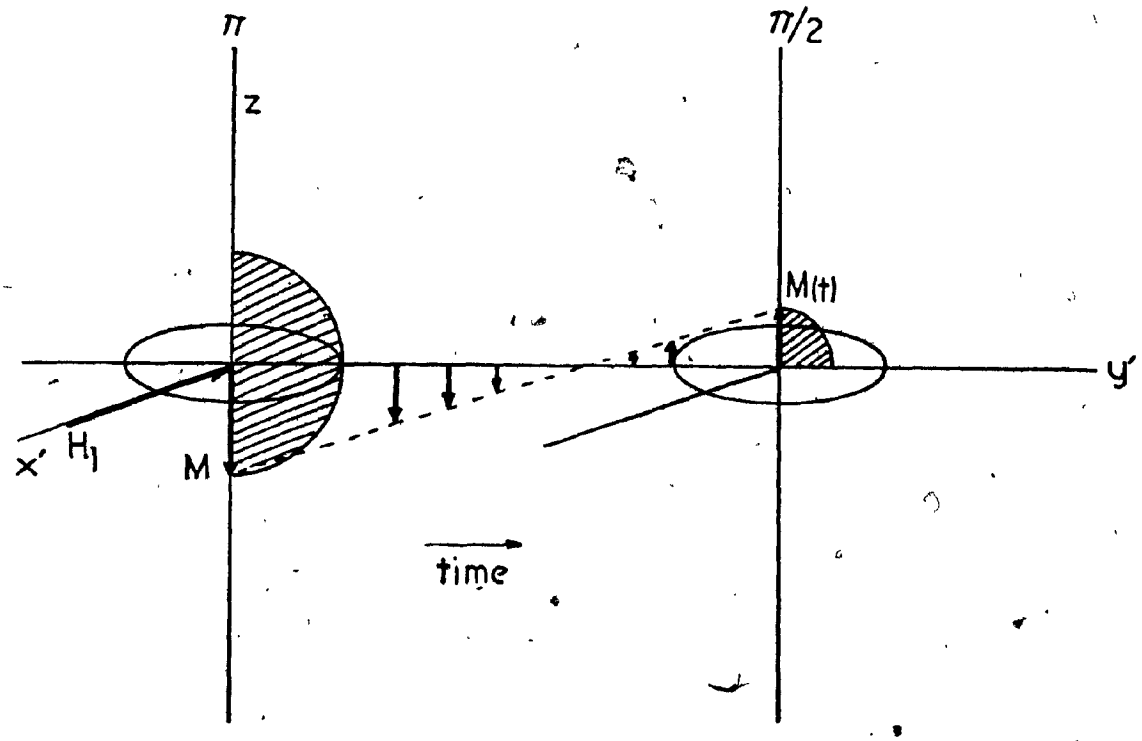


Figure 3-6 Diagram illustrating the principle of inversion recovery experiment.

This can be expressed mathematically as:

$$M_z = Mo_z \left[1 - 2 \exp\left(-t/T_1\right) \right]$$

Where M_z is the component of M along the-z-axis, t (sec) after the 180^0 pulse, Mo_z is its equilibrium value and T_1 is the spin-lattice relaxation time. Hence, at one point M_z will actually pass through zero and we have:

$$0 = Mo_z \left[1 - 2 \exp\left(-t_o/T_1\right) \right]$$

where to is the time at which $M_z = o$.

We have now:

$$2 \exp\left(-t_o/T_1\right) = 1$$

$$T_1 = \frac{t_o}{2.303 \log 2.}$$

$$T_1 = \frac{t_o}{0.693}$$

or

$$R_1 = \frac{0.693}{t_o}$$

Providing that spectrometers can detect signals along the -z-axis, this is a method to determine the T_1 (or R_1) values. But in practice, most spectrometers detect signals in the x'y' plane. Therefore, after a delay time of t (sec) a 90^0 pulse is applied which tips the magnetization onto the -y'-axis where it can be detected. The full sequence is shown in the 180^0 pulse - delay t - 90^0 pulse (Figure 3-7). The signal which has been inverted along the -z-axis gradually recovers its normal upright intensity, passing through the zero (also called "the null point").

The spectra obtained as a function of t may be displayed in the form of a stack plot (Figures 3-9, 3-10). However, at the end of the cycle, the magnetization lies along the -y'-axis and so before a second 180^0 pulse can be applied, it is necessary to wait a period of 5 T_1 to allow the magnetization vector to relax back to Mo_z.

After 5 T_1, we have:

$$M_z = 0.993\ Mo_z$$

Hence, the pulse delay (PD) (equal to 5 T_1) must be inserted between cycles and the sequence becomes:

$$\left[180^0 \text{ pulse} - t \text{ delay} - 90^0 \text{ pulse} - PD\right]$$

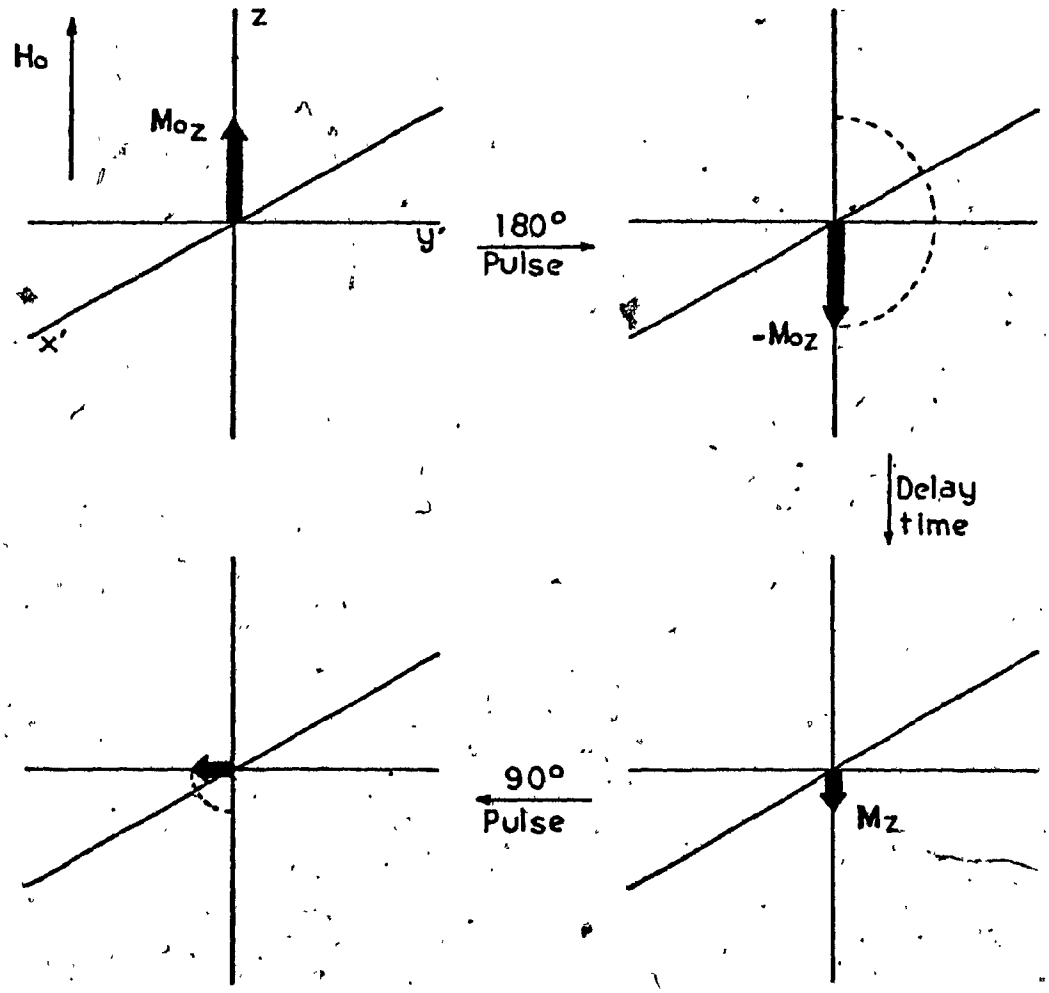


Figure 3-7 The rotating reference frame model for the measurement of spin-lattice relaxation time.

The timing of the pulses and the delays are normally performed automatically by the computer. The relaxation rates of individual nuclei may be obtained by fitting the theoretical expression for the exponential recovery of magnetization to the measured signal intensities as a function of the time delay:

$$M_z - Mo_z = -2\, Mo_z \exp(-t/T_1)$$

Taking logarithms:

$$\mathrm{Ln}(M_z - Mo_z) = \mathrm{Ln}\ 2\, Mo_z - t/T_1$$

Hence a plot of $\mathrm{Ln}(M_z - Mo_z)$ against t will give a straight line with a gradient of $-1/T_1$. In practice, at the end of the experiment, the accumulated free induction decay (FID) is Fourier transformed and the intensity of the signal is determined. Then these intensities (Figure 3-8 and Table 3-1) or the ln of the intensities of the signal are plotted as a function of t and the T_1 value is determined. The fitting process may be carried out using linear (semi-log) regression or graphically, or by non-linear regression, as in the present study. However, it is possible with a considerable saving of time, to estimate the T_1 value using the "null point" method on the stack plots, considering that at the "null point" we have

$$R_1 = \frac{1}{T_1} = \frac{0.693}{t_o}$$

NLNT1
FIT AFTER 4 ITERATIONS

2-NITROPHENYL COMPOUND: 8.2 PPM ARYL MULTIPLET

PARAMETERS: B(1) = 3978.65 (EQUILIBRIUM INTENSITY)
B(2) = .265 (RELAXATION RATE, R1, /SEC.)
T1 = 3.776 (RELAXATION TIME, T1, SEC.)

PARAMETER CORRELATION MATRIX

1	1.000	.629
2	.629	1.000

	STD ERROR	ONE-PARAMETER LOWER	ONE-PARAMETER UPPER	SUPPORT PLANE LOWER	SUPPORT PLANE UPPER
1	.2534E+02	.3928E+04	.4029E+04	.3907E+04	.4050E+04
2	.1632E-02	.2616E+00	.2681E+00	.2602E+00	.2695E+00

NONLINEAR CONFIDENCE LIMITS

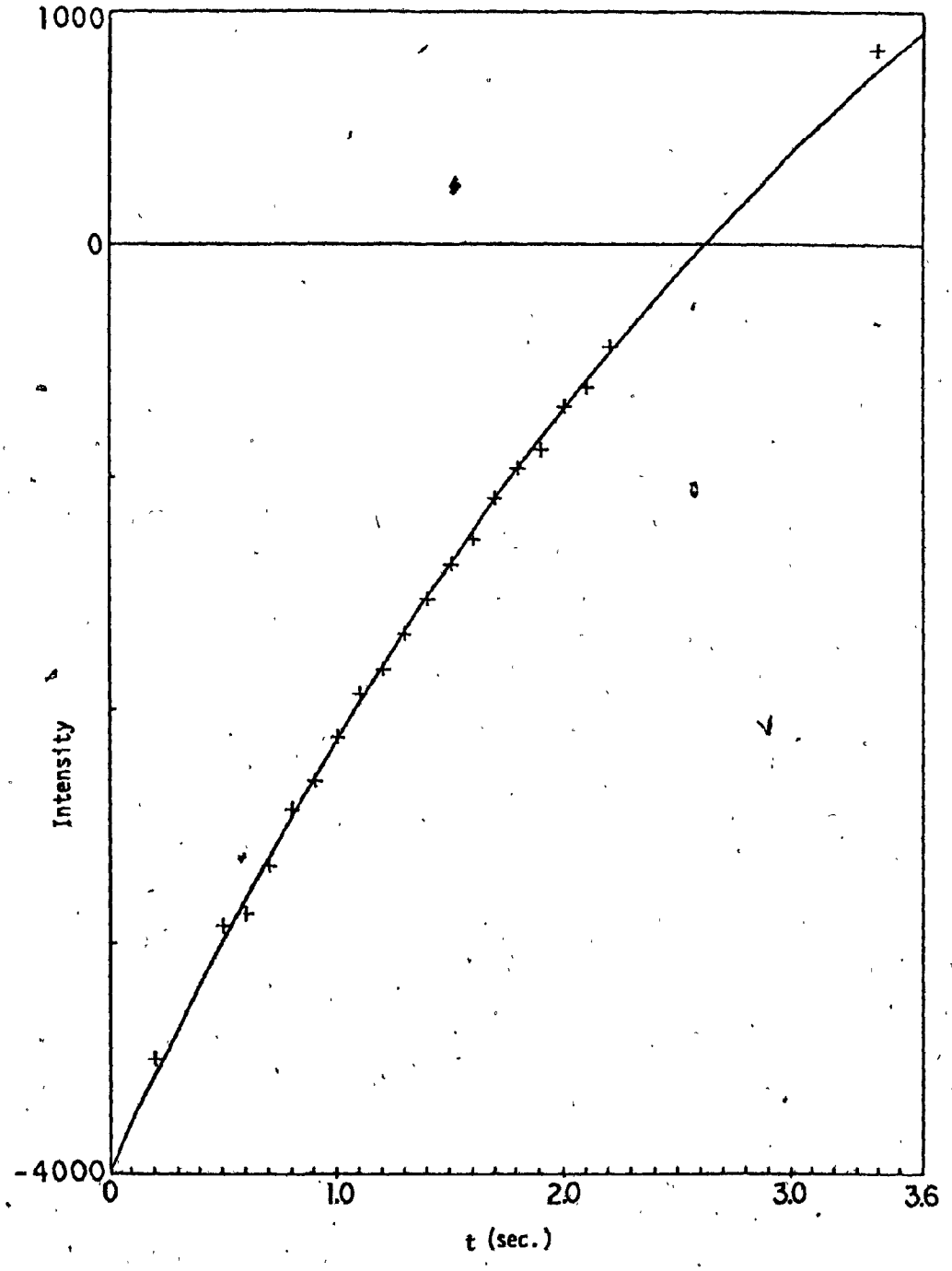
PHI CRITICAL = .45701000E+05

PARA	LOWER B	LOWER PHI	UPPER B	UPPER PHI
1	.392310E+04	.457167E+05	.403407E+04	.457009E+05
2	.261306E+00	.457044E+05	.268394E+00	.457187E+05

