CARBON-13 NMR STUDY OF 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES AND 3-ARYL-4(3H)-QUINAZOLINONES

This Thesis

is

Dedicated

to

My Beloved Husband Robert

and

My Parents Mr. & Mrs. M. A. Barnes

ACKNOWLEDGEMENT

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Patricia Musty

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

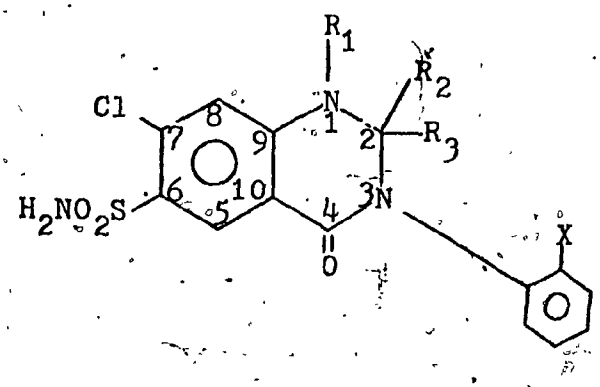
LIST OF SPECTRA

INTRODUCTION

INTRODUCTION

3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONE [5]

This research project was undertaken in order to obtain the carbon-13 spectra of a series of 3-aryl-2,3-dihydro-4(1H)-quinazolinones. The compounds investigated [2] are derivatives of 7-chloro-2,3-dihydro-3-phenyl-6-sulfamoyl-4(1H)-quinazolinone. (I)



I

Derivatives of structure I are diuretic agents, some of which are used in the treatment of diuresis, natriuresis and kaluresis. The diuretic activity is dependent on the various substituents on the quinazolinone nucleus. The highly active compounds have at least one hydrogen in the 2 position, a primary SO_2NH_2 in the 6 position and an ortho or para lower alkyl or CF_3 substituted aromatic ring in the 3 position of the quinazolinone nucleus [2]. The diuretic and natriuretic activity in quinazolinones is reduced if

a) the size of the substituent groups at the 1 position

and / or the second substituent groups at the 2 position is increased from the normal H or Me substituent (an exception to this trend is the 2-iC_3H_7 derivative).

b) both H's in the 2 position are replaced by a larger group.

c) an electron - rich group α to the 2 position is present (ie. 2-CH_2OCH_3)

d) the ortho or para methyl from the 3-aryl ring is removed; changing the alkyl substituent to the meta position or adding alkyl groups into the ring.

e) the methyl group in the 3-aryl ring is replaced by an electron withdrawing group:

f) the aryl group in the 3 position is separated from the quinazolinone nucleus by an alkyl bridge.

g) the primary SO_2NH_2 groups in the 6 position is changed to either a 2^o or 3^o amide.

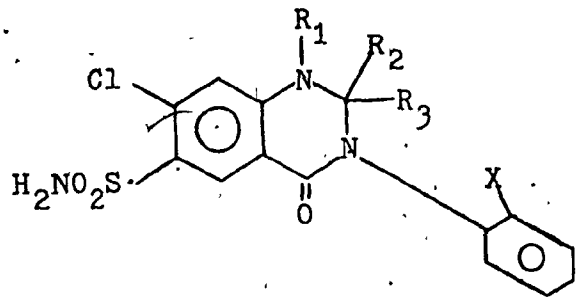
or

h) the 7-Cl group is removed or replaced with an electron-donating group.

The kaluretic activity parallels that of the natriuretic activity.

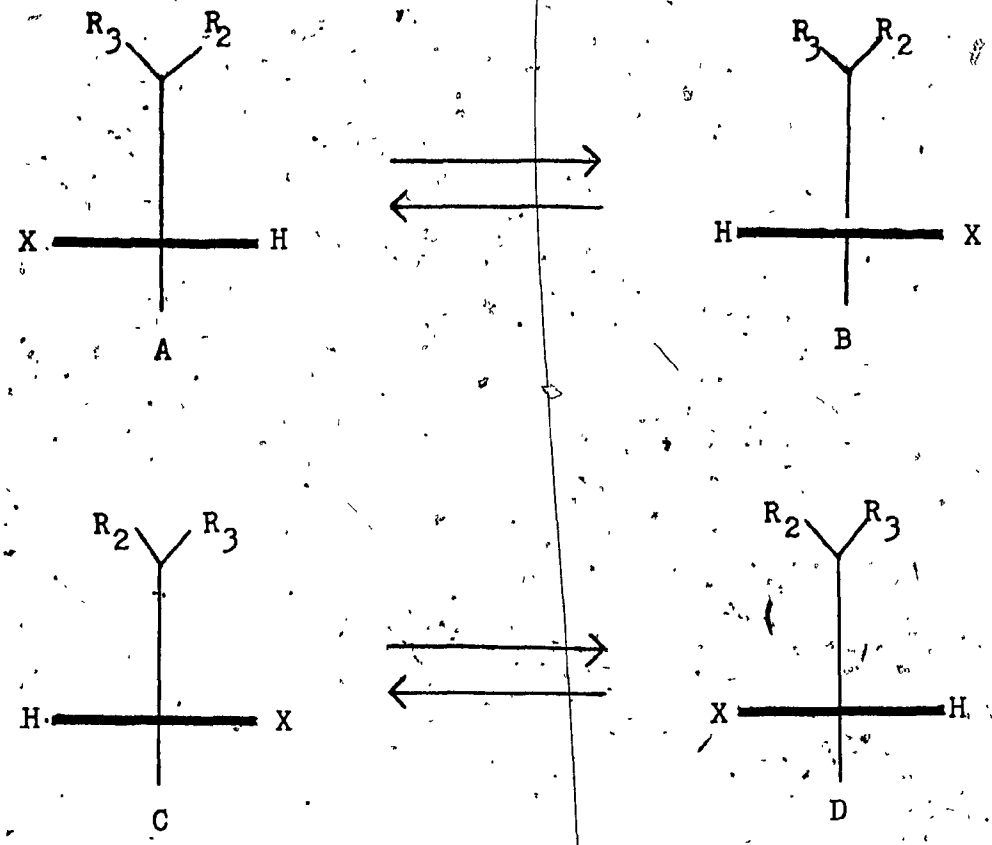
In view of the pharmacological interest in the compounds of the above type, it was considered that information on their stereochemistry might prove useful in aiding the understanding of their biological activity.

Their ^{1}H and ^{13}C NMR spectra show that the 3-aryl-2,3-dihydro-4(1H)-quinazolinones exist as mixtures of enantiomeric or diastereomeric rotational isomers at normal temperatures. The steric interactions between the ortho substituent on the 3-aryl group and the substituent on the 2 and 4 positions of the hetero ring in the 3-aryl-2,3-dihydro-4(1H)-quinazolinone (II) force the aryl group out of co-planarity with the rest of the molecule in the conformational ground state.



II

The isomers may be represented in the simplified form by A, B, C and D. The drawings represent a view of the molecule along the aryl C-N bond from the para position of the aryl ring.



The compounds may be classified into two stereochemical categories, depending on the nature of R_2 and R_3.

If $R_2 = R_3$ ($X \neq H$), the rotational isomers are enantiomers with identical spectra in achiral media. R_2 and R_3 are diastereotopic and, therefore, they will be expected to have different chemical shifts. When $R_2 = R_3 = H$ ($X \neq H$), the proton NMR is expected to show an AB quartet from these protons at low rates of rotation if the chemical shift is significant. The quartet should collapse to a singlet at high rates of rotation on the NMR time scale. This behavior has been observed by Fehlner[12] for compound II (Table II). If

$R_2 = R_3 = CH_3$ ($X \neq H$), the proton NMR spectrum should consist of two singlets and should collapse to one singlet at sufficiently high rotation rates. This behavior was observed by Fehlner[12] for compound I (Table II). The carbon-13 spectrum should consist of two distinct peaks and was observed for compound I (Table II).

If $R_2 \neq R_3$ ($X \neq H$), the rotational isomers are diastereomers and should give rise to distinctly different spectra at low rates of rotation. Such behavior has been observed in the present series for compounds VI, IX and X of Table II. Since the rotational isomers are diastereomers, they are present in unequal concentration at equilibrium and the two contributing spectra will be of unequal intensity.

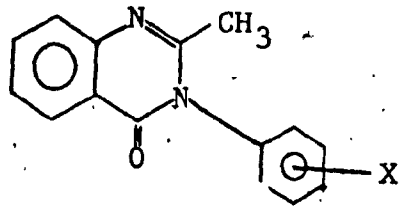
The hetero ring of 3-aryl-2,3-dihydro-4(1H)-quinazolinones should be flexible. Conformational changes in the hetero ring in response to changes in substituents are possible and should be reflected in the carbon-13 chemical shift changes.

A proton magnetic resonance study of 3-aryl-2,3-dihydro-4(1H)-quinazolinones was initiated by Colebrook[6] and Fehlner[12] in 1966. The thermodynamic activation parameters for restricted internal rotation about the C-N bond for a number of 3-aryl-2,3-dihydro-4(1H)-quinazolinones were determined by complete lineshape analysis of the temperature dependent proton NMR spectra. The thermodynamic activation parameters

reflect the difference between the ground state rotamers and the transition state. The present work deals with the ground state rotamers. The 7-chloro-2,3-dihydro-3-phenyl-6-sulfamoyl-4(1H)-quinazolinones were supplied by Strasenburg Laboratories, New York (now Pharmaceutical Division, Pennwalt Corp.)

3-ARYL-4(3H)-QUINAZOLINONES

A few 3-aryl-4(3H)-quinazolinones (III) were synthesized for the present study in order to obtain information on the effect of unsaturation on the carbon-13 chemical shifts.



III

CARBON-13 SPECTROSCOPY

CARBON-13 SPECTROSCOPY

The history of the development of carbon-13 nuclear magnetic resonance spectroscopy is well documented in the literature.[11, 29, 37, 39] The following is a summary of the relevant material:

Carbon-13 nuclear magnetic resonance spectroscopy is rapidly becoming an everyday technique in structure elucidation. The principles of carbon-13 spectroscopy are similiar to those of the more familiar proton NMR spectroscopy. The chemical shift and coupling constants of protons provide information about the structure of many organic compounds. However its usefulness is limited for two reasons: firstly, the center of interest in organic chemistry is not the proton, but the carbon skeleton. Secondly, numerous organic molecules contain nearly magnetically equivalent protons, thus producing overlapping signals, so that proton NMR provides little or no information about the carbon skeleton of such compounds. The chemical shift range of carbon is approximately 200 ppm, due to the large number of surrounding electrons, while the range for protons is only 10 ppm. Because of this large range in carbon chemical shifts, carbon-13 spectroscopy easily differentiates between complex molecules which may differ only in the rearrangement of a few carbon atoms. Similarly, in a non-^{13}C enriched molecule, the probability that more than one ^{13}C nucleus is present is very small, hence, the effect of carbon-

carbon spin - spin splitting is normally insignificant.

The first carbon-13 NMR spectrum was reported by Lauterbur [27] in 1957, however this technique was not widely employed until recently, due to difficulties in detecting the carbon-13 resonance signal. The lack of sensitivity was due to the low natural abundance of the carbon-13 isotope (1.11% as compared to 99.9% for hydrogen). Another factor which further lowered the sensitivity of the carbon-13 experiment was the magnetogyric ratio, γ, which is about 1/4 that of the hydrogen nucleus. The sensitivity of a nucleus in a magnetic resonance experiment is proportional to the cube of γ, thus a carbon-13 nucleus would give rise to 1/64 the signal intensity of a proton nucleus upon excitation. In consequence, the overall decrease in sensitivity in a natural abundance carbon-13 experiment would be about 10,000 relative to a proton experiment.

The first break through in experimental carbon-13 NMR came about in 1965, with the development of wide band proton decoupling. In a wide band proton decoupling experiment, all of the protons in the molecule are irradiated at a high radio frequency (RF) power at their resonance frequencies. Each non-equivalent carbon atom will give rise to a single peak. The added advantage of wide band proton decoupling is the increase in sensitivity as a result of the multiplet collapse as well as the Nuclear Overhauser effect. The disadvantage of this

technique is the suppression of the valuable information for assignments provided by the nature of the multiplets. Carbon-13 spectroscopy was further advanced in the early 1970's by employing pulse and Fourier Transform techniques. In the pulse NMR experiment, an intense RF field is applied to the sample and is left on only a very short time. This strong RF pulse excites a finite bandwidth of frequencies as compared to the decoupling experiment where only one excitation at one frequency is observed. The response of a sample to the excitation is absorption of individual frequency components by each nucleus. These frequencies, called precession frequencies, are detected by a receiver. The pattern or interferogram detected by the receiver is called a free induction decay (F.I.D.). An example of a F.I.D. is shown in Figure 1

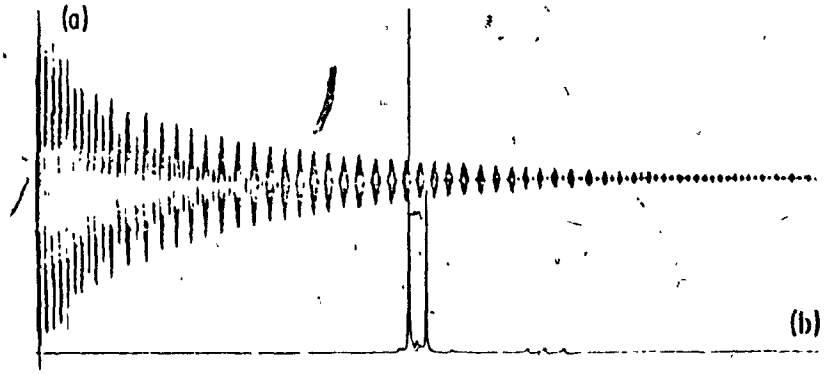


FIGURE 1 (a) Free induction decay and (b) frequency domain spectrum of $(CH_2=CH)_4Si$ (the small triplet is benzene-d_6 solvent).*

In order to abstract the spectral information from the F.I.D., a mathematical operation, a Fourier Transformation, is performed on the F.I.D.. The Fourier Transformation abstracts all frequency components from the complex wave form present in the F.I.D..

A detailed description of continuous wave NMR techniques and pulse and Fourier Transform techniques and a comparison of the two techniques are noted in the literature. [10, 11, 22, 28, 39]

The development of carbon-13 spectroscopy is illustrated in Figures 2 to 4.

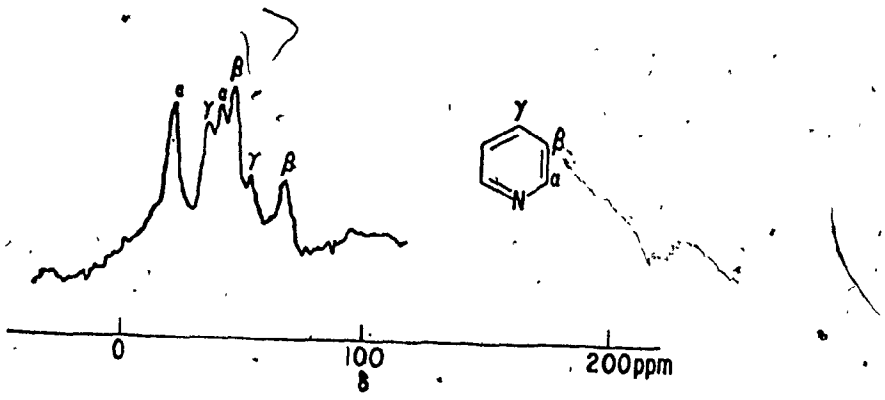


FIGURE 2 CMR spectrum of pyridine. Chemical shift scale in ppm upfield from CS_2. Spectrum obtained without ^1H decoupling; before 1958*

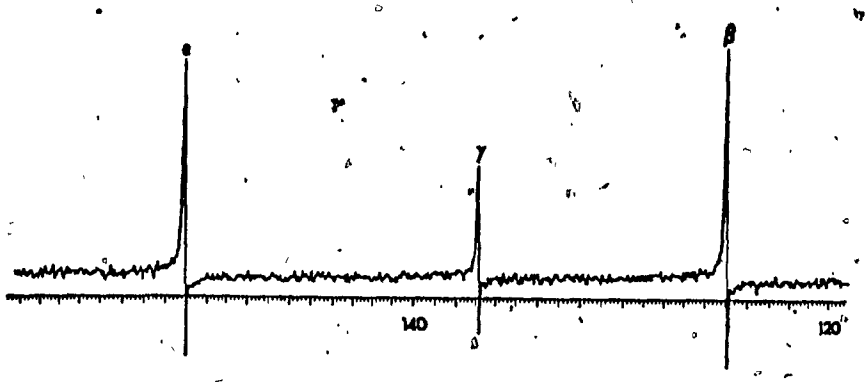


FIGURE 3 CMR spectrum of pyridine (^{1}H decoupled).*

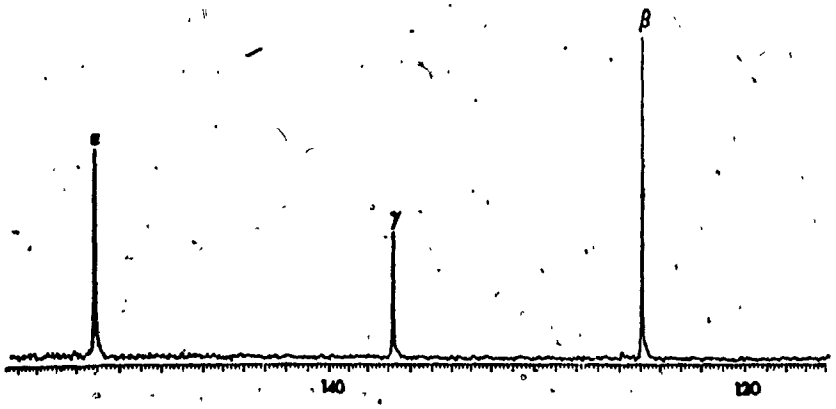


FIGURE 4 Fourier transform CMR spectrum of pyridine.*

* Figures 1 to 4 courtesy of John Wiley & Sons Inc.

THEORY

THEORY

Resonance frequencies for chemically non-equivalent nuclei differ because the magnetic field at the nucleus differs from the applied field. The applied field, H_o, is reduced by a factor $(1 - \sigma_c)$, where σ_c is the screening constant, to a value H_c, the carbon-13 magnetic field, due to the electrons surrounding the nucleus. Thus

$$H_c = H_o(1 - \sigma_c) \quad 39$$

The screening constant, σ_c, is a function of the chemical environment of a nucleus.

Components of the Screening Constant

Saika and Slichter [36] have divided the screening constant into three components.

$$\sigma_c = \sigma_d + \sigma_n + \sigma_p$$

where σ_d is the diamagnetic term, σ_n, the neighboring atom term and σ_p, the paramagnetic term.

The diamagnetic term, σ_d, results from the circulation of local electrons induced by the applied field about the nucleus being considered. The value, σ_d, is computed using Lamb's formula [25]:

$$\sigma_d = \frac{e^2}{3mc^2}\sum\langle r_i^{-1}\rangle$$

where e is the electron charge, m is the mass of the electron, c is the velocity of light, and r_i^{-1} is the reciprocal of the distance from the nucleus of interest to the overall electrons. Slater atomic orbital calculations have shown that the influence of σ_d on the variation in shielding of the carbon nucleus of interest is negligiable.[36]

The neighboring atom term, σ_n, arises from the circulation of electrons on neighboring atoms and specific anisotropic groups. The anisotropy term is dependent only on the spatial relationship between the nucleus whose shift is being considered and the anisotropic group.[28] This term is dependent on the geometry of the molecule and remains essentially constant regardless of the nucleus being considered. Although σ_n makes little contribution to the overall shielding, it is important in stereochemical analysis.

The principal factors affecting the paramagnetic term, σ_p, are charge polarization, variations in the π bond order and the average excitation energy required for the magnetic field to mix higher energy paramagnetic levels into the ground-state description of the molecule.[39] Karplus and Pople have demonstrated that the paramagnetic term is the dominant factor governing carbon-13 nuclear shielding.[21] This term is

computed using the following formula:

$$\sigma_p = \frac{e^2h^2}{2m^2c^2\Delta E} \langle r^{-3} \rangle_{2p} \sum_B Q_{AB}$$

where e is the electron charge, h is Planck's constant divided by 2π, m is the mass of the electron, c is the velocity of light, ΔE is the mean excitation energy, $\langle r^{-3} \rangle_{2p}$ is the mean inverse cube of the distance from the nucleus for the carbon 2p atomic orbital, and Q_{AB} is a term containing the elements of charge density and bond order in the MO description of the unperturbed molecule. Q_{AB} arises from an induced current flow on A, because the applied field acting on B mixes in certain excited electronic states. Jones and Grant [20] have demonstrated that ΔE is the dominant factor affecting σ_p.

Hydrocarbon Shieldings

The carbon-13 spectra of a wide variety of compounds have been reported in the literature.[3, 28, 32, 37, 39, 40, 43] The chemical shift values within a related series of compounds tend to follow additive relationships.[12]

The detailed study of linear alkanes by Grant and Paul [13] is a prime example of this additive relationship. Methyl substitution of hydrogen atoms in the α or β position produce a downfield shift of about 9 ppm; whereas methyl

substitution γ, causes an upfield shift of about 2.5 ppm. The deshieldings of α and β positions are mainly induced through bonds, while the γ effects operate through space. Methyl substitution of hydrogen on remote regions in alkanes have little effect on carbon shifts.

The carbon-13 chemical shifts of the alkanes obey Grant-Paul [13] additive relation:

$$\sigma_c^i = B + \sum_j A_j n_{ij}$$

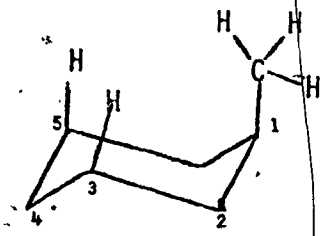
where σ_c is the shielding of the i^{th} carbon, A_j is the additive shift parameter, n_{ij} is the population factor and B is a constant which corresponds to the shielding of the parent compound.

This relation cannot be generalized to other organic structures due to the various differences; namely, steric effects, π electrons involved in ring currents, the presence of heteroatoms. The substituent parameters for a family of compounds are valuable in structure elucidation where information on steric and inductive polarization can be rationalized by stereochemical assignments.

The shielding effects of the following four factors can be interpreted through stereochemical assignments.

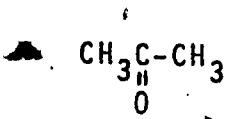
Steric interactions are due to the change in the polar-

ization of the carbon atom resulting from through-space repulsive interactions. Methyl cyclohexanes illustrate steric interactions:



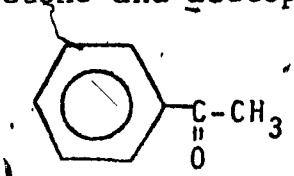
The chemical shifts of sterically perturbed carbon atoms 1, 3 and 5 are found at higher fields than similar carbon atoms which are not spatially crowded.[1, 13, 34] The electron density on the nuclei bonded to carbon decreases due to perturbation of the bond to the carbon atom, while the carbon atom becomes more shielded.

Conjugation effects result from the decrease in electron deficiency at the carbon atom due to the electrons released from conjugated π systems. This effect is well illustrated by carbonyl derivatives, for example, acetone and acetophenone.[9,27]



$\delta_c^{CH_3}$ = 28.1 ppm

$\delta_c^{C=O}$ = 204.1 ppm

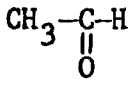


$\delta_c^{CH_3}$ = 24.9 ppm

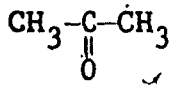
$\delta_c^{C=O}$ = 196.9 ppm

The carbonyl carbon signal in acetophenone shifts upfield due to the increase in electron density caused by delocalization of the π electrons from the phenyl ring. The methyl carbon signal also shifts upfield due to the reduced electron withdrawing effect of the carbonyl grouping on the carbon - methyl bond, thereby reducing the polarization of the bond and increasing the electron density at the methyl carbon nucleus.

The inductive effect results from substitution of a nucleus other than hydrogen on a carbon atom. The effect is dependent on the electron releasing or withdrawing ability of the substituent and the polarization of the bond between the carbon nucleus and the substituent. The chemical shieldings for methane, bromo, chloro and fluoromethane are -2.1, 10.2, 25.1 and 75.4 ppm respectively.[39] Increasing the electronegativity of the substituents causes the carbon atom to be deshielded; thereby causing a downfield shift. An increase in the electron releasing ability of the substituent shields the carbon atom, thereby causing an upfield shift as in the case of methyl iodide $\delta_c CH_3 = -20.5$ ppm.[39] Replacement of α and β hydrogens with methyl groups in alkanes cause a downfield shift due to the polarized C–C bond.[39] Similarly, replacing a directly bonded hydrogen with a methyl group in carbonyl compounds reduces the polarization of the π bond towards oxygen and causes a downfield shift of the carbonyl carbon.[39]



$\delta_{C}^{C=O}$ = 199.6 ppm



$\delta_{C}^{C=O}$ = 205.08 ppm

The majority of carbon-13 shielding values are obtained from measurements in solution. The contribution which the solvent can make to the shielding of a carbon atom must be considered. The shielding contribution of the solvent may be expressed as:[4]

$$\sigma_{solvent} = \sigma_b + \sigma_a + \sigma_w + \sigma_E$$

where σ_b is the contribution to screening which is proportional to the bulk magnetic susceptibility of the medium, σ_a is the anisotropy in molecular susceptibility of the solvent molecules, σ_w is due to Van der Waals interaction between the solute and solvent and σ_E is the polar effect on the electronic field due to the charge distribution in neighboring solvent molecules. It has been shown that σ_w and σ_E are dominant factors influencing the carbon-13 chemical shift.[5,30,31]

Overhauser Effect

The Overhauser effect, or Overhauser enhancement, results from decoupling of the protons on neighboring carbon atoms. Saturation of the neighboring protons give rise to a non-equilibrium polarization of the carbon-13 nuclei, greater than the thermal value, and results in an increase in the

observed signal strength. The magnitude of the Overhauser enhancement depends on the nature and environment of a specific carbon atom. The enhancement may vary for carbon atoms in the same molecule to a maximum of a three-fold enhancement being observed for a carbon atom substituted by protons.

The theoretical value of 2.98 for the Nuclear Overhauser Enhancement agrees with the experimental value of 2.98 ± 0.15 based on a dipole - dipole relaxation mechanism.[15] Taking into account competitive relaxation mechanisms, Jones et al[19] have developed the following equation for the ratio of relative intensities for a given carbon atom:

$$\frac{I}{I_0} = 1 + \{\alpha\gamma_H/2\gamma_c(\alpha + \chi)\}$$

$$\alpha = \sum(r_i^{CH})^{-6}$$

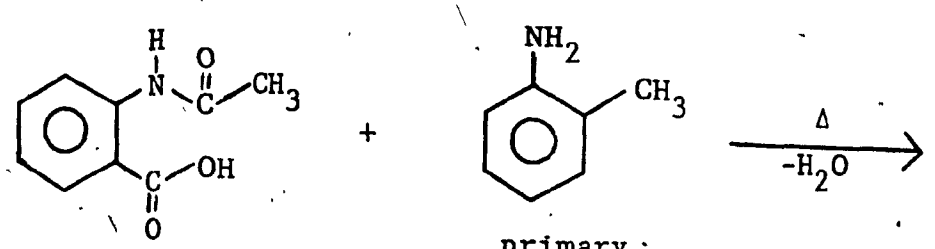
where r_i^{CH} is the distance between the directly bonded carbon and proton nuclei and χ measures the relative contribution of all other relaxation mechanisms. As illustrated above, the Overhauser enhancement will depend on the C-H separation when competing mechanisms are present.

EXPERIMENTAL

EXPERIMENTAL

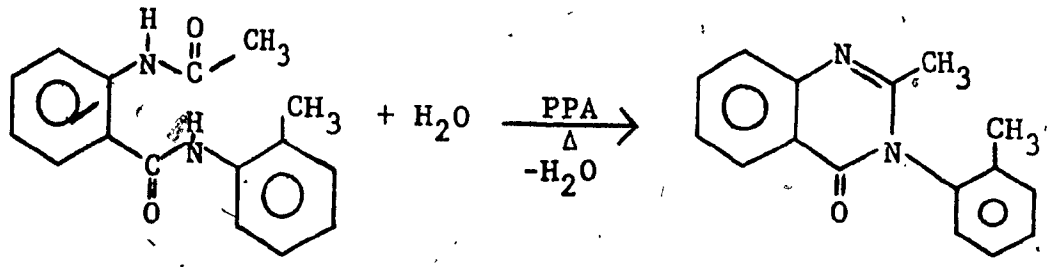
The 2-methyl-3-aryl-4(3H)-quinazolinones were prepared by an adaption of the Klosa Method.[23, 24] Compounds XXIX, XXXII and XXXIII are reported by Klosa,[23] however the melting point found for XXXIII differs considerably from that reported in the literature.[23]

The preparatory scheme of the 2-methyl-3-aryl-4(3H)-quinazolinones is shown below.



N-acetylanthranilic acid

primary aromatic amine



anilamide (not isolated)

2-methyl-3-aryl-4(3H)-quinazolinone + H_2O

Anthranilic acid and glacial acetic acid can be used as precursors to this reaction instead of N-acetyl anthranilic acid, however yields are greatly reduced.

N-acetyl anthranilic acid or anthranilic acid and glacial acetic acid were employed as the precursors. Reaction of either of these compounds with the appropriate primary aryl amine was carried out in the presence of polyphosphoric acid (PPA). The reaction was carried out under anhydrous conditions with the reaction temperature between 160° and 180°C and the reaction time between 30 and 60 minutes.

The compounds were recrystallized twice from methanol - water and were identified by elemental analysis and proton NMR. DMSO-d_6 was the solvent used for all proton NMR spectra, which were determined at 60 MHz using a Varian A-60A instrument. Melting points were measured on a Gallenkamp melting point apparatus and were uncorrected. Elemental analyses were performed by the Organic Microanalysis Laboratories, Montreal. Yields were calculated relative to the aniline.

PREPARATION OF 2-METHYL-3-ARYL-4(3H)-QUINAZOLINONES

2-Methyl-3(o-Tolyl)-4(3H)-Quinazolinone (XXIX)

N-acetyl anthranilic acid (Aldrich) (6.98 g, 0.039 moles) was mixed with o-toluidine (B.D.H.) (3.9 g, 0.037 moles) and polyphosphoric acid (40 g) in a 250 ml round bottom flask, fitted with a thermometer, drying tube and stirrer. The reaction mixture was heated to 180 °C with stirring, and kept at that temperature for 30 minutes. After cooling, the solution was poured into 200 ml distilled water and then neutralized by the addition of 20% sodium carbonate solution. Upon neutralization, a brown viscous oil formed, which solidified upon cooling overnight. The crude product was recrystallized twice from methanol - water to yield 4.7 g of yellowish brown crystals that were then dried under vacuum.

Yield: 4.7 g (50.8 %)

Melting Point: 111 - 112 °C (Lit.[23,24] 113 - 115 °C)

^{1}H NMR Data: Methyl proton on 3-aryl or methyl on C-2
2.03 ppm (singlet)
Methyl on C-2 or methyl proton on 3-aryl
2.10 ppm (singlet)
Aromatic protons 7.33 - 8.20 ppm (multiplet)
Spectrum I

^{13}C NMR Data: Tables VIII, XII, XVIII and XXIV
Spectrum II

The procedures were the same for the preparation of the following 2-methyl-3-aryl-4(3H)-quinazolinones.

