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APPLICATIONS OF NMR SPECTROSCOPY TO PROBLEMS IN ORGANIC CHEMISTRY

by

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Submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

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The University of Western Ontario
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ABSTRACT

The stereochemistry of the products obtained by Diels-Alder addition of maleic anhydride and dimethyl fumarate to 1,3,5,5-tetramethylcyclohexa-1,3-diene has been investigated by chemical and spectroscopic methods. It is found that proton magnetic resonance spectroscopy can be used to distinguish between _exo_ and _endo_ isomers, providing that due care is taken in evaluating electronic effects, anisotropy effects and Van der Waals interactions. The products of halogenation of the Diels-Alder adducts were also investigated and their NMR parameters examined.

Interaction between non-conjugated chromophores has previously been studied largely by ultraviolet spectroscopy and is widely thought to be essentially an excited state phenomenon. The interaction between the olefinic and carbonyl groups in seventeen (17) β,γ-unsaturated ketones has been investigated by ^{13}C nuclear magnetic resonance spectroscopy. The influence of the non-conjugated double bond on the ^{13}C chemical shift of the carbonyl carbon is compared with the

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Interaction between non-conjugated chromophores has previously been studied largely by ultraviolet spectroscopy and is widely thought to be essentially an excited state phenomenon. The interaction between the olefinic and carbonyl groups in seventeen (17) β,γ-unsaturated ketones has been investigated by ^{13}C nuclear magnetic resonance spectroscopy. The influence of the non-conjugated double bond on the ^{13}C chemical shift of the carbonyl carbon is compared with the effects of α,β-unsaturation. Evidence is provided for a ground state interaction between the chromophores. A theoretical basis is proposed for the stereochemical dependence of the interaction.

The temperature dependence of the formyl proton shieldings of 9-anthraldehyde and 9-phenanthraldehyde in chloroform solutions has been measured. Four concentrations in the range 0.5 to 5.0 mole % were examined over the temperature interval -60 to +90°C. From these results, the enthalpies and entropies of formation have been estimated for the complex formed by the self-association of two aldehyde molecules. The calculations indicate the ΔH and ΔS values to be -1.9 ± 0.3 kcal/mole and -6 ± 1 e.u., respectively. These results are compared with other available data.

The proton spectra of the vinyl groups in a series of 23 substituted styrenes have been analysed as ABC spin systems. The proton chemical shifts are compared with previously reported shielding data for the corresponding vinyl carbon nuclei. The series includes 12 meta- and para-substituted examples and 10 ortho-substituted examples. The effects of steric inhibition of conjugation on the vinyl proton parameters for some 2,6-disubstituted derivatives are considered in detail.

ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Professor J.B. Stothers whose example was a continuous source of inspiration and whose expert guidance and constant encouragement made this work possible.

The author also wishes to thank Dr. J.D. Talman of the Mathematics Department who constructed the computer program used in analysis of the data on styrenes and Dr. A.A. Bothner-By of the Mellon Institute (Pittsburgh) for providing a copy of the LAOCOON III computer program. Thanks are also due to Dr. D.R. Bidinosti for mass spectrometry, to Dr. W.A. Ayer of the University of Alberta (Edmonton) for 100 Mc/s spectra and to Dr. A. Stoessl of the Department of Agriculture for the use of a Varian A60A spectrometer.

Special thanks are due to my wife, Dahutie, who undertook the tedious task of typing this thesis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

GENERAL INTRODUCTION

In recent years, there has been an enormous increase in the number of publications dealing with the elucidation and confirmation of the structures of organic compounds. This increase is largely due to the availability of physical methods which frequently enable the chemist to circumvent the complicated, laborious and sometimes uncertain procedures of chemical degradation followed by synthesis. A series of reactions can now be carried out on small quantities of a particular compound and the products identified by a fusion of information derived from several spectral disciplines. One of the more recent and, perhaps, the most versatile of these, is nuclear magnetic resonance spectroscopy (NMR). This form of spectroscopy depends on the magnetic properties of a nucleus, arising from its axial spin, which cause radiofrequency radiation to be absorbed when the nucleus is in a magnetic field.

Brief Historical Review.

The first actual nuclear magnetic resonance signals were observed in 1945. Bloch[1] observed the hydrogen resonance in water, while Purcell[2] was successful in detecting hydrogen nuclear resonance absorption in paraffin wax. For the first few years after its discovery, the method was essentially a tool for physicists and physical chemists who studied the ways in which nuclei exchange energy with themselves and with their surroundings. It was soon discovered, however, that the resonance position for a given nucleus depends on its chemical environment. This phenomenon was observed first by Knight[3] for metals and metal salts and later by Proctor and Yu[4] for ^{14}N compounds and Dickinson[5] for ^{19}F compounds. The behaviour appeared to be a general one for all nuclei and was given the name "the chemical shift".

On examining spectra under high resolution, it is often found that the chemically shifted "peaks" are themselves composed of several lines. This added multiplicity was first noted by Proctor and Yu[6] for the ^{121}Sb resonance in $NaSbF_6$. A systematic study of multiplet splitting by Gutowsky and McCall[7] showed that fine structure may arise in any molecule containing two or more nuclei which resonate at different field strengths, that is, the nuclei are either of different isotopic species or have different chemical shifts. The spectrum of a nucleus A in a molecule AX_n, where A and X are non-equivalent, comprises $(2nI_x+1)$ lines where I_x is the spin quantum number of X. The multiplet lines are equally spaced and the magnitude of the splitting is known as the "coupling constant" or, more completely, as the "electron coupled nuclear spin-spin interaction constant".

The NMR Parameters

A. The Chemical Shift.

It can be shown[8] that the resonance frequency of a given nucleus is given by,

$$\nu = \frac{\gamma H}{2\pi} \qquad [1]$$

where H is the field strength experienced by the nucleus and γ is its gyromagnetic ratio. In terms of the applied field, H_o, the effective field at the nucleus is given by the expression,

$$H = H_o(1-\sigma) \qquad [2]$$

where σ is termed the "shielding coefficient" or the "screening constant". The screening constant for a nucleus depends on its electronic environment, and this is responsible for chemical shifts between nuclei of the same isotopic species. The measurement of absolute chemical shifts is not possible, since it would mean comparing the resonance frequency of an isotopic species in a given molecular environment with that of the same isotope stripped of all its electrons. For chemical applications, however, it is necessary to know only the shifts measured relative to some reference compound. Further, it is convenient to express the chemical shift as a parameter which is independent of the applied field strength and the oscillator frequency. One method of defining the chemical shift parameter is,

$$\delta = \frac{\Delta}{\nu_o} \text{ X } 10^6 \quad \text{p.p.m.} \qquad [3]$$

where Δ is the separation in cycles per second between the sample and reference peaks, and ν_o is the frequency of the oscillator in Mc/s.

In proton spectroscopy, the reference compound commonly used is tetramethylsilane (TMS). The line separation, Δ, is considered as positive when the sample absorbs at lower field than the reference, so that δ usually has a positive value. The chemical shifts obtained in this way are readily converted to the widely used τ-scale by the expression

$$\tau = 10 - \delta \qquad [4]$$

For carbon-13 spectroscopy, carbon disulphide is a suitable reference compound. In this case, however, the line separation, Δ, is considered positive when the resonance position for the sample occurs at higher field than that of the reference compound.

Factors affecting the Chemical Shift.

The chemical shifts have been interpreted in terms of the behaviour of the electrons in a magnetic field.[9] An external field sets up induced currents which give rise, in turn, to a secondary screening field which may have different values at non-equivalent nuclei. The theory leads to a distinction of three different types of currents:[10]

(a). There are local diamagnetic circulations at each atom, very similar to those that determine the diamagnetic susceptibility of a free atom. The magnitude of the corresponding magnetic field will increase with the electron density of the atom.

(b). Paramagnetic currents may be set up arising from the mixing of ground and excited electronic states by the magnetic field.

(c). There may be interatomic currents flowing in closed circuits around a molecular path.

Thus the total screening of a nucleus, A, may be given by,[11]

$$\sigma^{A} = \sigma_{d}^{AA} + \sigma_{p}^{AA} + \sum_{B(\neq A)} \sigma^{AB} + \sigma^{A,\mathrm{ring}} \qquad [5]$$

where σ_d^{AA} is the contribution due to the diamagnetic circulation on atom A, σ_p^{AA} is due to the opposing (paramagnetic) currents on this atom, $\sum\sigma^{AB}$ is the contribution from currents on other atoms and $\sigma^{A,\mathrm{ring}}$ the contribution from ring currents which cannot be localized in individual atoms.

For most isotopes, the screening of a particular nucleus is determined principally by its own local circulations. Protons are exceptional, however, in that the total electron density at the hydrogen atom is very small and circulations in other parts of the molecule can assume relatively greater significance. The most striking cases are, perhaps, the low-field shifts of the ring protons in aromatic systems and the high-field shift of acetylenic protons; the former is the 'ring-current' effect,[12] and the latter is thought of as being due to the large magnetic susceptibility of the cylindrically symmetrical triple bond in the direction of the bond axis.[9] In both the carbonyl group[10] and the carbon-carbon double bond[13] paramagnetic circulations can be induced by the in-plane components of the applied field and give rise to a deshielding effect in the plane of the π-system.

The anisotropy in the screening contribution due to interatomic currents can be utilized in structural elucidation. Some applications of this are dealt with in Chapter 2 and in Appendices I and II.

The screening of a nucleus can also be affected by permanent dipoles in the molecule which distort the electronic orbitals and, hence, affect the electron density at the nucleus.[14,15] In addition, the near approach of polarizable groups may lead to a non-vanishing mean square electric field at the nucleus and thus reduce its shielding.[16]

Nuclear magnetic resonance spectra are usually obtained in solution so that the observed screening of the nucleus is given by

$$\sigma = \sigma_{gas} + \sigma_{solvent} \qquad [6]$$

where σ_{gas} is the screening constant for the isolated molecule and $\sigma_{solvent}$ is the contribution due to the solvent. The solvent contributions may be further subdivided as follows:[17]

$$\sigma_{solvent} = \sigma_b + \sigma_a + \sigma_w + \sigma_E \qquad [7]$$

where σ_b is the contribution to σ proportional to the bulk magnetic susceptibility of the medium; σ_a arises from anisotropy in the magnetic susceptibility of the solvent molecules; σ_w is due to Van der Waal's forces between the solute and solvent and σ_E is the "polar effect", caused by the charge distribution in the neighbouring solvent molecules leading to an electric field E on the solute, thereby perturbing its electronic structure and hence the nuclear screening constant.

It is found[17] that σ_b and σ_w are negative, σ_a is positive for disc-shaped solvents such as benzene and negative for rod-shaped solvents such as carbon disulphide. σ_E can be either positive or negative depending on the position of the nucleus relative to polar groups in the solvent molecule.[18]

Strong specific interactions such as those arising from intermolecular hydrogen bonds,[19,20] and solute-solvent associations involving aromatic solvents[21,22] are of considerable importance in determining the observed chemical shifts in some compounds. In other cases, solute-solute associations determine the observed screening of a particular nucleus. In the work described in Appendix I, use is made of this fact in the investigation of the thermodymamic parameters of examples of such association.

B. Coupling Constants.

The coupling constant $J_{NN'}$ for a pair of nuclei N and N' is defined by the expression,[23]

$$\Delta E_{NN'} = hJ_{NN'}\,\vec{I}_N.\vec{I}_{N'} \qquad [8]$$

where $\Delta E_{NN'}$ is the energy of interaction between the two nuclei with spin I_N and $I_{N'}$, respectively. This expression may be rewritten as

$$\Delta E_{NN'} = hJ_{NN'} \, |I_N| \, |I_{N'}| \cos \theta \qquad [9]$$

where θ is the angle between the spin vectors. For two nuclei to show coupling, $\Delta E_{NN'}$ must be negative; since cos θ can vary between +1 and -1, the coupling constant $J_{NN'}$ can be either positive or negative. For two nuclei N and N' separated by n bonds, the coupling constant is often symbolized as $^{n}J_{NN'}$.

(a) Geminal Proton-Proton coupling Constants ($^2J_{HH}$)

The general trends found in the coupling interaction between two protons on the same carbon atom are as follows:[24]

1. In the simplest hydrocarbons, the geminal proton-proton coupling constant increases (becomes more positive) as the hybridization of the bonding orbitals to carbon becomes more s-like. Thus the value for methane (sp^3 hybridization) is -12.4 c/s while that for ethylene (sp^2 hybridization) is +2.5 c/s. The geminal coupling constant for cyclopropane protons in hydrocarbons (where the hybridization should be intermediate between sp^3 and sp^2) is about -4 c/s.

2. The substitution of an electronegative atom X in a position α to a CH_2 group leads to a positive shift in the geminal coupling constant. This applies both to protons

on sp^2 hybridized carbon (for example, J_{HH} for formaldehyde is more positive than that for ethylene) and to protons on sp^3 hybridized carbon, for which the trend was established in a series of substituted methanes by Bernstein and Sheppard.[25]

3. Substitution of an electronegative group at a position β to the CH_2 group leads to a negative shift in $^2J_{HH}$. This was demonstrated in a series of vinyl compounds by Banwell and Sheppard,[26] and there is some evidence[27] for similar effects for protons on sp^3 hybridized carbon.

4. The presence of a π-electron system next to a CH_2 group generally leads to a negative shift in $^2J_{HH}$. Barfield and Grant[28] have collected data which suggest that this effect is greatest when the H-H internuclear axis is perpendicular to the nodal plane of the π-electron system.

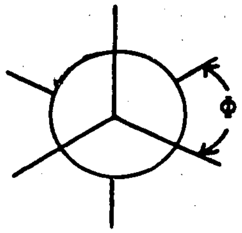
The variation of $^2J_{HH}$ has been examined both in terms of valence bond (VB) theory[28] and molecular orbital (MO)[24] theory. Both theoretical procedures predict positive geminal coupling constants for protons on sp^3 hybridized carbon atoms, while most of these are in fact negative. The MO method predicts an algebraic increase in $^2J_{HH}$ as the H-C-H angle is increased, while the VB method predicts a decrease. Experimentally, an increase is observed in going from a CH_2 fragment with an sp^3 hybridized carbon atom (H_2C_{IV}) to one having an sp^2 hybridized carbon atom (H_2C_{III}).

On the other hand the VB method correctly predicts a larger magnitude for the H_2C_{IV} coupling than for the H_2C_{III} coupling, while the MO method predicts the reverse. Clearly, neither theoretical treatment can be used to predict the general behaviour of geminal coupling constants.

(b) Vicinal Proton-Proton Coupling Constants ($^3J_{HH}$)

A greater measure of success has been realized in the theoretical treatment of the coupling interaction between two protons on adjacent carbon atoms ($^3J_{HH}$). A valence bond theory of vicinal proton-proton coupling has been presented by Karplus,[23,29,30] who made the following predictions:

1. $^3J_{HH}$ depends on the dihedral angle, Φ, between the two C-H bonds. The variation of the interaction is



given, approximately, by the expression,

$$^3J_{HH} = A + B\cos\Phi + C\cos 2\Phi \qquad [10]$$

with $A \approx 4$ c/s, $B \approx -\frac{1}{2}$c/s and $C \approx 4.5$ c/s. The near equality of A and C means that the coupling will be small

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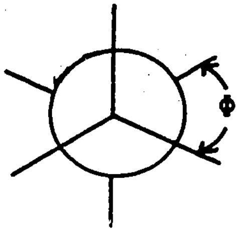


$$^3J_{HH} = A + B \cos \Phi + C \cos 2\Phi \qquad [10]$$

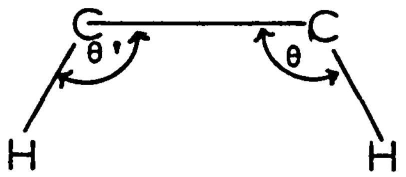
with A ≈ 4 c/s, B ≈ $-\frac{1}{2}$c/s and C ≈ 4.5 c/s. The near equality of A and C means that the coupling will be small when $\Phi \approx 90°$, and large when $\Phi \approx 0°$ and $180°$. The negative sign of B implies $^3J_{HH}$ (180°) is greater than $^3J_{HH}$ (0°). In addition, $^3J_{HH}$ (0°) and $^3J_{HH}$ (180°) are both positive.

2. The introduction of substituents causes hybridization changes on a carbon atom, and induces changes in $^3J_{HH}$. If the ^{13}C-H coupling constant is taken as a measure of the s-character in the carbon hybrid orbital, the measured coupling constants suggest that the introduction of electronegative substituents on methane increases the s-character of the C-H bonding orbitals.[31,32] In a series of substituted ethanes, the variation of $^3J_{HH}$ with the electronegativity of the substituent is given approximately by

$$^3J_{HH} = {}^3J^{\circ}_{HH}\ (1 - 0.07\ \Delta X) \qquad [11]$$

where $^3J^{\circ}_{HH}$ represents $^3J_{HH}$ for ethane itself and ΔX is the electronegativity difference between the substituent and hydrogen.

3. As the H-C-C bond angles, θ and θ', increase, $^3J_{HH}$ is expected to decrease for most values of Φ.



4. As the C-C bond length increases, ${}^3J_{HH}$ decreases.

It is clear that the above changes cannot be independent. For example, if a substituent is introduced, the changed hybridization on the carbon atom leads to changes in bond angles and bond lengths and, of course, dihedral angles may also be affected.

The results of molecular orbital calculations[33] are essentially in agreement with those obtained from the valence bond method.

(c) Long Range Proton-Proton Coupling Constants

Coupling interactions between nuclei separated by more than three bonds are referred to as long-range couplings. The observation of such a coupling often has stereochemical significance. In Chapter 2, the application of some of these couplings to problems of structural elucidation is illustrated.

Comments on Obtaining Nuclear Magnetic Resonance Parameters from Spectral Line Positions

Some nuclear magnetic resonance spectra comprise well-separated absorption bands possessing multiplet fine structure due to spin-spin interactions between differently shielded nuclei. If $J/\Delta\delta \leq 0.1$, first order spectra result, in which the multiplet splittings of the absorption bands are given by the simple (2nI + 1) rule and the intensities of the components are distributed symmetrically about the centre of each multiplet. The chemical shift and coupling constant parameters can be obtained directly from such spectra. A spectrum of this type is always obtained when the interaction is between different isotopic species. Thus methyl fluoride, CH_3F, has a ^{19}F resonance spectrum which consists of a symmetrical quartet with separations equal to the proton-fluorine coupling constant; the ^1H resonance spectrum is composed of two lines of equal intensity having a separation equal to the same proton-fluorine coupling constant. The necessary condition for the observation of a first order spectrum (that is, $\Delta\delta >> J$) is sometimes satisfied by interacting nuclei of the same isotopic species. A simple example of this type is the proton spectrum of 2-bromothiophene at 60 Mc/s[34] in which the chemical shift differences of the three non-equivalent hydrogen nuclei are much greater than the coupling constants involved.

When the magnitudes of the chemical shift differences are comparable to the coupling constants, the simple rules for analysing the spectra break down and the required parameters can only be obtained by subjecting the spectra to a full quantum mechanical analysis. The high-resolution Hamiltonian is given by,[35]

$$\mathcal{H} = \sum_{i=1}^{n} \nu_i I_{zi} + \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} J_{ij} \vec{I}_i \cdot \vec{I}_j \qquad [12]$$

where ν_i is the resonance frequency of nucleus i in the absence of other nuclei, I_{zi} is the z component of the angular momentum associated with the nucleus i, J_{ij} is the spin-spin coupling constant between nuclei, i and j, and $\vec{I}_i$ is the angular momentum operator for nucleus i. The summations are over all n nuclei and all pairs of nuclei ($j > i$).

For many simple cases (for example, all n equivalent spins or only two sets of equivalent spins present) the exact solutions for the eigenvalues of $\mathcal{H}$ may be found[36] as closed expressions in the fundamental NMR parameters, and the interpretation of the spectra proceeds in a straightforward manner. Many experimental cases, however, involve more than two sets of close-coupled equivalent spins, and in these cases numerical methods must be used. The most widely used methods[26,37,38] involve iterative techniques in which a starting estimate of the values of a set of parameters is successively improved until the calculated spectrum is "identical" with the observed spectrum.

Recently, Castellano and Bothner-By[35,39] have devised an iterative method making use of the least squares principle to obtain the best set of parameters from experimental line positions. Since more than one set of chemical shifts and coupling constants which reproduce the observed line positions can usually be found,[40,41] the correct solution is taken to be that which most closely reproduces the intensities as well as the line positions. One limitation of the iterative method is that there is no way to determine if all solutions have been found or even to determine that the best solution has been obtained. Arata, Shimuzu and Fujiwara[42] have developed a least squares refinement method that circumvents this uniqueness problem by including intensities as well as line positions as data which must be fitted by the refinement process.

A second approach to the problem is to obtain an exact algebraic solution giving the chemical shifts and coupling constants in terms of experimentally determined line positions or energy levels. Exact solutions are possible for only a limited number of cases, the most complex of these being the three-spin ABC system which was worked out by Castellano and Waugh.[43,44] The exact method has the advantage that it gives all possible sets of solutions, eliminating doubt about having found the correct solution. The choice of the best solution from the complete set of solutions is made by comparing calculated and observed intensities as is done for the iterative method. The method of analysis used to obtain the results presented in Appendix II employs the principles laid out by Castellano and Waugh but uses more accurate methods for the solution of the mathematical equations.[45,46]

One problem encountered in the use of experimental data in the exact solution of the ABC system arises from experimental uncertainties in the observed line positions introducing errors into the calculations which in turn may become magnified and produce much larger uncertainties in the final parameters. This problem may be minimised by adjusting the experimental line positions so that they conform exactly to a simple set of known relationships between lines of the spectrum. This adjustment is usually done by trial and error by hand but weighted least squares methods have recently been developed[46,47] to obtain the best set of internally consistent line positions from data which contain experimental uncertainties. Energy values required in the Castellano and Waugh formalism are expressable in terms of the adjusted line positions and therefore can be obtained directly from the least-squares results.

Applications of NMR Spectroscopy

From the preceeding survey, it is clear that the nuclear magnetic resonance parameters show a high specificity with respect to molecular structure and that methods are available by which these parameters can be obtained from simple as well as from more complex spectra. The applications of NMR have been reviewed by many authors,[8,13,16,48,49] and these reviews have proved invaluable in interpreting the results presented in this thesis. In subsequent chapters, the variation of the NMR parameters with the electronic environment of ^{1}H and ^{13}C nuclei, has been applied to the investigation of stereochemical, stereo-electronic and physico-chemical problems in organic chemistry.

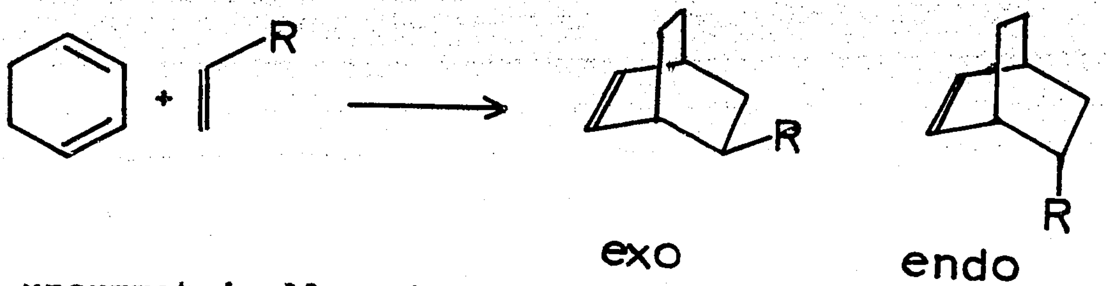
CHAPTER 2

PROTON MAGNETIC RESONANCE STUDIES OF THE BICYCLO[2.2.2]OCTANE SYSTEM

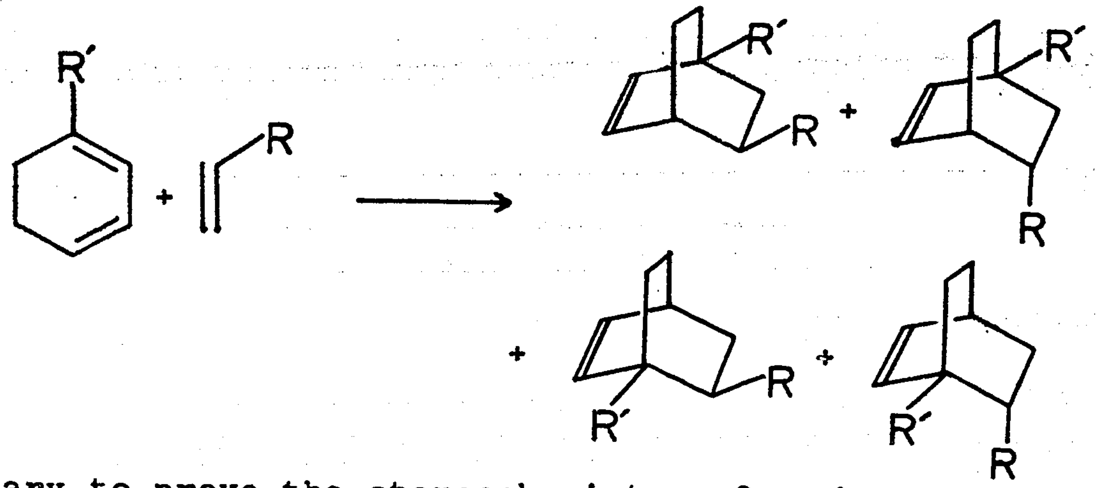
INTRODUCTION

Bicyclic compounds are a chemically intriguing group of compounds and an appreciable amount of recent research has been directed towards gaining a better understanding of their chemistry. The most thoroughly investigated are the derivatives of bicyclo[2.2.1]heptane (norbornane), probably because of the comparative ease of obtaining the simpler members of this series and, also, their close relationship to the naturally occurring terpenes.

One synthetic route to the bicyclic compounds involves the Diels-Alder addition of a suitable dienophile to a cyclic diene. With a vinyl derivative as dienophile, a simple cyclic diene can, in principle, produce either (or both) of two diastereoisomeric adducts - which are usually described as *exo* and *endo* isomers. These are illustrated below for adducts of 1,3-cyclohexadiene.



For an unsymmetrically substituted diene, a greater variety of products is possible, as shown below. It is, therefore,



necessary to prove the stereochemistry of each product obtained by this route.

Several chemical methods have been employed for this purpose. These include degradative oxidation,[50] lactonization,[51] halolactonization[52] and titrimetric analysis.[53] The classical degradative procedures are usually unambiguous, but are often very tedious. The lactonization methods suffer from the disadvantages that

(a) they depend on the presence of a carboxyl function and (b) skeletal rearrangements can occur in the course of the reactions.[54,55]

The use of physical methods obviates the above difficulties. However, these can be used advantageously only if their applicability and limitations are well established.

Since proton magnetic resonance spectroscopy has been shown to be very useful in determining the configuration of Diels-Alder adducts of cyclopentadiene,[56] it was proposed to investigate the applicability of this method to the elucidation of the stereochemistry of adducts of 1,3-cyclohexadiene.

The Stereochemical Significance of Proton Nuclear Magnetic Resonance Parameters

The chemical shift and coupling constant(s) observed for a particular proton depend on both intermolecular and intramolecular interactions and reflect the electronic as well as the steric environment of the nucleus being examined (see Chapter 1). Because of these facts, nuclear magnetic resonance spectroscopy is now one of the best methods available for conformational analysis of flexible systems such as cyclohexane derivatives.[57] Further, the technique can be used to give information about the spatial orientation of protons in fixed systems.

(a). Vicinal Coupling Constants.

The results of valence bond calculations indicate that the coupling constant between two vicinal protons is given by the expression,[30]

$$^3J_{HH} = A + B \cos \Phi + C \cos 2\Phi \qquad [10]$$

where Φ is the dihedral angle between the two C-H bonds. In the norbornane system, this dependence on the dihedral angle is reflected in the coupling interaction of 4-5 c/s for an *exo* proton with an adjacent bridgehead proton, while the *endo* proton has a smaller coupling constant (0-1 c/s). This characteristic has been widely used in assigning the structures of camphor derivatives.[58-60] In the bicyclo-[2.2.2]octenes, this method is less useful since a dihedral angle of about 60° (Fig. 1) is expected for both the *exo* and *endo* protons with the bridgehead proton.

Although the dihedral angle between both the *exo*-*exo* and *endo*-*endo* pairs of protons at C-5 and C-6 of the bicyclo-[2.2.1]heptene system is zero, there have been many reports[27,59,61,62] which claim that the *exo*-*exo* vicinal coupling constant is smaller thanthe corresponding *endo*-*endo* interaction. Recent work by Anet and coworkers[63] has shown, however, that the two interactions are virtually the same (about 9 c/s). In the bicyclo[2.2.2]octenes the transoid

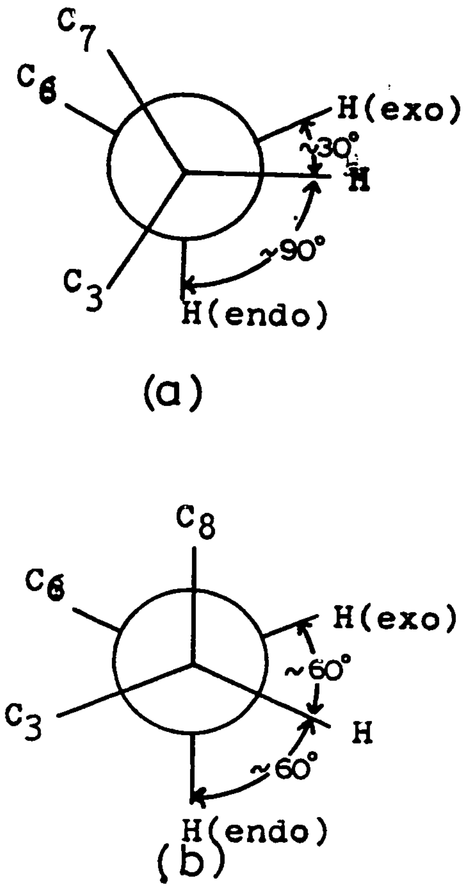
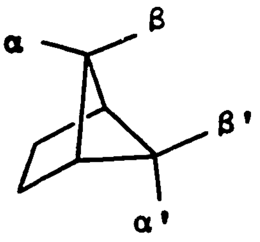


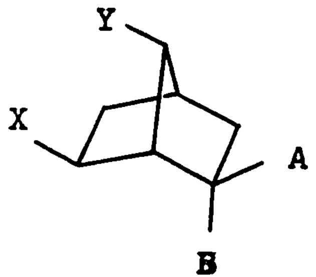
Figure 1. - The Dihedral Angle between the C-4 Proton and the C-5 Protons in (a) Bicyclo[2.2.1]heptene and (b) Bicyclo[2.2.2]octene.

vicinal coupling constant between protons at C-5 and C-6 is about 6.8 c/s while the cisoid interaction is about 10.2 c/s.[64,65,66] Clearly, the magnitude of the vicinal coupling constant in bicyclic systems can be used to indicate (approximately) the dihedral angle between the interacting protons but cannot differentiate between <u>exo</u>-<u>exo</u> and <u>endo</u>-<u>endo</u> coupling.

(b). Long Range Coupling Interactions.

In the majority of cases, spin-spin coupling interactions are not detectable between protons separated by four or more sigma (σ) bonds. In substituted bicyclo[2.1.1]-hexanes, however, a strong interaction (J = 7-8 c/s) is found between the protons labelled α and α'[67] while in the bicyclo[2.2.1]heptanols,[68] coupling across four σ bonds is





found between pairs of protons AX and BY. The stereospecificity of the interaction is indicated by the absence of resolved coupling between the pairs of protons αβ', ββ'; XB and YA. Further, in a study of heterocyclic analogues of bicyclo[2.2.1]heptane, Gagnaire and Payo-Subiza[69] found that a number of protons in the *exo*-*exo* relationship were coupled, while there was no evidence of coupling between '*endo*-*endo*' or '*exo*-*endo*' pairs of protons. Corresponding results for bicyclo[2.2.2]octane derivatives have been reported.[64]

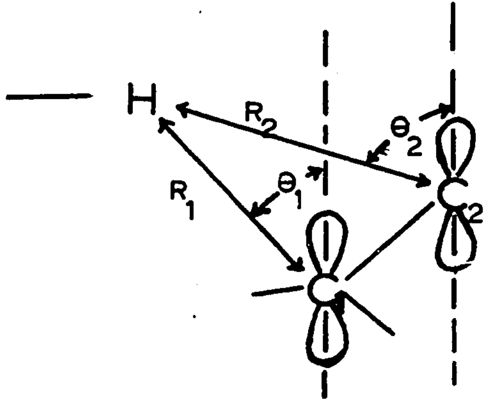
(c). Long Range Shielding Effects of the Carbon-Carbon Double Bond.

By analogy with Pople's theory[9,10] for the shielding effects of the carbonyl group, it has been proposed[13] that the long range shielding effects of the carbon-carbon double bond arise from paramagnetic currents induced by the in-plane component of the applied field. This results in anisotropy of the magnetic susceptibility of the sp^2 hybridized carbon atom.

It can be shown that, if the point dipole approximation[70] is assumed, the shielding contribution of an olefinic bond is given by the expression,[71]

$$\Delta\sigma = \frac{\Delta\chi}{3}\left\{\frac{1-3\cos^2\theta_1}{R_1{}^3} + \frac{1-3\cos^2\theta_2}{R_1{}^3}\right\} \qquad [13]$$

where the angles (θ) and the distances (R) are as shown in the diagram below, and $\Delta\chi$ is the difference between the



magnetic susceptibility of sp^2 hybridized carbon atom in the nodal plane of the π-orbital and perpendicular to that plane.

An investigation of a number of bicyclo[2.2.1]heptenes and their saturated equivalents[27,56,72] revealed that the double bond makes a positive (+0.04 p.p.m.) contribution to the shielding of the <u>endo</u> proton, but a negative contribution (-0.14 p.p.m.) to the shielding of a proton in the <u>exo</u> configuration.

For the bicyclo[2.2.2]octene system, the shielding contributions calculated from this relationship are +0.18 p.p.m. for the <u>endo</u> proton and -0.09 p.p.m. for the <u>exo</u> proton.[64] The magnitude and sign of the shielding contribution of the C=C double bond has been used in the determination of the configuration of protons in the norbornene[56] and the bicyclo[2.2.2]octene systems.[64-66,73,74]

Extreme caution must, however, be exercised in such analyses since the chemical shift of a proton depends on a number of factors other than anisotropy effects (see Chapter 1) and, therefore, this parameter cannot always be used as a direct indication of the latter factor. The shielding effect of a double bond is usually estimated as a difference in the proton chemical shifts between the saturated and the unsaturated compounds. Even in these cases, however, the dubious assumption is made that all other factors remain constant on introduction of a double bond.

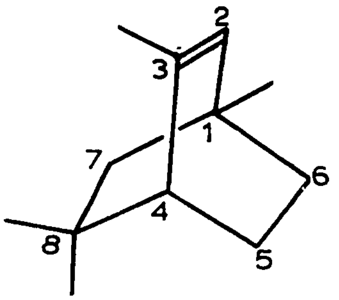
The Objectives of the Project

As stated previously (page 21), it was proposed to study the applicability of the NMR method to the stereochemical analysis of Diels-Alder adducts of cyclohexa-1,3-diene. It was expected that the magnitude of vicinal coupling constants would distinguish between cis and trans protons on adjacent carbon atoms while careful analysis of the shielding contribution of the double bond would help to distinguish between exo and endo protons. Further information about the configuration of the protons was to be obtained by taking advantage of the established stereospecificity of long range coupling interactions.

In addition to providing chemical evidence for the stereochemical assignments, the reactions carried out on the Diels-Alder adducts were designed to provide further systems containing the bicyclo[2.2.2]octane skeleton. From the data obtained from the spectra of these compounds, it was proposed to evaluate the effect of various factors on the spectral parameters.

The System Studied

The compounds studied include some 5,6-disubstituted derivatives of 1,3,8,8-tetramethylbicyclo[2.2.2]oct-2-ene (I), hereinafter referred to as "Bicyclo-octene A". Products obtained by hydrogenation and halogenation of these compounds were also examined.



These compounds were expected to have spectra in which the resonance patterns for the methine protons (C-4,5,6) are well resolved so that the nuclear magnetic resonance parameters can be determined by applying the criteria discussed above.

With identical substituents at C-5 and C-6, the inductive effect on the chemical shift of protons on these carbon atoms would be the same and observed differences should reflect other factors such as anisotropy effects and Van der Waal's interactions. It was hoped that the chemical shift differences between the methine protons (C-4,5,6) would be sufficient for first order analysis to be satisfactory, although it was anticipated that, in some cases, the pattern for the C-5 and C-6 protons will have to be treated as a perturbed AB system. A high-field AB pattern with some secondary splitting was expected for the C-7 methylene protons.

In assigning the absorption bands to specific protons extensive use was made of general references[8,13,16,48,75] containing data on NMR parameters as well as literature reports dealing specifically with bicyclic systems.[56,63-66,72] Where necessary, decoupling experiments were performed to provide additional data for assignments.

RESULTS AND DISCUSSION

For convenience, the results are discussed in two sections (a) and (b). In section (a) the methods of obtaining the chemical compounds are considered together with chemical and spectroscopic data which are essential to define their structures. A more detailed examination of the nuclear magnetic resonance parameters is presented in section (b). Summaries of the spectral parameters are given in Tables I to XV. All chemical shifts are quoted relative to internal tetramethylsilane and the δ scale defined in Chapter 1 is adopted.

The Chemical Compounds

The series of bicyclooctenes was prepared by Diels-Alder reactions of maleic anhydride or dimethyl fumarate with "1,3,5,5-tetramethylcyclohexa-1,3-diene". Hydrogenation and bromination reactions with the adducts furnished a series of derivatives having the bicyclo[2.2.2]octane skeleton. The chemical transformations involved are summarized in Figs. 2 and 3.

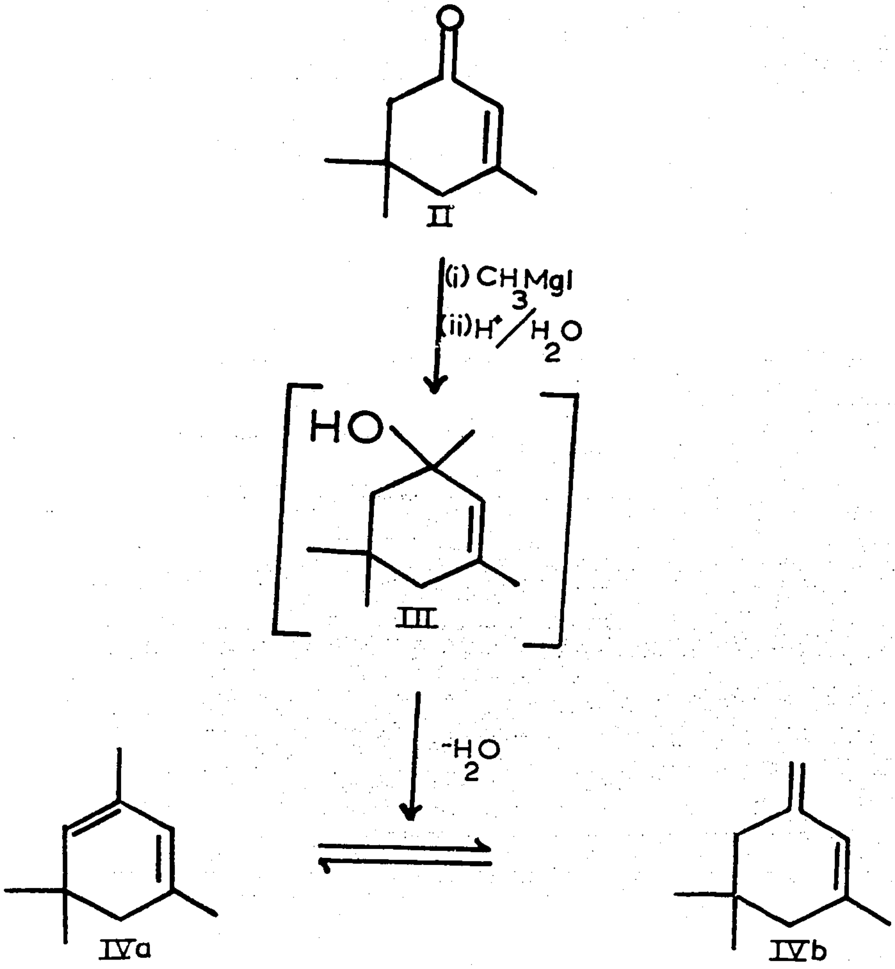


Figure 2. - Preparation of the "Diene".

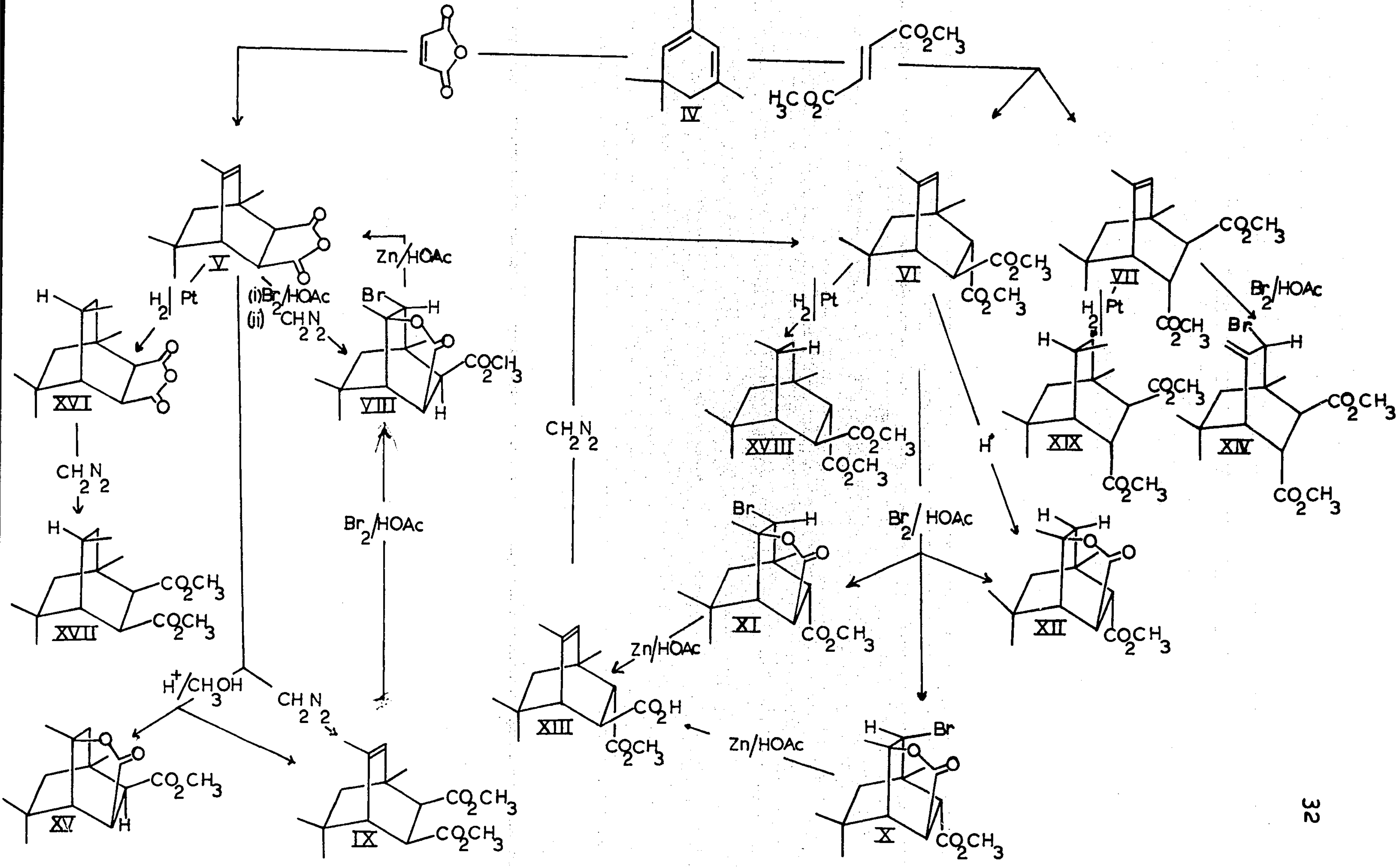


Figure 3. - Compounds obtained from 1,3,5,5-Tetramethyl-cyclohexa-1,3-diene.

(a) The "Diene" ("1,3,5,5-Tetramethylcyclohexa-1,3-diene")

The "diene" was prepared by reaction of the methyl Grignard reagent on isophorone (II) with subsequent elimination of the elements of water. Although the structure IVa (Fig. 1) was assigned to the "diene" by Kharasch,[76] the vapour phase chromatogram of the product indicates the presence of two compounds. The infrared spectrum shows three maxima in the C=C stretching region ($\nu_{max}^{CHCl_3}$ 1667 cm^{-1}, 1647 cm^{-1} and 1616 cm^{-1}) together with a peak at 900 cm^{-1} suggesting the presence of a terminal methylene group. Thus, the product appears to contain IVa and IVb.