#	TIME SEC	INTENSITY	REGRESSION DATA FIT	DIFF
1	.200	-3500.78	-3562.77	62.00
2	.500	-2928.89	-2979.36	50.47
3	.600	-2874.66	-2795.09	-79.57
4	.700	-2671.80	-2615.71	-56.09
5	.800	-2431.84	-2441.07	9.23
6	.900	-2306.66	-2271.06	-35.60
7	1.000	-2122.32	-2105.56	-16.76
8	1.100	-1934.60	-1944.43	9.83
9	1.200	-1829.26	-1787.57	-41.69
10	1.300	-1676.20	-1634.87	-41.33
11	1.400	-1525.35	-1486.21	-39.14
12	1.500	-1378.68	-1341.49	-37.19
13	1.600	-1269.26	-1200.60	-68.66
14	1.700	-1091.80	-1063.44	-28.36
15	1.800	-963.50	-929.91	-33.59
16	1.900	-885.58	-799.92	-85.66
17	2.000	-699.38	-673.37	-26.01
18	2.100	-614.80	-550.18	-64.62
19	2.200	-439.70	-430.24	-9.46
20	3.400	837.00	783.76	53.24

Table 3-1. Proton spin-lattice relaxation regression data obtained using the non-linear regression program NLNT1.

Figure 3-8 Plot of spin-lattice relaxation data (Intensity vs time) for 8.2 ppm aryl multiplet of 6, following the inversion - recovery pulse sequence. The best fit non-linear regression curve is shown.



In comparisons of R_1 values determined by the "null point" method and the regression methods, it has been demonstrated [38] that the null point method provides sufficient accuracy for qualitative studies such as the present one. The R_1 values reported in this thesis were measured by the "null point" method but a number of values were also determined by the non-linear regression computational method (Table 3-1).

R_1 values can provide direct information concerning molecular motion (3-6), both the overall tumbling of the molecule and any additional internal degrees of motional freedom for pendant substituents.

However, the fact that τ_c values also depend on the solvent, the solute concentration, temperature and on molecular weight and shape, creates problems whenever it is necessary to compare R_1 values for different molecules. It is possible to eliminate the above experimental variations by using the R_1 value of a selected proton to normalize the R_1 values of the remaining protons (see later).

EXRERIMENTAL

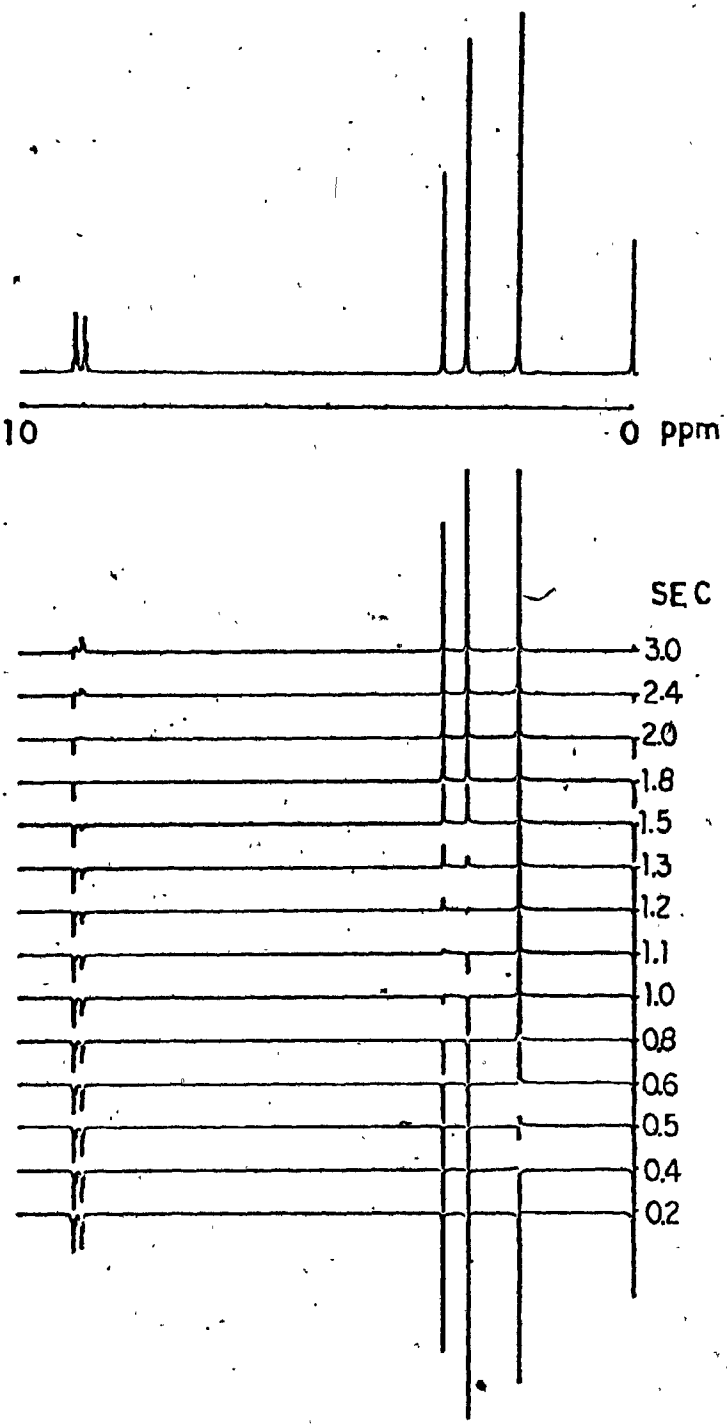
Spectra were determined at 270 MHz and 23°C, using a "home built" spectrometer, based on a Bruker WH-90 console, an Oxford Instruments superconducting magnet, and either a Nicolet-1080 or -1180 computer with a 16 K word data block. Relaxation rates were measured using the 180°, t, 90°, delay (inversion - recovery) pulse sequence [42], with averaging of four free induction decays. The delay between sequences was at least five times the estimated value of the longest T_1. Before each run, the 180° pulse length was optimized by finding the length which produced a null in the amplitude of the free induction decay. Typically, data for about thirty values of t, the maximum which could be accommodated, were averaged, filtered, Fourier transformed, phase corrected, and stored automatically on disc for later processing, the appropriate range of t values having been selected in a preliminary experiment. The longest value of t was chosen so that all peaks had relaxed through their null points. R_1 values were determined by the null point method[38], using extrapolation between data sets straddling the null point, and also in a number of cases by computer fitting the peak intensities by the exponential recovery curve using an iterative non linear regression program run on a Hewlett-Packard 1000 computer. This

program can sum the intensities of the components of a multiplet. Intensities were obtained either from computer print-outs or from measurements from the charts, and in every instance attempts were made to ensure that only the data from the initial slope region were used.

The spectra arising from the four aryl ring protons of 3, 4, 5 and 6 were analysed by the iterative program LAOCN3[19] using a CDC Cyber 172 computer. Chemical shifts were obtained directly from line positions measured by the system computer and spectral analysis of aryl multiplets. Computer simulated spectra and corresponding experimental spectra are shown in Tables 3-1 and Figures 3-8, 3-9, 3-10, 3-11 and 3-12.

Spectra and computerized data were obtained by Dr. L.D. Colebrook at the University of British Columbia.

Figure 3-9 Stack plot displaying a selected series of partially relaxed spectra of 2 taken for various delay times, t, in the 180°-t-90° pulse sequence. The delay times are marked on the right hand side of the figure. The normal (fully recovered) spectrum is displayed at the top of the stack.



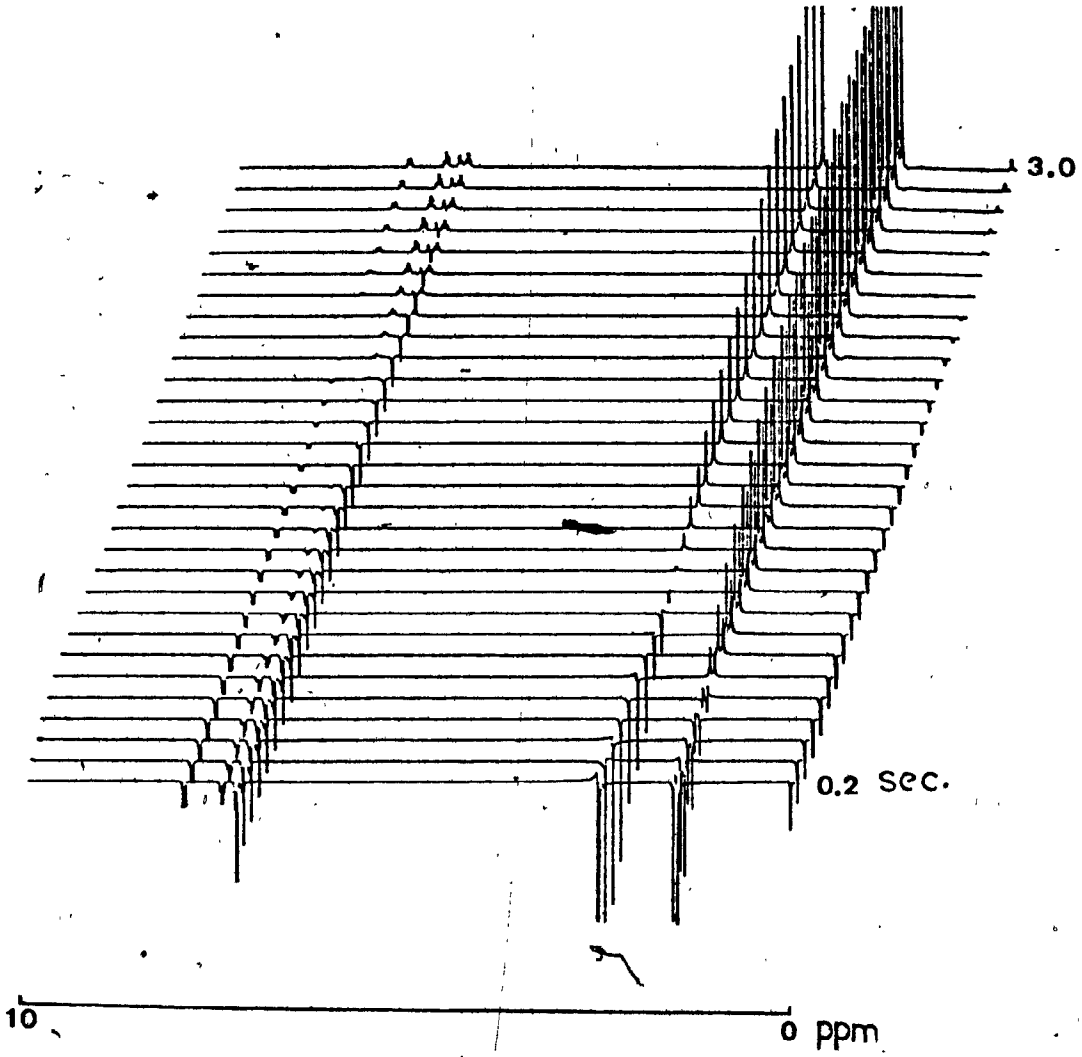
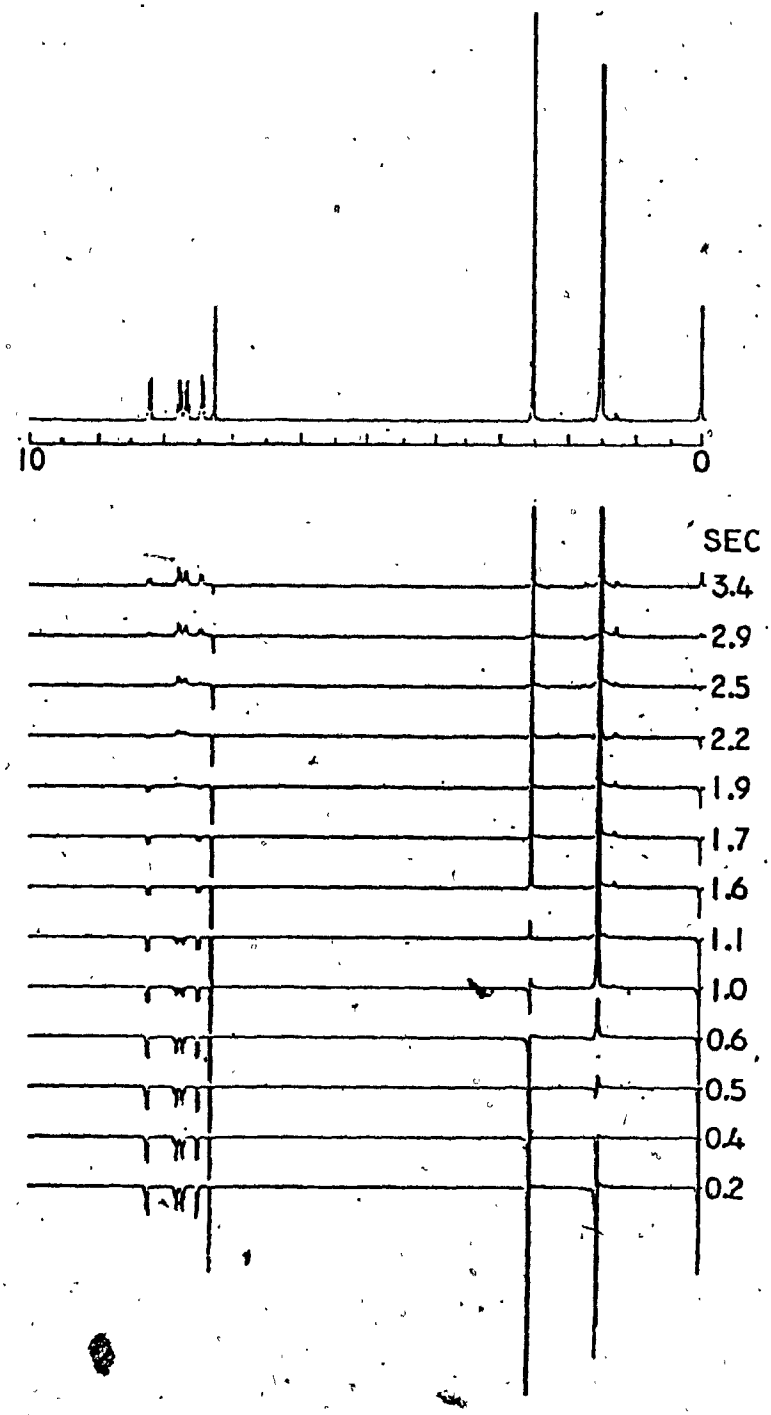