2-Methyl-3(2,5-Dimethylphenyl)-4(3H)-Quinazolinone (XXX)

Starting Materials: N-acetylanthranilic acid (Aldrich) (6.98 g, 0.039 moles), 2,5-dimethyl aniline (Eastman) (4.73 g, 0.039 moles), polyphosphoric acid (Baker) (40 g)

Yield: 5.4 g (52.4 %)

Melting Point: 101 - 103 °C

^{1}H NMR Data: Methyl protons on 3-aryl

5-methyl	2.00 ppm	(singlet)
2-methyl	2.13 ppm	(singlet)
C-2 methyl	2.37 ppm	(singlet)
Aromatic protons	7.28 - 8.27 ppm	(multiplet)

Spectrum LII

Elemental Analysis:	% C	% H	% N
Calculated:	77.25	6.10	10.60
Found:	77.26	6.77	10.28

^{13}C NMR Data: Tables VIII, XII, XVIII and XXIV

Spectrum IV

2-Methyl-3(2,4,6-Trimethylphenyl)-4(3H)-Quinazolinone (XXXI)

Starting Materials: Anthranilic acid (Baker) (7.0 g, 0.044 moles), glacial acetic acid (Baker) (4 ml), 2,4,6-trimethyl aniline (Aldrich) (5.3 g, 0.039 moles), polyphosphoric acid (Baker) (40 g)

Yield: 6.7 g (61.8 %)

Melting Point: 96 - 98 °C

^{1}H NMR Data: Methyl protons on 3-aryl

2 & 6-methyl	1.97 ppm	(singlet)
4-methyl	2.07 ppm	(singlet)
C-2 methyl	2.33 ppm	(singlet)

Aromatic protons 7.08 - 8.27 ppm (multiplet)

Spectrum V

Elemental Analysis:	% C	% H	% N
Calculated:	77.86	6.41	9.94
Found:	77.67	6.51	10.06

^{13}C NMR Data: Tables VIII, XII, XVIII and XXIV

Spectrum VI

2-Methyl-3(4-Chloro-2-Methylphenyl)-4(3H)-Quinazolinone (XXXII)

Starting Materials: Anthranilic acid (Baker) (7.0 g, 0.044 moles), glacial acetic acid (Baker) (4 ml), 4-chloro-2-methyl aniline (Eastman) (5.53 g, 0.039 moles), polyphosphoric acid (Baker)(40 g).

Yield: 4.4 g (39.6 %)

Melting Point: 106 - 107 °C (Lit.[23] 105 - 107 °C)

^{1}H NMR Data: Methyl on 3-aryl 2.05 ppm (singlet)

C-2 methyl 2.12 ppm (singlet)

Aromatic protons 7.50 - 8.27 ppm (multiplet)

Spectrum VII

^{13}C NMR Data: Tables VIII, XII, XVIII and XXIV

^{13}C NMR Data: Spectrum VIII

2-Methyl-3(5-Chloro-2-Methylphenyl)-4(3H)-Quinazolinone

(XXXIII)

Starting Materials: Anthranilic acid (Baker) (7.0 g, 0.044 moles), glacial acetic acid (Baker) (4 ml), 5-chloro-2-methyl aniline (Eastman) (5.53 g, 0.039 moles), polyphosphoric acid (Baker) (40 g)

Yield: 5.40 g. (48.6 %)

Melting Point: 140 - 142 °C (Lit.[23] 114 - 116 °C)

^{1}H NMR Data:

Methyl on 3-aryl	2.03 ppm (singlet)
C-2 methyl	2.13 ppm (singlet)
Aromatic protons	7.50 - 8.27 ppm (multiplet)

Elemental Analysis:

	% C	% H	% N
Calculated:	67.49	4.61	9.68
Found:	67.53	4.80	9.84

^{13}C NMR Data: Tables VIII, XII, XVIII and XXIV

2-Methyl-3(5-chloro-2-methylphenyl)-4(3H)-Quinazolinone

(XXXIII)

Alternate Procedure.

Starting Materials: N-Acetyl anthranilic acid (Aldrich) (6.98 g, 0.039 moles), 5-chloro-2-methyl aniline (Eastman) (5.53 g, 0.039 moles),

polyphosphoric acid (Baker) (40 g)

Yield: 6.00 g (54.1 %)

Melting Point: 140 - 142 °C

^{1}H NMR Data: Methyl 3-aryl protons 2.03 ppm (singlet)

C-2 methyl 2.13 ppm (singlet)

Aromatic protons 7.50 - 8.27 ppm (multiplet)

Spectrum IX

^{13}C NMR Data: Tables VIII, XII, XVIII and XXIV

Spectrum X

ATTEMPTED PREPARATIONS OF 2-METHYL-3-ARYL-4(3H)-QUINAZOLINONES

2-Methyl-3(2,4-Dimethylphenyl)-4(3H)-Quinazolinone

N-acetyl anthranilic acid (Aldrich) (6.98 g, 0.039 moles) was mixed with 2,4-dimethyl aniline (Eastman) (4.73 g, 0.039 moles) and polyphosphoric acid (Baker) (40 g) in a 250 ml round bottom flask, fitted with a thermometer, drying tube and stirrer. The reaction mixture was heated to 180 °C with stirring and kept at that temperature for 60 minutes. After cooling, the solution was poured into 200 ml distilled water and then neutralized by the addition of 20% sodium carbonate solution. Upon neutralization, a brownish yellow tar formed. The tar did not solidify upon prolonged cooling. The tar was separated from the solution and attempts to crystallize the product failed.

The preparation of the following compounds were attempted in the manner outlined for 2-methyl-3(2,4-dimethylphenyl)-4(3H)-quinazolinone.

2-Methyl-3(2,3-Dimethylphenyl)-4(3H)-Quinazolinone

Starting Materials: N-acetyl anthranilic acid (Aldrich) (6.98 g, 0.039 moles), 2,3-dimethyl aniline (Eastman) (4.73 g, 0.039 moles), polyphosphoric acid (Baker) (40 g)

Yield: 3.10 g (30.07 %)

Melting Point 158 - 160 °C (Lit.[23] 156 - 158)

^{1}H NMR Data: The ^{1}H NMR spectrum did not conform to the expected spectrum.

Expected ^{1}H NMR Data:

Methyl 3-aryl protons	2.14 ppm
C-2 methyl	2.19 ppm
Aromatic protons	7.10 - 8.00 ppm

2-Methyl-3(2,6-Dimethylphenyl)-4(3H)-Quinazolinone

Starting Materials: N-acetyl anthranilic acid (Aldrich) (6.98 g, 0.039 moles), 2,6-dimethyl aniline (Eastman) (4.73 g, 0.039 moles), polyphosphoric acid (Baker) (40 g)

Yield: 5.30 g (51.4 %)

Melting Point: 135 - 137 °C (Lit.[23] 134 - 136 °C)

^{1}H NMR Data: The ^{1}H NMR spectrum did not conform to the

expected spectrum.

Expected ^{1}H NMR Data:

Methyl 3-aryl protons	2.19 ppm
C-2 methyl	2.14 ppm
Aromatic protons	7.10 - 7.90 ppm

NMR SPECTRA

The ^{1}H NMR spectra of 3-aryl-2,3-dihydro-4(1H)-quinazolinones and 3-aryl-4(3H)-quinazolinones were taken on a Varian A-60A, 60 MHz spectrometer as concentrated DMSO-d_6 solutions.

The ^{13}C NMR spectra of the compounds were taken on a Varian HA 100, 25.1 MHz spectrometer as DMSO solutions. Methyl Iodide solution was employed as the external standard and lock signal./

The chemical shift values for both ^{1}H NMR and ^{13}C NMR are reported as ppm from TMS.

A sample of the ^{1}H NMR and ^{13}C NMR spectra of a 3-aryl-2,3-dihydro-4(1H)-quinazolinones are shown in Spectra XIII to XXII

In the ^{1}H NMR, the protons in the quinazolinone ring are found to absorb between δ 6.87 and δ 8.23, with the proton in the 8 position of the quinazolinone ring absorbing at the highest field (δ 6.86) of the aromatic protons, due to the effect of the adjacent chloro and sulfamoyl groups. The proton on C-5 is deshielded due to the sulfamoyl and carbonyl group and appears between δ 8.22 and δ 8.46 .

The proton on the N-1 position absorbs between δ 3.40

and δ 4.27. When a methyl group is in the N-1 position, the $N-CH_3$ protons absorb between δ 3.04 and δ 3.10. The sulfamoyl group hydrogens appear as broad peaks absorbing between δ 7.8 and δ 8.56.

In the ^{13}C spectrum, the highest field absorptions are usually caused by the N-3 o-tolyl carbon, while the lowest field absorptions are due to the carbonyl carbon.

Examples of the ^{1}H NMR and ^{13}C NMR spectra of 3-aryl-4(3H)-quinazolinones are shown in Spectra I to XII.

In the ^{1}H NMR spectrum, the highest field absorptions are usually caused by the C-2 methyl protons absorbing between δ 1.19 and δ 1.69. The tolyl methyl protons usually absorb in the region from δ 1.76 and δ 2.30. However, the chemical shifts of these protons are affected by substitution on the C-2 or N-1 position.

INSTRUMENTATION

INSTRUMENTATION

The Pulse and Fourier Transform NMR Spectrometer

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

Pulse Generation, Timing and Control Logic

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

Radiofrequency Pulse Control

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

R.F. Pulse Interval Timing

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

The 26G1 puts out a triggered pulse at the start of its delay ramp (i.e. immediately it is triggered). This pulse triggers the 26G3 Pulse Generator (see above) which controls the Digilab 400-2 Pulser (gated power amplifier) and also

triggers the 26G2 Ramp Generator which controls the computer starting and blanking timing. When the 26G1 delay ramp has been completed, the unit returns to the correct configuration for being re-triggered as the two free-running audio oscillators reach the relative phase angles which result in the maximum algebraic sum in the output from the audio frequency summing circuit. The 26G1 cannot be re-triggered until the delay ramp has ended.

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

The Computer Start and Receiver Blanking Timing

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

start of the delay is synchronous with the start of the pulse (from the 26G3) controlling the Digilab Pulser.

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

Computer Start Pulse

The computer start pulse (40 μsec. duration) is put out by the second 26G3 Pulse Generator, operating in the preset 1 volt level triggered mode. This unit is triggered when the ramp level from the 26G2 Ramp Generator rises to 1 volt. The output pulse is directed to the interrupt input on the D/A Converter card in the HP 2114 A Computer. At the time this pulse arrives, the computer is in a loop awaiting an interrupt from the D/A card. Immediately the interrupt occurs, the computer may start acquiring data. A further delay in the start of the data acquisition can be provided by computer software.

Blanking Amplifier

The blanking amplifier is a custom built unit mounted on a standard plug in unit for Tektronix 2600. In addition to

providing gain, it switches off the audio frequency output from the V-4311 r.f. Receiver during, and immediately following, the r.f. pulse. The output from the blanking amplifier is directed to the two audio frequency phase detectors (in the lock and analytical channels).

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

R.F. Transmitter

The Varian r.f. transmitter (25.12 MHz) has been changed slightly from its original configuration. The Attenuator/ Maximum switch, which is normally locked in the Attenuation

position has been replaced by a switch to facilitate the change between pulsed and c.w. modes of operation. This switch directs the transmitter output either directly to the probe (c.w. mode) or to the Digilab Pulser (pulse mode). The transmitter is normally operated with 10 DB of attenuation.

R.F. Receiver

The receiver section of the Varian V-4311 has been modified so that the r.f. pulse detector may be by-passed and replaced by a broad band phase detector. The i.f. (intermediate frequency) signal is taken from the end of the i.f. strip to J302. A Relcom M1C Double Balanced Mixer is employed as a phase detector, the signal being taken from J302, and the 5 MHz reference voltage from J103 of the V-4311 unit. The detected output from the M1C (audiofrequency signal) is fed to the blanking amplifier (see earlier).

Digilab 200-2 Pulser

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

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

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

Phase Detectors

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

Lock Channel

The original phase detector in the Varian V-4354 'lock box' is employed for the control (lock) channel. Broad band characteristics are not required for this phase detector. The reference signal is taken from the Wavetek 111 audio oscillator in the V-3530 wide sweep unit. The phase detector input is taken (via the standard Varian high pass filter) from the output of the blanking amplifier (see earlier).

Analytical Channel

A Princeton Applied Research (PAR) 128 phase detector, modified for broad band (> 5 KHz) characteristics, is employed as the analytical channel phase detector. It is referenced to an HP 4204 A analytical channel audio oscillator. The input is taken from the output of the blanking amplifier, and the output is fed to the audio frequency filter circuitry (see later). The phase detector section of the PAR 128 is preceded by a high pass filter (to remove spinning noise) whose characteristics have been modified to have a cut off frequency of 500 Hz. The filter circuitry of PAR 128, which follows the phase detector section, has been disabled; and the amplifier section has been modified to extend its band width. The unit has its own gain and phase selection controls.

Audio Frequency Filter

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

A/D converter is set at 1-2 volts peak to peak.

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

Audio Frequency Summing Circuit

In order that the lock channel and the analytical channel signals will be detected in constant phase following the r.f. pulse, the pulse must be timed so that it is generated when each audio reference frequency has reached a particular phase angle. This situation is achieved by summing the two audio reference frequencies and triggering the r.f. pulse when the summed a.f. signal is fed via a variable voltage divider to the trigger input of the 26G1 Rate/Ramp Generator which controls pulse interval timing. The input voltage to the 26G1 is adjusted so that it is just sufficient to cause triggering, thus ensuring that the r.f. pulse is generated when the algebraic sum of the audio reference signals is at maximum.

Audio Frequency Oscillators

Two a.f. oscillators are employed, one for each channel. In pulse operation, the oscillators supply reference voltage

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

Block Averaging

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

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

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

/NSxx	Number of scans per block
/NBxx	Number of blocks

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

preset value of NB is 1.

Important:

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

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

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

The Computer Program, FTNMR

The computer program , FTNMR, written by Colebrook [6] is designed specifically for use in high resolution pulsed Fourier Transform NMR Spectroscopy. Its basic functions include, but are not limited to, following data acquisition and data processing operations:

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

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

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

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

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

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

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

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

FTNMR Loading Procedures

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

A Paper Tape Procedure:

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

1 The computer and peripherals are switched on.

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

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

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

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

B Magnetic Tape Procedure:

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

1 The computer and peripherals are switched on.

2 FTNMR data tape (with FTNMR as file 1) is mounted and positioned at the load point (AUTO mode).

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

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

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

6 On pressing RUN, the computer should type *NEXT? . If so, step no. 7 should be overlooked.

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

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

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

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

11 Before switching off the computer, /ST should be typed or HALT pressed. Load 77_8 is addressed and RUN is pressed. The tape will rewind and the computer will type *NEXT? . In response, :PAUSE should be typed. This action returns control to the MTS

monitor and leaves the computer in the correct configuration for restarting from address 15606_8.

12 The peripherals and the computer should be switched off.

General Procedure:

Load Address Procedure:

1 The computer should be in HALT mode.

2 CLEAR REGISTER is pressed.

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

4 LOAD ADDRESS is pressed.

5 CLEAR REGISTER is pressed.

Re-Starting When FTNMR is Already Loaded:

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

1 Switch register (HALT mode) is cleared.

2 Load 2001_8 is addressed.

3 RUN is pressed.

Basic Binary Loader (BBL) Procedure:

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

1 Computer should be in HALT mode.

2 Paper tape is placed in reader.

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

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

Preparation of an FTNMR Magnetic Tape

FTNMR may be written on magnetic tape for loading using the Magnetic Tape System by following standard procedures as set out in the Hewlett Packard 2114A manual.

Command Formats

All commands are three characters in length. The first of three characters is required for certain interrupt operations, and is not decoded by the computer. It may be a slash (/), a period (.) or other character chosen by the operator. The second and third characters are decoded by the computer

and constitute an operation command. Commands which enter operating parameters are followed immediately by up to four numerals (the first of which may be replaced by a minus sign (-) for the TC command only).

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

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

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

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

Oscilloscope Display Modes

Three modes of 'scope display are available:

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

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

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

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

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

Plotting Modes:

The above remarks also apply to plotting modes.

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

PR (Plot Real) corresponds to DR.

PI (Plot Imaginary) corresponds to DI.

FTNMR Operating Parameters:

(N.B. Underlined commands initiate an action. Other commands,

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

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

Initialization:		Preset Value	Limits
/EXxx	Exponent, No. of points = 2**EX	12 ie. 4096 points	0<EX<12
/ZE	Zero array (control is transferred to DF)		

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

Display:		Preset Value	Limits
/DMxx	Display multiplier	1	≥1
/DF	Display FID		
/DR	Display real array		
/DI	Display imaginary array		

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

Array Manipulations:			
/ADxx	Array divider (for Fourier Transform)	4 ie. (2**4)	≥1
/DA	Divide array by 2 (control is transferred to DF)		
/MA	Multiply array by 2 (control is transferred to DR)		
/BC	Baseline correction (control is transferred to DF)		

Digital Filters:			
/TCxx	Time constant (for exponential multiplications)	1	none

		Preset Value	Limits
/TLxx	Trapezoidal filter limit	1	<2**EX
/EF	Exponential filter (control is transferred to DF)		
/TR	Trapezoidal filter (control is transferred to DR)		

Fourier Transform:

/FT	Fourier Transform (control is transferred to DR)		

Phase Correction:

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

Plotting:

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

	Preset Value	Limit

Stop:

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

Data Recovery:

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

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

2 Position the tape to the original start point.

3 Initiate recovery, using the command /RC .

Processing will then proceed in the usual way.

FTNMR Spectral Parameters Abbreviations:

NS	Number of scans
SI	Sampling interval (μsec)
AF	Analytical frequency (Hz)
LF	Lock frequency (Hz)
PW	Pulse width (μsec, duration of pulse)
PI	Pulse interval (sec) (time difference between two pulses)
NP	Number of points

AD Acquisition delay (after pulse, before the computer starts acquisition)

PA Zero order phase correction (degrees)

PB First order phase correction (degrees)

Description of Command Parameters

Selection of Data Acquisition Rate:

In the pulsed Fourier NMR experiment, the rate of data acquisition determines the frequency range or spectral width acquired by the data system. This is done by selection of appropriate values for the command CPxx and CMxx. The spectral width is determined by:

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

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

In the present study, for all compounds, CP = 0, ie. 100 μsec and CM = 1 so that:

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

Beginning Data Acquisition

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

Signal Conditioning:

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

TABLE I

FID ACQUISITION DATA

Sampling Interval (μsec)	Acquisition Time (sec.)			Highest Frequency (Hz)
	1K	2K	4K	
100	0.1	0.2	0.4	5000
200	0.2	0.4	0.8	2500
300	0.3	0.6	1.2	1667
400	0.4	0.4	1.6	1250
500	0.5	1.0	2.0	1000
600	0.6	1.2	2.4	833
700	0.7	1.4	2.8	714
800	0.8	1.6	3.2	625
900	0.9	1.8	3.6	556
1000	1.0	2.0	4.0	500
1100	1.1	2.2	4.4	454
1200	1.2	2.4	4.8	417
1300	1.3	2.6	5.2	385
1400	1.4	2.8	5.6	357
1500	1.5	3.0	6.0	333
1600	1.6	3.2	6.5	313
1700	1.7	3.4	6.8	294
1800	1.8	3.6	7.2	278
1900	1.9	3.8	7.6	263
2000	2.0	4.1	8.2	250
2500	2.5	5.1	10.2	200

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

Fourier Transform and Window Functions

A Baseline Correction...../BC

The signal averaged FID may contain a small residual DC bias that prevents the average value of the data points from being zero. If this is the case, a huge spike is produced at zero frequency which has no physical meaning. Hence, in all cases studied, a base line correction was performed before transformation. Base line correction was also performed before the command /EF , (exponential filter, see later). The command /BC takes the sum of all displayed data points, divided by

the number of points and subtracts this average value from all points, so that the average value is zero. This command is called automatically if the /TR command is used. /BC is required in these cases because the window function must operate on the data only and not on any constant DC offset.

B Exponential Filter...../EF

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

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

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

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

C Time Constant...../TC

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

D Fourier Transformation...../FT

The command /FT initiates a fast Fourier Transform of the acquired time domain data and replaces it with the frequency domain spectrum of N/2 real points and N/2 imaginary points corresponding to the Cosine and Sine transforms of the data. It is done by multiplying each data point by all possible Sine waves up to Nyquist frequency. This clearly requires N^2 multiplications, where N is the number of data points. However, the method elaborated by Cooley and Tukey [7] makes use of $2N \log_2 N$ multiplications and hence a great saving in time is achieved.

E Trapezoidal Window:..../TLxx and /TR

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

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

If a large value of /TLxx is used, eg. 30 or more, the peaks tend to settle in triughs in the baseline.

F Phase Correction...../PAxx, /PBxx and /PC

Before Fourier Transformetion, the digitized FID is stored in the computer as a real array of length 2^k where k=12 ie. the array has a maximum length of 4096 points.

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

1 Spectrometer phase detector setting,

2 Delay between pulses and start of data acquisition, and

3 Filter settings.

The spectrometer phase detector setting is usually optimized at the beginning of data acquisition, using the sharp peak of the solvent, DMSO. The smallest changes will

affect this parameter; variation in sample tubes, solvent or even spinning rate may affect the phase of the information entering the detector. This effect is a zero order one which causes the same shift in phase for each data point, regardless of frequency.

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

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

$$R_{NI} = R_{oi}\ \mathrm{Cos}\theta_i - I_{oi}\ \mathrm{Sin}\theta_i$$

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

where $i = 1, 2, 3, 4 \ldots\ldots 2^{k-1}$

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

I_{Ni} = new imaginary value for point i

R_{oi} = old real value for point i

I_{oi} = old imaginary value for point i

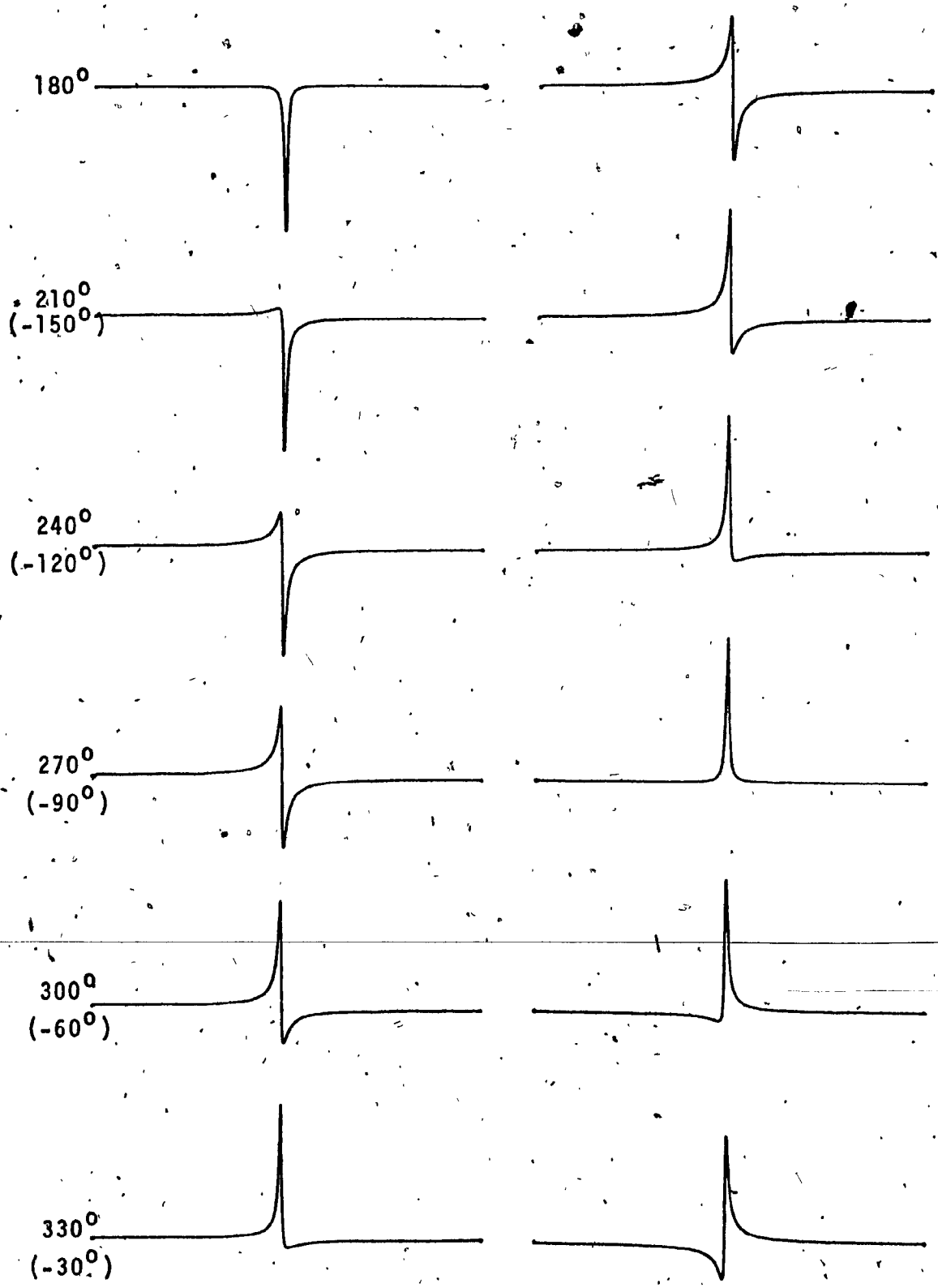


FIGURE 8 Phase correction curves.

RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

The Fourier Transformed carbon-13 nuclear magnetic resonance spectra for a series of 3-aryl-2,3-dihydro-4(1H)-quinazolinones and 3-aryl-4(3H)-quinazolinones were measured. The quinazolinones are divided into three groups according to the relationship between the rotamers. (Table II)

Group I includes the compounds in which two rotamers are enantiomers, and therefore have identical spectra in achiral media. In one case both C-2 positions are methyl, while in the other compounds, both C-2 substituents are hydrogens. Group II contains the compounds in which the two rotamers are diastereomeric and each rotamer in this series is expected to have its own individual spectrum. Group III includes miscellaneous compounds that do not fit into Groups I or II.

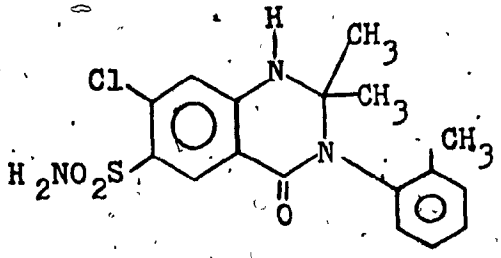
The chemical shift data are divided into tabular form according to the carbon position in order to compare the chemical shifts and to clarify the following discussion.

Dimethylsulfoxide (DMSO) was employed as a solvent in this study and provided the lock signal and internal reference. The concentrations of the quinazolinone solutions varied from 5 to 50 % w/v. Each sample was run using at least two analytical frequencies, with the number of scans varying

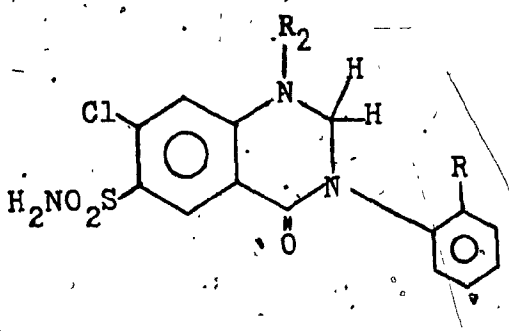
TABLE II

GROUP I

ISOMERIC RELATION : ENANTIOMERIC

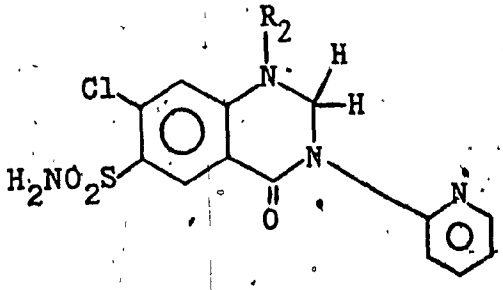


I



II R=CH_3, R_2=H

III R=C_2H_5, R_2=H



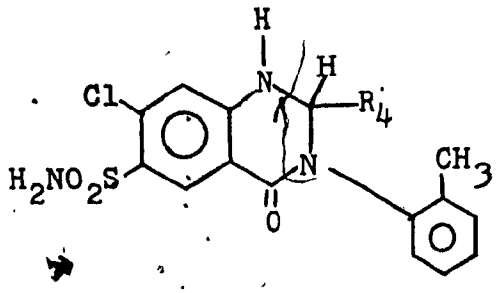
IV R_2=H

V R_2=CH_3

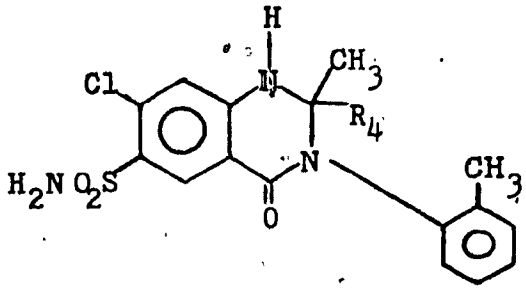
TABLE II (cont'd)

GROUP II

ISOMERIC RELATION : DIASTEREOMERIC



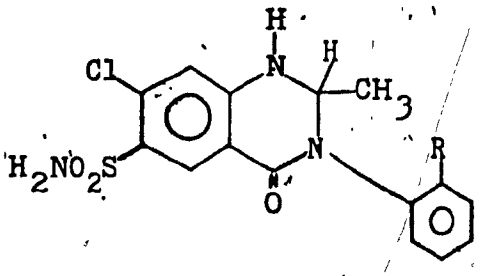
VI	$R_4=CH_3$
VII	$R_4=C_2H_5$
VIII	$R_4=n\text{-}C_3H_7$
IX	$R_4=CH_2Cl$
X	$R_4=CHCl_2$
XI	$R_4=CH_2OCH_3$
XII	$R_4=CO_2C_2H_5$
XIII	$R_4=C_6H_5$



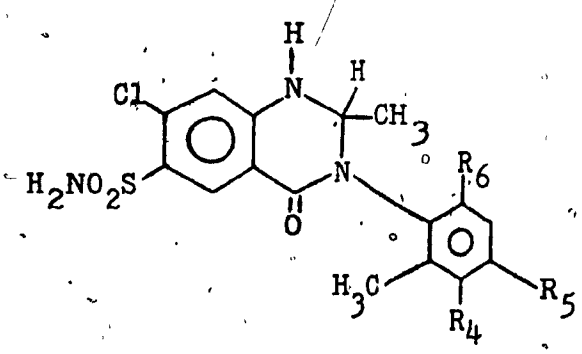
XIV	$R_4=CO_2C_2H_5$

TABLE II (cont'd)

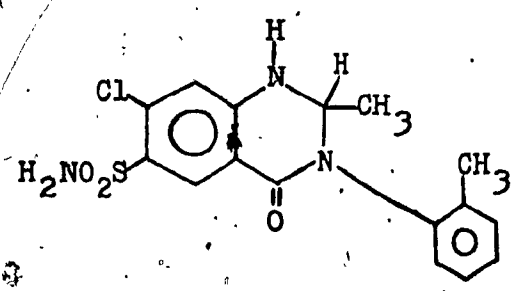
GROUP II (cont'd)



XV	$R=CH_2OH$
XVI	$R=C_2H_5$
XVII	$R=CF_3$



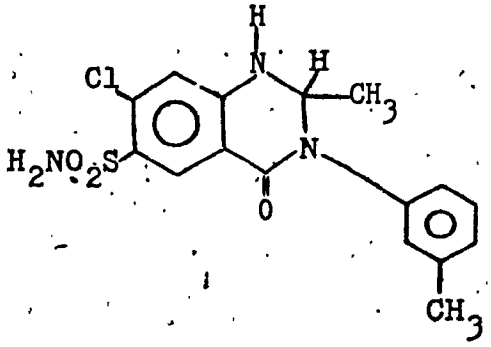
XVIII	$R_4=R_5=H,\ R_6=CH_3$
XIX	$R_4=H,\ R_5=R_6=CH_3$
XX	$R_4=R_6=H,\ R_5=OCH_3$



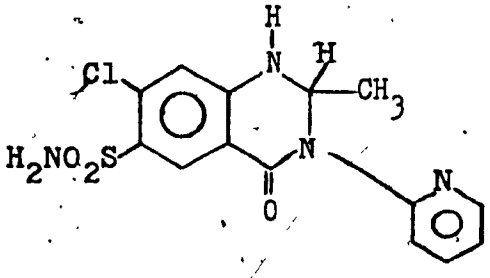
XXI	$R_2=CH_3$
XXII	$R_2=CH_2-\phi$

TABLE II (cont'd)

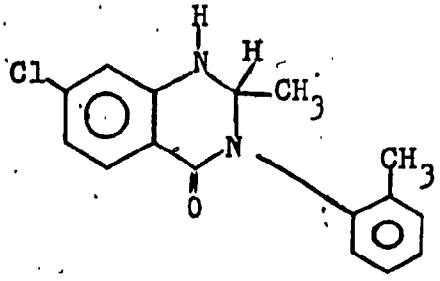
GROUP II (cont'd)



XXIII



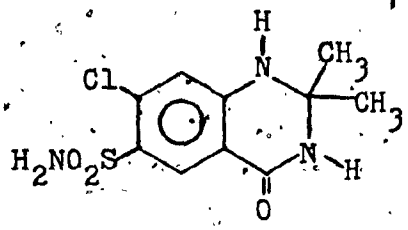
XXIV



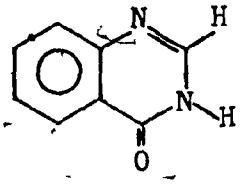
XXVI

TABLE II (cont'd)

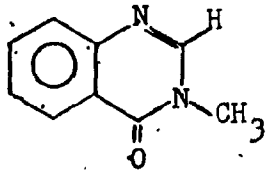
GROUP III



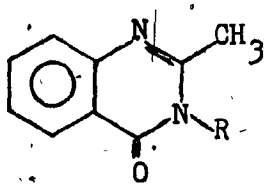
XXV



XXVII



XXVIII R_5=H



XXIX R=o-tolyl

XXX R=2,5-dimethyl-Ø

XXXI R=2,4,6-trimethyl-Ø

XXXII R=4-chloro-2-methyl-Ø

XXXIII R=5-chloro-2-methyl-Ø

between 4096 and 12,288, depending upon the concentration of the sample.

