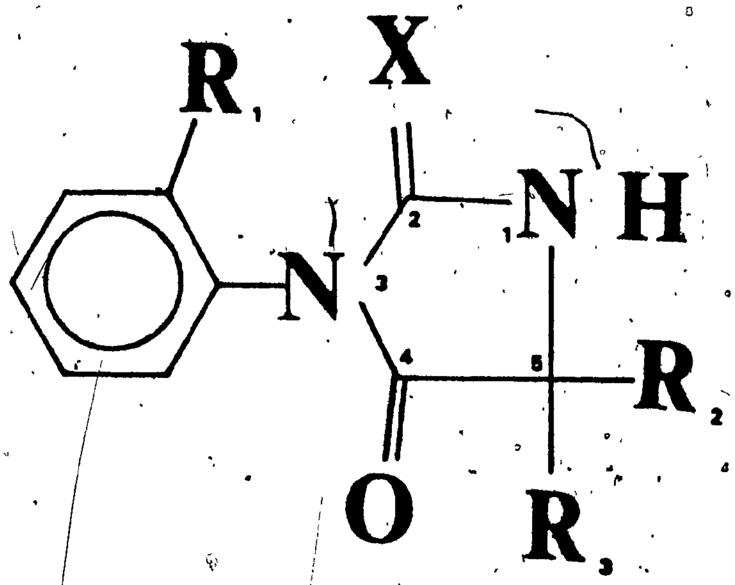
PULSE FAST FOURIER TRANSFORM C-13 NUCLEAR MAGNETIC RESONANCE STUDY OF THIOHYDANTOINS



X = O HYDANTOIN

X = S THIOHYDANTOIN

ABSTRACT

Author : **Mohammad Ashique Khadim.**

Title : Pulse Fast Fourier Transform C-13 Nuclear Magnetic Resonance Study of 2-Thiohydantoins.

The modifications and improvements introduced into the existing Varian HA-100 c.w. NMR instrumentation have been described.

A number of 3-N aryl substituted 2-thiohydantoins were synthesised from suitable aromatic isothiocyanates by condensation with amino acids. The ground state stereochemistry of 2-thiohydantoins has been discussed employing the data obtained by Pulse Fast Fourier Transform C-13 NMR. Definite assignments have been made to signals arising from carbons in the thiohydantoin moiety and those in the aryl substituents.

The upfield γ-methyl substituent effect on C-2 has been found to be 1.04 - 3.94 ppm compared with that in hydantoin, (1.0 - 1.2 ppm). The γ-effect on C-2 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. It is considered that variations in dihedral angle between the aryl and the hetero rings exert steric pressure on the asymmetric solvent shell around the C-2 and C-4 carbons, which in turn affects the variations in the chemical shifts of C-2 and C-4. The direction and magnitude of the solvent-induced variations in the chemical shift

of C-2 and C-4 have been estimated. The chemical shift of C-2 and C-4 in ortho halogen substituted thiohydantoins has been found to show a linear relationship with the electronegativity of the ortho halogen atom. The observation of deshielding, rather than shielding, resulting from the increased steric bulk of the N-3 substituent is rather unexpected and has been discussed in terms of δ-, ε-, solvent and steric bulk effects.

In the α-naphthyl thiohydantoins, as the tendency to release electrons by the C-5 substituents decreases, the C-2 carbons are found to be increasingly shielded whereas the C-4 carbons are increasingly deshielded.

The solvation, resonance and inductive effects have been discussed for the observed chemical shift of the C-5 carbon. The downfield β-effect upon the chemical shift of the C-5 methyl carbons has been found to be 7.8 ± 0.5 and 7.4 ± 0.3 ppm for the low and high field signals, respectively, and this information has been used, perhaps for the first time, to assign a particular peak to a given methyl carbon on C-5.

DEDICATION

TO

*********** My Parents Mr. & Mrs. Khadim

*********** My Beloved Wife Ummaysalma

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

Whose Patience and Encouragement
Has Made This Thesis Possible.

VITAE

The author was born on September 10, 1946 in Ambala, India and emigrated to Pakistan in August 1947 soon after the division of the sub-continent into two independent states. He received his B.Sc. Degree in Chemistry and Physics from Government College, Sargodha, Pakistan, in September 1967, and his M.Sc. Degree in Physical Chemistry, under the supervision of Dr. Mohammad Ali Khan, from the University of the Panjab, Lahore, Pakistan, in September 1969. He then joined the University of Islamabad as Research Fellow and received his M. Phil. Degree in Theoretical Physical Chemistry under the supervision of Dr. S. U. Malik in September 1970. Then he worked as Lecturer in Chemistry in the Cantonment Board College, Wah Cantt; Pakistan. In September 1971, he joined the Education Service of the Government of Sierra Leone, West Africa. In August 1972, the author undertook a graduate programme at Sir George Williams University, Montreal under the supervision of Dr. Lawrence David Colebrook.

ACKNOWLEDGEMENTS

I deem it a great pleasure to express my thanks to my learned guide Dr. Lawrence David Colebrook of the Department of Chemistry, Concordia University, Montreal, under whose able and kind guidance this investigation has been accomplished. I am highly greatful to him for his inspiring and encouraging smile throughout the course of this work.

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INTRODUCTION

INTRODUCTION

Pulsed NMR spectroscopy has been employed as a powerful tool by chemists for almost as long as the more conventional continuous wave (cw) nmr spectroscopy; however, the pulse technique is less familiar to most chemists. This situation is now changing rapidly.

^{13}C-nmr spectroscopy is probably the single most important tool in determining the structure of complex organic and biological molecules, and as such it is almost impossible to overestimate its importance. In an overwhelming number of cases, where little information is available from proton nmr because of overlapping signals, ^{13}C-nmr spectra easily show differentiation between two complex molecules which differ only in the subtle re-arrangement of a few carbon atoms. The reason for this lies partly in the fact that the range of ^{13}C chemical shifts (200 ppm or more) is much greater than for protons (about 20 ppm) and partly because in non-^{13}C-enriched molecules, the probability is small that more than one ^{13}C nucleus is present in any given molecule; hence, the effects of carbon-carbon spin-spin splitting are normally insignificant.

However, cw ^{13}C-nmr spectroscopy has its own limitations. The primary limitation has been a lack of sensitivity, due both to a relatively small magnetogyric ratio, and to the fact that ^{13}C has a natural abundance of only 1.1 %. By employing signal averaging methods and by taking advantage of proton noise-decoupling techniques (see later) with their attendent nuclear Overhauser effect (NOE) enhancement (see later), great advances have been made in increasing the signal to noise ratio (S/N) obtainable from ^{13}C-nmr spectrometers. This has been accomplished by signal averaging for long periods of time and by using large amounts of materials. The sensitivity inherent in ^{13}C-cw-nmr spectroscopy, even using proton noise-decoupling and long term signal averaging, is still inadequate. Fortunately, Fourier Transform techniques, especially when used in multiple pulse experiments, afford one a significant increase (in principle, upto a factor of 100 or more) in sensitivity for a given time.

Basically, pulsed FT-nmr spectroscopy is just a special form of interferometry and, as is usually the case, to interpret the results, it is necessary to go to a conventional form of spectral representation by means of a Fourier Transformation. This can be done either by an analogue Fourier analyzer or by collecting the interferogram digitally and performing the Fourier transformation on a digital computer. The technique consists of the application, to the sample, of a short, intense pulse of radio frequency (r.f.) energy and the measurement, as a function of time, of the resulting free induction decay (F.I.D.) signal from the nuclear spins in the sample.

Fourier transformation (F.T.) of the F.I.D. signals gives the ordinary high resolution spectrum (1, 2)

The advantage of the F T-nmr technique is that the F.I.D. signals are obtained rapidly (each one normally less than a second) so that in a given length of time it is possible to apply the pulse repetitively and add the F.I.D. signals coherently in a digital computer or other time-averaging device. The time, T, required to record a spectrum in the time domain is given by $T \simeq r^{-1}$ sec; where r is the resolution (see later) desired (usually about 1 Hz) ; T is independent of the width, Δ, of the frequency domain spectrum. The result is that the sensitivity is much higher for a given time than when using the cw method. The sensitivity enhancement factor, $\mathcal{E}_s$, is given by $\mathcal{E}_s \simeq (\Delta/r)^{1/2}$ or alternatively, the time enhancement factor, $\mathcal{E}_t$, is given by $\mathcal{E}_t \simeq \Delta/r$, since S/N improves only as the square root of the time, or as the number of scans in a time-averaged experiment. Thus the time required to obtain a spectrum of a given S/N ratio is shorter using the F T-nmr technique by a factor of $\mathcal{E}_t$. In ^{13}C-nmr studies, spectrum width, Δ, is typically 200 ppm and r is about 1 Hz, so that at 25 MHz (the frequency of operation of the nmr spectrometer), the time enhancement factor, $\mathcal{E}_t$, is given by

$$\mathcal{E}_t \simeq (200 \text{ ppm} \times 25 \text{ MHz} / 1 \text{ Hz})$$
$$\simeq 5000. \quad (3)$$

COMPARISON OF CW AND F T ^{13}C-NMR SPECTROSCOPY

The details of F T-nmr spectroscopy are abundantly available in the literature (4,5). It is sufficient, at the moment, to briefly compare the methods of F T-nmr and cw-nmr. They differ primarily in the duration and magnitude of the r.f. field employed in the experiments. In the pulsed F T-nmr experiment, an intense (upto about 200 G) r.f. field is applied to the sample but it is left on only for a very short time (typically, about 10-15 μsec). In the cw-nmr experiment, a rather weak (10^{-3} G or less) r.f. field is used, but is allowed to run continously. Its effect is such that in the cw-nmr experiment one produces an r.f. field, H_1 , at a single discrete frequency which perturbs only slightly that line in the spectrum which resonates at precisely that frequency. This r.f. frequency is then changed slowly at a rate comparable to the resolution desired (in a frequency sweep experiment).

In the pulsed nmr experiment, the sample is perturbed very strongly by a very large H_1 field. This has the effect of irradiating the sample, not with a single discrete frequency as is the case with the cw-nmr, but with a band of frequencies centered at 25 MHz and covering a range of about $1/4\tau$ Hz, where τ is the time duration, in sec, of the pulse used. For a 10 μsec pulse, then, the pulse covers the frequency range 25 MHz ± 20 kHz. The result is that the nuclei associated with the various lines in the spectrum are induced to radiate their characteristic r.f. signals simultaneously and, as is the case whenever one mixes a number of signals simultaneously with different frequencies, an interference pattern is obtained. This is usually referred to as an interferogram or the 'time domain' spectrum.

FOURIER TRANSFORMATION

Since the interferogram is almost impossible to interpret directly in other than very simple cases, some method of transforming the time-domain spectrum into the conventional frequency-domain spectrum is desirable. Such a transformation is accomplished through the application of Fourier analysis.

It is well known that an exponential in the time domain and a Lorentzian in the frequency domain are Fourier transforms of each other. Mathematically, we can write.(4)

$$\frac{T_2}{1 + T_2^2 (w - w_0)^2} = \int_0^\infty e^{-t/T_2} \cdot \cos (w - w_0) t \, dt \qquad \text{------Eq (1.1)}$$

where T_2 is transverse or spin-spin relaxation time

$w_0 = 2\pi y_0$, resonance frequency in radians per sec; and

t is time.

The Lorentzian function on the left hand side of Eq.(1.1) is the expression for the absorption mode that comes from solution of the Bloch equations. The corresponding sine transform of an exponential gives the dispersion mode, rather than the absorption mode.

Since Fourier transformation is carried out in a digital computer, the computation actually involves summing a series over a finite number of data points rather than evaluating the integral of Eq (1.1). This discrete Fourier transform can be defined by

$$A_f = \sum_{t=0}^{N-1} X_t \; e^{-2\pi ift/N} \qquad f = 0, 1, ---, N-1, \qquad \text{-------------Eq (1.2)}$$

where A_f is the coefficient of the fth point in the transform (frequency domain), X_t is the value of the data (i.e. free induction signal) at point t in the time domain, and N is the number of data points.

The transform of Eq (1.2) will be the complex sum of cosine and sine transforms since

$$e^{-iy} = \cos y - i \sin y \qquad \text{-----------Eq (1.3)}$$

Discrete Fourier transforms are computed by an algorithm first elaborated by Cooley and Tukey (6). This technique is often called the Fast Fourier Transform (FFT) because of the great saving in time over previously used methods of evaluating the A_f by direct multiplication and summation. The FFT method involves repetitive pairwise sorting of the data points; hence it works best for a number of data points, N, that is a power of 2. The saving in time arises from the smaller number of multiplications required by the FFT method compared with the direct method of transformation, $2N \log_2 N$ multiplications for N points with the FFT method, N^2 multiplications with the direct method. For 4096 points, these quantities are approximately 10^5 and 1.7×10^7, respectively; thus a time saving in this case of the order of 170 is obtained by FFT, and even greater savings are made with larger N. A further advantage of the FFT comes from its efficient use of computer memory. Because the co-efficients are evaluated by an iterative procedure, intermediate and final values can be written over original data values that are no longer needed. Thus, N (2^n) data points in computer memory can be transformed with only slightly more than N words of memory.

RESOLUTION

In general, the free induction decays with a time constant T_2^*, often determined largely by field inhomogeneity, and corresponding to a line width of $1/\pi T_2^*$. While we cannot improve the resolution below the line width corresponding to the decay time, we can artificially broaden the lines in the transformed spectrum by taking data during each F.I.D. for too short a time. It is known from F T theory that to achieve a resolution of r Hz, the time domain must be sampled for 1/r sec. Since T_2^*, as determined by the magnetic field inhomogeneity and/or the nucleus being observed, provides an upper limit to the resolution that can be achieved, there is little to be gained by extending the acquisition time beyond $3T_2^*$ ($\simeq \pi T_2^*$).

SAMPLING RATE

Since data are acquired in the time domain, the rate of data acquisition, or sampling frequency, is directly related to the frequency range, Δ, which can be observed by the computer. Data are stored in the computer memory as discrete points. Since it takes two points to define a sine wave, we must sample the F.I.D. at a rate at least 2Δ points sec^{-1}, for frequencies as high as Δ.

In practice, sampling rates greater than 2Δ are needed so that noise of frequency higher than 2Δ may not 'fold back' into the spectrum and add to noise already present at lower frequencies, thus reducing S/N. Practically, the required data acquisition rates can be quite appreciable e.g. 11,000 points sec^{-1} for ^{13}C at 25 MHz.

The spectral width, Δ, is determined by

$$\Delta = 10^6/ 2 \times (\text{pulse interval in } \mu\text{sec})$$

In the present study, for all compounds, the pulse interval of 100 μsec was employed so that the spectral width is $10^6/2 \times 100 = 5{,}000$ Hz.

SPIN DECOUPLING

With broad band or noise modulated proton decoupling of ^1H-^{13}C nuclei, all the protons in the molecule are irradiated at a high r.f. power at their resonance frequencies. Each non-equivalent carbon will thus give rise to a single peak. The added advantage of proton noise decoupling is an increase in sensitivity as a result of multiplet collapse and also by the nuclear Overhauser effect. The disadvantage is the suppression of the valuable information for assignments provided by the nature of the multiplets.

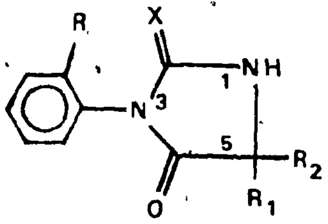
With off-resonance proton decoupling, the decoupling frequency is typically a few hundred Hz removed from the resonance frequencies of the protons in the molecule, and the proton decoupler r.f. power output is lower than for noise proton decoupling. The resulting ^{13}C spectrum consists of perturbed multiplets, corresponding to the multiplets of the non-decoupled ^{13}C spectrum. The nuclear Overhauser effect is still operative and thus some signal enhancement is provided without undue loss of spectral information.

NUCLEAR OVERHAUSER EFFECT

The Overhauser effect is a common term used in ^{13}C studies. It is referred to the enhancement in intensities of ^{13}C signals which occur when protons of neighbouring carbons are decoupled and also when the saturation of protons gives rise to a non-equilibrium polarization of the ^{13}C nuclei, greater than the thermal value. As a result, a 2-3 fold increase of the signal strength is observed. This phenomenon is very similar, in a theoretical sense, to the nuclear-electron Overhauser effect, which was observed by Overhauser in electron-spin resonance studies (7).

STUDY OF HYDANTOINS AND THIOHYDANTOINS

The study of compounds of the 3-aryl hydantoin type, structure A, was initiated by Colebrook and Fehlner (8) in 1970 to investigate, employing the technique of nmr Total Line Shape Analysis, the rates and mechanisms of hindered rotation, at different temperatures, about the aryl C-N bond in cyclic aromatic amides. It was considered that the interpretation should be more straightforward than in the case of acyclic amides in that the system was simplified by the pre-arrangement of the substituents that the aryl ring must pass in its rotation.



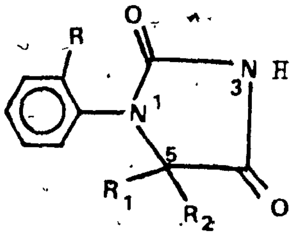
A : Hydantoin X = O

B : Thiohydantoin X = S

Colebrook and Granata (9) (1972) continued the study of 3-aryl hydantoins , employing nmr Total Line Shape Analysis, and obtained kinetic and thermodynamic data for a variety of substituents on the aryl and the hydantoin rings, to interpret the process of hindered rotation about the aryl C-N bond in these compounds.

Later, Colebrook and Giles (10) (1973) examined the barriers to rotation about the aryl C-N bond in some of 3N-(aryl)-5-methyl-2-thiohydantoins, structure B. In cases where the rotational stability was very high, the rotation was followed by equilibration of diastereomers, whereas in the compounds with lower rotational stabilities, the rotational barriers were determined by nmr Total Line Shape Analysis.

Colebrook and Icli (11) (1974) examined the stereochemistry and kinetics of conformational change of a series of 1-aryl substituted hydantoins, structure C, subject to restricted internal rotation about the aryl C-N bond, employing the ^{1}H nmr Total Line Shape Analysis method. Solvent effects on the thermodynamic parameters for restricted rotation were also studied.



(C)

Colebrook and Williams (12) (1972) extended the study of hydantoins by obtaining the ^{13}C continuous wave nmr spectra of a series of 3-aryl hydantoins with a variety of ortho substituents and the spectra were interpreted in terms of the ground state rotamers. They investigated the factors which may affect the chemical shift values for carbons in the hydantoin moiety. Also evidence was obtained in order to confirm the original idea of Granata (9) that in the 3N-aryl hydantoin series, a chlorine ortho substituent was effectively larger than a methyl ortho substituent.

Later, Colebrook and Icli (11) (1974), by employing the conventional cw technique, examined the ^{13}C shieldings of 1N-aryl hydantoins with reference to the stereochemistry of these molecules. The relative influences of steric, inductive and conjugation effects, due to aryl and C-5 methyl substituents, on the chemical shifts of various carbon atoms in these compounds were considered. By comparing the chemical shift values of various carbons in 1N-aryl hydantoins with those in the 3N-aryl hydantoins, they obtained additive shift parameters for 1N-aryl hydantoins.

Although the study of 3N-aryl hydantoins has received considerable attention in our laboratories, thiohydantoins were relatively less examined. It was considered that the study of corresponding 3N-aryl-2-thiohydantoins might reveal interesting and useful information concerning the stereochemistry of these molecules in the ground states for internal rotation. With this view in mind, a number of 3N-aryl substituted thiohydantoins were successfully synthesised. The structures of the molecules were confirmed by their elemental analysis, infra red spectra, proton nmr and Fourier Transformed ^{13}C-nmr spectra. The pulse and Fourier transform ^{13}C-nmr technique was employed, since it offers a significant increase (upto a factor of 100 or more) in sensitivity for a given time, allowing the number of scans as high as 10,000.

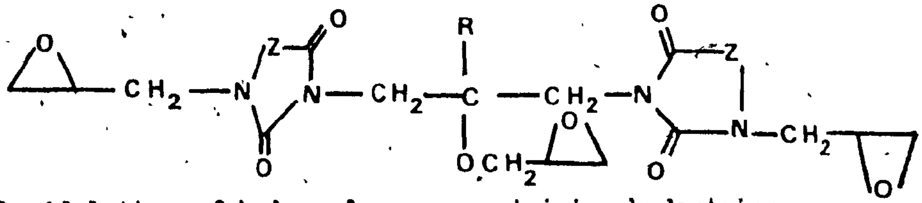
Hydantoins and thiohydantoins now find increasing applications in various fields, yet a survey of chemical literature has shown that a study of hydantoins or thiohydantoins, similar to that in the present work, has not been undertaken upto this date, except in these laboratories. It is hoped that the data concerning the ^{13}C shieldings of various carbons in the thiohydantoins, obtained in the present investigation, may provide information useful for research work to [illegible] carried out on hydantoins or thiohydantoins in the future. Some of the uses of these compounds are listed here to indicate the scope of their application :

a- In pharmacology, they have been used in the treatment of epilepsy and as anti-convulsants. (13,14)

b- Some of the hydantoins, thio- and dithio- hydantoins, substituted at the 5-position with alkyl, dialkyl or spiro cycloalkanes were found to possess a high protective effect against citrus canker disease and herbicidal effects against broad leaf weeds. (15)

c- Heat resistant polymers were obtained containing divalent hydantoin rings in their main chain. (16)

d- Light-stable plastics with surface leakage current resistance were prepared, of the type shown below : (17)



e- Glycidylation of hydroxyl group-containing hydantoins gave diepoxides, which when polymerised with phthalic anhydride or hexahydrophthalic anhydride gave polyesters with good mechanical properties. (18)

f- 1-Glycidyl hydantoin was used as a light and heat stabilizer for PVC and Vinyl acetate-Vinyl chloride co-polymers. (19)

g- Hardenable epoxy resins were prepared by using 5,5-dimethyl hydantoins with formaldehyde and certain polyamines e.g. such hardeners were used for joining concrete blocks in water. (20)

h- Hydantoins were used as one of the ingredients for the photo-sensitive resin compositions e.g. lithographic printing plates obtained with hydantoins gave superior printed copies. (21)

INSTRUMENTATION

THE PULSE AND FOURIER TRANSFORM NMR SPECTROMETER:

The Concordia University Pulse and Fourier Transform Nuclear Magnetic Resonance Spectrometer is a modified Varian HA-100 Unit. Before modification, the instrument was equipped with a Varian continous wave (c.w.) Carbon-13 accessory operating at 25.12 MHz. The V-3512 Heteronuclear Decoupler (100 MHz) and the V-4311 Transmitter-Receiver Units (in somewhat modified form) have been retained in the Pulse Configuration. Only switching and filtering circuity and the radio frequency and audio frequency sources have been retained in the V-3530 Wide Sweep Unit. (Fig. 1-1 & 1-11)

Pulse Generation, Timing and Control Logic.

The Pulsed Spectrometer is built around a Tektronix 2600-series Modular Pulse and Timing Control Unit. This unit consists of a 2601 Main frame and power supply, two 26G3 Pulse Generators, a 26 G1 Rate/Ramp Generator and a 26 G2 Ramp Generator. The two remaining slots are filled with custom built circuits (filtering circuity and blanking amplifier) built on standard plug in kits. Interconnection between units is carried out by means of a standard interconnection board.

MODIFICATIONS

IN

INSTRUMENTATION

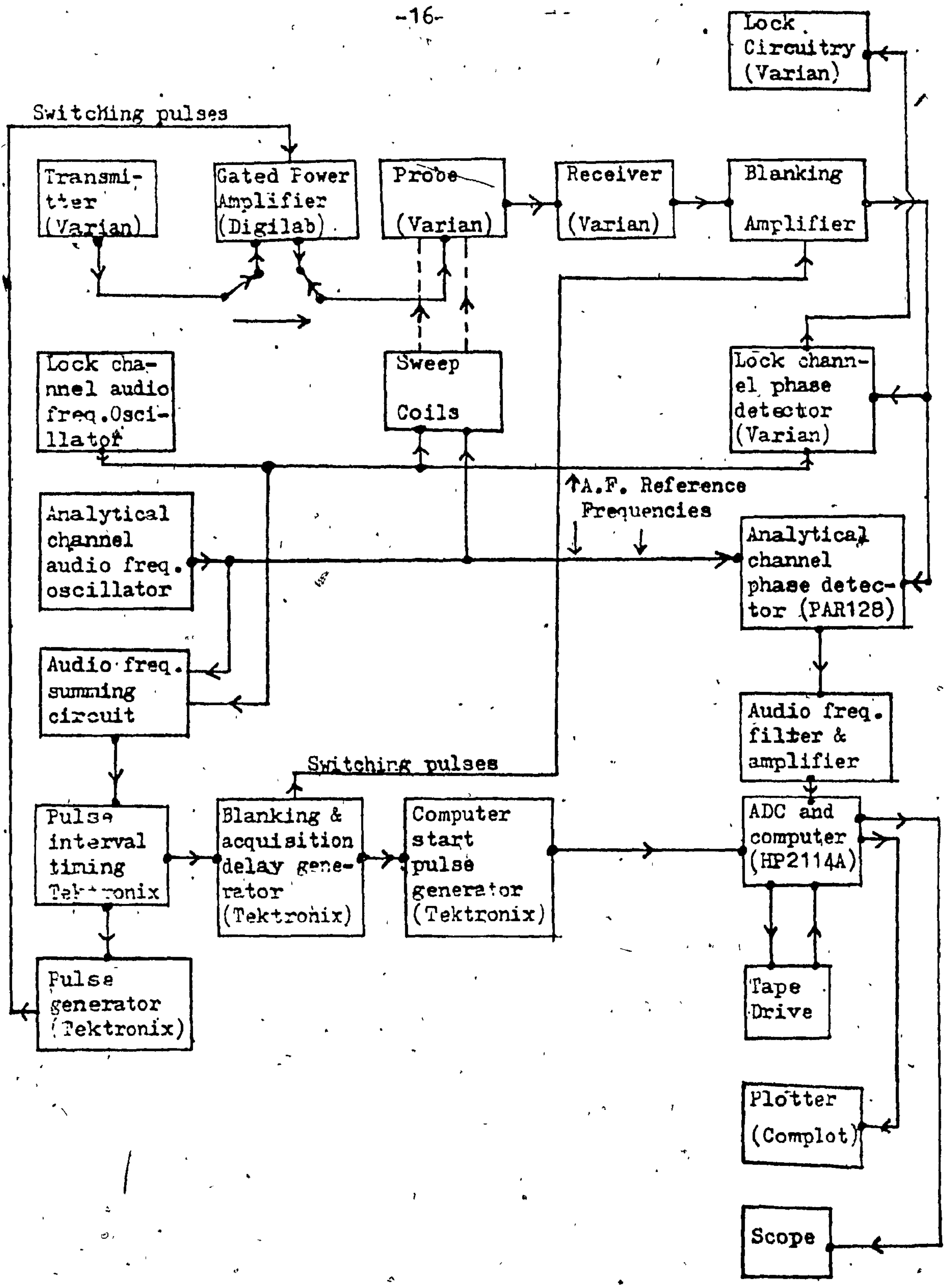


Fig.1-1 : Block Diagram of Fourier Transform NMR Spectrometer (Modified Varian HA-100)

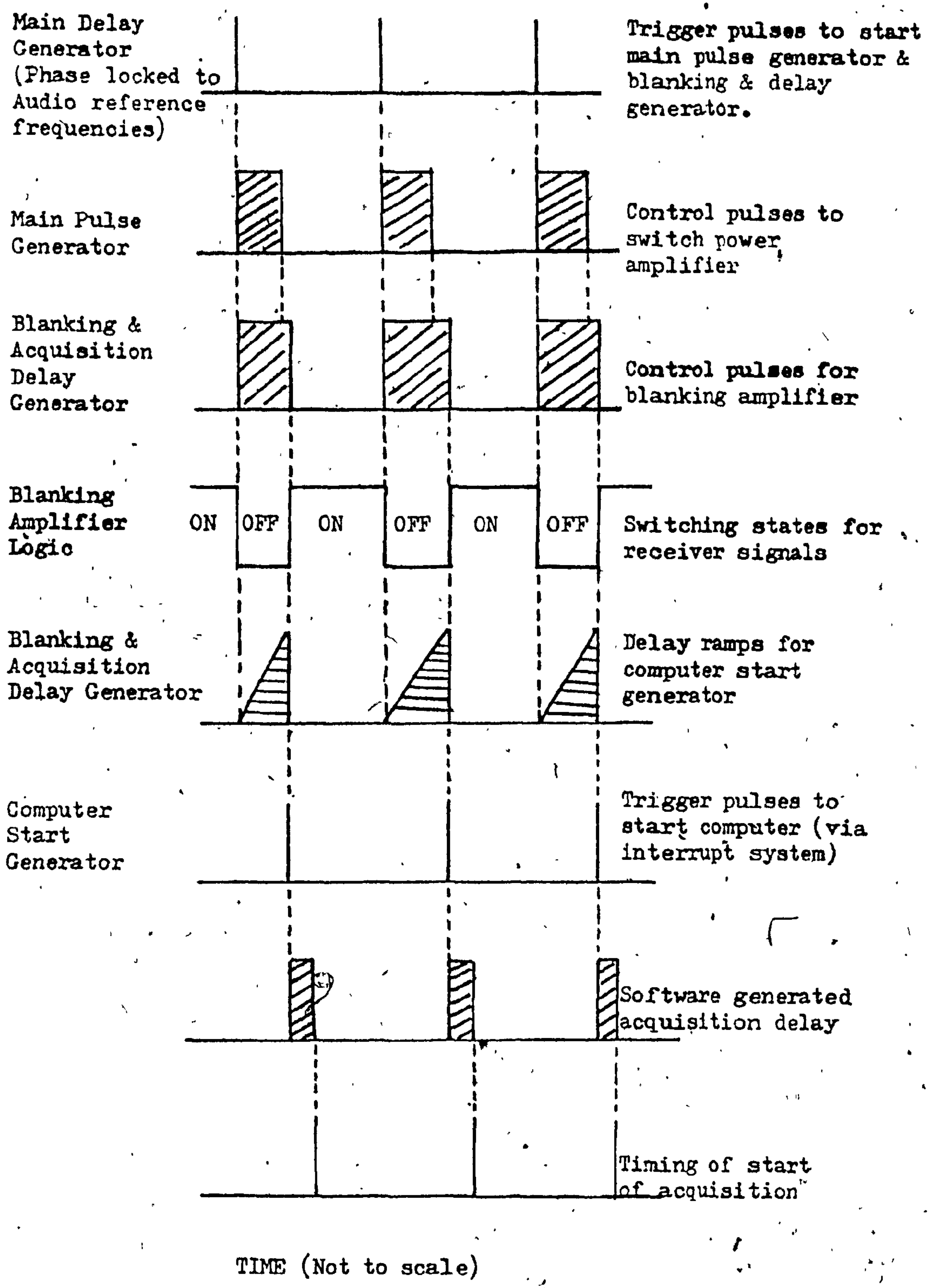


Fig. 1-2 : Timing and Logic Sequences for the Pulse Mode Operation of Varian HA 100 NMR Unit.

Radiofrequency Pulse Control.

The length of the r.f. pulse (≤90° for normal operation) is controlled by a 26 G3 Pulse Generator. The output pulse (+1 volt) from this generator is employed to switch a Digilab 200-2 Pulser (gate power amplifier) which gates and amplifies the r.f. signal from the 25.12 MHz Transmitter and directs the pulse train to the probe. In typical operation, 30-40 μsec. pulses are employed at a repetition period of 0.8-1.0 sec. The 26 G2 unit is triggered by a 26 G1 Rate/Ramp Generator at the start of its delay ramp.

R.F. Pulse Interval Timing.

The delay between pulses is set by means of a 26 G1 Rate/Ramp Generator operating in the triggered mode. The generator is triggered from the signal obtained by summing the two audio oscillator outputs in a summing circuit (see later). By this means the r.f. pulse is triggered at a constant phase angle with respect to both audio frequencies which are the reference frequencies for the two audio frequency phase detectors.

The 26 G1 puts out a triggered pulse at the start of its delay ramp (i.e. immediately it is triggered). This pulse triggers the 26 G3 Pulse Generator (see above) which controls the Digilab 400-2 Pulser (gated power amplifier) and also triggers the 26 G2 Ramp Generator which controls the computer start and blanking timing. When the 26 G1 delay ramp has been completed, the unit returns to the correct configuration for being re-triggered as the two free-running audio oscillators reach the relative phase angles which result in the maximum algebraic sum in the output from the audio frequency summing circuit. The 26 G1 cannot be retriggered until the delay ramp has ended.

The delay between r.f. pulses can be conveniently controlled by means of the Ramp Duration and the Duration Multiplier Controls on the 26 G1. Typically, the delay is set at 0.8 - 1.0 sec.