Figure 3-10 Stack plot displaying a selected series of partially relaxed spectra of 2 taken at various delay times, t, in the 180^{o}-t-90^{o} pulse sequence.

Figure 3-11 Stack plot displaying a selected series of partially relaxed spectra of 6, taken for various delay times, t, in the 180^0-t-90^0 pulse sequence. The delay times are marked on the right hand side of the figure. The normal (fully recovered) spectrum is displayed at the top of the stack.



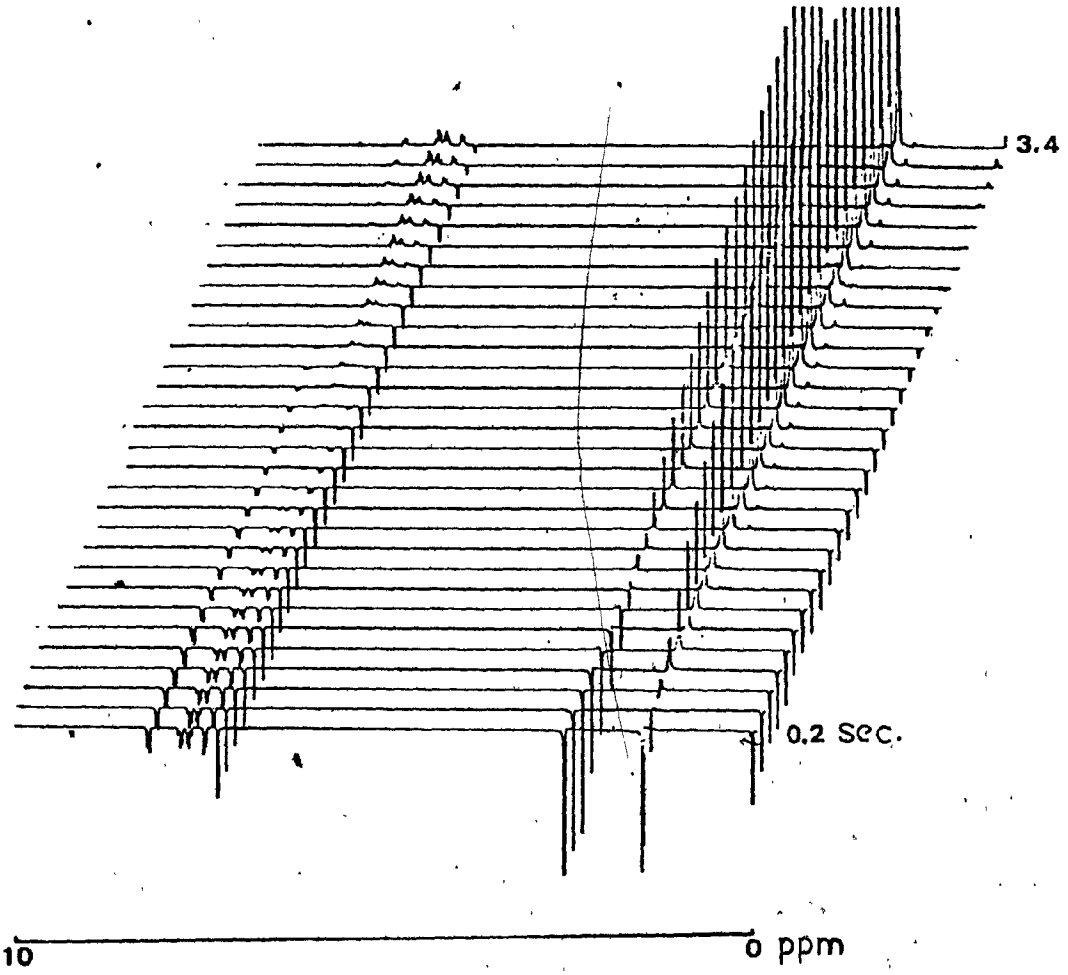


Figure 3-12 Stack plot displaying a selected series of partially relaxed spectra of $\underset{\sim}{6}$, taken for various delay times, t, in the 180^0-t-90^0 pulse sequence.

RESULT & DISCUSSION

The proton chemical shifts for derivatives 1-7 are summarized in Table (1-3).

All but one, 1, of the compounds with enantiomeric rotational isomers showed two sharp signals arising from the 4,4-dimethyl groups (Table 1-3), indicating that these groups are diastereotopic and anisochronous under the conditions of the experiments.

Since the barriers to internal rotation of these compounds are known to be high, it is assumed that the failure to observe separate 4,4-dimethyl group signals in 1 results from inadequate chemical shift differences rather than from the effects of fast internal rotation.

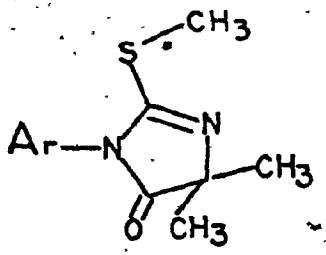
The aromatic proton signals are sufficiently dispersed at 270 MHz that R_1 values could be determined for all of these protons in 5 and 6. The multiplet arising from the aryl-3 proton was chemically shifted from the other aromatic proton signals in the remaining compounds, so that measurement of the R_1 value was possible in all cases except 7. Interference from the residual $CHCl_3$ signals from the 99.8% $CDCl_3$ solvent caused some problems, since this is one of the more intense signals when 0.01 M solutions are used. However, the relaxation rate ($R_1 = 0.18 sec^{-1}$) of this proton is very much slower than those of the aromatic protons so that its signal was always readily identifiable.

A comparison of the R_1 values obtained by the "null point" and by the regression (initial slope) methods was carried out for selected signals in most of the compounds in order to check the reliability of the former method in this series of compounds (Table 3-2). In general, excellent agreement was obtained, the range lying within the regression error limits (typically ±0.01 for all but the 4,4-dimethyl signals). Experimental conditions were not ideal for regression measurements on the fast relaxing 4,4-dimethyl signals, since a restricted range of t values was available. In consequence, these regression values are less reliable and have a larger error range than the other regression R_1 values.

It will be noted (Table 3-2) that the R_1 values of protons remote from the direct influence of changes in aryl group substituents, e.g. those of the 4,4-dimethyl groups, are not constant throughout the series. In particular, the R_1 values are largest for the compound, 7, with the largest aryl substituent. These data demonstrate the sensitivity of relaxation rates to change in rates (and possibly, preferred axes) of molecular tumbling. Fortunately, it proved possible to effectively eliminate these effects by using the R_1 values of the 4,4-dimethyl to normalize the relaxation rates of the other protons. The 4,4-dimethyl protons are chosen because their rates could not be directly affected by chemical changes in the aryl-substituents, and the normalized rates are shown in Table 3-3.

The fastest relaxing protons of these compounds are those of the geminal dimethyl group, which relax notably faster (2-2.4 times) than the $-SCH_3$ and aryl-CH_3 protons. The absolute relaxation rates of the $-SCH_3$ protons range from 0.61 to 0.72 $sec.^{-1}$, the fastest rate occurring in the 1'-naphthyl compound, 7, whereas the range of values in the remaining compounds is small. After normalization, the relative relaxation rates are seen to be

Table 3-2 Proton spin-lattice relaxation rates (R_1, sec^{-1}) determined by the null point method, and by non-linear regression[a]



	Ar	Aryl Protons 3'	4'	5'	6'	CH_3	$-SCH_3$	4-CH_3
1	2'-Tolyl					0.54(0.54)	0.62(0.62)	1.33(1.29)
2	2',6'-Dimethylphenyl	0.35	0.36	0.35		0.56(0.57)	0.65(0.64)	1.33(1.35)
3	2'-Chlorophenyl	0.27	0.38[b]		0.30		0.61(0.61)	1.28(1.28)
4	2'-Bromophenyl	0.27	0.38[b]		0.31		0.62	1.28
5	2'-Iodophenyl	0.28	0.38	0.41	0.30		0.63(0.64)	1.33(1.36)
6	2'-Nitrophenyl	0.28(0.27)	0.38(0.38)	0.42(0.41)	0.32(0.32)		0.65(0.64)	1.33(1.38)
7	1'-Naphthyl						0.72(0.71)	1.43(1.44) 1.54(1.57)

a) Regression data are enclosed in brackets. Null point precision was 5% or better.

b) Composite values for H_4' and H_5'.

Table 3-3 Relaxation rates relative to those of the 4-methyl protons

Ar	Aryl Protons 3'	4'	5'	6'	CH_3	$-SCH_3$	$4-CH_3$
1					0.41	0.47	1.00
2	0.26	0.27	0.26		0.43	0.48	1.00
3	0.21	0.30[a]		0.23		0.48	1.00
4	0.21	0.30[a]		0.24		0.48	1.00
5	0.21	0.29	0.31	0.23		0.48	1.00
6	0.21	0.29	0.32	0.24		0.48	1.00
7							1.05, 0.95

[a] Composite value for H_4, and H_5,

essentially identical. The faster uncorrected rate in 7 is evidently due to the reduced tumbling rate of the larger naphthyl compound. The small range of normalized rates in 1-7 indicates that the relaxation rates of -SCH_3 protons are insensitive to changes in the ortho substituents of the aryl group, even though the ortho methyl substituents of 1 and 2 might be capable of providing additional relaxation pathways.

The aryl methyl protons in 1 and 2 relax with almost identical rates (absolute and normalized) which are somewhat slower than those of the -SCH_3 groups in the same molecules, and much slower than those of the 4,4-dimethyl groups.

The aryl ring protons of 2 show well dispersed signals, so that their relaxation rates could be determined; these are almost identical. If the 3'-, 4'- and 5'- protons were an isolated system, tumbling isotropically, calculations based on distances measured from Dreiding models show that the 4'-proton should relax 1.93 times faster than 3'- and 5'- protons. It is clear, therefore, that the 3'- and the 5'- protons get some relaxation from the aryl methyl groups. Confirmation that this is so is seen in a comparison with the relaxation rates of the 3'- protons

of 2-6, which have identical normalized relaxation rates about 20% slower than that of H-3' (or H-5') in 2. The 4'- protons of 2-6 have very similar normalized relaxation rate, indicating, as expected, that their significant relaxation pathways are to H-3' and H-5'.

Excellent dispersion of the aromatic proton signals of 5 and 6 at 270 MHz permitted the measurement of the relaxation rates of all four aromatic protons. The relaxation rates (Tables 3-2 and 3-3) of corresponding protons in these two compounds are almost identical. If this four-proton system formed a completely isolated group which was tumbling isotropically, the 4'- and the 5'- protons would have identical relaxation rates, 1.94 times faster than the (identical) relaxation rates of the 3'- and 6'- protons. In fact, while the 4'- and the 5'- protons have very similar relaxation rates, an examination of the stack plots, and also regression analysis of the aryl proton intensities of 6 show that they are not identical, differing by 7-10%. Similarly, the relaxation rates of 3'- and 6'- protons differ by 10-14%. The greatest rate ratio ($R_{5'}/R_{3'}$) is only 1.5, further demonstrating that this group is subject to outside influences.

