A CARBON-13 NMR STUDY OF SOME 3-ARYL HYDANTOINS

Donald Frank Williams

A THESIS

in

The Department

of

Chemistry

Presented in Partial Fulfillment of the Requirements for
the Degree of Master of Science at
Sir George Williams University
Montreal, Canada

September, 1972

ABSTRACT

Donald Frank Williams. A CARBON-13 NMR STUDY OF SOME 3-ARYL HYDANTOINS.

The spectra of a series of 3-aryl hydantoins, with various ortho substituents, are interpreted in terms of the ground state rotamers.

The chemical shift values for carbons in the hydantoin moiety depend essentially on the number of methyls at the C-5 position. The trends in these values with the nature of the ortho substituent cannot be attributed to only one factor.

The carbonyl carbon chemical shift values may constitute confirmatory evidence that in the 3-aryl hydantoin series, a chlorine ortho substituent is effectively larger than a methyl ortho substituent.

The magnitude of the C-5 methyl peak separation indicates no important steric interaction with the ortho substituent. This peak separation for the diastereomeric C-5 methyl carbons is only slightly less than for the diastereotopic C-5 methyl carbons, for corresponding 3-aryl hydantoins. The C-5 methyl peak separations are about an order of magnitude larger (in ppm) for carbon-13 than for proton resonances.

ACKNOWLEDGEMENTS .

The author wishes to thank Dr. L.D. Colebrook for suggesting the project and for his interest throughout the course of this investigation.

In addition thanks are expressed to J. Fehlner for the gift of several hydantoins. Helpful discussions with members of the Department of Chemistry, and in particular with Mr. H.G. Giles, are gratefully acknowledged.

The author wishes to thank the Department of Chemistry for the facilities afforded and for financial assistance.

He wishes to thank his wife for her patience, understanding, and encouragement, and for her help in preparing the thesis.

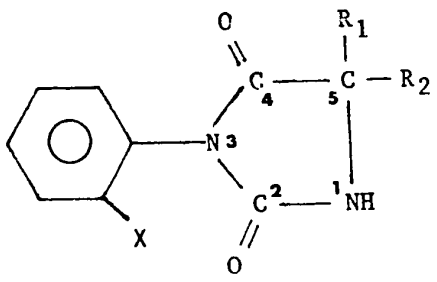
TABLE OF CONTENTS

LIST OF TABLES .

INTRODUCTION .

Hydantoins are of interest in pharmacology, and they have been used in the treatment of epilepsy and as anticonvulsants (1, 2).

The 3-aryl hydantoins investigated in the present work have an ortho substituent on the aryl ring. There is restricted rotation about the aryl C-N bond because of steric interaction between this ortho substituent and one or both of the hydantoin carbonyl groups:



R_1 = H, CH_3.

R_2 = H, CH_3.

Fehlner (3) has determined the thermodynamic activation parameters of a number of 3-aryl hydantoins, by a complete lineshape analysis of the temperature dependent proton nuclear magnetic resonance (nmr) spectra.

It was considered useful to seek further information on this series of compounds, from their carbon-13 nmr spectra. For a given hydantoin, the thermodynamic activation parameters reflect the differences between ground state rotamers and the transition state. The present work deals essentially with the ground state rotamers.

A number of Fehlner's 3-aryl hydantoins were chosen, with an assortment of polar and non-polar ortho substituents, and several new hydantoins were synthesised to complete the series.

The usefulness of proton nmr is often limited because many organic compounds contain too few non-equivalent protons. Also, the main center of interest in organic chemistry is not the protons, but the carbon skeleton of these compounds.

There are several advantages in the use of carbon-13 nmr as a probe for the elucidation of chemical structures. Carbon-13 chemical shift values cover a total range of about 250 ppm, and the peaks which correspond to non-equivalent carbons are usually resolved. Compounds with natural abundance carbon-13 (about 1.1 atom %) do not show carbon-carbon spin coupling because of the low probability (of the order of 1 in 10000) of having two adjacent carbon-13 atoms in the same molecule. Coupling to protons gives rise to first order spectra, and this provides a valuable assignment aid.

In the series of hydantoins studied, there are carbon atoms at several positions in the molecule which are of stereochemical interest.

The carbonyl carbon chemical shift values should be of interest because of the steric interaction between the aryl ortho substituent and the carbonyl groups. Furthermore, there is a possibility of conjugation between the hydantoin ring π-system, including the carbonyl groups, and the 3-aryl ring.

The C-5 methyl carbon chemical shift values may show effects due to steric interaction with the aryl ortho substituent. Of particular interest is the comparison of the methyl carbon resonances of diastereomeric and diastereotopic methyl groups, of corresponding 5-methyl and 5,5-dimethyl hydantoins, respectively, which have the same 3-aryl substituent. The stereochemistry and spectra of the hydantoins are more fully discussed below.

GENERAL INTERPRETATION OF CARBON-13 SPECTRA .

Assignment.

Assignment of the peaks in a carbon-13 spectrum can often be made on the basis of the chemical shift values, as in the case of many proton nmr spectra. Typical carbon-13 chemical shift values, for various classes of organic compounds, are given in several review

articles (4-9). The chemical shift values of suitable model compounds can often be used to resolve any remaining ambiguities in assignment.

The coupling constants between carbon-13 atoms and directly bound hydrogens are of the order of 100-250 Hz, and the interpretation of carbon-13 spectra is frequently difficult because of overlapping multiplets. In order to simplify the spectra, proton decoupling is commonly used.

With broad-band or noise modulated proton decoupling, all the protons in the molecule are irradiated at a high RF power at their resonance frequencies. Each non-equivalent carbon will thus give rise to a single peak. The added advantage of noise proton decoupling is an increase in sensitivity as a result of multiplet collapse and also by the nuclear Overhauser effect. A maximum nuclear Overhauser effect enhancement of approximately three-fold can be obtained in suitable cases (10). 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 frequency of the protons in the molecule, and the proton decoupler RF power output is lower than for noise proton decoupling. The resulting carbon-13 spectrum consists of perturbed multiplets, corresponding to the multiplets of the non-decoupled carbon-13 spectrum. The residual splitting or " reduced coupling constant ", J_r, is related to the coupling constant J by the expression (11):

$$J_r = \frac{J \ \Delta f}{\gamma H_2 / \ 2\pi}$$

where Δf is the frequency separation between the proton decoupler frequency and the resonance frequency of the proton which is being partially decoupled, and $\gamma H_2 / 2\pi$ is the effective spread in Hz of the proton decoupler frequency. With off-resonance proton decoupling the nuclear Overhauser effect is still operative and thus some signal enhancement is provided without undue loss of spectral information. In cases of multiplet overlap the assignment of peaks to a given multiplet can be made by comparing spectra with different proton decoupler power output settings. This corresponds to different values of H_2 and hence J_r.

The comparison of the carbon-13 spectra run under conditions of noise proton decoupling, and off-resonance proton decoupling, provides a valuable assignment aid. In the present work, quaternary aryl carbon peaks were identified in this way since they remain unsplit with off-resonance proton decoupling. Also all assignments were confirmed by the nature of the multiplets obtained with off-resonance proton decoupling.

Additivity and Substituent Parameters.

The carbon-13 spectra of a wide variety of compounds have been reported in the literature, and also the shielding effects of an assortment of substituents have been evaluated. A general finding is that within a related series of compounds, the chemical shift values tend to follow additive relationships(7).

The prime example is the work by Grant and Paul on the alkanes (12) where methyl substitution α or β to a carbon causes a downfield shift of about 9 ppm for the peak of that carbon. Similarly γ substitution causes an upfield shift of about 2.5 ppm. The carbon-13 chemical shifts of the alkanes obey the Grant-Paul additivity relation:

$$\delta_c(k) = B + \sum_l A_l n_{kl}$$

where δ_c (k) is the carbon-13 chemical shift values of the k^{th} carbon atom, B is a constant, n_{kl} is the number of carbon atoms in the l^{th} position relative to the k^{th} carbon, and A_l is the additive chemical shift parameter assigned to the l^{th} carbon atom.

For highly branched systems, sizable refinement parameters are required to allow for tertiary and quaternary carbon atoms. Thus for a methyl group adjacent to either a tertiary or quaternary carbon, the refinement parameters 1^o (3^o) and 1^o (4^o) are required, and similarly 4^o (1^o) for a quaternary carbon adjacent to a methyl group. The parameters used in the present work are listed in table I.

Table I. Grant-Paul Additivity Parameters for the Alkanes[a].

Carbon position	A_l	Refinement parameter	Coefficient
α	-9.1 ± 0.1	1^o (3^o)	1.1 ± 0.2
β	-9.4 ± 0.1	1^o (4^o)	3.4 ± 0.4
γ	2.5 ± 0.1	4^o (1^o)	1.5 ± 0.1

[a] Upfield shift in ppm.

The additivity parameters A_1 can equally be regarded as methyl substituent shift parameters. Similar parameters have been reported for other substituents (7).

Substituent parameters have been successfully applied to a series of amino acids by Horsley, Sternlicht and Cohen (13). Because of the similarity in the structure of amino acids and hydantoins, similar relationships between substituents and chemical shifts should also apply to the present series of compounds. The chemical shift values of the carbonyl carbons, the C-5 carbons and the C-5 methyl carbons should be related to the number of methyls at the C-5 position.

Although additivity or substituent parameters are determined empirically, the nature of the interactions have inevitably been rationalized. The current view is that the α-effect is largely inductive with some steric contribution. The β-effect has not been satisfactorily explained (9). The original explanation by Grant and Paul that the γ-effect is caused by steric perturbation caused by coiling is still accepted.

Carbonyl Carbon Chemical Shifts and Conjugation.

Stothers (14) has derived an empirical expression to estimate the angle of twist of the aryl ring relative to the carbonyl group in a series of ortho substituted acetophenones. Because of steric inhibition, the aryl ring and carbonyl group are not coplanar in these

compounds. The extent of the conjugation between the aryl ring and the carbonyl group depends on the angle of twist. An increase in angle of twist and consequent decrease in conjugation is reflected by a downfield shift of the carbonyl carbon peak. This effect is readily rationalized as caused by a decrease in the electron density at the carbonyl carbon with decreasing conjugation.

Carbon Chemical Shifts and Steric Perturbation.

The chemical shifts of sterically perturbed carbon atoms are generally found at higher magnetic fields than for similar carbons that are not sterically crowded (15). The initial observation of this phenomenon was by Grant and Paul in the case of the γ methyl substituent shift in the alkanes (12).

A striking example of the stereodependence of carbon-13 shielding is in the low temperature study by Roberts of 1,1,3,3-tetramethyl cyclohexane (16). The chemical shift difference between axial and equatorial methyl protons (at -91°C) is 0.075 ppm, whereas the corresponding shift difference for the methyl carbons (at -107°C) is 8.8 ppm. This shift difference is attributed to steric interaction of the two axial methyls.

Similarly Anet (17) has measured the carbon-13 spectrum of methyl cyclohexane (at -110°C), and the chemical shift of the methyl group of the less preferred axial methyl conformer is 6 ppm to higher field than for the equatorial methyl conformer. The

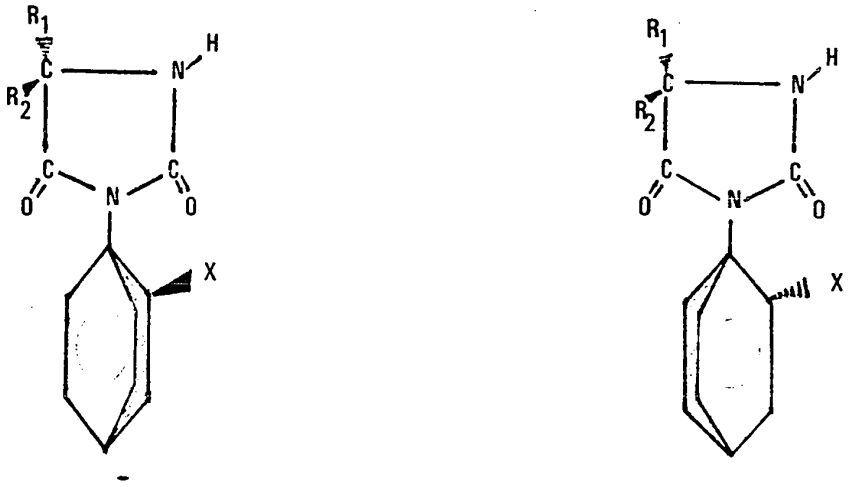
steric interaction in this case is between the axial methyl and the axial hydrogens at C-3 and C-5.

The effect of steric perturbation of the carbon-13 chemical shift has been rationalized by Grant and Cheney (15) on the basis of a sterically induced change in polarization in the perturbed carbon-hydrogen bond associated with non-bonded hydrogen-hydrogen repulsive interactions. Perlin and Koch (18) have found that for isomeric cyclohexane derivatives, the sum of the carbon-13 shieldings (shift values) increases additively with an increase in repulsive non-bonding interaction and thus with decreasing enthalpy in the series. By contrast, an inverse shielding pattern is found for the protons. This observation lends support to the proposed charge polarization mechanism for upfield steric shifts.

STEREOCHEMISTRY AND NMR SPECTRA OF THE HYDANTOINS .

For the 3-aryl hydantoins studied, the hydantoin ring is considered to be essentially planar. The crystal structure of 5,5-diphenyl hydantoin has been determined by Camerman (19). The five ring atoms and the two carbonyl oxygen atoms are coplanar: the average deviation from the plane through C-5 is 0.044 Å, the maximum being 0.1 Å. The small thermal parameters indicate that the calculated atom positions are not an average for several puckered conformations. Similar results were obtained for 2-thiohydantoin by Walker (20).

In the 3-aryl hydantoins, there is steric interaction between one or both of the hydantoin carbonyl groups and the aryl ortho substituent, and this causes restricted rotation about the aryl C-N bond. Because of this interaction, the hydantoin ring and the aryl ring are not coplanar in either of the two possible ground state rotamers:



Case 1: With two identical C-5 substituents R_1 and R_2, the two ground state rotamers are enantiomers and have indistinguishable spectra. The dihedral angle between the two rings must be the same for both rotamers, and similarly for the hydantoin ring conformation. For either ground state rotamer, the two identical C-5 substituents are diastereotopic and hence are magnetically non-equivalent.

In the present study the enantiomeric rotamers have either two diastereotopic hydrogens or two diastereotopic methyls at C-5. For carbon-13 spectra run with the protons fully decoupled (noise proton

decoupling), each carbon of the hydantoin should give rise to a single peak and in principle the two C-5 methyl carbons should give separate peaks. With the protons partially decoupled (off-resonance proton decoupling), carbons directly bound to hydrogen will show the predictable first order splitting. In practice, long range coupling was not observed.

Case 2. With two non-identical C-5 substituents R_1 and R_2, the two ground state rotamers are diastereomers, and in principle these have distinguishable spectra. The dihedral angle between the aryl and hydantoin rings is not necessarily the same for both rotamers, and similarly for the hydantoin ring conformation. One of the diastereomers will be thermodynamically preferred, and at equilibrium in solution the diastereomers will not be present in the ratio of 1:1, although this was found to be nearly so for the series of hydantoins studied (3). It should be noted that because C-5 is an asymmetric carbon, it can exist in either R or S configurations, and there are, therefore, two possible pairs of diastereomeric ground state rotamers. However, these four species also form two pairs of enantiomers, so that only two diastereomeric forms are, in principle, distinguishable in the spectra.

In the present study, the diastereomeric rotamers have one hydrogen and one methyl at C-5. For carbon-13 spectra run with noise proton decoupling each 5-methyl hydantoin should, in principle, show double peaks for each carbon, although these may not be resolved in

all cases. With off-resonance proton decoupling, carbons directly bound to hydrogen will show the predictable first order splitting. In practice, long range coupling was again not observed.

DIFFICULTIES IN INTERPRETATION OF THE SPECTRA .

There are several interdependent variables in the ground state structures of the aryl hydantoins:

- the nature of the aryl ortho substituent
- the dihedral angle between the aryl and hydantoin rings
- the conformation of the hydantoin ring
- the site and importance of solvation.

In the absence of any large effect clearly attributable to only one of the above factors, the interpretation of the spectral data for the series of hydantoins will depend on an often subjective evaluation of the relative importance of these factors.

The direct variable in the study is the nature of the ortho substituent: increase in the steric bulk or polarity of this group can be expected to increase the dihedral angle and will have qualitatively predictable effects on the spectrum. It is not known if there are significant differences in the dihedral angles of corresponding 5,5-dimethyl and 5-methyl hydantoins. The conformation of the hydantoin ring is thought to be planar, but the effects of the 3-aryl substituent or an asymmetrically substituted C-5 carbon could conceivably change

the conformation. Any change is expected to be small, however, because the eight π-electron hydantoin π-system must be planar for maximum orbital overlap, and consequent lowest energy. The C-5 carbon does not formally take part in the hydantoin π-system and may be above or below the plane of this π-system. The greatest unknown in this study is the extent and importance of solvation. All the measurements were carried out in the same solvent (DMSO), however, differences in solvation within the series of hydantoins may have appreciable effects on the spectra, and may invalidate any conclusions drawn from small trends in chemical shift values. An indication of the importance of solvation effects is obtained from the proton nmr spectra of the hydantoins: in general the C-5 methyl proton peak separations for solutions in pyridine are greater than in DMSO, where they are often zero. There may also be important differences in solvation between diastereomers: after several recrystallisations from ethanol, a pure diastereomer of 3-α-naphthyl-5-methyl-2-thiohydantoin has been obtained (21). The difference in solubility implies a difference in solvation, and this probably applies to DMSO as well as to ethanol solutions.

EXPERIMENTAL

GENERAL REQUIREMENTS FOR CARBON-13 SPECTROSCOPY.

In addition to the usual high-resolution requirement of magnetic field homogeneity and field/frequency stabilization, a carbon-13 spectrometer will require:

Wide Sweep Capability.

Carbon-13 chemical shifts cover a range of 250 ppm, compared to protons where the usual range is 10 ppm, and in order to obtain a spectrum it will often be necessary to sweep over a considerable range, typically 1000 Hz or more.

Frequency-sweep Mode of Operation.

This will allow the use of proton spin-decoupling, which may be necessary for signal enhancement by multiplet collapse and nuclear Overhauser effect, for spectrum simplification by the elimination of coupling to protons, and for spectral assignment.

Signal-to-noise Enhancement.

This is necessary because of the low natural abundance of carbon-13 (1.1%) and the inherent low detection sensitivity of carbon-13 relative to protons (1.59×10^{-2} at constant field for equal numbers of nuclei).

THE SPECTROMETER.

The present spectrometer is a Varian HA-100 continuous wave (C.W.) instrument operating at 25.15 MHz, equipped with a V-3530 wide sweep accessory and V-4335-1 probe, double-tuned to allow for proton spin-decoupling by means of a V-3512-1 heteronuclear decoupler. Spectra are recorded in the frequency-sweep mode using internal lock, and are accumulated in a C-1024 time average computer.

Principle of the Conventional HA-100 Spectrometer.

The HA-100 spectrometer operation is based on audio modulation of the applied magnetic field. With a transmitter radio frequency (RF) of ω and an audio frequency (AF) of m, the RF resonance signal obtained consists of a centerband together with upper and lower sidebands. The first upper sideband has frequency components $\omega + m$, and on RF phase detection gives rise to an AF signal of frequency m. This signal is actually a complex quantity, and is a mixture of absorption and dispersion mode signals, 90 degrees out of phase. An AF phase detector is used to select only signal components of frequency m, and also to discriminate between absorption and dispersion mode signals.

The HA-100 spectrometer in fact uses modulation at two different frequencies m_1 and m_2, one fixed, the other swept. This provides two separate signals, one for field/frequency stabilization (lock), the other recorded as the nmr spectrum. A simplified block diagram of the HA-100 operating in the frequency-sweep mode is shown in figure 1 .