Chemical shifts were measured with respect to the DMSO solvent signal (at 40.74 ppm) and were reported relative to TMS. The chemical shift values are estimated to approximately 0.05 ppm (2.0 Hz). The spectra were measured by double irradiation near the methyl region for noise modulated proton decoupling.

The quinazolinone samples were stable in DMSO

The carbon-13 chemical shift values of 3-aryl-2,3-dihydro-4(1H)-quinazolinones have not previously been reported in the literature.

The chemical shift values of the groups of corresponding carbons (C-2, C-2 substituents, carbonyl, aromatic, aryl substituents) are discussed with respect to conjugation, inductive, steric and polar interactions. The results are compared with the carbon-13 data in the literature.

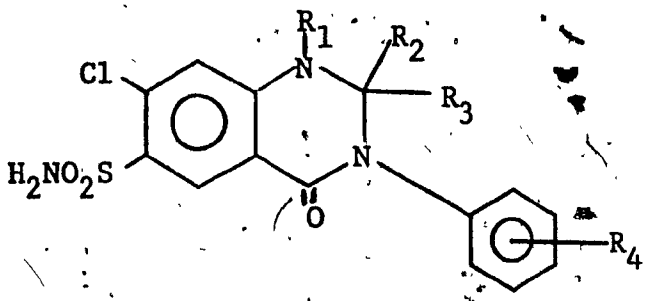
Assignment of the Peaks

Table III shows the ranges of chemical shift values for the various carbon positions of 3-aryl-2,3-dihydro-4(1H)-

TABLE III

RANGE OF CHEMICAL SHIFT VALUES IN

3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES [a]



C-2	C-2 METHYL	C-4	ARYL METHYLS
56.9	15.88	159.84	14.10
to	to	to	to
75.14	29.61	162.23	18.08

[a] ppm from TMS

quinazolinones. Table IV shows the range of chemical values for the various carbon positions of β-aryl-4(3H)-quinazolinones. These values agree with the chemical shift ranges found for similar compounds. Breitmaier et al[3] have reported carbon chemical shift values of 160 - 175 ppm for carbonyl carbons in amides. Williams [44] and Icli [17] have reported values of 52 - 66 ppm for the C-5 carbon group and 14.6 - 25 ppm for C-5 methyl in 1-aryl hydantoins.

The environment of these carbon atoms are similiar to the environment of the C-4, C-2 and C-2 methyl carbons in 3-aryl-2,3-dihydro-4(1H)-quinazolinones.

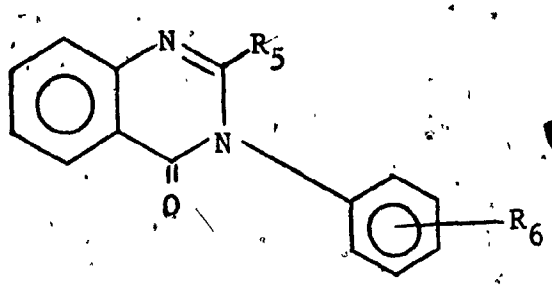
Aryl Quinazolinones

The chemical shift values for the peaks assigned to C-2 are shown in Tables V, VI, VII and VIII. The values range from 56.9 to 75.14 ppm for the saturated compounds and 145.33 to 147.51 ppm for the unsaturated compounds. These values agree with those found by Icli [17] for 1-aryl hydantoins (52 - 63 ppm) and Breitmaier [3] (62 - 76 ppm for the saturated compounds and 145 - 155 ppm for the unsaturated ones).

Chemical shift values for peaks assigned to the C-4 carbonyl carbon are shown in Tables IX, X, XI and XII. These values range from 159.44 to 163 ppm and are consistent with

TABLE IV

RANGE OF CHEMICAL SHIFT VALUES IN 3-ARYL-4(3H)-QUINAZOLINONES [a]

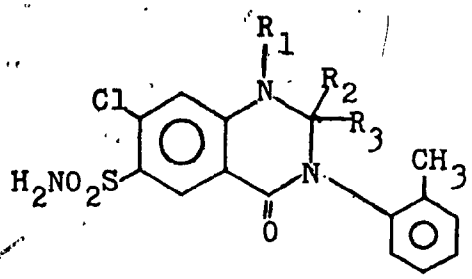


C-2	C-2 Me	C-4
145.33 to 147.51	22.69 to 23.36	160.44 to 160.83

[a] ppm from TMS

TABLE V

CARBON-13 CHEMICAL SHIFTS OF C-2 IN 3-(o-TOLYL) COMPOUNDS



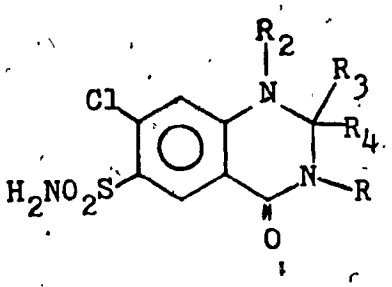
COMPOUND NUMBER	R_1	R_2	R_3	CHEMICAL SHIFT C-2 (ppm)
I	H	CH_3	CH_3	72.55
II	H	H	H	60.62
VI	H	H	CH_3	67.37 *
VII	H	H	C_2H_5	72.56 *
VIII	H	H	$n\text{-}C_3H_7$	70.56
IX	H	H	CH_2Cl	71.16 *
X	H	H	$CHCl_2$	73.75
XI	H	H	CH_2OCH_3	72.95
XII	H	H	$CO_2C_2H_5$	69.77
XIII	H	H	C_6H_5	73.74 *
XIV	H	CH_3	$CO_2C_2H_5$	75.04 *
XXI	CH_3	H	CH_3	73.75
XXII	$CH_2\emptyset$	H	CH_3	72.95

* center of doublet

TABLE VI

CARBON-13 CHEMICAL SHIFT OF C-2 IN

3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES

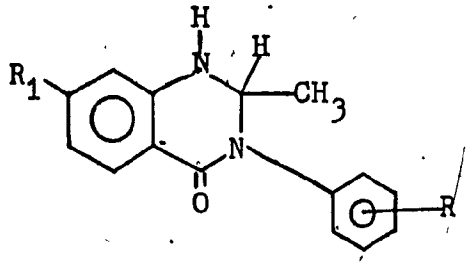


COMPOUND NUMBER	R	R_2	R_3	R_4	CHEMICAL SHITF C-2 (ppm)
III	o-C_2H_5-Ø	H	H	H	61.22
XVI	o-C_2H_5-Ø	H	H	CH_3	67.38
IV	α-PYRIDYL	H	H	H	56.85
V	"	CH_3	H	H	63.80
XXIV	"	H	H	CH_3	63.80
XV	o-CH_2OH-Ø	H	H	CH_3	67.78
XVII	o-CF_3-Ø	H	H	CH_3	67.38 *
XVIII	2,6-DIMETHYL-Ø	H	H	CH_3	66.59
XIX	2,4,6-TRIMETHYL-Ø	H	H	CH_3	66.59
XX	2-METHYL-4-METHOXY-Ø	H	H	CH_3	67.38 *
XXIII	m-TOLYL	H	H	CH_3	67.78
XXV	H	H	CH_3	CH_3	67.78

* center of doublet

TABLE VII

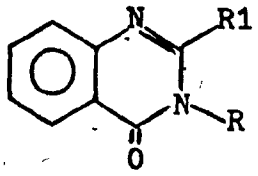
CARBON-13 CHEMICAL SHIFT OF C-2 IN 3-ARYL-7-CHLORO-2,3-DIHYDRO-4(1H)-QUINAZOLINONE



COMPOUND NUMBER	R	R_1	CHEMICAL SHIFT C-2 (ppm)
XXVI	o-CH_3	Cl	66.59

TABLE VIII

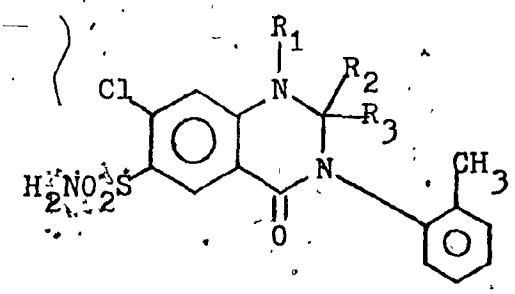
CARBON-13 CHEMICAL SHIFTS OF C-2 IN 4(3H)-QUINAZOLINONES AND 3-ARYL-4(3H)-QUINAZOLINONES



COMPOUND NUMBER	R_1	R'	CHEMICAL SHIFT C-2 (ppm)
XXVII	H	H	145.33
XXVIII	H	CH_3	147.51
XXIX	CH_3	o-TOLYL	147.51
XXX	CH_3	2,5-DIMETHYL-Ø	147.63
XXXI	CH_3	2,4,6-TRIMETHYL-Ø	147.63
XXXII	CH_3	4-CHLORO-2-METHYL-Ø	147.51
XXXIII	CH_3	5-CHLORO-2-METHYL-Ø	147.35

TABLE IX

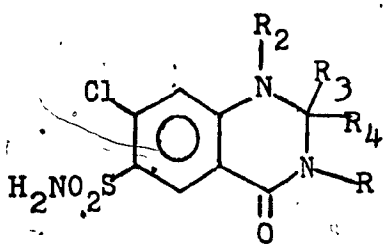
CARBON-13 CHEMICAL SHIFTS OF C-4 CARBONYL CARBONS OF 3-(o-TOLYL) COMPOUNDS



COMPOUND NUMBER	R_1	R_2	R_3	CHEMICAL SHIFT C-4 (ppm)
I	H	CH_3	CH_3	159.84
II	H	H	H	160.83
VI	H	H	CH_3	160.24
VII	H	H	C_2H_5	160.24
VIII	H	H	$n\text{-}C_3H_7$	159.84
IX	H	H	CH_2Cl	159.84
X	H	H	$CHCl_2$	159.44
XI	H	H	CH_2OCH_3	160.44
XII	H	H	$CO_2C_2H_5$	161.03
XIII	H	H	C_6H_5	160.24
XIV	H	CH_3	$CO_2C_2H_5$	160.83
XXI	CH_3	H	CH_3	159.64
XXII	$CH_2\text{-}\phi$	H	CH_3	160.04

TABLE X

CARBON-13 CHEMICAL SHIFTS OF C-4 CARBONYL CARBON IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES

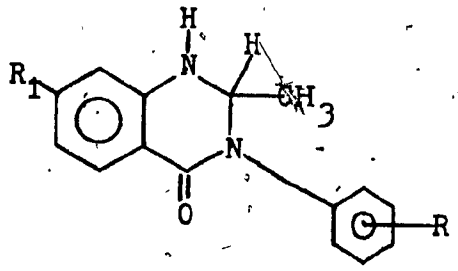


COMPOUND NUMBER	R	R_2	R_3	R_4	CHEMICAL SHIFT C-4 (ppm)
III	o-C_2H_5-Ø	H	H	H	161.23
XVI	o-C_2H_5-Ø	H	H	CH_3	160.44
IV	α-PYRIDYL	H	H	H	162.23
V	α-PYRIDYL	CH_3	H	H	161.43
XXIV	α-PYRIDYL	H	H	CH_3	161.23
XV	o-CH_2OH-Ø	H	H	CH_3	160.44
XVII	o-CF_3-Ø	H	H	CH_3	162.12 *
XVIII	2,6-DIMETHYL-Ø	H	H	CH_3	160.44
XIX	2,4,6-TRIMETHYL-Ø	H	H	CH_3	160.24
XX	2-METHYL-4-METHOXY-Ø	H	H	CH_3	160.83
XXIII	m-TOLYL	H	H	CH_3	160.64
XXV	H	H	CH_3	CH_3	161.63

* center of doublet

TABLE XI

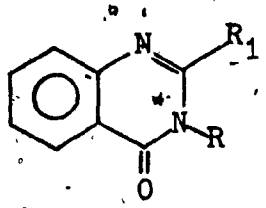
CARBON-13 CHEMICAL SHIFTS OF C-4 CARBONYL CARBONS IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



COMPOUND NUMBER	R	R_1	CHEMICAL SHIFT C-4 (ppm)
XXVI	o-CH_3	Cl	161.23

TABLE XII

CARBON-13 CHEMICAL SHIFTS OF C-4 CARBONYL CARBONS IN 4(3H)-QUINAZOLINONES AND 3-ARYL-4(3H)-QUINAZOLINONES



COMPOUND NUMBER	R_1	R	CHEMICAL SHIFT C-4 (ppm)
XXVII	H	H	160.83
XXVIII	H	CH_3	160.44
XXIX	CH_3	o-TOLYL	160.80
XXX	CH_3	2,5-DIMETHYL-Ø	160.83
XXXI	CH_3	2,4,6-TRIMETHYL-Ø	160.44
XXXII	CH_3	4-CHLORO-2-METHYL-Ø	160.75
XXXIII	CH_3	5-CHLORO-2-METHYL-Ø	160.64

those observed by Breitmaier [3] of 158.3 to 173.8 ppm for carbonyls of amides and Icli's [17] values of 155 and 172 ppm for 1-aryl hydantoins.

Methyl Peaks:

Lauterbur [26] has determined the chemical shift values for the methyl derivatives of anilines & N,N-dimethyl anilines (Table XIII). The aryl methyls in these compounds can be compared with the aryl methyls in quinazolinones.

Icli [17] has reported the chemical shift values of the aryl methyl carbon in 1-aryl hydantoins to be ≈ 16.74 ppm (Table XIV). The aryl methyls in these compounds can also be compared with the aryl methyls in quinazolinones.

Khadim [22], Icli [17] and Williams [44] have observed that in 3-aryl hydantoins, the aryl methyl carbons appear on the high field side as compared to the C-5 methyl carbons. This trend is also evident in the 3-aryl-2,3-dihydro-4(1H)-quinazolinones. In the 2,2-dimethyl-3-ortho tolyl quinazolinone compound (I), three peaks are observed in the methyl region. Based on enantiomeric and diastereomeric relationships, the high field signal at 18.47 ppm is assigned to the ortho methyl carbon, since the enantiomeric ortho methyl group is expected to exhibit a single absorption. The C-2 dimethyl groups are

TABLE XIII

CARBON-13 CHEMICAL SHIFTS OF METHYL DERIVATIVES OF ANILINES AND N,N-DIMETHYL ANILINES [26]

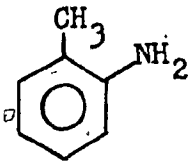
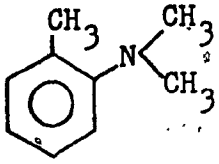
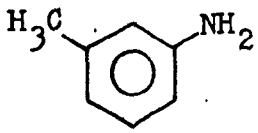
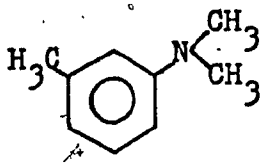
COMPOUND	C-13 CHEMICAL SHIFT OF ARYL METHYL (ppm)
	17.3
	18.5
	21.6
	21.6

TABLE XIII (cont'd)

CARBON-13 CHEMICAL SHIFTS OF METHYL DERIVATIVES OF ANILINES AND N,N-DIMETHYL ANILINES

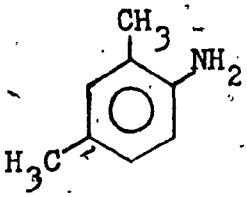
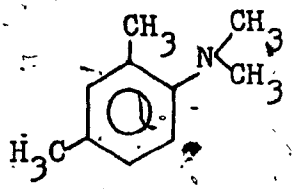
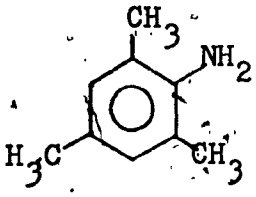
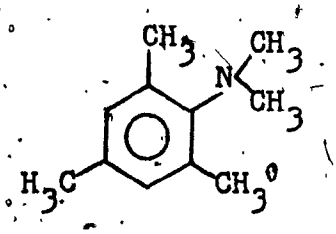
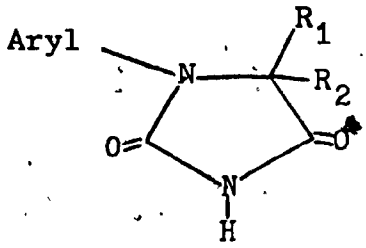
COMPOUND	C-13 CHEMICAL SHIFT OF ARYL METHYL (ppm)
	17.6
	19.0
	2,6 17.2 4 20.0
	2,6 19.8 4 19.8

TABLE XIV

CARBON-13 CHEMICAL SHIFTS OF 1-ARYL HYDANTOINS [17]



ARYL	R_1	R_2	CHEMICAL SHIFT OF ARYL METHYL (ppm)	CHEMICAL SHIFT OF C-5 METHYLS (ppm)
o-TOLYL	CH_3	H	18.1	15.7
o-TOLYL	CH_3	CH_3	18.5	22.38 25.05
2,3-DIMETHYL-Ø	CH_3	H	15.7[b] 20.4[b]	14.6
2,3-DIMETHYL-Ø	CH_3	CH_3	15.3 [b] 20.3 [b]	22.22 25.01

[b] meta methyl

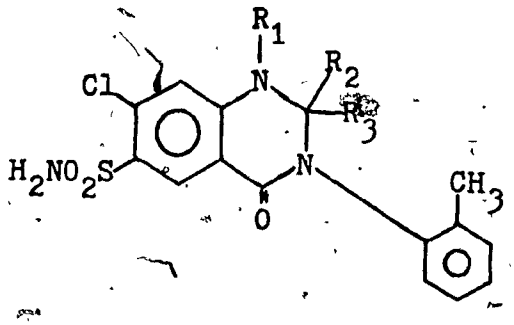
expected to show two signals of almost equal intensity and close to each other. The low field signals at 27.02 ppm and 28.41 ppm are believed to arise from the C-2 dimethyl carbons.

Table XV shows the chemical shift values of the aryl-o-methyl carbons. The chemical shift values range from 13.70 to 18.87 ppm. The chemical shift values of the aryl substituents are shown in Tables XVI, XVII and XVIII. Model compounds used to assign the aryl substituents are shown in Table XIX. The peaks assigned to o-ethyl range from 14.30 - 14.89 ppm for the terminal methyl group and 20.86 to 24.04 ppm for the α carbon. The ^{13}C chemical shift of the N-3 aryl substituent, CH_2OH (59.43 ppm), CF_3 (116.50 ppm), 2,4,6-trimethyl (18.07 & 18.47 ppm for the 2,6 methyl carbons and 20.26 ppm for the 4 methyl carbon), 4-methoxy (55.25 ppm) and meta- CH_3 (20.86 ppm) compare closely to those of the model compounds.

The C-2 methyl carbon chemical shifts are shown in Tables XX, XXI, XXII and XXIII. The mono-methyl carbon chemical shifts range from 15.69 to 20.86 ppm, while the dimethyl carbons are found further downfield, ranging from 27.22 to 29.61 ppm. These values are similar to those of 15.7 to 17.9 ppm for mono-methyl carbons and 24.12 to 25.27 ppm for dimethyl carbons found by Williams [44], Icli [17] and Khadim [22] in 1-aryl hydantoins. The substituted methyl carbons, Table XXIV, where one or more methyl hydrogens were

TABLE XV

CARBON-13 CHEMICAL SHIFTS OF N-3 ARYL o-METHYL SUBSTITUENTS OF 2,3-DIHYDRO-3-o-TOLYL-4(1H)-QUINAZOLINONES

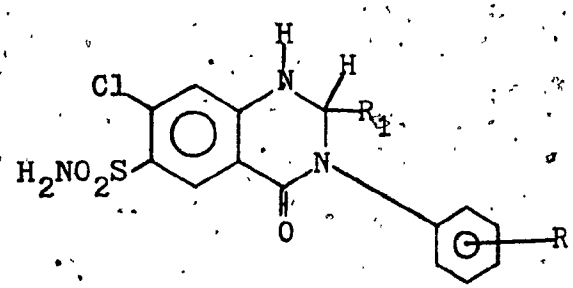


COMPOUND NUMBER	R_1	R_2	R_3	CHEMICAL SHIFT OF N-3 ARYL o-Me (ppm)
I	H	CH_3	CH_3	18.47
II	H	H	H	17.68
VI	H	H	CH_3	17.88 *
VII	H	H	C_2H_5	17.68
VIII	H	H	$n\text{-}C_3H_7$	17.28
IX	H	H	CH_2Cl	17.28
X	H	H	$CHCl_2$	18.08 *
XI	H	H	CH_2OCH_3	17.28
XII	H	H	$CO_2C_2H_5$	14.10
XIII	H	H	C_6H_5	15.89
XIV	H	CH_3	$CO_2C_2H_5$	13.90 *
XXI	CH_3	H	CH_3	17.28
XXII	$CH_2\text{-}\phi$	H	CH_3	17.28

* center of doublet

TABLE XVI

CARBON-13 CHEMICAL SHIFTS OF N-3 ARYL SUBSTITUENTS IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES

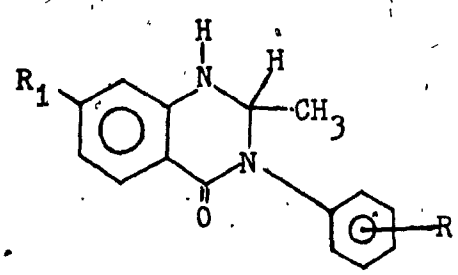


COMPOUND NUMBER	R	R_1	CHEMICAL SHIFT OF N-3 ARYL SUBSTITUENTS (ppm)
III	o-CH_2CH_3 (a b)	H	a 24.04 b 14.30
XV	o-CH_2OH	CH_3	59.43
XVI	o-CH_2CH_3 (a b)	CH_3	a 22.35 * b 14.69 *
XVII	o-CF_3	CH_3	116.50 *
XVIII	2,6-DIMETHYL	CH_3	18.37 *
XIX	2,4,6-TRIMETHYL	CH_3	C-2&6 18.87 * C-4 20.26
XX	2-CH_3-4-OCH_3 (a b)	CH_3	a 18.18 * b 55.25
XXIII	m-CH_3	CH_3	20.86

* center of doublet

TABLE XVII

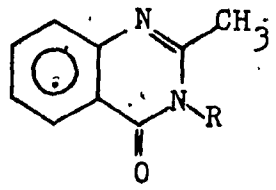
CARBON-13 CHEMICAL SHIFTS OF N-3 ARYL SUBSTITUENTS IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



COMPOUND NUMBER	R	R_1	CHEMICAL SHIFT OF N-3 ARYL SUBSTITUENTS (ppm)
XXVI	o-CH_3	Cl	17.68

TABLE XVIII

CARBON-13 CHEMICAL SHIFTS OF N-3 ARYL METHYL SUBSTITUENTS IN 3-ARYL-4(3H)-QUINAZOLINONES



COMPOUND NUMBER	R	CHEMICAL SHIFT OF N-3 ARYL METHYL SUBSTITUENTS (ppm)
XXIX	o-TOLYL	16.88
XXX	2,5-DIMETHYL-Ø	C-5 20.26 C-2 16.28
XXXI	2,4,6-TRIMETHYL-Ø	C-4 20.70 C-2,6 17.12
XXXII	4-CHLORO-2-METHYL-Ø	16.56
XXXIII	5-CHLORO-2-METHYL-Ø	16.36

TABLE XIX

CARBON-13 CHEMICAL SHIFT VALUES OF SOME SUBSTITUTED ARYL COMPOUNDS

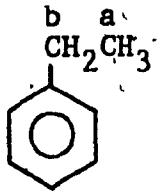
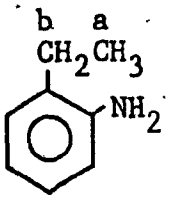
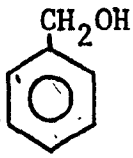
COMPOUND	C-13 CHEMICAL SHIFT OF ARYL SUBSTITUENT (ppm)	REFERENCE
	a 15.7 b 29.1	18
	a 12.9 b 23.9	18
	64.5	18
	124.6	18

TABLE XIX (cont'd)

CARBON-13 CHEMICAL SHIFT VALUES OF SOME SUBSTITUTED ARYL COMPOUNDS

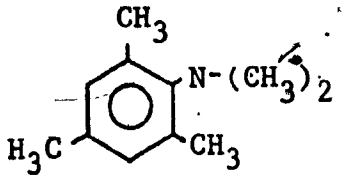
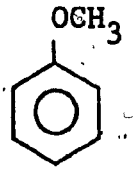
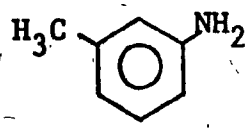
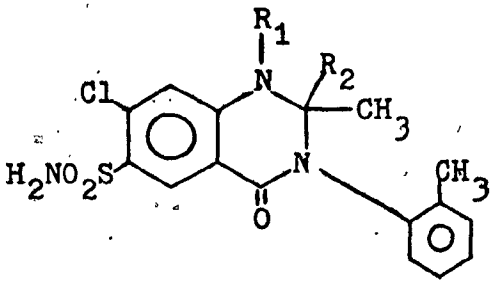
COMPOUND	C-13 CHEMICAL SHIFT OF ARYL SUBSTITUENT (ppm)		REFERENCE
	2,4,6	14.8	26
	$N-(CH_3)_2$	42.8	
		55.5	18
		21.6	26

TABLE XX

CARBON-13 CHEMICAL SHIFTS OF C-2 METHYL CARBONS IN 3-(o-TOLYL)-2,3-DIHYDRO-4(1H)-QUINAZOLINONES

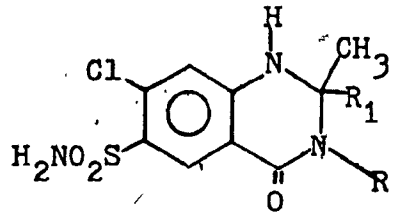


COMPOUND NUMBER	R_1	R_2	CHEMICAL SHIFT OF C-2 METHYL CARBON (ppm)
I	H	CH_3	27.02 , 28.41
VI	H	H	20.86
XIV	H	$CO_2C_2H_5$	18.27 *
XXI	CH_3	H	15.88 *
XXII	CH_2-Ø	H	16.88

* center of doublet

TABLE XXI

CARBON-13 CHEMICAL SHIFTS OF C-2 METHYL CARBONS IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES

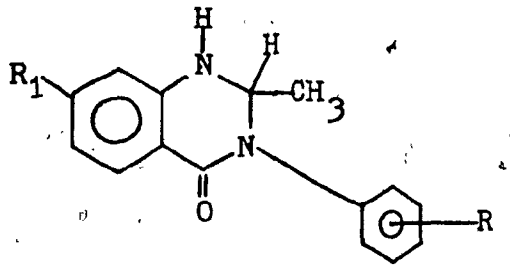


COMPOUND NUMBER	R	R_1	CHEMICAL SHIFT C-2 METHYL (ppm)
XV	o-CH_2OH-Ø	H	20.46
XVI	o-C_2H_5-Ø	H	20.86
XVII	o-CF_3-Ø	H	19.96 *
XVIII	2,6-DIMETHYL-Ø	H	20.06
XIX	2,4,6-TRIMETHYL-Ø	H	20.66
XX	2-METHYL-4-METHOXY-Ø	H	20.46
XXIII	m-CH_3-Ø	H	20.86
XXIV	α-PYRIDYL	H	20.66
XXV	H	CH_3	29.61

* center of doublet

TABLE XXII

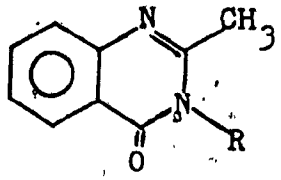
CARBON-13 CHEMICAL SHIFTS OF C-2 METHYL CARBONS IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



COMPOUND NUMBER	R	R_1	CHEMICAL SHIFT C-2 METHYL (ppm)
XXVI	o-CH_3	Cl	20.06

TABLE XXIII

CARBON-13 CHEMICAL SHIFT OF C-2 METHYL CARBONS IN 4(3H)-QUINAZOLINONES AND 3-ARYL-4(3H)-QUINAZOLINONES

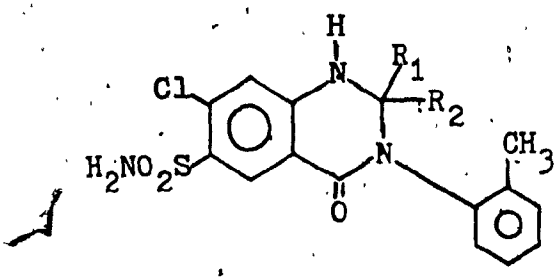


COMPOUND NUMBER	R	CHEMICAL SHIFT C-2 METHYL (ppm)
XXIX	o-TOLYL	23.36
XXX	2,5-DIMETHYL-Ø	23.24
XXXI	2,4,6-TRIMETHYL-Ø	22.69
XXXII	4-CHLORO-2-METHYL-Ø	23.24
XXXIII	5-CHLORO-2-METHYL-Ø	23.32

TABLE XXIV

CARBON-13 CHEMICAL SHIFTS OF C-2 SUBSTITUENTS OF

3-(o-TOLYL)-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



COMPOUND NUMBER	R_1	R_2	CHEMICAL SHIFT R_2 SUBSTITUENT (ppm)
VII	H	CH_2CH_3 (a b)	a 27.22 b 18.47
VIII	H	$CH_2CH_2CH_3$ (a b c)	a 36.17 b 13.50 c 12.11
IX	H	CH_2Cl	47.50
X	H	$CHCl_2$	75.34
XI	H	CH_2OCH_3 (a b)	a 69.37 b 58.63
XII	H	$CO_2CH_2CH_3$ (a b c)	a 169.58 b 62.01 c 25.68
XIII	H	C_6H_5	111 - 139
XIV	CH_3	$CO_2CH_2CH_3$ (a b c)	a 170.18 * b 62.14 * c 23.64

* center of doublet

replaced by Cl, Cl_2, OCH_3, range in value from 18.47 to 75.34 ppm.