Two external factors which may produce differential relaxation rates within this group of protons may be identified, namely anisotropic molecular motion and inter-ring relaxation. The most likely axis for preferred molecular rotation would be approximately parallel to the bond linking the aryl and the heterocyclic moieties. Thus, the relaxation vector between H-5' and H-6' would be approximately parallel to this axis, whereas the relaxation vector between H-3' and H-4', and H-4' and H-5', would make a large angle to this axis. The theory of dipole-dipole relaxation in anisotropically tumbling molecules predicts[43] that relaxation vectors which lie on, or parallel to, the principal axis of rotation are more efficient than vectors at an angle to the axis. It follows that the H_5'-$_6'$ pathway is expected to be more efficient than the H_3'-$_4'$ and the (similar) H_4'-$_5'$ pathways, in accord with observation. Similar effects of anisotropic molecular motion on proton R_1 values in chlorophyll derivatives[44] and in numerous carbon-13 studies[45] have been demonstrated.

The geometry of these molecules is such that a significant relaxation pathway may exist between the $-SCH_3$ group and H-6' of the aryl group. It is unlikely that this pathway would noticeably

affect the relaxation rate of the $-SCH_3$ protons, since methyl protons relax each other quite efficiently, but it should measurably increase the relaxation rate of H-6'. In all cases where measurements were possible, 3-6, the H-6' protons relax faster (10-14%) than the H-3' protons, which is in accord with this expectation. However, in view of the possibility that anisotropic motion could also make a contribution, it does not seem possible to pursue this point further.

CONCLUSIONS

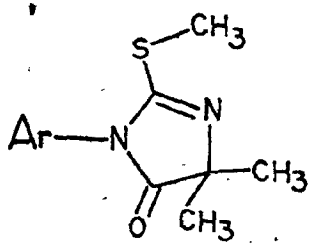
The data reported here clearly support an earlier contention[38] that under carefully controlled conditions, the "null point" method can provide a reliable source of proton spin-lattice relaxation data for natural products. It is also apparent that a substantial differential, in this case a five-fold one, can exist between the R_1 values of the protons of a single compound. Interpretation of these data in term of molecular-geometry and molecular-motion is feasible, but it can be difficult to distinguish between the effect of anisotropic motion and inter-ring relaxation. For some systems, this is a serious limitation. Although in principle, it is possible to eliminate some of these ambiguities by measuring the ^{13}C R_1 values, either lack of material or limited solubility (as in this case) will make such measurements impractical. The alternative procedure of specific deuteration[46] has some attractive possibilities which have to be considered.

CHAPTER IV

SYNTHETIC PROCEDURES

The 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones required for this study were prepared by methylation of the corresponding 3-aryl-5,5-dimethyl-2-thiohydantoins, using established procedures[47], and were characterized by elemental analysis, infrared, ^{13}C and ^{1}H n.m.r. spectra. Melting points and analytical data are listed in Table 4-1. The thiohydantoins were prepared from the appropriate aryl isothiocyanate and methylalanine using the procedure of Pujari and Rout[48].

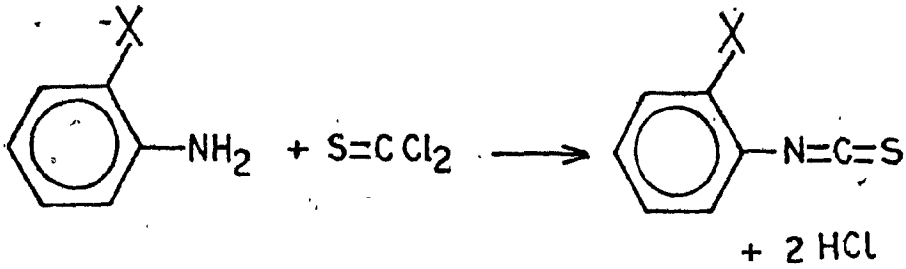
Table 4-1 Melting points and analytical data of the 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones.



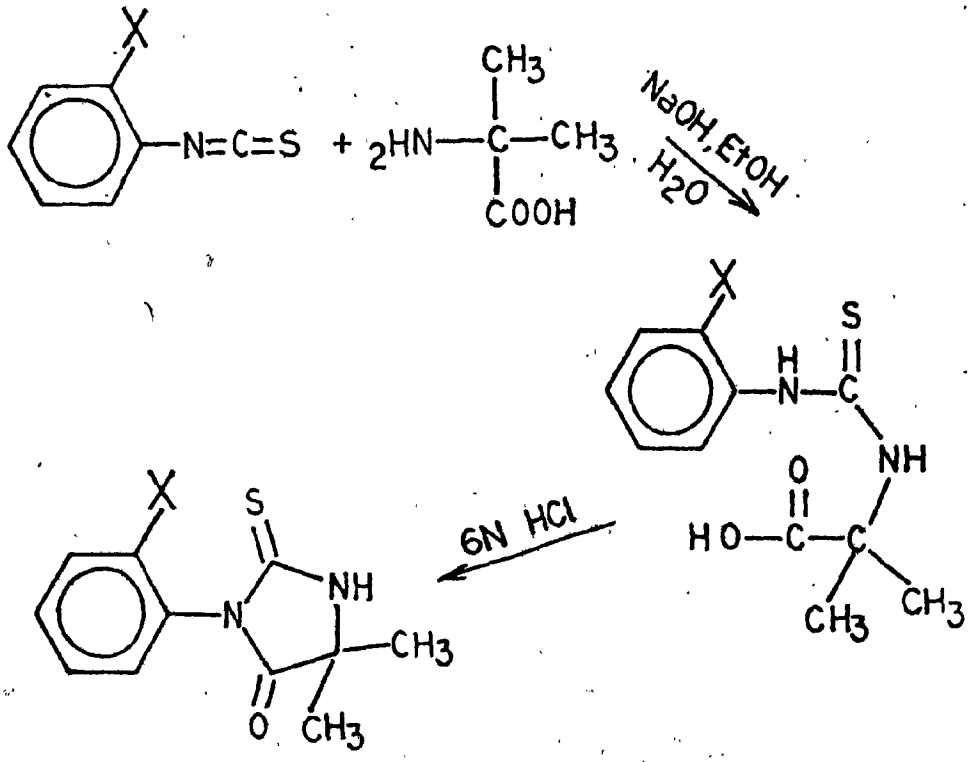
	Ar	Formula	Analytical Data						Melting points in °C
			% Calculated			% Found			
			C	H	N	C	H	N	
1	2'-Tolyl	$C_{13}H_{16}N_2OS$	62.87;	6.50;	11.28	62.63;	6.71;	11.48	84-85
2	2',6'-Dimethylphenyl	$C_{14}H_{18}N_2O_5$	64.09;	6.91;	10.28	64.04;	7.12;	10.55	91-92
3	2'-Chlorophenyl	$C_{12}H_{13}ClN_2OS$	53.63;	4.87;	10.43	53.44;	4.90;	10.46	123-125
4	2'-Bromophenyl	$C_{12}H_{13}B_2N_2OS$	46.01;	4.18;	8.95	46.05;	4.13;	8.93	140-141
5	2'-Iodophenyl	$C_{12}H_{13}IN_2OS$	40.01;	3.64;	7.77	39.85;	3.77;	7.93	144-145
6	2'-Nitrophenyl	$C_{12}H_{13}N_3O_3S$	51.60;	4.69;	15.04	51.66;	4.87;	14.95	143-145
7	1'-Naphthyl	$C_{16}H_{16}N_2OS$	65.57;	5.67;	9.85	67.40;	5.48;	9.69	143-144

The overall synthetic scheme was as follows:

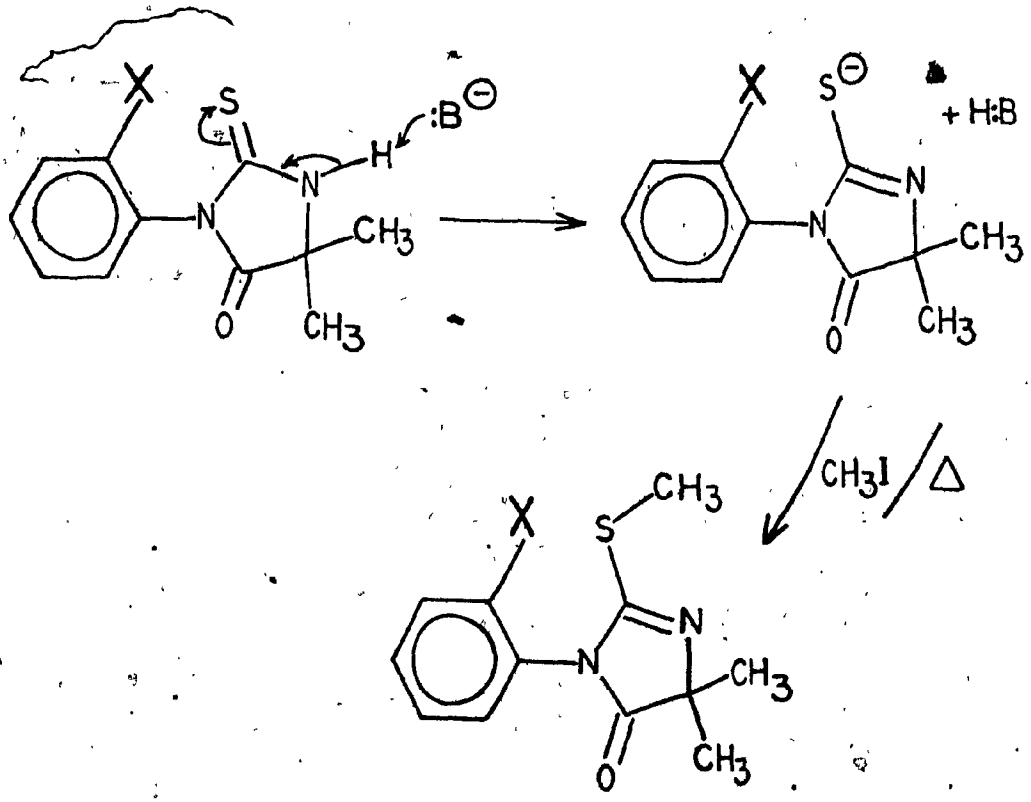
Preparation of isothiocyanates[49]



Preparation of 3-aryl-5,5-dimethyl-2-thiohydantoins[48]



Preparation of 1-aryl-4,4-dimethyl-2-methylthio-2- imidazolin-5-ones 50, 51, 52, 53.



GENERAL PROCEDURE FOR THE PREPARATION OF ARYL-ISOTHIOCYANATES

The method described by Coghill and Johnson[49] was followed. A typical example follows:

O-chlorophenyl-isothiocyanate:

O-chloroaniline (10 g, 0.08 mol) was dissolved in 200 ml of ethyl acetate in a round bottom flask and 14 g (0.12 mol) of thiophosgene was slowly added to the magnetically stirred solution, using a Pasteur pipet. All reactions and manipulations were carried out in a well ventilated fume hood. The mixture was stirred and heated under reflux for two hours to permit the removal of the hydrogen chloride evolved in the reaction. At the end of this period, the reaction mixture was cooled and the solvent evaporated under reduced pressure (rotary evaporator). An additional portion of solvent was added and then evaporated; this process was repeated until the excess of the thiophosgene had been completely removed. The deep brown oil which remained was characterized by the broad CNS band at 2075 cm^{-1} in its infrared spectrum (Figure 4-1). The O-chlorophenyl-isothiocyanate was used without further purification.