The two AF oscillators provide field modulation via the modulation coils, and supply reference signals to the AF phase detectors. The RF signal from the probe is amplified and phase detected to yield AF signals which are then applied to the control and analytical channels, where they are amplified and phase detected. In the frequency-sweep mode, the control channel AF phase detector is

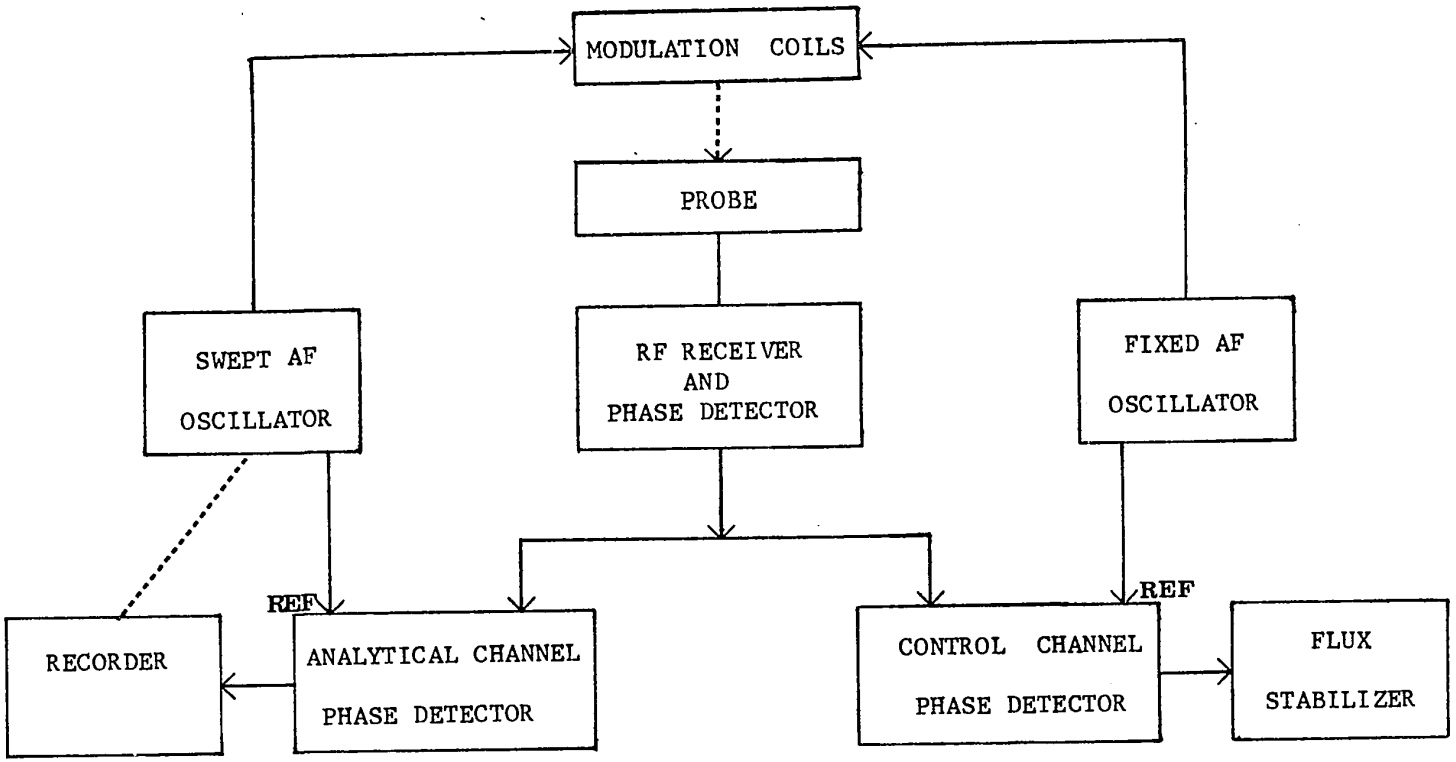


Figure 1 . Conventional HA-100 Internal Lock System Operating in the Frequency Sweep Mode.

(magnet not shown).

set to detect only signals in phase with the fixed frequency and the analytical channel phase detector is set to detect only signals 90 degrees out of phase with the swept frequency.

The phase of the RF phase detector can be varied to give a dispersion mode signal output from the control channel and an absorption mode signal from the analytical channel. The dispersion mode signal provides a dc error voltage to the flux stabilizer which adjusts the magnetic field to compensate for any change in the position of the lock signal due to field or frequency fluctuations. The swept AF provides frequency sweep, and the output from the analytical channel phase detector will be a series of absorption mode signals corresponding to the peaks in the nmr spectrum.

Principle of the Carbon-13 Spectrometer.

The combination of wide sweep capability and frequency-sweep operation introduces a serious problem in the case of the conventional spectrometer described above: as the observing AF is swept, the phase of the analytical channel phase detector also changes, resulting in an unacceptable spectrum. This problem is evident on proton spectra run with a frequency sweep of 1000 Hz. With proton spectra, frequency sweep is normally only used in decoupling experiments where a particular multiplet, extending over a small range, is observed. However in carbon-13 spectra, because of the large chemical shifts involved, sweeps of the order of 1000 Hz are common.

The solution adopted in the wide sweep accessory is as follows: instead of the conventional fixed RF and swept AF for the observing frequency, there is a fixed AF and a swept RF: the change in RF during the sweep is negligible compared to the value of the RF, and no problem arises at the RF phase detector stage.

In order to have a constant upper sideband frequency for the control channel, given a swept RF, it is necessary to have an AF which is swept by the same number of Hz as the RF, but in the opposite direction. The simultaneous AF and RF sweeps are generated in the V-3530 wide sweep accessory which consists of a Wavetek model 111 AF waveform generator and a Hallicrafter voltage controlled RF oscillator. These two units are both driven from the C-1024 time averaging computer (CAT) by the staircase ramp output which has 1024 discrete steps corresponding to the 1024 memory channels.

The Wavetek output is an AF whose start frequency is set on the Wavetek and whose positive going frequency sweep is controlled by the positive going ramp voltage. The staircase ramp also drives the Hallicrafter XVCO whose output is a negative going RF frequency sweep. The relationship between the RF, the two AF and the resultant upper sideband frequencies for the control and analytical channel signals are shown in figure 2 . The block diagram of the carbon-13 spectrometer is shown in figure 3 .

The C-1024 time averaging computer (CAT) settings control the sweepwidth, the sweeptime and the number of scans accumulated. The staircase ramp from the C-1024 CAT simultaneously

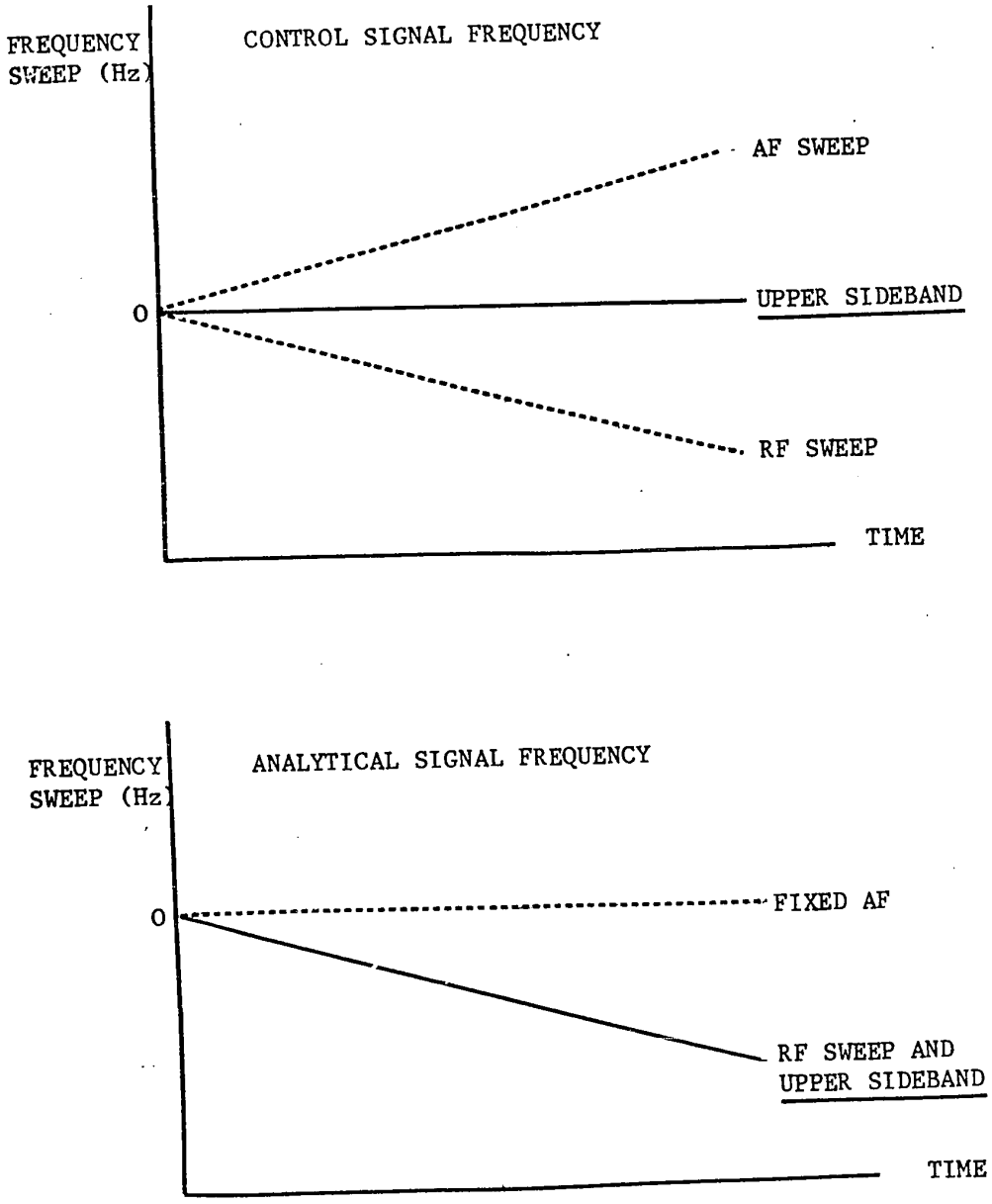


Figure 2 . Resultant Upper Sideband Frequencies for Carbon-13 Frequency Sweep Operation.

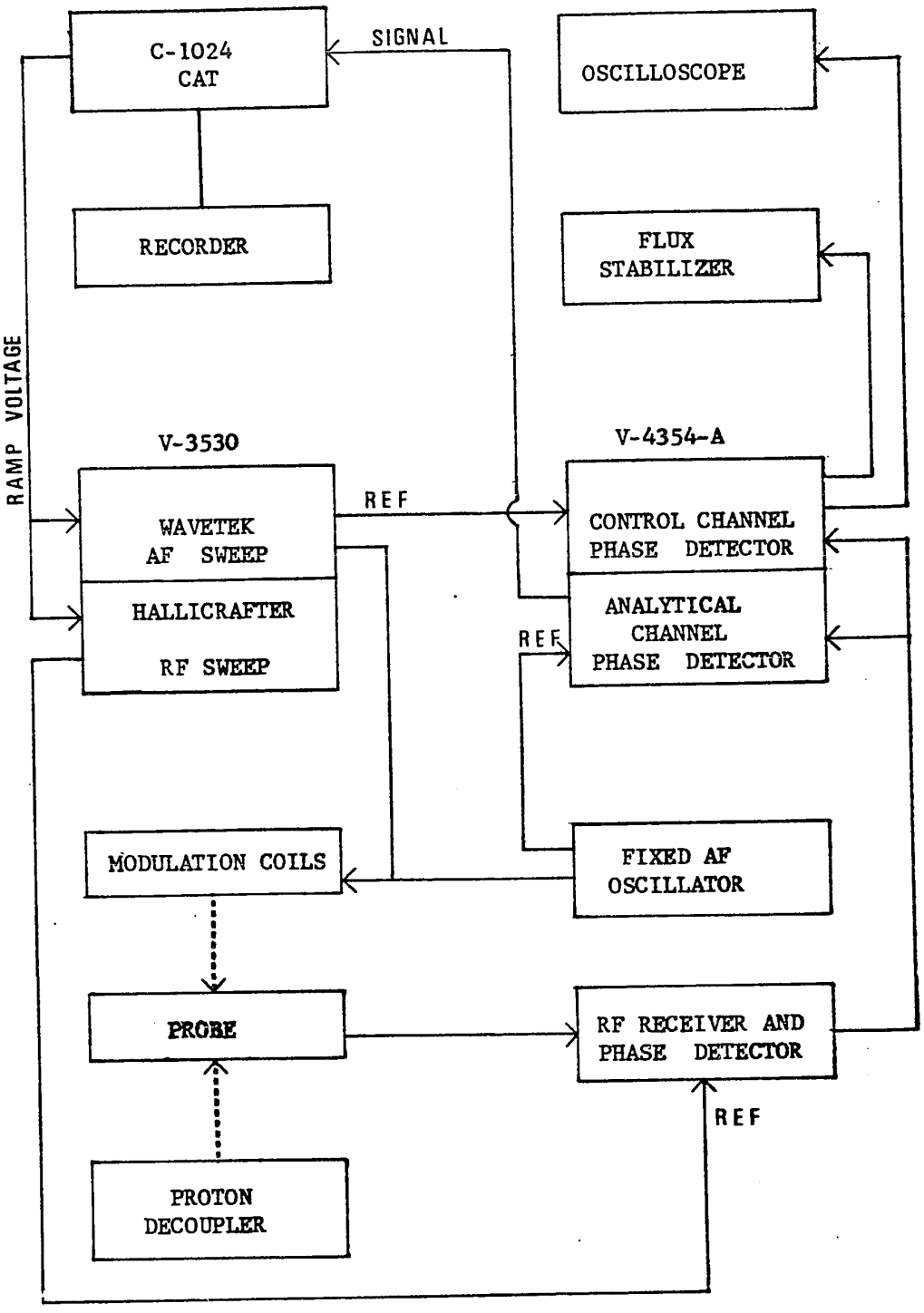


Figure 3 . Carbon-13 Spectrometer (magnet not shown).

serves to locate consecutive memory adresses for the spectral accumulation and drives the AF and RF sweeps as discussed above. As in the case of conventional HA-100, the AF oscillators provide field modulation and reference signals to the AF phase detectors, and the dispersion mode signal from the control channel is used for the lock. The absorption mode signals from the analytical channel are accumulated in the C-1024 CAT: for n scans, the signal-to-noise ratio is increased by a factor of $\sqrt{n}$. In order to provide a further signal enhancement, but at the expense of lower resolution, 8 mm diameter sample tubes are used instead of the 5 mm tubes used for protons.

The V-3512-1 heteronuclear decoupler can be used either in the coherent mode (single frequency irradiation) to decouple specific protons, or with a variable bandwidth noise modulation to decouple multiplets or all protons.

Two further features of the spectrometer are necessary because of the small signals obtained from natural abundance carbon-13:

- the C-1024 interlock, a sweep interrupt circuit which monitors the presence of a lock signal. When switched in, the interlock automatically prevents the C-1024 CAT from accumulating if there is no lock present. Thus data collected before the lock is lost are not destroyed by numerous additional scans of noise.

- for carbon-13, the conventional sine wave lock signal presentation on the oscilloscope is not observed above the noise,but a more sensitive lock dc level can be used to find the lock signal and to optimize homogeneity.

Choice of Audio Frequencies.

For proton nmr the HA-100 control and analytical channels operate at frequencies in the range 1.5 to 3.5 kHz. For carbon-13 operation the AF range used must extend from 1.5 to 8 kHz in order to cover the whole range of chemical shifts for one magnetic field setting. The audio frequencies chosen for locking onto or observing a series of compounds are given in table II .The audio frequencies used in this work are plotted as a function of carbon-13 chemical shifts in figure 4.

When locking onto a given resonance, the Wavetek AF start is selected according to table II or figure 4 . Choosing the AF start in this way ensures that the magnetic field will be the same for all samples, and hence the proton decoupler calibration will also remain constant for all samples.

Since the RF sweep is towards lower frequency, the analytical channel fixed AF is chosen from figure 4 to correspond to the upper frequency limit of the required sweep range.

SETTING UP THE SPECTROMETER.

Finding the Signal.

All setting up is done using a 60% carbon-13 enriched sample of methyl iodide in a 5 mm tube. This sample gives a signal large enough to be observed on the oscilloscope.

Table II. Carbon-13 Reference Compounds with their Chemical Shifts from Carbon Disulfide and the Audio Frequencies Used.

Compound	Chemical shift[a]	AF	AF (VARIAN)
Methyl iodide	213.9	3220	2500
TMS	192.8	3770	
Cyclohexane	167.2	4400	3676
DMSO	152.9	4780	4032
Dioxan	126.9	5430	4685
Benzene	65.7	6970	6220
Carbon disulfide	0	8600	7870

[a] Ppm upfield from carbon disulfide, from Refs. 22, 23.

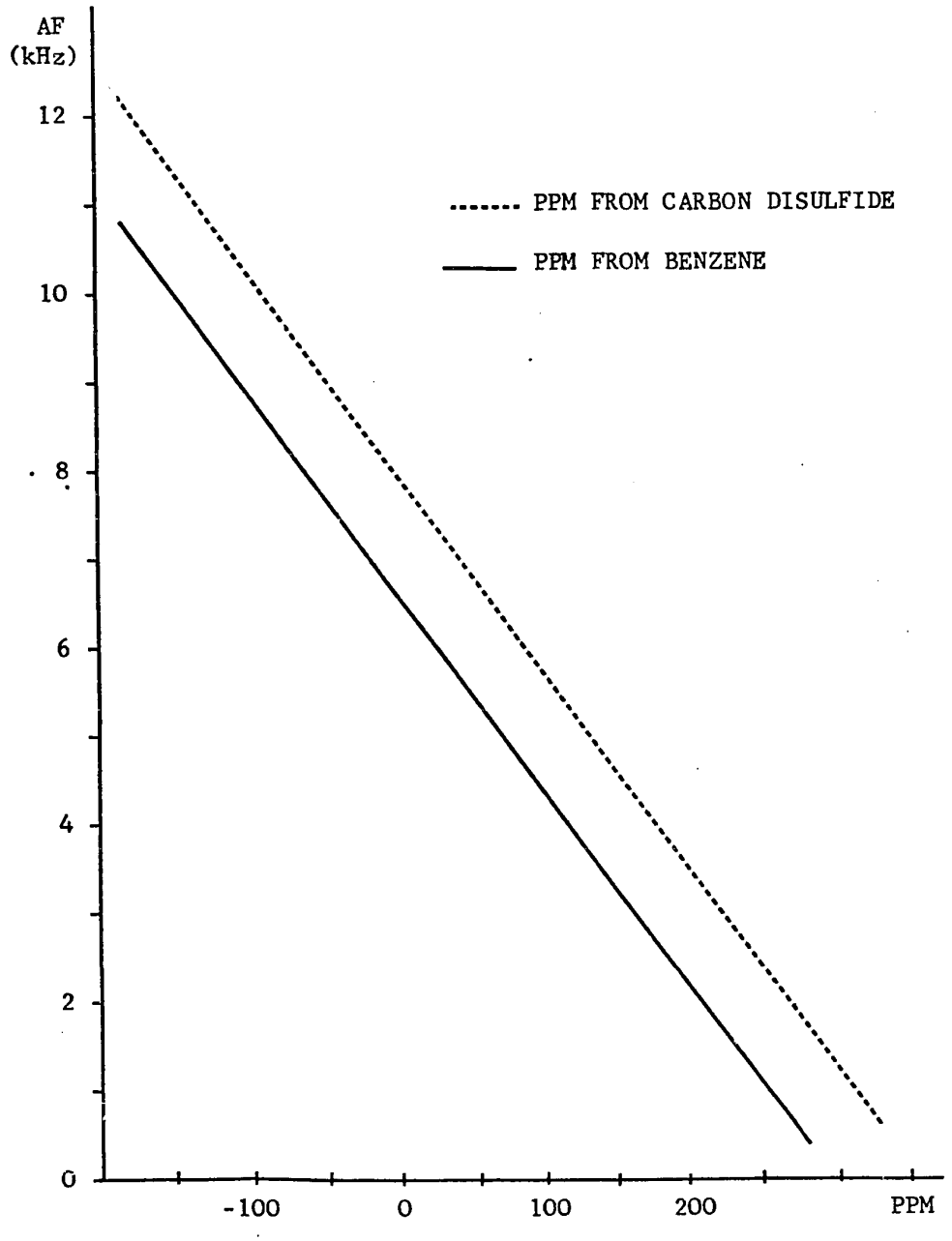


Figure 4 . Audio Frequencies Used, as a Function of Chemical Shift in PPM Upfield from Benzene or Carbon Disulfide.