Further support for the presence of a mixture was provided by the ultraviolet spectrum of the product. Calculations based on Woodward's Rules[77] predict absorption maxima at 236 mμ for IVb and at 263 mμ for IVa. The observed spectrum of the diene product exhibits maxima at 238 mμ and 261 mμ, in good agreement with these predictions.

The proton magnetic resonance spectrum of the "diene" in carbon tetrachloride, shown in Fig. 4, clearly substantiates this conclusion and provides an easy measure of the relative amounts of the components. The low-field absorption comprises four multiplets centred at 5.85, 5.43 4.98 and 4.62 p.p.m., respectively, and having intensity ratios of 1:1.2:1.2:2.3. The band at highest field, 4.62 p.p.m., is assigned to the terminal methylene protons

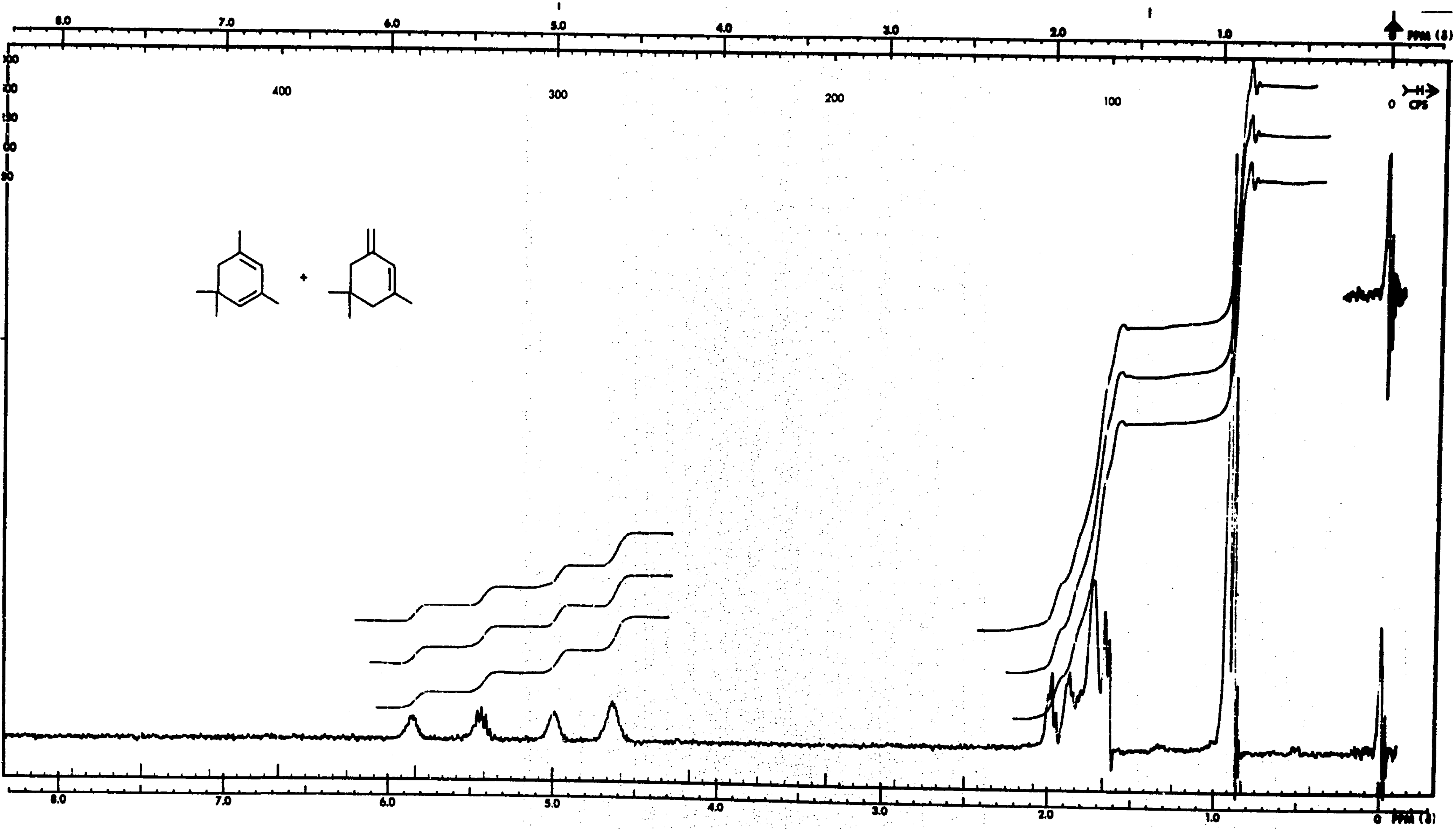


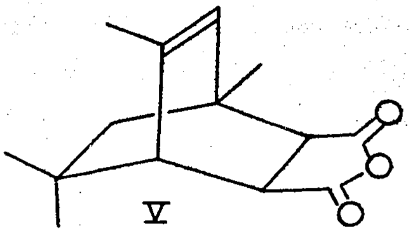
Figure 4. - Proton Magnetic Resonance Spectrum of the "Diene" in CCl₄.

in structure IVb by analogy with other terminal methylene groups and because of its relative intensity. The product, therefore, is a mixture of approximately equal amounts of the two olefins.

(b) The Diels-Alder Adducts

Although the diene is prepared as a mixture with the isomeric 1,5,5-trimethyl-3-methylenecyclohex-1-ene, the adduct formation is essentially quantitative.

With maleic anhydride as dienophile, the endo-5,6 anhydride (V) of bicyclo-octene A is obtained. The infrared spectrum of the adduct shown peaks characteristic of a five-membered ring anhydride ($\nu_{max}^{CHCl_3}$ 1780 cm^{-1}, 1855 cm^{-1})[78] as well as weak absorption in the C=C stretching region ($\nu_{max}^{CHCl_3}$ 1650 cm^{-1}). The presence of a double bond is confirmed by two features of the proton resonance spectrum (Figs. 5 and 6). Firstly, vinyl proton absorption appears as a low field multiplet (δ^{CDCl_3} = 5.52 p.p.m.) and, secondly, a methyl doublet (δ^{CDCl_3} = 1.75 p.p.m.) corresponding to the expected pattern for a methyl group attached to C-3 and


V

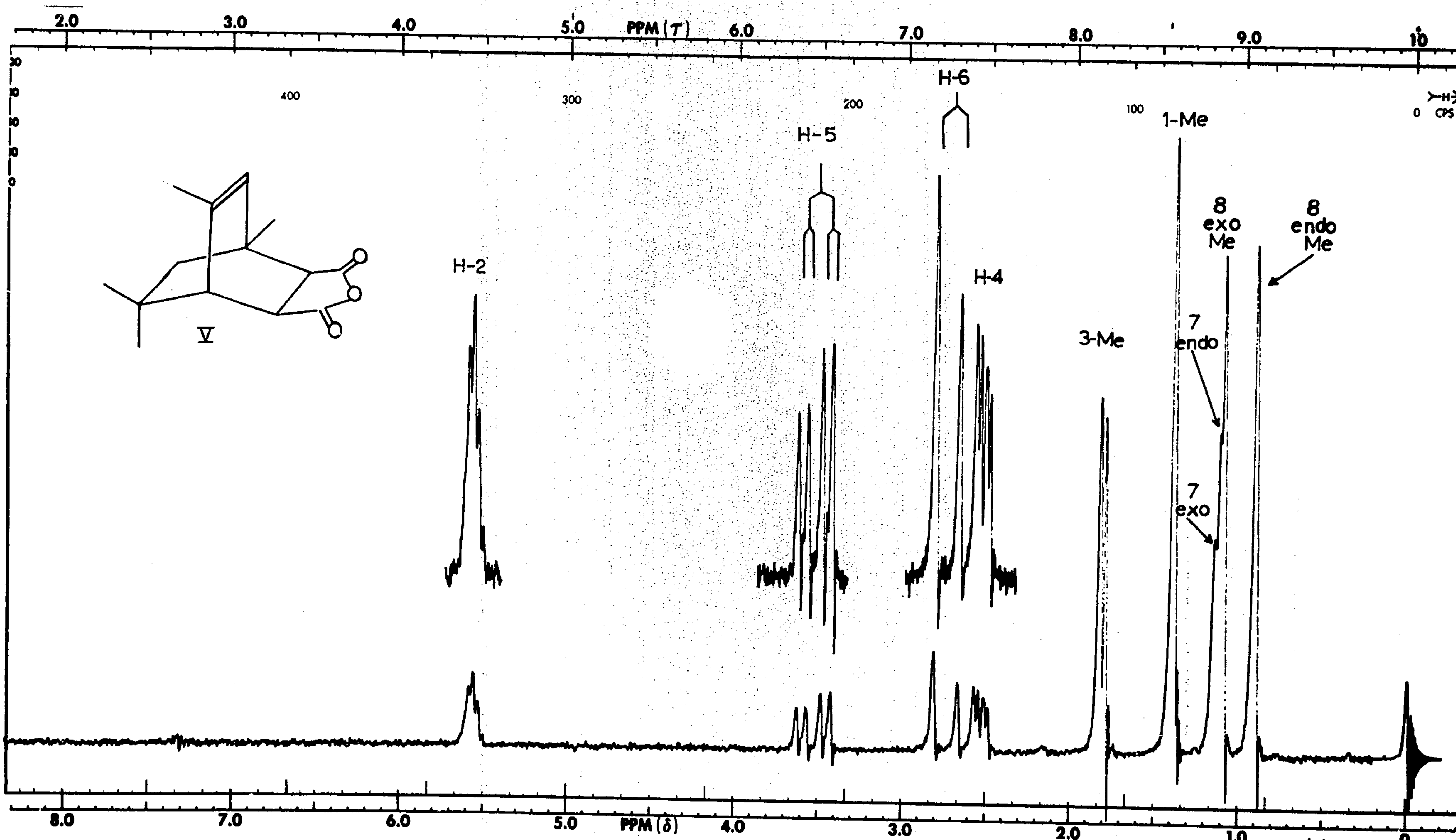


Figure 5. - Proton Magnetic Resonance Spectrum of the 5,6-endo Anhydride of Bicyclo-octene A (V). (5 mole % in $CDCl_3$).

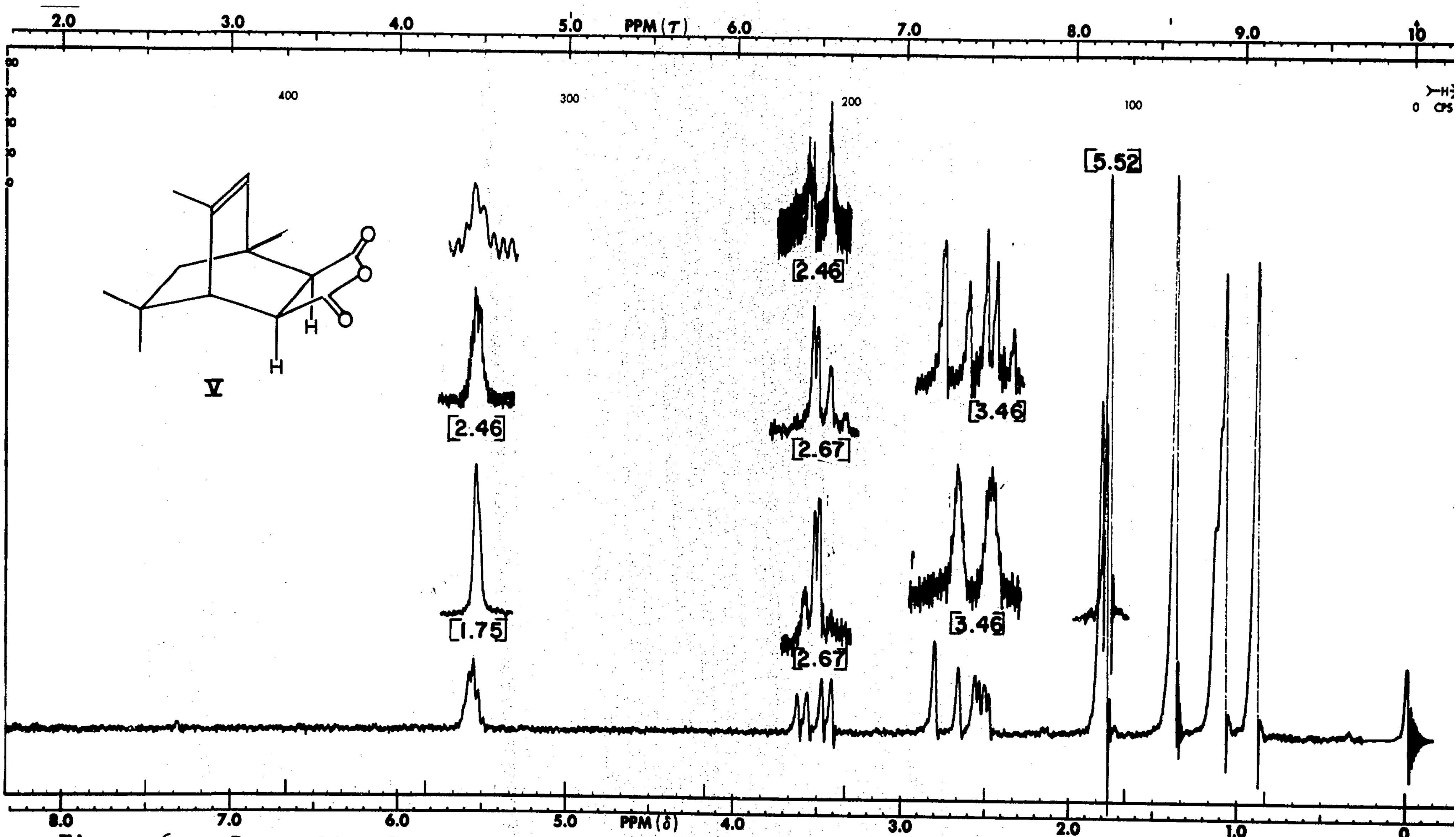
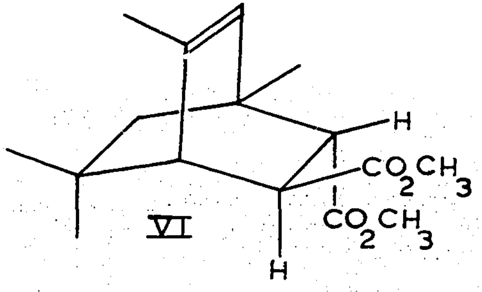


Figure 6. - Decoupling Experiments on the Proton Magnetic Resonance Spectrum of the 5,6-*endo* Anhydride of Bicyclo-octene A (V) in $CDCl_3$. Nos. in Square Brackets Indicate the Chemical Shift of the Proton Being Irradiated.

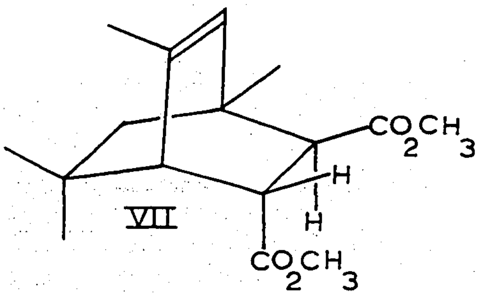
coupled to the vinyl proton ($J_{CH_3,H} = 1.8$ c/s).

The stereochemistry of the adduct is indicated by the absorption pattern for the proton at C-6 which appears as a clean doublet at 2.67 p.p.m. An <u>endo</u> proton at this position is expected to show long range "W" coupling to the <u>endo</u> proton at C-7. Since no such coupling is observed the proton at C-6 must be <u>exo</u> and, hence, the anhydride adduct must be <u>endo</u> as predicted by the Alder Rule.[79] The resonance pattern for the C-5 proton ($\delta^{CDCl_3} = 3.46$ p.p.m.) is a doublet of doublets showing coupling to the C-6 proton ($J_{5,6} = 8.5$ c/s) and the bridgehead proton ($J_{4,5} = 3.5$ c/s). These coupling interactions were confirmed by decoupling experiments (Fig. 6).

Addition of the "diene" to dimethyl fumarate does not take place as readily as the reaction with maleic anhydride. On refluxing a solution of the dienophile in the diene, a mixture of compounds was obtained from which two diesters VI and VII can be isolated by column chromatography, the former being the major product (≃ 10:1).



VI



VII

Both compounds show carbonyl absorption in the infrared ($\nu_{max}^{CHCl_3}$ 1725 cm^{-1} and 1720 cm^{-1}, respectively). The proton magnetic resonance spectra (Figs. 7 and 8) indicate that each compound possesses a vinyl proton, a vinyl methyl group and two carbomethoxyl groups. The chemical shifts and coupling constants are listed in Tables III to V and XII.

As in the case of the maleic anhydride adduct, V, the stereochemistry of each of the 5,6 diesters is readily determined from the resonance pattern of the C-6 proton. In compound VI, the absorption of this proton appears as a doublet of doublets (δ^{CDCl_3} = 2.60 p.p.m.) showing that the C-6 proton is coupled to two other protons, the vicinal proton at C-5 and one of the protons at C-7 ($J_{5,6}$ = 5.9 c/s, $J_{6,7}$ = 2.0 c/s). The larger splitting is clearly seen in the absorption pattern for the C-5 proton (δ^{CDCl_3} = 3.42 p.p.m.) while the smaller coupling interaction appears as secondary splitting in the high field portion of the AB pattern for the C-7 methylene protons. Further, the C-6 proton absorbs at higher field than the C-5 proton. Taken together, the above experimental evidence indicates clearly that the C-6 proton is in the <u>endo</u>-position and that compound VI is 5-<u>endo</u>-6-<u>exo</u>-dicarbomethoxybicyclo-octene A.

In the proton spectrum of compound VII, the positions of the C-5 and C-6 protons are reversed with the C-5 proton at higher field. Also the C-6 proton shows no long range

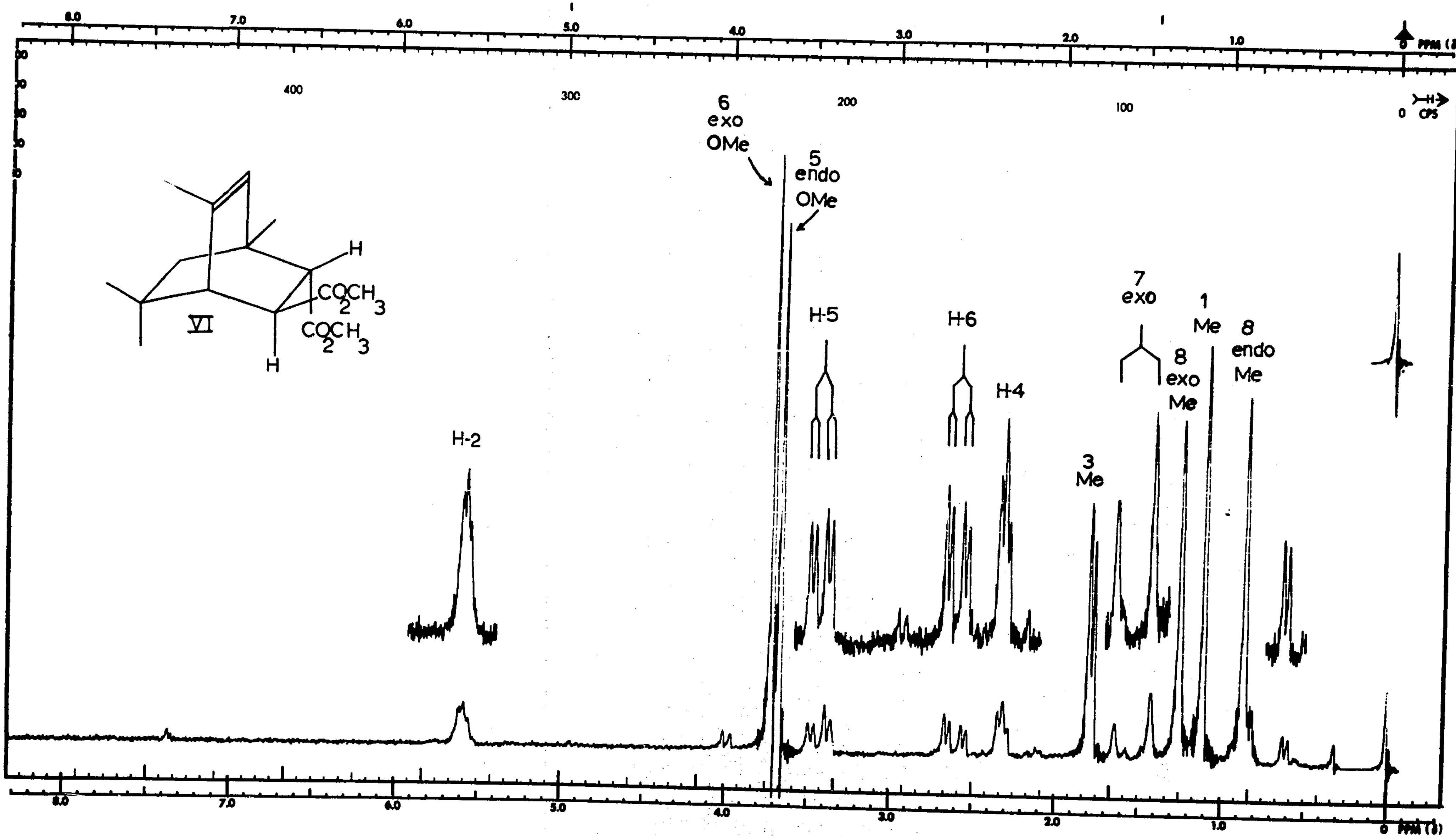


Figure 7. - Proton Magnetic Resonance Spectrum of 5-endo-6-exo-Dicarbomethoxybicyclo-octene A (VI) in $CDCl_3$.

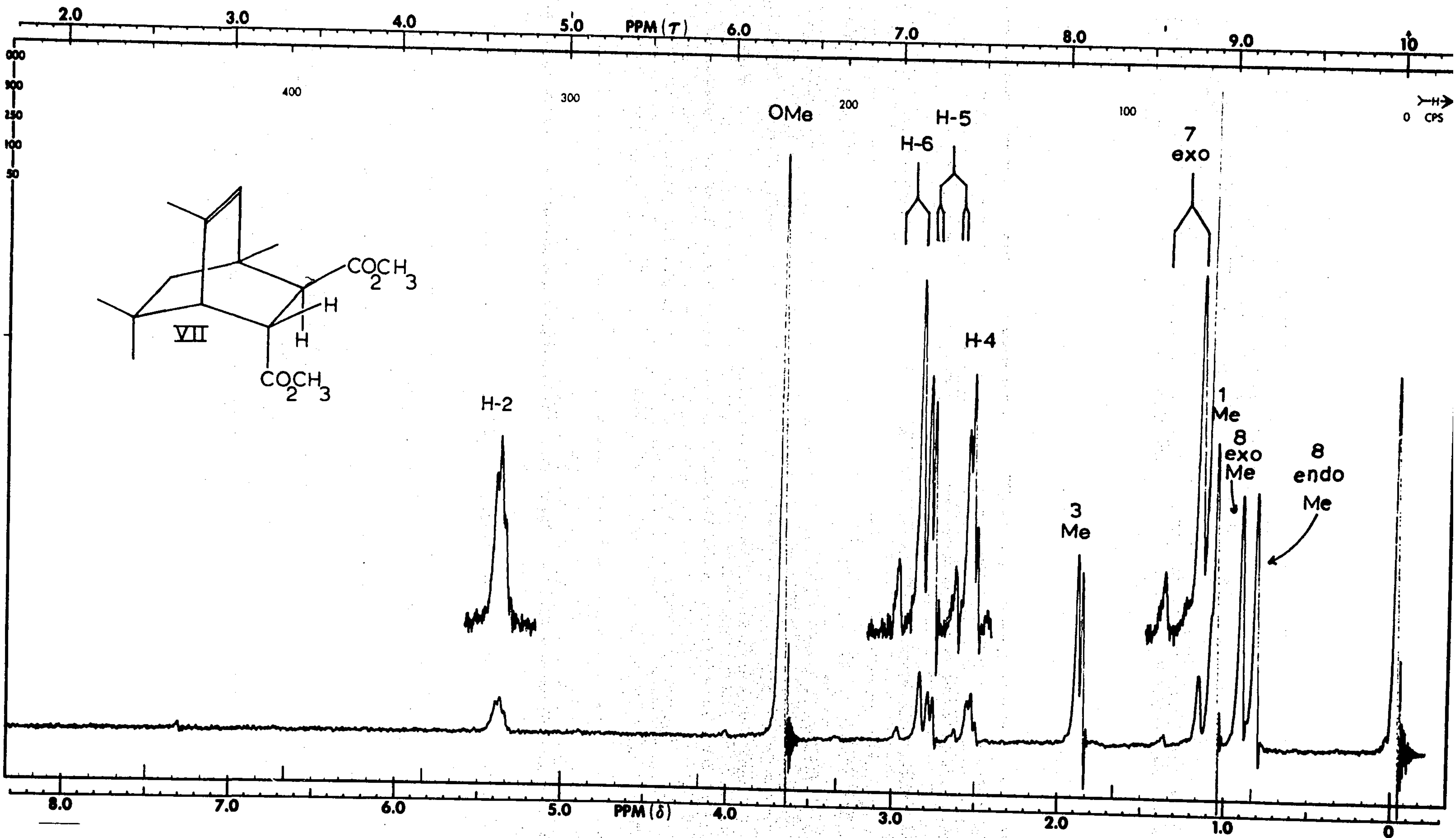


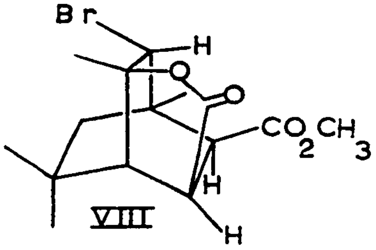
Figure 8.- Proton Magnetic Resonance Spectrum of 5-exo-6-endo-Dicarbomethoxybicyclooctene A (VII) in CDCl₃.

coupling. These spectral features are consistent with compound VII being 5-_exo_-6-_endo_-dicarbomethoxybicyclo-octene A.

(c) Bromination of the Diels-Alder Adducts.

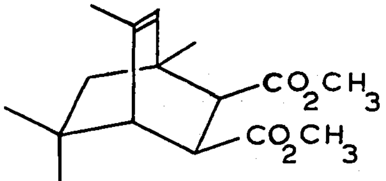
(i) Bromination of the endo-5,6-Anhydride of Bicyclooctene A (V)

Bromination of the _endo_-5,6-anhydride of bicyclooctene A (V), followed by methylation of the resulting carboxylic acid yields the _trans_-bromolactone VIII. This compound



VIII

is also obtained by methylation of the anhydride (V) to form the _cis_-diester (IX) and subsequent bromination of the _cis_-5,6-dister.



IX

The presence of a γ-lactone is shown by infrared spectroscopy ($\nu_{max}^{CHCl_3}$ 1783 cm^{-}) and its attachment to C-3 is readily deduced from the proton spectrum in deuteriochloroform (Fig. 9) in which the resonance of the C-3

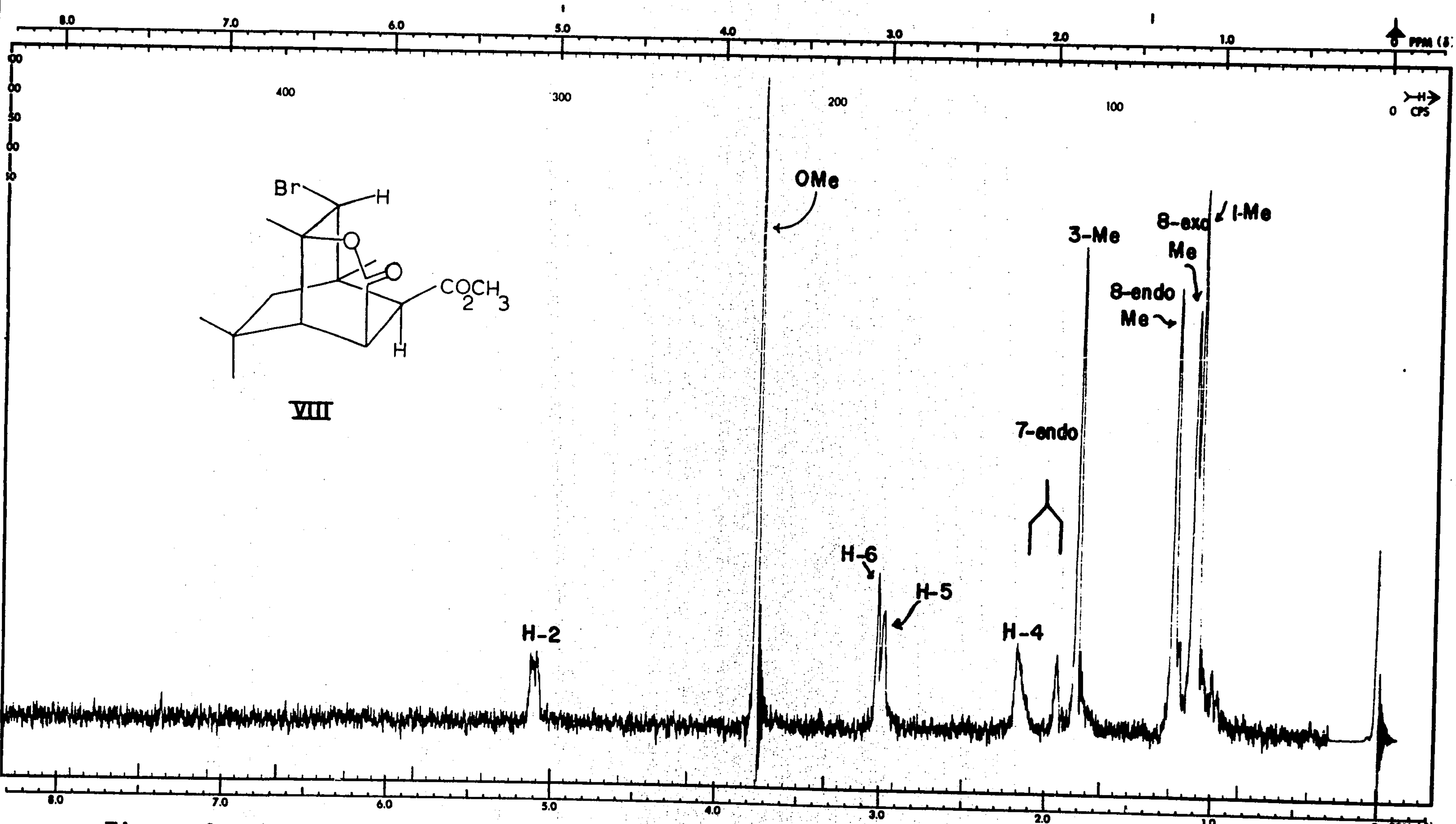


Figure 9. - Proton Magnetic Resonance Spectrum of the trans-Bromolactone (VIII) from the cis-endo Diester of Bicyclo-octene A in $CDCl_3$.

methyl group appears as a singlet with a chemical shift of 1.79 p.p.m.

The stereochemistry of the ester function is confirmed by the lack of long range coupling in the absorption pattern of the 7-endo proton while the presence of a long range coupling in the resonance pattern for the 7-exo proton shows that the C-2 proton must be in the position shown. Decoupling experiments proved conclusively that the C-2 proton is coupled to a C-7 proton (Fig. 10b). The double irradiation experiments also indicate the presence of a small coupling between the C-2 proton and the bridgehead proton at C-4 (Fig. 10c). This coupling is not unexpected since at least two factors can distort the bicyclo[2.2.2]-octane system so that the H-C-C-C-H fragment involving C-2, C-3 and C-4 approaches the "W" configuration. These factors are:

(a) steric repulsion between the methyl group at C-3 and the endo-methyl group at C-8, and

(b) the five-membered ring containing C-3 and C-5.

Other contributing factors may include interactions between bromine at C-2 and both the methyl group at C-3 and the 8-endo methyl group as well as steric interference between the C-2 proton and the carbomethoxyl group at C-6.

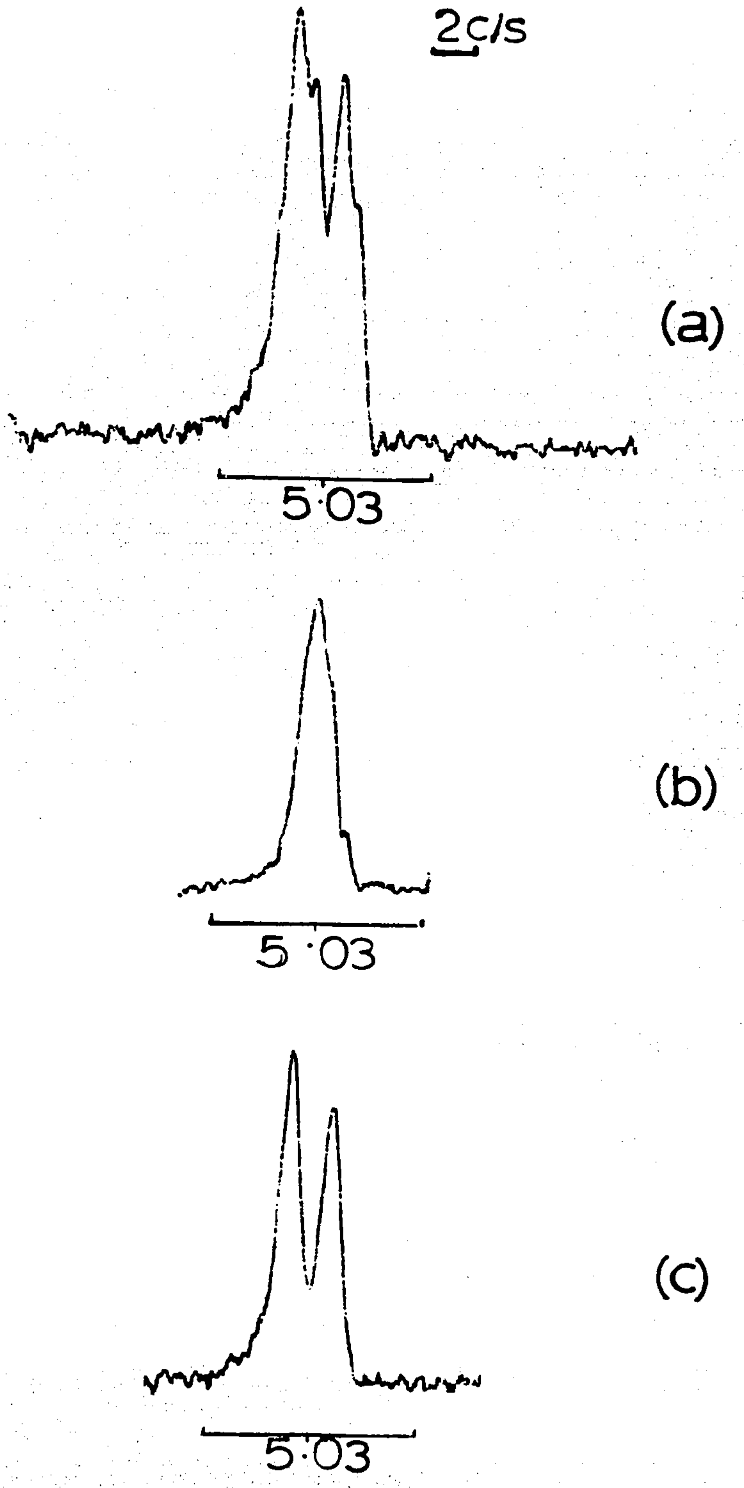
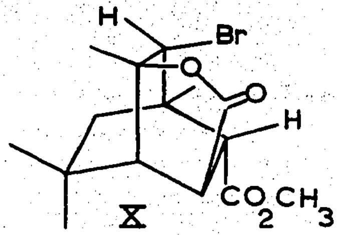


Figure 10. - The Resonance Pattern for the C-2 Proton in the Bromolactone (VIII). (a) Normal, (b) With the C-7 *exo* Proton (1.09 p.p.m.) Irradiated and (c) With the C-4 Proton (2.12 p.p.m.) Irradiated. (The Decoupling Experiments were Performed at 100 Mc/s.).

(ii) Bromination of 5-endo-6-exo-Dicarbomethoxybicyclo-octene A (VI)

Three compounds were isolated from the mixture obtained by adding bromine to 5-*endo*-6-*exo*-dicarbomethoxybicyclo-octene A (VI). The major product is the *cis*-bromolactone (X).



X

Infrared spectroscopy showed the presence of a γ-lactone ($\nu_{max}^{CHCl_3}$ 1786 cm^{-1}) as well as an ester function ($\nu_{C=O}^{CHCl_3}$ 1739 cm^{-1}). The stereochemistry of the ester function is assigned by the same criterion used for the parent compound (VI). In this case the absorption of the C-6 proton (Fig. 11) comprises an apparent "triplet" (δ^{CDCl_3} = 2.73 p.p.m.) and it is clear that the pattern for the *endo* C-7 proton is a doublet of doublets (δ^{CDCl_3} = 1.25 p.p.m.) although a portion of the band is obscured by methyl absorption. Decoupling experiments (Fig. 12) confirm the coupling between these two protons and the coupling constant for the interaction is 2.2 c/s. Thus, the C-6 proton must be *endo*, and hence the carbomethoxyl substituent is in the *exo* configuration. The singlet at 4.01 p.p.m. is assigned to the C-2 proton. No coupling interaction is found between this proton and that in the 7-*exo* position. The stereochemistry at C-2 must, therefore, be that indicated in structure X.

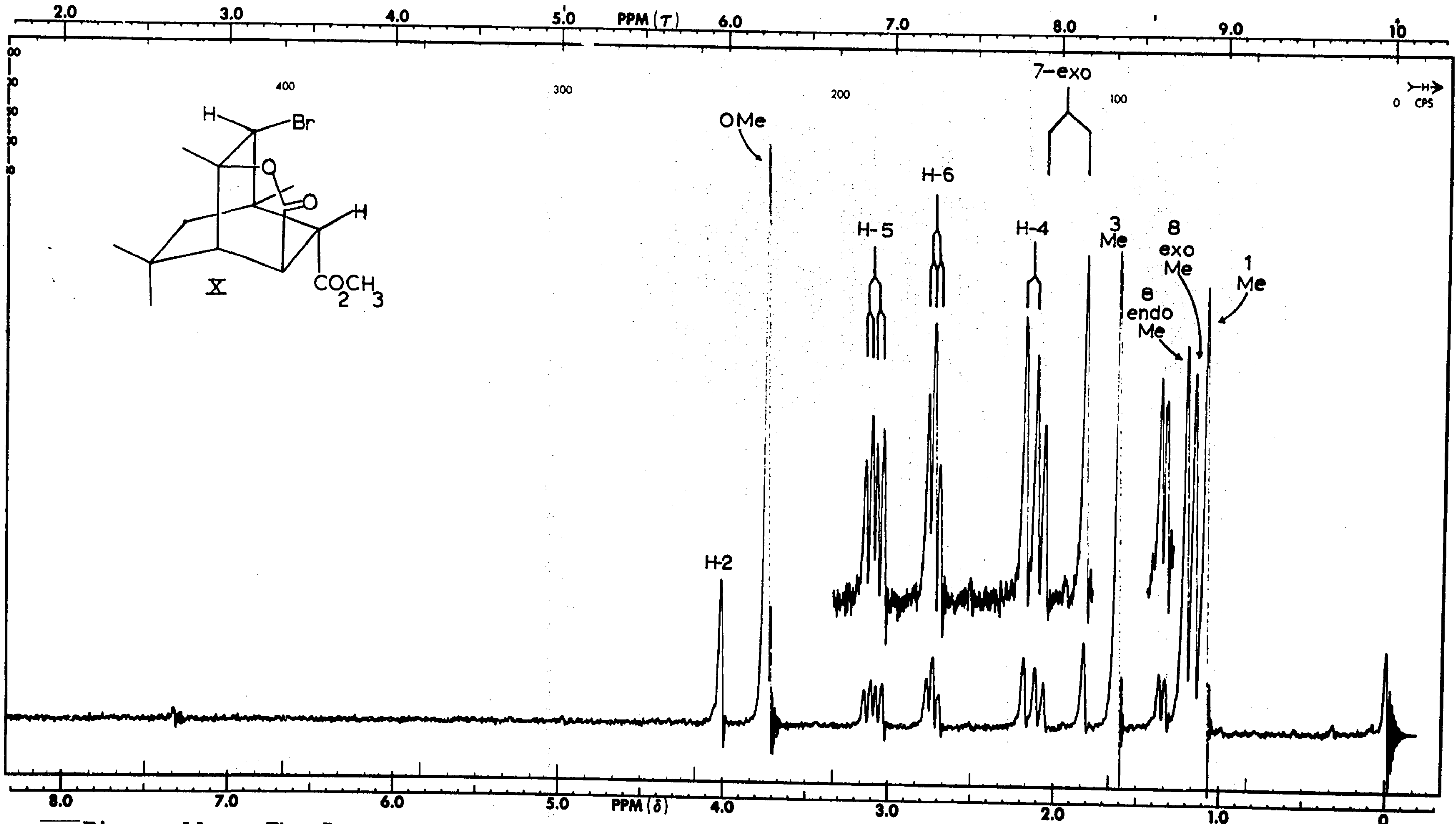


Figure 11. - The Proton Magnetic Resonance Spectrum of the *cis*-Bromolactone (X) Derived from 5-*endo*-6-*exo*-Dicarbomethoxybicyclo-octene *A* in $CDCl_3$.

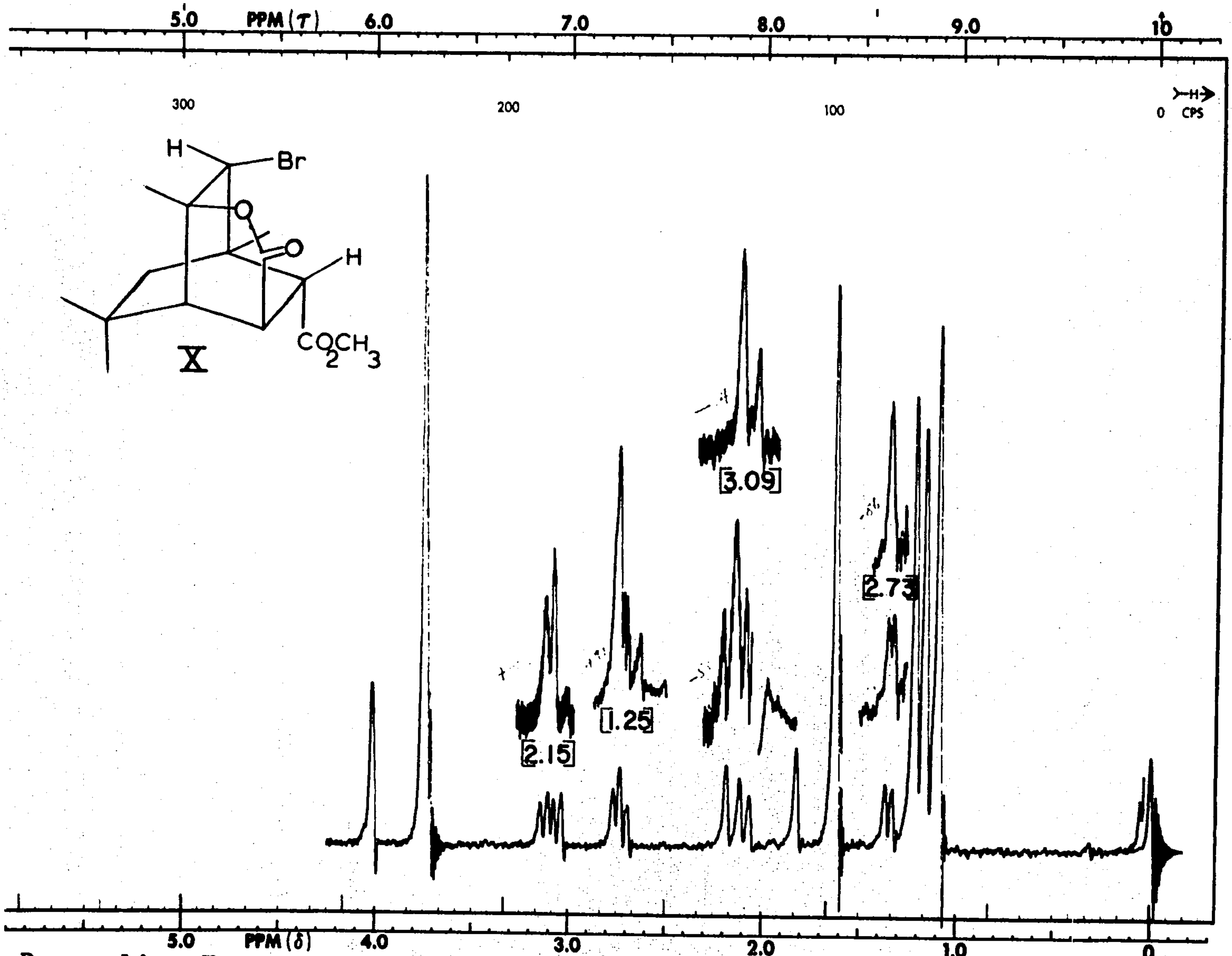
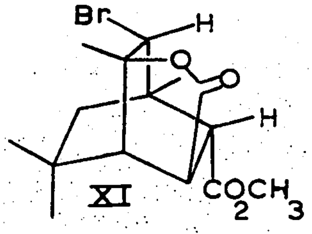


Figure 12. - Decoupling Experiments on the Proton Magnetic Resonance Spectrum of *cis*-Bromolactone X in $CDCl_3$.