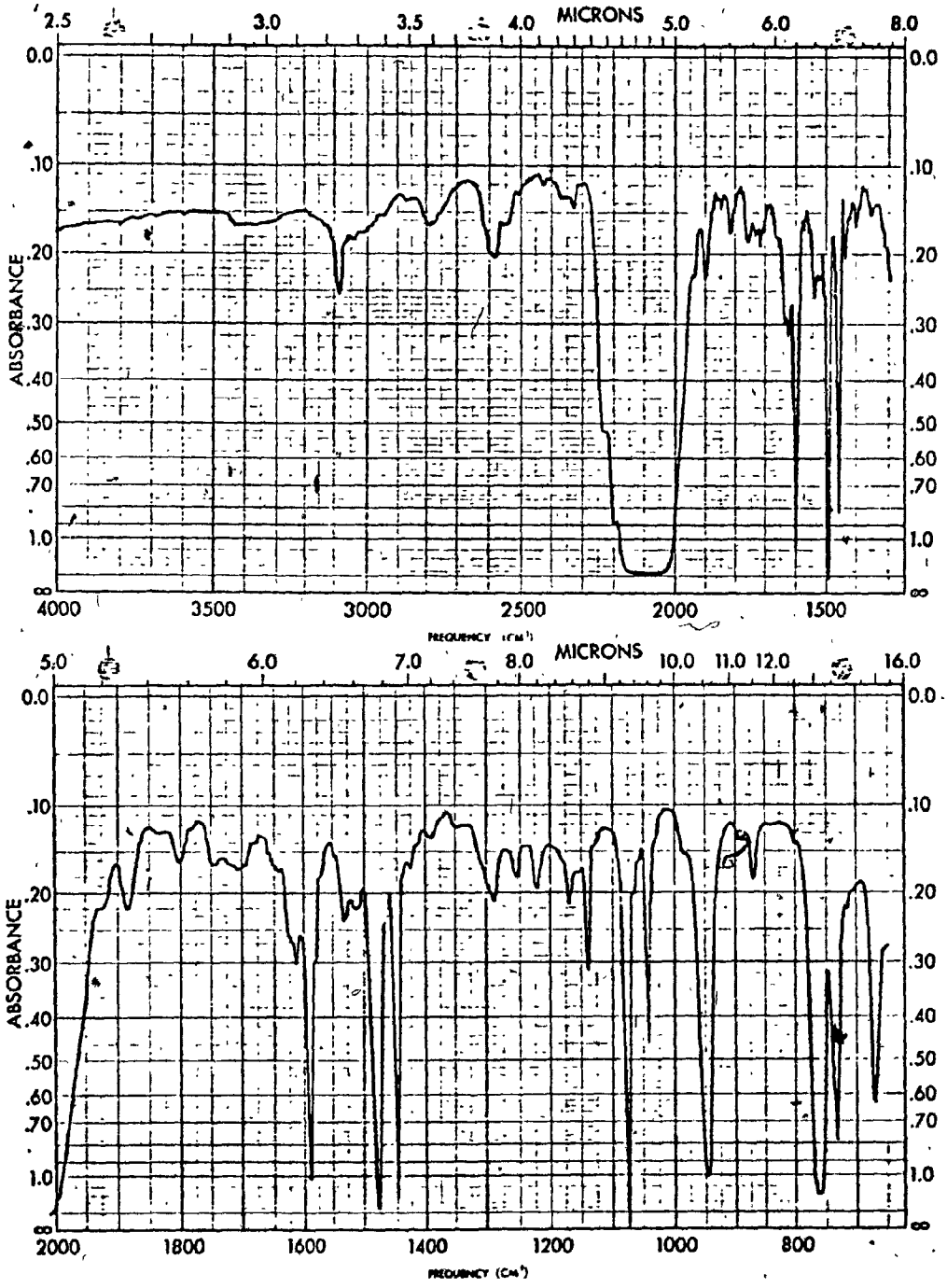


Figure 4-1 Infrared spectrum of O-chlorophenyl-isothiocyanate

GENERAL PROCEDURE FOR THE PREPARATION OF 3-ARYL-THIOHYDANTOINS

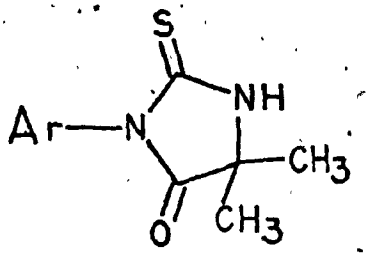
The method used for the preparation of these compounds has been described by Pujari and Rout [48]. A typical preparation was as follows:

3-(1'-naphthyl)-5,5-dimethyl-2-thiohydantoin:

A mixture of methylalanine (2.06 g, 0.02 mol), 15 ml of water, and 1.0 g (0.025 mol) of sodium hydroxide was magnetically stirred in a round bottom flask until solution was complete. A slight excess of α-naphthyl-isothiocyanate (4.6 g, 0.025 mol) in solution in 10 ml of ethanol was then added dropwise using a Pasteur pipet. The resulting mixture was heated under reflux for one hour, acidified with 6N hydrochloride acid, and heated under reflux again for a half hour. After the reaction mixture was cooled, the precipitate which formed was removed by filtration, dried, and recrystallized from absolute ethanol to yield 4.1 g (84%) of 3-(1'-naphthyl)-5,5-dimethyl-2-thiohydantoin, as white prisms (mp 259-269 ^{o}C with decomposition).

In certain cases, the thiohydantoin appeared as an oil when the solution was hot, or as a gum on cooling. In general, the precipitate was removed by filtration from the cooled solution, rinsed with acidified water, dried, then recrystallized several times from hot absolute ethanol. The thiohydantoins were obtained as colourless or off-white prisms, readily characterized by infrared (Figure 4-2) (see Table 4-2) and proton n.m.r. spectroscopy (Figure 4-3).

Table 4-2 Infrared characteristic bands and melting points of the 3-aryl-5,5-dimethyl-2-thiohydantoins



	Ar	Infrared Bands Position in cm-1 for: N-H	C=O	C=S	Melting Point in °C with decomposition
1	2'-Tolyl	3150	1760	1285	185
2	2',6'-Dimethylphenyl	3280	1725	1270	288 - 230
3	2'-Chlorophenyl	3150	1770	1285	210 - 212
4	2'-Bromophenyl	3175	1770	1285	191 - 193
5	2'-Iodophenyl	3240	1725	1275	235 - 238
6	2'-Nitrophenyl	3275	1735	1275	250 - 202
7	1'-Naphthyl	3145	1785	1285	259 - 269

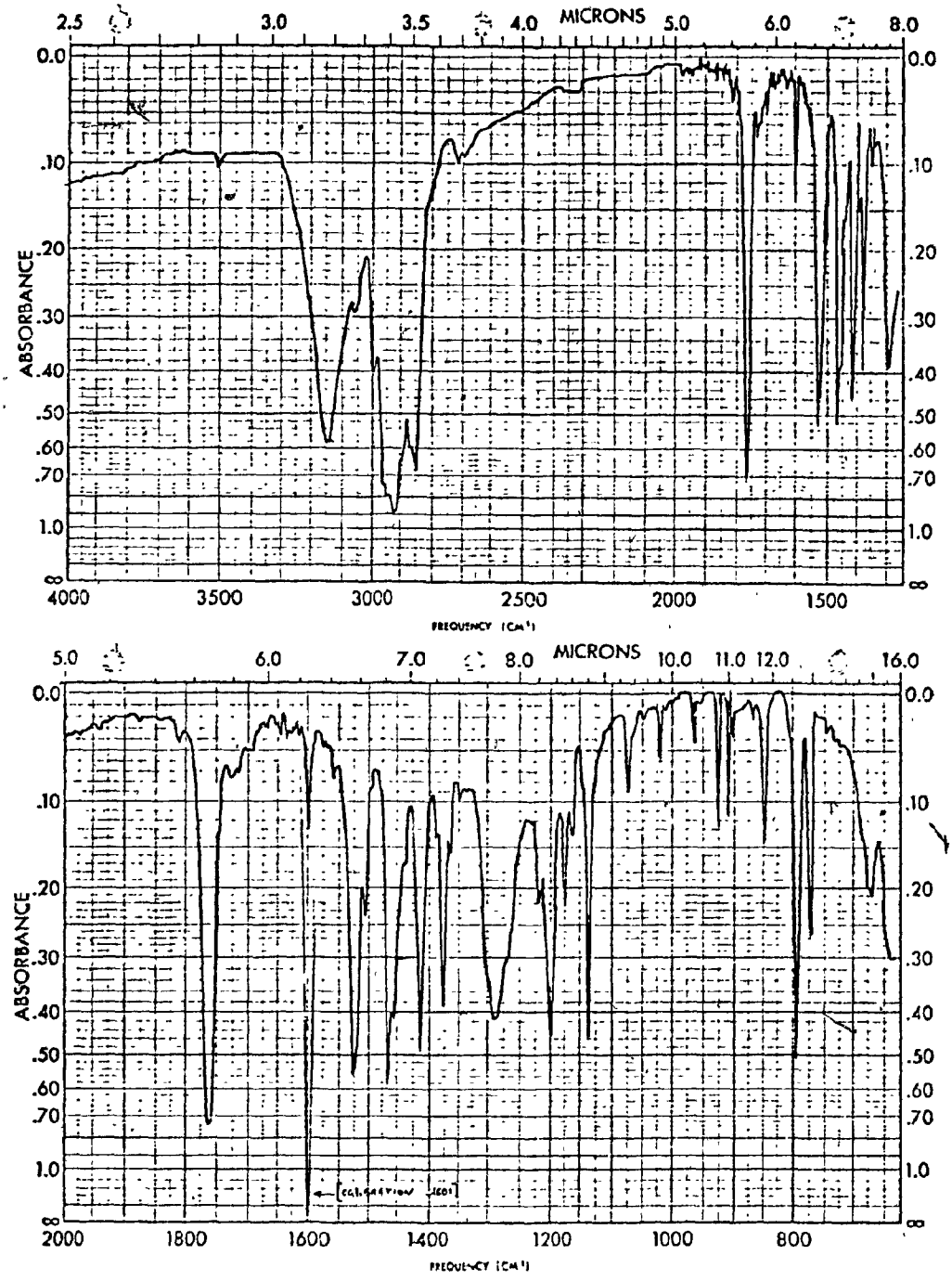


Figure 4-2 Infrared spectrum of 3-(1'-naphthyl)-5,5-dimethyl-2-thiohydantoin

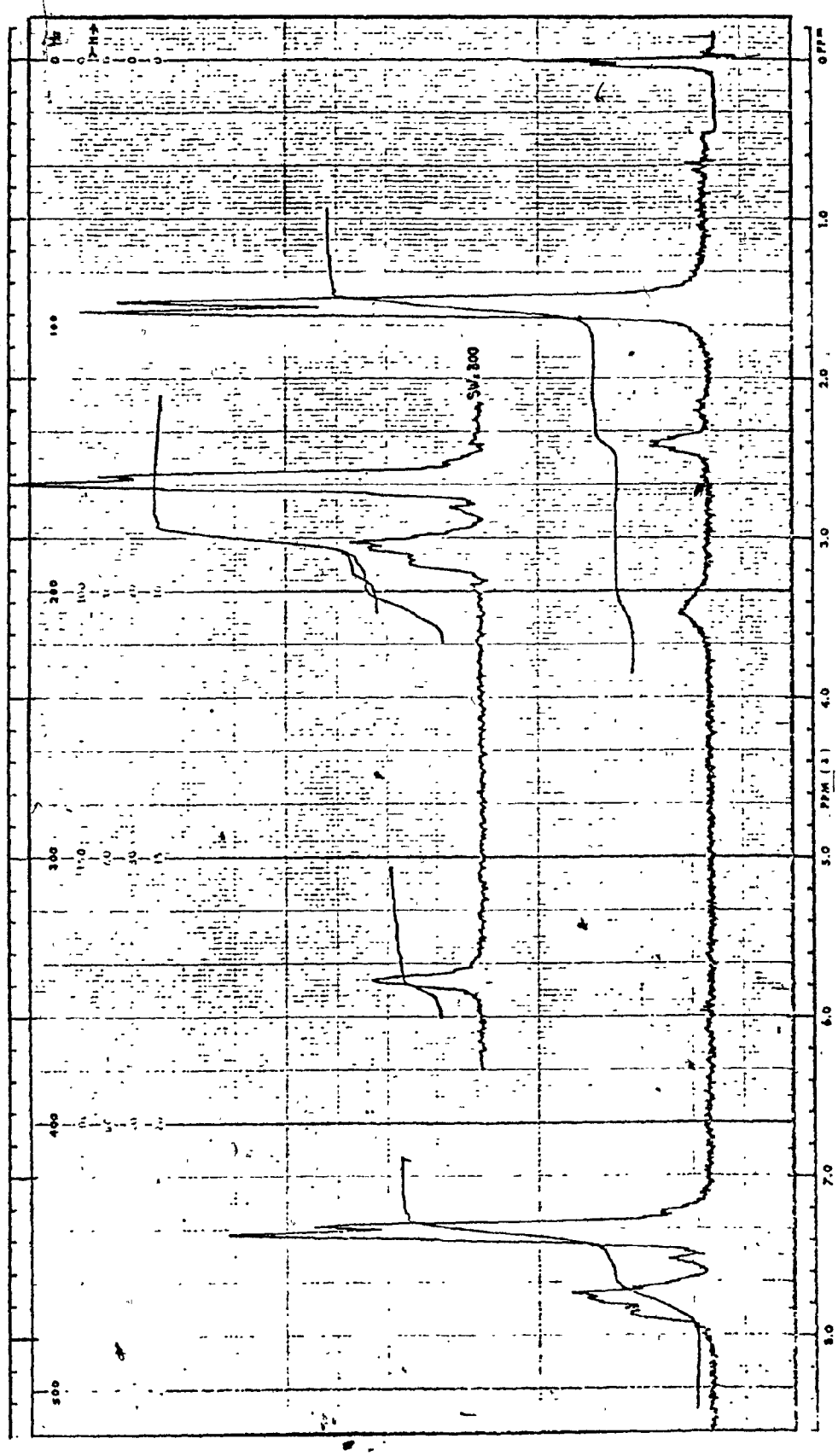
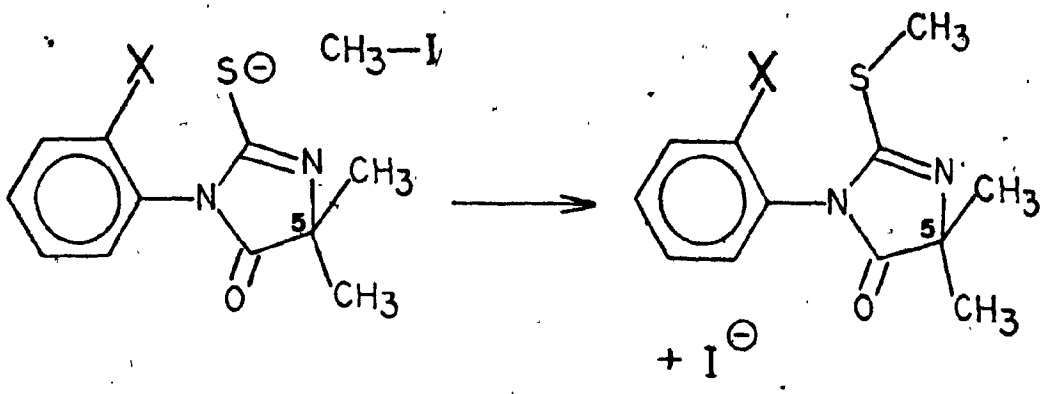


Figure 4-3 Proton n.m.r. spectrum (60 MHz) of 3-(1'-naphthyl)-5,5-dimethyl-2-thiohydantoin

GENERAL PROCEDURE FOR THE PREPARATION OF 1-ARYL-4,4-DIMETHYL-2-METHYLTHIO-2-IMIDAZOLIN-5-ONES

The method used for the preparation of these compounds has been described by Marckwalt, Newmark and Stelzner[50] Carrington and Waring [51], Komatsu [52] and Cattelin and Chabrier [53].

