

PROTON AND CARBON-13 NMR STUDIES OF SOME
5-MEMBERED HETEROCYCLIC COMPOUNDS

MOHAMMAD ASHIQUE KHADIM

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ ۝

اقْرَأْ بِاسْمِ رَبِّكَ الَّذِي خَلَقَ ۝

خَلَقَ الْإِنْسَانَ مِنْ عَلَقٍ ۝

اقْرَأْ وَرَبُّكَ الْأَكْرَمُ ۝

الَّذِي عَلَّمَ بِالْقَلَمِ ۝

عَلَّمَ الْإِنْسَانَ مَا لَمْ يَعْلَمُ ۝

In the name of Allah, the Beneficent, the Merciful.

Read: In the name of thy Lord who created.

Created man from a clot.

Read: And thy Lord is the Most Bounteous,

Who taught by the pen,

Taught man that which he knew not.

(Al-Quran, 96:1-5.)

ABSTRACT

PROTON AND CARBON-13 NMR STUDIES OF SOME
5-MEMBERED HETEROCYCLIC COMPOUNDS

Mohammad Ashique Khadim, Ph.D.

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SECTION 1.

Proton spin-lattice relaxation rates (R_1 values) have been measured, at 270 MHz and 23° , for a series of N-aryl-1-isindolinones. A normalization procedure has been used to enable comparison of R_1 values in different compounds by minimizing the effects on relaxation rates of changes in motional correlation times accompanying changes in substitution patterns. A substantial (4.3 fold) dynamic range of R_1 values has been observed, and individual values have been correlated with the molecular environments of the nuclei. There is evidence for an inter-ring relaxation process.

SECTION 2.

A series of 1,3-diaryl substituted 2-thio-4-imidazolidinones and N-aryl-1-isindolinones were synthesised. The barriers to internal rotation of the N-aryl moieties and their dependence on the nature of the N-aryl substituents have been examined. The

vicinal coupling constants between the 1- and 5-protons in the 2-thio-4-imidazolidinones appear to be fairly insensitive to the dihedral angle between the C-H and N-H bonds. It is concluded that the conformation of the hetero ring is insensitive to aryl group substituents.

SECTION 3.

From carbon-13 NMR data for a series of 1,3-diaryl-2-thio-4-imidazolidinones various effects of aryl substituents on the hetero ring carbon atoms have been examined. In these compounds, steric and polarity effects of aryl substituents appear to be negligible as compared to electronic effects. However, the reverse seems to be true for the 3-aryl analogues.

SECTION 4.

Consistently deshielding carbon-13 δ -shifts resulting from the presence of ortho aryl substituents have been measured for the 3-methylene carbon atoms of some N-aryl-1-isoindolinones (0.12 - 3.25 ppm) and for the carbonyl carbon atoms of these compounds and the corresponding N-aryl isoindole-1,3-diones (0.04 - 1.47 ppm). Low temperature (-75° and -150°) proton NMR studies indicate that steric barriers to internal rotation about the aryl C-N bonds in the N-aryl 1-isoindolinones are low. The compounds with the bulkiest ortho aryl substituents tend to show the largest δ -shifts (particularly for the 3-methylene carbons).

SECTION 5. EXPERIMENTAL.

DEDICATION

TO

***** My Parents Mr. and Mrs. Khadin

***** My Beloved Wife Ummaysalma

***** My Learned Prof. L.D. Colebrook

Whose Patience and Encouragement
Has Made This Thesis Possible.

and to my little Amma Nur.

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Praise be to Allah, Lord of the Worlds.

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GENERAL

INTRODUCTION

In our laboratories, considerable attention has been paid to the study of hindered internal rotation about the aryl C-N bond in N-aryl cyclic amides. As part of our continued interest in the study of barriers to internal rotation in heterocyclic compounds, we have synthesized a series of 1,3-diaryl-2-thio-4-imidazolidinones and 2-aryl-1-isoindolinones. We have investigated, in this study, proton and carbon-13 nuclear magnetic resonance spectra of these compounds in order to obtain information on barriers to internal rotation of the N-aryl groups and their dependence on the nature of the N-aryl substituents; and to study various interactions operative in these molecules in relation to their ground state stereochemistry.

Proton NMR line shape analysis is the most commonly employed technique to the solution of problems of structural isomerism involving restricted rotation. When applied to the 1,3-diaryl-2-thio-4-imidazolidinones, only

three compounds with bulky N-aryl moieties and methyl substituents at the C-5 carbon showed restricted internal rotation about the 1-aryl nitrogen bond. All other compounds in this series failed to exhibit individual signals corresponding to the diastereomeric rotamers at temperatures as low as -160° . In view of there being a substantially bulky and polar thiocarbonyl group in the vicinity of the N-aryl moiety, this observation is somewhat unexpected. We undertook a carbon-13 NMR study of these compounds and interpreted the spectra in terms of ground state rotamers. (Our aim was to look into the effects of substituents on the aryl moiety and establish if there were steric or electronic interactions between various segments of these molecules by examining their carbon-13 shielding data. These results have shown lack of detectable steric interaction between the aryl ortho substituents and the C-5 groups in the ground state. So it was decided to undertake a detailed investigation concerning the behaviour of these systems.

In view of the reports by Colebrook et. al. that the 5-methyl- and 5,5-dimethyl- 1-aryl-imidazolidine-2,4-diones show substantial barriers to rotation about the N-aryl bond, 11.0 - 12.6 (26), and 18.0 - 21.2 (28) kcal/mol, respectively, it was desirable to look for a system which should have molecular frame-work similar, at least partially, to these compounds. The N-aryl-1-isindolinones

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provided a good example. Particularly, we were encouraged to note that Levin et. al. (71) and Seymour and Jones (93) have observed non-equivalence of the N-benzyl protons in N-benzyl-1-isoindolinones and N-benzyl-N-(2-chlorophenyl) acetamide, respectively. It was of interest to us to investigate if slow rotation about the aryl C-N bond in N-aryl-1-isoindolinones at lower temperatures could render the methylene or bulky ortho substituents non-equivalent.

It was observed, unfortunately, that in all of the N-aryl-1-isoindolinones studied, the methylene or aryl ortho substituent protons exhibited rather sharp singlets with no indication of appearance of signals due to non-equivalency at temperatures as low as -160° . Thus, barriers to internal rotation in these compounds were found to be very low.

Under these circumstances, we were interested to further pursue the matter. In order to explain our results of very low barriers to internal rotation, we decided to look into the solution geometry of these molecules in detail. The phenomenon of proton spin-lattice relaxation is related to a variety of molecular properties, in particular, molecular motions. We decided to exploit the geometric dependencies to inter-proton relaxation contributions by measuring their R_1 - rates. The proton relaxation studies, in conjunction with their carbon-13 shielding data enabled us to establish the nature of intramolecular steric or electronic interactions in these systems.

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The division of the thesis under study into various sections is merely a matter of convenience to clearly present the results of our studies. This thesis consists of five (5) sections as listed below :

Section 1 : Proton Spin-Lattice Relaxation Studies on N-Aryl-1-Isoindolinones.

Section 2 : Proton NMR Line Shape Analysis of 1,3-Diaryl-2-Thio-4-Imidazolidinones.

Section 3 : Carbon-13 NMR Studies on 1,3-Diaryl-2-Thio-4-Imidazolidinones.

Section 4 : Carbon-13 NMR Studies on N-Aryl-1-Isoindolinones.

Section 5 : Experimental work.

SECTION 1.

A

PROTON SPIN-LATTICE

RELAXATION STUDY

OF

1-ISOINDOLINONES

INTRODUCTION

The study of spin-lattice relaxation is important for two reasons. Firstly, it provides information about the dynamics of the spin-bearing molecules and also the spin-dependent interactions which couple the nuclear spins to the environment, the lattice. Secondly, it provides a knowledge of spin-relaxation times which is necessary for the operation of NMR spectrometers and in the interpretation of many spectroscopic observations.

The conventional procedure using high-resolution NMR spectroscopy as a tool for studying the structure and stereochemistry of organic molecules in solution is well-known: three sets of NMR parameters, the chemical shifts, coupling constants, and integrated areas, are derived from the measured spectrum and these parameters are then used, either singly, or in some suitable combination, as the basis for the structural assignment. Powerful as it is, this approach neglects the fact that each spectrum contains, implicitly at least, two further sets of magnetic resonance parameters; these are the spin-lattice relaxation times (T_1 - values) and the spin-spin relaxation times (T_2 - values). These parameters may also be expressed as

relaxation rates, R_1 and R_2 , where $R_1 = 1/T_1$ and $R_2 = 1/T_2$. Recent instrumental developments have made possible the routine measurement of spin-lattice relaxation times.

The theory of nuclear spin-relaxation is well-developed and is described in the texts by Pople, Schneider and Bernstein (82), Abragam (1), Slichter (97), Goldman (45), Parrar and Becker (37), and more recently by Mullen and Pregosin (78).

The phenomenon of spin-lattice relaxation has long attracted the attention of physicists and some chemical physicists. Largely as a result of their effort, there is an extensive literature both on methods for measuring T_1 - values and on the theory that enables these parameters to be related to a wide variety of molecular properties and, importantly, molecular motions. Until recently, most practising chemists, even those with an active interest in NMR spectroscopy, have largely neglected the phenomenon of spin-lattice relaxation, with some exceptions. There have been many reasons for this neglect and of these the most cogent is that until very recently, the methods developed by physicists for measuring T_1 - values have been incompatible with studies of the complex molecular species which are of chemical interest. However, with the development of Fourier transform (FT) techniques, it has become possible to measure, on a routine basis, the T_1 - value of any resonance that can be clearly resolved in an NMR spectrum, and hence to study systems which are chemically quite complex.

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Several laboratories, notably that of Allerhand (2-4) and Levy (70) have measured the longitudinal relaxation times of carbon-13 in natural abundance using P T methods. It is interesting to note that the majority of the laboratories equipped with P T NMR spectrometers appear to have somewhat neglected relaxation studies of other magnetic nuclei, particularly of protons. However, recently a number of reports have been published on the experimental aspects of proton relaxation studies; most notable of these is a series of proton-relaxation studies on-mono-, di- and polysacchride molecules by Hall (50) showing the stereo-specific dependencies of relaxation times.

It is not appropriate to attempt to give here a full account of the phenomenon of spin-lattice relaxation; however, a brief description is important.

SPIN-LATTICE RELAXATION :

The phenomenon of spin-lattice relaxation is associated with the transfer of magnetic energy between the magnetic nuclei under study (the 'spins') and their environment (the 'lattice'). There are a number of distinct mechanisms, listed below, whereby this energy transfer can be effected :

1- Dipole-dipole relaxation

- a- intramolecular
- b- intermolecular
- c- paramagnetic

- 2- Spin-rotation relaxation
- 3- Quadrupolar relaxation
- 4- Scalar coupling
- 5- Chemical shift anisotropy

1- Dipolar Relaxation :

When the nucleus undergoing relaxation is directly bonded to a second nucleus possessing a magnetic spin, then we have the possibility of an efficient relaxation mechanism. e.g. when a proton is directly bonded to a carbon-13 nucleus, the two spins can each be considered as small dipoles oriented along the $^1\text{H} - ^{13}\text{C}$ bond. The proton will experience a small field due to the C-13 nucleus. The magnitude of this field depends on the magnitude of the two dipoles and the angle θ of their line of interaction with respect to the applied field. The magnitude of the field, H , created at the proton is given by

$$H \propto (3 \cos^2 \theta - 1) / r^3 \quad - - - \text{Eq. 1.}$$

As the molecule tumbles in solution, variation in θ will cause fluctuations in the field H . Relaxation can be induced by any oscillating electric or magnetic field which has a component at, or close to, the Larmor frequency of the nucleus concerned.

The contributions made by the dipolar mechanism are normally found to decrease with increasing temperature.

2- Spin-Rotation Relaxation :

This arises due to fluctuating magnetic fields generated by the movement of atoms within the molecule and is normally only important for small highly symmetrical groups such as short aliphatic side chains or methyl groups.

Although such segmental motion results in an increase in spin-rotation relaxation, it is normally accompanied by a decrease in the effectiveness of the dipolar relaxation mechanism and, since this is normally the dominant mechanism, by an over-all increase in the relaxation time (i.e. low rate of relaxation). In addition to this, spin-rotation relaxation does not give rise to NOE (nuclear Overhauser effect) enhancement (in the case of carbon signals) and, consequently, the signals arising from carbon-13 nuclei which undergo appreciable relaxation via this mechanism often possess characteristically low signal intensities.

3- Quadrupolar Relaxation :

This mechanism is important for nuclei with spins greater than $1/2$ (such as ^{14}N , ^2H , ^{35}Cl , ^{37}Cl , ^{79}Br and ^{81}Br). Such nuclei possess a quadrupolar moment which gives rise to an electric field gradient at the nucleus, providing a highly efficient relaxation mechanism. It is the effectiveness of this mechanism which is responsible for the lack of any observable ^1H or ^{13}C couplings to chlorine and bromine despite the fact that they both possess nuclear spin.

4- Paramagnetic Relaxation :

The presence of dissolved oxygen or any other paramagnetic impurities in a sample can have a marked effect on the relaxation times. This is because the magnetogyric ratio of an electron is ≈ 657 times greater than that of a proton. Consequently, the presence of even trace amounts of such impurities can provide very efficient relaxation by a dipolar mechanism. This effect is sometimes utilized by deliberately adding paramagnetic material [usually $\text{Cr}(\text{acac})_3$] to a sample possessing long relaxation times.

5- Scalar Coupling :

Scalar coupling of one magnetic nucleus to another may give rise to a fluctuating field at the site of the nucleus of interest, provided the interacting spin undergoes rapid change of its spin state, or, in other words, if it relaxes rapidly. On condition that $1/T_{1sc}$ (sc for scalar coupling) $\gg 2\pi J$, i.e. if the relaxation rate of the second nucleus of spin S is fast compared to $2\pi J$, where J stands for the scalar spin-spin coupling constant, no spin coupling will be observed. However, the nucleus of interest (proton) to which spin S is spin-coupled experiences a local field that fluctuates at a frequency $1/T_{1sc}$. This condition is often satisfied for such quadrupolar nuclei as ^{14}N , ^{35}Cl , ^{37}Cl , ^{79}Br , ^{81}Br etc. Scalar relaxation is frequently found to be a dominant mechanism for transverse relaxation, to the

extent where it manifests itself in appreciable line broadening.

6- Anisotropic Shielding :

If the chemical shielding is not isotropic, the secondary magnetic field due to electronic currents will not generally be parallel to the applied field, and there will, therefore, be a component in the perpendicular direction. As the molecule rotates or tumbles, this component will oscillate or fluctuate and may cause transitions between the nuclear spin states. This mechanism of relaxation requires the presence of an external field H_0 and will lead to a spin-lattice relaxation time dependent on the magnitude of H_0 even when the correlation time, τ_c , (see later) is small.

A rapidly fluctuating magnetic field, generated and located in the lattice, interacts with the rapidly precessing nuclei of interest and thereby mediates in the energy transfer process. In principle, and often in practice, several of these different relaxation mechanisms operate simultaneously; and in these circumstances, the spin-lattice relaxation time measured experimentally is a composite value and contains contributions from each of the several mechanisms. If this were always the case, then it is quite probable that this entire phenomenon would have little, or no, relevance to organic chemists since it is a difficult task to derive from the experimental value of T_1 the individual contributions from several different mechanisms.

Fortunately, it is often possible to conduct experiments in which one of these mechanisms, the intramolecular dipole-dipole (DD) mechanism, dominates the relaxation; and under optimum conditions is the only operative one. In practice, this requires the isotropic motion of the molecules to be studied as a dilute solution (~ 0.1 M) in a magnetically inert solvent; both of these requirements minimize contributions from intermolecular effects. The requirement of a magnetically inert solvent means that the solvent should contain neither fluorine nor proton substituents, and in practice, it suffices by using a deuterated substance, which has the added convenience of providing a heteronuclear-lock signal for the spectrometer. Experimental measurements under these conditions are convenient. The factors influencing dipole-dipole relaxation become apparent when one studies the mathematical form of the intramolecular DD mechanism, Equation 2, for the contribution that one donor nucleus, D, makes to the spin-lattice relaxation of a second receptor nucleus, R, (8).

$$R_1 = 1/T_1 \propto \frac{\gamma_D^2 \gamma_R^2}{(r_{D \rightarrow R})^6} \tau_c (D \rightarrow R) \quad \text{Eq. 2.}$$

where γ_D and γ_R are the magnetogyric ratios of the two nuclei involved, r is the internuclear distance between D and R, τ_c is a motional correlation time (see later) for the $D \rightarrow R$ vector, and R_1 is the relaxation rate (sec^{-1}). The first important point is that for the relaxation of a proton, R, the most probable source of relaxation is another proton, D; this follows from the

fact that only protons have significantly high values of γ . (The other nucleus of high magnetogyric ratio is Fluorine-19). Second, the efficiency of this inter-proton relaxation is critically dependent on the inter-nuclear distance; hence it may be anticipated that there will be geometric dependencies to inter-proton relaxation contributions, and consequently, to the composite T_1 (R_1) values. Third, the relaxation is dependent on the correlation time τ_c (see later) which is related to the rate of rotation of the molecule in solution.

Even if it is justifiable to assume that the intramolecular DD mechanism is the exclusive mechanism for proton relaxation, it is still not clear that a unique R_1 - value for an individual proton-transition can be defined: this is because the presence of cross-relaxation^{98,99,73} can cause (a) significant differences between the R_1 -values measured on the individual components of a spin-coupled multiplet, and (b) deviations from a pure, exponential rate of recovery of equilibrium magnetization (51, 108)

Correlation Time, τ_c :

The correlation time serves as a measure of the average time that two nuclei remain in a given relative orientation. For molecular rotation the correlation time may be thought of approximately as the length of time that the molecule requires on the average to rotate through an angle of a radian while for the translational motion, the correlation time is roughly the time it takes the molecule to move one molecular diameter. The rotational

process is related to intramolecular relaxation and the translational process is related to intermolecular relaxation.

The correlation time can also be defined as a measure of the time taken for the local fluctuating field to 'lose memory' of a previous value.

The correlation time is dependent on the temperature and the concentration of the sample, and the viscosity of the solvent, and can be further complicated by anisotropic motion of the molecule as a whole, and by the freer motion of any side chains and methyl groups. Complications associated with correlation time are not generally important for many small or simple molecules.

MEASUREMENT OF SPIN-LATTICE RELAXATION TIMES :

Pulse methods provide the most versatile technique for measuring T_1 -values over a wide range. The simplest conceptual model upon which a discussion can be based is the 'rotating reference frame' model. The most commonly employed procedure, 180 - t - 90 (inversion-recovery) sequence is illustrated in Fig. IN-1.

Consider an ensemble of magnetically equivalent nuclei (spins), subject to the influence of the laboratory magnetic field, H_0 . At thermal equilibrium between the spins and the lattice, this ensemble will have a net macroscopic magnetic moment which will, in the rotating reference frame, be directed along the z-axis, which is also the direction of H_0 . In Fig. IN-1 this magnetic moment is represented by a vector 'arrow', whose length is intended to indicate the total amount of magnetization present. When this vector lies along the z-axis, no signal is detected by the spectrometer, which is designed to respond to that component of the magnetization which lies in the x,y-plane. Thus, to assay the amount of magnetization along the z-axis at any particular time, it is necessary to tip the magnetization vector through 90° into the x,y-plane. This is easily done by applying suitable radiofrequency power at the appropriate frequency, in the form of a short pulse (a 90° -pulse), and providing this is done sufficiently rapidly compared with the rate of change of

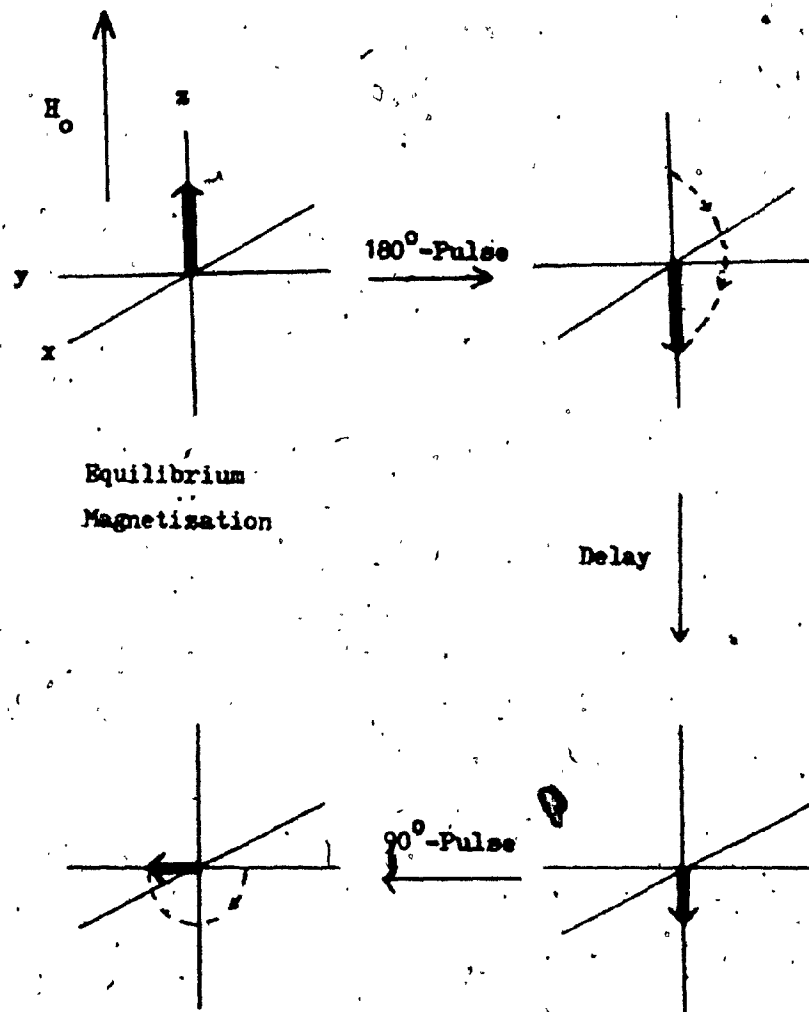


Fig. IM-1 : The Rotating Reference Frame Model for the Measurement of a Spin-Lattice Relaxation Time.

magnetization along the z-axis, this introduces no systematic error.

It is important to note that if twice the amount of power is applied, say, by doubling the length of pulse, then, the original magnetization vector will be tipped through 180° and will lie along the -z-axis.

In the rotating reference frame, spin-lattice relaxation refers to the rate at which magnetic energy is transferred from spins which are directed along the z-axis. Initially, as in Fig. III-1, the spin system is at thermal equilibrium with its lattice, and with its macroscopic magnetic moment directed along the z-axis. The equilibrium is then destroyed by applying a 180° -pulse which tips the magnetization rapidly into the -z-direction. Spin-lattice relaxation then restores the system to thermal equilibrium; this is accompanied initially by a decay in the magnetization intensity along the -z-direction, and subsequently by a recovery in the +z-direction. The amount of magnetization present at any given instant can be assayed by applying a 90° -pulse (sampling pulse) and so tipping the residual component up, or down, into the x,y-plane, where it induces a signal into the receiver of the spectrometer.

Quantitatively, the decay of M_z is given by the Bloch Equations (17.18) with $M_x = M_y = 0$:

$$dM_z / dt = -(M_z - M_0) / T_1 \quad \dots \dots \text{Eq. 3.}$$

Integration of Eq. 3 with $M_z = -M_0$ at $t = 0$ gives

$$M_z = M_0 (1 - 2 e^{-t/T_1}) \quad \dots \dots \text{Eq. 4.}$$

In practice, Eq. 4 is often re-cast into the form

$$\ln (M_0 - M_z) = \ln 2 M_0 - t / T_1 \quad \dots \text{Eq. 5.}$$

where M_z is the initial amplitude of the signal following the 90° -pulse at time t , and M_0 is the limiting value of M_z for a very long interval between the 180° - and 90° - pulses.

It can be seen from Eq. 5 that

$$M_z = 0 \text{ for } t = T_1 \ln 2 \text{ i.e.}$$

$$T_1 = t / 0.69 \quad \dots \text{Eq. 6.}$$

$$(\text{ Or } R_1 = 1/T_1 = 0.69 / t)$$

T_1 is determined from one of the equations Eq. 4, Eq. 5 or Eq. 6.

In practice, then, a 180° -pulse is used to destroy the thermal equilibrium, a known amount of time, t , is allowed to elapse, and the residual magnetization after that period is assayed by a 90° -pulse. This gives the first point on the 'decay-recovery' curve, Fig. IN-2 and 3, using Eq. 4. The system is left for more than $5 \times T_1$ sec (at $5T_1$, $M_z = 0.993 M_0$) to recover its equilibrium level of magnetization, and then a second 180° - t - 90° pulse sequence is applied, this time with a somewhat longer value for t . This gives the second point on the 'decay-recovery' curve, and so on. In normal practice, a minimum of ten such points must be determined. If necessary, spectra may be time averaged for each value of t .

Using Eq. 5, T_1 may be determined from the slope of a

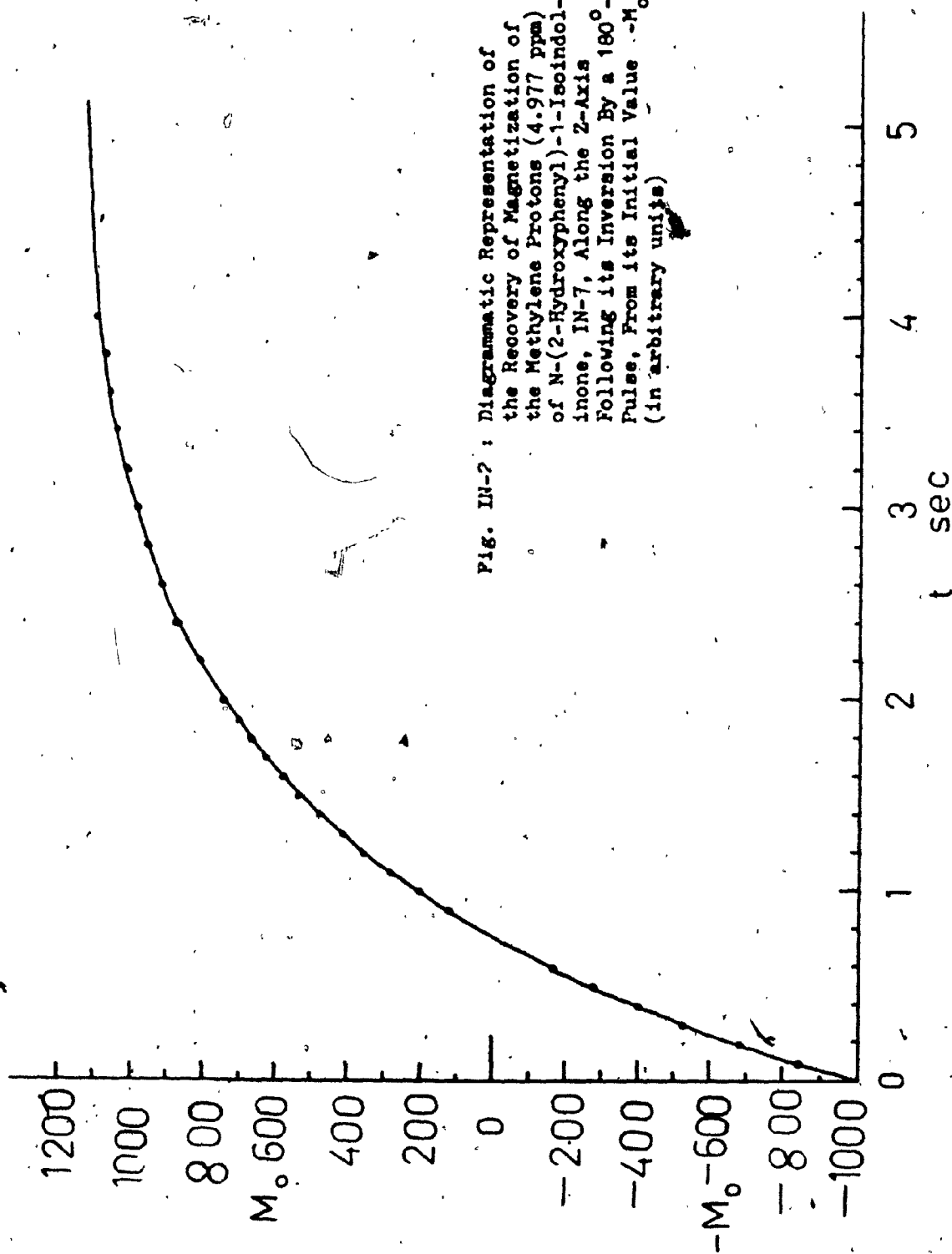


Fig. IN-2 : Diagrammatic Representation of the Recovery of Magnetization of the Methylene Protons (4.977 ppm) of N-(2-Hydroxyphenyl)-1-Isoindolinone, IN-7, Along the Z-Axis Following its Inversion By a 180° -Pulse, From its Initial Value $-M_0$ (in arbitrary units)

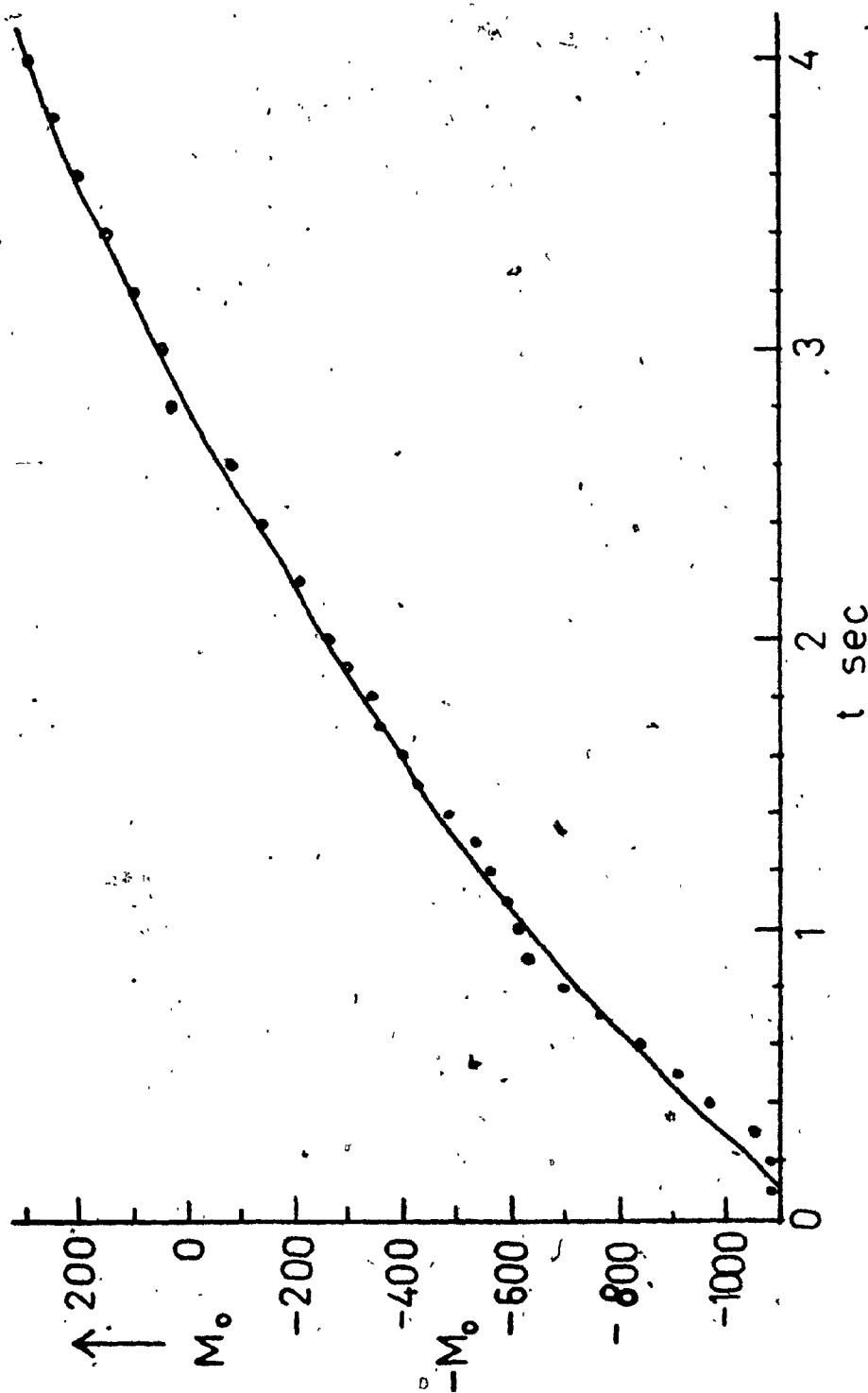


Fig. IN-3 : Diagrammatic Representation of the Recovery of Magnetization of the Methyl Protons of N-(2-Methyl-4-Methoxyphenyl)-1-isoindolinone, IN-10, Along the Z-Axis, Following its Inversion By a 180°-Pulse, From its Initial Value, $-M_0$ (in arbitrary units)

plot of $\ln (M_0 - M_z)$ vs t , Fig. IN-5 -7. Using Eq. 6, T_1 can be found from the best estimate of pulse spacing, t , that results in no PID signal following the 90° -pulse. This procedure is unsuitable for the most accurate determinations of T_1 , but may be adequate for routine measurements.

Fig. IN-4 illustrates a series of partially relaxed proton NMR spectra of N-(2,3-dimethylphenyl)-1-isoindolinone in chloroform- d_1 recorded following a 90° -pulse at various delay times, t sec.

One particular advantage of the pulse FT NMR method (inversion-recovery sequence) is that all resonant nuclei of a given magnetic type (e.g. proton or carbon-13) can be sampled simultaneously and repetitively. The Fourier transformation of the PID yields the time-dependent intensity of each line in the spectrum. The intensity may be negative, zero or positive, depending on the relative value of t and the T_1 governing the resonance line.

One particular experimental concern in this technique is the inversion of each line in the spectrum. A very short 180° -pulse is non-selective and simultaneously inverts all the nuclei with different chemical shifts, provided that the condition (72) $\gamma H_1 \gg (\omega_1 - \omega_0)$ holds, where $(\omega_1 - \omega_0)$ is the difference in frequency units between a given resonance line (ω_1) and the pulse carrier frequency (ω_0). The $\gamma H_1 \gg (\omega_1 - \omega_0)$ condition assures that while the actual resonance condition ($\omega_1 = \omega_0$) does not hold for any line in the spectrum, deviations are so slight

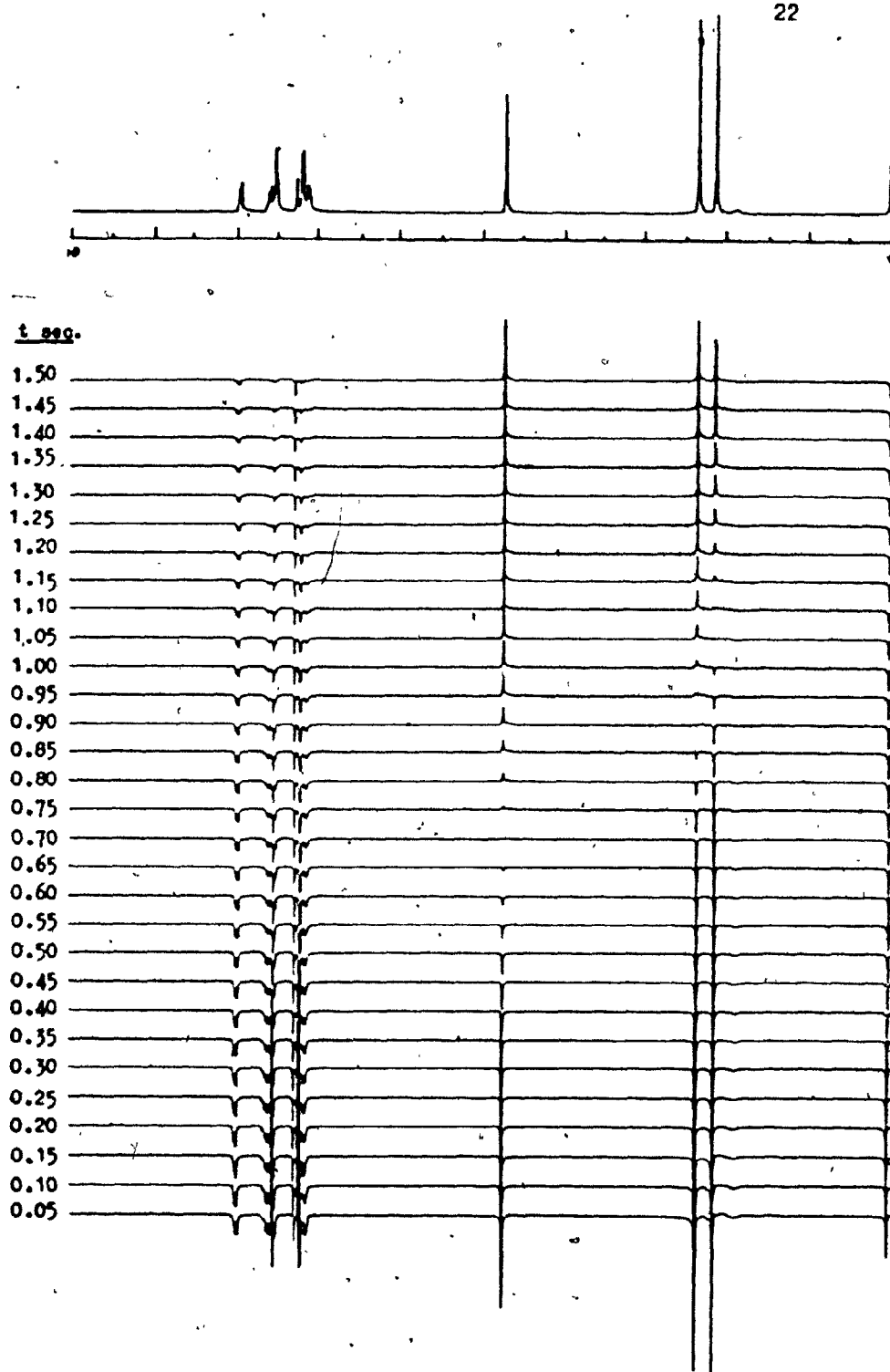


Fig. IM-4 : Partially Relaxed 270 MHz Proton NMR Spectra of
N-(2,3-Dimethylphenyl)-1-isoindolinone, IM-8, in CDCl_3 ,
Recorded Following a 90° -Pulse at Various Delay Times,
 t sec.

as to be negligible and the effective field for each nucleus in the rotating frame is approximately H_1 . If $\gamma H_1 \gg (\omega_1 - \omega_0)$ is not met for various lines, the measured T_1 may deviate from the true T_1 . Particularly large deviations will be observed for T_1 's calculated by the null-point method; it is recommended that complete $\ln(M_0 - M_2)$ -vs- t plots be used when γH_1 is not much larger than $(\omega_1 - \omega_0)$. Breakdown of this condition, of course, becomes of great concern at superconducting field strengths, where the frequency width of a proton (and particularly of carbon-13) spectrum may be quite large. A thorough treatment of the problem is given by Jones (59). Fig. IN-5, 6 & 7 represent plots of $\ln(M_0 - M_2)$ -vs- t , and assure that the experimental condition $\gamma H_1 \gg (\omega_1 - \omega_0)$ has been adequately met.

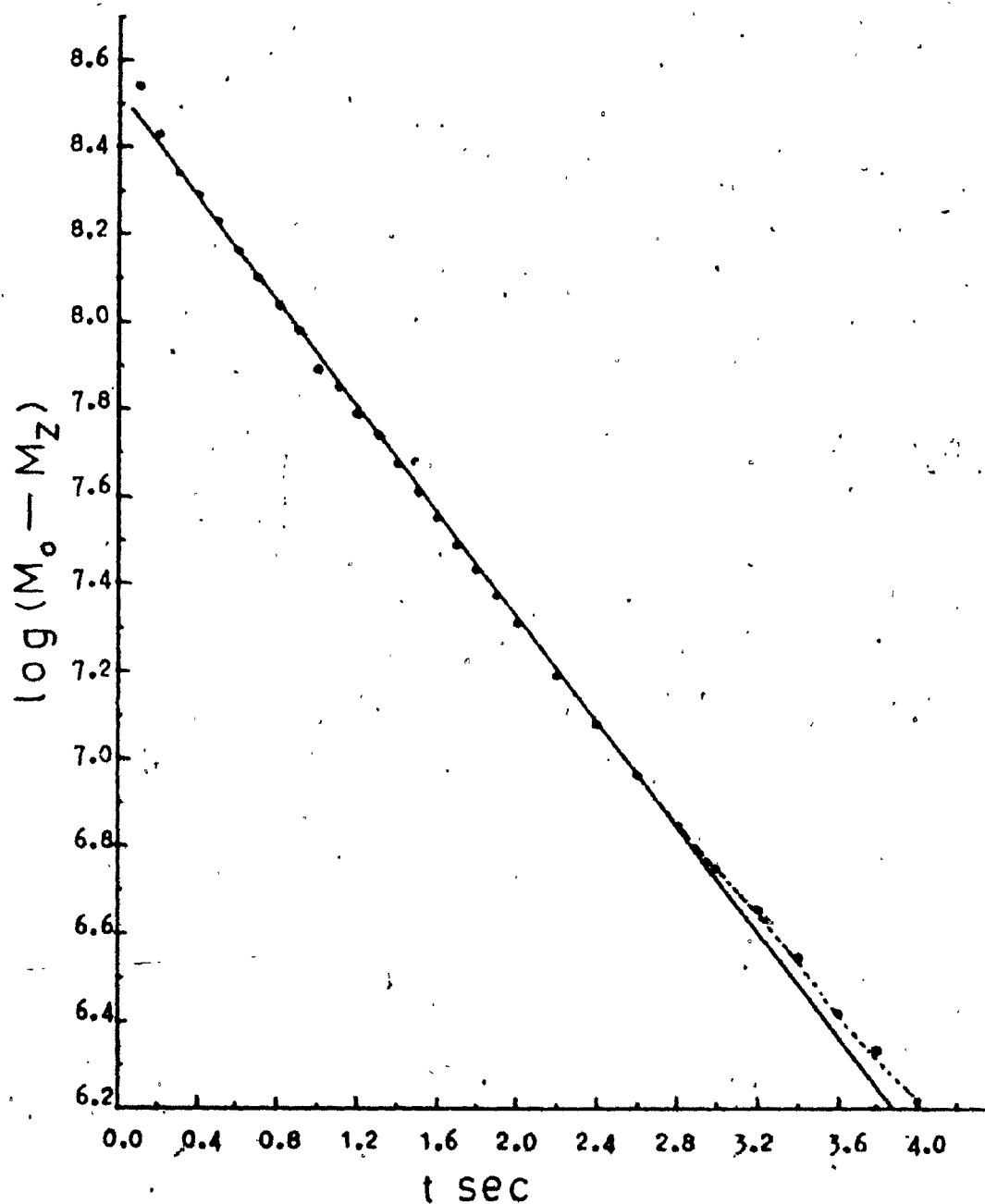


Fig. IN-5 : Decay Plot of $\ln(M_0 - M_z)$ versus t (sec) for the Methyl Resonance (2.226 ppm) of N-(2-Methyl-4-Methoxyphenyl)-1-isoindolinone, IN-10, 0.05 M Solution in CDCl_3 at 270 MHz and 23° .

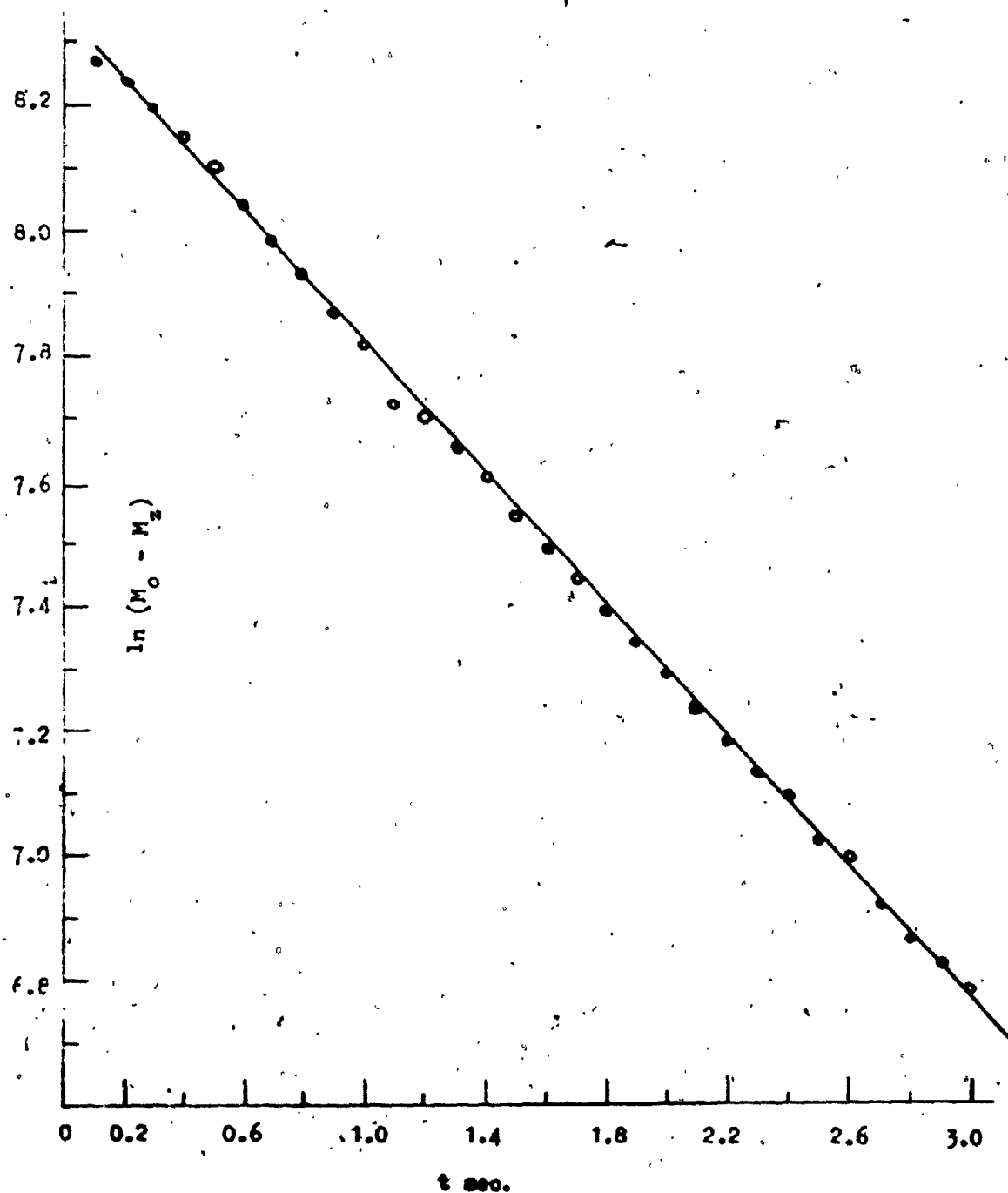


Fig. IN-6 : Decay plot of $\ln(M_0 - M_2)$ versus t (sec) for the Ortho Methyl Resonance (2.122 ppm) of N-(2,3-Dimethylphenyl)-1-isoindolinone, IN-8, 0.05 M Solution in CDCl_3 , at 270 MHz and 23° .

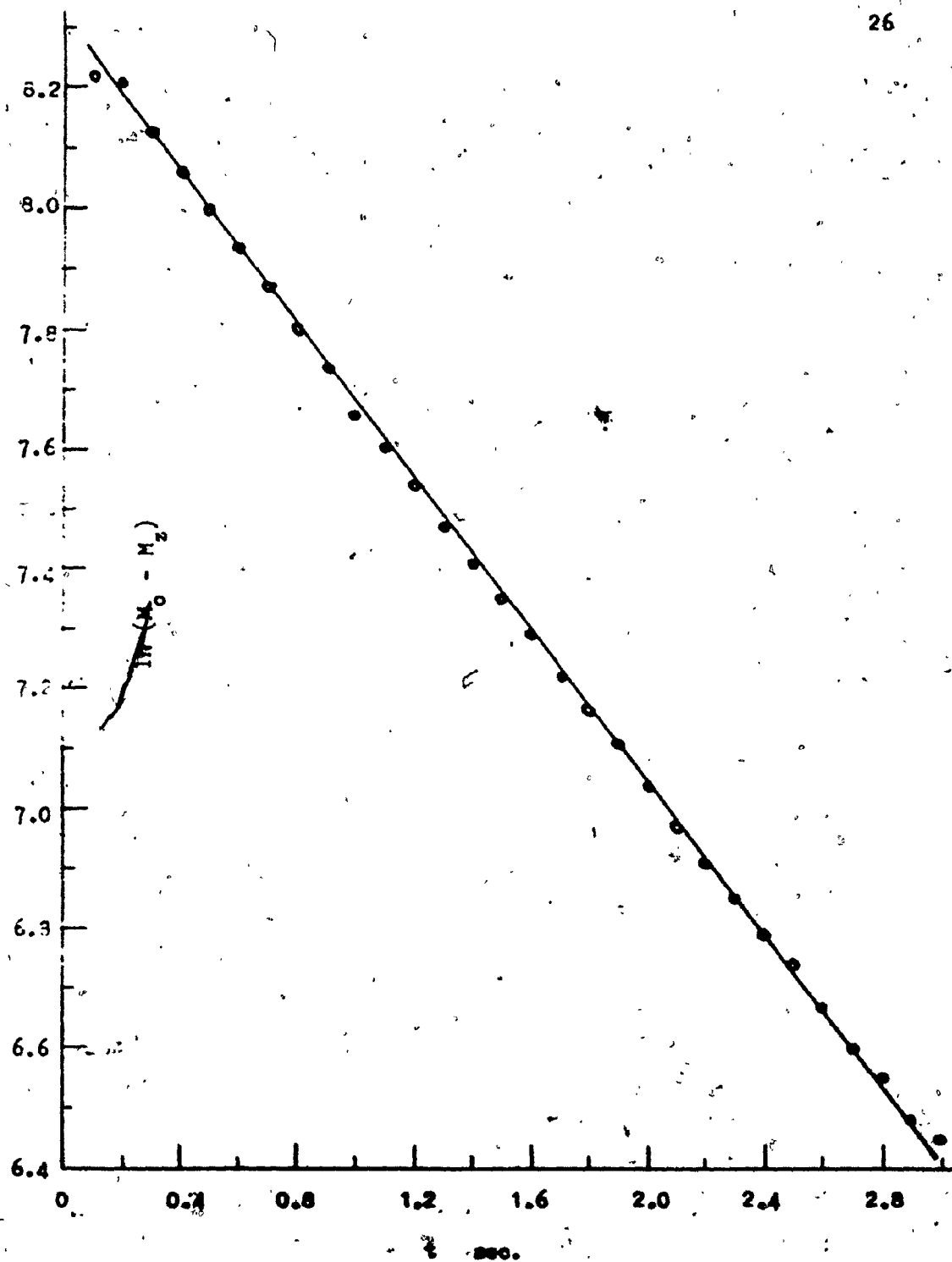


Fig. 1E-7 : Decay Plot of $\ln(M_0 - M_2)$ vs t (sec) for the Meta Methyl Resonance (2.336 ppm) of N-(2,3-Dimethylphenyl)-1-Isocindolinone, 1E-8, 0.05 M Solution in $CDCl_3$ at 270 MHz.

1-ISOINDOLINONES

The 1-isoindolinones were synthesized for the measurement of their spin-lattice relaxation rates which were expected to provide us with some insight into their solution geometry and various steric, inter- and intramolecular forces in operation. Although hydantoins and their thio analogues have been extensively studied in our laboratories, it was considered that their study employing the proton spin-lattice relaxation technique may be somewhat complicated for several reasons. Firstly, the N-aryl substituted hydantoins and thiohydantoins may not present conformationally rigid systems, and it may be difficult to analyse the contributions to their spin-lattice relaxation rates from a variety of sources, such as steric, changes in motional correlation times and conformational and configurational effects upon the correlation times, etc. Secondly, the effects of solvation about the carbonyl and/or thiocarbonyl groups in these compounds by solvents like chloroform or dimethylsulfoxide have been known to be quite significant and to affect the rotation of the N-aryl

moiety about the C-N bond as well as the relative orientations of the aryl ortho substituents. These effects may further complicate the analysis of the spin-lattice relaxation data. Finally, the hydantoins and their thio analogues show relatively low solubility in the less polar solvent chloroform as compared to highly polar solvent DMSO. A 99.8 atomic percent DMSO- d_6 solution of a compound is expected to enhance the intramolecular relaxation contributions through increased viscosity (with consequent long motional correlation times) and thus will exhibit a range of T_1 -values much smaller than that in chloroform.

The considerations mentioned above led us to investigate a system which should be fairly rigid to avoid conformational and configurational contributions to the relaxation of protons, be easily soluble in a less polar solvent and the solvation about any functional group present should not be significant. Moreover, a system similar to hydantoins or their thio analogues would be desirable in view of our experience with these compounds.

These requirements are best fulfilled by N-aryl substituted 1-isindolinones. The isindolinone moiety is fairly rigid, and configurational or conformational variations are not expected to be significant enough to produce large changes in their spin-lattice relaxation data (through changes in their correlation times). These compounds are expected to undergo preferred rotation about the longest molecular axis and, therefore, may provide a good case for a study of anisotropic motion of a heterocyclic system in solution.

The carbon-13 chemical shift data in DMSO showed that the carbonyl carbons in 1-isindolinones absorb over a narrow range, 167.0 ± 0.8 ppm, for a variety of N-aryl substituted moieties, Table CN-3. This suggested that variations due to solvation about the carbonyl group in these compounds by DMSO are almost negligible. Therefore, their study in the less polar solvent chloroform could be undertaken with confidence that intermolecular and viscosity effects are minimal. Moreover, by varying the nature and number of substituents on the N-aryl ring, the effect of conformational variations thus introduced in one part of the molecule (by keeping the second part as a rigid system) upon the over-all anisotropic molecular tumbling and the inter-ring relaxation between the aryl ortho substituents and the methylene protons could be investigated.

It was hoped that this strategy would provide us spin-lattice relaxation data for a heterocyclic system without complications.

EXPERIMENTAL CONSIDERATIONS :

1- Effect of Concentration and Temperature on T_1 -Values :

The intermolecular relaxation mechanism becomes important at increasing concentrations of the sample solution. The effect of concentration of solution on T_1 was not investigated in the present study. However, it is desirable to refer to a study of this effect in the case of sugar molecules (85). Fig. IN-8 represents the variation, with change in concentration, of the value of T_1 for the anomeric protons of D-glucose in degassed D_2O solution at 42° . This indicates that, over the range of 0.06 to 1.2 M, the T_1 -values change by about 35 %. The decrease in T_1 -values with increase in concentration has been considered to be probably due to the changes in correlation time with increase in the viscosity of the solution. It is clear that at a concentration of about 0.06 M, the contribution to the T_1 -values due to intermolecular relaxation is minimal.

The T_1 -values of the isoindolinones in the present study were all measured at 0.05 M solutions in $CDCl_3$ and, therefore, the intermolecular relaxation effects are considered to be minimal.

A study of T_1 -values of the anomeric protons of D-glucose (10 %, w/v in D_2O) as a function of temperature (85) revealed that a temperature increase of about 30° caused a greater

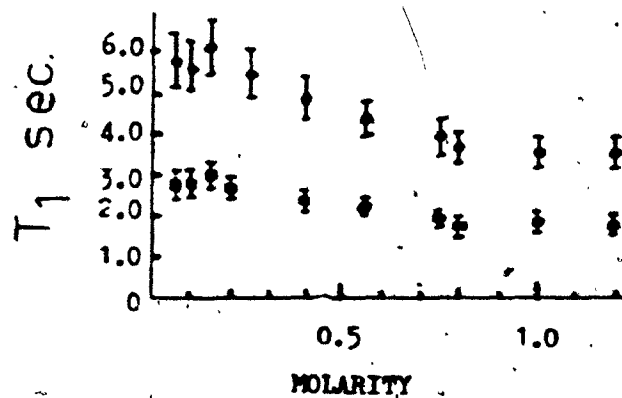


Fig. IN-8 : Graph Showing the Variation, With Change in Concentration, of the Value of T_1 for the Anomeric Protons of D-Glucose in Degassed D_2O Solution at 270 MHz and 42° .

Upper Curve : H (equatorial)

Lower Curve : H (axial) (85)

than two fold increase in the T_1 -values. Consequently, if data for different compounds are to be compared, it is necessary to keep the temperature constant. The R_1 -values of isoindolinones in the present study were measured at a constant temperature of 23° .

2- Effect of Choice of Solvent on R_1 -Values :

The polarity, solvation patterns, and viscosity characteristics of a solvent have marked influences on the magnitude of the R_1 -values. The effect of varying solvent has been studied by Colebrook (25) and is represented in Fig. IN-9 which shows the variation in the proton relaxation rates of a 0.1 M solution of vindoline (see Figure) in CDCl_3 , benzene- d_6 , and acetone- d_6 . It is clear that the relaxation rates are strongly affected in acetone- d_6 ; whereas in benzene- d_6 , the relaxation rates are comparable to those in CDCl_3 . Variations in viscosity are considered to be important upon change of one solvent to another, thereby affecting the correlation times and hence R_1 -values. A polar solvent may have an additional effect, namely, it can cause conformational variations by solvating around a polarizable group, e.g. such an effect could have been very significant in the case of N-aryl substituted -2-thiohydantoins (61) where a polar solvent, DMSO, strongly solvates the polarizable thiocarbonyl group. However, in the case of the 1-isoindolinones, the solvation effects arising from the less polar solvent, CDCl_3 , or the strongly polar solvent, DMSO, do not

VINDOLINE

0.1 M, NOT DEGASSED

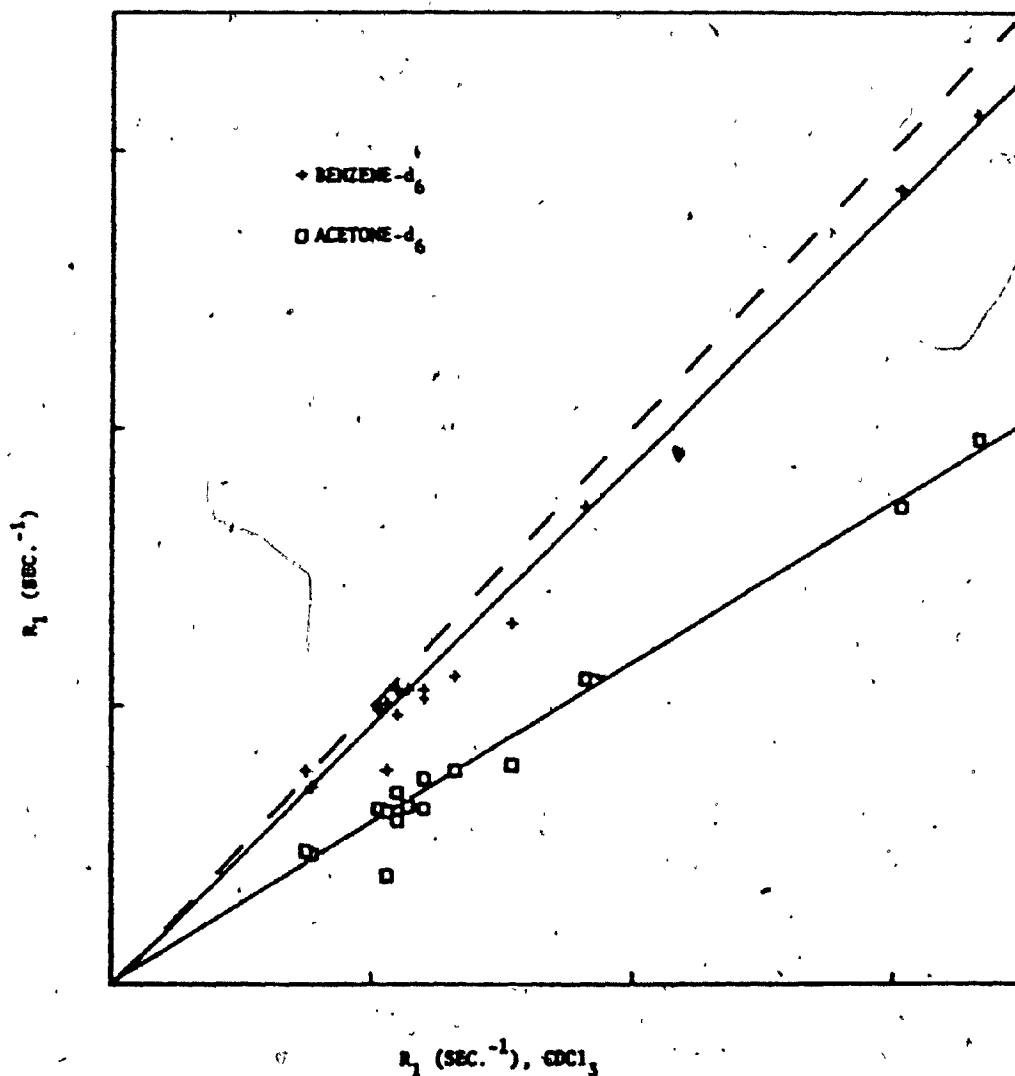


Fig. II-9 : Proton R_1 values for vindoline obtained by the null point method with the ordinate showing the data measured in CCl_3 solution (0.1 molar). The abscissa shows the data for 0.1 molar solutions in benzene- d_6 (+) and in acetone- d_6 (□), measured at the same temperature. (25)

seem to be important, as has been indicated by their C-13 chemical shift data (see Section 4). Therefore, CDCl_3 seems to be a reasonable solvent for studying these compounds.