The Computer Start and Receiver Blanking Timing

It is necessary to delay the start of data acquisition by the computer until after the r.f. pulse has ended, and the receiver electronics have recovered from any overload which may be present. Receiver overload may be minimized by switching the receiver off ('blanking') during and immediately after the r.f. pulse. The necessary delay is provided by a 26 G2 Ramp Generator, operating in the triggered mode. The trigger signal is provided by the 26 G1 Rate/Ramp Generator immediately it is triggered. The delay is normally set at $>100\,\mu$sec; i.e. larger than the normal pulse lengths. The start of the delay is synchronous with the start of the pulse (from the 26 G3) controlling the Digilab Pulser.

The 26 G2 puts out a ramp voltage (0-1 volt), used to trigger the second 26 G2 Pulse Generator (used to start the computer), and a +3 volt ramp gate signal, of the same duration as the ramp signal, used to switch the blanking amplifiers.

Computer Start Pulse.

The computer start pulse (40 μsec duration) is put out by the second 26 G3 Pulse Generator, operating in the preset 1-volt level triggered mode. This unit is triggered when the ramp level from the 26 G2

Ramp Generator rises to 1 volt. The output pulse is directed to the interrupt input on the D/A Converter ca[illegible] in the HP 2114 A Computer. At the time this pulse arrives, the computer is in a loop awaiting an interrupt from the D/A cord. Immediately the interrupt occurs, the computer may start acquiring data. A further delay in the start of the data acquisition can be provided by computer software.

Blanking Amplifier

The blanking amplifier is a custom built unit mounted on a standard plug in unit for Tektronix 2600. In addition to providing gain, it switches off the audio frequency output from the V-4311 r.f. Receiver during, and immediately following, the r.f. pulse. The output from the blanking amplifier is directed to the two audio frequency phase detectors (in the lock and analytical channels).

Switching is carried out by a DG 139 BL integrated circuit. Switching transients cause problems since they are summed coherently by the computer. Two approaches have been taken to minimize the amplitude of these transients. First, the switch is preceded by a μA741 operational amplifier, in order that the switch sees a large signal with peak to peak amplitude near its 20 volt limit. The signal following the switch is then attenuated by means of a voltage devider. By this means, the transient/signal ratio is significantly attenuated. Second, an unused switch position in the DG 139 BL is connected to the inverting input of a second μA741, operating as a unity gain differential amplifier, and following the DG 139 BL. Thus the remaining switching transients are largely cancelled out.

R.F. TRANSMITTER

The Varian r.f. transmitter (25.12 MHz) has been changed slightly from its original configuration. The Attenuator/Maximum switch, which is normally locked in the Attenuation position has been replaced by a switch to facilitate the change between pulse and the c.w. modes of operation. This switch directs the transmitter output either directly to the probe (c.w. mode) or to the Digilab Pulser (pulse mode). The transmitter is normally operated with 10 DB of attenuation.

R.F. RECEIVER

The receiver section of the Varian V-4311 has been modified so that the r.f. pulse detector may be bypassed and replaced by a broad band phase detector. The i.f. (intermediate frequency) signal is taken from the end of the i.f. strip to J302. A Relcom M1C Double Balanced Mixer is employed as a phase detector, the signal being taken from J302, and the 5 MHz reference voltage from J 103 of the V-4311 unit. The detected output from the M1C (audiofrequency signal) is fed to the blanking amplifier (see earlier).

Digilab 200-2 Pulser

This unit operates as a high power gated amplifier, switching to low level r.f. signal (25.12 MHz) from the V-4311 transmitter, and amplifying the resultant r.f. pulses before they enter the probe.

The original Digilab r.f. switch has been replaced by a more efficient Relcom S7 switch and its custom built driver. The switch is controlled by pulses from the Tektronix 26 G3 Pulse Generator (see earlier).

The Pulser operates at a constant power level (set by the attenuator buttons on the V-4311 transmitter). The tip angle of the nuclei during the pulse is controlled by adjusting the pulse duration (26 G2 unit).

Phase Detectors

Two audiofrequency phase detectors are employed, one for each channel (i.e. lock channel and analytical channel).

Lock Channel

The original phase detector in the Varian V-4353 'lock box' is employed for the control (lock) channel. Broad band characteristics are not required for this phase detector. The reference signal is taken from the Wavetek 111 audio oscillator in the V-3530 wide sweep unit. The phase detector input is taken (via the standard Varian high pass filter) from the output of the blanking amplifier (see earlier).

Analytical Channel

A Princeton Applied Research (PAR) 128 phase detector, modified for broad band (>5 KHz) characteristics, is employed as the analytical channel phase detector. It is referenced to an HP 4204 A analytical channel audio oscillator. The input is taken from the output of the blanking amplifier, and the output is fed to the audio frequency filter circuitry (see later). The phase detector section of the PAR 128 is preceded by a high pass filter (to remove spinning noise) whose characteristics have been modified to have a cut off frequency of 5000 Hz. The filter circuitry of PAR 128, which follows the phase detector section, has been disabled; and the amplifier section has been modified to extend its band width. The unit has its own gain and phase selection controls.

Audio-Frequency Filter

The audio frequency signal (analytical channel) from the PAR 128 phase detector is passed through a low pass filter setwork, consisting of a Frequency Devices 730 BT - 4 four-pole Butterworth active filter and its associated tuning resistors. A 1709 Operational Amplifier, followed by a variable voltage devider, is also employed to adjust the signal level to that required by the A/D Converter of the computer. In typical operation, the signal level (mainly noise) to the A/D converter is set at 1-2 volts peak to peak.

In normal operation, the filter cut off frequency is set to correspond to the Nyquist frequency for data acquisition.

Audio-Frequency Summing Circuit

In order that the lock channel and the analytical channel signals will be detected in constant phase following the r.f. pulses, the pulse must be timed so that it is generated when each audio reference frequency has reached a particular phase angle. This situation is achieved by summing the two audio reference frequencies and triggering the r.f. pulse when the summed a.f. signal is fed via a variable voltage divider to the trigger imput of the 26 Gl Rate/Ramp Generator which control pulse interval timing. The input voltage to the 26 Gl is adjusted so that it is just sufficient to cause triggering, thus ensuring that the r.f. pulse is generated when the algebraic sum of the audio reference signals is at maximum.

Audio-Frequency Oscillators

Two a.f. oscillators are employed, one for each channel. In pulse operation, the oscillators supply reference voltages to the two phase detectors and their summed output is employed to synchronize pulse timing with the reference frequencies. During instrument set up (c.w. mode), the lock channel oscillator modulates the magnetic field via the A.C. sweep coils in order to provide the a.f. side band required for observation of the signal. Field modulation is not required during pulse operation. The frequency of this oscillator (lock channel) is adjusted to centre the detector reference frequency on the signal being employed as a lock. The frequency of the analytical channel oscillator is adjusted to locate the analytical phase detector reference frequency to one side of the group of frequencies in the spectrum.

BLOCK AVERAGING

Block Averaging may be used to overcome problems associated with the filling of the computer memory by the relatively strong signals from solvent lines.

The computer will accumulate 'blocks' of data, writing each block on magnetic tape, when the preset number of scans have been averaged. When the preset number of blocks have been acquired, the computer will average the blocks, working in floating point mode to eliminate the problem of word overflows.

Each block is written on magnetic tape as three 1366 word records, followed by an end-of-file. When all blocks have been collected and written on tape, the computer back spaces the tape to the start point, reads the 1366 fixed points words of the first record of the first block, converts them to floating point and stores them in the remaining 2732 locations of available memory. It then spaces the tape to the first record of the second block, reads the record, floats the 1366 words and adds them to the numbers stored in the second area (2732 locations) of memory. The same procedure is followed for the remaining blocks. When the first records of all the blocks have been processed, the computer devides the floating point numbers by the number of blocks, converts the numbers to fixed point, and writes them on tape as a 1366 word record. It then back spaces the tape to the start of the second record of the first block, and processes the second record of each block in the same manner as before. The third and final record of each block is processed in the same way. The three averaged records are then read and the tape is back spaced to the start position. The permanent file may be written on the magnetic tape in the usual way, if necessary. The revelant commands are :

/NSxx Number of scans per block

/NBxx Number of blocks

If NB 1 is used (i.e. only one block) the computer does not write the block on the tape. Thus it is not necessary to have a data tape mounted or correctly positioned if NB = 1. The preset value of NB is 1.

Important :

The computer writes intermediate data (i.e. the blocks) on a long scratch area of tape beyond the start point. Care should be taken to position the tape one file beyond the last file to be preserved. The positioning is automatic once the process is started. The tape stops at the same position it started -- normally the correct position for writing the permanent file.

Attempt should not be made to block average with the tape positioned at the load point i.e. the beginning of the tape. The computer will halt when it backspaces the tape because the load point marker rather than an end-of-file is found. The situation can be recovered by pressing the start switch at once but this is inconvenient. If necessary, a dummy first file may be written and set the tape to file 2 (with an LF 2 command). The permanent file can be written as file 1 following a rewind (RW) command.

Data acquisition may be aborted as usual during accumulation (not during tape read, write or move operations) by setting switch 15. If the run is lost, it can be recovered by the command /<u>RC</u>.

THE COMPUTER PROGRAM, FTNMR

The computer program, FTNMR, written by Colebrook (41) is designed specifically for use in high resolution pulsed Fourier transform nmr spectroscopy. Its basic functions include, but are not limited to, the following data acquisition and data processing operations :

a- Acquisition of spectral data from the spectrometer through an analog-to-digital converter.

b- Improvement of spectral S/N by means of on-line ensemble averaging of repetitive time-series responses.

c- Off-line manipulation of the averaged data e.g. base line correction and exponential filtering.

d- Fast Fourier transformation (FFT) of averaged time-domain information to obtain frequency spectra.

e- Manipulation of real (absorption) and imaginary (dispersion) portions of the transformed spectra to yield phase- and amplitude-corrected absorption spectra.

f- Display of either the time-domain FID data or transformed spectra on the oscilloscope.

g- Multiplication and division of the acquired data points either in the time- or frequency domain.

h- Readout of the time domain FID and transformed spectra to an external X-Y plotter or computer compatible magnetic tape and to teletype paper.

FTNMR Loading Procedures :

FTNMR may be loaded into computer memory as an absolute program from (a) paper tape or (b) magnetic tape, using an FTNMR data tape with the program stored as File 1.

A- Paper Tape Procedure :

The program is loaded using the Basic Binary Loader (BBL).

1-The computer and the peripherals are switched on.

2-If required later, an FTNMR data tape may be mounted and positioned at the load point (AUTO mode)

3-The FTNMR absolute paper tape is placed in the reader.

4-With the computer in the HALT mode, PRESET and LOAD switches are pressed simultaneously.

5-When loading is complete, 2_8 in the switch register is set and RUN is pressed.

B- Magnetic Tape Procedure :

The program is loaded using the Magnetic Tape System (MTS).

1- The computer and the peripherals are switched on.

2- FTNMR data tape (With FTNMR as File 1) is mounted and positioned at the load point (AUTO mode).

3- With the computer in HALT mode, load 15606_8 is addressed and the switch register is cleared.

4- On pressing RUN, the computer should type *NEXT? If so, steps No. 5, 6 and 7 should be ignored.

5- If the computer should fail to respond, load 77_8 is addressed and the switch register (HALT mode) is cleared.

6- On pressing RUN, the computer should type *NEXT? If so, No. 7

should be overlooked.

7- If the computer fails to respond, MTS Bootstrap (paper tape) is loaded using the BBL. When the Bootstrap is loaded, the switch register is cleared, load 100_8 is addressed, the register is cleared again and RUN is pressed.

8- When the computer has typed *NEXT? , :PROG,FTNMR should be typed.

9- The program will load from the tape and automatically start running. The tape will rewind to the load point.

10- The tape should be positioned at the required file before proceeding. It should be noted that File 2 is of zero length. It is recommended that File 3 be written as a dummy (empty) file since it may be lost if an updated version of FTNMR is written at a later date. The first working file should, therefore, be File 4.

11- Before switching off the computer, /ST should be typed or HALT pressed. Load 77_8 is addressed and RUN is pressed. The tape will rewind and the computer will type *NEXT? In response, :PAUSE should be typed. This action returns control to the MTS monitor and leaves the computer in the correct configuration for re-starting from address 15606_8 .

12- The peripherals and the computer should be switched off.

General Procedures :

Load Address Procedure

1- The computer should be in HALT mode.

2- CLEAR REGISTER is pressed.

3- The address (octal) is set in the switch register.

4- LOAD ADDRESS is pressed.

5- CLEAR REGISTER is pressed.

Re-Starting When FTNMR is Already Loaded

If FTNMR is already in memory, the computer can be re-started without re-loading the program. The parameter values will be those used for the last run, not necessarily the standard set.

1- Switch register (HALT) mode is cleared.

2- Load 2001_8 is addressed.

3- RUN is pressed.

Basic Binary Loader (BBL) Procedure

BBL is used to load absolute programs (including the MTS Bootstrap) from paper tape.

1- Computer should be in HALT mode.

2- Paper tape is placed in reader.

3- PRESET and LOAD are pressed simultaneously. The paper tape will be read.

4- When the program has been loaded, a start address must be either loaded, or set in the switch register, before RUN is pressed.

PREPARATION OF AN FTNMR MAGNETIC TAPE :

FTNMR may be written on magnetic tape for loading using the Magnetic Tape System.

It is written as File 1 of an MTS tape. File 2, which normally consists of relocatable subroutines on an MTS tape, is empty.

Procedure

The tape is prepared using the paper tape system (PTS). Detailed instructions are given in the PTS manual.

1- The computer and the peripherals are switched on.

2- FTNMR data tape is mounted and set at the load point (AUTO mode).

3- If the HA-100 NMR Spectrometer is in operation (in particular, if the pulse control unit is switched on), the co-axial cable which connects at the junction box on the computer table, is disconnected.

4- The CONFIGURED PTS tape is loaded using the BBL.

5- Load 100_8 is addressed, the switch register is cleared to set 15_8 in the switch register and RUN is pressed.

6- In response to: PROGRAM INPUT DEVICE S.C. = ? , 14 should be typed.

7- In response to: I.D. NAME: .IPL. should be typed.
In response to: S.A. , 77 is typed.
In response to: *LOAD , .IPL. paper tape is placed in the reader and RUN is pressed.

8- In response to: I.D. NAME: , S.SIO is typed.

In response to: S.A. , 77 is typed.

In response to: *LOAD , the S.SIO paper tape is placed in the reader and RUN is pressed.

9- In response to: I.D. NAME: , FTNMR is typed.

In response to: S.A. , 2 is typed.

In response to: *LOAD , place the FTNMR paper tape in the reader and RUN is pressed. FTNMR will be read and written on magnetic tape.

10- In response to: I.D.NAME: , /E is typed.

The computer will write an end-of-file (EOF) and will be prepared to load and relocate library, which is not required.

11- In response to: *LOAD , switch 15 is set and RUN is pressed. An EOF will be written and the tape will rewind.

12- AUTO switch is set on the tape drive, and the MTS Bootstrap is loaded using the BBL (start address 100_8)

13- If FTNMR is to be loaded at this point, :PROG,FTNMR is typed in response to *NEXT? If FTNMR is not to be loaded, :PAUSE is typed, and the peripherals and the computer are switched off.

14- The co-axial cable is re-connected to the junction box.

COMMAND FORMAT :

All commands are three characters in length. The first of the three characters is required for certain interrupt operations, and is not decoded by the computer. It may be a slash (/), a period (.) or other character chosen by the operator. The second and third characters are decoded by the computer and constitute an operation command. Commands which enter operating parameters are followed immediately by up to four numerals (the first of which may be replaced by a minus sign (-) for the TC command only).

If an invalid command is entered, the computer will respond with a double question mark (??). The correct command should then be entered. This response is also given at start up, i.e. before the computer has received a valid command. If a typing error has been made, the command may be aborted without execution by typing an invalid character. The correct command can then be entered following the (??) response.

When the computer has received a valid command and has completed its response to the command, it will type (??) without a carriage return and line feed. The next command may then be typed (on the same line). The (??) is thus an acknowledgement by the computer of a completed action and a signal that a new command may be entered. It should be noted that a command can only be entered following the double question mark (??).

Oscilloscope display is automatically interrupted by the first (interrupt) character of a command. The computer outputs the double (??) indicating that it is ready for the next command, immediately before it enters the 'scope display subroutine.

Data acquisition may be interrupted, between scans, by typing any single character. This does not constitute a command. The computer will respond with a double (??), at which point next command may be entered. A teletype interrupt will not be accepted by the computer while it is waiting for a trigger pulse, so it may prove convenient to switch off the computer start trigger pulse (from the Tektronix pulse control unit) before interrupting data acquisition via the key board. Data acquisition may also be interrupted by setting switch 15 of the computer switch register.

OSCILLOSCOPE DISPLAY MODES :

Three modes of 'scope display are available :

DF (Display FID) Initiates display of the entire data array.

DR (Display Real) Initiates display of the real portion of the complex array generated by Fourier transformation. The contents of the odd numbered locations are displayed, starting with the first location.

DI (Display Imaginary) Initiates display of the imaginary portion of the complex array generated by Fourier transformation. The contents of the even numbered locations are displayed, starting with the second location.

The DF command is suitable only for the display of FID. If Fourier transformation has been carried out, the DF command will generate an uninterpretable display. The DF command should be used if a FID is to be examined closely. Use of the other two commands to display a FID is not recommended since half of the points will be missing and the display could be misinterpreted.

The display mode called automatically by the program following certain commands will normally be appropriate. Occasionally, however, an inappropriate display mode will be called, e.g. if a transformed spectrum rather than a FID is written on tape.

PLOTTING MODES :

The above remarks also apply to plotting modes.

PF (Plot FID) corresponds to DF. It should be used only to plot FID.

PR (Plot Real) Corresponds to DR.

PI (Plot Imaginary) Corresponds to DI.

FTNMR OPERATING PARAMETERS :

(N.B. Underlined commands initiate an action. Other commands, which must be followed by a number, change the stored values of parameters. Three commands, GO, RF, and FT cause the value of the display multiplier (accessed by the DMxx command) to be restored to 1).

An oscill oscope display is automatically initiated on completion of certain types of processing.

Initialization :

		Pre-set Value	Limits
/EXxx	Exponent , No. of points = 2**EX)	12 i.e.4096 points	0<EX<12
/ ZE	Zero array, Control is transferred to DF.		

Acquisition :

/NBxx	No. of blocks	1	None
/NSxx	No. of scans (per block)	100	None
/CPxx	Clock period (0 = 100 usec, 1 = 1 msec)	0	≥ 0
/ CMxx	Clock period multiplier	1	≥ 1
/PDxx	Post-pulse delay	1	≥ 1
/ GO	Go-start acquisition Control is transferred to DF		
/ RC	Recover (Control is transferred to DF		

Display

/ DMxx	Display multiplier	1	> 1
/ DF	Display FID		
/ DR	Display real array		
/ DI	Display imaginary array		

File Control

/ LFxx	Locate file xx		> 1
/ FB	File back		
/ RW	Rewind tape		
/ FF	File forward		
/ WR	Write file (control is transferred to DF		
/ ID	Identify file		
/ RF	Read file (control is transferred to DF)		

Array Manipulations

/ ADxx	Array divider (for Fourier transform)	4 (i.e. 2**4)	> 1
/ DA	Divide array by 2 (control is transferred to DF)		
/ MA	Multiply array by 2 (control is transferred to DR)		
/ BC	Baseline correction (control is transferred to DF)		

Digital Filters

/ TCxx	Time constant (for exponential multiplications)	1	None
/ TLxx	Trapezoidal filter limit	1	< 2**EX
/ EF	Exponential filter (control is transferred to DF)		
/ TR	Trapezoidal filter (control is transferred to DR)		

Fourier Transform

/ FT	Fourier Transform (control is transferred to DR)		

Phase Correction

/ PAxx	Zero order phase angles (degrees)	0	None
/ PBxx	First order phase correction	0	None
/ PC	Phase correction (control is transferred to DR)		

Plotting

/ PHxx	Plot height	4	≥ 1
/ PSxx	Plot scale (Length of plot)	1	≥ 1
/ PPxx	Points to be plotted	2048	≤ 2048
/ SIxx	Sampling interval (for tick marks)	100	
/ PF	Plot FID (control is transferred to DF)		
/ PR	Plot real array (control is transferred to DR)		
/ PI	Plot imaginary array (control is transferred to DI)		
/ SC	Scale (control is transferred to DR) (draw scale on plot)		

Stop

/ ST	Stop (Computer may be re-started by pressing RUN switch)

DATA RECOVERY :

To recover block averaging data from magnetic tape following a power interrupt, etc., use the following procedure:

1- Set the number of blocks to be recovered, using the command /NBxx

2- Position the tape at the original start point .

3- Initiate recovery, using the command / RC

Processing will then proceed in the usual way.

FTNMR SPECTRAL PARAMETERS ABBREVIATIONS :

NS	Number of scans
SI	Sampling interval (u sec)
AF	Analytical frequency (Hz)
LF	Lock frequency (Hz)
PW	Pulse Width (usec, duration of pulse)
PI	Pulse interval (sec) (time difference between two pulses)
NP	Number of points
AD	Acquisition delay (after pulse, before the computer srarts acquisition)
PA	Zero order phase correction (degrees)
PB	First order phase correction (degrees)

DESCRIPTION OF COMMAND PARAMETERS :

Selection of Data Acquisition Rate

In the Pulsed Fourier Transform NMR experiments, the rate of data acquisition determines the frequency range or spectral width acquired by the data system. This is done by selection of appropriate values for the commands CPxx and CMxx. The spectral width is determined by

$$\text{Spectral Width} = 10^6 / 2(\text{CPxx X CMxx})$$

The CPxx command sets the pulse interval of the computer time base generator. If CP = 0, the pulsed interval is 100 µsec; if CP = 1, the interval is 1000 µsec; etc. The CM command instructs the computer to skip pulses. If CM = 1, the computer responds to every pulse; if CM = 2, it responds to every second pulse; etc. Thus all multiples of 100 µsec may be selected by using these commands.

In the present study, for all compounds, CP = 0, i.e. 100 µsec; and CM = 1 so that

$$\text{Spectral Width} = 10^6 / 2 \times 100 = 5{,}000 \text{ Hz.}$$

Beginning Data Acquisition

Signal averaging is initiated by using 'GO' command. During data acquisition, the contents of the computer memory (the averaged free induction decay) are displayed on the oscilloscope as the newly averaged data are stored. Thus the FID may be examined as data acquisition is proceeding. During the time the computer is writing the 'block' on tape, the signal is not displayed. When the pre-set value of number of scans has been acquired, ending one block, the teletype writes FINIS, the block is recorded on the magnetic tape and the acquisition of the next block is started, (see earlier, Block Averaging). At the end of the acquisition the teletype writes ??, indicating that data acquisition has been completed. The data may then be transferred to the tape for permanent storage.

Signal Conditioning

Before beginning a long run of signal averaging, it is desirable to condition the input signal as much as possible. Before locking the spetrometer, the best level of homogeneity of the instrument is achieved. After the spectrometer is locked on the solvent or on $^{13}CH_3I$, the spinning rate, homogeneity controls, receiver gain, filter band width, decoupling frequency, pulse width and delay time following the pulse are re-adjusted to achieve the best locking conditions.

The signal should be centered on the 'scope indicating no DC bias to the signal. If DC bias is present, it will fill the memory word up quite rapidly, allowing only short term averaging. The pulse width and the delay after the pulse are carefully adjusted, normally pulse width : delay time are 1:20 to prevent any pulse-feed-through into the free induction signal. Pulse-feed-through can easily be detected by viewing the input signal and looking for spurious points at the beginning of the FID. The delay time on the 26 G2 Ramp Generator is adjusted until the spurious points disappear. In some cases, the spurious points appeared to persist. These were cut off by using the trapezoidal filter /TLxx and /TR before the Fourier Transform of the FID.

FOURIER TRANSFORMATION AND WINDOW FUNCTIONS :

A- Baseline Correction --- /BC

The signal averaged FID may contain a small residue DC bias that prevents the average value of the data points from being zero. If this is the case, a huge spike is produced near zero frequency which has no physical meaning. Hence in all cases studied a base line correction was performed before transformation and the command /EF, (exponential filter, see later). The command /BC takes a sum of all displayed data points, divided by the number of points and subtracts this average value from all points, so that the average value is zero. This command is called automatically if the /TR command is used. /BC is required in these cases because the window function must operate on the data only and not on any constant DC offset.

B- Exponential Filter, /EF

It is not always desirable to transform the FID without the application of certain smoothing functions. It is possible to improve signal to noise ratio (S/N) of a frequency domain spectrum by manipulations in the time domain. Smoothing can be accomplished in the frequency domain, but generally introduces more distortions.

Multiplication of the FID by an exponentially decaying function can increase apparent S/N markedly, but results in some additional line broadening. The command /EF multiplies the data by an exponential having a time constant entered by the command /TC. During this multiplication, each data point is multiplied by $e^{-iTC/N}$ where N is the number of data points and i is the index of the current point, i varying from zero to N-1. Thus the first point is multiplied by e^0 or 1.0 and the last data point by e^{-TC}. Base line correction, /BC, should be carried out before the /EF command.

It seems intuitively reasonable that multiplying by a decaying exponential would improve S/N, since most of this noise contribution appears in the tail of the FID where the signal has more or less died out. If this tail is forced toward zero, the amount of noise in the transformed spectrum will be less, but the lines will have broadened slightly.

The mathematical justification for this particular window function is simply that the Fourier Transform of an exponential decay is a line having a Lorentzian shape. This is not surprising since the FID is governed by the T_2^*, which is, indeed, exponential in nature, and which is the cause of the observed Lorentzian line shape in conventional c.w. NMR spectra.

C- Time Constant, /TC

The Time Constant, TC is entered by typing /TC and entering it just before /EF. It should be noted that /TC is usually entered as a positive number. Entering a negative number will allow multiplication by a negative exponential. This will increase noise level but will produce narrower lines or enhance the resolution.

D- Fourier Transformation, /FT

The command /FT initiates a Fast Fourier Transform of the acquired time domain data and replaces it with the frequency domain spectrum consisting of N/2 real points and N/2 imaginary points corresponding to the Cosine and Sine transforms of the data. It is done by multiplying each data point by all possible Sine waves upto the Nyquist frequency. This clearly requires N^2 multiplications, where N is the number of data points. However, as already described (see Introduction) the method elaborated by Cooley & Tukey (6) makes use of $2N \log_2 N$ multiplications and hence a great saving in time is achieved.

E- Trapezoidal Window, /TLxx and /TR

It is often found that a small amount of pulse-feed-through may exist even after introducing what is apparently a sufficient delay. This feed-through may manifest itself by a rippling base line having a frequency of 2-3 Hz in the transformed spectrum. This problem is cured easily by using the Trapezoidal window functions, /TLxx and /TR.

The transformed spectrum may sometimes have a small spike at the left end, at zero Hz, caused by a small residual D.C. bias, not removed by /BC. This spike may be removed by using the /TLxx and /TR command.

F-Phase Correction, /PAxx, /PPxx and /PC

Before Fourier Transformation, the digitized FID is stored in the computer as a real array of length 2^k where $k \leq 12$ i.e. the array has a maximum length of 4096 points.

The Fourier transform of a FID produces two stectra, each containing 2^{k-1} points. These are called the real and the imaginary parts, or the Cosine and the Sine transforms. Under ideal conditions, these two spectra should correspond to the absorption and the dispersion mode spectra, respectively. However, a number of physical phenomena may cause the absorption and dispersion mode phase information to be 'mixed' between the two spectra. There are three major causes of mixed phase information:

1- Spectometer phase detector setting,
2- Delay between pulses and start of data acquisition, and
3- Filter settings.

The specrometer phase detector setting is usually optimized at the beginning of acquisition of data, using the sharp peak of the solvent, DMSO. The smallest changes will affect this parameter: variation in sample tubes, solvents or even spinning rate may affect the phase of the information entering the detector. This effect is a ZERO ORDER one which causes the same shift in phase for each data point, regardless of frequency.

The remaining two factors, delay time and filters, have first order effects on the spectrum. That is, at frequency zero, the phase shift is zero, and at highest frequency in the spectrum, the phase shift is maximum. It is customary to refer to this phase shift in terms of the phase angle shift of the highest frequency e.g. a 170° first order phase shift is one in which the first frequency domain point has zero phase shift and the last one 170° of phase shift.

When a phase correction is carried out, the real and the imaginary points of the complex array are replaced as follows.

$$R_{Ni} = R_{oi} \, \mathrm{Cos}\, \theta_i \; - \; I_{oi} \, \mathrm{Sin}\, \theta_i$$

$$I_{Ni} = R_{oi} \, \mathrm{Sin}\, \theta_i \; - \; I_{oi} \, \mathrm{Cos}\, \theta_i$$

where $i = 1,2,3 \text{--------} 2^{k-1}$

and R_{Ni} = new real value for point i

I_{Ni} = new imaginary value for point i

R_{oi} = old real value for point i

I_{oi} = old imaginary value for point i

The phase angle θ_i is given by

$$\theta_i - A + \frac{B \cdot i}{2^{k-1}} \qquad i = 1,2,3 \text{----} 2^{k-1}$$

where A = Zero order phase correction, and

R = First order phase correction,

A and B are entered in degrees and are converted to radians/sec, in the calculation.

Phase Correction Algorithm:

Let $B' = B / 2^{k-1}$

For the first point, the phase angle, θ_1, is

$$\theta_1 = A + B^1$$

For the second point,

$$\theta_2 = (A + B') + B'$$

$$= {}_1\theta + B'$$

For each succeeding point, the phase angle is increased by B'.

Although it appears simple to calculate Sine θ_i and Cos θ_i for each point, this is an inefficient process because of the time taken to obtain the sines and cosines. It is more efficient in time to make use of the relations:

$$\sin\theta_{i+1} = \sin(\theta_i + B') = \sin\theta_i \cos B' + \cos\theta_i \cdot \sin B'$$

$$\cos\theta_{i+1} = \cos(\theta_i + B') = \cos\theta_i \cos B' - \sin\theta_i \cdot \sin B'$$

The computer initially calculates Sin A and Cos A, and Sin B' and Cos B' and stores these four values. Sin θ_i and Cos θ_i i.e. Sin (A+B') and Cos (A+B') are then calculated as above and stored in the locations previously holding Sin A and Cos A.

The phase correction for R_1 and I_1 is then carried out. θ_2 is then calculated using Sin θ_1 and Cos θ_1, together with the unchanged values of Sin B' and Cos B'. R_2 and I_2 are then calculated, and cycle repeated until the complex array is fully processed. The values for Sin θ_i and Cos θ_i are unchanged in each cycle.

Fig. 1-3 shows a complete listing of phase angles. The sign of the angles given is that required to bring the lines back into phase.

FIRST ORDER PHASE CORRECTION

The PDxx command sets a software delay counter which controls the computer delay before the start of acquisition. This software delay is in addition to the hardware delay set by the Tektronix pulse control unit.

The software delay is in multiples of the sampling interval (100 usec for 5000 Hz spectral width). Thus, for a 100 µsec sampling interval (CP 0, CM 1) the following delays occur :

Command	Delay (µsec)
PD1	100
PD2	200
PD3	300 etc...

A change of 1 in the PDxx command requires a change of 180° in the first order (PBxx) phase correction. For example, the first order phase correction required to compensate for PD3 is 3 x 180 = 540°. It should be noted that the first order phase correction required to compensate for a software delay may be predicted exactly. In contrast, the first order phase correction required to compensate for the hardware delay is more difficult to predict because of the finite length of the pulse (the pulse period is included within the hardware delay period).

The approximate overall first order phase correction is given by :

$$\text{Correction (deg)} = \frac{(\text{hardware + software delay } (\mu\text{sec}))}{\text{Sampling interval (usec)}} \times 180 - 180$$

Example : Hardware delay = 300 µsec

Software delay = 600 µsec

Total delay = 900 µsec

Sampling interval = 100 µsec

First order phase correction (PBxx) $= \frac{900}{100} \times 180 - 180$

$= 1440^{\circ}$

Experimentally determined value is 1410°.