Aryl Carbon Atoms

Quinazolinone Ring:

The aryl carbon peaks in the quinazolinone ring (ie carbons 5,6,7,8 & 9) are found between 110 and 150 ppm. The substituted aryl peaks are quite easily assigned, for example, the C-7 (–C–Cl) peak occurs at 131.0 ppm and the C-6 (–C–SO_2NH_2) peak occurs at 147.7 ppm. The quaternary carbon atoms, 9 and 10, give rise to signals at 135.8 and 130.0 ppm, respectively.

3-Aryl Carbon Atoms:

The substituted 3-aryl peaks are easily assigned; for example the C–OMe signal appears at 158.9 ppm, C–C_2H_5 at 127.8 ppm and C–CF_3 at 131.1 ppm.

The unsubstituted aryl peaks are of greater intensity than the substituted ones, due to the Nuclear Overhauser effect and shorter relaxation times.

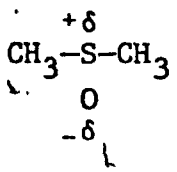
The aryl carbon atoms are not sensitive to stereochemical variation, thus they are of minor importance in this study.

Khadim [22] and Icli [17] have demonstrated that the solvent polarity and proton donor ability of the solvent molecules have pronounced effects on the carbon shieldings of hydantoin molucules. Prior to the correlation of the carbon-13 NMR data of 3-aryl-2,3-dihydro-4(1H)-quinazolinones, the solvent effects will be considered.

SOLVENT EFFECTS ON THE CHEMICAL SHIFT OF C-4 CARBONYL CARBON

SOLVENT EFFECTS ON THE CHEMICAL SHIFT OF THE C-4 CARBONYL CARBON

Dimethyl sulfoxide is a highly polarized molecule which



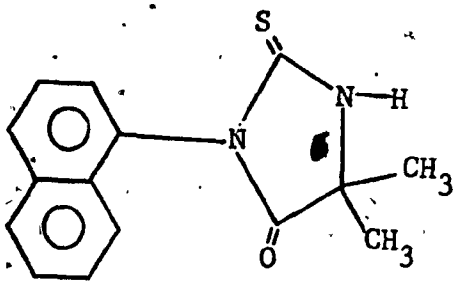
solvates cations and leaves anions relatively unencumbered. It is expected that in the C-2 monomethyl quinazolinones the oxygen atom of DMSO will approach and solvate the C-4 carbonyl carbon. Khadim [22] has determined the magnitude and direction of the solvent induced variation in the chemical shifts of 3-aryl hydantoins using chloroform as the non polar solvent and DMSO as the polar solvent. Table XXV shows the comparison of the ^{13}C chemical shifts of 3-(α-naphthyl)-5,5-dimethyl thiohydantoin in these two solvents. The DMSO induced shift of the carbonyl carbon signal is upfield.

Cisoid Conformers

If we consider the conformers in which the methyl group on the C-2 monomethyl is cisoid to the ortho aryl substituent, then the solvent molecule is expected to experience little steric hinderance in approaching the C-4 carbonyl carbon from the side transoid to the ortho substituent. The approach of the solvent molecules to the C-4 carbonyl carbon from the

TABLE XXV

COMPARISON OF CHEMICAL SHIFT DATA OF 3-(α-NAPHTHYL)-5,5-DIMETHYL THIOHYDANTOIN IN CHLOROFORM AND DMSO [22]

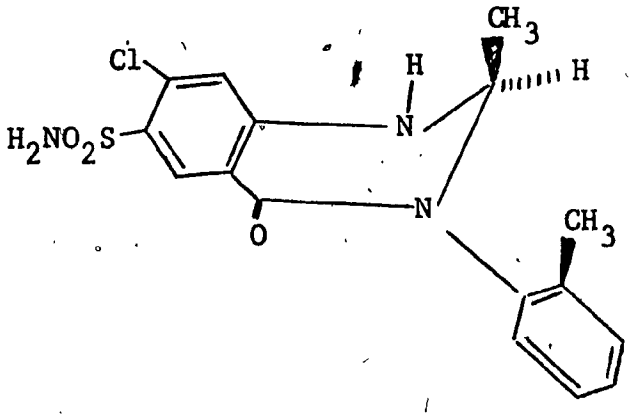


SOLVENT	CONCENTRATION (%)	CARBON POSITION C-2	C-4	C-5	C-5 METHYL
CHLOROFORM	25	182.80	176.76	61.91	24.14 [a]
DMSO	25	181.00	176.68	61.22	24.01 *
DIFFERENCE		1.80	0.08	0.69	0.13

[a] singlet observed

* center of doublet

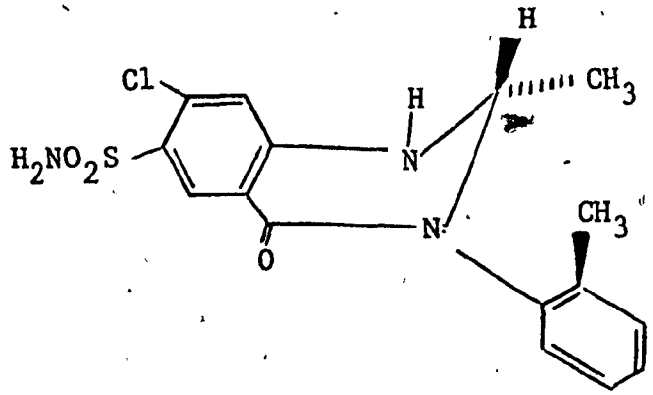
same side as that of the ortho substituent is also possible, but less likely because of some steric hinderance from the ortho and the cisoid C-2 methyl substituents. The extent of solvation around the C-4 carbonyl carbon from this side is expected to be dependent on the size of the ortho substituent. If the ortho substituent is sufficently large it may reduce solvation about C-4 from this side resulting in a smaller shielding contribution to the C-4 chemical shift and consequently a lower upfield γ effect. This in fact was observed on the compounds studied in this investigation.



Upon addition of a second methyl group which would occupy a position transoid to the ortho substituent, the solvent shell around C-4 would be sterically disturbed. An average upfield shift of 0.40 ppm was observed for the compounds studied.

Transoid Conformers

If the C-2 monomethyl quinazolinone molecule is assumed to exist in the transoid conformation (the C-2 methyl group being transoid to the ortho position), the solvation around the carbonyl carbon from the side 'transoid' to the ortho substituent would be reduced as compared to the 'cisoid' conformer, because of steric hinderance. The approach of the solvent molecule to the carbonyl carbon from the same side as that of the ortho substituent is still hindered, but less so compared to the 'cisoid' conformer. A weak solvent shell may develope around the carbonyl carbon.



Upon addition of a second methyl group at C-2 which would occupy the cisoid position with respect to the ortho substituent, the solvation around C-4 is expected to be unaffected.

In summary, when the C-2 monomethyl quinazolinone molecule exists in the cisoid conformation, then the addition

of a second methyl group at C-2 is expected to affect the chemical shift of C-4 by changing the extent of solvation. When the C-2 monomethyl quinazolinone molecule exists in the transoid conformation, then the addition of a second methyl group at C-2 would have little effect on the chemical shift of the C-4 carbonyl carbon.

CORRELATION OF CARBON-13 CHEMICAL SHIFTS IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES

CORRELATION OF CARBON-13 CHEMICAL SHIFTS IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES

Carbonyl Carbon Chemical Shifts

The carbon-13 chemical shift values of the C-4 carbonyl carbon atom are shown in Tables IX to XII

The C-4 carbonyl carbon ^{13}C chemical shift values for the 3-aryl-2,3-dihydro-4(1H)-quinazolinones fall into three more or less distinct regions, corresponding to the number of methyl groups at the C-2 position. For compounds where both C-2 substituents are hydrogen, the carbonyl carbon-13 shift values range from 160.83 ppm to 162.23 ppm. The monomethyl compounds range in value from 160.24 ppm to 162.12 ppm, while the carbonyl carbon shifts for the dimethyl compounds occur at 159.84 ppm. On the basis of their stereochemistry, all of the 3-aryl-2,3-dihydro-4(1H)-quinazolinones which have diastereomeric rotamers can be expected to show double peaks for the C-4 carbonyl carbon provided that the chemical shift difference is adequate and the rate of internal rotation is sufficiently slow. Some of the quinazolinones do show the splitting of the C-4 carbonyl carbon signal, for example in compound XIV (Spectrum XXII). The remainder of the quinazolinones did not show the diastereomeric splitting, probably for the following reasons. Firstly, the peaks corresponding to the diastereomeric rotamers may be lost in

the noise. Secondly, the temperature of the probe may have been sufficiently high to cause a collapse of the signals arising from the diastereomeric rotamers, due to fast internal rotation of the 3-aryl group. Finally, the chemical shift differences may have been too small for splitting to be observed.

The observed carbonyl carbon ^{13}C chemical shift values as reported are the net result of various factors. The carbonyl carbon will experience a normal γ effect from the C-2 methyl group. In addition, there will be δ effect contributions from the N-1 substituent and from the 3-aryl group. The latter effects can be expected to be dependent on the stereochemistry of the 3-aryl group. There is also a possibility of a conjugation effect which will be dependent on the stereochemistry of this group, and induction effects of the aryl substituents which will be independent of stereochemistry. Finally, there is a contribution from the solvent effect. The net chemical shift will be the sum of all these effects. These are the variable influences which are altered by changes in substitution patterns.

The Upfield γ-Methyl Substituent Effects on the C-4 Carbonyl Carbon

The observed upfield substituent shifts on the C-4

carbonyl carbon for the addition of a methyl group at C-2 are in the range of -0.2 ppm and -1.0 ppm. Table XXVI shows the upfield γ-methyl substituent effect on the carbon-13 chemical shift values of the carbonyl carbon in 3-aryl-2,3-dihydro-4(1H)-quinazolinones.

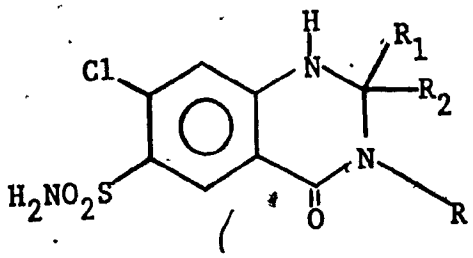
For 3-aryl hydantoins, Williams[44] has reported the observed substituent shift values of the C-2 carbonyl carbons to be -1.0 ppm to -1.2 ppm for the addition of a second methyl group at the C-5 position, for the hydantoins bearing α-naphthyl, o-chlorophenyl, o-trifluromethyl phenyl, or o-tolyl as the 3-aryl group. Icli[17] has reported γ-methyl substitution shifts of -1.1 ppm for 1-aryl hydantoins.

The increased shielding of the C-4 carbonyl carbon with the increase on the number of C-2 methyl groups might be attributed, in part, to the increase in the dihedral angle and decrease in conjugation between the quinazolinone ring and the N-3 aryl group, resulting in an increase in the electron density of the carbonyl carbon.

As mentioned earlier in the discussion on solvent effects, in the cis conformation, the solvent is expected to experience minimal steric perturbation in approaching the carbonyl carbon from the side transoid to the N-3 ortho substituent. The carbonyl carbon would experience effective solvation resulting in further shielding of the C-4 carbonyl

TABLE XXVI

THE UPFIELD γ METHYL SUBSTITUENT EFFECT ON THE ^{13}C CHEMICAL SHIFT VALUES OF THE C-4 CARBONYL CARBON IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



COMPOUND NUMBER	R	R_3	R_2
I	o-TOLYL	CH_3	CH_3
II	o-TOLYL	H	H
VI	o-TOLYL	H	CH_3
XII	o-TOLYL	H	$CO_2C_2H_5$
XIV	o-TOLYL	CH_3	$CO_2C_2H_5$
III	o-C_2H_5-Ø	H	H
XVI	o-C_2H_5-Ø	H	CH_3
IV	α-PYRIDYL	H	H
XXIV	α-PYRIDYL	H	CH_3

TABLE XXVI (cont'd)

THE UPFIELD γ METHYL SUBSTITUENT EFFECT ON THE ^{13}C CHEMICAL SHIFT VALUES OF THE C-4 CARBONYL CARBON IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES

QUINAZOLINONE	CHEMICAL SHIFT DIFFERENCE * ppm
II → VI	- 0.59
VI → I	- 0.40
XII → XIV	- 0.20
III → XVI	- 0.79
IV → XXIV	- 1.00

* negative shift upfield based on TMS convention

carbon. Compounds IV → XXIV, where the N-3 substituent is α-pyridyl, experience a greater γ-methyl substituent effect than the 3-o-tolyl compounds (VI → I). The nitrogen in the pyridyl group, produces by electron attraction, a deficiency of charge in the ring carbon atoms resulting in a greater γ-methyl substitution effect. Compounds XII → XIV, where the C-2 substituent is $CO_2C_2H_5$, experience a small γ-methyl upfield shift compared to compounds II → VI where the C-2 substituents are methyl, possibly due to the electronegativity of the substituent.

Upon addition of a second methyl group to C-2, the γ-methyl substituent effect is reduced from -0.59 to -0.40 ppm, respectively, in the N-3 o-tolyl compound, possibly due to the solvent effect. As mentioned earlier, in the cis conformation, the solvation around the carbonyl carbon by DMSO would be hindered from the side transoid to the ortho substituent, compared to the C-2 monomethyl compound, resulting in a deshielding contribution to the C-4 carbonyl carbon shift.

Icli [17] and Khadim [22] have shown that the γ-methyl substituent shifts for 3-aryl hydantoin carbonyl carbons are relatively insensitive to the polarity of the 3-aryl ortho substituents. In 3-aryl thiohydantoins, the o-tolyl and o-fluorophenyl thiohydantoins have γ-methyl substituent shifts of -3.97 and -3.47 ppm, respectively.

Stothers and Dhami [9] have found that (Table XXVII) both non polar and polar bulky ortho aryl substituents cause deshielding of the carbonyl carbon of methyl aryl ketones. The ortho substituent deshields the carbonyl carbon by up to 4 ppm due to decreasing conjugation associated with an increase in Van der Waals radius of the ortho substituent.

The γ-methyl substituent shift of 3-o-ethyl phenyl-2,3-dihydro-4(1H)-quinazolinone is slightly greater that that for 3-o-tolyl-2,3-dihydro-4(1H)-quinazolinone. This observation cannot be explained using the above arguments.

δ SUBSTITUENT EFFECT ON C-4 CARBONYL CARBON

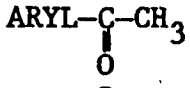
The δ effect will be discussed in two parts, namely, the upfield N-1 methyl substituent effect and the downfield N-3 ortho substituent effect.

The observed upfield N-1 methyl substituent shift on the carbonyl carbon (Table XXVIII) ranges from -0.60 ppm to -0.80 ppm.

Tarples and Goldstein have reported δ effects in uracils E and F.

TABLE XXVII

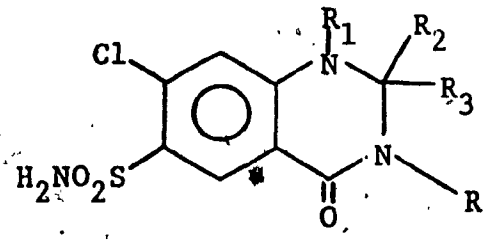
CARBONYL CARBON SHIELDINGS IN SOME KETONES [9,19]



ARYL	CHEMICAL SHIFT (ppm)
PHENYL	196.0
o-METHOXYPHENYL	197.8
o-CHLOROPHENYL	198.7
o-TOLYL	199.3
2,3-DIMETHYLPHENYL	200.6

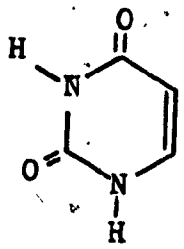
TABLE XXVIII

THE UPFIELD δ METHYL SUBSTITUENT EFFECTS ON THE C-4 CARBONYL CARBON OF SOME 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



COMPOUND NUMBER	R	R_1	R_2	R_3
VI	o-TOLYL	H	H	CH_3
XXI	o-TOLYL	CH_3	H	CH_3
IV	α-PYRIDYL	H	H	H
V	α-PYRIDYL	CH_3	H	H

QUINAZOLINONE	CHEMICAL SHIFT DIFFERENCE (ppm)
VI → XXI	- 0.60
IV → V	- 0.80

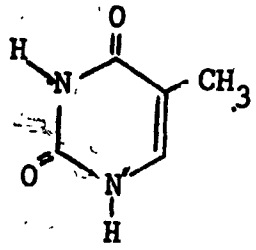


A

C-2

$\delta_{C=O}$ 152.8 ppm

E



B

C-2

$\delta_{C=O}$ 152.3 ppm

F

The 0.5 ppm upfield δ methyl substituent effect observed for uracils, where C-H is replaced by C-CH_3 is of similar magnitude as in the 3-aryl-2,3-dihydro-4(1H)-quinazolinones where N-H is replaced by N-CH_3.

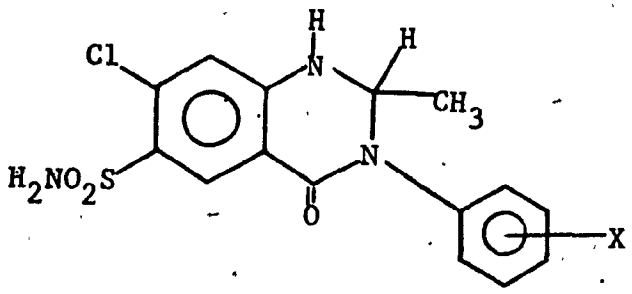
The observed downfield δ effects of the N-3 aryl substituent on the carbonyl carbon chemical shift range from 0.20 to 1.88 ppm, respectively.

On the basis of reports in the literature, the δ effect of the ortho aryl substituent would have been expected to cause an upfield shift on the C-4 carbonyl carbons. The downfield δ effect of N-3 aryl substituents on the carbonyl carbon chemical shifts are shown in Table XXIX.

3-o-Tolyl-2,3-dihydro-4(1H)-quinazolinone (compound VI) is the reference compound used to measure the δ effect of the

TABLE XXIX

DOWNFIELD δ CHEMICAL SHIFT OF CARBONYL CARBON OF 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



COMPOUND NUMBER	X	CHEMICAL SHIFT DIFFERENCE (ppm)
VI	CH_3	0.0
XVI	C_2H_5	0.20
XV	CH_2OH	0.20
XVII	CF_3	1.88
XVIII	2,6-DIMETHYLPHENYL	0.20
XIX	2,4,6-TRIMETHYLPHENYL	0.0
XX	2-METHYL-4-METHOXYPHENYL	0.59
XXIII	m-TOLYL	0.40

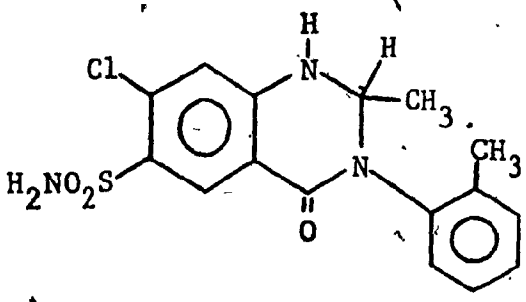
ortho aryl substituent in the series studied.

The C-4 carbonyl carbon chemical shifts are shifted to successively lower fields on replacement of the ortho methyl substituent in the order: C_2H_5 = CH_2OH , CF_3 . Icli[17] and Khadim[22] have observed downfield δ chemical shifts of 0.20 ppm and 0.70 ppm in 1-aryl hydantoins and 3-aryl thiohydantoins.

The ortho substituent is expected to be quite close to the C-2 methyl group. Due to the bulkier ortho aryl substituent, the dihedral angle could be expected to increase because of steric interaction between the C-2 methyl and the N-3 aryl substituent; similarly conjugation between the hetero ring and the aryl ring is expected to decrease. Due to the bulkier ortho aryl substituent, the solvation of the carbonyl carbon by DMSO would be hindered. The net result of the above effects should be to cause a deshielding of the carbonyl carbon. It should be noted that the o-trifluorophenyl C-4 chemical shift is greater (ie more deshielded) than that of either the o-ethyl or the o-CH_2OH phenyl compounds. This can be attributed to the electronegativity of the fluorine atoms which would increase the deshielding of the carbonyl carbon by inductive electron withdrawal.

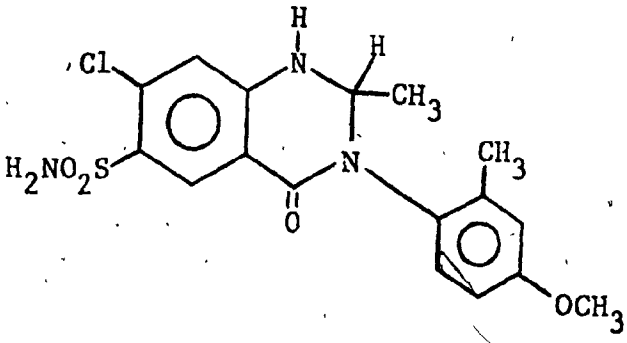
Apart from the steric bulk of the ortho substituent, the electron withdrawing substituent on the aryl ring seems to play an important role in the δ substituent shift values.

The deshielding effects caused by the presence of a polar group on the aryl ring can be examined by comparing the o-tolyl (VI) and 2-methyl-4methoxy phenyl (XX) compounds below. The presence of the methoxy group in the para position deshields the carbonyl carbon by 0.59 ppm compared to the o-tolyl (VI) compound.



VI

$\delta_{C=O}$ 160.24 ppm

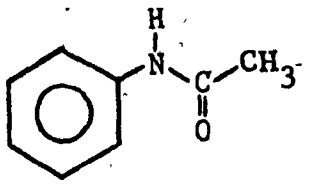


XX

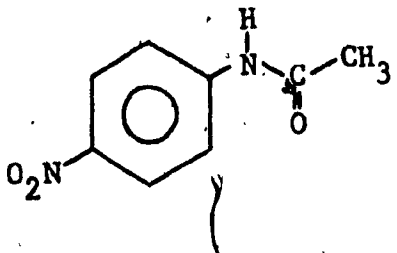
$\delta_{C=O}$ 160.83 ppm

Khadim [22] has reported a similar type of polar aryl substituent effect in 2-methyl-4-nitrophenyl hydantoin, in which the C-2 and C-4 carbonyl carbons are deshielded by 0.55 and 0.83 ppm, respectively, as compared to the corresponding carbonyl carbons in o-tolyl hydantoin.

The environment of the carbonyl carbon in 3-aryl-2,3-dihydro-4(1H)-quinazolinone can be compared to the environment of the carbonyl group in the following substituted acetamides.[29]



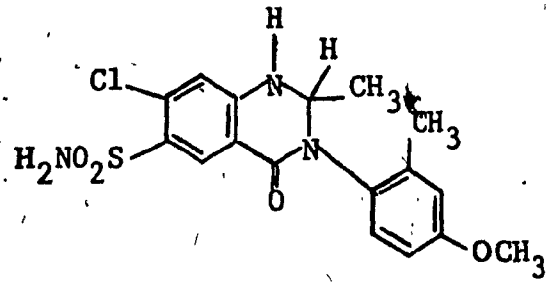
$\delta_{C=O}$ 168.3 ppm



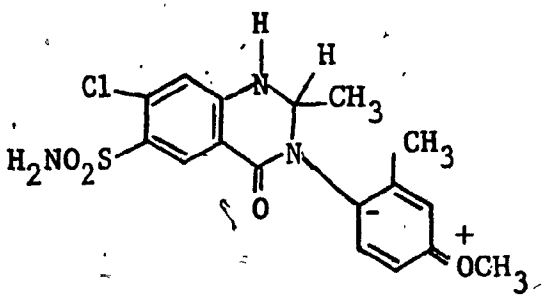
$\delta_{C=O}$ 169.2 ppm

The presence of the nitro group in the para position on the aryl ring deshields the carbonyl carbon in the acetamide by 0.9 ppm. Both resonance and inductive effects may be responsible for the observed deshielding of the carbonyl carbon in substituted acetamides; however the resonance effect would contribute only slightly to the deshielding of the carbonyl carbon in the 3-aryl-2,3-dihydro-4(1H)-quinazolinone, since the aryl and the hetero atom are expected to have a large dihedral angle between them. Although, the presence of the resonance effect is considered to be very small because of the large dihedral angle between the two rings, there is a possibility of resonance contribution to the carbonyl carbon from the resonance structure H in which the inductive effect can influence the carbonyl carbon shielding more forcefully than structure G.

The partial positive charge on H is expected to shield the carbonyl groups, which would imply the reversal of



G



H

direction or the retardation of the inductive effect.

As mentioned previously, the observed chemical shifts are the results of the various effects. Since the carbonyl carbon experiences a net downfield δ effect with the N-3 aryl para methoxy substituent, the solvent effect would be expected to contribute largely to these observstions.

Other Considerations Affecting the C-4 Carbonyl Cabron Chemical Shift

Due to the steric interaction between the ortho substituents of the N-3 aryl group and the substituents at the C-2 and C-4 position of the hetero ring, the aryl group is forced out of co-planarity with the rest of the molecule in

the ground state configuration. It is probable that the dihedral angle between the rings will be affected by the size of the C-2 substituent. These steric effects of the C-2 substituent could be transmitted to the carbonyl group via the 3-aryl group.

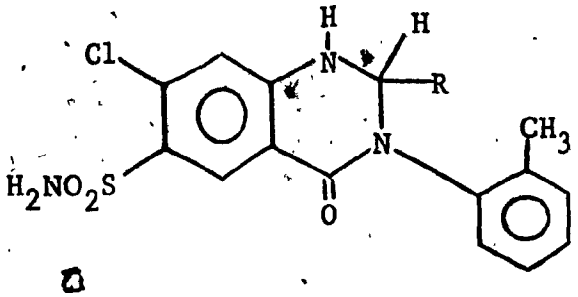
The chemical shifts, relative to 3-o-tolyl-2,3-dihydro-4(1H)-quinazolinone, of various C-2 substituted quinazolinones are shown in Table XXX.

Exchanging a hydrogen for a methyl group in the 2-ethyl compound (VII) does not affect the carbonyl carbon chemical shift. Further substitution to give the 2-isopropyl compound (VIII) causes a slight shielding effect. These data suggest that, since the methyl groups of the isopropyl group are fairly remote from the N-3 o-tolyl group, no steric interaction effects are observed. Exchanging a hydrogen for a chlorine atom causes a slightly shielding δ effect similar in magnitude to the shielding of the isopropyl group. Where two hydrogens have been replaced by two chlorines, the shielding of the carbonyl carbon further increases as expected.

The C-4 carbon signals of compounds XI and XII are shifted downfield. Pearson [33] has observed similar results in ortho substituted toluene compounds and attributed them to inductive effects, but this explanation does not appear to be adequate in the present case.

TABLE XXX

C-2 SUBSTITUENT EFFECT ON CARBONYL CARBON SHIFT IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



COMPOUND NUMBER	R
VI	CH_3
VII	CH_2CH_3
VIII	$CH_2CH_2CH_3$
IX	CH_2Cl
X	$CHCl_2$
XI	CH_2OCH_3
XII	$CO_2C_2H_5$
XIII	PHENYL

QUINAZOLINONE	CHEMICAL SHIFT DIFFERENCE (ppm)
VI + VII	0
VI + VIII	- 0.4
VI + IX	- 0.4
VI + X	- 0.8
VI + XI	+ 0.22
VI + XII	+ 0.79
VI + XIII	0

No chemical shift change was observed for the compound bearing the C-2 phenyl substituent.

Summary

The dominant effects on the shielding of the C-4 carbonyl carbon are obtained with C-2 substitution. Addition of methyl groups to the C-2 carbon results in the shielding of the carbonyl carbon by -0.2 to -1.00 ppm. Changes in the C-2 substitution pattern causes variable influences on the C-4 carbonyl carbon chemical shift.

N-1 methyl substitution causes a shielding of -0.60 to -0.80 ppm of the carbonyl carbon. The δ effect caused by N-3 aryl ortho substituent variation causes the carbonyl carbon to be shielded by 0.2 to 1.88 ppm.

C-2 METHYL CARBON CHEMICAL SHIFTS

The C-2 methyl carbon-13 chemical shift values for the 3-aryl-2,3-dihydro-4(1H)-quinazolinones are given in Tables XX to XXIV. Due to the large variety of substituents, the values cover a broad range from 15.88 ppm to 29.61 ppm.

On the basis of their stereochemistry, all of the 3-aryl-2,3-dihydro-4(1H)-quinazolinones which have diasteriomeric rotamers can be expected to show double peaks for the C-2 methyl carbon signal. Some of the quinazolinones do not show these doublets; however, the reasons the other compounds do not show the doublets have been discussed earlier.

As seen from Table XX, two peaks corresponding to the two C-2 methyls in compound I appear at 27.02 and 28.41 ppm. Since the ortho substituent on the aryl ring is well separated from the C-2 methyl group, non-bonded steric interactions between them is negligible. The effect of the steric crowding on the aryl ring should be transmitted to the C-2 methyl groups via re-orientation of the unsymmetrical solvent shell around the carbonyl carbon.

DMSO is a pyramidal molecule having a non-planar configuration. It is known from ^{1}H NMR measurements that the magnetic anisotropy in such solvent molecules leads to lower field shifts of the solute molecules.[4] The methyl group of

the 2,2'-dimethyl, transoid to the ortho substituent, may be considered as lying in close proximity to the solvent shell around the carbonyl group. Variations in dihedral angles arising from different substituents in the ortho position should give rise to different extents of interaction between the transoid C-2 methyl group and the DMSO solvent shell around C-4. Khadim [22] has determined the magnitude of deshielding of the transoid C-5 methyl carbon in 3-aryl thiohydantoin relative to the o-tolyl thiohydantoin to range from 7.14 to 7.66 ppm. Khadim [22] has shown that transoid C-5 methyl carbon of 3-aryl thiohydantoins is deshielded by approximately 1.2 ppm compared to the cisoid C-5 methyl carbon.

These results were confirmed in this present study where the transoid C-2 methyl carbon is deshielded by approximately 1.4 ppm compared to the cisoid C-2 methyl carbon.