This procedure takes advantage of the acidity of the NH group, which loses a proton when the thiohydantoin is treated with a strong base[47]. The resulting anion may undergo a nucleophilic substitution reaction on an alkyl halide, in this case, methyl iodide, to yield the $S\text{-}CH_3$ derivative.



This reaction cannot be successfully carried out if there is a hydrogen atom on C_5; in this case, C_5 and O-methylation may also occur[47]. For this reason, only C_5 dimethyl compounds could be prepared for this study.

A typical preparation is described as follows:

1-(1'-naphthyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one:

3-(1'-naphthyl)-5,5-dimethyl-2-thiohydantoin (1.65 g, 0.005 mol) was dissolved in 25 ml of ethanol containing 0.3 g of potassium hydroxide, the mixture being stirred in a round bottom flask until solution was completed. An excess of methyl iodide (1 ml, 0.009 mol) was added and the mixture was gently heated under reflux for one hour. The solvent and the excess of methyl iodide were then removed (rotary evaporator) under reduced pressure. On addition of water to the residue, a precipitate formed; this was removed by

filtration, rinsed with water, dried and recrystallized several times from absolute ethanol to yield 1.2 g (84%) of pale yellow prisms (mp 143-144°C).

The product was identified through the absence of an N-H band, and the presence of a C = O (1740 cm^{-1}) and a C-S (790 cm^{-1}) band in the infrared spectrum (see Table 4-3) (Figure 4-4) and proton n.m.r. spectroscopy (Figure 4-5).

In some cases, an oily residue separated on the addition of water, after trituration. This gummy material was recrystallized from absolute ethanol as many times as necessary to obtain pure material. The preparation of the 1-(2'-tolyl)-compound, 1, required a different procedure at this point. When water was added, a precipitate failed to form. The mixture was extracted with chloroform, the organic phase washed with water and dried over anhydrous sodium sulfate. The gummy residue obtained on removal of the solvent was left in a refrigerator (at about 4°C) for one week, and then triturated with petroleum ether to yield a precipitate (about 3.3 g, 70%). Recrystallization of this material several times from methanol yielded colourless prisms (about 3.0 g, 64%, mp. 84 - 85°C).

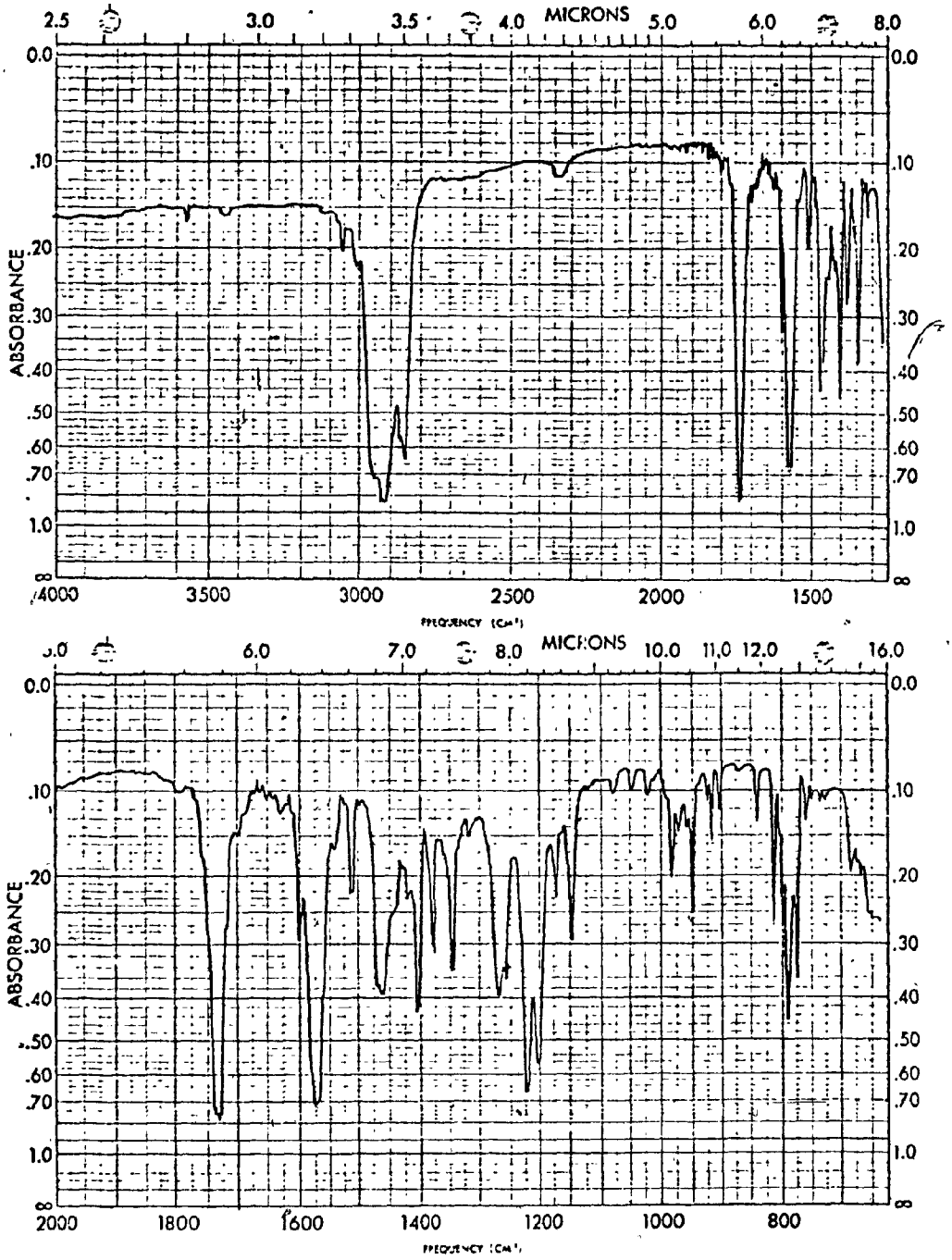


Figure 4-4 Infrared spectrum of 1-(1'-naphthyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (7).

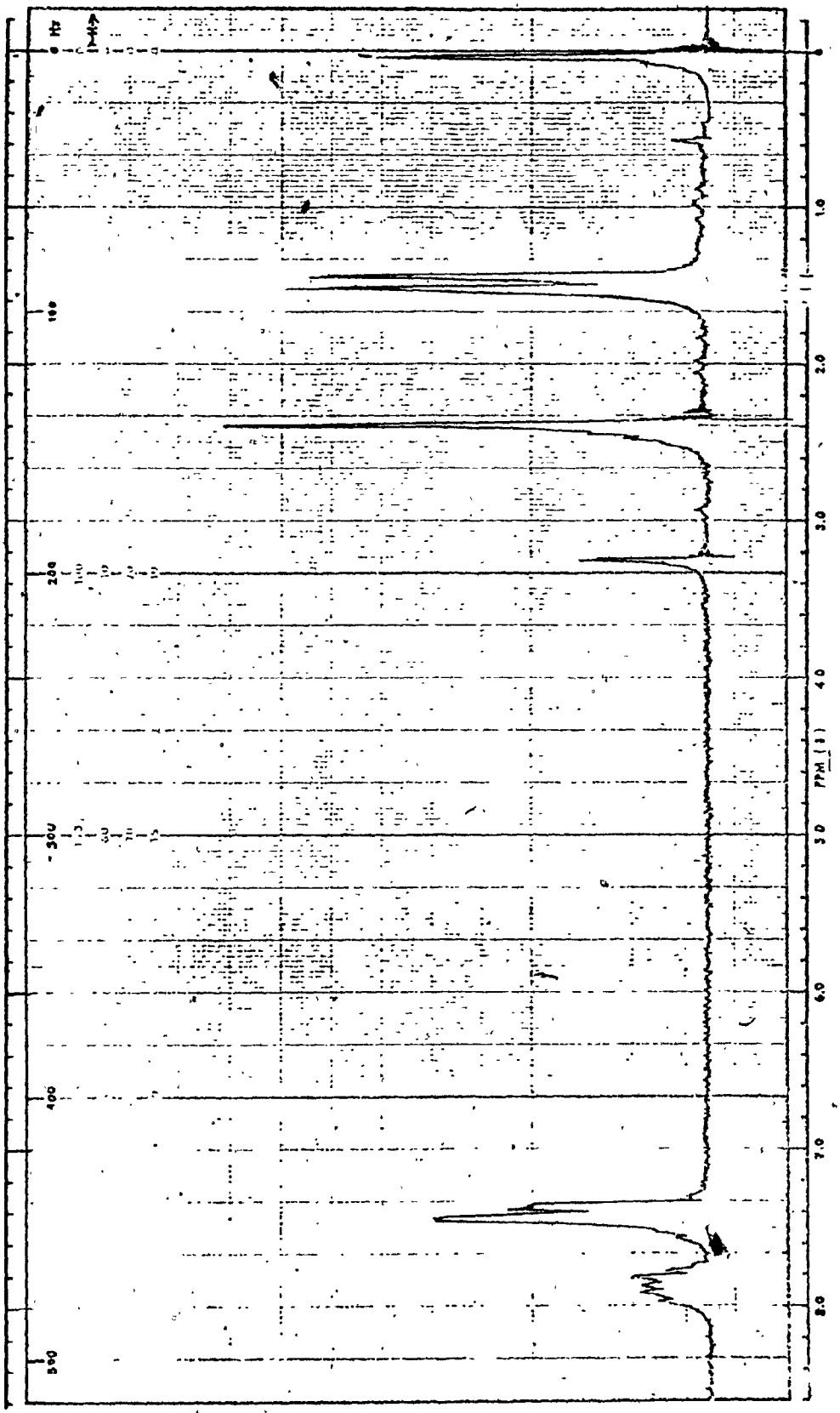
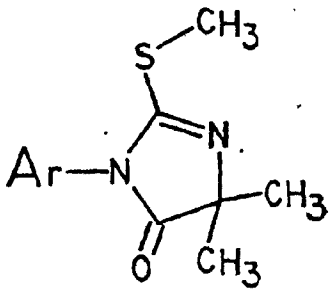


Figure 4-5 Proton n.m.r. spectrum (60 MHz) of 1-(1'-naphthyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (7).

Table 4-3 Infrared characteristic bands of 3-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones



	Ar	Infrared bands position in cm^{-1}				
		C=O		C-S-		NO_2
1	2'-Tolyl	1740	;	750	;	-
2	2',6'-Dimethylphenyl	1740	;	775	;	-
3	2'-Chlorophenyl	1740	;	760	;	-
4	2'-Bromophenyl	1735	;	760	;	-
5	2'-Iodophenyl	1730	;	760	;	-
6	2'-Nitrophenyl	1725	;	790	;	1530
7	1'-Naphthyl	1740	;	790	;	-

Melting Points:

Melting points were measured using a Gallenkamp melting point apparatus, and are uncorrected.

Elemental Analysis:

C, H and N analyses were carried out by Dr. C. Daesslé, 5757 Decelles street, Montreal. The previously recrystallized samples were dried at 60°C under reduced pressure (0.1 mm Hg) for two hours before being sent for analysis.

Thin layer chromatography:

At various stages during the syntheses, progress of the reaction was checked using thin layer chromatography on ready-made silica gel G or GF (fluorescent) plates (Analtech) of 250 micron thickness. The samples were dissolved in chloroform (if solid), or, if liquid, were used as such, and were spotted on a 0.5 cm band. The eluting system used was acetone-chloroform (1:9). Plates were developed in an unsaturated chamber, then dried in a stream of warm air.

The spots were identified using a short wave-length U.V. lamp (254 nm) or by developing in an iodine saturated chamber.

Infrared Spectra:

Infrared spectra were taken using a Perkin-Elmer model 237 B grating spectrophotometer. Solid samples were prepared as nujol mulls, while liquids were prepared as films between sodium chloride discs (Figures 4-1, 4-2 and 4-4).

Nuclear Magnetic Resonance Spectra:

60 MHz proton n.m.r. spectra were measured using a Varian A-60A spectrometer. Samples were prepared by dissolving approximately 50 mg of material in 0.5 ml of solvent (DMSO-d_6), and placing the solution in a clean n.m.r. tube. Prepared samples were stored in a refrigerator to prevent decomposition, and TMS was added to the solution, as an internal standard, before each spectrum was taken (Figures 4-3 and 4-5).

25.1 MHz carbon-13 n.m.r. spectra were measured as DMSO solutions, using an extensively modified Varian HA-100 spectrometer, operating in the pulse Fourier transform mode, with a homonuclear lock provided by the solvent signal, and interfaced to a Hewlett-Packard 2114A computer. The computer was used to time-average the free induction decays, and for Fourier transformation, phase correction, plotting, and other data processing. Two carbon-13 spectra were run at the University of British Columbia on a Varian CFT-20 spectrometer (20 MHz) as DMSO-d_6 solutions (Figures 4-6 and 4-7).