3- Comparison of Null Point vs Initial Slope Method for Measurement of R_1 -Values:

In this study, the proton R_1 values were measured by the conventional 'inversion-recovery' two pulse sequence, i.e. the magnetization was inverted by a 180° pulse, then, following a variable delay, t , a 90° sampling pulse was applied to monitor the residual magnetization. Following time averaging, exponential filtering, Fourier transformation, and phase correction, the partially relaxed spectra were plotted in the form of a 'stack plot', Fig. IN-4, more relaxed spectra, corresponding to longer delay times between pulses, were plotted higher on the figure. As the delay time, t , increases, the initially inverted signals decay from their negative maxima through zero intensity (null point) and eventually recover their normal, upright, intensity for sufficiently long delay times (of the order of $5 \times T_1$).

The R_1 value for the each resolved signal may be determined by fitting the theoretical exponential recovery function (25) to the measured time dependence of the signal intensity. This may be done graphically, in the form of a semi-log plot, or by linear (semi-log) or non-linear regression using a computer. If this procedure is followed, only the first portion of the recovery curve

(the 'initial slope') is employed, in order to avoid the possible effects of cross-relaxation^{98,99,73}, which lead to non-exponential decay. In the present study, the 'initial slope' is defined as the range from complete inversion to about $1.2 \times T_1$. This procedure is reasonably convenient when the signals are singlets, especially if the system computer can search the data set for the signal of interest, and print out the intensities or, better still, use the intensities directly to calculate R_1 by means of a regression routine. However, current commercial software is not satisfactory for the multiplets which are commonly encountered in proton spectra, since the summed intensities of the multiplets are required. Although the computer may print out the intensities of the components of a multiplet, these must be summed by the operator or by a computer in a separate program, then fitted in a regression program. This procedure can be very tedious and time consuming for a complex proton spectrum.

Colebrook (25) has investigated the use of the null point to evaluate R_1 , since at this point $R_1 = 0.69 \cdot t$, where t is the delay between the inversion and the sampling pulses. The R_1 values may be determined very quickly from the stack plot, usually by extrapolating between values of t which straddle the null point. Provided that the values of t chosen for the experiment are sufficiently close, the null point can be determined to within 0.1 sec. Using the null point method, an estimate of R_1 can often be made for partially overlapping signals under circumstances where the intensity method would fail. The control experiments

reported by Colebrook (25), using both procedures, indicate that agreement between the null point and the initial slope methods can be excellent, Fig. IN-10, and that, in general, use of the null point method is unlikely to compromise the significance of any R_1 values determined for a qualitative study, such as the present one. A further comparison of the two methods was made for a number of signals in the present series (see later).

If the intensity method is used, six to eight different partially relaxed spectra must be obtained within the 'initial slope' range so that sufficient points are available for the regression calculation. This can be a source of difficulty in the case of fast relaxing protons in a molecule with a large dynamic range of R_1 values, since data storage limitations, which govern the number of partially relaxed spectra which can be processed, may require that data be acquired in more than one experiment.

If the null point method is to be used, it is important that the duration of the 180° pulse must be set as accurately as possible, to ensure complete inversion of the magnetization, since errors in the pulse length are more serious than in the case when the intensity method is used. For some signals, the null point method may violate the initial slope approximation, in which case the intensity method should be employed. This was not the case in the present study.

Although each component of a multiplet has its own R_1 value, the dynamic range of values within a multiplet is likely to be small, so that the error in estimating an average R_1 value

VINDOLINE

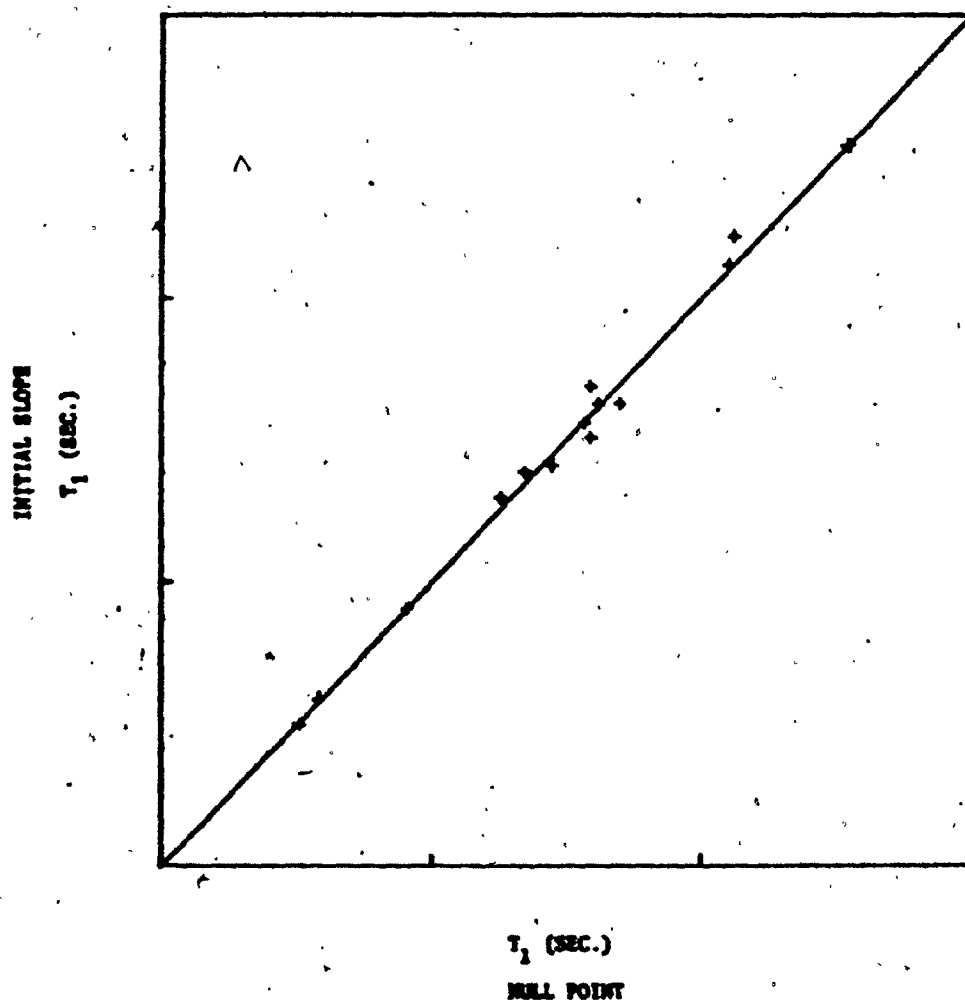
ACETONE- d_6 , 0.1 M, NOT DEGASSED

Fig. IM-10 : Plot of the R_1 values for vindoline (0.1 M in acetone- d_6), without degassing. The data on the ordinate were obtained by the null point method and those on the abscissa from the initial slope method using a least squares fit. (25)

for the multiplet will usually be insignificant in a qualitative study. Both methods for the estimation of R_1 may present problems in the limit of very close coupling between multiplets.

As pointed out earlier, the null point method is inadequate for accurate determination of T_1 values. Failure to meet some instrumental requirements such as non-uniformity or inhomogeneity of H_1 over the sample solution may give rise to errors in measurements by the null point method. A more common but less important source of error seems to be due to inaccurate judgement of the decay of magnetization to zero value in between the spacing of two pulses. Fig. IN-11 compares T_1 values obtained by the null point and the initial slope method using a linear regression program. It is clear that in the case of the 4-methoxy-2-methyl derivative, the null point furnishes T_1 values which are 5 - 14 % lower than those obtained by the initial slope method. In the case of 2,3-dimethylphenyl derivative, this difference is even larger i.e. about 16 - 25 %.

However, employing a non-linear regression program for the calculation of T_1 and R_1 values by the initial slope method furnishes values (Table IN-1) 2 - 10 % higher than those obtained by the null point method, well within the range of experimental error.

This analysis indicates that errors associated with the type of regression analysis employed may be greater than those introduced by the null point method. The linear regression method is subject to substantial errors resulting from an inaccurate estimate of the equilibrium magnetization, M_0 . Since the non-linear

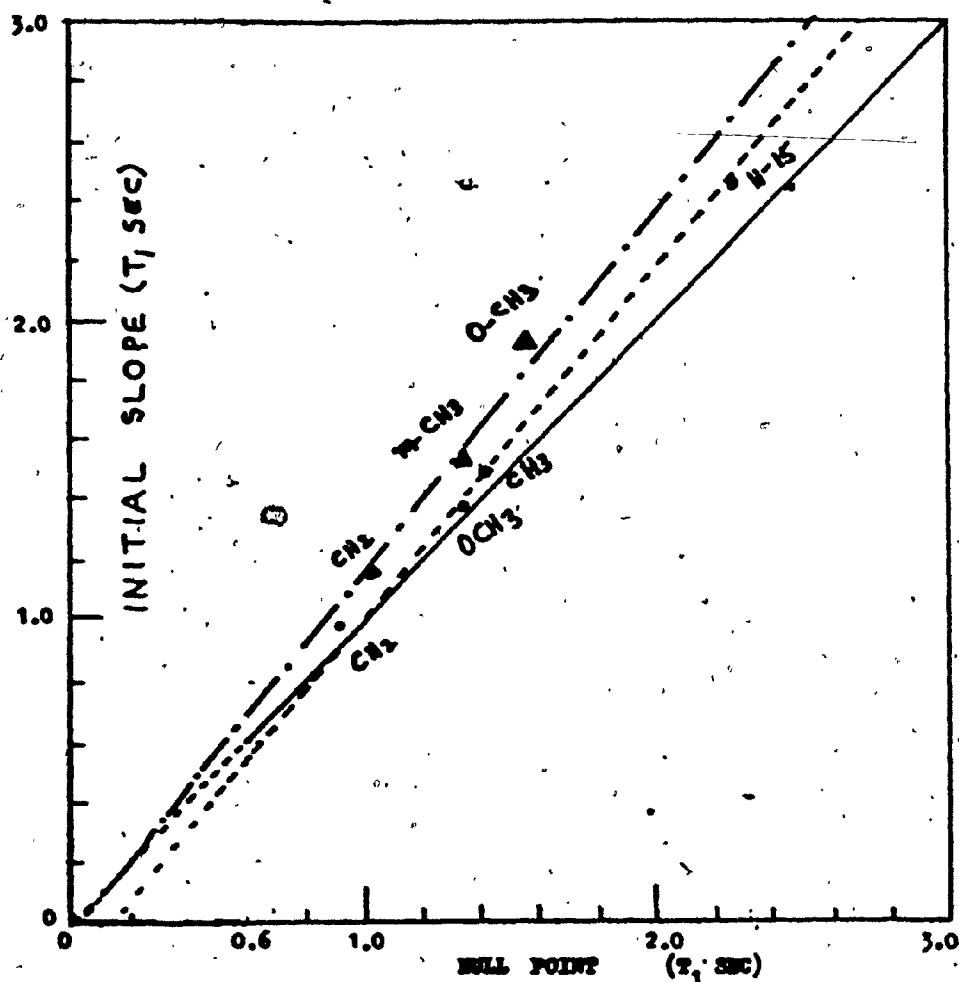
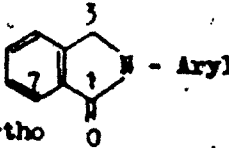
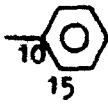


Fig. 11-11 : A comparison of T_1 values obtained by the Null point method and the initial slope method, using a Linear Regression program. (O) N-(2-Methyl-4-methoxyphenyl)-1-Isoindolinone, 11-10.
 (Δ) N-(2,3-Dimethylphenyl)-1-Isoindolinone, 11-8.
 (—) Excellent agreement.

TABLE IN-1

A Comparison of Spin-Lattice Relaxation Rates (Sec.^{-1})
 Obtained By Null-Point and Initial Slope^a Methods
 Using Non-Linear Regression Algorithms.

No.	ARYL	CH ₂				
			Ortho Group	H-15	H-7	
IN-1	Phenyl	0.78 (0.85)				
IN-4	O-P-Ph	0.74 (0.81)				
IN-5	O-Cl-Ph	0.78 (0.85)				
IN-7	O-OH-Ph	0.90 (1.00)	OH 0.25 (0.29)			
IN-8	2,3-Me ₂ -Ph	0.99 (1.01)	Me 0.64 (0.68)		7.963 ppm 0.31 (0.36)	
					7.936 ppm 0.31 (0.34)	
IN-10	** 2-Me-4-OMe-Ph	1.11 (1.17)	Me 0.71 (0.78)	7.145 ppm 0.44 (0.48)	7.960 ppm 0.32 (0.35)	
				7.177 ppm 0.44 (0.48)	7.932 ppm 0.32 (0.35)	
IN-13	1-Naphthyl	1.04 (1.11)				
IN-14	2-Naphthyl	1.11 (1.18)				

^aR₁ values in parentheses.

^{*}Meta Methyl Group : 0.75 (0.79)

^{**}Para Methoxy Group : 0.75 (0.79)

regression method does not require an estimate of M_0 , it should in principle, be more accurate than linear regression.

The T_1 and R_1 values reported in the present study are those obtained by the null point method. Most of these values have been compared with those obtained by the initial slope method using a non-linear regression program for calculation.

4- Effect of Dissolved Oxygen on R_1 Values :

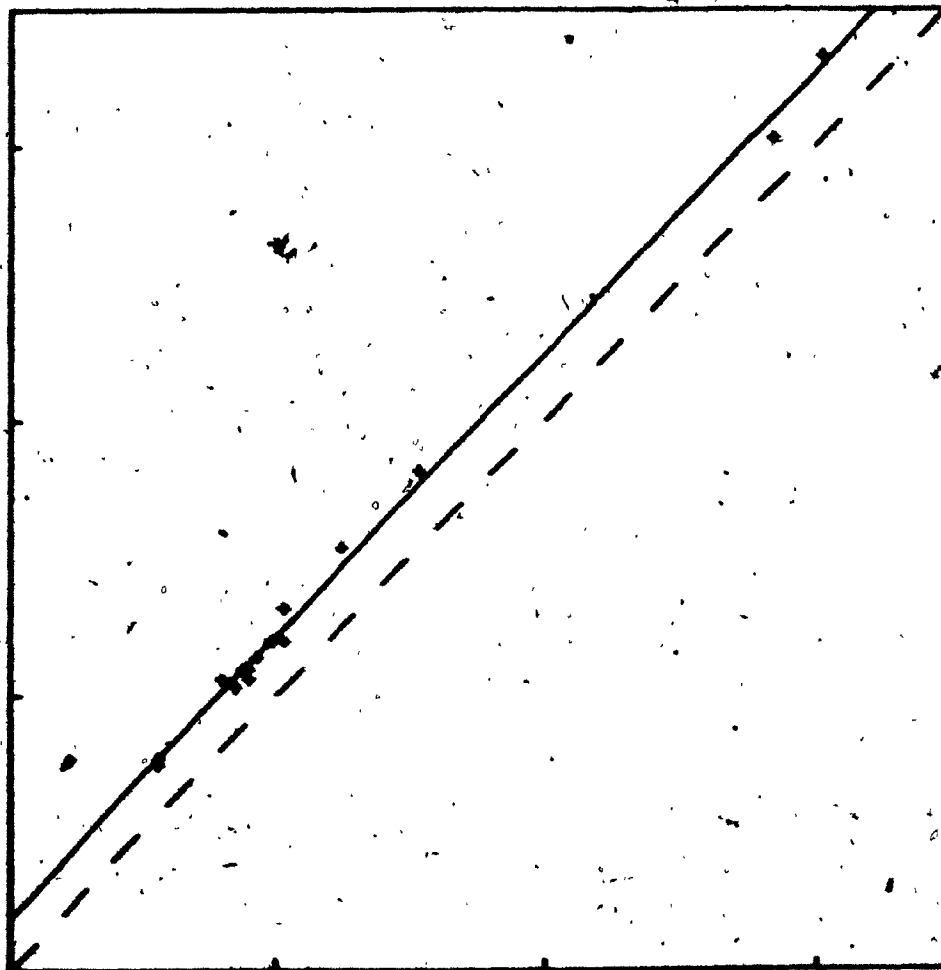
Molecular oxygen is a fairly effective paramagnetic relaxing agent and its presence in the dissolved state in the sample solution is expected to affect the R_1 values of various protons. Fig. D-12 represents a study by Colebrook (25) which determines the effect of non-degassing a 0.1 M solution of vindoline. It clearly shows that the rate of relaxation of all the protons in vindoline is increased, but notably, approximately to the same extent i.e. the rate constants for relaxation to oxygen are similar for all protons. The spectra of the 1-isindolinones in $CDCl_3$ were obtained without degassing, but under identical conditions. The relaxation effects due to the dissolved oxygen in these sample solutions are considered to be similar, and hence the comparison of R_1 values of these compounds is believed to be valid.

VINDOLINE

OCl_3 , 0.1 M

NOT DEPOSED

λ_1 (nm $^{-1}$)



λ_1 (nm $^{-1}$)

DEPOSED

Fig. 12-12 : Plot of the proton λ_1 values for vindoline (0.1 M in OCl_3 solution) determined by the mill point method. Solid circles values, measured without depositing; open circles values measured after six freeze-pump-thaw cycles followed by sealing under vacuum. (25)

RESULTS AND DISCUSSION

Fig. IM-13 to IM-26 represent a series of partially-relaxed inversion-recovery spectra of the 1-isocindolinones recorded with a non-selective 180° -t- 90° pulse sequence. These proton NMR spectra were run by Prof. L.D. Colebrook, while on sabbatical leave, at the Department of Chemistry, University of British Columbia, Vancouver, B.C., Canada. Spectra were determined at 270 MHz, using a 'homebuilt' spectrometer, based on a Bruker WM-90 console, an Oxford Instruments superconducting magnet, and a Nicolet 1080 or 1180 computer with a 16K word data block. Relaxation rates were measured using the 180° - t - 90° delay (inversion-recovery) pulse sequence, 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, 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 disk

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, using extrapolation between data sets straddling the null point, and also in a number of cases (Table IN-1) by computer fitting the peak intensities by the exponential recovery curve (25) 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 from computer print-outs. Non-degassed 0.05 M solutions in 98.8 % CHCl_3 were used throughout, the solvent having been stored over molecular sieves.

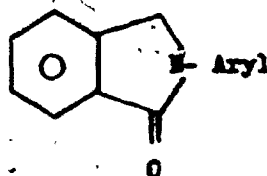
The N -aryl substituted 1-isobindolinones that are studied in this work are shown in Table IN-2.

Fig. IN-13 and IN-14 represent stack plots displaying partially relaxed spectra of two of the representative N -aryl-1-isobindolinones, IN-1 and IN-2. In all cases studied 0.05 molar solutions in chloroform- d , were measured at 270 MHz and 23° for various delay times, t , in the 180° - t - 90° pulse sequence. The delay times (sec.) are marked on the left hand of each figure.

For experimental conditions see page 43.

TABLE II-2

**N-Aryl 1-Isoindolinones Used for Spin-Lattice
Relaxation Studies.**



<u>No.</u>	<u>ARYL</u>
IN-1	Phenyl
IN-2	2-Tolyl
IN-3	2-Methoxyphenyl
IN-4	2-Fluorophenyl
IN-5	2-Chlorophenyl
IN-6	2-Bromophenyl
IN-7	2-Hydroxyphenyl
IN-8	2,3-Dimethylphenyl
IN-9	2,6-Dimethylphenyl
IN-10	4-Methoxy-2-Methylphenyl
IN-11	3-Chloro-2-Methylphenyl
IN-12	4-Chloro-2-Methylphenyl
IN-13	1-Naphthyl
IN-14	2-Naphthyl

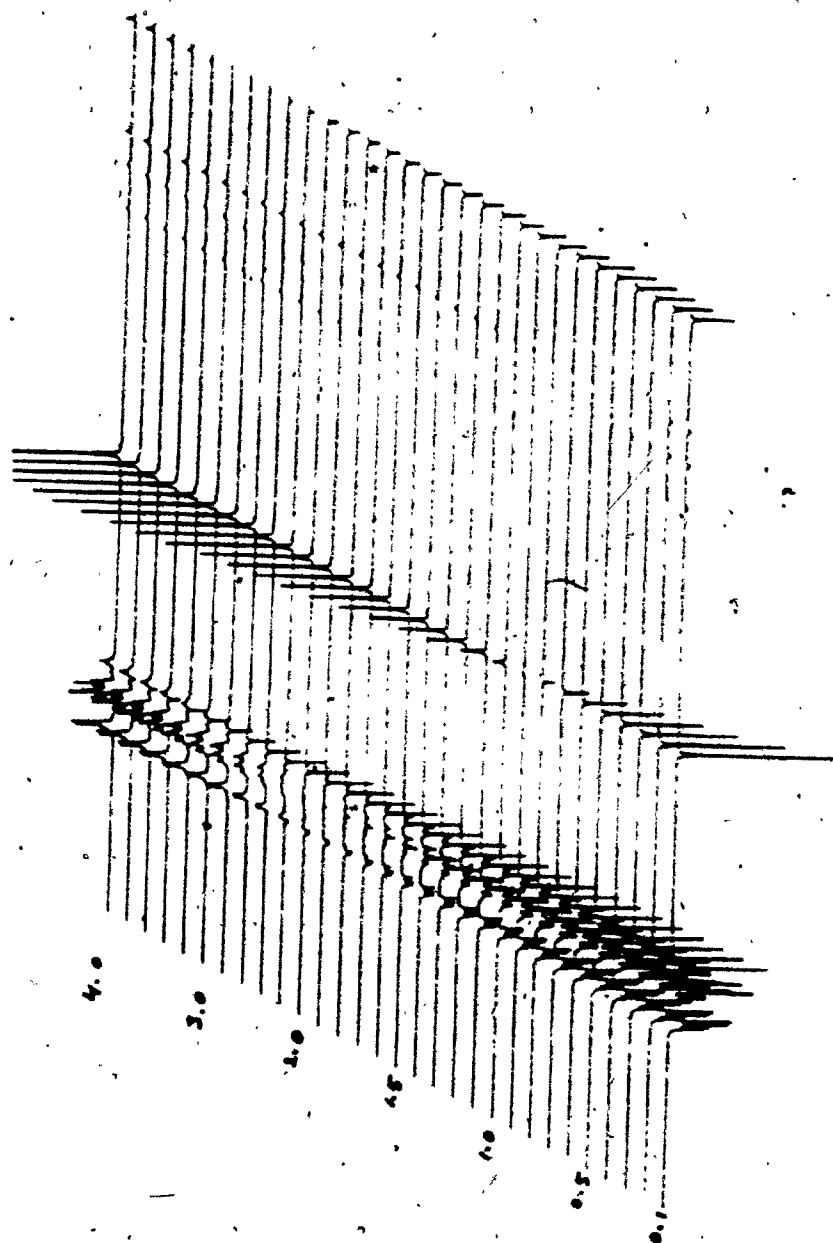


FIG. 12-13 : N-PENTYL-3-ISOINDOLINONE

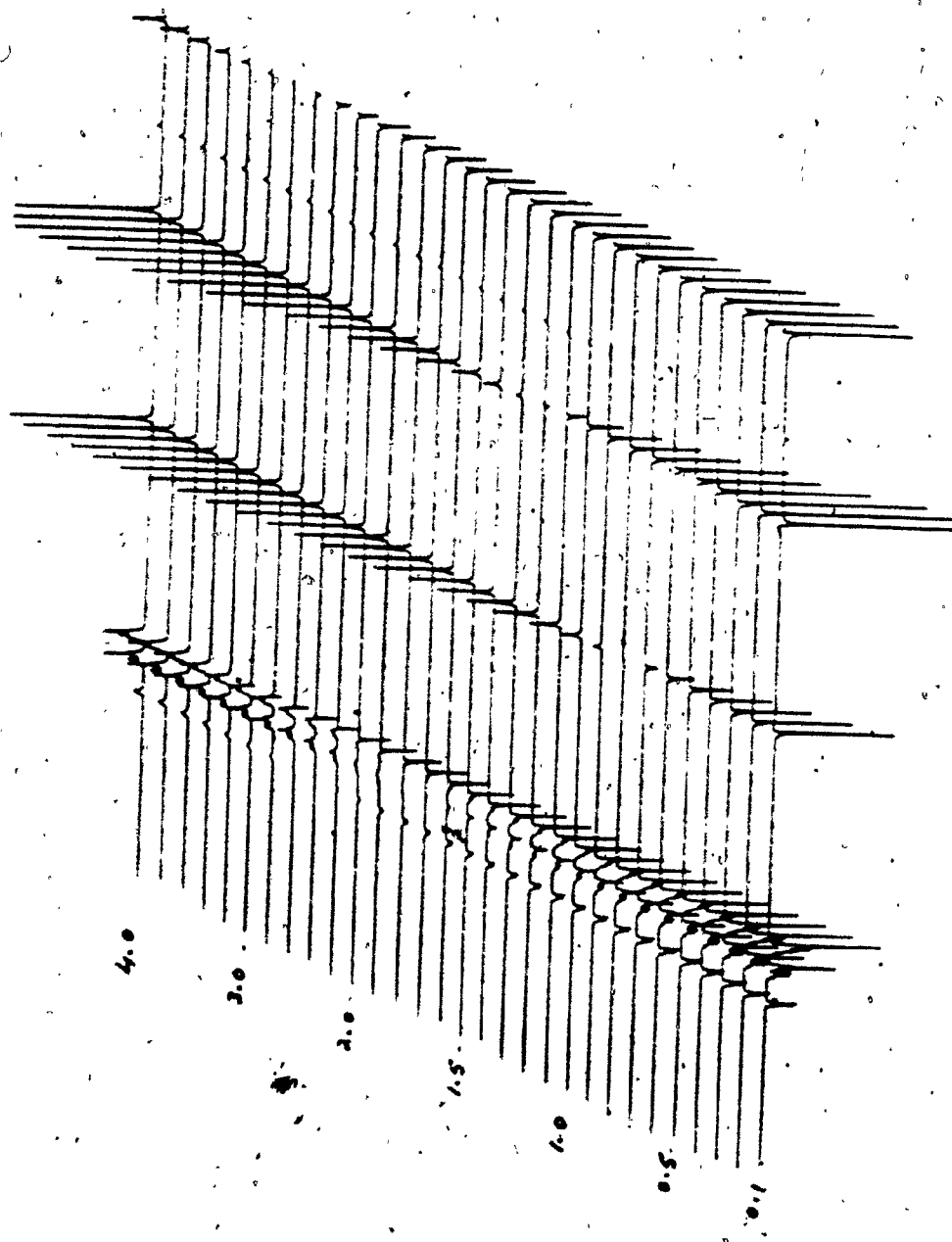


FIG. 14-14 : N-(2-TOLYL)-1-ISOINDOLINONE

Assignments :

The identification of the 3-methylene, methyl or methoxy groups in 1-isocindolinones is a trivial matter. The 3-chloro-2-methylphenyl, 4-chloro-2-methylphenyl, and 4-methoxy-2-methylphenyl derivatives were analysed as an ABC spin system, and signals were assigned to the appropriate protons of the H-aryl ring. In all other cases, no attempt was made to assign peaks to the aryl protons because of the complex nature of the multiplets, except that the lowest field multiplet is readily identifiable as arising from the H-7 proton.

In the case of the 2,3-dimethylphenyl compound, two signals are observed, at 2.132 and 2.346 ppm, arising from the ortho and meta methyl groups. In the related compound, 2,3-xylylidine hydrochloride, (87) the ortho and the meta methyl protons absorb at 2.31 and 2.36 ppm, respectively. In 4,6-dibromo-2,3-xylylidine (87) the ortho and meta methyl protons appear at 2.11 and 2.29 ppm, respectively. The carbon-13 chemical shifts of the ortho and meta carbon atoms in 2,3-xylylidine (64B) are 12.7 and 20.6 ppm, respectively, indicating that the meta carbon is highly deshielded as compared to the ortho carbon atom. Therefore, the signals at 2.132 and 2.346 ppm in the spectrum of 2,3-dimethylphenyl compound, IM-8, have been attributed to the ortho and the meta methyl protons, respectively.

The spin-lattice relaxation rates, R_1 , and times, T_1 , for the assignable protons of the 1-isocindolinones, IM-1 to IM-14, are shown in Fig. IM-15 and IM-16, respectively. These

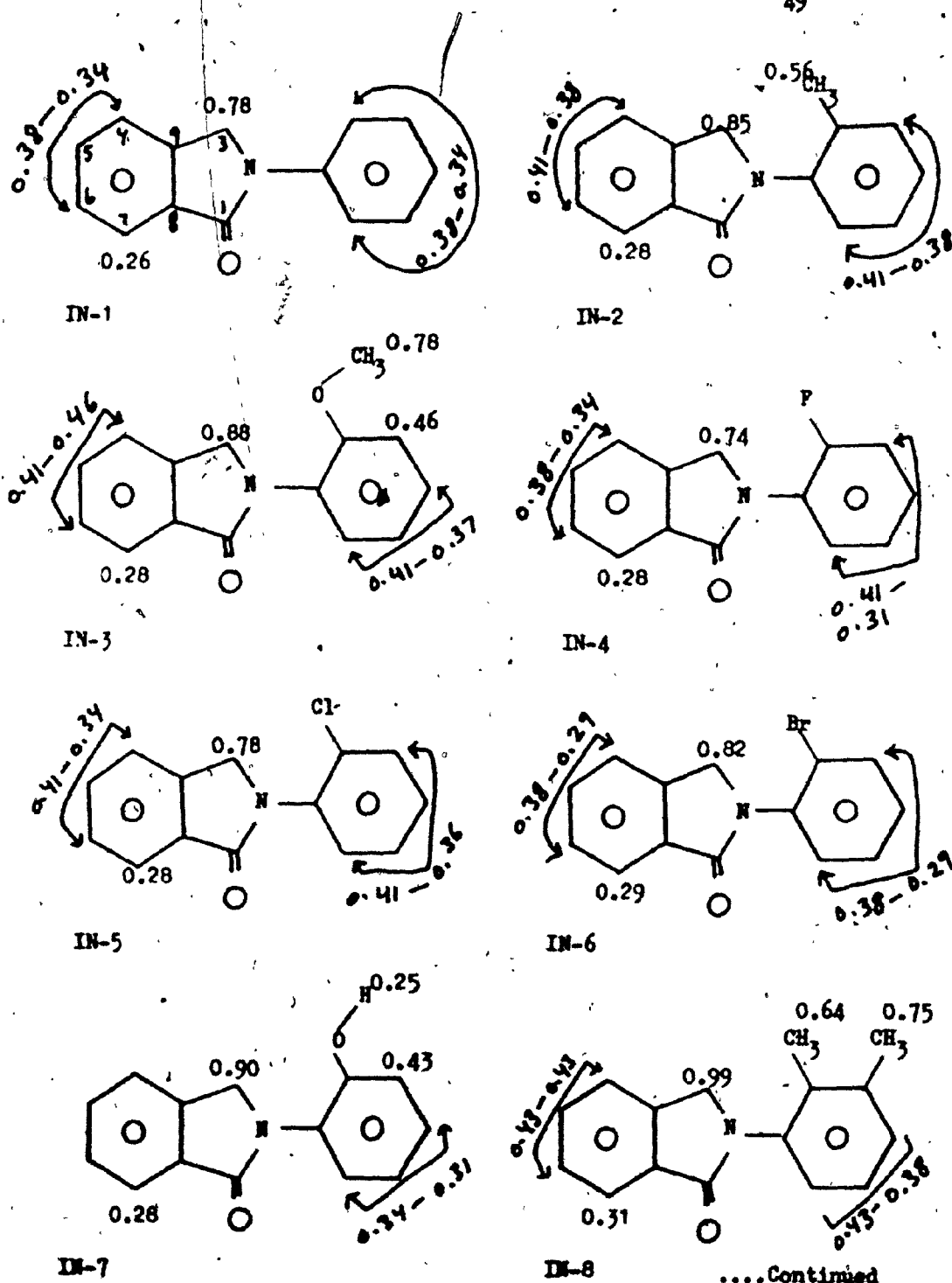
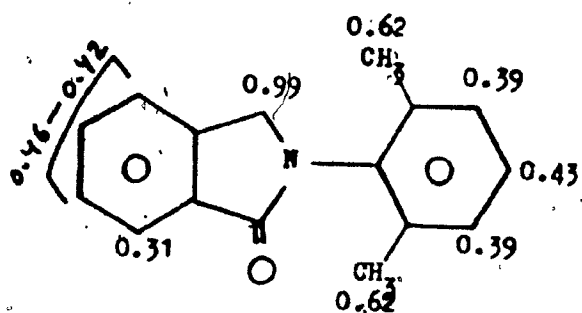
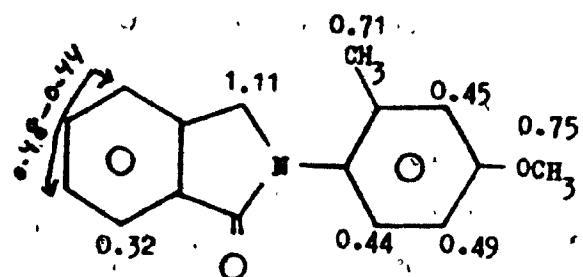


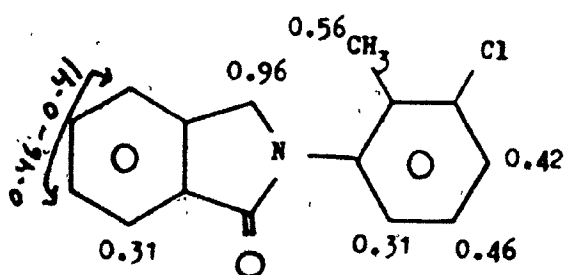
Fig. IN- 15: Spin-Lattice Relaxation Rates (sec⁻¹) for the Assignable Protons of 1-Isindolinones, IN-1 to IN-14, 0.05 M Solutions in CDCl₃, Measured at 270 MHz and at 25°.



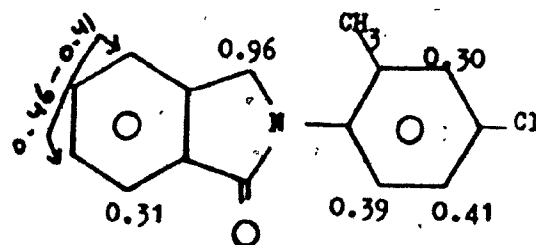
IN-9



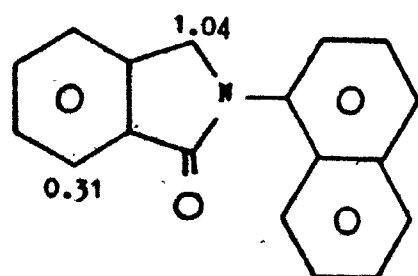
IN-10



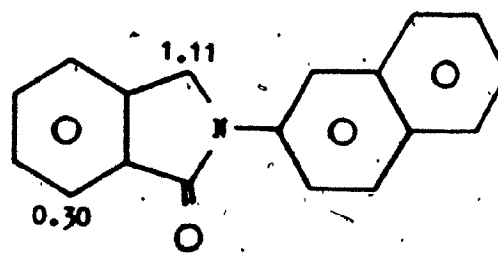
IN-11



IN-12



IN-13



IN-14

Fig. IN-15 : (Continued)

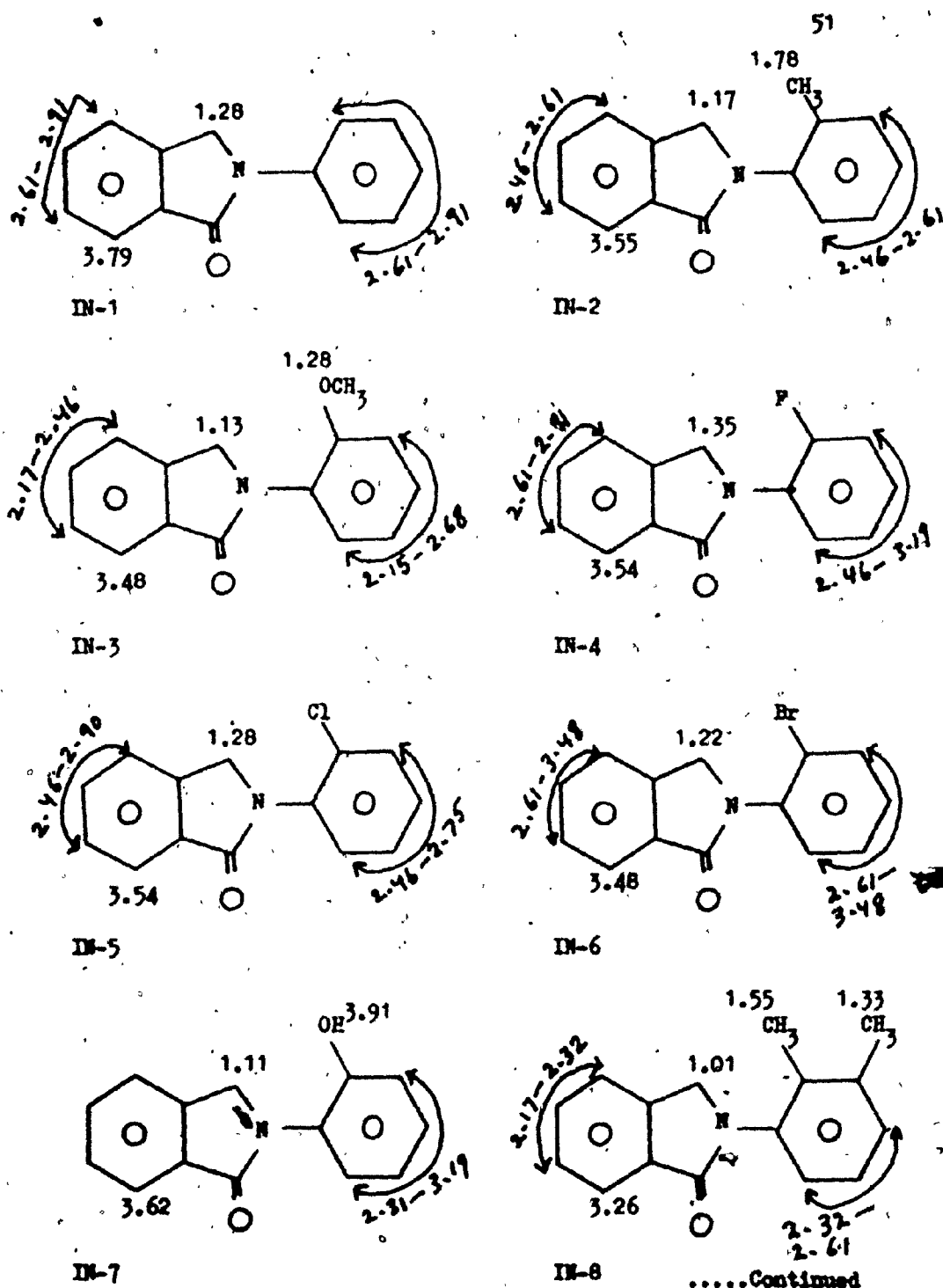


Fig. IN-16: Spin-Lattice Relaxation Times for the Assignable Protons of 1-Isindolinones, IN-1 to IN-14, 0.05 M Solutions in CDCl_3 , Measured at 270 MHz and at 23° .

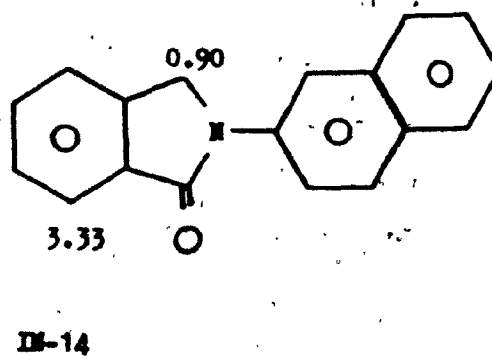
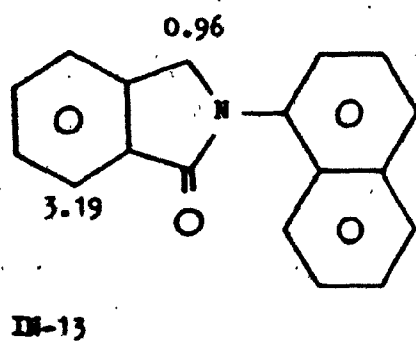
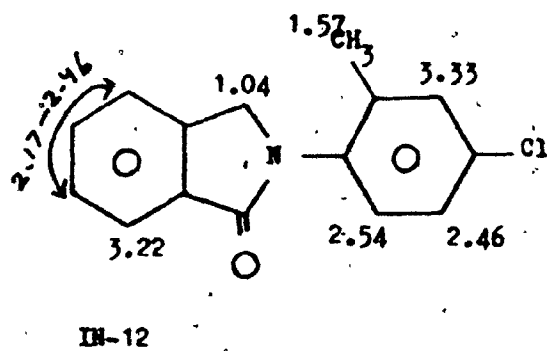
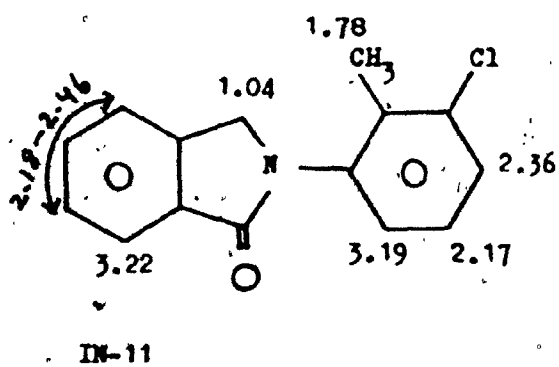
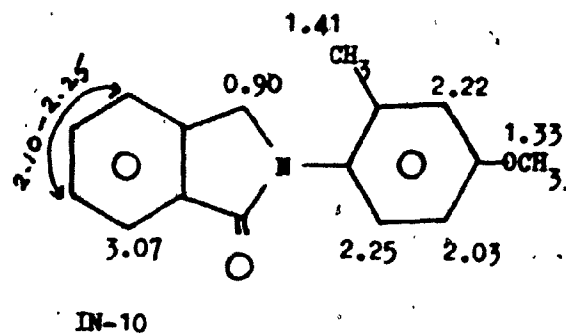
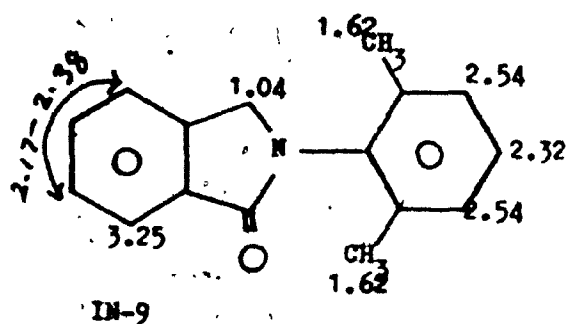


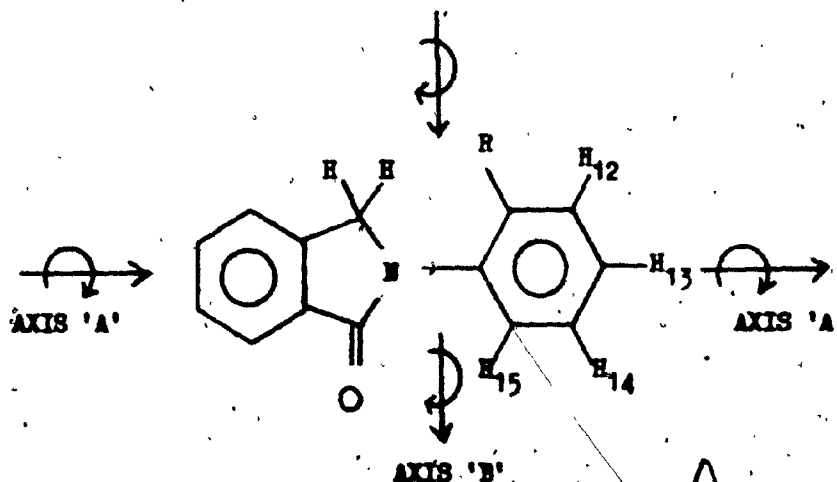
Fig. IN- 16 : (Continued)

measurements were made on 0.05 M solutions of samples in CDCl_3 , in order to minimize intermolecular and viscosity contributions to relaxation rates.

Molecular Motions :

Because the five-membered ring is fused to the benzene ring in 1-isoindolinone derivatives, the frame-work of the isoindolinone system is expected to be fairly rigid and strained. Keeping this fact in view, the following major molecular motions may be considered apart from the Brownian movement :

A- Rotation of the molecule as a whole about the longest axis is likely to be preferred than about the axis perpendicular to the longest axis i.e. rotation about axis a is preferable than that about b. Since under such circumstances, the correlation times of different protons will be different for rotation of the molecule about two different axes, the molecule would exhibit the effects of anisotropic motion in solution.




B- The internal rotation of the N-aryl moiety about the C-N bond,
and

C- The internal rotation of a substituent e.g. a methyl group,
on the aryl ring about the C - C bond.

Of the three types of molecular motions mentioned above, the motion described under A would be expected to be much faster than that described under B or C. The motion of N-aryl moiety about the C-N bond is also fast because even a highly substituted N-aryl moiety failed to show any diastereomeric splitting of either the diastereotopic methylene protons or the protons of a substituent on the aryl ring at temperatures as low as -161°C . The different types of molecular motions as described under A, B or C will have associated with them correlation times of different magnitudes, and their individual contributions to the overall spin-lattice relaxation rates can not be determined. These molecular motions will interact with the static local magnetic field, which at a nucleus i due to another nuclear moment j is given by (13)

$$H_{\text{local}} = \pm \frac{\mu}{r_{ij}^3} (3 \cos^2 \theta_{ij} - 1) \quad \text{Eq. 7}$$

where r_{ij} is the magnitude of a vector joining nuclei i and j , while θ_{ij} is the angle between this vector and the applied H_0 .

For the rotation of the molecule as a whole about the longest molecular axis (axis 'A' in ) or for the internal rotation of the N-aryl moiety about the C-N bond, the nuclear vector

H_{14} — H_{15} makes an angle $\theta = 0$ (parallel to the axis of rotation) and $\cos 0 = 1$ so

$$R_{\text{local}} = \pm \frac{2\mu}{r^3} \quad \dots \dots \text{Eq. 8.}$$

When $\theta = 90^\circ$ (e.g. for H_{13} - H_{14} approximately), $\cos 90 = 0$ and

$$R_{\text{local}} = \pm \frac{\mu}{r^3} \quad \dots \dots \text{Eq. 9.}$$

A comparison of Eqs. 8 and 9 shows that the protons H_{14} and H_{15} will relax each other faster as compared with H_{13} and H_{14} .

Normalization of Spin-Lattice Relaxation Rates :

If the R_1 values of protons in a series of compounds are to be compared, it is important that the effects of changes of substituents on the molecular tumbling rates be considered. Thus, an increase in molecular weight or molecular dimensions through the addition of a substituent may change the moments of inertia of the molecules, decreasing the tumbling rates (i.e. increasing T_0), sufficiently to increase the measured R_1 values. In consequence, it is desirable that relaxation rates of protons on different molecules be 'normalized' before being compared. On the assumption that the R_1 value of a proton remote from the site of substitution will not be affected by the substituent, but will be affected by a change in the molecular tumbling rate, the effects of changes in T_0 may be minimized

by comparing the ratios of the R_1 values of the protons of interest to that of the remote proton in each molecule. Molecular tumbling rates are also dependent on temperature and on the viscosity of the solvent, so it is important that both temperature and solvent be kept constant if R_1 values in different compounds are to be compared. These requirements have been fulfilled in the present study.

Fig. II-17 presents normalized spin-lattice relaxation rates of the assignable protons in 1-isindolinones, II-1 to II-14. In the individual molecules, the R_1 values of various nuclei are normalized with respect to H-7, since the relaxation rate of this proton should be the least affected in all the molecules under study ($0.26 - 0.32 \text{ sec}^{-1}$). Moreover, H-7 is not expected to have direct steric or other interactions with either the methylene protons or the aryl ortho substituent.

There are noticeable variations in the observed relaxation rates of various protons in these molecules, Fig. II-17 which survive in the normalized R_1 values. For example, the R_1 values of the 3-methylene protons cover the range $0.7 - 1.1 \text{ sec}^{-1}$, whereas the corresponding normalized R_1 values are $2.6 - 3.7$, after a magnification of about three times, $R_1(\text{CH}_2)/R_1(\text{H-7}) = \frac{0.78}{0.26} = 3$ in II-1

The behaviour of the normalized R_1 values parallel to the observed R_1 values suggests that changes in the molecular mass and shape do not affect their rotational correlational times to a large extent. Nevertheless, there is definite increase in the R_1 values of various protons in these molecules with the increase

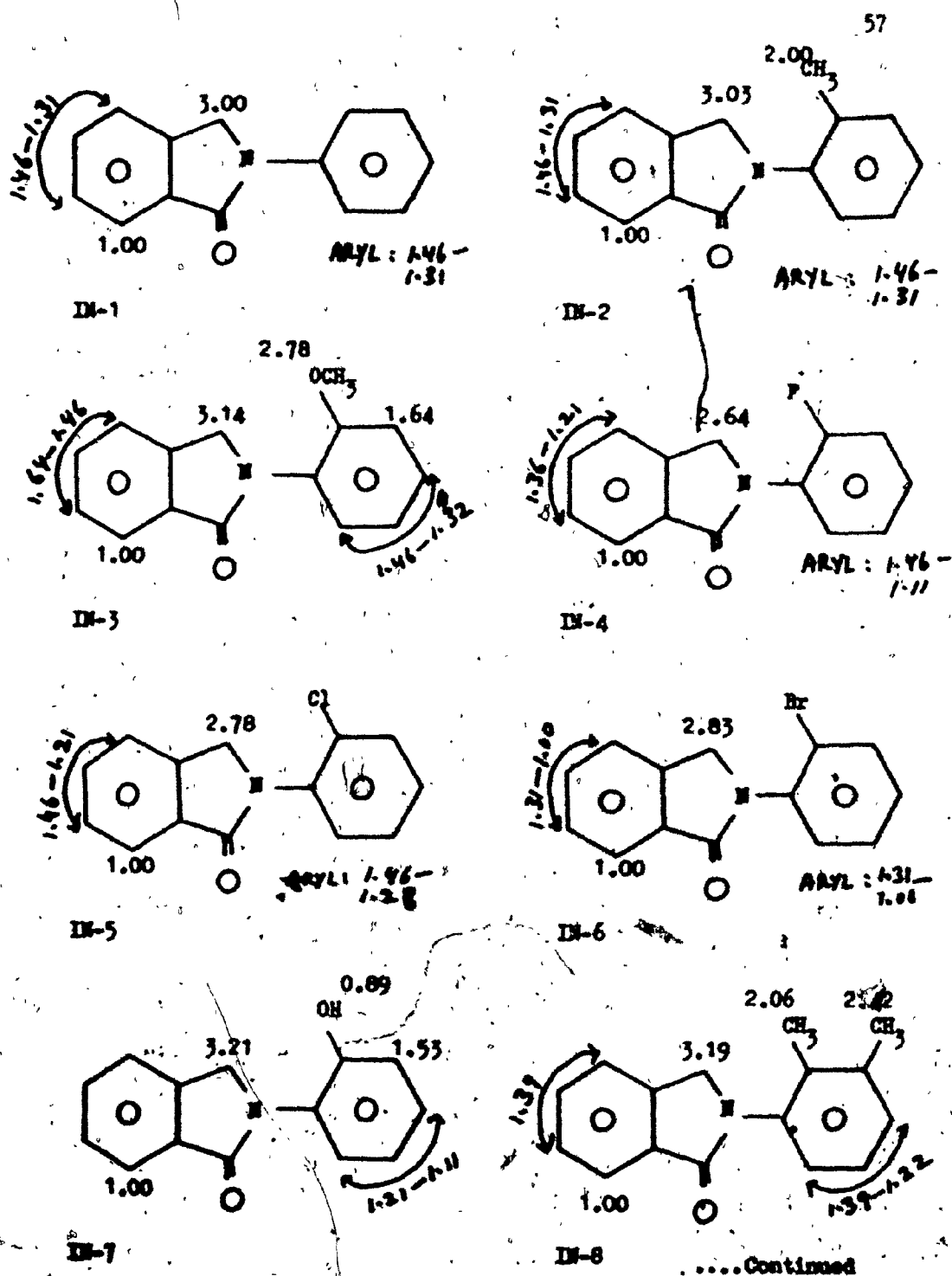


Fig. IN- 17: Normalized Spin-Lattice Relaxation Rates (sec^{-1})
 for the Assignable Protons of 1-Isindolinones,
 IN-1 to IN-14, 0.05 M Solutions in CDCl_3 ,
 Measured at 270 MHz and at 25° .

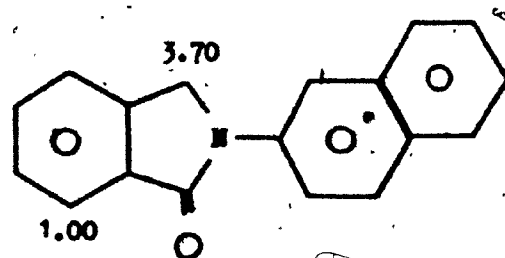
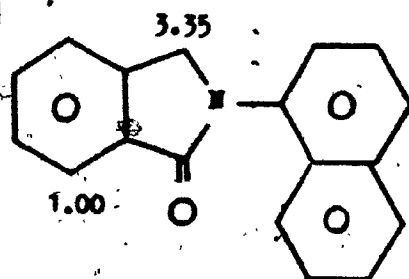
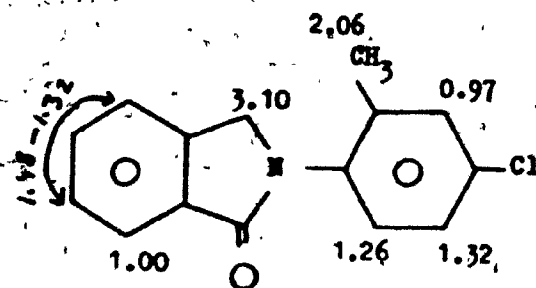
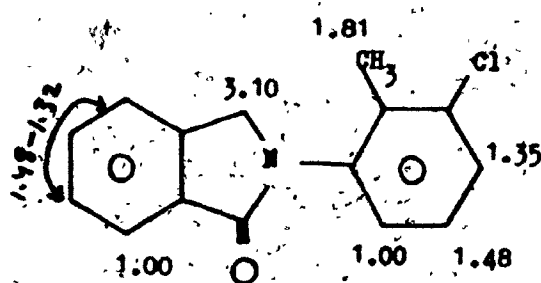
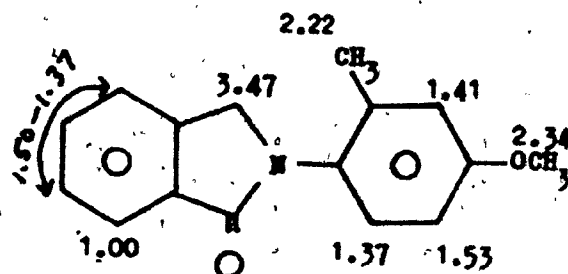
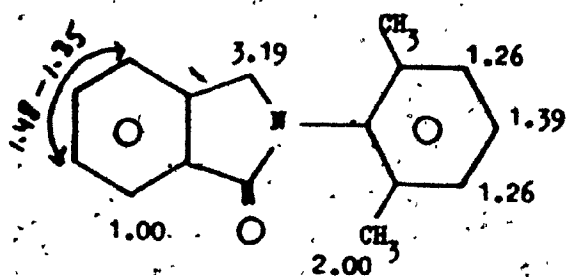


Fig. II-17 : (Continued)

in their steric bulk. This increase in the R_1 values is considered to arise from the longer rotational correlational times, rather than the steric effects leading to the intramolecular dipole-dipole relaxation.

PROTON RELAXATION RATES IN 1-ISOINDOLINONES :

The relaxation rates (R_1 values) in this series of compounds range from $0.26 - 1.11 \text{ sec}^{-1}$, a dynamic range of 4.3. Fastest relaxing are the 3-methylene protons, slowest are the more isolated aryl protons, in particular the 7-protons of the isoindolinone group, Tables IM-3 and IM-4.

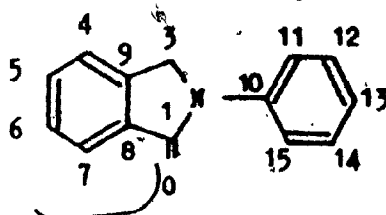
R_1 values determined by both the null point and the regression methods show reasonably good agreement except in the case of the fast relaxing 3-methylene protons. The chosen experimental conditions did not permit sufficient measurements for these protons to be taken within the 'initial slope' range to permit accurate regression analysis.

3-Methylene Protons :

The relaxation rates (R_1 values) of these protons fall within the range $0.74 - 1.11 \text{ sec}^{-1}$. These rates increase roughly in parallel with increasing molecular weight, indicating their sensitivity to changes in rates of molecular tumbling. After normalization with respect to the 7-proton rate, the 'normalized' rates fall within the range 2.64 - 3.70. Because of their short internuclear distance and their location in a rigid portion of the molecule, the 3-methylene protons relax each other efficiently and, in fact, the fastest relaxing nuclei in these molecules.

TABLE II-3

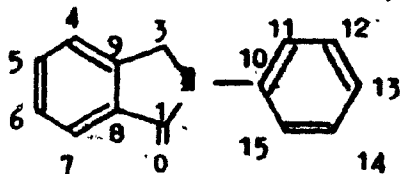
Observed Proton Spin-Lattice Relaxation Rates
(sec.⁻¹) of N-Aryl-1-Isosindolinones, Measured
at 270 MHz and 23° in CDCl₃ (0.05 M Solutions).



No	H-3	H-4 to H-6	H-7	H-12	H-13	H-14	H-15	Ortho Group	Other
IN-1	0.78	0.38-0.34	0.26	<u>0.38</u>	to	<u>0.34</u>			
IN-2	0.85	0.41-0.38	0.28	<u>0.41</u>	to	<u>0.38</u>		0.56	
IN-3	0.88	0.46-0.41	0.28	0.46	<u>0.41</u>	to	<u>0.37</u>		0.78
IN-4	0.74	0.38-0.34	0.28	<u>0.41</u>	to	<u>0.31</u>			
IN-5	0.78	0.41-0.34	0.28	<u>0.41</u>	to	<u>0.36</u>			
IN-6	0.82	0.38-0.29	0.29	<u>0.38</u>	to	<u>0.29</u>			
IN-7	0.90		0.28	0.43	<u>0.34</u>	to	<u>0.31</u>	0.25	
IN-8	0.99	0.46-0.43	0.31		<u>0.43</u>	to	<u>0.38</u>	0.64	0.75
IN-9	0.99	0.46-0.42	0.31	0.39	0.43	0.39		0.62	
IN-10	1.11	0.48-0.44	0.32	0.45		0.49	0.44	0.71	0.75
IN-11	0.96	0.46-0.41	0.31		0.42	0.46	0.31	0.56	
IN-12	0.96	0.46-0.41	0.31	0.30		0.41	0.39	0.64	
IN-13	1.04	-	0.31						
IN-14	1.11	-	0.30						

TABLE IN-4

Proton Spin-Lattice Relaxation Times* (sec) of
N-Aryl-1-Isocindolinones, Measured at 270 MHz and
23° in Chloroform-d₁, 0.05 M Solutions.



No	H-3	H-4 to H-6	H-7	H-12	H-13	H-14	H-15	Ortho Group Protons	Other Protons
IN-1	1.28	2.61-2.91	3.79	2.61	to	2.91			
IN-2	1.17	2.46-2.61	3.55	-	2.46	to	2.61	1.78	
IN-3	1.13	2.17-2.46	3.48	2.15	2.32	to	2.68	1.28	
IN-4	1.35	2.61-2.91	3.54	-	2.46	to	3.19		
IN-5	1.28	2.46-2.90	3.54	-	2.46	to	2.75		
IN-6	1.22	2.61-3.48	3.48	-	2.61	to	3.48		
IN-7	1.11	-	3.62	2.31	2.90	to	3.19	3.91	
IN-8	1.01	2.17-2.32	3.26	-	2.32	to	2.61	1.55	1.33
IN-9	1.04	2.17-2.38	3.25	2.54	2.32	2.54	-	1.62	
IN-10	0.90	2.10-2.25	3.07	2.22	-	2.03	2.25	1.41	1.33
IN-11	1.04	2.18-2.46	3.22	-	2.36	2.17	3.19	1.78	
IN-12	1.04	2.17-2.46	3.22	3.33	-	2.46	2.54	1.57	
IN-13	0.96	-	3.19						
IN-14	0.90	-	3.33						

* Observed Values.

Less efficient relaxation pathways which may also contribute to the relaxation rates are to the 4-protons of the isoindolinone moiety, and to protons attached directly or indirectly to the ortho positions of the N-aryl group. Since all of the compounds in this series have identical isoindolinone moieties, no information on the contribution of the relaxation pathway to the 4-proton can be obtained. Thus, external influences on the 3-proton relaxation rates must be due to relaxation to N-aryl substituents, modulated by the effect of changes in substituents on the over-all tumbling rates of the molecules in solution, changes in anisotropic contributions to the tumbling processes, and changes in rates of segmental motion, i.e. rotation about the aryl C-N bond.

Comparison of relaxation rates between compounds in the series is best done using the 'normalized' rates in Fig. IX-17 so as to reduce correlation time effects as much as possible. In the ortho fluorophenyl derivative, IX-4, the 3-methylene protons show the slowest relaxation rate, indicative of incapability of the ortho halogen substituent to relax these protons. It is evident from Eq. 2 that nuclei other than protons do not make significant contributions for relaxation to nearby protons because their magnetogyric ratios are small compared with that of the hydrogen atom. This has also been observed by Hall (50A) for 3,4,6-tri-O-acetyl-1-O-benzoyl-2-halogeno-2-deoxy- β -glucopyranosides, A to D, Fig. IX-18. The relaxation rates of protons are indicated in this Figure.