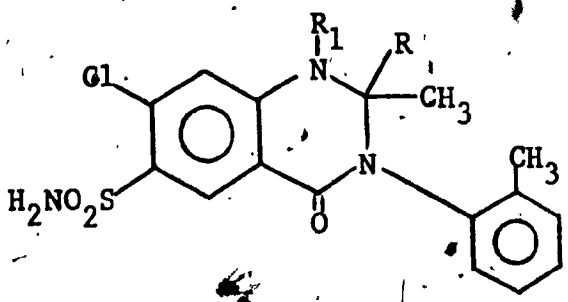
Downfield β-Methyl Substituent Shift Effect on the C-2 Methyl Carbon

The downfield β-methyl substituent shift effect on the C-2 methyl carbon for the addition of a second methyl group on C-2 was found to be 6.16 ppm. (Table XXXI)

Williams [44], Icli [17] and Khadim [22] have found β-methyl

TABLE XXXI

DOWNFIELD β METHYL SUBSTITUENT SHIFTS ON THE C-2 METHYL CARBON IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



COMPOUND NUMBER	R_1	R_2	CHEMICAL SHIFT DIFFERENCE (ppm)
VI	H	H	0
I	H	CH_3	+ 6.16

substituent shifts of 5.70, 4.48 and 7.28 ppm, respectively, for 3-aryl, 1-aryl and 2-thiohydantoins. Grant and Paul [13] have found a β-methyl substituent shift of 7.2 ppm in alkanes.

The downfield shifts of the methyl carbon in the 2,2-dimethyl quinazolinones with respect to the 2-monomethyl quinazolinones, are attributed to dominant through-bond inductive effects.

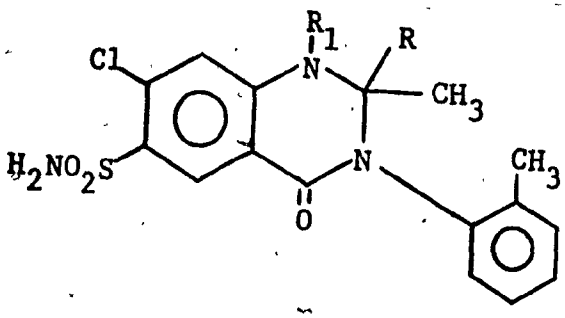
The Upfield γ Substituent Shift on the C-2 Methyl Carbon

The carbon-13 chemical shifts of the C-2 methyl carbons with N-1 substituents are shown in Table XX. As shown in Table XXXII, when the N-1 hydrogen substituent is replaced with a methyl group, an upfield shift of 4.98 ppm is observed, whereas when the N-1 hydrogen is replaced with CH_2-Ø, a 3.98 ppm upfield shift is observed.

Similar upfield γ substituent effects of 2.6 ppm were observed by Lauterbur [26] for substituted anilines. Grant and Paul [13] have observed γ substituent effects of 2.5 ppm in linear alkanes.

TABLE XXXII

UPFIELD γ-SUBSTITUENT SHIFTS ON THE C-2 METHYL CARBON IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLONONES



COMPOUND NUMBER	R_1	R_2	CHEMICAL SHIFT DIFFERENCE (ppm)
VI	H	H	0
XXI	CH_3	H	- 4.98
XXII	CH_2-Ø	H	- 3.98

The ε Upfield Substituent Effect on the C-2 Methyl Carbon

The C-2 carbon-13 chemical shifts of 3-aryl-2,3-dihydro-4(1H)-quinazolinones are shown in Table XXI.

As shown in Table XXXIII, the ε upfield substituent effects of the N-3 aryl ortho substituent on the C-2 methyl signals vary from 0.0 to 0.9 ppm. The C-2 methyl carbon chemical shifts are shifted to successively higher fields in the sequence CH_3 = C_2H_5 ; CH_2OH ; 2,4,6-trimethyl ; 2,6-dimethyl ; and CF_3.

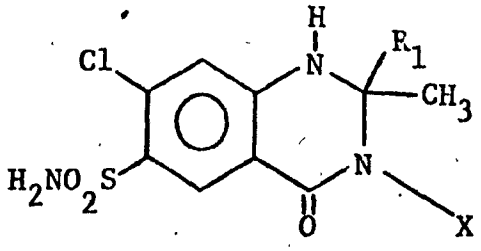
Icli [17] has observed ε upfield shifts of 1.1 ppm in similar compounds. Grant and Paul [13] have determined the ε shielding effect to be + 0.1 ±0.1 in alkanes.

The ε effect in 3-aryl-2,3-dihydro-4(1H)-quinazolinones is attributed to the steric bulk of the N-3 aryl ortho substituent, however solvent effects must also be considered.

Variations in the dihedral angle arising from the variation of the N-3 aryl ortho substituent would give rise to the changes in the degree of solvation of the C-4 carbonyl group. It has been previously shown that an increase in steric bulk of the N-3 aryl ortho substituent causes an increase in the deshielding of the carbonyl carbon, probably caused partly by changes in the degree of solvation. The

TABLE XXXIII

THE ε UPFIELD SUBSTITUENT EFFECT ON C-2 METHYL CARBON IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



COMPOUND NUMBER	R_1	X	CHEMICAL SHIFT DIFFERENCE (ppm)
VI	H	o-TOLYL	0
XV	H	o-CH_2OH-Ø	- 0.40
XVI	H	o-C_2H_5-Ø	0
XVII	H	o-CF_3-Ø	- 0.90
XVIII	H	2,6-DIMETHYLPHENYL	- 0.80
XIX	H	2,4,6-TRIMETHYLPHENYL	- 0.60
XX	H	2-METHYL-4-METHOXYPHENYL	- 0.40
XXIII	H	m-TOLYL	0.0
XXIV	H	α-PYRIDYL	- 0.20
XXV	CH_3	H	+ 8.75

shielding of the C-2 methyl group may also be somewhat dependent on the degree of solvation.

From the data presented in Table XXXIII, it is apparent that the steric bulk of the N-3 aryl ortho substituent and solvent effects are not the sole contributions for the ε effect. The chemical shifts of the C-2 methyl groups are probably somewhat dependent on the conformation of the hetero ring which, in turn, are likely to be affected by changes in substitution patterns. When the N-3 aryl substituent is replaced with hydrogen, a large downfield shift is observed due to the decrease in conjugation, in conjunction with a smaller contribution resulting from the anisotropy of the aryl group.

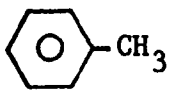
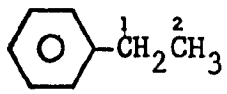
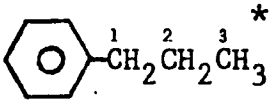
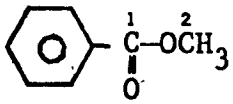
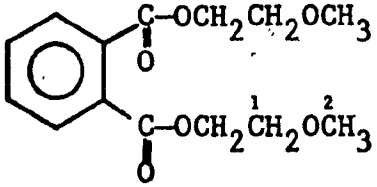
Other Considerations Affecting the C-2 Methyl Carbon

The carbon-13 chemical shifts of various C-2 substituents of 3-(o-tolyl)-2,3-dihydro-4(1H)-quinazolinones are shown in Table XXIV

The chemical shifts of these compounds are compared to model compounds (Table XXXIV). Exchanging a hydrogen for a methyl group in C-2 causes a downfield shift of 6.36 ppm, while further substitution to give the isopropyl substituent vauses a 15.31 ppm downfield shift. The inductive effect

TABLE XXXIV

THE CARBON-13 CHEMICAL SHIFT VALUES OF MODEL COMPOUNDS AND C-2 SUBSTITUENTS IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES

MODEL COMPOUND		CHEMICAL SHIFT (ppm)	C-2 SUBSTITUENT	CHEMICAL SHIFT (ppm)
	*	21.3	CH_3	20.86
	*	^{1} 29.3 ^{2} 16.8	$^1CH_2{}^2CH_3$	^{1} 27.22 ^{2} 18.47
	*	^{1} 38.5 ^{2} 25.2 ^{3} 14.0	$^1CH_2{}^2CH_2{}^3CH_3$	^{1} 36.17 ^{2} 13.50 ^{3} 12.11
CH_4	**	- 2.3	CH_3	20.86
CH_3Cl	**	24.9	CH_2Cl	47.50
CH_2Cl_2	**	54.0	$CHCl_2$	75.34
	*	^{1} 166.8 ^{2} 51.8	$^1CO_2{}^2CH_2{}^3CH_3$	^{1} 169.58 ^{2} 62.01 ^{3} 25.68
	*	^{1} 70.2 ^{2} 58.7	$^1CH_2{}^2OCH_3$	^{1} 69.37 ^{2} 58.63

* Reference 18 ** Reference 28

observed for these compounds is analogous to the α and β effect of 9.1 ppm observed by Stothers [39] and Johnson. [18]

The inductive effects are responsible for the downfield shift observed when the C-2 methyl hydrogens are successively replaced by chlorine groups. The downfield shift observed was 26.6 ppm for the mono chloro and 54.48 ppm for the di-chloro methyl substituent. Similarly, the inductive effect is responsible for the observed chemical shifts due to replacing the methyl hydrogen by OCH_3 and $O_2CH_2CH_3$.

Summary

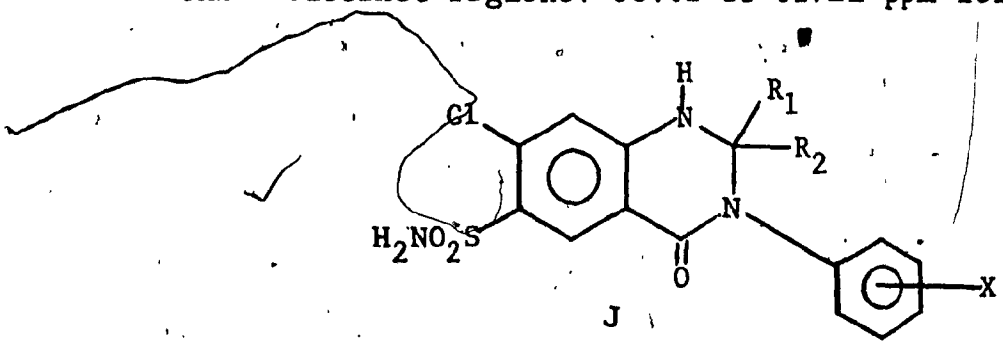
The C-2 methyl carbon lies out of the plane of the hetero ring, thus shielding changes are dominated largely by the steric interaction of the ortho aryl substituent, the β effect of the additional C-2 methyl and the γ effect of the N-1 methyl group.

C-2 CARBON CHEMICAL SHIFTS

The C-2 chemical shift values are shown in Tables V, VI and VII.

Due to the great variety of substituents on the quinazolinone ring, which affect the C-2 chemical shift, the C-2 carbon chemical shift values range from 56.85 ppm to 173.75 ppm.

The chemical shift values of compounds (J) where C-2 substituents are either H and/or methyl groups, fall into three distinct regions: 60.62 to 61.22 ppm for the dihydro



J

compounds, 66.59 to 67.98 ppm for the monomethyl compounds and 72.55 ppm for the dimethyl compounds.

On the basis of their stereochemistry, the C-2 carbon atoms of the diastereomeric rotamers can be expected to show double peaks. However, only a few compounds showed the double peaks for the C-2 carbon (compounds XII, XIV and XX). It is possible that the chemical shift difference between the C-2

carbon atoms in the diastereomeric rotamers is too small for resolution to be possible. The chemical shift differences which were resolvable ranged from 0.2 to 1.99 ppm.

Downfield α-Methyl Substituent Shift on C-2 Carbon

The observed α-methyl substituent shifts on the C-2-carbon for the addition of methyl groups are presented in Table XXXV.

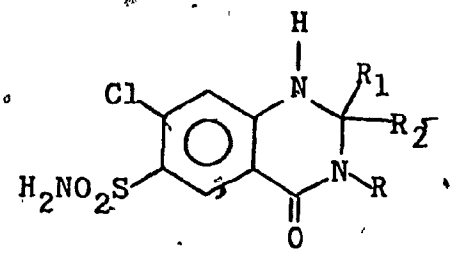
The α-methyl substituent shifts for the addition of one methyl group range in value from 6.16 to 6.95 ppm, while the shift for the addition of two successive methyl groups range from 5.16 to 5.27 ppm.

It should be noted that, as in the case of the downfield β and upfield γ methyl substituent effects, the α-methyl substitution effects as reported in Table XXXV are net effects of various factors, the true α effect being the major one. The variation in the degree of solvation around the carbonyl carbon as well as resonance and inductive effects could also contribute to the observed α-methyl substituent effect. The inductive effect would be the major contribution to the observed α-methyl substituent effect.

The α-substituent shift for the addition of a phenyl group was observed to be 13.12 ppm (compound XIII). This

TABLE XXXV

THE DOWNFIELD α-METHYL SUBSTITUENT EFFECT ON THE CARBON-13 C-2 CHEMICAL SHIFT VALUE IN 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONE



COMPOUND NUMBER	R	R_1	R_2	CHEMICAL SHIFT DIFFERENCE (ppm)
II	o-TOLYL	H	H	-
VI	o-TOLYL	H	CH_3	6.77
I	o-TOLYL	CH_3	CH_3	5.16
III	o-C_2H_5-Ø	H	H	-
XV	o-C_2H_5-Ø	H	CH_3	6.16
IV	α-PYRIDYL	H	H	-
XXIV	α-PYRIDYL	H	CH_3	6.95
XII	o-TOLYL	H	$CO_2C_2H_2$	-
XIV	o-TOLYL	CH_3	$CO_2C_2H_2$	5.27

downfield shift is due to the decrease in electron density on the C-2 carbon together with the contribution from the magnetic anisotropy of the phenyl group. Levy [28] has observed similar substituent values of 13.10 ppm for biphenyl.

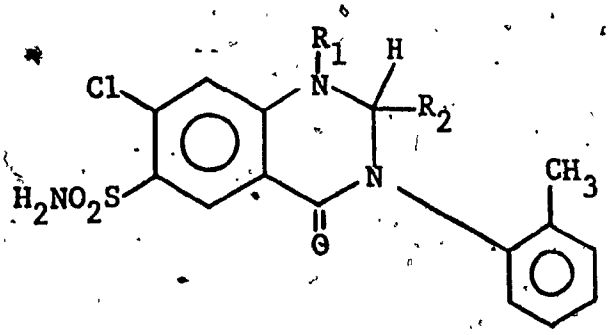
Downfield β-Substituent Shift Effects on C-2 Carbon

The observed β-substitution shift effects of the C-2 carbon are shown in Table XXXVI. The values range from 2.38 ppm to 6.95 ppm and are dependent on the particular C-2 substituent. Model compounds used to compare the observed chemical shift are shown in Table XXXVII.

Exchanging the β hydrogen by a methyl group deshields C-2 by 5.27 ppm to 6.95 ppm. The inductive effect observed for these compounds is analogous to β effects observed by Stothers.[39] When a β hydrogen is replaced ba a chlorine atom (compound IX) a 3.77 ppm downfield shift is observed, while a shift of 6.36 ppm is observed upon further chlorine substitution (compound X). Increasing the electronegativity of the substituent enhances the deshielding of the C-2 nucleus. These results are in agreement with those of the model compounds. The magnitude of the observed shielding differs from those of the model systems due to the different type of compounds involved.

TABLE XXXVI

DOWNFIELD β-SUBSTITUENT EFFECT ON C-2 CHEMICAL SHIFT OF 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONE

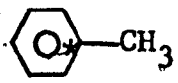
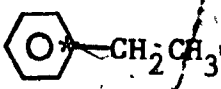
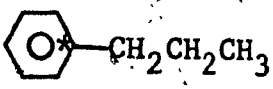
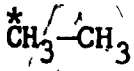
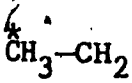
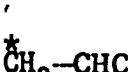
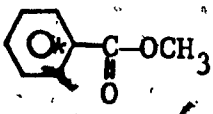
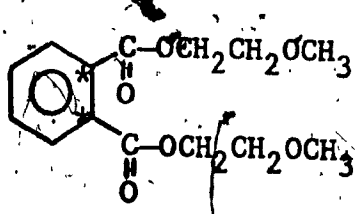
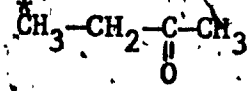


COMPOUND NUMBER	R_1	R_2	CHEMICAL SHIFT DIFFERENCE (ppm)
VI	H	H	-
XXI	CH_3	CH_3	6.11
VII	H	CH_2CH_3	5.17
IX	H	CH_2Cl	3.77
X	H	$CHCl_2$	6.36
XI	H	CH_2OCH_3	5.56
XII	H	$CO_2C_2H_5$	2.38
XIV	CH_3	$CO_2C_2H_5$	5.27 *
V	CH_3	α-PYRIDYL	6.95

* chemical shift of compound - chemical shift of monemethyl compound.

TABLE XXXVII

MODEL COMPOUNDS USED TO COMPARE THE OBSERVED C-2 CHEMICAL SHIFTS

COMPOUND	CHEMICAL SHIFT	CHEMICAL SHIFT DIFFERENCE (ppm)
	137.8 [a]	-
	144.1	6.3
	142.5	4.7
	5.9	0
	39.9	34.0
	62.2	56.3
	130.3	-7.5
	132.0	- 5.8
	45.7	51.6

The inductive effect may also be responsible for the variation in the observed chemical shift between C-2 substituents of CH_2CH_3 , CH_2Cl and $CH_2C_2H_5$ with shifts of 5.17 ppm, 3.77 ppm and 2.38 ppm, respectively. The differences are due to the differences in electronegativity of the particular substituent.

The upfield γ-methyl substituent shift observed for compound VIII, where the C-2 substituent was n-propyl was found to be - 2.00 ppm. This result is consistent with the - 2.5 ppm γ shift in alkanes.[13]

δ Effect on the Chemical Shift of C-2 Carbon

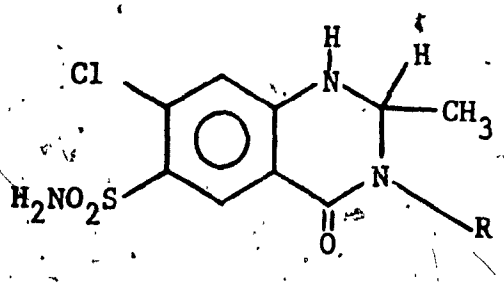
The observed δ chemical shifts of C-2 carbon are shown in Table XXXVIII. The chemical shift values range from - 0.80 to + 0.40 ppm.

Khadim[22], Icli[17] and Williams[44] have reported increasing deshielding effects with increasing bulkiness of the otho substituents in 3-aryl thiohydantoins, 1-aryl hydantoins and 3-aryl hydantoins, respectively. Lauterbur[26] has reported an increasing deshielding effect in N,N-dimethyl anilines as the ortho hydrogen is replaced with a methyl group.

TABLE XXXVIII

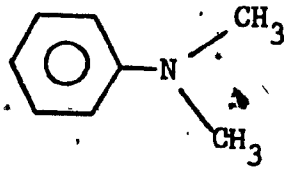
δ CHEMICAL SHIFT ON C-2 CARBON IN

3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES

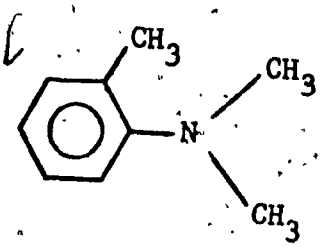


COMPOUND NUMBER	R	CHEMICAL SHIFT DIFFERENCE * (ppm)
VI	o-CH_3-Ø	0
XVI	o-CH_2CH_3-Ø	0
XV	o-CH_2OH-Ø	0.40
XVII	o-CF_3-Ø	0.01
XVIII	2,6-DIMETHYL-Ø	-0.80
XIX	2,4,6-TRIMETHYL-Ø	-0.80
XX	2-METHYL, 4-METHOXY-Ø	0.40
XXIII	m-CH_3	0.40
XXV	H	0.40

* Chemical shift of compound - chemical shift of N-3 o-tolyl compound.



δ_{CH_3} = 41.1 ppm



δ_{CH_3} = 45.2 ppm

The above observations were rationalized by assuming that electron release from the ring to the nitrogen nucleus is reduced in the hindered form, thus increasing the polarization of the N–CH_3 bond.

Both deshielding and shielding were observed for N-3 aryl substituents. As mentioned previously in the discussion on conformation and solvent effects, solvent effects do contribute to the observed shielding. If the inductive effect were the sole contribution to this shielding, then the C-2 carbon chemical shift would follow those shifts observed for C-2 methyl compounds. As mentioned previously under the discussion of the C-4 carbonyl carbon, increasing the steric bulk of the N-3 aryl ortho substituent causes an increase in deshielding of the carbonyl carbon. The steric pressure is transmitted via the N-3 aryl ortho substituent to the C-2 methyl carbon. Thus it is expected that the C-2 carbon would

be deshielded with the increasing size of the N-3 aryl ortho substituent due to steric bulk and solvent effects. However, such factors as electronegativity and resonance effects could contribute to the variance of results.

Summary

The variations in the shielding of the C-2 carbon are dominated largely by α and β effects. The δ effects are quite variable and are expected to contribute little to the overall changes in the C-2 carbon chemical shift.

ARYL CARBONS

The carbon-13 chemical shifts of the aryl carbon in the quinazolinone ring are presented in Table XXXIX. The different N-3 aryl ortho substituent effects the chemical shift of C-2 and C-4, while it has little or no effect on the shielding of the other carbon atoms.

Table XL shows the effect of the chloro and sulfamoyl groups on the chemical shielding of the quinazolinone carbons. The compound where no chloro or sulfamoyl groups are present was not available. The chemical shifts for this compound were calculated using model compounds.

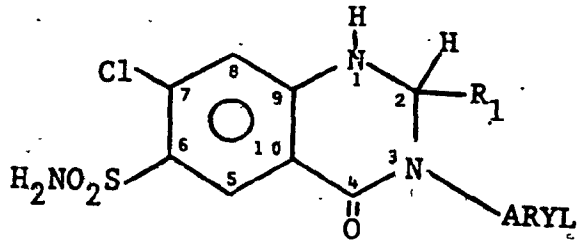
Aryl N-3 Carbon Chemical Shifts

The carbon-13 chemical shifts of the N-3 aryl carbons in 3-aryl-2,3-dihydro-4(1H)-quinazolinones are shown in Table XLI. With the exception of the methoxy carbon atom, all the carbons absorb between 110 and 151 ppm. The methoxy carbon atom absorbs at 158.85 ppm. The aryl carbon shieldings are sensitive to perturbations caused by the electronic effects of the substituents, small variations in shielding or deshielding of the heterocyclic ring could not be detected.

The N-3 nitrogen substituents of the hetero ring

TABLE XXXIX

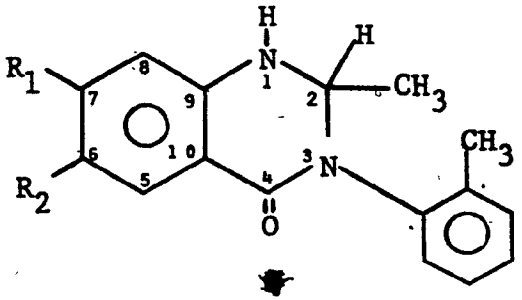
CARBON SHIELDING OF 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



QUINAZ-OLINONE	ARYL	R_1	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10
VI	o-TOLYL	CH_3	60.62	160.83	127.83	142.94	136.97	128.03	135.38	129.82
XVI	o-ETHYL	CH_3	67.38	160.44	127.83	142.54	137.77	128.62	135.78	129.82
XX	2-METHYL 4-METHOXY	CH_3	67.39	160.83	127.83	138.17	136.78	128.42	135.38	129.62

TABLE XL

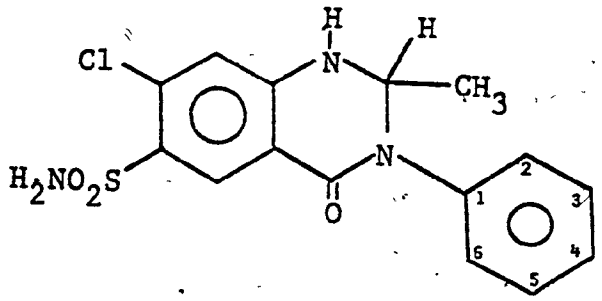
CARBON SHIELDING OF 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



QUINAZOLINONE	R_1	R_2	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10
VI	Cl	SO_2NH_2	60.62	160.83	127.83	142.94	136.97	128.03	135.38	129.82
XXIV	Cl	H	66.59	161.23	130.80	127.63	136.97	126.44	135.38	129.82
Calculated	H	H	62.82	161.23	122.40	126.70	127.50	125.40	135.38	129.82

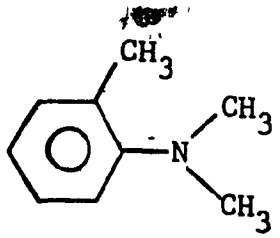
TABLE XLI

ARYL CARBON SHIELDING OF 3-ARYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



QUINAZOLINONE	ARYL	C-1	C-2	C-3	C-4	C-5	C-6
VI	o-TOLYL	150.10	131.01	138.76	116.30	126.83	112.32
XVI	o-ETHYL	150.49	130.21	138.37	116.69	126.63	112.52
XX	2-METHYL 4-METHOXY	150.49	131.01	115.90	158.85	112.12	111.92

reduce the electron density of the C-1 carbon thus it is deshielded to 150.10 ppm in compound VI, for example. Substitution on the phenyl ring either shields or deshields the carbon atom and depends on the electron withdrawing or electron releasing ability of the substituents. The results obtained for compound VI are in agreement with those obtained by Lauterbur [26] for methyl anilines.



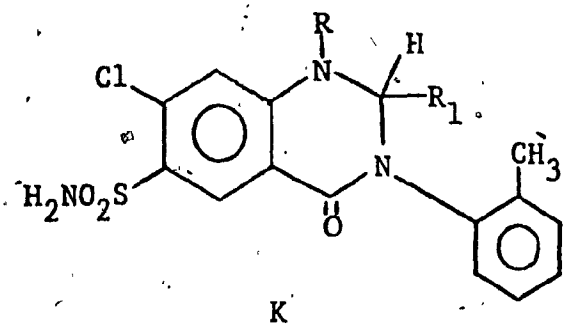
C-1	C-2	C-3	C-4	C-5	C-6
153.0	131.4	131.1	123.1	126.2	118.9

The through bond inductive effects of the C-2 methyl and C-2 substituents were the meaningful correlations which could be made between the aryl carbon chemical shift and the hetero ring substitution.

Carbon Chemical Shifts of Substituent Groups on the N-3 Aromatic Ring

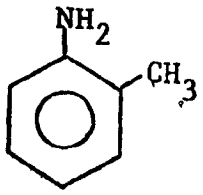
The carbon chemical shift values for the N-3 aryl substituents are shown in Table XVI and XVII.

For the compounds with structure K, the ortho methyl N-3 aryl substituent shift ranges from 14.10 to 18.08 ppm,

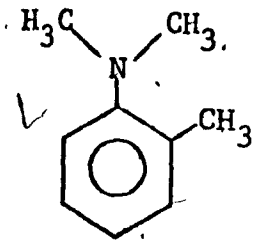


K

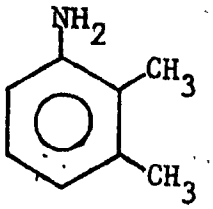
respectively. It can be seen from Table XLII, that an increase in steric bulk of the C-2 substituent does not cause a consistent upfield or downfield shift. Results similar to those which have been observed by Lauterbur [26] for the following methyl substituted anilines might have been expected.



$\delta_{o\text{-}CH_3}$ = 17.3 ppm

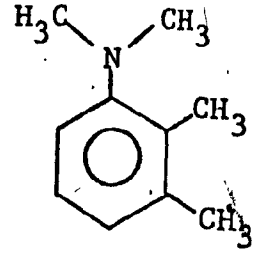


$\delta_{o\text{-}CH_3}$ = 18.5 ppm



$\delta_{o\text{-}CH_3}$ = 12.7 ppm

$\delta_{m\text{-}CH_3}$ = 20.6 ppm



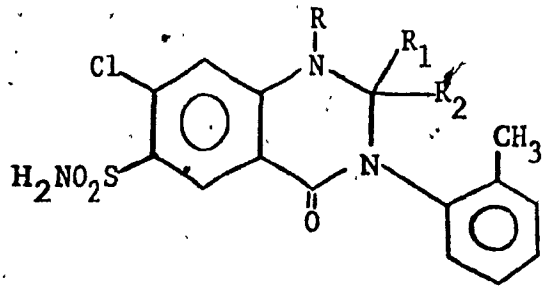
$\delta_{o\text{-}CH_3}$ = 14.1 ppm

$\delta_{m\text{-}CH_3}$ = 20.8 ppm

TABLE XLII

ARYL METHYL CARBON SHIELDINGS OF

3-o-TOLYL-2,3-DIHYDRO-4(1H)-QUINAZOLINONES



COMPOUND NUMBER	R	R_1	R_2	CHEMICAL SHIFT DIFFERENCE * (ppm)
II	H	H	H	- 0.20
VI	H	H	CH_3	0.00
I	H	CH_3	CH_3	0.59
VII	H	H	CH_2CH_3	- 0.20
VIII	H	H	$CH_2CH_2CH_3$	- 0.60
IX	H	H	CH_2Cl	- 0.60
X	H	H	$CHCl_2$	0.20
XI	H	H	CH_2OCH_3	- 0.60
XII	H	H	$CO_2C_2H_5$	- 3.78
XIII	H	H	C_6H_5	- 1.99
XIV	H	CH_3	$CO_2C_2H_5$	- 3.98
XXI	CH_3	H	CH_3	- 0.60
XXII	CH_2-Ø	H	CH_3	- 0.60

* chemical shift of compound - chemical shift of compound VI

compound XVII, where the N-3 ortho aryl substituent is CF_3, that no carbon-13 chemical shift difference was observed for the C-2 methyl carbon atoms of the diastereomers. The chemical shift differences are evidently too small to be observed. A significant rate of internal rotation at the probe temperature may also be a contributing factor.

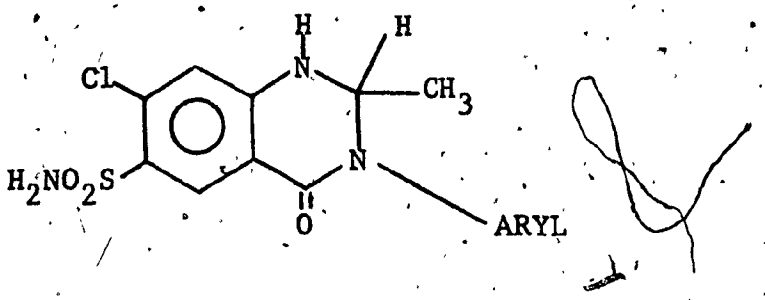
In compound XVII, where the N-3 ortho substituent is CF_3, two distinct peaks at 19.27 and 20.66 ppm are observed with a chemical shift difference of 1.39 ppm.

Rotation about the C-N bond is clearly slow on the NMR time scale in this case. It is not obvious why a chemical shift difference should be observed in this case and not in others.

The chemical shifts and chemical shift differences for the ortho methyl groups of N-3 aryl substituents of diastereomeric rotamers are shown in Table XLVI. The chemical shift difference was found to be 0.40 to 0.60 ppm. The diastereotopic carbons are distingushed from each other due to differences in the interactions with the C-2 and C-4 substituents in the diastereomeric forms. It should be noted that in the case of XIX, which has a symmetrical substitution pattern on the aryl group, rotational isomers do not exist, ie. this is a case of degenerate internal rotation.

TABLE XLVI

CHEMICAL SHIFTS OF ORTHO SUBSTITUENTS OF DIASTEREOMERIC ROTATIONAL ISOMERS



COMPOUND NUMBER	ARYL	CHEMICAL SHIFT (ppm)	CHEMICAL SHIFT DIFFERENCE (ppm)
VI	o-TOLYL	18.07 17.68	0.39
XVI	o-CH_2CH_3-Ø a b	a 23.84 b 14.49 14.89	- 0.40
XIX	2,4,6-TRIMETHYL-Ø	18.07 18.47	0.40

When $R_2 = R_3 = CH_3$, then A will be identical to D and B identical to C and A & B will be enantiomeric with identical spectra in achiral media. However R_2 and R_3 should be in different magnetic environments, therefore the two methyl groups will be expected to have different carbon-13 chemical shifts. The C-2 methyl signal of compound I were found at 28.41 and 27.02 ppm, with a chemical shift difference of 1.39 ppm.