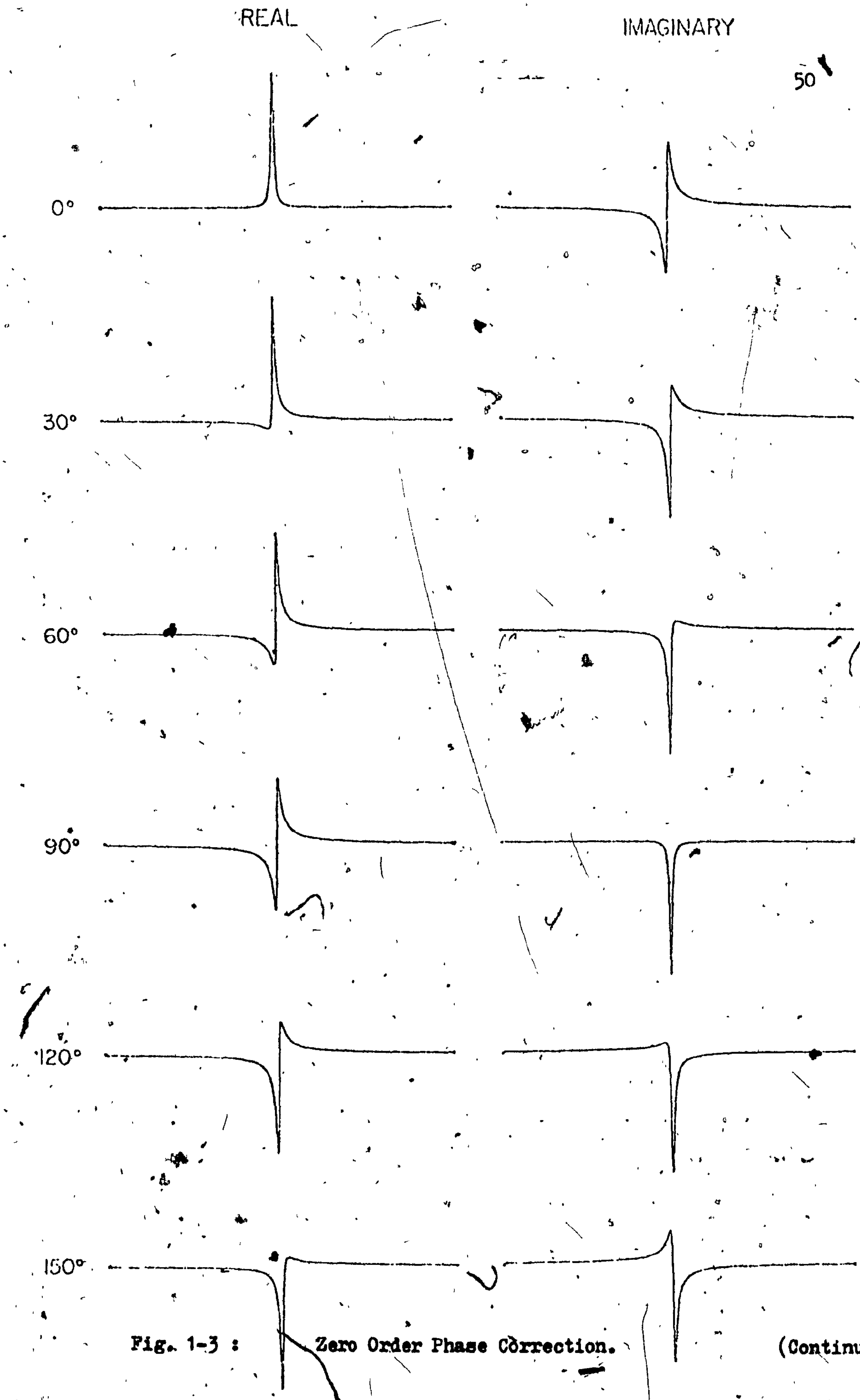


Fig. 1-3 : Zero Order Phase Correction. (Continued)

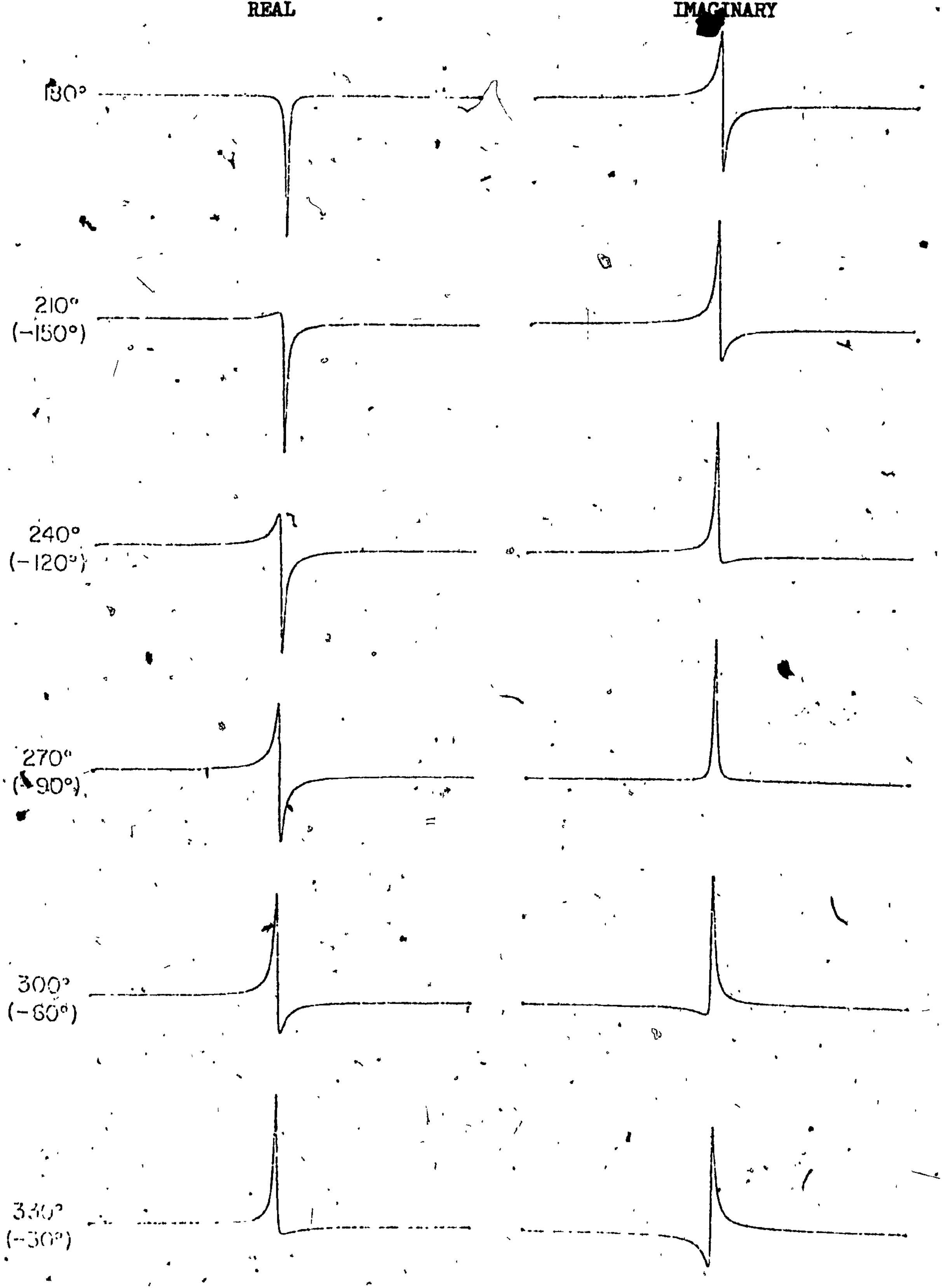


Fig. 1- 3 : Zero Order Phase Correction : The Sign of the Angles Given is that Required to Bring the Lines Back into Phase.

RESULTS

AND

DISCUSSION

RESULTS AND DISCUSSION

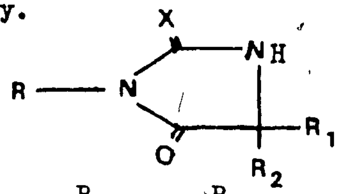
The Fourier Transformed ^{13}C nuclear magnetic resonance spectra are measured for a series of 3-Aryl substituted thiohydantoins and a hydantoin, as listed in Table 1. The thiohydantoins are divided into two groups corresponding to the number of methyl substituents at the C-5 position. The relationship between the rotamers, formed by the rotation about the aryl C-N bond, is also shown for each hydantoin.

For the purpose of comparison of the chemical shift values for a given carbon position throughout the series of thiohydantoins studied, the results are tabulated and discussed according to the carbon positions.

Dimethyl Sulfoxide (DMSO) was used as a solvent, which

TABLE 1-1

In the 3-N Aryl Thiohydantoin series, the following Compounds were synthesised and studied through the Fourier Transform ^{13}C nmr spectroscopy.



No.	R	R_1	R_2	X	Rotamers
1	O-Tolyl	H	CH_3	S	Diastereomer
11	2,3-Dimethylphenyl	H	CH_3	S	" " " "
111	α - Naphthyl	H	CH_3	S	" " " "
1V	O-Fluorophenyl	H	CH_3	S	" " " "
V	2-methyl-4-Nitrophenyl	H	CH_3	S	" " " "
V1	2-methyl-4-Nitrophenyl	H	CH_3	O	" " " "
V11	2-methyl-4-Methoxyphenyl	H	CH_3	S	" " " "
V111	β - Naphthyl	H	CH_3	S	" " " "
1X	O-Tolyl	CH_3	CH_3	S	Enantiomer
X	2,3-dimethylphenyl	CH_3	CH_3	S	" " " "
X1	α - Naphthyl	CH_3	CH_3	S	" " " "
X11	O-Fluorophenyl	CH_3	CH_3	S	" " " "
X111	2-methyl-4-Nitrophenyl	CH_3	CH_3	S	" " " "
X1V	O-Chlorophenyl	CH_3	CH_3	S	" " " "
XV	O-Bromophenyl	CH_3	CH_3	S	" " " "
XV1	α - Naphthyl	Phenyl	CH_3	S	Diastereomer

also provided the lock signal and the internal reference. The concentrations of the solutions of thiohydantoins in DMSO varied in the range of 20 - 40 % w/v. The number of scans varied from 2,000 to 10,000, each spectrum run with at least two different analytical frequencies.

Chemical shift values are reported relative to TMS and were calculated by taking the chemical shift of DMSO to be 40.40 ppm downfield from TMS. All chemical shift values are estimated to be accurate to 0.05 ppm (equivalent to 2.0 Hz), unless otherwise indicated. All the spectra were measured by doubly irradiating either near the aryl region or near the methyl region for noise proton decoupling of ^{13}C (^{1}H)

ASSIGNMENT OF THE PEAKS

Previously some investigation had been carried out in these laboratories for the ^{13}C chemical shift values for different carbon positions in the 3-Aryl (12) and 1-Aryl (11) hydantoins. Eberhard et al in a review article (22) have reported a range of ^{13}C chemical shifts of 190 - 202 ppm (TMS) for thioketones and of 160 - 175 ppm (TMS) for carbonyl carbons in esters and amides. Williams (12) has confirmed the assignments of the peaks of hydantoin by measuring its ^{13}C nmr spectrum in DMSO both by off-resonance proton decoupling and with noise proton decoupling and by comparing the results with the ^{13}C chemical shifts of carbons at various positions in acetamide and urea. Our measurements of chemical shift values of various carbons in hydantoin and thiohydantoin has reconfirmed his assignments. Table 1-2 shows the range of chemical shift values for various carbon positions in 3-Aryl- and 1-Aryl-hydantoins.

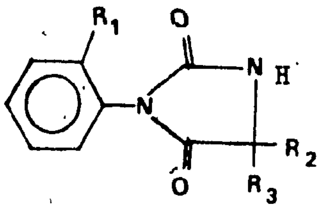
ASSIGNMENT OF THE PEAKS OF THE ARYL THIOHYDANTOINS

The peaks corresponding to the C-2 and C-4, thiocarbonyl and carbonyl carbons, respectively, and C-5 carbons are readily assigned from a comparison of their chemical shift values with values given in Tables 1-2 and 1-3.

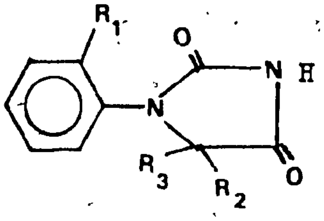
Chemical shift values for the peaks assigned to the carbonyl and the thiocarbonyl carbons of the hydantoins and the thiohydantoins are shown in Table 1-4. The values for the C-2 thiocarbonyl carbons of the aryl thiohydantoins vary over a range of 176.80 to 182.77 ppm

TABLE 1-2

Range of Chemical Shift Values for Various Positions of Carbons in 3- Aryl and 1- Aryl Hydantoins[a].



3-Aryl hydantoin



1-Aryl hydantoin

Type of Hydantoin	Carbon Chemical Shifts, ppm,[a] (TMS).				
	C-2	C-4	C-5	C-5 Methyl	Aryl Methyl
3- Aryl substituted	152.8 - 158.6	174.0 - 175.3	46.6 - 58.4	16.9 - 25.7	16.9 - 17.6
b	156.3 - 158.5	173.2 - 180.2	47.2 - 59.4	18.0 - 26.1	17.9
1- Aryl substituted[c]	155.4 - 157.6	172.8 - 179.4	52.0 - 66.0	14.6 - 25.0	15.3 - 20.4

a : ppm from TMS
b : solvent not reported
c : in morpholine

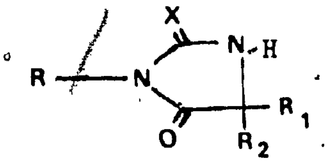
TABLE 1-3

Chemical Shift Values of Various Carbons in the Reference Compounds Listed therein.

Compound	Carbon Chemical Shift Values, ppm (TMS).			
	C-2	C-4	C-5	Methyl
Hydantoin	158.6	174.0	47.6	
Thiohydantoin	183.6	174.3		
Acetamide		172.0		22.2
Urea	160.4			
3-phenyl-5,5-dimethyl hydantoin (11)	157.2	179.3		17.9

TABLE 1-4

Carbonyl and Thiocarbonyl ^{13}C Chemical Shift Values of the Thiohydantoins and the Hydantoin V1.



No.	R	Isomeric Relation	R_1	R_2	X	C-2	C-4
1_o	H	-	H	H	S	183.60	173.70
1	0-Tolyl	Diastereomeric	H	CH_3	S	182.77	174.41
11	2,3-Dimethylphenyl	"	H	CH_3	S	182.78	174.73
111	α- Naphthyl	"	H	CH_3	S	182.52	175.41^d 175.21
1V	0-Fluorophenyl	"	H	CH_3	S	181.56	174.41^d 174.01
V	2-Methyl-4-Nitrophenyl	"	H	CH_3	S	180.38	174.01
V1	2-Methyl-4-Nitrophenyl	"	H	CH_3	O	162.08	178.79
V11	2-Methyl-4-Methoxyphenyl	"	H	CH_3	S	182.07	174.61
V111	β-Naphthyl	"	H	CH_3	S	182.07	174.81
1X	0-Tolyl	Enantiomeric	CH_3	CH_3	S	178.79	175.60
X	2,3-Dimethylphenyl	"	CH_3	CH_3	S	180.38	176.80
X1	α- Naphthyl	"	CH_3	CH_3	S	180.77	176.44
X11	0-Fluorophenyl	"	CH_3	CH_3	S	178.09	174.41
X111	2-Methyl-4-Nitrophenyl	"	CH_3	CH_3	S	179.34	176.43
X1V	0-Chlorophenyl	"	CH_3	CH_3	S	180.14	176.56
XV	0-Bromophenyl	"	CH_3	CH_3	S	181.77	176.80
XV1	α- Naphthyl	Diastereomeric	C_6H_5	CH_3	S	181.49	177.79^d 178.19

d : doublet

and agree quite closely with the value of 183.60 ppm for the thiocarbonyl carbon of 2-thiohydantoin and the range of 190 - 202 ppm for the thioketones (22). Similarly, the values for the C-4 carbonyl carbons of the aryl thiohydantoins vary over a range of 173.10 -178.19 ppm and again agree quite closely with the values of 174.3 and 174.0 ppm for the carbonyl carbons in thiohydantoin and hydantoin, respectively, and fall within the range of 160 - 175 ppm for carbonyl peaks in amides and esters, (22).

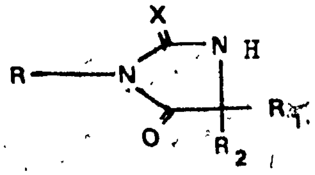
Chemical shift values for the peaks assigned to the C-5 carbons of the aryl thiohydantoins are shown in Table 1-5. These values vary over a range of 54.91 to 61.58 ppm and agree with the value of the C-5 carbon of hydantoin at 47.6 ppm, particularly, if α- methyl substituent effects are taken into consideration.

Methyl Peaks :

Toluene methyl carbon absorbs at 21.3 ppm. The chemical shifts of methyl carbons in various anilines and N,N- dimethyl anilines are shown in Table 1-6. The chemical shift values of methyl carbons in N-Aryl phthalimides and N- Aryl phthalimidines are shown in Table 1-7. The aryl methyls in these compounds can be compared with the aryl methyls

TABLE 1-5

^{13}C Chemical Shift Values of C-5 Carbons in Thiohydantoins and the Hydantoin V1.



No.	R	Isomeric Relation	R_1	R_2	X	C-5 Carbon ppm (TMS)
1	0-Tolyl	Diastereomeric	H	CH_3	S	55.01
11	2,3-Dimethylphenyl	"	H	CH_3	S	54.91
111	α- Naphthyl	"	H	CH_3	S	55.51
1V	0-Fluorophenyl	"	H	CH_3	S	55.10
V	2-Methyl-4-Nitrophenyl	"	H	CH_3	S	55.31
V1	2-Methyl-4-Nitrophenyl	"	H	CH_3	O	52.43
V11	2-Methyl-4-Methoxyphenyl	"	H	CH_3	S	54.91
V111	β- Naphthyl	"	H	CH_3	S	55.21
1X	0-Tolyl	Enantiomeric	CH_3	CH_3	S	59.49
X	2,3-Dimethylphenyl	"	CH_3	CH_3	S	60.68
X1	α- Naphthyl	"	CH_3	CH_3	S	60.98
X11	0-Fluorophenyl	"	CH_3	CH_3	S	61.00
X111	2-Methyl-4-Nitrophenyl	"	CH_3	CH_3	S	61.58
X1V	0-Chlorophenyl	"	CH_3	CH_3	S	61.24
XV	0-Bromophenyl	"	CH_3	CH_3	S	60.60
XV1	α- Naphthyl	Diastereomeric	Ph	CH_3	S	60.68

TABLE 1-6

Aryl Methyl ^{13}C Chemical Shift Values for Some Anilines and N,N-Dimethyl Anilines.

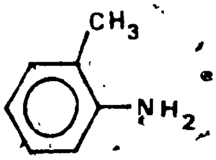
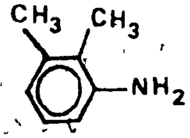
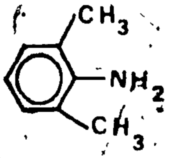
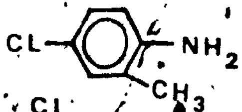
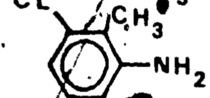
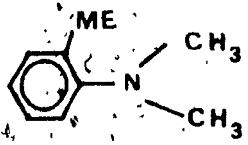
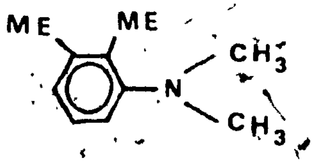
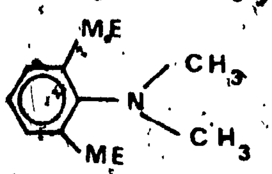
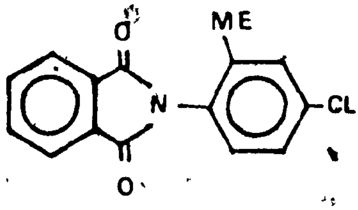
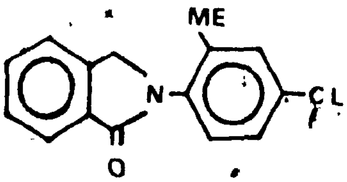
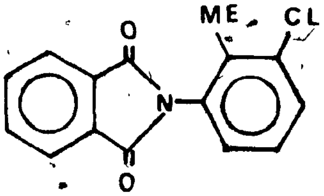
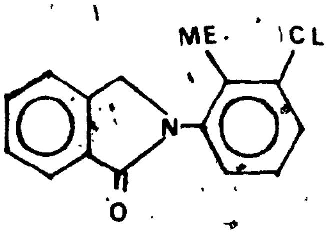
Aniline	Methyl Carbon		Ref.
		17.3	23
	2-CH_3 3-CH_3	12.7 20.6	23
	2-CH_3 6-CH_3	17.6 17.6	23
		16.88	27
		13.90	27
		18.5	23
	2-CH_3 3-CH_3	14.1 20.8	23
	2-CH_3 6-CH_3	19.0 19.0	23

TABLE 1-7

Aryl Methyl ^{13}C Chemical Shift Values in N- Aryl Phthalimidines and N- Aryl Phthalimides. (28)

Phthalimide	Methyl Carbon	Phthalimidine	Methyl Carbon
	18.27		18.27
	15.79		16.48

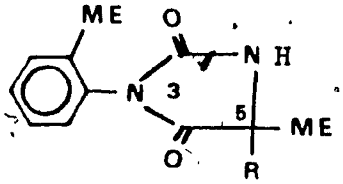
in hydantoins, since they have similar, at least immediate, surroundings.

Icli (11) has reported the Chemical Shift values of the aryl methyl carbons in 3-N Aryl hydantoins to be 17.9 ppm, regardless of the number of methyl substituents at the C-5 position. Williams(12) reported these values to be 16.87 and 16.90 ppm for the aryl methyl carbons in C-5 methyl and C-5 dimethyl hydantoins, respectively. These results along with the chemical shift values for C-5 methyl carbons as reported by Icli (11) and Williams (12) are presented in Table 1-8.

It is clear from Table 1-6 that the ortho methyl carbons in anilines and N,N-Dimethyl anilines show chemical shift values in the range of 16.88 - 19.0 ppm, and in the N-substituted phthalimides and N-substituted phthalimidines, Table 1-7, over a region of 15.79 -18.27 ppm. In 3-N aryl substituted hydantoins, the chemical shift values lie in the region of 16.9 to 17.9 ppm. The trend for the aryl methyl carbons to be on the high field side as compared to the C-5 methyl carbons is noteworthy. A knowledge of the enantiomeric and diastereomeric relationship is also a valuable guide in assigning a particular peak to an aryl methyl carbon or a C-5 methyl carbon. For example, in 3-(O-tolyl)-5,5-

TABLE 1-8

^{13}C Chemical Shifts of Aryl Methyl Carbons and C-5 Methyl Carbons in 3-Aryl Hydantoins.



R	Aryl Methyl Carbon	C-5 Methyl (a) Carbon	C-5 Methyl (b) Carbon	Ref.
H	17.9	18.10^{d} 18.61	-	(11)
H	16.9	17.10 17.61	-	(12)
CH_3	17.9	25.42	26.12	(11)
CH_3	16.90	24.12	25.12	(12)

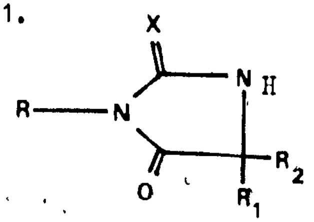
d : doublet for the diastereomers

dimethyl hydantoin, 1X, three peaks are observed in the methyl region. The high field signal at 16.14 ppm is clearly attributable to the ortho methyl since the enantiomeric ortho methyl group is expected to exibit a single absorption. On the other hand, the C-5 dimethyl groups are expected to show two signals, of almost equal intensity, and close to each other. This is indeed observed and the lower field signals at 24.12 and 25.32 ppm are believed to arise from the C-5 dimethyl carbons. Table 1-9 shows the chemical shift values of the aryl methyl carbons and the C-5 methyl carbons of the compounds studied in the present investigation. The chemical shift values of the aryl methyl carbons vary in the region of 13.26 to 17.14 ppm. The 3-methyls of the 2,3- dimethylphenyl moieties in the C-5 methyl and C-5 dimethyl hydantoins show chemical shifts of 20.02 and 19.52 ppm, respectively. The greater deshielding is expected because the 3-methyl carbons in 2,3-dimethyl anilines and N,N- dimethyl anilines show chemical shifts of 20.6 and 20.8 ppm, respectively. (23)

The C-5 methyl carbons show chemical shift values in two distinct regions. For C-5 mono methyl thiohydantoins, the range of the chemical shift values is from 15.35 to 17.34 ppm whereas for the C-5

TABLE 1-9

^{13}C Chemical Shift Values of Ortho Methyl Carbons and of C-5 Methyl Carbons in 3-N Aryl Thiohydantoins and the 3-N-Hydantoin, V1.



No.	R	R_1	R_2	X	Ortho Methyl Carbon	C-5 Methyl Carbon	
1	O-Tolyl	H	CH_3	S	15.94, 16.44^{d}	16.84	17.04^{d}
11	2,3-Dimethylphenyl	H	CH_3	S	13.26, 13.66^{d} 19.02, 20.02^{d}	16.04	16.44^{d}
111	α- Naphthyl	H	CH_3	S	-	16.30	16.80^{d}
1V	O-Fluorophenyl	H	CH_3	S	-	15.94	16.34^{d}
V	2-Methyl-4-Nitrophenyl	H	CH_3	S	16.94, 17.14^{d}	15.34	16.14^{d}
V1	2-Methyl-4-Nitrophenyl	H	CH_3	O	16.74, 16.94^{d}	16.04	16.34^{d}
V11	2-Methyl-4-Methoxyphenyl	H	CH_3	S	16.34, 16.74^{d}	16.94	17.34^{d}
V111	β- Naphthyl	H	CH_3	S	-	15.35	16.14^{d}
1X	O-Tolyl	CH_3	CH_3	S	16.14	24.12	25.32
X	2,3-Dimethylphenyl	CH_3	CH_3	S	13.50, 19.52	23.40	24.10
X1	α- Naphthyl	CH_3	CH_3	S	-	23.44	24.10
X11	O-Fluorophenyl	CH_3	CH_3	S	-	23.30	24.10
X111	2-Methyl-4-Nitrophenyl	CH_3	CH_3	S	16.84	23.00	24.20
X1V	O-Chlorophenyl	CH_3	CH_3	S	-	23.10	24.10
XV	O-Bromophenyl	CH_3	CH_3	S	-	23.50	24.57
XV1	α- Naphthyl	Ph	CH_3	S	-	22.70	23.70^{d}

d : diastereomeric doublet

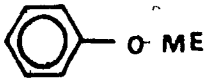
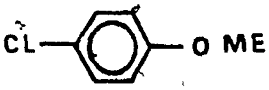
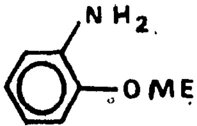
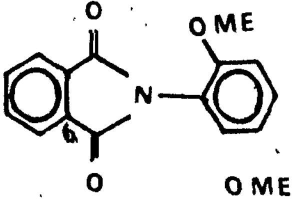
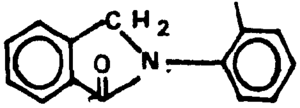
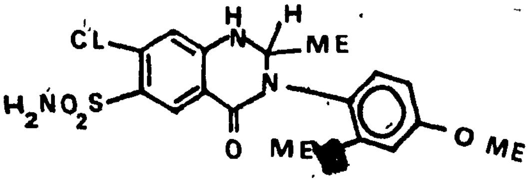
dimethyl thiohydantoins, this range is from 22.70 to 25.32 ppm, and agrees well with the range of 24.12 to 26.12 ppm as found by Williams (12) and Icli (11) for similarly substituted hydantoins.

In the case of 3-(2-methyl-4-methoxyphenyl)-2-thio-5-methyl hydantoin, V11, the signals due to the aryl methoxy carbon and the C-5 carbon of the hydantoin moiety overlap each other. In this case, the signals are observed at 54.91 and 55.11 ppm. In order to make a definite assignment to each peak, some comparisons of the chemical shift values of the methoxy carbon in this thiohydantoin can be made with the chemical shift values of the methoxy carbons in the compounds listed in Table 1-10.

It is clear from Table 1-10 that the chemical shift values of the methoxy carbons in these methoxy compounds appears in the region 54.7 to 56.1 ppm, usually greater than 55.25 ppm. Particularly in the substituted quinazolinone (25), the methoxy carbon is in an environment similar to that of the methoxy carbon in the thiohydantoin and therefore provides a useful comparison. Therefore, we may have reasonable confidence in assigning the peak at 55.11 ppm to the methoxy carbon in the thiohydantoin, and conclude that the peak at 54.91 ppm corresponds to the

TABLE 1-10

Chemical Shift Values of Aryl Methoxy Carbons

Compound	ppm (TMS)	Ref.
	54.70	24
	55.30	24
	55.25	27
	56.25	27
	56.07	27
	55.25	25

C-5 carbon.

Aryl Carbons :

A series of peaks corresponding to the aryl carbons occurs within the expected range of 110 - 140 ppm. The intensities of the peaks were greatly enhanced when the samples were irradiated close to the ^{1}H aryl absorption region, due to the more efficient spin - spin decoupling of ^{13}C - ^{1}H nuclei. For the purpose of ground state stereochemical studies, major consideration is given to the chemical shift values of different carbons in the thiohydantoin moiety, since aryl carbons are not expected to be very sensitive to stereochemical variations and therefore, no attempt was made to specifically assign various peaks to the aryl carbons. However, some of the peaks are quite easy to recognise. For example, peaks corresponding to the carbons of the C - N bond, or the C-OMe bond, or the C-Me bond. The unsubstituted aryl carbons would, because of the Nuclear Overhauser Effect, show peaks of much greater intensities than the substituted aryl carbons.

In summary, it can be seen that throughout the series of thiohydantoins studied, the chemical shift values for a given carbon position vary over quite a narrow region and the regions for different carbon positions are well separated. There is, thus, no ambiguity in the assignment of the peaks in the Fourier Transformed ^{13}C NMR Spectra.

THIOCARBONYL AND CARBONYL ^{13}C CHEMICAL SHIFT VALUES OF THE THIOHYDANTOINS.

The ^{13}C Chemical Shift values for both the C - 2 (Thiocarbonyl) and C - 4 (Carbonyl) carbons are shown in Table 1-4.

The C-2 thiocarbonyl ^{13}C chemical shift values of the aryl-thiohydantoins fall into two, more or less distinct regions corresponding to the number of methyl groups at the C-5 position. In the case of C-5 methyl thiohydantoins, the thiocarbonyl ^{13}C Chemical Shift values fall in the range of 180.13 to 182.77 ppm, whereas for the corresponding C-5 dimethyl thiohydantoins, the range of ^{13}C Chemical Shifts varies from 176.80 to 181.50 ppm.

Similarly, the ^{13}C Chemical Shifts of carbonyl carbons (C-4) of the thiohydantoins fall within the range of 173.70 to 175.40 ppm for one methyl at the C-5 position, whereas for two methyls at the C-5 position in the corresponding thiohydantoins, the range of Chemical Shifts varies from 173.10 to 178.20 ppm.

It is interesting to note that the thiohydantoins V11 (2-Methyl-4-Methoxyphenyl) and V111 (β- Naphthyl) both absorb at 182.07 ppm for the thiocarbonyl carbon and slightly differently for the carbonyl carbons i.e. 174.61 and 174.81 ppm, respectively.

The thiohydantoins X1V, XV and XV1 absorb over the range 176.80 - 181.50 ppm for the thiocarbonyl carbons; whereas the carbonyl carbons absorb over the range of 173.10 - 178.20 ppm.

The only hydantoin examined, V1, ((3-Methyl-4-Nitrophenyl)-5-Methyl hydantoin)) shows Chemical Shift values of 162.08 and 178.79 ppm for the C-2 and the C-4 carbonyl carbons, respectively.

On the basis of their stereochemistry, all the C-5 methyl thiohydantoins and also the hydantoin V1, which have diastereomeric rotamers, can be expected to show double peaks for both the C-2 and the C-4 carbonyl carbons. Some of the thiohydantoins studied did show splitting of the C-2 and the C-4 carbonyl carbon peaks because of diastereomeric rotamers when the spectra were run at higher concentrations, e.g. the thiohydantoins 111, 1V, X1, X1V, XV and XV1 are included in this group. The remaining thiohydantoins did not show diastereomeric splitting of either the C-2 or the C-4 carbons, probably for the two reasons : First, the concentrations of the thiohydantoin solutions may not be sufficiently high and consequently, the peaks corresponding to one of the diastereomeric

TABLE 1-12

The Downfield B-Methyl Substitution Effect on the C-13 Chemical Shift Values of the Carbonyl (C-4) Carbon in the Thiohydantoins.

Thiohydantoin		ppm
0-Fluorophenyl	1V and X11	0.0-0.2
0-Tolyl	1 and 1X	1.19
α-Naphthyl	111 and X1	1.13
2,3-Dimethylphenyl	11 and X	2.07
2-Methyl-4-Nitrophenyl	V and X111	2.42

SOLVENT EFFECTS ON THE CHEMICAL SHIFTS OF C-2 AND C-4 CARBONYL CARBONS :

The thiocarbonyl link is highly polarized ($>C=S \leftrightarrow \overset{+\delta}{C}-\overset{-\delta}{S}$). DMSO itself is a highly polarized molecule, $CH_3-\underset{\underset{O^{-\delta}}{|}}{\overset{+\delta}{S}}-CH_3$. It solvates cations strongly and leaves the anions relatively unencumbered. It is, therefore, expected that in a C-5 monomethyl thiohydantoin, the oxygen atom of DMSO will be close enough to the carbon atom of the C S bond to solvate the highly polarized thiocarbonyl bond. Solvation is also expected to occur on the C-4 carbonyl group. In an attempt to estimate the magnitute and the direction of the solvent induced variations in the chemical shifts of the C-2 and C-4 carbons, a 25% solution of 3- (α-Naphthyl)-5,5-Dimethyl-2-Thiohydantoin, XI, in chloroform, was run to obtain its Fourier Transformed NMR spectrum. The results are discussed later, but it should be mentioned here that not only the C-2 and C-4 carbonyl carbons, but also the C-5 and the C-5 dimethyl carbons showed significant upfield shifts in DMSO compared to chloroform, the largest shift being experienced by the thiocarbonyl carbon, C-2.