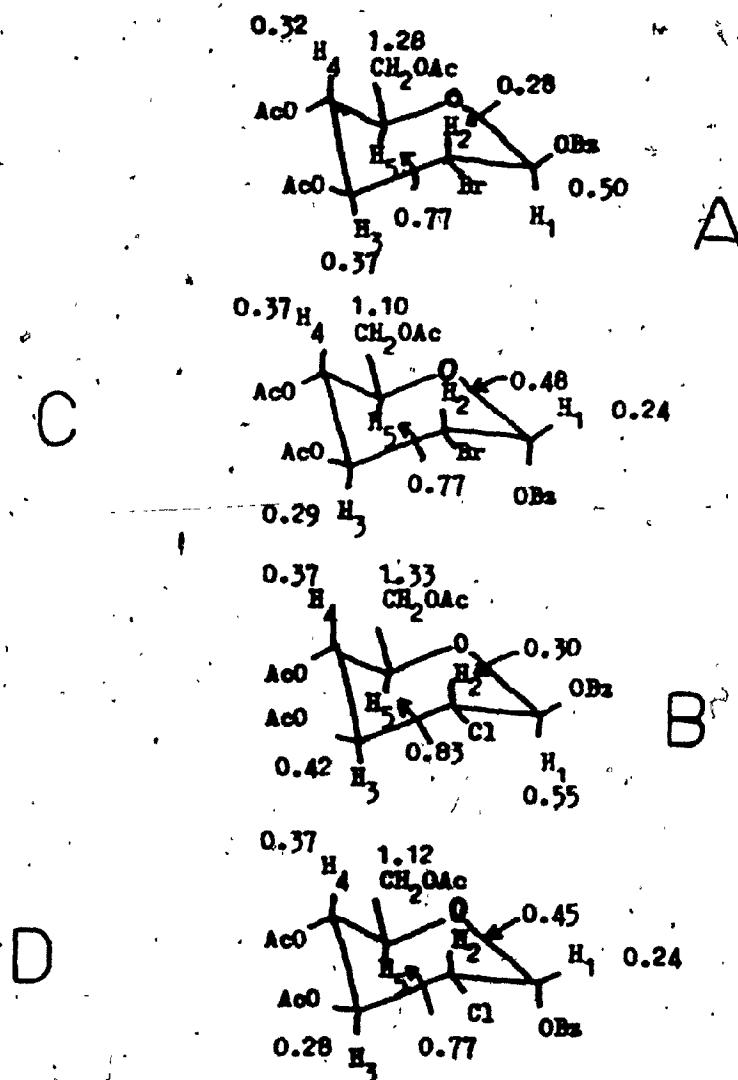


Fig. 18 : Proton Spin-Lattice Relaxation Rates of
3,4,6-Tri-O-Acetyl-1-O-Benzoyl-2-Halogeno-
2-Deoxy-D-Glucopyranoses in Benzene-d₆ (50A).

The close similarity between the individual relaxation times of the configurationally identical pairs of compounds A, B and C, D, shows that the C-2 halogen substituents do not contribute appreciably to the relaxation of the neighbouring proton.

It is interesting to note that the R_1 value of the 2-fluorophenyl compound, IN-4, is slightly lower as compared to that of the N-phenyl compound, IN-1, Table IN-3.

The most striking feature of the 'normalized' rates of the β -methylene protons is the low values for the three ortho-halo compounds, IN-4 to IN-6. In these compounds, the β -protons relax at a rate 88 - 94 % of the corresponding protons of the phenyl compound, IN-1. In contrast, the β -protons of all the other compounds, which have proton containing substituents in the ortho positions, relax faster than those of the reference compound, IN-1. It is evident that a significant inter-ring relaxation pathway exists between the β -methylene protons and proton containing ortho substituents on the aryl group. The presence of ortho halo substituents, which are less effective sources of relaxation than protons, reduces the contribution of the aryl group to the relaxation of the β -methylene protons. The increase in the 'normalized' relaxation rates of the β -protons with increased atomic weight of the halo substituent in IN-4 to IN-6 is attributed to a decrease in the rates of internal rotation, or of libration, about the aryl C-N bond as the steric bulk of the substituent increases. Thus, the molecules become more rigid as the size of the ortho substituent increases, and the effect of

segmental motion, which reduces the relaxation rate of involved moieties, becomes less important. This effect is also noticeable in other compounds with increasingly substituted aryl moieties. For example, in the 2-naphthyl derivative, IN-14, the β -methylene protons relax about 50 % faster than in the 2-fluorophenyl derivative, IN-4.

A comparison of IN-11 and IN-12 shows that the sterically compressed methyl group in IN-11 is unable to relax the β -methylene protons through the intramolecular DD relaxation mechanism, since the relaxation rates of methylene protons in particular, and the remaining protons in general, in IN-11 and IN-12 are essentially unchanged.

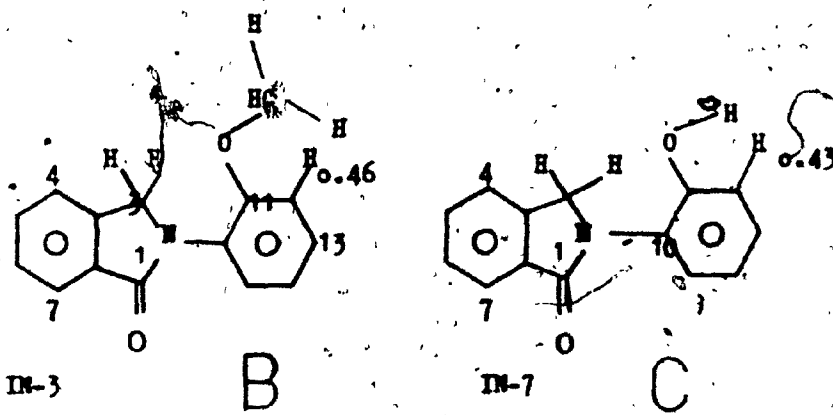
N-Aryl Protons :

In most cases, the protons on the N-aryl ring show complex multiplets and therefore, only protons on the trisubstituted benzene ring were assignable. However, the relaxation rates of the sufficiently resolved individual lines in a spin multiplet were measured and reported as the range of R_1 values in that multiplet (Table IN-3 and Fig. IN- 15, 16 & 17). The relaxation rates reported are average values, since the individual lines in a multiplet may have different relaxation rates. The range of values within a multiplet is likely to be small, so that the error involved in an over-all value is likely to be insignificant in a qualitative study such as the present one.

The relaxation rates of the N-aryl protons fall in the range $0.29 - 0.46 \text{ sec.}^{-1}$ (Table IN-3), and the normalized rates in the range $0.97 - 1.64$ (Fig. IN-17). It was not practicable to determine any rates for the two naphthyl compounds, IN-13 and IN-14, because of the complexity of their aryl spectra. The narrow range of these relaxation rates indicates that the nature of the substituent in either the ortho- or ortho and meta- or ortho and para- positions on the aryl ring has negligible effect on the over-all molecular tumbling in chloroform solutions.

There are, however, a number of instances in which ⁸ specific intramolecular dipole-dipole relaxation of N-aryl ring protons can be clearly illustrated. For example, in the 2-methoxyphenyl- and 2-hydroxyphenyl- compounds, IN-3 and IN-7,

respectively, the H-12 ring protons are relaxed by the protons on the substituents in the ortho position, as shown below :



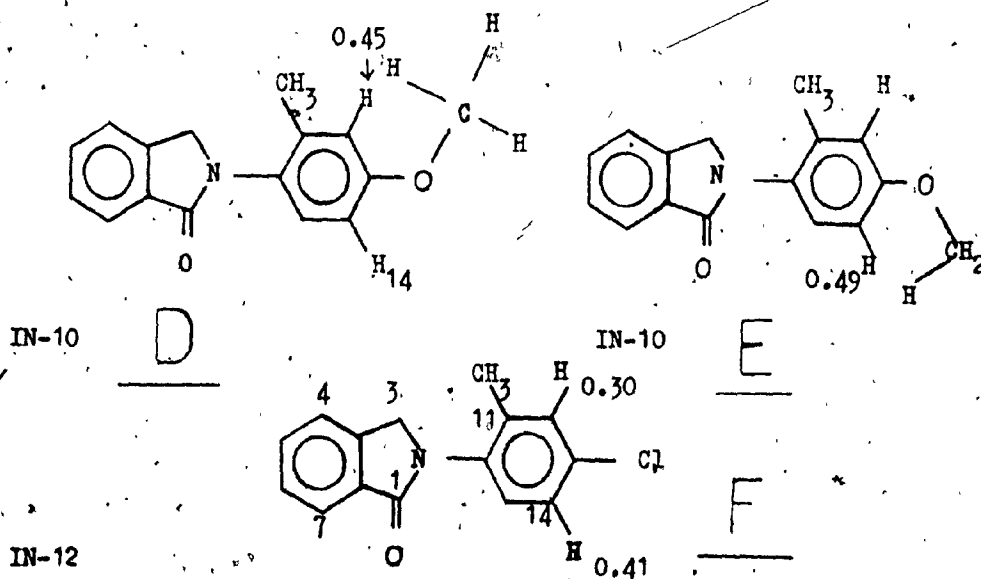
The relaxation contribution made by the methoxyl protons to nearby protons is now well-established. For example, Preston and Hall (85) observed that 2-acetamido-2-deoxy-D-hexopyranoses and methyl-D-hexopyranosides have pronounced differentials in the R_1 values of their anomeric protons. The replacement of a 2-hydroxyl group by a 2-acetamido group has little effect on the relaxation rate of H_1 , but the introduction of an anomeric methoxy group does cause an increase (of about 50%) in the R_1 value of the anomeric proton.

In another example, Hall and Preston (50H) have shown that in the case of the alkaloid vindoline, protons H-15 and H-17 (Fig. IN-19) relax mostly via the protons of the methoxyl group located at position 16. H-17 is also relaxed by a methyl group at position 1.

**Fig. 18-19: Structural Formula of Vindeline
Showing the Values (in seconds)
of the Longitudinal Relaxation
Times (T_1 Values), (50M).**

In view of the fore-going observations made by Hall and Preston, it is reasonable to consider that the 2-methoxyl or 2-hydroxyl protons make a significant contribution to the intramolecular dipole-dipole relaxation of the H-12 aryl protons in IN-3 and IN-7. In this respect, the contribution made by the hydroxyl group is expected to be less (1.53 sec^{-1} , normalized) than that of the methoxyl group (1.64 sec^{-1} , normalized). One can reasonably assume that the contribution to relaxation made by the 2-hydroxyl group will be approximately equal to that made by a 2-methyl group.

Similarly, the H-12 and H-14 aryl protons in IN-10 have a relaxation rate much higher (50% and 17%, respectively) than the corresponding protons in IN-12. Again, this is easily interpreted in terms of intramolecular DD relaxation provided by the para methoxyl protons to the H-12 and H-14 ring hydrogens, as shown below :



It should be mentioned that the halogen atom at C-13 is incapable of relaxing neighboring protons because of its low gyromagnetic ratio. The higher relaxation contribution to H_{12} (50 %) as compared to that of H_{14} (17 %) suggests that in $CDCl_3$ solution, the preferred conformation of the para methoxy group in IN-10 is the one in which it is closer to H-12 than to H-14.

The relaxation rates of the H-15 ring protons in the 1-isoindolinones, IN-1 to IN-14, do not show any correspondence with the increase in the molecular mass and dimension. These rates vary over the range $0.37 \pm 0.07 \text{ sec}^{-1}$, and are indicative of their insensitivity to the nature of one to three substituents on the aryl ring.

Similarly, the protons H-4 to H-6 on the 1-isoindolinone moiety lack sensibility of the variations in the environment of the other part of the molecule. Their variations cover the range $0.43 \pm 0.05 \text{ sec}^{-1}$ to $0.37 \pm 0.07 \text{ sec}^{-1}$. The spin-lattice relaxation rates of H-7 on the isoindolinone moiety are $0.29 \pm 0.03 \text{ sec}^{-1}$; and are indicative of the negligible variations in the motion of 1-isoindolinones in chloroform solution.

If the 12-, 13-, and 14-protons of the 2,6-dimethylphenyl compound, IN-9, formed an isolated spin system tumbling isotropically, it can be calculated from internuclear distances (obtained from Dreiding models) that the H-13 should relax 1.93 times faster than the other two protons. In fact, this proton relaxes only 10 % faster. Since these protons are approximately symmetrically disposed with respect to the most probable axis of anisotropic motion, it is unlikely that there will exist any

differential effects of tumbling motion. The relatively fast relaxation of the 12- and the 14-protons must, therefore, be attributed to the relaxation effects of the two dimethyl groups on the N-aryl moiety.

N-Aryl Substituents :

a. Methyl Groups.

The spin-lattice relaxation rates for the methyl substituents in the isoindolinones fall in the range 0.56 - 0.71 sec^{-1} (normalized : 1.81 - 2.42). They (and the methoxy protons) relax more slowly than the 3-methylene protons, despite the greater number of near neighbours of an individual proton within the group. This differential is a consequence of the freedom of segmental motion available to the methyl and methoxy groups.

Interpretation of the variations in the normalized relaxation rates of the aryl methyl groups within the series (Fig. IN-17) in terms of substituent effects is complicated by the possibility of concomitant changes in the rates of internal motion within the molecules. However, a number of interesting comparisons can be made. For example, the R_1 value of the ortho methyl groups in IN-2 and IN-11 is 0.56 sec^{-1} , (normalized: 2.00 and 1.81, respectively) leading to the following conclusions:

.... the meta chloro group does not relax the ortho methyl protons as expected.

.... the buttressing effect of the chlorine substituent apparently does not change the correlation time for the internal rotation of the methyl group, although steric interaction between these two substituents in IN-11 is greater than that between the ortho methyl group and the meta hydrogen in IN-2.

.... the buttressing effect of the meta chloro group upon the ortho methyl group in IN-11 is not sterically transmitted to the 3-methylene protons, since these (3-CH_2) protons have R_1 values of 0.96 sec^{-1} in both IN-11 and IN-12, where the steric influence on the o-methyl group in IN-12 is relieved. Therefore, the differential in the R_1 values of the 3-methylene groups in IN-2 and IN-11 (0.85 vs 0.96 sec^{-1} ; normalized: 3.03 vs 3.10 , respectively) does not result from the inter-ring relaxation. Rather, this differential is considered to arise from changes in the rotational correlation times upon increasing the mass of the molecule.

It is interesting to note that the buttressing effect of the m-methyl group upon the o-methyl group in IN-8, resulting in close proximity of protons, does not enhance the relaxation of these protons to any considerable extent. The o-methyl groups in IN-8 and IN-9 have R_1 values of 0.64 and 0.62 sec^{-1} (normalized: 2.06 and 2.00) respectively, whereas the o-tolyl methyl group in IN-2 has a slightly lower apparent rate of relaxation, 0.56 sec^{-1} ; (normalized: 2.00). In IN-9, where the buttressing effect is absent, the 3-methylene protons in particular, and all other protons in general, relax at rates similar to those of the

corresponding protons in IN-8. This clearly demonstrates that in IN-8 and IN-9 the inter-ring relaxation is operative for the 3-methylene protons to a similar extent and that it is not influenced by the bettressing effect of the meta methyl group. Moreover, changes in their correlation times also arise:

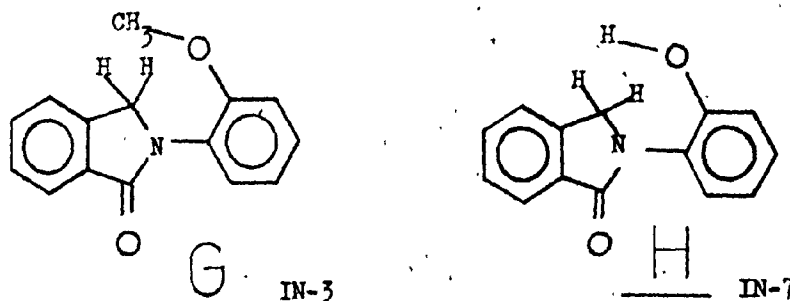
f r o m variations in molecular tumbling. These correlation times, as described earlier, are the resultant of individual correlation times for the internal free rotation of methyl group about C-C bond, of the N-aryl moiety about the C-N bond, and the anisotropic rotation of the whole molecule about the preferred axis of rotation. Presently, it is not possible to estimate these individual correlation times.

The most striking feature of the normalized relaxation rates is the relatively fast relaxation of the meta methyl group in IN-8. This group relaxes 17 % faster than the ortho methyl group in the same compound, whose normalized R_1 value is consistent with other ortho tolyl values within the series. In particular, since the relaxation rate of the ortho methyl protons in IN-8 is similar to that in IN-9, (2.06 vs 2.00), these protons may not be considered as a source for relaxation of the meta methyl group. Provided that the chemical shift assignment is correct, the origin of this relaxation rate enhancement is not clear. The assignment is based on reported assignments for related compounds, but in view of the relaxation data, it must be considered questionable.

b. The Methoxyl and Hydroxyl Protons :

As discussed earlier under the sub-title 'N-aryl substituents', the methoxyl and hydroxyl hydrogens relax the neighbouring aryl ring protons. Since the major source of relaxation of methoxy protons is within this group, the external influence of the aryl ring protons on the methoxy group may not be easily evident. Similarly, for the hydroxyl, which usually relax very slowly, the effect of relaxation from nearby protons is not readily apparent.

It is possible that the inter-ring relaxation process may be operative between the 3-methylene protons and the ortho methoxyl or hydroxyl hydrogens, IN-3 and IN-7, because of the prolated substituents as shown below :



For the same reasons mentioned above, an inter-ring relaxation of small magnitude may not easily be evident.

The methoxyl groups in IN-3 and IN-10 relax faster than any of the methyl groups, despite their apparently greater freedom for segmental motion. In particular, the normalized relaxation rate of the ortho methoxyl group in IN-3 is 39 %

faster than that of the ortho methyl group in IN-2, the most closely analogous compound. The origin of this rate enhancement is not clear at present.

SECTION 2.

BARRIERS TO INTERNAL

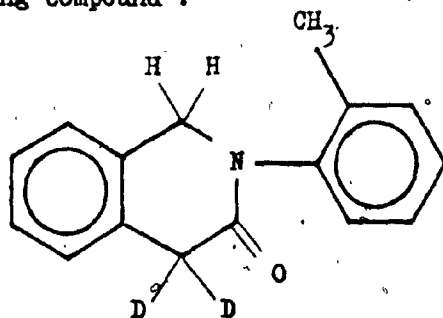
ROTATION IN 1,3-DIARYL-

2-THIO-4-IMIDAZOLIDINONES

INTRODUCTION

Barriers to rotation have been investigated by several methods (36,75) and their determination by DNMR has been the subject of a number of reviews (49,81,83). Amides in particular are reviewed by Siddall (102).

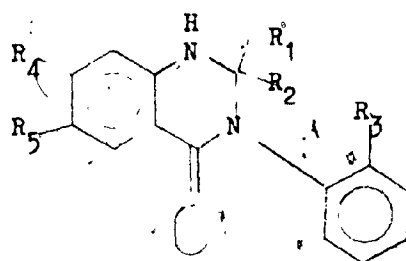
The first report on the study of hindered internal rotation about the aryl C-N bond in N-aryl cyclic amides appears to be the one reported by Shvo and co-workers (96). They determined a free energy of activation of 17.3 kcal/mole, at 73° for the following compound :



A

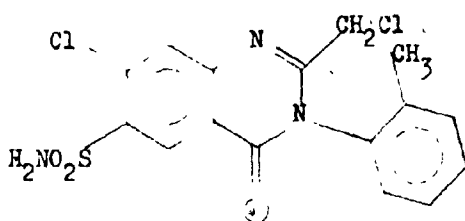
In our laboratories, considerable attention has been paid to the study of hindered internal rotation about the aryl C-N bond in N-aryl cyclic amides. A brief description is in order.

Fehlner (38) examined a series of 3-aryl substituted quinazolinones in order to study the barrier heights to rotation about the aryl C-N bond. However, interpretation of the results



B

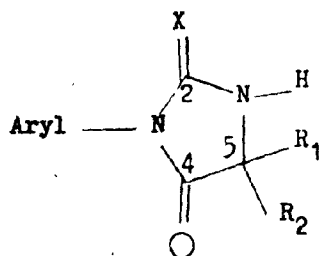
were complicated by the flipping of the non-planar heterocyclic ring. In an attempt to overcome this problem, he examined the following compound, C.



C

Unfortunately, there was no observable chemical shift difference between the diastereotopic methylene protons at the lowest temperature attainable in DMSO- d_6 .

Fehlner (26,38) also observed high rotational barriers in 3-aryl-2,4-imidazolidinediones, D, and 3-aryl-2-thio-4-imidazolidinones, E.



D

X = O

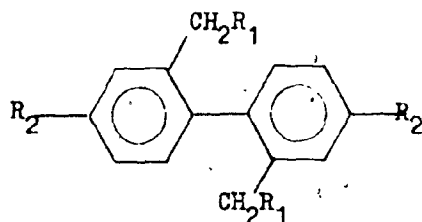
E

X = S

A slight conformational preference (when $R_1 \neq R_2$) between the diastereomeric rotational isomers in both series of compounds was

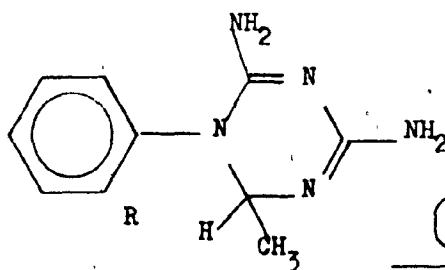
noted. It was also observed that in these compounds, an ortho chloro substituent on the aryl ring is more effective than an ortho methyl group in restricting the rotation in imidazolidinediones (X = O, S) although a methyl group is expected to exert a steric effect greater than that of a chlorine atom. This has been attributed to repulsion between the chlorine atom and a carbonyl oxygen atom in the torsional transition state of the 3-aryl compounds. It was also shown that the observed influence of an ortho chloro substituent is primarily a through-space, rather than a through-bond, effect.

Bentz (14) has examined hindered rotation about the phenyl-phenyl bond of several pairs of 2,2'-disubstituted biphenyls, F, by means of complete line shape analysis of their



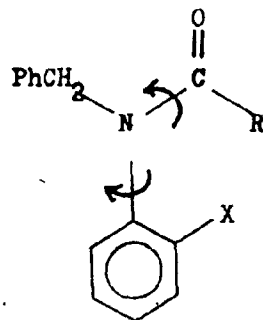
F

temperature-dependent NMR spectra. He also examined (14,15,27) hindered rotation about the aryl C-N bond in two s-triazines, G.



R = CH₃, Cl

G



H

It was found, in agreement with common observation, that a methyl group exerts a steric effect greater than that of a chlorine atom in restricting internal rotation about the aryl C-N bond.

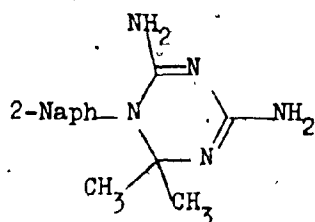
Hund (52) has examined a series of N-benzyl-N-aryl ortho substituted amides, H, in order to investigate the effect of structural changes on kinetic parameters. He concluded that the process which interchanges the magnetic environment of the methylene protons is not only rotation about the aryl C-N bond but also involves rotation about the C-N bond of the amide function. The extent of involvement of the latter process depends on the identity of the ortho and amide substituents and on solvent polarity.

Hund (52,28) also attempted to observe magnetic non-equivalence of enantiomeric solute pairs with various optically active solvents. This effect was observed with 3-(o-tolyl)-5,5-dimethyl-2,4-imidazolidinedione, D, using (-)-2,2,2-trifluoro-1-phenylethanol as the solvent.

Williams (109) made a preliminary investigation of the 3-aryl-2,4-imidazolidinediones, D, using the CW carbon-13 NMR technique. He studied the effect of various substituents on the chemical shifts of carbon atoms in the hetero and the aryl rings.

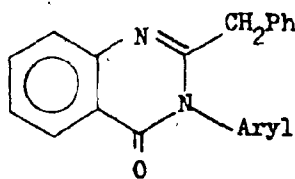
Giles (44) and Icli (53) have contributed significantly toward deeper understanding of hindered internal rotational processes about the aryl C-N bonds in various heterocyclic systems. Giles (29) observed high barriers to rotation

about the aryl C-N bond in the compounds I - K even though they lack bulky ortho substituents.



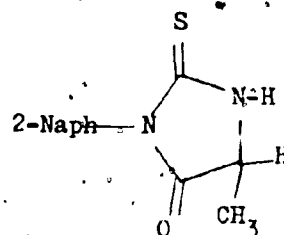
Solvent : Perfluorobutyric acid

I



Nitrobenzene

J



DMSO-d₆

K

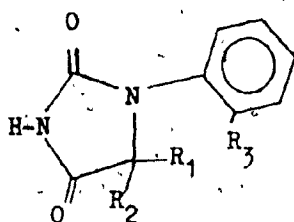
The free energies of rotation about the C-N bonds in these systems were found to be 18.9 to 23.1 kcal/mole in the solvents indicated.

In the case of ortho substituted 3-aryl-2-benzyl-4(3H)-quinazolinones, J, attempts to measure the rate of rotation of the aryl groups by line shape analysis of the AB quartets at elevated temperatures failed (30). No indications of collapse of the AB quartets through time-averaging were detectable at the highest temperatures employed (150° - 187°), even for compounds with small blocking substituents, such as fluoro, in the ortho position. The barriers to internal rotation about the aryl C-N bond of some 3-aryl-5-methyl-2-thio-4-imidazolidinones, E, were also examined.

An X-ray crystallographic study (16) of one of the diastereomeric rotational isomers of 3-(2-bromophenyl)-5-methyl-2-thio-4-imidazolidinone, E, revealed that the dihedral angle between the heterocyclic and aryl rings is 82°. The heterocyclic ring was found to be planar. It was also noted that in the

preferred rotational isomer, which should be the more highly solvated, the bromine atom would be transoid to the solvent shell and hence cisoid to the 5-methyl group.

Icll (53) has investigated the stereochemistry and kinetics of conformational changes in 1-aryl substituted-2,4-imidazolidinediones, L, following the restricted internal



L

rotation about the aryl C-N bond. Solvent effects on the thermodynamic parameters were also examined. He found (26) that in 1-aryl derivatives, an ortho methyl group is effectively larger than an ortho chloro substituent in restricting rotation about the aryl C-N bond, whereas in 3-aryl derivatives, the reverse order of sizes is observed. He also determined ¹H and C-13-NMR spectra of a number of 1- and 3-aryl-2,4-imidazolidinediones (28) in achiral and chiral solvents. Chemical shifts between corresponding protons on the pairs of rotamers, induced by diastereomeric solute-solvent interactions in the chiral solvent, are strongly dependent on the location of the protons in the solute molecules. In conjunction with proton and carbon-13 chemical shifts, the geometry of the solvated species has been discussed.

Khadim (61) has studied the ground state stereochemistry of 3-aryl substituted-2-thio-4-imidazolidinones, E, employing the

data obtained by Pulse Fast Fourier Transform Carbon-13 NMR spectroscopy. The upfield γ -methyl substituent effect on the C-2 thiocarbonyl carbon has been observed to be related to the steric bulk of the ortho substituent as well as the substituents in the para position of the aryl ring. The direction and magnitude of the solvent-induced variations in the chemical shifts of C-2 and C-4 carbons have been estimated. The chemical shifts of the C-2 and C-4 carbons have been found to show a linear relationship with the electronegativity of the ortho halogen atom. The δ -, ϵ -, solvent, inductive, and steric effects on the chemical shifts of various carbons have been discussed.

Recently, Musty (79) has concluded a C-13 NMR study of a series of 3-aryl-2,3-dihydro-4(1H)-quinazolinones and the results were interpreted in terms of the ground state isomers resulting from the restricted internal rotation about the aryl C-N bond. The influence of steric, conjugation, and inductive effects due to the C-2 substituents and the N-3 aryl substituents on the chemical shifts of various carbon atoms in these compounds were considered.

The investigation of barriers to hindered internal rotation about the aryl C-N bonds in 1,3-diaryl-2-thio-4-imidazolidinones, M, and N-aryl substituted-1-isoindolinones, N, in relation to the stereochemistry of conformational change is the subject of this study.

The 1,3-diaryl-2-thio-4-imidazolidinones and N-aryl-1-isoindolinones, which were synthesised for this DNMR study, are listed in Tables IZ-1 and IZ-2, respectively.

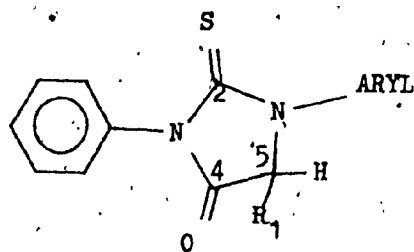
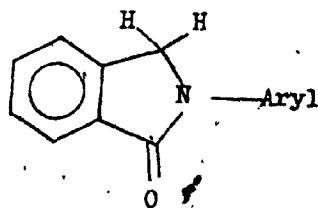
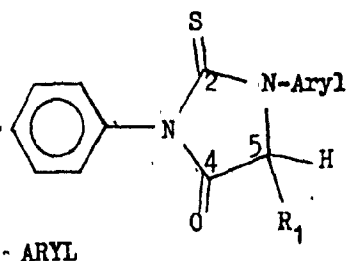
MN

TABLE IZ-1

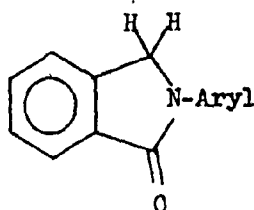
1,3-Diaryl-2-thio-4-imidazolidinones



No.	ARYL	R
IZ-1	H	H
IZ-2	Phenyl	H
IZ-3	2-Tolyl	H
IZ-4	2-Methoxyphenyl	H
IZ-5	2-Fluorophenyl	H
IZ-6	2-Chlorophenyl	H
IZ-7	2-Bromophenyl	H
IZ-8	2,3-Dimethylphenyl	H
IZ-9	1-Naphthyl	H
IZ-10	H	CH ₃
IZ-11	Phenyl	CH ₃
IZ-12	2-Tolyl	CH ₃
IZ-13	2-Methoxyphenyl	CH ₃
IZ-14	2-Fluorophenyl	CH ₃
IZ-15	2,3-Dimethylphenyl	CH ₃
IZ-16	1-Naphthyl	CH ₃

TABLE IZ-2

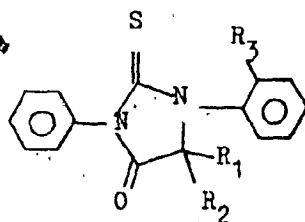
N-Aryl-1-Isoindolinones



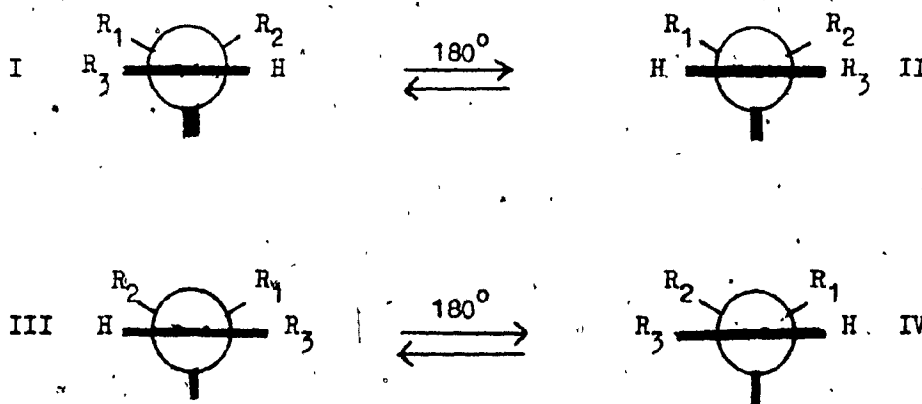
No.	ARYL
IN-1	Phenyl
IN-2	2-Tolyl
IN-3	2-Methoxyphenyl
IN-4	2-Fluorophenyl
IN-5	2-Chlorophenyl
IN-6	2-Bromophenyl
IN-7	2-Hydroxyphenyl
IN-8	2,3-Dimethylphenyl
IN-9	2,6-Dimethylphenyl
IN-10	4-Methoxy-2-Methylphenyl
IN-11	3-Chloro-2-Methylphenyl
IN-12	4-Chloro-2-Methylphenyl
IN-13	1-Naphthyl
IN-14	2-Naphthyl

Causes of Non-Equivalence in the NMR Spectra :

The internal bond rotation about the C-N bond joining the aryl and hetero rings results in formation of diastereomeric and enantiomeric rotational isomers in 1-aryl-thioimidazolidinones.



Asymmetry is introduced by the ortho substituted aryl and the C-5 substituents. The aryl and the hetero rings of the rotamers are shown at right angles to each other in the figures below, the molecule being viewed along the C-N bond rotational axis. Due to steric and electronic effects the planes are expected to deviate from 90° angles. In order to simplify the schematic drawings, these effects are not considered here, but they are discussed later in the thesis.



A 180° rotation of the ortho substituted aryl ring around the C-N rotational axis forms isomer II from I, and isomer IV from III. When the R_1 and R_2 groups are identical, I and IV, and II and III will be identical. I will be enantiomeric to II. Enantiomers have similar physical properties, so one may expect indistinguishable spectra for the I and II enantiomers. However, R_1 and R_2 are non-equivalent (diastereotopic) due to the presence of asymmetry caused by the ortho aryl substituent R_3 . Hence they reside in different magnetic environments and they are expected to show chemical shift differences in the NMR spectra. If R_1 and R_2 are protons, an AB spin system will be present. The protons will couple to each other so that an AB quartet is expected to be observed at slow rates of rotation. In this work an AB quartet was not exhibited by the thioimidazolidinones studied even at the lowest possible temperatures ($\approx -150^\circ$), presumably because of low barriers to hindered rotation.

Diastereomeric species may be present only when R_1 and R_2 are not identical. Under these circumstances, I will be diastereomeric to II, and III will be diastereomeric to IV. I and III, and II and IV, will be enantiomeric, with indistinguishable spectra. R_1 and R_2 were chosen to be a proton and a methyl group, respectively, in the thioimidazolidinone diastereomeric series. The lifetimes of the diastereomers were found to be unequal, due to certain steric interactions in these molecules, resulting in unequal intensities of the signals arising from corresponding

protons on the diastereomeric rotamers. The spectrum is further complicated by coupling of the methine proton to the methyl protons. The methine proton shows a pair of quartets, while the methyl protons show a pair of doublets under conditions of slow rotation.

Theory of Line Shape Analysis :

The line shape theory based on the Bloch equations (17,18) to derive the line shape equations for an exchange process between two sites has been dealt in detail by Jackman and Cotton (55).

Comparison of Spectra :

Theoretical spectra can be calculated for any given set of lifetimes, chemical shift, and coupling constant parameters for the exchanging sites, using the equations based on the Gutowsky-Holm (49) formulation. In order to obtain the most accurate lifetime values or rate constants for rotamers, at given temperatures, one has to achieve a good fit between the experimental and theoretical spectra. This may be done point by point by computer. A spectrum calculated from initial estimates of the parameters can be compared with the observed spectrum by a least squares method. New parameters are then calculated based upon the differences between observed and calculated intensities, and a resulting new theoretical spectrum is compared with the experimental spectrum. The non-linear

regression procedure continues to calculate new parameters and make comparisons until the best fit is obtained. The programs NLINGH and NLINDD2, which are suitable for this non-linear least squares regression analysis, were developed by Colebrook (25) from the program NLIN2 which was originally obtained from the SHARE library (110). The basic non-linear regression program is used in combination with sub-routines containing the line-shape equations for the system being considered.

The process of fitting the theoretical spectra to the experimental ones was carried out in two steps. First, in order to get reasonably good initial estimates of exchange lifetimes and the chemical shift difference, only the coupling constants and the experimental linewidths were held constant and the chemical shift differences were allowed to vary. This was considered to be important, since the experimental spectra obtained at higher temperatures posed difficulty in determining the chemical shift differences accurately because of line-broadening due to the exchange process. Second, based on these initial estimates from above, theoretical spectra were again fitted to the experimental ones, now keeping coupling constants, linewidth and the chemical shift differences constant during the fitting process. The value of the chemical shift (in Hz) determined from the experimental spectra at or near the room temperature for a given molecule was held constant during the fitting process and thus more accurate exchange lifetimes were calculated.

CALCULATION OF ACTIVATION PARAMETERS :

The Arrhenius and Eyring activation parameters for the rotational process are calculated through the use of mean lifetimes or rate constants which are obtained from line-shape analysis. A computer program, ACTPAR, (25) has been written to calculate all the activation parameters and 90 % confidence limits from given lifetimes and temperatures.

The Arrhenius activation energy, E_a , is defined in the Arrhenius equation :

$$K = A \exp (- E_a / RT)$$

where K is the rate constant for the rotation process, A is the frequency factor, R is the gas constant, and T is the temperature in degrees Kelvin. The slope of the plot of

$$\ln K \text{ versus } 1/T (K^0)$$

gives the energy of activation, see Fig. IZ-1 to IZ-3.

The temperature dependent activation parameters, enthalpy of activation (ΔH^\ddagger), free energy of activation (ΔG^\ddagger), and entropy of activation (ΔS^\ddagger), are calculated by the use of the Eyring equations by ACTPAR. These equations are reproduced below :

$$\Delta H^\ddagger = E_a - R T$$

$$\Delta G^\ddagger = 2.303 RT (10.319 + \log T + \log \tau)$$

$$\Delta S^\ddagger = (\Delta H^\ddagger - \Delta G^\ddagger) / T$$

ACTPAR finds the best straight line for the plot of $\ln K$, versus $1/T$ (K°) through the use of a linear regression method, and also calculates the Eyring parameters for a specified temperature.

The activation parameters reported in this study are calculated at $298.1 K^\circ$ ($25 C^\circ$).

Preparation of NMR Samples :

The NMR samples of 1,3-diaryl-2-thio-4-imidazolidinones with high coalescence temperatures ($> 25^{\circ}$) were prepared in a mixture (3 : 2 or 3 : 1) of DMSO- d_6 and 2-chloropyridine.

2-Chloropyridine has a boiling point higher than pyridine.

Moreover, it is a good solvent for these compounds. The samples were prepared as concentrated as possible (2 - 3 M solutions).

The sample solutions which coalesced below room temperature, were dissolved either in mixtures of DMSO- d_6 and 2-chloropyridine, or acetone- d_6 and pyridine, or acetone- d_6 and DMSO- d_6 . Contrary to the report by Icli (53), the solutions in acetone- d_6 containing 15 - 20 % DMSO- d_6 froze in the vicinity of -50° to -55° .

N-aryl-1-isindolinones are easily soluble in acetone and chloroform. Approximately 2M solutions were prepared in a mixture of chloroform- d_1 and acetone- d_6 (5 : 2)

In some cases, NMR spectra were measured at or near -150° . 30-40 mg of the sample was dissolved in chlorodifluoromethane, $CHClF_2$, (Freon-22) at acetone-dry ice temperature. The solution was then frozen by immersing the sample tube in liquid nitrogen and subjected to high vacuum for a few minutes. The solution was thawed in acetone-dry ice mixture, frozen by liquid nitrogen and again connected to high vacuum. The thaw-freeze-high vacuum procedure was repeated 5-6 times until all dissolved gases were removed. The sample tube, being immersed in liquid nitrogen, was sealed under 0.05 - 0.1 torr, and the NMR spectrum was run at

100 MHz at temperatures in the vicinity of -150° on a JEOL-JNM-4H-100 NMR spectrometer. TMS was used as internal reference, but generally, the spectra were run by locking the NMR spectrometer on the central peak of Freon-22.

Tetramethylsilane (TMS) and hexamethyldisiloxane (both from NMR Specialities, Kensington, Pa, USA) were added in small portions as internal standards to the low and high temperature NMR samples, respectively.

TEMPERATURE DEPENDENCE OF CHEMICAL SHIFT DIFFERENCES :

The temperature dependence of the chemical shift differences between non-equivalent diastereomeric and enantiomeric protons of 3-aryl-2,4-imidazolidinediones was found to be relatively small in the line shape analysis studies by Fehlner (38) and Granata (45 A). For all the cases studied in those projects, there was not enough evidence because of limitations in the precision of the experiment to show whether the chemical shift difference had increased or decreased with increasing temperatures. In the present study, the calculated chemical shift difference dependence upon temperature becomes evident when the fitting process is carried out by keeping the linewidth constant and allowing the chemical shift difference to vary. The chemical shift differences returned by the computer in the coalescence region become very large and unacceptable. Therefore, the exchange lifetimes were calculated by keeping both the linewidth and the chemical shift difference constant during the fitting process of the spectra.

DATA AND RESULTS

The N-aryl-1-isoindolinones, IN-1 to IN-14, failed to show individual signals from the enantiomeric ortho group protons or the diastereotopic 3-methylene protons at low temperatures. Even the N-(2,3-dimethylphenyl)- and N-(1-naphthyl)- derivatives, IN-8 and IN-13, respectively, did not show any diastereomeric or diastereotopic splitting of the methyl or methylene resonances at the lowest temperatures attainable in chloroform- d_1 and acetone- d_6 mixtures ($\approx 1M$ solutions). These compounds will be discussed in detail in a separate section following the present one.

A behaviour similar to the 1-isoindolinones was also observed for the 2-thio-4-imidazolidinones unsubstituted at the C-5 position or substituted at C-5 but having a small ortho substituent on the aryl ring. In view of there being a substantially bulky and polar thiocarbonyl group in the vicinity of the N-aryl moiety, this observation is somewhat unexpected.

Line shape analysis data and results for some of the C-5 monomethyl-2-thio-4-imidazolidinones, which did show individual diastereomeric signals, are presented in the following Tables and Figures. The lifetimes, together with their associated standard errors, were calculated from the best fits of calculated and digitized experimental spectra using the computer program NLINDD. In one set of calculations, the fitting process was carried out by holding only the linewidth as a constant parameters. In another set of calculation, the fitting procedure was carried out by keeping both the linewidth and the chemical shift difference constant. Rate constants are given as reciprocals of lifetimes. For all of these compounds two well-separated spin-doublets were observed which collapsed to a very broad singlet in the coalescence region. A doublet appeared when the samples were heated much beyond the coalescence temperature. Since the temperature range is $25^{\circ} - 150^{\circ}$, the quality of the fitting of the spectra is quite acceptable. This can also be seen from the computer print-out after the fitting process is complete.

The range of the Arrhenius plots are chosen to present a convenient display, rather than for purpose of comparison. All the Arrhenius plots of the C-5 monomethyl imidazolidinones are drawn on the same scale.

Tables of kinetic data are shown following the experimental data. Arrhenius and Eyring parameters and 90 % confidence limits were calculated by the program ACTPAR. Equilibrium constants were obtained from the ratio of rate

constants for diastereomeric equilibrium at 25°.

Table IZ-6 is included to show kinetic parameters and equilibrium constants for rotation for the thio-imidazolidinones when the chemical shift is not held constant during the fitting process. (cf. Table IZ-6A). It is evident that the enthalpies and entropies of activation are about 10 - 20 % higher when only the linewidth is a constant parameter, than when both the linewidth and the chemical shift parameters are held constant. The free energies of activation show little variations (about 0.3 - 2.3 %).

The lifetimes, Tau A and Tau B, for the collapse of the C-5 methyl signals are chosen for the upfield and low field peaks in the NMR spectrum, respectively.

Lifetimes and Rotational Rates for 1-(2-Tolyl)-3-Phenyl-5-Methyl-2-Thio-4-Imidazolidinone, IZ-12, in DMSO-d₆ + 2-Chloropyridine (3:2), 3M Solution, at Various Temperatures. Linewidth (1.0 Hz) and Chemical Shift Difference (10.5 Hz) Were Held Constant During the Fitting Process.

Temp. (C°)	Lifetime (sec.)	Standard Error, x10 ²	Rate Constant (1/sec.)
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TAU A. COLLAPSE OF C-5 METHYL (UPFIELD) SIGNALS.

34.0	0.3172	3.381	3.15
48.0	0.2869	2.642	3.48
57.0	0.2236	1.234	4.47
62.5	0.1780	0.514	5.38
64.5	0.1536	0.424	6.51
67.0	0.1384	0.392	7.22
70.0	0.1116	0.412	8.96
72.0	0.0883	0.468	11.32
75.0	0.0560	0.422	17.86
83.0	0.0422	0.199	23.70
89.5	0.0367	0.108	27.25

TAU B. COLLAPSE OF C-5 METHYL (LOW FIELD) SIGNAL.

34.0	0.2320	2.615	4.31
48.0	0.2277	2.157	4.39
57.0	0.1872	1.082	5.34
62.5	0.1462	0.448	6.84
64.5	0.1297	0.392	7.71
67.0	0.1204	0.357	8.31
70.0	0.1005	0.386	9.95
72.0	0.0846	0.443	11.82
75.0	0.0641	0.452	15.60
83.0	0.0477	0.216	20.96
89.5	0.0379	0.111	26.38

TABLE IZ-4

100

Lifetimes and Rotational Rates for 1-(2,3-Dimethylphenyl)-3-Phenyl-5-Methyl-2-Thio-4-Imidazolidinone, IZ-15, in DMSO-d₆ + 2-Chloropyridine (4:1), 2M Solution, at Various Temperatures. Linewidth (1.0 Hz) and Chemical Shift Difference (10.0 Hz) Were Held Constant During the Fitting Process.

Temp. (C°)	Lifetimes (sec)	Standard Error, x 10 ²	Rate Constant (1/sec)
---------------	----------------------	--------------------------------------	--------------------------

TAU A, COLLAPSE OF C-5 METHYL (UPFIELD) SIGNALS.

81.0	0.3603	4.098	2.77
91.5	0.2403	1.872	4.16
101.0	0.1843	1.544	5.42
106.0	0.1363	0.597	7.34
108.0	0.1150	0.388	8.70
110.0	0.1271	0.521	7.87
117.5	0.0855	0.126	11.70
127.0	0.0752	0.132	13.30
133.0	0.0477	0.047	22.34

TAU B, COLLAPSE OF C-5 METHYL (LOW FIELD) SIGNALS.

81.0	0.2425	2.842	4.12
91.5	0.1690	1.411	5.92
101.0	0.1414	1.296	7.07
106.0	0.1075	0.573	9.30
108.0	0.0943	0.350	10.60
110.0	0.0919	0.463	10.88
117.5	0.0684	0.115	14.62
127.0	0.0557	0.113	17.95
133.0	0.0401	0.043	24.94 ✓

TABLE IZ-5

101

Lifetimes and Rotational Rates for 1-(1-Naphthyl)-3-Phenyl-5-Methyl-2-Thio-4-Imidazolidinone, IZ-16, in DMSO- d_6 + 2-Chloropyridine (3:2), 2.5 M Solution, at Various Temperatures. Linewidth (1.0 Hz) and Chemical Shift Difference (9.4 Hz) Were Held Constant During the Fitting Process.

Temp. ($^{\circ}$ C)	Lifetimes (sec.)	Standard Error, $\times 10^2$	Rate Constant (1/sec.)
--------------------------	---------------------	----------------------------------	---------------------------

TAU A, COLLAPSE OF C-5 METHYL (UPFIELD) SIGNALS.

34.0	0.4878	1.145	2.05
51.5	0.2961	1.543	3.38
61.8	0.2560	1.125	3.89
71.0	0.1932	0.734	5.18
77.0	0.1850	0.832	5.40
81.0	0.1718	0.474	5.82
84.5	0.1372	0.335	7.29
87.5	0.1355	0.419	7.38
99.0	0.0720	0.070	13.89
104.0	0.0514	0.122	19.45
108.5	0.0449	0.041	22.27

TAU B, COLLAPSE OF C-5 METHYL (LOW FIELD) SIGNALS.

34.0	0.4554	0.973	2.20
51.5	0.2787	1.406	3.59
61.8	0.2350	1.025	4.25
71.0	0.1825	0.691	5.48
77.0	0.1742	0.784	5.74
81.0	0.1614	0.445	6.20
84.5	0.1316	0.328	7.56
87.5	0.1180	0.375	8.47
99.0	0.0659	0.067	15.17
104.0	0.0530	0.126	18.87
108.5	0.0437	0.039	22.88

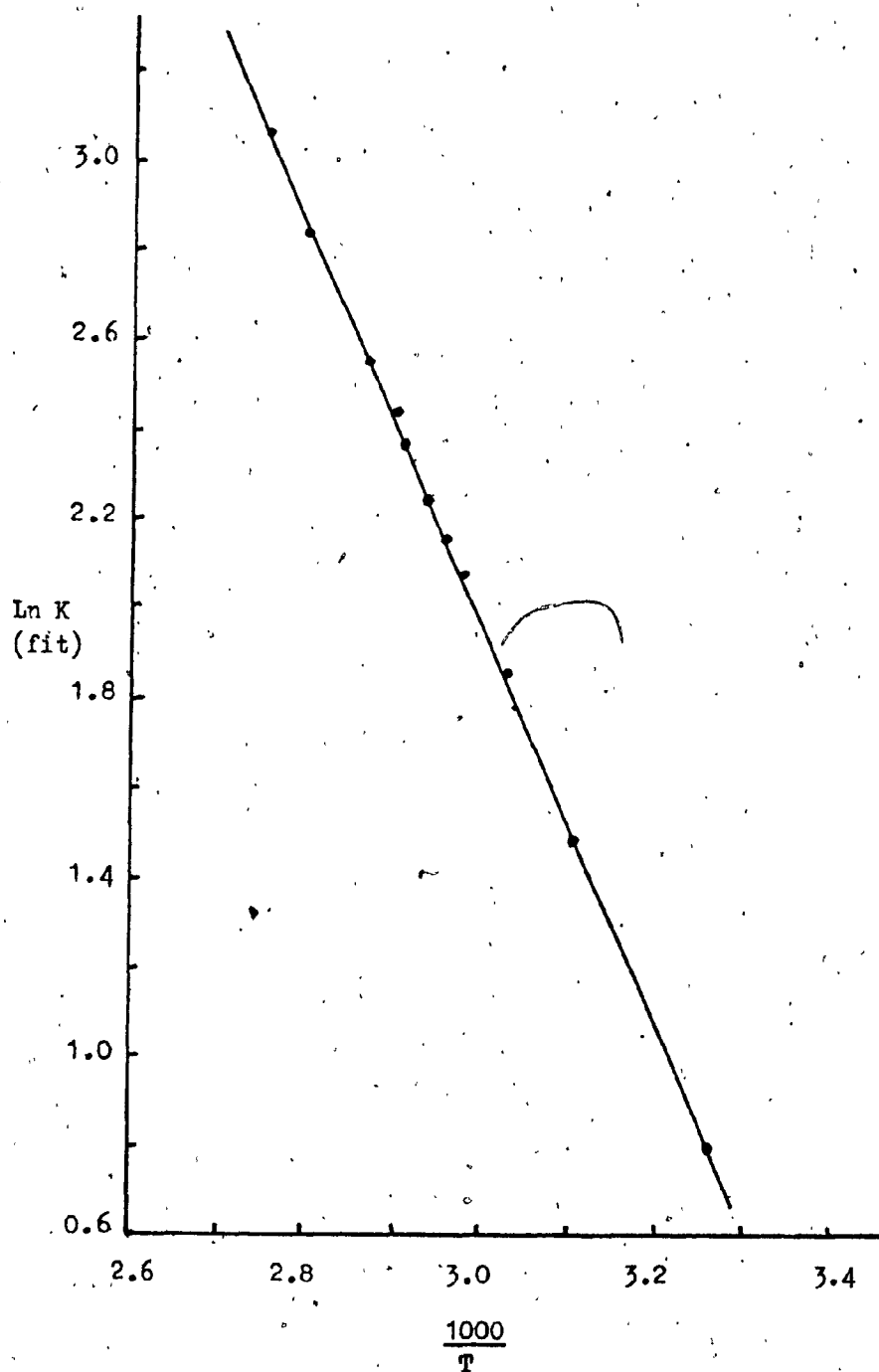


Fig. IZ-1 : Arrhenius Plot for 1-(2-Tolyl)-3-Phenyl-5-Methyl-2-Thio-4-Imidazolidinone, IZ-12, in DMSO-d₆ + 2-Chloropyridine (3:2), 3M Solution.

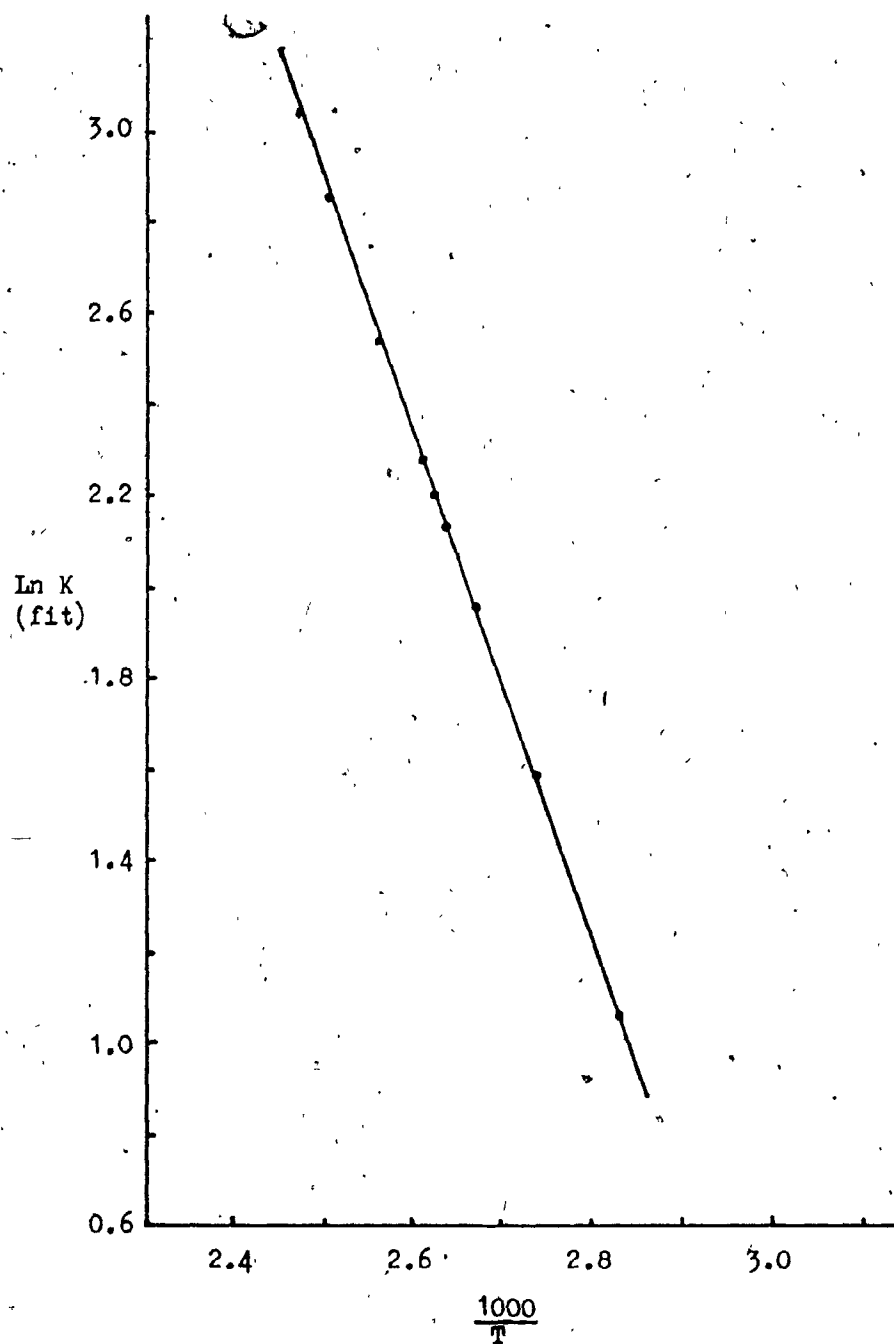


Fig. IZ-2 : Arrhenius Plot for 1-(2,3-Dimethylphenyl)-3-Phenyl-5-Methyl-2-Thio-4-Imidazolidinone, IZ-15, in DMSO-d_6 + 2-Chloropyridine (4:1), 2M Solution.

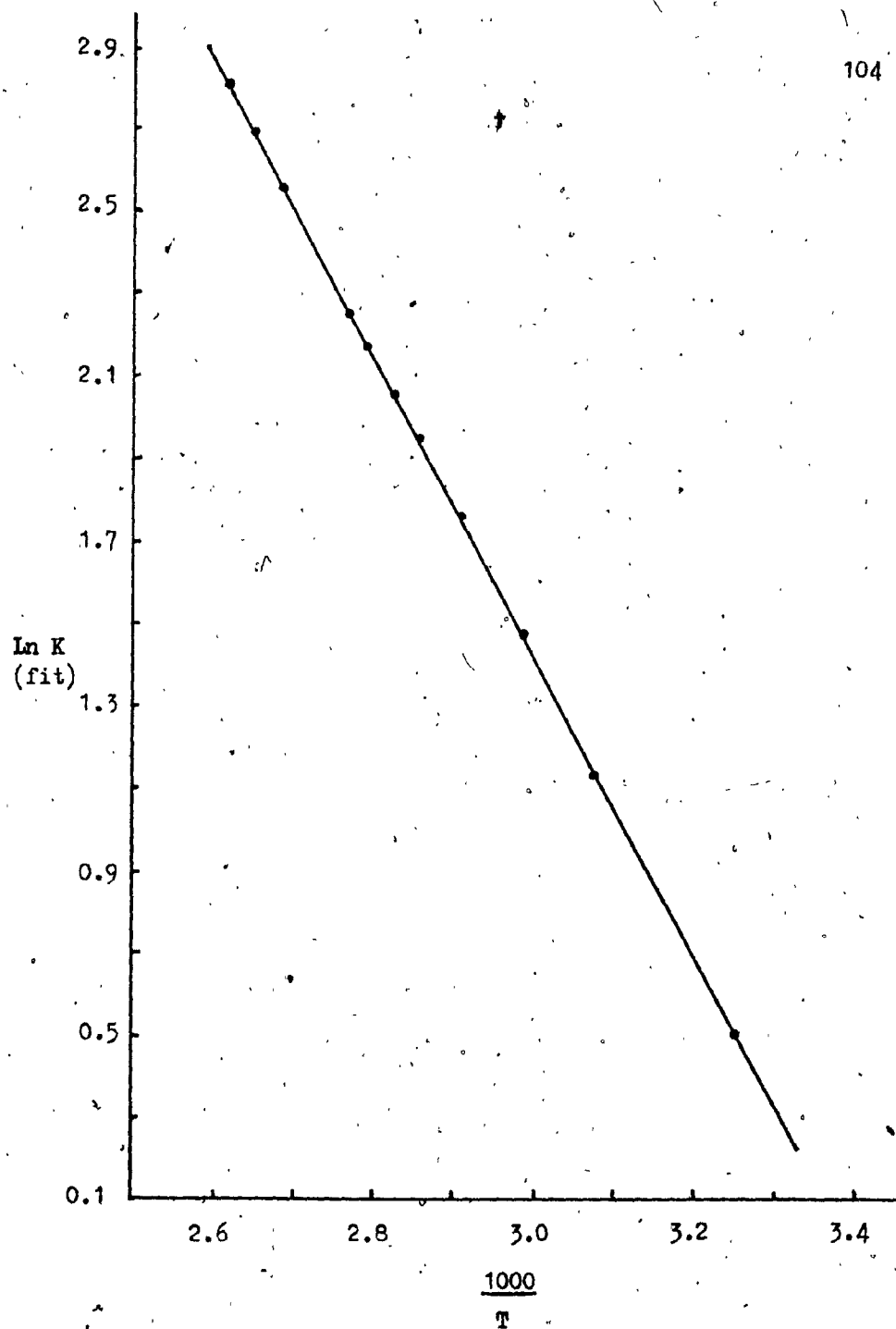


Fig. IZ-3 : Arrhenius Plot for 1-(1-Naphthyl)-3-Phenyl-5-Methyl-2-Thio-4-Imidazolidinone, IZ-16, in DMSO-d_6 + 2-Chloropyridine (3:2), 2.5 M Solution.

T A B L E I Z - 6

KINETIC PARAMETERS^a AND EQUILIBRIUM CONSTANTS FOR ROTATION IN SOME 1,3-DIARYL-2-THIO-4-IMIDAZOLIDINONES IN DMSO-d₆ + 2-CHLOROPYRIDINE, CALCULATED AT 298.1 K.*

No.	1-Aryl	T _c	Site	E _a ^b	A ^c x10 ⁷	ΔH ^b	ΔS ^d	ΔG ^b	T _{25°} ^(sec)	Rate Constant (Sec ⁻¹) 25°	K _{eq} (25°)
IZ-12	2-Tolyle	89.5°	T _A	10.5 ± 3.4	6.53	9.9 ± 3.4	-25 ± 10	17.30 ± 0.4	0.7709	1.297	1.51
			T _B	9.2 ± 2.9	1.05	8.6 ± 2.9	-28 ± 8	17.00 ± 0.3	0.5111	1.956	
IZ-15	2,3-ME ₂ -PH ^f	133.0	T _A	12.0 ± 2.3	5.51	11.4 ± 2.3	-25 ± 6	18.85 ± 0.5	10.84	0.092	1.09
			T _B	12.2 ± 2.5	8.80	11.6 ± 2.5	-24 ± 6	18.80 ± 0.5	9.970	0.100	
IZ-16	1-Naphthyl ^g	108.5	T _A	8.4 ± 2.1	0.11	7.8 ± 2.1	-33 ± 6	17.54 ± 0.3	1.192	0.838	1.05
			T _B	8.5 ± 2.2	0.15	7.9 ± 2.2	-32 ± 6	17.52 ± 0.4	1.135	0.881	

^aErrors are 90 % Confidence Limits; ^bkcal/mol; ^cFrequency Factor, ^dEntropy Units.

^eSolvent Ratio (3 : 2), 2 M; ^fSolvent Ratio (4 : 1), 2 M, ^gSolvent Ratio (3 : 2), 2.5 M.

*Calculated by keeping only the linewidth constant during the fitting process, (cf. Table IZ-6A).

TABLE 1Z-6A

KINETIC PARAMETERS^a AND EQUILIBRIUM CONSTANTS FOR ROTATION IN SOME
 1,3-DIARYL-2-THIO-4-IMIDAZOLIDINONES IN DMSO-d₆ + 2-CHLOROPYRIDINE, CALCULATED
 AT 298.1 K. (LINEWIDTH AND CHEMICAL SHIFT DIFFERENCE HELD CONSTANT DURING THE
 FITTING PROCEDURE.)