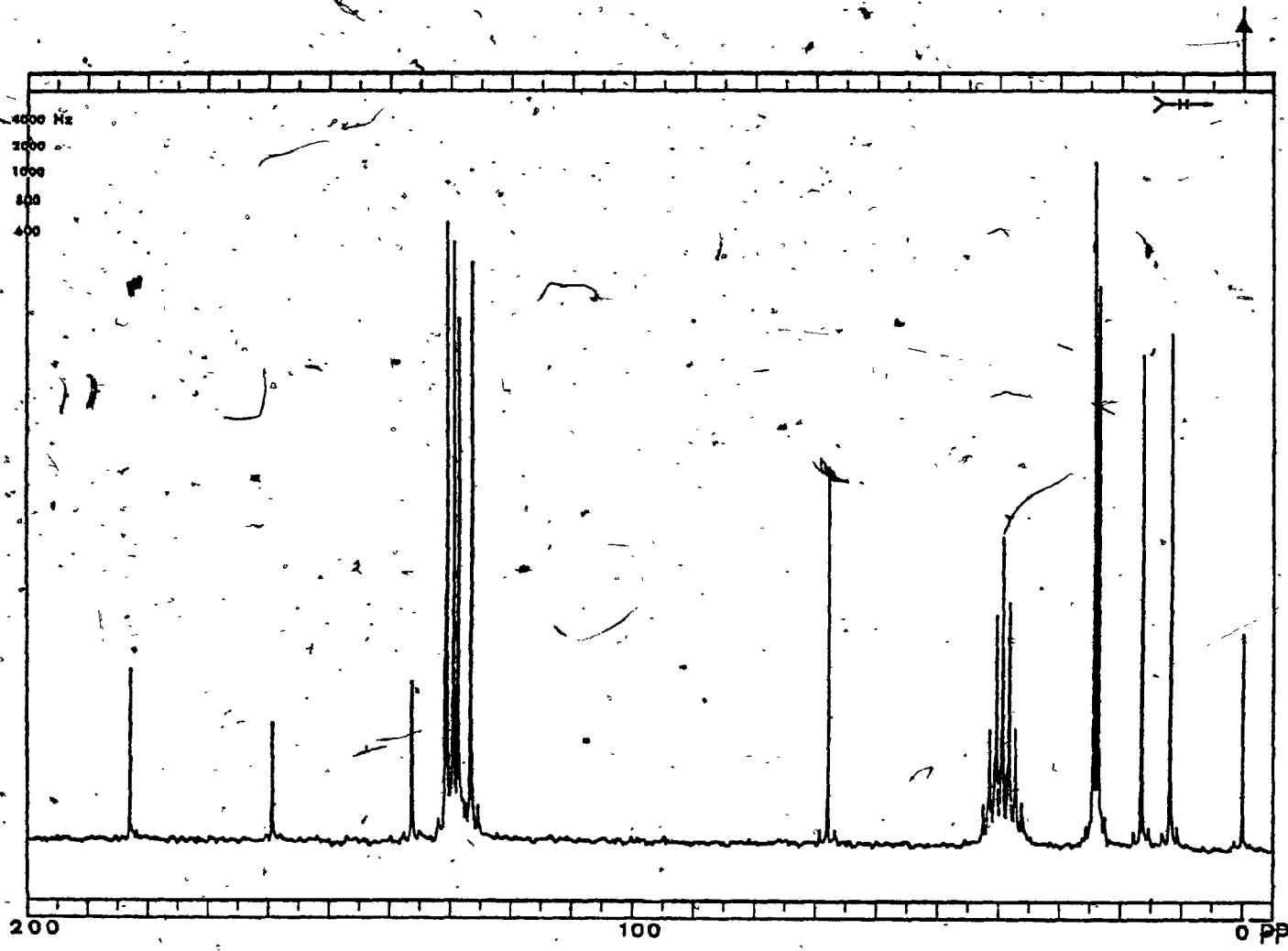


Figure 4-6 Carbon-13 n.m.r. spectrum of 1-(2'-tolyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (2).

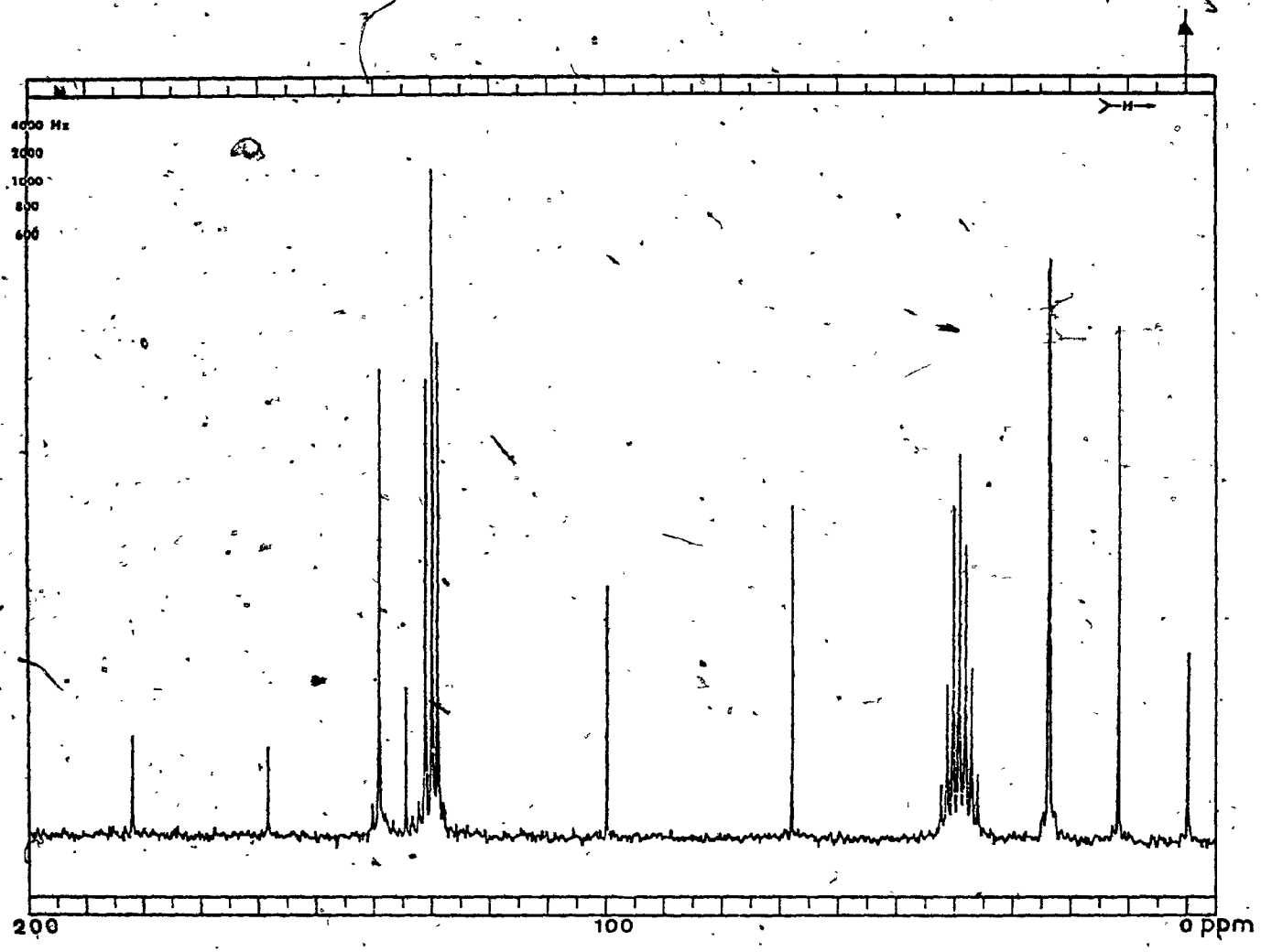


Figure 4-7 Carbon-13 n.m.r. spectrum of 1-(2'-iodophenyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (5).

270 MHz proton n.m.r. spectra were run at the University of British Columbia using a "home-built" spectrometer based on a Brucker WH-90 console, an Oxford Instruments superconducting magnet, and a Nicolet data system. $CDCl_3$ solutions were used (Figures 4-8, 4-9, 4-10, 4-11 and 4-12).

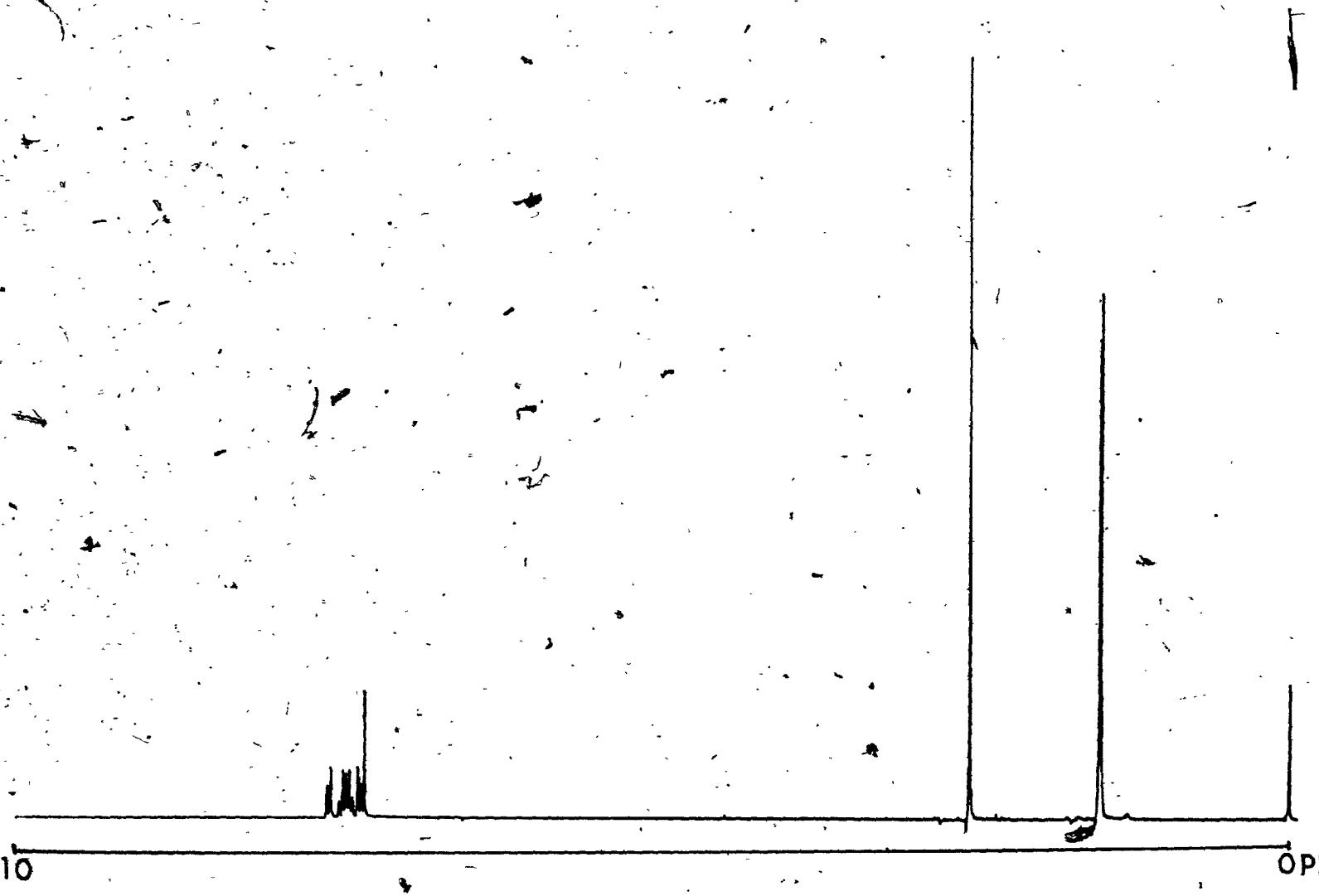


Figure 4-8 270 MHz proton n.m.r. spectrum of 1-(2'-chlorophenyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (3)

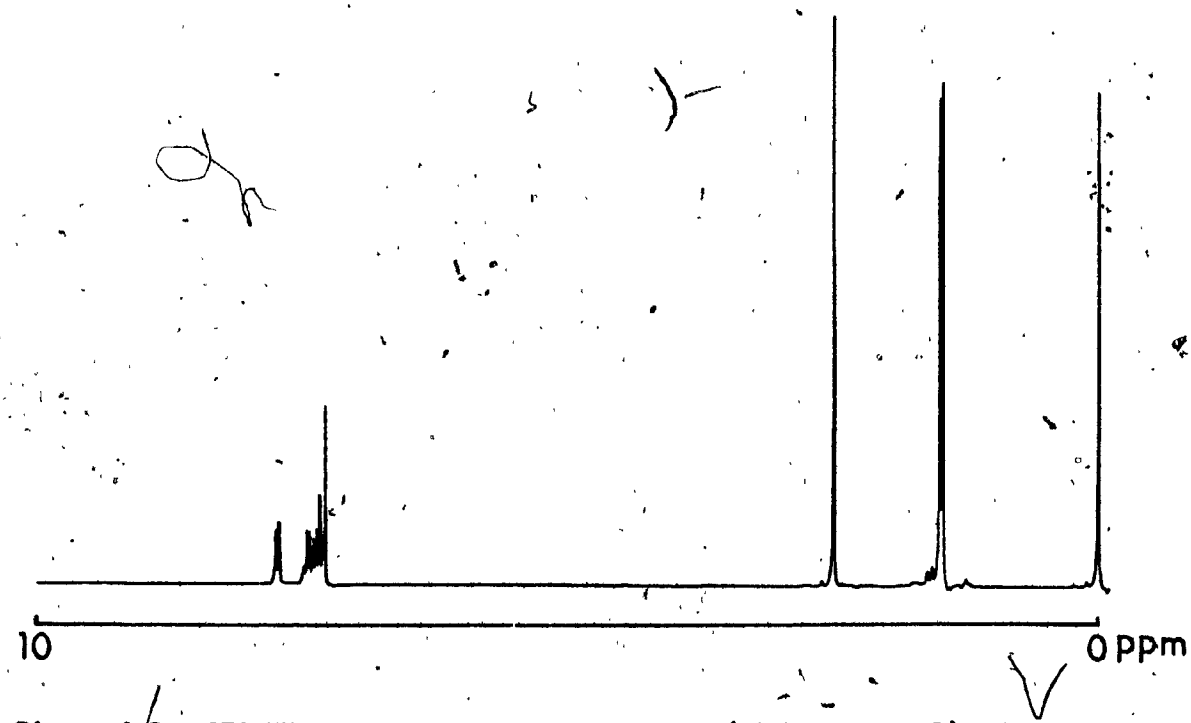


Figure 4-9 270 MHz proton n.m.r. spectrum of 1-(2'-bromophenyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (4).