In order to obtain maximum signal-to-noise, the probe receiver circuit is tuned for each sample at equilibrium temperature, and the probe leakage is balanced to a mimimum.

The signal displayed on the oscilloscope is from the control channel, and for methyl iodide the AF start frequency of the Wavetek is selected from table II to be 3220 Hz.

The first upper sideband signal from the methyl iodide is centered on the oscilloscope by adjusting the magnetic field, and the magnet homogeneity is maximized while observing the ringing from the peak of the methyl iodide quartet.

AF/RF Tracking.

It is necessary to ensure that the AF and RF sweeps are both of exactly equal magnitude, otherwise the upper sideband lock signal frequency will not be constant and calibration errors will be introduced. The AF/RF sweep check is made by observing a peak of the methyl iodide quartet on the oscilloscope, and then sweeping the AF/RF frequencies from the C-1024 CAT. If the AF/RF sweeps are of the same number of Hz, then the peak position will not move laterally on the oscilloscope during the sweep. A small lateral displacement is most easily detected by observing the peak position just before the end of a 1000 Hz sweep, and then again the beginning of the next sweep. The AF/RF tracking is adjusted with the RF sweep width calibration.

Homogeneity.

The final adjustment of the magnetic field homogeneity is carried out after locking on one peak of the methyl iodide quartet, by optimizing the RF phase detector and shim coil setting for a maximum lock dc level.

Spin Decoupler.

The proton spin decoupler operates at 100 MHz variable over a range of ± 0.045%. The output can be noise-modulated with a bandwidth adjustable between 0.1 and 8 kHz.

To set the exact frequency of the decoupler, the methyl iodide quartet is observed on the oscilloscope, with a noise modulation of 1-2 kHz and maximum output. The frequency is adjusted to collapse the quartet to a singlet. The spectrometer is locked onto this decoupled line and the final adjustment of the decoupler frequency is carried out in the coherent mode with a low output by obtaining a maximum for the lock dc level. A low level coherent output is necessary for this adjustment because the audio field modulation produces an effect equivalent to audio sidebands of the decoupler frequency: methyl iodide protons can be decoupled by such a " sideband " at high coherent output levels, but on reducing the output or switching to noise modulation there is no longer sufficent power at the proton resonance frequency to provide decoupling.

This method of optimising the proton decoupler frequency by means of the decoupled methyl iodide lock dc level was found to be very sensitive and was used in calibrating the fine frequency dial against protons decoupled in ppm downfield from TMS. Protons that absorb 1 ppm downfield from methyl iodide protons will absorb at a frequency 1 ppm higher on frequency sweep. A method was found to increase the decoupler frequency by exactly 1 ppm, using the carbon-13 enriched methyl iodide sample. The lock signal AF was increased by 1 ppm (25 Hz for carbon-13) and to observe the methyl iodide resonance, the magnetic field had then to be increased by 1 ppm. The decoupler frequency also had to be increased by 1 ppm (100 Hz for protons) to collapse the quartet to a singlet. The spectrometer was locked onto this decoupled line and the decoupler frequency adjusted for maximum lock dc level as described above. Carrying out this process at several lock signal audio frequencies, the decoupler fine frequency dial was calibrated: the most useful range of protons is covered with the fine frequency dial set at 2.00 for methyl iodide using an AF of 3220 Hz.

By means of the calibration graph shown in figure 5, protons whose chemical shift is known can be selectively decoupled, or using noise modulation, the decoupler can readily be set to cover a given range of protons. For each new sample the decoupler fine frequency setting is optimized for the lock resonance used, and the setting is taken as the reference in using the calibration graph.

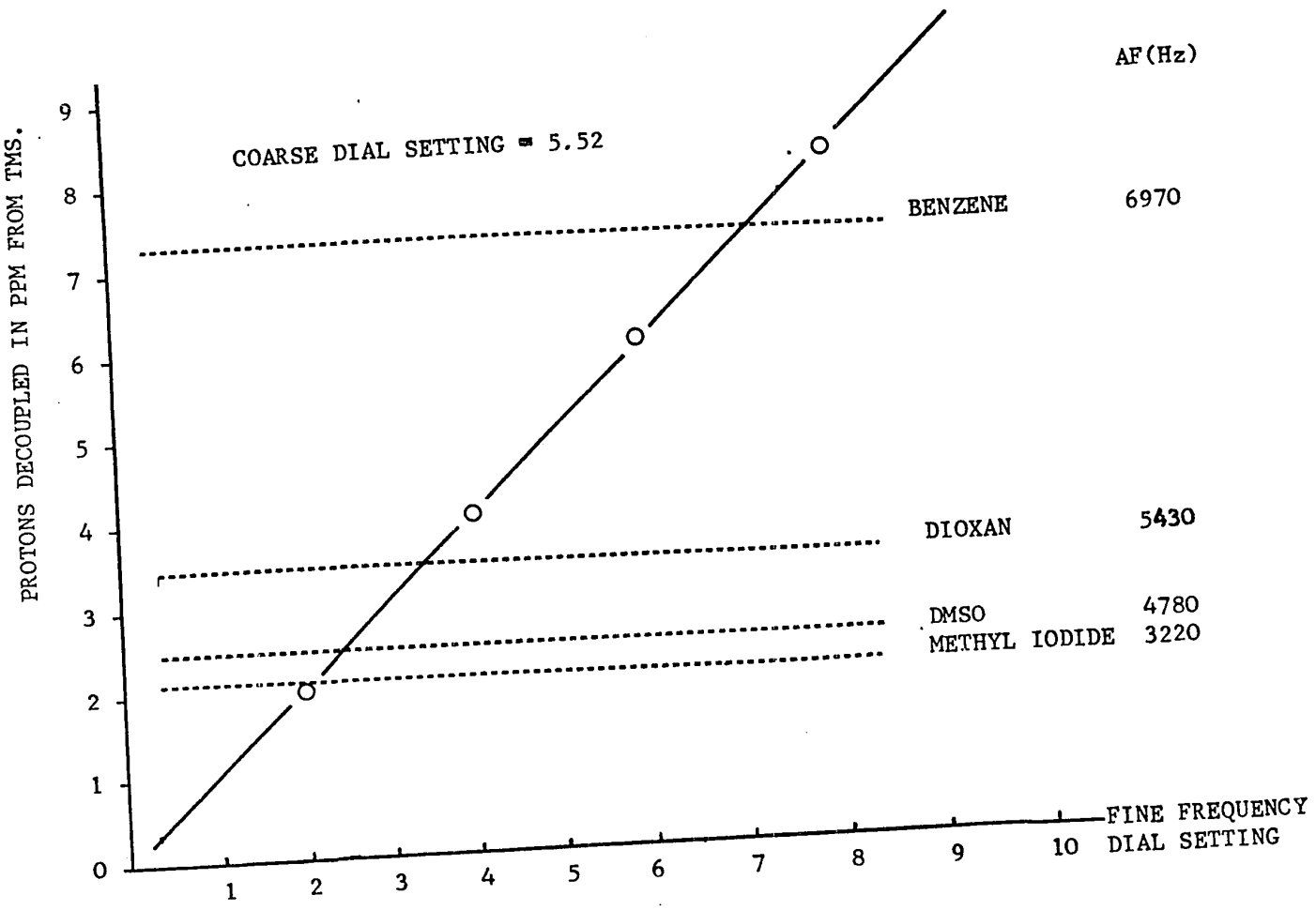


Figure 5 . Proton Decoupler Fine Frequency Dial Calibration.

SPECIFICATIONS AND TESTS.

Wavetek (AF).

The specifications of the Wavetek AF sweep are as follow:

- ramp linearity $>99\%$
- amplitude and frequency stability $\pm$ 0.05% for 10 min,
  $\pm$ 0.25% for 24 hours
- jitter (cycle to cycle stability) $\pm$ 0.025%

(For an AF of 5 kHz, $\pm$ 0.05% = $\pm$ 2.5 Hz)

The AF stability was found experimentally to be better than specified: the AF start was counted before and after each accumulation and did not vary by more than $\pm$ 1 Hz. The AF start was sometimes checked during a long accumulation and if necessary readjusted to the correct value.

Sweepwidth.

The AF start is counted on an HP 5512A counter, the sweep is triggered from the C-1024 CAT, and the highest frequency counted is recorded. The measurement was repeated several times, sweeping at the slowest possible rate towards the end of the scan, and the AF sweep determined in this way is estimated to $\pm$ 1 Hz, which is about the frequency stability of the Wavetek during an accumulation. There is a provision for reading the sweep end point directly, but this only worked intermittently and was not trusted.

Resolution.

The resolution for the carbon-13 enriched methyl iodide sample in a 5 mm spinning tube was determined by locking onto one peak of the quartet and observing one of the other peaks. The resolution was measured to be 1.5 Hz for a single scan. For samples in an 8 mm spinning tube, the resolution was measured by locking onto decoupled benzene and observing decoupled dioxan. The sample contained 80% benzene and 20% dioxan, both with natural abundance carbon-13, and the accumulated spectrum gave a peak width of 2.5 Hz. Typically, carbonyl groups in the hydantoins gave peak widths of 2.5 Hz. Over long accumulations, the resolution stability sometimes proved troublesome, but the resolution could be optimized between scans using the lock dc level.

AF/RF Tracking.

The AF/RF tracking as set up using the oscilloscope presentation can be estimated to be correct to within ½ of the peak width as seen on the oscilloscope, or ± 0.5 Hz. This was checked using the methyl iodide sample by locking on one peak of the quartet and observing one of the other peaks: the observing fixed AF was first chosen to display the signal near the start of a sweep, and then changed to display the signal near the end of a sweep. for a change in position of 950 Hz along the sweep, the calculated peak frequency was the same to within ± 1 Hz which is the precision of the reading.

It was concluded that the AF/RF tracking as set up using the oscilloscope is adequate.

Hallicrafter (RF).

The specifications were not supplied, but it can be seen that the absolute frequency and jitter stability are taken care of by the field/frequency stabilization . Only the RF sweepwidth stability is critical and as the AF/RF tracking and the AF sweep stabilities are both of the order of $\pm$ 0.5 Hz over a day, then the RF sweep stability must also be of the same order.

The frequency of the Hallicrafter was measured on a HP 5255A counter to be 25.144126 MHz, thus the effective upper sideband frequency with AF modulation in the range 1.5 to 10 kHz is 25.15 MHz. The V-4311 RF receiver was tuned to the Hallicrafter RF in order to ensure maximum signal-to-noise.

Readout.

The accumulated spectra are read out of the memory and displayed on the HA-100 recorder. The readout time can be adjusted in the C-1024 CAT and this was attempted in order to calibrate the readout with the graph paper, using the known coupling constant of methyl iodide. However, it was found that the C-1024 CAT readout times were very temperature dependent and also varied from day to day.

The solution adopted was to start the recorder pen sweep before the C-1024 memory readout: the 1024 channels were taken to extend over the region displaying noise, and the peak positions were calculated by interpolation, knowing the frequencies corresponding to the sweep start and sweep end.

Readout tests were run by accumulating the carbon-13 methyl iodide quartet, and then reading out the memory at different speeds. It was found that a sweep time of 250 seconds was necessary to allow the pen to follow the signal without distortion. Successive scans gave identical separation between first and fourth peaks, within the precision of reading the peak positions (0.2 Hz in 453 Hz).

Sweep Linearity.

Overall sweep linearity was tested for by locking on one peak of the methyl iodide quartet and measuring the frequencies of the other peaks, with a range of sweep AF values selected so that a given peak appeared at different positions on the sweep.

The peak frequency was calculated to be constant over the whole range of the 1000 Hz sweep to within $\pm$ 1 Hz, the precision of the measurements.

Sample Temperature.

With the heteronuclear decoupler in operation, ice-cold air is passed through the probe to avoid heating damage. The sample

temperature was measured under operating conditions using an iron-constantan thermocouple in a non-spinning sample tube containing DMSO, the solvent normally used. The sample temperature was found to depend markedly on the decoupler output level but not on the noise modulation bandwidth. The maximum change in the flow of the cooling air produced a change of only ± 2° C. With an RF attenuation of 20 dB and the usual settings for AF modulation, the temperatures recorded for different decoupler output levels are given below:

output level	sample temperature °C ± 2°C.
3.00 (maximum)	55
1.00	35
0.80	34
0.60	32

Conclusion.

It was shown that the readout is reproducible and the overall sweep is linear for the sweep widths employed.

With the AF/RF tracking correctly set, the calculated peak positions can therefore be estimated to within the stability of the audio frequencies (± 1 Hz) and the error of reading the peak position, which will depend on the peak width and the sweep range.

PROCEDURE FOR RUNNING SPECTRA.

General Conditions.

The combination of low sensitivity and relatively long spin-lattice relaxation times, T_1, for carbon-13 causes the experimental conditions for obtaining carbon-13 spectra to be critical, particularly in the case of natural abundance samples.

For a maximum signal-to-noise a high RF power level is desirable, but if too high, the Boltzmann distribution will be disturbed, leading to saturation of the signal.

The RF power level, the AF modulation levels and the sweep rate were determined for maximum signal-to-noise without saturation. Typical conditions used for setting up and for running spectra are given in tables III and IV.

Lock Signal.

For the lock signal a capillary containing 86.5% carbon-13 enriched methyl iodide can be used, held coaxially in the 8 mm tube by means of a Teflon insert. In order to allow non-decoupled spectra to be obtained, it was originally intended to lock onto one peak of the quartet from this sample. However this was found to be unfeasible, probably due to spinning wobble of the capillary. The proton decoupled

Table III. Instrument Parameters for Setting Up using the Carbon-13 Enriched Methyl Iodide Sample.

	Homogeneity		Proton decoupler	
	oscilloscope	spectrum	oscilloscope	lock dc level
RF attenuation (dB)	20	30	30	30
AF start (Hz)	3220	3220	3220	3220
(mG)	0.7	0.1	0.7	0.1
Fixed AF (Hz)	a	3400	a	a
(mG)	a	1	a	a
RF phase detector	25	34	25	34
Spectrum Amplitude	3000	1000	3000	500
Sweep (Hz)	a	100	a	a
Sweeptime (sec)	a	25	a	a

[a] Not applicable.

Table IV. Typical Instrument Parameters for Spectra with Natural Abundance or Capillary Lock[a].

	To find lock	To record spectrum
RF attenuation (dB)	20	20
AF start (mG)	1	0.1
Fixed AF (mG)		1
RF phase detector	26	26
Spectrum amplitude	3000	3000
Sweeps (Hz)	off	200, 1000
Sweep time (sec)	off	10, 50

[a] Proton decoupler frequency centered on lock sample protons. Noise decoupling: bandwidth 1.5 kHz, output setting 3.00. Off-resonance proton decoupling: coherent, output setting 1.00.

signal from the capillary sample is strong enough to use for the lock but it was found more convenient to lock onto the natural abundance carbon-13 of the solvent, DMSO in the present work.

To lock onto the decoupled solvent or capillary resonance, the instrument conditions are set as given in table IV . Using the slow sweep unit, the field is swept until the lock dc level, observed with maximum sensitivity, gives a positive excursion. The instrument is then immediately locked and the AF sweep level is reduced.

Final Adjustments with the Sample.

The decoupler frequency, the RF phase detector and the field homogeneity shim coils are successively adjusted for maximum lock dc level.

The modulation audio frequencies are counted and the sweepwidth determined for accurate spectrum calibration. The RF phase detector is set for the correct spectrum absorption mode phase, as previously determined by trial and error, and finally the accumulation is initiated at the C-1024 CAT.

Readout.

The accumulated spectrum is read out of the memory onto the recorder with readout and pen sweep times of 250 seconds. The spectra included in this thesis were obtained directly with appropriately chosen readout and pen sweep times.

PREPARATIONS .

Proton nmr spectra were recorded on Varian HA-100 and Varian A-60 Spectrometers. The chemical shifts are reported in ppm relative to TMS, the coupling constants are in Hz. Infrared spectra were obtained from KBr pellets on a Perkin Elmer Model 457. Melting points were measured on a Gallenkamp melting point apparatus, and are uncorrected. The elemental analyses were performed at the Alfred Berhart Microanalytisches Laboratorium, Elbach-uber-Engelskirchen, West Germany. Yields are calculated on the basis of the amino acid, since the isocyanate was present in excess in all preparations.

o-Trifluoromethylphenyl isocyanate:

The procedure followed was that of Shriner, Horne and Cox (24).This reaction involved the use of phosgene and was carried out in a hood in the presence of test paper to detect phosgene (25). The apparatus was maintained under reduced pressure by means of a water pump.

Phosgene (Matheson), dried by passing through concentrated H_2SO_4, was bubbled through ethyl acetate (Baker)(30 ml), previously dried over molecular sieves. The excess of phosgene was destroyed by bubbling through a 20% solution of NaOH.

o-Aminobenzotrifluoride (Aldrich) (6.2 g, 0.038 mole) dissolved in dry ethyl acetate (50 ml), was added dropwise to the saturated phosgene solution. The amine hydrochloride precipitate, kept

in suspension by means of a magnetic stirrer, was allowed to react before more amine was added.

After complete reaction of all of the amine, phosgene was passed through the solution for another 15 minutes. The ethyl acetate was then removed by distillation at atmospheric pressure and the crude trifluoromethylphenyl isocyanate was used, without further purification, in the preparation of the hydantoin. The ir spectrum of the isocyanate showed a characteristic strong broad band at 2260 cm^{-1}.

3-o-Trifluoromethylphenyl-5-methyl hydantoin:

The procedure followed was that of Behr and Clarke (26) D,L-Alanine (Eastman) (2.0 g, 0.0022 mole) was dissolved in 0.4 N NaOH solution (80 ml). The o-trifluoromethylphenyl isocyanate prepared above was added, and the suspension was stirred with a magnetic stirrer for one hour,

The insoluble urea, formed by reaction of the isocyanate with water, was filtered off and the filtrate was acidified to Congo red with 6N HCl. During the acidification the hydantoic acid precipitated from solution. The solution was cooled, and the hydantoic acid was collected by filtration.

The hydantoic acid was dissolved in a hot solution of water (350 ml) and 12N HCl (100 ml). This solution was refluxed for 1½ hours, was reduced to about 200 ml, and was partially neutralized with solid sodium carbonate.

The hydantoin, which precipitated upon cooling, was collected by filtration and was recrystallised from an ethanol-water mixture.

Yield 2.4 g (41%), mp 135.5-136.5°C, lit. 139.5-141.0°C (3). Proton nmr (60 MHz, DMSO-d_6) δ 1.40 (doublet, J = 7 Hz) and 1.47 (doublet, J = 7 Hz) (3H), 4.15-4.50 (multiplet centered at 4.32, 1 H), 7.40-8.00 (multiplet, 4H), 8.40 (1H). Analysis calculated for $C_{11}H_9F_3N_2O_2$: C, 51.17; H, 3.51; N, 10.85. Found: C, 50.97; H, 3.49; N, 11.04.

The procedure was the same for the following compounds:

3-o-Trifluoromethyl-5,5-dimethyl hydantoin:

The starting materials were 2-methyl alanine (Baker) (1.0 g, 0.010 mole) and o-trifluoromethylphenyl isocyanate.