No	I-ARYL	T _c ^h (C°)	E _a ^b	A ^c x10 ⁷	H ^b	S ^d	G ^b	τ (sec; 25°) 1/sec; 25°
1Z-12	2-Tolyl ^e	89.5°	8.9 ± 1.5	0.50	8.3 ± 1.5	-30 ± 4	17.2 ± 0.2	0.672 1.488
1Z-15	2,3-ME ₂ -PH ^f	133.0°	10.3 ± 1.0	0.73	9.7 ± 1.0	-29 ± 3	18.4 ± 0.2	4.826 0.207
1Z-16	1-Naphthyl ^g	108.5°	7.2 ± 0.9	0.02	6.6 ± 0.9	-36 ± 2	17.4 ± 0.1	0.868 1.152

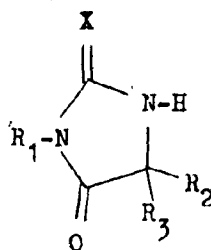
^aErrors are 90 % Confidence Limits; ^bkcal/mol., ^cFrequency Factor; ^dEntropy Units;

^eSolvent Ratio (3:2), 2M; ^fSolvent Ratio (4:1), 2M; ^gSolvent Ratio (3:2), 2.5 M;

^hCoalescence Temperature.

Conformational Variations in the 2-Thio-4-Imidazolidinone Ring :

Before we discuss conformational processes in detail, it seems important to look into the geometry of these molecules. From the X-ray crystallographic structure determination of 2-thio- (106) and 5,5-diphenyl-2,4-imidazolidinediones (23); O and P, in the solid state, the heterocyclic rings were found to be planar.



<u>O</u>	$R_1 = R_2 = R_3 = H, X=S$
<u>P</u>	$R_1 = H, R_2 = R_3 = Ph,$ $X = O$
<u>E</u>	$R_1 = (2\text{-Bromophenyl}),$ $R_2 = H, R_3 = CH_3, X=S$

In our laboratories, X-ray studies (16) of the thermodynamically less stable (in solution) diastereomeric rotational isomer of 3-(2-Bromophenyl)-5-methyl-2-thio-4-imidazolidinone, E, has shown the following important features :

- a- the heterocyclic ring was found to be planar.
- b- the dihedral angle between the heterocyclic and aryl rings is 82° .
- c- the bromine atom is transoid to the 5-methyl group. This implies that, in the preferred rotational isomer which should be more highly solvated, the bromine atom would be transoid to the solvent shell and hence cisoid to the 5-methyl group.

The solution geometry of a molecule may very well be different from that in the solid state ; and unfortunately, not much is known about this particular aspect of these molecules. Recent developments in the NMR literature have established, among many other things, correlation of coupling constants with other physical properties such as hybridization, dihedral bond angles, and electronegativity of substituents. The theory has suggested (67) and the experiments have largely confirmed that the relation between the torsional angle defined by vicinal hydrogens (or lately, a vicinal $^{13}\text{C}-^1\text{H}$ group) and their coupling constants $^3J_{\text{H-H}}$ or $^3J_{\text{C-H}}$ (6,21,32,60,67-69,91-2) have a profound influence on elucidation of configuration and conformational analysis. Particularly, Bystrov and co-workers (21) have extensively studied the relationship between three bond coupling constants and the dihedral angle between the involved nuclei, in the case of -CO - NH - CH- structural unit in dipeptide systems. Fortunately, this structural unit is also present in the compounds under study.

Bystrov et. al. (21) have determined the stereochemical dependence of the spin-coupling constants of the vicinal -CO - NH - CH- protons by the relation :

$$^3J_{\text{NH-CH}} \text{ (Hz)} = (8.9 \pm 0.9) \cos^2 \theta - (0.9 \pm 0.9) \cos \theta + (0.9 \pm 0.9) \sin^2 \theta$$

where θ is the dihedral angle between the H-N-C and C-C-H planes.

Fig. IZ-7 shows the calculated stereochemical dependence on θ of the vicinal proton coupling constants of the $-\text{CO} - \text{NH} - \text{CH}-$ fragment (solid line) as defined above. For comparative purpose, similar Karplus-type (60) plots are also shown for $\text{C} = \text{CH} - \text{CH} <$ (dotted line) and $\text{H}_a - \text{C} - \text{C} - \text{H}_b$ fragments based on equations by Bothner-By (19) and Garbisch (43).

Poupaert and co-workers (84) have reported the dihedral angular dependence of the three bond coupling constants in hydantoins (2,4-imidazolidinediones) and 3-phenyl-2-thiohydantoins bearing various alkyl and aryl substituents at the C-5 carbon atom. They observed values for $^3J_{\text{H}_1 - \text{H}_5}$ ranging from 1.10 - 1.25 Hz which corresponds to a dihedral angle of about 70° between the nuclei involved. Also from values of $^3J_{\text{C}-4 - \text{H}-1} = 7 \text{ Hz}$ ($\Phi = 180^\circ$); $^3J_{\text{C}-2 - \text{H}-5} = 3 \text{ Hz}$ ($\Phi = 125^\circ$) in the C-13 NMR spectra, they inferred the planarity of the hydantoin and 3-phenyl-2-thiohydantoin rings in solution, a conclusion in agreement with X-ray analysis. Table IZ-7 shows a summary of their results.

We have had the opportunity* to examine the structural features of some of the 3-aryl substituted-2-thio-4-imidazolidinones in more detail by obtaining their proton NMR spectra at 270 MHz. Although these compounds incorporate the structural unit $-\text{CS} - \text{NH} - \text{CH}$ instead of $-\text{CO} - \text{NH} - \text{CH}-$, Poupaert and co-workers,

*Prof. L.D. Colebrook's sabbatical leave at the Department of Chemistry, University of British Columbia, Vancouver, B.C., December 1977 - July 1978, where these spectra were run.

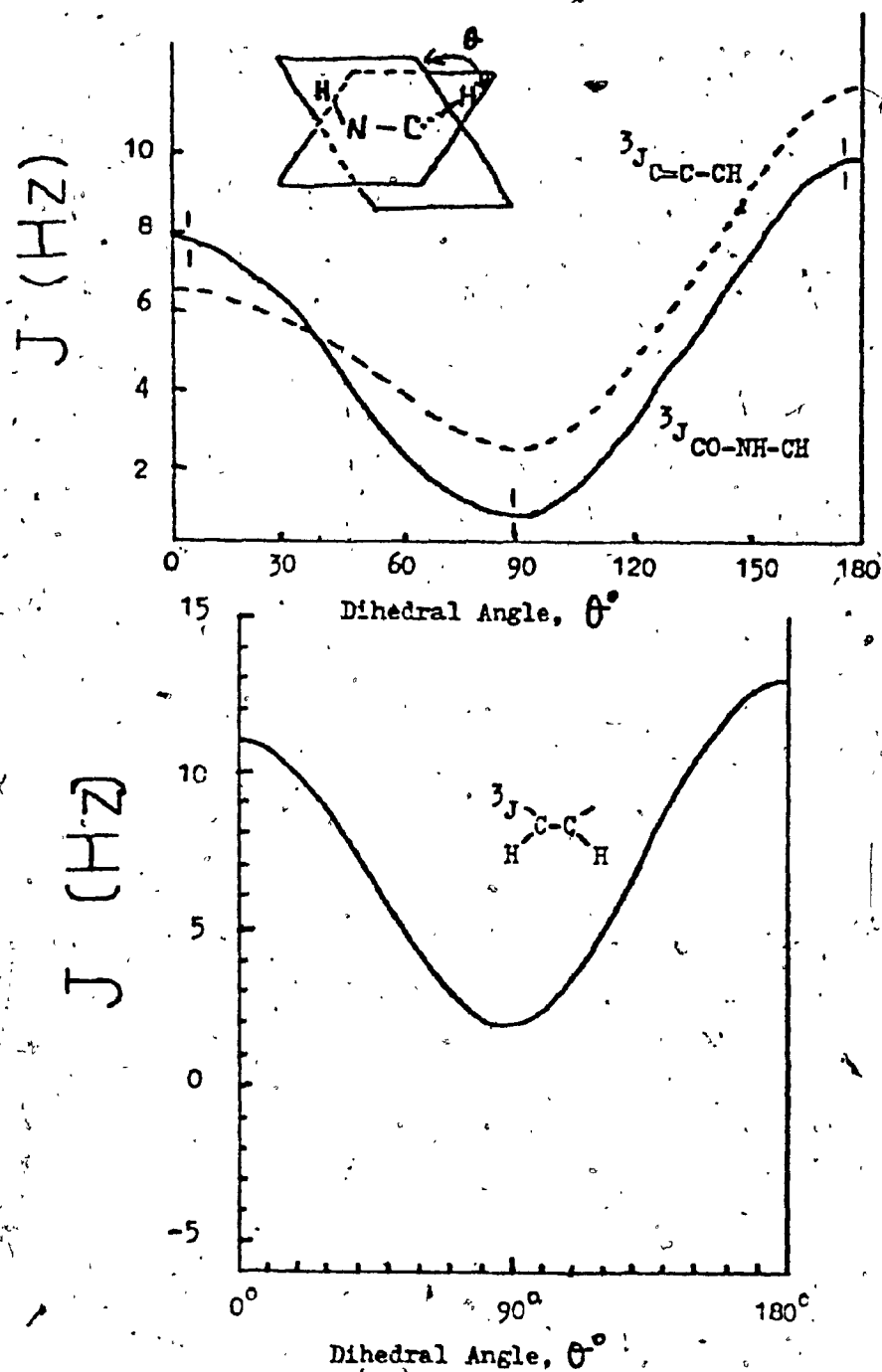


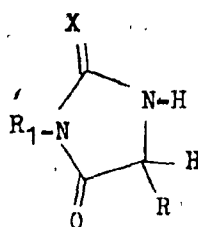
Fig. 1Z-4 : Stereochemical Dependence of Vicinal Proton Coupling Constants (J) of the CO-NH-CH and C=CH-CH²¹ and H-C-C-H (13) Fragments. θ - The Dihedral Angle Between the H-N-C and C-C-H Planes.

have shown that the correlation between the three bond coupling constants and the dihedral angle between the involved nuclei is applicable to hydantoins and 3-phenyl-2-thiohydantoin. The vicinal coupling constants ($^3J_{N_1-H-C_5-H}$) measured at 270 MHz in $CDCl_3$ solutions (0.05 M) are shown in Table IZ-8. It should be emphasized here that the $^{13}J_{CO-NH-CH}$ measured by Bystrov (21) for a number of dipeptides in $CDCl_3$, $DMSO-d_6$, or CCl_4 are almost identical.

Our data and those obtained by Poupaert et. al. (84) clearly indicate that in a given series of imidazolidinediones or their 2-thio analogues, conformational and configurational changes are either absent or negligible, if present at all. For example, the dihedral angle between $N_1-H - C_5-H$ in the hydantoins or thiohydantoins studied is about 70° which is independent of the size and nature of the C-5 substituents. Similarly, in the 3-aryl-5-methyl-2-thio-4-imidazolidinones, the dihedral angle between the N_1-H-C_5-H is about 90° which is independent of the steric bulk of the aryl moiety or nature and position of the substituents on the aryl ring. This conclusion is supported by an observation by Colebrook et. al. (26) that the electronic influence of a chlorine substituent on the rotational barriers in 3-aryl hydantoins (with a methyl or phenyl substituent at C-5) is primarily a 'through-space' effect rather than a 'through bond' effect which might influence the electron distribution in

TABLE 12-7

^1H - ^1H and ^{13}C - ^1H Three-Bond Coupling Constants and the Dihedral Angles Between the Involved Nuclei in 5-Substituted 2,4-Imidazolidinediones (A) and 3-Phenyl-2-Thio-4-Imidazolidinones (B), (84).



A $R_1 = \text{H}$, $X = \text{O}$.

B $R_1 = \text{Ph}$, $X = \text{S}$.

R	$^3J_{\text{H}_1-\text{H}_5}$		$^3J_{\text{C}_4-\text{H}_1}$		$^3J_{\text{C}_2-\text{H}_5}$	
	A	B	A	B	A	B
CH_3	1.10	1.20	7.3	7.0	3.2	2.8
cyclo- C_6H_{11}	1.25	1.10	7.5	-	3.0	-
$\text{CH}_2 - \text{C}_6\text{H}_5$	1.10	-	-	-	-	3.6
C_6H_5	1.25	1.10	7.5	7.0	3.0	3.3

Φ calculated solution

70°

180°

$\approx 125^\circ$

Φ X-rays solid (106)

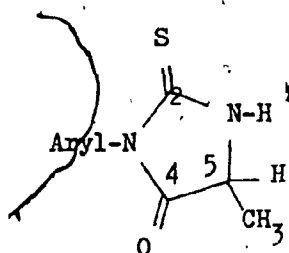
68°

180°

112°

TABLE IZ-8

Proton-Proton Three-Bond Coupling Constants (Hz)
 (Measured at 270 MHz) and the Dihedral Angles (Inferred)*
 Between the Involved Nuclei in 3-Aryl Substituted-2-Thio-
 4-Imidazolidinones, (0.05 M in Chloroform- d_1).



No.	ARYL	$^3J_{N_1H-C_5H}$
IZ-17	2-Tolyl ..	0.82
IZ-18	2-Chlorophenyl ..	0.88
IZ-19	2-Fluorophenyl ..	0.86
IZ-20	2-Methyl-4-Methoxyphenyl ..	0.80
IZ-21	2-Methyl-4-Nitrophenyl ..	0.72
<hr/>		
Dihedral Angle, θ , (Inferred)* ..		$80^\circ \pm 10^\circ$
Dihedral Angle, θ , (X-rays, solid state) (44)		66°

* From Eq. at page 124 (21) and Fig. IZ-7.

the hetero ring. It was expected to result in significant changes in bond lengths and bond angles in the ground and transition states to influence the free energies of activation.

Barriers to Internal Rotation in Imidazolidinediones :

In the present study of the 1,3-diaryl-2-thio-4-imidazolidinediones series, only three compounds IZ-12, IZ-15 and IZ-16 showed restricted internal rotation about the 1-aryl-nitrogen bond. The 1-aryl derivatives with o-methoxy or o-fluoro substituents, IZ-13 and IZ-14 respectively, failed to exhibit individual signals from the diastereomeric C-5 methyl protons in their NMR spectra

at temperatures as low as -150° . The thioimidazolidinones lacking a substituent in the 5-position behaved in a similar manner.

It is important to note that the C-5 methyl or methine proton signals corresponding to the individual diastereomers of the 2-methoxyphenyl derivative, IZ-13, were observable below -152° . These signals coalesced to a very broad singlet, at -152° , which changed to a relatively less broad signal at -143° , Fig. IZ-8. At -137° , a clearly resolved spin doublet ($J = 7$ Hz) appeared under the conditions of fast rotation. Because of very broad singlet at temperatures below -152° , an estimate of the chemical shift difference of the two diastereomers was not possible. The sample solution froze at about -162° . The 2-fluorophenyl compound, IZ-14, failed to show similar behaviour at about -150° .

The thioimidazolidinones with 1-(2-tolyl), 1-(2,3-dimethylphenyl), and 1-(1-naphthyl) as aryl moieties, IZ-12, IZ-15 and IZ-16, respectively, showed internal rotation sufficiently slow that two doublets (with large chemical shift differences) were observed, corresponding to the C-5 methyl protons, when the samples were at normal probe temperatures ($34 \pm 1^{\circ}$). These doublets collapsed to singlets as time-averaging of the environments of the methyl groups became significant at higher probe temperatures. Their coalescence temperatures are in the range 89.5° - 133.0° , and their free energies of activation for restricted rotation are 17.0 - 18.9 kcal/mole. Variations in the ΔG^{\ddagger} values of these compounds are consistent with the steric bulk of the aryl moieties.

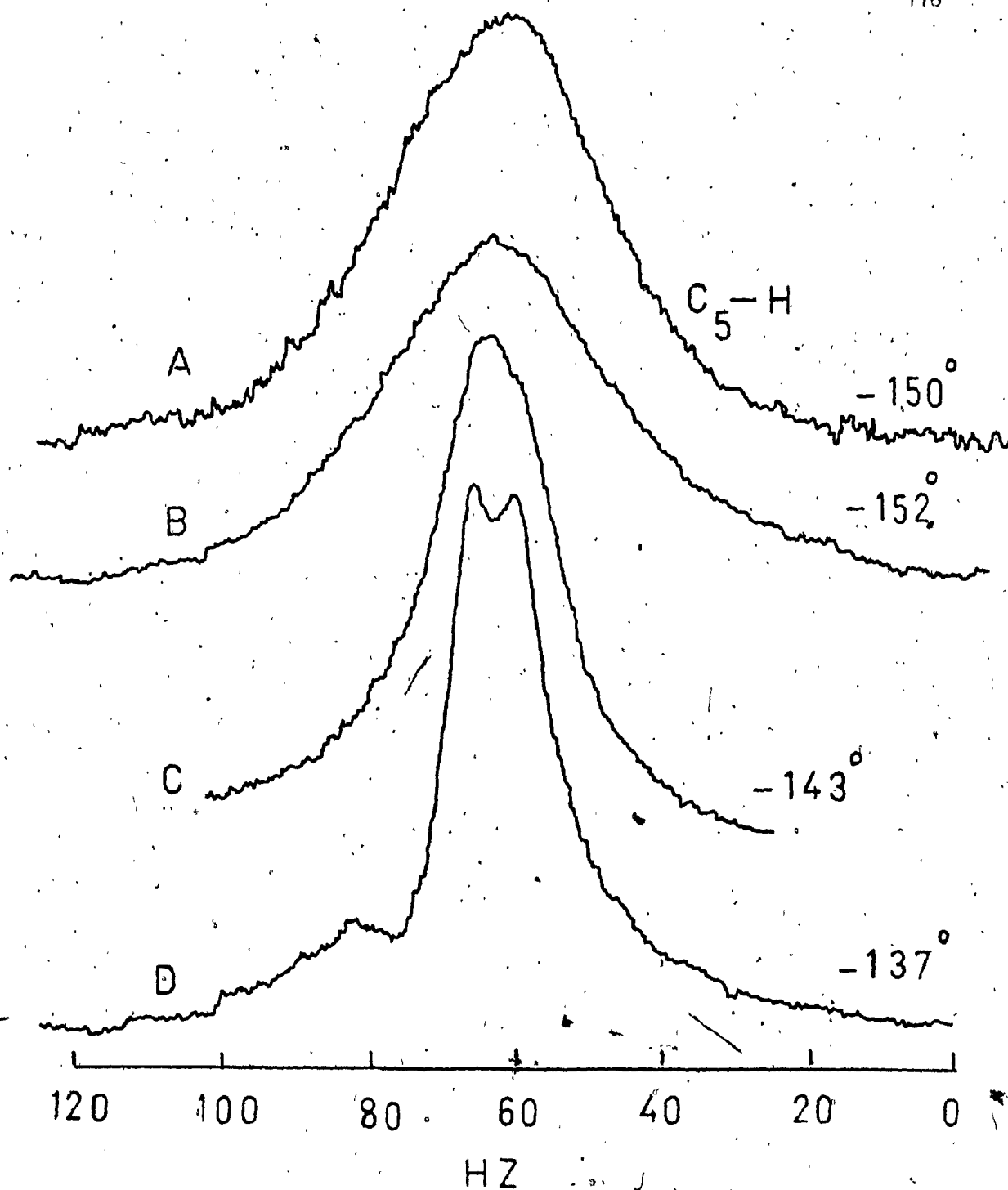


Fig. IZ-5: 100 MHz ^1H -NMR Spectrum of 1-(2-Methoxyphenyl)-3-Phenyl-5-Methyl-2-Thio-4-Imidazolidinone, IZ-15, at Various Temperatures. A: C_5 Methine Proton at its Coalescence Point, B-D: C_5 Methyl Proton Signals at the Temperatures Shown.

COMPARISON OF 1-ARYL-2-THIOIMIDAZOLIDINONES
WITH THEIR OXO ANALOGUES.

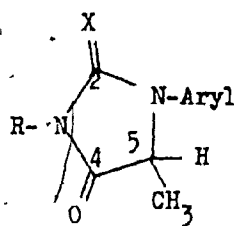
The barriers to internal rotation about the aryl-N bond in IZ-12, IZ-13, IZ-15 and IZ-16 are similar in magnitude to those in 1-aryl-2,4-imidazolidinediones. Table IZ-9 compares kinetic parameters and equilibrium constants in some of the 1-aryl-5-methyl-2,4-imidazolidinediones (53) and their thio analogues.

Whereas the coalescence temperatures of the diones are much below the room temperature (-0.2° to -32.0°), the thio analogs demonstrate rotational stability at room temperature. A striking feature of these derivatives is their higher coalescence temperatures, in the region 89.5° - 133.0° . Consequently, the barriers to internal rotation about the C-N bond are considerably higher.

In the case of 1-(2-methoxyphenyl)-5,5-dimethyl-imidazolidinedione, the diastereotopic C-5 methyl groups did not exhibit any splitting of the NMR signals, even at -78° , thus showing that the barrier to internal rotation is very low. In the 1-(2-methoxyphenyl)-5-methyl dione, the barrier to rotation is expected to be even lower. Its thio analogue did not show individual signals corresponding to the two diastereomers at -75° . However, at very low temperature (-152°), the coalescence point for this compound, IZ-13, was observed.

TABLE IZ-9

Comparison of Kinetic Parameters and Equilibrium
 Constants for Rotation in 1-Aryl-5-Methyl-
 Imidazolidinediones (X = O, S)



X = O*
 X = S**

Aryl	R	Site	ΔE	ΔH^\ddagger	ΔS^\ddagger	ΔG^\ddagger	K_{eq}
2-Tolyl ^a	H*	A	5.2 ± 2.3	4.7 ± 2.3	-33 ± 6	12.7 ± 0.1	1.26
		B	4.5 ± 1.4	4.0 ± 1.4	-36 ± 10	12.6 ± 0.1	
	C ₆ H ₅ **	A	10.5 ± 3.4	9.0 ± 3.4	-25 ± 10	17.3 ± 0.4	1.51
		B	9.2 ± 2.9	8.6 ± 2.9	-28 ± 8	17.0 ± 0.3	
2,3-Me ₂ φ ^b	H*	A	10.7 ± 0.6	10.2 ± 0.6	-16 ± 2	14.6 ± 0.1	1.26
		B	7.1 ± 0.8	6.6 ± 0.8	-29 ± 3	14.5 ± 0.1	
	C ₆ H ₅ **	A	12.0 ± 2.3	11.4 ± 2.3	-25 ± 6	18.8 ± 0.5	1.09
		B	12.2 ± 2.5	11.6 ± 2.5	-24 ± 6	18.8 ± 0.5	
1-Naphthyl ^c	H*	A	6.1 ± 1.0	5.6 ± 1.0	-31 ± 4	13.6 ± 0.1	1.25
		B	5.6 ± 0.6	5.1 ± 0.6	-33 ± 2	13.2 ± 0.1	
	C ₆ H ₅ **	A	8.4 ± 2.1	7.8 ± 2.1	-33 ± 6	17.5 ± 0.3	1.05
		B	8.5 ± 2.2	7.9 ± 2.2	-32 ± 6	17.5 ± 0.3	

Coalescence Temp: X = O (a, -32.0 ; b, -0.2 ; c, -24.0)

X = S (a, 89.5 ; b, 133.0 ; c, 108.5)

* X = O in DMSO-d₆ + acetone-d₆ ; **X = S, in DMSO-d₆ + 2-chloropyridn.

The X-ray crystal structure of 3-(2-bromophenyl)-5-methyl-2-thio-4-imidazolidinone (44) shows that the thiocarbonyl bond length is considerably greater than the carbonyl bond length (1.67 vs 1.23 Å⁰). In addition, sulfur is larger than oxygen (1.85 vs 1.40 Å⁰). In consequence, there occurs a stronger repulsive interaction between the sulfur atom and the groups in the ortho position on the aryl ring when the thio compound is in its rotational transition state than is the case in the 2,4-dione molecule. Since a thiocarbonyl group is more polarizable than a carbonyl group (especially in a highly polar solvent, e.g. DMSO), the solvation around a thiocarbonyl group is expected to occur to a considerable extent. The C-13 NMR study of 3-aryl-2-thio-4-imidazolidinones (61) shows that it is indeed the case.

In imidazolidinones, the bulky ortho substituent must pass over the C-5 substituent while the ortho hydrogen atom passes over the thiocarbonyl group (26) in the preferred transition state for rotation. Therefore, it may be concluded that the differences in rotational stabilities of these thio-imidazolidinones and 2,4-dione analogues principally result from differences in repulsive interactions between the ortho hydrogen atom and the thiocarbonyl group; and the ortho hydrogen atom and the carbonyl group, respectively. Thus, the larger, highly polarizable and hence solvated thiocarbonyl group firmly "locks" the N-aryl moiety out-of-plane, giving extra stability to the ground state of these compounds. This mutual locking of groups into position is quite important and it frequently occurs in

amides and thionamides. This effect is evident in the values of lifetimes of diastereomeric rotamers, τ_{25} , and their equilibrium constants, K_{eq} , at 25°, Table IZ-6.

For the o-tolyl compound, IZ-12, the τ_{25} are 0.51 and 0.77 sec, with $K_{eq} = 1.51$. This value of K_{eq} is similar to those obtained previously by Giles (26, 44) and Icli (26, 53), i.e. 1.25 - 1.70. The value of the equilibrium constant being non-unity has been attributed to preferential solvation of one diastereomer over the other (44) as well as steric interaction between the 3-aryl ortho substituent and the C-4 carbonyl group. In 3-aryl-2-thio-4-imidazolidinones, the cis relationship of the 5-methyl substituent to the bulky ortho group (16) results from such preferential solvation. However, in the 1-aryl-2,4-dione series, it has been shown (53) that the trans isomer corresponds to the more stable ground state conformation.

Because of the medium steric bulk of the ortho substituent, the 'locking' effect of the thiocarbonyl group is not very strong in the ortho tolyl compound, IZ-12. This is seen from the relatively small values of τ_{25} in Table IZ-6. However, greater preferential solvation in one diastereomer over the other does appreciably influence the equilibrium constant.

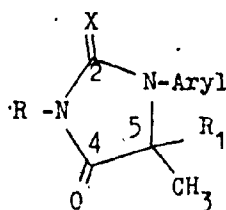
This situation is different with the other two derivatives, IZ-15 and IZ-16, with the 2,3-dimethylphenyl and 1-naphthyl moieties, respectively. In the 1-naphthyl compound, the equilibrium constant is only 1.05 for the interconversion

of rotamers. The thiocarbonyl group and preferential solvation around it in one of the stereoisomers (probably the one in which the bulky ortho substituent occupies a trans position with respect to the C-5 methyl substituent) result in considerable hindrance to rotation of the aryl moiety in the ground state. In the 2,3-dimethylphenyl derivative, IZ-15, this rotation of the 1-aryl moiety should become very severe since the barrier to rotation is very high for this compound. The appreciable hindrance to rotation of the 1-aryl moiety in the ground state is supported by the following two observations :

- a- The rotational lifetimes in the ground state, τ_{25} , are very large, 1.19 and 1.13 sec. for the 1-naphthyl and 10.84 and 9.97 sec. for the 2,3-dimethylphenyl derivatives, respectively. These rotational lifetimes are 1.5 - 2.2 and 14.0 - 19.5 times the corresponding lifetimes, τ_{25} , of the ortho tolyl compound. Table IZ-10 shows ground state rotational lifetimes in 2,4-imidazolinediones and their thio analogues, and compares these values with τ_{25} for the diastereomeric rotamers of the corresponding o-tolyl analogue. It is clear that, when the hindrance to internal rotation of the aryl ring is sufficiently high, the ground state rotational lifetimes in such compounds are 14-20 times larger than those in the corresponding o-tolyl compounds. This represents a situation when the aryl moiety is 'locked' in the ground state and hindrance

TABLE IZ-10

Ground State Rotational Lifetimes in
2,4-Imidazolidinediones (53) and Their 2-Thio Analogues
and Their Comparison with 2-Tolyl Derivatives.



Aryl		X	R	R ₁	Site (τ)	τ_{25} (sec)	Ratio ^a
2-Tolyl ^b	IZ-12	S	C ₆ H ₅	H	A	0.7709	-
					B	0.5111	-
2,3-Me ₂ Φ ^b	IZ-15	S	C ₆ H ₅	H	A	10.84	19.51
					B	9.97	14.06
1-Naph ^b	IZ-16	S	C ₆ H ₅	H	A	1.192	2.22
					B	1.135	1.54
2-Tolyl ^c		O	H	H	A	0.062	-
					B	0.049	-
2,3-Me ₂ Φ ^c		O	H	H	A	0.087	1.41
					B	0.069	1.40
1-Naphthyl ^c		O	H	H	A	0.102	1.67
					B	0.082	1.64

....continued

TABLE IZ-10 Continued...

Aryl	X	R	R ₁	Site (τ)	τ_{25} (sec)	Ratio ^a	
2-Tolyl	(d)	O	H	CH ₃	-	0.0083	-
	(e)	O	H	CH ₃	-	0.0059	-
2,3-Me ₂ Φ	(d)	O	H	CH ₃	-	0.163	19.64
	(f)	O	H	CH ₃	-	0.121	20.51
1-Naphthyl	(d)	O	H	CH ₃	-	0.031	3.73
	(f)	O	H	CH ₃	-	0.024	4.07

^aratio of τ_{25} for a given 1-aryl derivative to τ_{25} for the corresponding 2-tolyl analogue.

^bin DMSO-d₆ + 2-chloropyridine (3 : 2)

^cin DMSO-d₆ + acetone-d₆ (1 : 4)

(d) DMSO-d₆ only

(e) pyridine only

(f) 2-chloropyridine only

to rotation becomes very important. In compounds where this hindrance is not very large, the ground state rotational lifetimes in these compounds are comparable to those in the corresponding 2-tolyl analogues. This represents the situation when hindrance to internal rotation (either steric or solvent-induced) is not very much different from that in the o-tolyl compound.

b- Fourier transform C-13 NMR data on the thioimidazolidinones (see Section 3) have revealed that in their ground state conformation, these molecules do not have noticeable steric or any other direct or indirect interaction between the C-5 substituent and the bulky ortho group. Note, for example, that although diastereomeric splitting of C-13 resonances from the C-2, C-4 or C-5 carbons have been observed, their chemical shift values are very close to the corresponding carbons in the 1,3-diphenyl-2-thio-4-imidazolidinone, 1Z-11, Tables CN-6 and CN-4 of Section 3 . These molecules are expected to adopt conformations with large dihedral angles between the aryl and the heterocyclic ring systems because of steric interaction of the bulky ortho substituent and the C-5 group on the hetero ring in the transition state as well as the 'locking' effect of the thiocarbonyl group and the solvent shell around it. The existence of significant chemical shift

difference between carbons and protons in the diastereomeric rotamers, in C-13 and ¹H NMR, respectively, is considered to originate from anisotropic shielding of the unsymmetrical aryl moiety which is more or less 'locked' in a position in the ground state. Since the molecules should have significant flexibility in the ground state to minimize steric repulsions between the two ring systems, it is probable that most of the influence on the values of ΔG^\ddagger in these compounds arises from interactions in the transition state for rotation.

ROTATIONAL FREE ENERGIES OF ACTIVATION :

All attempts directed to observe slow rotation, on the NMR time scale, about the aryl C-N bond in the C-5 unsubstituted thioimidazolidinones failed. Various combinations of mixtures of acetone-d₆, DMSO-d₆, CDCl₃ and pyridine were tried at the lowest possible temperatures attained ($\sim -78^{\circ}$) on the Varian HA-100 NMR spectrometer. Finally, we hoped that slow rotation may be observed at still lower temperatures. The 30 mg sample of 1-(2,3-dimethylphenyl)-2-thio derivative, IZ-8, (selected because of its expected large hindrance to rotation about the C-N bond) was dissolved in chlorodifluoromethane (Freon-22) at acetone-dry ice temperature and the dissolved gases were evacuated under high vacuum by immersing the sample solution in liquid nitrogen. About 5-6 cycles of freeze-thaw-high vacuum procedure effected removal of dissolved gases and the sample tube was sealed under high vacuum ($\approx 0.1 - 0.05$ torr). The 100 MHz NMR spectrum of this compound at -150° showed time-averaged environments of the C-5 methylene or ortho methyl group protons.

The situation was more encouraging with the C-5 methyl derivatives. IZ-12, IZ-15 and IZ-16, with o-tolyl, 2,3-dimethylphenyl, and 1-naphthyl moieties, which showed doublets for the diastereomeric methyl signals when the samples were at normal probe temperatures. These two doublets collapsed to a very broad singlet at the coalescence temperature and finally changed to a single doublet as time-averaging of the environments

of the methyl group protons became significant at still higher probe temperatures.

The behaviour of the 2-methoxyphenyl derivative, IZ-13, was strikingly different from those mentioned above. Whereas IZ-12, IZ-15, or IZ-16 showed quite a high coalescence temperature ($89.5 - 133.0^\circ$), it was expected that slow rotation in the case of 2-methoxyphenyl derivative might be observable at somewhat lower temperatures. However, this compound failed to show any spectral modification at the lowest temperature attainable ($\approx -78^\circ$) on the Varian HA-100 probe. As a last resort, a 30 mg sample of the 2-methoxyphenyl derivative, IZ-13, in chloro-difluoromethane was prepared following the method described above for the C-5 unsubstituted 2,3-dimethylphenyl compound, IZ-8. The C-5 methyl or methine proton signals i.e. two doublets or two quartets, respectively, corresponding to the individual diastereomers of IZ-13 were observable below -152° . The methyl or methine proton signals coalesced to a very broad singlet at -152° and -150° , respectively, which changed to a relatively less broad singlet at -143° . At -137° , a clearly resolved spin-doublet ($J = 7$ Hz) appeared for the C-5 methyl protons under the conditions of fast rotation on the NMR time scale.

The 2-fluorophenyl derivatives, IZ-14, failed to show, under similar conditions, slow rotation about the aryl C-N bond at a temperature as low as -150° .

The free energies of activation of the three compounds which behaved favorably are shown in Table IZ-6A. From the

foregoing discussion, it is apparent that the steric bulks of the ortho and C-5 substituents should have a certain lower limit in order to observe slow rotation. This lower limit is probably provided by the 2-methoxy group on the aryl ring and the methyl group at the C-5 position. The barriers to rotation increase in other compounds in the expected order. This observation is in agreement with the earlier finding (26) that in the 1-aryl-imidazolidine-2,4-diones, the more bulky ortho substituent must pass the 5-position in the preferred transition state for rotation.

VARIATIONS IN ENTROPY OF ACTIVATION :

The entropy of a state represents the randomness of that state. Thus, the entropy of activation represents the difference in degree of order between the ground state and the transition state. A negative ΔS^\ddagger , therefore, implies that the transition state is more ordered than the ground state.

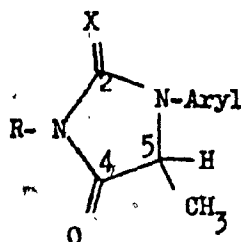
It has been assumed (44) that when the molecule is in the transition state, one or more solvent molecules are added to the solute-solvent complex, so that the system becomes more ordered. Since solvation is an exothermic process, a higher degree of solvation in the activated state would lower the transition state energy level and hence lower ΔH^\ddagger assuming

that solvent-induced steric effects are absent. On the other hand, a more solvated transition state would be a more ordered one, corresponding to a more negative rotational entropy of activation. Steric hindrance to solvation of a polar group in the ground state and/or large size of substituent, small degree of polarity or unfavorable geometry of the solvent molecule would affect the ΔH^\ddagger and ΔS^\ddagger values.

Table IZ-11 compares the enthalpies and entropies of activation in the 1-aryl-5-methyl-2,4-imidazolidinediones and their 2-thio analogues. It is seen from Table IZ-11 that in the thioimidazolidinones listed, there is a large entropy change associated with the transition state. This indicates that the rotational transition state is probably more highly solvated than the ground state. Also, the variations in ΔS^\ddagger in the thioimidazolidinones and their 2,4-dione analogues are almost similar in going from ground to the rotational transition state.

It is noteworthy that there is an appreciable increase in the enthalpy of activation of the thio compounds over the 2,4-dione series, the increase being in the range 1-5 kcal/mole. The large van der Waals radius of sulfur and increased solvation in the transition state probably increases the transition state energy levels of these compounds as compared to the 2,4-dione derivatives, thereby increasing ΔH^\ddagger .

Comparison of Enthalpies, ΔH^\ddagger , and Entropies, ΔS^\ddagger ,
of Activation in 1-Aryl-5-Methyl-2-Thio-4-Imidazoli-
dinones* and Their 2,4-Dione Analogues**.



ARYL	ΔH^\ddagger		ΔS^\ddagger	
	R = H, X = O	R = Phenyl X = S	R = H, X = O	R = Phenyl X = S
2-Tolyl	4.7 \pm 2.3		-33 \pm 6	
		8.3 \pm 1.5		-30 \pm 4
	4.0 \pm 1.4		-36 \pm 10	
2,3-Dimethylphenyl	10.2 \pm 0.6		-16 \pm 2	
		9.7 \pm 1.0		-29 \pm 3
	6.6 \pm 0.8		-29 \pm 3	
1-Naphthyl	5.6 \pm 1.0		-31 \pm 4	
		6.6 \pm 0.9		-36 \pm 2
	5.1 \pm 0.6		-33 \pm 2	

* In DMSO-d₆ + 2-Chloropyridine (3:2)

** In DMSO-d₆ + Acetone-d₆ (1:4) (53)

BUTTRESSING EFFECT :

The enthalpy, ΔH^\ddagger , and free energy of activation, ΔG^\ddagger , are significantly higher in 1-(2,3-dimethylphenyl)-5-methyl-2-thio-4-imidazolidinone, IZ-15, compared with the 1-(2-tolyl) derivative, IZ-12. The ΔH^\ddagger and ΔG^\ddagger values in IZ-15 are higher by 1.4 and 1.2 kcal/mole, respectively, whereas the entropies of activation are almost unaffected in both the compounds. In the 1-aryl-2,4-dione series, similar variations have been observed. The increase in ΔH^\ddagger and ΔG^\ddagger in 2,3-dimethylphenyl compound is attributed to the buttressing effect of the meta methyl substituent which is capable of restricting the ability of the ortho methyl group to bend back in the rotational transition state in order to relieve steric strain.

COMPARISON OF 3-ARYL AND 1-ARYL-2,4-IMIDAZOLIDINEDIONES :

In 3-aryl-2,4-imidazolidinediones, the bulky ortho substituent must pass the C-2 or C-4 carbonyl group in the rotational transition state. The free energies of activation for internal rotation in these compounds (38,45A) in DMSO- d_6 solutions have been found in the range 17 - 20 kcal/mole. These studies have shown that changes in the steric bulk of the C-5 substituent does not have an appreciable effect on the rotational barriers.

In contrast, the barriers to internal rotation in the 1-aryl-2,4-diones (as well as 2-thio-4-ones) are significantly affected by the steric bulk of the C-5 substituent. This is expected since the C-5 substituents in the 1-aryl series are capable of interacting directly with the bulky ortho group. As mentioned earlier, the more bulky ortho substituent must pass the 5- position in the preferred transition state for rotation in 1-aryl derivatives (26). When the C-5 position is unsubstituted these compounds (C=O, or C=S) fail to exhibit individual signals from the enantiotopic C-5 protons in their NMR spectra at temperatures as low as -150° . When the C-5 substituent is a phenyl group, similar behaviour is observed. However, with the C-5 methyl derivatives, the ΔG^{\ddagger} values calculated at the coalescence point for this group of compounds (X=O) ranged from 11.1-14.5 kcal/mole; the T_c being in the range 0° to -63° . The compounds with the 2-methoxyphenyl or 2-fluorophenyl moieties, however, failed to show slow rotation even at very low temperatures.

In the 1-aryl-5-methyl-2-thio series, the barriers to rotation are substantially higher, 17-19 kcal/mol, than the corresponding 2,4-diones, as discussed earlier. With the 2-fluorophenyl moiety, the internal rotation about the aryl C-N bond is fast even at -150° ; but for the 2-methoxyphenyl compound the coalescence temperatures of the C-5 methyl and C-5 methine proton signals are -152° and -150° , respectively, in chlorodifluoromethane.

In 1-aryl-5,5-dimethyl derivatives, there occurs substantial steric interaction between the bulky ortho substituent and the C-5 methyl group and consequently the barriers to rotation are quite high, in the region of 17 - 20 kcal/mol.

^ In the 3-aryl-5-methyl-2-thio-4-imidazolidinones, the rotational barriers are very high because the ortho substituent must pass the carbonyl oxygen in the transition state. The minimum value of the rotational barriers in these compounds is about 25 kcal/mole (26).

Giles (44) has compared in detail the barriers to rotation about the aryl C-N bond in 3-aryl-5-methyl-2-thio-4-imidazolidinones with the corresponding 2,4-dione analogues.

Icli (53) has elaborated on rotational behaviour of the 1-aryl-2,4-imidazolidinediones. The present investigation on 1,3-diaryl-2-thio-4-imidazolidinones essentially complements earlier studies and provides further understanding of the effects of substituents and the associated rotational behaviour on the various positions on this heterocyclic molecule.

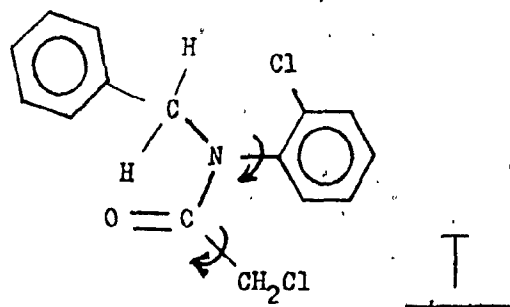
INTERNAL ROTATION IN N-ARYL-1-ISOINDOLINONES.

Lewin, Lipowitz and Cohen (71) have reported that the NMR spectrum of 3-methyl- or 3-phenyl-N-benzyl-1-isoindolinone, S, in carbon tetrachloride reveals the benzyl methylene protons as an AB spin system, approaching an AX system. The unusually large chemical shift difference, 1.75 and 1.05 ppm for R = phenyl and R = methyl, respectively, has been explained on the basis of

R	δ (ppm)		$\Delta\delta$
	H_x	H_y	
CH ₃	5.85	4.80	1.05
C ₆ H ₅	6.33	4.58	1.75

some reasonable assumptions about the lowest energy conformations of these molecules.

Seymour and Jones (93) have shown that in benzene, toluene, or DMSO solution the chloroacetyl methylene protons of T are non-equivalent, but in some other solvents they are



equivalent.

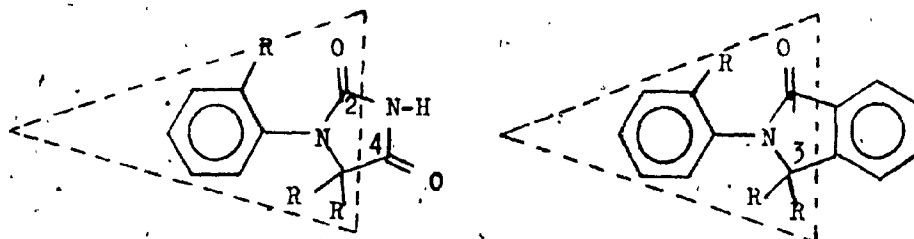
It was proposed that the non-equivalence is due to slow rotation around the C(O)-CH₂Cl bond induced by complexation of T with solvent molecules. However, an alternative and more plausible explanation was also given i.e. the non-equivalence is due to slow rotation about the N-aryl bond. The benzyl methylene protons were found to be non-equivalent in all solvents studied, indicating that the N-aryl rotation was slow, and thus the chloroacetyl methylene protons should be non-equivalent in all solvents. However, the observability of the non-equivalence depends upon the field gradients due to anisotropic groups in the molecule; in the solvents which gave no observable non-equivalence, the methylene proton shifts could be accidentally degenerate. The three solvents in which non-equivalency was observed may, by their weak complexation with the amide group, destroy the degeneracy and lead to the expected AB spin-pattern.

In this case, an AB pattern could be observed for the methylene protons, even with rapid rotation around the $C(O)-CH_2Cl$ bond.

It was also reported that the chloroacetyl methylene protons become equivalent in benzene, toluene and DMSO by replacing the N-(2-chlorophenyl) moiety by an N-methyl group. Therefore, the latter explanation accounts for this observation better than the former.

The measurement of the proton spin-lattice relaxation times at 270 MHz and 23° (see Section 1. . .); and Fourier transform C-13 NMR at 25.12 MHz and 34° (see Section 4) has established unambiguously that in the ground state conformation of the N-aryl-1-isoindolinones, IN-1 to IN-14, there does not exist any detectable steric, electronic or any other type of direct or indirect interaction between the bulky ortho substituent on the aryl ring and the methylene protons or the carbonyl group on the hetero ring.

The N-aryl-1-isoindolinone frame-work is partially



similar to 1-aryl-2,4-imidazolidinedione system. (Note the portions under the closed curve).

In view of observation of non-equivalence of the benzyl protons by Lewin et. al. (71), and by Seymour and Jones

(93), as mentioned earlier, it was of interest to us to investigate if slow rotation about the aryl C-N bond in 1-isindolinones at lower temperatures could render the methylene or bulky ortho substituent non-equivalent. It should be mentioned that the 100 MHz or 270 MHz proton NMR spectra of these compounds in DMSO- d_6 or $CDCl_3$ show that the methylene protons or the protons on the bulky ortho substituent are equivalent at normal probe temperatures. The solutions of N-(2,3-dimethylphenyl)- and N-(1-naphthyl)- derivatives, IN-8 and IN-13, respectively, in $CDCl_3$ and acetone- d_6 mixtures did not show any non-equivalency between the protons mentioned above at temperatures as low as -75° at 100 MHz.

Finally, an attempt was made to observe the behaviour of these compounds at about -150° , using degassed samples of IN-8 and IN-13. (100 MHz NMR spectra, Fig. IZ-6 and IZ-7.)

It was observed, unfortunately, that in the N-(2,3-dimethylphenyl), IN-8, and N-(1-naphthyl), IN-13, derivatives, the methylene protons exhibited a rather sharp singlet with no indication of splitting of signals due to non-equivalency. Similarly, the ortho and meta methyl group protons in 2,3-dimethylphenyl compound gave rise to a sharp

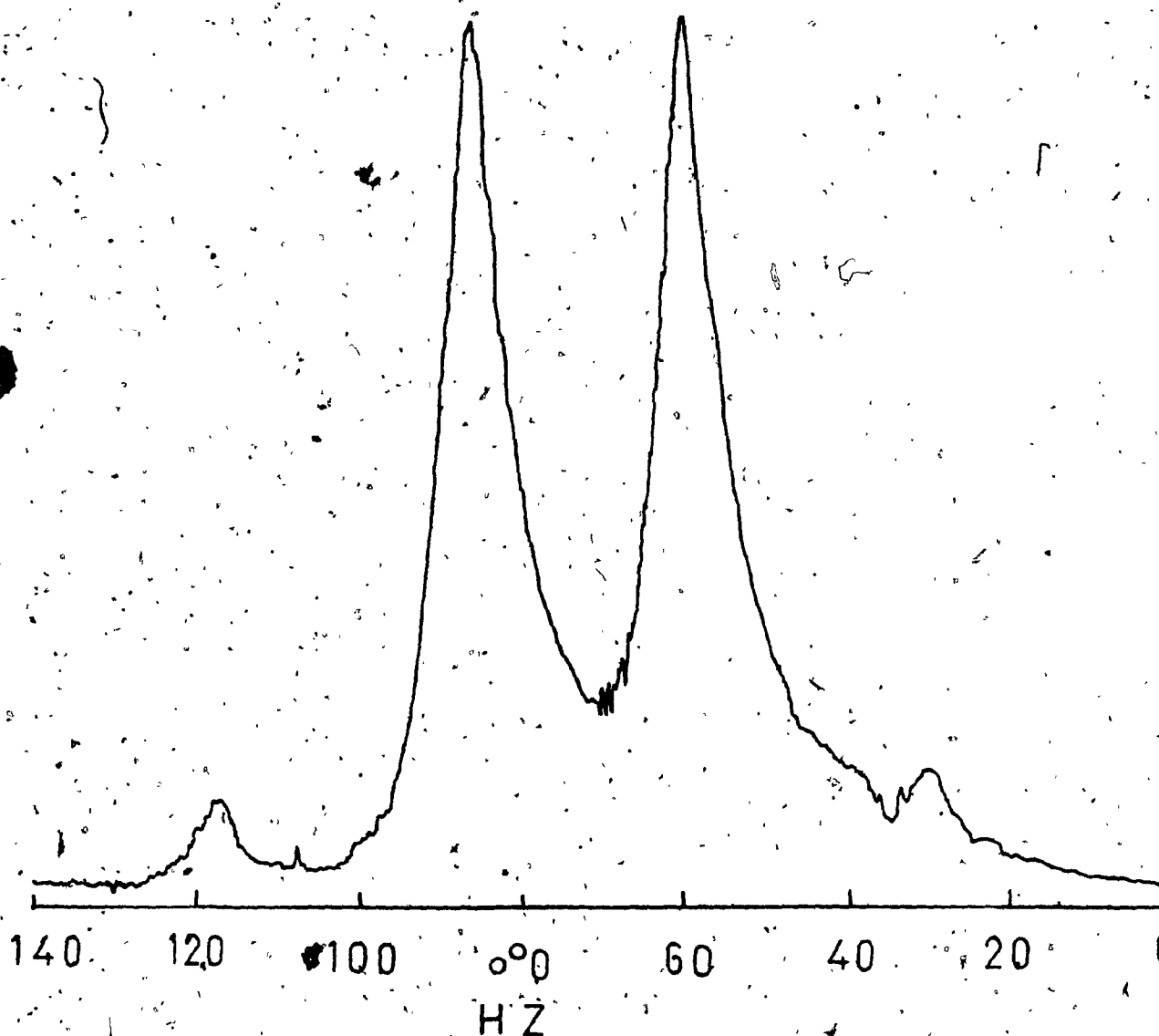


Fig. IZ- 6: 100 MHz Proton NMR Spectrum of N-(2,3-Dimethylphenyl)-1-Isindolinone, IN-8, at -150° . Ortho Methyl (2.108 ppm), and Meta Methyl (2.372 ppm) Proton Signals in CHClF_2 .

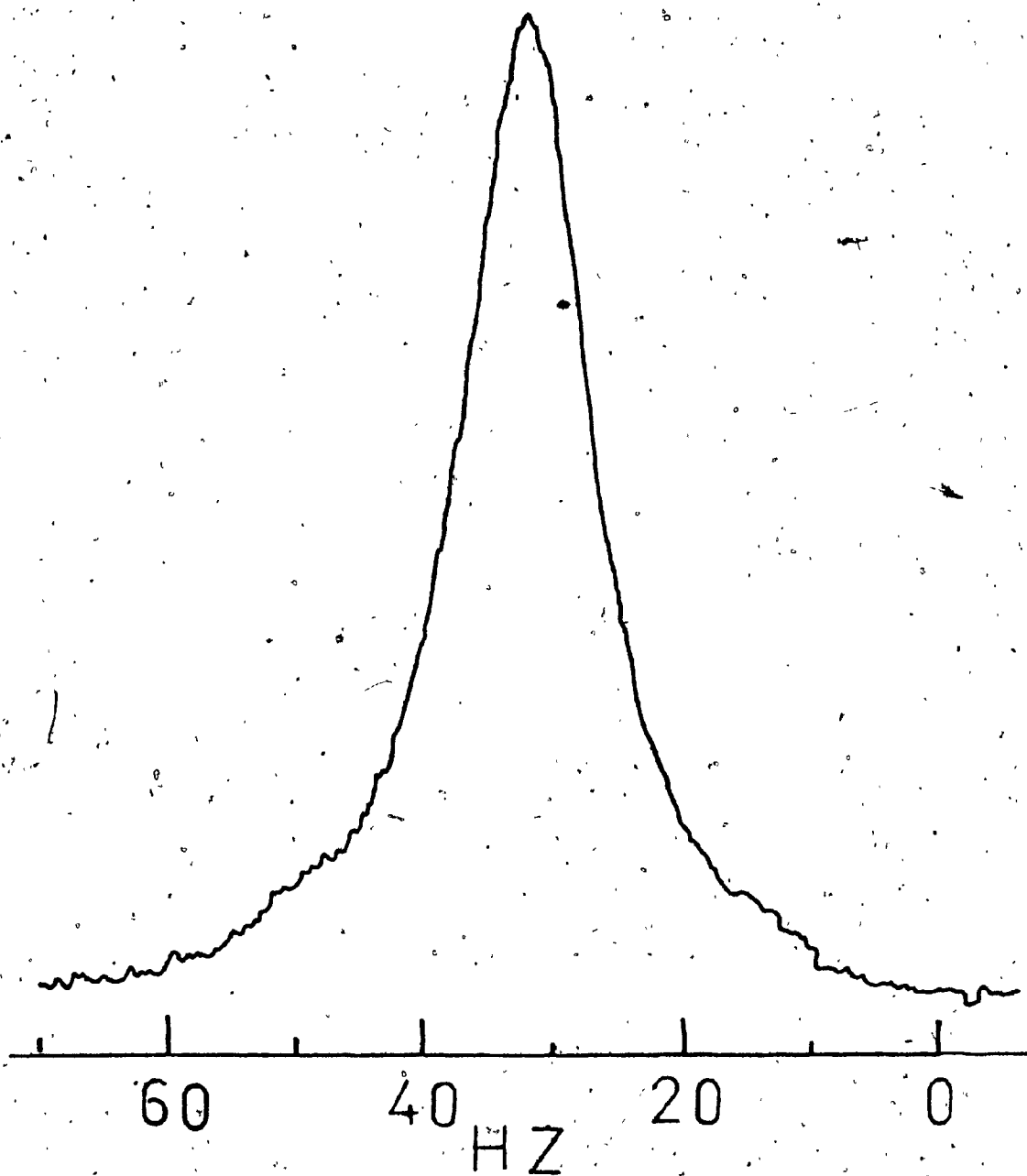


Fig. IZ-7 : 100 MHz Proton NMR Spectrum of N-(2,3-Dimethylphenyl)-1-Isoindolinone, IN-8, at -150° . Methylene Proton Signal at 4.77 ppm in CHClF_2 .

singlet at -150° in chlorodifluoromethane.

It is unlikely that failure to observe splitting of signals at low temperatures is due to very small chemical shift difference between the two methylene protons.

These observations lead to the conclusion that internal rotation about the aryl C-N bond in N-aryl-1-isindolinones is quite fast even at -150° . An alternate conclusion is that there may be accidental equivalence of chemical shifts. Consequently, the barriers to internal rotation in these compounds are very low. This line shape study of these molecules in conjunction with their carbon-13 NMR data shows that there is not any detectable steric, electronic or any other type of direct or indirect interaction between the bulky ortho substituent and the methylene protons or the carbonyl group in their ground as well as rotational transition state. In this respect, these compounds exhibit a rotational behaviour similar to 1-aryl-imidazolidine-2,4-diones or their 2-thio analogs.

SECTION 3.

A

CARBON-13 NMR STUDY OF

2-THIO-4-IMIDAZOLIDINONES

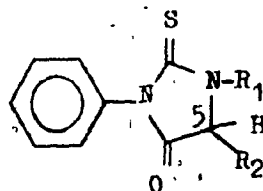
RESULTS AND DISCUSSION

For introduction to this section of thesis, the reader is referred to Section 2 (Proton NMR Line Shape Analysis).

The Fourier transformed C-13 nuclear magnetic resonance spectra, presented in Fig. NC-5 to NC-15, were measured for a series of 3-aryl- and 1,3-diaryl substituted 2-thio-4-imidazolidinones, as listed in Table CN-1. These spectra were run on Bruker WH-90 (22.628 MHz) NMR spectrometers located at the University of Montreal, and the Pulp and Paper Institute of Canada, Montreal, using the instrumental parameters as shown below :

<u>Spectrometer Location</u>	<u>Pulse Width</u>	<u>Repetition Time</u>	<u>Sweep Width</u>	<u>Number of Scans.</u>
University of Montreal	5 μ sec	0.7 sec.	6024 Hz.	5,000 to 10,000.
Pulp & Paper Institute	5 μ sec.	0.9 sec.	4500 Hz.	2500-6400.

N-Aryl Substituted-2-Thio-4-Imidazolidinones Used
for C-13 NMR Study.



No.	R_1				R_2
IZ-1	H	H
IZ-2	Phenyl	H
IZ-3	2-Tolyl	H
IZ-4	2-Methoxyphenyl	H
IZ-5	2-Fluorophenyl	H
IZ-6	2-Chlorophenyl	H
IZ-7	2-Bromophenyl	H
IZ-8	2,3-Dimethylphenyl	H
IZ-9	1-Naphthyl	H
IZ-10	H	CH ₃
IZ-11	Phenyl	CH ₃
IZ-12	2-Tolyl	CH ₃
IZ-13	2-Methoxyphenyl	CH ₃
IZ-14	2-Fluorophenyl	CH ₃
IZ-15	2,3-Dimethylphenyl	CH ₃
IZ-16	1-Naphthyl	CH ₃

The number of scans varied from 2,500 - 10,000 depending upon the concentration for all of the compounds except the 1-(2-tolyl)-, IZ-3, and the 1-(2-fluorophenyl)-, IZ-14, derivatives, where the concentration of these solutions was very low. IZ-14 was available in small quantity, but its 0.2 M solution in DMSO- d_6 , using 46,664 scans, yielded a reasonably good and clearly resolved C-13 spectrum. Although IZ-3 was abundantly available, its unexpectedly low solubility in DMSO- d_6 yielded a very dilute solution, so much so that even a large number of scans, as high as 50,000, failed to produce a reasonably good C-13 spectrum. The signals corresponding to C-5, the C-5 methyl, and the aryl carbons can easily be recognized, but the carbonyl and thiocarbonyl signals can not be identified.

Dimethylsulfoxide- d_6 (DMSO- d_6) was used as a solvent for all of the compounds in the present study. Besides being a relatively good solvent for these compounds as compared with chloroform or other commonly used solvents, it provided the heteronuclear (deuterium) lock signal for the NMR spectrometer. The concentrations of the solutions of the N-aryl-2-thio-4-imidazolidinones in DMSO- d_6 varied in the range 0.60-1.0 M; except for the IZ-3 and IZ-14 for the reasons mentioned earlier. All chemical shifts are reported relative to TMS, and were measured by taking the chemical shift of DMSO- d_6 to be

39.560* ppm downfield from TMS. All chemical shift values are estimated to be accurate to 0.005 ppm, unless otherwise indicated. The broad band noise-decoupled spectra were obtained for all of the compounds, IZ-1 to IZ-16. Off-resonance proton-decoupled spectra were run for the ortho methoxyphenyl derivatives, IZ-4 and IZ-13. The off-resonance decoupled spectra provided valuable aid in distinguishing resonances arising from the C-5 and the ortho methoxy carbons in these compounds (see later).

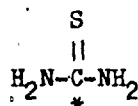
For the purpose of comparison of the chemical shift values, the results are tabulated and discussed according to the carbon positions.

* In the case of 1-isoindolinones and isoindole-1,3-diones, the FT C-13 NMR spectra were measured on a Varian HA-100 NMR spectrometer housed at Concordia University. On this instrument, the chemical shift of DMSO was found to be 40.64 ppm downfield from TMS.

ASSIGNMENTS OF THE RESONANCES :

Carbonyl and Thiocarbonyl Carbon Signals :

The chemical shift values of the thiocarbonyl carbons in the thioureas (A) to (C) are shown below :



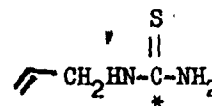
183.2 ppm (109)

(A)



182.8 ppm (70)

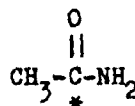
(B)



184.4 ppm (70)

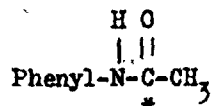
(C)

The carbonyl chemical shift values in the acetamides (D) to (F) are indicated below :



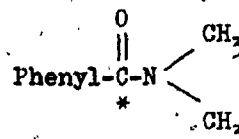
171.4 ppm (109)

(D)



169.2 ppm (70)

(E)



170.8 ppm (70)

(F)

The chemical shift values of the thiocarbonyl and carbonyl carbons in N-aryl-2-thio-4-imidazolidinones are found to be 180.0-183.5 and 169-174 ppm, respectively, and are in close

agreement with the model compounds (A) to (F) as well as those listed in Table CN-3. The observed values closely correspond to those previously studied for 1-aryl- (53), 3-aryl- (109) and 3-aryl-2-thio-4-imidazolidinones (61).

C-5 Carbon Signals :

The signals corresponding to the C-5 carbons were observed in the expected region 50-60 ppm; in close agreement to our previous findings (61).

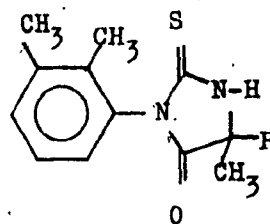
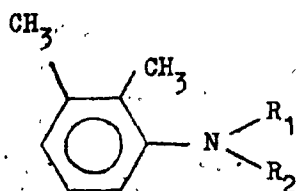
In the case of 1-(2-methoxyphenyl)-3-phenyl-2-thio-4-imidazolidinone, IZ- 4, the signals due to the aryl methoxy carbon and the C-5 carbon of the hetero ring appear close to each other; at 54.626 and 55.841 ppm. The off-resonance proton-decoupled spectrum showed a triplet overlapped by a quartet, such that the resonance at 54.626 ppm remains un-displaced. This is possible only if the signal at 54.626 ppm is one of the components of the triplet arising from the C-5 carbon. The partially collapsed components of the quartet from the methoxy carbon signal can easily be recognized. In fact, three spin-components of the multiplet from the methoxyl quartet are superimposed on the triplet due to the C-5 carbon resonance, Fig. NC-6.

In the case of the ortho methoxyphenyl derivative with a C-5 methyl substituent; IZ-13, the signal corresponding

to the methoxy carbon absorbs at 55.872 ppm (un-affected), whereas the peak due to the C-5 carbon shifted about 6 ppm downfield due to the α -methyl effect as compared to IZ-4.