In summary, the C-2 methyl carbons from the diastereomeric rotamers of quinazolinones showed distinguishable peaks in only a single case when the barriers to internal rotation were sufficiently high that rates of rotation were slow at probe temperatures. From pmr line shape analysis, it was shown that the above compounds had low coalescence temperature. [12]

The carbon-13 spectra must have similar coalescence temperatures if the chemical shift differences (in Hz) are similar. It may be concluded that with the one exception noted, the chemical shift differences between diastereotopic C-2 methyl carbon atoms are small.

The enantiomeric rotational isomers of quinazolinones showed distinguishable C-2 methyl peaks as did the N-3 ortho aryl substituents of diastereomeric rotamers; pmr line shape analyses have shown that these carbon atoms have a high coalescence temperature. [12]

It may be concluded from the present carbon-13 NMR study, and previously reported proton NMR data, that carbon-13 NMR spectroscopy is less capable than proton NMR spectroscopy of distinguishing between nuclei in diastereotopic environments in this series of compounds.

UNSATURATED 4(3H)-QUINAZOLINONES

The 3-aryl-4(3H)-quinazolinone compounds were prepared in order to determine the effects that unsaturation would have on the C-2 and C-4 chemical shifts.

The C-2 carbon chemical shifts are shown in Table VIII. The values range from 147.5 ppm to 147.35 ppm.

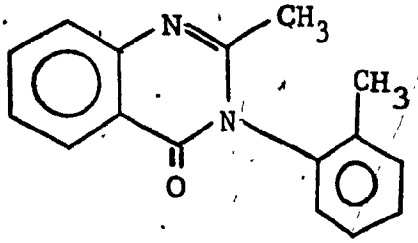
The C-4 carbon chemical shifts are shown in Table XII. The values range from 160.80 ppm to 160.44 ppm.

It should be noted that the unsaturated system does not show the variation in chemical shift of the C-2 and C-4 carbons with variation in the N-3 aryl substituents as do the saturated systems. The variation in the C-4 carbonyl chemical shielding is due mainly to the bulkiness of the N-3 aryl substituents. The different substituents on the N-3 aryl ring do not seem to cause any substantial changes in the C-4 carbonyl carbon chemical shielding in 3-aryl-4(3H)-quinazolinones.

The C-2 chemical shift of the 3-aryl-4(3H)-quinazolinone is shifted downfield compared to the 3-aryl-4(1H)-quinazolinone compounds (Table XLVII). These results are comparable to those observed for the alkene vs alkane system.

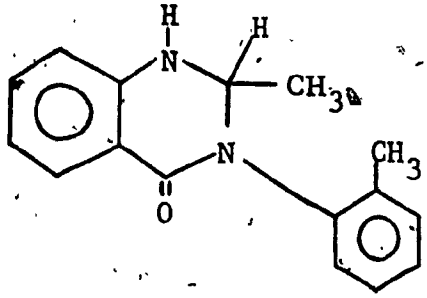
TABLE XLVII

COMPARISON BETWEEN C-2 & C-4 CARBON CHEMICAL SHIELDING IN 3-ARYL-4(3H)-QUINAZOLINONES AND 3-ARYL-[illegible](1H)-QUINAZOLINONES



C-2 147.51 ppm

C-4 160.83 ppm



C-2 67.38 ppm

C-4 160.24 ppm

It is interesting to note the lack of variation of chemical shift in the 3-aryl-4(3H)-quinazolinone compounds compared to the saturated 3-aryl-2,3-dihydro-4(1H)-quinazolinones. The different behavior of the two groups of compounds could result in part from the increased rigidity of the hetero ring of the less saturated compound. The hetero ring of the dihydro compounds must be flexible. Perhaps conformational changes in this ring in response to changes in substituents are partly responsible for chemical shift changes.

In summary, 3-aryl-4(3H)-quinazolinones show little variation in chemical shift for different substituents on the N-3 aryl ring. The lack of variation in chemical shift is probably due to the rigidity of the hetero ring.

CONCLUSION

CONCLUSION

For the series of 3-aryl-6-sulfamoyl-7-chloro-1,2,3,4-tetrahydro-4(1H)-quinazolinones and 3-aryl-4(3H)-quinazolinones studied, the carbon-13 chemical shift values for a given carbon position were found and substituent effects were examined.

The C-4 carbonyl carbon chemical shift values vary from 160.24 ppm to 162.23 ppm. The chemical shifts are influenced by the degree of solvation around C-4, the δ effects and the steric bulk of the N-3 aryl substituent. A mean value of 0.60 ppm was found for the additive γ methyl shift parameter.

The C-2 methyl carbon chemical shifts vary from 15.88 ppm to 27.32 ppm. Variation in the chemical shifts are introduced by the β effect of the C-2 substituent, the γ effect of the N-1 substituent, and the ε effect of the N-3 aryl ortho substituent. A mean value of 6.16 ppm was found for the additive β methyl shift parameter.

The chemical shifts of other C-2 substituents vary over a range of 12.11 ppm to 170.18 ppm and are dependent upon the particular substituent. For example, the chemical shift of $\underline{C}H_2Cl$ was found to be 47.50 ppm while the carbon chemical shift of $\underline{C}O_2C_2H_5$ was found to be 169.58 ppm. The C-2

substituent values are influenced by the α effect and the ε effects of the N-3 aryl substituents.

The C-2 carbon chemical shifts range from 60.62 ppm to 73.75 ppm. Variations in the chemical shieldings are produced by the α and β substituents. The α methyl additive shift parameter was found to be 5.88 ppm and the β substituent additive shift parameter was found to be 6.11 ppm.

The N-3 aryl substituent shifts vary over a larger range from 14.10 to 116.69 ppm. The values depend largely upon the substituent, for example the chemical shift of o-$\underline{C}H_3$ was found to absorb at 17.88 ppm while the chemical shift of o-$\underline{C}F_3$ was found to be 116.69 ppm. The N-3 aryl substituent carbon shieldings are influenced by the ε effect of the C-2 substituents.

The N-3 aryl carbon chemical shifts vary from 110 to 151 ppm. Aryl carbon shieldings are most sensitive to the perturbations caused be electronic effects of the substituents. The signals of the strongly deshielded aromatic carbons bonded to the methoxy group absorb at 158.85 ppm.

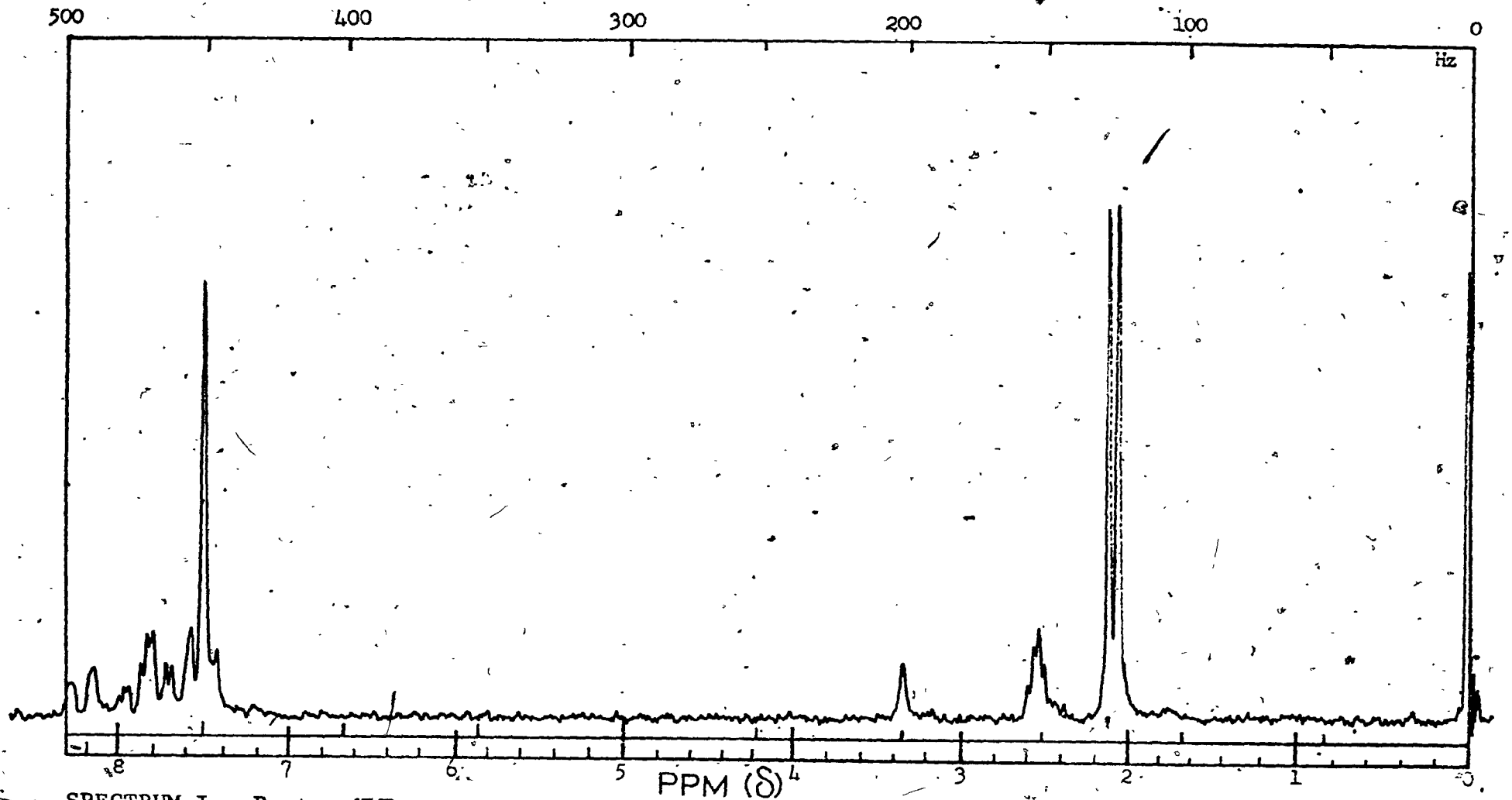
The aryl carbon atoms in the quinazolinone ring absorb over the range of 60.62 ppm to 142.9 ppm. The most prominent signals are observed for the aromatic carbons bound to chlorine and sulfamoyl groups which absorb at 136.9 and 142.9

ppm, respectively. Quaternary carbons are distinguished from the other aromatic carbons due to decrease in intensity caused by larger relaxation times and possibly by Overhauser effects and absorb at 129.82 (C-10) and 135.38 ppm (C-9).

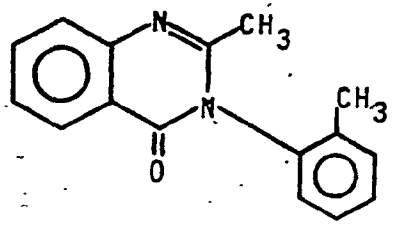
The carbon chemical shift of the quinazolinone rings in 3-aryl-4(3H)-quinazolinones range from 120.43 to 160.83 ppm. The major difference observed between 3-aryl-4(3H)-quinazolinones and 3-aryl-4(1H)-quinazolinones is seen in the C-2 chemical shift from 60.62 ppm in the 4(1H)-quinazolinone to 145.83 ppm in the 4(3H)-quinazolinones. Carbon chemical shifts in this series of compounds show little sensitivity to the effects of substituents.

APPENDIX I

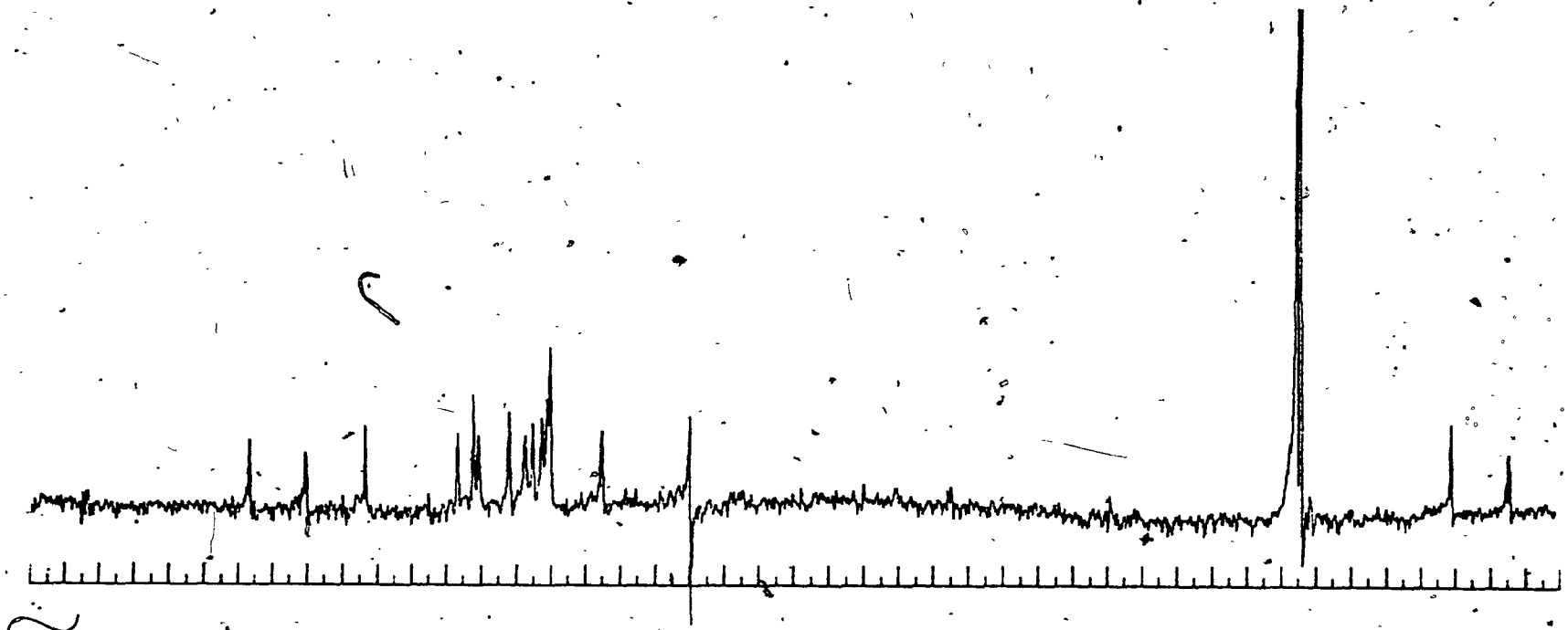
^{1}H NMR AND ^{13}C NMR SPECTRA



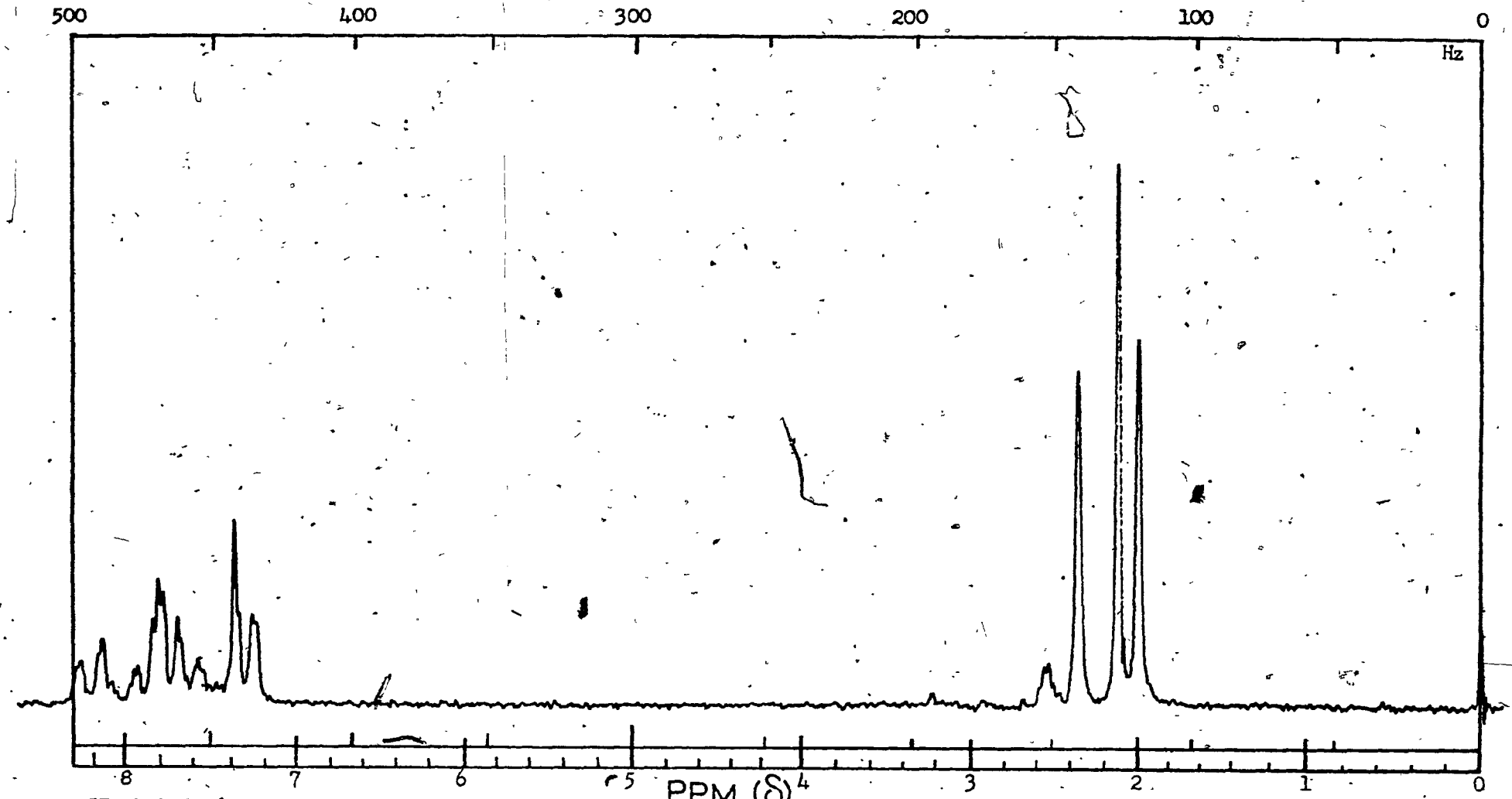
SPECTRUM I Proton NMR spectrum of 2-methyl-3(o-tolyl)-4(3H)-quinazolinone (XXIX) in DMSO-d_6 solution (500 Hz scan)



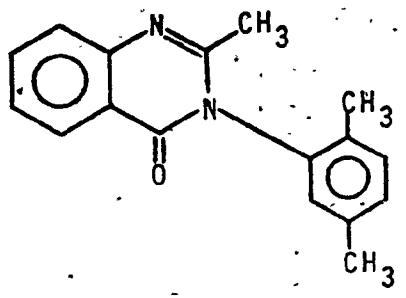
Sample	OTQ
Solvent	DMSO
Lock	Solvent
AF	11000 Hz
LF	6750 Hz
NB	8
NS	512
PD	1
SI	100 µsec



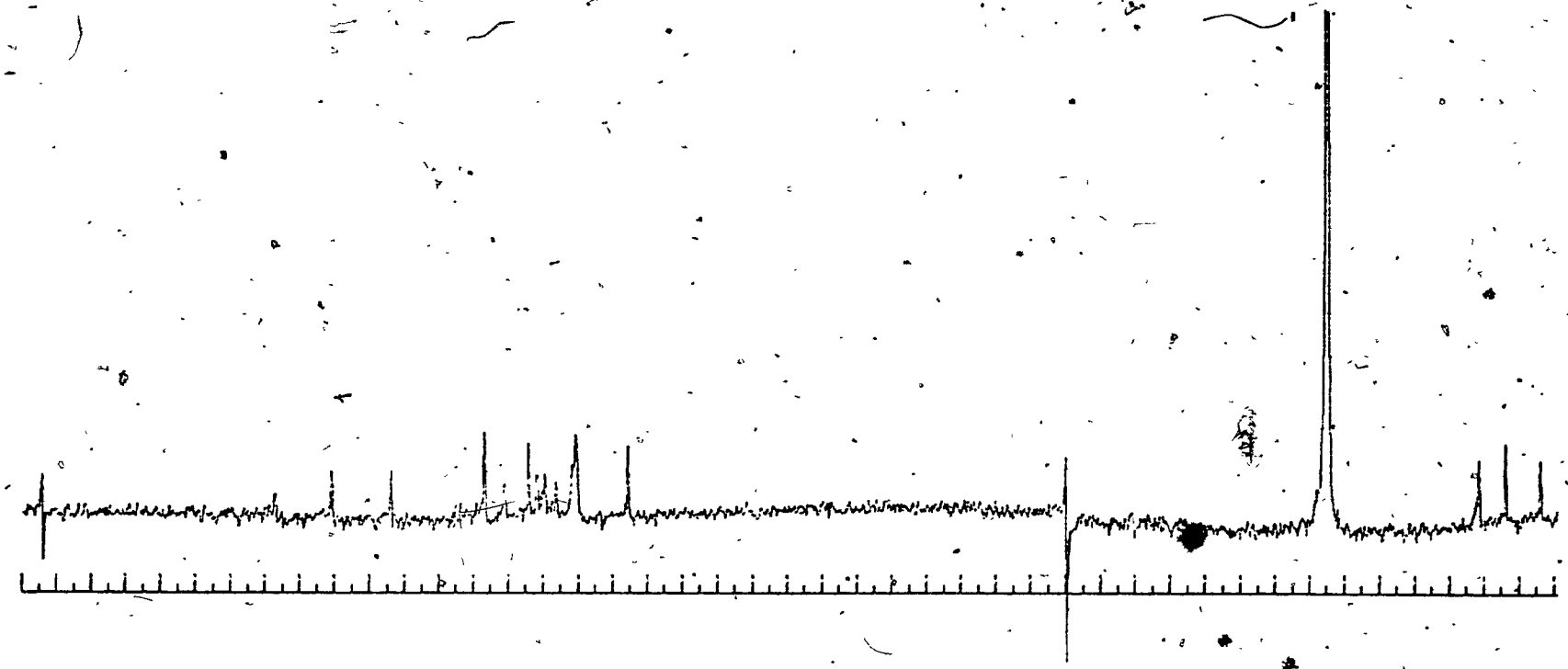
SPECTRUM II Carbon-13 spectrum of 2-methyl-3(o-tolyl)-4(3H)-quinazolinone (XXIX) in DMSO solution (5000 Hz scan)



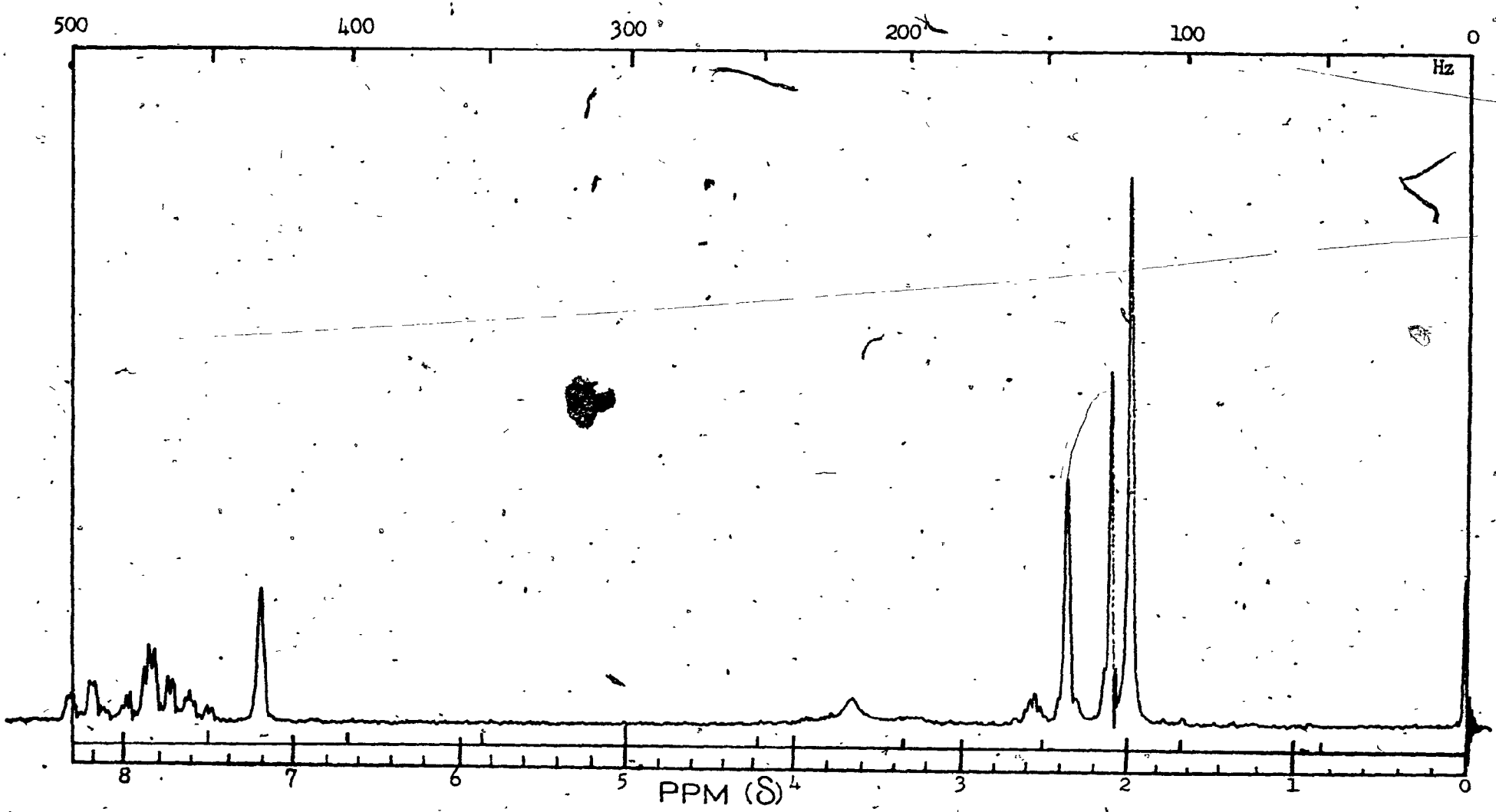
SPECTRUM III Proton NMR spectrum of 2-methyl-3(2,5-dimethyl phenyl)-4(3H)-quinazolinone (XXX) in DMSO-d_6 solution (500 Hz scan)



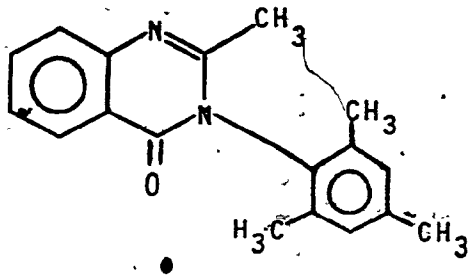
Sample	DMQ
Solvent	DMSO
Lock	Solvent
AF	11000 Hz
LF	6750 Hz
NB	8
NS	516
PD	1
SI	100 µsec



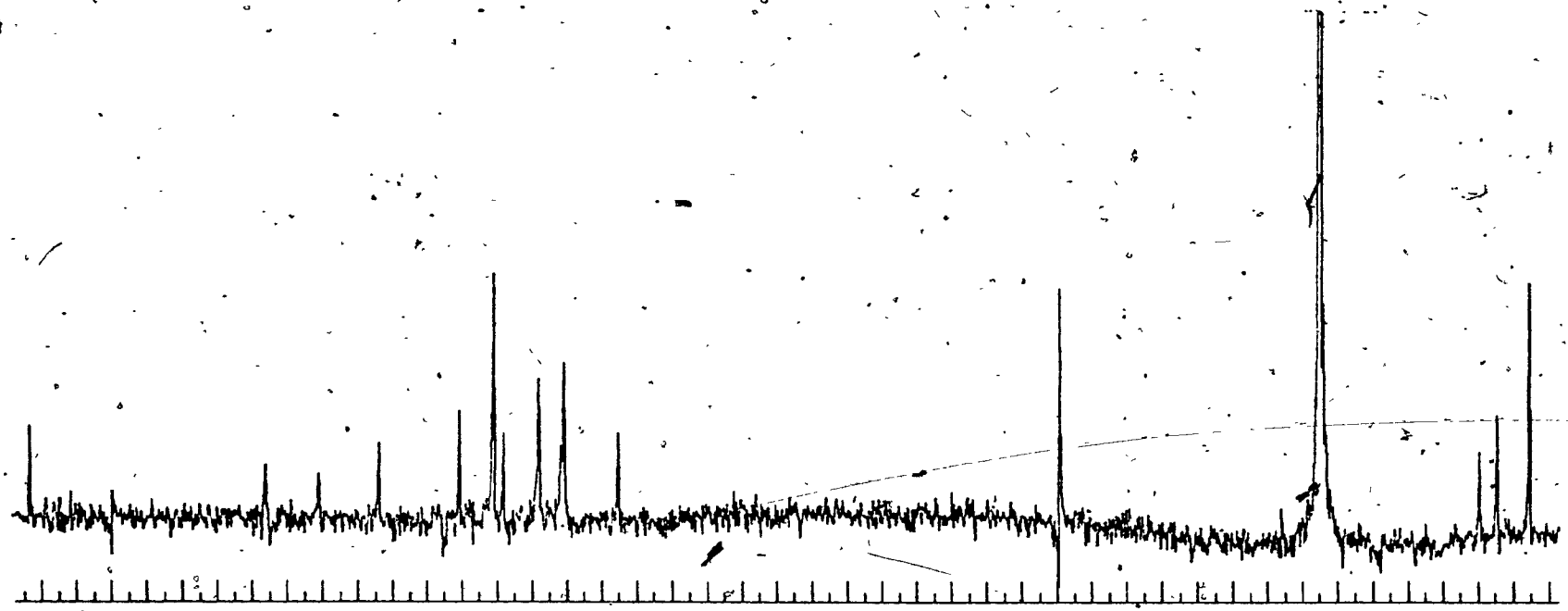
SPECTRUM IV Carbon-13 spectrum of 2-methyl-3(2,5-dimethyl phenyl)-4(3H)-quinazolinone (XXX) in DMSO solution (5000 Hz scan)