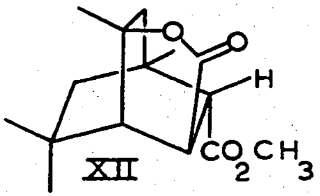
The attachment of the lactone ring at C-3 is indicated by singlet resonance of the methyl group at 1.63 p.p.m.

A second bromolactone was isolated from the bromination of compound VI. This product is 6-exo-carbomethoxybicyclo-octene-A-trans-bromolactone (XI). Carbonyl absorption in the infrared shows the presence of a γ-lactone ($\nu_{max}^{CHCl_3}$ 1775 cm^{-1}) and an ester group ($\nu_{max}^{CHCl_3}$ 1730 cm^{-1}). The position of the lactone ring is indicated by the absorption of the C-3 methyl group (singlet, δ^{CDCl_3} = 1.79 p.p.m.). The stereochemical difference between the cis-bromolactone (X) and the trans-bromolactone (XI) is clearly reflected in their proton spectra. For example, the C-3 methyl group of the trans-bromolactone is deshielded by 0.16 p.p.m. relative to the corresponding group in the cis-bromolactone. It is interesting to note that its chemical shift in XI (1.79 p.p.m.) is identical to that found for the C-3 methyl group in 6-endo-carbomethoxybicyclo-octene-A-trans-bromolactone (VIII). Further evidence of the orientation of the C-2 proton in XI is given by its own resonance pattern, which is a doublet (δ^{CDCl_3} = 4.15 p.p.m.) showing coupling with the 7-exo proton.



XI

The third component isolated from the product mixture contains no halogen and is assigned structure XII.

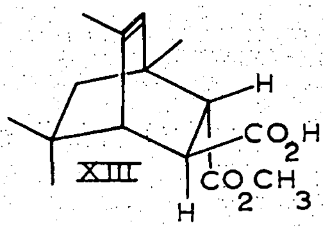


XII

Infrared spectroscopy indicated the presence of a γ-lactone ($\nu_{max}^{CHCl_3}$ 1770 cm^{-1}) and an ester group ($\nu_{C=O}^{CHCl_3}$ 1735 cm^{-1}). From the proton spectrum (Fig. 13), it is concluded that the lactone bridge is attached to C-3 because of the singlet at 1.56 p.p.m. (in $CDCl_3$) for the C-3 methyl group. Three peaks are seen for the C-6 proton (δ^{CDCl_3} = 2.42 p.p.m.) which arise from coupling with the C-5 proton and the <u>endo</u> proton at C-7.

<u>Debromination of Bromolactones X and XI</u>

Treatment of either the <u>cis</u>-bromolactone X or the <u>trans</u>-bromolactone XI with zinc and acetic acid gives 6-<u>exo</u>-carbomethoxybicyclo-octene-A-5-<u>endo</u>-carboxylic acid (XIII).



XIII

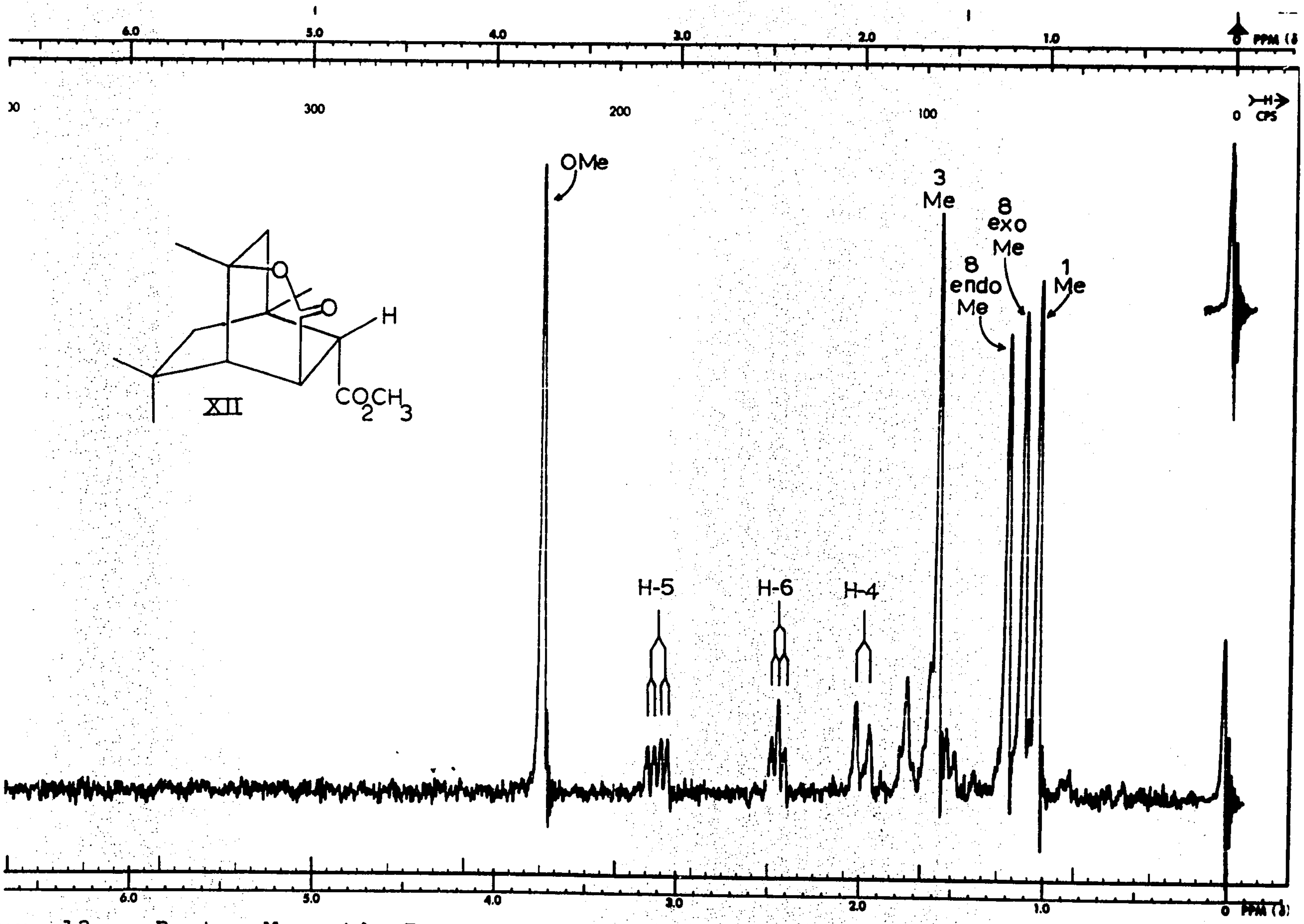


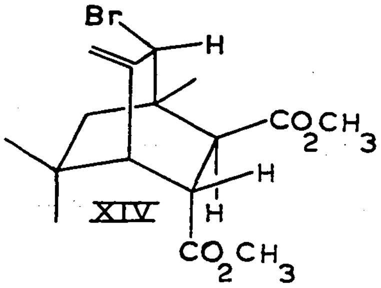
Figure 13. - Proton Magnetic Resonance Spectrum of the γ-lactone (XII) Derived from 5-endo-6-exo-Dicarbomethoxybicyclo-octene A in $CDCl_3$.

The infrared spectrum of this compound shows a broad hydroxyl absorption band (2400 cm^{-1} - 3600 cm^{-1}), characteristic of carboxylic acids, as well as carbonyl absorption indicating an ester group ($\nu_{C=O}^{CHCl_3}$ 1720 cm^{-1}) and a carboxylic acid group ($\nu_{C=O}^{CHCl_3}$ 1700 cm^{-1}). Comparison of the proton spectra of compounds VI and XIII reveals that the chemical shifts and coupling constants for the protons in the two compounds are almost identical, establishing that the geometry of the bicyclo[2.2.2]octene system is the same in the two cases.

The half-ester is readily converted to 5-_endo_-6-_exo_-dicarbomethoxybicyclo-octene A (VI) by treatment with diazomethane.

(iii) Bromination of 5-exo-6-endo-Dicarbomethoxybicyclo-octene A (VII)

A single crystalline compound is obtained when the _trans_-diester VII is treated with bromine in acetic acid. The product is 1,8,8-trimethyl-3-methylene-5-_exo_-6-_endo_-dicarbomethoxy-2-_trans_-bromobicyclo[2.2.2]octane (XIV).



XIV

The mass spectrum of this compound has a parent peak at m/e = 358 with a peak of almost equal intensity at m/e = 360. This is consistent with the molecular formula $C_{16}H_{23}O_4Br$. The infrared spectrum shows carbonyl absorption ($\nu_{C=O}^{CHCl_3}$ = 1730 cm^{-1}) and the presence of an olefin ($\nu_{C=C}^{CHCl_3}$ = 1620 cm^{-1}). Proton spectroscopy (Fig. 14) suggests two carbomethoxyl groups (δ^{CDCl_3} = 3.66 and 3.69 p.p.m.) and three tertiary methyl groups (δ^{CDCl_3} = 0.84, 0.95 and 1.11 p.p.m., respectively). The multiplet at low field is assigned to the C-2 proton (δ^{CDCl_3} = 5.84 p.p.m.), the configuration of which is indicated by its coupling to the exo proton at C-7 (δ^{CDCl_3} = 0.82 p.p.m.). The presence of such an interaction was confirmed by decoupling experiments. The two proton pattern centred at 4.08 p.p.m. is assigned to the terminal methylene protons while the complex pattern at about 2.90 p.p.m. is due to the protons at C-4, C-5 and C-6. Better separation of the latter absorption band is achieved by changing the solvent to benzene, in which the C-5 and the C-6 protons are deshielded ($\delta^{C_6H_6}$ = 3.16 p.p.m.) relative to the bridgehead proton ($\delta^{C_6H_6}$ = 2.91 p.p.m.).

Attempts to add bromine to the exocyclic double bond were partially successful, but gave a mixture of products. Further evidence for the exocyclic double bond was obtained by ozonolysis which yielded a ketonic product which formed a 2,4-dinitrophenylhydrazone. Under the conditions used, ozonolysis of an internal (2,3) double bond would give a

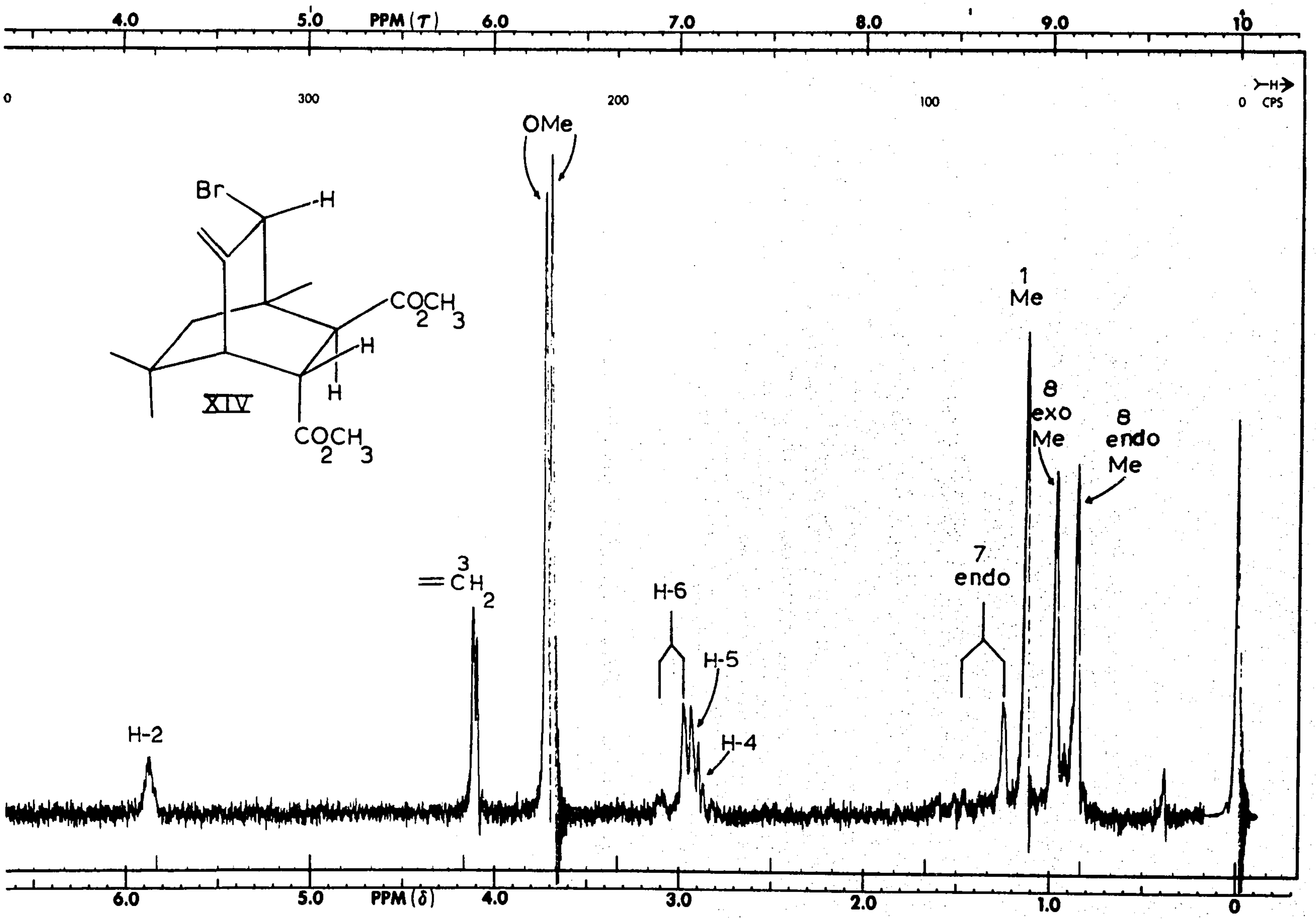
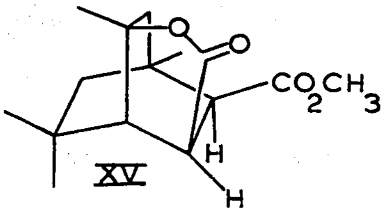


Figure 14. - Proton Magnetic Resonance Spectrum of 1,8,8-Trimethyl-3-methylene-5-exo-6-endo-dicarbomethoxy-2-trans-bromo-bicyclo[2.2.2]octane (XIV) in $CDCl_3$.

product containing a carboxylic acid function as well as an acetyl (CH_3CO) group. Infrared and proton spectroscopy show the absence of any such groups.

(d) Esterification of the 5,6-endo-Anhydride of Bicyclooctene A

As mentioned previously (page 42), methylation of the anhydride yields the *cis*-*endo* diester IX. If the esterification is carried out with an ethereal solution of diazomethane, the *cis*-*endo* diester IX is the sole product. If acidified methanol is used, a γ-lactone (XV) (ν^{CHCl_3} = 1780 cm^{-1}) is obtained in addition to the *cis*-*endo* diester.



XV

Although the proton spectrum of this compound appears complex, the pattern for each proton (or group of protons) can be assigned (see Table IX). The position of the lactone-bridge is determined by the same criterion as before ($\delta^{CDCl_3}_{3Me}$ = 1.57 p.p.m.) and the *endo* position of the C-6 substituent is confirmed by the coupling of the *exo* C-6 proton to the *trans* C-2 proton.

product containing a carboxylic acid function as well as an acetyl (CH_3CO) group. Infrared and proton spectroscopy show the absence of any such groups.

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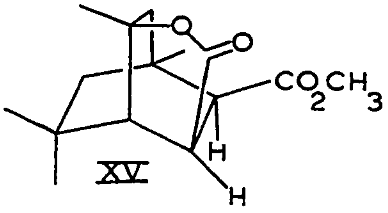
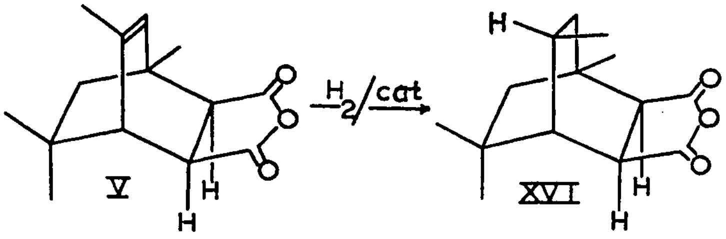


XV

(e) Hydrogenation of the Unsaturated Compounds

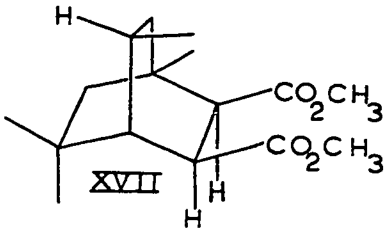
Catalytic hydrogenation of the 5,6-cis-endo-anhydride V gave the saturated compound XVI,



V XVI

with the C-3 methyl group in the syn-position as illustrated. The proton spectrum of this compound is shown in Fig. 15. The stereochemistry at C-3 was determined by decoupling experiments which revealed coupling between the C-3 and C-5 protons. Since the latter is in the exo-position the C-3 proton must be anti to the C-5 substituent.

Attempts to remove the double bond catalytically from the cis-endo-diester IX gave mixtures containing large amounts of the saturated anhydride XVI. Samples of 1,3-syn-8,8-tetramethyl-5-endo-6-endo-dicarbomethoxybicyclo[2.2.2]octane XVII were obtained by methylation of the saturated anhydride (XVI) with an ethereal solution of diazomethane.



XVII

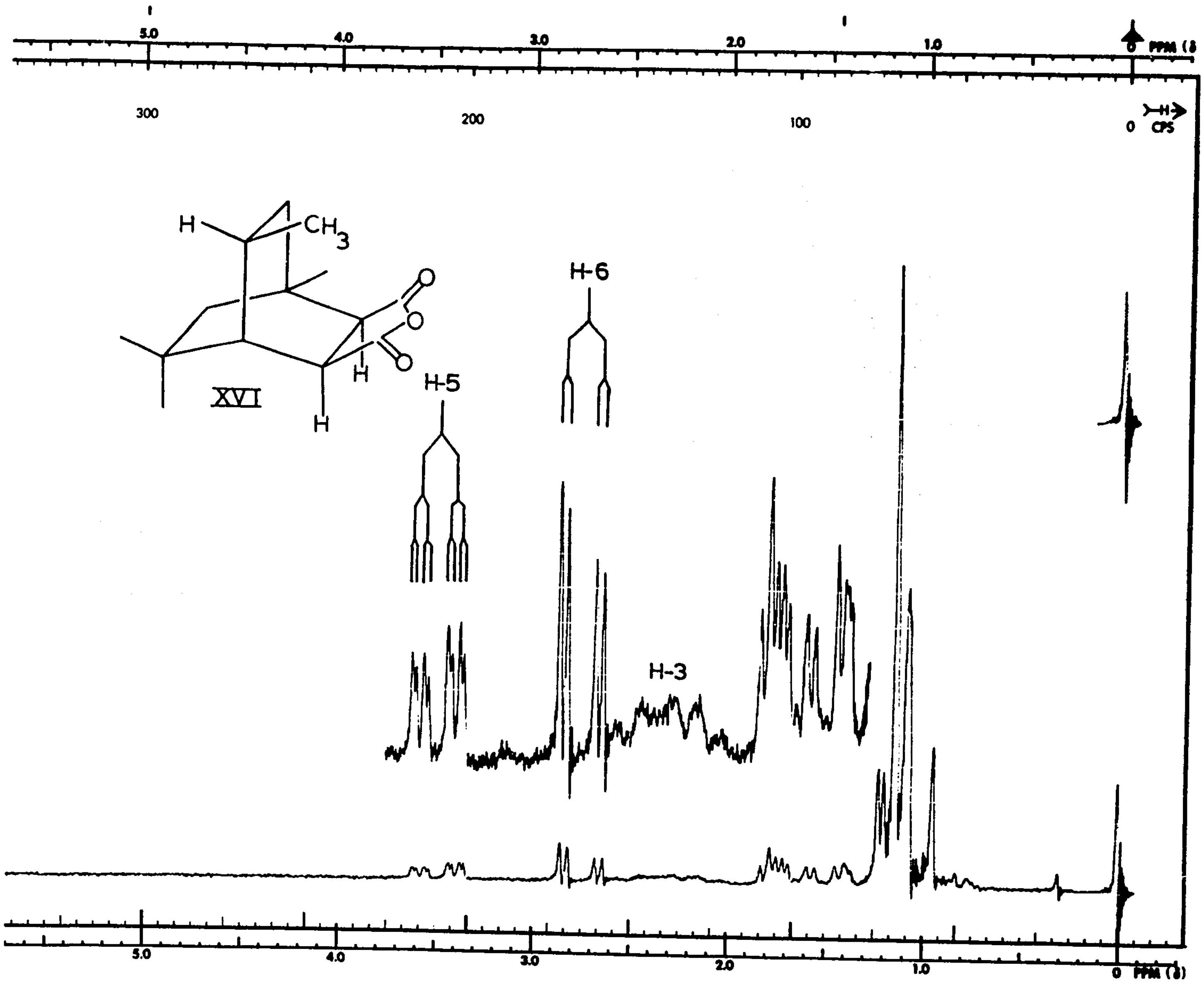
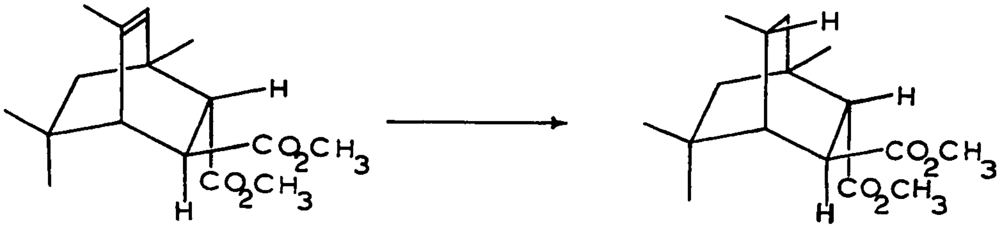


Figure 15. - Proton Magnetic Resonance Spectrum of the Saturated Anhydride XVI in $CDCl_3$.

The stereochemistry at C-3 was again readily demonstrated by irradiating the C-3 proton while the C-5 proton absorption was being observed. The disappearance of the small long range coupling from the resonance pattern of the latter proton indicates that the C-3 proton is anti to the 5,6-ethano bridge.

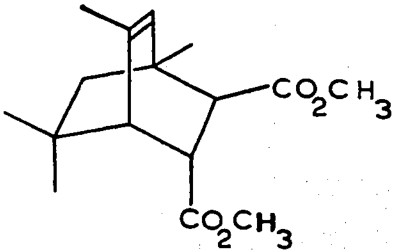
When the 5-endo-6-exo-dicarbomethoxy compound VI is hydrogenated, the saturated product has the methyl group anti to the 5,6 ethano bridge (XVIII).



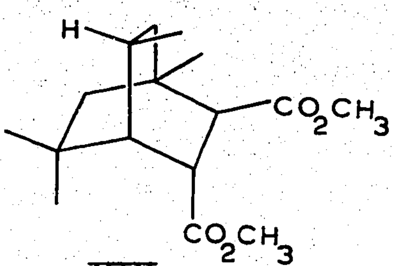
VI XVIII

This stereochemical assignment is based on the resonance pattern for the C-5 proton. This band comprises a doublet of doublets with the C-5 proton coupled to the protons at C-4 and C-6 but showing no coupling with the C-3 proton.

The product obtained by catalytic hydrogenation of 5-exo-6-endo-dicarbomethoxybicyclo-octene A is thought to have structure XIX. The C-3 methyl group is assigned a configuration syn to the 5,6 ethano bridge because of the large downfield shift (0.47 p.p.m.) of the 5-endo proton (δ^{CDCl_3} = 3.22 p.p.m.) compared with the corresponding shift (0.11 p.p.m.) of the 6-endo proton (δ^{CDCl_3} = 2.71 p.p.m.) upon hydrogenation of the 5-endo-6-exo-dicarbomethoxy compound (VI). The proton spectrum of compound XIX is shown in Fig. 16.



VII



XIX

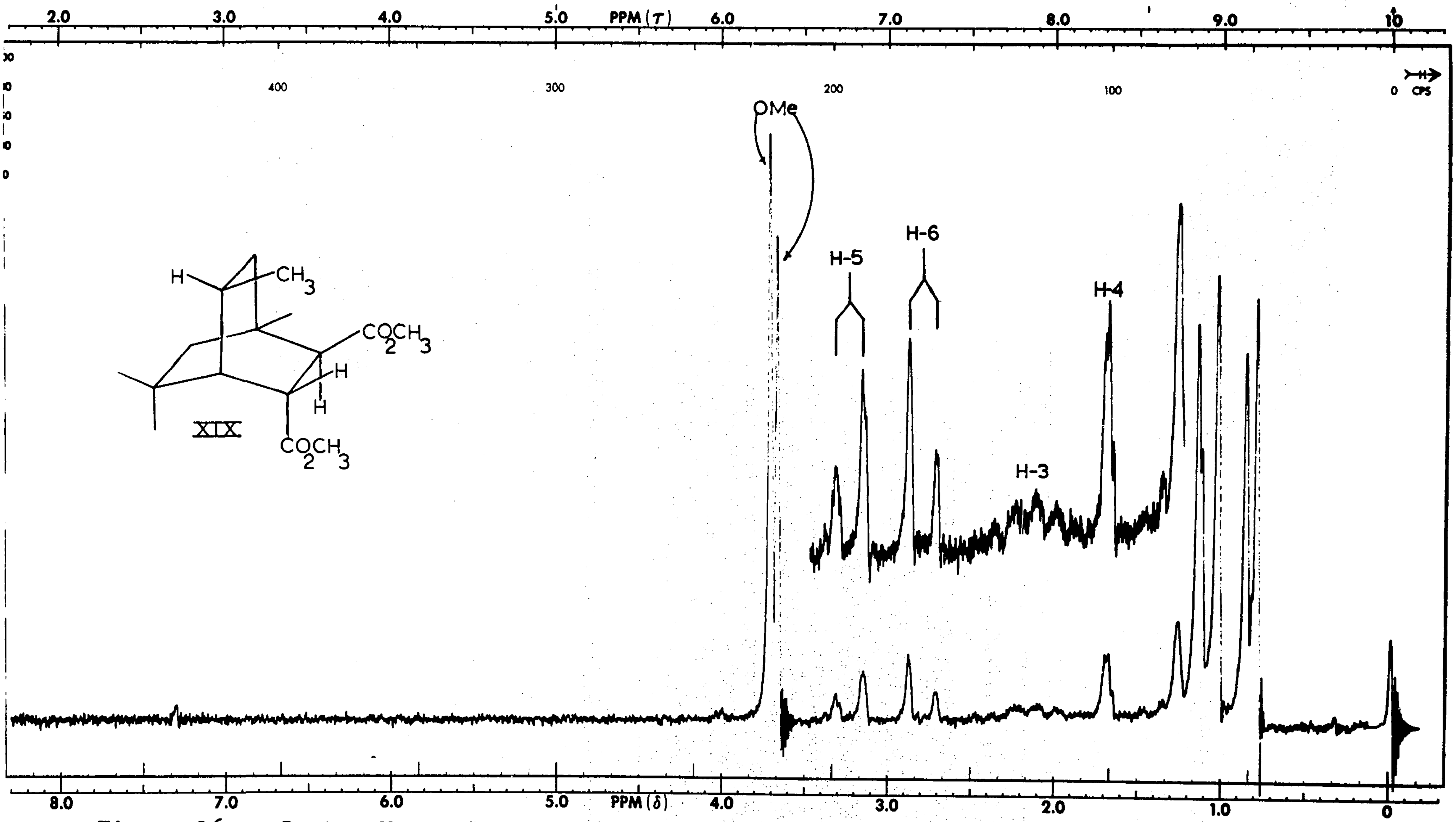


Figure 16. - Proton Magnetic Resonance Spectrum of the Saturated 5-*exo*-6-*endo*-Diester (XIX) in $CDCl_3$.

Mechanistic Considerations

(a) Formation of the trans-Bromolactone VIII from 5-endo-6-endo-Dicarbomethoxybicyclo-octene A

Mechanistic pathways which can lead to the formation of bromolactone VIII are illustrated in Fig. 17. Essentially, the two alternatives involve either the bromonium ion XX or the carbonium ion XXI. The products obtained can be readily explained in terms of either intermediate.

In view of the favourable spatial disposition of the ester function, as well as the steric hindrance to attack on the carbonium ion XXI by an external agent, the absence of dibromide XXII in the product is not surprising.

(b) Formation of the Bromolactones from 5-endo-6-exo-Dicarbomethoxybicyclo-octene A

The *trans* bromolactone XI arises in a manner analogous to that postulated for the corresponding derivative of 5-*endo*-6-*endo*-dicarbomethoxybicyclo-octene A.

In this case, however, the stereochemistry of the hydrogenation product (XVIII) indicates that the ethano bridge containing C-7 is on the more hindered side of the double bond. Initial attack from the less hindered side gives the major product - the *cis*-bromolactone (X). For the same reasons stated in the previous case, the formation of a dibromide is unlikely.

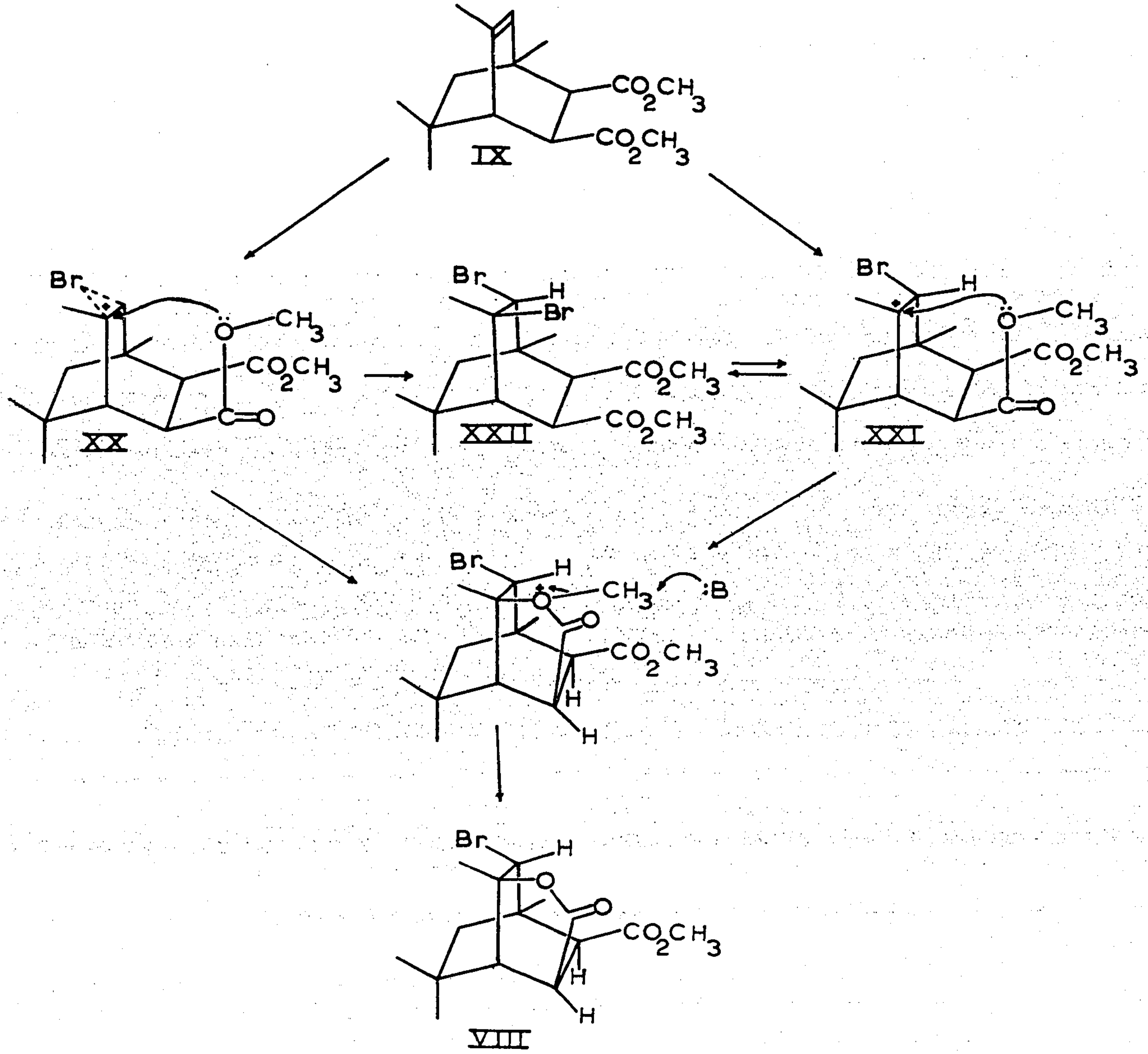


Figure 17. - Mechanistic Pathways for the Formation of <u>trans</u>-Bromolactone VIII.

(c) Bromination of 5-exo-6-endo-Dicarbomethoxybicyclo-octene A.

Fig. 18 illustrates a possible mechanism for the formation of the observed product. From the configuration of C-3 in the hydrogenation product, XIX, it can be concluded that the 7,8-ethano bridge is on the less hindered side of the double bond. Again the intermediate may be either a bromonium ion (XXIII) or a carbonium ion (XXIV) although elimination of a proton from the latter is more readily visualized. An alternative mechanism involves the formation of a dibromide and subsequent solvolysis of the tertiary halide.

(d) The Origin of Compound XII.

In the reaction of 5-endo-6-exo-dicarbomethoxybicyclo-octene A (VI) with bromine in acetic acid, the lactone, XII, is probably formed by protonation of the carbon-carbon double bond to give a tertiary carbonium ion at C-3 with subsequent attack by the C-5-endo carbomethoxyl group. The alternative synthesis of this lactone by refluxing the unsaturated diester (VI) in glacial acetic acid lends some support to this postulate.

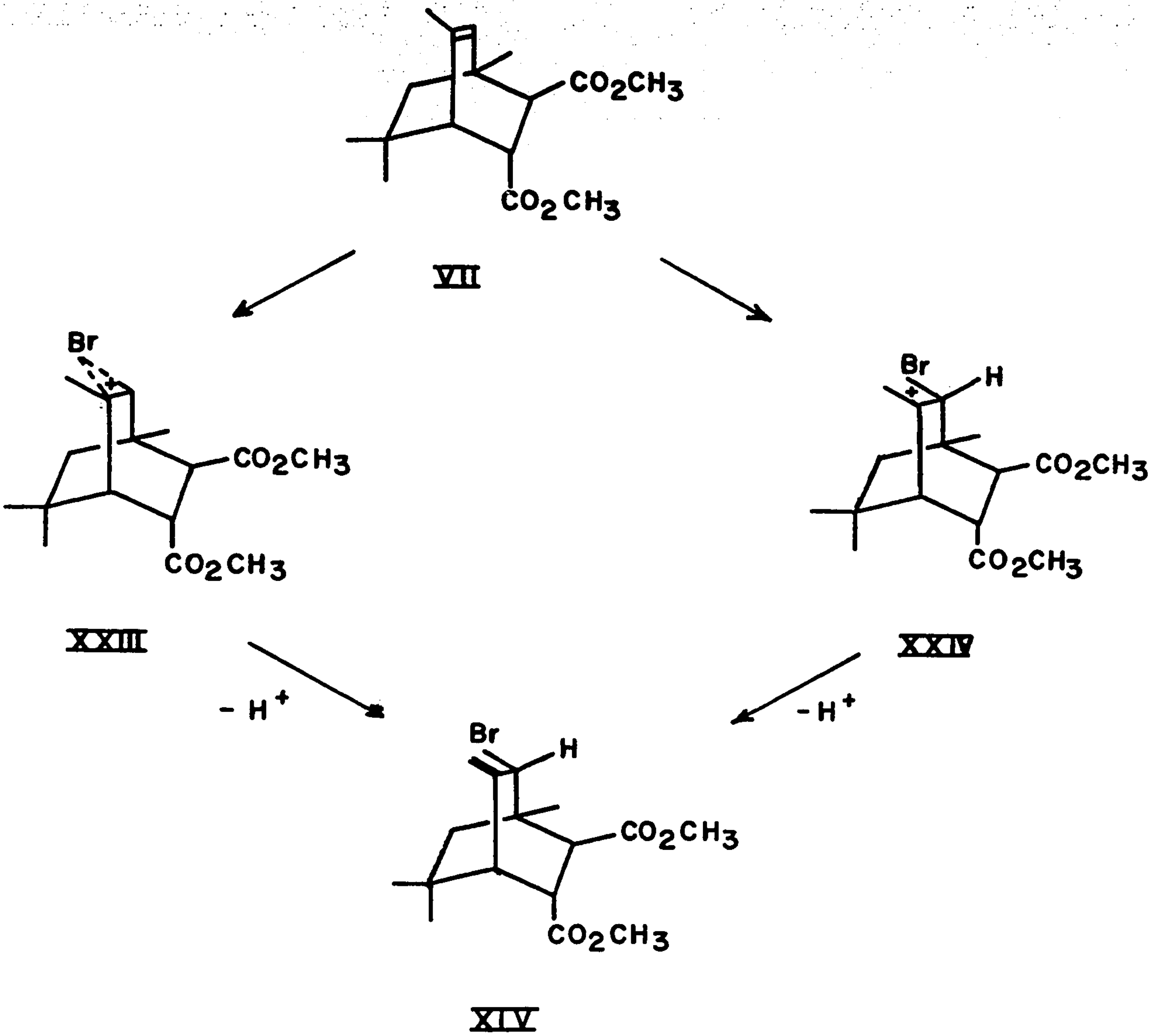


Figure 18. - A Mechanism for the Bromination of 5-*exo*-6-*endo*-Dicarbomethoxybicyclo-octene A (VII).

Examination of the Proton Magnetic Resonance Parameters

The nuclear magnetic resonance parameters of protons in the bicyclo[2.2.2]octane system are sensitive to the nature and stereochemistry of the substituents and, in some cases, to the solvent. The variations observed are discussed below.

(a) Chemical Shifts

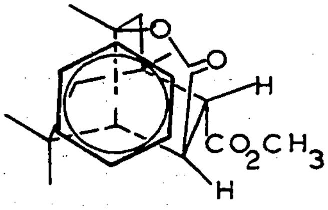
(i) Vinyl Protons

With deuteriochloroform or carbon tetrachloride as solvent, the vinyl proton absorption is at highest field in the 5-exo-6-endo-diester (δ^{CDCl_3} = 5.38 p.p.m.) and at lowest field in the 5-endo-6-exo-diester (δ^{CDCl_3} = 5.57 p.p.m.). Comparison of the chemical shifts suggests that a carbomethoxyl group in the 6-endo configuration shields the vinyl proton by 0.1 p.p.m., whereas this group in the 5-endo position has a deshielding effect of the same magnitude. When the spectra are obtained in benzene, the highest field vinyl proton is that of the cis-endo anhydride (V). This solvent shift suggests a difference in solvation between the anhydride and the diesters.

(ii) Bridgehead Protons

In the unsaturated compounds, the C-4 protons absorb in the range 2.18 - 2.54 p.p.m. An endo-carbomethoxyl group at C-5 shields the C-4 proton by 0.21 p.p.m. compared with the same substituent in the exo configuration. The relative shielding contribution of the C-6 endo-carbomethoxyl group is 0.08 p.p.m.

Hydrogenation of the double bond results in a relative shielding of between 0.53 and 0.88 p.p.m., the smallest change being found for the cis-endo diester (the spectrum of which is shown in Fig. 19) and the largest for the 5-exo-6-endo diester. Except in benzene solution, removal of the double bond by lactonization results in a comparatively small relative shielding of 0.1 p.p.m. In the aromatic solvent, the observed shielding is much larger, being 0.72 p.p.m. in the case of the cis-endo-diester and 0.95 p.p.m. for the 5-endo-6-exo diester. These results suggest that benzene solvates the lactones in a stereospecific manner. One possible orientation is shown below.



Effects of stereospecific solvation on NMR parameters are of considerable interest and have been discussed by many authors (see, for example, reference 75).

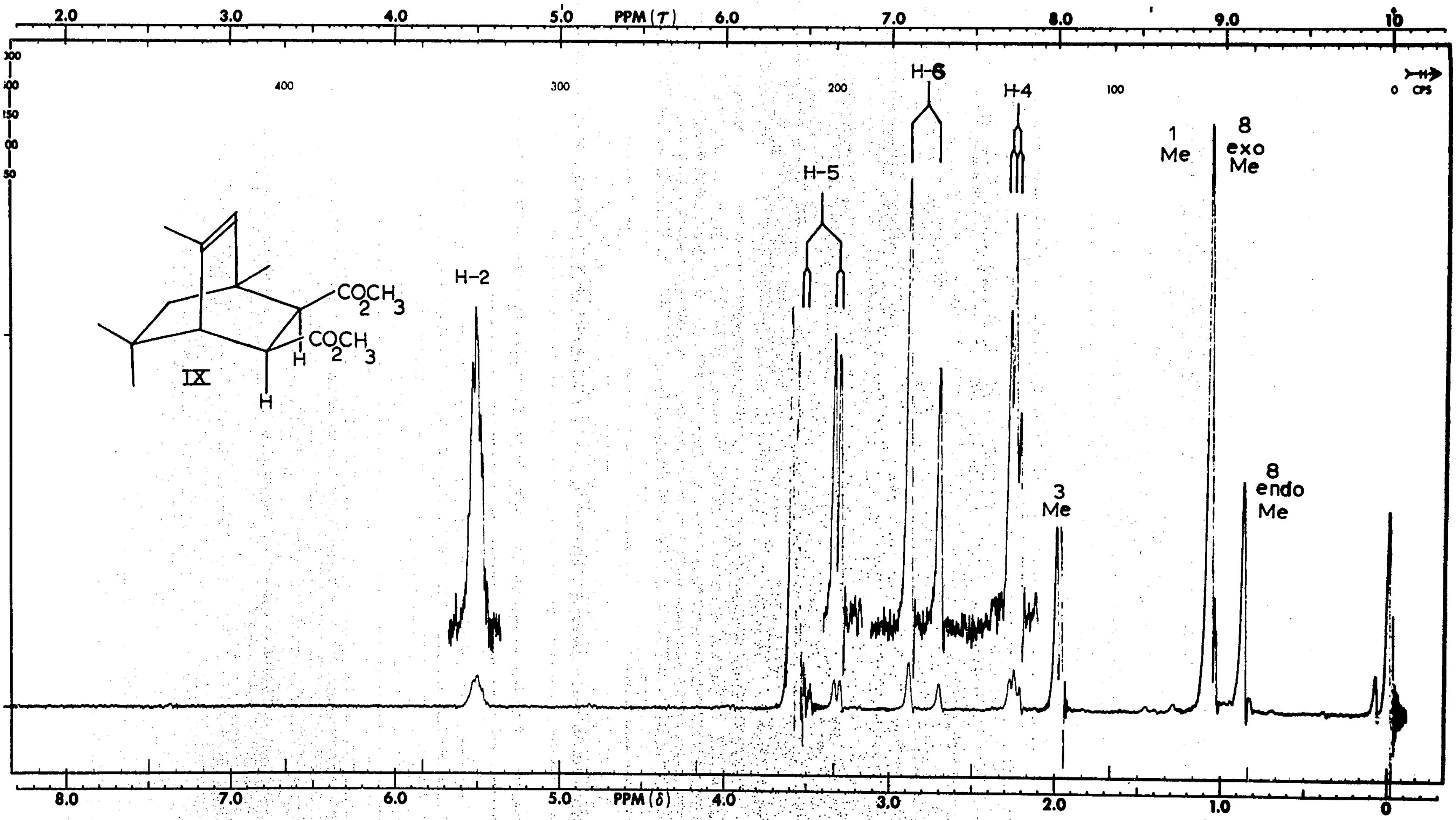


Figure 19. - Proton Magnetic Resonance Spectrum of 5-_endo_-6-_endo_-Dicarbomethoxy-bicyclo-octene A (IX) in $CDCl_3$.

An investigation of the related phenomenon of solute-solute interaction is described in Appendix I.

(iii) The exo and endo Protons at C-5 and C-6

In each unsaturated compound, the *exo* proton at C-5 or C-6 absorbs at lower field than the *endo* proton. Since the two carbon atoms are similarly substituted, this difference is probably a reflection of the anisotropy of the double bond although a contribution from the C-8 *exo* methyl group cannot be excluded. For a series of substituted bicyclo[2.2.2]octenes, Tori and coworkers[64] found that the downfield shift of the *endo* proton on hydrogenation of the double bond varied from 0.11 to 0.25 p.p.m. while the upfield shift of the *exo* proton was in the range of 0.01 to 0.19 p.p.m. The present results are summarized in Table Ia where some reported values are also listed. Although there is qualitative agreement with the trends predicted by the Nakagawa equation[71] (eq. [13], page 25), the wide range of shielding changes emphasizes the need for caution in the use of this criterion for assigning configuration. Shifts in the "wrong" direction are observed for the C-6 *exo* proton in XVI and comparable results have been reported by Huitric and coworkers.[63] These apparent anomalies clearly indicate that the shielding effect of an olefinic bond cannot always be evaluated by taking the difference between the shielding of a particular proton in the saturated and unsaturated compounds, One possible contribution to the unusually large change in the shielding of the C-5 endo proton in XIX has already been mentioned (page 59). The steric compression of this proton by the C-3 methyl group in the saturated compound is absent in the corresponding unsaturated compound VII. Others may include anisotropy effects of functional groups (such as the carbomethoxyl group) and solvation of the solute.