Yield 1.2 g (46%), mp 178.0-180.0°C. Proton nmr (100 MHz, DMSO-d_6) δ 1.37 (3H), 1.44 (3H), 7.47-7.84 (4H), 8.60 (1H). Analysis calculated for $C_{12}H_{11}F_3N_2O_2$: C, 52.95; H, 4.07; N, 10.29. Found: C, 52.83; H, 4.10; N, 10.43.

3-o-Tolyl-5-methyl hydantoin:

The starting materials were D,L-alanine (2.7 g, 0.030 mole) and o-tolyl isocyanate (Eastman) (5.4 g, 0.041 mole).

Yield 1.3 g (21%), mp 112.0-113.0°C. Proton nmr (100 MHz, DMSO-d_6) δ 1.37 (doublet, J = 6 Hz , 3H), 2.09 and 2.12 (3H), 4.20-4.40 (multiplet centered at 4.30, 1H), 7.06-7.36 (multiplet, 4H), 8.40 (1H). Analysis calculated for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.71; H, 5.90; N, 13.72.

3-o-Tolyl-5,5-dimethyl hydantoin:

The starting materials were 2-methyl alanine (3.1 g, 0.030 mole) and otolyl isocyanate (4.3 g, 0.032 mole).

Yield 1.1 g (17%), mp 165.0-166.0°C, lit. 168.0-169.2°C (3) Proton nmr (100 MHz, DMSO-d_6) δ 1.42 (6H), 2.10 (3H), 7.10-7.37 (4H), 8.55 (1H). Analysis calculated for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.90. Found: C, 66.03; H, 6.42; N, 12.92.

3-Phenyl-5,5-dimethyl hydantoin:

The starting materials were 2-methyl alanine (3.0 g, 0.030 mole) and phenyl isocyanate (4.9 g, 0.041 mole).

Yield 2.4 g (39%), mp 160.0-161.5°C, lit. 171°C corrected (27) Proton nmr (100 MHz, DMSO-d_6) δ 1.42 (6H), 7.41 (5H), 8.54 (1H). Analysis calculated for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.52; H, 5.82; N, 13.66.

For all the above hydantoins the ir spectra showed a broad N-H band between 3180 and 3310 cm^{-1}. The carbonyl group gave rise to a weak band at 1780-1790 cm^{-1}, and a strong broad band at 1720 cm^{-1}.

The solvent and the model compounds were reagent grade chemicals, unless otherwise indicated, and were obtained from standard sources: DMSO (Fisher), hydantoin (Eastman), urea (Fisher), acetamide (Eastman), 2-thiohydantoin (Eastman, practical grade), thiourea (Eastman, practical grade), phenyl urea (Baker),

1,3-diphenyl urea (Aldrich), o-tolyl urea (Eastman), m-tolyl urea (Eastman).

The hydantoin was recrystallised from ethanol, and the 2-thiohydantoin was recrystallised three times from water. The other compounds were not further purified.

With the exception of the aryl hydantoins for which the preparations have been given above, the aryl hydantoins investigated in the present work were donated by J. Fehlner and were measured without further purification.

RESULTS AND DISCUSSION.

Carbon-13 nuclear magnetic resonance spectra were measured for a series of model compounds listed in table V and for the series of 3-aryl substituted hydantoins listed in table VI. The hydantoins are divided into three groups corresponding to the number of methyls at the C-5 position. The relationship between the rotamers formed by rotation about the aryl C-N bond is shown for each hydantoin.

The peaks of the carbon-13 nmr spectra of the hydantoins were assigned by comparison of their chemical shift values to the values measured for model compounds.

In order to compare the chemical shift values for a given carbon position throughout the series of hydantoins studied, the

Table V .

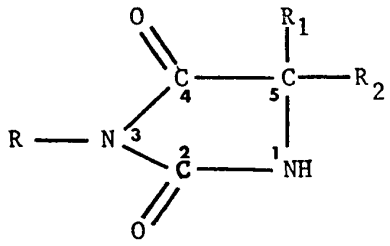
Carbonyl Carbon-13 Chemical Shifts of Hydantoin (I) and some Model Compounds[a].

Compound	Concentration mole% in DMSO	C-2	C-4
Hydantoin (I)	20.6	34.8	19.4
Urea	21.4	33.0	
Acetamide	24.5	21.4	
2-Thiohydantoin	17.3	9.8	19.1
Thiourea	21.3	9.6	
Phenylurea	13.9	37.1	
1,3-Diphenyl urea	8.5	39.9	
o-Tolyl urea	9.8	37.2	
m-Tolyl urea	14.0	37.2	

[a] Ppm upfield from carbon disulfide.

Table VI

The Series of Hydantoins Studied, with the Relationship Between Rotamers.



Hydantoin	R	R_1	R_2	Rotamers
I	H	H	H	a
II	α-Naphthyl	H	H	enantiomers
III	o-Chlorophenyl	H	H	enantiomers
IV	α-Naphthyl	H	CH_3	diastereomers
V	o-Tolyl	H	CH_3	diastereomers
VI	o-Trifluoro-methylphenyl	H	CH_3	diastereomers
VII	o-Chlorophenyl	H	CH_3	diastereomers
VIII	α-Naphthyl	CH_3	CH_3	enantiomers
IX	Phenyl	CH_3	CH_3	a
X	o-Tolyl	CH_3	CH_3	enantiomers
XI	o-Trifluoro-methylphenyl	CH_3	CH_3	enantiomers
XII	o-Chlorophenyl	CH_3	CH_3	enantiomers
XIII	o-Bromophenyl	CH_3	CH_3	enantiomers
XIV	o-Nitrophenyl	CH_3	CH_3	enantiomers

[a] Not applicable

results are tabulated and discussed according to the carbon position.

The solvent used was dimethyl sulfoxide (DMSO) which also provided a lock signal and internal reference. Concentrations expressed as mole% in DMSO, are listed in table V for the model compounds and in table VII for the hydantoins.

Chemical shift values are reported relative to carbon disulfide, and were calculated by taking the chemical shift of DMSO to be 152.9 ppm upfield from carbon disulfide. All chemical shift values are estimated to be internally accurate to $\pm$ 0.1 ppm unless otherwise indicated. For spectra measured with off-resonance proton decoupling, the chemical shift corresponding to the center of a multiplet is reported, followed in parentheses by J_r, the residual splitting or " Reduced Coupling Constant " (28) expressed to the nearest 1 Hz.

ASSIGNMENT OF THE PEAKS OF HYDANTOIN (I).

The carbon-13 nmr spectrum of hydantoin (I) is shown in figure 6 . Three peaks are observed with noise proton decoupling: two of these peaks remain unsplit with off-resonance proton decoupling and are assigned to the two carbonyl carbons.

The carbonyl carbon-13 chemical shifts of hydantoin (I) and some model compounds are listed in table V . The two carbonyl peaks of hydantoin (I) have chemical shift values of 34.8 ppm and

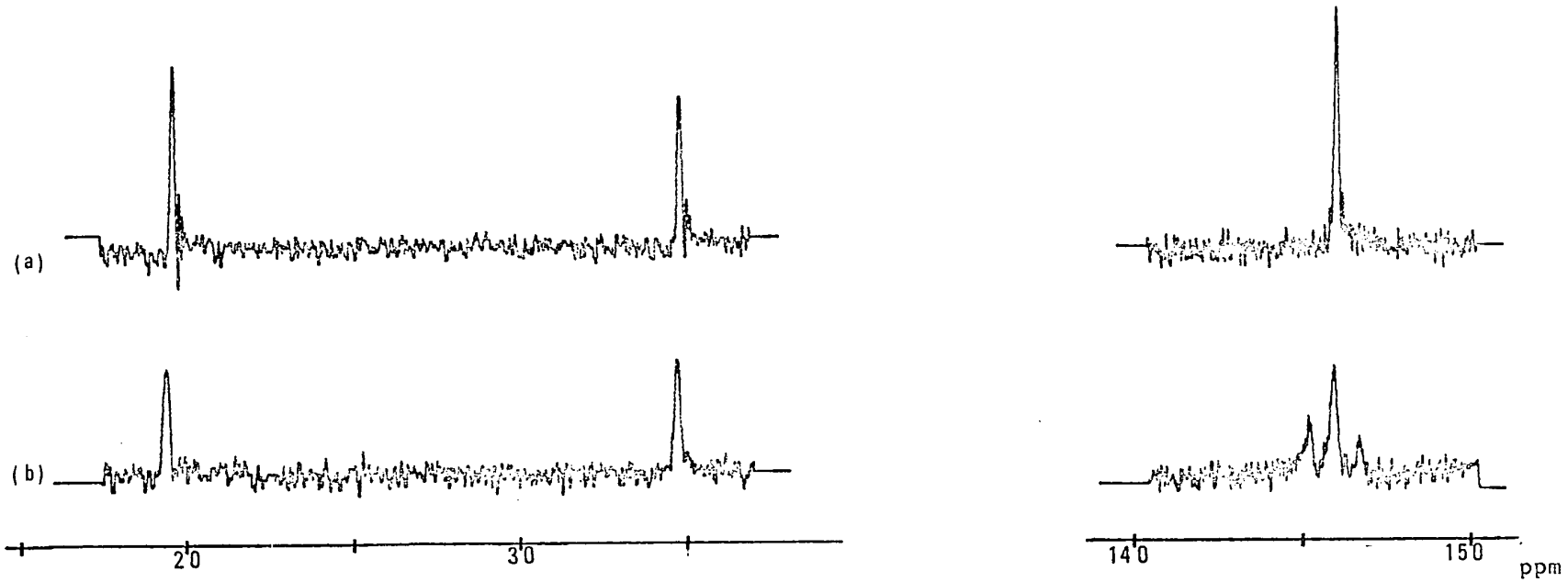


Figure 6 . Carbon-13 nmr Spectra of Hydantoin (I).

(a) With noise proton decoupling
(b) With off-resonance proton decoupling.

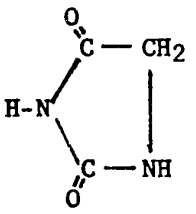
Table VII . Carbonyl Carbon-13 Chemical Shifts of the Hydantoins[a].

Hydantoin	Substituent at N-3	Relationship between rotamers	Concentration mole% in DMSO	C-2	C-4
I	H	b	20.6	34.8	19.4
II	α-Naphthyl	enantiomers	6.3	36.8	22.2
III	o-Cl-Ph	enantiomers	8.7	37.9	23.2
IV	α-Naphthyl	diastereomers	7.2	37.7	18.8
V	o-Tolyl	diastereomers	8.6	38.2	19.5
VI	o-CF_3-Ph	diastereomers	12.3	38.19 38.33	19.4
VII	o-Cl-Ph	diastereomers	5.6	38.89 39.01	19.8
VIII	α-Naphthyl	enantiomers	9.4	38.7	16.2
IX	Phenyl	b	11.8	39.2	17.1
X	o-Tolyl	enantiomers	9.9	39.3	17.1
XI	o-CF_3-Ph	enantiomers	9.5	39.5	17.1
XII	o-Cl-Ph	enantiomers	3.9	40.1	17.8
XIII	o-Br-Ph	enantiomers	6.1	40.2	17.9
XIV	o-NO_2-Ph	enantiomers	3.0	40.6	18.1

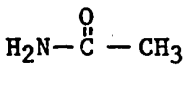
[a] Ppm upfield from carbon disulfide, with noise proton decoupling, ± 0.1 ppm. Separation of double peaks, ± 0.05 ppm. [b] Not applicable.

19.4 ppm and are in or near the amide carbonyl region of 19 to 33 ppm (6).

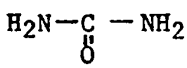
In order to assign each of these two peaks specifically to the C-2 or C-4 carbonyl carbon, the model compounds urea and acetamide were chosen respectively.



(I)



acetamide



urea

The spectrum of acetamide with noise proton decoupling shows two peaks, one from the methyl carbon, the other from the carbonyl carbon. With off-resonance proton decoupling, the peak at 171.2 ppm gives a 1:3:3:1 quartet with J_r = 7 Hz and is assigned to the methyl carbon. The peak at 21.4 ppm remains unsplit and is assigned to the carbonyl carbon of acetamide. The spectrum of urea shows one peak at 33.0 ppm.

The chemical shift values of these model compounds agree closely with the values for the carbonyl peaks of hydantoin (I) at 34.8 ppm and 19.4 ppm which are accordingly assigned to the C-2 and C-4 positions, respectively, as shown in table V . This assignment is confirmed by a comparison of the thiocarbonyl and carbonyl peaks of 2-thiohydantoin at 9.8 ppm and 19.1 ppm, with the peak of thiourea at 9.6 ppm and the peak assigned to the C-4 carbonyl of hydantoin (I) at 19.4 ppm.

The remaining peak in the spectrum of hydantoin (I) observed with noise proton decoupling must be due to the C-5 carbon. With off-resonance decoupling this peak is split to give a 1:2:1 triplet, thus identifying it unambiguously as the C-5 carbon resonance by the coupling to the C-5 geminal hydrogens. Furthermore, this peak occurs at 145.8 ppm, within the 135-150 ppm region expected for a methylene carbon adjacent to nitrogen (6).

ASSIGNMENT OF THE PEAKS OF THE ARYL HYDANTOINS .

The peaks corresponding to the C-2 and C-4 carbonyl carbons and the C-5 carbon are readily assigned from a comparison of their chemical shift values with the values for the previously assigned peaks of hydantoin (I).

Chemical shift values for the peaks assigned to the carbonyl carbons of the hydantoins are shown in table VII. The values for the C-2 carbonyl carbons of the aryl hydantoins vary over a range of 36.8 to 40.6 ppm, and agree quite closely with the value of 34.8 ppm for hydantoin (I). Similarly the values for the C-4 carbonyl carbons of the aryl hydantoins vary over a range of 16.2 to 23.2 ppm, and again agree quite closely with the value of 19.4 ppm for hydantoin (I).

Chemical shift values for the peaks assigned to the C-5 carbons of the aryl hydantoins are shown in table VIII. These values

Table VIII . The C-5 Carbon-13 Chemical Shifts of the Hydantoins[a].

Hydantoin	Substituent at N-3	Relationship between rotamers	Noise proton decoupling	Off-resonance proton decoupling ppm	J_r (Hz)
I	H	e	145.8	145.6[b]	(17)
II	α-Naphthyl	enantiomers	147.1	146.8[b]	(24)
III	o-Cl-Ph	enantiomers	147.2	147.0[b]	(24)
IV	α-Naphthyl	diastereomers	140.73 140.93	140.6[c]	(23)
V	o-Tolyl	diastereomers	141.06 141.17	140.9[c]	(26)
VI	o-CF_3-Ph	diastereomers	140.57 140.68	140.4[c]	(25)
VII	o-Cl-Ph	diastereomers	141.1[d]	140.7[c]	(24)
VIII	α-Naphthyl	enantiomers	135.0	134.8	
IX	Phenyl	e	135.8	135.6	
X	o-Tolyl	enantiomers	135.4	135.2	
XI	o-CF_3-Ph	enantiomers	135.0	134.8	
XII	o-Cl-Ph	enantiomers	135.2	135.0	
XIII	o-Br-Ph	enantiomers	135.1	134.9	
XIV	o-NO_2-Ph	enantiomers	135.2	135.0	

[a] Ppm upfield from carbon disulfide, ± 0.1 ppm. Separation of double peaks, ± 0.05 ppm.
[b] Center of triplet. [c] Center of doublet [d] Unresolved broad peak. [e] Not applicable

are seen to vary over a range of 135.0 to 147.2 ppm, and agree well with the value for the C-5 carbon of hydantoin (I) at 145.8 ppm, particularly if α methyl substituent effects are taken into consideration.

A series of peaks corresponding to the aryl carbons occurs within the expected 60-80 ppm region (6). The number of peaks observed both with noise proton decoupling and with off-resonance proton decoupling are as expected except in cases of unresolved peak overlap.

For the hydantoins IV to XIV the remaining peaks in the spectrum with noise proton decoupling must correspond to the C-5 methyl carbons, and are shown in table IX. The chemical shift values are seen to vary over a range of 167.9 to 176.3 ppm, within the expected 164 to 190 ppm region (6). Assignment of these peaks to methyl carbons is confirmed as each peak corresponds to a 1:3:3:1 quartet in the spectrum with off-resonance proton decoupling.

In summary, it can be seen that throughout the series of hydantoins studied, the chemical shift values for a given carbon position vary over a narrow region, and that the regions for different carbon positions are well separated. There is thus no ambiguity in the assignment of the peaks in the spectra. However, the individual aryl carbon peaks cannot be assigned with confidence to a particular aryl carbon. Also, in the case of 3-o-tolyl-5-methyl hydantoin VII, there is an overlap of the C-5 methyl and the tolyl methyl peaks.

Table IX. The C-5 Methyl Carbon-13 Chemical Shifts of the Hydantoins[a].

Hydantoin	Substituent at N-3	Relationship between rotamers	Noise proton decoupling ppm		Off-resonance proton decoupling	
IV	α-Naphthyl	diastereomers	175.76 176.36	0.60	175.76 (17) 176.23 (18)	0.47
V	o-Tolyl	diastereomers	175.79[c] 176.30[c] 176.53[c]	0.51 0.23	d	
VI	o-CF_3-Ph	diastereomers	176.08 176.46	0.38	175.88 (12) 176.28 (11)	0.40
VII	o-Cl-Ph	diastereomers	175.92 176.40	0.48	175.64 (12) 176.12 (12)	0.48
VIII	α-Naphthyl	enantiomers	168.13 168.76	0.63	167.89 (14) 168.56 (16)	0.67
IX	Phenyl	g	168.7	g	168.6 (14)	g
X	o-Tolyl	enantiomers	168.28 168.98 176.5[f]	0.70 g	168.10 (13) 168.87 (12) 176.3[f] (4)	0.63 g
XI	o-CF_3-Ph	enantiomers	168.79 169.43	0.64	168.52 (13) 169.25 (13) e	0.73
XII	o-Cl-Ph	enantiomers	168.47 169.27	0.80	168.24 (14) 169.08 (14)	0.84
XIII	o-Br-Ph	enantiomers	168.41 169.16	0.75	e	
XIV	o-NO_2-Ph	enantiomers	169.3	0.00		

a Ppm upfield from carbon disulfide ± 0.1 ppm, ± 0.05 ppm. b Center of the quartet (J_r in parentheses).
c Overlap of C-5 methyl and tolyl methyl peaks. d Unresolved. e Not measured. f Tolyl methyl.
g Not applicable

DEPENDENCE ON CONCENTRATION OF THE CHEMICAL SHIFT VALUES FOR THE HYDANTOINS .

It might be expected that the carbon-13 chemical shift values, particularly of the polar carbonyl groups, could be dependent on the concentration of the hydantoin in a polar solvent such as DMSO (29).

The dependence on the concentration in DMSO of the carbon-13 chemical shift values of hydantoin (I) is reported in table X and the data are plotted in figure 7. It can be seen that this dependence is a small downfield shift with increasing concentration of about 0.035 ppm per mole% for the two carbonyl carbons and 0.030 ppm per mole% for the C-5 carbon.

Carbon-13 spectra of the hydantoins VI and X were each obtained at two different concentrations: VI at 6.6 and 12.3 mole%, X at about 6 and 9.9 mole%. The concentration dependence of the chemical shift values of the C-2, C-4 and C-5 carbons was essentially the same as for hydantoin (I). The dependence on concentration of the C-5 methyl carbon chemical shift values was of the same order of magnitude as for the C-5 carbon of hydantoin (I), and the separation of the two C-5 methyl peaks remained constant. The two values of Δ measured for VI were 0.39 and 0.38 ppm, and similarly for X they were 0.68 and 0.70 ppm.

The concentrations of the aryl hydantoins studied varied only over a small range, as seen in table VII, and the chemical shift

Table X .

Dependence on Concentration of the Carbon-13 Chemical Shifts of Hydantoin(I)[a].