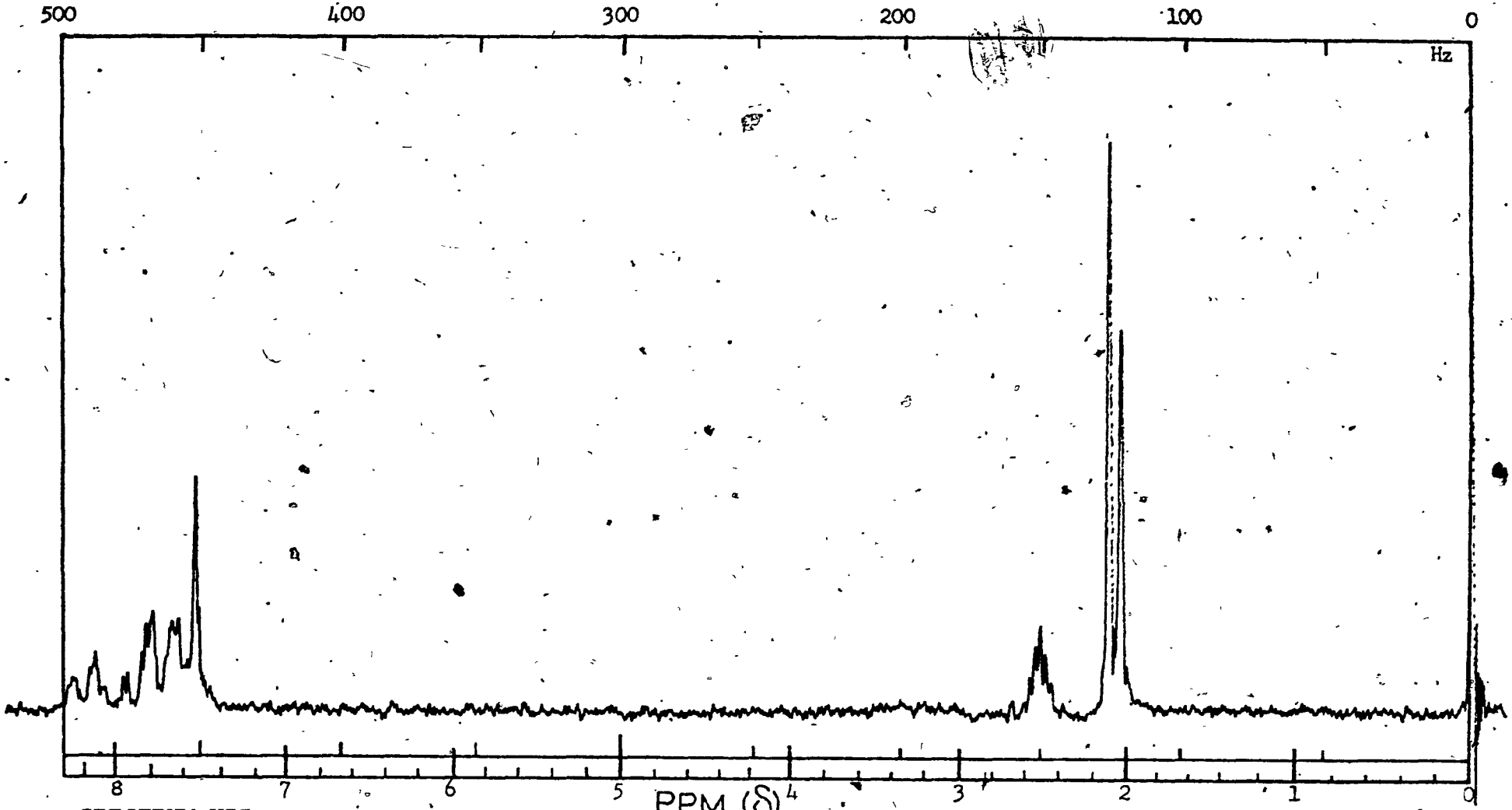
SPECTRUM V Proton NMR spectrum of 2-methyl-3(2,4,6-trimethyl phenyl)-4(3H)-quinazolinone (XXXI) in DMSO-d_6 solution (500 Hz scan)



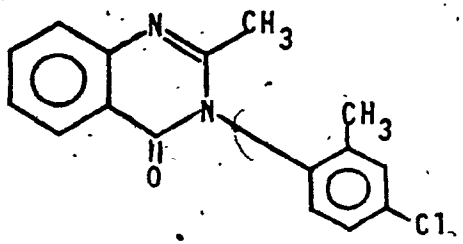
Sample	TMQ
Solvent	DMSO
Lock	Solvent
AF	10500 Hz
LF	6752 Hz
NB	8
NS	512
PD	1
SI	100 µsec



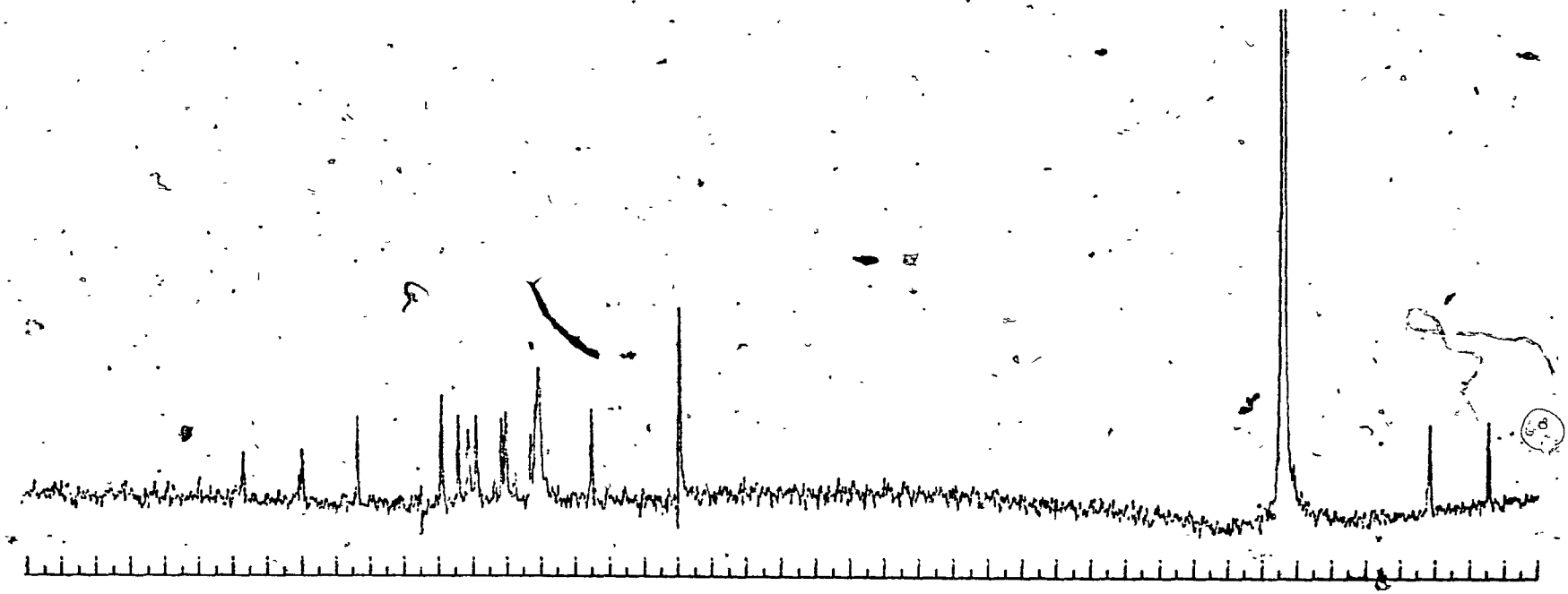
SPECTRUM VI Carbon-13 spectrum of 2-methyl-3(2,4,6-trimethyl phenyl)-4(3H)-quinazolinone (XXXI) in DMSO solution (5000 Hz scan)



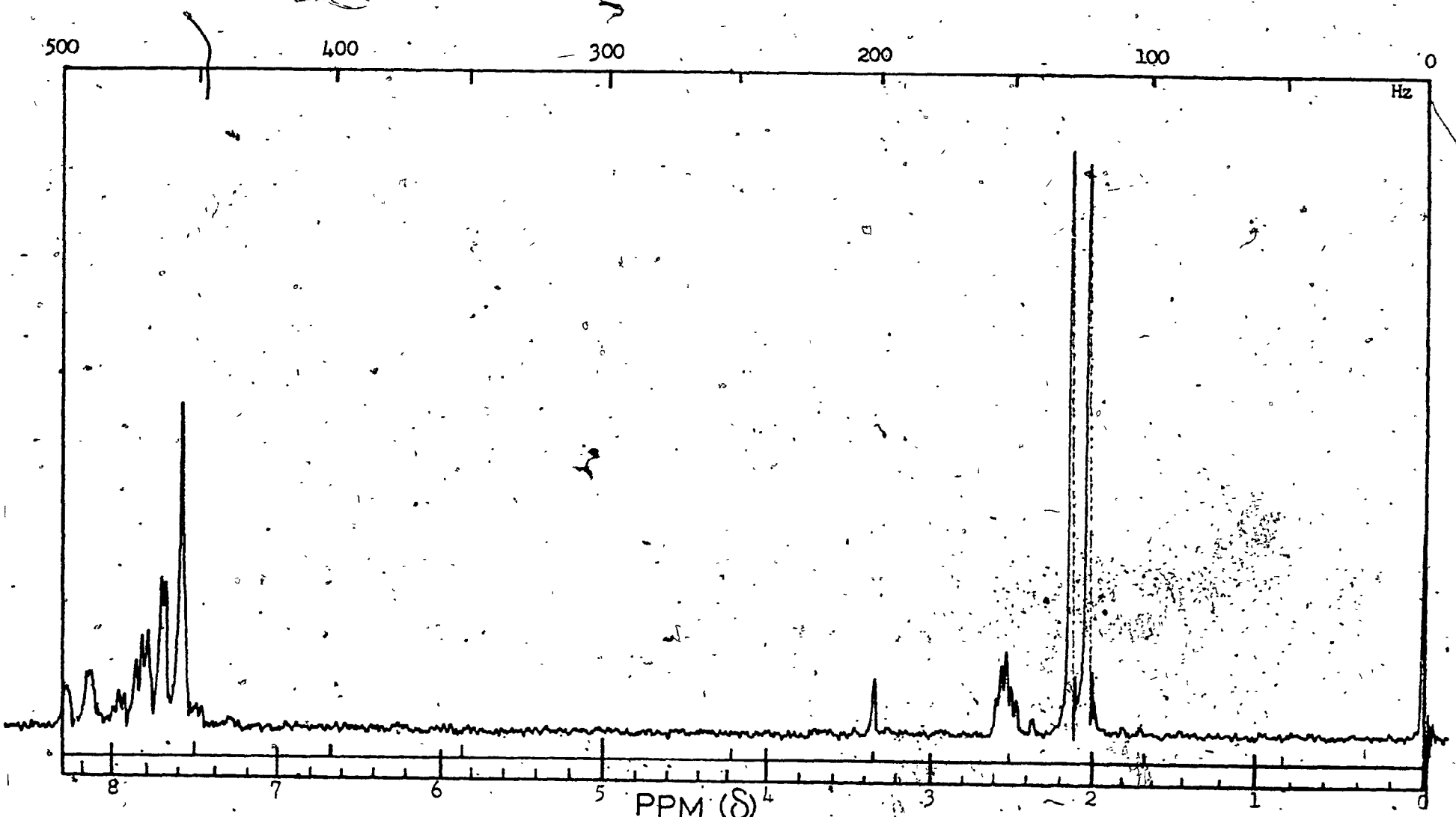
SPECTRUM VII Proton NMR spectrum of 2-methyl-3(4-chloro-2-methyl phenyl)-4(3H)-quinazolinone (XXXII) in DMSO-d_6 solution (500 Hz scan)



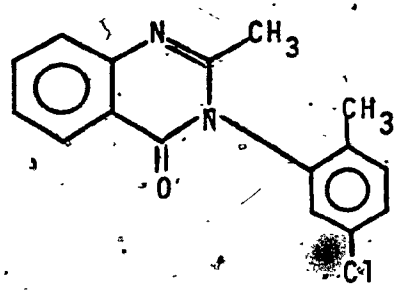
Sample	4-CMQ
Solvent	DMSO
Lock	Solvent
AF	10500 Hz
LF	6750 Hz
NB	8
NS	512
PD	1
SI	100 µsec



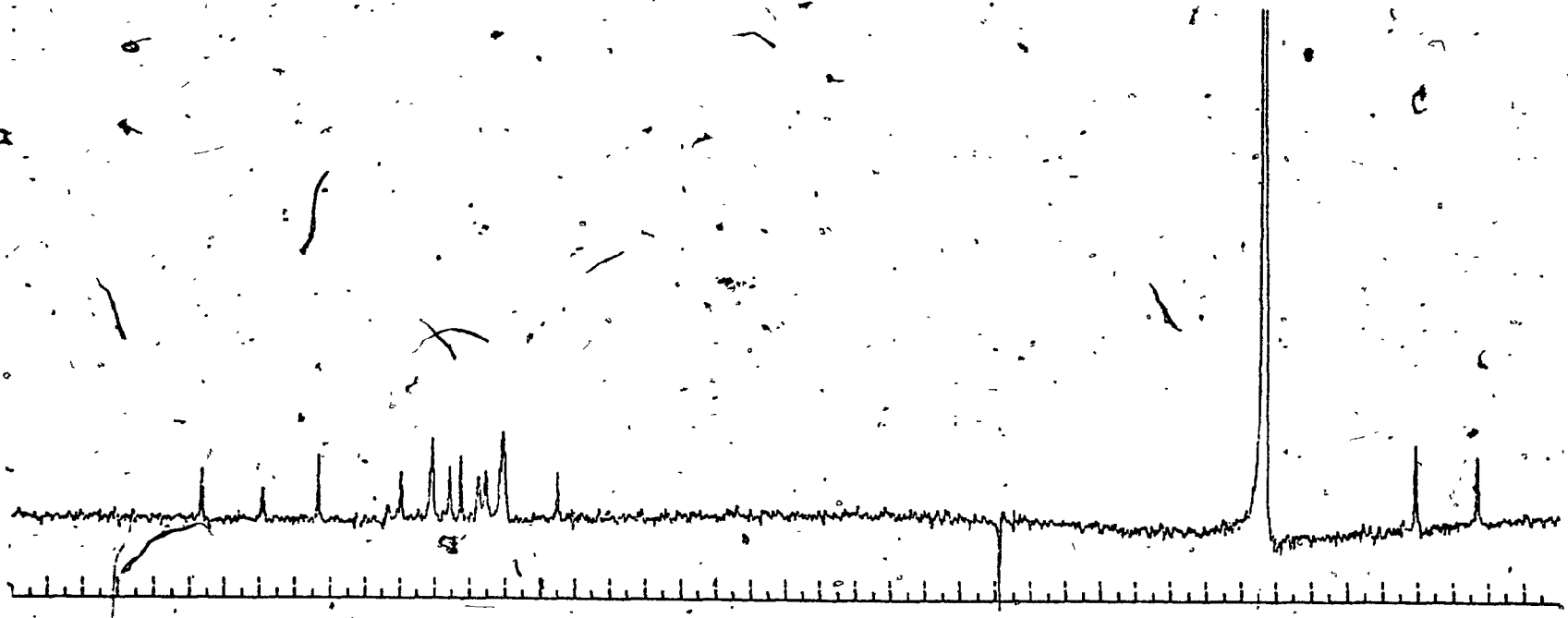
SPECTRUM VIII Carbon-13 spectrum of 2-methyl-3(4-chloro-2-methyl phenyl)-4(3H)-quinazolinone (XXXII) in DMSO solution (5000 Hz scan)



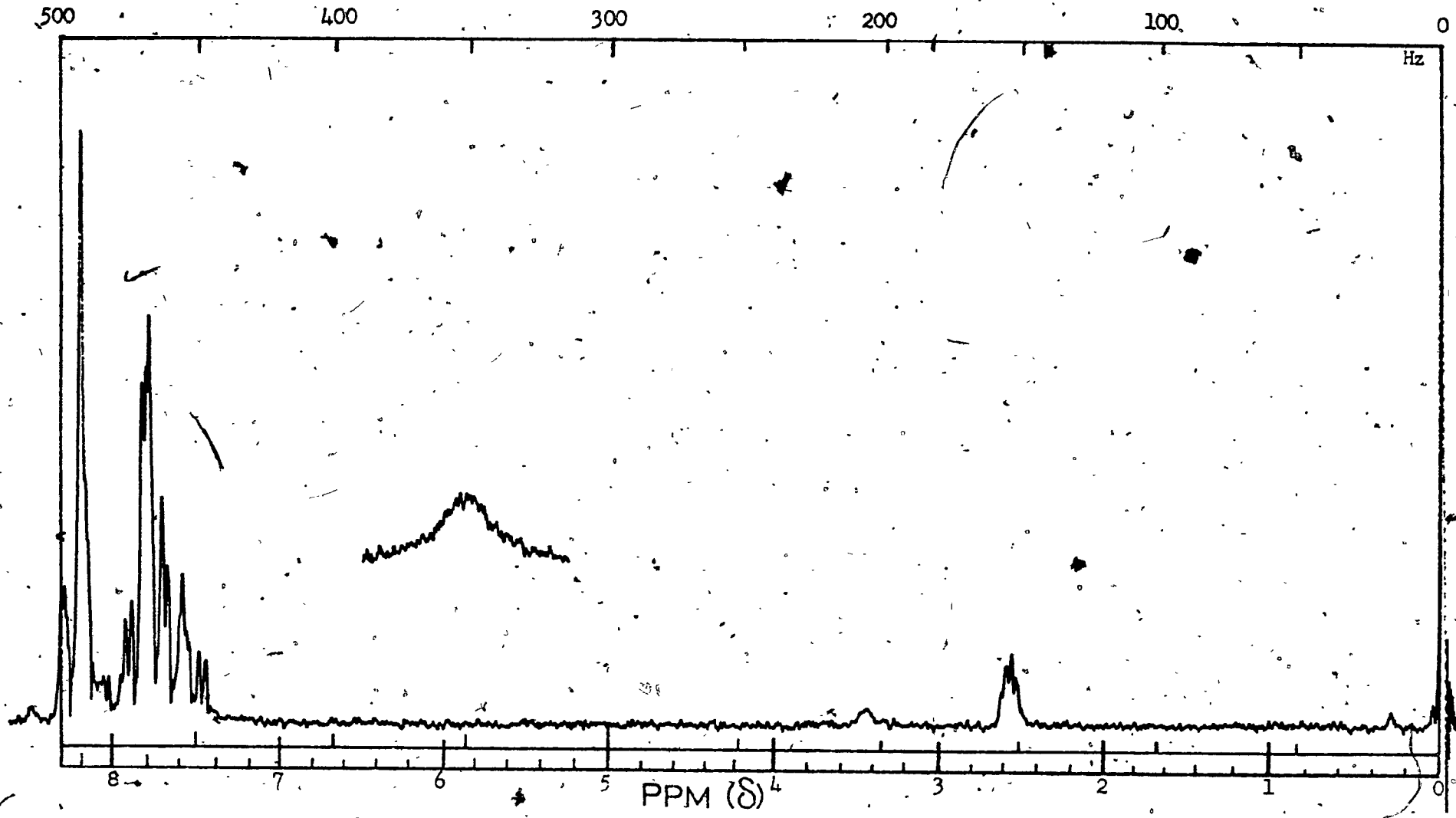
SPECTRUM IX Proton NMR spectrum of 2-methyl-3(5-chloro-2-methyl phenyl)-4(3H)-quinazolinone (XXXIII) in DMSO-d_6 solution (500 Hz scan)



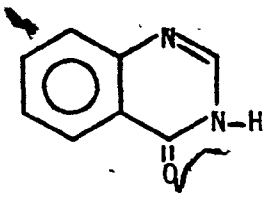
Sample	5-CMQ
Solvent	DMSO
Lock	Solvent
AF	10500 Hz
LF	6750 Hz
NB	6
NS	512
PD	1
SI	100 μsec



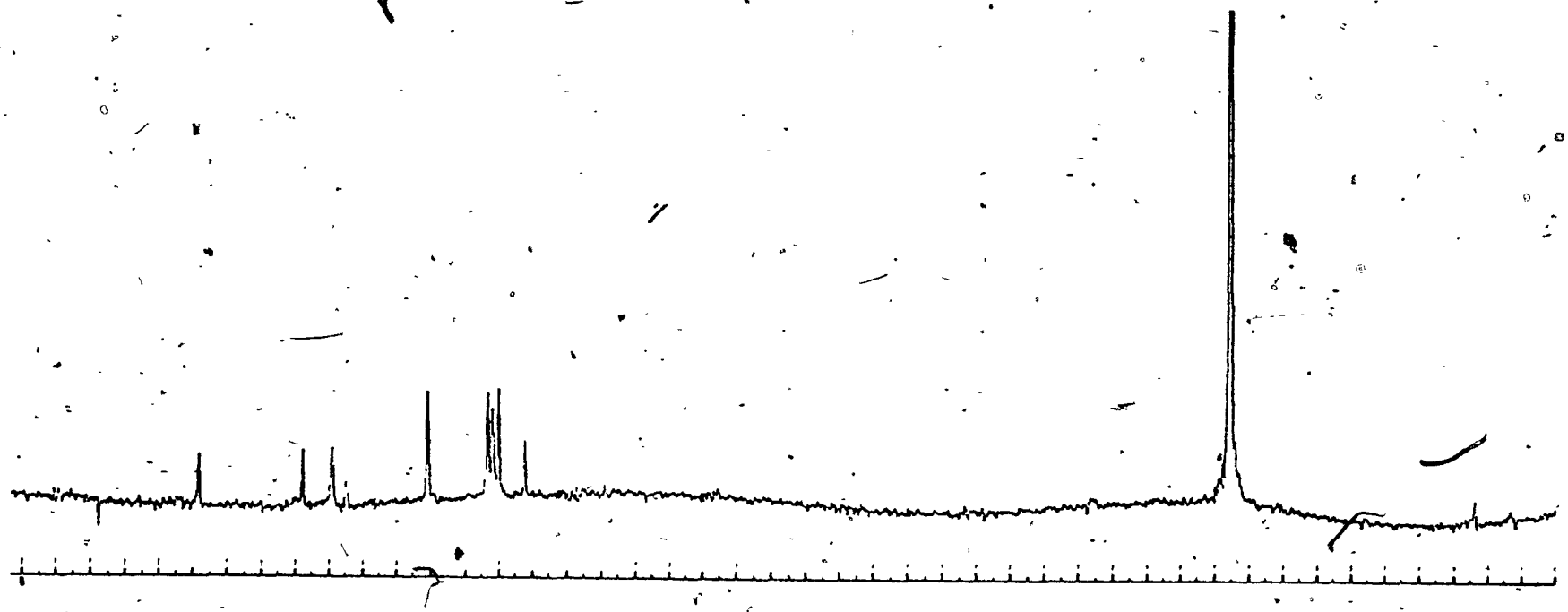
SPECTRUM X Carbon-13 spectrum of 2-methyl-3(5-chloro-2-methyl phenyl)-4(3H)-quinazolinone (XXXIII) in DMSO solution (5000 Hz scan)



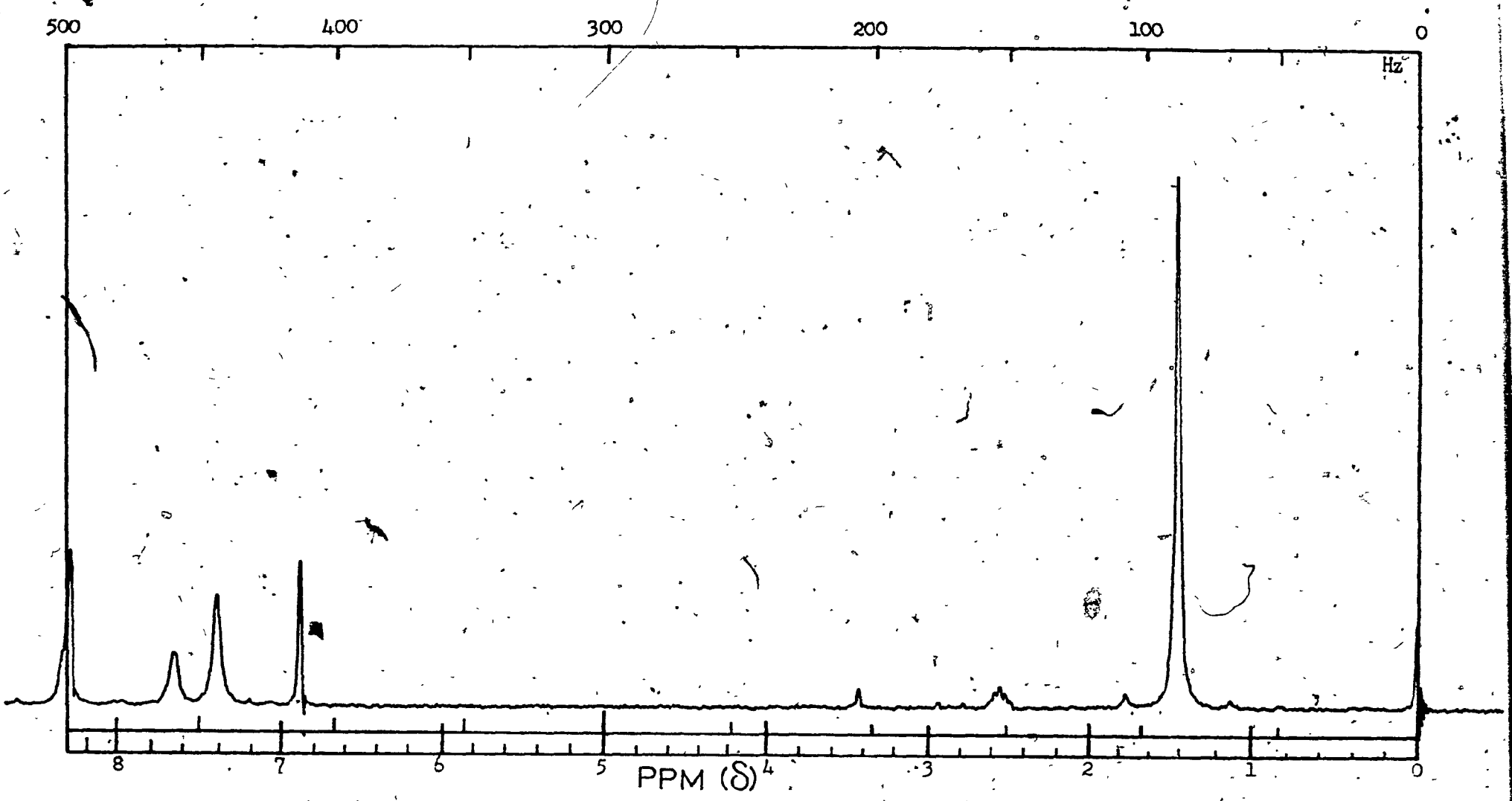
SPECTRUM XI Proton NMR spectrum of 2,3-dihydro-4(3H)-quinazolinone (XXVII) in DMSO-d_6 solution (500 Hz scan)



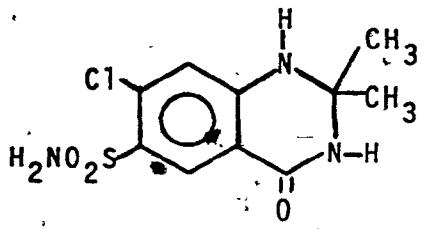
Sample	'D'
Solvent	DMSO
Lock	Solvent
AF	8800 Hz
LF	4760 Hz
NB	8
NS	512
PD	1
SI	100 usec



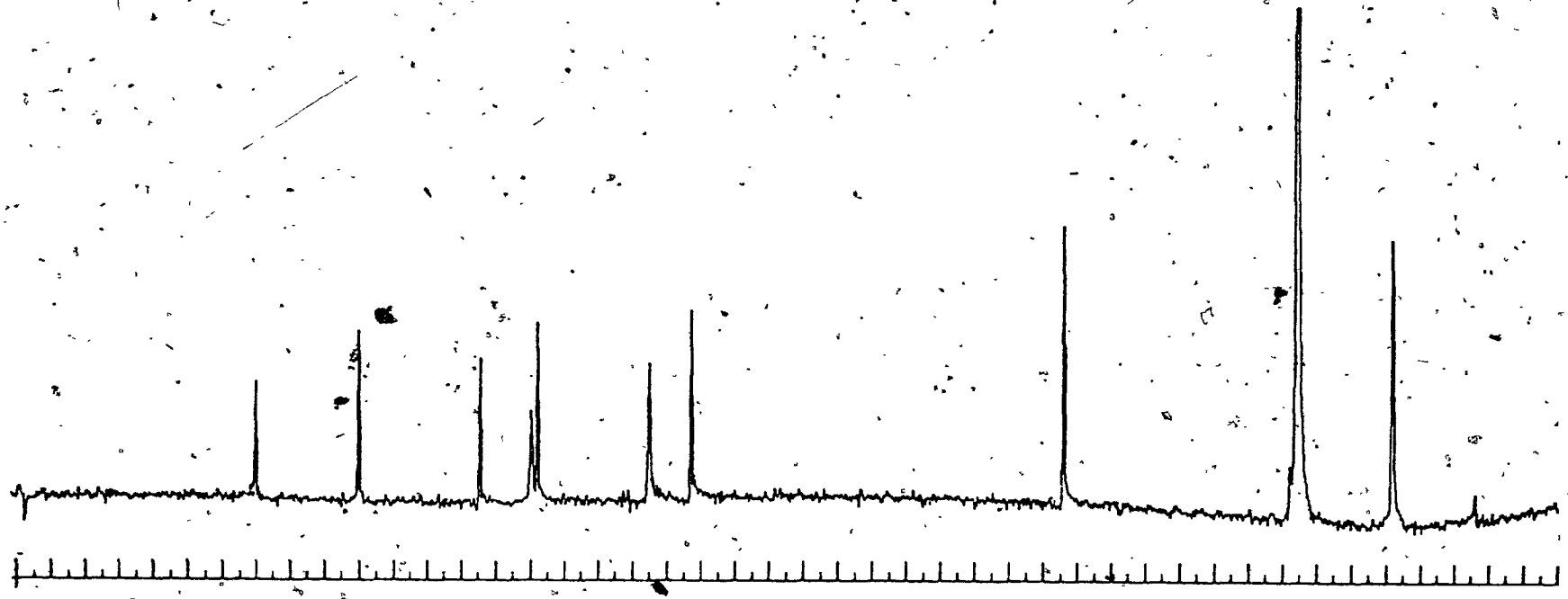
SPECTRUM XII Carbon-13 spectrum of 2,3-dihydro-4(3H)-quinazolinone (XXVII) in DMSO solution (5000 Hz scan)