(iv) C-7 Protons

In the NMR spectrum of each unsaturated compound, the higher field half of the AB pattern for the C-7 protons is assigned to the endo proton by analogy with the behaviour of the C-5 and C-6 protons. The situation obtaining in the bicyclo[2.2.2]octanes is more complex and the assignments were made by studying the coupling interactions exhibited by these protons. Where necessary, decoupling experiments were used to establish the protons giving rise to the observed couplings.

The study of the effect of removal of the double bond by hydrogenation was hindered by the fact that the relevant absorption signals for many of the saturated compounds coincide with the resonance positions of the methyl groups. The available data are summarized in Table Ib.

TABLE I(a)

SHIFTS IN POSITIONS OF SIGNALS OF ENDO AND EXO PROTONS AT C-5 AND C-6 UPON HYDROGENATION OF SOME BICYCLO [2.2.2]OCTENES.

Octene → Octane	Solvent Shifts: $\delta_{octane} - \delta_{octene}$ (p.p.m.)	endo Proton		exo Proton	
		5	6	5	6
V → XVI	$CDCl_3$	-	-	-0.02	+0.07
	CCl_4	-	-	-0.04	+0.06
VI → XVIII	$CDCl_3$	-	+0.11	-0.10	-
	CCl_4	-	+0.15	-0.10	-
VII → XIX	$CDCl_3$	+0.47	-	-	-0.09
	CCl_4	+0.46	-	-	-0.07
IX → XVII	$CDCl_3$	-	-	-0.14	-0.24
	CCl_4	-	-	-0.06	-0.29
Tori and coworkers[64]		+0.11 to +0.25		-0.11 to -0.19	
Huitric et al.[65]		+0.12 to +0.43		-0.06 to +0.14	
Calculated[72] from eq. [13][71]		+0.18		-0.08	

TABLE I(b)

SHIFTS IN POSITION OF SIGNALS OF ENDO AND EXO PROTONS AT C-7 UPON HYDROGENATION OF SOME BICYCLO[2.2.2]OCTENES.

Octene → Octane	Solvent Shifts: $\delta_{octane} - \delta_{octene}$ (p.p.m.)	endo Protons	exo Proton
V → XVI	$CDCl_3$	+0.16	-0.04
VI → XVIII	CCl_4	+0.15	-0.36

Even from these limited results it is clear that factors other than anisotropy effects of the olefinic bond are contributing to the differences in shielding between the unsaturated and saturated species. Some of these factors have been mentioned in discussing the C-5 and C-6 protons.

The effect of an adjacent bromine atom is demonstrated in the bromolactones. For example, the endo-C-7 proton in the trans-bromolactone of 5-endo-6-endo-dicarbomethoxybicyclo-octene A (IX) absorbs at 0.77 p.p.m. to lower field than the corresponding proton of the lactone XV. A similar deshielding effect is observed for the endo-C-6 proton in the cis-bromolactone of 5-endo-6-exo-dicarbomethoxybicyclo-octene A (X) although the shift, in this case, is only 0.29 p.p.m. (relative to the corresponding proton in lactone XII). The deshielding influence of the neighbouring halogen atom may be due to intramolecular Van der Waals dispersion interactions.[80,81]

(v) Methyl Groups

In the compounds examined, unambiguous assignments of the methyl absorption signals is possible only for the C-3 methyl groups. The chemical shift assignments reported (Tables II to X and XV) for the other methyl groups (C-1, C-8-exo and C-8-endo) are those which are most consistent with the expected behaviour of such groups. In each spectrum, the sharp singlet is assigned to the C-1 substituent while the somewhat broadened signals are assigned to the C-8 methyl groups which are thought to be weakly coupled. Recent literature provides ample support for coupling between geminal methyl groups.[82,83]

C-1 Methyl

The resonance position of this methyl group in the unsaturated compounds varies between 1.05 and 1.35 p.p.m. On hydrogenation, the absorption peak moves 0.24 ± 0.05 p.p.m. upfield while removal of the double bond by lactonization gives a relative shielding of 0.09 p.p.m. (in $CDCl_3$) in the case of the 5-endo-6-exo lactone ester XII and 0.15 p.p.m. (in $CDCl_3$) in the case of the 5-endo-6-endo lactone ester XV.

C-3 Methyl

In deuteriochloroform or carbon tetrachloride solutions of the unsaturated compounds, the C-3 methyl group gives rise to a doublet between 1.74 and 1.97 p.p.m., showing allylic coupling with the vinyl proton ($J = 1.6 \pm 0.2$ c/s). A somewhat larger range is found in benzene solutions (1.59 to 2.03 p.p.m.). Hydrogenation results in an upfield shift of 0.80 to 0.95 p.p.m. The absorption for the C-3 methyl group in the saturated compounds is readily distinguished from those of the C-1 and C-8 methyl groups because of the coupling with the C-3 proton (J = 6.8 to 7.5 c/s).

The resonance position of this methyl group is 1.56 and 1.57 p.p.m., respectively, for the lactones XII and XV (in $CDCl_3$ solution). This is at lower field than the absorption of the other methyl groups because of the oxygen atom bonded to C-3. A bromine atom at C-2 deshields the methyl group by 0.23 p.p.m. when it is cis to this group. relative to the effect of a proton in the corresponding position in the lactone lacking halogen. This effect is similar to that on the endo-C-7 proton in the trans-bromolactone IX and on the endo-C-6 proton in the cis-bromolactone X.

C-8 Methyl Groups

In the unsaturated compounds, the higher field absorption is assigned to the endo group because of the shielding effect of the olefinic bond. In many of the saturated compounds the resonance positions of the exo and endo groups coincide. A difference is, however, present in the spectra of the diester XIX in which the higher field signal has been assigned to the endo methyl protons since the presence of a 5-exo carbomethoxyl group results in steric compression (see Appendix II) and consequent deshielding of the 8-exo methyl group. The lower field absorption in the lactone esters is assigned to the endo methyl group because these protons are expected to be deshielded by the C-3 methyl group.

It must be emphasized that these distinctions between the exo and endo methyl groups at C-8 are tentative and firm assignments cannot be made without further experiments. With the assignments made as described above, the resonance position of the endo C-8 methyl group is similar for all the unsaturated cases (δ^{CDCl_3} = 0.84 p.p.m. to 0.87 p.p.m.) but the relative shift on hydrogenation varies from 0.02 p.p.m. to lower field for the 5-exo-6-endo diester to 0.23 p.p.m. downfield in the 5-endo-6-endo anhydride. Lactonization and halolactonization also result in a shift to lower field (δ^{CDCl_3} = 1.11 to 1.23 p.p.m.).

Carbomethoxyl Groups

Methods used to establish the configuration of the carbomethoxyl group(s) in each compound have been discussed in the section dealing with the chemical compounds. In the proton spectra, the absorption for a carbomethoxyl group is readily recognized as a sharp singlet between 3.5 and 4.0 p.p.m. In the unsaturated compounds the protons of the exo-carbomethoxyl groups absorb at lower field (δ^{CDCl_3} = 3.54 to 3.68 p.p.m.). This difference disappears on hydrogenation. In the lactone-esters, the resonance positions of these methoxyl protons do not show any significant trends.

TABLE II

PROTON CHEMICAL SHIFTS* IN SOME 5,6-DISUBSTITUTED DERIVATIVES OF BICYCLO-OCTENE A†

Proton(s)	2	4	5x	5n	6x	6n	7x	7n	1 Me	3 Me	8x Me	8n Me	OMe
Compound													
V	5.52	2.46	3.46	-	2.67	-	1.19	1.10	1.32	1.75	1.03	0.84	-
VI	5.57	2.31	3.42	-	-	2.60	1.51	0.73	1.11	1.77	1.24	0.86	3.65(5n) 3.70(6x)
VII	5.38	2.54	-	2.75	2.90	-	1.24	1.05	1.08	1.89	0.93	0.84	3.68(5x) 3.68(6n)
IX	5.47	2.23	3.38	-	2.80	-	1.12	0.98	1.08	1.97	1.08	0.87	3.57(5n) 3.54(6n)
XIII	5.57	2.34	3.46	-	-	2.57	1.50	0.73	1.10	1.79	1.24	0.85	3.71(6x)

* in p.p.m. from internal tetramethylsilane

† 5 mole % solution in $CDCl_3$

x = exo, n = endo.

TABLE III

PROTON CHEMICAL SHIFTS* IN SOME 5,6-DISUBSTITUTED DERIVATIVES OF BICYCLO-OCTENE A†

Proton(s)	2	4	5x	5n	6x	6n	7x	7n	1 Me	3 Me	8x Me	8n Me	OMe
Compound													
V	5.51	2.46	3.42	-	2.63	-	¶	¶	1.35	1.79	1.09	0.89	-
VI	5.49	2.24	3.29	-	-	2.46	1.48	0.67	1.07	1.74	1.23	0.84	3.59(5n) 3.66(5x)
VII	5.30	2.47	-	2.64	2.77	-	1.21	0.98	1.05	1.90	0.90	0.83	3.61 (5x) 3.64 (6n)
IX	5.37	2.18	3.26	-	2.69	-	1.08	0.97	1.07 or 1.03	1.93	1.03 or 1.07	0.85	3.51(5n) 3.48(6n)

* In p.p.m. from internal tetramethylsilane

† 5 mole % solution in CCl$_4$

¶ Obscured by methyl absorption

x = *exo*, n = *endo*.

TABLE IV

PROTON CHEMICAL SHIFTS* IN SOME 5,6-DISUBSTITUTED DERIVATIVES OF BICYCLO-OCTENE A†

Proton(s)	2	4	5x	5n	6x	6n	7x	7n	1 Me	3 Me	8x Me	8n Me	OMe
Compound													
V	5.14	2.21	2.79	-	1.98	-	¶	¶	1.22	1.59	0.67	0.57	-
VI	5.43	2.37	3.62	-	-	2.85	1.66	0.69	1.10	1.79	1.32	0.81	3.30 (5n) 3.36 (6x)
VII	5.31	2.55	-	2.93	3.00	-	1.13	0.93	1.07	1.77	0.92	0.76	3.39 (5x) 3.42 (6n)
IX	5.48	2.21	3.28	-	2.76	-	¶	¶	1.05	2.03	0.87	0.78	3.43(5n) 3.39(6n)

* In p.p.m. from internal tetramethylsilane

† 5 mole % solution in benzene

¶ Obscured by methyl absorption

x = exo, n = endo.

TABLE V

PROTON CHEMICAL SHIFTS* IN SOME SATURATED DERIVATIVES OF BICYCLO-OCTENE A†

Proton(s)	4	5x	5n	6x	6n	7x	7n	1 Me	3 Me	8x Me	8n Me	OMe
Compound												
XVI	1.72	3.44	-	2.74	-	1.26	1.15	1.12	0.97	1.07	1.07	-
XVII	1.70	3.24	-	2.56	-	¶	¶	0.87	1.03	1.07	1.07	3.63 (5n) 3.67 (6n)
XVIII	1.56	3.32	-	-	2.71	¶	¶	0.84	n.a.	n.a.	n.a.	3.72(5n) 3.72(6x)
XIX	1.68	-	3.22	2.81	-	¶	¶	0.80	1.09	1.05	1.05	3.66 (5x) 3.70 (6n)

* In p.p.m. from internal tetramethylsilane

† 5 mole % solution in $CDCl_3$

¶ Obscured by methyl absorption.

n.a. = not assigned.

x = exo, n = endo.

TABLE VI

PROTON CHEMICAL SHIFTS* IN SOME SATURATED DERIVATIVES OF BICYCLO-OCTENE A†

Proton(s)	3 anti	4	5x	5n	6x	6n	7x	7n	1 Me	3 Me	8x Me	8n Me	OMe
Compound													
XVI	n.a.	1.68	3.38	-	2.69	-	1.13	1.24	1.11	0.98	1.11	1.11	-
XVII	n.a.	1.64	3.20	-	2.44	-	¶	¶	0.84	0.98	1.08	1.08	3.59(5n) 3.59(6n)
XVIII	-	1.55	3.19	-	-	2.61	1.12	0.82	0.83	n.a.	n.a.	n.a.	3.64(5n) 3.64(6x)
XIX	2.04	1.62	-	3.10	2.70	-	¶	¶	0.76	1.16	1.01	0.84	3.62 (5x) 3.64 (6n)

* In p.p.m from internal tetramethylsilane

† 5 mole % solution in CCl_4

¶ Obscured by methyl absorption

n.a. = not assigned

x = exo, n = endo.

TABLE VII

PROTON CHEMICAL SHIFTS* IN SOME SATURATED DERIVATIVES OF BICYCLO-OCTENE A†

Proton(s)	4	5x	5n	6x	1 Me	3 Me	8x Me	8n Me	OMe
Compound									
XVII	1.69	3.17	-	2.54	0.84	1.19	0.91	0.91	3.39 (5n) 3.57 (6n)
XIX	1.77	-	3.48	3.01	0.81	1.12	0.96 or 0.98	0.96 or 0.98	3.34 (5x) 3.44 (6n)

* In p.p.m. from internal tetramethylsilane

† 5 mole % in benzene

x = <u>exo</u>, n = <u>endo</u>

TABLE VIII

PROTON CHEMICAL SHIFTS* IN SOME γ-LACTONES DERIVED FROM BICYCLO-OCTENE A†

Proton(s)	2 syn	2 anti	4	5x	6x	6n	7x	7n	1 Me	3 Me	8x Me	8n Me	OMe
Compound													
VIII	5.03	-	2.12	~2.93	~2.99	-	1.09	2.02	1.07	1.79	1.10	1.21	3.71(6n)
X	-	4.01	2.15	3.09	-	2.73	1.92	1.25	1.10	1.63	1.16	1.21	3.74(6x)
XI	4.12	-	2.02	3.02	-	2.55	1.55	1.66	1.13	1.79	1.23	1.23	3.75(6x)
XII	n.a.	n.a.	1.97	3.01	-	2.44	¶	¶	1.02	1.56	1.10	1.18	3.72(6x)
XV	2.52	1.33	2.07	2.92	2.64	-	1.33	1.21	0.93	1.57	1.08	1.11	3.67(6n)

* In p.p.m. from internal tetramethylsilane.

† 5 mole $ in $CDCl_3$

n.a. = not assigned

¶ Obscured by methyl absorption

x = _exo_, n = _endo_.

TABLE IX

PROTON CHEMICAL SHIFTS* IN SOME γ-LACTONES DERIVED FROM BICYCLO-OCTENE A†

Proton(s)	2 anti	4	5x	6n	7x	7n	1 Me	3 Me	8x Me	8n Me	OMe
Compound											
XI	4.15	1.98	2.87	2.49	1.54	1.62	1.12	1.75	1.22	1.22	3.74(6x)
XII	n.a.	1.89	2.90	2.32	¶	¶	0.99	1.52	1.08	1.16	3.69(6x)

* In p.p.m. from internal tetramethylsilane

† 5 mole % in CCl_4

n.a. = not assigned

¶ Obscured by methyl absorption

x = _exo_, n = _endo_.

TABLE X

PROTON CHEMICAL SHIFTS* IN SOME γ-LACTONES DERIVED FROM BICYCLO-OCTENE A†

Proton(s)	2 syn	2 anti	4	5x	6x	6n	7x	7n	1 Me	3 Me	8x Me	8n Me	OMe
Compound													
VIII	5.22	-	1.44	2.59	2.68	-	0.58	1.70	0.96	1.56	0.58	0.85	3.41(6n)
X	-	3.49	1.46	2.98	-	2.79	1.69	0.71	0.95	1.25	0.62	0.94	3.24(6x)
XII	n.a.	n.a.	1.42	3.07	-	2.37	¶	¶	0.77	1.24	0.68	1.02	3.26(6x)
XV	n.a.	n.a.	1.49	2.45	2.72	-	¶	¶	0.80	1.27	0.64	0.69	3.49(6n)

* In p.p.m. from internal tetramethylsilane

† 5 mole % in benzene.

n.a. = not assigned

¶ Obscured by methyl absorption

x = exo, n = endo.

(b) Coupling Constants

The coupling constants found for the bicyclo[2.2.2]-octene and bicyclo[2.2.2]octane systems are summarized in Tables XII to XV. In the discussion below, the significance of these interactions are considered.

(i) Geminal Coupling Constants

The largest geminal coupling interactions (J = 15.0 c/s) is found between the C-2 protons in the γ-lactone XV derived from *cis*-*endo* diester IX while the smallest (J = 12.9 c/s) is that observed for the C-7 protons in the unsaturated 5-*endo*-6-*exo* diester, VI. In general, the coupling is larger in the saturated compounds. For example, $J_{7x,7n}$ = 12.9 c/s in the 5-*endo*-6-*exo* diester, VI, increases to 13.5 c/s on hydrogenation (XVIII).

Geminal coupling constants of 13.6 to 13.8 c/s were reported by Tori and coworkers[64] while Huitric[65] found the coupling constant to be 10.0 c/s in the compounds examined by his group. Although it is recognized that these variations must be due to a combination of steric and electronic factors, it is not possible to separate their contributions in a meaningful manner.

(ii) Vicinal Coupling Constants

Cis Vicinal Couplings

In the unsaturated anhydride V an exo-exo coupling, $J_{5,6}$, of 8.5 c/s is observed. Esterification removes the constraint imparted by the five-membered ring and results in increased coupling between the protons (J = 10.9 c/s in XVII). Examination of molecular models (Fieser) indicates that the H-C-C angles at C-5 and C-6 decrease on cleaving the anhydride ring; such a decrease may account for the increased coupling between the two protons (see Chapter 1, page 12).

Hydrogenation of the ester causes a further increase of about 1 c/s in the cis vicinal interaction. A similar increase (0.8 c/s) was reported by Huitric[65] while Tori[64] found a difference of about 1.6 c/s. These results may be compared with the increase in exo-exo coupling observed in norbornyl compounds.[61]

It has been suggested[65,84] that this increase is due to the greater flexibility of the saturated system allowing the dihedral angle between H-5 and H-6 to be larger than it is in the "non-distorted" unsaturated system. While this rationale is feasible for trans vicinal coupling constants where an increase in dihedral angle to a value greater than the "normal" 120° will result in increased coupling, it is unacceptable for cis coupling constants where any increase in dihedral angle from 0° will result in a decrease of the coupling constant. Further, examination of Barton, Dreiding and Fieser molecular models suggests that there is no increase in exo-exo or endo-endo dihedral angle when bicyclo[2.2.2]octene is hydrogenated. These changes may represent variation in the "constants" of Karplus equation [10].[30] One possible source of such a change is a variation in the H-C-C angles due to redistribution of the strain in the bicyclic system.

Since vicinal coupling constants depend on the electronegativity of the substituent(s),[27,85] a direct comparison with literature values is not meaningful. It is, however, interesting to note that the reported values (Table XIa) are not unlike those found in the present study being 8.3 to 11.1 c/s for unsaturated systems and 9.0 to 11.0 c/s for saturated systems.

A decrease of 2.3 c/s in the exo-exo coupling is observed when the 5-endo-6-endo diester (XVII) is converted to the lactone. Examination of models (Fieser) suggests that lactonization results in a dihedral angle of about 22° between the exo protons (Fig. 20b) and, therefore, the decreased coupling is not unexpected.

Trans Vicinal Couplings

Associated with the increase of dihedral angle between the exo protons in the lactones (see previous paragraph) is

TABLE XI(a)

CIS VICINAL COUPLING CONSTANTS (c/s) IN THE BICYCLO[2.2.2]-OCTENE AND BICYCLO[2.2.2]OCTANE SYSTEMS.

Substituent(s) (C-5 and/or C-6)	J_{octene}	J_{octane}	Reference
OH	8.3	9.0	64
OAc	8.4	9.0	64
2 COOMe	11.0	-	73
2 COOMe	8.5 to 10.9	10.8 to 11.9	This study
p-Cl-phenyl CN	10.2	11.0	65

TABLE XI(b)

TRANS VICINAL COUPLING CONSTANTS (c/s) IN THE BICYCLO[2.2.2]-OCTENE AND BICYCLO[2.2.2]OCTANE SYSTEMS.

Substituent(s) (C-5 and/or C-6)	J_{octene}	J_{octane}	Reference
OH	2.6	2.8	64
OAc	2.6	3.0	64
2 COOMe	6.0	-	64
2 COOMe	6.0	-	73
2 COOMe	5.9 to 8.5	8.3 to 9.9	This study
p-Cl-phenyl NO_2	5.3 to 5.7	6.9	84
p-Cl-phenyl CN	6.8	8.2	65

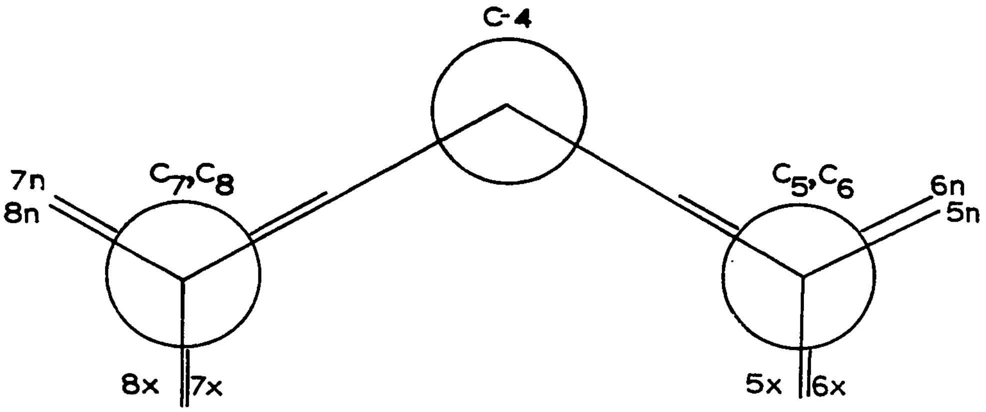
an equivalent decrease of the dihedral angle between the 5-*exo* proton and the 6-*endo* proton (Fig. 20b). This is reflected in a decrease of 2.7 c/s in the 5-*exo*-6-*endo* coupling constant when the 5-*endo*-6-*exo* diester is converted to the lactone.

Mutual steric interaction between the 8-*exo* and the 5-*exo* substituents increase the dihedral angle between the 5-*endo* and 6-*exo* protons (Fig. 20c). As a result, the coupling constant between the 5-*endo* and 6-*exo* protons is larger than that between the 5-*exo* and 6-*endo* protons. In the latter case, the dihedral angle appears to be "normal" (Fig. 20a). For the unsaturated compounds, the difference is about 2.5 c/s. A smaller difference is observed in the saturated compounds - probably because of the steric interactions of the C-3 methyl group.

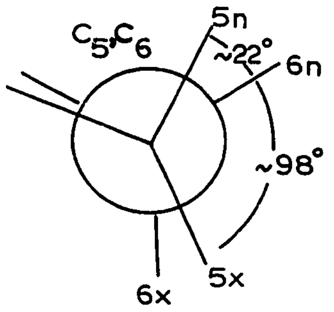
The data shown in Table XIb clearly demonstrate the substituent dependence of the *trans* vicinal coupling constants and, taken with the results obtained in this study, indicate that substituents other than those on C-5 and C-6 can affect the interaction between protons on these two carbon atoms.

Vicinal Coupling with the Bridgehead Proton

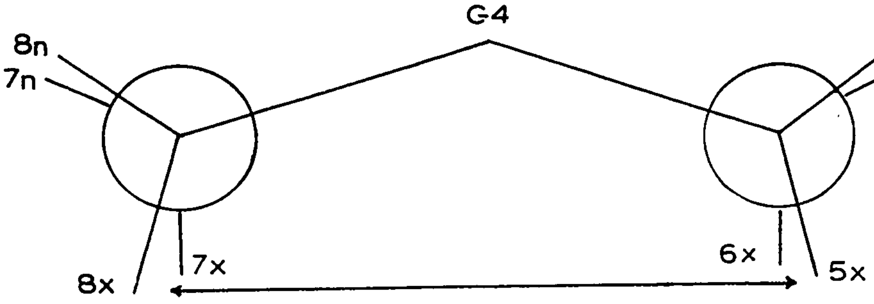
The 4,5 coupling constant in the unsaturated esters and the lactones is remarkably constant, being 1.95 ± 0.05 c/s



(a) Normal



(b) Distorted by 3,5 Lactone Bridge



(c) Distorted by Mutual Repulsion of *exo*-Substituents at C_5 and C_8

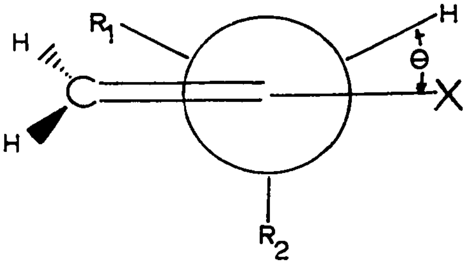
Fig. 20 - The Dihedral Angles between the C-5 and C-6 Protons in the Bicyclo[2.2.2]octane Systems.

in the former group of compounds and 4.3 ± 0.1 c/s in the latter. In the saturated compounds, however, a wider range is observed (1.2 - 2.3 c/s). This is thought to be due to the greater flexibility of the saturated ring system and the concomitant increased sensitivity of the equilibrium conformation to the steric interactions of the substituents.

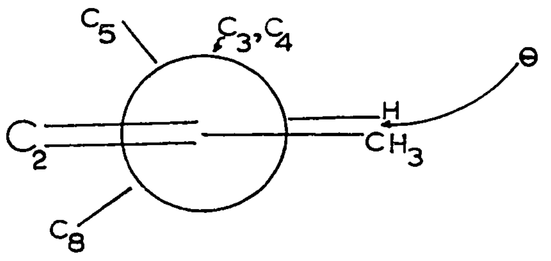
(iii) Long Range Couplings

Allylic Coupling

$J_{2,4}$ was found to be 1.6 ± 0.1 c/s. The present results agree well with those found by Tori and coworkers[64] (J = 1.5 - 1.8 c/s), but are unexpectedly large in view of the previous success of the theoretical predictions.[86] According to theory,[87] the allylic coupling is at a maximum when the angle θ (see diagram below) is 90° and at a minimum when θ is either 0° or 180°. As is indicated in the diagram, the value of θ in the bicyclooctene system



Generalized Allylic System



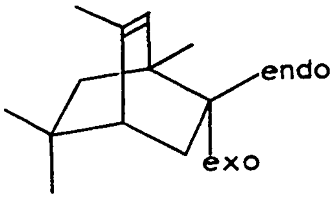
Bicyclooctene System

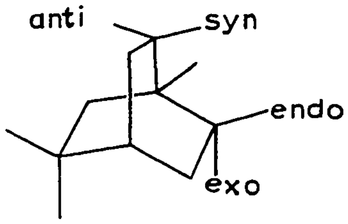
is 0° and a small coupling is predicted. It is interesting to note that similar "anomalous" allylic coupling constants are reported for the photodimers of α-pyridone.[88] In both of these cases, the stereochemical relationship in the H-C-C-C-H fragment is that required for the "W" coupling which involves the σ framework. One rationale of the apparent anomaly is, therefore, that allylic coupling involves contributions from both the σ bond transmission and the σ-π interactions.[89]

The allylic coupling between the C-2 proton and those of the methyl group at C-3 varied between 1.4 c/s and 1.8 c/s. This variation is probably due to substituent effects on the average rotameric configuration of the methyl group. A similar coupling (J = 1.7 c/s) was observed for the photodimers of N-Methyl-4-methyl-pyridone.[88]

"W" Couplings across four Single Bonds

The geometric requirements for this type of long range coupling (see page 24) are satisfied by the 6-endo, 7-endo pairs of protons in both the saturated and the unsaturated compounds. The coupling constant is 1.6 c/s in the former group and 2.0 c/s in the latter group. Both Barton and





Dreiding models indicate no difference between the geometry of the H-C-C-C-H fragment in the unsaturated and saturated compounds. The difference in coupling may be due to electronic factors involving the π-orbitals of the double bond. The magnitude of the coupling is also sensitive to the presence and the configuration of bromine at C-2, being 1.4 c/s with bromine anti and 2.2 c/s with bromine syn. The sensitivity to the configuration of the substituent at C-2 suggests that both electronic and steric perturbations are caused by the halogen atom.

Long range couplings of this type also occur between the following pairs of protons: 2-syn,7-exo; 2-anti,6-exo; 3-anti,5-exo. In one case, a coupling is observed between the 2-syn proton and the bridgehead proton at C-4. Possible reasons for this coupling have already been mentioned (see page 44).

TABLE XII

COUPLING CONSTANTS (c/s) IN SOME 5,6-DISUBSTITUTED DERIVATIVES OF BICYCLO-OCTENE A

Coupling Constant	7x,7n gem	4,5x vic	4,5n vic	5x,6x vic	5x,6n vic	5n,6x vic	2,4 allylic	CH_3,H allylic	6n,7n W
Compound									
V	-	3.5	-	8.5	-	-	1.5	1.8	-
VI	12.9	2.0	-	-	5.9	-	1.7	1.6	2.0
VII	13.0	-	1.9	-	-	8.5	1.5	1.8	-
IX	13.7	2.0	-	10.9	-	-	1.7	1.6	-
XIII	13.1	2.2	-	-	6.1	-	1.6	1.4	2.0

x = *exo*, n = *endo*

TABLE XIII

COUPLING CONSTANTS (c/s) IN SOME SATURATED DERIVATIVES OF BICYCLO-OCTENE A

Coupling Constant	7x,7n gem	4,5x vic	4,5n vic	5x,6x vic	5x,6n vic	5n,6x vic	3,4 vic	CH_3,H vic	2,6x W	6n,7n W	3,5x W
Compound											
XVI	-	3.5	-	10.8	-	-	2.0	7.5	2.3	-	1.0
XVII	-	2.3	-	11.9	-	-	2.2	7.2	2.2	-	-
XVIII	13.5	1.2	-	-	8.3	-	-	6.8	-	1.6	-
XIX	-	-	1.5	-	-	9.9	1.5	6.7	0.7	-	-

x = *exo*, n = *endo*

TABLE XIV

COUPLING CONSTANTS (c/s) IN SOME γ-LACTONES DERIVED FROM BICYCLO-OCTENE A

Coupling Constant	2,2 gem	7x,7n gem	4,5x vic	5x,6x vic	5x,6n vic	2,6x W	2,7x W	6n,7n W
Compound								
VIII	-	13.9	≈1.1	≈9.7	-	-	2.0	-
X	-	14.5	4.3	-	2.2	-	-	2.2
XI	-	-	4.2	-	2.3	-	<0.6	1.4
XII	-	13.7	4.3	-	2.1	-	-	2.0
XV	15.0	-	4.4	9.7	-	1.5	1.6	-

x = <u>exo</u>, n = <u>endo</u>

TABLE XV

PROTON MAGNETIC RESONANCE PARAMETERS FOR COMPOUND XIV

Proton(s)	Chemical Shift (p.p.m.)	
	$CDCl_3$	Benzene
2-H	5.84	5.54
3-CH_2=	≈4.07,≈4.09	≈3.73,≈3.75
4-H	obscured	2.91
5n-H	≈2.90	3.16
6x-H	≈2.95	3.16
7x-H	0.82	0.81
7n-H	1.32	1.06
1-CH_3	1.11	0.99
8x-CH_3	0.95	0.90
8n-CH_3	0.84	0.64
5x,6n-OCH_3	3.66,3.69	3.66,3.69

Coupling Constants

$J_{7x,7n}$ = 12.5 c/s;

$J_{2,7x}$ = 1.8 c/s.

x = exo, n = endo

EXPERIMENTAL

(a) Proton Nuclear Magnetic Resonance Spectroscopy

Most of the proton nuclear magnetic resonance parameters reported in this chapter were calculated from spectra obtained on a Varian A60 spectrometer. The chart calibration was checked regularly using audiofrequency sidebands of tetramethylsilane. The decoupling experiments were performed on a Varian A60A spectrometer using a Varian decoupling accessory. A few double irradiation experiments were carried out using a Varian DP60 spectrometer in conjunction with either a circuit similar to the Varian V3521 integrator or a single sideband homonuclear decoupler model HD60 (NMR Specialties, Inc.). One set of spin decoupling experiments was performed at 100 Mc/s for which the author is grateful to Professor W.A. Ayer, University of Alberta.

(b) Preparation of Compounds

(i) Synthesis of 1,3,5,5-Tetramethylcyclohexa-1,3-diene (IV)

The diene was prepared by a slight modification of the method described by Kharasch.[76] A typical run is as follows:

Magnesium turnings (20 g.) were placed in a one-litre flask equipped with a condenser bearing a calcium chloride drying tube, a mercury-sealed stirrer and a dropping funnel. About 10 ml. of a solution of 114 g. of methyl iodide (50 ml.)

in 150 ml. of diethyl ether was added to the magnesium. When the initial reaction had subsided, 210 ml. of diethyl ether was added to the reaction flask. The rest of the alkyl halide was added at a rate such that gentle reflux was maintained. Stirring and refluxing was continued for an additional thirty minutes after the alkyl halide had been added.

The Grignard reagent was then cooled in an ice-bath and a solution of 96.7 g. (105 ml.) of isophorone is 135 ml. of diethyl ether was added in the course of one and three-quarters hours. The reaction mixture was allowed to stand for four hours, refluxed for one hour and then allowed to stand overnight.

The Grignard Complex was poured onto 400 g. of crushed ice and 46.5 ml. of glacial acetic acid added with stirring. After standing for a short while, the ether layer was separated and the aqueous layer extracted with two portions of ether. The combined ether extracts were washed twice with a 10% aqueous sodium carbonate solution and then with two portions of water to remove excess base. The organic solution was then dried over anhydrous magnesium sulphate, filtered, and the solvent stripped on a thin film evaporator. The residual liquor was fractionated on a spinning band column and yielded 65 g. of product. Compound IV has the following physical properties:

Boiling Point: 45.5°C - 48.0°C/12 mm.
(lit.[76] 151°C - 155°C/760 mm.).
Infrared Spectrum: ν^{CHCl_3} 1667 cm^{-1}, 1647 cm^{-1}, 1616 cm^{-1}, 900 cm^{-1}.
Ultraviolet Spectrum: λ_{max}^{EtOH} 238 mμ, 261 mμ.

(ii) Preparation of the Maleic Anhydride Adduct V of Compound IV

To 13.6 g. of compound IV was added a solution of 9.8 g. of maleic anhydride in about 15 ml. of benzene. The reaction mixture was warmed until a deep yellow coloration developed when heating was discontinued until the rate of reaction had reduced considerably.

Refluxing the reaction mixture for one hour resulted in the complete disappearance of the yellow colour. Removal of the solvent left a white solid which was recrystallized from a 50/50 mixture of petroleum ether (boiling point 35°C - 60°C) and benzene.

The first crop weighed 13.1 g. and has the following physical properties:

Melting Point: 99.5°C - 100.5°C (lit.[76] 98 - 99°C).
Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1780 cm^{-1}, 1855 cm^{-1};
$\nu_{C=C}^{CHCl_3}$ 1650 cm^{-1}.

(iii) Hydrogenation of Compound V (→ XVI)

A solution of 1 g. of anhydride adduct V in 25 ml. glacial acetic acid was added to 250 mg. platinum oxide (Engelhard). Three drops of perchloric acid were added and the mixture shaken for about 84 hours with hydrogen at 50 p.s.i.

The catalyst was filtered off and the solvent removed. The residue was dissolved in diethyl ether and the solution washed four times with water. After filtration through anhydrous magnesium sulphate, the ether was removed leaving 1.25 g. of a syrupy liquid.

Crystallization from methanol yield 600 mg. of a white solid (XVI), melting in the temperature range 72 - 76°C. After recrystallization from chloroform compound XVI had the following physical properties:

Melting Point: 76.0°C - 77.0°C;

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1775 cm^{-1}, 1855 cm^{-1}.

Analysis Calculated for $C_{14}H_{20}O_3$: C, 71.2%; H, 8.5%.

Found: C, 70.7%; H, 8.6%.

(iv) Esterification of Compound V (→ IX)

Anhydride adduct (4 g.) was dissolved in 100 ml. of methanol and 2.4 g. of concentrated sulphuric acid added. The mixture was refluxed overnight.

After removing most of the excess alcohol (*in vacuo*) the reaction mixture was extracted with diethyl ether. The extract was washed once with water, once with 10% aqueous sodium bicarbonate solution and then with portions of water until the washings were neutral. Anhydrous magnesium sulphate was used to dry the extract.

Removal of drying agent and solvent yielded 3.6 g. of a colourless viscous liquid. The product was chromatographed on 150 g. of B.D.H. Silica Gel with anhydrous ether as eluent. A yield of 3.2 g of purified material was obtained. Compound IX has the following physical properties:

Refractive Index: n_D^{25} 1.4802

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1740 cm^{-1}.

Analysis Calculated for $C_{16}H_{24}O_4$: C, 68.5%; H, 8.6%

Found: C, 68.0%; H, 8.8%.

(v) Esterification of Compound XVI (→ XVII)

Saturated anhydride (1.2 g. containing a small amount of unsaturated anhydride because of incomplete hydrogenation) was dissolved in about 30 ml. of methanol and excess of an ethereal solution of diazomethane added to the cooled solution. After several hours reaction appeared to have occurred and the solvent was removed leaving a viscous, pale yellow liquid.

To remove the unsaturated material, the liquid was redissolved in glacial acetic acid and a slight excess of a solution of bromine in glacial acetic acid added.

The mixture was allowed to stand for one hour and then diluted with water and extracted with several portions of ether. The extract was washed free of acid with 10% aqueous sodium carbonate. It was then washed once with water and then with brine until neutral. After drying the organic solution over anhydrous magnesium sulphate, the drying agent and solvent were removed. On cooling the residue and adding a few ml. of anhydrous ether, a white crystalline solid (216 mg.) separated out. The crystals were separated off and the volatile portions of the filtrate evaporated leaving a viscous yellow liquid (0.67 g.) whose NMR spectrum showed the absence of unsaturated material. The product was further purified by column chromatography followed by distillation along a horizontal tube. Compound XVII has the following physical properties:

Refractive Index: n_D^{25} 1.4812

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1730 cm^{-1}.

Analysis Calculated for $C_{16}H_{26}O_4$: C, 68.05%; H, 9.28%

Found: C, 67.72%; H, 9.09%.

(vi) Reaction of Compound IV with Dimethyl Fumarate.

Preparation of Dimethyl Fumarate

Dimethyl fumarate was prepared by a method analogous to that described by Vogel[90] for diethyl fumarate.

A mixture of 50 g. of fumaric acid, 100 ml. of methanol, 200 ml. of benzene and 8 ml. of concentrated sulphuric acid was refluxed for about 20 hours. On cooling, white crystals precipitated. The crystals were filtered off, washed thoroughly with water, and dried in a vacuum desiccator.

Recrystallization from chloroform gave 61 g. of product. This compound has the following melting point: 101°- 102°C. (lit.[91] 101.2 - 101.4°C.).

Diels-Alder Reaction

A mixture of 18.5 g. of compound IV and 14.5 g. of dimethyl fumarate was refluxed for about eleven hours. The excess diene was removed by distillation at 20 mm. Hg. and the residue fractionated at 1 mm. Hg. The portion of product distilling between 105°C and 120°C was collected. The weight of this fraction was 20.2 g.

Isolation of Compound VI

On addition of a small amount of petroleum ether (boiling point 35° - 60°C) to the material collected, a white crystalline solid (Compound VI) separated out. After several recrystallization from petroleum ether, the product has the following physical properties:

Melting Point: 71.0° - 72.0°C

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1725 cm^{-1}, $\nu_{C=C}^{CHCl_3}$ 1650 cm^{-1}.

Analysis Calculated for $C_{16}H_{24}O_4$: C, 68.5%; H, 8.6%.

Found: C, 68.6%; H, 8.8%.

Isolation of Compound VII

After the crystallization of Compound VI 6.05 g. of mother liquor remained. Separation of the components of this mixture was effected by gradient elution from a column of alumina (Woelm Neutral, Activity 1). The material was applied as a concentrated solution in petroleum ether (boiling point 35° - 60°C) which was also the initial eluent. This was replaced by increasing concentrations of benzene in petroleum ether until the eluent was pure benzene. Material still remaining on the column was then removed with anhydrous diethyl ether.

Further amount of Compound VI was obtained as early fractions while a new compound (VII) appeared in the benzene rich solutions. This latter material was crystallized by cooling to about 10°C and then adding a small amount of methanol. The product was then recrystallized from petroleum ether. Compound VII has the following physical properties:

Melting Point: 50°C-51°C.

Infrared Spectrum: $\nu_{C=C}^{CHCl_3}$ 1658 cm^{-1}.

Analysis Calculated for $C_{16}H_{24}O_4$: C, 68.5%; H, 8.6%

Found: C, 68.6%; H, 8.7%

(vii) Hydrogenation of Compound VI (→ XVIII)

The unsaturated compound (0.9 g. in 25 ml. of glacial acetic acid) was hydrogenated over a platinum catalyst (150 mg.). A Parr low pressure hydrogenation apparatus was used at a hydrogen pressure of 48 p.s.i. for 36 hours.

The catalyst was filtered off and the bulk of the solvent removed on a film evaporator. The residue was then dissolved in ether, washed free of acid with sodium bicarbonate solution and then washed with water until neutral. Subsequent drying over anhydrous magnesium sulphate followed by removal of drying agent and solvent yielded a colourless liquid which was crystallized by cooling to below 0°C and then adding a small amount of methanol. The product was subsequently recrystallized from petroleum ether (boiling point 35°C - 60°C). Compound XVIII has the following physical properties:

Melting Point: 44.0°C - 45.5°C.

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1720 cm^{-1}.

Analysis Calculated for $C_{16}H_{24}O_4$: C, 68.05%; H, 9.28%.

Found: C, 68.44%; H, 9.47%.

(viii) Hydrogenation of Compound VII (→ XIX)

The diester VII (450 mg.) was dissolved in 15 ml. of glacial acetic acid and hydrogenated over a platinum catalyst in the presence of two drops of perchloric acid.

A Parr low pressure hydrogenation apparatus was used and the reaction mixture shaken for 72 hours with hydrogen at a pressure of 58 p.s.i.

After the catalyst was filtered off and the solvent removed by thin film evaporation, the crude product was redissolved in diethyl ether. The ethereal solution was washed once with water, once with 5% aqueous sodium bicarbonate and then again with water until neutral. The washed solution was dried over anhydrous magnesium sulphate. Removal of the drying agent and solvent yielded 0.45 g. of product.

The saturated diester (XIX) was further purified by column chromatography on silica gel (BDH). A sample for analysis was prepared by distilling a small quantity under reduced pressure along a horizontal tube. Compound XIX has the following physical properties:

Refractive Index: n_D^{25} 1.4742

Infrared Spectrum: $^{CHCl_3}_{C=O}$ 1720 cm^{-1}.

Analysis Calculated for $C_{16}H_{26}O_4$: C, 68.05%; H, 9.28%.

Found: C, 68.68%; H, 8.93%.

(ix) <u>Bromination of trans-Diester VI</u>

To a solution of 7.3 g. of the diester (VI) in about 50 ml. of glacial acetic acid was added a 5% (v/v) solution of bromine in glacial acetic acid, the addition being

A Parr low pressure hydrogenation apparatus was used and the reaction mixture shaken for 72 hours with hydrogen at a pressure of 58 p.s.i.

After the catalyst was filtered off and the solvent removed by thin film evaporation, the crude product was redissolved in diethyl ether. The ethereal solution was washed once with water, once with 5% aqueous sodium bicarbonate and then again with water until neutral. The washed solution was dried over anhydrous magnesium sulphate. Removal of the drying agent and solvent yielded 0.45 g. of product.

The saturated diester (XIX) was further purified by column chromatography on silica gel (BDH). A sample for analysis was prepared by distilling a small quantity under reduced pressure along a horizontal tube. Compound XIX has the following physical properties:

Refractive Index: n_D^{25} 1.4742

Infrared Spectrum: $\overset{CHCl_3}{C{=}O}$ 1720 cm^{-1}.

Analysis Calculated for $C_{16}H_{26}O_4$: C, 68.05%; H, 9.28%.

Found: C, 68.68%; H, 8.93%.

(ix) Bromination of trans-Diester VI

To a solution of 7.3 g. of the diester (VI) in about 50 ml. of glacial acetic acid was added a 5% (v/v) solution of bromine in glacial acetic acid, the addition being carried out dropwise and with continuous stirring. When a pale orange colour remained for more than one minute, addition was stopped and the reaction mixture allowed to stand for some time.