Methyl Carbon Signals :

The ortho methyl carbon in IZ-3 absorbs at 17.593 ppm; whereas the C-5 methyl carbon resonates at 15.059 ppm in the 1,3-diphenyl derivative, IZ-11. The C-5 methyl carbons in IZ-10 - IZ-16 absorb at 14.0 - 16.2 ppm; and can be easily distinguished from the aryl ortho methyl carbons. In the case of the 2,3-dimethylphenyl derivatives, IZ-8 and IZ-15, the resonances corresponding to the ortho and meta methyl carbons were compared to the compounds (G) to (J) listed below :



- (G) $R_1 = R_2 = H$, 2-CH₃ (12.7 ppm), 3-CH₃ (20.6 ppm)
 (H) $R_1 = R_2 = CH_3$, 2-CH₃ (14.1 ppm), 3-CH₃ (20.8 ppm)
 (I) $R = H$, 2-CH₃ (13.46 ppm), 3-CH₃ (19.52 ppm)
 (J) $R = CH_3$, 2-CH₃ (13.50 ppm), 3-CH₃ (19.52 ppm)

(66)

(61)

The signals at 14.094 and 19.780 ; and 14.149 and 19.998 ppm were assigned to the ortho and meta methyl carbons in IZ-8 and IZ-15, respectively.

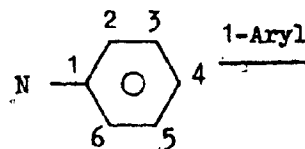
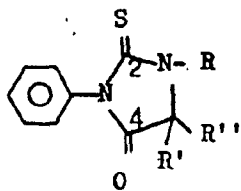
Aryl Carbon Signals :

The aryl carbons attached to N-3 in 3-phenyl-2-thio-4-imidazolidinones absorb at 133.5 - 134.0 ppm in all the compounds studied in this series, IZ-1 to IZ-16. The signals corresponding to the remaining carbons in the 3-phenyl moieties appear at 128.5-129.0 ppm, and their assignment to specific carbons was not attempted. However, the 1-aryl carbon resonances in many of these compounds were assigned to the respective carbons by taking into consideration the substituent effects on the benzene ring. The shielding data for the model compounds IZ-1,2,10 and 11 as well as those listed in Table CN-3 provided the basis for these assignments. In this way, a reasonably good comparison was obtained between the estimated and the observed chemical shifts for aryl carbons in most of the 2-thio-4-imidazolidinones. These results are shown in Table CN-2.

In summary, it can be seen that throughout the series of N-aryl-2-thio-4-imidazolidinones studied, the chemical shift values for given carbon positions in the hetero ring vary over quite a narrow region and that the ranges for different carbon

TABLE CN-2

Aryl Carbon Shieldings (ppm, TMS) of 1-Aryl Moieties in
1,3-Diaryl-2-Thio-4-Imidazolidinones in DMSO-d₆.



No	C-1	C-2	C-3	C-4	C-5	C-6
IZ-2	138.462	125.389	128.742	127.138	128.742	125.389
IZ-3	136.862					
IZ-4	126.458 (124.1)	154.841 (156.9)	112.704 (114.3)	129.957 (128.1)	120.480 (121.0)	129.714 (126.2)
IZ-5	125.583 (125.5)	157.352 (160.0)	116.592 (115.7)	130.565 (128.5)	124.972 (124.2)	126.069 (126.7)
		¹ J=250.0*	² J=19.8*	³ J= 7.7*	⁴ J= 3.3*	
IZ-6	135.741 (138.8)	132.069 (131.6)	130.686 to 128.353			
			(129.1)	(128.4)	(126.7)	(126.7)
IZ-7	139.386 (141.9)	122.424 (119.9)	130.783 (132.1)	128.937 to 128.305		
				(126.8)	(127.1)	(127.1)
IZ-8	137.782 (139.0)	134.963 (135.0)	137.296 (138.2)	129.960 (127.7)	126.215 (125.7)	125.292 (122.4)
IZ-9	135.303	134.040 to 123.493				

..... Continued.

() Estimated Chemical Shifts

* C-F Spin-Doublet (Hz)

TABLE CN-2 (Continued)

No	C-1	C-2	C-3	C-4	C-5	C-6
IZ-11	136.980	128.921 to 127.166				
IZ-12	137.297 ^d 136.567 (137.6)	136.130 ^d 135.352 (136.5)	131.124 ^d 130.783 (129.2)	130.054 (127.5)	126.604 (125.5)	126.993 (127.0)
IZ-13	125.022 (124.1)	155.372 (156.8)	112.738 (114.3)	132.105 (129.5)	120.667 (121.0)	130.286 (129.5)
IZ-14	124.489 ² J=12.1* (124.5)	158.000 ¹ J=250.7* (163.3)	116.568 ² J=19.9* (115.6)	130.905 ³ J=7.7* (129.9)	125.170 ⁴ J=3.3* (124.1)	130.359 (129.9)
IZ-15	138.217 ^d 137.890 (137.8)	135.335 ^d 135.160 (135.0)	136.135 ^d 136.005 (137.3)	130.286 ^d 129.896 (129.9)	126.451 ^d 125.996 (126.2)	124.567 (125.3)
IZ-16	134.445 ^d 134.250	133.015 ^d to 122.386 ^d				

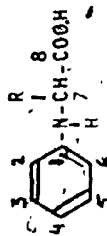
() Estimated Chemical Shifts

* C-F Spin-Doublet (Hz)

^d Diastereomers.

TABLE CN-3

CARBON-13 SHIELDING DATA FOR SOME GLYCINES, ALANINES AND SOME MODEL COMPOUNDS IN DMSO-d₆ (PPM FROM TMS)
 FOR ASSIGNMENT OF SIGNALS TO CARBONS IN 1,3-DIARYL-2-THIO-4-IMIDAZOLIMONES.




N-ARYL	SCANS	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	ARYL ORTHO
PHENYL (GLYCINE)	1500	148.112 (146.8)	112.107 (115.2)	128.745 (129.4)	116.137 (118.7)	128.745 (129.4)	112.107 (115.2)	44.878	172.613	
2-TOLYL (GLYCINE)	1500	145.772 (148.8)	121.610 (124.0)	129.720 (129.4)	116.267 (116.0)	126.730 (125.8)	109.183 (112.0)	44.908	172.678	17.352
2-METHOXYPHENYL (GLYCINE)	1500	137.324 (133.7)	146.357 (143.5)	109.768 (114.3)	116.202 (117.0)	120.946 (121.0)	109.378 (113.1)	44.583	172.483	55.241
2-FLUOROPHENYL (GLYCINE)	2500	136.544 136.024 2J=11.76	156.171 145.708 J=236.8	114.772 113.927 2J=19.12	116.267 116.007 3J=5.89	124.651	112.237 112.042 3J=4.41	44.323	172.353	
2-CHLOROPHENYL (GLYCINE)	2500	N (148.5)	N (118.3)	128.810 (129.2)	116.917 (117.4)	127.900 (128.8)	111.393 (113.4)	44.323	172.028	
2-BROMOPHENYL (GLYCINE)	2500	144.343 (151.5)	108.468 (106.6)	132.059 (132.1)	117.567 (117.8)	128.485 (127.1)	111.458 (113.8)	44.583	171.898	

.....CONTINUED.

TABLE CN-3 (CONTINUED)

N-ARYL	SCANS	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	R-ME.
2,3-DIMETHYL-A PHENYL (GLYCINE)	5000	145.707 (145.2)	119.841 (122.9)	135.699 (138.9)	118.671 (117.4)	125.755 (126.6)	107.558 (107.1)	45.233	172.808	
1-NAPHTHYL (GLYCINE)	2000	143.498 (146.1)	103.139 (112.6)	126.600 (126.9)	C-4 TO C-7 : 116.1-125.6			44.973	172.613	
		C-8 127.965 (129.1)	C-9 122.961 (120.4)	C-10 134.009 (134.7)	(118.3)	(118.3)	(125.9)			
PHENYL (ALANINE)	2000	148.093 (140.8)	112.802 (118.8)	129.246 (129.0)	116.703 (123.1)	129.246 (129.0)	112.802 (118.8)	51.388	176.426	18.569
2-TOLYL (ALANINE)	2000	145.315 (148.8)	122.181 (121.8)	130.006 (130.0)	116.738 (116.6)	126.750 (126.0)	109.982 (112.7)	51.322	175.836	18.419
2-FLUOROPHENYL (ALANINE)	2000	135.959* 135.439 2 J=11.77 (135.2)	156.106* 145.642 140=236.8 (146.9)	114.902* 114.057 2 J=19.12 (115.8)	116.592* 116.267 3 J=7.35 (117.5)	124.521 3 J un- resolved (124.2)	112.562 (113.5)	50.822	175.343	18.002
2-CHLOROPHENYL (ALANINE)	2000	143.368 (148.5)	117.957 (118.3)	129.655 (129.2)	117.957 (117.4)	128.550 (128.8)	112.367 (113.4)	51.277	175.538	18.717

TABLE CN-3 (CONTINUED)

N-ARYL	SCANS	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	R=ME:
2-BROMOPHENYL (ALANINE)	2000	143.628 (151.5)	108.988 (106.6)	132.319 (132.1)	118.022 (117.8)	128.680 (127.1)	111.913 (113.8)	50.822	174.888	18.197
2,3-DIMETHYLPHENYL (ALANINE)	2000	145.187 (145.2)	118.022 (122.9)	135.829 (138.9)	118.931 (117.4)	125.690 (126.6)	108.273 (107.1)	51.537	175.993	18.457
1-NAPHTHYL (ALANINE)	2000	143.108 (146.1)	103.724 (112.6)	127.900 (126.9)	C-4 TO C-9 : 116.3-126.5 (118.3)	125.690 (118.3)	108.273 (125.9)	51.472	175.853	18.002
C-10		134.009 (134.7)								
H - N - C-  CH ₂ CH ₃	2000	138.344	124.761	128.660	122.226	128.660	124.761	(C-S) 187.606	(CH ₂) 67.179	(CH ₃) 14.019

^A ORTHO METHYL, 12.413 PPM; META METHYL, 20.276 PPM. ^B ORTHO METHYL, 17.447 PPM.

^C ORTHO METHYL, 12.543 PPM; META METHYL, 20.341 PPM. ^N SIGNAL NOT OBSERVED. ^{*} C-F SPIN-DOUBLET.

VALUES IN PARENTHESES ARE ESTIMATED CHEMICAL SHIFTS.

positions of interest are well-separated. There is, thus, no ambiguity in the assignment of signals to carbons in the heterocyclic ring, and the substituted carbons either on the C-5 position or on the aryl ring. Moreover, peaks corresponding to various aryl carbons in most of these compounds are assigned with a reasonable degree of confidence.

Dependence of Carbon Shieldings on Concentration :

It might be expected that the carbon-13 shieldings, particularly of the polar carbonyl groups, could be dependent on concentration of imidazolidinones in a polar solvent such as DMSO. This effect of concentration was not investigated for the present series of compounds, since an earlier study by Williams (109) and Icli (53) on related compounds shows the trends of such effects. With increasing concentration, Williams has observed a small downfield shift of about 0.03 ppm per mole % for all the carbons in the 5-membered heterocyclic ring. Icli has observed that, for the 1-aryl imidazolidine-2,4-diones, the concentration dependence of the chemical shifts of hetero ring carbons (C-2, C-4, C-5, and the C-5 methyl) is about 0.01 ppm per mole percent in morpholine.

The effect of concentration of solutes on the carbon shieldings in 1- and 3-aryl imidazolidine-2,4-diones is, thus, negligible. In the case of 1,3-diaryl-2-thio-4-imidazolidinones, the dependence of chemical shifts of the C-2 thiocarbonyl carbons

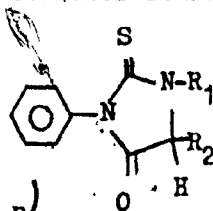
is expected to be somewhat larger than in the corresponding 2,4-diones. However, one would expect to correlate the C-13 shifts for these compounds in DMSO independently of the concentration effects for the following two reasons: First, the concentrations of the imidazolidinones in this study vary over a small range, 0.6-1.0 M, (Table CN-6). Second, the C-2 thiocarbonyl and C-4 carbonyl carbons are expected to have almost similar solvation patterns by DMSO. As will be shown later, these carbons do not experience direct non-bonded steric interactions from the aryl moieties to any considerable extent.

C-5 CARBON-13 CHEMICAL SHIFT VALUES :

The C-5 carbon-13 shielding data of N-aryl-2-thio-4-imidazolidinones are presented in Table CN-4. These values are seen to fall into two narrow regions corresponding to the number of substituents at the C-5 carbon: 54.8-56.7 ppm for the un-substituted C-5 carbon, and 60.0-62.8 ppm for the C-5 methyl derivatives.

On the basis of their stereochemistry, the C-5 carbons in all the compounds with a C-5 methyl substituent, which have diastereomeric rotamers, can be expected to show double peaks. This splitting was observed only for the compounds with 2-tolyl, 2,3-dimethylphenyl- and 1-naphthyl moieties, IZ-12, IZ-15 and IZ-16, respectively.

Carbon-13 Chemical Shift Values of C-5 Carbons in N-Aryl-2-Thio-4-Imidazolidinones in DMSO-d₆ (ppm, TMS).



No	<u>B₁</u>			<u>R₂</u>	<u>PPM</u>
IZ-1	H	H	49.086
IZ-2	Phenyl	H	55.210
IZ-3	2-Tolyl	H	55.807
IZ-4	2-Methoxyphenyl	H	54.626
IZ-5	2-Fluorophenyl	H	55.210
IZ-6	2-Chlorophenyl	H	54.869
IZ-7	2-Bromophenyl	H	54.821
IZ-8	2,3-Dimethylphenyl	H	55.841
IZ-9	1-Naphthyl	H	56.668
IZ-10	H	CH ₃	55.157
IZ-11	Phenyl	CH ₃	60.486
IZ-12	2-Tolyl	CH ₃	62.062, 59.584 ^d
IZ-13	2-Methoxyphenyl	CH ₃	59.966
IZ-14	2-Fluorophenyl	CH ₃	60.702
IZ-15	2,3-Dimethylphenyl	CH ₃	62.241, 60.031 ^d
IZ-16	1-Naphthyl	CH ₃	62.761, 60.616 ^d

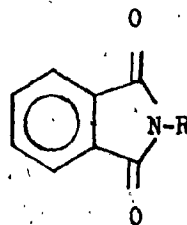
^dDiastereomers.

The Downfield β -Phenyl Substitution Effect :

The downfield β -phenyl substitution effect in linear and branched alkanes is known to be about 7-9 ppm, (107). In the case of imidazolidinones, IZ-1,2 ; and IZ-10, 11, the β -effect upon the C-5 carbon by the addition of a phenyl group at N-1, is 6.12 and 5.33 ppm, respectively, downfield. This deshielding effect upon the C-5 carbon may result from changes in the hybridization of the nitrogen atom. Such changes are not un-reasonable to consider. For example, from the measurements of dipole-moments of phthalimide and its derivatives, Lumbroso and Dabhard (65) estimated that the N-R (alkyl) bonds make angles between fifty and sixty degrees in relation to the planes of the imide ring. The angles correspond to the case where the nitrogen atom uses orbitals close to sp^3 -hybridization. Lumbroso et. al. (9,10) also suggested that N-phenyl-phthalimide takes a planar conformation, implying sp^2 -hybrid orbitals for the nitrogen atom. The change of hybridization from the sp^3 - to sp^2 - type facilitates the electron release from the nitrogen atom to carbonyl groups. The carbon-13 NMR data (70) on phthalimides, as given below, also show that the carbonyl carbon shieldings increase in the order



<u>R</u>	<u>ppm</u> <u>C=O</u>
(N) H	169.7
(O) n-Propyl	168.5
(P) ^o Phenyl	167.5



The carbonyl carbon in N-phenylphthalimide (P) is shielded by 2.2 ppm, compared to phthalimide (N) itself, indicating greater electron release from the nitrogen atom to the carbonyl groups, in agreement with the results from the dipole-moment measurements and the I.R. data. In the imidazolidinones, the β - and the γ -phenyl substitution effects upon the thiocarbonyl and carbonyl carbons have been found to be 1.1-2.2 ppm (see later) upfield. This has been attributed to the increase in electron densities at the carbonyl carbons arising from increased conjugation in 1,3-diaryl compounds. The deshielding of the C-5 carbon may also arise, to some extent, from conformational changes in the heterocyclic ring resulting from the substitution of a phenyl group at N-1.

The observed deshielding β - effects of 5-6 ppm by a phenyl substituent (at N-1) upon the C-5 carbon probably arises from enhanced through-bond inductive effects of the slightly increased electron density at N-1 from conjugation.

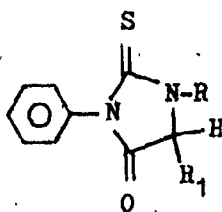
The Downfield α -Methyl Substitution Effect :

The observed α -methyl substitution effects on the C-5 carbon are presented in Table CN-5. The C-5 carbon shieldings, Table CN-4, in both the C-5 unsubstituted and the C-5 methyl derivatives decrease on increasing the steric bulk of the 1-aryl moieties. For example, δ_{C-5} for 2-chlorophenyl-, 2-tolyl-, 2,3-dimethylphenyl- and 1-naphthyl- derivatives are 54.87, 55.80, 55.84, and 56.67 ppm, respectively, in the unsubstituted series. The small differences in the C-5 carbon shieldings may arise either from the steric interactions between the substituents at C-5 and the aryl moiety, or from the δ -effects of the ortho substituents. The methyl group at C-5 in all of these compounds exerts an almost constant effect, either electronic or steric, i.e. it may be seen from Table CN-5 that the α -methyl effect is almost constant at 5.2 ± 0.2 ppm. Steric interactions between the ortho substituents and the C-5 methylene groups are considered to be almost negligible (from proton NMR line shape analysis) and thus the factor contributing to the variations in the α -methyl shifts appears to be the δ -effect of the ortho substituents and the accompanying variation in conjugation from changes in dihedral angles.

The chemical shifts of the unsubstituted C-5 carbons in the 2-tolyl- and 2,3-dimethylphenyl derivatives, 1Z-3 and

TABLE CN-5

Downfield α -Methyl Substitution Effects
on the C-13 Chemical Shift Values of C-5 Carbons in
N-Aryl-2-Thio-4-Imidazolidinones in DMSO-d₆.



R	No	PPM
H	IZ-1, IZ-10	6.071
Phenyl	IZ-2, IZ-11	5.276
2-Tolyl	IZ-3, IZ-12	5.016
2-Methoxyphenyl	IZ-4, IZ-13	5.340
2-Fluorophenyl	IZ-5, IZ-14	5.492
2,3-Dimethylphenyl	IZ-8, IZ-15	5.295
1-Naphthyl	IZ-9, IZ-16	5.020

IZ-8, are 55.81 and 55.84, respectively. This suggests that the buttressing influence of the meta methyl group in IZ-8 has apparently no effect upon the shielding of the C-5 carbon. However, in the C-5 methyl series, the C-5 carbon in the 2,3-dimethylphenyl derivative, IZ-15, is deshielded by 0.313 ppm as compared to that in the 2-tolyl compound, IZ-12. This deshielding effect may arise either from steric interactions and the buttressing effect of the meta methyl group or from the ϵ - effect upon the C-5 carbon. As will be seen shortly, the latter is more probable.

The ortho halogens show interesting effects upon the C-5 carbon shieldings in both the unsubstituted and the C-5 methyl series. With the chloro or bromo group as the ortho substituents, the C-5 carbon shieldings are very similar, 54.87 and 54.82 ppm, respectively; whereas in the ortho fluorophenyl compound, IZ-5, it is 55.210 ppm, deshielding the C-5 carbon by 0.3 - 0.4 ppm as compared to the chloro or bromo compounds. The unsubstituted C-5 shieldings in the ortho fluorophenyl and the phenyl derivatives are 55.210 ppm, whereas in the C-5 methyl series, the C-5 carbon in the ortho fluorophenyl compound is about 0.2 ppm deshielded. The C-5 nucleus in IZ-5 (2-Fluorophenyl compound) is shielded by about 0.6 ppm as compared with the ortho tolyl compound, IZ-4, but is almost unaffected by changes in substitution in the C-5 methyl series. The gradual increase in the steric bulk from F \rightarrow Cl \rightarrow Br is obviously not important

in this respect. It seems that the δ -effect due to a strongly electronegative fluorine atom affecting the conjugation may exert some deshielding influence on the C-5 carbon. It should be pointed out that, for the ortho-fluorophenyl and the ortho methoxyphenyl derivatives, the α -methyl substituent effects (Table CN-5) are 5.49 and 5.34 ppm, somewhat higher than for the non-polar ortho substituents, and in agreement with the trend in electronegativities of these atoms (F : 4.0; O : 3.5; and C : 2.5).

It seems important to consider the chemical shift difference between the C-5 carbons in the diastereomeric rotamers of the 2-tolyl, 2,3-dimethylphenyl and 1-naphthyl derivatives, IZ-12, IZ-15, and IZ-16, respectively. The chemical shift differences, between the low and high field rotamers, are shown below :

IZ-12 :	2-tolyl	2.478 ppm
IZ-15 :	2,3-Dimethylphenyl	2.210 ppm
IZ-16 :	1-Naphthyl	2.145 ppm

An increase in the steric bulk of 1-aryl moiety might be expected to increase the chemical shift difference of the C-5 carbons in the corresponding diastereomeric rotamers. However, no corresponding increase in the diastereomeric splitting has been observed. The α -methyl effect upon substitution at the C-5 carbon, as already shown, is almost

invariable, 5.2 ± 0.2 ppm.

The foregoing discussion clearly indicates that non-bonded steric interactions between the C-5 methyl group and substituents on the aryl moiety do not occur to any considerable extent. This deduction is further supported by the fact that the C-5 methyl carbon shieldings also remain indifferent (14.9 ± 0.2 ppm) to variations in the steric bulk of the ortho substituents.

Thus, any variation in the shielding of carbons in the hetero ring is expected to reflect changes in dihedral angles (and so in conjugation) arising from variable steric bulk of the aryl moieties. For example, the deshielding (0.3 ppm) of the C-5 carbon in 2,3-dimethylphenyl derivative, IZ-15, as compared with the ortho tolyl compound, IZ-12, is not considered to arise from the buttressing influence of the meta methyl group, but probably from the σ -effect upon the C-5 carbon as a result of increase in dihedral angle between the two rings.

Since the C-5 carbon shieldings depend upon the dihedral angle, and hence on conjugation, the electron releasing or withdrawing nature of an ortho substituent is expected to give rise to small variations in the shielding trends of the C-5 carbons.

CHEMICAL SHIFT VALUES OF CARBONYL AND THIOCARBONYL CARBONS :

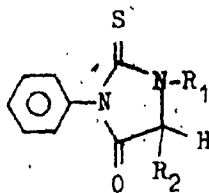
The carbon-13 chemical shift values for both the C-2 (thiocarbonyl) and C-4 (carbonyl) carbons are shown in Table CN-6. The C-2 thiocarbonyl chemical shifts vary over the narrow region 181.0-183.5 ppm for all the imidazolidinones studied; whereas the C-4 carbonyl chemical shift values are much more sensitive to the substitution at the C-5 carbon. The C-4 chemical shifts are 169.9-172.1 ppm for the unsubstituted C-5 carbon in IZ-1 to IZ-9; and 173.0-175.0 ppm for the C-5 monomethyl derivatives, IZ-10 to IZ-16. The C-4 carbons are slightly more deshielded in 3-aryl-2-thio-4-imidazolidinones (61). The chemical shifts for the mono- and dimethyl derivatives at C-5 are 173.7-175.4 ppm, and 173.1-178.2 ppm, respectively. The C-2 thiocarbonyl carbons in 3-aryl compounds also show distinct regions for mono and dimethyl substituents at C-5. These are 180.1-182.8 ppm, and 176.8-181.5 ppm for the C-5 methyl and C-5 dimethyl derivatives, respectively.

On the basis of their stereochemistry, all the C-5 methyl thioimidazolidinones, which have diastereomeric rotamers, can be expected to show double peaks for both the C-2 and the C-4 carbonyl carbons. The thioimidazolidinones with bulky aryl ortho substituents in the C-5 methyl series, i.e. IZ-12, IZ-15, IZ-16, did show the splitting of resonances corresponding to

Carbonyl and Thiocarbonyl Carbon-13 Chemical Shift

Values of N-Aryl-2-Thio-4-Imidazolidinones in DMSO-d₆

(PPM, TMS).



No	R ₁		R ₂	Conc. (M)	C-2	C-4
IZ-1	H	..	H	1.0	183.418	172.143
IZ-2	Phenyl	..	H	1.0	181.279	169.907
IZ-3	2-Tolyl	..	H	< 0.2	a	a
IZ-4	2-Methoxyphenyl		H	0.75	182.592	170.442
IZ-5	2-Fluorophenyl		H	0.75	182.640	170.199
IZ-6	2-Chlorophenyl		H	0.25	182.592	170.101
IZ-7	2-Bromophenyl		H	0.60	182.446	169.956
IZ-8	2,3-Dimethylphenyl		H	0.75	181.863	170.442
IZ-9	1-Naphthyl		H	0.70	183.126	170.636
IZ-10	H	..	CH ₃	1.5	182.147	174.998
IZ-11	Phenyl	..	CH ₃	1.0	181.043	173.179
IZ-12	2-Tolyl	..	CH ₃	0.75	181.377*	173.455*
					180.599	173.309
IZ-13	2-Methoxyphenyl		CH ₃	1.0	181.823	173.504
IZ-14	2-Fluorophenyl		CH ₃	0.2	181.960	173.163
IZ-15	2,3-Dimethylphenyl		CH ₃	1.0	181.474*	173.569*
					180.924	173.439
IZ-16	1-Naphthyl		CH ₃	1.0	182.603*	173.699*
					182.018	173.659

*Not observed upto 50,000 scans. *Diastereomers.

the C-2 and C-4 carbonyl carbons in the diastereomeric rotamers. No diastereomeric splitting or broadening of the C-2 and C-4 resonances, was observed in compounds having aryl ortho substituents of effectively low steric bulk e.g. OCH_3 , and F in IZ-11, IZ-13, and IZ-14, respectively. Proton line shape analysis of these compounds (see Section 2) has shown that the fast internal rotation about the aryl C-N bond would render such observation difficult.

The Downfield δ - and ϵ - Effects:

Table CN-7 shows the downfield δ - and ϵ - effects on the C-2 thiocarbonyl and C-4 carbonyl carbons, respectively, arising from the aryl ortho substituents in N-aryl-2-thio-4-imidazolidinones. These effects have been calculated by comparing the chemical shift values of the C-2 and C-4 carbons in IZ-3 to IZ-9 with the corresponding carbons in IZ-2 for the C-5 unsubstituted derivatives. For the C-5 methyl substituted compounds, the chemical shifts of the C-2 and C-4 carbons are compared with the corresponding carbons in IZ-11. Table CN-7 shows that the δ - and ϵ - effects vary over the range 0.0-1.9 and 0.0-0.7 ppm, respectively.

The 5-membered heterocyclic ring has 8 π -electrons (the lone pair electrons of N-1 and N-3 and the π -electrons of the C-2 and C-4 carbonyl groups). Through amide-type resonance the carbonyl carbons should have quite a high π -electron

Downfield δ - and ϵ - Effects* (PPM) on the C-2 Thiocarbonyl and C-4 Carbonyl Carbon-13 Chemical Shifts, Respectively, Arising From 1-Aryl Ortho Substituents in 1,3-Diaryl-2-Thio-4-Imidazolidinones in DMSO-d₆.

No.	Aryl	R	δ - (C-2)	ϵ - (C-4)
IZ-3	2-Tolyl	H	-	-
IZ-4	2-Methoxyphenyl ..	H	1.313	0.535
IZ-5	2-Fluorophenyl ..	H	1.361	0.292
IZ-6	2-Chlorophenyl ..	H	1.313	0.194
IZ-7	2-Bromophenyl ..	H	1.167	0.049
IZ-8	2,3-Dimethylphenyl ..	H	0.584	0.535
IZ-9	1-Naphthyl ..	H	1.847	0.729
IZ-12	2-Tolyl	CH ₃	-0.075 ^a	0.203 ^a
IZ-13	2-Methoxyphenyl ..	CH ₃	0.780	0.325
IZ-14	2-Fluorophenyl ..	CH ₃	0.917	-0.016
IZ-15	2,3-Dimethylphenyl ..	CH ₃	0.156 ^a	0.325 ^a
IZ-16	1-Naphthyl ..	CH ₃	1.267 ^a	0.500 ^a

*The Phenyl derivatives, IZ-2 and IZ-11, were used as reference compounds for the C-5 unsubstituted and the C-5 methyl substituted compounds, respectively. (a) from centre of the doublet.
(-) shielding.

density. The phenyl rings in the 1,3-diaryl derivatives, IZ-2 and IZ-11, are expected to favour a planar conformation so that the dihedral angles between the aryl and the hetero rings should be very small. The same conclusion about the dihedral angles may also be inferred from proton NMR line shape analysis of these compounds, which has shown lack of steric interactions between the C-5 substituents and the aryl ortho groups, (see Section 2). Under such conditions, it can be concluded that the conjugation effects between the aryl and the hetero rings are operative. However, it should be pointed out that in the case of the thermodynamically less stable isomer of 3N-(2-bromophenyl)-5-methyl-2-thio-4-imidazolidinone, the dihedral angle between the aryl and the hetero rings in the solid state has been observed to be 82° . (16). It has also been observed that in the 3-aryl systems (61,84) the dihedral angles between an aryl ring with a bulky ortho substituent and the hetero ring are quite large even in the solution state (see Section 2). However, the reverse is probably true for the 1-aryl derivatives.

The molecular frame-work of N-aryl-2-thio-4-imidazolidinones is such that the conjugative effects are operative over a large portion of the molecule. Such effects are expected to increase the shielding of the C-2 and C-4 carbonyl carbons. Taking into account the large β - and small γ -effects of the phenyl ring upon the C-2 and C-4 carbons, respectively, it is clear from Table CN-6 that these carbons

are rather shielded (by 1 - 2.5 ppm) in IZ-2 and IZ-11 as compared to IZ-1 and IZ-10.

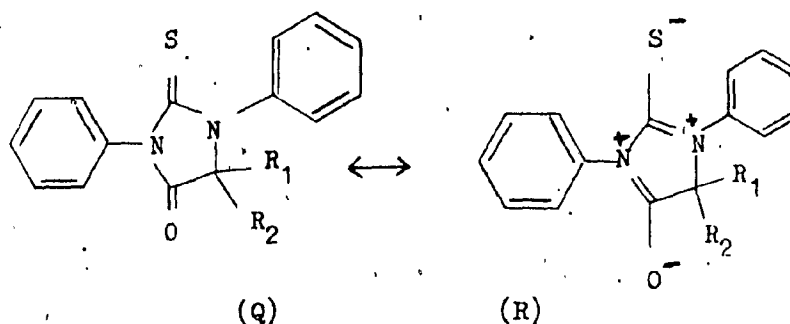
After having established that conjugation effects are important in these compounds, it is necessary to examine the steric and polarity effects associated with the aryl substituents. It appears that in the 1,3-diaryl-2-thio-4-imidazolidinones, the polarity of the 1-aryl ortho substituent does not affect the shielding of the C-2 and C-4 carbons, (Table CN-6, see IZ-4 to IZ-7).

Table CN-7 shows that the δ - and ϵ - effects of the 1-aryl substituents upon the C-2 and C-4 carbonyl carbons are affected by the steric bulk of the aryl moiety in these compounds. With increasing steric bulk of the aryl moiety, the dihedral angle between the aryl and the hetero rings is expected to increase, and therefore, a corresponding decrease in conjugation could deshield the C-2 and C-4 carbons. The downfield δ - effects are the largest for the 1-(1-naphthyl) derivatives. The effect of decreasing conjugation is clearly noticeable in the downfield ϵ -effects, in which the C-4 carbon shifts show a regular increase with increasing steric bulk of 1-aryl moiety.

The 2,3-dimethylphenyl derivatives, IZ-8 and IZ-15, show relatively small δ - effects upon the C-2 thiocarbonyl carbon. A considerable upfield ϵ - effect (about 0.5-1.0 ppm) arising from the meta methyl group on the aryl ring may offset the downfield δ - effect. The ϵ - effect upon C-4 (0.5 ppm)

does not seem to be affected by the δ -effect of the meta methyl group in IZ-8 and IZ-15.

The imidazolidinones, IZ-1 to IZ-16, all contain highly polarizable thiocarbonyl and carbonyl groups. It appears important to consider the contribution of the structure such as (R), shown below, toward the overall representation of these molecules.

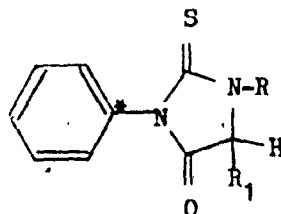


The presence of an aryl ring on N-1 is expected to stabilize the positive charge on nitrogen atoms in (R) as compared to the unsubstituted N-1. This stabilization of charge may depend upon variations in dihedral angles resulting from various N-aryl moieties. The downfield δ - and ϵ -effects (Table CN-7) of various ortho substituents upon the thiocarbonyl and carbonyl carbons, respectively, are rather small; 0.0 - 1.8 ppm and 0.0 - 0.7 ppm, which cast doubt on the importance of the polarized structure such as (R).

More direct evidence may be obtained from variations in the shielding of aryl carbons directly bonded to N-3 (C-N3) in compounds with and without N-1 substituents, Table CN-8.

TABLE CN-8

The 3N-C_{aryl} Carbon Chemical Shifts in N-Aryl
2-Thio-4-Imidazolidinones in DMSO-d₆ (PPM, TMS).



No	R		R ₁	PPM*
IZ-1	H	..	H	133.505
IZ-2	Phenyl	..	H	133.984
IZ-3 to IZ-9	H	133.5 - 133.9
IZ-10	H	..	CH ₃	133.470
IZ-11	Phenyl	..	CH ₃	133.795
IZ-12 to IZ-16	CH ₃	133.6 - 133.8

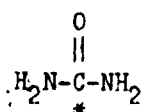
* for carbons directly attached to N-3.

Replacement of a hydrogen atom by aryl moieties at N-1 gives rise to a negligible deshielding effect on the C-N3 carbons. Its magnitude is 0.0 - 0.5 ppm downfield in the C-5 unsubstituted as well as the C-5 methyl derivatives. This small deshielding effect may arise from a number of diverse, but uncertain, sources like the δ - effect of either the N-1 aryl moiety or the C-5 methyl group, changes in hybridization of the nitrogen atom resulting from substitution of a hydrogen atom by a phenyl ring and any accompanying change in conformation, and the unpredictable variations in the solvation patterns around the C-2 and C-4 carbons.

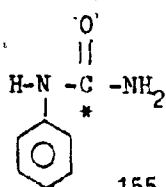
The foregoing considerations suggest that the contribution of a resonance structure such as (R) toward overall representation of 2-thioimidazolidinones is undetectable.

The Upfield β - and γ - Phenyl Substitution Effects :

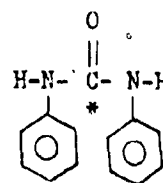
The substitution of a hydrogen atom by a phenyl group in linear and branched alkanes is known to deshield the β -carbon strongly (by about 7-9 ppm) (107). However, an examination of the shielding of certain amides (70) and ureas (109), as shown in Fig. CN-1, indicates the opposite trends.



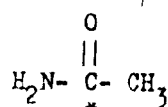
159.8 ppm



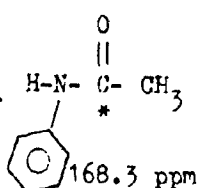
155.7 ppm



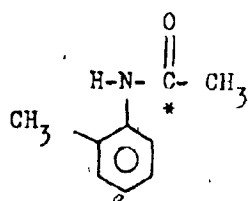
152.9 ppm



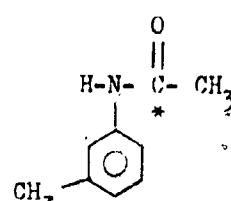
172.7 ppm



168.3 ppm

 $(\Delta\delta = 4.4 \text{ ppm})$ 

155.6 ppm



155.6 ppm

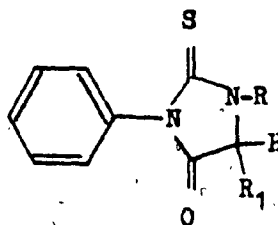
Fig. CN-1 : Carbon-13 Carbonyl Chemical Shifts in Some
Amides and Ureas.

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The replacement of a hydrogen atom by a phenyl group in the amides and ureas listed in Fig. CN-1 gives rise to an upfield β -effect on the carbonyl carbon by about 4 ppm. This is attributed to the increased conjugation which would increase the electron density at the carbonyl carbon atom. The upfield β - and γ -effects of the 1-phenyl ring upon the C-2 and C-4 carbonyl carbons, as shown in Table CN-9, are 2.1 and 2.2 ppm, respectively, for the C-5 unsubstituted derivatives, and 1.1 and 1.8 ppm, respectively, for the C-5 methyl compounds. In the absence of a 1-aryl moiety, as in IZ-1 or IZ-10, the electron density over the hetero ring is already fairly high because of its own 8 π -electron system, and conjugation with the 3-phenyl ring. The addition of another phenyl ring does increase the electron density over the whole molecule, but the shielding effect is only about 1-2 ppm. A similar trend is observed in urea and its phenyl derivatives. The carbonyl carbon in N-phenyl urea is shielded by about 4.2 ppm as compared to urea itself; but the addition of another phenyl group in 1,3-diphenyl urea further shields the carbonyl carbon by only 2.8 ppm.

TABLE CN-9

The Upfield β - and γ - Phenyl Substitution
Effects Upon the C-2 and C-4 Carbonyl Carbons
in N-Aryl-2-Thio-4-Imidazolidinones in DMSO- d_6 (PPM).



<u>R</u>	<u>No</u>	<u>β-</u>	<u>γ-</u>
H, Phenyl	IZ-1, IZ-2	2.139	2.236
H, Phenyl	IZ-10, IZ-11	1.104	1.819

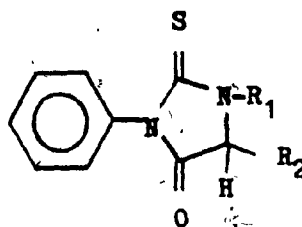
The Upfield γ - and the Downfield β - Effects of Substituents at C-5 :

The C-2 and C-4 carbonyl carbon shieldings are quite sensitive to substitution at the C-5 carbon which gives rise to the γ - effect upon the thiocarbonyl carbon and the β - effect upon the carbonyl carbon. These γ - and β - effects are calculated by comparing the chemical shifts of the corresponding carbons in imidazolidinones with C-5 unsubstituted and the C-5 methyl substituted derivatives, both having the same type of aryl moieties. This would ensure that the γ - and β - effects are free from any other effect e.g. β -phenyl or δ - or ϵ - effects etc. The downfield β - and the upfield γ - effects upon the C-2 and C-4 carbons resulting from the addition of a methyl group at the C-5 carbon are shown in Table CN-10.

Table CN-10 shows that the γ -effect on the thiocarbonyl carbon in imidazolidinones with 1-aryl moieties such as 2-methoxyphenyl, 2-fluorophenyl, 2,3-dimethylphenyl and 1-naphthyl groups is 0.74 ± 0.08 ppm. The downfield β - effect upon the carbonyl carbon in these compounds is 3.0 ± 0.2 ppm. It suggests that the γ - and the β - methyl substitution effects in 2-thio-4-imidazolidinones are fairly insensitive to the polarity of the ortho substituent. This is similar to the findings of Williams (109) that the γ -methyl effect upon the C-2 carbonyl carbons in 3-aryl substituted imidazolidine-2,4-diones are 1.0-1.2 ppm for a variety of ortho substituents. However, unlike

TABLE CN-10

The Upfield γ - and the Downfield β -Effects (PPM) Upon the C-2 Thiocarbonyl and C-4 Carbonyl Carbon Chemical Shift Values, Respectively, By the Addition of a Methyl Group at C-5 in 1,3-Diaryl-2-Thio-4-Imidazolidinones in DMSO- d_6 .



R_1	No	γ - (C-2)	β - (C-4)
H	IZ-1, IZ-10	1.271	2.835
Phenyl	IZ-2, IZ-11	0.236	3.272
2-Tolyl	IZ-3, IZ-12	-	-
2-Methoxyphenyl	IZ-4, IZ-13	0.769	3.062
2-Fluorophenyl	IZ-5, IZ-14	0.680	2.964
2,3-Dimethylphenyl ...	IZ-8, IZ-15	0.664	3.062
1-Naphthyl	IZ-9, IZ-16	0.816	3.043

3-aryl-2-thio-4-imidazolidinones (61) where the β - and γ -effects were found to be related to the steric bulk of 3-aryl moieties, these effects in 1,3-diaryl analogues seem to be quite independent of the steric bulk of the 1-aryl moiety. For example, the γ -effects in the 2-fluorophenyl and 2,3-dimethylphenyl derivatives are 0.68 and 0.66 ppm, respectively. The magnitude of the γ -effects in 1,3-diaryl compounds is smaller (0.6 - 0.8 ppm) as compared with the corresponding effects in 3-aryl-, 1-aryl- diones or 3-aryl-2-thio analogues (1.0 - 4.0 ppm). However, the β -substitution effects in these compounds (3.0 ± 0.2 ppm) are almost comparable to those found in the 3-aryl-, and 1-aryl-diones (2.0-3.4 ppm), but not with 3-aryl-2-thio-4-ones (0.0-2.4 ppm).

Table CN-10 shows that the γ -effect in 1,3-diphenyl derivatives, (IZ-2, IZ-11) is only 0.2 ppm compared with 0.74 ± 0.08 ppm in all other cases studied. This shows that the effect solely from the C-5 methyl substitution upon the C-2 thiocarbonyl carbon seems to be about 0.2 ppm; whereas the difference between the observed γ -effect and this 0.2 ppm (i.e. $\approx 0.7 - 0.2 = \approx 0.5$ ppm) appears to be contributed from some other factor. The only variable factor in calculating the γ -effects is the addition of a methyl group at the C-5 carbon. It is probable that an increase in the steric bulk of the aryl moiety followed by an increase in the dihedral angle between the two rings affects the through-bond inductive

contributions of the C-5 methyl group to the C-2 and C-4 carbonyl carbons by about 0.5 and 0.2 ppm, respectively.

The C-13 shielding data on the γ -effects do not suggest non-bonded steric interaction between the aryl ortho substituents and the C-5 methyl groups to be significant. This is in agreement with the results obtained by proton line shape analysis. More direct and conclusive evidence can be obtained from a study of the proton spin-lattice relaxation rates of these compounds which is expected to show not only the existence but also the relative magnitudes of such non-bonded steric interactions, if any. It is hoped that in near future such a study may be undertaken when the facilities for spin-lattice relaxation measurements become available at Concordia University.

For the ortho halogen substituents in 3-aryl-2-thio-4-imidazolidinones (61) interesting trends were observed for the C-2 thiocarbonyl and C-4 carbonyl carbon chemical shifts in the 5,5-dimethyl derivatives. In these compounds, both the C-2 and C-4 carbons become increasingly deshielded and their carbon chemical shifts show an approximately linear relationship with the electronegativity of the ortho halogen substituent. The increase in deshielding of the C-2 and C-4 carbons (with ortho substituents as $F \rightarrow Cl \rightarrow Br$) has been attributed to the slightly increased atomic covalent radii of the halogens which would increase the possibility of electrostatic interaction between the ortho halogen

substituent and either the C-2 thiocarbonyl and/or the C-4 carbonyl group or the DMSO solvent shell around these groups.

In 1,3-diaryl-2-thio-4-imidazolidinones, however, the C-2 and C-4 carbon shieldings are almost invariant to the ortho halogen substituents (F, Cl, and Br) on the 1-aryl ring, suggesting that these ortho substituents do not have direct non-bonded steric interactions with either the C-2 and C-4 carbonyl groups or solvent shells around them.

C-5 METHYL CARBON CHEMICAL SHIFTS :

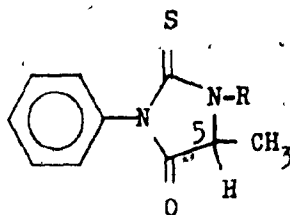
The C-5 methyl carbon-13 chemical shift values are shown in Table CN-11. These values fall within the range 14.7-16.3 ppm. The thioimidazolidinones with C-5 methyl groups are expected to show double signals corresponding to the diastereomeric rotamers. However, only those compounds which possess relatively bulky aryl moieties showed such a splitting of resonances. These include the ortho tolyl-, 2,3-dimethylphenyl-, and 1-naphthyl- derivatives, IZ-12, IZ-15, and IZ-16, respectively.

Since the C-5 methyl group lies out of the plane of the hetero ring, shielding changes are expected to be dominated by the steric interaction of the ortho aryl substituents. Shielding contributions from the hetero ring, such as through conjugation, are expected to be less important. As already discussed, the steric interaction between the C-5 methyl groups and the ortho substituents are not significant in 1,3-diaryl-2-thio-4-imidazolidinones. This is also apparent from the chemical shift values of C-5 methyl carbons in Table CN-11 being 14.9 ± 0.2 ppm for all the compounds.

The shieldings of the C-5 methyl carbons in 1,3-diaryl-2-thio-4-imidazolidinones are insensitive to the polarity of

TABLE CN-11

Carbon-13 Chemical Shift Values of C-5 Methyl
Carbons in N-Aryl-2-Thio-4-Imidazolidinones in
DMSO-d₆ (PPM, TMS).



No	R		PPM
IZ-10	H	..	16.293
IZ-11	Phenyl	..	15.059
IZ-12	2-Tolyl	..	15.357, 14.142*
IZ-13	2-Methoxyphenyl	..	14.929
IZ-14	2-Fluorophenyl	..	14.823
IZ-15	2,3-Dimethylphenyl		15.449, 14.799*
IZ-16	1-Naphthyl	..	15.579, 14.604*

*Diastereomers.

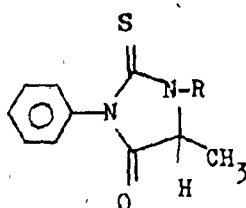
the aryl ortho substituents, Table CN-11. This is expected since the C-5 methyl group is at 5-bonds distance from the ortho substituent. However, Ioli (53) has reported a maximum of 0.3 ppm upfield shift by polar ortho substituents (Cl, F, OCH₃) in 1-aryl-2,4-imidazolidinediones, in morpholine, employing the continuous wave (C.W.) NMR technique. In 3-aryl-imidazolidine-2,4-diones (109), the C-5 methyl carbon shieldings have been observed to be insensitive to the polarity or the steric bulk of the ortho substituents. However, in 3-aryl-2-thio-4-imidazolidinones (61), though the polarity effects are negligible, the steric effects of the bulky ortho substituents on the C-5 methyl carbons are considerable. A gradual increase in the shielding of the C-5 carbons has been observed with an increase in the steric bulk of the 3-aryl moieties, up to a maximum of about 1.0 ppm. Since the ortho substituents on the 3-aryl ring are well-separated from the C-5 methyl groups so as not to have non-bonded steric interactions between them, it was deduced that the effect of the steric crowding of the aryl ring might be transmitted to the C-5 methyl group via re-orientation of the un-symmetrical solvent shell around the carbonyl carbons.

Substitution of the N-1 hydrogen atom, IZ-10, by a phenyl ring, IZ-11, gives rise to an upfield γ -effect of 1.23 ppm on the C-5 methyl carbon. It may be recalled that the same effect for the C-4 carbonyl carbons is 1.8-2.2 ppm upfield.

Table CN-12 shows the effect of the C-5 methyl group upon the aryl carbons bonded to N-1 and N-3. It shows that the methyl group does not exert any steric or electronic influence upon the aryl carbons attached to N-3, the δ - effects being 0 to 0.1 ppm. However, the γ - methyl substitution effect on the aryl carbons attached to N-1, in most cases, is 1.0-1.5 ppm upfield. This effect in the ortho tolyl derivative is almost zero, whereas in the 2,3-dimethylphenyl compound, a small deshielding effect (0.27 ppm) is observed.

TABLE CN-12

Upfield γ - and δ - Effects of C-5 Methyl Group
 Upon the Aryl Carbons Directly Bonded to the
 Nitrogen Atoms in DMSO- d_6 (PPM, TMS).



R		No	γ - (C-N ₁)	δ - (C-N ₃)
H	..	IZ-1, IZ-10	-	0.035
Phenyl	..	IZ-2, IZ-11	1.482	0.189
2-Tolyl	..	IZ-3, IZ-12	-0.070	-0.170
2-Methoxyphenyl	..	IZ-4, IZ-13	1.436	0.115
2-Fluorophenyl	..	IZ-5, IZ-14	1.094	0.146
2,3-Dimethylphenyl	..	IZ-8, IZ-15	-0.270	0.099
1-Naphthyl	..	IZ-9, IZ-16	0.956	0.083

(-) deshielding effect.

ARYL CARBON CHEMICAL SHIFTS :

A series of peaks corresponding to the aryl carbons occurs within the expected range of 110-160 ppm. Useful information about conjugation to the hetero ring or about the dihedral angles and the intramolecular steric interactions could not be obtained from the shielding data of the aromatic carbons. Aryl carbon shieldings are most sensitive to perturbations caused by the electronic effects of the substituents.

A meaningful correlation which could be made between the aryl carbon chemical shifts and the hetero ring substitution pattern was a through-bond inductive effect of the C-5 methyls; the upfield γ -effect on the carbon directly attached to N-1 being 1.0-1.5 ppm.

The invariant chemical shifts of carbons attached to N-3 have shown (see earlier) that the contribution of a highly polarized resonance structure, such as (R), is not detectable in the over all representation of these molecules.

It is interesting to note that the aryl carbons in bulky substituents at N-1 i.e. IZ-12, IZ-15 and IZ-16, show splitting of signals corresponding to the diastereomeric rotational isomers. The aryl carbons in the ortho fluorophenyl derivatives, IZ-5 and IZ-14, show spin-spin splitting over one to four bonds. The carbon-fluorine coupling constants ($^nJ_{C-F}$),

in Hz, as listed below, are in good agreement with those reported

	$^1J_{C-F}$	$^2J_{C-F}$	$^3J_{C-F}$	$^4J_{C-F}$
IZ-5	250.00	19.80	7.70	3.30
IZ-14	250.74	18.70	7.70	3.30
Literature	245.3	21.0	7.7	3.3

in the literature (70) for fluorobenzene.

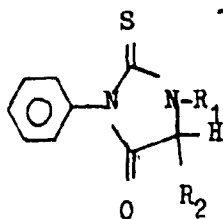
CARBON-13 CHEMICAL SHIFTS OF ARYL SUBSTITUENTS :

Shielding data for the methyl and methoxyl carbons on the aromatic ring are shown in Table CN-13. The ortho tolyl carbons in these compounds absorb at 17.6-17.9 ppm. The substitution of methyl group at C-5 gives rise to a downfield ϵ - effect of ≈ 0.3 ppm. The carbon shieldings of the methoxyl (IZ-4, IZ-13) or 2,3-dimethylphenyl (IZ-8, IZ-15) carbons are not affected by substitution at C-5. The chemical shifts of the tolyl, methoxyl, and the meta methyl carbons in these compounds are about 0.3-0.6 ppm upfield, and of the ortho methyl carbon in the 2,3-dimethyl derivative is about 1.3-1.7 ppm upfield, with respect to the corresponding carbons in the 1-aryl-imidazolidine-2,4-diones (53). The increased carbon shieldings may be attributed to the presence of 3-phenyl-2-thio moiety in the present series of compounds which result in greater degree of conjugation than in the diones. Similar aryl substituents in the 3-aryl-2-thio-4-imidazolidinones are deshielded by about 0.5-1.5 ppm as compared to the corresponding carbons in the diaryl series. Large dihedral angles between the 3-aryl and the hetero rings with a consequent decrease in conjugation have been considered to give rise to deshielding effects in the 3-aryl-2-thio series of imidazolidinones (61).

The insensitivity of the aryl substituents in 1,3-diaryl-2-thio-4-imidazolidinones to the steric, polar and inductive effects of the 5-membered hetero ring precludes any

TABLE CN-13

Aryl Methyl and Methoxyl Carbon-13 Shieldings of
1,3-Diaryl-2-Thio-4-Imidazolidinones in DMSO-d₆
(PPM, TMS).



No	R ₁		R ₂	PPM
IZ-3	2-Tolyl	..	H	17.593
IZ-4	2-Methoxyphenyl	..	H	55.841
IZ-8	2,3-Dimethylphenyl	..	H	2-CH ₃ : 14.094 3-CH ₃ : 19.780
IZ-12	2-Tolyl	..	CH ₃	17.884, 17.253*
IZ-13	2-Methoxyphenyl	..	CH ₃	55.872
IZ-15	2,3-Dimethylphenyl	..	CH ₃	2-CH ₃ : 14.149*, 13.709 3-CH ₃ : 19.998

* Diastereomers.

useful stereochemical information to be drawn from the shielding data, The chemical shifts of these carbons are influenced largely by other substituents on the aromatic ring, whereas relatively minor correlations are observable with the hetero ring substituents.

SECTION 4.

A

CARBON-13 NMR STUDY OF

1-ISOINDOLINONES

INTRODUCTION

The various factors contributing to the shielding of a carbon nucleus generally combine in a complex manner. Type and number of substituents as well as the nature of the functional group the carbon under consideration is part of are the determining factors. An outstanding feature of C-13 chemical shifts is the finding that substituent contributions are additive. This is particularly so for aliphatic carbons, where practice shows that carbon shieldings can be divided up into a number of additive contributions produced by substituents in α -, β -, γ -, and δ - positions with respect to the site of substitution. Unsaturated carbon shifts are generally more straightforward to interpret because they primarily depend on the local π -electron density, which is more easily predictable. Other contributions are often of secondary importance.

Like so many features of C-13 NMR, many of the main patterns and ideas of substituent effects on C-13 chemical shifts

can be found in the early work, especially by Lauterbur (63-4). Although the resolution of early C-13 NMR techniques was not sufficient to display effects at carbons remote from the site of substitution, the main empirical features of substituent effects manifested at the substituted α - carbon and the adjacent β - carbon were known by 1963 from the work of Lauterbur, (63-4), of Spiesscke and Schneider (100,101), and of Savitsky and Namikawa (89,90). Of course, more accurate data that display the same trends as were found in the early work are available from more recent experiments.

The dominant feature of the early C-13 NMR work on substituent effects were usually discussed as an 'electronegativity effect', 'the neighbor anisotropy effect', and 'the methyl effect' (i.e. the decrease in shielding at both the α - and β - carbons caused by substitution of a methyl group for a hydrogen atom). The electronegativity effect was typically introduced by means of plots of chemical shifts versus the electronegativities of the substituents.

Stothers (103) has reviewed the course of development of the history of the theory of carbon-13 shieldings in hydrocarbons as well as in heterocyclic systems. It is not appropriate to attempt here such a theoretical discussion.

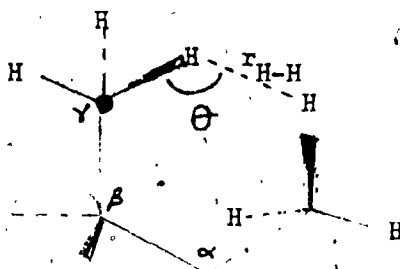
Although a satisfactory theoretical explanation of the β - substituent effect is still lacking, both the α - and β - effects are thoroughly documented in the C-13 NMR literature.

The γ -effect, also universally accepted, has been utilized for stereochemical purposes in a wide variety of systems. Though small in magnitude (~ 2.5 ppm upfield in hydrocarbons, as compared with $\sim 9-10$ ppm downfield α - and β -effects), the γ -effect has, probably, been the most important and the most interesting of substituent effects since it appears to be primarily operative through space rather than through the bonds of the molecule.

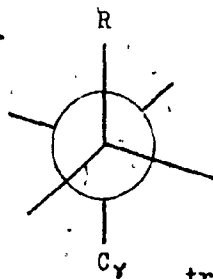
It has become a widely accepted practice to rationalize steric C-13 shift effects in terms of the repulsive forces between closely spaced atoms. They arise from locally crowded electron distributions within a molecule and they influence the shielding constants of involved nuclei in two ways. Apart from causing distortions of the electron distribution, the interactions also affect the shielding constants indirectly by producing small changes in molecular geometry. These two components of the steric effects are very difficult to separate and, therefore, any quantitative rationalization remains doubtful.

Grant and Cheney (46) have rationalized the γ -effects in terms of a model of steric interactions between the neighboring C-H moieties. Qualitatively, the principal idea is that the C-H bonds associated with hydrogen atoms suffering appreciable non-bonded interactions are perturbed such that the charge density at the carbon nucleus is altered. There will be a force associated with the non-bonded interaction energy

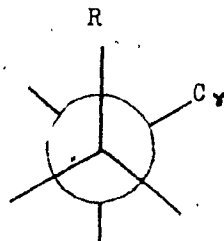
which has a component along the C-H bond axis. According to the model, it is this component of the force which affects the shielding of the carbon nucleus of interest. Thus, the steric perturbation of the C-H bond will depend upon internuclear separations as well as on the angle θ between the C-H bond axis and a line drawn between the interacting hydrogen atoms, as shown below :



The Y- effect has been found to be very sensitive to the relative orientations of the sterically interacting groups. The Y- gauche or eclipsed arrangements produce an upfield shift of the signal relative to the shielding of a corresponding carbon in the anti form. In rigid, cyclic systems, the Y-trans effect has been found to be almost zero for a methyl, chloro or sulfur substituent; whereas for the



trans



gauche

first row hetero atom substituents ($R = N, O, F$), it is 1-8 ppm upfield compared with the unsubstituted parent compound. The

γ -gauche effects for heteroatoms are almost twice as much (35,107). In conformationally rigid systems, very large γ -gauche effects have been observed, e.g. 18 ppm upfield in 1,2,3-trimethylcyclohexane (31). In conformationally mobile systems, the γ -gauche effect is also observed, though to a lesser extent since more stable conformations are favored; e.g. 2-6 ppm in n-alkanes (107).

Since the effects arising from interactions of more remote nuclei (separated by four or more bonds) tend to be much smaller and variable, less attention has been given to their detailed examination. The δ - and ϵ - effects were known from earlier studies to be remarkably constant, but their magnitude was considered to be very small, e.g. $\sim 0.1 - 0.3$ ppm. However, in a report of the effects of molecular asymmetry on C-13 shieldings (56), it was observed that significant deshielding effects (1.5 - 6.9 ppm) occur over four bonds in isopropylalkylcarbinols. It was also noted that the 1,5- interaction, which resulted in a downfield shift, was especially interesting in view of the usual upfield shifts associated with the steric effects.

It was pointed out by Grover et. al. (47) that nuclei separated by four bonds can exist in orientations in which non-bonded internuclear distances are comparable to or shorter than for the γ -gauche arrangement. They demonstrated that the syn-axial orientation of sterically interacting δ - nuclei produced appreciable downfield δ - shifts, as large as 5-6

ppm, in rigid, cyclic systems. In another study of the substituent effects of the hydroxyl group on the C-13 shieldings of the trans-decalols, 10-methyl-trans-decalols, and some sterols, Grover and Stothers (48) showed definitive evidence of appreciable downfield shifts for syn-axial steric interaction between carbon nuclei having positions δ - with respect to each other. This finding was in striking contrast to the general trend for gauche interactions, and clearly violated the general premise which associates steric crowding with upfield shifts.

In acyclic compounds, the populations of gauche-gauche conformers (separated by four bonds) are generally very low because of the high gauche-gauche interaction energy, ~ 3 Kcal/mole (41). Batchelor (12) has reported downfield shifts in acyclic hydrocarbons produced by $g(+)g(-)$ substituents, those in which consecutive C-C bonds have gauche rotations of opposite sign (41). Appreciable downfield δ - shifts of C-1 resonances of the tertiary butyl group in acyclic hydrocarbons were observed, and it was concluded that the downfield direction of the shift appeared to be a property of δ - interactions in general rather than the cyclic systems and hydroxyl interactions considered previously by Grover and Stothers (47,48).

The existence of such downfield δ - shifts casts doubt (12) on the interpretation of steric shifts by Grant and Cheney (46) in terms of polarization of electrons along interacting C-H bonds. It was suggested that there must be a

competing mechanism which must be dominant at short distances. It was shown that the second order electric field effects due to fluctuating magnetic dipoles were large enough to explain the observed downfield shifts.

PRESENT INVESTIGATION :

Isoindole-1,3-diones (phthalimides) have been known to the organic chemist for long time. Most of the earlier work generally involved their preparations and reactions. However, over the past twenty years, these compounds gained the interest of many workers because of their plant-growth regulatory and fungicidal actions, tranquillizing and anti-convulsant effects, and formation of thermally stable polyimide polymers. Consequently, most of the studies on isoindole-1,3-diones were directed in these directions.

We noticed that the N-arylisindolinones and N-arylisoindolediones could provide good examples of systems to study δ - shifts of the carbonyl or heterocyclic ring methylene carbons arising from the aryl ortho substituents. Because the 5-membered hetero ring is fused to the benzene ring in these compounds, the frame-work of the imide and imidine systems constitute cyclic rigid systems with the advantage that shielding

effects arising from conformational interconversions may be avoided.

Lumbroso and Dabard (65) , Arcoria et. al. (9-10), and Barassin (11) measured the dipole-moments of a number of cyclic imides with a five-membered ring. They concluded that N-phenylphthalimide takes a planar conformation. The I.R. studies by Matsuo (74) on a series of N-aryl substituted phthalimides showed that the high and low frequency absorption bands of the carbonyl groups in a number of N-aryl substituted-1,3-isoindolediones are 1784 ± 4 and $1727 \pm 5 \text{ cm}^{-1}$, respectively. This suggests that the magnitudes of conjugation (and hence the dihedral angles) between the aryl and the hetero rings in these molecules are not affected to any considerable extent by the nature of the substituents on the aryl ring. (Alternatively, the carbonyl frequencies are not sensitive to conjugation in these compounds).

The I.R. and the C-13 NMR data of isoindole-1,3-diones and isoindolinones suggests that the magnetic environments of the carbonyl groups in both types of compounds are not much different (see later).