Concentration mole% in DMSO	C-2	C-4	C-5
20.6	34.81	19.44	145.83
15.1	34.94	19.64	146.00
11.6	35.10	19.73	146.07
7.8	35.28	19.89	146.22
3.8	35.36	20.06	146.27

[a] Ppm upfield from carbon disulfide ± 0.05 ppm.

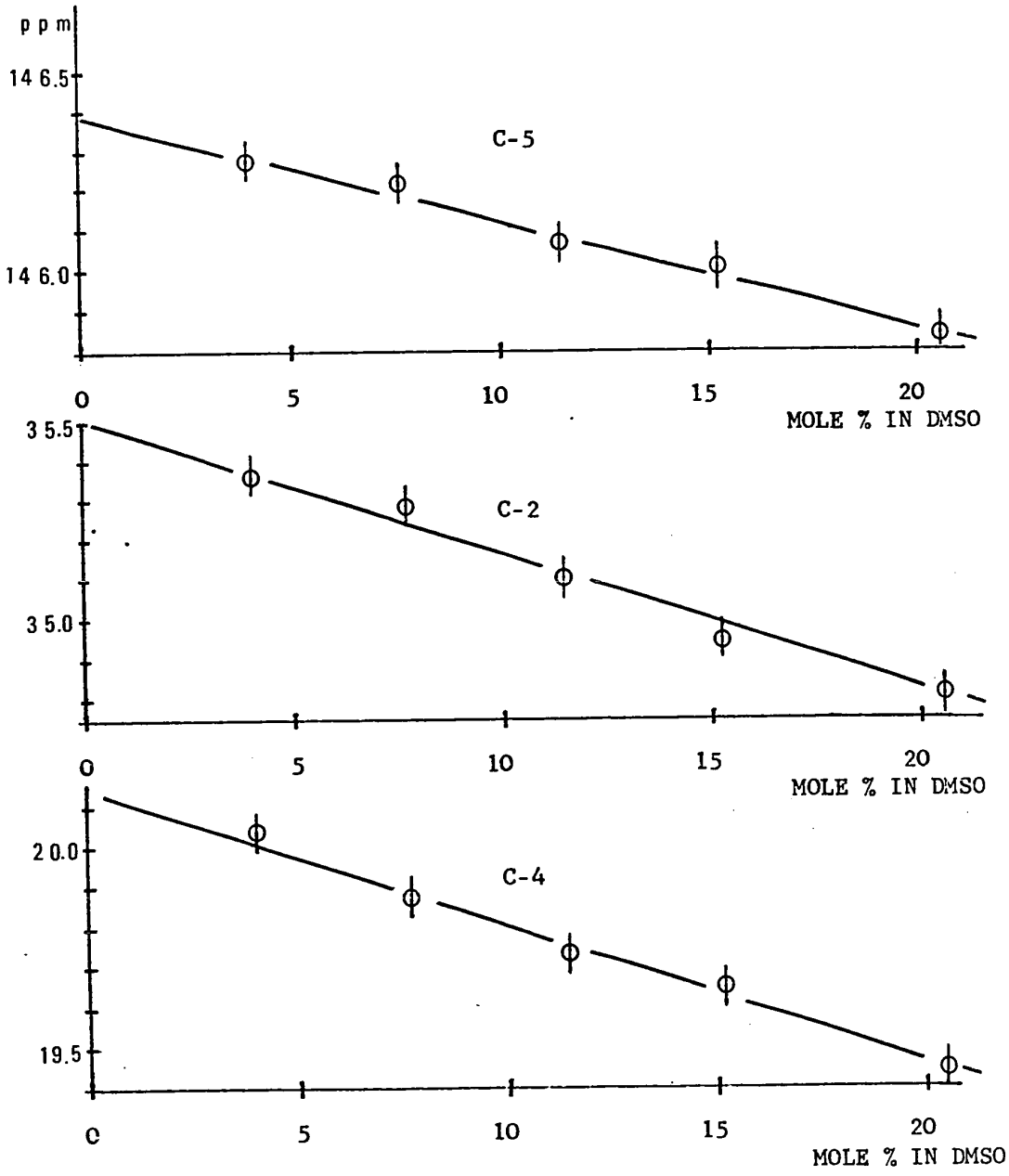


Figure 7 . Dependence on Concentration of the Carbon-13 Chemial Shifts of Hydantoin (I).

values are comparable. Errors in the chemical shift values due to concentration effects are rarely more than the precision of the measurements of these chemical shifts, and in no case is there a change in the order of a trend in chemical shift values.

DEPENDENCE ON TEMPERATURE OF THE CHEMICAL SHIFT VALUES FOR THE HYDANTOINS .

An examination of the chemical shift values throughout the tables shows that there is a consistent downfield shift of about 0.2 ppm on going from noise proton decoupling to off-resonance proton decoupling.

No direct measurement of temperature effects on the chemical shift values for the hydantoins can be made because the instrument is not equipped with a variable temperature probe for carbon-13. However, the chemical shift values of the C-5 carbon of hydantoin (I) measured at the three different proton decoupler output power settings given in table XI , show that these values vary directly with the proton decoupler output power setting and the temperature of the sample. Furthermore the values are independent of the decoupler mode (noise modulated or coherent). The temperature of the sample was previously found to be independent of decoupler mode. For a given proton decoupler output power setting, the magnitude of a Bloch-Siegert shift would be dependent on the decoupler power at the

Table XI. Dependence on Proton Decoupler Output Power Setting of the C-5 Carbon-13 Chemical shift of Hydantoin (I)[a].

Proton decoupler power output setting	Sample temperature °C ± 2°C	Noise proton decoupling	Off-resonance proton decoupling[b]
3.0	55	145.78	145.80 (9)
2.0	c	145.73	145.72 (11)
1.0	35	145.65	145.62 (19)

[a] Ppm upfield from carbon disulfide ± 0.03 ppm.

[b] Center of triplet (J_r in parentheses).

[c] Not measured.

frequency of the decoupled protons (30) , and thus on the bandwidth of the noise modulation. It is deduced that the small shifts cannot be due to a heteronuclear Bloch-Siegert shift.

It is, therefore, concluded that the small consistent downfield shift observed throughout the tables on going from noise proton decoupling to off-resonance proton decoupling must be due to a temperature effect governed by the proton decoupler output power setting.

STABILITY OF THE HYDANTOINS IN DMSO .

The temperature of the samples during the accumulation of the spectra was often about 55°C, but between measurements the samples were kept refrigerated. Over the course of more than a year the solutions showed no obvious color change. Repeat measurements of several samples showed no significant changes in chemical shifts and no appearance of extra peaks was observed. All the peaks in the spectra were accounted for by the hydantoin and it is concluded that the hydantoins were stable in DMSO.

CARBONYL CARBON-13 CHEMICAL SHIFT VALUES OF THE HYDANTOINS .

Chemical shift values are shown for both the C-2 and C-4 carbonyl carbons in table VII.

The C-2 carbonyl carbon-13 chemical shift values of the aryl hydantoins are seen to fall into three overlapping ranges corresponding to the number of methyls at the C-5 position: 36.8 and 37.9 ppm for the hydantoins II and III with no C-5 methyls, 37.7 to 39.0 ppm for the hydantoins IV to VII with one C-5 methyl, and 38.7 to 40.6 ppm for the hydantoins VIII to XIV with two C-5 methyls.

Similarly, the C-4 carbonyl carbon-13 chemical shift values of the aryl hydantoins fall into three ranges: 22.2 and 23.2 ppm for the hydantoins II and III with no methyls at C-5, 18.8 to 19.8 ppm for the hydantoins IV to VII with one methyl at C-5 and 16.2 to 18.1 ppm for the hydantoins VIII to XIV with two methyls at C-5.

The C-2 and C-4 chemical shift values for hydantoin (I) are 34.8 and 19.4 ppm, about 3 ppm lower than for the aryl hydantoins with no methyl at the C-5 position. This discrepancy is readily rationalized as due to an upfield aryl substituent shift. The carbonyl carbon-13 chemical shifts of urea and some aryl ureas are given in table V and similarly show an upfield aryl substituent shift of about 4.2 ppm.

On the basis of their stereochemistry, the hydantoins IV to VII, which have diastereomeric rotamers, can be expected to show double peaks for both C-2 and C-4 carbonyl carbons. However, only

the hydantoins VI and VII, with polar ortho substituents, show double peaks for the C-2 carbonyl carbon, and in no case are double peaks observed for the C-4 carbonyl carbon.

Upfield γ Methyl Substituent Shifts on C-2.

The observed substituent shifts on the C-2 carbonyl carbon for the addition of two successive methyls at C-5 are both about 1.0 ppm. From the α-naphthyl hydantoins II, IV and VIII the values are 0.9 and 1.0 ppm. From the ortho chlorophenyl hydantoins III, VII and XII they are 1.1 and 1.2 ppm. Similarly from the hydantoins V and X the value for the addition of a second methyl is 1.1 ppm, and from the hydantoins VI and XI it is 1.2 ppm.

Although the shift is in the correct direction and of about the same value as observed in the alkanes, it is difficult to attribute this formal γmethyl substituent shift to steric crowding as in the case of the alkanes.

Downfield βMethyl Substituent Shifts on C-4.

The observed substituent shifts on the C-4 carbonyl carbon for the addition of two successive methyls at C-5 are about 4.4 and 2.3 ppm. From the α-naphthyl hydantoins II, IV and VIII the values are 4.4 and 2.6 ppm. From the ortho chlorophenyl hydantoins III, VII and XII they are 4.4 and 2.0 ppm. Similarly, from the hydantoins V and

X the value for the addition of a second methyl at C-5 is 2.4 ppm, and from the hydantoins VI and XI it is 2.3 ppm. The discrepancy of about 2 ppm between the substituent shift on C-4 for the addition of the first and second methyls at C-5 can probably be attributed to refinement terms such as are found to apply to the highly branched alkanes (12) There is, however, a possibility that it reflects a change in conformation of the heterocyclic system involving a displacement of C-5 from the plane of the hydantoin ring.

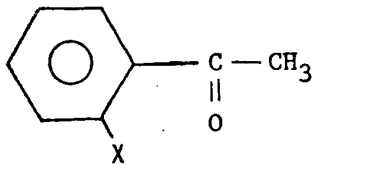
Carbonyl Carbon-13 Chemical Shifts and the Dihedral Angle between the Aryl and Hydantoin Rings.

It has been shown (p.7) that the angle of twist of the aryl ring relative to the carbonyl group can be estimated for a series of ortho substituted acetophenones, from the carbonyl carbon chemical shift values. For the series of ortho substituted acetophenones with the same ortho substituents as in the present study, the carbonyl carbon-13 chemical shifts varied between -3.2 ppm for acetophenone and -6.5 ppm for ortho-bromoacetophenone, a total range of 3.3 ppm. (31). In the case of the aryl hydantoins the aryl group is not α to the carbonyl group as with the acetophenones. However, both of the carbonyl groups take part in an extensive eight π-electron system which includes the lone pairs on N-1 and N-3. It can be expected that the extent of the conjugation between the aryl ring and the hydantoin π-system will depend on the dihedral angle between these two rings.

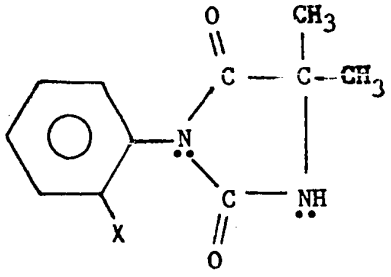
The C-2 and C-4 carbonyl carbon-13 chemical shifts may show a dependence on the extent of this conjugation as was found for the acetophenones and for similar systems (32, 33).

The largest group of hydantoins suitable for a similar study are the 5,5-dimethyl hydantoins VIII to XIV, which have enantiomeric rotamers. The phenyl hydantoin IX is taken as the basis for comparing the ortho substituted aryl hydantoins. This is because the unsubstituted phenyl ring can be considered to be most nearly coplanar with the hydantoin ring and will show consequent maximum conjugation with the C-2 and C-4 carbonyls. The α-naphthyl hydantoin VIII is considered a special case because the naphthyl ring could be expected to provide more extensive conjugation with the carbonyls for a given dihedral angle than would be the case for the other aryl substituents.

From the data in table VII it is seen that the carbonyl carbon chemical shift values show a trend which may correspond to an increase in steric hindrance to conjugation between the two rings. The most striking feature of this trend is that with decreasing conjugation there is an upfield shift of both C-2 and C-4 carbonyl carbon peaks, contrary to the downfield shift observed for the acetophenones. This discrepancy is, however, rationalized by a consideration of the electron shifts involved in the process of conjugation, for the two cases:



ortho substituted acetophenone



ortho substituted 3-aryl-5,5-dimethyl hydantoin.

In the case of the acetophenones, two electrons from the polar carbonyl group form an extended π-system with the aryl ring, and the resultant electron density at the carbonyl carbon is increased, causing an upfield shift with increasing conjugation.

In the case of the hydantoins, the two carbonyls are already involved in an eight π-electron conjugated system. Further conjugation with the aryl ring results in sharing of the two p-electrons of N-3 with the aryl ring. The result is less overall electron density in the hydantoin π-system, and in particular at the carbonyl carbons, causing a downfield shift with increasing conjugation.

Excluding the α-naphthyl hydantoin VIII, the C-2 and C-4 hydantoin peaks vary over a range of 1.4 and 1.0 ppm, respectively, about one third the range for the corresponding acetophenones. The upfield peak shifts relative to the phenyl hydantoin IX for the C-2

and C-4 carbonyl carbon, respectively, are in the same ratio of 1.4:1.0, within experimental error, for each of the 5,5-dimethyl hydantoins, with the exception of the α-naphthyl hydantoin VIII. The observation that the upfield shift of the C-2 peak is consistently larger than the upfield shift of the C-4 peak lends support to the proposed π-electron displacement with increasing conjugation. The C-2 carbon may be expected to have a greater π-electron density than C-4, because the C-2 carbonyl can share p-electrons with N-1 and N-3, whereas the C-4 carbonyl can only share with N-3. An overall decrease in π-electron density in the hydantoin ring would then be expected to affect the relative electron density at C-2 more than C-4.

Both the C-2 and C-4 carbonyl carbon-13 peaks are shifted to successively higher fields for ortho substituents in the order: -H, $-CH_3$, $-CF_3$, -Cl, -Br, $-NO_2$. This appears to be a reasonable order of increase in effective bulk size of the ortho substituents, and consequent increase in dihedral angle. The same order is found within experimental error for the other aryl hydantoins studied. The order found for the carbonyl shifts of similar ortho substituted acetophenones was somewhat different: -H, $-NO_2$, -Cl, -Br, $-CH_3$, and the corresponding estimated angles of twist were 0, 20, 22, 24 and 24 degrees (31) This order corresponds to the Van der Waals radii (34) . However, the values given for -Cl, -Br and $-CH_3$ are very similar (1.8, 1.95, 2.0 Å) and it is difficult to estimate a value for the $-NO_2$ group. It is also not certain that Van der Waals radii are an accurate measure of the steric hindrance between the ortho substituents and the carbonyl groups.

It is interesting to note that for a series of 3-aryl hydantoins, the thermodynamic activation parameters indicate that the hindrance to free rotation about the aryl C-N bond is essentially an effect of the ortho substituent (35). Furthermore, from the free energies of activation, it has been deduced that a chlorine atom is effectively larger than a methyl group in this series, and similarly for the corresponding 2-thiohydantoins (21) . However, for the 1-aryl hydantoins a methyl group is effectively larger than a chlorine ortho substituent, as was observed for the acetophenones (36).These conclusions are based on the assumption that the energies of the ground state rotamers are very similar for either a chlorine or a methyl ortho substituent.

The C-2 and C-4 chemical shifts of the ortho tolyl hydantoin X do not differ significantly from those of the phenyl hydantoin IX. This indicates that either the conjugation is about the same in both cases, or alternatively that the carbonyl shifts are not sensitive to the extent of conjugation, but rather to some other factor. The ortho methyl substituent is clearly not polar, and the Van der Waals radii of -H and $-CH_3$ are 1.2 and 2.0 $\mathring{A}$, respectively (34). It appears from a comparison of these two hydantoins that the carbonyl carbon peak shifts observed for the other hydantoins may be caused directly by polar effects rather than by steric inhibition to conjugation between the aryl and hydantoin rings.

Even if it is assumed that the observed C-2 and C-4 carbonyl carbon-13 peak shifts relative to the values for the phenyl

hydantoin IX are a measure of the dihedral angle in the series of 5,5-dimethyl hydantoins, it has not been found possible to evaluate this dihedral angle. The reason is that an empirical equation cannot be obtained for the hydantoins as was possible in the case of the acetophenones. The difficulty lies in evaluating the C-2 and C-4 carbonyl carbon shifts for an aryl 5,5-dimethyl hydantoin with no conjugation between the aryl and hydantoin rings.

Other Attempted Correlations of the Carbonyl Carbon-13 Shifts.

The C-2 and C-4 carbonyl carbon shifts do not correlate with either meta or para Hammett substituent constants. This is hardly surprising since the aryl group is ortho substituted. Also the Hammett equation is particularly unreliable in the case of ortho substitution because of proximity effects near the site of reaction (37).

The carbonyl carbon chemical shift values may correlate with the polarities of the ortho substituents. For the acetophenones, Stothers (31) found a total variation of the carbonyl carbon chemical shift for polar para substituents covering the range para-$N(CH_3)_2$ to para-NO_2 of only 1.2 ppm. He concluded that the carbonyl shielding in the acetophenones is relatively insensitive to through bond polar effects of the substituents. The carbonyl shifts in the present study showed a variation of this same order, but for a far more restricted range of polar ortho substituents. It is assumed that the carbonyl shieldings are similarly insensitive to through bond polar effects of

substituents in the hydantoins. However with ortho substituents, polar effects are more likely to occur through space than via the bonding electrons of four bonds. Carbon-13 chemical shifts are affected by both the magnetic anisotropy and electric field effects of neighboring groups.

The two 5-methyl hydantoins VI and VII with polar ortho substituents showed double peaks for the C-2 carbonyl carbon and only single peaks for the C-4 carbonyl carbon. If this is due to a through space effect it is probable that in the ground states of these hydantoins, the ortho substituent is nearer to the C-2 than to the C-4 carbonyl group. However, it was noted earlier that the range of the C-2 carbonyl carbon shifts is larger than that of the C-4 carbonyl carbon shifts, and any C-4 carbonyl carbon double peak may not be resolved.

Overall Information Provided by the Carbonyl Carbon-13 Chemical Shifts.

In summary, the observed carbonyl carbon chemical shifts are consistent with β and γ methyl substituent shifts, and there is no strong evidence of a change in conformation of the hydantoin ring on the addition of successive methyls at C-5.

The aryl ortho substituent appears to be located near to the C-2 carbonyl carbon in the ground states. The carbonyl carbon shifts of the 5,5-dimethyl hydantoins probably reflect either an increase in the dihedral angle between the aryl and hydantoin rings

with the effective bulk of the ortho substituent, or alternatively these shifts may be directly a function of the polarity of these substituents.

THE C-5 CARBON-13 CHEMICAL SHIFT VALUES OF THE HYDANTOINS .

These chemical shift values are shown in table VIII. The C-5 chemical shift values for the aryl hydantoins are seen to fall into three narrow ranges corresponding to the number of methyls at the C-5 position: 147.1 and 147.2 ppm for the hydantoins II and III with no C-5 methyls, 140.6 to 141.2 ppm for the hydantoins IV to VII with one C-5 methyl, and 135.0 to 135.8 ppm for the hydantoins VIII to XIV with two C-5 methyls. The chemical shift of the C-5 carbon of hydantoin (I) at 145.6 ppm is a little lower than for the hydantoins II and III, and this is attributed to an aryl substituent shift.

On the basis of their stereochemistry the hydantoins IV to VII, which have diastereomeric rotamers, can be expected to show double peaks for the C-5 carbons. Double peaks were observed except in the case of the ortho chlorophenyl hydantoin V which shows an unresolved broad peak.