After dilution with water, the product was extracted with several portions of chloroform. The extract was washed once with water, three times with 5% aqueous sodium carbonate solution and then with water until it was neutral. It was then dried over anhydrous magnesium sulphate.

The drying agent was filtered off and the chloroform removed by flash evaporation. The residue was then cooled and a small amount of anhydrous ether added; immediate crystallization of part of the product resulted.

From a total crude yield of 8.8 g., 3.5 g. of crystalline material (Compound X) was obtained. Recrystallization from diethyl ether gave material with the following physical properties:

Melting Point: 176.0 - 177.0°C.

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$: 1786 cm^{-1}, 1739 cm^{-1}.

Analysis Calculated for $C_{15}H_{21}O_4Br$: C, 52.18%; H, 6.13%; Br, 23.15%.

Found: C, 52.02%; H, 6.04%; Br, 23.08%.

Chromatography of Residual Liquor after removal of Compound X

Gradient elution of a silica column (BDH) gave very little separation of the components. A portion of the resultant material was chromatographed on a column made from silicic acid (Fisher) which had been heated at 135°C for five days. The column was eluted with 10% diethyl ether in benzene.

The crude material (2.85 g.) gave fractions which were combined into three groups on the basis of their proton magnetic resonance spectra.

Group Number	Weight(g.)
1	1.20
2	1.23
3	0.39

Group 1 comprised several components, some of which were identical to those found in Group 2. The group was not investigated further.

From Group 2, 220 mg. of a crystalline material was obtained (Compound XI) with the following physical properties:

Melting Point: 128°C (decomposition)

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1730 cm^{-1}, 1775 cm^{-1}.

Analysis Calculated for $C_{15}H_{21}O_4Br$: C, 52.18%; H, 6.13%; Br, 23.15%.

Found: C, 52.05%; H, 6.18%; Br, 23.34%.

Group 3 yielded 195 mg. of a white crystalline solid (Compound XII) which has the following physical properties:

Melting Point: 99.5° - 100.5°C.
Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1735 cm^{-1}, 1770 cm^{-1}.
Analysis Calculated for $C_{15}H_{22}O_4$: C, 67.64%; H, 8.33%.
Found: C, 67.58%; H, 8.06%.

(x) Alternative Synthesis of Compound XII

Compound VI (1 g.) was dissolved in a few ml. of glacial acetic acid and 100 ml. of 5% sulphuric acid added. Some solid separated out and enough methanol was added to redissolve the solid. The mixture was warmed overnight on a steam bath. On cooling, starting material was recovered unchanged.

The recovered material was dissolved in 50 ml. of glacial acetic acid and refluxed for about one hour. The solvent was removed on a rotary evaporator and the residue dissolved in ether. After washing with 10% aqueous sodium carbonate followed by water, the neutral ether solution was dried over anhydrous magnesium sulphate.

Removal of drying agent and solvent yielded 0.7 g. of a white crystalline material. Recrystallization from petroleum ether (boiling point 35°C - 60°C) gave a product, with the melting point 100.5 - 101.0°C, whose infrared spectrum and proton magnetic resonance spectrum were identical in every respect with those of Compound XII.

(xi) Debromination of Compound X

The bromolactone X (500 mg.) was dissolved in about 10 ml. of methanol and 5 ml. of glacial acetic acid was added. The solution was swirled with 200 mg. of zinc dust for about ten minutes. No reaction occurred.

The mixture was then refluxed for two hours. After cooling, the zinc was removed by filtration. The filtrate was diluted with water and extracted with several portions of chloroform. The chloroform extracts were washed twice with water, once with 10% aqueous sodium carbonate solution and then with water until neutral. After drying the organic solution over anhydrous magnesium sulphate, the solvent was removed to give a syrupy liquid (275 mg.) which crystallized on standing (Compound XIII).

Acidification of the alkaline extracts gave a further 76 mg. of product. Compound XIII has the following physical properties:

Melting Point: 148.0° - 149.0°C.

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1700 cm^{-1}; 1720 cm^{-1}, broad hydroxyl absorption.

Analysis Calculated for $C_{15}H_{22}O_4$: C, 67.64%; H, 8.33%.

Found: C, 67.72%; H, 8.59%.

(xii) Methylation of Compound XIII

A solution of 100 mg. of the half ester (XIII) in anhydrous ether was cooled in an ice-bath and a slight excess of an ethereal solution of diazomethane added dropwise. (Diazomethane was prepared from p-tolylsulphonylmethyl nitrosamide as described by Vogel).[90]

Removal of excess diazomethane and evaporation of solvent gave a quantitative yield of Compound VI the identity of the two compounds being established by mixed melting point, infrared spectroscopy and proton magnetic resonance spectroscopy.

(xiii) Isolation of Compound XV

Column chromatography of the product obtained by treatment of the anhydride adduct V with sulphuric acid-methanol gave, in addition to the diester IX, a later fraction 0.4 g. which crystallized on standing. After recrystallization from anhydrous ether, Compound XV has the following physical properties:

Melting Point: 87.5°C - 88.5°C.

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1745 cm^{-1}, 1780 cm^{-1}.

Analysis Calculated For $C_{15}H_{22}O_4$: C, 67.64%; H, 8.33%.

Found: C, 67.97%; H, 8.19%.

(xiv) Debromination of Compound XI

This reaction was carried out in a manner similar to that described for the dehalogenation of Compound X. The product was identified as Compound XIII by mixed melting point (147.5°C - 148.5°C) as well as by infrared spectroscopy and proton magnetic resonance spectroscopy.

(xv) Debromination of Compound VIII

A solution of 275 g. of the bromocompound in 10 ml. of glacial acetic acid was refluxed with 200 mg. of zinc dust for fifteen minutes. A crystalline solid separated out on cooling. The organic material was dissolved in chloroform and water added to the mixture. After filtering off the zinc, the organic layer was isolated, washed once with water, once with 5% aqueous sodium carbonate and then with water until neutral. The solution was dried by shaking with anhydrous magnesium sulphate. Removal of drying agent and solvent gave 210 mg. of crude product. After recrystallization from a petroleum ether/benzene mixture, the product was identical with the *cis*-*endo* anhydride V as indicated by mixed melting point (99.0° - 100.0° C), infrared spectroscopy and proton NMR.

(xvi) Bromination of trans-Diester VII (→ XIV)

The bromination was carried out in the manner described for the halolactonization of the 5-*endo*-6-*exo*-diester. Reaction of 135 mg. of 5-*exo*-6-*endo*-diester gave 136 mg. of crude product (melting point 115°C - 120°C). After two recrystallizations from anhydrous ether, Compound XIV has the following physical properties:

Melting Point: 127.5°C - 129.5°C.

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1730 cm^{-1}, $\nu_{C=C}^{CHCl_3}$ 1620 cm^{-1}.

Analysis Calculated for $C_{16}H_{23}O_4Br$: C, 53.49%; H, 6.45%; Br, 22.24%

Found: C, 53.88%; H, 6.33% Br, 22.20%.

(xvii) Ozonolysis of Compound XIV

The ozonization was carried out on 27 mg. of the compound in ethyl acetate at -70°C. Work up with formic acid/hydrogen peroxide (3:1) mixture gave 25 mg. of crude product which was crystallized from chloroform.

The proton NMR spectrum showed no peaks corresponding to $CH_3-C = O$, -COOH or $-\overset{\overset{O}{\|}}{C}-H$.

The infrared spectrum showed $\nu_{C=O}^{CHCl_3}$ 1725 cm^{-1}.

The compound gave a 2-4-dinitrophenylhydrazone (melting point 121°C - 122°C).

CHAPTER 3

^{13}C CHEMICAL SHIFTS OF THE CARBONYL CARBON OF β,γ-UNSATURATED KETONES

INTRODUCTION

The ^{13}C Chemical Shifts of Carbonyl Compounds

The resonance positions of carbonyl carbons occur over a total range of 70 p.p.m. at the low field end of the ^{13}C spectral region.[92,93] The carbonyl group in aliphatic aldehydes and ketones absorbs in the low field portion of this range (-25 to -5 p.p.m. with respect to carbon disulphide), while the resonances of the carbonyl carbon in conjugated aldehydes and ketones are shifted to higher field and, for the most part, are found in the range -5 p.p.m to +5 p.p.m.

Alkyl substitution on a carbonyl carbon deshields it by about 5 p.p.m. while electronegative substituents have the opposite effect. It has been suggested[93] that inductive electron withdrawal from the carbonyl carbon depolarizes the carbon-oxygen π-bond and thus causes an effective increase in the net π-electron density at the carbonyl carbon. Using equations developed by Karplus and Pople,[94,95] it was found that the local paramagnetic term in these systems is given by,[96]

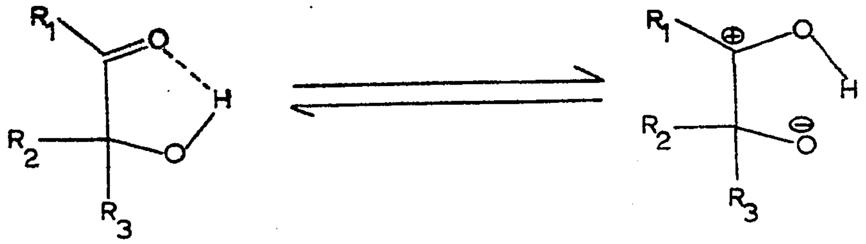
$$\sigma_p^{AA} = -(296 + 95.7\lambda)[1 + 0.273(1-\lambda^2)^{\frac{1}{2}}] \qquad [14]$$

where λ is the bond polarity parameter defined by the expression for the π-bond orbital in a polar carbonyl bond.

$$\psi(\pi,CO) = [(1-\lambda)/_2]^{\frac{1}{2}}\ \Phi_{pz(C)} + [(1+\lambda)/_2]^{\frac{1}{2}}\ \Phi_{pz(O)} \qquad [15]$$

The form of the expression for σ_p^{AA} clearly indicates a dependence on the polarity of the C=O bond as had been previously suggested.[93]

A hydroxyl group α to a carbonyl group deshields the carbonyl carbon. This effect is thought to be due to hydrogen bonding.[93,97,98] The formation of a hydrogen bond can be considered to increase the polarity of the carbonyl bond[99] and thus enhance the local paramagnetic term (σ_p^{AA}).



The conjugative effects indicated in the early studies[93] are substantiated by an extensive investigation of a number of α,β-unsaturated ketones.[100-102] In addition, the results of these studies showed that the carbonyl chemical shift is dependent on the stereochemical relationship between the two chromophores. Further, ^{13}C spectroscopy provided some evidence for ground state interaction between a carbonyl group and a cyclopropyl ring.[103] In view of these results, it was considered likely that examination of the chemical shifts of the carbonyl carbon in a series of β,γ-unsaturated ketones would give useful information about the interaction between the two chromophores in the ground state. Such information would supplement knowledge gained through ultraviolet spectroscopy (see page 118).

Some authors have suggested that the interaction between non-conjugated chromophores is essentially an excited state phenomenon. A lowering of the energy of the excited state(s) gives a smaller value for the average electronic transition energy (ΔE) and enhances the local paramagnetic term (σ_p^{AA}) of the shielding constant, the _zz_-component of which is given by the expression,[95]

$$(\sigma_p^{AA})_{zz} = -\frac{e^2h^2}{2m^2c^2(\Delta E)}\langle r^{-3}\rangle_{2p}\left\{(Q_{AA})_{zz} + \sum_{B\neq A}(Q_{AB})_{zz}\right\} \qquad [16]$$

where $\langle r^{-3}\rangle_{2p}$ is the mean inverse cube radius for carbon

2p orbitals and Q_{AA} and Q_{AB} are related to the charge density and bond order matrix in the molecular orbital description of the unperturbed molecule. If the transition energy term (ΔE) is dominant, then conjugation should result in a deshielding of the carbonyl carbon. On the other hand, it has been proposed[104] that minor changes in the electron density about a nucleus create variations in the repulsions between electrons. An increase of negative charge (by conjugation) would be associated with a general electron expansion about the nucleus and the smaller value $< r^{-3} >$ would decrease the paramagnetic term, causing the resonance position of the carbonyl carbon to shift upfield.

Intramolecular Interactions Involving Non-conjugated π-Electron Systems

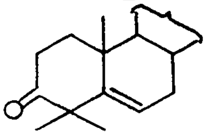
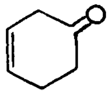
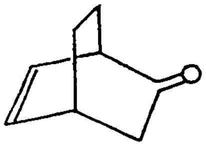
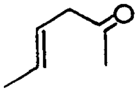
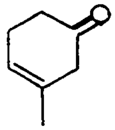
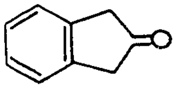
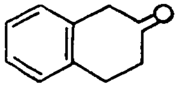
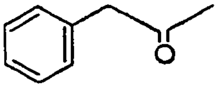
It is known that π-electron systems situated beta to a developing carbonium ion centre can significantly influence the course and the rate of the reaction. This anchimeric acceleration of rate has been ascribed to delocalization of the π-electron cloud of the neighbouring π-electron substituent in the rate-determining step. Simonetta and Winstein[105] used a semi-empirical molecular orbital theory to calculate the stabilization energies in homoallyl, β-dienyl and β-phenyl systems. The values obtained followed the same trend as the rate-enhancing effect of these substituents in solvolytic reactions.

Another somewhat analogous manifestation of π-electron interaction, is the alteration of characteristic ultraviolet spectra by interactions between non-adjacent chromophores. The consequences of this interaction do not follow a simple trend. In some cases, for example, Δ^5-bicyclo[2.2.1]heptenone-2 (dehydronorcamphor) (XXV), the n → π* transition is shifted to longer wavelengths;[106] in $\Delta^{3,5}$-cycloheptadienone (XXVI) the wavelength is unchanged and the intensity increases,[107] while a hypsochromic shift of the n → π* band has been observed in the case of Δ^2-bicyclo[2.2.1]hepten-7-one (XXVII).[108] Particularly striking intensities are reported for parasantonide[109] (XXVIII) (ε 1170) and 5-phenyl-bornenone (XXIX) (ε≈6000).[110] The wavelength and intensity of the n → π* transition of a number of β,γ-unsaturated ketones are shown in Table XVI.

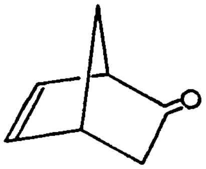
The first rationalization of this phenomenon was given by Labhart and Wagniere,[111] who considered both conjugated and non-conjugated ketones and attributed the intensified n → π* absorption to mixing of the non-bonding p-orbital on oxygen with the olefinic π-orbital of nearly the same energy. Cookson and coworkers[112] have suggested that the intensification of the n → π* transition will be controlled by two factors:

TABLE XVI

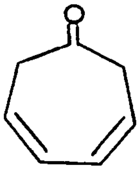
THE WAVELENGTH AND INTENSITY OF THE n → π* TRANSITION IN SOME β,γ-UNSATURATED KETONES

Compound (Structure)	$\lambda_{max}(n \rightarrow \pi^*)$ mμ	ε_{max}	Reference
XXV	305^{a}	290	111
	295^{b}	315	109
XXVI	290	562	107
XXVII	275^{c}	33	113
XXVIII	300	1170	109
XXIX	315^{b}	6070	114
	290^{a}	51	111
	277^{a}	107	111
	292^{a}	107	111
	290^{b}	80	115
	280^{b}	19	116
	293^{b}	10	117
	327^{b}	18	117
	288^{b}	145	118

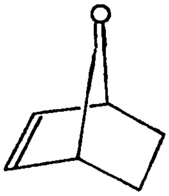
a. cyclohexane solvent; b. ethanol; and c. iso-octane.



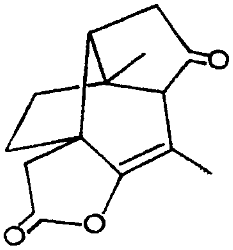
XXV



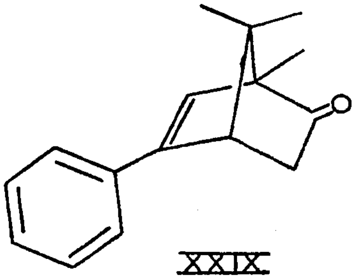
XXVI



XXVII



XXVIII



XXIX

(a) the oscillator strength of the charge transfer band, and

(b) the overlap between the non-bonding orbitals on oxygen and the 2p-π orbitals of the olefin.

Accordingly, two extreme conditions are visualized for which the $n \rightarrow \pi^*$ transition will not have an enhanced intensity. These are, respectively, the cases of no charge transfer, and that of no overlap. Thus, both XXV and XXVII show the charge transfer band only XXV has an intensified $n \rightarrow \pi^*$ band. Examination of models indicates that, in the case of XXVII, the nodal planes of the relevant p- and π-orbitals are orthogonal and the overlap requirement is not satisfied. There has been some success in correlating computed overlap integrals with the exaltation of $n \rightarrow \pi^*$ absorption in flexible as well as rigid molecules.[119]

The compounds exhibiting enhanced $n \rightarrow \pi^*$ absorption also show high optical rotation and Cotton effect curves with high amplitudes.[120] These 'anomalies' are considered to share a common basis with the exaltation of the n → π^* transition[109] and have been interpreted in a similar manner.[121] The results of some more detailed calculations indicate that the mixing of the carbonyl n → π^* transition with the olefinic $\pi_{CC} \rightarrow \pi^*_{CC}$ transition may be due mainly to electrostatic coupling of the two local transitions.[122]

The Stereochemical Dependence of the Interaction

For α-conjugation, the maximum interaction is expected when the nodal planes of the two π-systems are coplanar so that 2p-π overlap is at its maximum value. A fundamentally different relationship is expected in the case of β,γ-unsaturation. The basis of this relationship is best understood by considering simple models for the overlap between 2p orbitals.

In a simple case where the axes of the 2p orbitals lie in parallel planes at a distance r (Fig. 21a) the overlap integral is given by,[123]

$$S_{ij} = S_{\pi\pi} \cos \gamma \qquad [17]$$

where $S_{\pi\pi}$ is the overlap integral of parallel 2p orbitals overlapping in a π manner (Fig. 21b) at a distance r, and

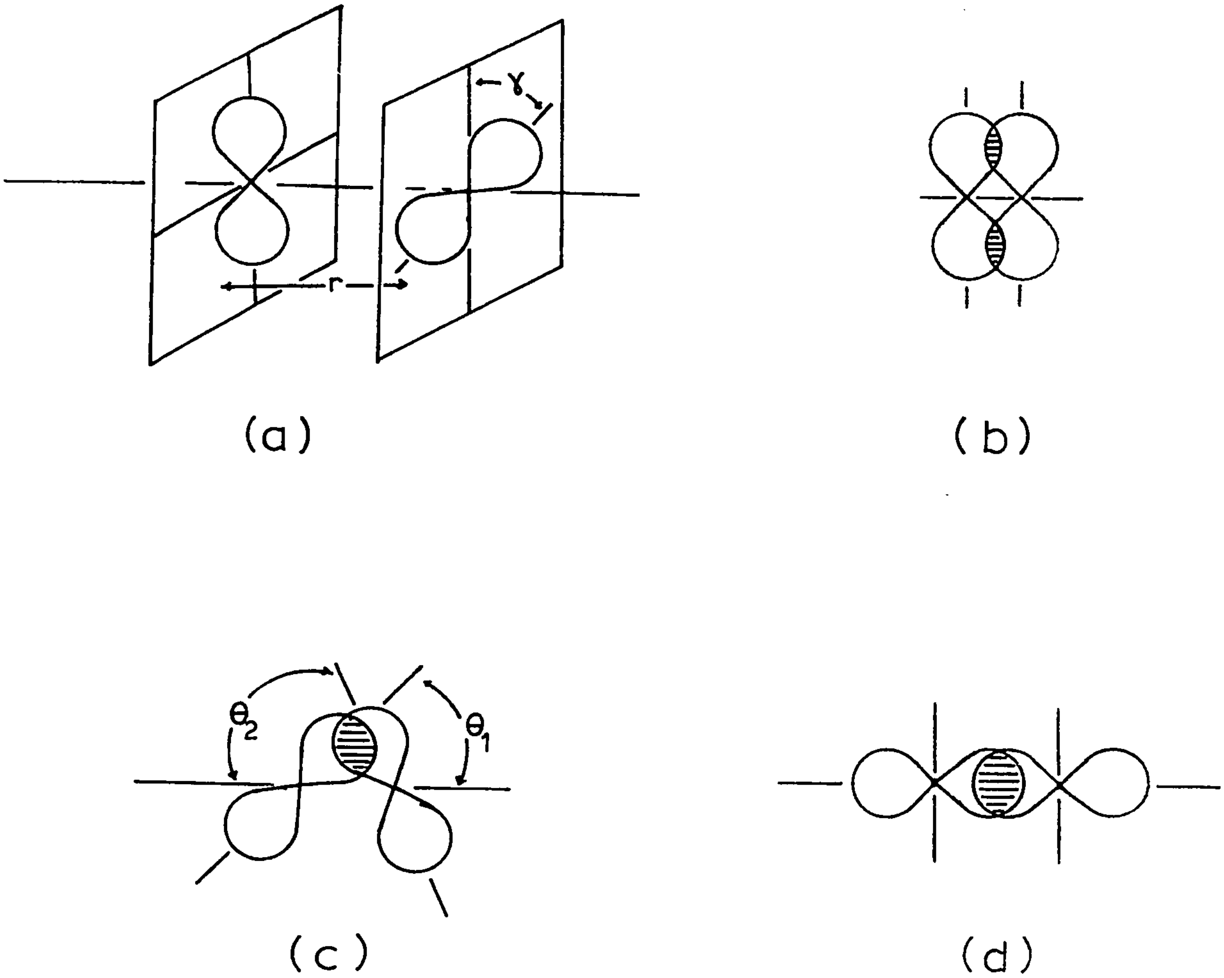


Figure 21. - Modes of Overlap of p-Orbitals.(a) Generalized Form with Orbitals in Parallel Planes, (b) ππ Overlap, (c) Orbitals Slanted towards One Another and (d) σσ Overlap.

γ is the angle between the axes of the p-orbitals (Fig. 21a). When the axes of the p orbitals lie in a plane ($\gamma = 0$) but are slanted towards one another at angles θ_1 and θ_2 with respect to the internuclear line (Fig. 21c), the overlap can be resolved into $\sigma\sigma$ contributions (Fig. 21d) and $\pi\pi$ contributions (Fig. 21b). The overlap integral is then given by,

$$S_{ij} = S_{\sigma\sigma} \cos\theta_1 \cos\theta_2 + S_{\pi\pi} \sin\theta_1 \sin\theta_2 \qquad [18]$$

if, in addition, γ is non-zero, the expression becomes,

$$S_{ij} = S_{\sigma\sigma} \cos\theta_1 \cos\theta_2 + S_{\pi\pi} \sin\theta_1 \sin\theta_2 \cos\gamma. \qquad [19]$$

For two directly bonded carbon atoms, the axes of the p orbitals can be assumed to be perpendicular to the bond axis so that $\theta_1 = \theta_2 = 90°$. The maximum overlap condition is therefore $\gamma = 0$, so that

$$S_{12} = S_{\pi\pi} \qquad [20]$$

This is the condition for maximum overlap in α,β-unsaturated systems and also the requirement for maximum conjugative shielding of the carbonyl carbon in α,β-unsaturated ketones. Use of this model for the interaction also provides an explanation for the fact that there is no difference in shielding for the s-cis and the s-trans configurations in which the $\pi\pi$ overlap contributions are identical.

For the p-orbitals of two sp^2-hybridized carbon atoms separated by an sp^3-hybridized carbon atom, it is readily apparent that little orbital overlap is possible in planar conformations such as those shown in Figs. 22a and 22b. More overlap is expected in non-planar conformations (Figs. 22c and 22d) where the p-orbitals lie in the same plane. If the problem is considered in terms of overlap integrals, the 1,3 overlap integral for the planar conformations is given by,

$$S_{1,3} = S_{\pi\pi} \qquad [21]$$

in the non-planar conformations with the p-orbitals axes in the same plane ($\gamma = 0$),

$$S_{1,3} = S_{\sigma\sigma} \cos\theta_1 \cos\theta_2 + S_{\pi\pi} \sin\theta_1 \sin\theta_2 \qquad [22]$$

where θ_1 and θ_2 are about 55°. At the 1,3 internuclear distances in β,γ-unsaturated ketones (about 2.5 Å), $S_{\sigma\sigma}$ is larger than $S_{\pi\pi}$ by at least a factor of 3. The first term is therefore expected to assume considerable importance. Similar arguments hold for the overlap between p-orbitals on sp^2-hybridized carbon atoms separated by more than one sp^3-hybridized carbon; the geometry for maximum 1,4 overlap is indicated in Fig. 22e.

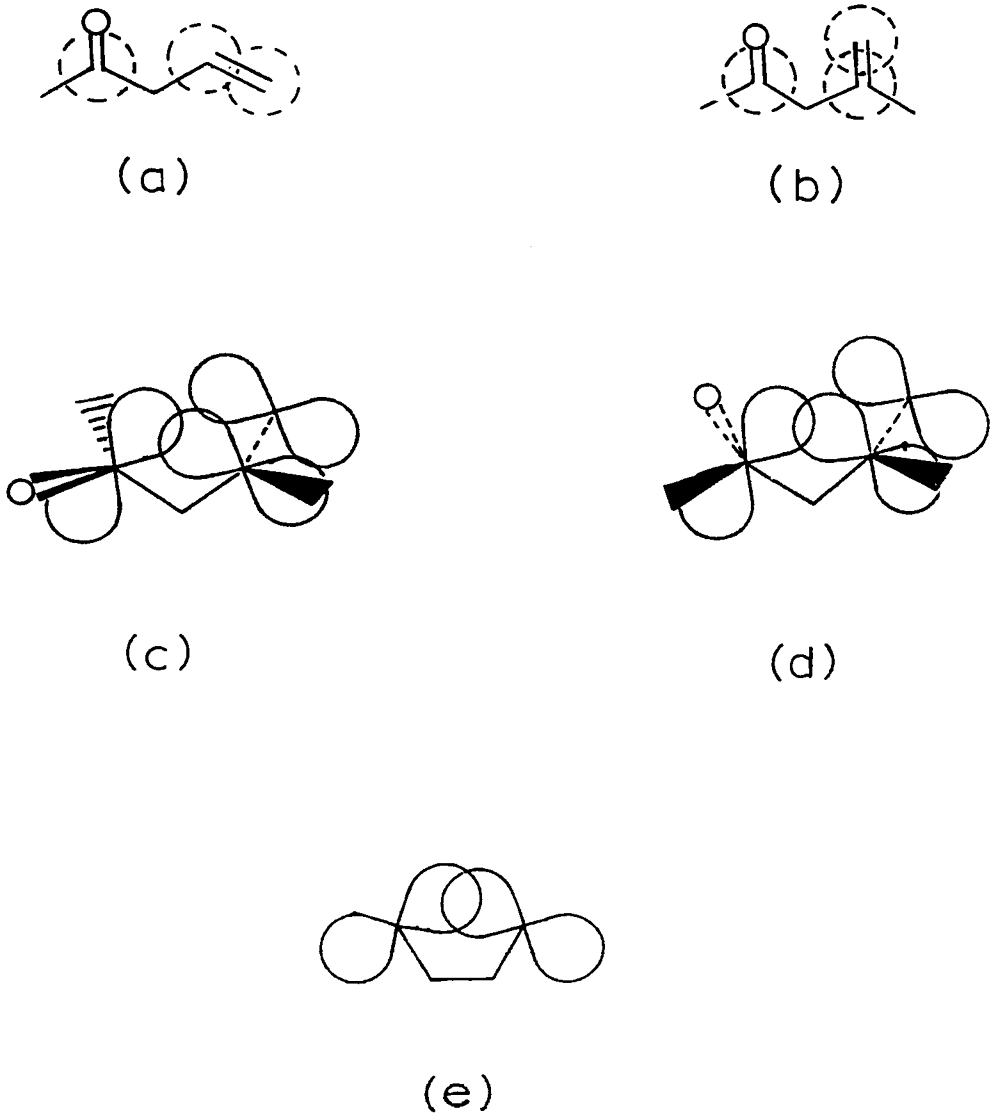

(a) (b) (c) (d) (e)

Figure 22. - 1,3 and 1,4 Overlap of *p*-Orbitals. (a) and (b) Conformations with the Nodal Planes of the *p*-Orbitals Parallel, (c) and (d) Non-planar Conformations with the Axes of the *p*-Orbitals (1,3) in the same Plane, and (e) Conformation for Maximum 1,4 Overlap.

RESULTS AND DISCUSSION

The ^{13}C chemical shifts of the carbonyl carbon in the β,γ-unsaturated ketones examined are listed in Tables XVII to XIX. Corresponding data for some related saturated and α,β-unsaturated compounds are also shown. In Table XX, the relative shielding of a carbonyl carbon by β-conjugation is compared with that caused by α-conjugation.

From the data shown in Table XX, it is clear that a π-system β to a carbonyl carbon has shielding effect. The amount of shielding is usually considerably less than that caused by α,β-unsaturation in the same nuclear framework but varies from one example to another. The observed chemical shift changes are in the _opposite_ direction to the shift to _lower_ field that would be predicted if changes in ΔE are assumed to determine the relative shift. It must, therefore, be concluded that the _changes in ^{13}C chemical shift of the carbonyl carbon reflect interactions in the ground state of the molecule_.

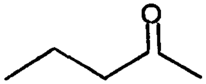
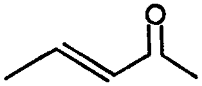
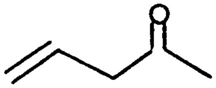
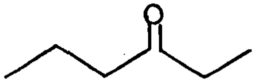
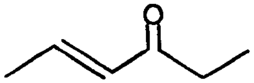
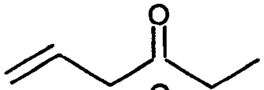
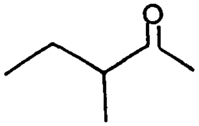
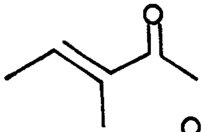
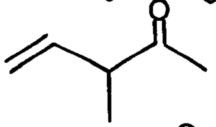
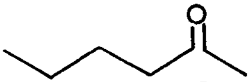
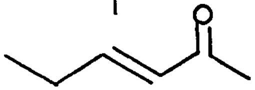
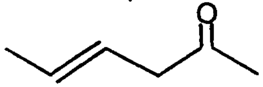
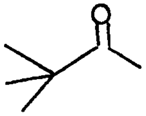
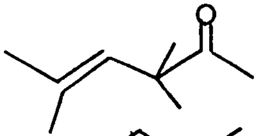
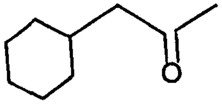
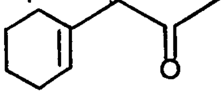
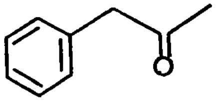
On the assumption that ΔE plays a dominant role in determining carbonyl carbon chemical shifts, a linear expression of the type[124]

$$\delta_{CO} = a\lambda_{max}^{n \rightarrow \pi^*} + b \qquad [23]$$

was proposed. The absence of such a relationship has been

TABLE XVII

^{13}C CHEMICAL SHIFTS (δ) OF THE CARBONYL CARBON OF SOME ACYCLIC KETONES†

SATURATED KETONES			α,β-UNSATURATED KETONES			β,γ-UNSATURATED KETONES		
Number	Structure	δ	Number	Structure	δ	Number	Structure	δ
XXX		-13.8	XXXVI		-3.7[a]	XL		-11.9
XXXI		-15.8	XXXVII		-6.2	XLI		-13.9
XXXII		-16.4	XXXVIII		-4.8[b]	XLII		-13.9
XXXIII		-14.3	XXXIX		-2.8[a]	XLIII		-11.4
XXXIV		-18.2				XLIV		-16.9
XXXV		-12.4				XLV		-11.6
						XLVI		-12.1

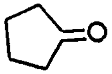
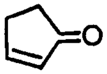
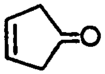
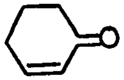
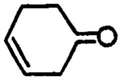
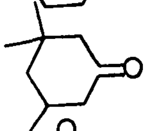
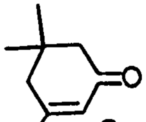
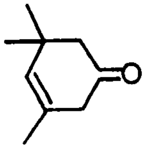
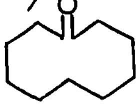
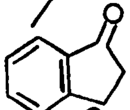
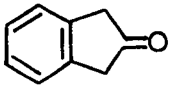
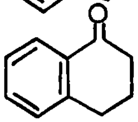
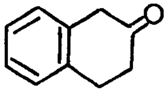
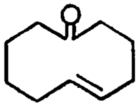
† In p.p.m. from CS_2

a Taken from reference 102

b Taken from referance 103.

TABLE XVIII

^{13}C CHEMICAL SHIFTS(δ) OF THE CARBONYL CARBON OF SOME MONOCYCLIC KETONES[†]

SATURATED KETONES			α,β-UNSATURATED KETONES			β,γ-UNSATURATED KETONES		
Number	Structure	δ	Number	Structure	δ	Number	Structure	δ
XLVII		-24.4	LI		-15.3[a]	LVI		-23.1
XLVIII		-16.1	LII		-4.3[a]	LVII		-15.1
XLIX		-15.2	LIII		-3.8	LVIII		-14.1
L		-18.9[b]	LIV		-12.9*	LIX		-20.0*
			LV		-3.2*	LX		-16.1*
						LXI		-17.5

† In p.p.m from CS_2

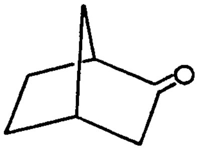
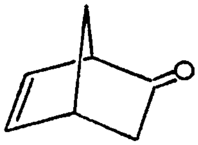
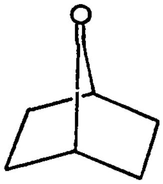
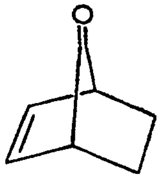
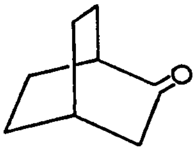
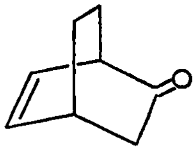
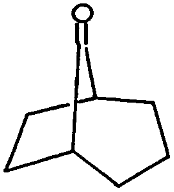
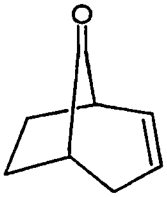
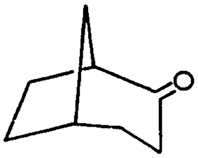
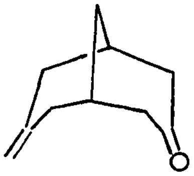
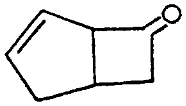
* Considered as substituted monocyclic compounds

a Taken from reference 102

b Taken from reference 93.

TABLE XIX

^{13}C CHEMICAL SHIFTS(δ) OF THE CARBONYL CARBON OF SOME BICYCLIC KETONES†

SATURATED KETONES			β,γ-UNSATURATED KETONES		
Number	Structures	δ	Number	Structures	δ
LXII		-21.8	XXV		-20.4
LXIII		-21.1	XXVII		-10.5
LXIV		-20.0[a]	LXVII		-20.2
LXV		-26.0	LXVIII		-22.0
LXVI		-18.6[b]	LXIX		-17.8*
			LXX		-12.4

† In p.p.m. from CS$_2$

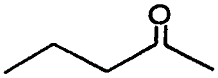
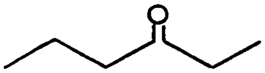
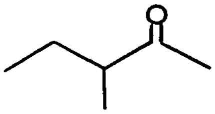
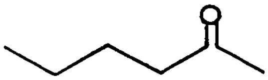
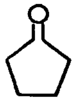
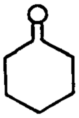
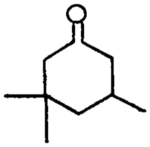
* Included for convenience

[a] Taken from reference 124

[b] Personal communication by G.W. Buchanan and J.B. Stothers.

TABLE XX

THE EFFECTS OF α,β- AND β,γ-UNSATURATION ON THE CHEMICAL SHIFT[†] OF A CARBONYL CARBON

Saturated Compound	$\Delta\delta(\beta)$*	$\Delta\delta(\alpha)$‡
	+1.9	+8.2
	+1.9	+9.6
	+2.5	+11.6
	+2.9	+11.5
	+1.3	+9.1
	+1.0	+11.8
	+1.1	+11.4

[†] In p.p.m.

* $\Delta\delta(\beta)$ = (δ_{CO} for β,γ-unsaturated compound - δ_{CO} for saturated compound)

‡ $\Delta\delta(\alpha)$ = (δ_{CO} for α,β-unsaturated compound - δ_{CO} for saturated compound).

demonstrated by Marr and Stothers,[103] and the data for β,γ-unsaturated ketones support the conclusions of the latter authors. These observations may be taken as additional evidence against the postulate that changes in ΔE are mainly responsible for the changes in ^{13}C chemical shifts.

On the basis of the arguments presented earlier, it is expected that the largest shielding effects for non-conjugated systems will be observed in non-planar systems. This postulate is supported by the relative shielding of 10.6 p.p.m. observed in the case of 7-ketonorbornene (XXVII) compared with the value of 1.3 p.p.m. found for Δ^3-cyclopentenone. In the former case, the geometric parameters determining the overlap integral are,[125]

$\theta_2 = 68°.10'$, $\theta_7 = 58°.55'$, $\gamma = 17°.29'$ and $r = 2.296$ Å

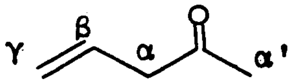
and S_{27} is calculated to be 0.0802. For the same internuclear distance $S_{\pi\pi}$ is less than 0.06.

While it is clear that this simple treatment is qualitative, it does indicate the stereochemical dependence of the interaction and gives a basis for the difference between the stereochemical dependence in this series and that observed for the α,β-unsaturated ketones.

Examination of the Experimental Data

(a) Acyclic Compounds.

Comparison of the results for the acyclic saturated and β,γ-unsaturated ketones (Table XVII) shows that methyl substitution at the α'-carbon has the same deshielding effect (2 p.p.m.) in both series. In addition, there is no difference between the substitution effects at the α- and α'-carbon atoms in the β,γ-unsaturated compounds.



This is in keeping with the postulate that the effects of the olefinic system on the chemical shift of the carbonyl carbon does not involve transmission through the α-carbon atom.

Methyl substitution at the γ-carbon has a small shielding effect on the carbonyl carbon. This can be explained in terms of an increased electron density at the β carbon resulting in more efficient 1,3 overlap.

(b) Monocyclic Compounds

In the five-membered ring, the β-double bond shields the carbonyl carbon by 1.3 p.p.m., while in the six-membered ring system a shielding of 1.0 p.p.m. is found. Measurements on Fieser molecular models indicate that, in the former case, the 1,3 internuclear distance (which is also "1,4" separation) is about 2.25 Å. In the latter ring system, the 1,3 distance varies from 2.35 Å to 2.40 Å, depending on the conformation, while the 1,4 distance is in the range 2.65 to 2.75 Å. The five-membered ring is planar so that the overlap is of the π-type with $\gamma = 0$. In Δ^3-cyclohexenone, the nodal planes of two π-systems are not coincident so that some contribution from σσ overlap is possible. This is probably responsible for the observed similarity of the shielding effect in the two ring systems, despite the larger internuclear distances in the six-membered ring system.

When the unsaturated bond in the six-membered ring forms a part of an aromatic system, the observed relative shielding is zero. Since the shape of the alicyclic ring in tetralin is analogous to that in cyclohexene,[126] this result suggests that the aromatic π-system interacts less efficiently than the simple vinyl group. This trend is in accord with the results obtained in solvolyses of β,γ-unsaturated compounds where the rate enhancement caused by a β-phenyl group is less than that found for a β-vinyl system.[108] In the case of 2-indanone, however, an increased shielding of 3.1 p.p.m. is observed. This anomaly serves to emphasize the inadequacy of the simple model proposed for the nature of the interaction, but the reason for the deviation is not clear.

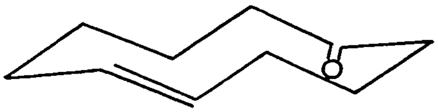
(c) Bicyclic Systems

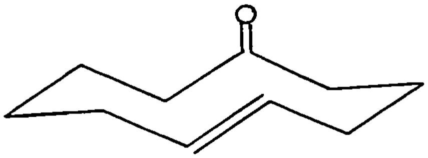
The large shielding effect observed in 7-ketonorbornene has already been mentioned (page 131). In keeping with the proposed model for the interaction, a smaller shift to higher field is found for Δ^2-bicyclo[3.2.1]octen-8-one where the internuclear distances are larger and both the σσ and the ππ contributions to the overlap are smaller. (C_2-C_8 = 2.31 Å; C_3-C_8 = 2.63 Å). An even smaller shielding is found for Δ^5-norbornen-2-one. In this compound, the 1,3 internuclear distance is about the same as that in the previous example (C_2-C_6 = 2.31 Å) but the 1,4 distance is larger (about 2.69 Å). In addition, the relevant *p*-orbitals are not tilted towards one another to the same extent and the contribution of the σσ term is reduced.

Since the proposed model for the interaction is analogous to that used in rationalizing the rate enhancing effect of non-adjacent π-systems in solvolytic reactions,[105] it is encouraging to find corresponding trends in the shielding contribution of the olefinic system to the chemical shift of the carbonyl carbon in β,γ-unsaturated ketones and the anchimeric assistance factor[127] in the acetolysis of the corresponding p-toluene sulphonates (Table XXI). Further, the fact that a β-aromatic group has a smaller effect than a β-vinyl group in both the ^{13}C spectroscopic investigation and the kinetic studies, gives additional credibility to the existence of a relationship between the two phenomena.

trans-Δ^5-Cyclodecenone

The shielding effect (1.4 p.p.m.) of the Δ^5-olefinic bond on the chemical shift of the carbonyl carbon in the ten-membered ring system clearly indicates a ground state interaction between the two chromophores, contrary to the conclusion drawn from the infrared spectrum of the compound. On the basis of current ideas on the conformation of ten-membered rings, two main spatial relationships between the two chromophores can be considered as shown in the diagram below.


(a)


(b)

In (a) the 1,5 and 1,6 distances are about 2.75 and 3.0 Å, respectively, while in (b) the corresponding internuclear

TABLE XXI

COMPARISON OF $\Delta\delta(\beta)^{\dagger}$ AND THE ANCHIMERIC ASSISTANCE FACTOR IN THE ACETOLYSIS OF THE CORRESPONDING p-TOLUENESULPHONATES

SYSTEM	log. anchimeric* assistance factor	$\Delta\delta(\beta)^{\dagger}$
anti-7-Norbornenyl	12.9	10.6
anti-8-Bicyclo[3.2.1]-oct-2-enyl	6.0	4.0
exo-2-Norbornenyl	3.8	1.4

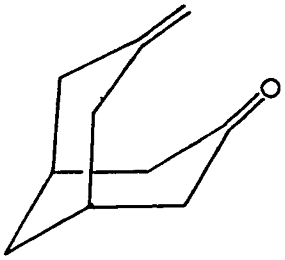
* Taken from reference 127.

† $\Delta\delta(\beta)$ is defined in Table XX.

distances are 2.1 and 2.5 Å. Since the observed shielding effect is of similar magnitude to that observed for Δ^3-cyclopentenone it seems reasonable to conclude that conformations dominate in which the two chromophores are oriented as in (b).

3-Methylene-bicyclo[3.3.1]nonanone-7

The chemical shift of the carbonyl carbon of 3-methylene-bicyclo[3.3.1]nonanone-7 is -17.6 p.p.m. In the conformation shown below, the distance between C-3 and C-7 is about 2.7 Å and that between C-7 and the terminal methylene carbon is about 2.9 Å. The interaction is therefore expected to be small. Unfortunately, attempted



hydrogenation of the unsaturated bond resulted in the formation of an unidentified alcohol, so that the corresponding saturated compound is not available for direct comparison.

EXPERIMENTAL

(a) Spectroscopy

(i) Infrared Spectra were obtained either on a Beckmann-IR5A or on a Beckmann- IR10. In each case a polystyrene strip was used to calibrate the chart paper.

(ii) Proton Magnetic Resonance Spectra were obtained on a Varian A-60 spectrometer. From time to time the calibrated chart was checked by generating audio sidebands of a tetramethylsilane signal. The sidebands were produced by a Hewlett-Packard model 241A audio oscillator the output of which was continuously monitored with an HP522B frequency counter.

(iii) ^{13}C Nuclear Magnetic Resonance Spectra

The spectra were obtained by using material containing ^{13}C in natural abundance and were measured on a Varian DP-60 Spectrometer operating at 15.0837 Mc/s. The reference was usually external methyl iodide (enriched to 58% ^{13}C) contained in a 5 mm. outside diameter tube inserted in the larger 15 mm. tube which contained the sample. In a few instances a concentric cell was used with the sample being placed in the outer bulb and the enriched CH_3I in the inner bulb.

Each spectrum was calibrated by generating audio sidebands of the reference signal on the spectrum, so that peak positions could be measured by interpolation. The output of the oscillator (either a Hewlett-Packard Model 200 CDR Wide Range oscillator or a General Radio Type 1310-A oscillator) was continuously monitored by a Hewlett-Packard Model 5245 Electronic Counter.