The foregoing observation encouraged us to undertake a C-13 NMR study of these heterocyclic systems. The δ - shifts upon the carbonyl and methylene carbons arising from the aryl ortho substituents are expected to be fairly independent of the steric interactions between the groups involved, since

proton NMR line shape analysis has shown (see Section 2) that the barriers to internal rotation about the aryl C-N bond in these molecules are very low. . It was also expected that the use of a less polar solvent like chloroform will not solvate the carbonyl group (C = O is part of fairly strained 5-membered ring) to any considerable degree so as to avoid complications because of the solvent-induced variations in chemical shifts. This situation may be contrasted to the observed pronounced solvation effects in the case of N-aryl-2-thio-4-imidazolidinone (61).

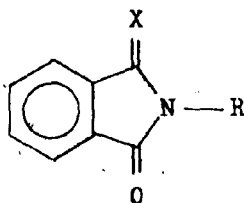
The δ - effects reported so far and discussed in the preceding sections were considered to arise from the steric interaction. It was considered desirable to investigate the δ - effects in systems which lack large steric interactions. It is fortuitous that the solvent effects upon the shielding of various carbons in compounds in this study were later found to be negligible. Since electron delocalization can occur over a major portion of these molecules, and the steric and solvent effects are minimal, it was expected that the δ - shifts would mostly be governed by variations in the electron densities in these molecules depending upon the nature and number of substituents on the aryl moieties.

RESULTS AND DISCUSSION

The Fourier transformed carbon-13 nuclear magnetic resonance spectra are measured for a series of N-aryl-isoindole-1,3-diones, ID-1 to ID-14, and N-aryl-1-isoindolinones, IN-1 to IN-14, as listed in Table NC-1. For the purpose of comparison, the chemical shift values are tabulated and discussed according to the carbon positions. The solvents employed were dimethylsulfoxide (DMSO) and chloroform. When chloroform was used, the lock signal and the external reference were derived from $^{13}\text{CH}_3\text{I}$ in an external capillary. The data were not corrected for bulk magnetic susceptibility. DMSO itself provided the lock signal as well as the internal reference. The number of scans varied from 7,000 - 10,000 depending upon the concentration of the solution. A pulse width of 50 μsec was used with a delay time of 0.7 sec. Each spectrum was run with at least two different analytical frequencies. The chemical shifts are reported relative to TMS and were calculated by measuring the chemical shift of

TABLE NC-1

N-Aryl Substituted-1H-Isoindole-1,3-Diones, (X=O)
and Isoindolinones, (X=H₂), Synthesised for the
Present Study.

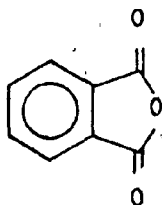


<u>X = O</u>	<u>X = H₂</u>	<u>R</u>
ID-1	IN-1	Phenyl
ID-2	IN-2	2-Tolyl
ID-3	IN-3	2-Methoxyphenyl
ID-4	IN-4	2-Fluorophenyl
ID-5	IN-5	2-Chlorophenyl
ID-6	IN-6	2-Bromophenyl
ID-7	IN-7	2-Hydroxyphenyl
ID-8	IN-8	2,3-Dimethylphenyl
ID-9	IN-9	2,6-Dimethylphenyl
ID-10	IN-10	2-Methyl-4-Methoxyphenyl
ID-11	IN-11	3-Chloro-2-Methylphenyl
ID-12	IN-12	4-Chloro-2-Methylphenyl
ID-13	IN-13	1-Naphthyl
ID-14	IN-14	2-Naphthyl

DMSO to be 40.64 ppm downfield from TMS. All chemical shifts are estimated to be accurate to 0.05 ppm (equivalent to 2.0 Hz).

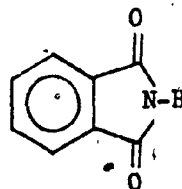
ASSIGNMENTS :

The carbon-13 carbonyl chemical shift values of N-aryl isoindolediones and N-aryl-isoindolinones, ID-1 to ID-14 and IN-1 to IN-14, respectively, fall within the expected range 160-170 ppm. These values in the compounds under study vary from 166.0 - 168.0 ppm; and are in close agreement with the chemical shifts of the carbonyl carbons in some related compounds, as shown below :



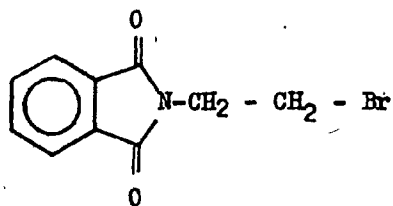
(1)

163.1 (DMSO- d_6) (58)



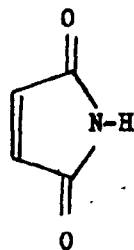
(2)

167.6 (42)



(3)

167.5 (CDCl₃) (58)



(4)

172.5 (70),

The assignment of carbon chemical shift values to the substituents on the aryl ring is straight-forward. The methyl signals are easily identifiable in the methyl region of the spectrum. The methoxy and β -methylene carbons in 1-isoindolinones appear over the range 50 - 55 ppm; but these resonances are easily distinguished by the off-resonance proton decoupling technique. Thus, signals at 50-53 ppm in the spectra of the isoindolinones are assigned to the methylene carbons, whereas those at 55-56 ppm are assigned to the methoxy carbons on the aryl ring.

A series of peaks corresponding to the aryl carbons occurs within the expected range of 110-155 ppm. Since the chemical shift values of the carbonyl and the β -methylene carbons, which were thought to be susceptible to stereochemical variations, vary over relatively limited range, the aryl carbons of the heterocyclic moieties are not expected to be very sensitive to the varying pattern of substitution on the N-aryl group. Therefore, no attempt was made to specifically assign various peaks to the aryl carbons. However, some of the aryl peaks are quite easy to recognize i.e. peaks corresponding to the carbons of C-N, C-OH, C-OMe, C-halogens, or C-CH₃ bonds. The unsubstituted aryl carbons would, because of the nuclear Overhauser effect and shorter relaxation times, show peaks of much greater intensities than the substituted aryl carbons.

The chemical shift values of the carbonyl carbons and those in the substituents on the aryl ring for the

isoindole-1,3-diones are shown in Table NC-2. Tables NC-3 and NC-4 show the chemical shifts of the carbons of interest in 1-isoindolinones.

EFFECT OF CONCENTRATION AND SOLVENT :

Some of the 1-isoindolinones with varying degrees of N-aryl steric bulk were dissolved in dimethylsulfoxide and chloroform at different concentrations and their C-13 FT NMR spectra were run at almost a constant temperature ($\sim 30^\circ$). The results show that for small as well as large steric bulk of N-aryl moieties in IN-1, 11, and 13, the shielding of all the carbons in these molecules are practically un-affected at a concentration range of 0.1 - 0.9 M, either in a polar solvent, dimethylsulfoxide, or in a relatively less polar solvent, chloroform. This shows that either chloroform or DMSO does not solvate these molecules to any considerable extent.

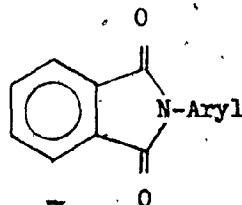
If chloroform is employed as a relatively non-polar reference solvent, the direction of polar solvent-induced shifts may be determined by comparison with the observed chemical shifts in the more polar solvent, DMSO.

The C-1 carbonyl and C-3 methylene carbons in the 3-chloro-2-methylphenyl derivative, IN-11, are deshielded by 1.12 and 0.70 ppm, respectively, in chloroform as compared with DMSO; while the ortho methyl carbon is least affected,

(by 0.23 ppm). The effect on the shielding of aryl carbons is intermediate (0.2 - 0.7 ppm). It seems that dimethylsulfoxide solvates the carbonyl group slightly more effectively than chloroform; and causes variation of electron densities over the whole conjugated system; the primary effect being upon the 5-membered hetero ring.

TABLE NC-2

The Carbon-13 Carbonyl Chemical Shifts (PPM, TMS)
of N-Aryl-Substituted-1H-Indole-1,3-Diones in
DMSO (0.4 - 1.0 M Solutions) at $\sim 30^\circ$.

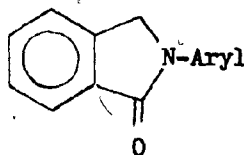


No	Aryl	C=O	Aryl Substituents.
ID-1	Phenyl	166.27	
ID-2	2-Tolyl	166.71	CH ₃ : 17.14
ID-3	2-Methoxyphenyl	167.02	OCH ₃ : 55.97
ID-4	2-Fluorophenyl	166.46	
ID-5	2-Chlorophenyl	166.31	
ID-6	2-Bromophenyl	166.36	
ID-7	2-Hydroxyphenyl	167.34	
ID-8	2,3-Dimethylphenyl	167.25	2-CH ₃ : 14.34 3-CH ₃ : 20.16
ID-9	2,6-Dimethylphenyl	166.74	2,6-Me ₂ : 17.58
ID-10	2-Methyl-4-Methoxyphenyl	167.37	2-CH ₃ : 17.80 4-OCH ₃ : 55.49
ID-11	3-Chloro-2-Methylphenyl	166.70 (DMSO) 166.70 (CHCl ₃)	2-CH ₃ : 15.23
ID-12	4-Chloro-2-Methylphenyl	166.92	2-CH ₃ : 17.46
ID-13	1-Naphthyl	167.57	
ID-14	2-Naphthyl	not observed	

(range : 166.92 \pm 0.65)

TABLE NC-3

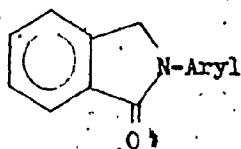
The Carbon-13 Carbonyl Chemical Shifts (PPM, TMS)
of N-Aryl Substituted-1-Isoindolinones in DMSO
(0.4 - 0.6 M Solutions) at $\sim 30^\circ$.



No.	ARYL	PPM
IN-1	Phenyl	166.26
IN-2	2-Tolyl	166.34
IN-3	2-Methoxyphenyl ..	167.20
IN-4	2-Fluorophenyl ..	166.90
IN-5	2-Chlorophenyl ..	166.94
IN-6	2-Bromophenyl ..	166.86
IN-7	2-Hydroxyphenyl ..	167.73
IN-8	2,3-Dimethylphenyl ..	166.72
IN-9	2,6-Dimethylphenyl ..	166.78
IN-10	2-Methyl-4-Methoxyphenyl	166.98
IN-11	3-Chloro-2-Methylphenyl	166.73 (DMSO) 167.85 (CHCl ₃)
IN-12	4-Chloro-2-Methylphenyl	166.50
IN-13	1-Naphthyl ..	167.61
IN-14	2-Naphthyl ..	not observed

(range : 167.05 ± 0.80)

The Carbon-13 Chemical Shifts of 3-Methylene and Aryl Ring Substituent Carbons in N-Aryl-1-Isoindolinones in DMSO (0.4 - 0.6 M Solutions) .



No	ARYL	3-CH ₂	Ortho Substituent	Other Substituents.
IN-1	Phenyl ..	50.50		
IN-2	2-Tolyl ..	52.49	17.73	
IN-3	2-Methoxyphenyl	51.96	55.91	
IN-4	2-Fluorophenyl	52.01		
IN-5	2-Chlorophenyl	52.01		
IN-6	2-Bromophenyl	52.01		
IN-7	2-Hydroxyphenyl	52.17		
IN-8	2,3-Dimethylphenyl	52.89	14.41	3-Me : 20.20
IN-9	2,6-Dimethylphenyl	50.62	17.62	
IN-10	2-Methyl-4-Methoxy-phenyl	53.04	18.21	4-OCH ₃ : 55.53
IN-11	3-Chloro-2-Methyl-phenyl	52.71 53.41	15.54 15.77 (CHCl ₃)	
IN-12	4-Chloro-2-Methyl-phenyl	52.44	17.81	
IN-13	1-Naphthyl	53.75		
IN-14	2-Naphthyl	50.80		

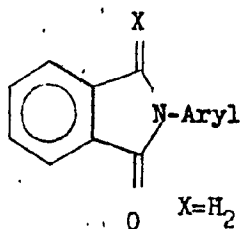
CARBONYL CARBONS :

The carbon-13 chemical shift values for the carbonyl carbons are 166.9 ± 0.7 ppm for isoindole-1,3-diones, and 167.0 ± 0.8 ppm for 1-isoindolinones, in DMSO. These relatively narrow ranges of shielding, however, do not preclude certain inferences to be drawn.

It appears that the magnetic environment at the carbonyl carbons in isoindolinones is very similar to that in the isoindole-1,3-diones. This is apparent from the examination of the I.R. and C-13 NMR data of these two types of compounds, Table NC-5. It shows that, with due consideration of experimental errors, the lower frequencies of absorption, ν_L , of the carbonyl groups in isoindole-1,3-diones are comparable to those of the isoindolinones. More direct and conclusive evidence is provided by the carbon-13 NMR data. For example, the carbonyl carbon chemical shift in both N-phenyl-isoindole-1,3-dione, ID-1, and N-phenyl-1-isoindolinone, IN-1, is 166.26 ppm. The range of chemical shift values of carbonyl carbons in the diones as well as in the isoindolinones is 167.0 ± 0.7 ppm. These observations suggest that the over-all influence of various factors operative in the dione series (e.g. ring strain, steric and electronic effects) is, un-expectedly, not much different from those in the isoindolinone compounds.

TABLE NC -5

Infra Red Absorption Frequencies of Carbonyl Groups
in N-Aryl Substituted-Isoindole-1,3-Diones, ID-1 to
ID-14; and 1-Isoindolindiones, IN-1 to IN-14, (KBr,
 cm^{-1}).



No.	ARYL	$\nu_{\text{C=O}}$	No.	X = (C = O)	
				High $\nu_{\text{C=O}}$	Low $\nu_{\text{C=O}}$
IN-1	Phenyl ..	1675	ID-1	1750	1700
IN-2	2-Tolyl ..	1660	ID-2	1750	1700
IN-3	2-Methoxyphenyl	1660	ID-3	1740	1680
IN-4	2-Fluorophenyl	1675	ID-4	1800	1725
IN-5	2-Chlorophenyl	1670	ID-5	1760	1700
IN-6	2-Bromophenyl	1670	ID-6	1720	1700
IN-7	2-Hydroxyphenyl	1670	ID-7	1800	1710
IN-8	2,3-Dimethylphenyl	1700	ID-8	1750	1690
IN-9	2,6-Dimethylphenyl	1655	ID-9	1750	1690
IN-10	2-Methyl-4-Methoxy-phenyl	1675	ID-10	1740	-
IN-11	3-Chloro-2-Methyl-phenyl	1640	ID-11	1740	1680
IN-12	4-Chloro-2-Methyl-phenyl	1665	ID-12	1740	1680
IN-13	1-Naphthyl	1670	ID-13	1750	1675
IN-14	2-Naphthyl	1690	ID-14	1770	1700

The negligible difference in carbonyl chemical shift values in 1-isoindolinones and isoindole-1,3-diones indicates that the carbonyl group in these molecules is not solvated to any considerable extent by chloroform or DMSO solvent molecules. Had there been significant solvation, the carbon shielding would have been expected to depend upon the steric interaction between the aryl ortho substituent and the solvent shell around the carbonyl group. Nevertheless, small differences in the solvation patterns about the carbonyl group are expected to affect their shielding to small extent, (e.g. $\sim 0.2 - 0.4$ ppm) depending upon changes in the dihedral angle between the aryl and hetero rings, and changes in the over-all molecular motion.

The following factors may be considered which would affect variations in the carbonyl chemical shift values in 1-isoindolinones and isoindole-1,3-diones.

A: Steric Effects :

Should steric interaction between the aryl ortho substituent (e.g. methyl, hydroxyl, or methoxy group) and the carbonyl group environment be significant, the effect on the carbonyl shielding is expected to be a function of the nature and size of the ortho substituent. Tables NC-2 and NC-3 show that the carbonyl carbon shieldings in these compounds are almost un-affected. This indicates that there is little or

negligible steric interaction between the ortho substituent and the carbonyl groups. Further conclusive evidence has been obtained from the proton spin-lattice relaxation rates, and from the line shape analysis of these compounds (see later).

The measurement of proton spin-lattice relaxation rates of isoindolinones at 270 MHz and at 23° has provided useful information on such steric interferences. For example, the "normalized" relaxation rates of 3-methylene protons in IN-3 and IN-7 are 3.14 and 3.21 sec⁻¹, respectively. This indicates that the ortho hydroxy or ortho methoxy substituents on the aryl ring are not prolate enough to exert a steric influence upon the methylene protons; and also on the carbonyl carbons.

The carbonyl carbons in ID-8, ID-11; and IN-8, IN-11 do not seem to be affected by the buttressing influence on the ortho methyl group by the meta methyl substituent in ID-8 and IN-8; and by the meta chloro group in ID-11 and IN-11; because the carbonyl shieldings in these compounds are almost un-affected when the buttressing influence is relieved in ID-9, IN-9; and ID-12, IN-12.

Further direct and conclusive evidence for the lack of steric interaction between the aryl ortho substituents and the methylene and/or the carbonyl groups in isoindolinones has been obtained from the proton spin-lattice relaxation rates of methylene protons in these compounds. For example, the spin-lattice relaxation rates (R_1 values) at 270 MHz and

at 23° for 3-methylene protons in IN-2 and IN-3 (with 2-tolyl and 2-methoxyphenyl moieties, respectively,) are 0.85 and 0.88 sec⁻¹; ("normalized" rates : 3.03 and 3.14, respectively), indicating that the methylene protons in these molecules do not relax via the intramolecular dipole-dipole relaxation mechanism provided by the aryl ortho methyl or ortho methoxy protons. Similarly, the relaxation rates of methylene protons in IN-8, IN-9, IN-11 and IN-12, (with 2,3-dimethylphenyl, 2,6-dimethylphenyl, 3-chloro-2-methylphenyl, and 4-chloro-2-methylphenyl-, respectively, as aryl moieties on the nitrogen atom) are 3.19, 3.19, 3.10 and 3.10 ("normalized"), respectively, indicating that the aryl ortho substituents are incapable of providing an intramolecular dipole-dipole relaxation pathway to the methylene protons through steric interactions. It should be noted that small differences in the relaxation rates of methylene protons are considered to originate from variations in the rotational correlational times of these molecules as a result of changes in their mass and dimensions.

The line shape analysis of these molecules has shown that even at temperatures as low as -150° to -160°, the internal rotational process about the aryl C-N bond in 1-isoidolinones is very fast. The lack of observation of spectral changes even at -160° is considered as an evidence that, in the rotational transition state, there is no large steric interaction between the aryl ortho substituent and either 3-methylene protons or the carbonyl group (see Section 2).

B : Electronic Effects :

The downfield δ - effects of the aryl ortho substituents upon the carbonyl and methylene carbons in 1-isoinolinones and isoindole-1,3-diones are presented in Table NC-6.

The molecular frame-work in these compounds is such that the lone pair on the nitrogen atom can be delocalized because of the adjacent carbonyl or aryl groups. Before going any further into a discussion of electronic effects in these compounds, it is appropriate, at this stage, to turn our attention to conjugation effects in enamide-type systems.

Mondelli (77) has reported nitrogen and carbon chemical shift values in some enamides, as shown below. The chemical shift values of respective nitrogen or carbon atoms are also indicated.

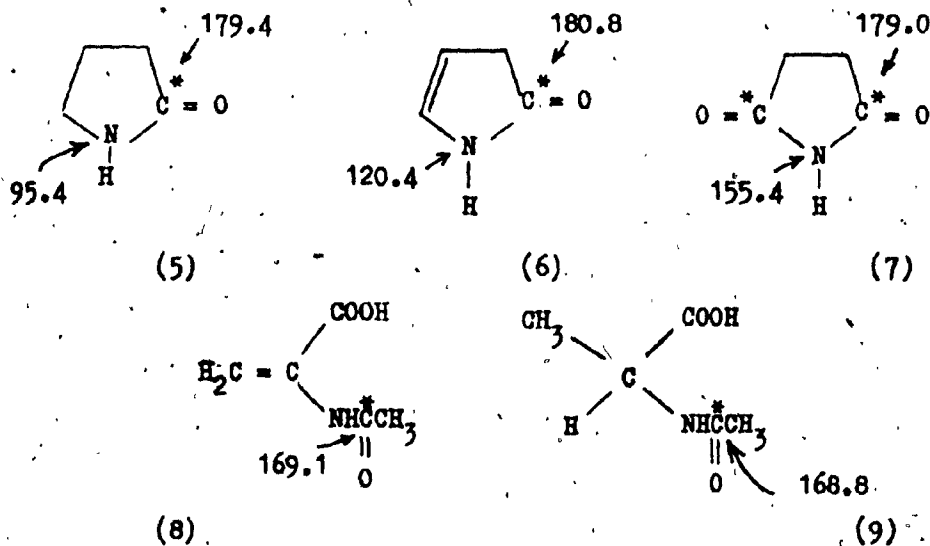
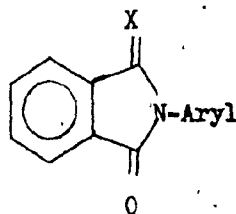


TABLE NC-6

Downfield δ - Effect (PPM) of Ortho Substituents on the Carbonyl and Methylene Carbons With Reference to the Corresponding N-Phenyl Derivatives, in N-Aryl-Substituted-Isoindole-1,3-Diones and 1-Isoindolinones in IMSO.



No. IN/ID	ARYL	C = O Carbons		CH ₂ ^a
		X=H ₂ ^a	X=O ^b	
1	Phenyl	-	-	-
2	2-Tolyl	0.08	0.44	1.99
3	2-Methoxyphenyl	0.94	0.75	1.46
4	2-Fluorophenyl	0.64	0.19	1.51
5	2-Chlorophenyl	0.68	0.04	1.51
6	2-Bromophenyl	0.60	0.09	1.51
7	2-Hydroxyphenyl	1.47	1.07	1.67
8	2,3-Dimethylphenyl	0.46	0.98	2.39
9	2,6-Dimethylphenyl	0.52	0.47	0.12
10	2-Methyl-4-Methoxy-phenyl	0.72	1.10	2.54
11	3-Chloro-2-Methyl-phenyl	0.47	0.43	2.21
12	4-Chloro-2-Methyl-phenyl	0.24	0.65	1.94
13	1-Naphthyl	1.35	1.30	3.25
14	2-Naphthyl	c	c	(0.30 [*])

^aWith reference to IN-1 ; ^bWith reference to ID-1 ;

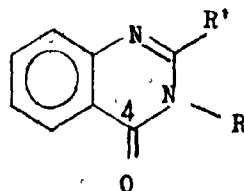
^cCarbonyl signals not observed ; ^{*} ϵ - effect rather than δ - effect.

As shown in Fig. PN-1, the enamide structural unit is also shared by Δ^3 -cephalosporins, 10-12, (biologically active), and Δ^2 -cephalosporin, 13, (inactive). The chemical shift values of carbons bearing an asterisk (*) are indicated (77) for cephalosporins as well as for the penicillins, 14-16, in Fig. CN-5. The substituent R in 10-16 has a position δ - with respect to the β -lactam carbonyl group. It should be noted that in these compounds, 10-16, the chemical shift values of the β -lactam carbonyl carbons are almost invariant.

The enamide structural unit in 4(3H)-quinazolinones, 17-18; and 3-aryl-4(3H)-quinazolinones, 19-23, (79), although left un-noticed by the author, is of particular

- (17) R = H
 (18) R = CH₃
 (19) R = 2-Tolyl
 (20) R = 2,5-Dimethylphenyl
 (21) R = 2,4,6-Trimethylphenyl
 (22) R = 4-Chloro-2-Methylphenyl
 (23) R = 5-Chloro-2-Methylphenyl

R' (H, CH₃)



$$\delta_{C=O} = 160.6 \pm 0.2 \text{ (ppm)}$$

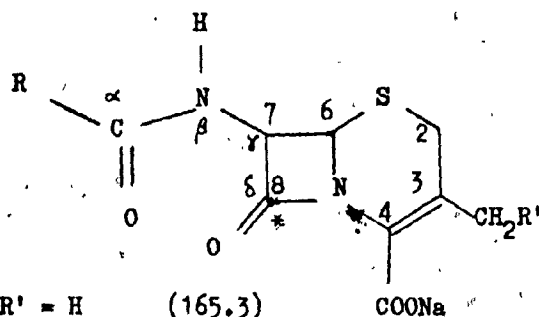
interest, since the 4-carbonyl carbons in these compounds absorb at 160.6 ± 0.2 ppm; and provides a good example of the invariant nature of carbonyl chemical shifts in enamides. The aryl ortho substituent in 19-23, again, occupies a position δ - with respect to C-4.

Chemical shift (ppm):

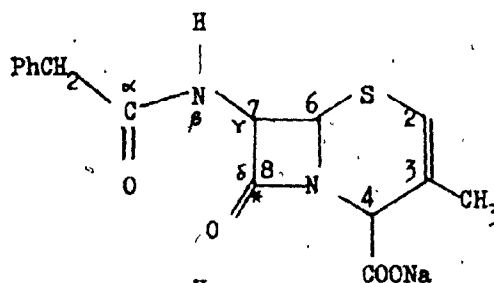
(10) $R = \text{PhCH}_2$; $R' = \text{H}$ (165.3)

(11) $R = \text{PhCH}_2$; $R' = \text{OAc}$ (165.6)

(12) $R = \text{PhCHNH}_2$; $R' = \text{H}$ (164.9)



(13) (166.4)



(14) $R = \text{PhCH}_2$ (175.3)

(15) $R = \text{PhOCH}_2$ (174.8)

(16) $R = \text{PhCHNH}_2$ (175.8)

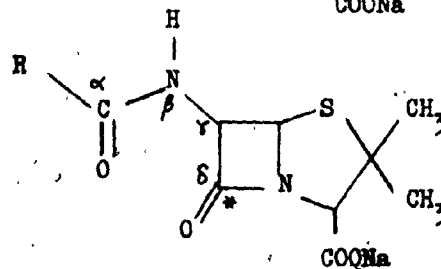
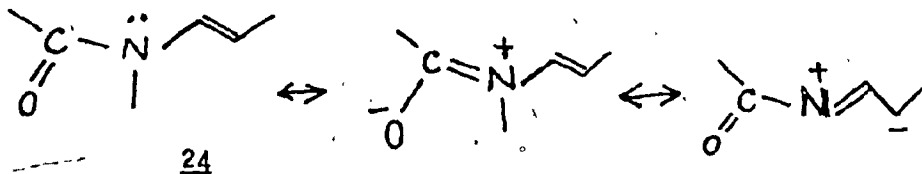


Fig. PM-1 : Chemical Shift Values of Carbonyl Carbons

(*) in Cephalosporins and Penicillins,

(77).

As mentioned earlier, the carbonyl chemical shift values in isoindole-1,3-diones and 1-isoindolinones vary over a limited range, i.e. 167.0 ± 0.8 ppm. It is clear from the foregoing discussion that the presence of 'enamide-type' delocalization involving the lone pair of the amide nitrogen, 24, does not affect the situation at the carbonyl group to any



considerable extent, but only at the nitrogen atom, since the electron availability at the nitrogen atom to supply the electron density as demanded by the adjacent π -system is affected. This effect seems to be particularly significant in those compounds where the substituent, e.g. methoxy, hydroxy, 1-naphthyl, or 2-naphthyl, promotes delocalization of the lone pair of electrons on nitrogen which is expected to deshield the carbonyl carbon. Such an effect may also be present in ortho halogen substituents but to a lesser extent. Table NC-6 shows that the carbonyl carbons are most deshielded in IN-3, 7, 10, and 13, with methoxy, hydroxy and naphthyl substituents, but to a lesser extent with ortho halogen substituents. The relatively large carbonyl δ -shifts in both 2-hydroxyphenyl compounds, ID-7 and IN-7, may result from internal hydrogen bonding between the hydroxyl and carbonyl groups. The δ -effects on the carbonyl carbons in

isoindole-1,3-diones also follow a pattern similar to that of 1-isoindolinones. In the latter series, the magnitude of the δ -effect on the carbonyl carbon is somewhat larger than that in the isoindolinone series. No consistent correlation with the expected electronic properties of the aryl group substituents is evident.

C : Effect of Chemical Shift Anisotropy :

It is well-known that a nucleus placed in a field H_0 , which is generated by a laboratory magnet, experiences a field H_{local} , given by

$$H_{\text{local}} = H_0 - \delta H_0 = H_0 (1 - \delta)$$

where δ is called the shielding factor. The magnitude of the shielding (or chemical shift) at a nucleus is dependent upon the orientation of molecule in the magnetic field. The rapid molecular motions of molecules in the liquid state average

these values out and one is then usually only concerned with the average value δ where

$$\delta = 1/3 (\delta_{xx} + \delta_{yy} + \delta_{zz})$$

Although the nucleus on the average sees a chemical shift value represented by δ , on a larger time scale (where e.g. rotational correlational times are of the order of $10^7 \text{ rad.}^2 \text{ sec}^{-1}$), it sees fluctuations in the local magnetic field. Thus, if δ_{xx} , δ_{yy} , δ_{zz} are not equal, i.e. if the chemical shift tensor is anisotropic, this may affect the shielding of some carbons in a molecule.

With the increase in the molecular mass and dimensions the isoindole-1,3-diones and 1-isoindolinones will be expected to have larger rotational correlational times. This has been observed from a study of the proton spin-lattice relaxation rates, at 270 MHz and at 23°, of these compounds, (see Section 1). In a situation where τ_c values are large, the nucleus will sense fluctuations in local magnetic field which may affect its shielding. It is possible that these variations in chemical shift anisotropy may contribute to some extent toward large downfield δ -effect of substituent upon the carbonyl carbons. It has been shown (12, 107) that second order electric field effects due to fluctuating magnetic dipoles are large enough to explain the observed downfield δ -shifts.

3-METHYLENE CARBONS :

The carbon-13 chemical shift values of ~~the~~ methylene carbons in 1-isocindolinones, IN-1 to IN-14, are presented in Table CN-4. The downfield δ - effect of aryl ortho substituents upon methylene carbons are presented in Table CN-6. The corresponding N-phenyl derivative has been used as a reference compound for the calculation of δ - effects in isocindole-1,3-diones and 1-isocindolinones.

It is clear from Table CN-6 that the δ - effect of the ortho substituents on methylene carbons is much larger than that on the carbonyl carbons, indicating that the methylene carbons are more susceptible to variations in the N-aryl moiety. It has already been discussed (see discussion on carbonyl carbons, and also Section 1) that the methylene groups in these compounds are not sensitive, to any considerable extent, to the steric effects of aryl substituents or to solvent effects. For example, the downfield δ - effect on the methylene carbon arising from the fluoro-, chloro-, or bromo-derivatives, IN-4 to IN-6, is 1.51 ppm. As mentioned under the "electronic effects", the presence of a methylene group, instead of a carbonyl group, would slightly reduce delocalization of the lone pair of electrons on the nitrogen atom over the hetero ring. This is expected to deshield the methylene carbons considerably.

Table NC-6 shows that the downfield δ - effect on methylene carbons increases as the asymmetrical substitution at the aryl ring increases. In 2,6-dimethylphenyl derivative, IN-9, the δ - effect is only 0.12 ppm ; which is un-expected, since the ortho tolyl derivative, IN-2, shows a δ - effect of 1.99 ppm. However, the δ - effects on carbonyl carbons in the ortho tolyl and 2,6-dimethylphenyl compounds are seen to be normal in both the isoindole-1,3-dione and 1-isoindolinone series, Table NC-6. The 'normalized' proton relaxation rates of the corresponding protons in IN-2 and IN-9 are very similar to each other, indicating that the small magnitude of the δ - effect in IN-9 does not arise from the steric interaction between the methylene protons and 2,6-dimethyl groups. The same conclusion is drawn from a study of line shape analysis of these compounds. The δ - effects from the two ortho methyl substituents appear to oppose each other. The effect of the symmetrical nature of the N-aryl moiety on the δ - shifts is not clear. It should be noted, however, that the increase in molecular dimensions and massive un-symmetrical substitution on the aryl moiety further enhances large downfield δ - effects on methylene and carbonyl carbons in both the isoindole-1,3-dione and 1-isoindolinone series. For example, in the 1-naphthyl derivative, IN-13, the δ - effect on the methylene carbon is as large as 3.25 ppm.

The downfield ϵ - effect on the methylene carbon by the 2-naphthyl moiety, IN-14, is 0.30 ppm. The ϵ - effects arising from the steric polarization of a group are generally observed to be upfield. The deshielding of the methylene carbon in 2-naphthyl derivative may be due to its reduced electron density resulting from delocalization of the lone pair of electrons on nitrogen over the aromatic system. The 'normalized' proton spin-lattice relaxation rates for the methylene protons in 1- and 2-naphthyl derivatives are 3.35 and 3.70, respectively. This shows that environments, and hence delocalization effects of the lone pair of electrons, are almost identical in both the compounds, IN-13 and IN-14.

ARYL SUBSTITUENTS :

The chemical shift values for the substituents on the aryl ring in isoindole-1,3-diones and 1-isoindolinones are presented in Tables NC-2 and NC-4, respectively. It should be noted that the shielding of the methoxy carbons are un-affected whereas methyl carbons are deshielded by about 0.3-0.6 ppm in isoindolinones as compared with the diones. In general, the carbon chemical shifts of aryl substituents in 1-isoindolinones are similar to the corresponding carbons in the 1,3-dione series.

SECTION 5

EXPERIMENTAL

Thin Layer Chromatography

The reactions were occasionally followed and the products identified employing TLC using Fisher Redi/Plate precoated with Silica Gel GF of 250 microns thickness. This also helped in determining the purity of the product.

The compound was usually dissolved in acetone and the TLC plate was developed in the TLC chamber containing benzene-acetone (10 : 1). After spraying the plate with conc. sulfuric acid in fume hood, characteristic spots were developed on moderate heating. The following observations are note-worthy.

3-Phenyl-2-thio-4-imidazolidinones : R_f (0.3 - 0.5)

Yellow brown spots.

1-Aryl-5-methyl-3-phenyl-2-thio-4-imidazolidinones

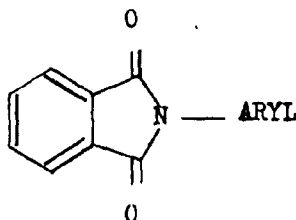
Yellow to deep yellow to R_f (0.80 - 0.85)
brown to brick red.*

1-aryl-3-phenyl-2-thio-4-imidazolidinones R_f (0.70-0.76)

Yellow to brown to red.*

* Changes in color of the spot corresponding to the product.

Synthesis of N-Aryl-1H-Isoindole-1,3-Diones.



The N-aryl substituted 1H-isoindole-1,3-diones were prepared by the general method described by Vogel (105).

Phthalic anhydride (Anachemia, AC-7478) (0.10 mole) was dissolved in 60 ml. of glacial acetic acid on warming. Then the aromatic primary amine (0.11 mole) was added slowly and the mixture was refluxed for 1 - 1.5 hours. The N-aryl substituted 1,3-isoindolediones separated out on cooling in ice-water mixture. The ppt. was filtered and the mother liquor was recycled. The ppt. was washed three times with ethanol, three times with water and three times with hexane. The final ppt. was dried at 50-60° under high vacuum.

The following 1,3-isoindolediones were prepared by the general method described above.

TABLE EXT 1

N-aryl Isoindol-1,3-diones		(Yields & Melting Points)		
	Aryl	M.P.	M.P. (lit.)	Yield
ID-1	Phenyl	207.0-208.0	205 -207	88.3
ID-2	2-Tolyl	180.5-181.5	180 -182	93.4
ID-3	2-Methoxyphenyl	156.5-157.0	158.5-159	89.8
ID-4	2-Fluorophenyl	186.0-186.2	184 -186	85.6
ID-5	2-Chlorophenyl	140.0-140.5	140 -142	75.0
ID-6	2-Bromophenyl	127.0-128.0	127 -128	68.9
ID-7	2-Hydroxyphenyl	222.0-223.0	223	92.9
ID-8	2,3-Dimethylphenyl	173.0-173.5	172.4	89.5
ID-9	2,6-Dimethylphenyl	210.0-202.0	203 -204	79.3
ID-10	2-Methyl-4-methoxyphenyl	---		
ID-11	3-Chloro-2-methylphenyl	215.0-215.5	215 -216	82.8
ID-12	4-Chloro-2-methylphenyl	138.0-138.5	136 -137	62.6
ID-13	1-Naphthyl	182.5-183.0	180 -181	86.7
ID-14	2-Naphthyl	214.0-214.5	216 -217	95.6

Ref.

24a

24a

24b

24a

24a

24a

24a

24a

24a

24a

24a

24a

24a

24a

TABLE EXP 2

Spectral Characteristics of N-Aryl-Isoindole-1,3-Diones,
ID-1 to ID-14.

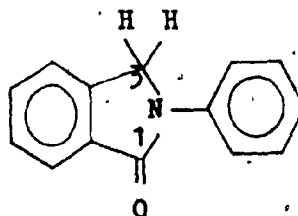
No.	$^1\text{H-NMR}$ (CDCl_3 , δ)	$^{13}\text{C-NMR}$ (DMSO , δ)	IR (KBr , cm^{-1})
1 ^a	7.50s N-aryl 7.70-8.00 phthalic	167.57 carbonyl 134.49 C-10 (N-aryl) 131.5-123.0 aryl	1700s, 1720w, 1750w, carbonyl 1600s, 1500s, aryl vib 755s, 710-790s, C-H bend
2	1.83s o-methyl 7.20-7.47m aryl	166.71 carbonyl 136.04 C-10 (N-aryl) 126.30 C-11 (C-Me) 135.0-123.2 aryl 17.14 o-Methyl	1700s, 1720w, 1750w, carbonyl 1600m, 1500s, aryl vib 770s, 712s, C-H bend
3	3.77s o-Methoxy 6.93-7.40 N-aryl 7.45-8.0 phthalic	167.02 carbonyl 155.50 C-11 (C-OMe) 134.87 C-10 (N-aryl) 131.7-112.6 aryl 55.97 o-Methoxy	1680s, 1740w, C=O 1580s, 1475s, aryl vib 690-710sb, 735-745sb, C-H bend
4	7.37-7.70m N-aryl 7.97-8.20m phthalic	166.46 carbonyl 152.62 C-11 (C-F) 143.00 C-10 (N-aryl) 135.1-116.0 aryl	1800m, 1725s, C=O 1600s, 1500s, aryl vib 795s, 760s, 715s, C-H bend
5	7.30-7.53m N-aryl 7.67-8.03m phthalic	166.31 carbonyl 135.1-123.7 aryl	1700s, 1760s, 1720w, carbonyl 1600m, 1500s, aryl vib 765s C-H bend 708s C-Cl stretch
6	7.28-7.55m N-aryl 7.62-8.05m phthalic	166.36 carbonyl 135.1-123.0 aryl	1700s, 1760s, 1720w, carbonyl 1600m, 1480s, aryl vib 710s, 755s, 790m, C-H
7 ^b	6.92-7.57m N-aryl 7.83-8.20m phthalic 9.67sb o-OH	167.34 carbonyl 154.33 C-11 (C-OH) 132.36 C-10 (N-aryl) 134.9-117.0 aryl	3400s aryl-O-H 1230s aryl-C-O 1800s, 1710s, C=O 1600s, 1500s, aryl vib 795s, 750s, 720s, C-H

No.	$^1\text{H-NMR}$ (CDCl_3 , δ)	$^{13}\text{C-NMR}$ (DMSO , δ)	IR (KBr , cm^{-1})
8	2.12s o-Methyl 2.38s m-Methyl 7.12-7.45m N-aryl 7.75-8.17m phthalic	167.25 carbonyl 134.0-123.0 aryl 14.34 o-Methyl 20.16 m-methyl	
9	2.17s 2,6-Dimethyl 7.20m N-aryl 7.67-8.08 phthalic	166.74 carbonyl 136.70 C-10 (N-aryl) 134.9-123.6 aryl 17.58 2,6-Dimethyl	1690s, 1750w, C=O 1570s, 1450s, aryl vib 710s, 785s, C-H bend
10	2.20s o-Methyl 3.83 p-Methoxy 6.90-7.33m N-aryl 7.83-8.08m phthalic	167.37 carbonyl 137.83 C-10 (N-aryl) 159.86 C-13 (C-OMe) 134.7-112.1 aryl 55.49 p-OMe 17.80 o-Me	1740s carbonyl 1600s, 1510s, aryl vib 880s, 865s, 815s, 795m, 720s, C-H bend
11	2.23s o-Me 7.13-7.57 N-aryl 7.77-8.10 phthalic	166.70 carbonyl 134.03 C-10 (N-aryl) 134.7-123.5 aryl 15.23 o-Methyl	1680s, 1740w, C=O 1550m, 1450m, aryl vib 705b, 775s, C-H bend 705b, C-Cl (overlap)
12	2.18s o-Me 7.17-7.47m N-aryl 7.77-8.10m phthalic	166.92 carbonyl 138.98 C-10 (N-aryl) 134.9-123.6 aryl 17.46 o-Me	1680s, 1740w, C=O 1600m, 1450s, aryl vib 785m, 810s, 865sb, C-H 700 sb C-Cl
13	7.13-8.07 complex aryl multiplet	167.57 carbonyl 134.8-122.8 aryl	1675s, 1750s, C=O 1600s, 1500s, aryl vib 705s, 760s, 790s, C-H
14	7.50-8.33 complex aryl multiplet	--	1770m, 1700s, C=O 1570m, 1620m, 1500m, aryl vibration 850-870 (m-s) C-H.

For $^1\text{H-NMR}$: a, DMSO-d_6 ; b, ($\text{DMSO-d}_6 + \text{CDCl}_3$ 1 : 1) ; s, singlet;
m, multiplet.

For IR : s, strong ; m, medium ; w, weak ; b, broad

Synthesis of N-Aryl-1-Isoindolinones.



Method 1.

The method described by Brewster and co-workers (20) for the preparation of N-alkyl-1-isoindolinones was found unsatisfactory for the synthesis of N-aryl derivatives. The isolation of the product from the semi-viscous brown oily mass posed difficulty and in many cases yields were low. However, a modification in the isolation procedure yielded, in some cases, the desired product conveniently and in reasonably good yields. The following method was employed for the synthesis of some of the N-aryl-1-isoindolinones.

The N-aryl-1H-isoindole-1,3-dione (0.10 mole) was dissolved in 200 ml. of glacial acetic acid by heating to 60-70 C° and 36.0g (0.55g atom) of zinc dust was added all at once. The reaction mixture was heated at reflux for 5 hours and then filtered hot on a sintered glass Buchner-type funnel with suction. The filter cake was washed with two 25 ml. portions of glacial acetic acid. The combined filtrate was evaporated to small volume at 60-70° and 250-300 ml. of saturated sodium

bicarbonate solution was slowly added in 40-50 ml. portions. The PH (alkaline) was checked at this stage and then stirred at room temperature for 6-8 hours. The lumps of the ppt. was successively washed with water and hexane thoroughly. The ppt. was dissolved in 80-100 ml. of chloroform and filtered to remove any insoluble material. The filtrate was evaporated to dryness on rotary evaporator (35-40°). This white ppt. and some brown resinous material was dissolved in small quantity of methanol (usually 15-20 ml.) and water was added dropwise (5-8 ml.) until brown oil began to reappear. Methanol was added dropwise (1-2 ml.) until clear and transparent solution was obtained. This mixture was refrigerated for 3-4 hours when white ppt. appeared along with brown supernatant. The ppt. was filtered and washed three times with 10 ml. of methanol: water (3:7); washed twice with 20 ml. of water and three times with 30 ml. of hexane. The white ppt. was kept under high vacuum (60-65°) for 10-12 hours. The lumps were broken, if any, and the fine powder was again kept under high vacuum (60-70°) for a day.

In cases, when the product was obtained in low yields (10-40%); attempt was made to isolate a second crop from the mother liquor of the major ppt.

The following compounds were prepared by the method described above.

IN-1, IN-3, IN-10, IN-11 and IN-12.

Method 2.

As described earlier under Method 1, the procedure adapted by Brewster and co-workers resulted in semi-viscous, brown oily mass which caused difficulty in isolation of some of the desired N-aryl-1-isoindolinones. In such cases, application of Clemmensen reduction proved successful and convenient.

The amalgamated zinc dust was prepared following the method of Caesar (22) as described by Fieser and Fieser (39). 10.0 g of zinc dust was added to a stirred solution of 1.0 ml. conc. HCl acid and 1.0 g of mercuric chloride in 30 ml. of water. After stirring for 15 min. lumps were crushed and zinc dust was collected and washed with a total of 50 ml. of water containing 1.0 ml. of conc. HCl acid. It was then washed three times with 5 ml. of ethanol and three times with 10 ml. of ether and dried in hot oven.

The Clemmensen reduction was carried out in the following manner: To 11.2 g of dried zinc amalgam were added 2.0 g (0.0084 mole) of N-(0-Tolyl)-1H-isoindole-1,3-dione and 10.0 ml. of glacial acetic acid, all in a 100 ml. round bottom flask fitted with a condenser. 10.0 ml. of conc. HCl acid was added in small portions through the top of the condenser over 5—6 minutes. The reaction mixture was

heated on reflux for 2 - 4 hours depending on the steric bulk of N-aryl moiety. The reaction mixture was filtered hot on a sintered glass Buchner-type funnel with suction. The filter cake was washed twice with 5 ml. portions of glacial acetic acid. The solution was reduced to less than half of the original volume on rotary evaporator (70 - 80°) and then cooled to room temperature. 20 ml. of water was added and white oily drops appeared. The solution was neutralized with saturated solution of sodium bicarbonate. At about pH = 6, the oily drops changed to granular white ppt. The excess of saturated sodium bicarbonate solution was added to ensure basic medium. The mixture was extracted four times with 20 ml. of either ether or chloroform and combined extract was washed with 20 ml. of water, dried over anhydrous magnesium sulfate and the solvent removed to almost dryness on rotary evaporator (30 - 35°), giving out white ppt. This ppt. was dissolved in 4 ml. of ether and petroleum ether was added dropwise until slight turbidity persists. At this stage ether was added dropwise until the turbidity just disappeared. The solution was slightly warmed and refrigerated for 1 - 2 hours when bright white ppt. crystallised out. The ppt. was filtered and washed three times with minimum amount of 1 : 10 ether : petroleum ether and dried under high vacuum at 50 - 55° for 8 - 10 hours.

The following N-aryl-1-isoidolinones were prepared by the method described above.

IN-2, 4-9, 13, 14.

TABLE EXP 3

Analytical Data, Melting Points, and Yields of N-Aryl isoindolinones, IN-1 to 14.

Molecular Formula	Calculated % C H N	Found % C H N	M.P. °C	Yield (Z)
1- C ₁₄ H ₁₁ NO	80.36 5.30 6.69	79.97 4.87 7.15	157.0-158.5	79
2- C ₁₅ H ₁₃ NO	80.69 5.87 6.27	80.44 6.07 6.27	95.5-96.5	57
3- C ₁₅ H ₁₃ NO ₂	75.30 5.47 5.85	74.96 5.68 6.13	122.5-124.0	23
4- C ₁₄ H ₁₀ FNO	74.00 4.44 6.16	74.64 4.75 6.34	132.0-133.0	43
5- C ₁₄ H ₁₀ ClNO	69.00 4.14 5.75	68.22 4.40 5.71	122.5-123.5	81
6- C ₁₄ H ₁₀ BrNO	58.35 3.50 4.86	58.57 4.10 5.03	122.0-123.0	73
7- C ₁₄ H ₁₁ NO ₂	74.69 4.92 6.22	74.79 4.75 6.24	157.5-159.0	78
8- C ₁₆ H ₁₅ NO	80.98 6.37 5.90	80.91 6.44 6.16	138.5-139.5	73
9- C ₁₆ H ₁₅ NO	80.98 6.37 5.90	80.80 6.40 5.91	138.5-139.5	68
10- C ₁₆ H ₁₅ NO ₂	75.87 5.99 5.53	75.13 6.12 5.74	152.0-154.0	53
11- C ₁₅ H ₁₂ ClNO	69.90 4.69 5.43	70.19 5.25 5.26	139.0-140.0	23
12- C ₁₅ H ₁₂ ClNO	69.90 4.69 5.43	69.61 4.91 5.63	173.5-175.0	39
13- C ₁₈ H ₁₃ NO	83.37 5.05 5.40	83.20 5.12 5.61	187.0-188.0	49
14- C ₁₈ H ₁₃ NO	83.37 5.05 5.40	83.12 5.20 5.68	177.5-178.5	12

TABLE EXP 4

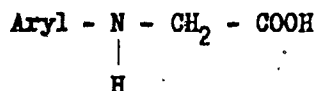
Spectral Parameters of N-Aryl-1-Isoindolinones, IN-1 to IN-14.

No.	$^1\text{H-NMR}$ (CDCl_3 , δ)	$^{13}\text{C-NMR}$ (DMSO-d_6 , δ)	IR (KBr , cm^{-1})
1	4.868s 3-methylene 7.15-7.95 aryl	166.26 carbonyl 141.06 C-10 (N-aryl) 139.5-119.5 aryl 50.44 3-methylene	1675s carbonyl 1590m, 1490s aryl 748s, 728s C-H bend 1460w methylene
2	2.269s o-methyl 4.736s 3-methylene 7.24-7.34m N-aryl 7.50-7.97 Phthalic	166.34 carbonyl 142.34 C-10 (N-aryl) 137.4-123.0 aryl 52.49 3-methylene 17.73 o-methyl	1660s carbonyl 1600m, 1475m, aryl vib. 1445s 3-methylene 755m, 745m, 725s, 715m, C-H bends
3	3.832s o-methoxy 4.815s 3-methylene 7.02-7.97m aryl	167.27 carbonyl 51.96 3-methylene 55.91 o-methoxy 155.21 C-OMe (C-11) 142.30 C-10 (N-aryl) 132.6-111.8 aryl	1660s carbonyl 1590m, 1485s, aryl vibrations 1440s 3-methylene 755s, 725s, C-H bend
4	4.880s 3-methylene 7.16-8.00m aryl	166.90 carbonyl 142.28 C-11 (C-F) 131.35 C-10 (N-aryl) 132.26-116.24 aryl 52.01 3-methylene	1675s carbonyl 1600s, 1590s, aryl vibrations 1450s 3-methylene 785s, 750s, 725s C-H bends
5	4.819s 3-methylene 7.31-8.00m aryl	166.94 carbonyl 142.10 C-10 (N-aryl) 136.02 C-Cl 132.00-123.47 aryl	1670s carbonyl 1600m, 1470s aryl vibrations 725s C-Cl stretch

No.	$^1\text{H-NMR}$ (CDCl_3 , δ)	$^{13}\text{C-NMR}$ (DMSO-d_6 , δ)	IR (KBr , cm^{-1})
		52.01 3-methylene	695m, 752s, 785w, C-H Bends 1440s 3-methylene
6	4.810s 3-methylene 7.25-8.00m aryl	166.86 carbonyl 142.06 C-10 (N-aryl) 137.6-122.4 aryl 52.01 3-methylene	1670s carbonyl 1590m, 1460s, aryl vib 785w, 730s, 710m, C-H bend 1445s 3-methylene
7	4.980s 3-methylene 7.0-8.0m aryl 8.814sb o-OH	167.73 carbonyl 52.17 3-methylene	1670s carbonyl 3200sb aryl-O-H 1590m, 1620m, 1500s, aryl vibration 1460-1450 3-CH ₂ 1230s aryl-C-O 790s, 750s, 740s, C-H bend
8	2.132s o-methyl 2.346s m-methyl 4.712s 3-methylene 7.09-7.20m N-aryl 7.49-8.00 phthalic	166.72 carbonyl 148.28 C-10 (N-aryl) 137.61 C-12 (C-m-Me) 134.65 C-11 (C-o-Me) 131.7-123.3 aryl 52.89 3-methylene 20.20 m-Methyl 14.41 o-Methyl	1700s carbonyl 1590s, 1475s aryl vib 1460s 3-CH ₂ 800s, 790s, 765s, 735s, 725s, 715s C-H bend
9	2.194s 2,6-Me ₂ 4.601s 3-CH ₂ 7.14-7.26m N-aryl 7.51-7.99m phthalic	166.78 carbonyl 142.30 C-10 (N-aryl) 136.52 C-11 + C-15 128.09 C-12 + C-14 135.89-123.15 aryl 50.62 3-CH ₂ 17.62 o & m - Me ₂	1655s carbonyl 1600m, 1460s, aryl vib 1450s 3-CH ₂ 875, 785, 765, 725, 715, all s, C-H bends

No.	$^1\text{H-NMR}$ (CDCl_3 , δ)	$^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$, δ)	IR. (KBr , cm^{-1})
10	2.228s o-methyl 3.823s p-methoxy 4.684s 3- CH_2 6.786-7.96 aryl	166.98 carbonyl 158.91 C-13 (C-OMe) 142.55 C-10 (N-aryl) 137.6-111.0 aryl 55.53 p-methoxy 18.21 o-methyl	1675s carbonyl 1600s, 1490s, aryl vib 1230s aryl-C-O 1465m 3-Methylene 860, 815, 795, 740, all s, C-H bends
11	2.278s o-methyl 4.725s 3- CH_2 7.2-7.4m N-aryl 7.5-8.0m phthalic	166.73 carbonyl 142.44 C-10 (N-aryl) 139.14 C-12 (C-Cl) 134.30 C-11 (C-Me) 132.0-123.4 aryl 52.71 3- CH_2 15.54 o-methyl	1650s carbonyl 1580m, 1440s, aryl vib 785s, 765s, 725s, 705m, 695m, C-H bend 1450s 3- CH_2
12	2.245s o-methyl 4.712s 3- CH_2 7.2-7.4m N-aryl 7.5-8.0 phthalic	166.50 carbonyl 142.34 C-10 (N-aryl) 138.50 C-13 (C-Cl) 136.46 C-11 (C-Me) 131.9-123.3 aryl 52.44 3- CH_2 17.81 o-Me	1665 carbonyl 1600m, 1450m, aryl vibrations 795m, 780s, 738s C-H bend 1430s 3- CH_2 deform.
13	4.893s 3- CH_2 7.4-8.0m aryl	167.61 carbonyl 134.2-123.4 aryl 53.75 3- CH_2	1670s carbonyl 1600m, 1450m, aryl vib 870s, 885s, 820s, 795m, 740s, C-H bend 1430s 3- CH_2
14	4.986s 3- CH_2 7.4-8.2 aryl	carbonyl unobserved 50.80 3- CH_2	1690s carbonyl 1600s, 1500s, aryl vib 1465s, 1460s, 3- CH_2 800s, 740w, 725s, C-H.

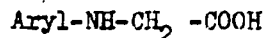
Synthesis of α -N-Aryl Glycines.



The α -N-aryl glycines were synthesised following the method reported by Zygmunt Eckstein, Jan Plenkiewicz and Marek Sak (34). The mixture of monochloroacetic acid (0.10 mole), ethanol (20 ml.), water (10 ml.) and sodium acetate trihydrate (0.10 mole) was heated to about 50 - 60° until clear solution was obtained. The aromatic primary amine (0.10 mole) was slowly added and the solution was heated to reflux for 10 - 16 hours depending on the steric bulk of the aryl moiety. The reaction mixture was cooled to room temperature and then in ice-water mixture for about two hours. The ppt. so obtained was filtered and washed three times with 10 ml. of water, three times with 4 - 5 ml. of ethanol. In some cases the ppt. was colored at this stage, so 10 - 15 ml. of ethanol was added, heated to boil, and cooled to room temperature. The ppt. was filtered, washed successively three times with 5 - 6 ml. of ethanol, and 15 ml. of hexane. The bright white ppt. thus obtained was dried under high vacuum (50 - 55°) for 10 - 12 hours.

TABLE EXP 5

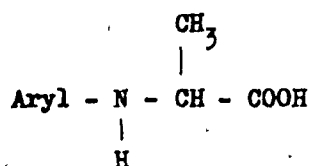
Proton NMR (DMSO- d_6 , δ) and IR (KBr, cm^{-1}) for α -N-Aryl-Glycines.*



<u>Aryl</u>	<u>M.P.</u>	<u>Yield</u> %	<u>$^1\text{H-NMR}$</u>	<u>IR</u>
Tolyl	147-8 148 (53)	24	2.17s o-Me 3.97s α -CH ₂ 6.50-7.33m N-aryl 8.33-9.33sb NH & OH	3480m N-H 1740s C=O 3200-2500 COOH
o-Methoxy-phenyl	148-9	59	3.93s o-OMe 4.00s α -CH ₂ 6.53-7.20m N-aryl 8.60-9.60sb NH & OH	3470m N-H 1725s C=O 3200-2500b COOH
o-Fluoro-phenyl	120-1	17	4.00s α -CH ₂ 6.67-7.50m N-aryl NH & COOH not observed	3470m N-H 1725s C=O 3200-2500b COOH
o-Chloro-phenyl	165-6 169 (53) 171-3 (76)	18	4.07s α -CH ₂ 6.67-7.77m N-aryl NH & OH unobserved	3500m N-H 1750s C=O 3200-2500b COOH
o-Bromo-phenyl	165.5- 166.5	31	4.03s α -CH ₂ 6.57-7.77m N-aryl NH & OH unobserved	3470m N-H 1725s C=O 3200-2500b COOH
2',3'-Dimethyl-phenyl	150-1	32	2.13s o-Me 2.32s m-Me 4.00s α -CH ₂ 6.37-7.33m N-aryl 8.67-9.33sb NH & OH	
1-Naphthyl	187-9	56	4.23s α -CH ₂ 6.57-8.57m N-aryl 9.33-10.17sb NH & OH	3470m N-H 1725s C=O 3200-2500b COOH

* For carbon-13 NMR data see Table CN-3, page 151.
s, singlet; m, multiplet; b, broad; (s, strong; m, medium; b, broad.)
Methylene deformation (IR) 1440-1450 cm^{-1} (strong)

Synthesis of α -N-Aryl Alanines.



The procedure described by Miller and Sharp (76) for the preparation of N-aryl alanines, was found to be unsatisfactory. The yields were low (10 - 20 %). The N-aryl alanines were prepared following the method of Fliedner (40) who adapted the general method of preparation of these compounds described by Eade and Earl (33). Thus, a mixture of aromatic primary amine (0.10 mole), sodium acetate trihydrate (0.10 mole), 3 - 4 ml. of ethanol and ethyl-2-bromopropionate (0.10 mole) was stirred and heated to reflux for 20 - 24 hours. After cooling and diluting with 40 ml. of water, the mixture was extracted with ether (3 X 50 ml.) and the combined extracts were evaporated on rotary evaporator. The residual oil was refluxed with 70 - 80 ml. of 10 % aqueous NaOH for two hours, cooled and the mixture was washed with ether (3 X 25 ml.). The aqueous layer was cooled in ice-water mixture and the solution was acidified with slow addition of conc. HCl acid, until pH was 2 - 3. The resulting suspension (or in some cases, slurry) was cooled in ice-water mixture for 2 - 3 hours, filtered, washed successively with water and hexane and dried under high vacuum. Finally, the ppt. was recrystallised from chloroform, washed with hexane and again

dried under high vacuum for several hours.

The following anilines were used for the synthesis of various alanines (see later).

Aniline (Fisher, A-740) : 18.64 g (0.20 mole)

O-Toluidine (BDH-30467) : 10.71 g (0.10 mole)

O-Anisidine (Aldrich, A-8818-2) : 24.632 g (0.20 mole)

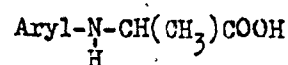
2,3-Dimethylaniline (Eastman, 1041) : 36.206 g (0.20 mole)

2-Fluoroaniline (Eastman, 7556) : 22.224 g (0.20 mole)

2-Chloroaniline (Aldrich, C2,239-3) : 12.75 g (0.10 mole)

2-Bromoaniline (Aldrich, B5,642-0) : 34.406 g (0.20 mole)

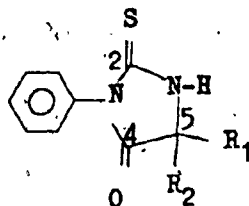
1-Naphthylamine (Eastman, 172) : 28.638 g (0.20 mole)

Experimental Data for α -N-Aryl-Alanines

Aryl	Yield (%)	M.P.	Proton NMR (DMSO-d ₆ , δ)	Infrared (KBr)
Phenyl	69.9	159.0-160.0	1.42d methyl 4.08a methine 6.5-7.5m aryl 9.0-9.7b OH, NH	3000-2600 OH 3450w NH 1600s C=O 1500m aryl 695, 755 CH bend
o-Tolyl	58.3	111.0-111.5	1.50d methyl 2.15s methyl 4.17a methine 6.6-7.4m aryl 8.40-9.17 NH, OH	3450m OH 3200-2900 OH 1730s C=O 1600s, 1510s aryl 745s CH bend
2-Methoxyphenyl	62.6		1.46d methyl 3.92s methoxy 4.17a methine 8.4-9.4b NH, OH 6.6-7.1a aryl	3450 N-H 3200-2850b OH 1740s C=O 1610s, 1520s aryl 750-720sb CH bend
2,3-Dimethylphenyl	58.9	124.0-125.0	1.47d methyl 2.10s 2-methyl 2.27s 3-methyl 4.12a methine 6.5-7.2 aryl 8.4-9.1b NH, OH	3410m NH 3250-2750sb OH 1725s C=O 1600s, 1500s aryl 770s, 712s CH bend
2-Fluorophenyl	55.7	122.5-123.0	1.49d methyl 4.04a methine 6.7-7.5m aryl	3440m NH 3200-2500mb OH 1750s C=O 1640s, 1525s aryl 740s, 720w CH bend
2-Chlorophenyl	52.2	147.5-148.0	1.48d methyl 4.30a methine 6.7-7.6m aryl	3450m NH 3300-2900b OH 1745s C=O 1600s, 1500s aryl 742s CH bend
2-Bromophenyl	47.4	163.5-164.5	1.50d methyl 4.31a methine 6.7-7.8m aryl	3450m NH 3200-2500mb OH 1720s C=O 1600s, 1500s aryl 740s CH bend
1-Naphthyl	81.7	146.0-147.0	1.62d methyl 4.26a methine 6.5-8.7m aryl	3500m NH 3200-2500mb OH 1725s C=O 1600s, 1500s, 1485s 790s, 775s CH bend

For carbon-13 NMR data see Table CN-3, page 151.

Synthesis of 3N-Aryl-2-Thio-4-Imidazolidinones.