A- Cisoid Conformers

If we consider the conformers in which the methyl group in the C-5 monomethyl thiohydantoins is 'cisoid' to the ortho substituent, then the solvent molecule is expected to experience little steric hindrance if approaching the C-4 carbonyl carbon from the side 'transoid' to the ortho substituent, thereby causing an increase in the shielding of the C-4 carbonyl carbon. It is less likely on the steric grounds that the solvent molecule would approach between the ortho and the C-5 methyl substituents.

In the conformers mentioned above, the extent of solvation around the C-2 thiocarbonyl carbon is expected to be much greater compared to that around the C-4 carbonyl carbon, based on the following two considerations:

a- The thiocarbonyl linkage is highly polarized as well as the DMSO molecule. The oxygen atom of DMSO would have relatively strong 'electrostatic solvent bonding' with the positively polarized carbon atom of the C=S bond.

b- Sterically, the C-2 thiocarbonyl link offers no resistance to the solvent molecule to approach it from the least hindered side i.e. 'transoid' to the ortho substituent. The solvation at the C-2 site would be very effective and the chemical shift of the C-2 carbon is expected to experience a large perturbation. This is in agreement with the observation that the chemical shift of the C-2 thiocarbonyl carbon of the thiohydantoin XI is 1.80 ppm. to higher field in DMSO than in chloroform.

The approach of the solvent molecule to the C-2 thiocarbonyl carbon from the same side as that of ortho substituent is also possible, but less likely because of some steric hindrance from the ortho and the 'cisoid' C-5 methyl substituents. The extent of solvation around C-2 from this side is expected to be somewhat dependent on the size of the ortho substituent. If the ortho substituent is sufficiently large, it may considerably reduce solvation about C-2 from this side, resulting in a smaller shielding contribution to the C-2 chemical shift and consequently a lower upfield γ- effect (see later).

Upon the addition of a second methyl group, which would occupy a position 'transoid' to the ortho substituent, the solvation around C-4 by DMSO would be hindered from the side 'transoid' to the ortho substituent compared with the C-5 monomethyl compound. This should result in a deshielding contribution to the C-4 carbonyl carbon chemical shift. The solvation of C-4 from the side 'cisoid' to the ortho substituent is still greatly hindered and would be highly probable.

Because of the incoming 'transoid' C-5 methyl group, the solvent shell around C-2 would also be sterically disturbed. However, solvation around the C-2 thiocarbonyl carbon should be affected to a lesser degree than that about C-4 because of the greater distance from the site of introduction of the methyl group.

In summary, when the C-5 monomethyl thiohydantoin molecule exists in the preferred 'cisoid' conformation, then, the addition of a second methyl group at C-5 may have a significant effect upon the chemical shift of the C-4 carbonyl carbon through hindering the ability of the solvent molecule to solvate the C-4 carbon. The addition of a second methyl group is also expected to affect, but to a smaller extent, the chemical shift of the thiocarbonyl carbon.

B- Transoid Conformers

If the C-5 monomethyl thiohydantoin molecule is assumed to exist in the less preferred conformation i.e. the C-5 methyl group being transoid to the ortho substituent, the solvation around the C-4 carbonyl carbon from the side 'transoid' to the ortho substituent would be greatly reduced, as compared to the 'cisoid' conformer, because of the steric hindrance. The solvation around C-4 from the side 'cisoid' to the ortho substituent is still hindered, but less so compared to the 'cisoid' conformer and a weak solvent shell may be developed around C-4. However, the solvation around the C-2 thiocarbonyl carbon would be slightly affected.

Upon the addition of a second methyl group at C-5, so that this methyl group occupies a 'cisoid' position with respect to the ortho substituent, solvation around C-4 from the side 'cisoid' to the ortho group becomes almost impossible, but from the side 'transoid' to the ortho substituent remains almost unchanged. The solvent shell around the C-2 carbon is expected to be unaffected since the environment, almost similar to that in the C-5 monomethyl compound, would be prevalent.

In summary, the addition of a second methyl group at the C-5 carbon in the C-5 monomethyl thiohydantoins, which has preferred 'cisoid' conformation, would drastically reduce the solvation about the C-4 carbonyl carbon, resulting in its considerable deshielding. The addition of a second methyl group at C-5 should have a relatively smaller effect on the shielding of the C-2 thiocarbonyl carbon.

In the less preferred conformation of the C-5 methyl thiohydantoins i.e. the C-5 methyl group being 'transoid' to the ortho substituent, the addition of a second methyl group at C-5 would have little effect on the chemical shifts of either the C-4 or C-2 carbonyl carbons.

EFFECT OF POLARITY OF SOLVENT:

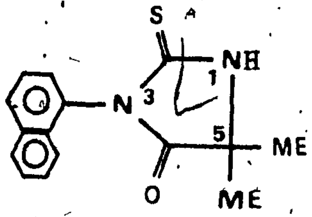
If cholorform is employed as a relatively non-polar reference solvent, the direction of polar solvent induced shifts may be determined by comparison with the observed chemical shifts in the more polar solvent, DMSO. A significant (1.80 ppm) upfield shift was observed for the C-2 carbon signal in DMSO. The shielding of the C-4 carbonyl carbon (0.08 ppm) in DMSO is within the range of experimental error.

Table 1-13 shows the comparison of the ^{13}C chemical shifts of 3-(α-Naphthyl)-5,5-Dimethyl-2-thiohydantoin, XI, in chloroform and DMSO. Approximately 25% solution of the thiohydantoin in each solvent was employed.

At this stage, the direction of the variations in chemical shifts induced by the polar solvent has been defined. The magnitude of the solvent induced chemical shifts is relatively more difficult to estimated. The shieldings of the C-2 and C-4 carbonyl carbons by 1.80 and 0.08 ppm, respectively, as induced by the polar solvent, DMSO, could serve as a guide to such estimation, but the possibility of different magnitudes of the upfield γ- and the downfield β-effects caused by the less polar solvent, chloroform, should not be ignored.

TABLE 1-13

Comparison of Chemical Shift Data of 3-(α-Naphthyl)-5,5-Dimethyl-2-Thiohydantoin, X1, in Chloroform and DMSO, (Each 25 % Solution)



Solvent	Chemical Shift (PPM From TMS)			
	C-2	C-4	C-5	C-5 Methyls
Chloroform	182.80	176.76	61.91	24.14[a]
DMSO	181.00	176.68	61.22	23.68, 24.34[b]
Difference:	1.80	0.08	0.69	0.46, 0.20

[a] Singlet observed

[b] Doublet observed

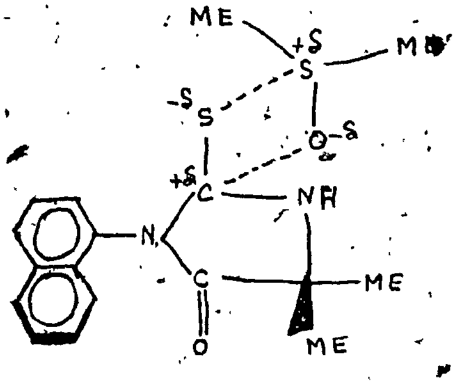
It is important to note that upon changing the solvent from chloroform to DMSO, the shielding of the C-2 thiocarbonyl carbon is large (1.80 ppm) as compared to that of the C-4 carbonyl carbon (0.08 ppm). At least the following two factors may be considered to be responsible for this observation:

1- The C=S bond is more polar than the C-O bond and is expected to be more subject to solvation by a polar solvent.

2. The steric crowding around the C-4 carbonyl carbon is expected to be quite large as compared to that around the C-2 thiocarbonyl carbon. In the latter case, the steric interference may be between one of the dimethyl groups of the DMSO molecule around the C-2 carbon and the C-5 methyl group transoid to the ortho substituent, and also between the aryl ortho hydrogen atom and the second methyl group of DMSO around the C-2 carbon. In the case of the C-4 carbonyl carbon, the distance between the naphthyl group and the C-5 methyl group may not be very small, but at the same time, may not be sufficient to permit quite a free approach of the DMSO molecules to the C-4 carbon.

The contribution from both the factors mentioned above seems to be important toward the observation of much smaller, if any, (0.08 ppm), shielding of the C-4 carbon in DMSO as compared to the quite large (1.80 ppm) shielding of the C-2 carbon.

The observation of large shielding of the C-2 thiocarbonyl carbon in DMSO (Table 1-13) shows that the highly polar solvent, DMSO, may interact with the polarizable C=S group by forming an electrostatic band between the electronegative oxygen atom and partially positively charged carbon of the C=S bond. However, the possibility of the formation of a weak sulfur to sulfur linkage may not be ignored:

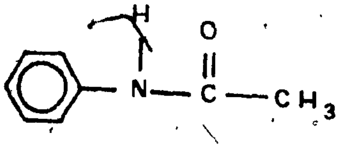


The formation of weak sulfur to sulfur bond would further facilitate the polarization of the thiocarbonyl bond, and hence promoting stronger interaction between the carbon of the C=S bond and the oxygen atom of DMSO.

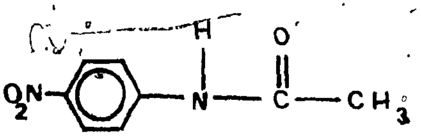
POLARITY OF SUBSTITUENTS ON THE ARYL RING :

The shielding effects caused by the presence of polar groups on the aryl rings can be examined from Table 1-4. Comparing the O-Tolyl and 2-Methyl-4-Nitrophenyl thiohydantoins in the C-5 methyl series, 1 and V, it is clear that the presence of a nitro group in the para position of the aryl ring strongly shields the C-2 thiocarbonyl carbon (by 2.40 ppm) and slightly shields the C-4 carbonyl carbon (by 0.40 ppm). This is contrary to the effect observed in the C-5 dimethyl series e.g. thiohydantoins 1X and X111 with O-Tolyl and 2-Methyl-4-Nitrophenyl moieties, respectively. Both the C-2 and C-4 carbons in X111 are deshielded by 0.55 and 0.83 ppm, respectively, as compared to the corresponding carbons in O-Tolyl compound, 1X.

The environment around the C-4 carbon in the thiohydantoins may usefully be compared with that of the carbonyl group in the following substituted acetamides (30).



(A) δ (C = O) 168.3 ppm



(B) δ (C = O) 169.2 ppm

The presence of the nitro group in the para position on the aryl ring deshields the carbonyl carbon in the substituted acetamide,(B), by 0.9 ppm. The deshielding of both the C-2 and C-4 carbonyl carbons, caused by the para nitro group, is indeed observed but only in the C-5 dimethyl compounds 1X and X111. The deshielding of the C-4 carbon by 0.83 ppm is very close to that observed in the substituted acetamide (B) mentioned above. Although both the resonance and the inductive effects may be held responsible for the observed deshielding of the carbonyl carbon in the substituted acetamide, the resonance effect should be considered to contribute very little, if any, to the deshielding of the C-4 carbonyl carbons in thiohydantoins, since the aryl and the hetero rings are known (29) to have a large dihedral angle.

In the 2-Methyl-4-Nitrophenyl thiohydantoins, V and X111, at least the following four factors can be considered to contribute toward the C-2 and C-4 carbon shieldings :

a- The solvent effect, depending on the extent of approach of the DMSO molecules to effectively solvate the C-2 and C-4 carbons.

b- The upfield γ-Methyl substitution effect on C-2 arising from the addition of a second methyl group at the C-5 carbon.

c- The downfield β-Methyl substitution effect on C-4, arising from the addition of a second methyl group at the C-5 carbon. Although the downfield β-effect is almost constant at 2.3 ± 0.3 ppm in the case of hydantoins[12], it varies from 0.0 to 2.4 ppm in the thiohydantoins studied in the present investigation, Table 1-12.

d- The effect due to the presence of electron withdrawing substituents on the aryl ring.

Of the four factors mentioned above, the direction of the solvent effect, whose magnitude is difficult to determine in this study, has been investigated. As discussed earlier, when chloroform was employed as a relatively non-polar solvent for reference, a significant upfield shift was observed for the C-2 carbon signal in DMSO in the case of α-Naphthyl 5,5-dimethyl thiohydantoin, X1. However, the shielding of the C-4 carbonyl carbon was not significantly affected.

The deshielding contribution of about 0.9 ppm by the para nitro group has already been discussed.

The downfield β-Methyl substitution effect is expected to be the main factor governing the chemical shift of the C-4 carbonyl carbon in the 5,5-dimethyl thiohydantoin, X111, which is 2.42 ppm.

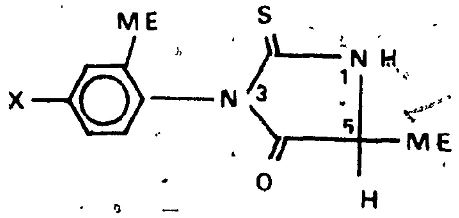
It should be pointed out that the downfield β-Methyl substitution effects as reported in Table 1-12 and also the upfield γ-Methyl substitution effects as reported in Table 1-11, should be regarded as a 'balanced' effect of the four factors mentioned above.

Comparison of the thiohydantoins 1 and V11 would reveal the effect of a methoxy group on the ^{13}C shieldings. From Table 1-4 it is clear that the C-2 thiocarbonyl carbon is shielded by 0.70 ppm and the C-4 carbon is deshielded by 0.20 ppm in V11 as compared to the corresponding carbons in the thiohydantoin 1. In order to compare this observation with that observed in the case of para nitro compound, V, it may be useful to refer to Table 1-14. The dipole moments for the nitro group (3.97) as well as for the methoxy group (1.16) are also included.

The comparison (Table 1-14) is made with reference to the O-Tolyl compound. The presence of the resonance effect is considered to be negligible because of a large dihedral angle between the two rings. However, there is a possibility of contribution to the

TABLE 1-14

Comparison of the Shielding Effects in Para Substituted Aryl Thiohydantoins With Respect to the Corresponding O-Tolyl Thiohydantoin, 1X.

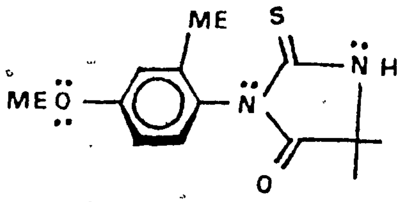


Substituent X	C-2 ppm	C-4 ppm	Dipole moment
NO_2	+ 2.40	+ 0.40	3.97
OCH_3	+ 0.70	- 0.20	1.16

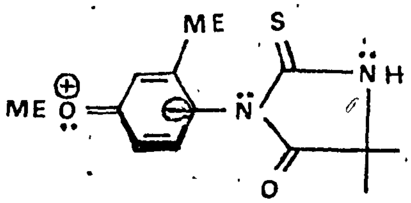
+ Shielding

\- Deshielding

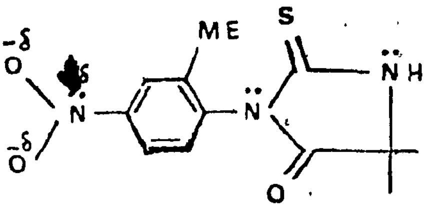
shielding of the C-2 and C-4 carbons from the resonance structure like (D) in which the inductive effect can influence the C-2 and C-4 carbon shieldings more forcefully than the structure (C). This implies the reversal of direction or at least the retardation of the inductive effect. Similar resonance structures e.g. (E) and (F) can be written for the para nitrophenyl thiohydantoin, but their contribution to the carbon shieldings seems to be negligible; since the partial positive charge in (F) is expected to help deshielding of the C-2 and C-4 carbons through the inductive effect; whereas these carbons are fairly shielded (2.40 and 0.40 ppm, respectively).



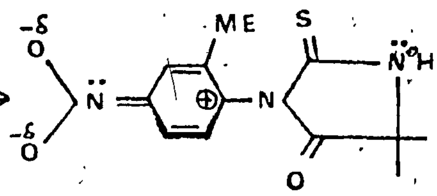
C



D



E



F

For the ortho halogen substituents, interesting trends are observed for the C-2 and C-4 carbon chemical shift values in 5,5-dimethyl thiohydantoins. The shielding decreases from O-Fluorophenyl- to O-Bromophenyl thiohydantoin. Both the C-2 and C-4 carbon chemical shift values show an approximately linear relationship with the electronegativity of the ortho halogen substituents, Fig. 1-4.

In contrast to the shielding of the C-2 and C-4 carbons by 0.70 and 1.19 ppm, respectively, in O-Fluorophenyl thiohydantoin, X11, these carbons in the O-Chlorophenyl compound, X1V, are strongly deshielded (1.35 and 0.96 ppm, respectively) as compared to the O-Tolyl compound, 1X. Similarly, the C-2 and C-4 carbons in the O-Bromophenyl thiohydantoin, XV, are even more strongly deshielded (3.0 and 1.2 ppm, respectively) as compared to the corresponding carbons in the O-Tolyl compound, 1X. Since electronegativity decreases from fluorine to bromine atoms, the increase in deshielding of the C-2 and C-4 carbons may be attributed to the slightly increased atomic covalent radii of the halogens, which increases the possibility of electrostatic interaction between the ortho halogen substituent and either the C-2 thiocarbonyl sulfur and/or C-4 carbonyl oxygen. Also the possibility of interaction between the ortho halogen substituent and the oxygen atom of DMSO, solvating the C-2 and C-4 carbonyl groups, may not be ignored.

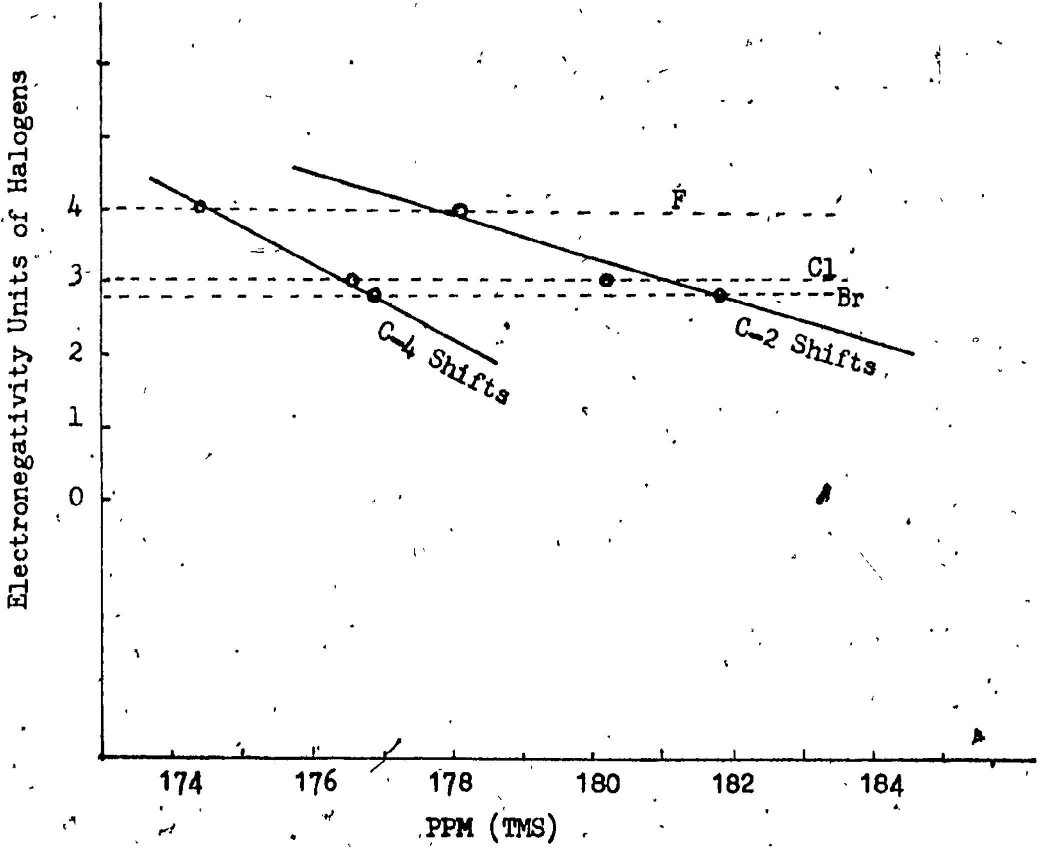


Fig. 1-4 : Relative Electronegativity of Halogens versus C-13 Chemical Shift Values of 3-Aryl Ortho Halogen Substituted C-5 Dimethyl Thiohydantoins.

STERIC BULK EFFECT :

Since steric crowding has been shown to affect the shielding of the carbon in question,[31] a substantial increase in the total steric bulk of the aryl substituent on N-3 is expected to result in changes in the shielding of the C-2 and C-4 carbons. The increase in the total steric bulk of the aryl moiety can be achieved by either replacing the N-phenyl group with N-Naphthyl (α-β) or by introducing a substituent on the phenyl ring in the meta position.

Useful information on steric bulk effects can be extracted for a series of hydantoins from the data obtained by Williams (12) for DMSO solutions and Icli (11) for morpholine solutions. Table 1-15 shows the steric bulk effects on the carbonyl carbons in hydantoins and thiohydantoins in different solvents. The effect is measured in ppm from TMS, using the O-Tolyl compound as reference.

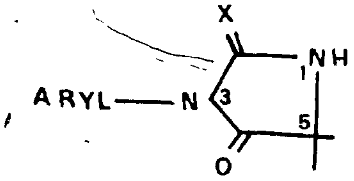
From the data obtained by Williams in DMSO (12) and by Icli (11) in morpholine, it becomes apparent that for both the C-5 methyl and 5,5-dimethyl series, the C-2 and C-4 carbonyl carbons in the α-Naphthyl compounds are deshielded by 0.5-0.9 ppm as compared to the corresponding carbons in O-Tolyl hydantoins.

The C-2 thiocarbonyl carbon in 2,3-dimethylphenyl 5-methyl thiohydantoin, 11, is unaffected whereas that in the α-Naphthyl compound, 111, is shielded by only 0.25 ppm. However, the C-4 carbonyl carbons in these thiohydantoins, 11 and 111, are deshielded by 0.32 and 0.90 ppm, respectively.

In the C-5 dimethyl series, the C-2 thiocarbonyl carbons in

TABLE 1-15

Sterio Bulk Effect (ppm) on the Carbonyl Carbons in the Hydantoins (Compared With O-Tolyl Hydantoin) and Thiohydantoins (Compared With O-Tolyl Thiohydantoin) in DMSO and Morpholine.



N-Aryl Moiety		C-5 Methyl	Hydantoins[a] in DMSO		Hydantoins[b] in Morpholine		Thiohydantoins[c] in DMSO	
			C-2	C-4	C-2	C-4	C-2	C-4
∝-Naphthyl	111	Mono	-0.5	-0.7	d	d	+0.25	-0.90
∝-Naphthyl	X1	di	-0.6	-0.9	-0.6	-0.9	-1.96	-0.84
2,3-Dimethyl-Phenyl	11	Mono	d	d	d	d	0.00	-0.32
2,3-Dimethyl-phenyl	X	di	d	d	d	d	-1.59	-1.20

Ref.

a	11
b	12
c	27
d	DATA NOT AVAILABLE

the 2,3-dimethylphenyl and α-naphthyl compounds, X and X1, are deshielded by 1.59 and 1.96 ppm, respectively, and the C-4 carbons are deshielded by 1.20 and 0.80 ppm, respectively. As expected, the C-2 carbon in the α-Naphthyl compound, X1, is more deshielded than that in the 2,3-dimethylphenyl compound, X, but it is interesting to note that the C-4 carbon is much less deshielded in X1 than in X. It should also be noted that the deshieldings observed in the C-2 thiocarbonyl carbons are greater than those for the C-4 carbonyl carbons in these thiohydantoins.

The observation of deshielding, rather than shielding resulting from the increased steric bulk is rather unexpected. The following three factors may be considered to affect the deshielding under observation :

a- δ -Effect.

In direct contrast to the well established trends for γ-effects, steric crowding of δ-nuclei frequently causes marked downfield shifts (31). The C-2 and C-4 carbonyl carbons occupy positions δ to the ortho substituents. Naturally, the shielding effects of the aryl ring upon the C-2 and C-4 carbons may be examined depending on whether or not these carbons experience the 'steric pressure' from the aryl moiety on N-3. The C-2 and C-4 carbons are expected to experience the steric bulk of the N-aryl substituents and hence, the δ-effect would contribute toward the deshielding of the C-2 and the C-4 carbons.

Although the δ-effect is considered to be small, its magnitude is variable, so that its influence is difficult to estimate under present circumstances.

The substitution at the meta position on the aryl ring will give rise to ε-effects which are known to contribute to the shielding of the carbon in question (31). The downfield δ-effect upon the C-2 and C-4 carbons may be nullified by the ε-effect. However, it should be noted that the relatively small δ- and ε-effects may be either offset or greatly enhanced by the effective solvation of these carbons by a polar solvent like DMSO.

b- Solvent Effect :

As already discussed, solvation around the C-4 carbonyl carbons in the C-5 dimethyl thiohydantoins is less significant than in the C-5 methyl series. Therefore, considerable solvation around the C-4 carbon in C-5 methyl series is expected to contribute toward its shielding. The C-2 carbon in both the C-5 methyl and dimethyl series is expected to be solvated effectively by DMSO and therefore greater shieldings of the C-2 carbons are expected.

If the solvent effect is the only significant factor to affect the shielding of the carbonyl carbons, the deshielding of the C-4 carbons by 1.20 and 0.84 ppm in the 2,3-dimethylphenyl and α-naphthyl compounds, respectively, in the C-5 dimethyl series, can probably be explained on the basis of the reduced extent of solvation around the C-4 carbons. However, solvation around the C-2 carbon, even in the C-5 dimethyl series, is expected to be significant, and thus the large deshieldings of 1.59 and 1.96 ppm in X and X1 cannot be rationalized on the basis of only solvation phenomena.

c- Steric Bulk Effect.

The large deshieldings of the C-2 and C-4 carbons in 2,3-dimethylphenyl and α-naphthyl thiohydantoins is obviously a direct manifestation of the presence of larger aryl moieties on N-3 as compared to the O-Tolyl group. The enhanced steric bulk of the aryl moiety on N-3 may be considered to obstruct the approach of the solvent molecules to the C-2 and particularly C-4 carbonyl carbons, affecting their significant deshielding. Moreover, such a steric crowding in conjunction with the neighbouring solvent shell would be expected to encourage deshielding of the C-2 and C-4 carbonyl carbons through the δ-effect.

In summary, the observation of very large deshielding of the C-2 carbons in X and X1 is difficult to attribute solely to either the δ-effect or solvent effect or the steric bulk effect. Although it is obvious that large deshielding of the C-2 and C-4 carbons arises from the presence of bulky aryl substituents on N-3, the relative contributions of the δ-, solvent-, and the steric bulk effects to influence the carbonyl carbon shieldings so strongly in X and X1 in the C-5 dimethyl series may not be quite clear.

NAPHTHYL COMPOUNDS :

The C-2 thiocarbonyl and the C-4 carbonyl carbon chemical shifts for the naphthyl thiohydantoins are listed in Table 1-4. It is clear that the α-naphthyl moiety in 111 exerts slightly a greater steric influence than the β-naphthyl group in V111 upon the C-2 and C-4 carbonyl carbons i.e. 0.45 and 0.50 ppm, respectively. The observation of the models and the experimental chemical shift values suggest that, in the activated state, the second ring in the α-naphthyl moiety would have strong steric interaction with the C-4 carbonyl carbon and the solvent shell around it, but less so with the C-2 thio-carbonyl carbon. The greater deshieldings of the C-2 and C-4 carbonyl carbons in the α-naphthyl thiohydantoin compared with the β-naphthyl compound suggest that the approach of solvent molecules around both the carbonyl carbons may be slightly more hindered in the α-naphthyl compound as compared with the β-naphthyl thiohydantoin.

For the α-naphthyl thiohydantoins, the upfield γ-methyl substitution effect on C-2 is 1.75 ppm and the downfield β-methyl substitution effect on C-4 is 1.13 ppm. In the C-5 disubstituted series the C-2 thiocarbonyl carbons in the α-naphthyl compounds, X1 and XV1, are shielded whereas the C-4 carbonyl carbons are deshielded as compared with the corresponding carbons in the C-5 methyl series.

In the α-naphthyl 5-methyl-5-phenyl thiohydantoin, XV1, the C-2 thiocarbonyl carbon is shielded by 1.03 ppm compared to the C-5 methyl compound, 111, and is deshielded by 0.72 ppm compared to the

C-5 dimethyl thiohydantoin. This is expected, since the tendency to release electrons falls in more or less the following order:

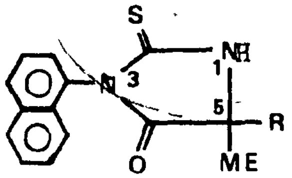
$$CH_3 > Phenyl > H$$

From Table 1-16 it becomes apparent that the shielding decreases in the same order i.e. Methyl-Phenyl-Hydrogen.

The C-4 carbonyl carbon chemical shifts are also listed in Table 1-16. From this Table it can be concluded that for the α-naphthyl thiohydantoins, as the tendency to release electrons by the C-5 carbon substituents decreases, the C-2 thiocarbonyl carbons are increasingly deshielded, whereas the C-4 carbonyl carbons are increasingly shielded. The observed large deshielding of the C-4 carbonyl carbon in α-naphthyl 5-methyl-5-phenyl-thiohydantoin, XV1, seems to be a function of the large steric bulk of the C-5 phenyl substituent which is sufficient to prevent the DMSO molecules effectively building up a solvent shell around the C-4 carbonyl carbon.

TABLE 1-16

The ^{13}C C-2 Thiocarbonyl and C-4 Carbonyl Carbon Chemical Shift Values in α-Naphthyl Thiohydantoins in Relation to the Substituents at the C-5 Carbon.



Thiohydantoin	Substituent at C-5, R	Chemical Shift (ppm)
For C-2 Thiocarbonyl Carbons :		
X1	Methyl	180.77
XV1	Phenyl	181.49
111	H	182.52
For C-4 Carbonyl Carbons :		
XV1	Phenyl [a]	177.79, 178.19
X1	Methyl	176.44
111	H	175.41, 175.21

[a] : Tendency to release electrons falls in more or less the following order : Methyl $\gg$ Phenyl $>$ H

C-5 . ^{13}C-CHEMICAL SHIFT VALUES OF THIOHYDANTOINS.

The C-5 ^{13}C chemical shift values are shown in Table 1-5. These values are seen to fall into two narrow ranges corresponding to the number of methyl groups at the C-5 position : 54.91 - 55.51 ppm for the thiohydantoins with one C-5 methyl; and 59.49 - 61.58 ppm for C-5 dimethyl thiohydantoins. The C-5 ^{13}C chemical shift value for the hydantoin V1 is 52.43 ppm.

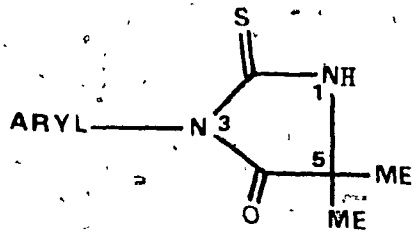
On the basis of their stereochemistry, the C-5 carbons in all the thiohydantoins with one C-5 methyl, which have diastereomeric rotamers, can be expected to show double peaks. It is noteworthy that even at a very large expansion of the spectrum, only rather sharp single peaks appeared for the C-5 carbon. It is possible that the elevated temperature of the probe did not permit the observation of separate peaks corresponding to diastereomeric rotamers because of internal rotation, but it is more likely that the chemical shift difference between the C-5 carbon atoms in diastereomeric rotamers is too small for resolution to be possible.

Downfield α-Methyl Substitution Shifts On C-5.

The observed α-methyl substituent shifts on the C-5 carbon for the addition of a methyl group at C-5 vary over the range 4.48 - 6.27 ppm and are presented in Table 1-17. For similarly substituted hydantoins, the substituent shifts for the addition of a second methyl group at C-5, as reported by Williams (12), are 5.7 ± 0.2 ppm.

T A B L E 1-17

The Downfield α-Methyl Substitution Effect on the ^{13}C Chemical Shift Values of the C-5 Carbon in Thiohydantoins.



Aryl Moiety	R = H,		R = Me.	ppm[a]
O-Tolyl	1	and	1X	4.48
2,3-Dimethylphenyl	11	and	X	5.77
α-Naphthyl	111	and	X1	5.47
O-Fluorophenyl	1V	and	X11	5.90
2-Methyl-4-Nitrophenyl	V	and	X111	6.27

[a] ppm from TMS

Contrary to the proposal by Williams (12) and Icli (11), the trend in the C-5 carbon chemical shift values is unlikely to be caused by the varying degree of conjugation between the aryl and the hetero rings, for the dihedral angle between these two rings has been observed to be about 82°(29) in one compound and is likely to be large in all compounds in the series.