The C-5 peaks of the hydantoins were also recorded with off-resonance proton decoupling. Residual coupling was observed between the C-5 carbon and the C-5 hydrogens. Triplets, doublets and singlets, respectively were observed for the C-5 carbons, according to

the number of hydrogens at the C-5 position, and the values of J_r are shown in table VIII. Residual coupling between the C-5 carbon and the C-5 methyl protons was not observed for any of the 5-methyl or 5,5-dimethyl hydantoins. The reason for this is attributed to a small value of J_{CCH}, below the resolution of the spectrometer.

In order to estimate a value for the expected residual splitting between C-5 and the C-5 methyl hydrogens, the model compound ethane is considered. The coupling constants J_{CH} and J_{CCH} for ethane have been measured from the carbon-13 satellite spectrum to be 129.9 Hz and -4.5 Hz respectively (38). For the hydantoins, the values of J_r will be proportional to $J\Delta f$ in each case, where Δf is the difference between the proton decoupler frequency and the resonance frequency of the particular hydrogen (11). The proton decoupler frequency is set to decouple DMSO hydrogens at 2.48 ppm, and the C-5 hydrogen and C-5-methyl hydrogens are found at about 4.3 and 1.4 ppm respectively. Since the observed residual splitting J_r corresponding to J_{CH} is about 24 Hz, then the expected value of J_r corresponding to J_{CCH} will be of the order of 0.6 Hz, at the limit of resolution of the spectrometer.

With off-resonance proton decoupling, the C-5 carbons of the hydantoins IV to VII showed doublets with very broad peaks. The peak separation is J_r, the residual coupling to the C-5 hydrogen, and each peak must be an unresolved double quartet.

Downfield αMethyl Substituent Shifts on C-5.

The observed substituent shifts on the C-5 carbon for the addition of two successive methyls at C-5 are about 6.2 and 5.8 ppm. From the α-naphthyl hydantoins II, IV and VIII the values are 6.3 and 5.8 ppm. From the ortho chlorophenyl hydantoins III, VII and XII they are 6.1 and 5.9 ppm. Similarly from the hydantoins V and X the value for the addition of a second methyl at C-5 is 5.7 ppm, and from the hydantoins VI and XI it is 5.6 ppm.

For the alkanes, the calculated downfield α methyl substituent shifts for the addition of two successive methyls to a secondary carbon are 9.1 and 6.1 respectively. The difference between these two values is due to a refinement term, found necessary for the highly branched alkanes (12).

For the hydantoins, the observed α methyl substituent shifts are somewhat smaller but this can readily be attributed to the difference between alkanes and hydantoins. Also, the ratio of the refinement term to the substituent shift is about the same in both cases.

The C-5 Carbon-13 Shifts and Correlation with Structure.

The range of chemical shift values within each of the three groups of hydantoins is small, and the order in the trend of these values with the ortho substituent is not the same for

corresponding 5-methyl and 5,5-dimethyl hydantoins. The separations of the C-5 carbon double peaks of the 5-methyl hydantoins IV to VI are small and not significantly different.

For the 5,5-dimethyl hydantoins, the C-5 chemical shift values do show a downfield trend, similar to the carbonyl carbons but in the opposite direction. The highest value, 135.8 ppm, is for the phenyl hydantoin IX: this cannot be attributed to maximum conjugation, and is probably due to an absence of either steric or polar effects. The hydantoins with polar ortho substituents all have low C-5 carbon chemical shifts, around 135.1 ppm. The non-polar ortho tolyl hydantoin X has a C-5 carbon shift of 135.4 ppm, half way between the values for phenyl hydantoin IX and for the hydantoins with polar ortho substituents. The α-naphthyl hydantoin VIII is again considered a special case: the C-5 carbon chemical shift has a low value, 135.0 ppm, and this could be attributed to either a steric effect or to the ring current from the α-naphthyl group.

In summary, the α methyl substituent shifts show no evidence of conformational changes in the hydantoin ring. The trend in the C-5 carbon chemical shifts cannot be caused by the variation in conjugation between the aryl and hydantoin rings. If real, this trend is probably due directly to the polar effects of the aryl ortho substituents, or to their steric effects.

THE C-5 METHYL CARBON-13 CHEMICAL SHIFT VALUES OF THE HYDANTOINS .

The C-5 methyl carbon-13 chemical shift values for the hydantoins IV to XIV are given in table IX . These values are seen to fall clearly into two narrow ranges: 175.8 to 176.5 ppm for the hydantoins IV to VII which all have one C-5 methyl, and 168.1 to 169.4 ppm for the hydantoins VIII to XIV which all have two C-5 methyls. The 5-methyl hydantoins have diastereomeric rotamers and the 5,5-dimethyl hydantoins have enantiomeric rotamers.

The other striking feature of the results is that the hydantoins IV to XIII all show double peaks for the C-5 methyl carbons. The phenyl hydantoin IX showed only one C-5 methyl carbon peak as expected from the stereochemistry since it has no ortho substituent to restrict rotation about the aryl C-N bond and cause non-equivalence of the two C-5 methyl groups. In the case of the ortho tolyl hydantoin VII, three peaks are observed due to an overlap of the C-5 methyl and tolyl methyl peaks. The ortho nitrophenyl hydantoin XIV showed only one singlet for the C-5 methyl carbons, in accord with the proton spectrum of the C-5 methyl protons measured by Fehlner (3). This could be attributed to unresolved peaks, or to collapse of the two peaks because of fast rotation about the C-N bond.

In all cases where the data are shown for the C-5 methyl spectra run with off-resonance proton decoupling, a quartet was observed to correspond to each peak of the spectrum with noise proton decoupling. Overlapping 1:3:3:1 quartets were submitted to first order

analysis to yield the chemical shifts corresponding to the centers of the quartets, and also the residual splittings J_r as shown in table IX.

Although the 5,5-dimethyl hydantoins VIII to XIV show, as expected, one quartet for each peak in the noise proton decoupled spectrum, the 5-methyl hydantoins IV to VII would be expected to show twice this number of quartets because of coupling to the C-5 hydrogen. That this further splitting is not observed is attributed to the small value of J_{CCH}.

As before, in order to estimate the value of the expected residual splitting J_r due to the hydrogen at C-5, the model compound ethane is considered. Since the observed residual splitting J_r corresponding to J_{CH} is about 15 Hz, then the expected value of J_r corresponding to J_{CCH} will be of the order of 0.9 Hz, which is at the limit of resolution of the spectrometer.

Downfield βMethyl Substituent Shifts on the C-5 Methyl Carbons.

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

The average value of the downfield βmethyl substituent shift is 7.4 ppm and is independent of relative assignment. The values obtained from the α-naphthyl hydantoins IV and VIII are 7.6 and

7.6 ppm. From the ortho trifluoromethylphenyl hydantoins VI and XI they are 7.3 and 7.0 ppm. From the ortho chlorophenyl hydantoins VII and XII they are 7.5 and 7.1 ppm. The average value from the overlapping peaks of the ortho tolyl hydantoin V and the two peaks of the ortho tolyl hydantoin X is 7.5 ppm.

It can be seen that for the two hydantoins with polar ortho substituents, there are discrepancies of 0.3 and 0.4 ppm between the two βmethyl substituent shift values, whereas for the non-polar α-naphthyl substituent, two equal values are obtained. It is unfortunate that the overlap of the C-5 methyl and tolyl methyl peaks for the hydantoin V so drastically reduces the statistical validity of this observed trend. Crossover of relative peak assignments in the three possible cases give discrepancies of 1.0 to 1.3 ppm between the two βmethyl substituent shifts.

For the alkanes, the β methyl substituent shift can be calculated for the addition of a second methyl to a tertiary carbon (12). Using the notation of Grant and Paul:

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

Thus in all cases, the experimental substituent shift coincides with the result predicted from Grant-Paul parameters for the alkanes. These same parameters were used with success by Sternlicht in a study of the amino acids (13) and they may be considered to apply to the C-5 methyls of the hydantoins.

Any change in conformation of the hydantoin ring on addition of a second methyl at the C-5 position might be expected to produce a further alteration in the hybridisation 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 and calculated substituent shifts coincide, it is concluded that, on addition of a second methyl at the C-5 position, either the hydantoin ring conformation does not change, or alternatively, that the methyl carbon-13 shifts are not sensitive to such a change in conformation. It was noted that the α methyl substituent shifts on the C-5 carbons likewise showed no evidence of change in conformation of the hydantoin ring.

The C-5 Methyl Carbon-13 Chemical Shifts and Correlation with Structure.

The range of the C-5 methyl chemical shift values is small. This is true for the 5-methyl hydantoins, which have diastereomeric rotamers, and also for the 5,5-dimethyl hydantoins, which have enantiomeric rotamers. The order of the trend of the average value for each doublet with the ortho substituent is the same for corresponding 5-methyl and 5,5-dimethyl hydantoins, within experimental error. The same is true for all the corresponding upfield peaks and similarly for the downfield peaks.

The upfield trend in the chemical shift values with the ortho substituent is similar to the carbonyl carbons, and in the same direction. This trend is investigated from a consideration of the

average chemical shift values of the 5,5-dimethyl hydantoins VIII to XIV, which have enantiomeric rotamers. The α-naphthyl hydantoin VIII is again considered a special case and has the lowest C-5 methyl chemical shift value at 168.5 ppm, attributed to the ring current of the α-naphthyl group. The phenyl and ortho tolyl hydantoins IX and X have similar values at 168.7 and 168.6 ppm. The hydantoins with polar ortho substituents all have shifts of about 168.9 ppm with the exception of the ortho nitrophenyl hydantoin XIV at 169.3 ppm.

If real, this observed trend in chemical shift values is probably due directly to the polar effects of the aryl ortho substituents.

Assignment of the Methyl Peaks of the ortho Tolyl Hydantoin V.

On the basis of the consistency in trend of the C-5 methyl carbon-13 chemical shifts a very tentative assignment could be made for the three methyl peaks of the hydantoin V. The double intensity peak at 176.30 ppm is assigned to the tolyl methyl carbon, and the other two peaks to the C-5 methyl carbons of the two diastereomers. The separation of these two peaks would then be 0.74 ppm. However, there is a very serious objection to this assignment. In the proton nmr spectrum run in DMSO-d_6 the tolyl methyl peaks of the two diastereomers are resolved and show a separation of 3 Hz or 0.03 ppm. It is considered unlikely that the corresponding carbon-13 peaks should not be resolved, so the three observed peaks must rather

consist of two overlapping doublets. The final possibility, the assignment of the double intensity peak at 176.30 ppm to the C-5 methyl, is discounted because the C-5 methyl peaks in the corresponding ortho tolyl hydantoin X were resolved in the carbon-13 spectrum. The question remains which doublet to assign to the C-5 methyl and tolyl methyl carbons, respectively. On the basis of the tendency for the C-5 methyl peak separations of the 5-methyl hydantoins to be approximately 30% less than for the corresponding 5,5-dimethyl hydantoins, the upfield doublet with a peak separation of 0.51 ppm is assigned to the C-5 methyl of the ortho tolyl hydantoin V. Support is lent to this assignment by the average chemical shift value of 176.4 ppm for the tolyl methyl doublet: the tolyl methyl carbon chemical shift of the corresponding 5,5-dimethyl hydantoin, X, is 176.5 ppm. The contrary assignment of the two doublets would, however, only introduce a discrepancy of Q.5 ppm between these tolyl methyl chemical shift values.

Steric Perturbation of the C-5 Methyl Carbon-13 Shifts.

It has been shown (p.8) that the chemical shifts of sterically perturbed carbon atoms are generally found at higher magnetic fields than for similar carbons that are not sterically crowded.

In the case of the aryl hydantoins, a large shift due to steric interaction can be expected for one of the C-5 methyl peaks,

providing that one of these C-5 methyl groups is sterically crowded by the aryl group as a whole, or by the ortho substituent on the aryl group.

Of the aryl hydantoins studied, the 5,5-dimethyl hydantoins provide the best examples to test for steric interaction of the C-5 methyl groups with the aryl group or the ortho substituent. This is because the rotamers are enantiomeric. The anisotropy associated with the aryl ring and the aryl ortho substituent and also the hydantoin ring conformation must be the same for the two rotamers. In addition, the C-5 methyl group farther from the aryl ortho substituent provides a suitable reference for a non-hindered methyl at the C-5 position: the presence or absence of steric interaction can thus be determined from the magnitude of the peak separation of diastereotopic C-5 methyl carbons.

However, for a meaningful discussion of the C-5 methyl peak separations in terms of the stereochemistry of the aryl substituted hydantoins, it is necessary to establish for each hydantoin that the observed spectrum corresponds to the two ground state rotamers. That is, that the observed peak separations do not correspond to a reduced value caused by partial collapse of the doublets at intermediate rates of rotation about the aryl C-N bond.

Ground State Rotamers and C-5 Methyl Carbon-13 Peak Separations.

Fehlner (3) has determined the thermodynamic activation parameters of some of the hydantoins of this study, by complete

lineshape analysis of the temperature dependent proton nmr spectra. These parameters were found to be solvent independent for the hydantoin VI (in 2-chloro pyridine and 1,1,2,2 tetrachloroethane) and for the hydantoin VIII (in pyridine and 1,1,2,2 tetrachloethane).

Except for the hydantoins V, IX and X the C-5 methyl protons of the hydantoins IV to XIII all showed doublets (or pairs of doublets) collapsing to singlets, with coalescence temperature near or above 100°C.

For a doublet collapsing to a singlet, the rate of rotation k at the coalescence temperature, can be determined (39) by the one-point kinetics expression:

$$k = \frac{\Delta \nu}{\sqrt{2}}$$

where $\Delta\nu$ is the separation in Hz of the two peaks under conditions of slow rotation, which corresponds to the spectrum of the two ground states. This expression is valid for equal lifetimes of the two rotamers, and large transverse relaxation times T_2: these conditions are probably met in the present case.

Table XII shows the separation between the two C-5 methyl peaks for some of the hydantoins. For each hydantoin this peak separation in ppm is an order of magnitude larger in the carbon-13 spectrum than in the proton spectrum, but is only two or three times larger in Hz. Nonetheless, from the above expression for k, it is clear that with a larger peak separation $\Delta\nu$, k should be larger at the coalescence temperature in the carbon-13 spectrum than at the

Table XII. Carbon-13 and Proton Peak Separations for the C-5 Methyl Doublet of the Hydantoins.

Hydantoin	Substituent at N-3	Relationship between rotamers	Δ Carbon-13[a] Hz	Δ Carbon-13[a] ppm	Δ Proton[b] Hz	Δ Proton[b] ppm	Δ Carbon-13 (ppm) / Δ Proton (ppm)
IV	α-Naphthyl	diastereomers	15.0	0.60	6.3	0.063	10
VI	o-CF_3-Ph	diastereomers	9.1	0.38	2.5	0.025	15
VII	o-Cl-Ph	diastereomers	12.0	0.48	4.1	0.041	12
VIII	α-Naphthyl	enantiomers	16.0	0.63	8.4	0.084	8
X	o-Tolyl	enantiomers	17.5	0.70	3.5	0.035	20
XI	o-CF_3-Ph	enantiomers	16.0	0.64	7	0.07[c]	9
XII	o-Cl-Ph	enantiomers	20.0	0.80	5.6	0.056	14
XIII	o-Br-Ph	enantiomers	19.0	0.75	9	0.09	8
XIV	o-NO_2-Ph	enantiomers	0.0	0.00	0.0	0.00	

[a] Measured in DMSO at 55°C with noise proton decoupling ± 0.05 ppm.
[b] Measured in pyridine at 30-60°C, from Ref.3.
[c] Measured in DMSO-d_6.

coalescence temperature in the proton spectrum. Since the rate of rotation increases with temperature, then the coalescence temperature should be higher in the carbon-13 spectrum than in the proton spectrum, providing the natural linewidths have comparable effects on the coalescence points. This appears to be true.

The carbon-13 spectra were measured at 55°C or less, and it is probable that this is well below the coalescence temperature of the C-5 methyl carbon-13 peaks of all the 5-methyl and 5,5-dimethyl hydantoins in table XII except possibly X and XIV. The spectra are thus obtained under conditions of slow rotation so the chemical shift values of the observed peaks should correspond closely to the spectra of the ground state rotamers for these seven hydantoins.

It can be seen in table IX that in all cases where the C-5 methyl carbon-13 peak separations were measured both with noise proton decoupling (55°C) and with off-resonance proton decoupling (35°C), these separations were equal within experimental error. This indicates that the observed separations correspond to the ground state rotamers except possibly for the ortho tolyl hydantoin V. In particular this will be true for the ortho tolyl hydantoin X, whose methyl proton spectrum showed a coalescence temperature of about 50°C (3).

There is one further qualitative and fairly subjective indication that the peak separations observed correspond to the ground state rotamers. This is that in all cases, including the ortho tolyl hydantoin V, the observed peaks are not noticeably broadened and thus do not correspond to the spectra run at intermediate rates of rotation about the aryl C-N bond, near the coalescence temperature.

It should be emphasized that the above analysis of the evidence for spectra corresponding to the ground state rotamers applies only to the C-5 methyl carbon-13 peaks. For the hydantoins IV to VII, corresponding carbon atoms of the two diastereomeric rotamers may have chemical shifts which are very nearly equal. The coalescence temperature for a smaller peak separation $\Delta\nu$ will be lower than for the C-5 methyls, and the observed peak separations may not correspond to the spectra of the ground state rotamers.

In summary, it can be said that the spectra of the C-5 methyl carbons of the hydantoins correspond to the ground state rotamers, with the possible exceptions of 3-o-tolyl-5-methyl hydantoin, V, and 3-o-nitrophenyl-5,5-dimethyl hydantoin, XIV.

The C-5 Methyl Carbon-13 Peak Separations and Steric Interaction.

An attempt can now be made to determine the presence or absence of steric interaction at the C-5 methyls from the magnitude of the C-5 methyl carbon-13 peak separations of the enantiomeric hydantoins VIII to XIII whose C-5 methyl carbon-13 spectra have been shown to correspond to the ground state rotamers.

From table XII it is seen that the C-5 methyl carbon-13 peak separations for these hydantoins fall in the range 0.6 to 0.8 ppm, an order of magnitude less than the separations observed for the methyl cyclohexanes. It is concluded that any steric interaction between the C-5 methyls and the aryl ring as whole, or the ortho substituent on

the aryl ring, must be substantially less than in the case of methyl cyclohexane where the steric repulsion energy of the axial methyl conformer is estimated to be 1.8 kcal/mole (40).

It should be noted that the upfield shift of sterically perturbed carbons has been determined for methyl groups interacting either with other methyls or with hydrogens (15). In the present study many of the ortho substituents are other than methyl or hydrogen and, depending on the mechanism of this shift, steric crowding might fail to induce an upfield shift on one of the C-5 methyl carbons. However a shift would certainly have been induced in the case of the two α-naphthyl hydantoins, IV and VIII, and of the two ortho tolyl hydantoins, V and X.

The conclusion of the absence of steric crowding of the C-5 methyls also assumes that separate factors are not causing compensating shifts in opposite directions. Since the magnitude of the peak separations is of the same order for either polar or non-polar ortho substituents, a compensating shift due to polar effects is ruled out. The same cannot necessarily be said for any effects due to the conformation of the hydantoin ring. No evidence has been found of changes in the conformation of the hydantoin ring on the addition of successive methyls at C-5, but this provides no information on the actual conformation of this ring.

The C-5 Methyl Carbon-13 Peak Separations and Changes in Conformation of the Hydantoin Ring.

The C-5 methyl carbon-13 peak separations for the 5-methyl hydantoins IV to VII, which have diastereomeric rotamers, fall in the range 0.4 to 0.6 ppm, hardly less than in the case of the 5,5-dimethyl hydantoins VIII to XIII, which have enantiomeric rotamers. It is more interesting to compare the C-5 methyl carbon-13 peak separations of corresponding 5-methyl and 5,5-dimethyl hydantoins having the same aryl substituent.