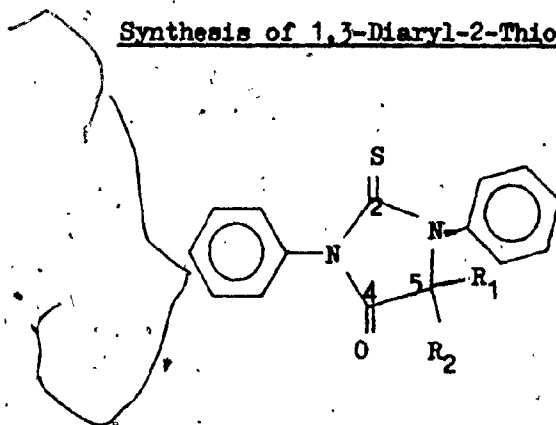


These compounds were prepared following the method of Pujari and Root (86).

Glycine (6.306 g., 0.084 mole) was dissolved in 10.0 ml. of water and 3.60 g. (0.09 mole) of NaOH was added. To this solution, a solution of phenylisothiocyanate (ICN. K & K, 16662) (10.0 g., 0.074 mole) in 70 ml. of absolute ethanol was added dropwise. The resulting solution was refluxed for two hours, then, cooled to room temperature and added 50 ml. of conc. HCl acid, and refluxed for another 15 minutes. The reaction mixture was cooled in refrigerator for two hours, filtered, the mother liquor was recycled, and the ppt. was washed three times with 20 ml. of water, once with 20 ml. of 10 % aq. ethanol, and finally three times with 25 ml. of hexane. The product was recrystallized from 95 % ethanol, ppt. was washed with hexane and dried under high vacuum for several hours.

The following compounds were prepared by the method described above.

Synthesis of 1,3-Diaryl-2-Thio-4-Imidazolidinones :



The procedure adapted by Pujari and Root (86), as described earlier, was found unsatisfactory for the preparation of 1,3-diaryl-2-thio-4-imidazolidinones. For this purpose, the procedure followed was that of Shirai et.al. (94). Thus, N-phenyl glycine (2.0 g, 0.0132 mole) was dissolved in 15 ml. of 95 % ethanol and warmed. Phenyl isothiocyanate (ICN. K & K, 16,662) (1.80 g. 0.0132 mole) was added dropwise and the reaction mixture was refluxed for one hour. It was cooled to room temperature and then in ice-water mixture. The ppt. thus separated was filtered and the mother liquor was recycled. The ppt. was washed twice with 5 ml. of 0.10 N NaOH solution, three times with 5 ml. of water, three times with one ml. of ethanol and finally three times with 10 ml. of hexane; and dried under high vacuum at 60 - 65° for several hours.

The following compounds were prepared by the method described above.

TABLE EXP 7

Analytical Data and Melting Points for
N-Aryl-2-Thio-4-Imidazolidinones, IZ-1 to IZ-16.

No.	Molecular Formula	Calculated %			Found %			M.P. °C	Yield %
		C	H	N	C	H	N		
1	C ₉ H ₉ N ₂ OS	56.23	4.20	14.57	57.03	5.15	14.06	237.5-238.5	92
2	C ₁₅ H ₁₂ N ₂ OS	67.14	4.51	10.44	67.15	4.41	10.60	212.0-212.5	82
3	C ₁₆ H ₁₄ N ₂ OS	68.06	5.00	9.92	67.69	5.51	9.68	253.0-254.0	38
4	C ₁₆ H ₁₄ N ₂ O ₂ S	64.41	4.73	9.39	64.49	5.11	10.12	193.5-194.5	46
5	C ₁₅ H ₁₁ FN ₂ OS	62.92	3.87	9.79	62.68	3.78	10.03	238.5-239.5	13
6	C ₁₅ H ₁₁ ClN ₂ OS	59.50	3.66	9.25	59.70	3.98	9.40	226.5-227.5	9
7	C ₁₅ H ₁₁ BrN ₂ OS	51.88	3.19	8.07	51.79	4.31	8.09	195.5-196.5	17
8	C ₁₇ H ₁₆ N ₂ OS	68.89	5.44	9.45	68.04	5.32	9.67	214.5-215.0	74
9	C ₁₉ H ₁₄ N ₂ OS	71.67	4.43	8.80	70.58	5.40	9.40	215.5-216.5	31
10	C ₁₀ H ₁₀ N ₂ OS	58.22	4.89	13.58	58.79	5.40	12.95	183.5-184.5	92
11	C ₁₆ H ₁₄ N ₂ OS	68.05	5.00	9.92	67.73	4.71	9.91	148.0-149.0	30
12	C ₁₇ H ₁₆ N ₂ OS	68.89	5.44	9.45	68.24	5.09	9.51	154.0-155.0	41
13	C ₁₇ H ₁₆ N ₂ O ₂ S	65.36	5.16	8.97	64.85	5.13	9.20	126.0-126.5	45
14	C ₁₆ H ₁₃ FN ₂ OS	63.98	4.36	9.33	62.56	4.73	9.58	180.5-181.5	27
15	C ₁₈ H ₁₈ N ₂ OS	69.64	5.84	9.03	69.22	5.77	9.12	152.5-153.5	36
16	C ₂₀ H ₁₆ N ₂ OS	72.26	4.85	8.43	71.24	5.08	8.36	177.5-178.5	20

TABLE EXP 8

Proton NMR data for N-Aryl-2-Thio-4-Imidazolidinones, IZ-1 to IZ-16

No.	5-H	5-CH ₃	Aryl Substituent	Aryl	N-H
1	4.30s	-	-	7.20-7.60 m	10.25b
2	5.00s	-	-	7.50-8.17 m	
a	4.628s	-	-	7.354-7.625 m	
3	4.85s	-	2.37s	7.47-7.80 m	
a	4.500s	-	2.344s	7.320-7.566 m	
4	4.83s	-	4.00s	7.30-7.87 m	
a	4.566s	-	3.907s	7.042-7.529 m	
5	4.90s	-	-	7.43-8.00 m	
a	4.582s	-	-	7.269-7.603 m	
6	4.90s	-	-	7.20-7.93 m	
a	4.435s	-	-	6.549-7.312 m	
7	4.88s	-	-	7.30-8.17 m	
8	4.83s	-	2.25s, 2.38s	7.40-7.83 m	
9	5.00s	-	-	7.67-8.50 m	
10	4.47q	1.42d	-	7.20-7.63 m	10.50sb
11	5.29q	1.41d	-	7.57-7.97 m	
12	5.18q	1.37d	2.40s	7.60-7.72 m	
13	5.00q	1.39d	3.95s	7.12-7.93 m	
14b	4.70q	1.56d	-	7.47-7.83 m	
15*	4.90q	1.36d	2.22s	7.42-7.83 m	
	5.15q	1.47d	2.25s		
16*	5.05q	1.37d	-	7.67-8.57 m	
	5.33q	1.50d	-		

Solvent : DMSO-d₆ at 60 MHza : CDCl₃ , 0.05 M solution at 270 MHzb : CDCl₃ at 60 MHz

*Diastereomeric signals.

TABLE EXP 9

IR data for N-Aryl-2-Thio-4-Imidazolidinones, IZ-1 to IZ-16

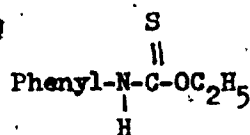
No.	N-H	C=O	C=S	Aryl skeletal Vibrations	Aryl C-H Bends
1.	3200s	1780s	1200s	1600m, 1525m	770s, 718s, 700s
2	-	1770s	1160s	1600s, 1500s	762s, 700s, 692s
3	-	1780s	1170s	1600m, 1500s	770s, 758s, 725s, 698s
4*	-	1780s	1170s	1610m, 1500s	775-735s, 695s
5	-	1770s	1150s	1600s, 1500s	790m, 758s, 695s
6	-	1780s	1170s	1600w, 1500s	825m, 765s, 725w, 700s
7	-	1785s	1170s	1510m, 1490m	825s, 765s, 698s
8	-	1775s	1180s	1610m, 1490s	795m, 762m, 715-735, 700s
9	-	1775s	1170s	1605m, 1505m	800m, 775s, 745s, 700m
10	3200s	1770s	1200s	1600m, 1525s	770s, 740s, 710s, 690s
11	-	1770s	1170s	1600s, 1500s	805m, 760s, 740s, 692s
12	-	1760s	1170s	1610s, 1510s	820m, 755s, 740s, 725s, 695s
13	-	1775s	1170s	1615s, 1510s	818s, 758s, 742s, 692s
14	-	1760s	1175s	1600m, 1500s	828m, 785m, 765s, 745m 692s
15	-	1760s	1180s 1200w	1610m, 1500s	790m, 772m, 740-715mb, 695m
16	-	1760s	1170s	1610s, 1510s	800m, 775s, 740s, 692s

*Aryl-O-C stretch 1240s

3-methylene deformations for 1-16: 1460-1470s.

Unsuccessful Syntheses :

Attempts to synthesise 1-(2-Chlorophenyl)- or 1-(2-Bromophenyl)- 5-methyl-3-phenyl-2-thio-4-imidazolidinones, following the method of either Pujari and Root (86) or Shirai (94) resulted in the formation of ethyl N-phenyl thiocarbamate :



The $^1\text{H-NMR}$ and the Thin Layer Chromatography did not show the formation of even small amount of the desired products. The data for the ethyl N-phenyl thiocarbamate are given below :

Elemental analysis : calculated for $\text{C}_9\text{H}_{11}\text{NOS}$:

% calc. : C, 59.63 ; H, 6.12 ; N, 7.73

% found : C, 57.29 ; H, 6.23 ; N, 5.78

$^1\text{H-NMR}$:

(DMSO-d_6 , δ) 1.25, 1.38, 1.50 (3H, triplet, methyl protons); 4.50 - 5.85 (2H, quartet, methylene protons); 7.33 - 7.90 (5H, multiplet, phenyl protons); and 11.43 (1H, broad singlet, N-H proton).

C-13 NMR : The C-13 FTNMR spectrum is presented in Fig. NC-16:

(DMSO-d_6 , 1.5 M, 9,000 scans, δ_{TMS}) 187.606 (thiocarbonyl carbon); 138.344 (N-C_{aryl}); 128.660 (aryl meta carbons); 124.761 (aryl ortho carbons); 122.226 (aryl para carbon); 67.179 (broad, multiplet 3 methylene carbon); and 14.019 (sharp singlet, methyl carbon).

I.R. : KBr, cm^{-1} :

N-H stretch, 3230 (s); aryl stretching vibrations, 1600 (s), 1500 (s); aryl C-H bends, 765 (m), 745 (s) and 688 (m); aryl mono substitution pattern; C=S, 1200 (s).

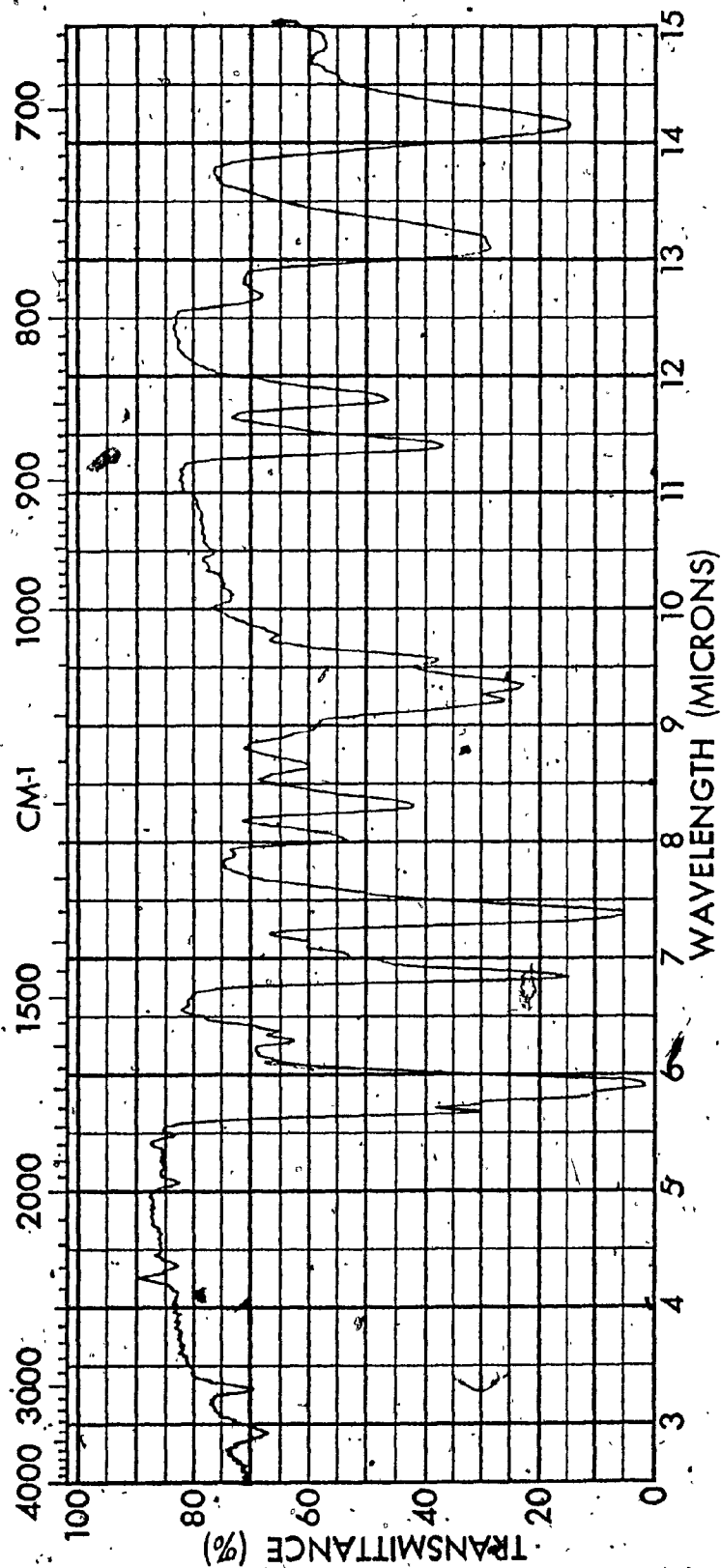


Fig. IR-1: Infra Red Spectrum (KBr) of N-(2-Chlorophenyl)-1H-

Indole-1,3-Dione.

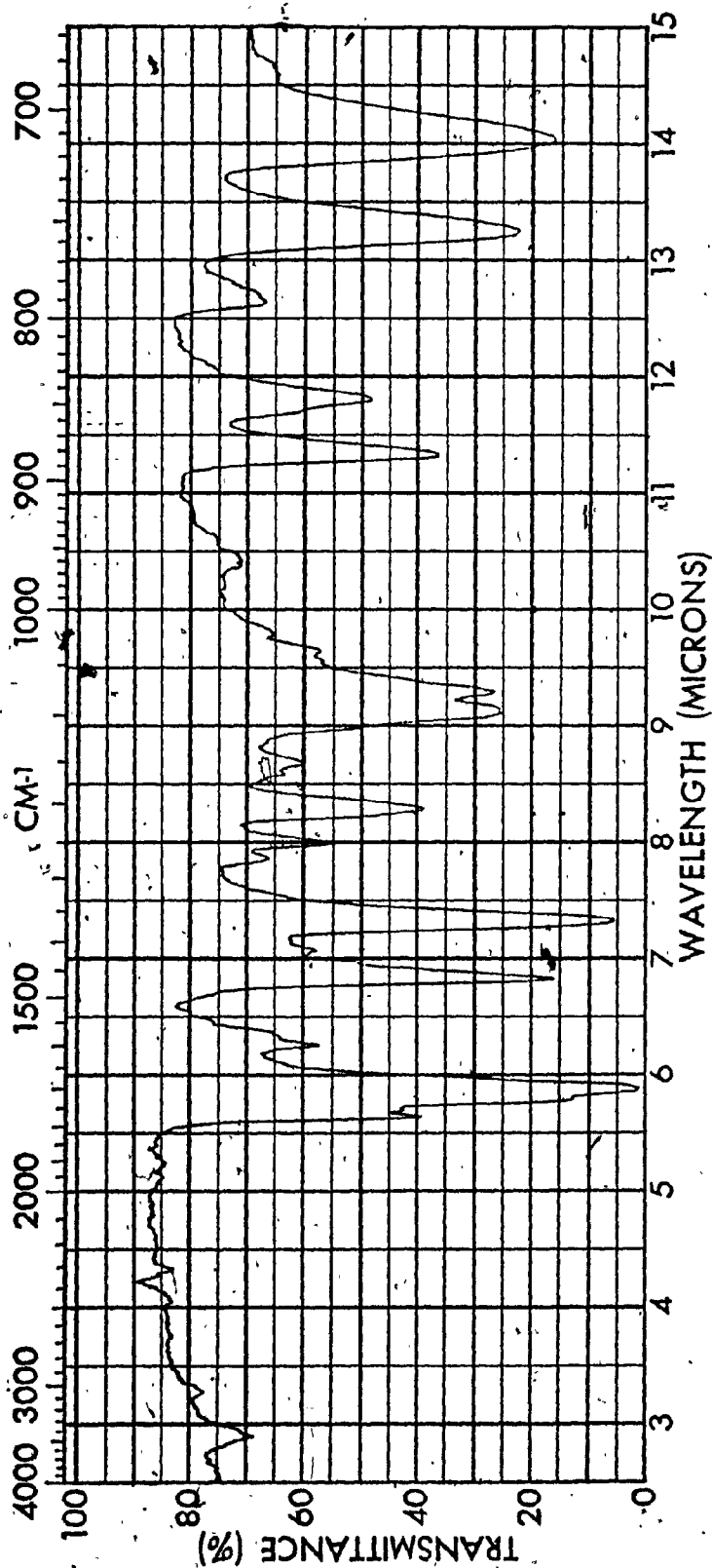


Fig. IR-2: Infra Red Spectrum (KBr) of N-(2-Bromophenyl)-1H-
Isoindole-1,3-Dione.

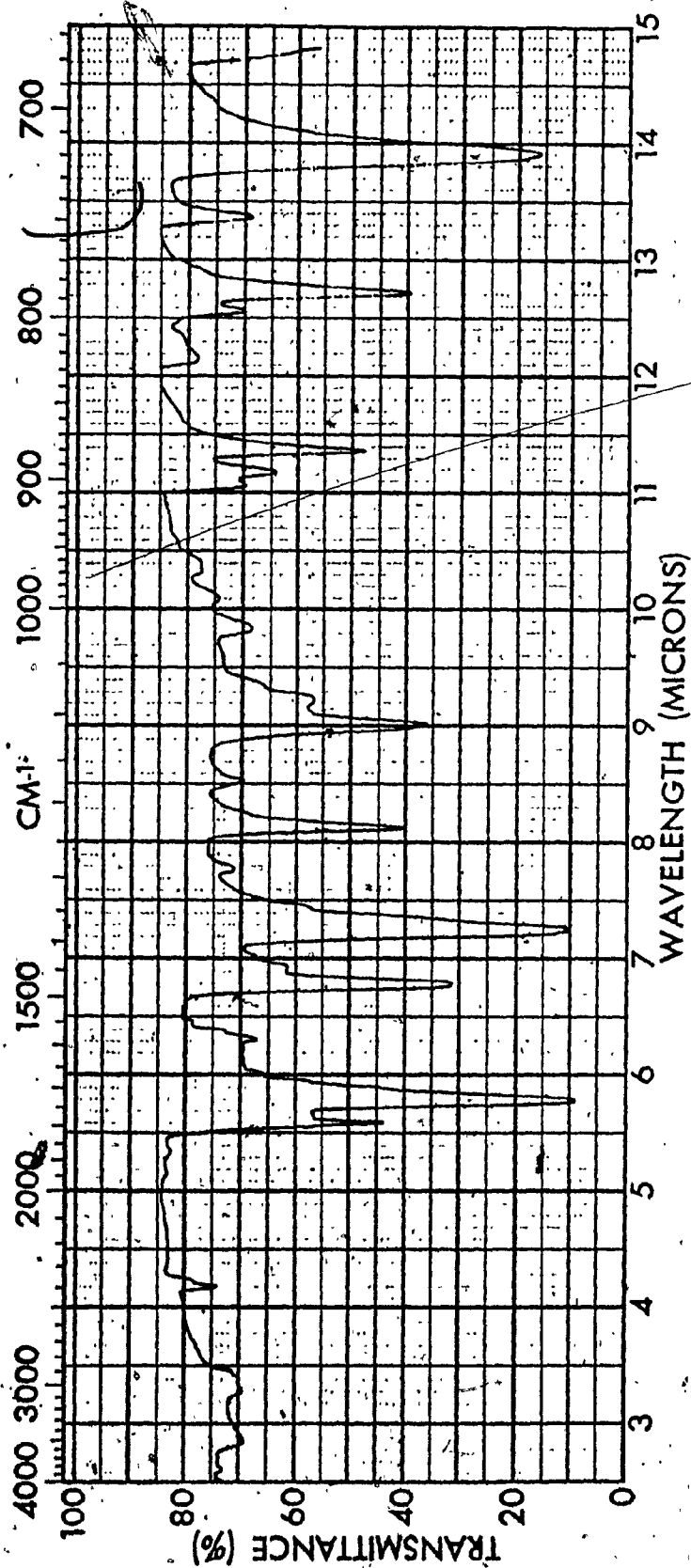


Fig. IR-3: Infra Red Spectrum (KBr) of N-(2,3-Dimethylphenyl)-1H-Indole-1,3-Dione.

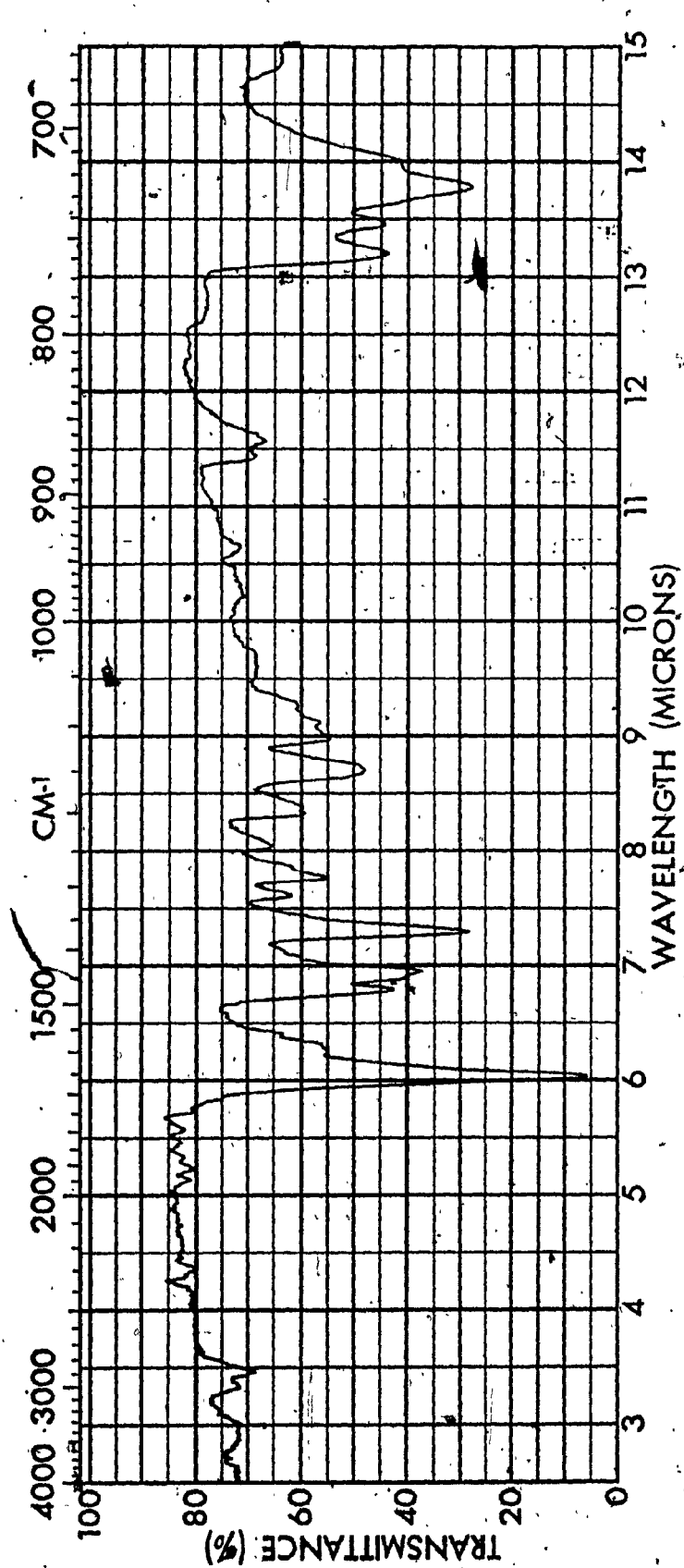


FIG. IR-41: INFRARED SPECTRUM (KBr) OF N-(2-TOLYL)-1-ISOINDOLINONE.

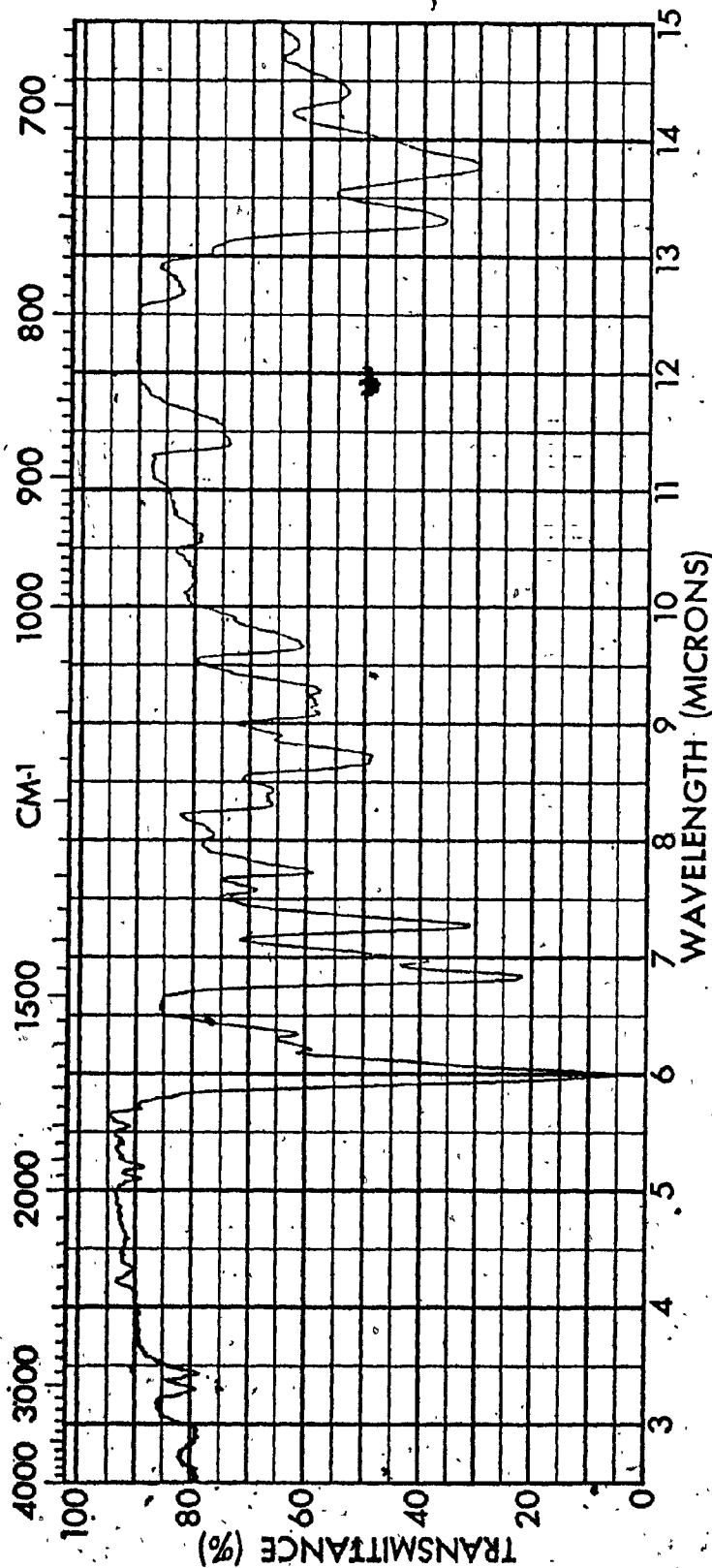


FIG. IR- 5 : INFRA RED SPECTRUM (KBr) OF N-(2-CHLOROPHENYL)-1-ISOINDOLINONE.

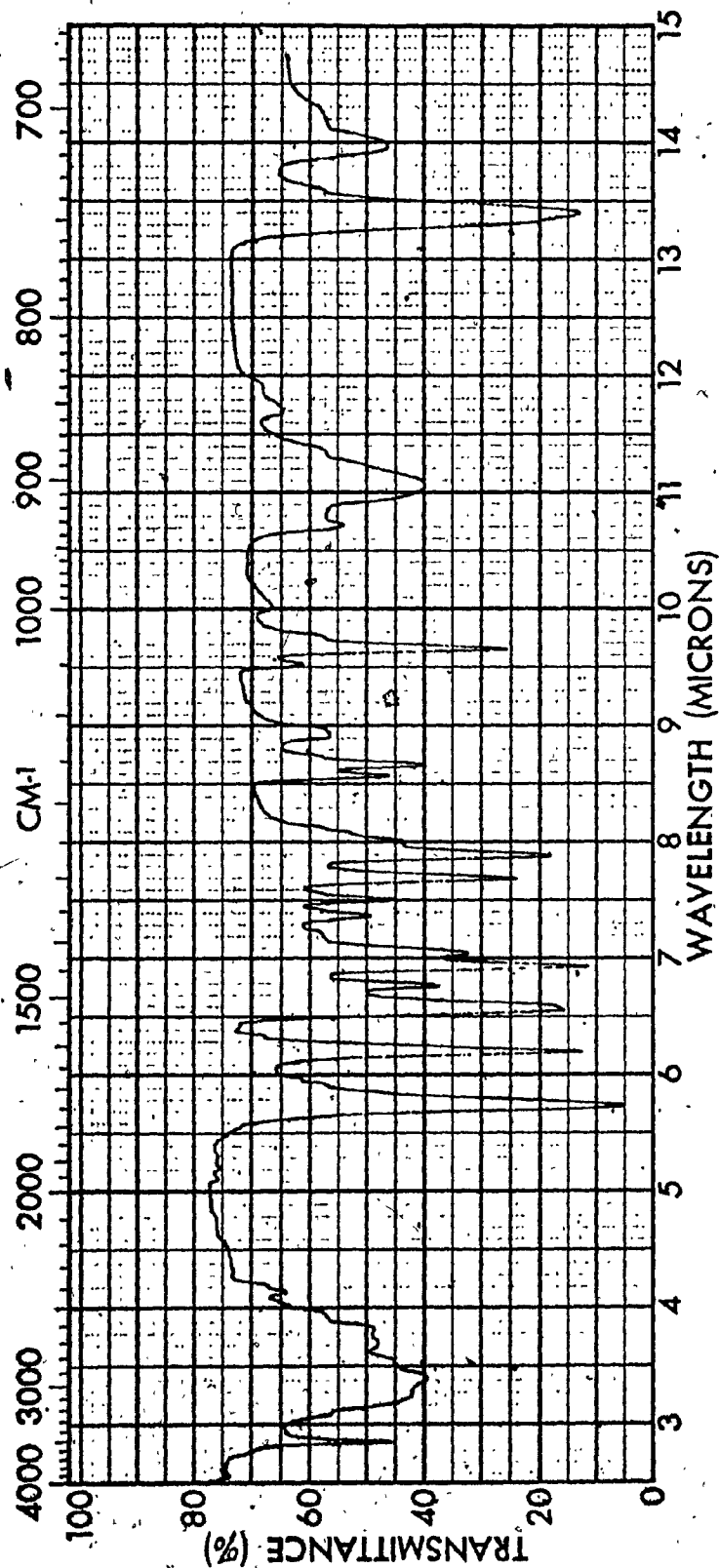


FIG. IR-6 : INTRA RED SPECTRUM (KBr) OF N-(2-CHLOROPHENYL)-GLYCINE.

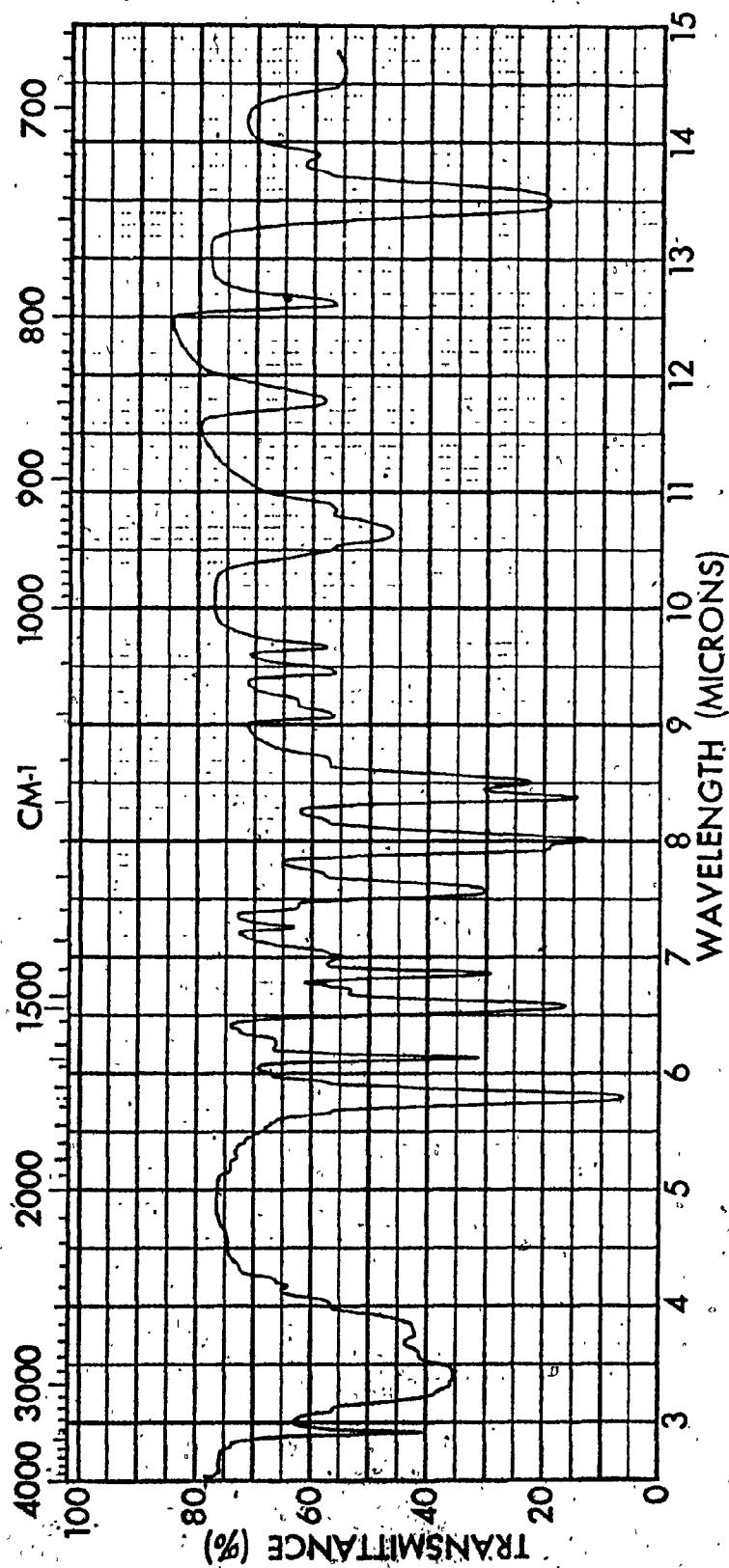


FIG. IR-7 : INFRA RED SPECTRUM (KBr) OF N-(2-FLUOROPHENYL)-ALANINE.

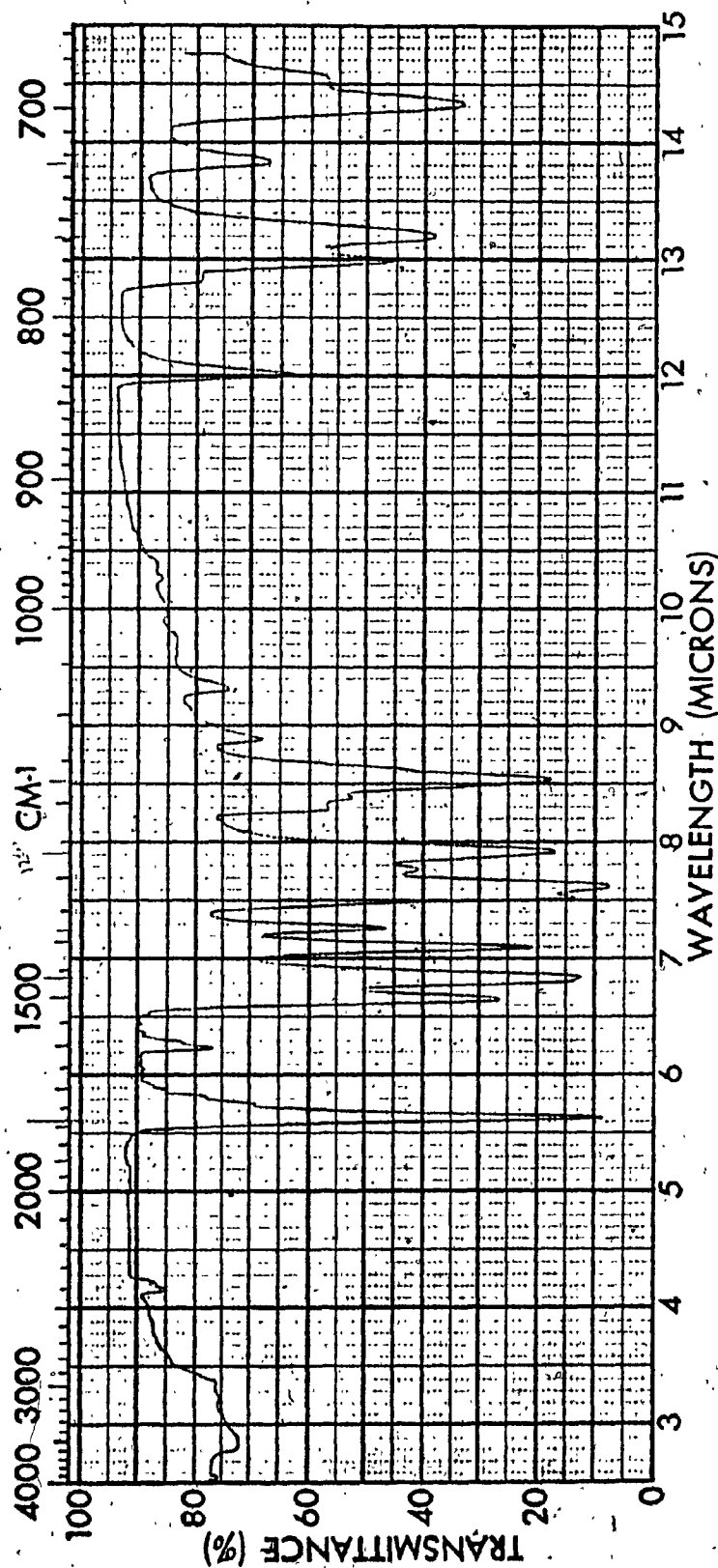


FIG. IR-8 : INFRA RED SPECTRUM (KBr) OF 3-PHENYL-1-(2-TOLYL)-2-THIO-4-IMIDAZOLIDINONE.

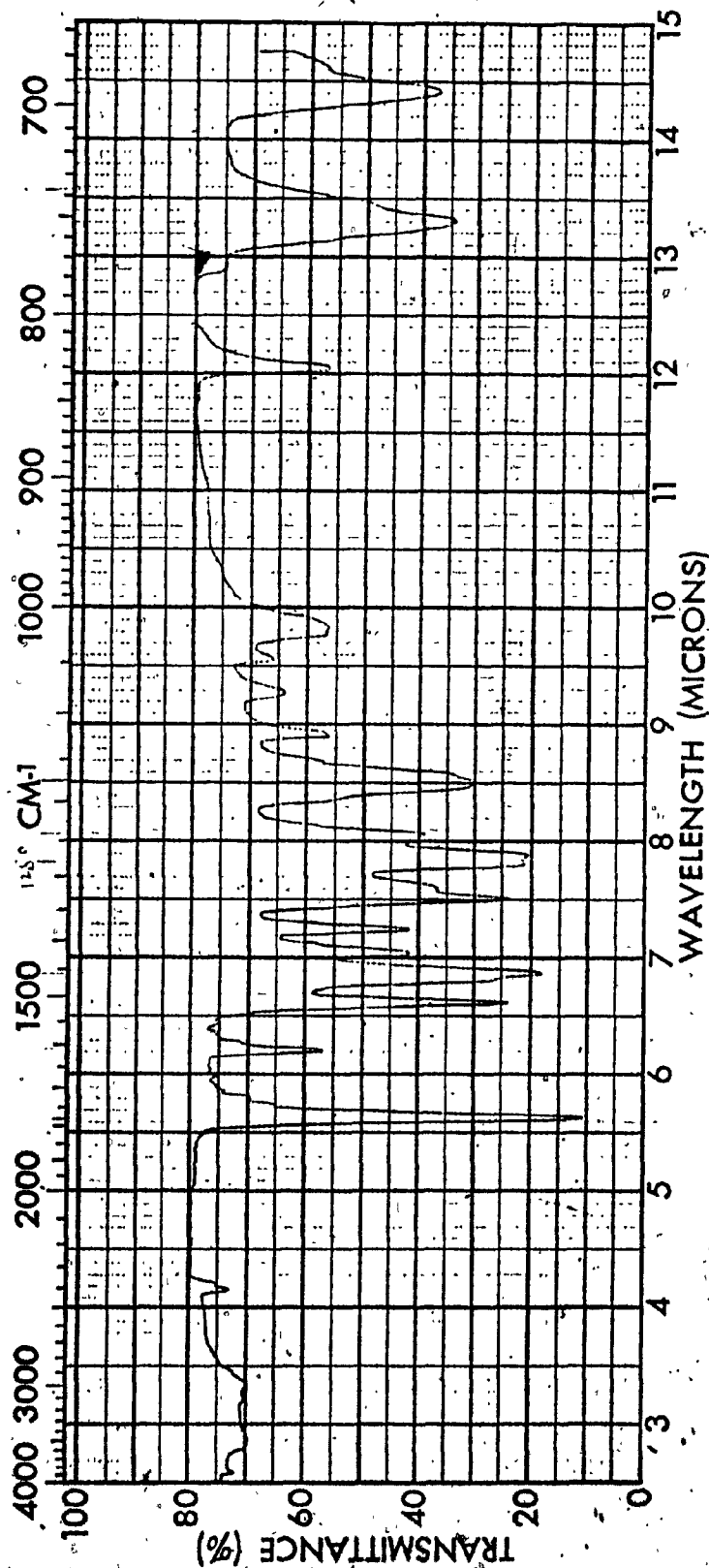


FIG. IR-9 : INFRA RED SPECTRUM (KBr) OF 3-PHENYL-1-(2-METHOXYPHENYL)-2-THIO-4-IMIDAZOLIDINONE.

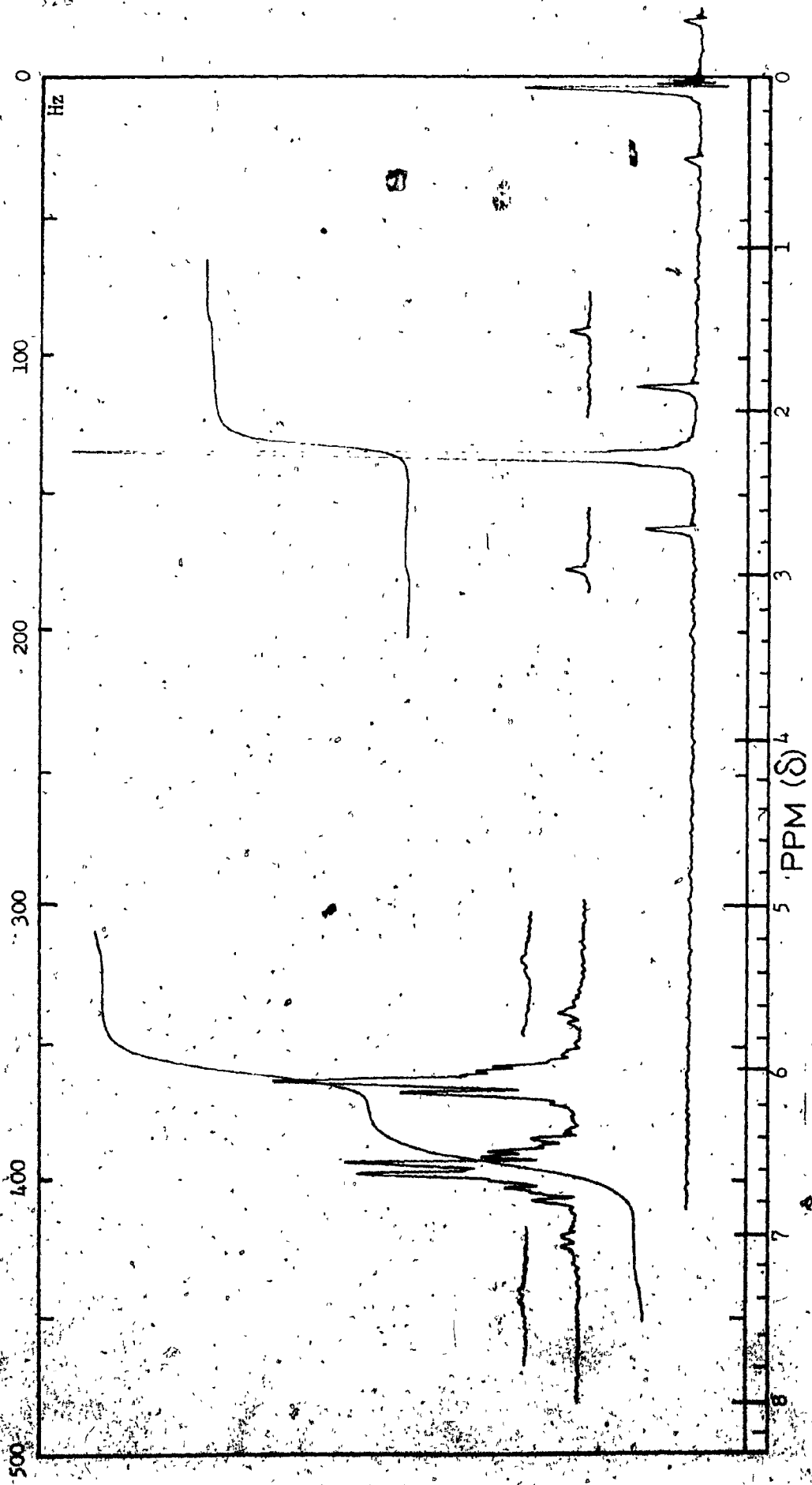
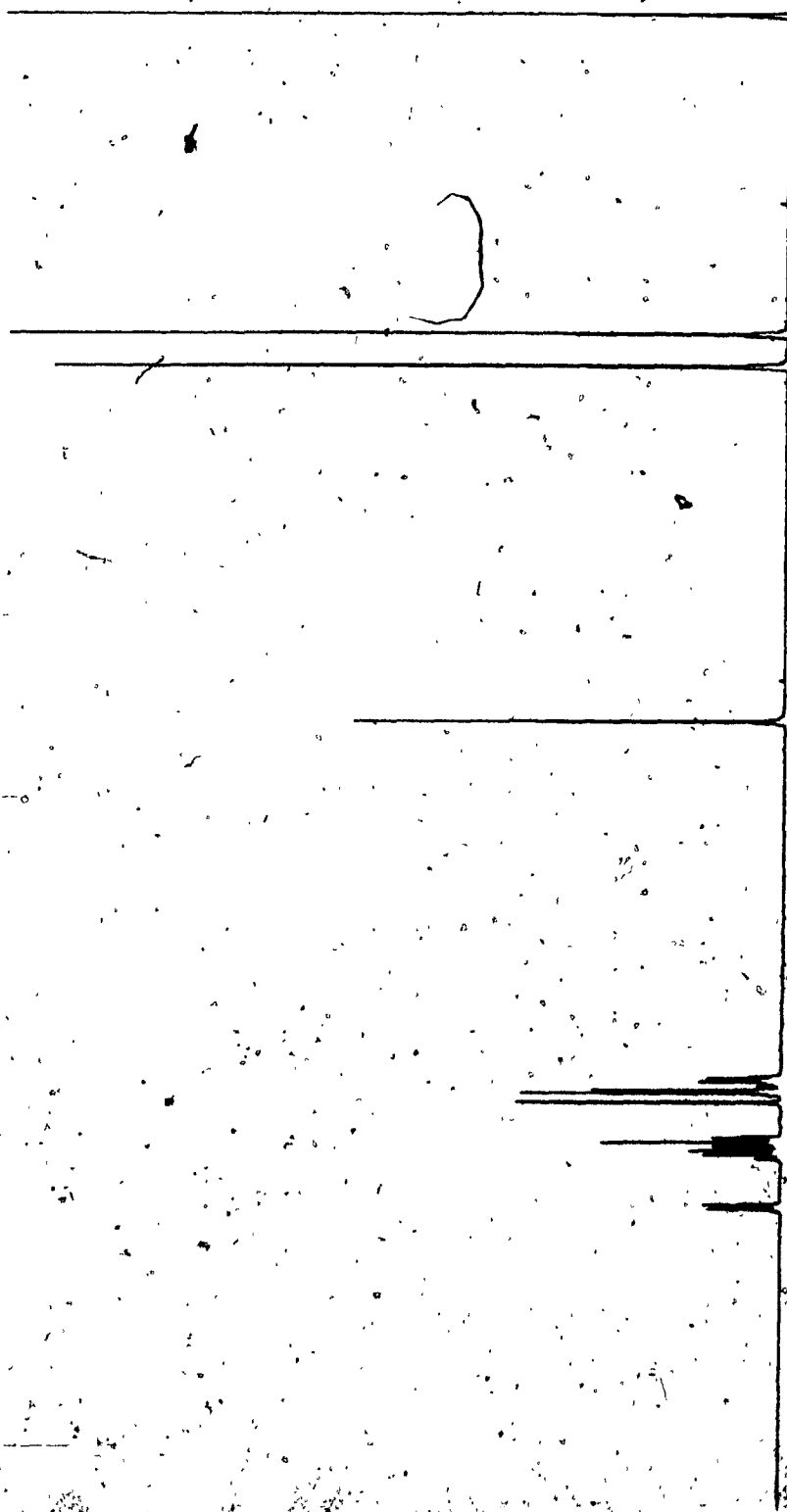
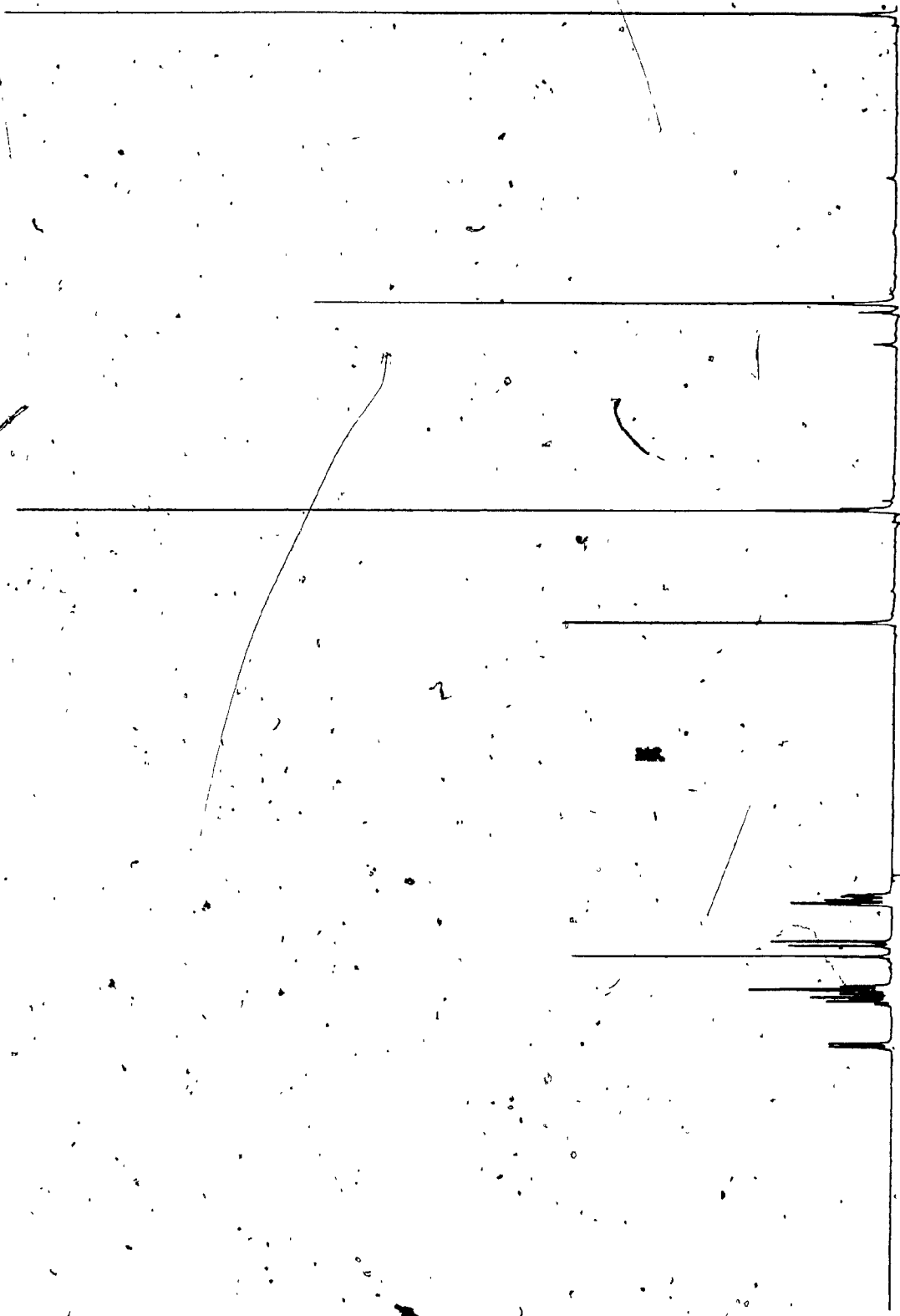


Fig. NH-1 : 60-MHz Proton NMR Spectrum of N-(2-Tolyl)-1H-Indole-1,3-Dione, ID-2, in CDCl_3 . Sweep Offset: 80 Hz, Spinning Rate : 26 and 46 rpm.

Fig. MH-11 : 270 MHz Proton NMR Spectrum of N-(2,3-Dimethylphenyl)-1-Isoindolinone, IN-8, 0.05 M Solution in CDCl_3 at 23° .





10 20 0

Fig. NH-13 : 270 MHz Proton NMR Spectrum of N-(2-Methyl-4-Methoxyphenyl)-1-Isolindolinone, IN-10, 0.05 M Solution in CDCl_3 at 23° .

Fig. NH-19 : 60-MHz Proton NMR Spectrum of N-(Phenyl)-Alanine in
DMSO- d_6 . Sweep Offset (for OH) : 42 Hz.



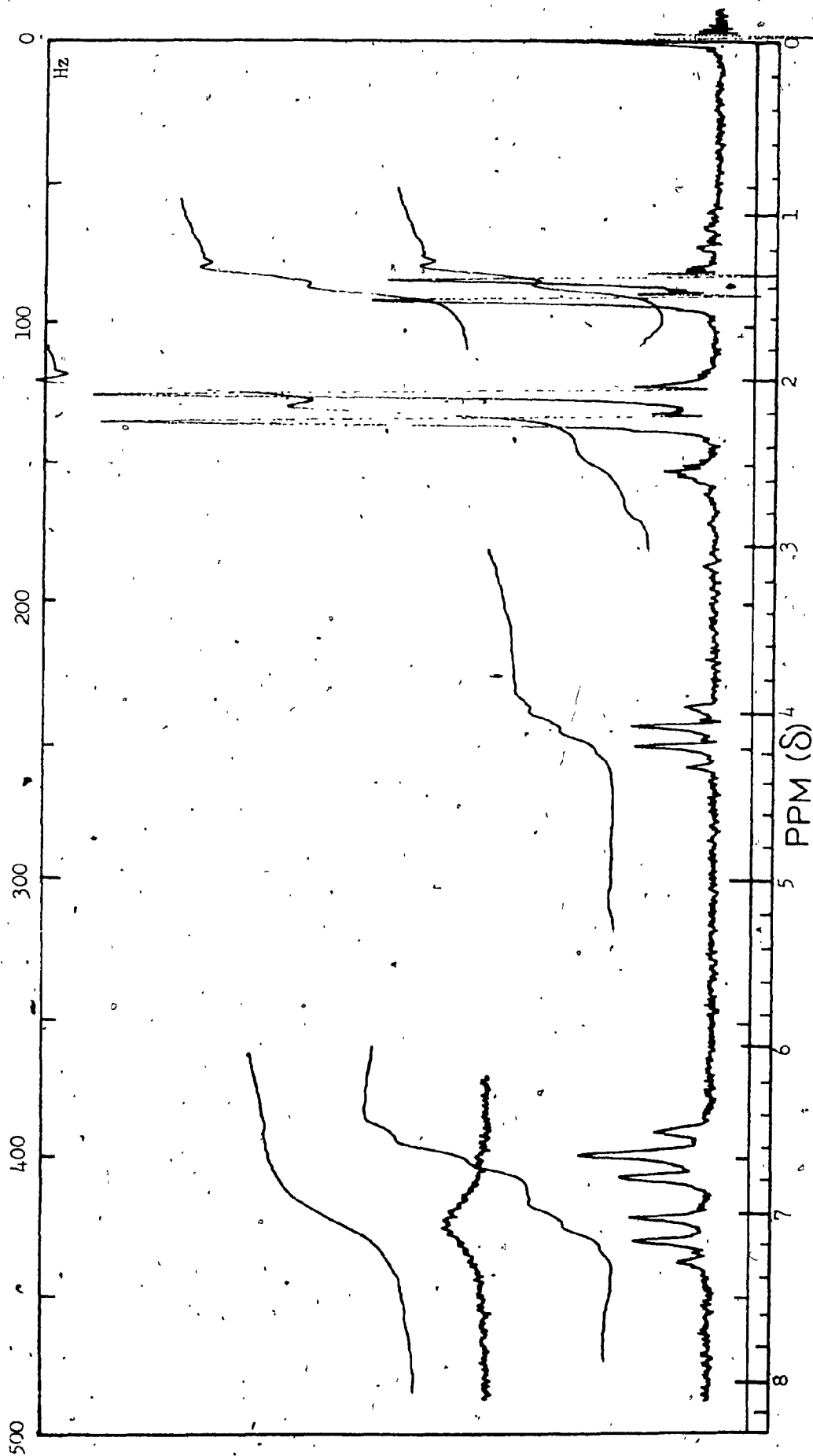


Fig. NH-22 : 60-MHz Proton NMR Spectrum of N-(2,3-Dimethylphenyl)-Alanine
in DMSO-d₆ . Sweep Offset (for OH) : 100 Hz.

Fig. NH-25 : 270-MHz Proton NMR Spectrum of 3-Phenyl-1-(2-Tolyl)-2-Thio-4-Imidazolidinone, 0.05 M Solution in CDCl_3 at 23° .

Fig. NH-26 : 270-MHz Proton NMR Spectrum of 3-Phenyl-1-(2-Methoxyphenyl)-2-Thio-4-Imidazolidinone, 0.05 M Solution in CDCl_3 at 23° .

10

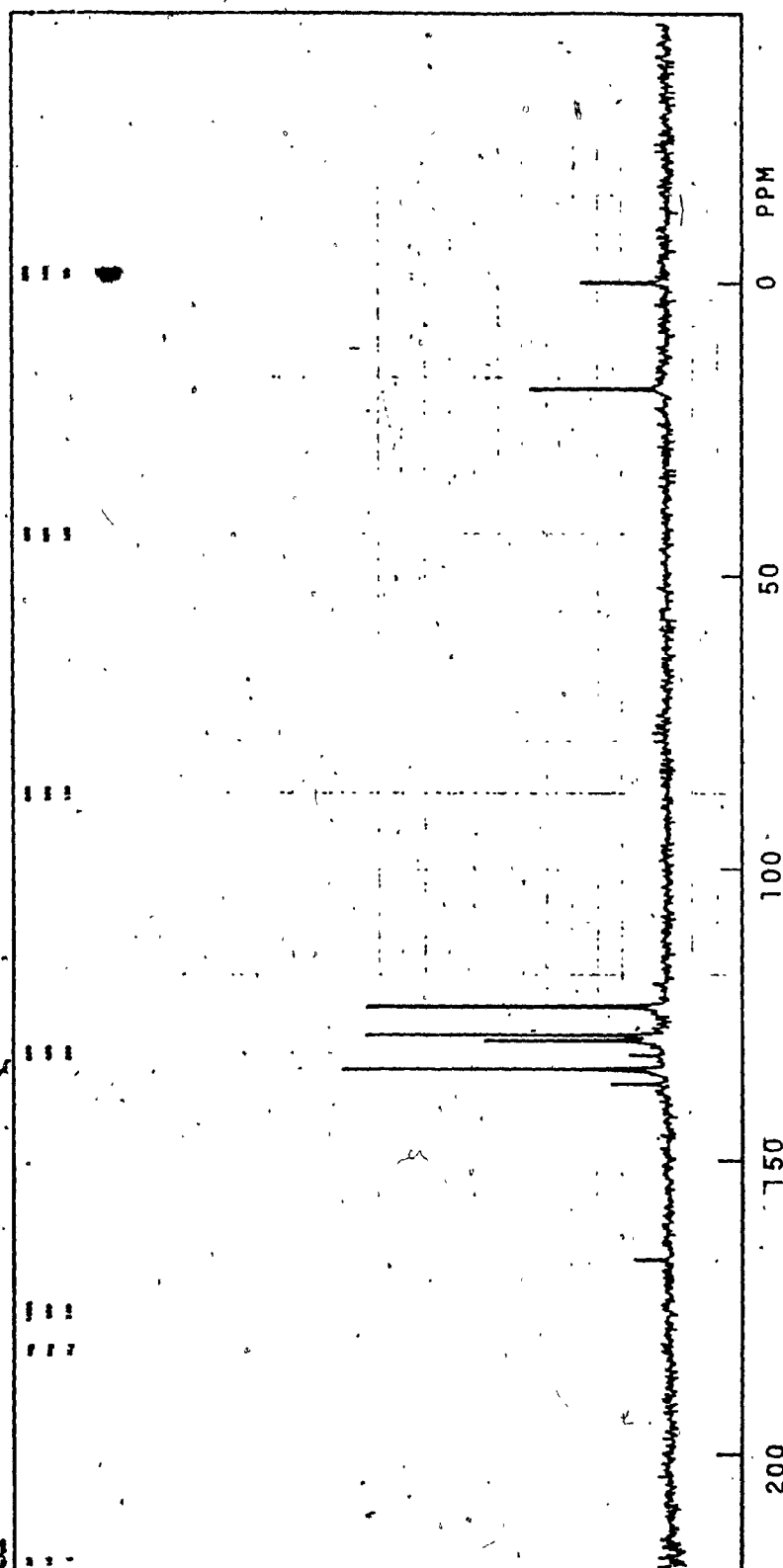


Fig. NC-1 : ^{13}C -NMR Spectrum of N-(2,6-Dimethylphenyl)-Isoindole-1,3-Dione; 300 mg/1.5 ml CDCl_3 , 2000 Scans at 27°.