It should be pointed out, as in the case of downfield β- and upfield γ-methyl substitution effects, that the α-methyl substitution effects as reported in Table 1-17 are the 'net' effects of various factors, the α-effect being the major one. Possibly, the variation in degree of solvation around the C-4 carbon is also important to some extent (about 1-2 ppm). The resonance and inductive effects, if any, are expected to contribute very little to the observed α-effects.

a- <u>2,3-Dimethylphenyl Thiohydantoins, 11 & X.</u>

The C-5 chemical shift values for the O-Tolyl, 1, and 2,3-Dimethylphenyl, 11, thiohydantoins with one C-5 methyl group are 55.01 and 54.91 ppm, respectively. The methyl group at the 3-aryl position exercises its buttressing influence upon the ortho methyl group and affects shielding of the C-5 carbon by 0.10 ppm. The magnitude of this shielding is low. However, in the C-5 dimethyl thiohydantoins, the C-5 carbon in X is deshielded, rather than shielded, by 1.19 ppm as compared to the corresponding carbon in 1X. The C-5 dimethyl groups are quite remote from the ortho methyl substituent and any direct steric interaction between them is highly improbable. As mentioned earlier under the discussion of 'cisoid' and 'transoid' conformers, the solvation at the carbonyl carbon, C-4, in the C-5 dimethyl compounds is not expected to occur to any significant level. In the absence of an effective solvent shell around C-4, the steric 'pressure' of the ortho substituent is unlikely to be transmitted to the C-5 carbon via its interaction with the C-5 'cisoid' methyl group. This is expected to deshield the C-5 carbon in X, as is observed.

b- Para Substituted-2-Methyl Thiohydantoins, V, V1, V11 & X111.

In the C-5 methyl series, the C-5 carbon in the 2-Methyl-4-Nitrophenyl thiohydantoin, V, is deshielded by 0.30 ppm as compared with the C-5 carbon in the O-Tolyl compound. From the comparison of shielding caused by the 'enhanced' steric bulk of ortho methyl in the 2,3-dimethylphenyl compound, 11, it is clear that the smaller shielding of the C-5 carbon in V cannot be attributed to the steric bulk of the aryl ortho substituent alone, but the polar substituent in the para position on the aryl ring may claim a significant contribution in the deshielding. That the polar substituent in the para position on the aryl ring has an important role to play in determining the shielding of the C-5 carbon, is evident from the examination of V and V11. Using the O-tolyl compound, 1, as reference, the C-5 carbon in V i.e. the 2-methyl-4-nitrophenyl compound, is deshielded by 0.30 ppm, whereas the C-5 carbon in V11 i.e. 2-methyl-4-methoxyphenyl compound is shielded by 0.10 ppm. Since conjugation between the aryl and the hetero rings is not likely to be important the shielding or deshielding effects are not transmitted to the C-5 carbon via changes in electron density over the hetero rings through resonance. The aryl ortho or the para substituent is too far away from the C-5 carbon to affect it in any direct way. One may imagine that variations in dihedral angle between the two rings, which are expected to depend on the nature of the aryl group substituent, could affect the C-5 carbon through disturbing the solvent shell around the C-4 carbonyl carbon. Apparently, the differences in the solvent shells around the C-2 and C-4 carbons in V and V11 are expected to be negligible and therefore, may not be considered to account for shielding of the C-5 carbon in V11 and deshielding of C-5 in V.

Perhaps the observed shieldings of the p-nitrophenyl and the p-methoxyphenyl thiohydantoins, V and V11, respectively, can be better rationalized on the basis of the inductive effect. In this connection, the resonance structures C to F (page 94) may be considered. The inductive effect in structures D and F is greater as compared to C and E. Moreover, D would be expected to enhance and F to reduce the shielding of the C-5 carbon through induction. The observation of a small shielding of the C-5 carbon in V11 and deshielding of the C-5 carbon in V lends support to this suggestion.

It is interesting to note that the 2,3-dimethylphenyl- and the 4-methoxy-2-methylphenyl thiohydantoins, 11 and V11 respectively, show identical chemical shift values at the C-5 carbon i.e. 54.91 ppm.

This observation may suggest that the shielding effect arising from the inductive effect (resonance structure D) in the thiohydantoin V11 is equivalent to the slight variations in the dihedral angle in the thiohydantoin 11 arising from the steric bulk effect of the meta methyl group, which in turn may cause variations in the solvent shells around the C-2 and C-4 carbons.

The C-5 carbon in the 2-methyl-4-nitrophenyl hydantoin V1, is deshielded by 0.14 ppm as compared to the O-tolyl hydantoin. Apparently, the difference in the solvation of C-2 and C-4 carbons in the thiohydantoins 1 and V is similar to that in the corresponding hydantoins. Moreover, conjugation between the aryl and the hetero rings is probably negligible in both the thiohydantoins and the hydantoins. Also the inductive effects of substituents are expected to be similar in the thiohydantoins and the hydantoins. Therefore, the greater deshielding, 0.30 ppm, of the C-5 carbon in V (with reference to the O-tolyl thiohydantoin, 1) as compared to the deshielding (0.14 ppm) of the C-5 carbon in the hydantoin V1 (with reference to the O-tolyl hydantoin) is apparently attributable to the presence of sulfur atom in the C-2 thiocarbonyl carbon.

A deeper look into the C-5 carbon chemical shift values in the C-5 dimethyl thiohydantoins is interesting. The C-5 carbon in the 2-methyl-4-nitrophenyl compound, X111, is strongly deshielded (2.09 ppm with respect to the O-tolyl compound, 1X, compared with 0.30 ppm in the C-5 methyl series.). This observation cannot be rationalized on the basis of the steric bulk of the ortho substituent alone. The resonance spread over both the aryl and the hetero rings is almost negligible because of the large dihedral angle between the two rings. The inductive effect of the para nitro group on the aryl ring, even in the structure like F is not likely to be the only factor responsible for such a large deshielding. It is conceivable that the reduced extent of solvation around C-4 is largely responsible for the deshielding of the C-5 carbon in the C-5 dimethyl thiohydantoin, X111.

c- Naphthyl Thiohydantoins, 111, V111, X1 and XV1.

The C-5 carbon in the α-naphthyl-5-methyl thiohydantoin, 111, is deshielded by 0.50 ppm as compared to the O-tolyl compound, 1; whereas the C-5 carbon in the β-naphthyl compound, V111, is deshielded by only 0.20 ppm. In the C-5 dimethyl series, the C-5 carbon in the α-naphthyl compound, X1, is deshielded by 1.49 ppm as compared to the O-tolyl compound, 1X. This large difference in deshielding i.e. 1.49 vs 0.50 ppm is considered to be mainly due to variations in the solvation pattern around the C-4 carbonyl group because the resonance and inductive effects in the C-5 dimethyl series are expected not to be considerably different from those in the C-5 methyl series.

When the C-5 chemical shifts of the C-5 disubstituted α-naphthyl compounds, X1 and XV1, are compared, the C-5 carbon in XV1, with 5-phenyl-5-methyl substituents, is 0.30 ppm more shielded than that in X1 with C-5 dimethyl groups, possibly because of the greater electron releasing tendency of the C-5 phenyl ring in XV1 as compared to that of the C-5 methyl group in X1.

d- Ortho Halogen Substituted Thiohydantoins, 1V, X11, X1V and XV.

In the C-5 methyl series, the C-5 carbon in the O-fluorophenyl compound, 1V, shows absorption almost similar to the O-tolyl compound, 1; but in the C-5 dimethyl series, the C-5 carbon in the O-fluorophenyl compound, X11, is 1.51 ppm deshielded as compared to that in the O-tolyl compound, 1X. The C-5 carbon in the O-chlorophenyl compound, X1V, is still more strongly deshielded, 1.75 ppm as compared with the O-Tolyl compound, 1X. However, the C-5 carbon in the O-bromophenyl thiohydantoin, XV, is less strongly deshielded i.e. by 1.11 ppm. It is possible that the electronic repulsion between the ortho halogen substituent and the oxygen atom of the C-4 carbonyl group and/or the oxygen of DMSO solvating the C-4 carbonyl group may change the dihedral angle between the aryl and the hetero rings significantly, resulting in variation in solvation around the carbonyl groups. The greater deshielding in the O-chlorophenyl thiohydantoin as compared with the O-fluorophenyl compound may be due to larger covalent radius of the chlorine atom as compared to the fluorine atom, resulting in larger interaction with the C-4 carbonyl group and/or the solvent shell around it. Although the bromine atom has larger covalent atomic radius than the chlorine atom, its smaller electronegativity, and therefore interaction, may cause slightly less deshielding of the C-5 carbon as compared to the O-chlorophenyl compound, as has been observed.

Comparison of C-5 ^{13}C Chemical Shifts of Thiohydantoins With Those of Hydantoins.

In C-5 methyl hydantoins with α-naphthyl, O-tolyl, O-trifluoromethylphenyl and O-chlorophenyl as aryl moieties, the C-5 chemical shifts are in the range of 50.67 - 52.83 ppm, and the double peaks corresponding to the two C-5 carbon chemical shifts in diastereomeric rotamers have been reported (12). In C-5 dimethyl hydantoins, the C-5 carbons have been reported to absorb over the range 57.6 - 58.4 ppm, Table 1-18.

In the C-5 methyl thiohydantoins, the C-5 carbons absorb over the region of 54.91 - 55.51 ppm, approximately 4 ppm downfield. The striking feature is that the double peaks corresponding to the C-5 carbons in diastereomeric rotamers were not observable, even with higher number of scans (4000-8000), higher commands to the computer for plotting the spectra at higher intensities and at very large expanded scale (about 4 feet). This is unexpected, since the C-2 thiocarbonyl group in thiohydantoins, because of its larger steric bulk than that of the C-2 carbonyl group in hydantoins, would be expected to force the aryl moiety to adapt a more restricted ground state conformation, hence rendering the diastereomeric rotamers to be observable more distinctly. The failure to observe separate peaks corresponding to the diastereomeric rotamers may possibly be due to slightly higher temperature of the probe, about 55-60 C^0, but it is more probable that the chemical shift difference of the diastereomeric C-5 carbons is too small for resolution to be possible.

The C-5 dimethyl series gave chemical shift values for the C-5 carbons over the range 59.49 - 61.58 ppm, approximately a range of 2.1 ppm as compared to the range of 0.8 ppm in corresponding hydantoins, Table 1-18. This absorption is about 2.3 ppm downfield compared to the hydantoins. The deshielding of the C-5 carbon by about 4 ppm in the C-5 methyl series and by about 2.3 ppm in the C-5 dimethyl series may be attributed to the presence of the C-2 thiocarbonyl group in thiohydantoins instead of the C-2 carbonyl group in the hydantoins and to the variations in the degree of solvation around the thiocarbonyl carbon.

In hydantoins, studied by Williams (12), the α-methyl substitution effect on the C-5 carbon is 5.8 ± 0.1 ppm for both the polar and non-polar orthosubstituents. For 2-thiohydantoins, the α-methyl substitution effect is 5.4 ± 1.0 ppm.

It has been suggested (12) that the trend in the C-5 carbon chemical shifts in the hydantoins may be due directly to the polar effects of the aryl substituents or to their steric effects. The C-5 carbons in the hydantoins with polar ortho substituents are deshielded over the range 0.4 - 0.6 ppm in the C-5 methyl series and 0.2 - 0.4 ppm in the C-5 dimethyl series; whereas in the thiohydantoins, the C-5 carbons are deshielded over the range 0.1 - 0.5 ppm in the C-5 methyl series and 1.1 - 2.1 ppm in the C-5 dimethyl series, Table 1-18.

In summary, the C-5 carbon chemical shift values in thiohydantoins are found to be dependent on the polarity of the

TABLE 1-18

Comparison of Regions of Absorption of C-5 ^{13}C Chemical Shifts (PPM) in Hydantoins (12) and 2-Thiohydantoins.

Type of Compound	Region	Range	Range of deshielding compared with corresponding O-Tolyl compound.
C-5 methyl hydantoin	50.67-52.83	2.16	0.4 - 0.6
C-5 methyl thiohydantoin	54.91-55.51	0.60	0.1 - 0.5
C-5 dimethyl hydantoin	57.60-58.40	0.8	0.2 - 0.4
C-5 dimethyl thiohydantoin.	59.49-61.58	2.1	1.1 - 2.1

ortho substituents and their steric effects, experienced by the C-5 carbons possibly through the perturbed and re-oriented unsymmetrical solvent shells around the C-4 carbonyl carbons. The large dihedral angles between the two rings do not allow the C-5 chemical shifts to be affected by variations in conjugation between the aryl and the hetero rings.

C-5 METHYL ^{13}C CHEMICAL SHIFT VALUES OF THIOHYDANTOINS.

The C-5 methyl ^{13}C chemical shift values are shown in Table 1-9. These values are seen to fall in two distinct regions: 15.34-17.34 ppm for the thiohydantoins 1-V and V11-V111 in the C-5 methyl series; and 22.70-25.32 ppm for the thiohydantoins 1X-XV1 in the C-5 dimethyl series. The only hydantoin, V1, showed chemical shift of 16.04 and 16.34 ppm for the diastereomeric C-5 methyl carbons.

As expected, all of the thiohydantoins in the C-5 methyl series showed double peaks corresponding to the diastereomeric C-5 methyl carbons. In the case of the thiohydantoin V111, β-naphthyl-5-methyl, the diastereomeric C-5 methyl carbon peaks appeared as singlet at the probe temperature 55-60 C°. At room temperature, after the achievement of efficient probe cooling, two peaks were distinctly observable at 15.35 and 16.14 ppm corresponding to the diastereomeric C-5 methyl carbons in V111.

Because of the larger steric bulk of the thiocarbonyl group in thiohydantoins as compared to the C-2 carbonyl group in the hydantoins, it is expected that the C-5 methyl peaks, corresponding to the diastereomeric rotamers in the C-5 methyl series and enantiomeric rotamers in the C-5 dimethyl series, may be well separated, since internal rotation is expected to be slow. The effect of the replacement of the oxygen atom is clearly observed in the Fourier Transform ^{13}C - nmr spectra of the thiohydantoins V, V1 and X11, Fig. 1-17, 1-18, and 1-24. The C-5 methyl signals for the respective rotamers are separated by only 0.30 ppm in V1. In the thiohydantoin V, C-5 methyl peaks separation is 0.80 ppm, and in the thiohydantoin X111, it is 1.20 ppm. In the FT-^{13}C-nmr spectrum of thiohydantoin X111, all peaks show a splitting of 5 Hz (0.20 ppm) due to ^{1}H-^{13}C spin-spin interaction as a result of incomplete decoupling. In this case, the centre of each doublet was taken for the purpose of comparison with other cases.

Downfield β-Methyl Substitution Effect on the C-5 Methyl Carbons.

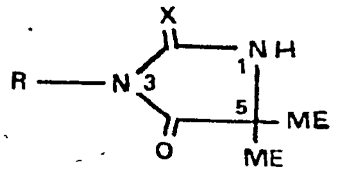
Because the C-5 methyl carbons show double peaks, the experimental β-methyl substituent shifts are taken as the chemical shift difference between the upfield peaks of the corresponding C-5 methyl and C-5 dimethyl thiohydantoins, and similarly for the downfield peaks. This assumes no crossover in relative assignments of the two peaks in each set of double peaks.

In the thiohydantoins, the average value of the downfield β-methyl substituent shift is 7.4 ± 0.3 and 7.8 ± 0.5 ppm for the high field and the low field signals, respectively, and is independent of relative assignments, and listed in Table 1-19.

In C-5 methyl and C-5 dimethyl hydantoins with the aryl moieties α-naphthyl, O-trifluoromethylphenyl, and O-chlorophenyl-, the β-methyl substituent shift on the C-5 methyl has been reported to be 7.6, 7.6 ; 7.3, 7.0 ; and 7.5, 7.1 ppm, respectively, (12). These results are included in Table 1-19. It has been suggested (12) that the unequal values of the β-methyl substituent shifts are due to the polarity of the ortho aryl substituents. In the present

TABLE 1 - 19

The β-Methyl Substituent Shift Differences of the C-5 Methyl Carbons in the 2-Thiohydantoins and the Hydantoins (12)



R		X	Low field (A) ppm	High field (B) ppm	A-B ppm	(β-Shift$_t^a$) - (β-Shift$_h^b$) Low Field	(β-Shift$_t^a$) - (β-Shift$_h^b$) High Field
0-Tolyl	1 & 1X	S	8.28	7.28	1.00	Nil	Nil
2,3-Dimethylphenyl	11 & X	S	7.66	7.36	0.30	+ 0.62	- 0.08
α-Naphthyl	111 & X1	S	7.30	7.14	0.16	+ 0.98	+ 0.16
0-Fluorophenyl	1V & X11	S	7.76	7.36	0.40	+ 0.52	- 0.08
2-Me-4-Nitrophenyl	V & X111	S	8.06	7.66	0.40	+ 0.22	- 0.38
α-Naphthyl		0	7.6	7.6	0.00		
0-CF$_3$-phenyl		0	7.0	7.3	0.3		
0-Chlorophenyl		0	7.45	7.13	0.32		
0-Tolyl		0	7.5	7.5	0.0		

b β-methyl substituent shift of the thiohydantoin
a β-methyl substituent shift of the 0-tolyl thiohydantoin

study, the O-tolyl thiohydantoins show unequal β-methyl substituent shift differences of 7.28 and 8.28 ppm, for the high field and the low field peaks, respectively. Similarly, the unequal values in the thiohydantoins 11 and X, 2,3-dimethylphenyl compounds, cannot be attributed to the polar effects of the ortho substituent, though as a special case, the increased steric bulk effect can be considered. Although the unequal β-methyl substituent shift values for the thiohydantoins V and X111, 2-methyl-4-nitrophenyl compound, can also be included in this discussion, the presence of p-nitro group on the aryl ring may need further consideration for its electron attracting character.

The difference between the β-methyl substituent shifts (for both the low and high fields) for four sets of compounds, relative to the low, and high field β-methyl effect in the O-tolyl thiohydantoins, 1 and 1X, are also included in Table 1-19. For example, it is clear from this Table that one of the C-5 methyl groups in the α-naphthyl compounds is strongly shielded (0.98 ppm) as compared to the corresponding C-5 methyl in the O-tolyl compound; whereas the remaining C-5 methyl in the α-naphthyl compound is slightly shielded (0.16 ppm) as compared to the remaining C-5 methyl group in the O-tolyl compound.

Since, as a general rule, the ^{13}C-shieldings have been observed to increase as the extent of steric crowding increases (31), the greater shielding of one of the C-5 dimethyl carbons in the α-naphthyl compound (0.98 ppm) compared to 0.62 ppm of one of the C-5 dimethyl carbons in the 2,3-dimethylphenyl compound, is not unexpected, because the α-naphthyl moiety should possess a larger steric bulk than the 2,3-dimethylphenyl moiety. In the case of the α-naphthyl compound, the steric crowding caused by the α-naphthyl moiety is so great that not only one of the C-5 methyl carbons is shielded but the other C-5 methyl carbon also feels the presence of the α-naphthyl group, since it is shielded (+ 0.16 ppm, Table 1-19).

In the 2,3-dimethylphenyl compound, the steric influence of the ortho methyl is experienced, via the solvent shell, by only one of the C-5 methyl groups and hence only that carbon is shielded ; whereas the other C-5 methyl carbon is slightly deshielded.

The buttressing effect of the aryl 3-methyl on the ortho methyl in 2,3-dimethylphenyl compound is greater than that of aryl-3-hydrogen on the ortho methyl in 2-methyl-4-nitrophenyl compound, therefore, a smaller value of β-methyl substituent effect is expected for the latter compound. This is indeed observed. One of the C-5 methyl carbons is shielded by only 0.22 ppm in X111 relative to the O-tolyl compound, whereas in X, 2,3-dimethylphenyl compound, it is shielded by 0.62 ppm. From these observations, one may conclude that the general rule of increasing shielding with the increase in steric crowding is also operative in the shieldings of the C-5 methyl and C-5 dimethyl thiohydantoins.

The greater shielding of one of the C-5 methyl carbons in the O-fluorophenyl compound, X11, as compared with that in the thiohydantoin X111, 2-methyl-4-nitrophenyl, may be attributed to the stronger electronegative character of the fluorine atom, although its steric bulk is much smaller than that of a methyl group. The relatively lower magnitude of shielding of the C-5 methyl carbon in X111 might also result from the presence of an electron withdrawing substituent in the para position on the aryl ring.

Since the ortho substituent on the aryl ring is well separated from the C-5 methyl groups so as not to have a non-bonded steric interaction between them, we may deduce that the effect of the steric crowding on the aryl ring should be transmitted to the C-5 methyl groups via re-orientation of the unsymmetrical solvent shell around the C-4 carbonyl carbon.

DMSO is like a rod-shaped molecule (33) and is different from acetone in having a non-planar configuration. It is well known from ^{1}H nmr measurements that the magnetic anisotropy in rod-shaped solvent molecules leads to low field shifts of the solute molecules (26). The methyl group of the 5,5-dimethyls, transoid to the ortho substituent, may be considered as lying in close proximity to the solvent shell around the thiocarbonyl group, where solvation is expected to be more effective as compared with the C-4 carbon. The variations in dihedral angles, arising from different substituents in the ortho positions, would give rise to different extents of interaction between the 'transoid' C-5 methyl group and the rod-shaped DMSO solvent shell around the C-2 carbon. The magnitude of deshielding of the 'transoid' C-5 methyl carbon, relative to the 0-tolyl compound and listed in Table 1-19, is expected to depend on the extent of such an interaction.

Another point of interest may be noted. No attempt seems to have been made so far to assign a particular peak to a given methyl group on the C-5 carbon. Fig. 1-5 shows β-methyl substitution shift differences on the C-5 methyl carbons in 2-thiohydantoins with respect to the β-methyl shifts in the 0-tolyl compounds, 1 and 1X. It shows that the C-5 methyl carbons in the α-naphthyl compounds, 111 and X1, experience the greatest shielding as compared to the other thiohydantoins, upon the addition of second methyl group at C-5. Further, it should be noted that in the thiohydantoins, the C-5 methyl carbons experience shielding in the order Naphthyl > 2,3-Dimethylphenyl > 2-Methyl-4-Nitrophenyl.

It is important to note that the low field signals corresponding to one of the C-5 methyl carbons in thiohydantoins show more pronounced displacement to higher field than the high field signals do to the lower field. Since steric crowding has been shown to increase shielding of the carbon under consideration (31) and the steric bulk is expected to increase in the order

Methyl > 2,3-Dimethylphenyl > α-Naphthyl

it may be inferred from Table 1-19 and Fig. 1-5 that the signals on the low field side correspond to those C-5 methyl carbons which are 'cisoid' to the ortho substituent. This idea is supported by the observation, Table 1-9, that the high field signals

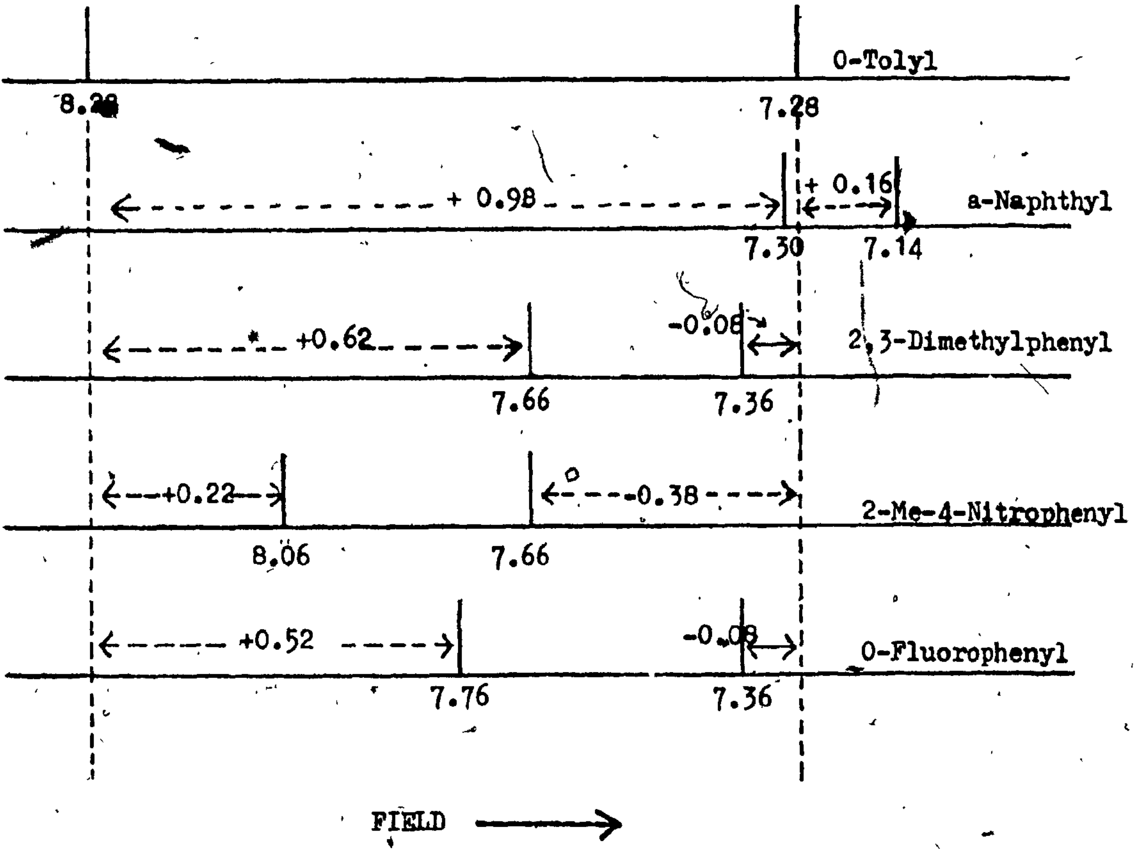


Fig. 1-5 : β-Methyl Substitution Shift Differences[a] on the C-5' Methyl Carbons in 2-Thiohydantoins With Respect To the β-Methyl Shifts in O-Tolyl Thiohydantoins.

[a] ppm (TMS)
+ = Shielding
- = Deshielding

corresponding to one of the C-5 methyl carbons consistently appear at 24.10 -24.20 ppm in almost all of the C-5 dimethyl thiohydantoins, whereas the low field signals show noticeable variations with respect to the aryl moieties. Thus, the assignments made on this basis are presented in Table 1-20.

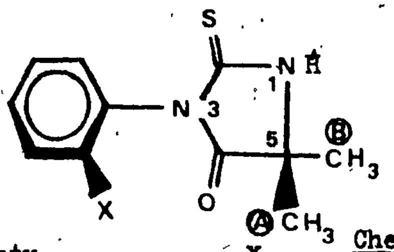
For the alkanes, the β-methyl substituent shift can be calculated for the addition of a second methyl group to a tertiary carbon (34). Using the notation of Grant and Paul :

$$\Delta\delta = \beta + 1^{\circ}\ (4^{\circ}) - 1^{\circ}\ (3^{\circ}) = 7.2 \pm 0.7 \text{ ppm}$$

In the thiohydantoins studied, the experimental β-substituent shifts, 7.78 ± 0.5 ppm, coincide with the result predicted from Grant-Paul parameters for the alkanes. Any change in conformation of the thiohydantoin ring upon addition of a second methyl group at the C-5 position might be expected to produce a further alteration in the hybridization of the C-5 carbon and in the bonding to the C-5 methyls, resulting in a shift from the predicted C-5 methyl chemical shift values. Since the experimental (7.78 ± 0.5 ppm) and the calculated, 7.2 ± 0.7 ppm, are in close agreement, it may be concluded that upon the addition of a second methyl group at C-5, either the thiohydantoin ring conformation does not change, or alternatively, that the methyl ^{13}C-chemical shifts are not sensitive to such a change in conformation.

TABLE. 1-20

Assignment of Signals to Each Methyl Carbon of the C-5 Dimethyl Groups in 2-Thiohydantoins.



No.	Aryl Moiety	X	Chemical Shift, ppm	
			CH$_3$ (A)	CH$_3$ (B)
1X	O-Tolyl	CH$_3$	24.12	25.32
X	2,3-Dimethylphenyl	CH$_3$	23.40	24.10
X1	α-Naphthyl	Naphthyl	23.44	24.10
X11	O-Fluorophenyl	F	23.30	24.10
X111	2-Methyl-4-Nitrophenyl	CH$_3$	23.00	24.20
X1V	O-Chlorophenyl	Cl	23.10	24.10
XV	O-Bromophenyl	Br	23.50	24.57

C-5 Methyl Peak Separations in Diastereomeric Rotamers.

It is interesting to compare the peak separation in the diastereomeric as well as enantiomeric rotamers in the thiohydantoins with those in the hydantoins. Table 1-21 shows the peak separations in ppm of the isomeric rotamers in both the hydantoins and the thiohydantoins, as well as the differences in the chemical shifts of the low and high field isomers in thiohydantoins relative to the hydantoins.

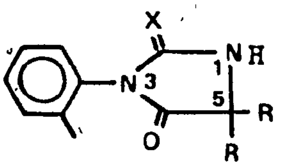
Table 1-21 shows that in the C-5 methyl thiohydantoins, the rotamers absorbing on the low as well as the high field side, are shielded by 0.2 - 0.9 ppm as compared to the corresponding rotamers in the hydantoins. In the C-5 dimethyl thiohydantoins, the C-5 carbons in both the low and the high field rotamers are shielded by 0.7 - 1.20 ppm, except in the O-tolyl compound, as compared to the corresponding rotamers in the hydantoins.

a- O-Tolyl Compounds :

The diastereomeric rotamers in the O-tolyl thiohydantoin and the O-tolyl hydantoin give rise to signals at 16.84, 17.04 ; and 17.10, 17.60 ppm, respectively, as shown in Fig. 1-6. It is clear from Fig. 1-6 that the diastereomeric separation of peaks for the C-5 methyl carbons in the O-tolyl thiohydantoin is smaller (0.20 ppm) as compared to the corresponding hydantoin (0.50 ppm). In the O-tolyl thiohydantoin, the C-5 methyl carbon

TABLE 1-21

C-5 Methyl ^{13}C-Chemical Shift Difference (PPM) in the Low and the High Field Isomeric Rotamers in 2-Thiohydantoins, Relative to the Corresponding Isomers in the Hydantoins;[12] and Their Respective Peak Separations (PPM).



ARYL	R_1	R_2	Low Field	High Field	Separation in Isomeric peaks X: O	Separation in Isomeric peaks X: S
DIASTEREOMERIC ROTAMERS :						
O-Tolyl	H	CH_3	+0.56	+0.26	0.50	0.20
α-Naphthyl	H	CH_3	+0.84	+0.74	0.60	0.50
2-Me-4-NO_2 -Ph	H	CH_3	+0.20	+0.70	0.30	0.80
ENANTIOMERIC ROTAMERS:						
O-Tolyl	CH_3	CH_3	-0.20	+0.30	0.70	1.20
α-Naphthyl	CH_3	CH_3	+1.20	+1.20	0.63	0.66
O-Chlorophenyl	CH_3	CH_3	+0.80	+1.00	0.80	1.00
O-Bromophenyl	CH_3	CH_3	+0.90	+0.74	0.76	0.60

+ = Shielding
- = Deshielding

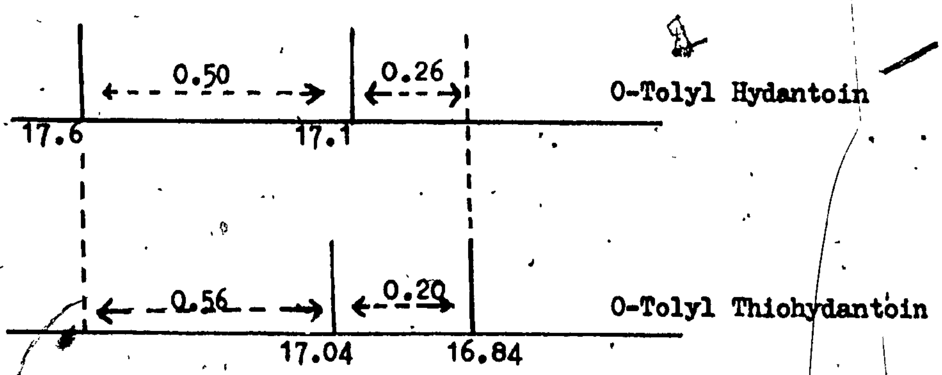


Fig. 1-6 : Diastereomeric C-5 Methyl Signals in the O-Tolyl Hydantoin and O-Tolyl Thiohydantoin.

in the high field diastereomer is shielded by 0.26 ppm ; whereas in the low field diastereomer, it is shielded by 0.56 ppm.

b- <u>2-Methyl-4-Nitrophenyl Compounds</u> :

With the 2-methyl-4-nitrophenyl moieties in the hydantoins and the thiohydantoins, the peak positions corresponding to the diastereomeric C-5 methyl carbons are shown in Fig. 1-7. It is clear from Fig. 1-7 that the separation in the peaks of the diastereomeric C-5 methyl carbons in the hydantoin is less (0.30 ppm) than in the thiohydantoin (0.80 ppm). The C-5 methyl carbon in the high field diastereomer is shielded by 0.70 ppm whereas in the low field diastereomer, it is shielded by 0.20 ppm.