Except in the case where a solvent is indicated in the results presented, the spectra were obtained on neat liquids. The chemical shifts were calculated relative to CS_2 and no corrections were made for bulk susceptibility differences.

(b) Preparation of Compounds

The following compounds were obtained from commercial sources: norcamphor, β-tetralone, 1-indanone, 2-pentanone, 3-methyl-2-pentanone and 3-hexanone (Aldrich Chem. Co.); Δ^1-cyclohexenyl acetone (K & K Laboratories). A sample of α-tetralone was provided by Dr. W.C. Howell while phenyl acetone was prepared by K.S. Dhami. The other compounds examined were prepared as described below.

(i) Synthesis of Δ^4-Pentenone-2 (XL)

The ketone was obtained by oxidation of the corresponding unsaturated alcohol, using the mild oxidation technique developed by Brown.[128]

1-Penten-4-ol (8.4 g. Aldrich) was dissolved in 50 ml. of ether and cooled in an ice-bath. To this was added 75 ml. of a solution containing 14.9 g. of sodium dichromate dihydrate (B.D.H. reagent) and 11.2 ml. of concentrated sulphuric acid. The addition was done with continuous stirring over a period of three hours. Stirring at 0°C was continued for about 2.5 hours after addition had been completed.

After removal of the organic layer, the aqueous layer was saturated with sodium chloride and extracted with several portions of ether. The combined ether extracts were washed once with ice-cold 10% aqueous sodium carbonate solution to remove any acid and then with saturated sodium chloride solution until the washings were neutral. Drying was accomplished by shaking with anhydrous magnesium sulphate and allowing the solution to stand overnight over fresh desiccant.

The drying agent was filtered off and the bulk of the solvent was distilled at atmospheric pressure through a Vigreux column. Fractional distillation of the product on a 46 cm. spinning band column yielded 3.0 g. (36%) of product. This compound has the following physical properties:

Boiling Point: 104°C - 107°C (lit.[129] b.p. 107°C - 108°C).

Refractive Index: n_D^{25} 1.4125

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1718 cm^{-1}, $\nu_{C=C}^{CHCl_3}$ 1639 cm^{-1}.

Proton NMR Spectrum: $\delta_{CH_3}^{neat}$ 2.08 p.p.m. (singlet), δ_{CH_2} 3.17 p.p.m. (doublet[J = 7 c/s] with each portion of the doublet showing smaller couplings), the vinyl protons appear as a complex pattern between 290 and 380 c/s below tetramethylsilane.

(ii) Synthesis of Δ^5-Hexenone-3 (XLI)

Preparation of 1-Hexen-4-ol

Allyl magnesium chloride was prepared by the techniques described by Kharasch.[130]

To 8 g. of magnesium turnings in 100 ml. of anhydrous diethyl ether was added 23 g. of allyl chloride in 100 ml. of ether. The flask was cooled in an ice-bath and the reaction mixture stirred vigorously during the addition. Halide was added at a rate such that there was little or no evolution of gas. Stirring was continued for about three hours after addition had been completed.

Propionaldehyde (11.6 g.) in 50 ml. of anhydrous ether was added dropwise to the cooled Grignard Reagent. When all the aldehyde had been added the reaction mixture was allowed to attain room temperature - stirring being continued in the interim.

Decomposition of the complex was accomplished by pouring onto 160 g. of chipped ice and then adding 10 ml. of 15% aqueous sulphuric acid with vigorous stirring. The organic layer was removed and the aqueous layer extracted three times with ether. The combined organic solutions were washed twice with water, once with 10% aqueous sodium carbonate solution and then again with water until neutral. This was followed by washing with brine.

After drying over anhydrous magnesium sulphate and subsequent separation of the drying agent, the solvent was distilled through a Vigreux column. Fractional distillation of the residue (15.0 g.) on a spinning band column yielded 8.7 g. (43.5%) of the alcohol. This compound has the following physical properties:

Boiling Point: 132°C - 133°C (lit.[131] b.p. 132°C).

Refractive Index: n_D^{25} 1.4300 (lit.[131] n_D^{25} 1.4302).

Oxidation of 1-Hexen-4-ol

Oxidation of the alcohol was carried out by the method described by Brown.[128] Reaction of 8.6 g. of alcohol yielded 5.7 g. (68%) of ketone; this has the following physical properties:

Boiling Point: 125°C - 127°C (lit.[129] b.p. 126°C - 127°C).

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1710 cm^{-1}, $\nu_{C=C}^{CHCl_3}$ 1635 cm^{-1}.

(iii) Synthesis of 3-Methyl Δ^4-Pentenone-2 (XLII)

Preparation of 3-Methyl-1-penten-4-ol

The required butenyl magnesium halide was prepared according to the method of Kharasch[130] using crotyl chloride and stirring for about ten hours. Subsequent addition of acetaldehyde and normal work up yielded the alcohol.

In a typical run 9 g. of acetaldehyde yielded 4.5 g. of alcohol. This compound has the following physical properties:

Boiling Point: 122°C - 123°C.

Refractive Index: n_D^{25} 1.4272.

Oxidation of 3-Methyl-1-penten-4-ol

Oxidation of 10.6 g. alcohol by the dichromate-ether method[128] yielded 6.8 g. (75%) ketone. This has the following physical properties:

Boiling Point: 112°C - 115°C.

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1710 cm^{-1}, $\nu_{C=C}^{CHCl_3}$ 1635 cm^{-1}.

Proton NMR Spectrum: $\delta_{CH_3CO}^{CDCl_3}=2.05$ p.p.m., $\delta_{CH_3CH}^{CDCl_3}=1.1$ p.p.m. (J = 7 c/s), the vinyl protons absorb between 280 c/s and 370 c/s below TMS.

(iv) Preparation of Δ^4-Hexenone-2 (XLIII)

The ketone was produced by the steam distillation of acidified 3-hexen-2,5-diol as reported by Morrison.[132]

Reaction of 25 g. of the diol (Aldrich; 70% purity) gave 10.5 g. of crude product which on fractional distillation yielded 4.5 g. of ketone. This compound has the following physical properties:

Boiling Point: 127°C - 130°C (lit.[132] b.p. 45°C/29 mm.).
Infrared Spectrum: $\nu_{max}^{CHCl_3}$ 1710 cm^{-1}, 970 cm^{-1}. (lit.[132] ν_{max} 1712 cm^{-1}, 966 cm^{-1}).

(v) Preparation of Δ^4-Hexenone-3 (XXXIX)

4-Hexen-3-ol (10 g.) was oxidized in ether by aqueous acid dichromate solution.[128] From 10 g. of crude product 5 g. of pure ketone was obtained by fractional distillation. This compound has the following physical properties:

Boiling Point: 139°C - 141°C (lit.[133] b.p. 136°C - 137°C).
Refractive Index: n_D^{25} 1.4324.

(vi) Synthesis of 3,3,5-Trimethyl-Δ^4-hexenone-2 (XLIV)

Preparation of 2,4,4-Trimethyl-Δ^4-hexen-5-ol

Grignard reaction of methyl magnesium iodide and 2,2,4-trimethyl-Δ^3-pentenal followed by acid hydrolysis gave 2,4,4-trimethyl-Δ^2-hexen-5-ol.

In a typical run, 4.3 g. aldehyde yielded 2.9 g. of alcohol. This compound has the following physical properties:

Boiling Point: 75.5°C/15 mm.
Infrared Spectrum: $\nu_{C=C}^{CHCl_3}$ 1661 cm^{-1}.

Oxidation of 2,4,4-Trimethyl-Δ^2-hexen-5-ol

The alcohol (4.97 g.) was oxidized by Sarett's reagent[134] to yield 4.3 g. of crude ketonic product. Fractional distillation of the crude material gave 2.9 g. of 3,3,5-trimethyl-Δ^4-hexenone-2. This compound has the following physical properties:

Boiling Point: 72°C - 74°C/33 mm.
Infrared Spectrum: $\nu_{C=C}^{CHCl_3}$ 1667 cm^{-1}.
Proton NMR Spectrum: δ_{CH_3C} 0.47 p.p.m., δ_{CH_3C} 0.76 p.p.m. and 0.99 p.p.m., δ_{CH} 4.62 p.p.m.

(vii) Cyclohexyl Acetone (XXXV)

Catalytic hydrogenation of 1.0 g. of Δ^1-cyclohexenyl acetone over 10% palladium-charcoal gave 0.9 g. of cyclohexyl acetone. This compound has the following physical properties:

Boiling Point: 89°C/19 mm. (lit.[135] 194 - 195°C/761 mm.).
Proton NMR Spectrum: $\delta_{CH_3CO}^{neat}$ 2.01 p.p.m.

(viii) Synthesis of Δ^3-Cyclopentenone (LVI)

Synthesis of Δ^3-Cyclopentenol

Δ^3-Cyclopentenol was prepared by the diborane reduction-peroxide oxidation method described by Winstein.[136,137]
This compound has the following physical property:

Infrared Spectrum: $\nu_{C=C}^{CHCl_3}$ 1610 cm^{-1}, ν_{OH} 3600 cm^{-1}, 3420 cm^{-1}.

Oxidation of Δ^3-Cyclopentenol

Conversion of the alcohol into the corresponding ketone was carried out by the dichromate-ether method. This compound has the following physical properties:

Boiling Point: 132°C - 133°C (lit.[138] 133 - 135°C).
Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1740 cm^{-1}.
Proton NMR Spectrum: δ^{CDCl_3} 5.57 p.p.m. (vinyl protons);
δ^{CDCl_3} 2.27 p.p.m. (methylene protons).

(ix) Synthesis of Δ^3-Cyclohexenone (LVII)

Cyclohexane-1,4-diol (30 g. mixture of <u>cis</u>- and <u>trans</u>; Aldrich) was distilled from a few drops of 65% sulphuric acid at a temperature of 200°C (bath temperature). The upper phase of the crude distallate (20 g.) was fractionally distilled and 9.6 g. of material boiling between 146°C and 160°C was collected. This fraction was shown to contain an alcohol by infrared spectroscopy ($\nu_{OH}^{CHCl_3}$ 3650 cm^{-1}, 3401 cm^{-1}).

Oxidation of the alcohol liquid by Brown's two phase method[128] gave 2.5 g. of ketone. This compound has the following physical properties:

Boiling Point: 61°C/15 mm, (lit.[139,140] 38 - 40°C/ mm).
Refractive Index: n_D^{25} 1.4720.
Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1712 cm^{-1}.
Proton NMR Spectrum: the vinyl protons appear as a multiplet centred at 347 c/s below tetramethylsilane.

(x) Synthesis 3,5,5-Trimethyl-Δ^3-cyclohexenone (LVIII)

Isophorone was deconjugated by the reaction discovered by Kharasch.[76] The Grignard reagent was prepared from methyl iodide. To the ethereal solution of methyl magnesium iodide was added 250 mg. anhydrous ferric chloride and the mixture stirred at room temperature for forty-five minutes.

At the end of this time the reagent was cooled in an ice-bath and a solution of 24.2 g. of isophorone in 36 ml. anhydrous ether was added dropwise. The reaction mixture was then refluxed for 30 minutes, cooled, and poured onto 130 g. cracked ice. Glacial acetic acid (13 ml.) was then added slowly to the mixture which was stirred vigorously.

After allowing the mixture to stand for a short while, the organic phase was separated and the aqueous layer extracted several times with ether. The combined ethereal extracts were washed with 10% aqueous sodium carbonate solution and then with water until neutral.

Drying over anhydrous magnesium sulphate, separation of drying agent by filtration and removal of solvent by distillation at atmospheric pressure left 20 g. of crude product.

Proton NMR of the residue indicated the presence of isophorone and the mixture of dienes expected from the

Grignard reaction in the absence of the metallic salt. Infrared spectroscopy indicated two carbonyl compounds, one of which was isophorone ($\nu_{C=O}^{CHCl_3}$ 1667 cm^{-1} and the other having $\nu_{C=O}^{CHCl_3}$ 1718 cm^{-1}).

Two fractional distillations yielded material enriched in the non-conjugated ketone. The entire reaction (including distillation, but excluding the normal work-up stages) was carried out in an atmosphere of nitrogen. The compound has a boiling range of 92°C - 95°C/25 mm. (lit.[76] 32°C/3.5 mm).

(xi) Preparation of 3,3,5-Trimethylcyclohexanone (XLIX)

Freshly distilled isophorone (5 g.) was hydrogenated at atmospheric pressure over 200 mg. of 10% palladium-charcoal catalyst. The catalyst was removed by filtration and the solvent distilled off at atmosperic pressure.

Fractional distillation of the crude product (4.4 g.) yielded 2.7 g. of saturated ketone. This compound has a boiling point of 73°C/12 mm. (lit.[141] 67°C/14 mm).

(xii) Preparation of Δ^5-Bicyclo[2.2.1]heptenone-2 (Dehydronorcamphor XXV)

Dehydronorborneol was oxidized with Sarett's reagent[134] in the manner described by Atkinson *et al.*[142]

Reaction of 20 g. of mixture of *exo*- and *endo*-

alcohol (Aldrich) yielded 10.45 g. of ketone which has the following physical properties:

Boiling Point: 59°C - 60°C/15 mm. (lit.[106]
59°C - 59.3°C/18 mm.).
Refractive Index: n^{25}_{D} 1.4855 (lit.[106] 1.4839).
Infrared Spectrum: $\nu^{CHCl_3}_{C=O}$ 1742 cm^{-1} (lit.[142]
$\nu_{C=O}$ 1740 cm^{-1}).

(xiii) Synthesis of 7-Ketonorbornene (Δ^2-Bicyclo[2.2.1]-heptenone-7 XXVII)

The unsaturated ketone was obtained by the fourstep synthesis published by Gassman and Pape.[143]

Preparation of 5,5-Dimethyoxy-1,2,3,4-tetrachlorocyclopentadiene

The procedure adopted for this step is that of McBee.[144] A solution of 69 g. of patassium hydroxide in 300 ml. methanol was added to a solution of 128.5 g. of hexachlorocyclopentadiene (Aldrich) during a period of about two hours. The rate of addition was adjusted so that the temperature of the reaction mixture remained below the boiling point of methanol. Stirring was continued for one hour after completion of addition and the reaction mixture allowed to stand overnight.

The contents of the flask were transferred to a large separating funnel and diluted with 1500 ml. of water. A heavy oil separated out and was collected. The aqueous layer was then extracted with several portions of ether and the extracts added to the oil. The combined organic material was then washed with three portions of water and dried over anhydrous magnesium sulphate.

After filtering off the drying agent, the solvent was removed on a thin-film evaporator and the residual liquid fractionated on a spinning band column. The product was obtained as a yellow liquid (108 g.). This compound has the following physical properties:

Boiling Point: 115°C - 118°C/13 mm. (lit.[144]
118°C - 110°C/11 mm.).
Refractive Index: n_D^{20} 1.5270.
Infrared Spectrum: $\nu_{C=C}^{CHCl_3}$ 1618 cm^{-1}
Proton NMR Spectrum: $\delta_{OCH_3}^{CCl_4}$ = 3.33 p.p.m.

Preparation of 7.7-Dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]heptene-2

This stage was carried out in the manner reported by Hoch.[145]

The substituted cyclopentadiene (103 g.) was placed in a gas washing bottle equipped with a condenser, drying tube and a magnetic stirrer. With nitrogen flowing through the apparatus, the dienophile was heated to 180°C (oil bath). A mixture of ethylene and nitrogen was then bubbled through for 12 hours.

Fractional distillation of the crude product yielded 88.3 g. of distillate of which 44.0 g. has the following physical properties:

Boiling Point: 76°C - 79°C/0.06 mm. Hg. (lit.[145] 75°C - 90°C/0.02 mm).
Infrared Spectrum: $\nu_{C=C}^{CHCl_3}$ 1610 cm^{-1},
Proton NMR Spectrum: $\delta_{CH_3(syn)}^{CCl_4}$ 3.50 p.p.m.
$\delta_{OCH_3(anti)}^{CCl_4}$ 3.56 p.p.m.

Preparation of 7,7-Dimethoxybicyclo[2.2.1]heptene

The tetrachloro compound was dehalogenated by a modification of Winstein's method.[146]

Into a one-litre three-necked flask (equipped with a stirrer, condenser, constant pressure dropping funnel and a nitrogen inlet) was placed 636 ml. of dry tetrahydrofunan, 55 g. of diced sodium and 81 ml. of <u>t</u>-butanol. The mixture was stirred vigorously and brought to gentle reflux. The ethylene adduct (44 g.) was then added dropwise and the mixture refluxed for 36 hours.

After cooling, the reaction mixture was filtered through a wire mesh to remove unreacted sodium. The filtrate was then refiltered through a bed of Kieselguhr in a large

Buchner funnel. The liquid thus obtained was mixed with one litre of chopped ice and 250 ml. of diethyl ether. Separation of the organic phase left a dark aqueous solution which was extracted with two portions of ether. Saturated sodium chloride solution was used to wash the combined ether extracts until the washings were neutral. The ether solution was dried over anhydrous magnesium sulphate.

The drying agent was filtered off and the solvent removed by distillation at atmospheric pressure through a Vigreux column. Fractional distillation of the residue yielded 11 g. of a colourless liquid. This compound has the following physical properties:

Boiling Point: 61°C - 62°C/12 mm. (lit.[143] b.p. 61 - 71°C/18 mm.).

Refractive Index: n_D^{20} 1.4640 (lit.[143] n_D^{25} 1.4598).

Proton NMR Spectrum: $\delta_{OCH_3}^{neat}$ 3.02 p.p.m. (<u>syn</u>), $\delta_{OCH_3}^{neat}$ 3.10 p.p.m. (<u>anti</u>), the vinyl protons appear as a triplet centred at 5.95 p.p.m. with a splitting of 2 c/s.

Conversion of the Ketal to Ketone[143]

The product from the previous stage was stirred for 24 hours with 20 ml. of a 5% aqueous solution of sulphuric acid. The resultant product was extracted with pentane and the extract dried over anhydrous magnesium sulphate.

Removal of the drying agent and solvent left 8.7 g. of crude product. The ketone was purified by fractional distillation (yield 6.1 g.). This compound has the following physical properties:

Boiling Point: 92°C - 97°C/115 mm. (lit.[143] 96°C - 100°C/115 mm.).

Infrared Spectrum: $\nu_{max}^{CHCl_3}$ 1869 cm^{-1}, 1792 cm^{-1}, 1776 cm^{-1} (lit.[147] ν_{max} 1862 cm^{-1}, 1792 cm^{-1}, 1779 cm^{-1}).

(xiv) Hydrogenation of 7-Ketonorbornene (→ LXIII)

The unsaturated ketone (3 g.) in glacial acetic acid (25 ml.) was hydrogenated at atmospheric pressure over 500 mg. of 10% palladium-charcoal.

After the catalyst had been filtered off, most of the acetic acid was removed by fractional distillation at about 80 mm. The residue was then dissolved in ether and washed twice with water, once with 10% aqueous sodium carbonate and then with brine until neutral.

Drying over anhydrous magnesium sulphate followed by removal of drying agent and solvent gave 2.55 g. product. This compound shows the following infrared absorption:

$\nu_{max}^{CHCl_3}$ 1840 cm^{-1}, 1770 cm^{-1}, 1740 cm^{-1}. (lit.[147] ν_{max} 1832 cm^{-1}, 1783 cm^{-1}, 1745 cm^{-1}).

(xv) Synthesis of Δ^2-Bicyclo[3.2.1]octen-8-one (LXVIII)

A five stage synthesis was used to obtain this compound.

Preparation of the Morpholine Enamine of Cyclopentanone

The procedure used is an adaptation of those used by Hunig[148] and Kuehne.[149]

Morpholine (90 g.) and cyclopentanone (84 g.) were dissolved in 375 ml. benzene and a few crystals of *p*-toluenesulphonic acid added. The solution was flushed with nitrogen for a few minutes and then refluxed in a Dean and Stark apparatus until no more water separated out. A slow flow of nitrogen was maintained throughout the reaction which took about ten hours.

The benzene was distilled off at atmospheric pressure (Vigreux column) and the residual liquid was fractionated *in vacuo* to yield 110 g. of product. This compound has the following boiling point: 103.0°C - 105.0°C/10 mm.

Preparation of 2-N-Morpholinobicyclo[3.2.1]octan-8-one

The amino-ketone was prepared by the addition of acrolein to 1-N-Morpholino-cyclopentene by the method of Stork.[150] Condensation of 110 g. of the enamine yielded 70 g. of amino-ketone having the following physical properties:

Boiling Point: 180°C - 193°C/0.8 mm. (lit.[151] b.p. 127 - 140°C/0.2 mm.).

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1740 cm^{-1} (lit.[151] $\nu_{C=O}^{CHCl_3}$ 1748 cm^{-1}).

Formation of the Ethylene Ketal of the Amino-ketone

Conversion of 70 g. of amino-ketone into its corresponding ethylene ketal as described by Woodward and Foote[151] yielded 4.5 g. of crude ketal which was used in the next stage without further purification.

The methylene protons of the ketal function appear as a singlet at 3.82 p.p.m. (in CCl_4).

Preparation of Δ^2-Bicyclo[3.2.1]octen-8-ethylene Ketal

Elimination of the morpholine group was carried out by way of oxidation to the N-oxide and subsequent pyrolysis.[151] A crude product (9.7 g.) was obtained. The ketal has the following physical properties:

Infrared Spectrum: $\nu_{max}^{CHCl_3}$ 3030 cm^{-1}, 1635 cm^{-1}, 1100 cm^{-1} to 1000 cm^{-1}, 690 cm^{-1} to 660 cm^{-1}, (lit.[151] 3030 cm^{-1}, 1639 cm^{-1}, 1111 cm^{-1} to 1000 cm^{-1}, [complex] 690 cm^{-1}, 671 cm^{-1}).

Proton NMR Spectrum: $\delta_{CH_2}^{CCl_4}$ (of ethylene ketal function) = 3.83 p.p.m., the vinyl protons appear as a complex pattern between 310 c/s and 355 c/s from tetramethylsilane.

Preparation of Δ^2-Bicyclo[3.2.1]octen-8-one (LXVIII)

Generation of the ketone from the ethylene ketal was accomplished by refluxing the latter compound for four hours in aqueous methanolic hydroghloric acid. Reaction of 9.5 g. of ethylene ketal gave 7.41 g. of crude ketone.

Purification of the crude material by fractional distillation gave 4.6 g. of product. This compound has the following physical properties:

Boiling Point: 85°C - 86°C/16 mm. (lit.[152] 69°C - 70°C/5 mm.; lit.[151] 130°C(pot)/25 mm.).

Infrared Spectrum: ν^{CHCl_3} 1745 cm^{-1}, 1630 cm^{-1}, 1185 cm^{-1}, 1110 cm^{-1}, 1030 cm^{-1}, (lit.[151] ν^{CCl_4} 1758 cm^{-1}, 1189 cm^{-1}, 1115 cm^{-1}, 1032 cm^{-1}; lit.[151] ν^{CCl_4} 3030 cm^{-1}, 1733 cm^{-1}, 1639 cm^{-1}, 690 cm^{-1}, 667 cm^{-1}).

Proton NMR Spectrum: The vinyl protons appear as a multiplet between 323 c/s and 363 c/s from tetramethylsilane (in $CDCl_3$).

(xvi) Preparation of Bicyclo[3.2.1]octan-8-one (LXV)

Hydrogenation of 2.2 g. of unsaturated ketone (LXVIII) in methanol (using a platinum catalyst) gave 2.0 g. of the saturated ketone. After crystallization from petroleum ether (b.p. 35°C - 60°C) the product has the following physical properties:

Melting Point: 138°C - 140°C (lit.[151] 140°C - 141°C).

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1733 cm^{-1}.

(xvii) Synthesis of Δ^5-Bicyclo[2.2.2]octen-2-one (LXVII)

The synthetic route was patterned after that used by Mislow and Berger.[153]

Diels-Alder Addition of Vinyl Acetate and Cyclohexa-1,3-diene

This reaction was carried out on a mixture of 20 g. of diene and 21.6 g. of dienophile with a small amount of hydroquinone sealed *in vacuo* in Carius tubes and heated to 180°C for six days. Removal of the more volatile portions of the product mixture by distillation at atmospheric pressure was followed by fractional distillation to give 9.6 g. of material which was shown to contain acetates. This compound has the following physical properties:

Boiling Point: 108°C - 119°C/19 mm. (lit.[153] 91°C/9 mm.).

Infrared Spectrum:: $\nu_{C=O}^{CHCl_3}$ 1721 cm^{-1}.

Proton NMR Spectrum: $\delta_{CH_3CO}^{neat}$ 1.82 p.p.m. and 1.89 p.p.m.

Saponification of Mixture of Acetates

The material containing acetates was refluxed with aqueous methanolic sodium hydroxide (0.5 N) for several hours. The resultant mixture was diluted with water, saturated with sodium chloride and extracted with several portions of diethyl ether. The residual aqueous methanolic layer was concentrated to about one-third its volume on a rotary evaporator and then again extracted with ether.

The combined ether extracts were washed with brine until the washings were neutral to litmus and then dried over anhydrous magnesium sulphate. Removal of drying agent and solvent yielded 6.8 g. of dark liquid which failed to give any crystalline material.

The crude product was chromatographed on 200 g. of silica gel (BDH). The dimer of cyclohexadiene was removed by elution with benzene and the eluent was then gradually changed to diethyl ether (via several dilutions of ether/benzene) and 2.25 g. of alcohol material (yellow crystals) was obtained ($\nu_{OH}^{CHCl_3}$ 3600 cm^{-1}, 3450 cm^{-1}).

The proton magnetic resonance spectrum indicated a mixture of exo- and endo- alcohols with the protons on carbon bearing oxygen appearing as perturbed triplets at 227 c/s (-OH exo) and 232 c/s (-OH endo) from tetramethylsilane.

Oxidation of the Mixture of Alcohols

Oxidation was accomplished by the method of Brown.[128] A small yield of the ketone was obtained having carbonyl absorption in the infrared spectrum ($\nu_{C=O}^{CHCl_3}$ 1720 cm^{-1}).

(xviii) Synthesis of 2-Indanone (LXIX)

Preparation of 2-Bromo-1-indanol

The bromohydrin of indene was prepared by the method reported by Suter and Milne.[154] Reaction of 25 g. of indene yielded 41 g. of bromohydrin which has a melting point of 127°C - 128°C. (lit.[154] m.p. 126°C - 127°C).

Preparation of 2-Methoxy-1-indanol

The method of Levin[155] was used to convert the bromohydrin into the corresponding methoxy compound. Reaction of 30 g. of 2-bromo-1-indanol gave 13.9 g. of product which has a boiling point of 150°C - 155°C/12 mm. (lit.[155] 149°C - 152°C/11 mm. - 12 mm.).

Preparation of 2-Indanone

2-Methoxy-indanol-1 (6.6 g.) was refluxed for 1 hour with a solution of 11 ml. concentrated sulphuric acid in 64 ml. water. The reaction mixture was steam distilled and the product isolated as white crystalline compound precipitating from the cooled distillate. This compound yielded 3.1 g. and has the following physical properties:

Melting Point: 56°C - 57°C (lit.[155] 56°C - 57°C).
Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1751 cm^{-1}.
Proton NMR Spectrum: δ^{CDCl_3} 7.29 p.p.m. (aromatic protons), 3.52 p.p.m. (methylene protons).

(xix) Synthesis of Δ^5-Cyclodecenone (LXI)

The four stage synthesis was carried out in a manner similar to that used by Goering and Closson.[156]

Preparation of 11-Oxabicyclo[4.4.1]undec-1-yl-acetate

Decalin was oxidized in the presence of acetic anhydride by the method developed by Holmquist.[157]

Acetic anhydride (620 g.) and 1,1'-azodicyclohexanecarbonitrile (5 g. Aldrich) was dissolved in 1840 g. of decalin (Fisher) and oxygen passed through the solution for fourteen hours, the temperature being maintained between 115°C and 120°C.

The resulting solution was washed four times with water, twice with 250 ml. portions of 5% aqueous sodium hydroxide solution and again with two portions of water (250 ml. each). The organic layer was then dried over anhydrous magnesium sulphate and distilled to give the following:

(a) unchanged decalin - 1272 g., b.p. 80°C/20 mm.,

(b) a fraction boiling between 80°C and 140°C.,

(c) a dark coloured residue.

No crystals were obtained from the residue but some crystals (m.p. 102°C - 103°C) separated out from fraction (b). Continuation of the distillation under reduced pressure gave material from which 19 g. of crystalline material was obtained. Recrystallization from ethanol gave product having the following physical properties:

Melting Point: 103.5°C - 104.5°C (lit.[157] 104°C).

Infrared Spectrum: $\nu_{C=O}^{CHCl_3}$ 1730 cm^{-1}.

Proton NMR Spectrum: $\delta_{CH_3CO}^{CDCl_3}$ 2.05 p.pm.

A second run, with oxygen being passed through for 24 hours, gave 34 g. of the acetate.

Preparation of 6-Keto-cyclodecanol

Conversion of 46 g. 11-oxabicyclo[4.4.1]undec-1-yl acetate to the alcohol by Goering's procedure[156] gave 38 g. of crude product. Recrystallization from 50:50 petroleum ether/ether gave 25.4 g. of product (first crop) having the following physical properties:

Melting Point: 66.5°C - 68.5°C (lit.[156] 70.5 - 71.5°C).

Infrared Sepctrum: $\nu_{C=O}^{CHCl_3}$ 1695 cm^{-1}, 3425 cm^{-1}.

Preparation of 6-Ketocyclodecyl p-Toluenesulphonate

The p-toluenesulphonate of 6-ketocyclodecanol was made as described by Cope and Holzman.[158] Reaction of 25.4 g. of alcohol yielded 41.3 g. of the derivative, and has a melting point of 69.5°C - 70.5°C (lit.[158] 69.5°C - 71.0°C).

Preparation of Δ^5-Cyclodecenone[158] (LXI)

A mixture of 41.3 g. of tosylate and 290 ml. diethylaniline was heated at 160°C - 170°C for one hour. The solution was cooled, diluted with 2 litres of ether and washed three times with 200 ml. portions of 10% sulphuric acid and then with water until neutral. The ether solution was then dried over anhydrous magnesium sulphate, concentrated on a rotary evaporator and fractionated on a spinning band column. A yield of 6.8 g. of Compound LXI was obtained having the following physical properties:

Boiling Point:	103°C - 105°C/9 mm. (lit.[156] 90°C - 105°C/17 mm.; lit.[518] 79 - 84.5°C/ 4.3 mm. - 5.5 mm.).
Refractive Index:	n_D^{25} 1.4925 (lit.[156] trans-Δ^5-cyclodecenone n_D^{25} 1.4983).
Infrared Spectrum :	$\nu_{C=O}^{CHCl_3}$ 1690 cm^{-1}.

(xx) Synthesis of 3-Methylene-bicyclo[3.3.1]nonanone-7 (LXIX)

The procedure used to obtain this bicyclic ketone is that of Stetter and Tache.[159]

Bromination of 1-Adamantane Carboxylic Acid

1-Adamantane carboxylic acid (15 g.) was halogenated with bromine and aluminium bromide (anhydrous) as described by Stetter and Mayer.[160]

A yield of 11 g. of product was obtained which gave a positive Beilstein test for halogen and showing carbonyl absorption in the infrared spectrum ($\nu_{C=O}^{CHCl_3}$ 1700 cm^{-1}).

Preparation of 3-Bromoadamantane Carboxamide

The bromoacid (10 g.) was converted to the carboxamide via the acid chloride according to the precedure reported by Stetter.[159] A yield of 10.6 g. of product was obtained having the following physical properties:

Boiling Point: 130 - 135°C (lit.[159] 154 - 155°C).

Infrared Spectrum: $\nu_{NH}^{CHCl_3}$ 3540 cm^{-1}, 3410 cm^{-1},

$\nu_{C=O}^{CHCl_3}$ 1680 cm^{-1}.

The material was used without further purification.

Preparation of N[3-bromo-adamantyl-1]methyl Urethane

The carboxamide (9 g.) was treated with sodium methoxide in absolute methanol in the presence of bromine.[159] A yield of 9.5 g. of crude rearrangement product was obtained. After recrystallization from ethanol the urethane melted at 82°C. (lit.[159] m.p. 82.5°C - 83.5°C).

Preparation of 3-Methylene-Bicyclo[1.3.3]nonanone-7

The crude urethane was refluxed with 100 ml. 10% aqueous sodium hydroxide for about six hours; a crystalline solid separated out and was isolated.

Yield of crude material was 1.0 g. After recrystallization from ethanol 0.6 g. of ketone was obtained. This compound has the following physical properties:

Melting Point: 160°C - 161°C (sealed tube)
(lit.[159] m.p. 162°C).
Infrared Spectrum: $\nu_{max}^{CHCl_3}$ 1695 cm^{-1}, 1715 cm^{-1}.
Proton NMR Spectrum: δ^{CDCl_3} 4.8 p.p.m. (broad singlet, terminal methylene).

(xxi) Hydrogenation of 3-Methylenebicyclo[3.3.1]nonan-7-one

The unsaturated ketone (336 mg.) was hydrogenated at atmospheric pressure and room temperature using 75 mg. of 10% palladium-charcoal as catalyst and methanol as solvent. Filtration to remove the catalyst followed by evaporation of the solvent yielded 322 mg. of a white solid. The proton NMR spectrum of the product indicated the absence of vinyl protons while the infrared spectrum showed strong hydroxyl absorption and only weak carbonyl absorption ($\nu_{C=O}^{CHCl_3}$ 1700 cm^{-1}).

(xxii) Preparation of Δ^2-Bicyclo[3.2.0]hepten-7-one (LXX)

A mixture containing this compound was obtained by the photolysis of dehydronorcamphor.[161]

A solution of 5 g. of dehydronorcamphor in diethyl ether was placed in a photolysis chamber and purged for

30 minutes with oxygen-free nitrogen. The solution was then irradiated for 90 minutes with a 450 watt Hanovia mercury-quartz lamp using a pyrex filter. A flow of nitrogen was maintained throughout the irradiation.

After the solvent was removed by distillation at atmospheric pressure, the residue was distilled under reduced pressure, and 1.8 g. of a mixture (b.p. 61.0°C - 63.5°C) was collected.

The infrared spectrum showed a new carbonyl absorption band at 1773 cm^{-1} in addition to that due to dehydronorcamphor (1742 cm^{-1}).

APPENDIX I

SELF-ASSOCIATION IN TRICYCLIC ALDEHYDES

INTRODUCTION

The intensity of each absorption band in a nuclear magnetic resonance spectrum is a measure of the relative number of nuclei giving rise to that band. In mixtures, therefore, intensity measurements can be used to determine the relative amount of each component - providing the bands corresponding to each entity are sufficiently separated. One application of this technique is in the study of the proportion of keto and enol forms in acetylacetone at various temperatures.[162]

Keto-enol equilibrium can be considered as an example of proton exchange between two non-equivalent sites, A and B. In the case of acetylacetone, the exchange is slow, so that

$$\tau_A >> (\nu_A - \nu_B)^{-1} << \tau_B \qquad [24]$$

where $(\nu_A-\nu_B)$ is the chemical shift difference between the two sites; τ_A and τ_B are the first order lifetimes of the nucleus at site A and B, respectively. It can be shown that equation [24] represents the condition for separate lines to be observed for the proton in each of the two environments (see for example, reference 8, page 484).

If the rate of exchange is accelerated, the line for each site broadens and the maxima approach one another until these coalesce. An early example of this phenomenon is the behaviour of the proton absorption of the hydroxyl groups in a solution of acetylacetone in acetic acid.[163] At room temperature, the hydroxyl protons give rise to two slightly broadened peaks whereas, at 64°C, a single broad peak is seen.

When rapid exchange occurs, a single line is observed. The chemical shift of this peak is given by the expression[164]

$$\nu_{obs} = p_A\nu_A + p_B\nu_B$$

where p_A and p_B represent the fractional populations of the two sites. The resonance position can, therefore, be used as a measure of the position of the equilibrium and it is possible to obtain values for the equilibrium constant under the prevailing conditions. By observing the chemical shift changes over a wide temperature range, one can determine the temperature dependence of the equilibrium constant and, hence, evaluate the thermodynamic parameters for the process, ΔH and ΔS.

This technique has been utilized in the study of the phenomenon of solute-solvent association.[165-170] Self association can also be studied in a similar manner and Emsley, Feeney and Sutcliffe[8] discuss several examples of the study of hydrogen bonding by proton spectroscopy.

The Chemical Shift of the Formyl Proton

The formyl proton is observed at relatively low field - at about 9 - 12 p.p.m. from tetramethylsilane.[171] This low shielding is due, in part, to the electrophilic nature of the carbonyl carbon which results in a polarization of the C-H bond reducing the electron density about the formyl proton. Electron releasing groups bonded to the carbonyl group decrease the positive character of the carbonyl carbon resulting in a decrease of the polarization of the C-H bond and a relative shielding of the formyl proton.

Pople[10] showed, however, that a major contribution to the observed shielding arises from the magnetic anisotropy of the carbonyl group. Since the formyl proton lies in the plane of the trigonal carbon, a strong deshielding effect will be experienced from this source.

In the case of aromatic aldehydes, a further deshielding influence is exerted by the ring current effect of the aromatic ring. Several theoretical treatments of interatomic currents have appeared,[172-178] the general conclusion being that nuclei in the plane of the aromatic ring are deshielded whereas those above or below the plane of the ring are shielded.

In general, the chemical shifts of the formyl proton in aromatic aldehydes show little concentration dependence in non-aromatic solvents. When an aromatic solvent is used, however, a marked dilution effect is observed. This result has been interpreted in terms of a specific solute-solvent interaction with the aromatic solvent molecule acting as an electron donor to an electron deficient site(s) in the solute molecule.[167,170,171]

By analogy with the tendency of benzene molecules to stack one above the other, a planar complex was postulated by Klinck and Stothers.[167] Ronayne and Williams[170] support Schneider's suggestion[21] that the solvent molecules orient themselves in such a manner that they are as far as possible from the negative end of the dipole while interacting with the positive end. The latter authors imply that the observed behaviour can be readily explained by a non-planar complex but offer no concrete evidence in support of this idea.

The thermodynamic parameters obtained for these solute-solvent associations indicate that the complex is very loose, in the case of aromatic aldehydes, $\Delta H = -0.9$ to -1.6 kcal/mole. It was assumed that the solute-solvent ratio was 1:1. Since no direct measure of this ratio is available, no firm statement of the stoichiometry of the association has been attempted.

Earlier studies on polycyclic aromatic aldehydes established that, contrary to the behaviour of the monocyclic aromatic aldehydes, the formyl proton absorption for 9-anthraldehyde and 9-phenanthraldehyde shifts to lower field on dilution in deuteriochloroform. This result was considered to be indicative of self-association of these tricyclic aldehydes. The purpose of the present work was to investigate the nature of this interaction and to evaluate its thermodynamic parameters.

Treatment of Experimental Data

In these systems, the self-association of the solute molecules can be represented as a dynamic equilibrium,

$$X \text{ aldehyde (A)} \overset{K_{eq}}{\rightleftarrows} \text{complex (C)} \qquad [25]$$

where C is A_X. The number of molecules involved in the complex, on the average, is X. The equilibrium constant, K_{eq}, is defined by equation [26].

$$K_{eq} = \frac{[\text{complex}]}{[\text{aldehyde}]^X} = \frac{[C]}{[A]^X} \qquad [26]$$

It is expected that the complex C will be the more stable species and that the relative amount of complex will increase as the temperature is lowered.

The observed resonance position of the formyl proton will be the weighted average of those corresponding to the two magnetic environments available to this proton. At very low temperatures the observed shift will be that characteristic of the complex; it follows that this value, ν_C, can be obtained by extrapolation to 0°K of plots of the chemical shift vs temperature. The formyl proton resonance position for unassociated molecules will be observed at high temperatures; this value, ν_A, for "free" aldehyde can be obtained by extrapolation to infinite dilution of the plots of shift vs concentration obtained at the highest temperature used.

From these two limiting values and measurements of the formyl chemical shift, ν, under various conditions, the equilibrium constants K_{eq} can be evaluated as shown below.

Let n_A° = initial number of moles of aldehyde,

n_S° = initial number of moles of solvent,

n_A = number of moles of "free" aldehyde at equilibrium,

n_C = number of moles of "complex" at equilibrium,

also, $n_C = pn_A^\circ$.

Now the observed chemical shift, ν, can be equated to the shifts of "free" and associated aldehyde by,

$$n_A^\circ \nu = n_A \nu_A + X n_C \nu_C \qquad [27]$$

substituting for n_C,

$$n_A^\circ \nu = (1-Xp) n_A^\circ \nu_A + Xp n_A^\circ \nu_C \qquad [28]$$

for convenience, we may take $\nu_A = 0$ whence,

$$\nu = Xp\nu_C \qquad [29]$$

or,

$$p = \frac{\nu}{X\nu_C} \qquad [30]$$

Rewriting [27] in terms of mole fractions

$$K = \frac{p n_A^\circ}{(1 + p-Xp) n_A^\circ + n_S^\circ} \times \frac{[(1 + p-Xp) n_A^\circ + n_S^\circ]^X}{[(1-Xp) n_A^\circ]^X} \qquad [31]$$

which, for dilute solution, reduces to

$$K = \frac{p}{(1-Xp)^X} \times \frac{n_S^{\circ(X-1)}}{n_A^{\circ(X-1)}} \qquad [32]$$

$$= \frac{p}{(1-Xp)^X M_A^{\circ(X-1)}} \qquad [33]$$

where M_A°, the mole fraction of solute = $\frac{n_A^\circ}{n_S^\circ}$

Thus,

$$\ln K = \ln p - X \ln (1-Xp) - (X-1) \ln M_A^\circ \qquad [34]$$

or,

$$\ln \nu = X \ln (1-Xp) + (X-1) \ln M_A^\circ + \ln K + \ln X\nu_C \qquad [35]$$

In equation [35], two of the terms on the right hand side are constant at a specified temperature, and, since p is small, the first term is essentially constant; therefore, a plot of ln ν vs ln M_A° at each temperature yields a straight line of slope (X-1) - providing a means of evaluating X.

The equilibrium constant, K_{eq}, can be calculated from equation [31], or, for the case X = 2, from the relation

$$K = \frac{\nu\nu_C}{2M_A^\circ(\nu_C - \nu)^2} \qquad [36]$$

derived from equations [30] and [31].

Plots of ln K vs 1/T allow the evaluation of ΔH and ΔS in the usual way.

As a further test of the results and the analytical method, the calculated values of ΔH and ΔS were used together with the ν_C values to generate theoretical curves for comparison with the experimental results.

From equation [36],

$$\nu = \frac{\nu_C(4M_A^\circ K_{eq} + 1)}{4M_A^\circ K_{eq}} \pm \sqrt{\frac{(8M_A^\circ K_{eq} + 1)\nu_C^2}{16M_A^{\circ 2} K_{eq}}} \qquad [37]$$

A computer program was written which generates values of K_{eq} from the expression

$$K = e^{\Delta S/R}\, e^{-\Delta H/RT} \qquad [38]$$

and computes values of ν using equation [37].

RESULTS

The variations of the formyl proton chemical shift with temperature are shown in Table XXII and in Figs. 23 and 24. (The results for the 5 mole% solutions were obtained by R.E. Klinck).[179]

Extrapolation of the plots in Figs. 23 and 24 to 0°K gave values for ν_C of 578 ± 20 c/s (from tetramethylsilane) for anthraldehyde and 530 ± 20 c/s for phenanthraldehyde.

From the results at +80°C, the chemical shift for unassociated aldehyde, ν_A, was obtained by extrapolation to infinite dilution. For 9-anthraldehyde, ν_A was found to be 690.0 c/s whereas ν_A for 9-phenanthraldehyde was 624.9 c/s. Taking $\nu_A = 0$ gives ν_C values of 113 ± 20 c/s, and 95 ± 20 c/s for 9-anthraldehyde and 9-phenanthraldehyde, respectively.

From plots of ln ν vs ln M_A° (where ν is the difference between the observed chemical shift and the ν_A value) values for X are obtained. Seven plots for each system gave average values of 2.23 and 1.77. X = 2 was taken as the most probable value of the number of solute molecules in the complex.

From equation [36], K_{eq} was calculated for each point in Figs. 23 and 24. The results are listed in Tables XXIII - XXX.