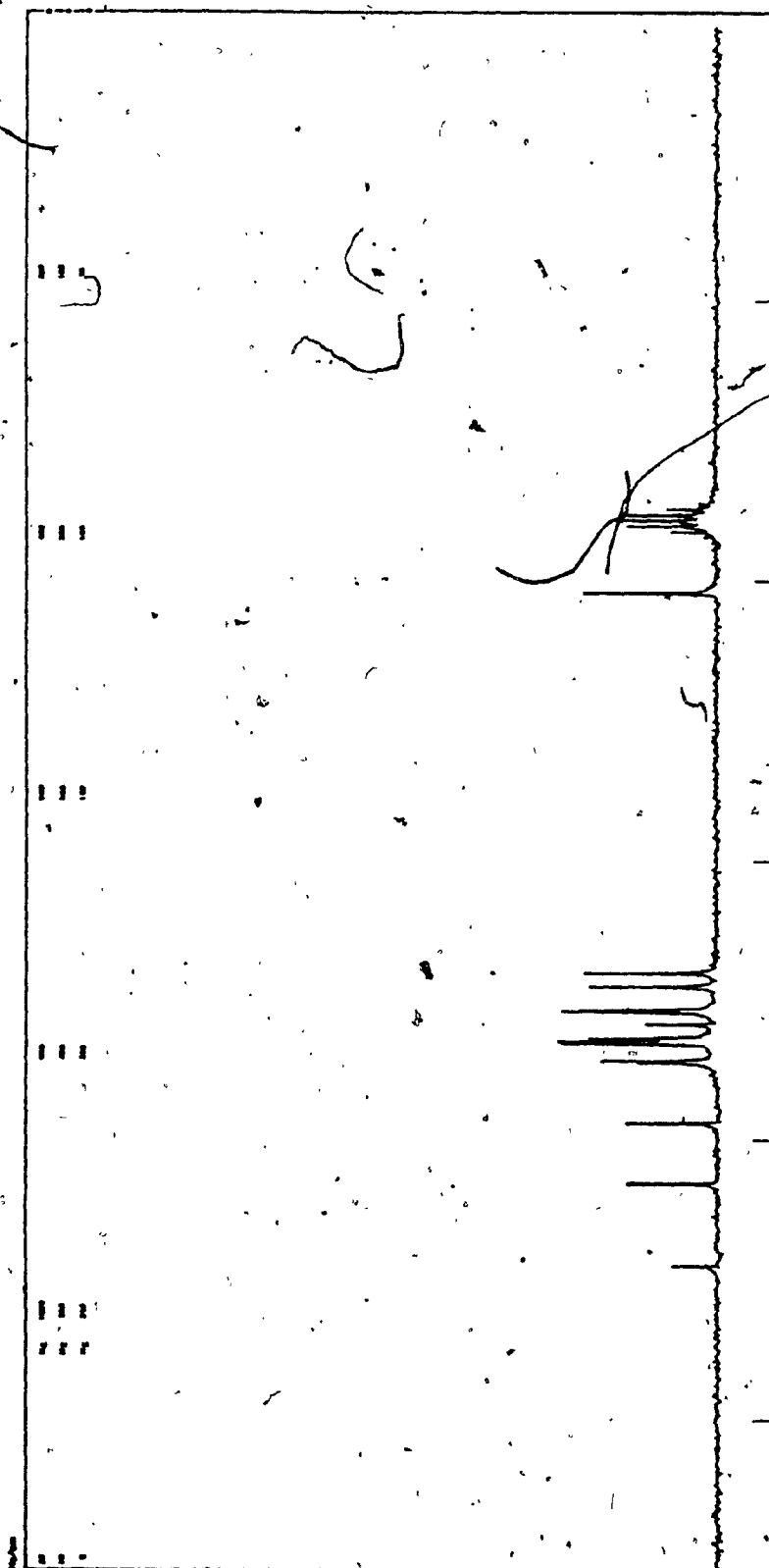
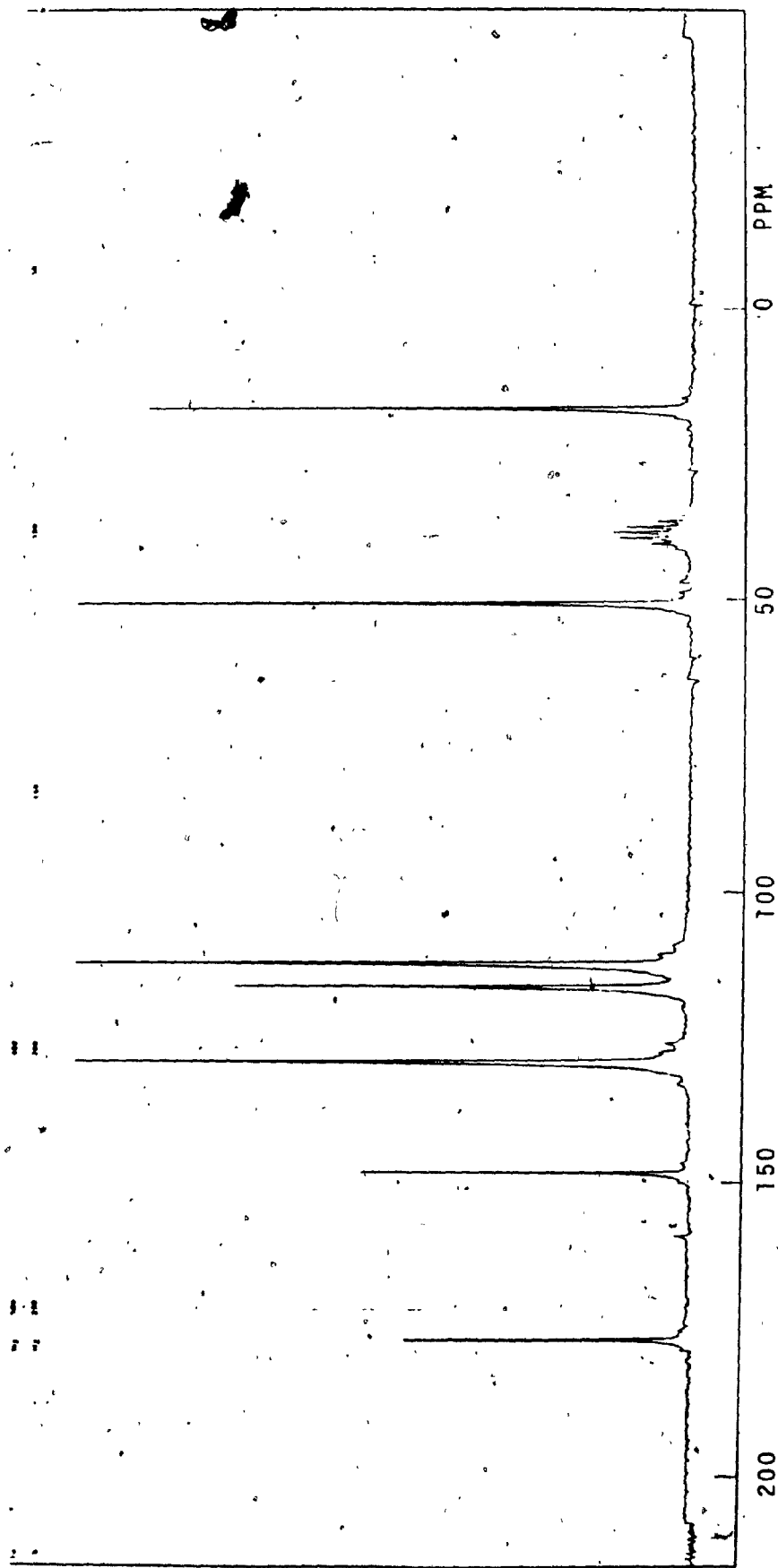


Fig. NC-2 : ^{13}C -NMR Spectrum of N-(2-Hydroxyphenyl)-1-isoindolinone,
1.0 M in DMSO-d_6 , 2500 Scans at 27° .



267

Fig. NC-3 : C-13 NMR Spectrum of N-Phenyl Alanine, 2.0 M in DMSO- d_6 , 7500 Scans at 27°.

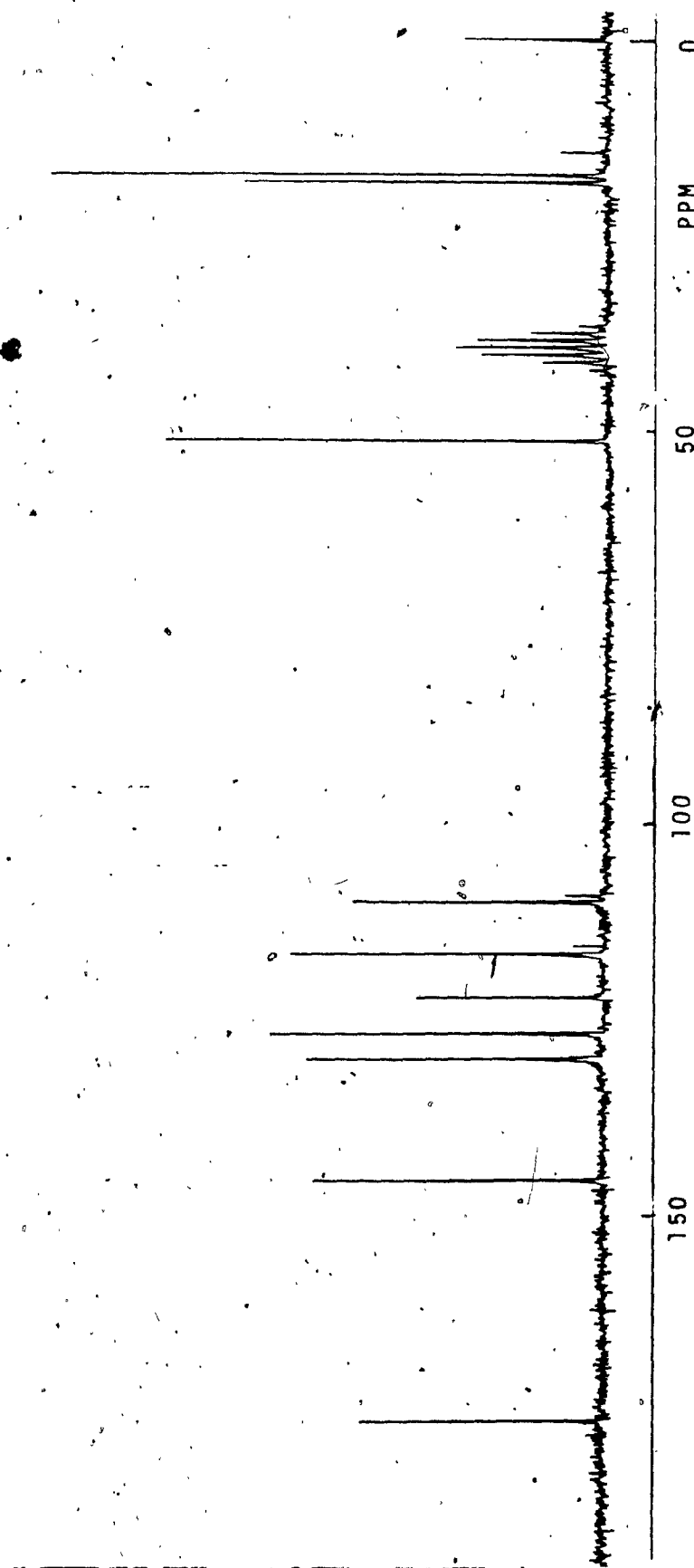


Fig. NC-4 : C-13 NMR Spectrum of N-(2-Tolyl)-Alanine, 270 mg/1.5 ml DMSO-d₆
4114 Scans at 35°

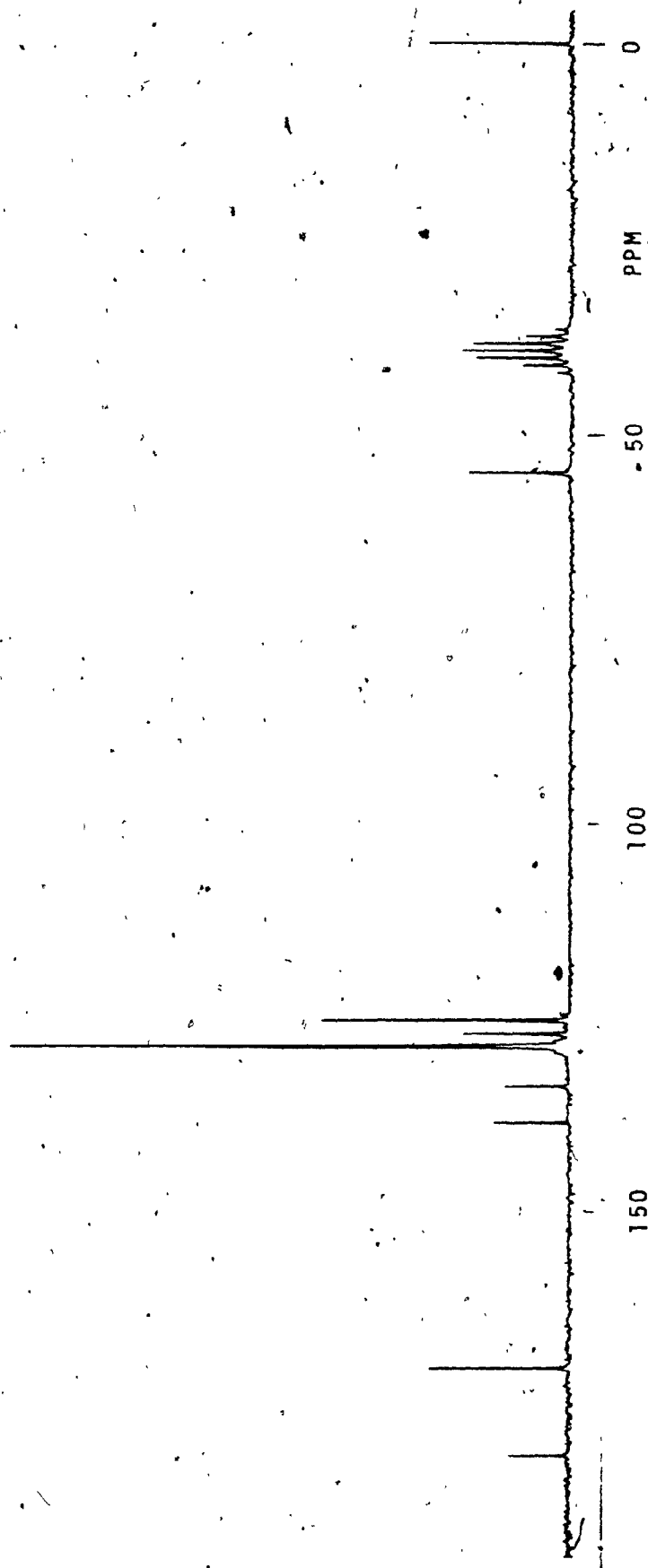


Fig. NC-5 : ^{13}C -NMR Spectrum of 1,3-Diphenyl-2-Thio-4-Imidazolidinone,
1.0 M in DMSO-d_6 , 2500 Scans at 35° .

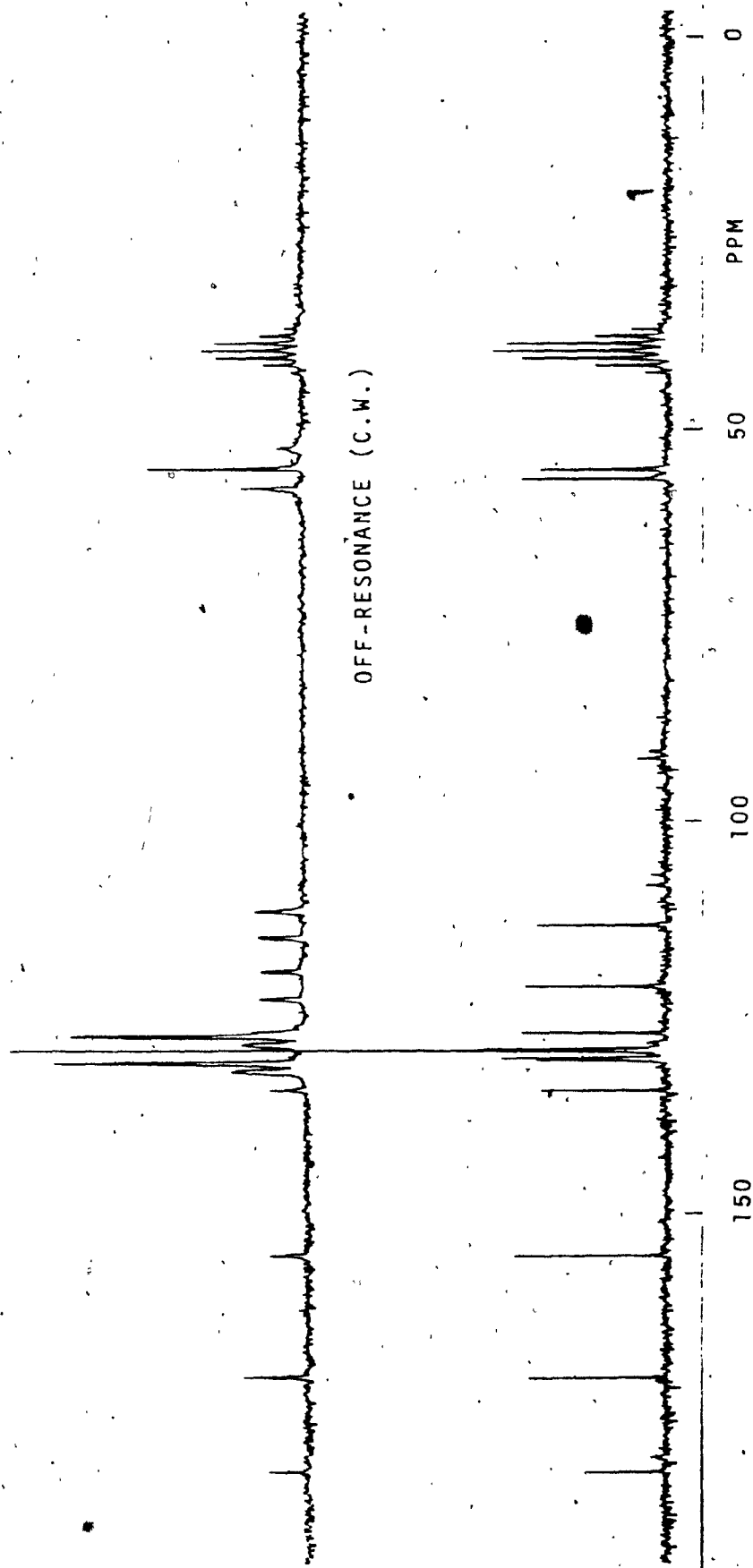


Fig. NC-6 : C-13 NMR Spectrum of 3-Phenyl-1-(2-Methoxyphenyl)-2-Thio-4-Imidazolidinone, 0.75 M. in DMSO-d₆, 2600 Scans at 35°.

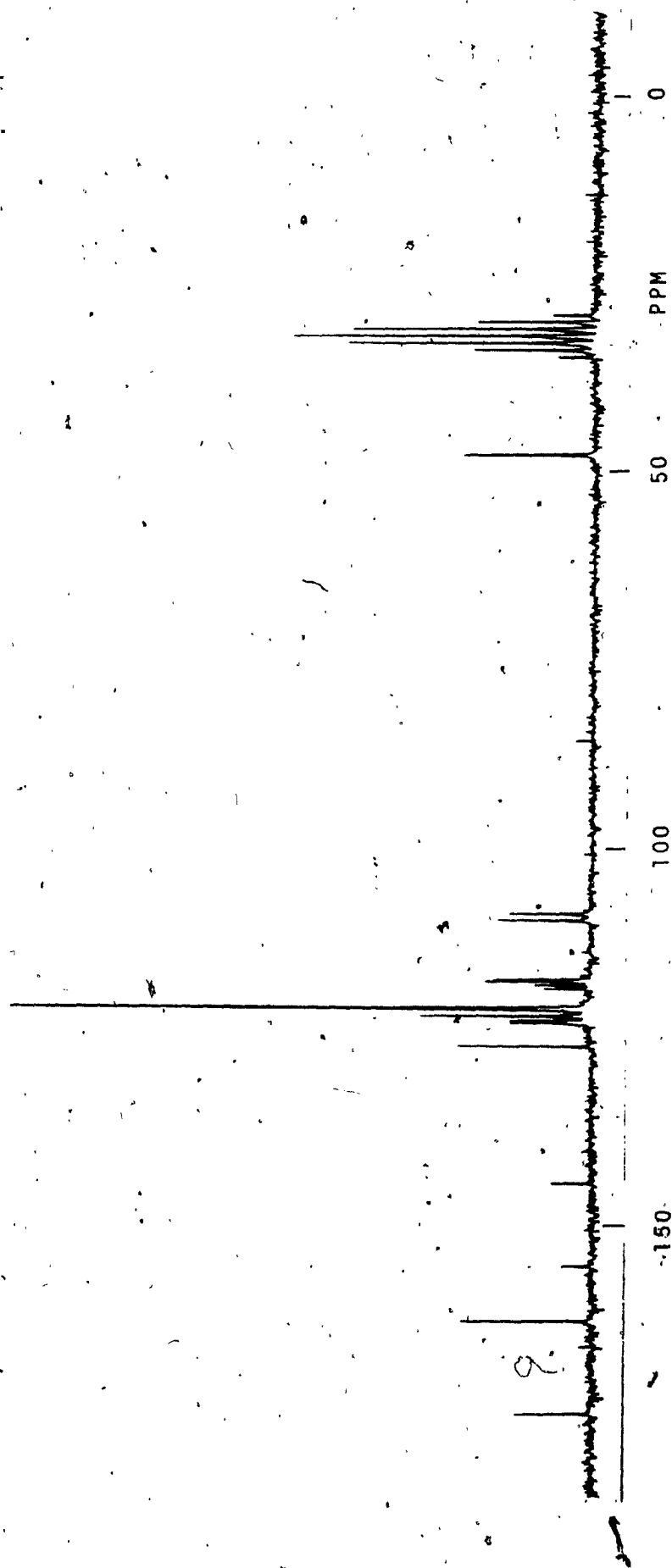


Fig. NC-7 : ^{13}C -NMR Spectrum of 3-Phenyl-1-(2-Fluorophenyl)-2-Thio-4-Imidazolidinone, 0.75 M in DMSO-d_6 , 4800 Scans at 35° .

271

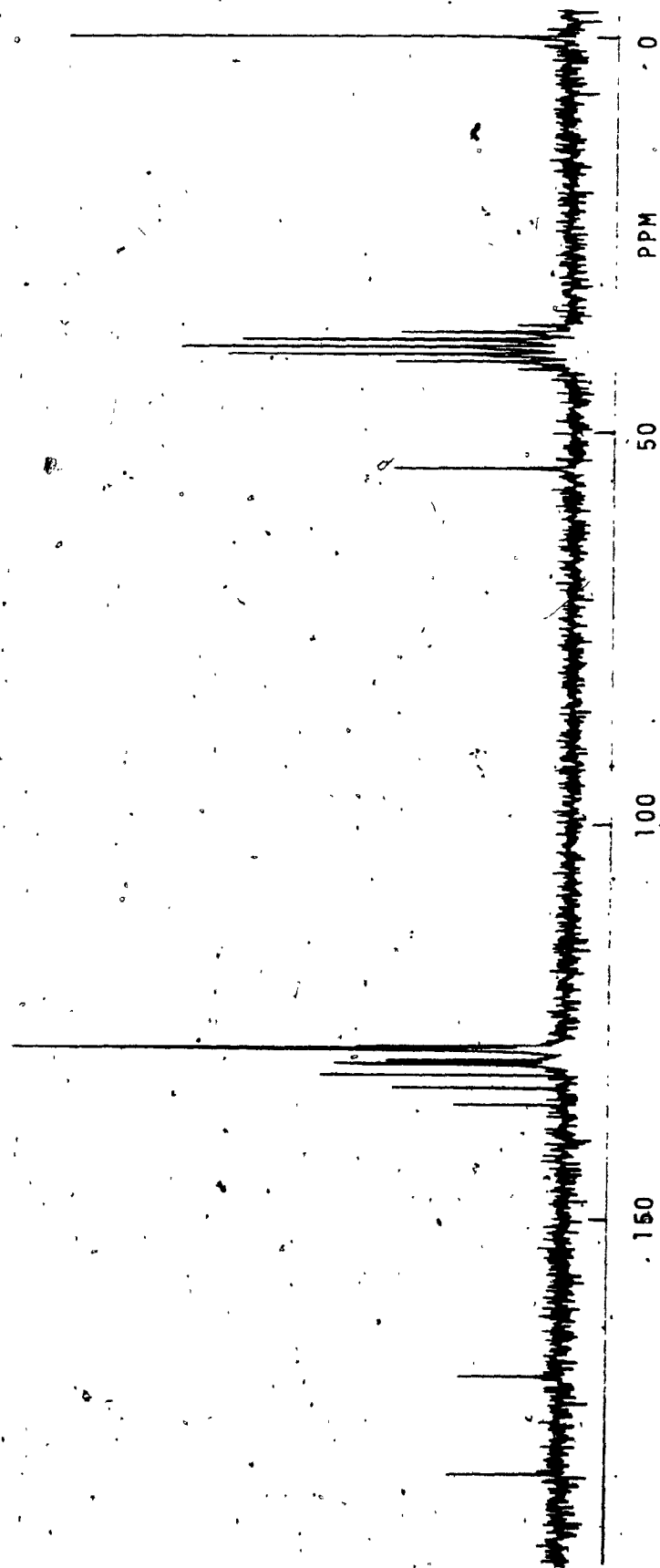


Fig. NC-8 : ^{13}C -NMR Spectrum of 3-Phenyl-1-(2-Chlorophenyl)-2-Thio-4-Imidazolidinone, 0.25 M in $\text{DMSO}-d_6$, 6060 Scans at 35°

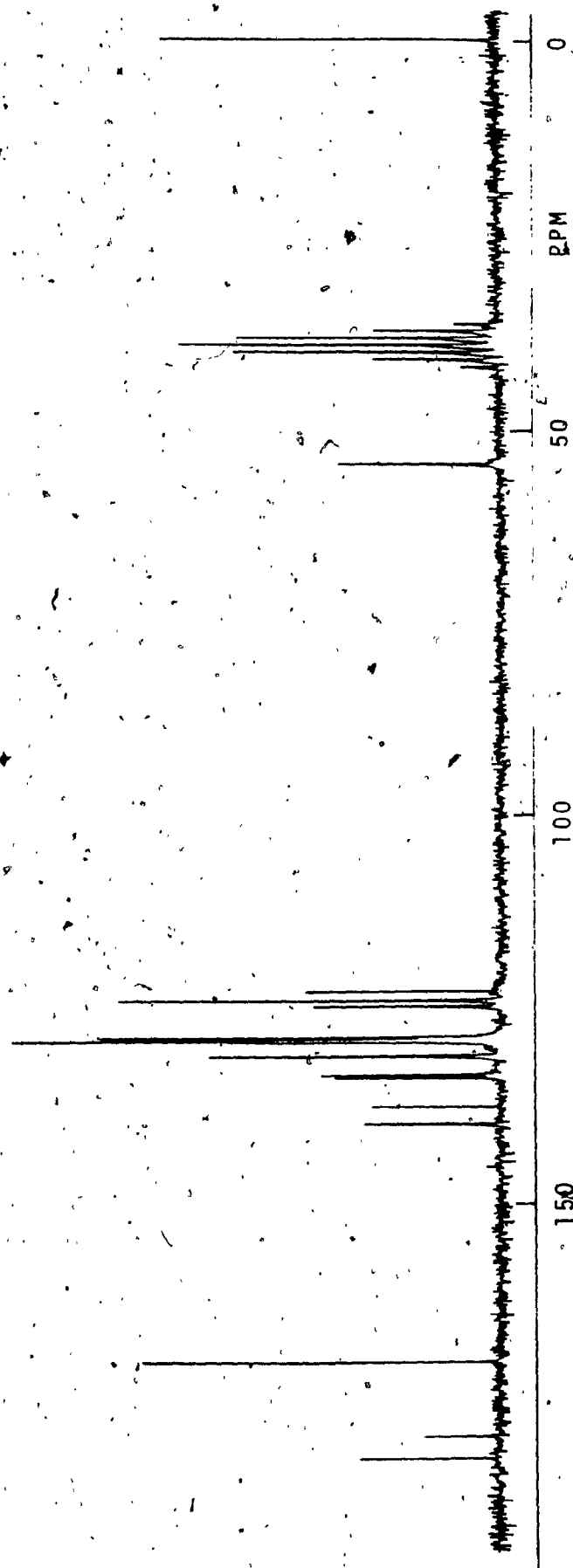


Fig. NC-9 : ^{13}C NMR Spectrum of 3-Phenyl-1-(2-Bromophenyl)-2-Thio-4-Imidazolidinone, 0.60 M in $\text{DMSO}-d_6$, 6400 Scans at 35° .

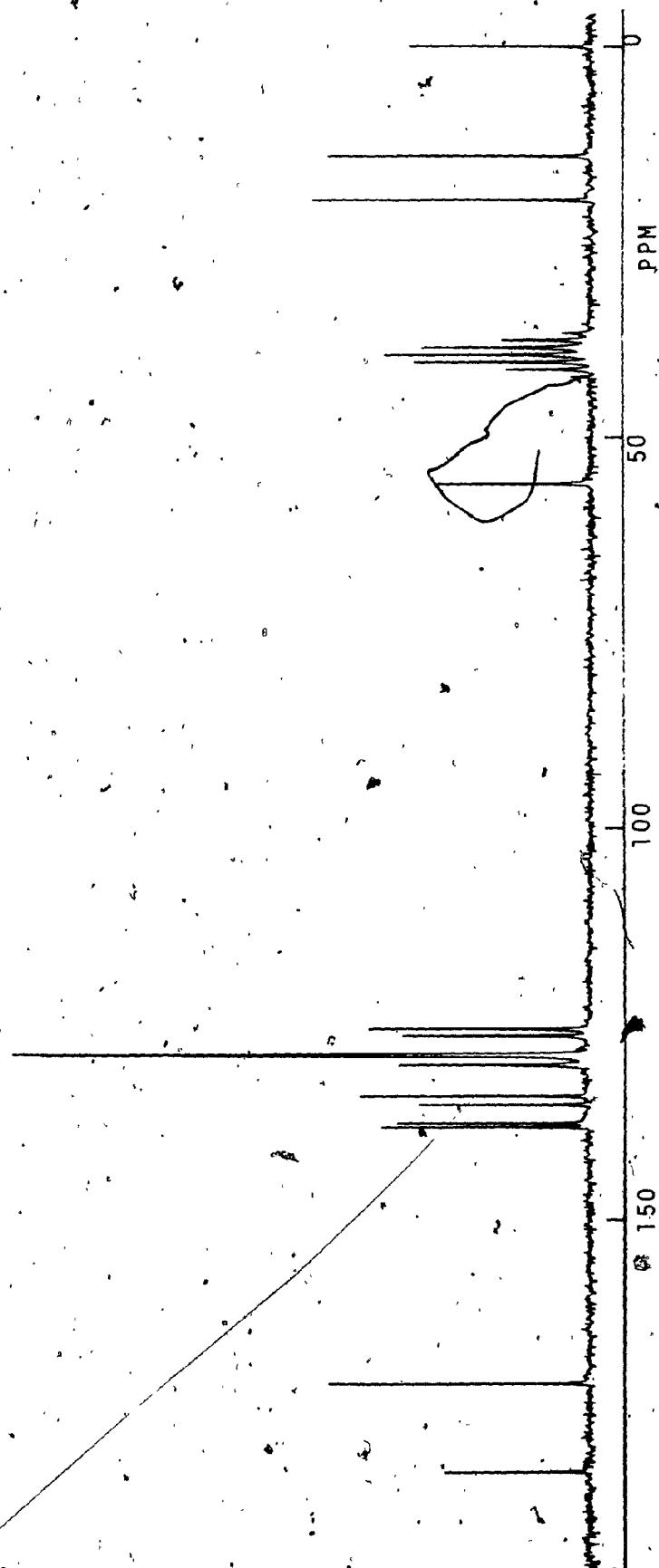


Fig. NC-10 : ^{13}C NMR Spectrum of 3-Phenyl-1-((2,3-Dimethylphenyl)-2-Thio-4-Imidazolidinone, 0.75 M in DMSO-d_6 , 2500 Scans at 35° .

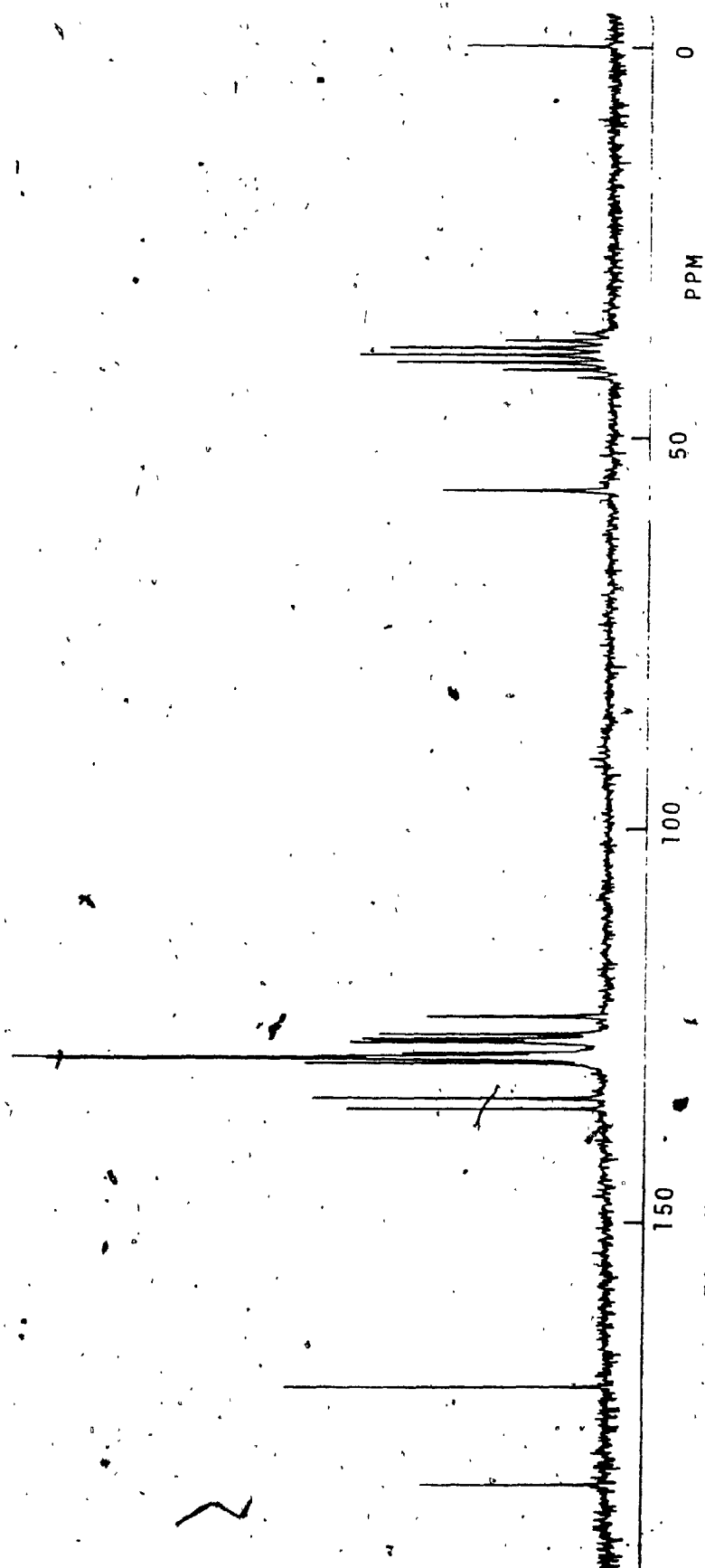
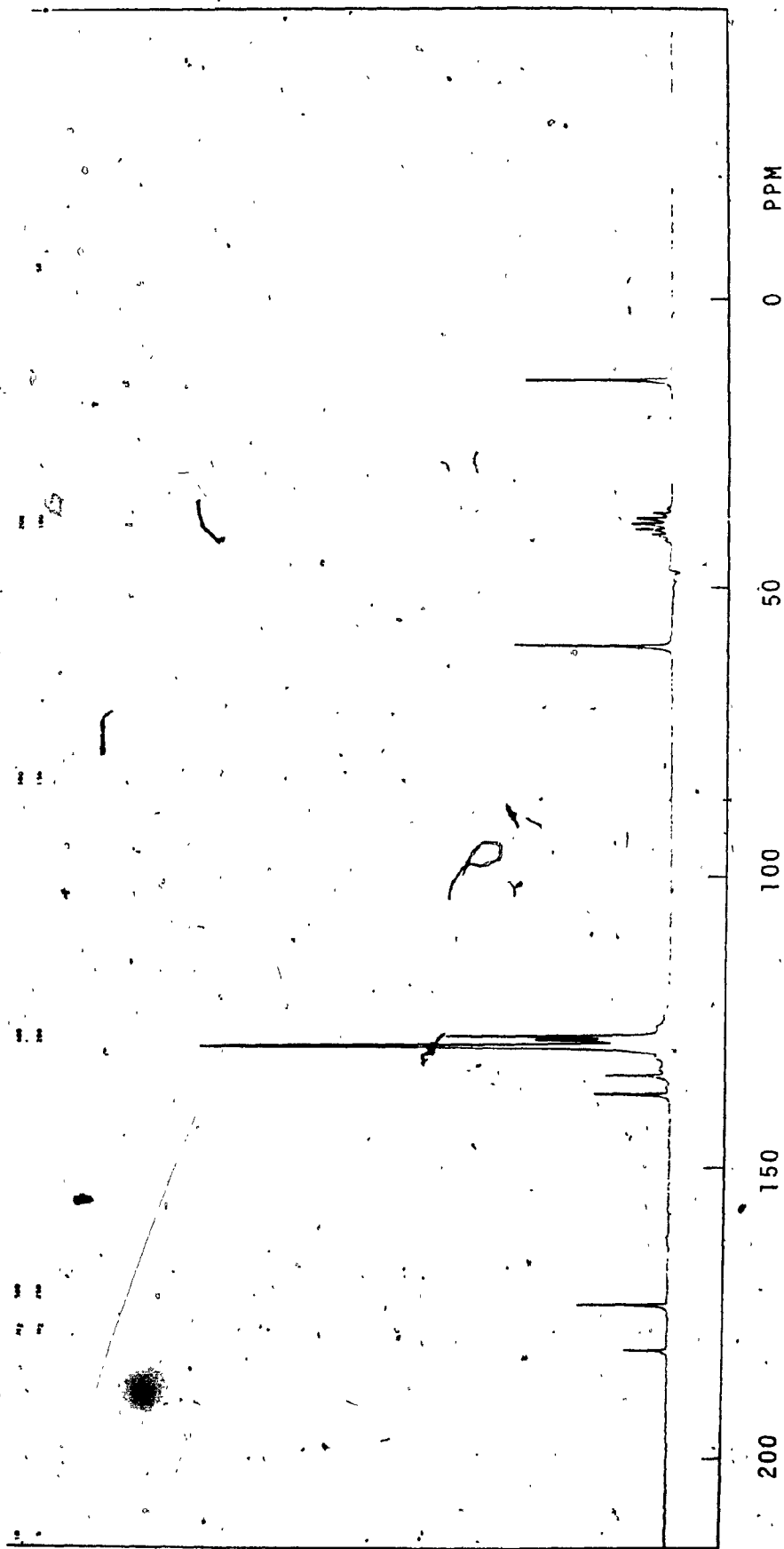


Fig. NC-11 : ^{13}C -NMR Spectrum of 3-Phenyl-1-(1-Naphthyl)-2-Thio-4-Imidazolidinone, 0.70 M in DMSO-d_6 , 2500 Scans at 35°



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Fig. NC-12 : C-13 NMR Spectrum of 1,3-Diphenyl-5-Methyl-2-Thio-4-Imidazolidinone, 1.0 M in DMSO-d₆, 10,000 Scans at 27°.

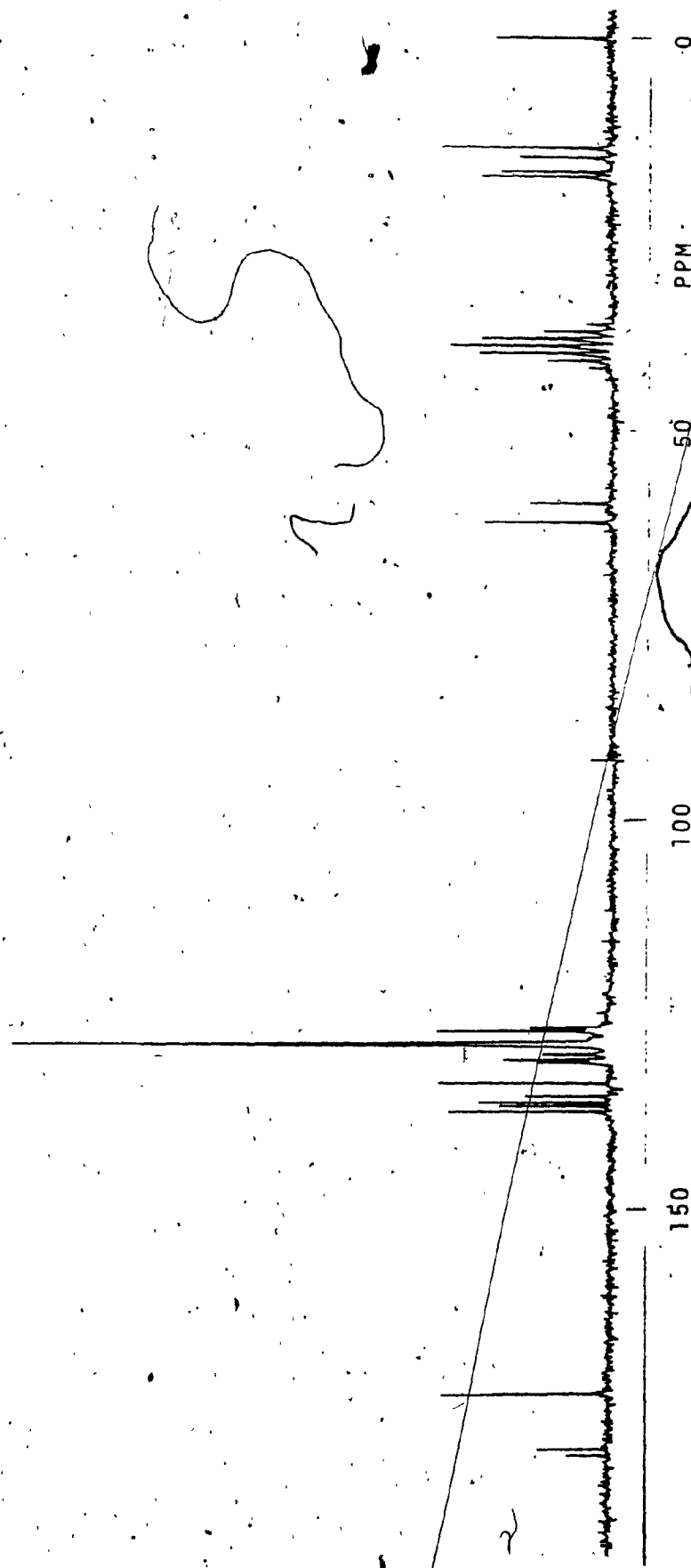


Fig. NC-13 : C-13 NMR Spectrum of 3-Phenyl-1-(2-Tolyl)-5-Methyl-2-Thio-4-Imidazolidinone, 0.75 M in DMSO-d_6 , 5000 Scans at 35° .

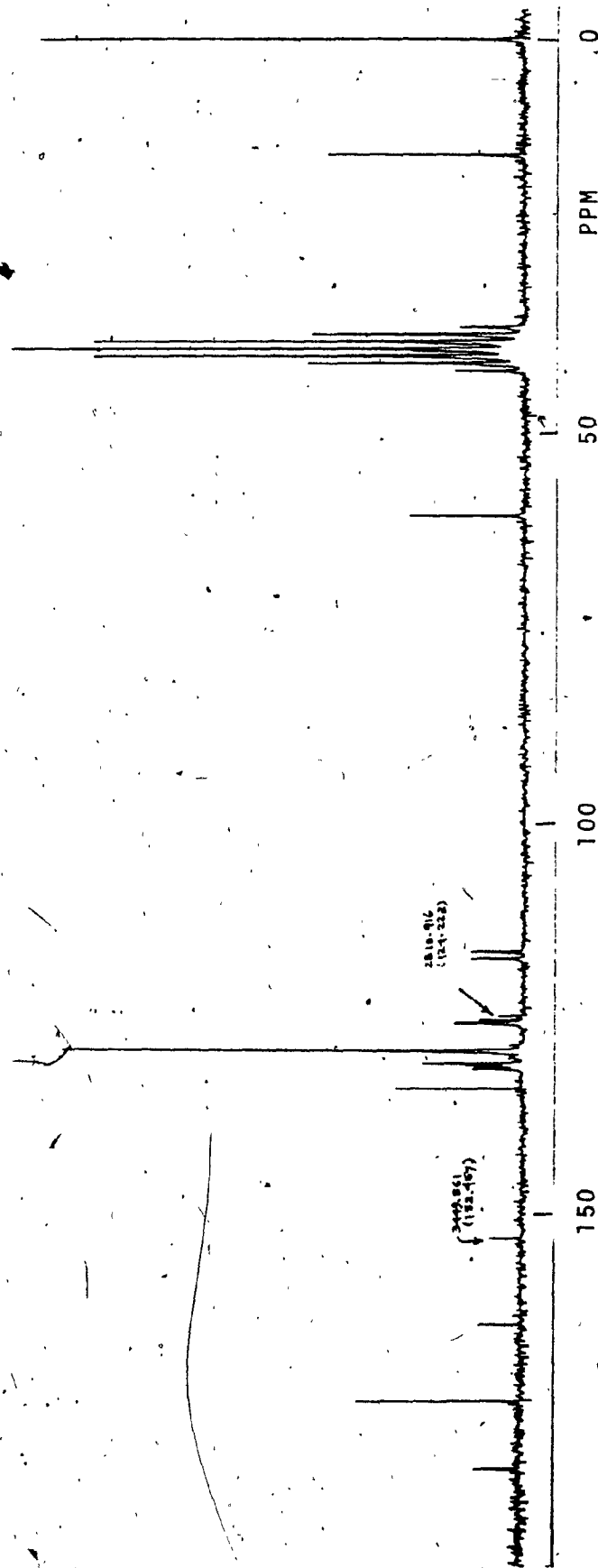


Fig. NC-14 : ^{13}C -NMR Spectrum of 3-Phenyl-1-(2-Fluorophenyl)-5-Methyl-2-Thio-4-Imidazolidinone, 0.20 M in $\text{DMSO}-d_6$, 46,664 Scans at 35° .

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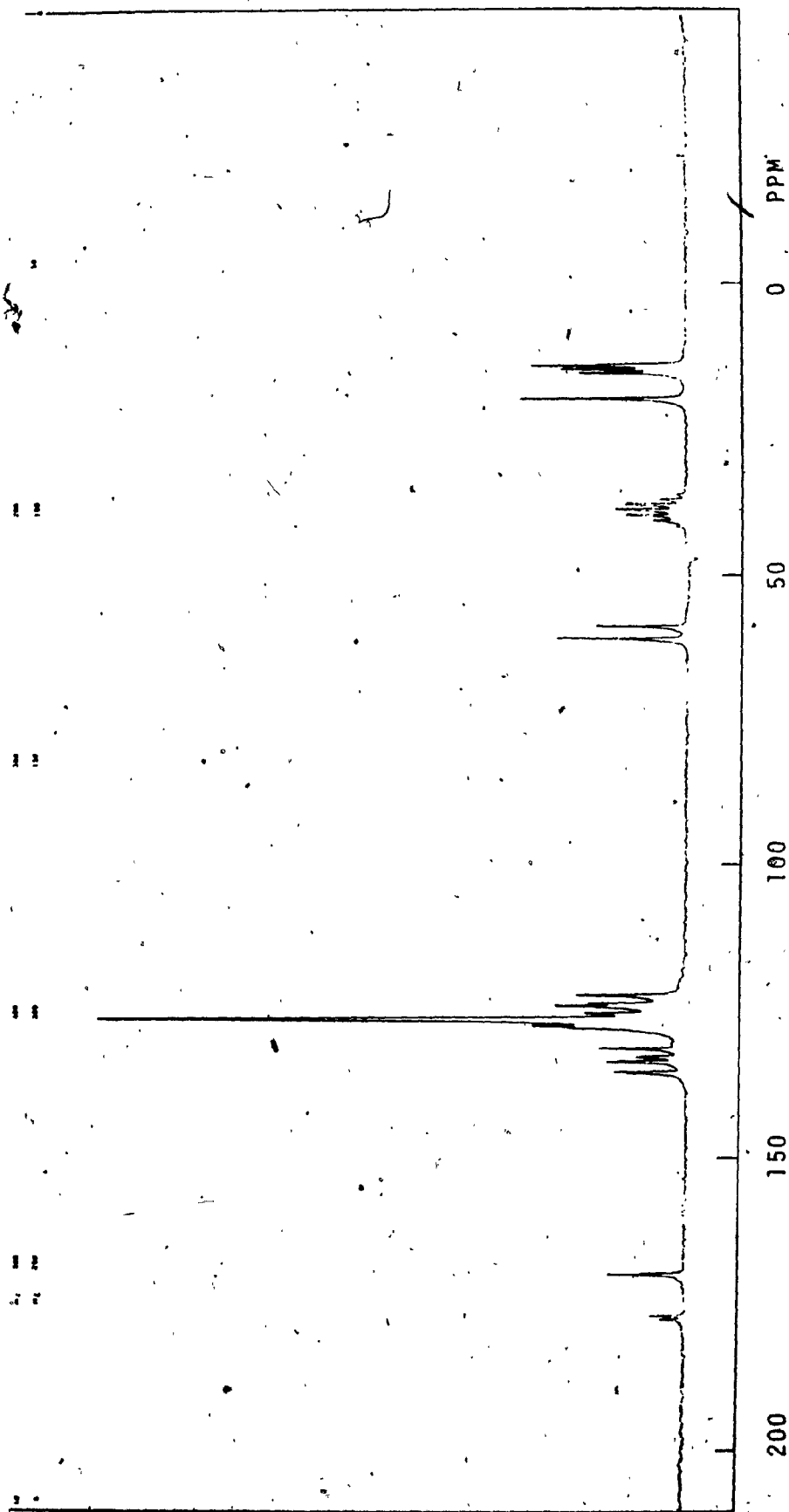


Fig. NC-15 : ^{13}C NMR Spectrum of 3-Phenyl-1-(2,3-Dimethylphenyl)-5-Methyl-2-Thio-4-Imidazolidinone, 1.0 M in $\text{DMSO}-d_6$, 10,000 Scans at 27° .

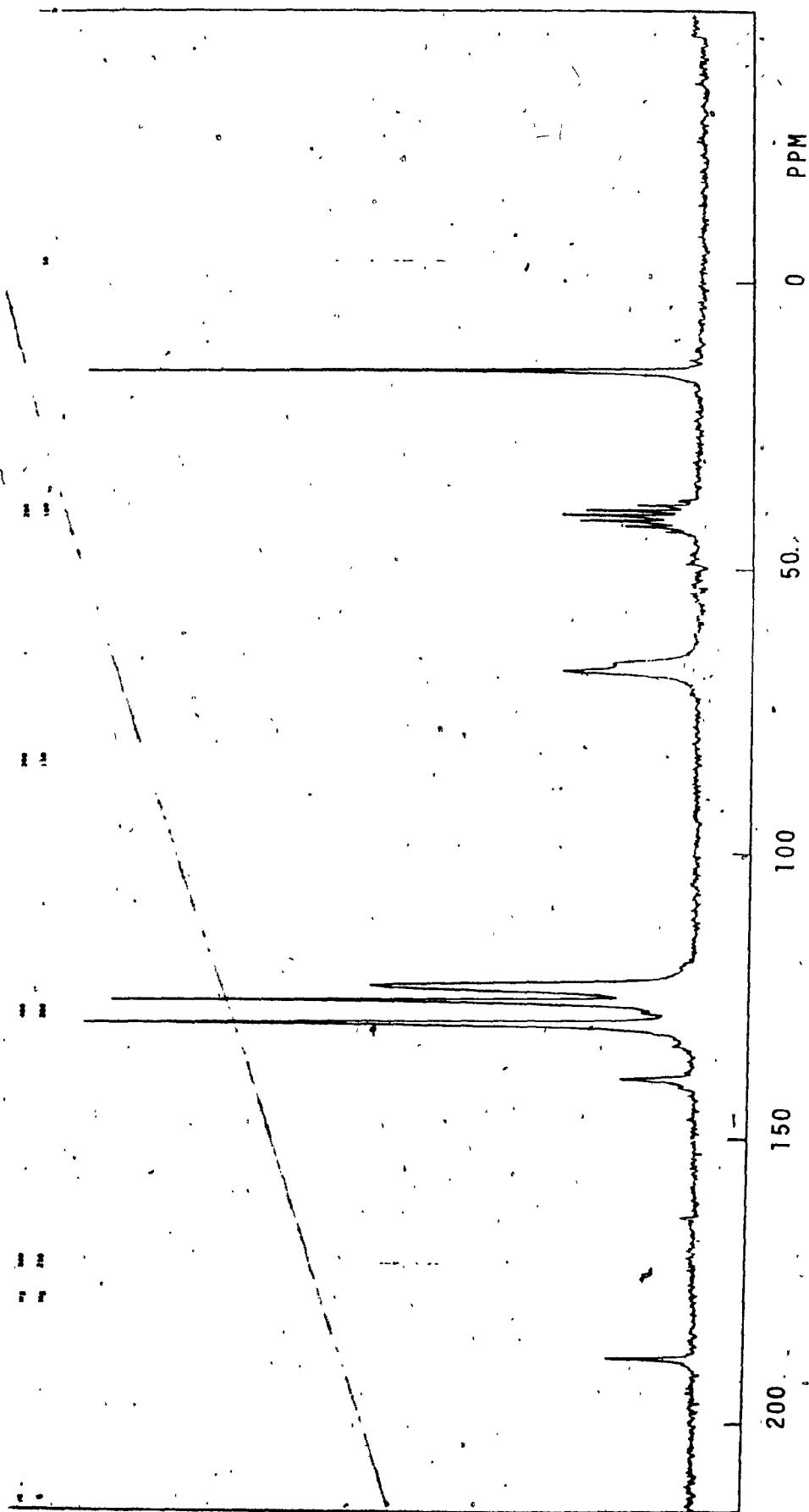


Fig. NC-16 : C-13 NMR Spectrum of N-Phenyl Thiocarbamate, 1.0 M in DMSO-d₆, 9000 Scans at 27°.

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LIST

78/08/11. 10.48.26.

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PROGRAM T1IR      T1IR
10 REM PROGRAM T1IR
100 DIM R(30),X(30),Y(30),Z(30),C(30),H(30)
120 PRINT
130 PRINT "TL BY INVERSION-RECOVERY SEQUENCE, CALCULATED"
140 PRINT "USING LINEAR (SEMI-LOG) REGRESSION"
150 PRINT
160 PRINT "N.B. RESPOND TO QUESTIONS WITH 'Y' OR 'N'"
170 PRINT "N.B. FOR INITIAL SLOPE CALCULATION, DATA PAIRS"
180 PRINT "MUST BE INCREASING IN TIME"
190 PRINT "N.B. MINIMUM ALLOWED NO. OF DATA PAIRS = 3"
200 PRINT
210 PRINT "ENTER EQUILIBRIUM INTENSITY (MO) ";
220 INPUT MO
230 PRINT "ENTER NO. OF DATA PAIRS (1-30) ";
240 INPUT N
250 LET NJ=N
260 PRINT "ENTER 'N' DATA PAIRS (TIME, INTENSITY)"
270 FOR I=1 TO N
280 PRINT "I ";I;
290 INPUT X(I),Z(I)
300 NEXT I
310 FOR I=1 TO N
320 LET H(I)=MO-Z(I)
330 LET Y(I)=LOG(H(I))
340 NEXT I
350 LET M1=0
360 LET M2=0
370 LET M3=0
380 LET S1=0
390 LET S2=0
400 LET S3=0
410 LET S6=0
420 LET S7=0
430 LET S8=0
440 LET S9=0
450 FOR I=1 TO N
460 LET M1=M1+X(I)/N
470 LET M2=M2+Y(I)/N
480 LET M3=M3+H(I)/N
490 NEXT I
500 FOR I=1 TO N
510 LET T1=M1-X(I)
520 LET T2=M2-Y(I)

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530 LET S1=S1+I1*Y1
540 LET S2=S2+I2*Y2
550 LET S3=S3+I1*Y2
560 NEXT I
570 LET R=S3/S1
580 LET A=M2-B*M1
590 FOR I=1 TO N
600 LET C(I)=A+B*X(I)
610 LET R(I)=H(I)-EXP(C(I))
620 LET RT=Y(I)-A-B*X(I)
630 LET S8=S8+R(I)*R(I)
640 LET S9=S9+R(I)*RT
650 LET S4=S4+(M3-H(I))*(M3-H(I))
660 LET X1=X(I)
670 LET S7=S7+(M3-EXP(A+B*X1))*(M3-EXP(A+B*X1))
680 NEXT I
690 LET D=1/(N-2)
700 LET RL=SQR((S9/S1)*CONCORDIA UNIVERSITY)
710 LET A1=SQR((S9*S1+S9*M1*M1*M1)/(N-2)*M1)
720 LET A1=(EXP(A+A1)-EXP(A-A1))/2
730 PRINT
740 PRINT
750 PRINT "SPIN-LATTICE RELAXATION DATA:"
760 PRINT "INVERSION-RECOVERY SEQUENCE"
770 PRINT
780 PRINT "EQUILIBRIUM INTENSITY = "A0
790 PRINT "REGRESSION DATA:"
800 LET P1=INT(10000*A1/EXP(A)+0.5)/100
810 PRINT " INITIAL INT. = "EXP(A);TAB(30);"STD ERR ="A1;
820 PRINT TAB(52);" "ABS(P1);"%
830 PRINT " RATIO OF INITIAL INTENSITIES = "EXP(A)/M0
840 LET P2=INT(10000*B1/B+0.5)/100
850 PRINT " R1 = "ABS(B);TAB(20);"/SEC.";TAB(30);"STD ERR ="B1;
860 PRINT TAB(52);" "ABS(P2);"%
870 PRINT " T1 = "ABS(1/B);TAB(20);"SEC."
880 PRINT " STANDARD DEVIATION = "SQR(S8/(N-2))
890 PRINT
900 PRINT "I";TAB(7);"TIME";TAB(18);"INTENSITY";
910 PRINT TAB(35);"REGRESSION DATA"
920 PRINT TAB(7);"(SEC)";TAB(30);"EXP.";TAB(40);"FIT";TAB(50);"DIFF."
930 FOR J=1 TO N
940 PRINT I;TAB(5);X(I);TAB(10);Y(I);TAB(20);Y(I);
950 PRINT C(I);TAB(10);Y(I)-C(I)

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```

960 NEXT I
970 PRINT
980 PRINT
990 PRINT
1000 PRINT
1010 PRINT "SHORTEN DATA SET FOR INITIAL SLOPE CALCULATION ? ";
1020 INPUT I$
1030 IF I$="Y" THEN 1120
1040 PRINT "ENTER LAST DATA PAIR # FOR INITIAL SLOPE ";
1050 INPUT N
1060 IF N=N1 THEN 1080
1070 LET N=N1
1080 PRINT
1090 PRINT
1100 PRINT "INITIAL SLOPE CALCULATION"
1110 GOTO 350
1120 PRINT "IS THERE A FURTHER DATA SET ? ";
1130 INPUT F$
1140 IF F$="Y" THEN 200
1150 STOP
1160 REM WRITTEN BY ROLAND BORTON AT UBC, VANCOUVER, CANADA
1170 REM CHECKED AGAINST UBC TRIP PROGRAM 8 SEPT '75
1180 REM REVISED FOR NICOLET 1180 BY LAURIE COLEBROOK, JUNE, 1978
1185 REM REVISED FOR CONCORDIA UNIVERSITY COMPUTER, JULY, 1978
1190 END
READY.

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BYE

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