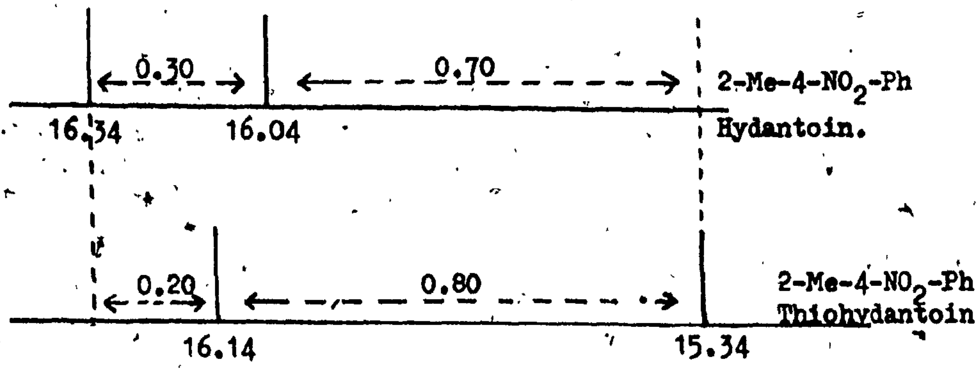


Fig. 1-7 : Diastereomeric C-5 Methyl Signals With 2-Methyl-4-Nitrophenyl moiety in Hydantoin and Thiohydantoin.

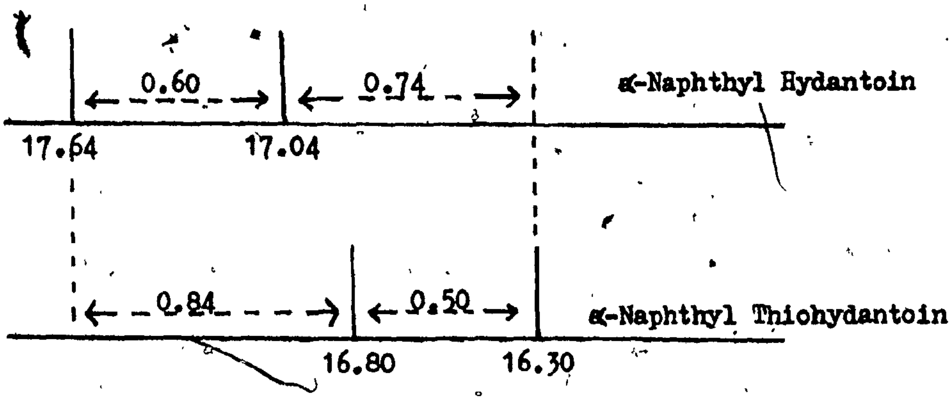


Fig. 1-8 : Diastereomeric C-5 Methyl Signals in α-Naphthyl Hydantoin and α-Naphthyl Thiohydantoin.

c- α-Naphthyl Compounds :

With the α-Naphthyl moieties in the hydantoin and the thiohydantoin, the peak positions corresponding to the diastereomeric C-5 methyl carbons are shown in Fig. 1-8. It can be seen from this Fig. that in the hydantoin, the C-5 methyl carbons in the diastereomers are separated by 0.60 ppm, whereas in the corresponding thiohydantoin, they are separated by 0.50 ppm. Furthermore, in the thiohydantoin, the C-5 methyl carbon in the high field diastereomer is shielded by 0.74 ppm ; whereas in the low field diastereomer, it is shielded by 0.84 ppm as compared to the corresponding carbons in the α-naphthyl hydantoin.

C-5 METHYL PEAK SEPARATIONS IN ENANTIOMERIC ROTAMERS :

a- O-Tolyl Compounds.

The peak positions for the enantioneric C-5 methyl carbons in the hydantoin and the thiohydantoin with O-tolyl moieties are shown in Fig. 1-9. The enantiomeric C-5 methyl groups in the hydantoin are separated by 0.70 ppm, whereas in the corresponding thiohydantoin, they are separated by 1.20 ppm. In the thiohydantoin the C-5 methyl carbon in the high field enantiomer is shielded by 0.30 ppm; whereas in the low field enantiomer, it is deshielded by 0.20 ppm.

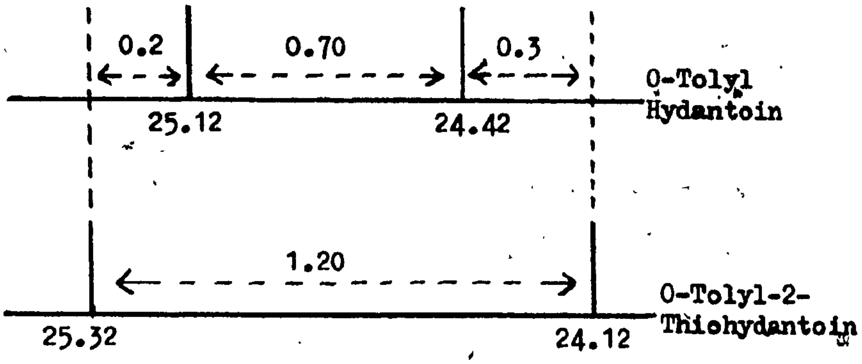


Fig. 1-9 : Enantiomeric C-5 Methyl Signals in the O-Tolyl Hydantoin and the O-Tolyl-2-Thiohydantoin.

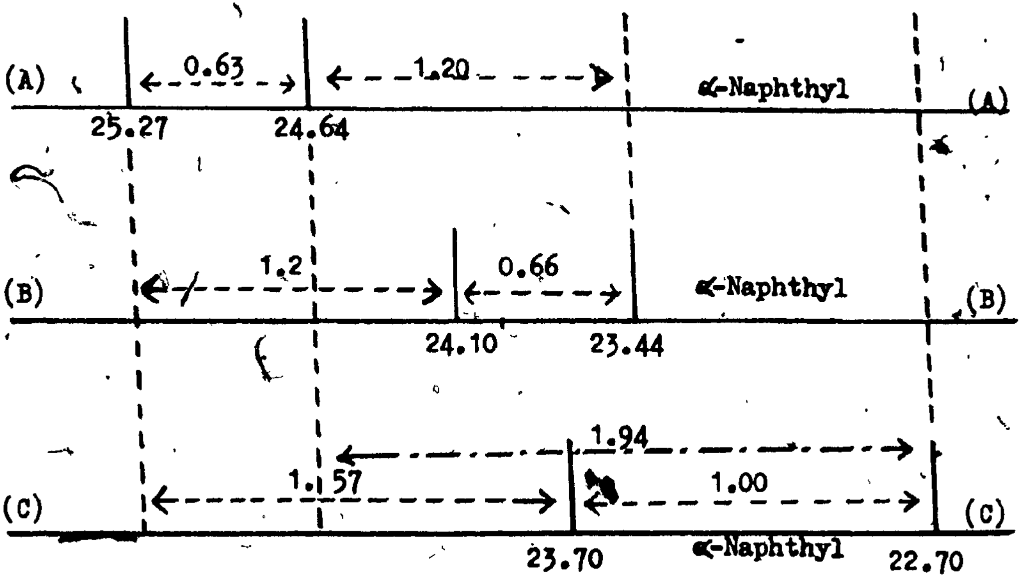


Fig. 1-10 : C-5 Methyl Signals in the C-5 Dimethyl α-Naphthyl Hydantoin (A), C-5 Dimethyl-2-Thio-Hydantoin (B) and the 5-Methyl-5-Phenyl-2-Thiohydantoin (C)

b- α-Naphthyl Compounds.

The peak positions for the enantiomeric C-5 methyl carbons in the α-naphthyl hydantoin and the α-naphthyl thiohydantoins, X1 and XV1, are shown in Fig. 1-10. The C-5 methyl carbons in the enantiomer are almost equally separated in the α-naphthyl hydantoin and the α-naphthyl thiohydantoin i.e. 0.63 and 0.66 ppm, respectively. The C-5 methyl carbon in each of the low and high field enantiomeric rotamers in thiohydantoin is shielded by 1.20 ppm as compared to the corresponding hydantoin.

The C-5 diastereomeric methyl carbons in the α-naphthyl 5-methyl-5-phenyl thiohydantoin, XV1, are separated by 1.00 ppm. The C-5 methyl carbon in the high field diastereomer is shielded by 1.94 and 0.74 ppm compared with the 5,5-dimethyl hydantoin and the thiohydantoin, respectively ; whereas the C-5 methyl carbon in the low field diastereomer in XV1 is shielded by 1.57 and 0.47 ppm compared to the 5,5-dimethyl hydantoin and the thiohydantoin.

c- Halogen Compounds.

The enantiomeric C-5 methyl peak separations in the hydantoin and the thiohydantoin each with O-chlorophenyl and O-bromophenyl moieties are shown in Fig. 1-11 and 1-12, respectively. The peak separations in the enantiomeric C-5 methyl carbons in the O-chlorophenyl and the O-bromophenyl

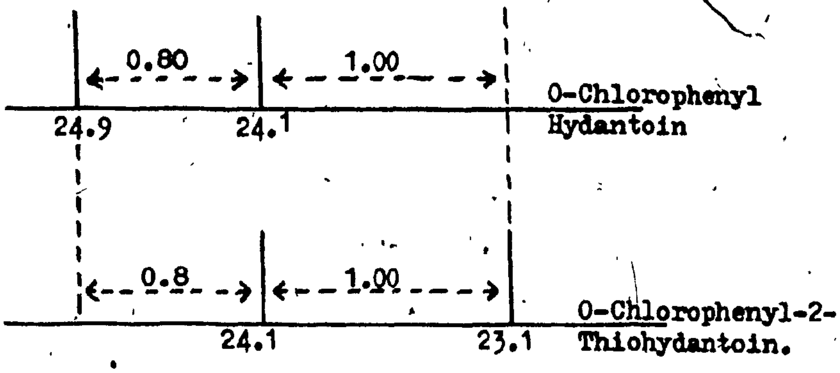


Fig. 1-11 : Enantiomeric C-5 Methyl Signals in the O-Chlorophenyl Hydantoin and the O-Chlorophenyl-2-Thiohydantoin.

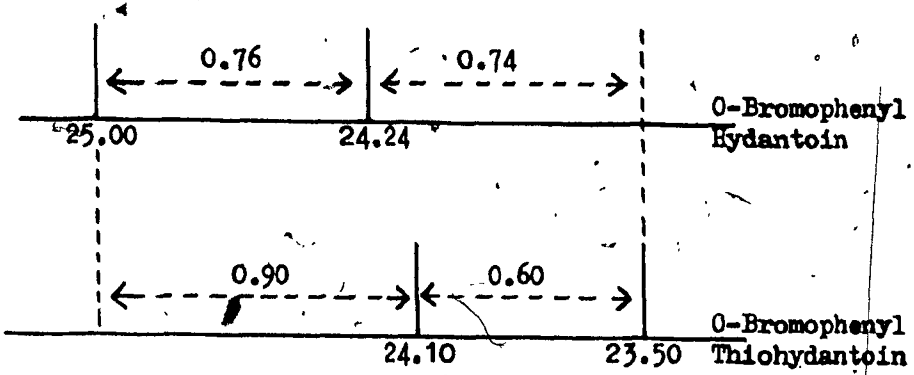


Fig. 1-12 : Enantiomeric C-5 Methyl Signals in the O-Bromophenyl Hydantoin and the O-Bromophenyl-2-Thiohydantoin.

hydantoins are 0.80 and 0.76 ppm, respectively; whereas in the corresponding thiohydantoins, they are 1.0 and 0.60 ppm, respectively. In the thiohydantoins, the C-5 methyl carbons in the high field enantiomers are shielded by 1.0 and 0.74 ppm in X1V and XV, respectively; whereas in the low field enantiomers, they are shielded by 0.8 and 0.9 ppm, respectively.

In 3-aryl-5-methyl hydantoins, the C-5 methyl carbons absorb over the range 17.2 ± 0.2 ppm ; and the 5,5-dimethyl carbons absorb over the range 24.6 ± 0.6 ppm. The C-5 methyl carbons in the corresponding thiohydantoins show chemical shift values over the range 16.3 ± 1.0 ppm and the C-5 dimethyl carbons in the range 24.0 ± 1.3 ppm. Thus it is clear that in the thiohydantoins, the C-5 methyl carbons absorb about 1.1 ± 0.6 ppm to high field and the C-5 dimethyl carbons about 0.5 - 1.0 ppm to high field as compared to the corresponding hydantoins.

Table 1-21 shows that the chemical shift separations between the two isomeric rotamers of a given hydantoin are generally comparable to those in the corresponding thiohydantoins.

It is interesting to note that in the thiohydantoins, the high field shifts of the two isomeric rotamers of a given compound relative to the chemical shift of the similar isomers in the hydantoin, are not equal, except for the α-naphthyl-5,5-dimethyl thiohydantoin, X1. The equal displacement of the chemical shifts, to the high field, of both the isomers in the α-naphthyl thiohydantoin, X1, seems to be associated with the equal peak separations of the isomers in both the hydantoin and the thio-

-hydantoin, since a similar trend is also observable in other compounds , Table 1-21.

Fig. 1-9 for the enantiomeric C-5 methyl signals for the O-tolyl thiohydantoin shows deviations from the regular pattern set by other thiohydantoins studied in this work. Generally, both the isomeric rotamers of a given thiohydantoin are shielded relative to the corresponding isomeric rotamers in the hydantoins. In the O-tolyl thiohydantoin, the high field enantiomeric rotamer is shielded by 0.30 ppm relative to the corresponding high field rotamer in the hydantoin ; whereas the low field rotamer is deshielded by 0.20 ppm relative to the corresponding low field rotamer in the hydantoin.

ASSIGNMENT OF THE ORTHO METHYL PEAKS IN THE THIOHYDANTOINS :

The methyl region of the C-13 F T ~~NMR~~ spectrum may contain a number of peaks which may lead to confusion. Therefore, one should be careful in the assignment of these peaks to a given methyl carbon.

In thiohydantoins 1X -XV1, which have 5,5-dimethyl groups, a number of methyl signals appear. Fortunately, methyl signals at the C-5 carbon are very well separated (by about 7-8 ppm) from the aryl methyl signals. In the case of X, the signals for the 2,3-dimethyl carbons on the aryl ring can easily be recognized at 13.50 and 19.52 ppm, Fig. 1-22, since in 2,3-dimethyl-aniline, these appear at 12.70 and 20.60 ppm and in the N,N-2,3-tetramethylaniline, these signals appear at 14.1 and

20.8 ppm (23). The α-naphthyl (Fig. 1-23), the O-fluorophenyl, the O-chlorophenyl (Fig. 1-25) and the O-bromophenyl thiohydantoins have only C-5 dimethyl groups, which can be identified immediately. The O-methyl group in X111 can easily be recognized because it is much separated from the double peaks of equal intensities corresponding to the C-5 dimethyl groups, Fig. 1-24. The ortho tolyl peak in 1X is clearly well separated from the two peaks of equal intensity corresponding to the C-5 dimethyl groups, Fig. 1-21.

Thus in the case of the C-5 dimethyl thiohydantoins, the assignment of methyl peaks is straightforward and simple, and therefore, no ambiguity can arise from their spectra.

The complications may arise in the case of C-5 methyl thiohydantoins 1-V and V11-V111 and the hydantoin V1. The α-naphthyl, 111, Fig. 1-15, O-fluorophenyl, 1V, Fig. 1-16, and the β-naphthyl, V111, Fig. 1-20, thiohydantoins do not present any problem because they lack any ortho methyl substituent, and the peaks corresponding to their C-5 methyl diastereomers can easily be identified. Similarly, for the thiohydantoin 11, Fig. 1-14, the situation is simplified by considering the highest and the lowest field peaks corresponding to the 2-methyl and the 3-methyl carbons on the aryl ring (23). Thus the remaining peaks should correspond to the diastereomeric rotamers of the C-5 methyl carbons.

The ortho methyl peak in X111, Fig. 1-24, appears at 16.84 ppm, therefore, in the corresponding C-5 methyl compounds V, Fig. 1-17, and V1, Fig. 1-18, the methyl peaks at 16.94, 17.14 ;

and 16.74, 16.94 ppm should correspond to the ortho methyl carbons in V and V1, respectively. The remaining peaks at 15.34, 16.14 ppm ; and 16.04, 16.34 ppm, then, should correspond to the respective C-5 methyl carbons in the diastereomers of V and V1, respectively.

In Fig. 1-21, the O-tolyl peak in 1X appears at 16.14 ppm. Therefore, in the thiohydantoin 1, Fig. 1-13, the tolyl peaks (for the diastereomeric rotamers) would be at 15.94 and 16.44 ppm, and unlikely to be at 16.84 and 17.04 ppm. Similarly, in the thiohydantoin V11, Fig. 1-19, the ortho methyl peak is assigned to 16.34 and 16.74 ppm for the rotamers, since the ortho methyl peaks have been generally found to absorb in the range 16.0 - 17.0 ppm, and the variations in their chemical shifts are very small e.g. Icli (11) has reported the chemical shift of 17.9 ppm for the ortho methyl groups in the hydantoins regardless of the C-5 carbon bearing mono or dimethyl substituents. Similarly, Williams (12) has reported that the ortho methyl substituents in hydantoins absorb over the range 16.87 - 16,90 ppm.

In summary, although a number of methyl peaks appear in the methyl region of the F T C-13 nmr spectra, it was found relatively easy to assign these peaks to a given methyl carbon with confidence. Thus, there is no ambiguity in the assignment of peaks in the FT C-13 nmr spectra of 3-aryl-2-thiohydantoins.

EXPERIMENTAL

General Procedures :

A Gallenkamp melting point apparatus was used for the determination of melting points. The reported figures are uncorrected.

All the Infrared spectra of the products that are solid were taken through fused KBr discs. The spectra of the liquid products were taken through neat liquid films held between NaCl plates. In all cases, the spectra were recorded on a Perkin-Elmer 457 spectrometer. The peak positions reported are within ± 5 cm^{-1}.

^{1}HNMR spectra were recorded on Varian A-60 NMR spectrometer. The concentration of the samples were never noted but were always adjusted to give a reasonable S/N ratio. Usually Dimethyl sulfoxide-d_6 was used as solvent but in some cases, other solvents e.g. $CDCl_3$ or Pyridine were also used in addition to DMSO-d_6. In such cases, solvents are reported along with the NMR data.

^{13}C NMR spectra were obtained by employing Varian-HA-100 NMR spectrometer in conjunction with various auxiliaries e.g. Hewlett-Packard (HP) 2114 A computer, HP 2020 Digital Tape Unit, HP 7001 AM X-Y Recorder, HP 4204 A Oscillator (10 Hz - 1 MHz), HP 5255 Frequency Converter (3 - 12.4 GHz), HP Oscill-oscope Model 120 B, COMPLOT Plotter, Tektronix Pulse Generator (2600 series), Tektronix Oscill-oscope Type 561 A, Digital to Analog Convertor, Varian 3512-1 Heteronuclear Decoupler, Varian RF/AF Sweep Unit, Varian V-4311 Fixed Frequency RF Unit (25.1 MHz), Digilab Radio frequency Pulse Amplifier (Pulser 400-2) e.t.c. The chapter entitled "Modifications in Instrumentation" briefly describes the improvements and modifications performed in the conventional Varian HA-100 NMR spectrometer in order to carry out faster and more accurate Fourier transform ^{13}C NMR studies.

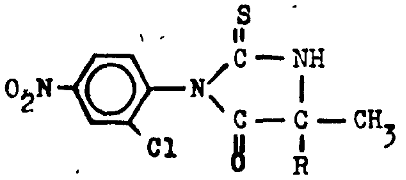
In all cases, DMSO was used as solvent which also provided the lock signal and the internal reference. The concentrations of the solutions of thiohydantoins in DMSO varied in the range of 20-40 % w/v. The number of scans varied from 2,000 - 10,000, and each spectrum was run with at least two different analytical frequencies.

Chemical shift values are reported relative to TMS and were calculated by taking the chemical shift of DMSO to be 40.40 ppm downfield from TMS. All chemical shift values are estimated to be accurate to 0.05 ppm (2.0 Hz) unless otherwise indicated. All the spectra were measured by doubly irradiating either near the aryl region or near the methyl region for noise proton decoupling of ^{13}C(H).

One of the compounds studied, 3-(1-Naphthyl)-5,5-dimethyl-2-thiohydantoin, X1, was also run in $CDCl_3$ to estimate the direction and magnitude of solvent-induced chemical shifts on the carbons in the thiohydantoin ring.

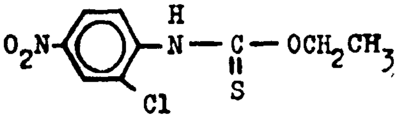
UNSUCCESSFUL SYNTHESES :

The syntheses of 3N-(2-chloro-4-nitrophenyl)-5-methyl-2-thiohydantoin (A) and 3N-(2-chloro-4-nitrophenyl)-5,5-dimethyl-2-thiohydantoin (B) did not turn out to be successful, but resulted in the formation of thiocarbamate (C). Yellow crystals, mp 109.0-110.0 C^{o}. Elemental Analysis : Calculated % : C, 41.46; H, 3.48;



(A) R = H

(B) R = CH_3



(C)

N, 10.75; O, 18.41; Cl, 13.60 and S, 12.27., Found : C, 41.20; H, 3.62; N, 10.93; O, 18.04; Cl, 14.53 and S, 11.70.

^{1}HNMR ($CDCl_3$, δ TMS) 1.60 (1:2:1 triplet, 3H, methyl protons), 4.84 (1:3:3:1 quartet, 2H, methylene protons), 8.10-8.83 (multiplet, 4H, phenyl protons and N-H), Fig. 1-26.

^{13}C-NMR ($CDCl_3$, δ TMS) 187.10 (thiocarbonyl carbon of predominant isomer), 188.24 (thiocarbonyl carbon of minor isomer), 143.85 (C-1), 140.10 (C-4), 125.4 (C-3), 124.06 (C-2), 123.40 (C-5) and 121.90 (C-6), Fig. 1-27. These assignments were compared with the values calculated from ' ^{13}C-Substituent Effects of Substituted Benzenes', (30, pp 81), 68.95 (CH_2) and 14.49 (CH_3).

The observation of two distinct signals in the ^{13}C-NMR spectrum (Fig. 1-27) corresponding to two thiocarbonyl carbons suggests the presence of syn- and anti- rotational isomers.

The IR spectrum (KBr) showed the absence of carbonyl peak in the region 1600 - 1800 Cm^{-1}.

ARYL ISOTHIOCYANATES

The following aryl isothiocyanates were commercially available and used as such :

a- O-Fluorophenyl isothiocyanate (PFALTZ & BAUER, Inc. N.Y.), M.Wt. 153.176

b- O-Tolyl isothiocyanate (ICN, K & K Labs. Inc.) M. Wt. 150.222

c- 1-Naphthyl isothiocyanate (Eastman), M. Wt. 185.24

d- 2-Naphthyl isothiocyanate (PFALTZ & BAUER) M. Wt. 185.24

The following aryl isothiocyanates were synthesised.

1- 2-Chlorophenyl Isothiocyanate (M. Wt. 169.633)

The method followed was that of Coghill and Johnson (36). 2-chloroaniline (B.D.H; M. Wt. 127.57) 8.292 g (0.065 mole) was added to 300 ml of dry ethyl acetate to which 20.0 g (0.174 mole) of thiophosgene (Baker, M. Wt. 114.98) was added little by little. The reaction was carried out in a fume hood. The reaction mixture was refluxed for about one hour until the hydrochloride went into the solution. The solvent was evaporated under reduced pressure and 50 ml of hot toluene was added. It was further evaporated employing reduced pressure, and the isothiocyanate so obtained was used as such for the preparation of the corresponding thiohydantoin.

IR spectrum showed a broad band (CNS) centered at 2100 cm^{-1}. The yield of the isothiocyanate was 7.032 g or 63.77 %.

11- 2,3-Dimethylphenyl Isothiocyanate (M. Wt. 163.24)

This compound was prepared by the method described above. Starting materials: 2,3-dimethylaniline (Eastman, M. Wt. 121.18) 12.118 g (0.10 mole), thiophosgene (Baker, M. Wt. 114.98) 25.8 g (0.224 mole), dry ethyl acetate 100 ml, reflux time two hours. The IR spectrum showed a broad band (CNS) centered at 2100 cm^{-1}. The yield of the isothiocyanate was 6.982 g or 42.77 %.

III - 2 Methyl-4-Nitrophenyl Isothiocyanate (M. Wt. 194.22)

This compound was prepared by the method described above. Starting materials: 2-Methyl-4-Nitroaniline (Eastman, M. Wt. 152.16) 6.086 g (0.040 mole), Thiophosgene (Baker, M.Wt. 114.98) 8.0 g (0.069 mole). The IR spectrum showed a broad band (CNS) centered at 2075 cm^{-1}. The yield of the isothiocyanate was 3.340 g or 43.0%.

IV- 2 Methyl-4-Methoxyphenyl Isothiocyanate (M. Wt. 179.24)

This compound was prepared by the method described above. Starting materials: 4-Methoxy-2-Methylaniline (Aldrich, M.Wt. 137.18) 10.0 g (0.073 mole), Thiophosgene (Baker, M.Wt. 114.98) 15.0 g (0.130 mole). The IR spectrum showed a broad band (CNS) at 2100 - 2150 cm^{-1}. The yield of the isothiocyanate was 5.82 g or 44.5%.

V- 2-Bromophenyl Isothiocyanate (M. Wt. 214.09)

This compound was prepared by the method described above. Starting materials: 2-Bromoaniline (Baker, M. Wt. 172.03) 10.0 g (0.058 mole), Thiosphosgene (Baker, M. Wt. 114.98) 12.0 g (0.104 mole). The IR spectrum showed a broad band (CNS) centered at 2100 cm^{-1}. The yield of the isothiocyanate was 7.242 g or 58.32%.

ARYL ISOCYANATE

V1- 2-Methyl-4-Nitrophenyl Isocyanate (M. Wt. 178.154)

The procedure followed is an adaptation of that used by Shriner, Horne and Cox (37).

Dry ethyl acetate (150 ml) was saturated with phosgene at room temperature. A solution of 15.216 g (0.1 mole) of 2-methyl-4-nitroaniline (Eastman, M. Wt. 152.16) in 100 ml of dry ethyl acetate was added slowly. Toward the end of addition, the reaction mixture was heated gently to dissolve the lumps of aniline added. The ethyl acetate solvent was removed under reduced pressure as much as possible and the remaining isocyanate was kept overnight in a dessicator under vacuum at room temperature. It was then used for the preparation of the corresponding hydantoin. The yield of the isocyanate was 6.79 g or 38.1 %.

PREPARATION OF 3-ARYL THIOHYDANTOINS

1- 3-(o-Tolyl)-5-Methyl-2-Thiohydantoin (M. Wt. 220.30)

The procedure followed was that of Pujari and Rout (38).

DL-Alanine (Aldrich, M. Wt. 89.09) 1.336 g (0.015 mole) was dissolved in 2 ml (0.111 mole) of water and 1.0 g (0.025 mole) of NaOH was added. To this solution, a solution of o-tolyl isothiocyanate (2.984 g, 0.020 mole) in 20 ml of absolute ethanol was added dropwise. The resulting solution was refluxed for 2 hrs, then 25 ml of hot 6N HCl was added. The thiohydantoin precipitated and was crystallised twice from 95% ethanol-water mixture. The yield of the thiohydantoin was 0.4 g or 12.12%; mp 215-16 C^{o}. ^{1}H nmr (DMSO-d_6, δ) 1.41 (3H, doublet, C-5 methyl protons, J=7 Hz, each peak shows diastereomeric splitting of 0.9 Hz i.e. 0.015 ppm), 2.07 (3H, singlet, o-methyl protons, diastereomeric splitting of 2.4 Hz i.e. (0.04 ppm), 4.5 (1H, quartet, C-5 hydrogen), 7.25 (4H, multiplet, phenyl protons). ^{13}C nme (DMSO, δ_{TMS}) 182.77 (C-2 thiocarbonyl carbon), 174.41 (C-4 carbonyl carbon), 55.01 (C-5 carbon), 15.94 and 16.44 (diastereomeric O-methyl carbons), 16.84 and 17.04 (diastereomeric C-5 methyl carbons).

11 - <u>3-(2,3-Dimethylphenyl)-5-Methyl-2-Thiohydantoin</u> (M.Wt. 234.32)

This compound was prepared by the method described above. Starting materials: DL-Alanine (Aldrich, M. Wt. 89.09) 1.782 g (0.020 mole), 2,3-Dimethylphenyl isothiocyanate (4.080 g, 0.025 mole). The yield of the thiohydantoin was 0.425 g or 9.07%.

^{1}H nmr (DMSO-d_6, δ) 1.43 (3H, doublet, C-5 methyl protons, J=7 Hz), 1.93 (3H, singlet, aryl methyl protons, diastereomeric splitting of 8.0 Hz i.e. 0.13 ppm), 2.30 (3H, singlet, aryl methyl protons, diastereomeric splitting of 4.0 Hz i.e. 0.066 ppm), 4.46 (1H, quartet, C-5 hydrogen), 7.17 (3H, multiplet, phenyl protons).

^{1}H nmr (pyridine, δ) 1.60 (3H, doublet, C-5 Methyl protons, J=7 Hz, diastereomeric splitting of 1.5 Hz i.e. 0.025 ppm), 2.17 (3H, singlet, aryl methyl protons), 2.52 (3H, singlet, aryl methyl protons), 5.83 (1H, quartet, C-5 hydrogen), 7.2 - 7.8 (multiplet, phenyl and pyridyl protons). ^{13}c nmr (DMSO, δ_{TMS}) 182.77 (C-2 thiocarbonyl carbon), 174.73 (C-4 carbonyl carbon), 54.91 (C-5 carbon), 13.26 and 13.66 (diastereomeric O-methyl carbons), 19.02, 20.02 (diastereomeric m-methyl carbons), 16.04, 16.44 (diastereomeric C-5 methyl carbons).

111 - <u>3-(α-Naphthyl)-5-Methyl-2-Thiohydantoin</u> (M. Wt. 256.24)

This compound was prepared by the method described above. Starting materials: DL-Alanine (Aldrich, M. Wt. 89.09) 2.4 g (0.027 mole), α-Naphthyl isothiocyanate (Eastman, M. Wt. 185.24) 4.631 g (0.025 mole). The yield of the thiohydantoin was 4.30 g or 67.12%: mp 235-6 C^o; ^{1}H nmr (DMSO-d_6, δ) 1.58 (3H, doublet, C-5 methyl protons, J = 7 Hz, diastereomeric splitting is 1.8 Hz i.e. 0.03 ppm), 7.58 (7 H, multiplet, Naphthyl protons). ^{13}C nmr (DMSO, δ_{TMS}) 182.52 (C-2 thiocarbonyl carbon), 175.41, 175.21 (diastereomeric splitting of C-4 carbonyl carbon), 55.51 (C-5 Carbon), 16.30, 16.80 (diastereomeric splitting of C-5 methyl carbon).

1V- <u>3-(O-Fluorophenyl)-5-Methyl-2-Thiohydantoin</u> (M. Wt. 224.26)

This compound was prepared by the method described above. Starting materials : DL-Alanine (Aldrich, M. Wt. 89.09) 2.40 g (0.027 mole); O-Fluorophenyl isothiocyanate (Pfaltz & Bauer, M. Wt. 153.176) 3.83 g (0.025 mole). The yield of the thiohydantoin was 3.7 g or 66.0 %. mp 170.0-171.0 C^{o}.

^{1}H nmr (DMSO-d_6 , δ) 1.33, 1.45 (3H, doublet, C-5 methyl protons, J = 7 Hz, diastereomeric splitting is 2.0 Hz i.e. 0.033 ppm), 4.55 (1H, quartet, C-5 hydrogen, diastereomeric splitting of 2.0 Hz i.e. 0.033 ppm) 7.4 (4H, multiplet, phenyl protons).

^{13}C nmr (DMSO, δ_{TMS}) 181.56 (C-2 thiocarbonyl carbon), 174.41, 174.01 (diastereomeric splitting of C-4 carbonyl carbon), 55.10 (C-5 carbon), 15.94, 16.34 (diastereomeric splitting of C-5 methyl carbon).

V- <u>3-(2-Methyl-4-Nitrophenyl)-5-Methyl-2-Thiohydantoin</u> (M. Wt. 265.28)

This compound was prepared by the method described above, but instead of 2 ml of water, 5 ml of DMF was used. When water was used, the synthesis of this thiohydantoin was always unsuccessful.