TABLE XXII

THE TEMPERATURE DEPENDENCE OF THE CHEMICAL SHIFT OF THE FORMYL PROTON

9-Anthraldehyde 2.5 mole%		9-Anthraldehyde 1.0 mole %		9-Anthraldehyde 0.5 mole%	
t°C	δ(c/s)	t°C	δ(c/s)	t°C	δ(c/s)
-60.50	674.1	-59.2(5)	683.0	-58.0	686.8
-53.0	675.7	-50.0	684.6	-45.0	688.6
-40.0	678.1	-38.0	685.6	-36.5	688.5
-28.75	679.8	-28.0	686.2	-30.0	688.4
-23.0	682.5	-23.0	687.8	-21.0	689.0
-20.0	680.9	-19.8	686.7	-10.2(5)	689.5
-14.0	683.6	-14.0	688.2	-23.0	689.7
-9.75	682.0	-8.0	687.6	-14.0	690.2
0.0	684.1	0.0	688.6	-1.5	690.1
+10.0	684.8	+10.0	688.9	+10.0	690.4
+21.7(5)	685.4	+21.7(5)	689.1	+23.0	690.4
+28.5	685.6	+28.5	689.1	+28.5	690.5
+40.0	685.9	+40.0	689.3	+40.0	690.6
+53.0	686.3	+53.0	689.4	+53.0	690.6
+60.0	686.6	+60.0	689.4	+60.0	690.5
+71.0	686.7	+71.0	689.5	+71.0	690.5
+80.0	686.8	+80.0	689.4	+81.0	690.5

TABLE XXII (Cont'd)

THE TEMPERATURE DEPENDENCE OF THE CHEMICAL SHIFT OF THE FORMYL PROTON

9-Phenanthraldehyde 2.5 mole%		9-Phenanthraldehyde 1.0 mole%		9-Phenanthraldehyde 0.5 mole%	
t°C	δ(c/s)	t°C	δ(c/s)	t°C	δ(c/s)
-55.5	609.1	-61.2(5)	614.1	-58.5	618.7
-46.7(5)	609.8	-48.5	615.6	-51.0	618.6
-34.2(5)	612.3	-39.0	616.4	-39.0	619.4
-26.5	613.2	-26.5	617.6	-29.5	619.8
-23.0	614.6	-17.0	618.1	-18.0	620.5
-15.5	614.3	-9.0	618.6	-10.0	620.9
-13.0	616.0	-23.0	618.7	-23.0	621.1
-4.5	615.4	-13.0	619.6	-13.0	621.6
-1.5	616.7	-1.5	620.2	-1.5	621.9
+10.0	617.6	+9.0	620.7	+9.0	622.4
+23.0	618.3	+23.0	621.2	+23.0	622.8
+28.5	618.9	+28.5	621.6	+28.5	623.0
+40.0	619.2	+40.0	621.8	+40.0	623.3
+53.0	620.0	+53.0	622.3	+53.0	623.7
+60.0	620.3	+60.0	622.7	+60.0	623.9
+71.0	621.0	+71.0	623.1	+71.0	624.3
+80.5	621.6	+80.5	623.5	+80.5	624.7

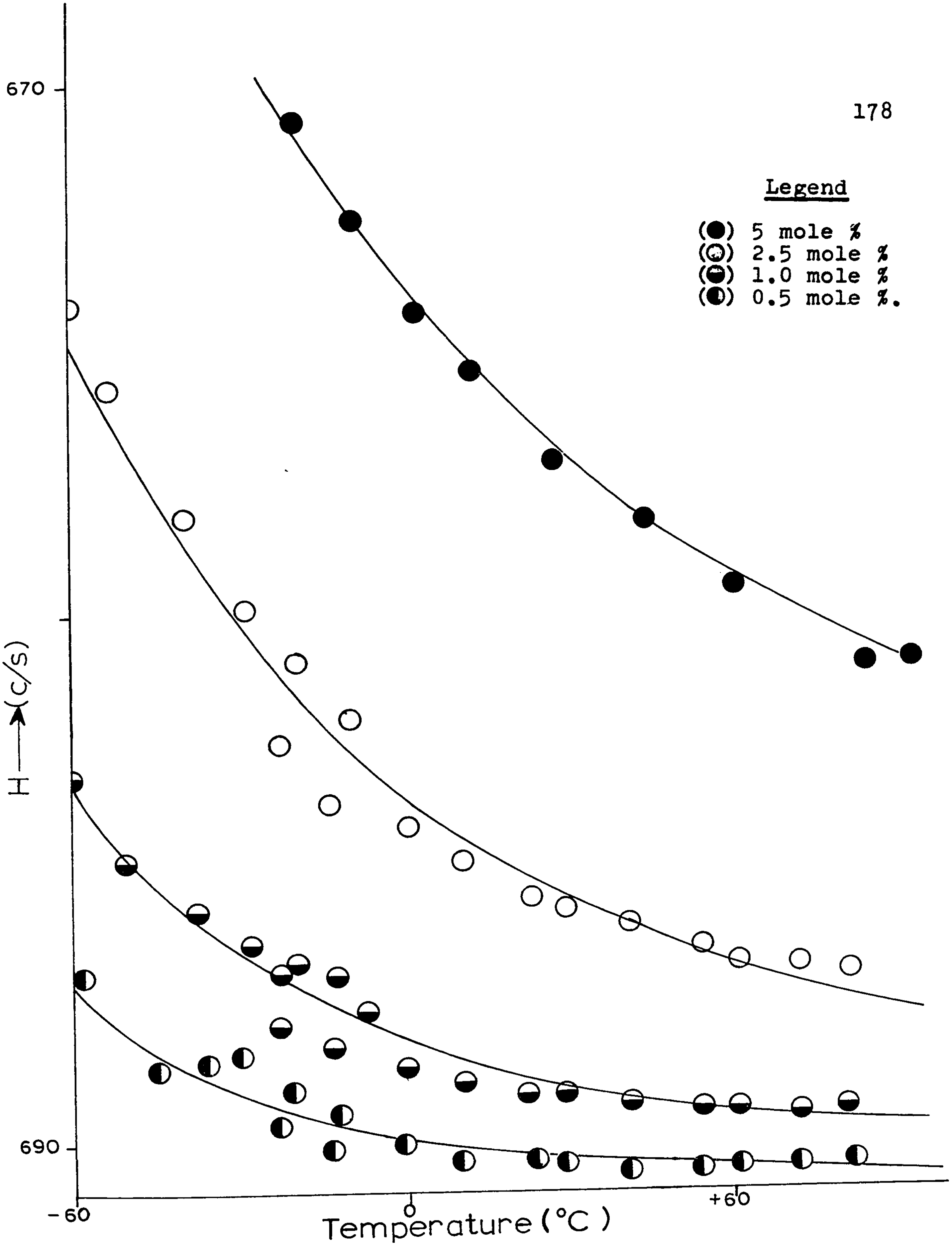


Figure 23. - Temperature Dependence of the Formyl Proton Shifts for Solutions of 9-Anthraldehyde in Chloroform-d (in c/s from TMS at 60 Mc/s).

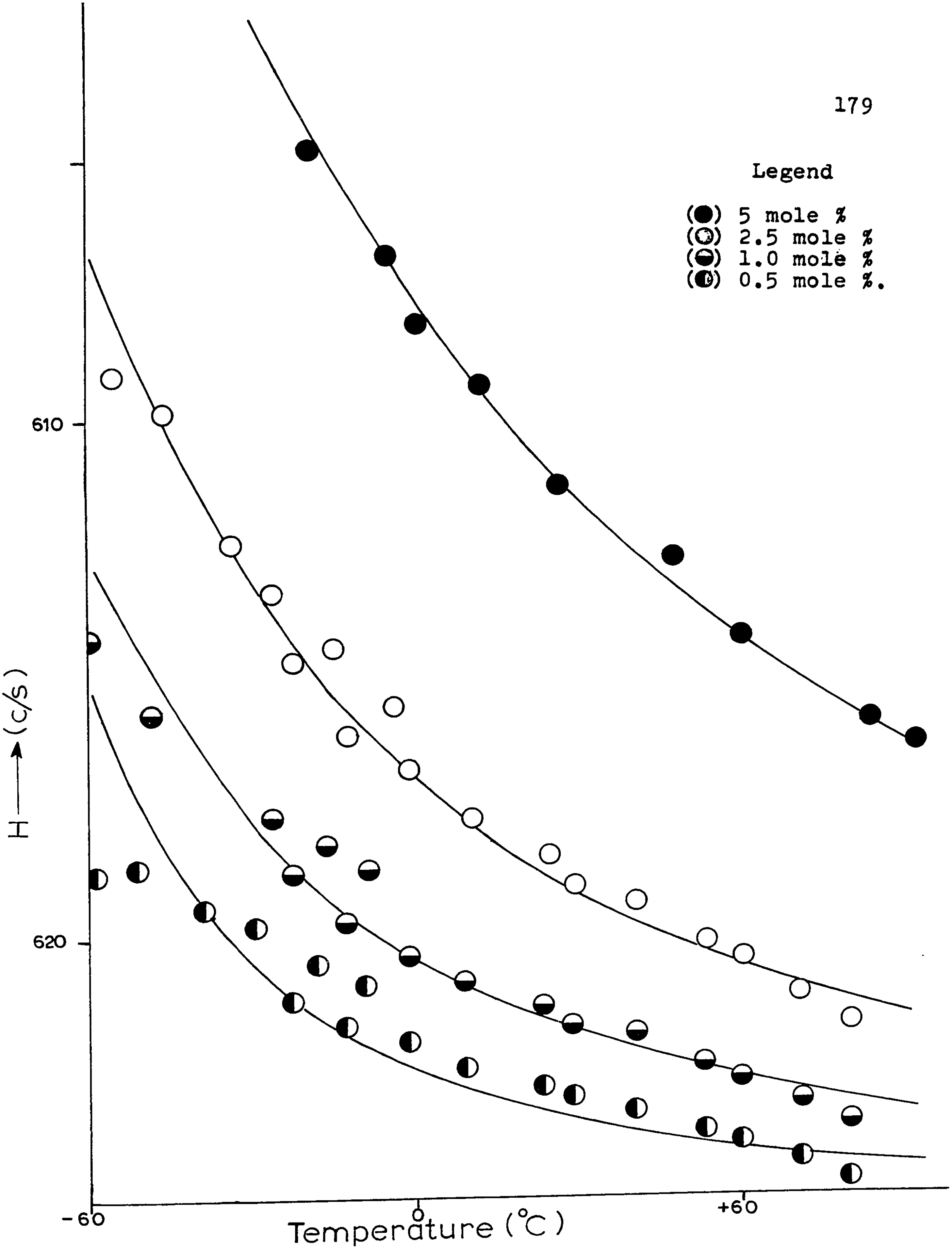


Figure 24. - Temperature Dependence of the Formyl Proton Shifts for Chloroform-d Solutions of 9-Phenanthraldehyde (in c/s from TMS at 60 Mc/s).

TABLE XXIII

RESULTS FOR THE FORMYL PROTON IN 9-ANTHRALDEDYDE

(0.5 mole % in $CDCl_3$)

Temp. (°K)	ν_{obs} (c/s)	ν (c/s)	$\frac{1}{T}X10^3$	K_{eq}	ln K
215.2	686.8	4.1	4.65	3.910	1.3610
228.2	688.2	2.3	4.38	2.123	0.7528
235.4	688.5	2.4	4.25	2.219	0.7970
243.2	688.4	2.5	4.11	2.315	0.8393
250.2	689.7	1.2	4.00	1.085	0.0818
252.2	689.0	1.9	3.97	1.742	0.5550
259.2	690.2	0.7	3.86	0.627	-0.4668
262.9	689.5	1.4	3.80	1.271	0.2398
271.7	690.1	0.8	3.68	0.718	-0.3313
283.2	690.4	0.5	3.53	0.446	-0.8074
296.2	690.4	0.5	3.38	0.446	-0.8074
301.7	690.5	0.4	3.31	0.356	-1.0328
313.2	690.6	0.3	3.19	0.267	-1.3205
326.2	690.6	0.3	3.07	0.267	-1.3205
333.2	690.5	0.4	3.00	0.356	-1.0328
344.2	690.5	0.4	2.91	0.356	-1.0328
354.2	690.5	0.4	2.82	0.356	-1.0328

TABLE XXIV

RESULTS FOR THE FORMYL PROTON IN 9-ANTHRALDEHYDE

(1.0 mole % in $CDCl_3$)

Temp. (°K)	ν_{obs} (c/s)	ν (c/s)	$\frac{1}{T}X10^3$	K_{eq}	ln K
213.9	683.0	7.9	4.67	4.044	1.3972
223.2	684.6	6.3	4.48	3.129	1.1407
235.2	685.6	5.3	4.25	2.584	0.9494
245.2	686.2	4.7	4.08	2.266	0.8181
250.2	687.8	3.1	4.00	1.451	0.3723
253.4	686.7	4.2	3.95	2.006	0.6960
259.2	688.2	2.7	3.86	1.255	0.2271
265.2	687.6	3.3	3.77	1.550	0.4383
273.2	688.6	2.3	3.66	1.061	0.0593
283.2	688.9	2.0	3.53	0.917	-0.0866
294.9	689.1	1.8	3.39	0.823	-0.1948
301.7	689.1	1.8	3.31	0.823	-0.1948
313.2	689.3	1.6	3.19	0.729	-0.3161
326.2	689.4	1.5	3.07	0.682	-0.3827
333.2	689.4	1.5	3.00	0.682	-0.3827
344.2	689.5	1.4	2.91	0.635	-0.4541
353.2	689.4	1.5	2.83	0.682	-0.3827

TABLE XXV

RESULTS FOR THE FORMYL PROTON IN 9-ANTHRALDEHYDE

(2.5 mole % in $CDCl_3$)

Temp. (°K)	ν_{obs} (c/s)	ν (c/s)	$\frac{1}{T} \times 10^3$	K_{eq}	ln K
212.7	674.1	16.8	4.70	4.107	1.4127
220.2	675.7	15.2	4.54	3.595	1.2796
233.2	678.1	12.8	4.29	2.884	1.0592
244.4	679.8	11.1	4.09	2.418	0.8829
250.2	682.5	8.4	4.00	1.736	0.5515
253.2	680.9	10.0	3.95	2.132	0.7570
259.2	683.6	7.3	3.86	1.478	0.3908
263.4	682.0	8.9	3.80	1.858	0.6195
273.2	684.1	6.8	3.66	1.363	0.3097
283.2	684.8	6.1	3.53	1.207	0.1879
294.9	685.4	5.5	3.39	1.076	0.0734
301.7	685.6	5.3	3.31	1.033	0.0325
313.2	685.9	5.0	3.19	0.969	-0.0315
326.2	686.3	4.6	3.07	0.885	-0.1222
333.2	686.6	4.3	3.00	0.823	-0.1948
344.2	686.7	4.2	2.91	0.803	-0.2194
353.2	686.8	4.1	2.83	0.782	-0.2459

TABLE XXVI

RESULTS FOR THE FORMYL PROTON IN 9-ANTHRALDEHYDE

(5.0 mole % in $CDCl_3$)

Temp. (°K)	ν_{obs} (c/s)	ν (c/s)	$\frac{1}{T}X10^3$	K_{eq}	ln K
253.4	670.3	20.6	3.95	2.729	1.0039
264.0	672.5	18.4	3.79	2.326	0.8442
274.4	674.2	16.7	3.65	2.037	0.7114
284.7	675.3	15.6	3.51	1.860	0.6206
299.7	677.0	13.9	3.34	1.601	0.4706
313.5	678.1	12.8	3.19	1.442	0.3660
332.2	679.4	11.5	3.01	1.262	0.2327
355.7	680.8	10.1	2.81	1.079	0.0763
364.4	680.0	10.1	2.75	1.079	0.0763

TABLE XXVII

RESULTS FOR THE FORMYL PROTON IN 9-PHENANTHRALDEHYDE

(0.5 mole % in $CDCl_3$)

Temp. (°K)	ν_{obs} (c/s)	ν c/s	$\frac{1}{T}$X10^3	K_{eq}	ln K
214.7	618.7	6.2	4.66	7.460	2.0096
222.2	618.6	6.3	4.50	7.597	2.0277
234.2	619.4	5.5	4.27	6.515	1.8741
243.7	619.8	5.1	4.10	5.987	1.7896
250.2	621.1	3.8	4.00	4.335	1.4668
255.2	620.5	4.4	3.92	5.086	1.6265
260.2	621.6	3.3	3.84	3.723	1.3145
263.2	620.9	4.0	3.80	4.583	1.5224
271.7	621.9	3.0	3.68	3.363	1.2128
282.2	622.4	2.5	3.54	2.772	1.0195
296.2	622.8	2.1	3.38	2.309	0.8367
301.7	623.0	1.9	3.31	2.080	0.7324
313.2	623.3	1.6	3.19	1.740	0.5539
326.2	623.7	1.2	3.07	1.294	0.2578
333.2	623.9	1.0	3.00	1.073	0.0706
344.2	624.3	0.6	2.91	0.639	-0.4479
353.7	624.7	0.2	2.83	0.211	-1.5559

TABLE XXVIII

RESULTS FOR THE FORMYL PROTON IN 9-PHENANTHRALDEHYDE

(1.0 mole % in $CDCl_3$)

Temp. (°K)	ν_{obs} (c/s)	ν (c/s)	$\frac{1}{T}X10^3$	K_{eq}	ln K
211.9	614.1	10.8	4.72	7.226	1.9777
224.7	615.6	9.3	4.45	6.007	1.7930
234.2	616.4	8.5	4.27	5.389	1.6844
246.7	617.6	7.3	4.5	4.502	1.5055
250.2	618.7	6.2	4.00	3.730	1.3164
256.2	618.1	6.8	3.90	4.147	1.4224
260.2	619.6	5.3	3.84	3.125	1.1394
264.2	618.6	6.3	3.79	3.798	1.3355
271.7	620.2	4.7	3.68	2.734	1.0058
282.2	620.7	4.2	3.54	2.416	0.8720
296.2	621.2	3.7	3.38	2.106	0.7447
301.7	621.6	3.3	3.31	1.861	0.6211
313.2	621.8	3.1	3.19	1.741	0.5545
326.2	622.3	2.6	3.07	1.444	0.3674
333.2	622.7	2.2	3.00	1.212	0.1922
344.2	623.1	1.8	2.91	0.983	-0.0172
353.7	623.5	1.4	2.83	0.758	-0.2771

TABLE XXIX

RESULTS FOR THE FORMYL PROTON IN 9-PHENANTHRALDEHYDE

(2.5 mole % in $CDCl_3$)

Temp. (°K)	ν_{obs} (c/s)	ν (c/s)	$\frac{1}{T}\times 10^3$	K_{eq}	ln K
217.7	609.1	15.8	4.59	4.778	1.5640
226.4	609.8	15.1	4.42	4.487	1.5012
238.9	612.3	12.6	4.19	3.521	1.2588
246.7	613.2	11.7	4.05	3.124	1.1391
250.2	614.6	10.3	4.00	2.724	1.0021
257.7	614.3	10.6	3.88	2.823	1.0378
260.2	616.0	8.9	3.84	2.278	0.8234
268.7	615.4	9.5	3.72	2.465	0.9022
283.2	616.7	8.2	3.68	2.065	0.7251
271.7	617.6	7.0	3.53	1.715	0.5394
296.2	618.3	6.6	3.38	1.602	0.4712
301.7	618.9	6.0	3.31	1.437	0.3625
313.2	619.2	5.7	3.19	1.356	0.3045
326.2	620.0	4.9	3.07	1.145	0.1354
333.2	620.3	4.6	3.00	1.068	0.0659
344.2	621.0	3.9	2.91	0.891	-0.1154
353.7	621.6	3.3	2.83	0.744	-0.2957

TABLE XXX

RESULTS FOR THE FORMYL PROTON IN 9-PHENANTHRALDEHYDE

(5.0 mole % in $CDCl_3$)

Temp. (°K)	ν_{obs} (c/s)	ν (c/s)	$\frac{1}{T} \times 10^3$	K_{eq}	ln K
253.9	604.6	20.3	3.94	3.450	1.2384
267.4	606.7	18.2	3.74	2.926	1.0736
273.2	608.0	16.9	3.66	2.628	0.9662
284.7	609.2	15.7	3.51	2.368	0.8621
299.7	611.1	13.8	3.34	1.985	0.6857
313.9	612.5	12.4	3.19	1.724	0.5446
332.9	614.0	10.9	3.00	1.462	0.3798
357.0	615.6	9.3	2.80	1.201	0.1831
365.2	616.1	8.8	2.74	1.123	0.1159

Plots of the results for ln K_{eq} vs 1/T were constructed for each solution and values of ΔH and ΔS were obtained, for each case, by least-squares analysis. The plots for the 5.0, 2.5 and 1.0 mole % solutions of 9-anthraldehyde are shown in Fig. 25, in which the lines are those given by a least-squares treatment. In Fig. 26, the results for 5.0 mole % and 2.5 mole % solutions of 9-phenanthraldehyde are illustrated. The data for the 1 mole % solutions have been omitted from the diagram because the points lie between those shown in Fig. 26, and would result in a cluttered diagram. Since the total change in the chemical shift for the formyl proton in the 0.5 mole % solutions is much less than that for the other solutions (see Figs. 23 and 24), the range over which K_{eq} values can be obtained reliably is reduced and the scatter in the plots of ln K vs 1/T is considerably greater; these have, therefore, been omitted from the composite diagrams.

The ΔH and ΔS values calculated for each solution are given in Tables XXXI and XXXII. Because of the greater uncertainty for the most dilute solutions, the "best" values are taken as the averaged value for the three higher concentrations. These are included in Tables XXXI and XXXII.

From the results for ΔH and ΔS for each solution, the theoretical curves were generated using equations [38] and [39];these are shown as solid lines in Figs. 23 and 24.

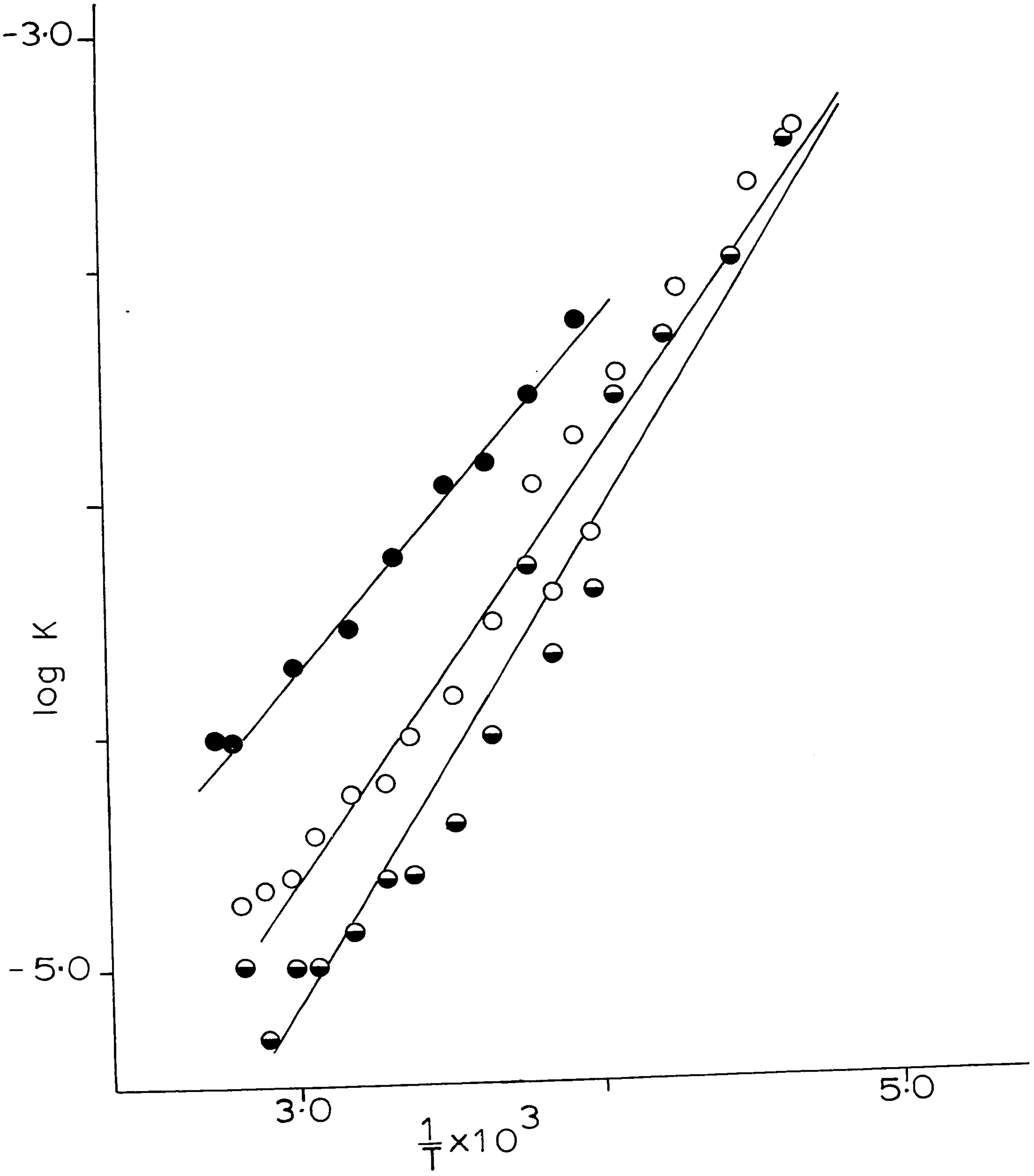


Figure 25. - Plots of log K *vs.* $^1/T$ for the Self-association of 9-Anthraldehyde in Chloroform-*d*. Concentrations are 5(●), 2.5(○) and 1.0(⊖) mole %.

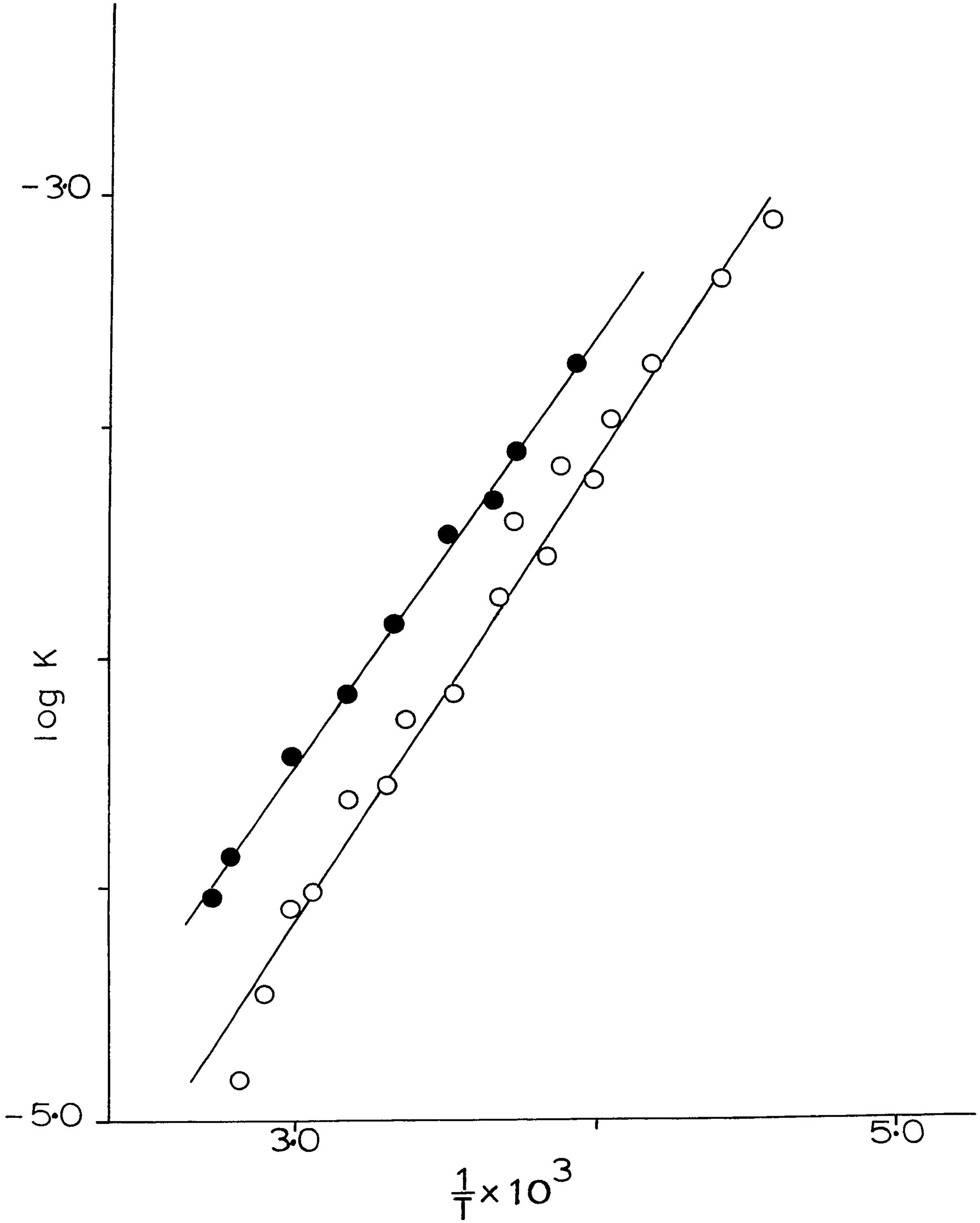


Figure 26. - Plots of log. K vs. $^1/T$ for the Self-association of 9-Phenanthraldehyde in Chloroform-d. Concentrations are 5(●) and 2.5(○) mole %.

TABLE XXXI

THERMODYNAMIC PARAMETERS FOR SELF-ASSOCIATION OF 9-ANTHRALDEHYDE IN CHLOROFORM-d

Solution Concentrations (mole %)	Temp. range (°K)	$-\Delta H$ (kcal/mole)	$-\Delta S$ (e.u.)
0.5	213-353	2.96	20.4
1.0	213-353	2.12	16.4
2.5	213-353	1.84	15.1
5.0	253-363	1.49	13.1
	Averaged Values*	1.82 ± 0.2	14.9 ± 1.2

* Excluding the 0.5 mole % solution (see text), the mean deviations are shown.

TABLE XXXII

THERMODYNAMIC PARAMETERS FOR SELF-ASSOCIATION OF 9-PHENANTHRALDEHYDE IN CHLOROFORM-d

Solution Concentrations (mole %)	Temp. range (°K)	-ΔH (kcal/mole)	-ΔS (e.u.)
0.5	213-353	3.10	18.6
1.0	213-353	2.29	15.6
2.5	213-353	2.06	15.3
5.0	253-363	1.87	14.0
	Averaged values*	2.07 ± 0.14	15.0 ± 0.6

* Excluding the 0.5 mole % solution (see text), the mean deviations are shown.

DISCUSSION

(a) Comments on the Precision of the Investigation

The determination of the ν_C values, the formyl shifts of the complexes, involves the use of a long extrapolation from the measured temperature range to 0°K. A fairly large error can, therefore, be expected. Trial calculations indicate, however, that a 10 - 15% error in these ν_C values produces changes of less than 5% in the ΔH values calculated. Inspection of the curves in Figs. 23 and 24 for the most dilute solutions suggests that the values chosen for ν_A are reasonable - especially in the case of 9-anthraldehyde. It, therefore, seems reasonable to conclude that the chemical shift changes arising from association are far greater than those arising from other mechanisms and, further, that the ΔH values obtained are within 0.3 kcal/mole of the true magnitude. Although the ΔS parameters obtained are subject to rather larger errors,[180] the fact that their values are somewhat larger than those for a number of solute-solvent interactions does suggest a higher degree of stereospecificity.

(b) The Nature and Stoichiometry of the Interaction

The results are in accord with previous interpretation of the interaction as an intermolecular self-association of molecules of the tricyclic aldehydes. It is further established that the most probable number of units in the complex is two. Contrary to the situation obtaining in previous studies in this series, it was possible to compute the stoichiometry of the interaction from the experimental data.

(c) The Strength of the Association

From the thermodynamic parameters calculated for the association (ΔH = -1.8 and -2.0 kcal/mole for 9-anthraldehyde and 9-phenanthraldehyde, respectively), it can be seen that the interaction is somewhat stronger than the solute-solvent associations of monocyclic aromatic aldehydes which have ΔH values in the range -0.9 to -1.6 kcal/mole. The difference between the parameters obtained for the two polycyclic aldehydes are, however, too small to justify any meaningful evaluation of their relative strengths.

(d) The Stereochemistry of the Complex

Even though the strength and stoichiometry of the association are known, it is still not possible to give a concrete description of the stereochemistry of the complex. It seems likely, however, that the aryl ring(s) of one unit will tend to interact with the electron deficient carbon of the carbonyl group of the second unit. One possible orientation of the 9-anthraldehyde "dimer" is a "head to tail" situation with the aryl rings in parallel planes.

Crystallographic analysis of anthracene shows that much of the intermolecular interaction involves the hydrogen atoms and that there is little direct carbon-carbon approach except at C-9 and C-10.[181] Extrapolation of this fact to solutions of the carboxaldehyde - or even to solutions of the hydrocarbon - may be completely unjustified. If, however, such a projection is permissible, then one can suggest that the stereochemistry of the two complexes would be very similar since the spatial disposition of the molecular units in phenanthrene is almost identical with that found in anthracene.[182]

EXPERIMENTAL

(a) Purification of Samples

(i) 9-Anthraldehyde

Commercial 9-anthraldehyde (Aldrich Chem. Co. Ltd.) was recrystallized from glacial acetic acid (2.5 g. in 5 ml.). The crystals were washed with methanol and dried over anhydrous calcium chloride in a vacuum desiccator. The purified product melted in the range 104.0°C - 105.0°C (lit.[183] 104°C - 105°C).

(ii) 9-Phenanthraldehyde

The sample of 9-phenanthraldehyde was recrystallized from glacial acetic acid (1 g./0.9 ml.) and then from ethanol (1 g./3 ml.). After recrystallization 9-phenanthraldehyde melted in the range 101.5°C - 102.5°C (lit.[184] 100°C - 101°C).

(b) Preparation of Samples for NMR Studies

A 2.5 mole % solution of each aldehyde was prepared in deuteriochloroform (51.5 mg. in 1.174 g. $CDCl_3$). The 1.0 mole % and 0.5 mole % solutions were prepared by volumetric dilution.

Tetramethylsilane was added to each sample which was then degassed and sealed *in vacuo*.

(c) NMR Spectroscopy

Spectra were obtained on the Varian DP60 Spectrometer over the temperature range -5°C to -60°C. A modified V4340 probe accessory was used with the spectrometer. A Varian A60 Spectrometer was used for the spectra in the range -20°C to +80°C. Peak positions were obtained by interpolation between the audiofrequency sidebands of an internal tetramethylsilane reference signal generated on either side of the peak to be measured.

A copper-constantan thermocouple was used for the temperature measurements with the DP60. In the case of the A60, the relative shift of the two peaks in a sample of methanol was used as an indication of temperatures below 40°C while the relative shifts of the two peaks of ethylene glycol were used to measure temperature above 40°C. Correlation charts of temperature (°C) vs relative shift (c/s) are provided in the A60 manual.

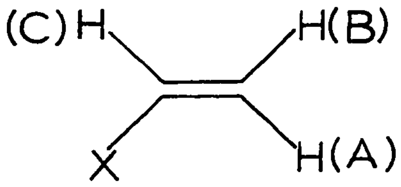
APPENDIX II

THE VINYL PROTON CHEMICAL SHIFTS AND COUPLING CONSTANTS OF SOME SUBSTITUTED STYRENES

INTRODUCTION

The Chemical Shift of Vinyl Protons

Olefinic protons absorb in the spectral region between 4.5 p.p.m. and 8.0 p.p.m. from tetramethylsilane. In vinyl compounds (LXXI) the three magnetically non-equivalent protons give rise to nuclear magnetic resonance spectra of the type described as ABC in the notation of Bernstein *et al.*[185]



LXXI

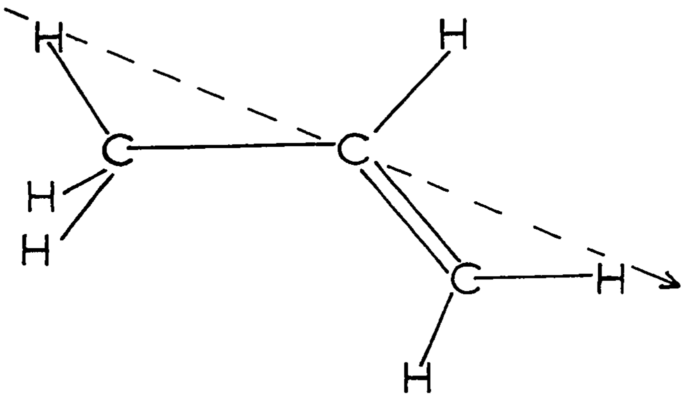
This type of spectrum can be subjected to exact analysis to yield the three chemical shifts (δ_A, δ_B and δ_C) and three coupling constants (J_{AB}, J_{BC} and J_{AC}).

Attempts to correlate the observed chemical shifts with the electronegativity of the substituent, X, have met with limited success. Banwell and Sheppard[26] chose, as chemical shift parameters,

$$\delta_C$$
$$\Delta_1 = \tfrac{1}{2}(\delta_A + \delta_B)$$
$$\Delta_2 = \delta_C - \tfrac{1}{2}(\delta_A + \delta_B)$$

No correlation was found between any of these parameters and the electronegativity of the substituent. However, Δ_2 gave a good linear correlation with the Taft σ_R constants.

Permanent dipoles within the molecule have a profound effect on the observed chemical shift. In the case of 1-alkenes the dipole moment is thought to lie parallel to the line indicated in LXXII, propylene.[186] If it is assumed that



LXXII

this dipole can be replaced by a uniform electric field in the same direction, such an electric field may be expected to "push" electron density along the double bond and onto the terminal hydrogen nuclei, thus increasing their shielding. This hypothesis predicts the correct relative magnitudes of the vinyl proton chemical shifts for 1-alkenes. Further, since little change of dipole moment is expected in a series of 1-alkenes, a corresponding invariance of their vinyl proton chemical shifts should be observed. The experimental data support this argument.[187] In substituted ethylenes, a linear correlation is found between the proton chemical shifts of the terminal methylene group and the group dipole moment of the substituents.[188] Solvent effects observed for the olefinic protons in vinyl bromide and <u>cis</u>- and <u>trans</u>-1,2-dichloroethylene have been explained in terms of dipole moment variations which accompany changes in the dielectric constant of the medium.[18]

A shielding contribution due to the approach of a polarizable group was evaluated from the following expression,[187]

$$\Delta\sigma = 1.5 \text{ X } 10^{-18}\ \alpha\varepsilon/r^6$$

where $\Delta\sigma$ is the change in shielding (dimensionless),

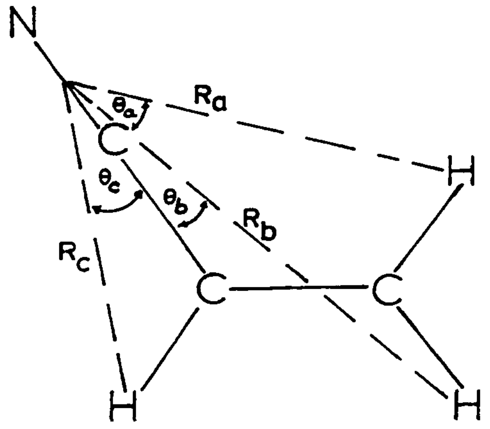
α is the polarizability of the group in cm ,

ε is the ionization energy in ergs

and r is the distance of approach in cm.

Analysis showed that r must be less than 2A before this effect is appreciable. In Bothner-By's treatment of 1-alkenes,[187] consideration of this effect gave chemical shifts which are qualitatively in agreement with those observed. However, any realistic choice for α and ε yields chemical shifts which are much too small.

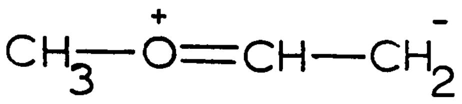
Magnetic anisotropy of the substituent can have significant effects on proton chemical shifts. In the case of vinyl cyanide, the strong diamagnetic anisotropy of the triple bond of the cyano group results in a shielding of all the protons. The magnitude of this screening depends on the distance (R) of each atom from the electrical centre of gravity of the -C≡N bond and the angle (θ) between the line joining this centre with the hydrogen nucleus and the axis of the -C≡N bond. The relevant lines and angles are indicated in the diagram below.



LXXIII

The relative chemical shifts of the terminal protons in vinyl ethers have been discussed in terms of the anisotropy of the C-O bond.[26,189]

Anomalous chemical shifts may also be due to delocalization effects. For example, in vinyl ethers, resonance form LXXIV would result in an enhanced electron density at the



$$CH_3-\overset{+}{O}=CH-\overset{-}{C}H_2$$

LXXIV

terminal carbon relative to that found in ethylene, leading to increased shielding of the methylene group. The presence of such delocalization effects is indicated by the unusually high chemical shifts ($\delta = 3.80$ to 4.88 p.p.m.[189]) of the terminal methylene protons in vinyl ethers.

The Coupling Constants in the Vinyl System

The relative magnitudes of the three coupling constants in the vinyl system can be deduced by examining the spectra of various disubstituted olefins. It is found that the geminal coupling constant ($J_{gem} = -3.5$ to $+2.5$ c/s) is much smaller than the cis vicinal coupling constant ($J_{cis} = +4.0$ to $+12.0$ c/s) which is less than the trans vicinal coupling constant ($J_{trans} = +12.0$ to $+19.0$ c/s).

Application of valence-bond theory to alkenes shows that J_{gem} should decrease with increasing H-C-H bond angle.[190]

Unfortunately, the theoretical curve obtained is in poor agreement with experimental data. Calculations of H-H vicinal couplings have met with more success. Karplus[23] predicted that J_{trans} and J_{cis} for ethylene would have σ-bond contributions of +11.9 and +6.1 c/s together with π-bond contributions of +1.5 and +1.5 c/s respectively. Although the total calculated values (J_{trans} = +13.4 c/s and J_{cis} = +7.6 c/s) are low compared with the observed values (J_{trans} = 19.0 c/s and J_{cis} = 11.7 c/s),[191] the predicted J_{cis}/J_{trans} ratio is correct.

In vinyl compounds, J_{cis} and J_{trans} depend linearly on the electronegativity of the substituent X according to the relationships,[26]

$$J_{trans} = 19.0 - 3.3\Delta E \text{ c/s}$$
$$J_{cis} = 11.7 - 4.0\Delta E \text{ c/s}$$

where ΔE is the difference in electronegativity between the substituent X and the hydrogen atom. A more comprehensive survey by Schaefer[192] indicates that the sum of the coupling constants ($J_{gem} + J_{cis} + J_{trans}$) lies in the range 14 to 50 c/s and there is an inverse proportionality between the sum of the coupling constants and the electronegativity (E_X) of the substituent. This correlation holds true over a range of E_X values from 1.0 to 4.0. The best correlation of an individual coupling constant with E_X, is obtained with J_{trans}. Theoretical support for the correlation with E_x is given by Karplus[30] who showed that the primary cause was the substituent-induced change in the hybridization of the carbon atoms in the H-C-C-H fragment. (It had previously been proposed that the correlation was due to a direct inductive effect on the polarity of the C-H bond).[193,194] Karplus further suggested that the proton coupling constants in these compounds would be affected by changes in bond angle, C=C length, exchange integrals, bond excitation energies, π-bonding, and molecular vibrations.[23]

Previous Work on Styrenes

From the preceding survey, it is clear that considerable effort has been expended in evaluating the parameters of the vinyl system both from a theoretical and an experimental standpoint. It is, therefore, very surprising that little work has been done on the styrene system, especially in view of the correlation found between the chemical shift parameter (Banwell's Δ_2) and the Taft σ_R constants[26] - which indicates a dependence on π-electron distribution.

The work presented here comprises a determination of the nuclear magnetic resonance parameters of a number of substituted styrenes and an examination of these parameters in terms of previous work on vinyl compounds. The compounds were chosen so that both electronic and steric factors could be investigated. It was also proposed to seek a correlation between the ^1H spectral parameters and the ^{13}C parameters recently determined.[195]

Treatment of Experimental Data

The vinyl proton spectra were analysed as ABC systems using an analytical method based on that described by Castellano and Waugh.[43,44] A Fortran IV program was written for an IBM 7040 computer to carry out the calculations. The program is essentially that described by Stothers, Talman and Fraser,[45] although a modification was incorporated to improve the determination of the eigenvectors. Error analysis was carried out to calculate the maximum possible deviations of the results.