The 5,5-dimethyl hydantoins have enantiomeric rotamers, which must both have the same conformation of the hydantoin ring. The 5-methyl hydantoins each have two diastereomeric rotamers which may take up different hydantoin ring conformations.

It is conceivable that for a given 5-methyl hydantoin, the diastereomeric rotamer with the ortho substituent nearer the C-5 methyl group will experience steric interaction which will cause the C-5 methyl group to be bent away from the ortho substituent. The consequent conformation of the hydantoin ring should be essentially the same as for the corresponding 5,5-dimethyl hydantoin.

In the case of the rotamer of the 5-methyl hydantoin with the aryl ortho substituent nearer the C-5 hydrogen, any steric interaction is expected to be reduced, so that the C-5 hydrogen would probably be bent away from the ortho substituent through a smaller angle, if at all. The hydantoin ring conformation may therefore be

expected to be different from the case of the other diastereomeric rotamer and the corresponding 5,5-dimethyl hydantoin.

The determination of possible conformational changes of the hydantoin ring by a comparison of the chemical shift values for corresponding 5-methyl and 5,5-dimethyl hydantoins involves the use of empirical substitution parameters. The comparison of the C-5 methyl peak separations for this determination eliminates the uncertainties associated with these parameters. The peak corresponding to the methyl carbon nearer to the ortho substituent can be taken as the reference for the conformation of the 5,5-dimethyl hydantoin and the appropriate rotamer of the 5-methyl hydantoin. The effect of steric interaction on these reference peaks has been shown to be most likely small, and should be about the same in the two cases.

Any difference in peak separations of corresponding 5-methyl and 5,5-dimethyl hydantoins can then possibly be attributed to a difference in the conformation of the hydantoin ring for the two diastereomeric rotamers of the 5-methyl hydantoin. This assumes that the dihedral angle between the aryl ring and the heterocyclic ring is about the same for the two diastereomers and for the corresponding 5,5-dimethyl hydantoin. It also assumes that solvation effects on the C-5 methyl carbon chemical shift values are negligible or constant for a given aryl substituent.

The observed peak separations for the α-naphthyl hydantoins IV and VIII are 0.60 and 0.63 ppm, identical within experimental error. For the hydantoins with polar ortho substituents the separations are

smaller for the 5-methyl than for the corresponding 5,5-dimethyl hydantoin. For the hydantoins VI and XI the separations are 0.38 and 0.64 ppm, for the hydantoins VII and XII they are 0.48 and 0.80 ppm. The separation for the ortho tolyl hydantoin X is 0.70 ppm. The separation for the ortho tolyl hydantoin V is either 0.73, 0.51 or 0.23 ppm, depending on the chosen assignment.

If the unlikely separation of 0.73 ppm is chosen, then the conclusion from the trend in peak separations must be that only with polar ortho substituents is there a difference in the hydantoin ring conformation of the two diastereomeric rotamers of the 5-methyl hydantoins. Alternatively, the difference in peak separations could be attributed directly to the effects of the polar ortho substituents.

If a more likely smaller separation is chosen, then the conclusion from the peak separations must be that for all the 5-methyl hydantoins, there is probably a difference in the hydantoin ring conformation of the two diastereomers, and that the α-naphthyl hydantoin IV is possibly a special case.

Comparison of the Carbon-13 and Proton C-5 Methyl Peak Separations.

These peak separations are given in table XII for a number of the hydantoins. The proton values are from Fehlner (3) and were obtained from line shape analysis: the directly observed separations may have been slightly smaller.

For each hydantoin, the peak separation in ppm is an order of magnitude larger for the carbon-13 spectrum than for the proton spectrum. This apparent advantage for the resolution of two peaks is however greatly reduced for a small peak separation because on the present instrument the peak widths are about four times greater for carbon-13 than for proton spectra.

Only an order of magnitude comparison can be made of the carbon-13 and proton peak separations. This is because the solvent was not the same for both measurements. In general, the proton peak separations were greater for solutions in pyridine than in DMSO-d_6, where they were often zero. Even from the order of magnitude comparison of the carbon-13 and proton peak separation, however, it is clear that these separations are not a function of only magnetic anisotropic effects (41).

The trifluoromethyl Carbon-13 Peaks.

The thermodynamic activation parameters for the hydantoin VI were obtained from a line shape analysis of the trifluoromethyl doublet in the fluorine-19 nmr spectrum (3). The separation of the fluorine-19 peaks from the two diastereomers was 0.15 ppm, rather similar to the separation of 0.23 ppm between the peaks assigned to the ortho tolyl carbon from the two diastereomers of the hydantoin V.

A comparison of the peak separations of the carbon-13 and fluorine-19 doublets from the trifluoromethyl group of the hydantoin V

would have been interesting. However the peaks from the trifluoromethyl carbon peaks could not be detected for the hydantoins V or XI, nor for a concentrated solution of the model compound α,α,α-trifluorotoluene. This failure may perhaps be attributed to a large coupling constant J_{C-F} of the order of 300 Hz (42), which would give a widely spaced quartet. Another possibility may be a long relaxation time T_1 with consequent saturation of the signal.

Overall Information from the C-5 Methyl Chemical Shifts.

The observed trend in chemical shift values is most likely due directly to the polar effects of the ortho aryl substituents.

There is no evidence from the β methyl substituent effects of a change in conformation of the hydantoin ring for the addition of successive methyls at the C-5 position. There is, however, some evidence of a change in the hydantoin ring conformation for the two diastereomeric rotamers of the 5-methyl hydantoins.

The magnitudes of the C-5 methyl carbon peak separations indicate no steric perturbation of the C-5 methyls.

THE ARYL CARBON-13 CHEMICAL SHIFT VALUES OF THE HYDANTOINS .

These chemical shift values are shown in tables XIII to XVIII. Hydantoins with the same 3-aryl substituent are reported together in the same table for purposes of comparison. Aryl carbon-13 chemical shift values for the series of model compounds are shown in table XIX.

Very little information is available from the aryl carbon-13 chemical shift values, and they are reported principally for the sake of completeness.

With noise proton decoupling each non-equivalent aryl carbon will in principle show one peak. With off-resonance proton decoupling, an aryl carbon directly bound to one hydrogen will show a doublet. The chemical shift corresponding to the center of the doublet is reported, followed in parentheses by the residual splitting, J_r, to the nearest 1 Hz. Chemical shift values not followed by a value of J_r correspond to quaternary aryl carbons, since these give single peaks. The method used to assign the peaks to a particular doublet was to run the spectrum with several different proton decoupler output power settings. Successively lower output settings produce successively larger values of J_r. This is illustrated by the data for 3-o-naphthyl-5,5-dimethyl hydantoin, VIII, listed in table XIII and shown in figure 8. The quarternary aryl carbons are immediately identified at 59.8, 63.6 and 64.9 ppm since they do not show doublets with off-resonance

Table XIII. Aryl Carbon-13 Chemical Shifts of 3-α-Naphthyl-5,5-dimethyl hydantoin VIII[a].

Noise proton decoupling	Off-resonance proton decoupling[b]			
3.0[c]	2.0[c]	1.5[c]	1.0[c]	0.6[c]
59.8	59.7	59.7	59.7	59.6
63.6	63.5	63.5	63.5	63.5
64.3	64.3 (54)	64.3 (76)	64.2 (76)	64.1 (114)
64.9	64.9	64.9	64.9	64.8
65.2	65.1 (51)	65.2 (63)	65.1 (77)	65.1 (114)
66.4	66.3 (49)	66.4 (57)	66.3 (70)	66.2 (108)
67.1	67.1 (49)	67.1 (57)	67.1 (68)	67.0 (108)
68.1	68.1 (49)	68.1 (60)	68.0 (70)	67.9 (111)
71.4	71.4 (50)	71.4 (58)	71.4 (72)	71.3 (109)

[a] Ppm upfield from carbon disulfide.
[b] Center of doublet (J_r in parentheses) except for carbons not directly bound to hydrogen.
[c] Proton decoupler output power setting.

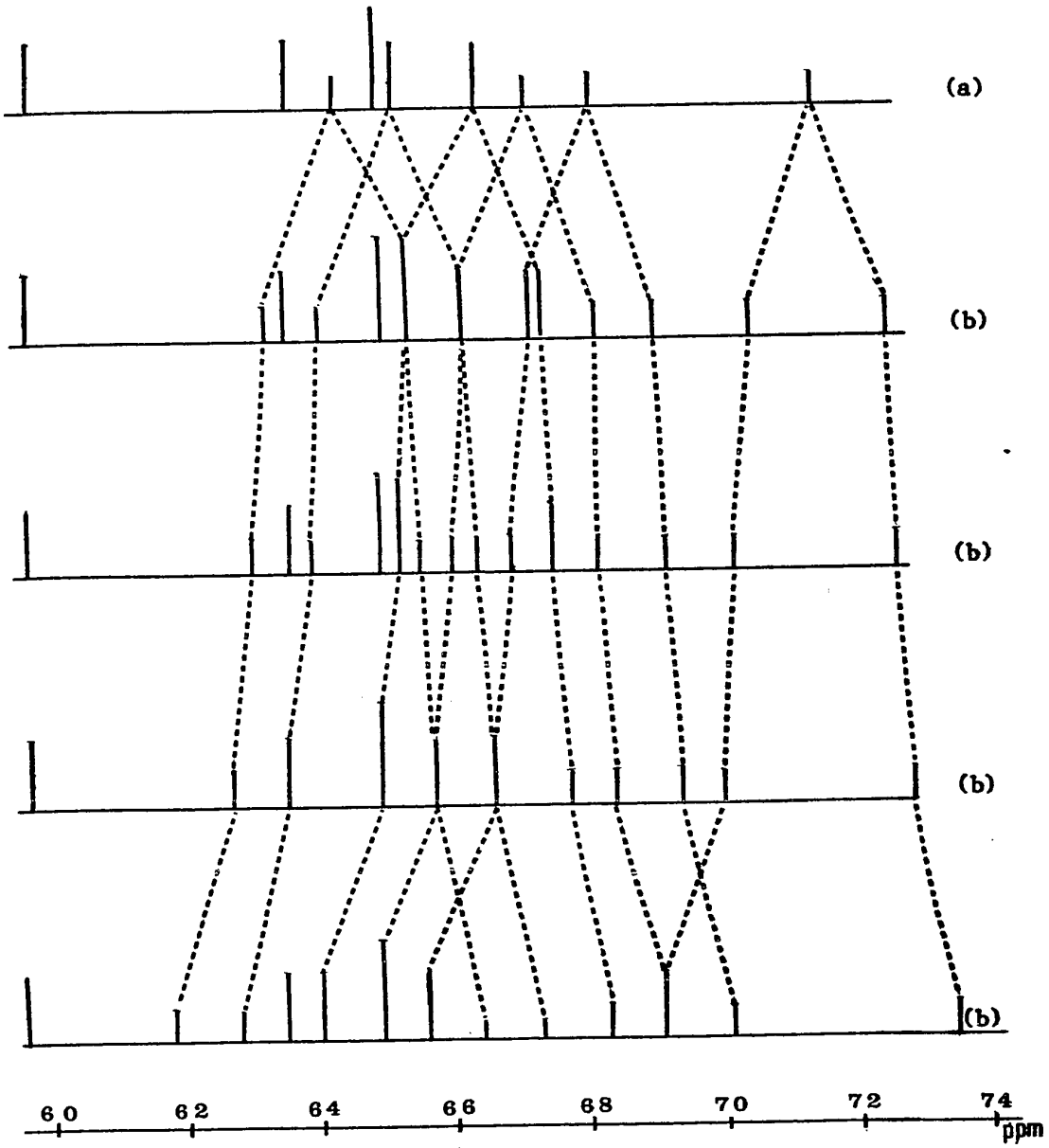


Figure 8. 3-α-Naphthyl-5,5-dimethyl Hydantoin VIII.

(a) With noise proton decoupling.
(b) With off-resonance proton decoupling.

Table XIV.

Aryl Carbon-13 Chemical Shifts of 3-Phenyl-5,5-dimethyl hydantoin IX [a].

Noise proton decoupling	Off-resonance proton decoupling[b]
61.3	61.3
65.1	64.9 (75)
66.1[c]	65.9[c] (72)
67.0	66.9 (75)

[a] Ppm upfield from carbon disulfide.
[b] Center of doublet (J_r in parentheses) except for carbon not directly bound to hydrogen.
[c] Carbon in <u>para</u>- position.

Table XV. Aryl Carbon-13 Chemical Shifts of 3-(ortho-Bromophenyl)-5,5-dimethyl hydantoin XIII.

Noise proton decoupling 3.0[c]	Off-resonance proton decoupling[b] 2.0[c]	1.5[c]
60.7	60.7 (49)	60.8 (60)
62.1	62.1	62.2
62.3	62.3 (47)	62.3 (54)
62.5	62.6 (46)	62.6 (57)
65.0	65.0 (48)	65.1 (55)
70.6	70.6	70.6

[a] Ppm upfield from carbon disulfide
[b] Center of doublet (J_r in parentheses) except for carbons not directly bound to hydrogen.
[c] Proton decoupler output power setting.

Table XVI .

Aryl Carbon-13 Chemical Shifts of the 3-o-Tolyl hydantoins V and X[a].

Noise proton decoupling		Off-resonance proton decoupling[b]	
V	X	V	X
57.6	57.6	57.4	57.5
62.4	62.5	62.3	62.5
63.2	63.2	63.0 (68)	63.0 (68)
64.9[c]	64.8[c]	64.6[d] (65)	64.6[d] (67)
67.2	67.2	66.9 (67)	66.9 (69)

[a] Ppm upfield from carbon disulfide.
[b] Center of doublet (J_r in parentheses) except for carbons not directly bound to hydrogen.
[c] Two unresolved peaks.
[d] Two unresolved doublets.

Table XVII. Aryl Carbon-13 Chemical Shifts of the 3-o-Chlorophenyl hydantoins III, VII and XII[a].

Noise proton decoupling			Off-resonance proton decoupling[b]	
III	VII	XII	XII	XII
61.5	61.5	61.4	61.3	61.2
62.6	62.6	62.5	62.3 (53)	62.5 (70)
63.0	63.0	63.1	62.7 (50)	62.9 (72)
63.6	63.8	63.8	63.5	63.5
63.9	64.0	64.0	63.7 (49)	63.6 (60)
65.8	65.8	65.8	65.6 (37)	65.5 (55)

[a] Ppm upfield from carbon disulfide.
[b] Center of doublet (J_r in parentheses) except for carbons not directly bound to hydrogen, with proton decoupler output power settings of 2.0 and 1.5 respectively.

Table XVIII. Aryl Carbon-13 Chemical Shifts of the 3-α-Naphthyl Hydantoins II, IV and VIII[a].

Noise proton decoupling			Off-resonance proton decoupling[b]					
II	IV	VIII	II		IV		VIII	
59.8	59.8	59.8	59.8		59.6		59.7	
63.6	63.7	63.6	63.6		63.5		63.5	
64.5	64.5	64.3	64.4	(79)	64.2	(61)	64.3	(64)
64.7	64.7		64.6		64.7			
65.4	64.9	64.9					64.9	
66.6	65.3	65.2	65.2	(81)	65.3	(63)	65.2	(63)
66.8	66.6	66.4[c]	66.5[d]	(72)	66.4	(58)	66.4[d]	(57)
67.2	67.2	67.1	67.0	(72)	67.0	(59)	67.1	(57)
68.1	68.1	68.1	68.0	(73)	67.9	(60)	68.1	(60)
70.9	70.9		70.8	(71)	70.6	(61)		
	71.5	71.4			71.4	(58)	71.4	(58)

[a] Ppm upfield from carbon disulfide.
[b] Center of doublet (J_r in parentheses) except for carbons not directly bound to hydrogen.
[c] Two unresolved peaks
[d] Two unresolved doublets.

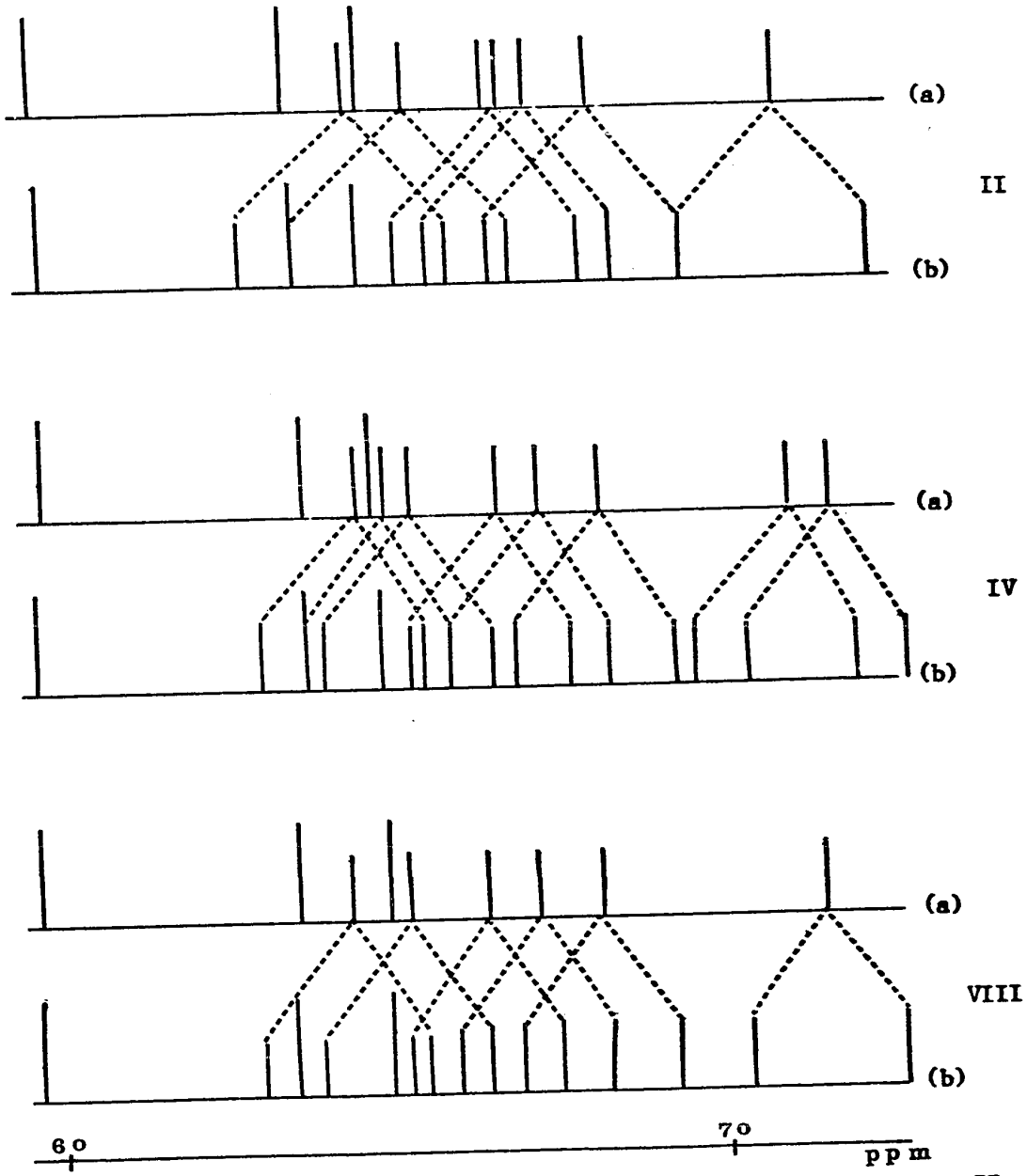


Figure 9. Aryl Carbon-13 Spectra of the 3-α-Naphthyl hydantoins II, IV and VIII.

(a) With noise proton decoupling.
(b) With off-resonance proton decoupling.

Table XIX. Aryl Carbon-13 Chemical Shifts of some Aryl Ureas[a].