Starting materials : DL-Alanine (Aldrich, M. Wt. 89.09) 2.673 g (0.03 mole), 2-Methyl-4-Nitrophenyl isothiocyanate (M. Wt. 194.22) 6.435 g (0.03 mole). The yield of the thiohydantoin was 0.337 g or 4.23 %. mp 206.0-206.5 C°.

Analysis. Calculated for $C_{11}H_{11}N_3O_3S$: C, 49.80 %; H, 4.18 %; N, 15.84 %; O, 18.09 %; S, 12.09 %. Found % : C, 49.58 ; H, 4.87 ; N, 15.47; O, 18.51 ; S, 11.73.

^{1}H nmr (DMSO-d_6 , δ) 1.45 (3H, doublet, C-5 methyl protons, J = 7 Hz, diastereomeric splitting is 0.9 Hz i.e. 0.015 ppm), 2.25 (3H, singlet, ortho methyl protons, diastereomeric splitting is 2.5 Hz i.e. 0.04 ppm), 4.53 (1H, quartet, C-5 hydrogen), 8.33 (3H, multiplet, phenyl protons).

^{1}H nmr (Pyridine) 1.50, 1.63 (3H, doublet, C-5 methyl protons, J = 7 Hz, diastereomeric splitting of 2 Hz i.e. 0.033 ppm), 2.30 (3H, singlet, ortho methyl protons), 7.33 (multiplet, phenyl and pyridyl protons).

^{13}C nmr (DMSO, δ_{TMS}) 180.38 (C-2 thiocarbonyl carbon), 174.01 (C-4 carbonyl carbon), 55.31 (C-5 carbon), 16.94, 17.14 (diastereomeric splitting of ortho methyl carbon), 15.34, 16.14 (diastereomeric splitting of C-5 methyl carbon).

V1- 3-(2-Methyl-4-Nitrophenyl)-5-Methylhydantoin

This compound was prepared by Alessandro Granata (9) employing the method of Wheeler et al (39).

mp 168.0-169.0 C°. ^{1}H nmr (DMSO-d_6 , δ) 1.4 (3H, doublet, C-5 methyl protons), 2.2 (3H, doublet, ortho methyl protons), 4.5 (1H, quartet, C-5 proton) ; IR (KBr, Cm^{-1}) 1705 (CO), 1760 (CO), 3240 (NH).

V11- 3-(2-Methyl-4-Methoxyphenyl)-5-Methyl-2-Thiohydantoin (M. Wt. 250.32)

This compound was prepared by the general method described earlier. Starting Materials : DL-Alanine (Aldrich, M. Wt. 89.09) 2.4 g (0.027 mole) and 4-Methoxy-2-Methylphenyl isothiocyanate (M. Wt. 179.24) 4.8 g (0.027 mole). The yield of the thiohydantoin was 1.6 g or 23.8 %. mp 146.5-147.0 C°. ^1H nmr (DMSO-d_6 , δ) 1.46 (3H, doublet, C-5 methyl protons, J = 7 Hz, diastereomeric splitting is 0.6 Hz i.e. 0.01 ppm), 2.08 (3H, singlet, ortho methyl protons, diastereomeric splitting is 2.5 Hz i.e. 0.04 ppm), 3.8 (3H, singlet, p-methoxy protons), 4.3 (1H, quartet, C-5 hydrogen, diastereomeric splitting of 2.0 Hz i.e. 0.03 ppm), 7.0 (3H, multiplet, phenyl protons).

^{13}C nmr (DMSO, δ_{TMS}) 182.07 (C-2 thiocarbonyl carbon), 174.61 (C-4 carbonyl carbon), 54.91 (C-5 carbon), 16.36, 16.74 (diastereomeric splitting of o-methyl carbon), 16.94, 17.34 (diastereomeric splitting of C-5 methyl carbon), 55.11 (p-methoxy carbon).

V111- 3-(β-Naphthyl)-5-Methyl-2-Thiohydantoin

This compound was prepared by the general method described earlier. Starting materials : DL-Alanine (Aldrich, M. Wt. 89.09) 2.4 g (0.027 mole), β-Naphthyl isothiocyanate (Pfaltz & Bauer Inc., M. Wt. 185.20) 5.55 g (0.03 mole).

^{13}C nmr (DMSO, δ_{TMS}) 182.07 (C-2 thiocarbonyl carbon), 174.81 (C-4 carbonyl carbon), 55.21 (C-5 carbon), 15.35, 16.14 (diastereomeric splitting of C-5 methyl carbon).

1X- 3-(O-Tolyl)-5,5-Dimethyl-2-Thiohydantoin (M.Wt. 234.33)

This compound was prepared by the general method described earlier. Starting materials : Methyl alanine (Aldrich, M. Wt. 103.13) 3.10 g (0.030 mole), O-Tolyl isothiocyanate (ICN, K & K Lab. Inc. M. Wt. 150.22) 4.476 (0.030 mole). The yield of the thiohydantoin was 1.85 g or 26.31 %. mp 153.0-155.0 C^{o}. Elemental Analysis, calculated for $C_{12}H_{14}N_{2}OS$, % : C, 61.50 ; H, 6.02 ; N, 11.96
Found, % : C, 61.24 ; H, 5.88 ; N, 12.08 .
^{1}H nmr (Pyridine, δ) 1.57 (3H, singlet, C-5 methyl protons), 1.60 (3H, singlet, C-5 methyl protons), 2.3 (3H, singlet, ortho methyl protons), 7.08-7.83 (multiplet, phenyl and pyridyl protons).
^{13}C nmr (DMSO , δ_{TMS}) 178.79 (C-2 thiocarbonyl carbon), 175.60 (C-4 carbonyl carbon), 59.49 (C-5 carbon), 16.14 (ortho methyl carbon), 24.12, 25.32 (C-5 methyl carbons).

X- 3-(2,3-Dimethylphenyl)-5,5-Dimethyl-2-Thiohydantoin (M. Wt. 248.35)

This compound was prepared by the general method described earlier. Starting materials : Methyl alanine (Aldrich, M. Wt. 103.13) 2.784 g (0.027 mole) and 2,3-Dimethylphenyl isothiocyanate (M. Wt. 163.24) 4.897 g (0.030 mole). The yield of the thiohydantoin was 0.21 g or 2.82 % . mp 190-191 C^{o}. Elemental analysis calculated for $C_{13}H_{16}N_{2}OS$. % : C, 62.83 ; H, 6.49 ; N, 11.28. Found % : C, 59.82, H, 6.21 ; N, 10.79.

^{1}H nmr (DMSO-d_6 , δ) 1.37, 1.48 (3H, doublet, C-5 methyl protons, 1.95 (3H, singlet, ortho methyl protons), 2.32 (3H, singlet, meta methyl protons), 7.2 (3H, multiplet, phenyl protons).

^{1}H nmr (Pyridine) 1.57 (3H, singlet, C-5 methyl protons), 1.62 (3H, singlet, C-5 methyl protons), 2.12 (3H, singlet, aryl methyl protons), 2.17 (3H, singlet, aryl methyl protons), 7.0- 7.8 (multiplet, phenyl and pyridyl protons).

^{13}C nmr (DMSO , δ_{TMS}) 180.38 (C-2 thiocarbonyl carbon), 176.80 (C-4 carbonyl carbon), 60.68 (C-5 carbon), 13.50 (O-methyl carbon), 19.52 (m-methyl carbon), 23.40, 24.10 (C-5 dimethyl carbons).

X1- 3-(α-Naphthyl)-5,5-Dimethyl-2-Thiohydantoin (M. Wt. 270.35)

This compound was prepared by the general method described earlier. Starting materials : Methyl alanine (Aldrich, M. Wt. 103.13) 3.094 g (0.030 mole) and α-Naphthyl isothiocyanate (Eastman, M. Wt. 185.24) 7.408 g (0.040 mole). The yield of the thiohydantoin was 5.60 g or 69.0 % . mp 188-190 C°. Analysis calculated for $C_{15}H_{14}N_{2}OS$. % : C, 66.63 ; H, 5.22 ; N, 10.36 . Found % : C, 66.99 ; H, 5.44 ; N, 10.28 .

^{1}H nmr (DMSO-d_6 , δ) 0.92 (3H, singlet, C-5 methyl protons), 1.33 (3H, singlet, C-5 methyl protons), 7.42 (7H, multiplet, α-Naphthyl protons). ^{1}H nmr (CDCl$_3$, δ) 0.97 (3H, singlet, C-5 methyl protons), 1.40 (3H, singlet, C-5 methyl protons), 7.33 (7H, multiplet, α-Naphthyl protons). ^{1}H nmr (Pyridine) 1.20 (3H, singlet, C-5 methyl protons), 1.47 (3H, singlet, C-5 methyl protons), 7.17 multiplet, α-Naphthyl and pyridyl protons)

^{13}C nmr (DMSO , δ_{TMS}) 180.77 (C-2 thiocarbonyl carbon), 176.44 (C-4 carbonyl carbon), 60.98 (C-5 carbon), 23.44, 24.10 (enantiomeric C-5 dimethyl carbons).

X11- 3-(O-Fluorophenyl)-5,5-Dimethyl-2-Thiohydantoin (M. Wt. 238.29)

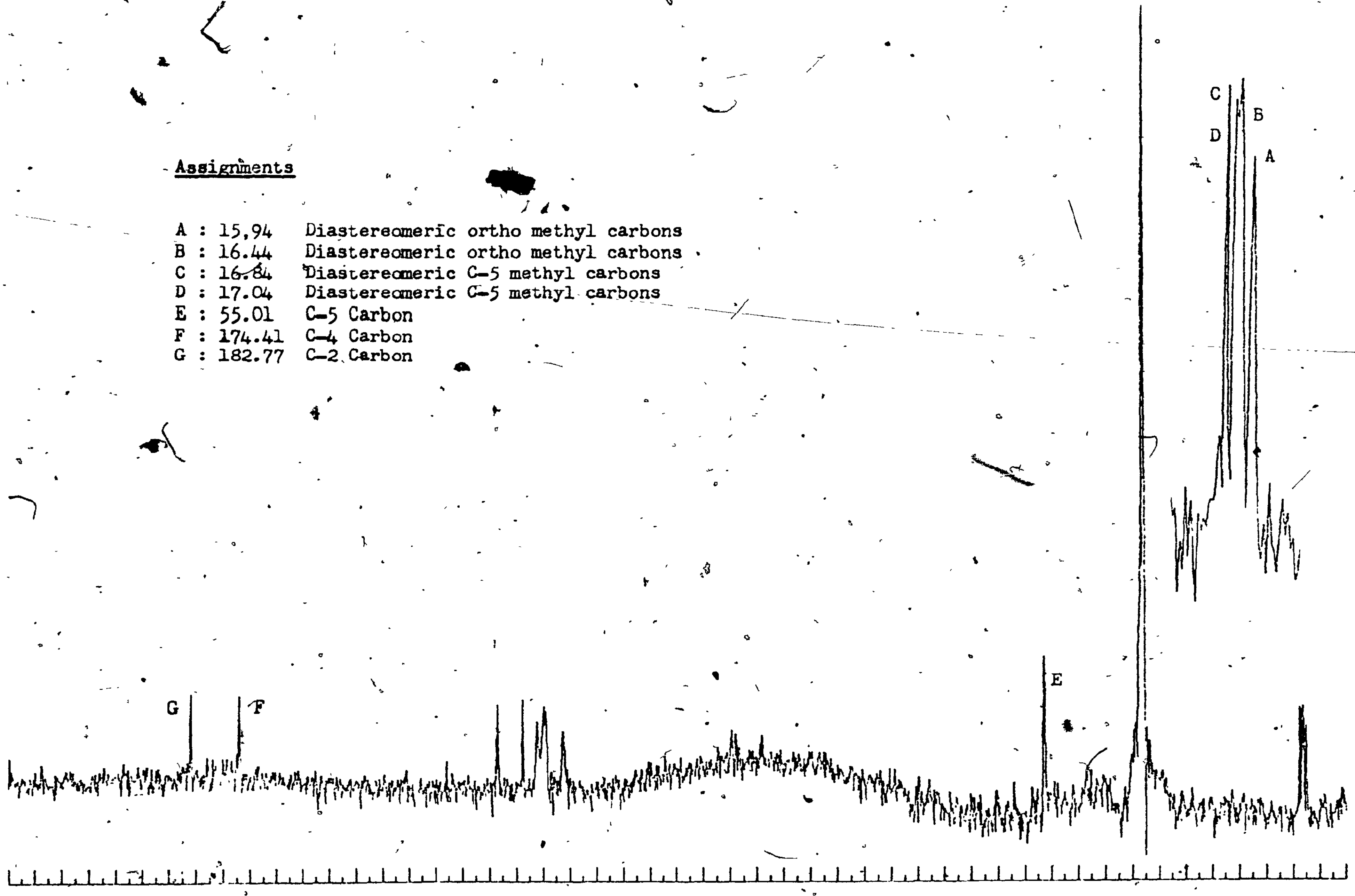
This compound was prepared by the general method described earlier. Starting materials : Methyl alanine (Aldrich, M.Wt. 103.13) 2.062 g (0.020 mole) and O-Fluorophenyl isothiocyanate (Pfaltz & Bauer Inc. M. Wt. 153.176) 4.595 g (0.030 mole). The yield of the thiohydantoin was 1.2 g or 25.18 % . mp. 248.0 - 251.0 C°.
Elemental analysis calculated for $C_{11} H_{11} N_2 O S F$. % : C, 55.44 ; H, 4.65 ; N, 11.76 . Found % : C, 55.17 ; H, 4.60 ; N, 11.50 .
^{1}H nmr (DMSO-d_6 , δ) 1.40 (3H, singlet, C-5 methyl protons), 1.45 (3H, singlet, C-5 methyl protons), 7.4 (4H, multiplet, phenyl protons).
^{1}H nmr (Pyridine) 1.58 (6H, singlet, C-5 dimethyl protons), 7.1 (multiplet, phenyl and pyridyl protons)
^{13}C nmr (DMSO , δ_{TMS}) 178.09 (C-2 thiocarbonyl carbon), 174.41 (C-4 carbonyl carbon), 61.00 (C-5 methyl carbon), 23.30, 24.10 (C-5 dimethyl carbons).

X111- 3-(2-Methyl-4-Nitrophenyl)-5,5-Dimethyl-2-Thiohydantoin

(M. Wt. 279.31)

This compound was prepared by the general method described earlier. Starting materials : Methyl alanine (Aldrich, 103.13) 2.50 g (0.024 mole) and 2-Methyl-4-Nitrophenyl isothiocyanate (M. Wt. 194.22) 6.435 g (0.033 mole). The yield of the thiohydantoin was 0.412 g or 6.15 % . mp 217.0-218.0 C^{o}. Elemental analysis calculated for $C_{12} H_{13} N_{3} O_{3} S$. % : C, 51.60 ; H, 4.69 ; N, 15.04 . Found % : C, 51.42 ; H, 4.53 ; N, 15.31 .

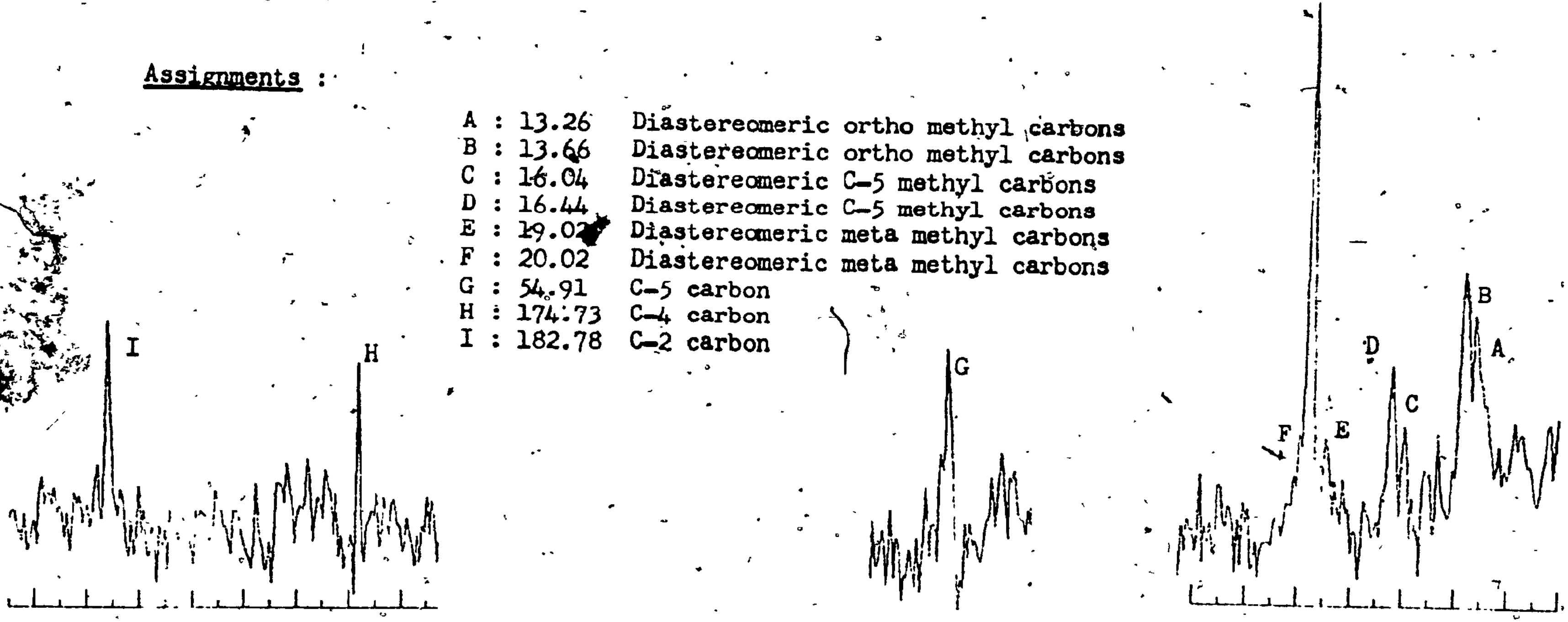
^{1}H nmr (DMSO-d_6 , δ) 1.52 (6H, singlet, C-5 dimethyl protons), 2.20 (3H, singlet, ortho methyl protons), 7.4-8.0 (3H, multiplet, phenyl protons). ^{1}H nmr (Pyridine) 1.58 (3H, singlet, C-5 methyl protons), 1.68 (3H, singlet, C-5 methyl protons), 2.32 (3H, singlet, ortho methyl protons), 7.2 (multiplet, phenyl and pyridyl protons). ^{13}C nmr (DMSO , δ_{TMS}) 179.34 (C-2 thiocarbonyl carbon), 176.43 (C-4 carbonyl carbon), 61.58 (C-5 carbon), 16.84 (O-methyl carbon), 23.00, 24.20 (C-5 dimethyl carbons).



Assignments

A : 15,94 Diastereomeric ortho methyl carbons
B : 16.44 Diastereomeric ortho methyl carbons
C : 16.84 Diastereomeric C–5 methyl carbons
D : 17.04 Diastereomeric C–5 methyl carbons
E : 55.01 C–5 Carbon
F : 174.41 C–4 Carbon
G : 182.77 C–2 Carbon

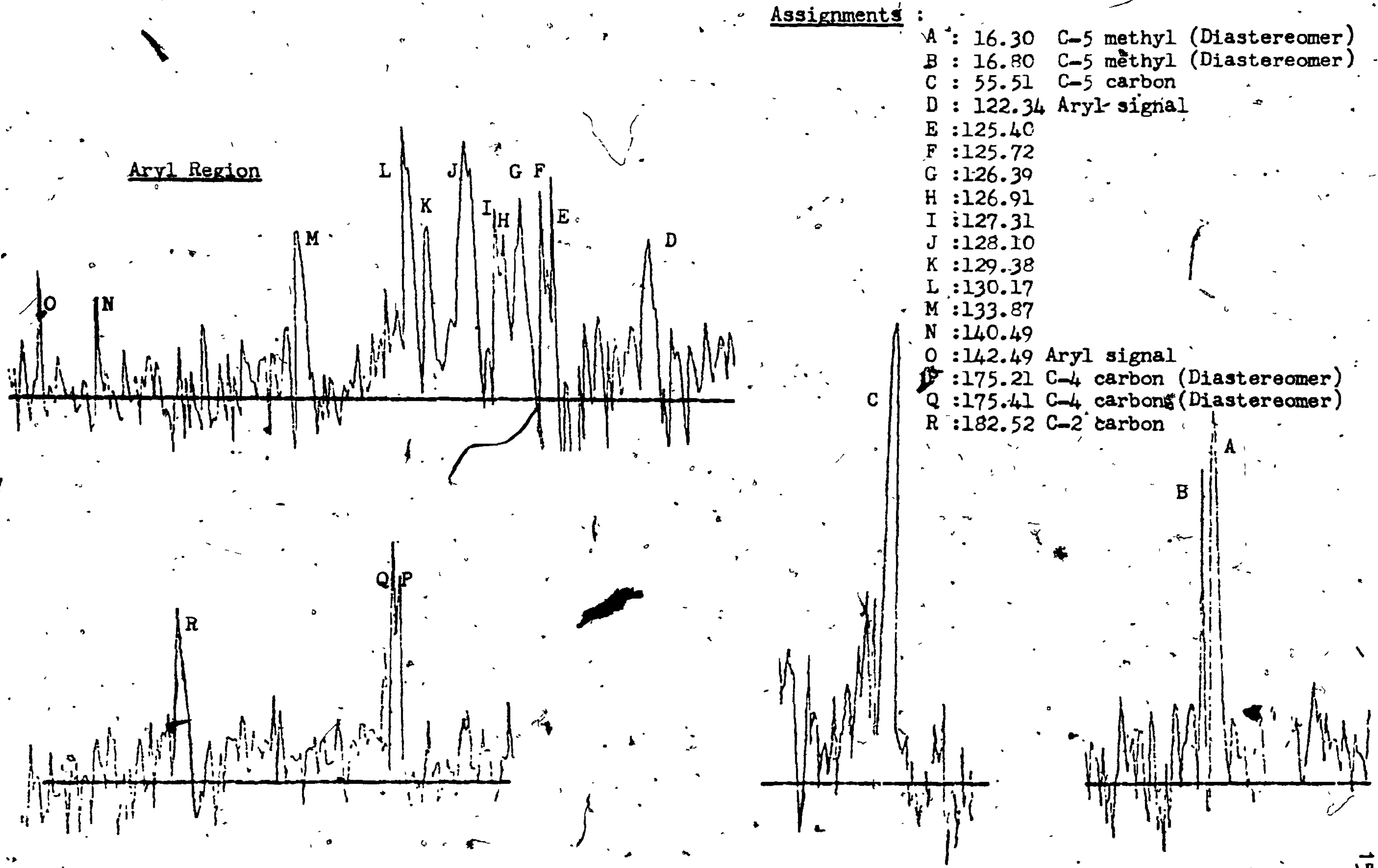
Fig. 1-13 : Fourier Transformed C–13 NMR 25.1MHz Spectrum of 3N-(o-Tolyl)-5-Methyl-2-Thiohydantoin in DMSO.



Assignments :

A : 13.26 Diastereomeric ortho methyl carbons
B : 13.66 Diastereomeric ortho methyl carbons
C : 16.04 Diastereomeric C-5 methyl carbons
D : 16.44 Diastereomeric C-5 methyl carbons
E : 19.02 Diastereomeric meta methyl carbons
F : 20.02 Diastereomeric meta methyl carbons
G : 54.91 C-5 carbon
H : 174.73 C-4 carbon
I : 182.78 C-2 carbon

Fig. 1-14 : Fourier Transformed C-13 NMR 25.1 MHz Spectrum of 3N-(2,3-Dimethylphenyl)-5-Methyl-2-Thiohydantoin in DMSO.



Assignments :

A : 16.30 C-5 methyl (Diastereomer)
B : 16.80 C-5 methyl (Diastereomer)
C : 55.51 C-5 carbon
D : 122.34 Aryl signal
E :125.40
F :125.72
G :126.39
H :126.91
I :127.31
J :128.10
K :129.38
L :130.17
M :133.87
N :140.49
O :142.49 Aryl signal
P :175.21 C-4 carbon (Diastereomer)
Q :175.41 C-4 carbon (Diastereomer)
R :182.52 C-2 carbon

Fig. 1-15 Fourier Transformed C-13 NMR 25.1 MHz spectrum of 3N-(1-Naphthyl)-5-Methyl-2-Thiohydantoin in DMSO

Assignments :

A : 15.94 Diastereomeric C-5 methyl carbon
B : 16.34 Diastereomeric C-5 methyl carbon
C : 40.40 DMSO solvent signal
D : 55.10 C-5 carbon
E : 116.21 Aryl signal
F : 124.41
G : 131.41
H : 144.51
I : 174.41 C-4 carbon
J : 181.56 C-2 carbon

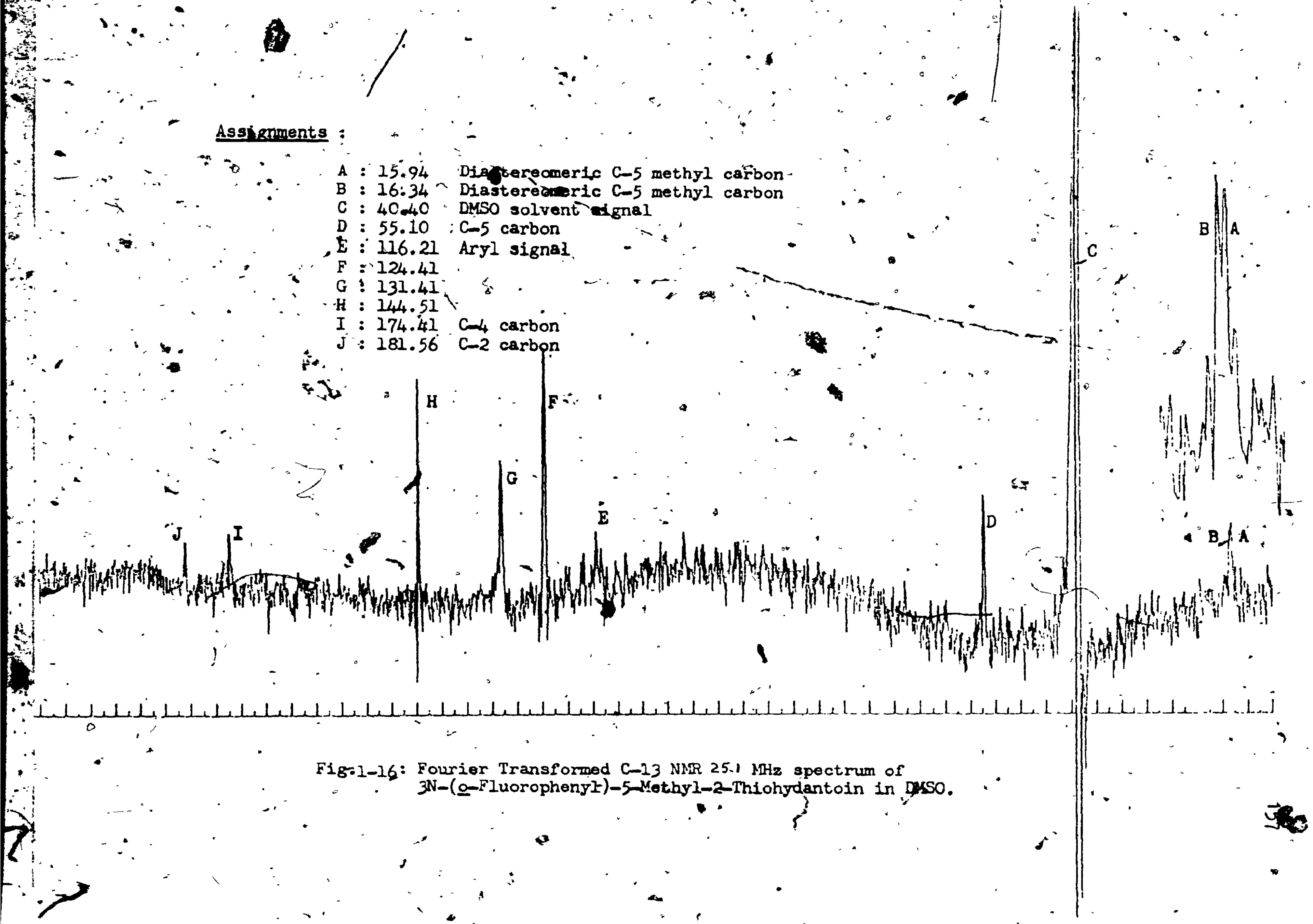


Fig-1-16: Fourier Transformed C-13 NMR 25.1 MHz spectrum of 3N-(o-Fluorophenyl)-5-Methyl-2-Thiohydantoin in DMSO.

Assignments :

A : 15.34 Diastereomeric C-5 methyl carbons
B : 16.14 Diastereomeric C-5 methyl carbons
C : 16.94 Diastereomeric ortho methyl carbons
D : 17.14 Diastereomeric ortho methyl carbons
E : 55.31 C-5 carbon
F : 174.01 C-4 carbon
G : 180.38 C-2 carbon

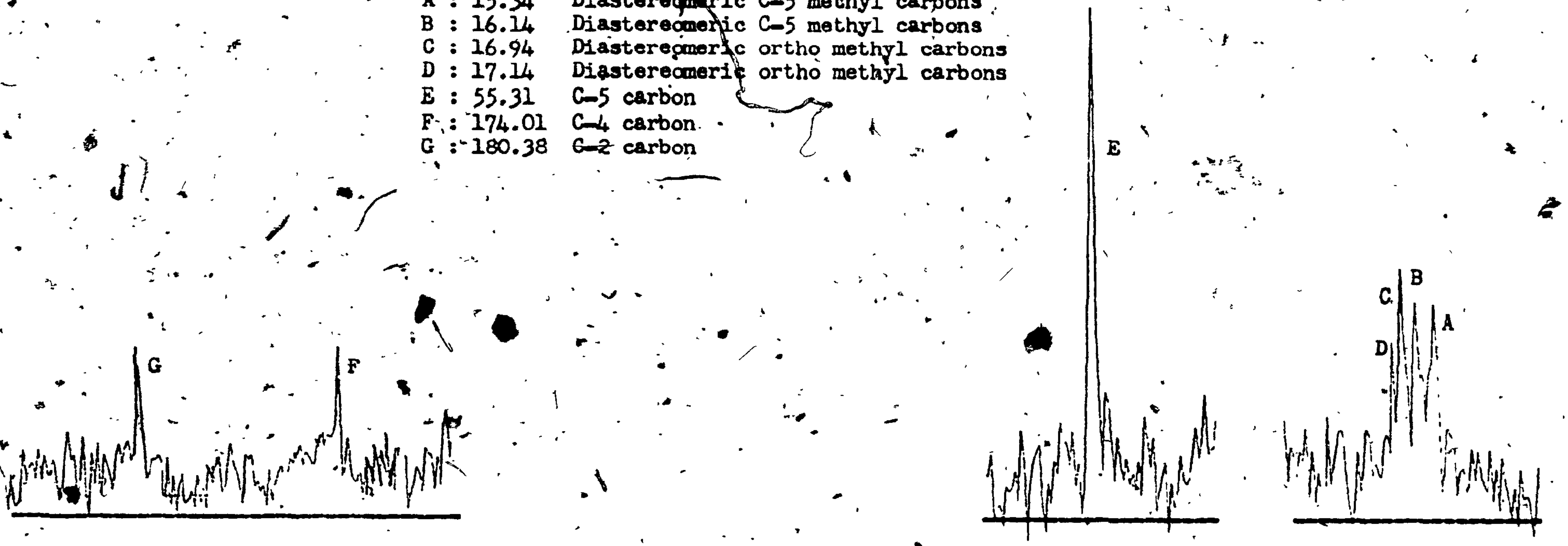


Fig. 1-17 : Fourier Transformed C-13 NMR 25.1 MHz Spectrum of 3N-(2-Methyl-4-Nitrophenyl)-5-Methyl-2-Thiohydantoin in DMSO.