A check on the empirical sum rules was made by using a weighted least-squares method to calculate the set of eigenvalues used as input parameters. As an additional check, theoretical spectra were computed from the calculated chemical shifts and coupling constants with the LAOCOON III program written by Bothner-By and Castellano.[39]

For each compound, the ABC analysis produced five sets of eigenvalues. [A set of eigenvalues comprises a numerical value (E_i) for each of the eight energy states (Table XXXIIIa) such that the transition frequencies can be generated as differences between the eigenvalues of the states involved in the allowed transitions.] One

TABLE XXXIIIa

THE ENERGY STATES IN A THREE SPIN (ABC) SYSTEM

Eigenfunction	Spin Orientations ABC	Total Spin	Eigenvalue
ψ_1	$\alpha\alpha\alpha$	$+\frac{3}{2}$	E_1
ψ_2	$\alpha\alpha\beta$	$+\frac{1}{2}$	E_2
ψ_3	$\alpha\beta\alpha$	$+\frac{1}{2}$	E_3
ψ_4	$\beta\alpha\alpha$	$+\frac{1}{2}$	E_4
ψ_5	$\alpha\beta\beta$	$-\frac{1}{2}$	E_5
ψ_6	$\beta\alpha\beta$	$-\frac{1}{2}$	E_6
ψ_7	$\beta\beta\alpha$	$-\frac{1}{2}$	E_7
ψ_8	$\beta\beta\beta$	$-\frac{3}{2}$	E_8

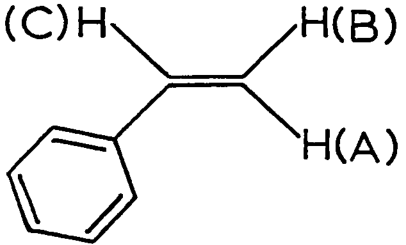
TABLE XXXIIIb

	A	B	C
1	$E_1 \leftarrow E_4$	$E_1 \leftarrow E_3$	$E_1 \leftarrow E_2$
2	$E_2 \leftarrow E_6$	$E_2 \leftarrow E_5$	$E_3 \leftarrow E_5$
3	$E_3 \leftarrow E_7$	$E_4 \leftarrow E_7$	$E_4 \leftarrow E_6$
4	$E_6 \leftarrow E_8$	$E_6 \leftarrow E_8$	$E_7 \leftarrow E_8$
Combination	$E_4 \leftarrow E_5$	$E_3 \leftarrow E_6$	$E_2 \leftarrow E_7$

possible grouping of these transitions is shown in Table XXXIIIb . Two groups of chemical shifts and coupling constants arise from each *set* of eigenvalues; only one *set* of eigenvalues, however, gives physically reasonable chemical shifts and coupling constants. The two groups of parameters arising from this *set* differ in the relative sign of the geminal coupling constant. In all cases, a comparison of the observed intensities with those calculated revealed that the group in which all three coupling constants have the same sign gives better agreement with the experimental spectrum. For this comparison, there were found to be at least two pairs of lines whose intensities are significantly different for the alternative assignment.

RESULTS

For discussion purposes, the three vinyl protons are labelled A, B and C as shown in LXXV. The results



LXXV

for the meta- and para-substituted styrenes are collected in Table XXXIV, and Table XXXV contains the data for the ortho-substituted examples. For each compound the α-proton (C) absorbs at lowest field and, in most cases, the expected four lines are found. In a few instances, one of these transitions is masked by the aryl proton absorption; the position of such a line is readily determined from the requirement of repeated spacings within the ABC pattern. For the meta- and para-substituted examples, the four lines for each of the A and B proton are well separated and the assignment is straightforward because of the larger <u>trans</u> vicinal coupling for A with C. With ortho substitution, the shielding of proton A increases and that of proton B decreases so that these multiplets overlap; the lines belonging to each "quartet" were, however, readily assigned by the same criterion as before. The intensities of the three possible combination transitions are too weak to be observed so that

TABLE XXXIV

PROTON CHEMICAL SHIFTS AND COUPLING CONSTANTS OF SOME META- AND PARA-SUBSTITUTED STYRENES

(10 mole % solutions in $CDCl_3$)

Substituent	Coupling Constants (c/s)*			Chemical Shifts (p.p.m.)*†		
	J_{AC}	J_{BC}	J_{AB}	δ_B	δ_A	δ_C
H	17.6_9	10.8_8	0.9_5	5.20_8	5.70_8	6.69_0
4-Me	17.6_1	11.0_2	1.0_8	5.18_3	5.69_5	6.66_3
4-OMe	17.6_1	10.9_2	0.9_8	5.08_8	5.57_4	6.63_5
4-N(Me)$_2$	17.5_3	10.9_7	1.2_3	4.98_8	5.50_7	6.61_1
4-Cl	17.5_7	10.9_0	0.8_3	5.22_5	5.67_4	6.62_6
4-Br	17.6_0	10.9_1	0.8_6	5.23_4	5.68_5	6.60_9
4-NO$_2$	17.4_3	10.9_0	0.7_6	5.47_6	5.90_3	6.76_9
3-Me	17.6_1	10.9_3	1.0_6	5.18_6	5.69_7	6.66_6
3-Cl	17.6_1	10.9_3	0.9_1	5.26_1	5.71_2	6.61_9
3-Br	17.6_7	10.9_1	0.7_5	5.25_1	5.70_2	6.60_2
3-NO$_2$	17.4_7	10.8_0	0.3_9	5.41_6	5.86_1	6.74_4
3,4-Cl$_2$	17.6_0	10.8_9	0.7_6	5.28_1	5.69_3	6.57_1
4-vinyl	17.6_6	10.9_8	0.9_5	5.19_4	5.69_8	6.66_1

* A,B, and C as shown in LXXV. † measured from internal TMS.

TABLE XXXV

PROTON CHEMICAL SHIFTS AND COUPLING CONSTANTS OF SOME ORTHO-SUBSTITUTED STYRENES

(10 mole % solution in $CDCl_3$)

Substituent	Coupling Constants (c/s)*			Chemical Shifts (p.p.m.)*†		
	J_{AC}	J_{BC}	J_{AB}	δ_B	δ_A	δ_C
2-Me	17.3_{6}	11.0_{7}	1.6_{2}	5.25_{1}	5.59_{3}	6.91_{7}
2-Cl	17.4_{3}	11.0_{6}	1.1_{8}	5.34_{4}	5.59_{8}	7.09_{6}
2-Br	17.4_{5}	10.9_{8}	1.1_{1}	5.32_{0}	5.65_{8}	7.04_{6}
2,4-Me_2	17.6_{0}	11.0_{9}	1.5_{5}	5.19_{9}	5.55_{6}	6.88_{6}
2,5-Me_2	17.4_{6}	10.9_{8}	1.5_{5}	5.22_{7}	5.58_{5}	6.89_{8}
2,6-Me_2	17.9_{8}	11.4_{8}	2.1_{4}	5.49_{8}	5.22_{9}	6.66_{8}
2,4,6-Me_3	17.9_{8}	11.5_{6}	2.1_{4}	5.46_{0}	5.20_{7}	6.64_{8}
2,3,5,6-Me_4	17.1_{0}	11.2_{6}	2.2_{5}	5.50_{2}	5.10_{5}	6.69_{2}
2,4,6-Et_3	17.9_{1}	11.4_{4}	2.2_{1}	5.46_{0}	5.21_{1}	6.73_{0}
2,4,6-$(iPr)_3$	17.9_{8}	11.3_{0}	2.3_{6}	5.47_{0}	5.15_{7}	6.76_{8}

* A, B, and C as shown in LXXV.

† measured from internal TMS.

each compound gives rise to spectra having only 12 lines. The parameters given in the Tables are estimated to be accurate to better than 0.01 p.p.m. for the chemical shifts and 0.2 c/s for the coupling constants.

DISCUSSION

It is convenient to discuss the proton magnetic resonance spectra of substituted styrenes in three groups as follows:

(a) Meta- and para-substituted styrenes.

(b) Styrenes bearing one ortho-substituent.

(c) Styrenes bearing two ortho-substituents.

(a) Meta- and Para-substituted Styrenes

(i) The Chemical Shifts of the Vinyl Protons

Examination of the results presented in Table XXXIV shows that the most shielded protons in the vinyl system of the meta- and para-substituted styrenes are those labelled B, while the α-protons (labelled C) absorb at lowest field. It is also immediately apparent that the β-nuclei (A and B) are more susceptible to the effects of polar substituents than the α-protons. This fact is indicated by the total ranges of the absorption of the three nuclei which are 0.5 p.p.m. for the B-protons, 0.4 p.p.m. for the A-protons and 0.2 p.p.m. for the nuclei labelled C. It is reasonable to assume that the predominant conformation throughout this group is that in which the nodal plane of the carbon-carbon double bond is coincident with the plane of the aryl ring, permitting extensive delocalization of the π-electron system. The comparatively small variation of the chemical shift of proton C is then readily understood since the α-carbon is not at the terminus of the conjugated system and the changes in π-electron density about this carbon atom will be smaller than at the terminal β-carbon.

Although the total ranges of absorption differ in magnitude, the shielding of each of the nuclei follows a similar trend in that the most shielded protons are those in the p-N,N-dimethylamino derivative and the least shielded are those in p-nitrostyrene. Plots of these proton shieldings against Hammett σ constants show, however, that fairly good correlations exist for protons A and B, but not for proton C. The Hammett plots are shown in Fig. 27; the lines were obtained by least-squares analysis of the data. The best relationship appears to be that for the B protons. This is not unexpected, because its greater separation from the aryl ring and the substituents suggests that it would be less affected by through-space effects of these groups. The somewhat larger scatter exhibited by the points for the A nucleus may be due to weak through-space effects since proton A is considerably closer to the ring and the substituents. In styrene itself, the A and B protons are calculated to be 3.8Å and 4.9Å, respectively from the centre of the aryl ring.[26] The contribution of the ring current effect to the deshielding

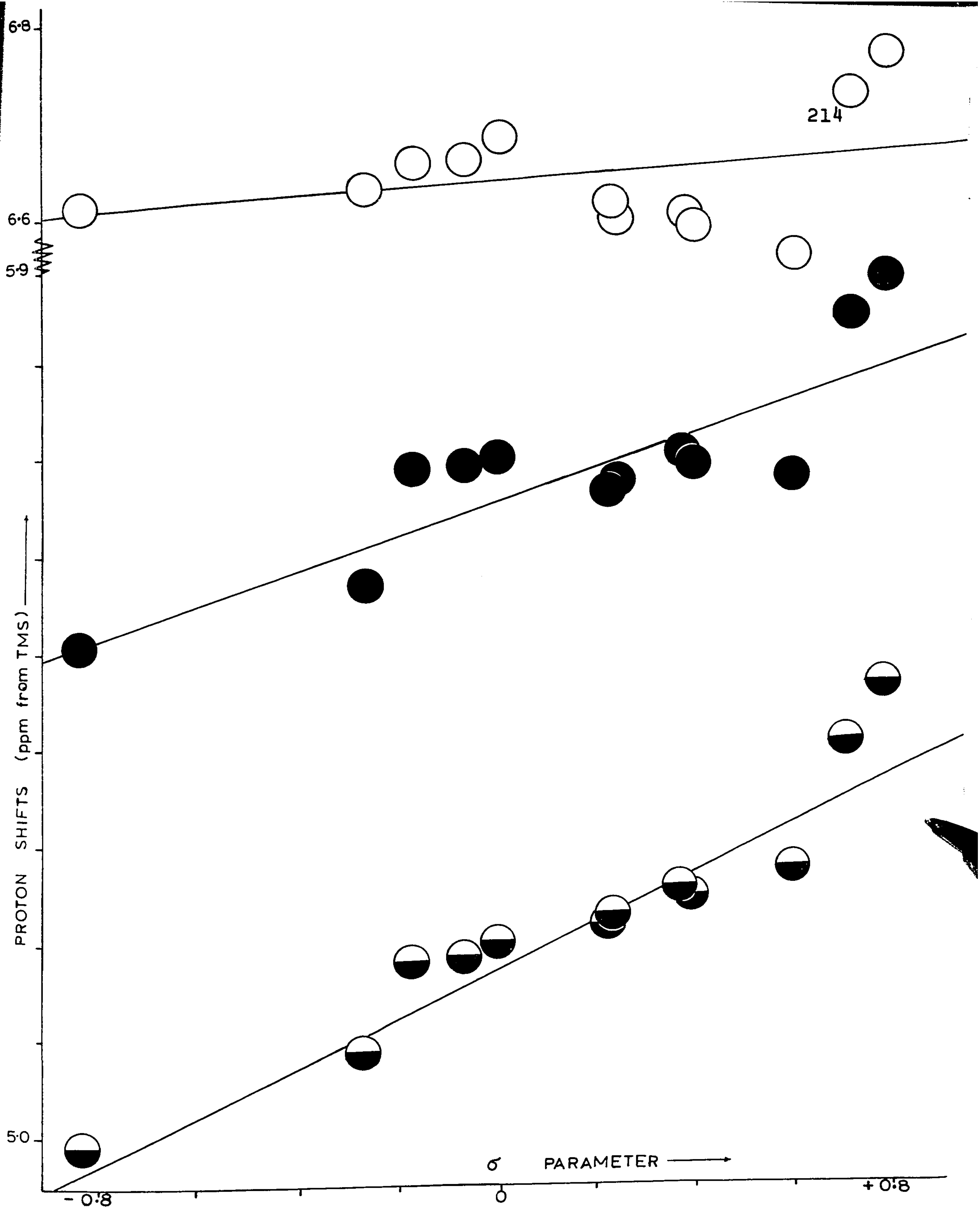


Figure 27.- Plots of Vinyl Proton Shieldings of some Meta- and Para- substituted Styrenes vs. Hammett σ Parameters. (A, ●; B, ●; C, O.)

of the β-protons was calculated[26] to be 0.55 p.p.m. for the A nucleus, but only 0.2 p.p.m. for the proton B. Since the secondary magnetic field arising from the ring current effect varies inversely as R^3 (where R is the distance from the centre of the ring)[12] proton A is expected to be more sensitive than the B nucleus to changes in this effect. However, the absence of any definitive work on the effect of substituents on the ring current effect prevents any quantitative assessment of this factor.

The α-proton in styrene is about 3.5Å from the centre of the ring and the correction for the ring current effect has been calculated to be +0.7 p.p.m.[26] Since the overall variation in electron density is small, it is not surprising that through-space effects assume a greater importance and the correlation with Hammett σ constants (which are assumed to reflect electronic effects anly) is poor. However, if the halogen compounds are neglected, a line can be drawn which correlates the chemical shifts of α-protons with deviations of less than 0.03 p.p.m. The anomalous behaviour of the halogen compounds is reminiscent of previous studies on vinyl halides, but a satisfactory explanation of this phenomenon is not available.

In a recent study of the ^{13}C spectra of styrenes,[195] the β-carbon shieldings were found to be correlated with the Hammett σ parameter with a total change of 10 p.p.m.

between the p-N,N-dimethylamino derivative and p-nitrostyrene. Compared to the range of 0.5 p.p.m. observed for the B protons, this gives a factor of 20 between the sensitivity of the ^{1}H and ^{13}C resonances to changes in the polarity of the substituents. This value compares reasonably well with those previously obtained for ^{1}H and ^{13}C shieldings in other systems where the controlling factor is thought to be the π-electron density.[196,197] Fig. 28 shows the relationships between the ^{1}H results for protons A and B and the ^{13}C shieldings of the β-carbon. The better correlation is again that for the B protons for which, with the exception of m-nitrostyrene, all the proton shifts are within 0.04 p.p.m. of the correlation line. There appears to be no satisfactory correlation between the α-proton and the α-carbon shieldings.

(ii) Coupling Constants

The apparent invariance of the ^{13}C-H couplings in the vinyl system of the meta- and para-substituted styrenes (161 ± 4 c/s)[195] indicates that hybridization of the olefinic carbons is not affected appreciably by the substituents. The dihedral angles between the vicinal protons, together with the H-C-C angles, are expected to be constant for the series and, hence, valence bond theory predicts that the vicinal H-H couplings are insensitive to meta and para substitution. This prediction is in accord with the ob-

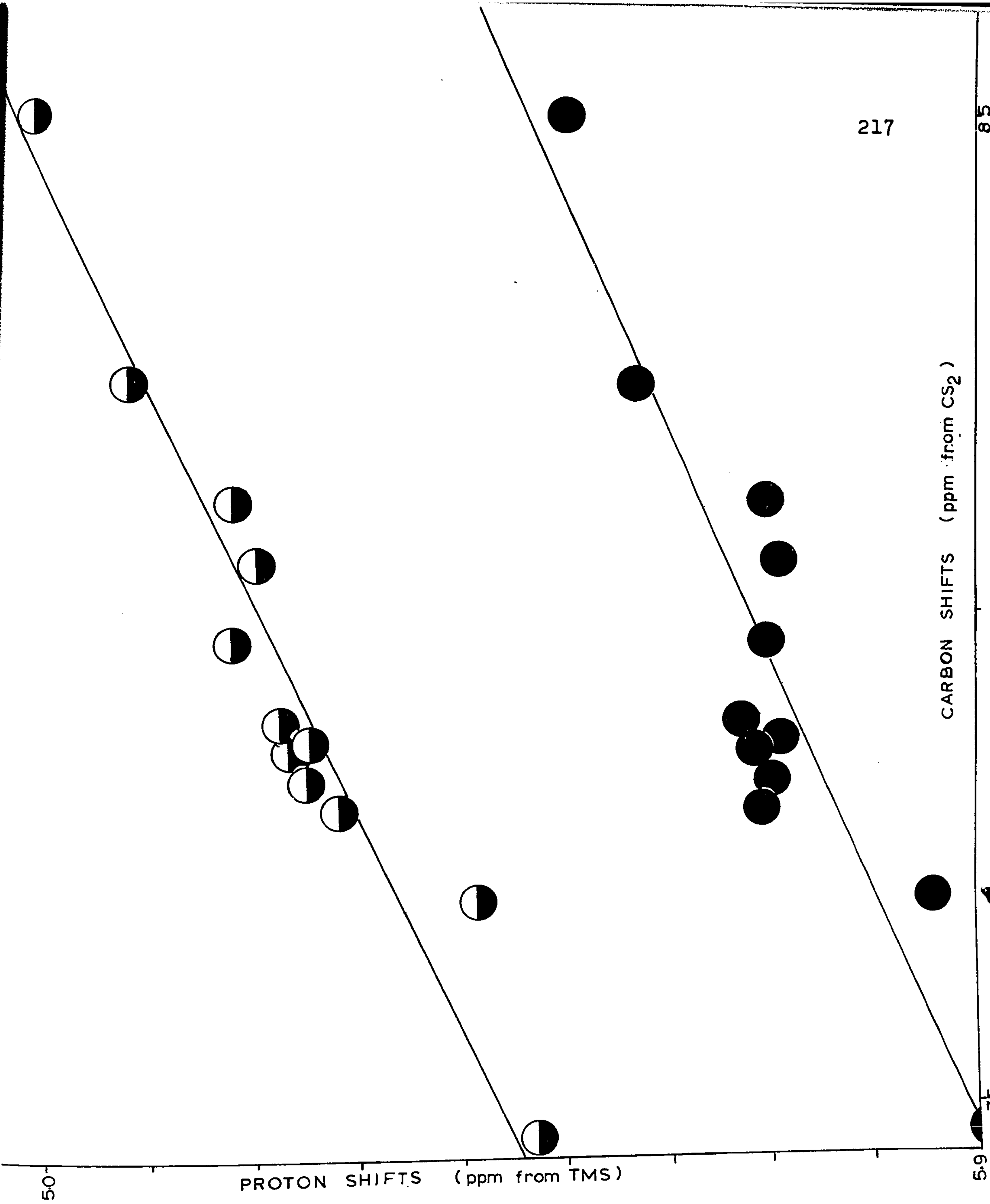


Figure 28. - Plots of ^{1}H and ^{13}C Chemical Shifts for the β-Nuclei in Meta- and Para- substituted Styrenes. (A, ●; B, ◐.)

served values of 10.91 ± 0.11 c/s for the <u>cis</u> coupling (J_{BC}) and 17.55 ± 0.12 c/s for the <u>trans</u> coupling (J_{AC}).

Styrene itself has been examined by a number of authors, the most recent being the work of Snyder[198] (who analysed the system by an iterative technique) and that of Dubois and coworkers[199] who employed the method of Swalen and Reily[200] which also involves iteration of the line frequencies. Satisfactory agreement exists between the reported values and those obtained here; the small differences observed could have arisen from dilution effects, solvent effects or simply from calibration errors.

In contrast to the vicinal interactions, the geminal proton-proton couplings (J_{gem}) exhibit appreciable sensitivity to substitution varying from +0.39 c/s to +1.23 c/s for this series. Calculations based on molecular orbital theory lead to the conclusion that electron withdrawal by the aryl ring should produce an algebraic decrease in the geminal coupling constant. Experimental support for this theoretical prediction is illustrated in Fig. 29, where Hammett σ constants are taken as a measure of the electron-withdrawing or electron-donating capacity of the substituent. Unfortunately, a relatively large error is possible in measuring the small geminal coupling so that the significance of differences (such as a value of 0.39 c/s for <u>m</u>-nitrostyrene, but 0.76 c/s

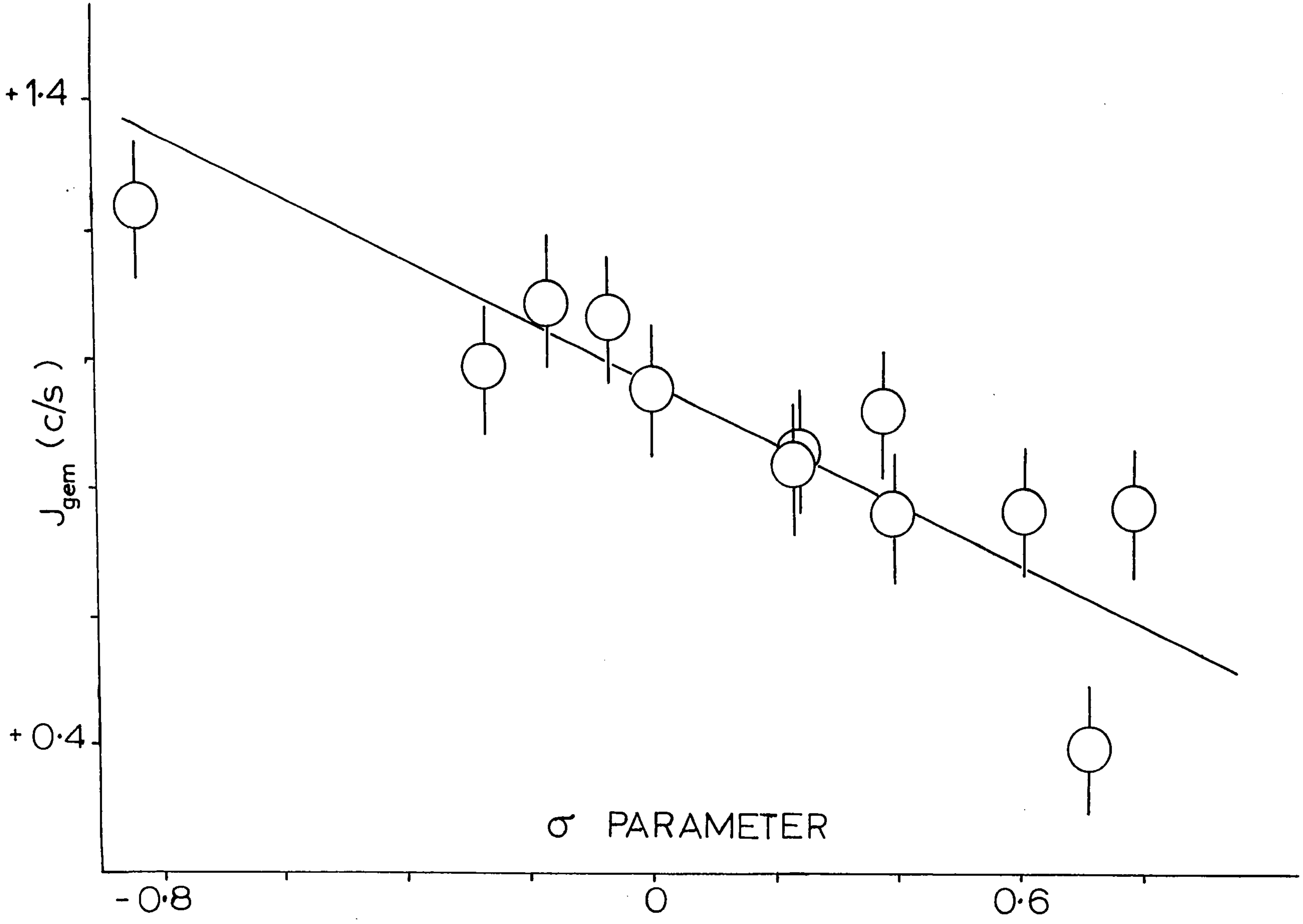
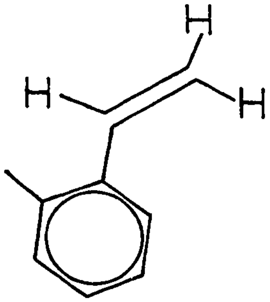


Figure 29. - Variation of J_{gem} with the σ Parameter for some Meta- and Para-substituted Styrenes.

for p-nitrostyrene) cannot be evaluated with certainty.

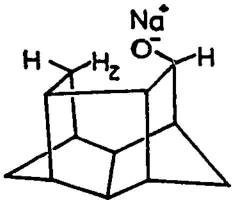
(b) Styrenes bearing one ortho-Substituent

In the mono-orthosubstituted styrenes, the preferred planar conformation is undoubtedly that in which the β-carbon is as far as possible from the ortho substituent.



In such a conformation the α-proton lies close to the substituent and experiences a deshielding effect. In the compounds bearing a methyl group in the ortho position, the α-protons are deshielded by 0.22 p.p.m. relative to the corresponding meta- and para-substituted compounds. For the halo-substituted compounds, the observed relative shift is 0.45 p.p.m. to low field. This reduced screening of the α-protons is in qualitative agreement with the results obtained for the amino-proton shifts in substituted anilines[201] where the ortho-substituted compounds follow a correlation line which is approximately 0.5 p.p.m. to lower field relative to the line correlating the meta- and para-substituted anilines.

The fact that the magnitude of the effect increases with Van der Waals radius of the substituent suggests that the low field shift may be due to "steric compression" or, "Van der Waals' interactions". The most striking example of this effect is the low field shift of about 4 p.p.m. suffered by proton Z in the cage compound (LXXVI).[202]

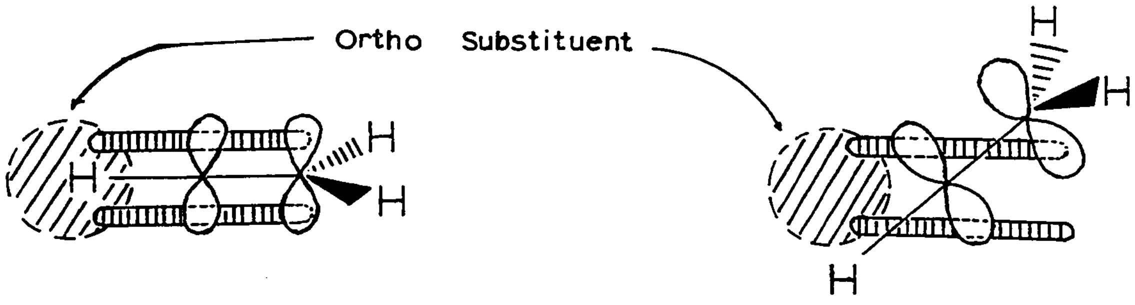


LXXVI

Many other examples of such interactions have been reported[80] and a theoretical treatment has been attempted.[81] However, the exact nature of the interaction is not certain and several obstacles hinder quantitative assessment of the effect.

The chemical shifts of the protons on the β-carbon show comparatively small changes. In the case of the A protons, a relative shielding of about 0.1 p.p.m. is observed, except in the case of ortho-bromostyrene where the shift for this proton is almost identical to that observed in the corresponding meta- and para-substituted compounds. Most of the B protons show a small deshielding of about 0.1 p.p.m. when compared with the previous series. From the ^{13}C spectral results, it was concluded that a single ortho substituent offers some steric hindrance to conjugation.[195] A likely equilibrium conformation is that in which the vinyl system has been twisted out of the plane of the benzene ring by rotation about the bond joining the two systems. From a study of its electronic spectrum, Suzuki[203] proposed that the angle of twist in o-methylstyrene is about 33°.

The changes observed in the chemical shifts of the β-protons seem to be related to the degree of displacement from the planar conformation. Since both protons move away from the plane of the aryl ring, the changes in the ring current effect should give rise to a relative shielding at each proton, although a larger change is expected for the A proton. The observed shift of the B proton to lower field is testimony to the importance of other factors. One such factor may be the through-space effects of the ortho substituents towards which the $2p_z$-orbitals of the ethylene system are tilted in the non-planar conformation.



Planar

Non-planar

In this series, the vicinal couplings closely resemble those observed for the meta- and para-substituted compounds. The _trans_ interactions are slightly smaller in the ortho-substituted compounds. In contrast to the vicinal coupling constants, the geminal interactions show appreciable changes. These are larger by 0.2 to 0.5 c/s for the ortho-substituted compounds. For the non-planar conformation, a larger H-C-H bond angle is expected because of decreased steric interaction between the A nucleus and the _ortho_ proton of the benzene ring. The observed increase in geminal coupling is, therefore, in agreement with the predictions based on valence bond theory.

According to the molecular orbital theory of geminal coupling,[204] increased electron density in the aromatic nucleus should result in increased geminal interaction for a styrene in the planar conformation. Such an increase is experimentally observed for _p_-methylstyrene. A deviation from coplanarity results in reduced electron donation to the antisymmetric orbitals of the CH_2 fragment. For this situation, the theory predicts an algebraic decrease in the geminal coupling constant. The observed result is an algebraic increase, suggesting that other factors may be more important. It appears that the ortho-substituent interacts directly with the electrons of the vinyl system in such a way that there is an effective withdrawal of electrons from ψ_1 - the symmetric bonding orbital, leading to the observed algebraic increase in the geminal interaction.

(c) Styrenes bearing two ortho-Substituents

For the 2,6-disubstituted compounds, the chemical shifts of the β-protons change in opposite directions such that the B nuclei are deshielded and the A protons are shielded relative to their positions in the less highly substituted compounds. The net result is a reversal of the relative positions of the patterns for the A and B protons from those in the spectra of the two previous series, with the absorption for the A nucleus now appearing at higher field. This is illustrated in Fig. 30 in which the AB patterns for styrene and 2,4,6-tri-isopropyl styrene are shown. For the five compounds studied the shifts of both β-protons are remarkably constant. The value for the A nuclei is 5.18 ± 0.04 p.p.m. and for the B nuclei 5.48 ± 0.02 p.p.m. (average deviations are given). As before, the spacings of the lines in each "quartet" (the apparent coupling constants), permit an easy distinction between the <u>cis</u> and <u>trans</u> β-protons and the assignments are unequivocal. The total range of absorption for the α-protons is slightly larger (6.71 ± 0.06 p.p.m.) and the absorption is shifted progressively to lower field

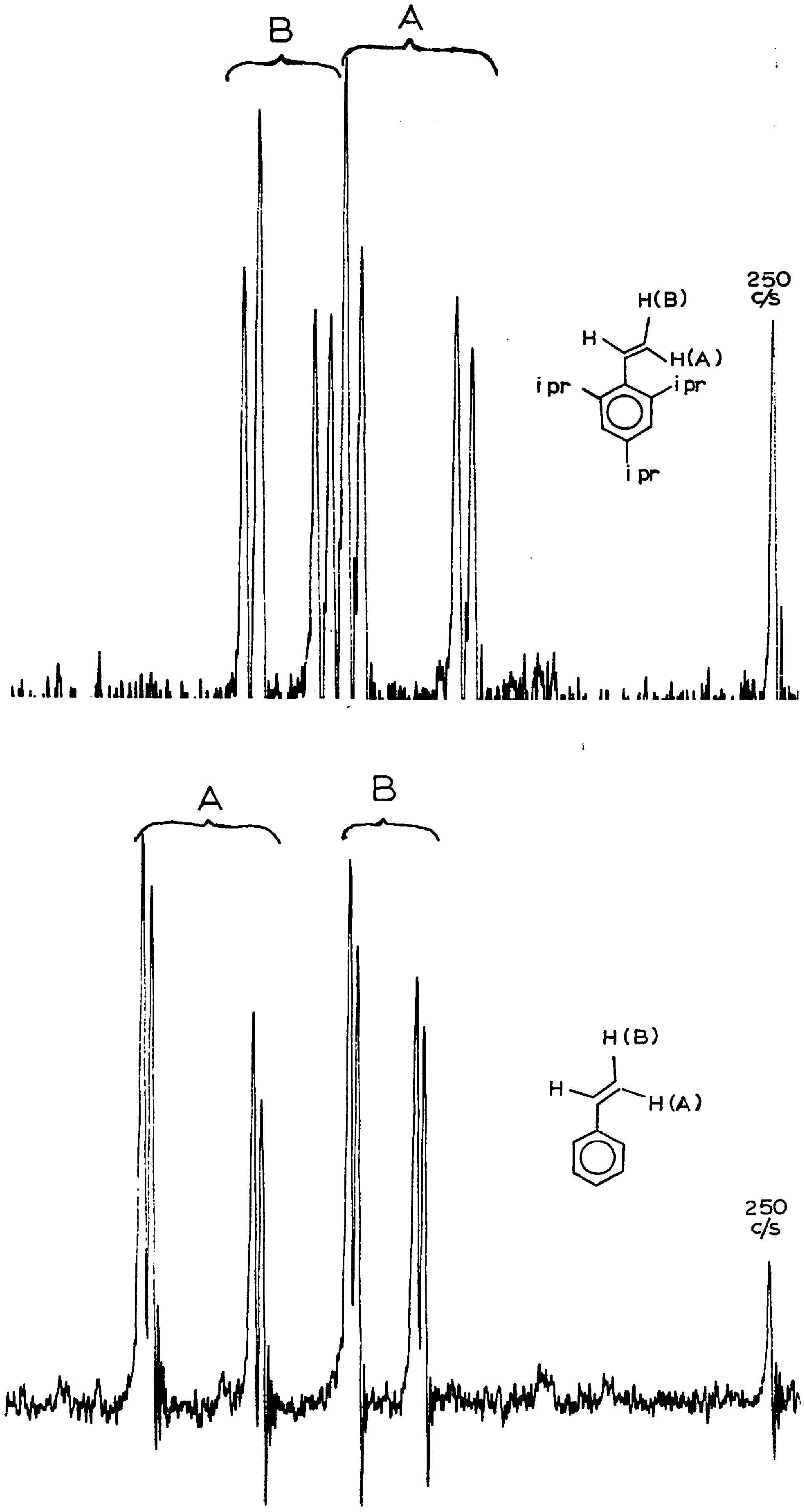


Figure 30. - The AB Portion of the ABC Resonance Pattern for (a) 2,4,6-Triisopropyl Styrene and (b) Styrene.

with increasing bulkiness of the ortho substituents. This trend suggests that Van der Waals interactions are important.

The chemical shift data, especially for the terminal methylene protons, indicate that there is a significant difference in the environment of these protons from that prevailing in the previous examples. The relative shielding of the A nuclei supports the non-planar conformation indicated by other evidence. For the B protons, however, a deshielding effect is observed, the resonance positions being comparable to that for the B nucleus in p-nitrostyrene. A rationalization for this apparent anomaly can be found by examining the steric environment of the B nucleus in the planar and non-planar conformations. In the former conformation, this nucleus is well separated from other groups in the molecule and Van der Waals interactions make a negligible contribution to the chemical shift. In the non-planar conformation, however, the distance between the B proton and the ortho-substituents is greatly reduced and "through" space effects are more significant.

It can also be noted that the shifts for the β-protons can be correlated with the β-carbon shieldings. The trends are illustrated in Fig. 31 in which the β-proton shifts for styrene, o-methyl styrene and 2,6-dimethylstyrene are plotted against the β-carbon shieldings. The slope of the line

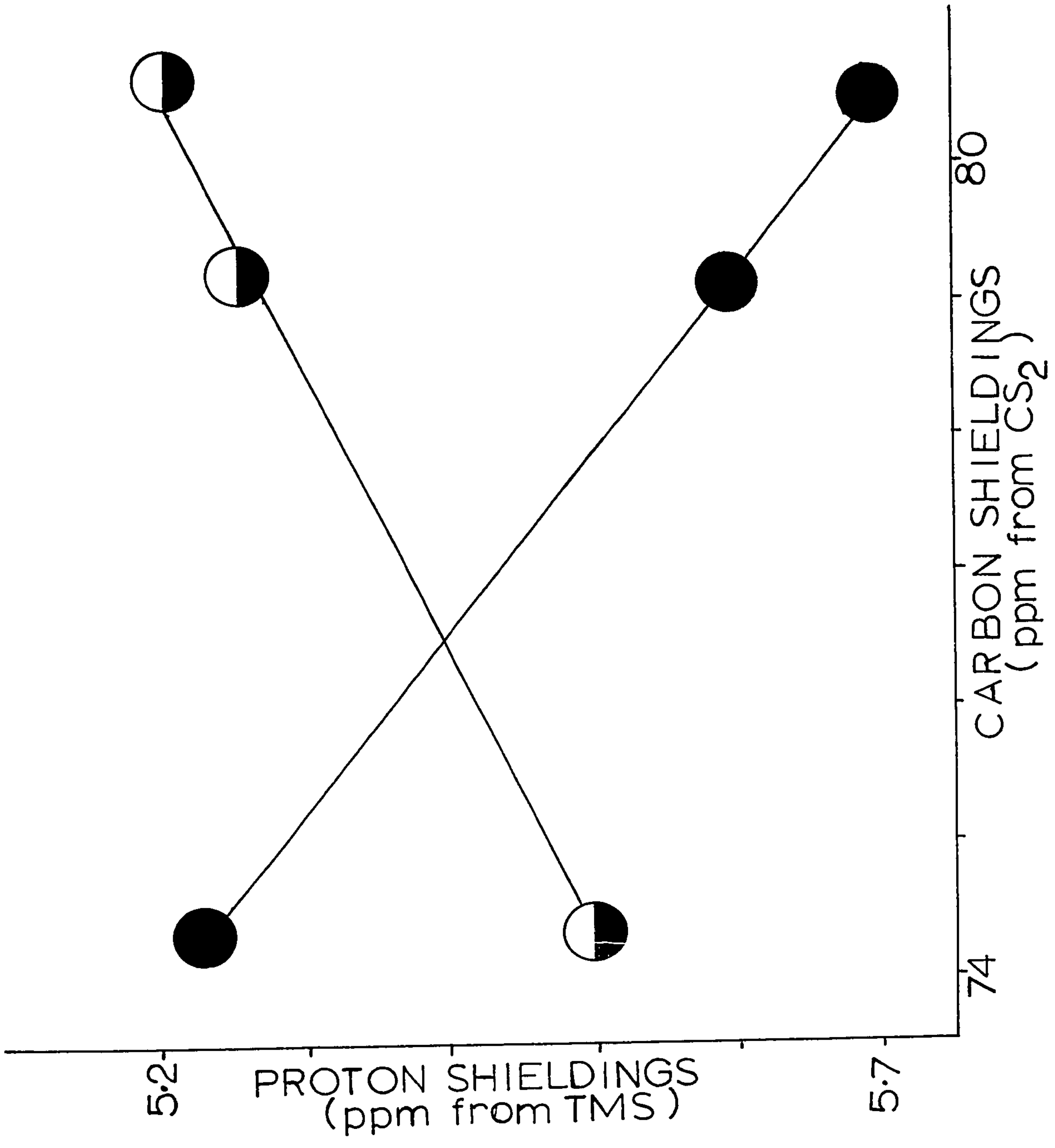


Figure 31. - Variations of β-Proton Shifts of Styrene, *o*-Methyl Styrene and 2,6-Dimethyl Styrene Relative to the β-Carbon Shieldings. (A, ●; B, ◐.)

for the B nuclei is the same as that found in Fig. 28, suggesting that the reduced chemical shift for the B proton is associated with a decrease in the π-electron density at the β-carbon.

From the above, it can be seen that although the effects of π-electron density, neighbouring anisotropic groups (the aryl ring and the substituents) and Van der Waals interactions are factors in determining the observed chemical shifts, it is not possible to assess the contribution of each factor.

The coupling constants found for 2,6-dimethylstyrene, vinyldurene and the 2,4,6-trisubstituted examples are larger than those for the less highly substituted compounds. The <u>trans</u> vicinal coupling constants are 18.00 ± 0.09 c/s, the <u>cis</u> vicinal interactions are 11.41 ± 0.15 c/s, and the geminal couplings are 2.25 ± 0.11 c/s. Thus, the vicinal coupling constants are 0.5 c/s larger than those in the compounds considered previously while the geminal interactions are approximately doubled. The latter trend may be related to the extent of deviation from coplanarity, especially since the geminal coupling constant increases with increasing substitution at the ortho position, and also because the magnitude of the increase roughly correlates with the decrease in the intensity of the ultraviolet absorption maximum for a series of methylated derivatives.

Some examples which illustrate this trend are shown in Table XXXVI.

Examination of the coupling constants for the series of styrenes reveals that the results for the most hindered system tend towards the values reported for ethylene, namely,

$$J_{trans} = +19.1 \text{ c/s}, J_{cis} = +11.7 \text{ c/s and } J_{gem} = +2.5 \text{ c/s.}$$

This trend is indicative of the progressive loss of the effect of the aromatic ring.

TABLE XXXVI

COMPARISON OF J_{gem} VALUES WITH ε_{max} DATA FOR SOME STYRENES

Compound	J_{gem}(c/s)	ε^{*}_{max}
Styrene	1.0	15600
2-Methyl	1.6	12000
α-Methyl	1.5	9800
2,6-Dimethyl	2.1	5400
2,3,5,6-Tetramethyl	2.2	4000

* Intensity data taken from reference 195 except that for α-methyl styrene (reference 203).

EXPERIMENTAL

(i) Sources and Purification of Compounds.

With the exception of p-divinylbenzene, the styrenes investigated were those used for the ^{13}C studies reported by Dhami and Stothers.[195] 2,4-Dimethylstyrene, 2,5-dimethylstyrene, 2,4,6-trimethylstyrene, 2,3,5,6-tetramethylstyrene, 4-methylstyrene and 3-nitrostyrene were obtained from Aldrich Chem. Co.; 2-chlorostyrene, 3-chlorostyrene, 4-chlorostyrene, 2-bromostyrene, 3-bromostyrene, 4-bromostyrene, 2-methylstyrene and 3-methylstyrene from Columbia Organic and styrene itself was obtained from Matheson, Coleman and Bell. Samples of 3,4-dichlorostyrene and 4-vinylstyrene were provided by Professor K. Yates and Professor J.W Lorimer, respectively. 4-Methoxystyrene, 4-nitrostyrene, 4-N,N-dimethylaminostyrene and 2,4,6-triethylstyrene were prepared by Dr. K.S. Dhami.[205]

The methods used to purify the styrenes are summarized in Table XXXVII which also lists the physical properties of the compounds. The samples of 3-nitrostyrene, 2,4,6-triethylstyrene and p-vinylstyrene were used without further purification.

(ii) Preparation of NMR Samples

A 10 mole % solution of each compound was prepared in deuteriochloroform. After addition of a few drops of

TABLE XXXVII

METHODS OF PURIFICATION AND PHYSICAL CONSTANTS FOR SOME SUBSTITUTED STYRENES

Substituent	M*	Observed Values			Reported Values			Ref.
		m.p.°C	b.p.°C/mm	n_D(°C)	m.p.°C	b.p.°C/mm	n_D(°C)	
Nil	A	-	38-39/15	-	-	60/40	-	206
p-OMe	A	-	89.0-90.0/10	1.5590(20)	-	78-80/3	1.5586(20)	207
p-Me	A	-	58.5-59.5/10	1.5405(18)	-	65-66/18	1.5402(20)	208
p-Cl	A	-	71-72/11	1.5655(18)	-	53-54/3	1.5658(20)	209
p-Br	A	-	83/11	1.5950(20)	-	88/13	-	210
p-N,N-Me$_2$	A	-	45.0-46.0/0.03	-	-	85-90/2.5	-	211
p-NO$_3$	B	25-26	-	-	21-22	-	-	212
		-	-	-	29	-	-	210
o-Me	A	-	58.5-59.0/11	-	-	51/9	-	213
o-Cl	A	-	70.5-71.0/11	-	-	60-61/4	-	209
o-Br	A	-	80.0-81.0/10	-	-	102-104/22	-	214
m-Me	A	-	57.0-58.0/13	-	-	50-51/3	-	211

TABLE XXXVII (Continued)

METHODS OF PURIFICATION AND PHYSICAL CONSTANT FOR SOME SUBSTITUTED STYRENES

Substituent	M*	Observed Values			Reported Values			Ref.
		m.p.°C	b.p.°C/mm	n_D(°C)	m.p.°C	b.p.°C/mm	n_D(°C)	
m-Cl	A	-	71.5/11	-	-	62-63/6	-	209
m-Br	A	-	86.0/10	-	-	48.1-48.5/0.5	-	215
2,4-Me_2	A	-	74.0-75.0/13	-	-	79-80/12	-	216
2,5-Me_2	A	-	78.0/13	-	-	69/10	-	216
2,6-Me_2	A	-	71.5-72.5/12	-	-	65-66/10	-	206
3,4-Cl_2	A	-	100-102/11	-	-	63-64/1.5	-	208
2,4,6-Me_3	A	-	88.0/11	-	-	92/14	-	
2,4,6-(i-Pr)$_3$	A	-	51.5-52.0/0.05	-	-	85-86/0.4	-	205
2,3,5,6-Me_4	B	32-33		-	34.10	-	-	217

* M denotes the method of purification; A = Fractional distillation, B = Recrystallization.

tetramethylsilane, the samples were degassed and sealed *in vacuo*.

(iii) Proton Magnetic Resonance Spectra

A Varian A60 spectrometer was employed for these measurements. The spectral line positions were determined by interpolation between audio sidebands of tetramethylsilane. A Hewlett-Packard model 241A audio oscillator was used to generate the sidebands, and its output was continuously monitored with an HP522B frequency counter. A minimum of six separate spectra were obtained at the 250 or 100 c/s sweep width for each case.

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