XV	Phenyl urea	XVII	o-Tolyl urea
XVI	1,3-Diphenyl urea	XVIII	m-Tolyl urea

Noise proton decoupling				Off-resonance proton decoupling[b]			
XV	XVI	XVII	XVIII	XV	XVI	XVII	XVIII
53.4	54.0	55.7	53.3	53.2	54.0	55.5	53.2
65.2	65.1	63.7	55.8	65.0 (68)	65.1 (69)	63.5 (64)	55.7
72.4[c]	71.8[c]	66.7	65.2	72.3[c] (67)	71.9[c] (64)	66.2	65.0 (66)
75.5	75.2	67.8	71.4	75.5 (71)	75.3 (72)	67.7 (60)	71.3 (61)
		71.3	74.7			71.3 (63)	74.7 (67)
		72.1	78.1			72.2 (80)	78.1 (69)

[a] Ppm upfield from carbon disulfide.
[b] Center of doublet (J_r in parentheses) except for carbons not directly bound to hydrogen.
[c] Carbon in para- position.

proton decoupling. These three peaks correspond to the aryl carbon at the point of attachment to N-3 and to the two naphthyl bridgehead carbons, not necessarily assigned in that order.

Similarly, the quaternary aryl carbons throughout the series of hydantoins can be identified as they show single peaks with off-resonance proton decoupling. The specific assignment of these quaternary aryl carbons is only possible in two cases.

For 3-phenyl-5,5-dimethyl hydantoin, IX, the aryl carbon data are listed in table XIV. There is only one quaternary aryl carbon, at the point of attachment to N-3 and this is easily identified at 61.3 ppm. The aryl carbon at the para position can also be distinguished, since the peak intensity is about half that observed for the two equivalent ortho position carbons or the two equivalent meta position carbons.

For 3-(ortho bromophenyl)-5,5-dimethyl hydantoin, XIII, the aryl carbon data are listed in table XV. The peak at 70.6 ppm is assigned to the quaternary aryl carbon at the point of bromine substitution, from the characteristic chemical shift value (43). The peak at 62.1 ppm is then assigned to the quaternary aryl carbon at the point of attachment to N-3.

In a similar way for the model compounds listed in table XIX, some aryl peaks can be assigned with confidence. For phenyl urea, the peak at 53.4 ppm is assigned to the aryl carbon at the point of attachment to N-3, and the peak at 72.4 ppm to the aryl carbon in the para position. The corresponding peaks of 1,3-diphenyl urea are at

54.0 and 71.8 ppm, respectively.

For the ortho tolyl hydantoins V and X, the aryl carbon chemical shift values are listed in table XVI. The quaternary aryl carbons give peaks at 57.6 and 62.4 ppm for both hydantoins, however, it is not possible to specifically assign these peaks.

Similarly, the three ortho chlorophenyl hydantoins III, VII and XII listed in table XVII have corresponding quaternary aryl carbon peaks with essentially identical chemical shift values. The same is true for the three α-naphthyl hydantoins II, IV and VIII, listed in table XVIII.

The one point of stereochemical interest in the aryl carbon chemical shifts of the hydantoins is to be found in the data for the α-naphthyl hydantoins listed in table XVIII, and shown in figure 9.

For the hydantoins III and VIII which both have enantiomeric rotamers, a maximum of ten aryl carbon peaks is expected, corresponding to the ten non-equivalent α-naphthyl carbons. The hydantoin III shows ten peaks, the hydantoin VIII only nine resolved peaks.

For the hydantoin IV which has diastereomeric rotamers, a maximum of twenty peaks is expected, two for each of the ten non-equivalent α-naphthyl carbons. Since eleven aryl carbon peaks are observed, the peaks corresponding to the two diastereomeric rotamers are resolved for the carbon of least at one position of the α-naphthyl group.

The two peaks corresponding to this carbon can be identified with confidence as the peaks at 70.9 and 71.5 ppm. These peaks are

nearly three ppm upfield from the other aryl carbon peaks, and they correspond to similarly isolated peaks at 70.9 and 71.4 ppm for the hydantoins II and VIII respectively.

With off-resonance proton decoupling, these two peaks of the hydantoin IV and the corresponding peaks of the hydantoins II and VIII all give doublets. Therefore, the carbon which shows resolved peaks for the two diastereomeric rotamers must have one attached hydrogen. This carbon is tentatively assigned to the 8-position of the 1-naphthyl group, as this position must have the hydrogen nearest to the C-5 asymmetric center.

It is noteworthy that the isolated upfield aryl peak for the 5,5-dimethyl hydantoin VIII is at 71.4 ppm, 0.5 ppm upfield from the peak at 70.9 ppm of the hydantoin II with no C-5 methyls. This is attributed to an upfield shift caused by steric perturbation in the case of the 5,5-dimethyl hydantoin VIII, and also for the corresponding diastereomeric rotamer of the 5-methyl hydantoin IV.

In the case of the α-naphthyl hydantoin IV, it is interesting to compare the magnitude of the peak separations for the C-5 doublet (0.20 ppm), the C-5 methyl doublet (0.60), and the aryl carbon doublet (0.68 ppm). A fairly large neighbor group anisotropy is expected from the α-naphthyl ring current, but less would be expected to be associated with the C-5 asymmetric carbon. Because the peak separations for the C-5 methyl and for the aryl carbon are similar, and three times as large as for the C-5 carbon, the mechanism is probably attributed to steric perturbation rather than only neighbor group anisotropy effects.

No other aryl carbon of a hydantoin with diastereomeric rotamers was resolved into two peaks. In the case of the 3-ortho-tolyl-5-methyl hydantoin, V, however, the tolyl methyl carbon peaks of the two diastereomers were probably resolved, according to the previous analysis of the spectrum.

The aryl carbon peaks of the ortho nitrophenyl hydantoin XIV were not recorded, because of the low concentration of this compound. The aryl carbon peaks of the ortho trifluoromethylphenyl hydantoins VI and XI were not fully resolved, and the spectrum could not be analysed.

In summary, the aryl carbon chemical shifts of the hydantoins provide little useful information with the exception of the α-naphthyl hydantoins. Resolution of the two peaks from corresponding aryl carbons of the diastereomeric rotamers of the 5-methyl hydantoin IV is attributed to steric perturbation, and probably indicates a large dihedral angle between the α-naphthyl group and the hydantoin system.

CONCLUSION

For the series of 3-aryl hydantoins studied, the carbon-13 chemical shift values for a given carbon position in the hydantoin moiety are found to depend essentially on the number of methyls at the C-5 position.

Predictable methyl substituent shifts are observed, and the magnitudes of these shifts show no evidence of changes in conformation of the hydantoin ring with methyl substitution.

With a fixed number of methyls at the C-5 position, the chemical shift values of the carbon at a given position only varies over a range of about 2 ppm or less, for the different 3-aryl substituents. None of the trends in chemical shift values with the

nature of the ortho substituent can be attributed with confidence to only one factor.

The trend in the carbonyl carbon chemical shift values with the nature of the ortho substituent may be due to a variation in the dihedral angle between the aryl and hydantoin rings. If this is the case, this trend constitutes further evidence that in the 3-aryl hydantoins, a chlorine ortho substituent is effectively larger than a methyl ortho substituent. However this trend might be due directly to the polarity of the ortho substituent.

The trend in C-5 methyl carbon chemical shift values is most likely due directly to the polar effects of the ortho substituent.

For the 5,5-dimethyl hydantoins, which have enantiomeric rotamers, the magnitude of the C-5 methyl peak separation between diastereotopic C-5 methyl carbons indicates no important interactions with the ortho substituent.

The C-5 methyl peak separations for the 5-methyl hydantoins, which have diastereomeric methyl carbons, are slightly less than for the corresponding 5,5-dimethyl hydantoins, which have diastereotopic methyl carbons. The small differences in peak separations might be attributed to differences in conformation of the hydantoin ring, or alternatively to differences in solvation or in the dihedral angle between the aryl and hydantoin rings.

The C-5 methyl peak separations are about an order of magnitude larger (in ppm) for carbon-13 than for proton resonances.

BIBLIOGRAPHY

1.- E. Testa and R. Ettorre, Arch. Pharm., 290, 532 (1957).

2.- Imperial Chemical Industries Ltd., Belgian Patent 629-79 (1963); Chem. Abstr., 60, 14512 f (1965).

3.- J. Fehlner, Ph. D. Thesis, Department of Chemistry, University of Rochester, Rochester, N.Y. 1970.

4.- J.B. Stothers, Quart. Rev. (London), 19, 144 (1965).

5.- E.F. Mooney and P.H. Winson, in "Annual Review of NMR Spectroscopy", vol II, E.F. Mooney, Ed., Academic Press, N.Y., 1969, p. 153.

6.- E. Breitmaier, G. Jung and W. Voelter, Angew. Chem. internt. Ed., 10, 673 (1971).

7.- J.B. Stothers, Appl. Spectrosc., 26, 1 (1972).

8.- G.C. Levy and G.L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, N.Y., 1972.

9.- E.W. Randall, Chem. Brit., 7, 371 (1971).

10.- K.F. Kuhlmann and D.M. Grant, J. Amer. Chem. Soc., 90, 7355 (1968).

11.- R.A. Archer, R.D.G. Cooper, P. Demarco and L.F. Johnson, Chem. Commun., 1291 (1970).

12.- E.G. Paul and D.M. Grant, J. Amer. Chem. Soc., 86, 2984 (1964).

13.- W. Horsley, H. Sternlicht and J. Cohen, J. Amer. Chem. Soc., 92, 680 (1970).

14.- K.S. Dhami and J.B. Stothers, Tetrahedron Letters, N° 12, 631 (1964).

15.- D.M. Grant and B.V. Cheney, J. Amer. Chem. Soc., 89, 5315 (1967).

16.- D.Doddrell, C. Charrier, B.L. Hawkins, W.O. Crain, Jr., L. Harris and J.D. Roberts, Proc. Nat. Acad. Sci. U.S., 67, 1588 (1970).

17.- F.A.L. Anet, C.H. Bradley and G.W. Buchanan , J. Amer. Chem. Soc., 93, 258 (1971).

18.- A.S. Perlin and H.J. Koch, Can. J. Chem., 48, 2639 (1970).

19.- A Camerman and N. Camerman , Acta Cryst., B27, 2205 (1971).

20.- L.A. Walker, K. Folting and L.L. Merrit Jr., Acta Cryst., B25, 88 (1969).

21.- H.G. Giles, Sir George Williams University, Montreal, Quebec, Canada, personal communication, 1972.

22.- J.W. Emsley, J. Feeney and L.H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy", vol II, Pergamon Press Ltd., Oxford, 1965. p 990.

23.- G.C. Levy and J.D. Cargioli, J. Magn. Res., 143 (1972).

24.- R.L. Shriner, W.H. Horne and R.F.B. Cox, Organic Synthesis, Col. vol II, p 453.

25.- The Merck Index, 8th Ed., 1968, p 823.

26.- L.D. Behr and H.T. Clarke, J. Amer. Chem. Soc., 54, 1630 (1932).

27.- J.R. Bailey, J. Amer. Chem. Soc., 30, 1415 (1908).

28.- W. McFarlane, Chem. Brit., 5, 142 (1969).

29.- G.E. Maciel and J.J. Natterstad, J. Chem. Phys., 42, 2752 (1965).

30.- J.H. Noggle and R.E. Schirmer, "The Nuclear Overhauser Effect", Academic Press, N.Y., 1971, p 108.

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

32.- K.S. Dhami and J.B. Stothers, Can. J. Chem., 43, 498 (1965).

33.- D.H. Marr and J.B. Stothers, Can. J. Chem., 43, 596 (1965).

34.- J. Hine, "Physical Organic Chemistry", Mc Graw-Hill, N.Y., 2nd Ed.,1962, p 28.

35.- A. Granata, M.Sc. Thesis, Department of Chemistry, Sir George Williams University, Montreal,P.Q., Canada, 1972.

36.- S. Icli, Sir George Williams University, Montreal, Quebec,Canada, personal communication, 1972.

37.- L.P. Hammett,"Physical Organic Chemistry", McGraw-Hill, N.Y., 2nd Ed., 1970, p 357.

38.- J.H. Goldstein, V.S. Watts and L.S. Rattet in "Progress in Nuclear Magnetic Resonance Spectroscopy", J.W. Emsley, J. Feeney and L.H. Sutcliffe. Eds., vol VIII, col. 1971, pp 128,143.

39.- E.D. Becker, "High Resolution NMR", Academic Press, N.Y., 1969 , p. 218.

40.- D.K. Dalling and D.M. Grant, J. Amer. Chem. Soc., 89, 6612 (1967).

41.- W. McFarlane, Chem. Commun., 418 (1970).

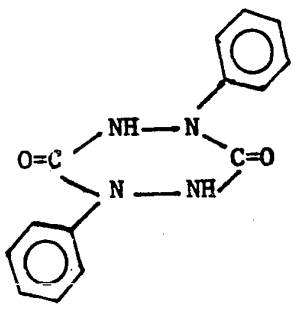
42.- E.D. Becker, "High Resolution NMR", Academic Press, N.Y., 1969 p 101.

43.- R.K. Jensen and L. Petrakis, J. Magn. Res., 6, 105 (1972).

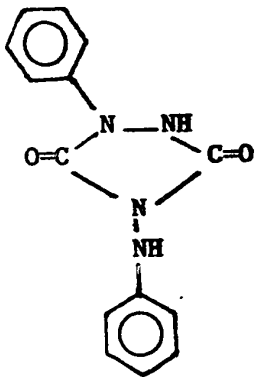
APPENDIX .

Elucidation of the Structure of 1-Phenyl-4-anilinourazole[a].

Two possible structures have been proposed for this compound:



(I)



(II)

[a] J.A. Lenoir, L.D. Colebrook and D.F. Williams, Can.J.Chem., in press. A sample of this compound was provided by J.A.L.

A distinction between these two possible structures may be made on the basis of the number of peaks appearing in the carbon-13 nmr spectrum.

With noise-modulated proton decoupling, all magnetically distinct (non-equivalent) carbon atoms must give rise to individual single peaks.

With off-resonance proton decoupling, only those carbons not directly bound to hydrogen will give rise to single peaks: these correspond to the carbonyl carbons and the aryl carbons at the points of attachment. The other aryl carbons in these compounds are all directly bound to one hydrogen. Because of coupling to the hydrogen they will give rise to perturbed doublets, with separation J_r.

In structure (I) both carbonyl groups and both aryl groups are equivalent since the molecule has a center of symmetry. Providing that accidental peak overlap is absent, five peaks (one carbonyl and four aryl) are predicted for the spectrum with noise proton decoupling. Two of these peaks should remain unsplit in the spectrum with off-resonance proton decoupling, for which eight peaks are predicted.

Structure (II) is less symmetrical, and ten peaks are predicted for the spectrum with noise proton decoupling. Four of these peaks should remain unsplit in the spectrum with off-resonance proton decoupling, for which a maximum of sixteen peaks is predicted.

The observed spectrum is shown in the figure, and the data are summarized in the table. Seven peaks are observed in the spectrum with noise proton decoupling. Of these peaks, four remain unsplit in

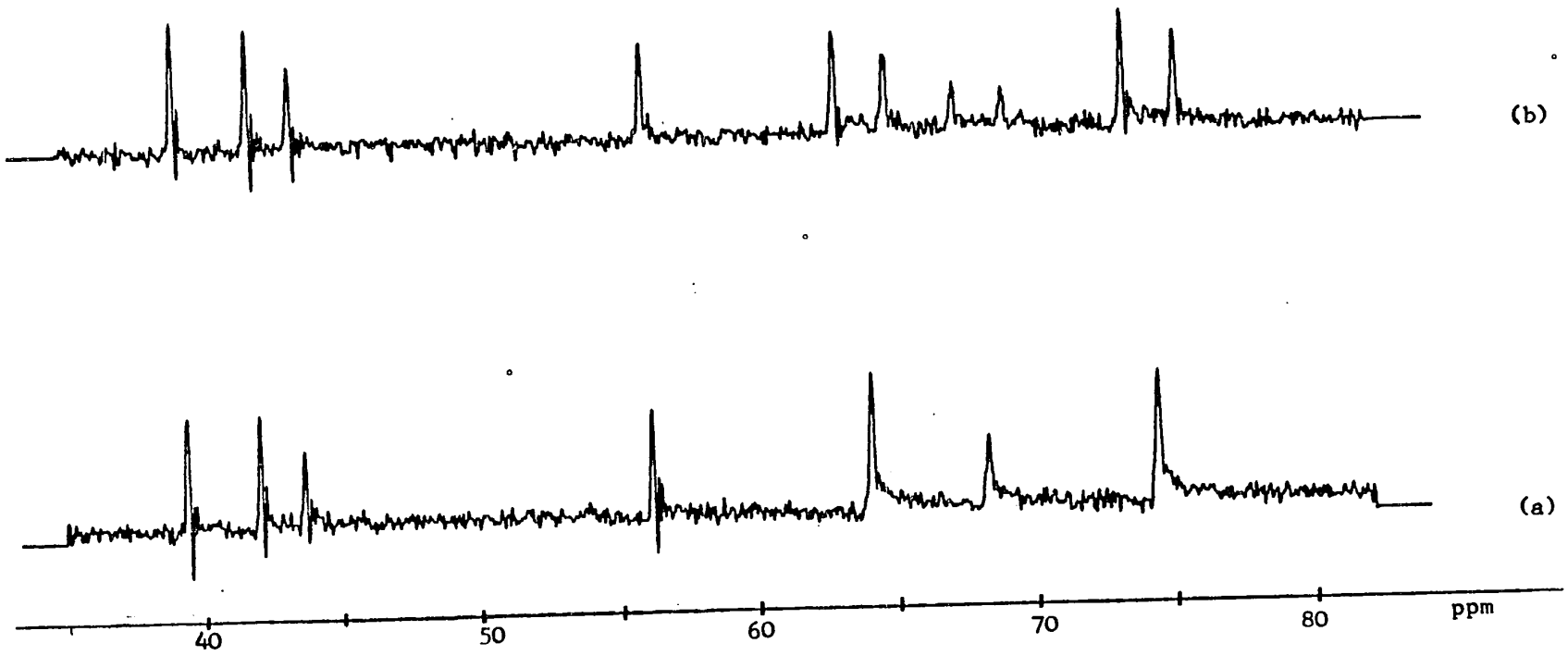


Figure . Carbon-13 nmr Spectrum of 1-Phenyl-4-anilinourazole.

(a) With noise proton decoupling
(b) With off-resonance proton decoupling.

Table .

Carbon-13 Chemical Shift Values of 1-Phenyl-4-anilinourazole[a].

Peak	Noise proton decoupling	Off-resonance proton decoupling[b]
1	39.3	39.1
2	42.0	41.9
3	43.6	43.4
4	56.4	56.3
5	64.5	64.3 (47)
6	68.7	68.6 (46)
7	75.0	75.0 (49)

[a] Ppm upfield from carbon disulfide ± 0.1 ppm.

[b] Center of doublet (J_r in parentheses) except for carbons not directly bound to hydrogen.

the spectrum with off-resonance proton decoupling, which shows ten resolved peaks. No further peaks were observed in the 10-140 ppm region which extends well beyond the usual 60-80 ppm aryl carbon region.

The data are consistent only with structure (II). Fewer peaks are observed than are predicted for this structure because of overlap between peaks from corresponding carbons of the non-equivalent aryl groups: only the peaks from the carbon atoms at the points of attachment are fully resolved. However, four of the peaks in the spectrum with noise proton decoupling remain unsplit in the spectrum with off-resonance proton decoupling.

Structure (I) must be excluded because both the spectrum with noise proton decoupling and the spectrum with off-resonance proton decoupling show more than the predicted maximum number of peaks.

Of the two possible structures (I) and (II), the symmetrical tetrazine structure (I) is quite inconsistent with the experimental spectra, whereas the five-membered ring 1,2,4-triazole structure (II) is fully consistent with these spectra.