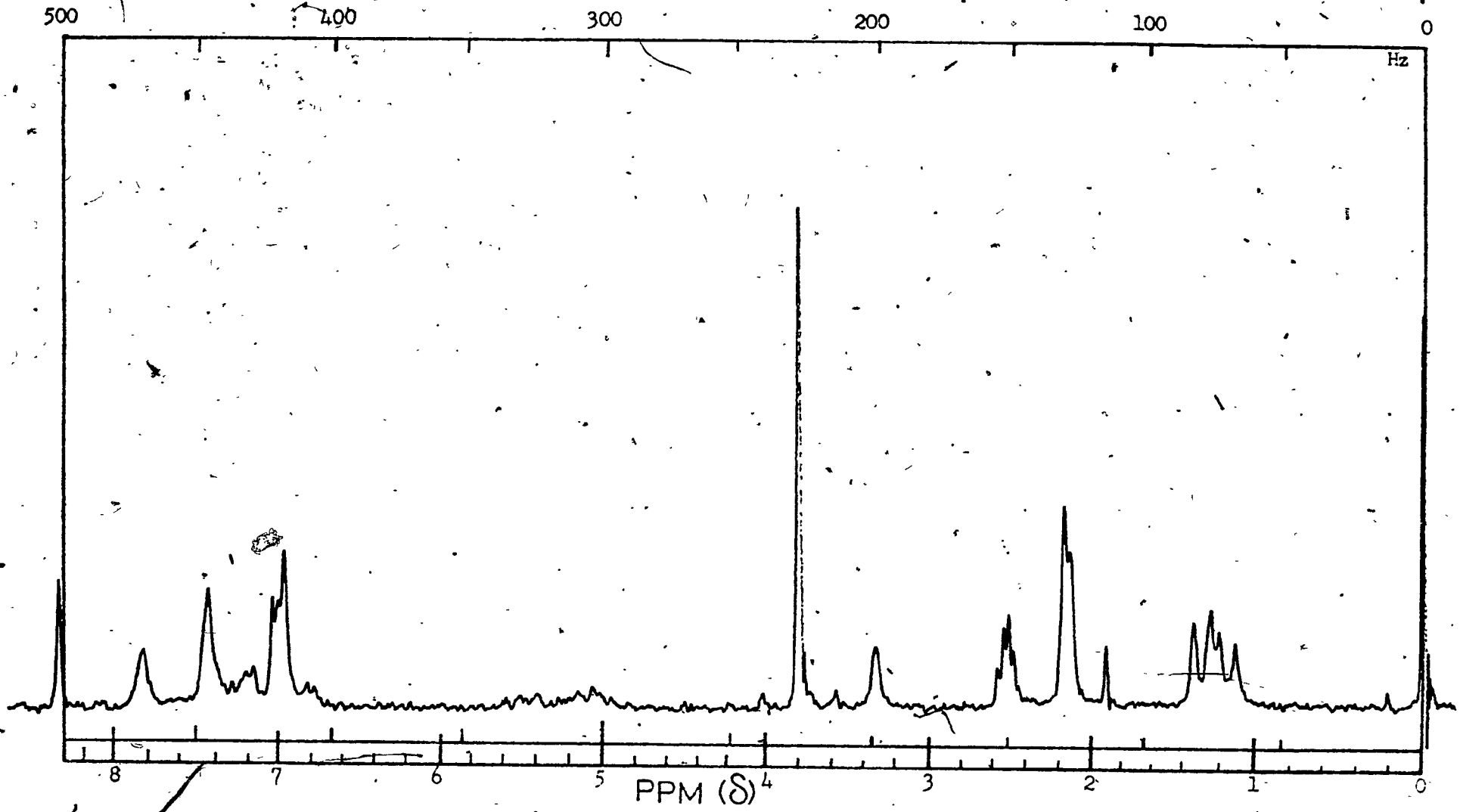
SPECTRUM XIII Proton NMR spectrum of 2,2-dimethyl-6-sulfamoyl-7-chloro-1,2,3,4-tetrahydro-4(1H)-quinazolinone (XXV) in DMSO-d_6 solution (500 Hz scan)



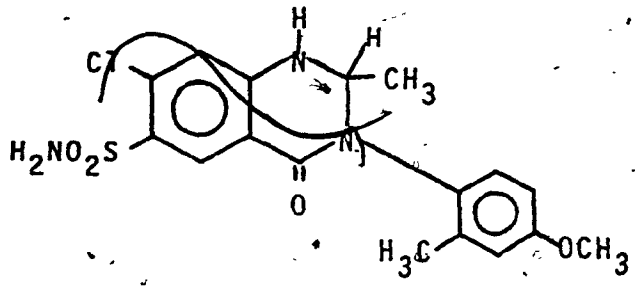
Sample	HMS
Solvent	DMSO
Lock	Solvent
AF	9000 Hz
LF	4760 Hz
NB	8
NS	512
PD	1
SI	100 μsec



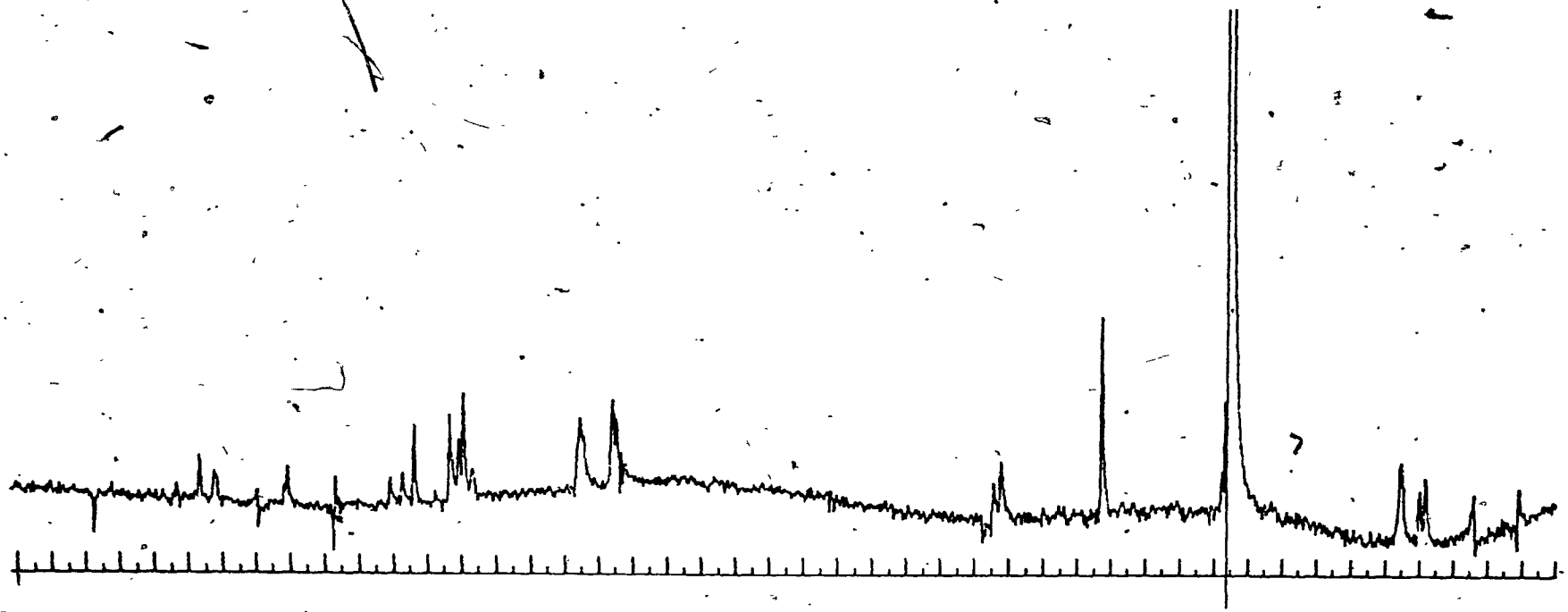
SPECTRUM XIV Carbon-13 spectrum of 2,2-dimethyl-6-sulfamoyl-7-chloro-1,2,3,4-tetrahydro-4(1H)-quinazolinone (XXV) in DMSO solution (5000 Hz scan)



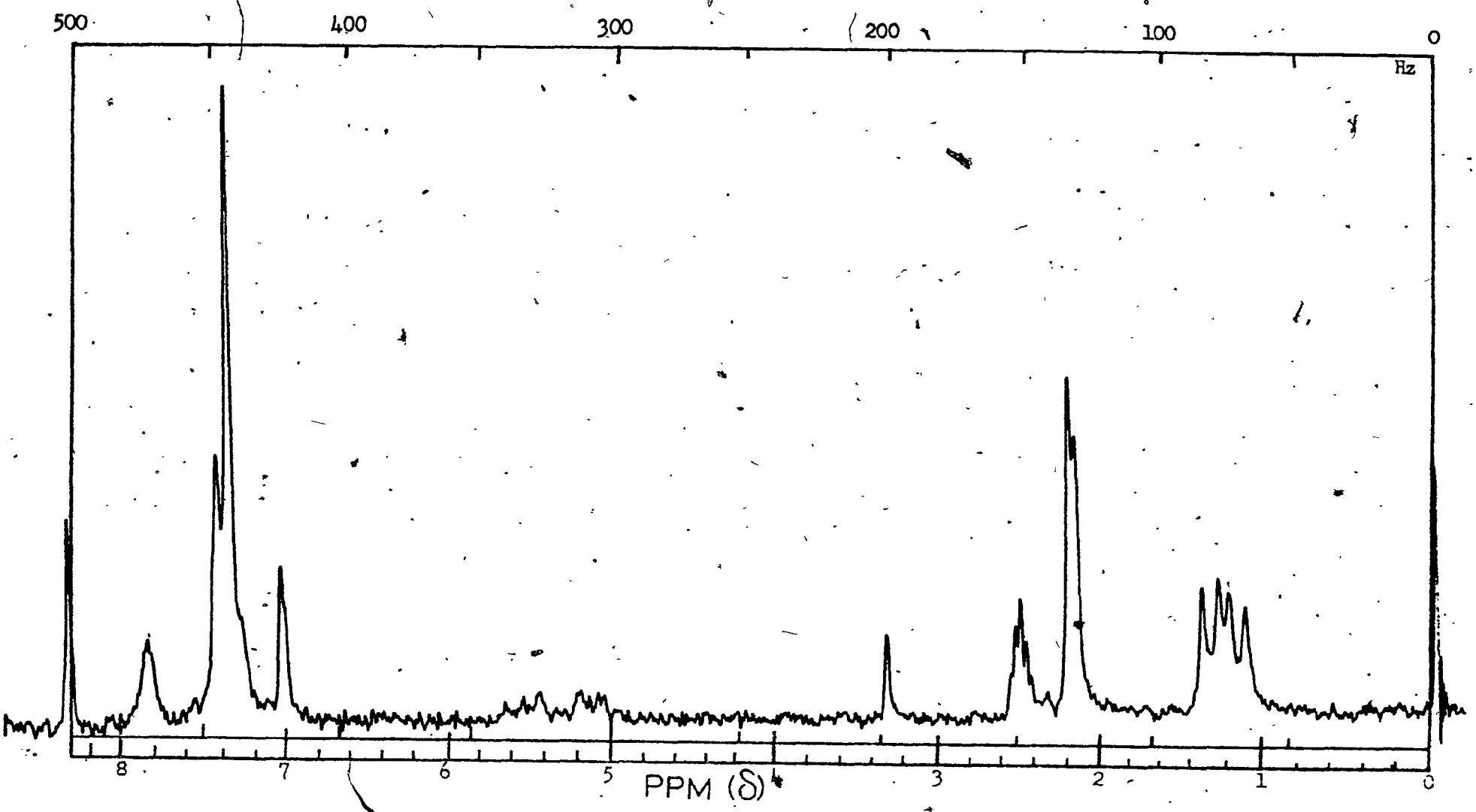
SPECTRUM XV Proton NMR spectrum of 2-methyl-3(2-methyl-4-methoxy phenyl)-6-sulfamoyl-7-chloro-1,2,3,4-tetrahydro-4(1H)-quinazolinone (XX) in DMSO-d_6 solution (500 Hz scan)



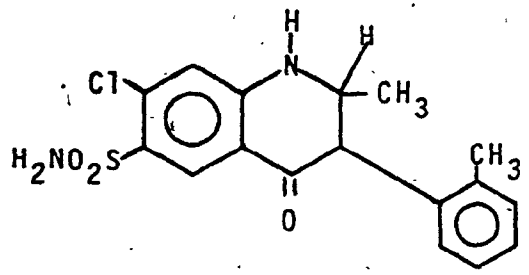
Sample	THQ
Solvent	DMSO
Lock	Solvent
AF	8800 Hz
LF	4760 Hz
NB	8
NS	512
PD	1
SI	100 µsec



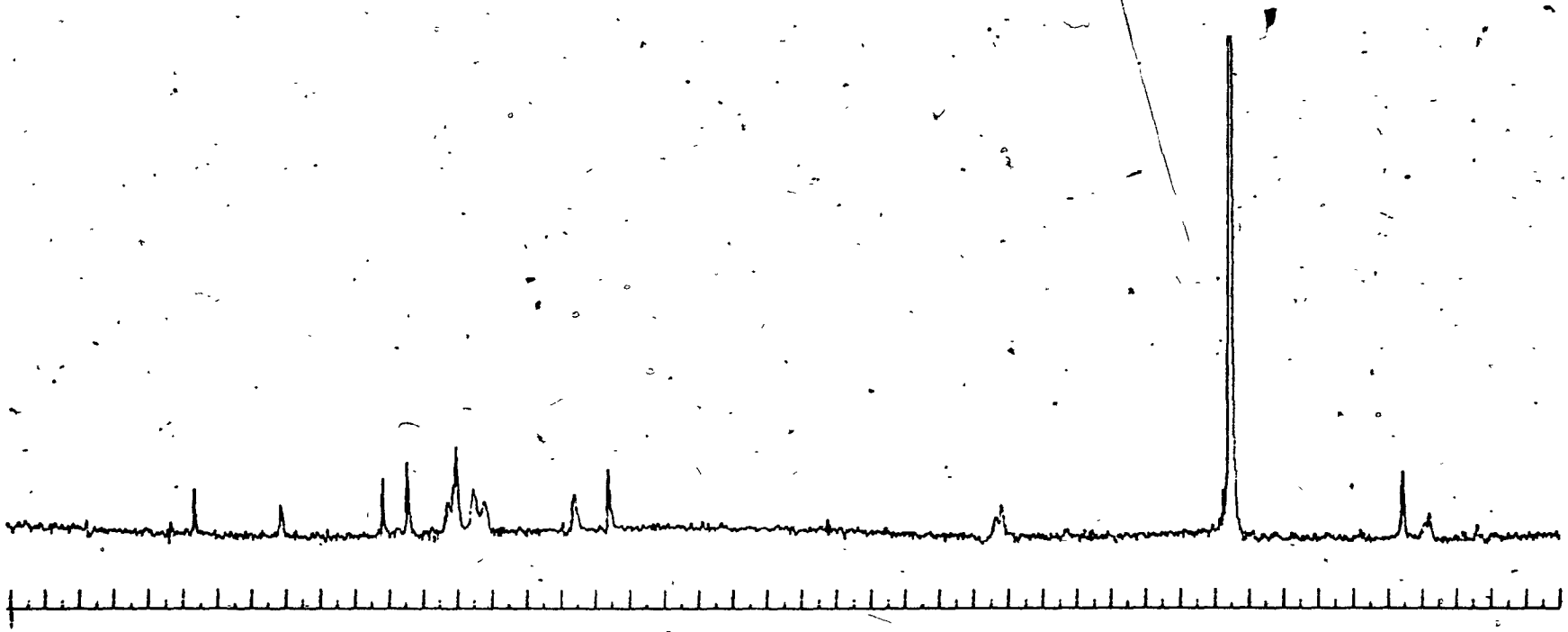
SPECTRUM XVI Carbon-13 NMR spectrum of 2-methyl-3-(2-methyl-4-methoxy phenyl) 6-sulfamoyl-7-chloro-1,2,3,4-tetrahydro-4(1H)-quinazolinone (XX) in DMSO solution (5000 Hz scan)



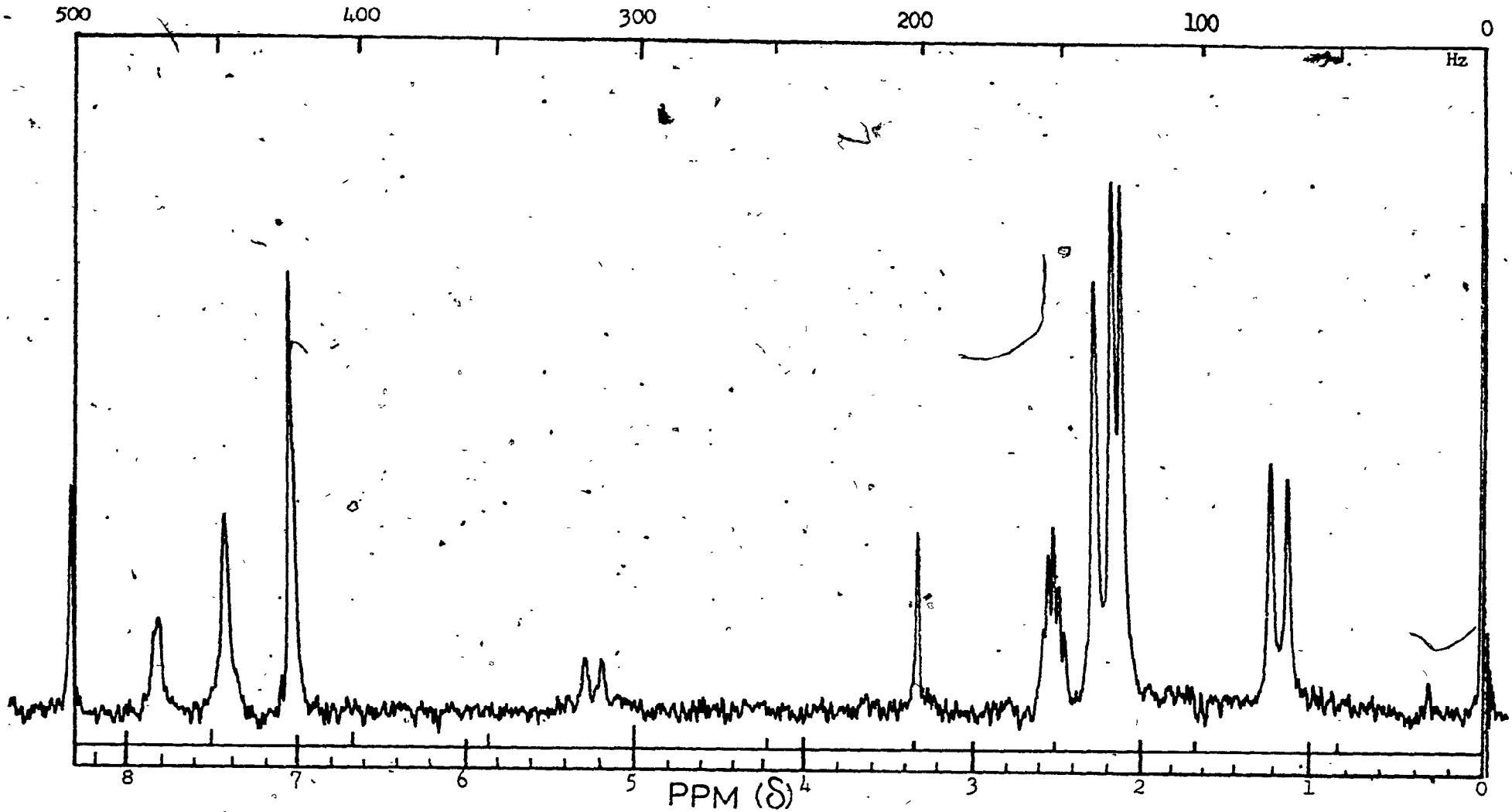
SPECTRUM XVII Proton NMR spectrum of 2-methyl-3(o-tolyl)-6-sulfamoyl-7-chloro-1,2,3,4-tetrahydro-4(1H)-quinazolinone (VI) in DMSO-d_6 solution (500 Hz scan)



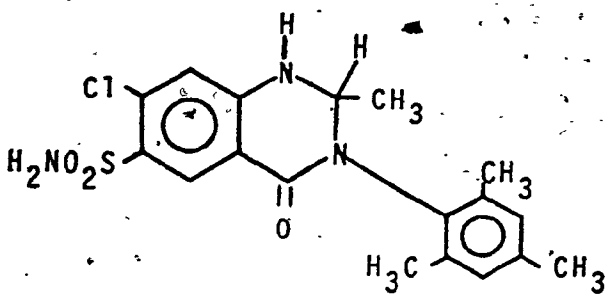
Sample	EDS
Solvent	DMSO
Lock	Solvent
AF	8800 Hz
LF	4760 Hz
NB	8
NS	512
PD	1
SI	100 µsec



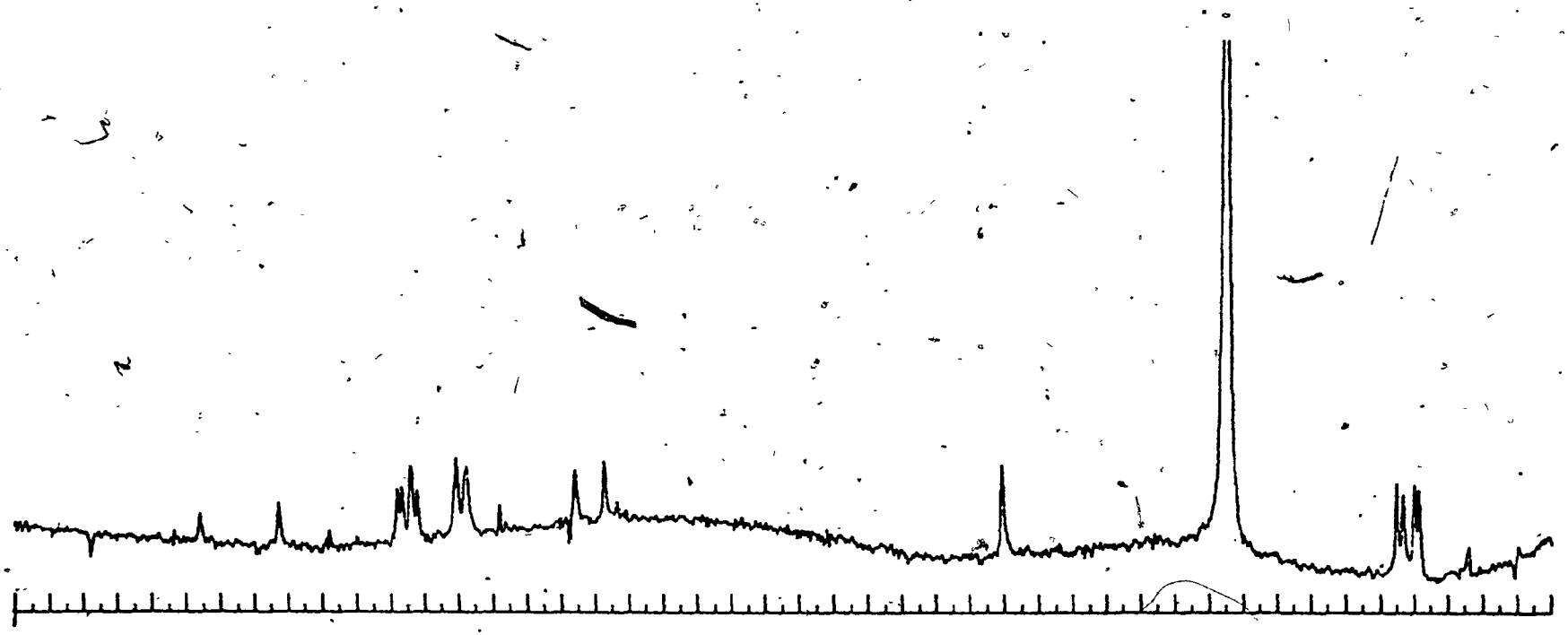
SPECTRUM XVIII Carbon-13 spectrum of 2-methyl-3-(o-tolyl)-6-sulfamoyl-7-chloro-1,2,3,4-tetrahydro-4(1H)-quinazolinone)VI in DMSO solution (5000 Hz scan)



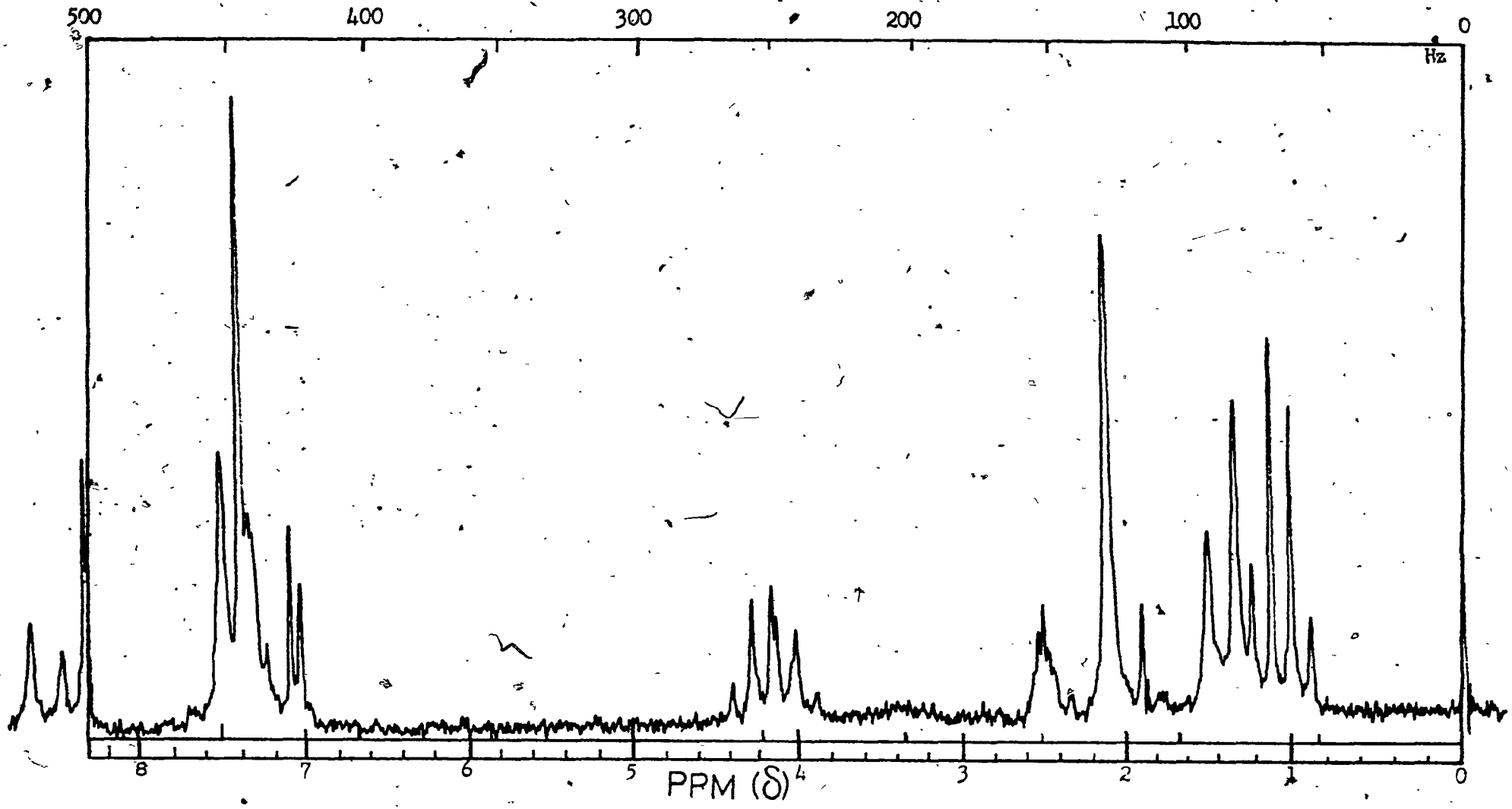
SPECTRUM XIX Proton NMR spectrum of 2-methyl-3(2,4,6-trimethyl phenyl)-6-sulfamoyl-7-chloro-1,2,3,4-tetrahydro-4(1H)-quinazolinone (XIX) in DMSO solution (500 Hz scan)



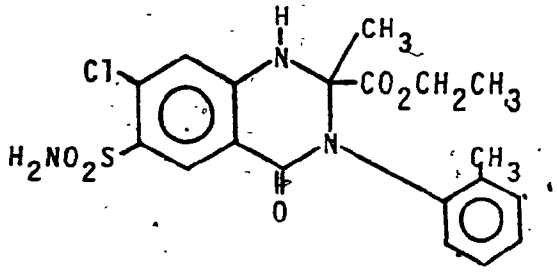
Sample	WAB
Solvent	DMSO
Lock	Solvent
AF	8800 Hz
LF	4760 Hz
NB	8
NS	512
PD	1
SI	100 µsec



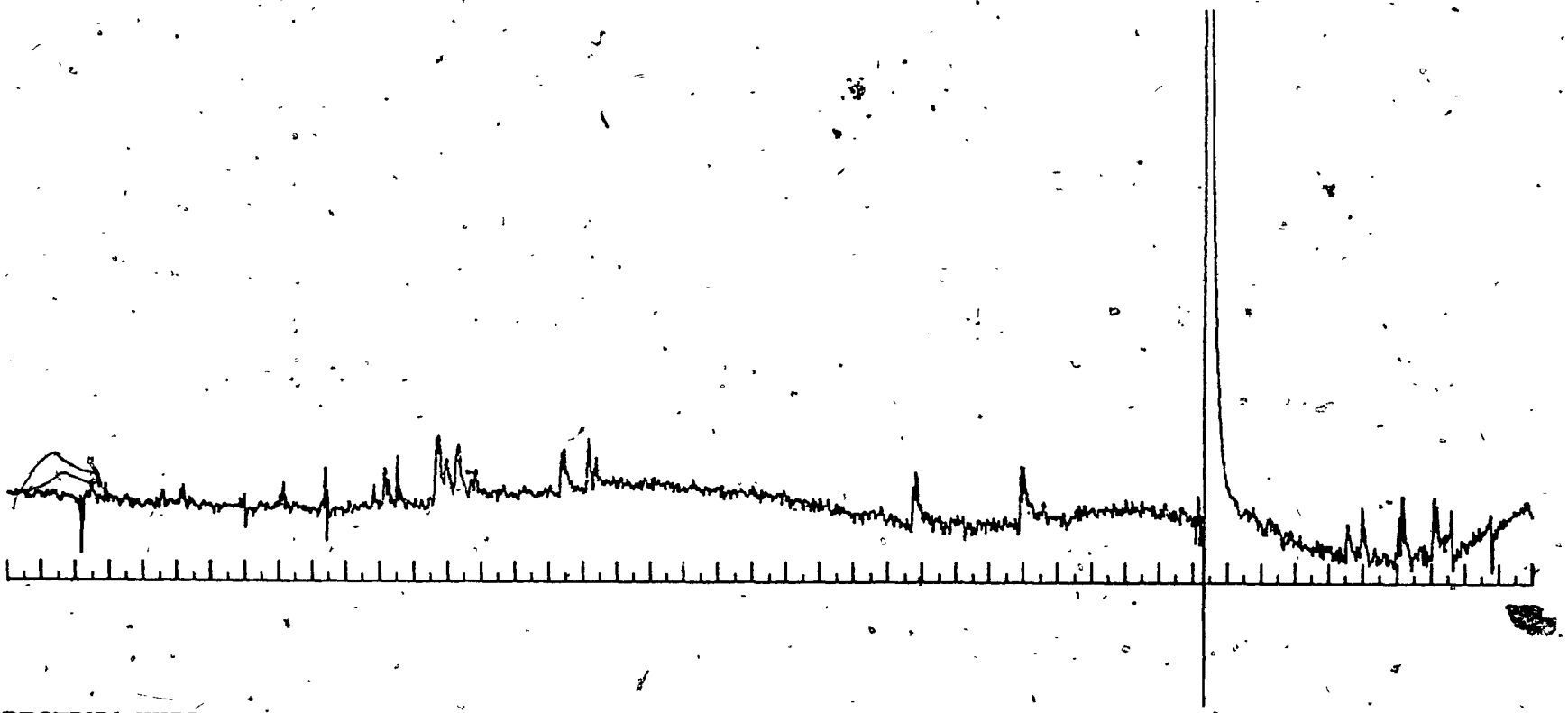
SPECTRUM XX Carbon-13 NMR spectrum of 2-methyl-3(2,4,6-trimethyl-phenyl)-6-sulfamoyl-7-chloro-1,2,3,4-tetrahydro-4(1H)-quinazolinone (XIX) in DMSO solution (5000 Hz scan)



SPECTRUM XXI Proton NMR spectrum of 2-methyl-2-carbethoxy-3(o-tolyl)-6-sulfamoyl-7-chloro-1,2,3,4-tetrahydro-4(1H)-quinazolinone (XIV) in DMSO-d_6 solution (500 Hz scan)



Sample	MCO
Solvent	DMSO
Lock	Solvent
AF	8800 Hz
LF	4760 Hz
NB	8
NS	512
PD	1
SI	100 μsec



SPECTRUM XXII Carbon-13 NMR spectra of 2-methyl-2-carbethoxy-3(o-tolyl)-6-sulfamoyl-7-chloro-1,2,3,4-tetrahydro-4(1H)-quinazolinone (XIV) in DMSO solution (5000 Hz scan)

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