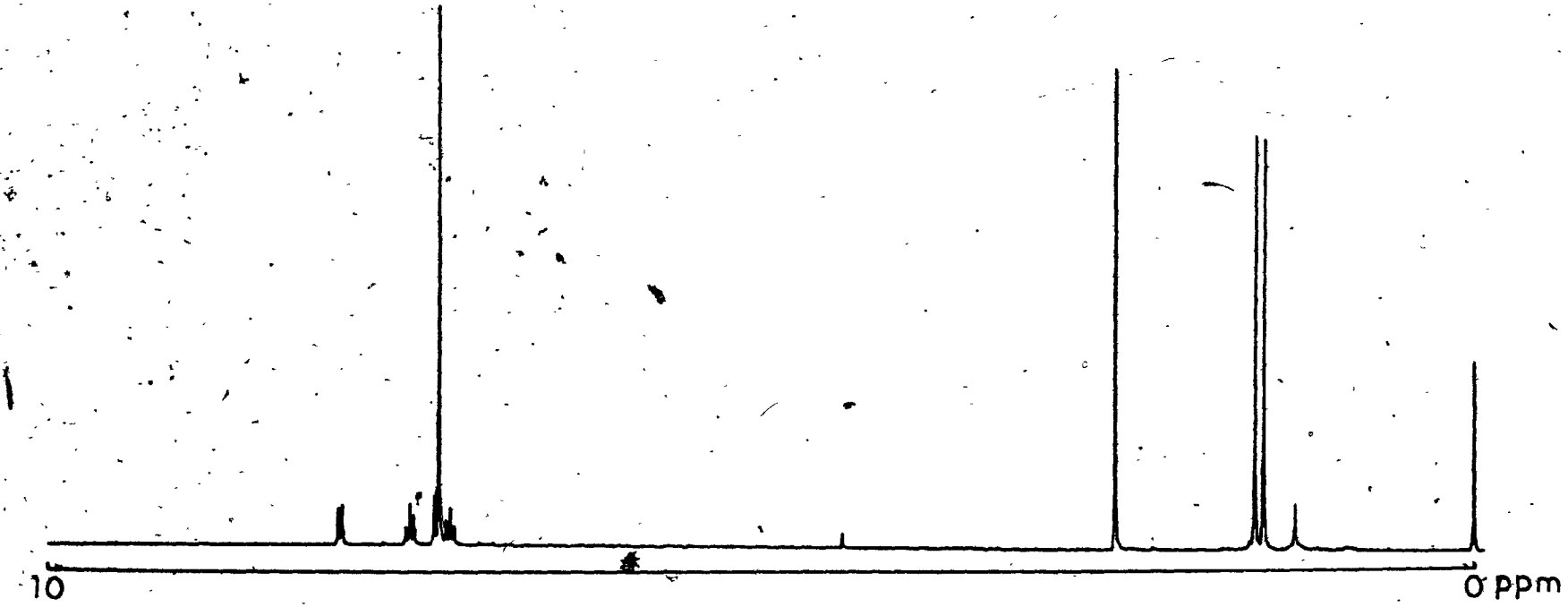


Figure 4-10 270 MHz proton n.m.r. spectrum of 1-(2'-iodophenyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (5).

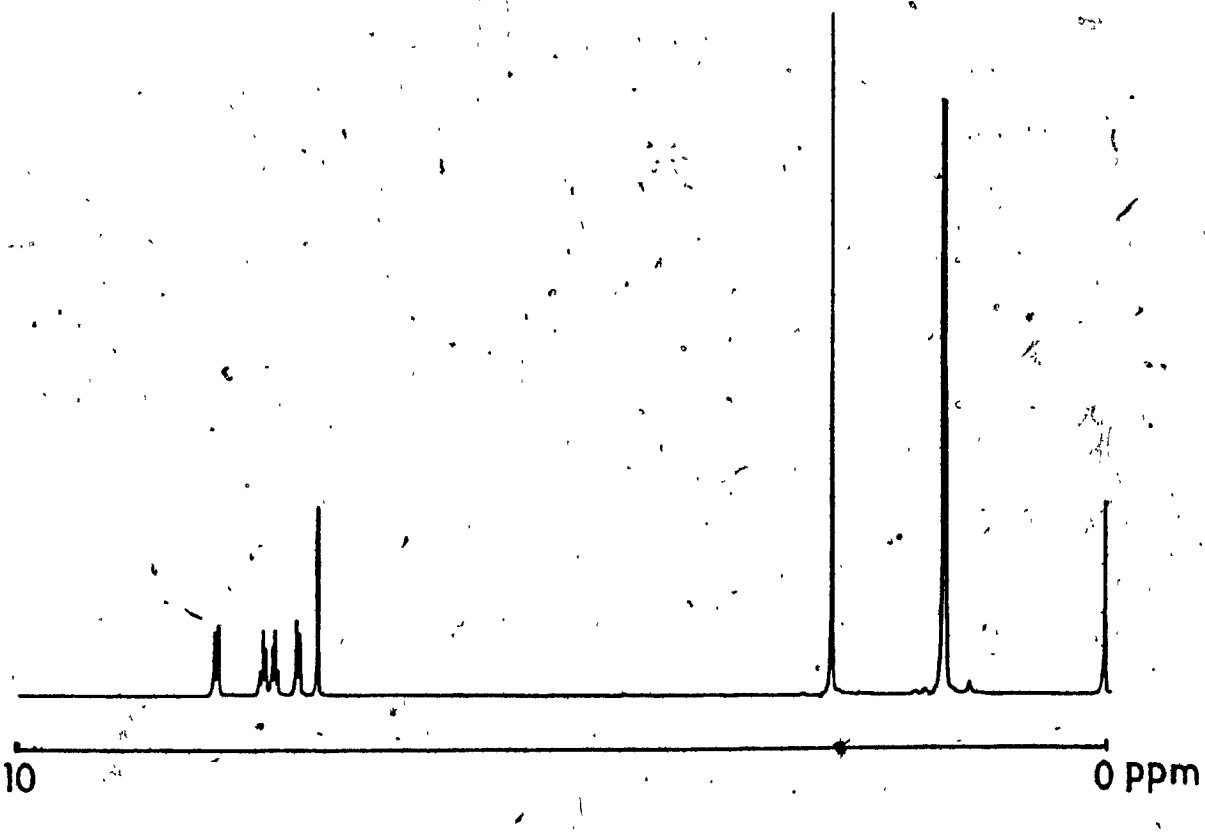


Figure 4-11 270 MHz proton n.m.r. spectrum of 1-(2'-nitrophenyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (6)

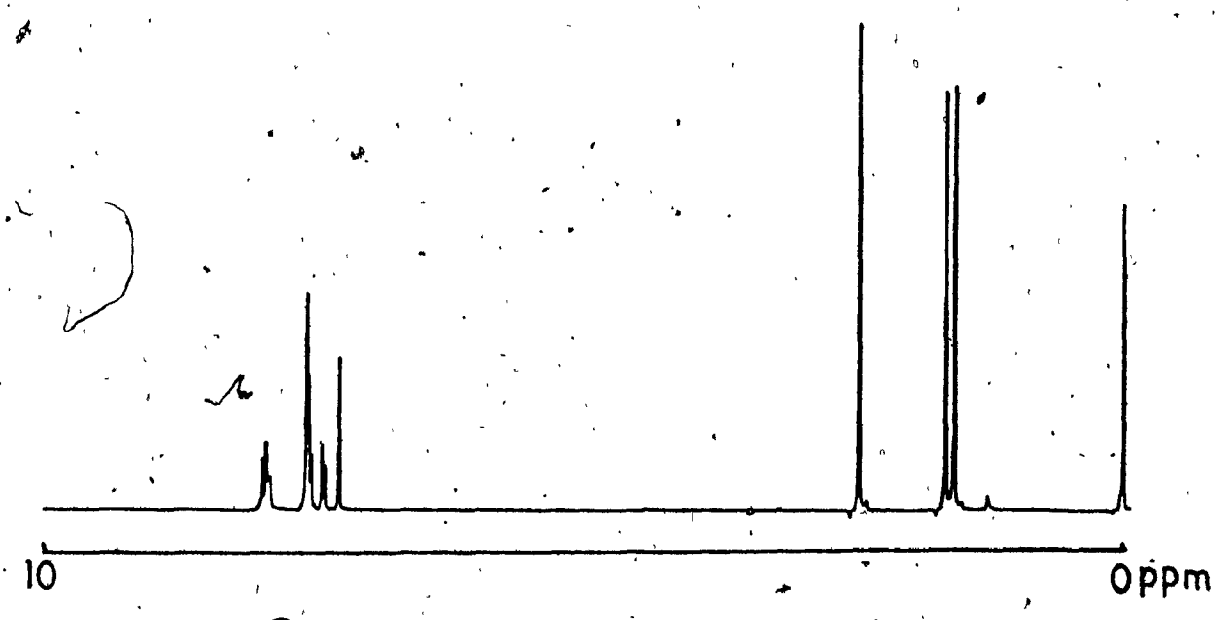


Figure 4-12 270 MHz proton n.m.r. spectrum of 1-(1'-naphthyl)-4,4-dimethyl-2-methylthio-2-imidazolin-5-one (7).

SUMMARY

A series of 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones has been prepared for the first time and their ^{1}H and ^{13}C n.m.r. spectra investigated. These compounds are potentially capable of undergoing biphenyl-like isomerism through restricted internal rotation about the aryl C-N bond. When the aryl group is unsymmetrically substituted, the rotational isomers are enantiomers, and the geminal dimethyl groups are diastereotopically related and should have distinct ^{1}H and ^{13}C chemical shifts under conditions of slow internal rotation. Slow rotation has been detected in the ^{1}H spectrum of three compounds, and in the ^{13}C spectrum of all but one compound.

Free energies of activation, $\Delta G^{\ddagger}$, were determined at the coalescence temperatures of the three compounds which showed separate gem dimethyl signals at 60 MHz. Rotational barriers are substantially lower in the imidazolinones than in similarly constituted thiohydantoins. These differences are interpreted in terms of differences in molecular geometries and the greater

ability of single than double bonds to relieve steric strain in the rotational transition state by bond bending.

Chemical shift differences between the gem dimethyl groups are a function of the anisotropic effects of substituents and of the aryl system; the latter is dependent on the dihedral angles between the ring systems. Dihedral angles are dependent on the steric bulk of the aryl group substituents, and also on their ability to affect conjugation between the ring systems.

The high dispersion of the 270 MHz ^{1}H spectra permitted complete computer-aided analysis of the aryl proton spectra of four compounds, so that the effects of substituents on aryl proton chemical shifts could be established.

The ^{13}C spectra of these compounds have well dispersed signals, and the heterocyclic group signals can be assigned readily. Assignment of the aryl group signals is more difficult, with the exception of the 1'- and 2'- carbons. Substituent effects on heterocyclic carbon chemical shifts have been identified.

With one exception, ^{13}C chemical shift differences between diastereotopically related gem dimethyl groups have been observed. The effects of aryl group substituents on the chemical shifts of the heterocyclic group carbon atoms have been interpreted in terms of the steric influence of the substituents on dihedral angles, with consequent influences on conjugation between the rings, and on the electronic influences of the substituents.

A survey of the ^{1}H spin-lattice relaxation rates (at 270 MHz) of the imidazolinones has been carried out in order to ascertain the sensitivity of the rates to the molecular environments of particular protons. A substantial dynamic range of relaxation rates was observed, indicating that these rates have considerable diagnostic potential. Individual relaxation rates have been interpreted in terms of the number and proximity of closely neighbouring protons. Some evidence was found for anisotropic motion of the molecules, and possibly for inter-ring relaxation.

Over all, this investigation has provided information on N-aryl imidazolinones which complements that already available on N-aryl thiohydantoins; it has provided ^{13}C data also related to restricted internal rotation, plus data characteristic of these compounds; finally, it has provided the first data on ^{1}H spin-lattice relaxation rates of heterocyclic compounds of this type, and has indicated the potential of the technique for supplying information on molecular structure.