Assignments :

A : 16.04 Diastereomeric C–5 methyl carbons
B : 16.34 Diastereomeric C–5 methyl carbons
C : 16.74 Diastereomeric ortho methyl carbon
D : 16.94 Diastereomeric orhto methyl carbon
E : 52.43 C–5 carbon
F : 162.08 C–2 carbon
G : 178.79 C–4 carbon

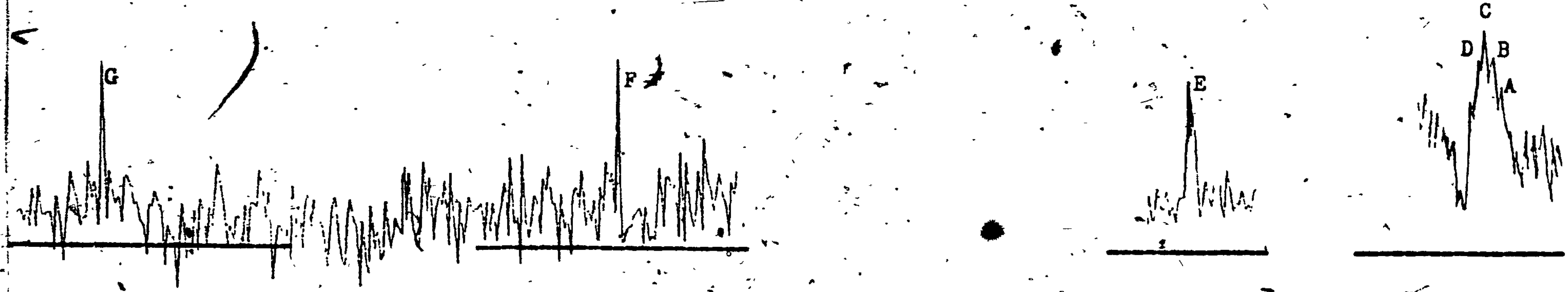
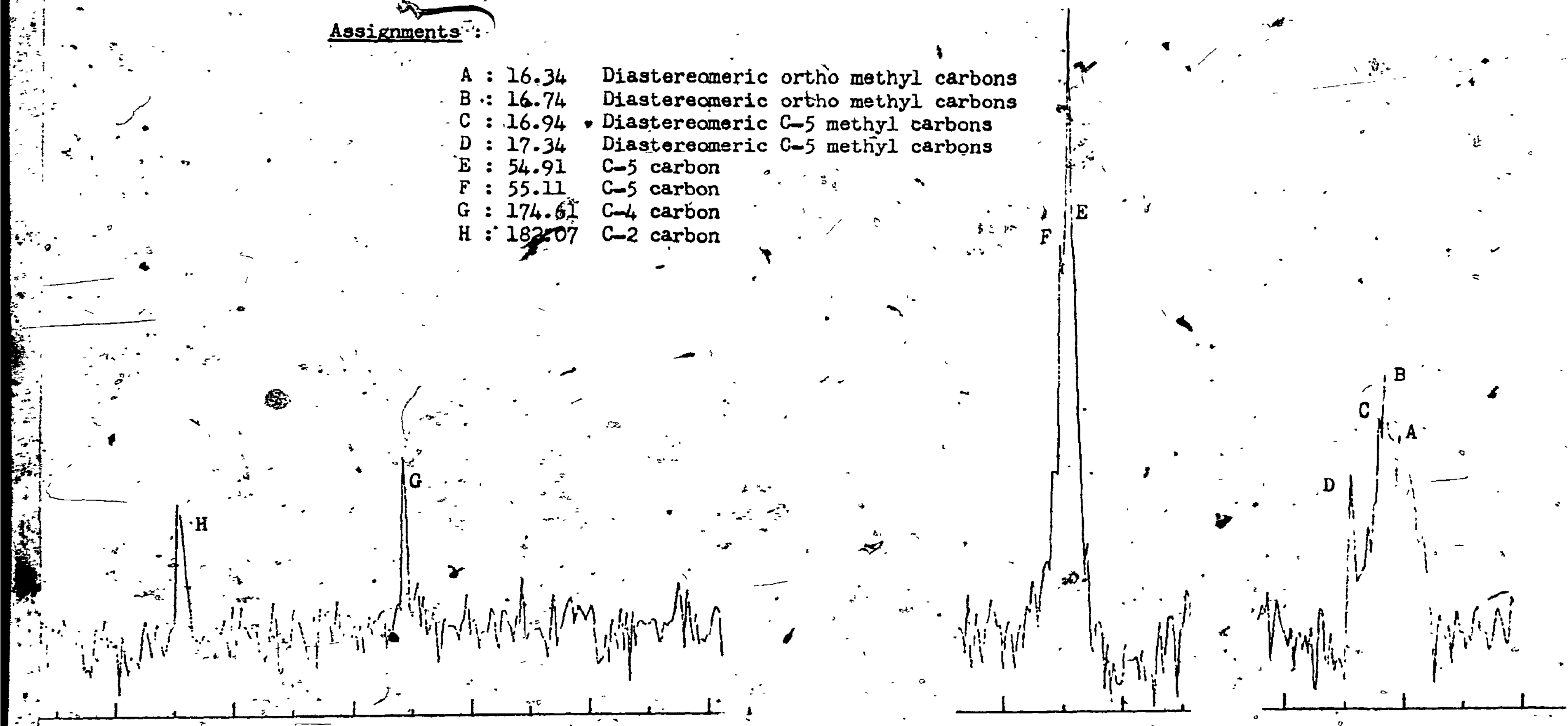


Fig. 1-18 : Fourier Transformed C–13 NMR 25.1 MHz spectrum of 3N–(2–Methyl–4–Nitrophenyl)–5–Methyl Hydantoin in DMSO.



Assignments :

A :	16.34	Diastereomeric ortho methyl carbons
B :	16.74	Diastereomeric ortho methyl carbons
C :	16.94	Diastereomeric C-5 methyl carbons
D :	17.34	Diastereomeric C-5 methyl carbons
E :	54.91	C-5 carbon
F :	55.11	C-5 carbon
G :	174.61	C-4 carbon
H :	182.07	C-2 carbon

Fig.1-19 : Fourier Transformed C-13 NMR 25.1 MHz Spectrum of 3N-(2-Methyl-4-Methoxyphenyl)-5-Methyl-2-Thiohydantoin in DMSO.

Assignments :

A : 15.35 Diastereomeric C-5 methyl carbon
B : 16.14 Diastereomeric C-5 methyl carbon
C : 55.21 C-5 carbon
D : 174.81 C-4 carbon
E : 182.07 C-2 carbon

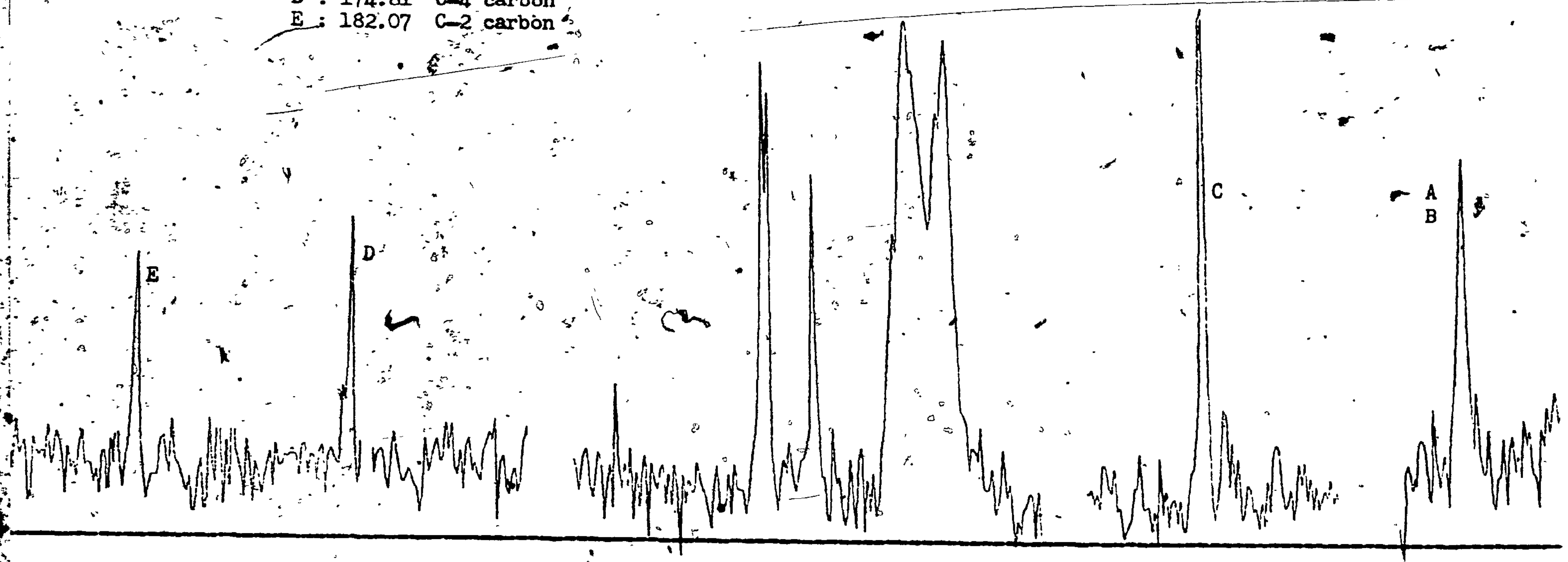


Fig. 1-20 : Fourier Transformed C-13 NMR 25.1 MHz Spectrum of 3N-(2-Naphthyl)-5-Methyl-2-Thiohydantoin in DMSO.at 55-60°. At room temperature, peaks A and B are split into diastereomeric doublet at 15.34 and 16.14 ppm.

Assignments :

A : 16.14 Ortho methyl carbon
B : 24.12 C-5 methyl carbon
C : 25.32 C-5 methyl carbon
D : 59.49 C-5 carbon
E : 175.60 C-4 carbon
F : 178.79 C-2 carbon

Fig, 1-21 : Fourier Transformed C-13 NMR 25.1 MHz spectrum of 3N-(o-Tolyl)-5,5-Dimethyl-2-Thiohydantoin in DMSO.

Assignments :

A :	13.50	Ortho methyl carbon
B :	19.52	Meta methyl carbon
C :	23.40	C-5 methyl carbon
D :	24.10	C-5 methyl carbon
E :	60.68	C-5 carbon
F :	125.50	
G :	127.09	
H :	130.27	
I :	132.26	
J :	134.84	
K :	137.03	
L :	153.34	
M :	176.80	C-4 carbon
N :	180.38	C-2 carbon

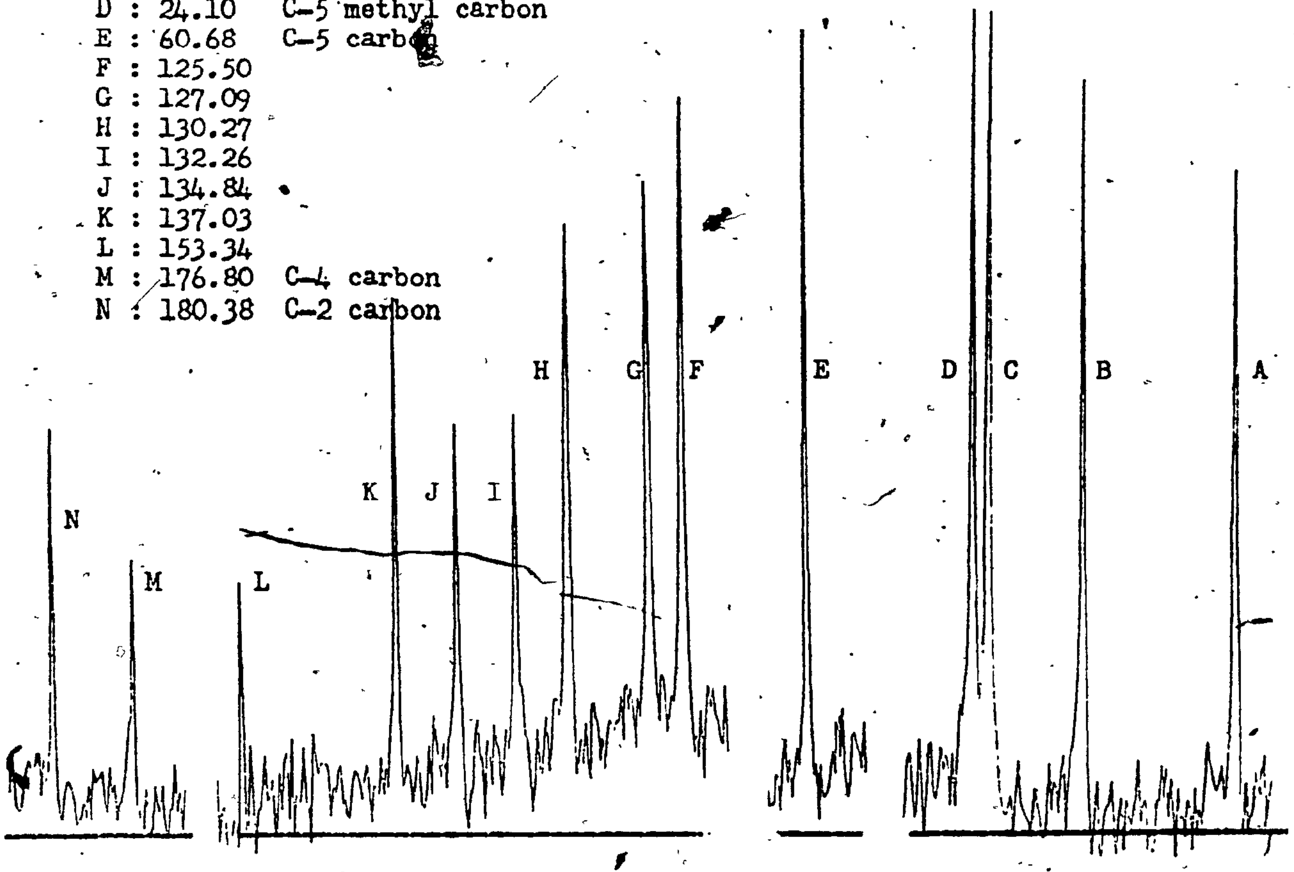


Fig. 1-22: Fourier Transformed C-13 NMR 25.1 MHz spectrum of 3N-(2,3-Dimethylphenyl)-5,5-Dimethyl-2-Thiohydantoin in DMSO.

Assignments :

A : 23.44, 24.10 C-5 methyl carbons
B : 41.54 C-13 CH_3I capillary lock
C : 60.98 C-5 carbon
D : 78.12 Chloroform (Solvent)
E : 128.23
F : 128.62
G : 129.02
H : 130.61
I : [illegible]1.21
J : 140.95
K : 142.54
L : 176.44 C-4 carbon
M : 180.77 C-2 carbon

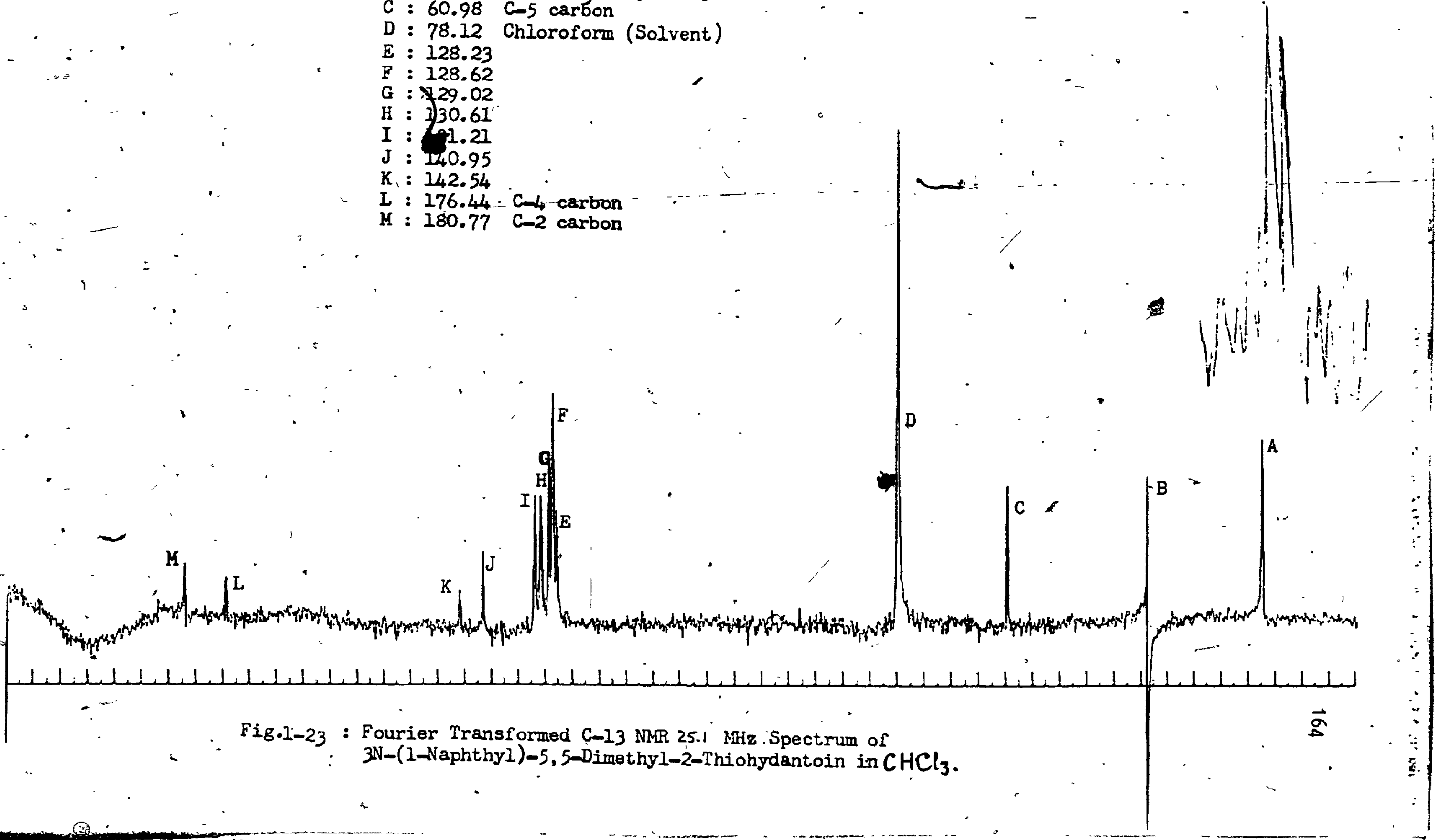


Fig.1-23 : Fourier Transformed C-13 NMR 25.1 MHz Spectrum of 3N-(1-Naphthyl)-5,5-Dimethyl-2-Thiohydantoin in $CHCl_3$.

Assignments:

A : 16.84 Orhto methyl carbon
B : 23.00 C-5 methyl carbon
C : 24.20 C-5 methyl carbon
D : 61.58 C-5 carbon
E : 176.43 C-4 carbon
F : 179.34 C-2 carbon

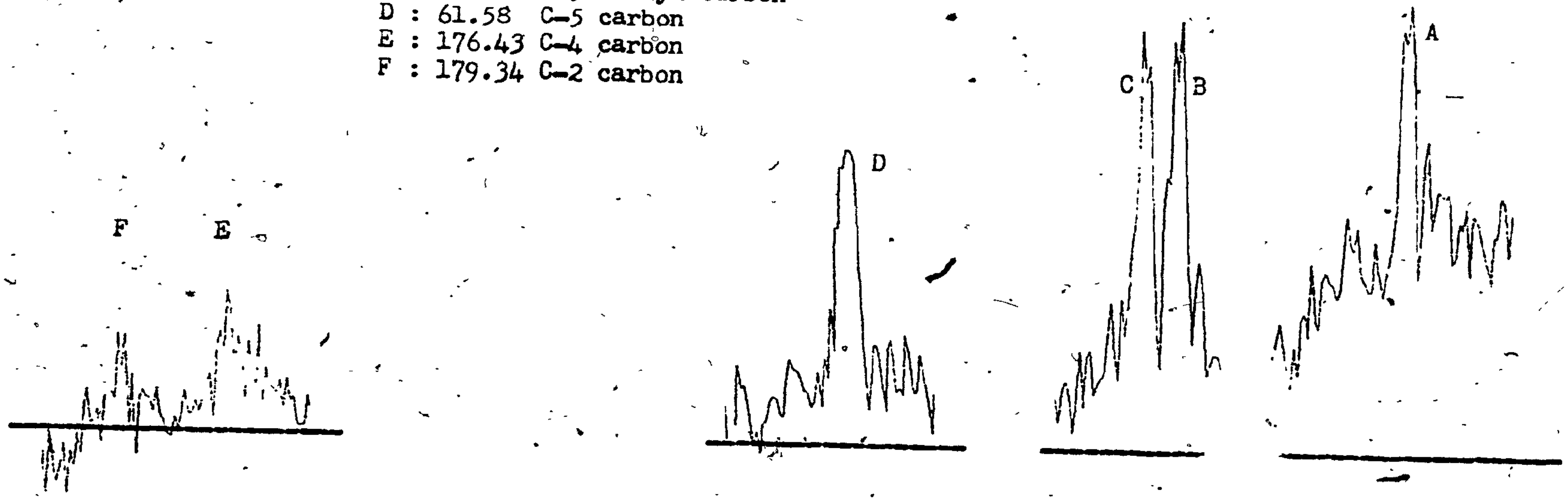


Fig. 1-24 : Fourier Transformed C-13 NMR 25.1 MHz spectrum of 3N-(2-Methyl-4-Nitrophenyl)-5,5-Dimethyl-2-Thiohydantoin in DMSO. The C-H spin-spin splitting may be noticed,

Assignments :

A : 23.10 C-5 methyl carbon
B : 24.10 C-5 methyl carbon
C : 40.40 DMSO solvent signal
D : 61.24 C-5 carbon
E : 129.00 Aryl signal
F : 130.57
G : 131.72
H : 132.52
I : [illegible]33.35
J : 144.77
K : 176.56 C-4 carbon
L : 180.18 C-2 carbon

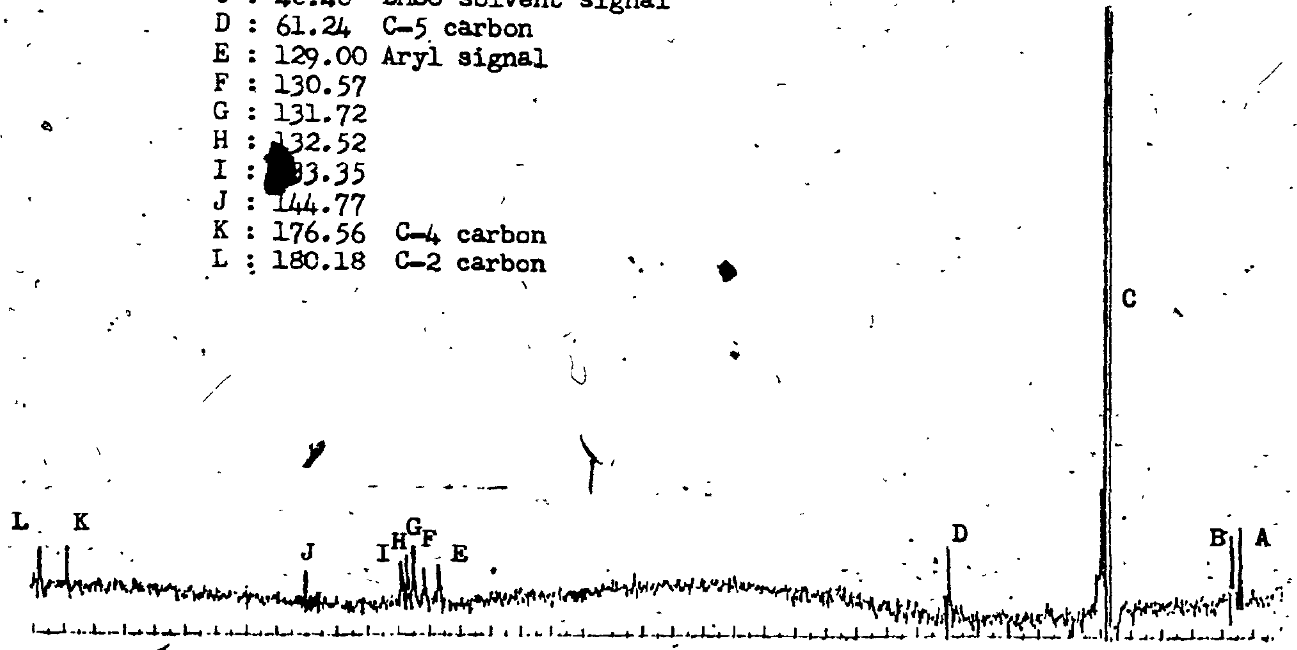


Fig. 1-25 : Fourier Transformed C-13 NMR 25.1 MHz spectrum of 3N-(o-Chlorophenyl)-5,5-Dimethyl-2-Thiohydantoin in DMSO.

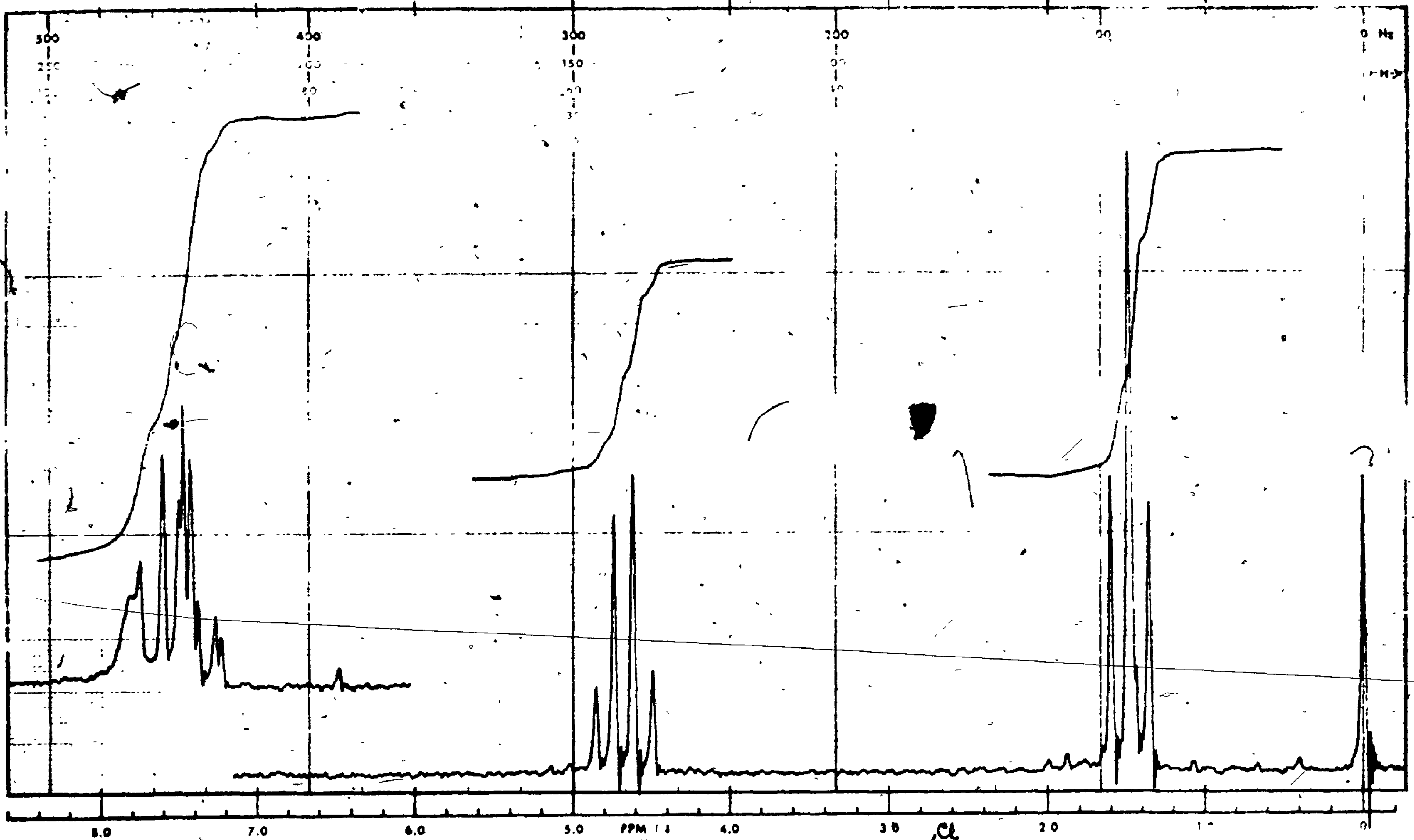


Fig. 1-26 : Varian A-60 MHz NMR Spectrum of $O_2N{-}C_6H_3(Cl){-}NH{-}C(=S)OEt$ in $CDCl_3$ Resulted on Unsuccessful Synthesis of 3N-(2-Chloro-4-Nitrophenyl)-5,5-Dimethyl-2-Thiohydantoin, Sweep Width = 1000 Hz, Sweep Offset = 50 Hz.

ASSIGNMENTS :

A-	14.49	CH_3
B-	41.54	CH_3I (C-13) folded back
C-	68.95	CH_2
D-	76.20	$CDCl_3$
E-	77.50	" "
F-	78.82	" "
G-	121.90	(C-6)
H-	123.40	(C-5)
I-	124.06	(C-2)
J-	125.40	(C-3)
K-	140.10	(C-4)
L-	143.85	(C-1)
M-	187.10	(C = S, major isomer)
N-	188.24	(C = S, minor isomer)

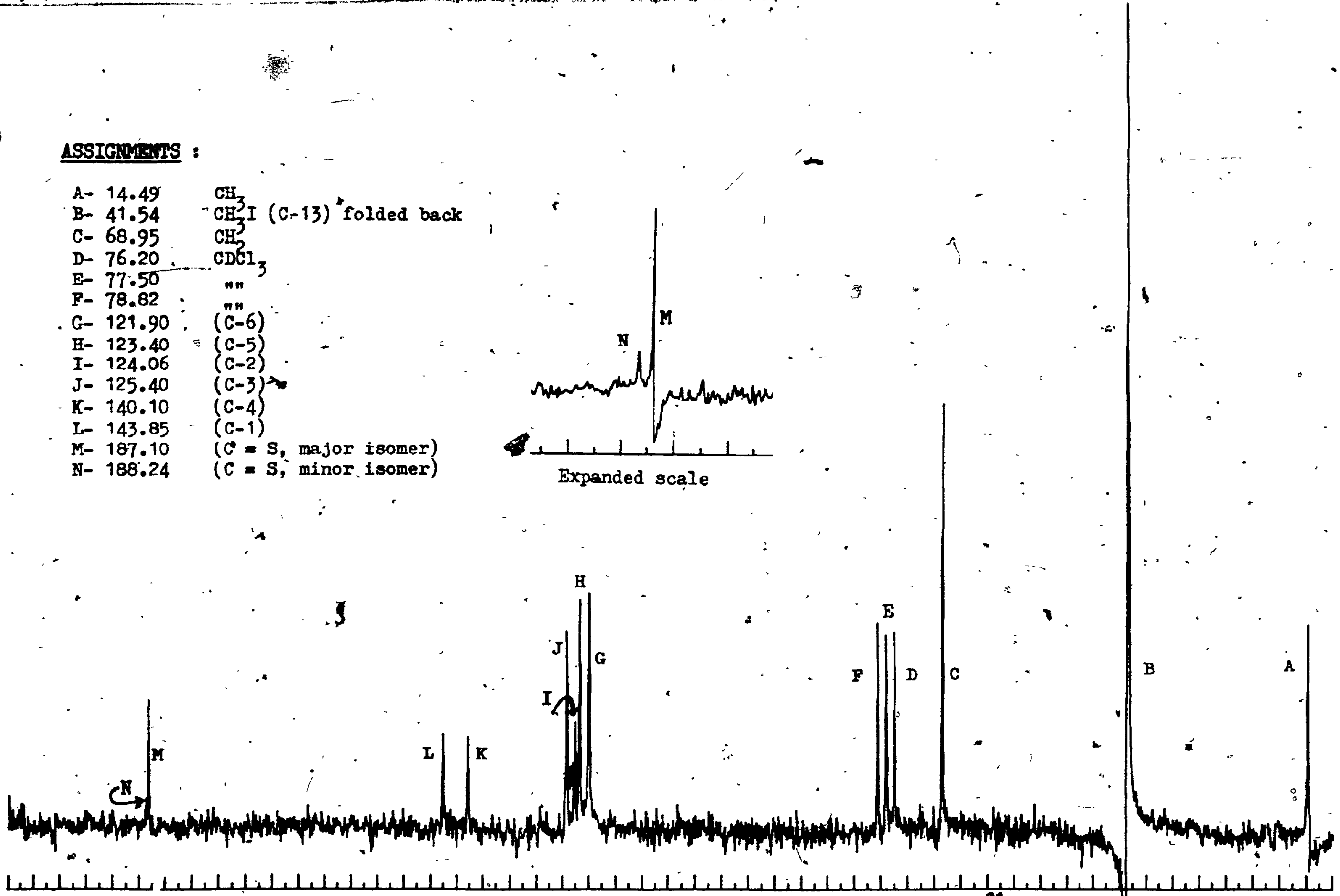
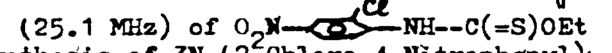


Fig. 1-27: Fourier Transformed C-13 NMR Spectrum (25.1 MHz) of  $O_2N-C_6H_3(Cl)-NH--C(=S)OEt$ in $CDCl_3$ Resulted on Unsuccessful Synthesis of 3N-(2-Chloro-4-Nitrophenyl)-5,5-Dimethyl-2-Thiohydantoin, Sweep Width = 1000 Hz.