SUBSTITUENT EFFECTS ON THE GEMINAL COUPLING CONSTANT IN AN ALLYLIC METHYLENE GROUP

by

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PREFACE

More and more use has been made of proton-proton coupling constants in determining the structure and conformation of an organic molecule. Many correlations between the structure and/or conformation of a molecule and the magnitude of the coupling constant have been established for vicinal and long-range interactions. Few such correlations have been developed for geminal coupling constants. In a methylene group adjacent to a benzene ring, it has been found that the substituent effect on J_{gem} depends on the orientation of the methylene group relative to the adjacent pi-orbital. The aim of this thesis is to examine the effect of substituents on the geminal proton-proton coupling constant in an allylic methylene group.

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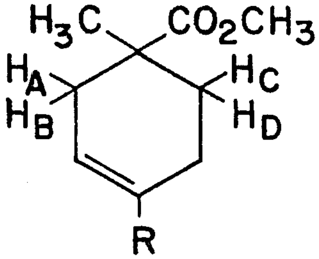
ABSTRACT

A series of substituted methyl 1-methylcyclohex-3-ene-1-carboxylates of the general formula



have been synthesized and the proton magnetic resonance spectra measured. The ring protons were extensively coupled to each other and gave complex spectra. The 3, 5, 5'-trideutero analogues have also been synthesized. The geminal coupling constant J_{AB}, was obtained from the AB pattern produced by the magnetically non-equivalent protons in the allylic methylene group. J_{AB} has been found to depend on the nature of the substituent R. A Hammett correlation between J_{AB} and σ_p, the Hammett substituent constant, had a slope or rho value of -2.9. Resonance effects were shown to be much more predominant than field effects.

Long-range coupling over four bonds has been measured between the allylic proton at C_2 and the homoallylic proton at C_6. The low field proton of each AB group has been tentatively assigned as being <u>cis</u> to the carbomethoxy group.

The low field proton of the allylic methylene group showed a larger S. C. S. than the high field proton. Since the low field proton is predominantly in the pseudoequatorial position, this result is opposite to that predicted by a hyperconjugative type of interaction.

The chemical shift of the olefinic proton of each compound has been found to obey the additivity scheme of Sternhell and co-workers.

INTRODUCTION

The splitting effect of one proton on the absorption of another proton or group of equivalent protons in n.m.r. spectroscopy is referred to as proton-proton coupling. It generally depends in a predictable manner on the number and kind of intervening bonds and on the stereochemical relationships of interacting groups.

Three classes of proton-proton coupling constants can be distinguished. These are geminal, vicinal and long-range coupling constants respectively (Figure I).

Spin-spin coupling constants between protons fall off rapidly in magnitude as the number of intervening bonds increase. However with high resolution n.m.r., couplings over four and more bonds may be measured. Most of the long-range coupling constants are observed between protons separated by four or five bonds and have magnitudes which are less than 3 Hz.

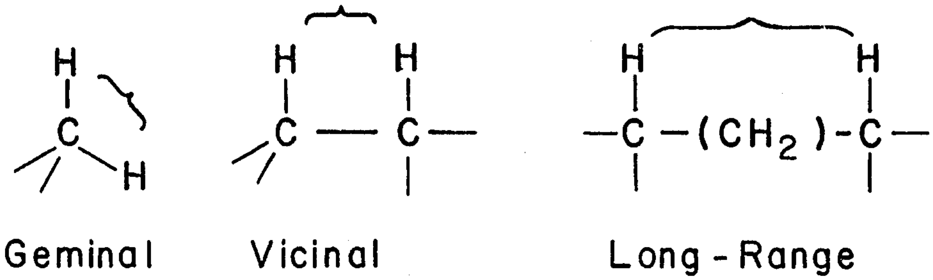


Figure 1. Classes of proton-proton coupling constants

The magnitude of long-range coupling constants depends on the type of bonds and on the conformations taken up by the bonds between the interacting nuclei. Coupling over four single bonds as discussed by Barfield[1] is maximal when the system adopts a coplanar **W** arrangement. The presence of several paths between the interacting nuclei or the introduction of unsaturation or heteroatoms in the path also increase the coupling. Allylic and homoallylic coupling exhibit angular dependence[2, 3] and may be used to aid in conformational analysis[4, 5].

Vicinal coupling constants are found to be a function of the electronegativity of substituents, the H-C-C bond angles and C-C bond lengths and ϕ, the dihedral angle between the interacting nuclei[6]. The Karplus relation[7, 8] between the magnitude of vicinal proton-proton coupling constants and ϕ is well known and has been used to elucidate stereochemical features in many compounds. This property has been widely used in rigid ring systems such as steroids and in rings with bulky substituents that exist in predominately one conformation.

Geminal coupling constants[*] are found to be sensitive to the type and conformation of adjacent groups and the strain in adjacent bonds. Coupling constants between protons of saturated CH_2 groups have been treated theoretically by the valence bond method,[7, 9-13] by the molecular orbital method[14] and by a modified

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[*] The geminal coupling constant will be referred to as J throughout this work. Only geminal coupling constants in tetrahedral methylene groups will be examined. Methane whose J is -12.4 Hz serves as a reference.

molecular orbital method[15]. Initial valence bond calculations met with significant deviations from experimental values,[16,17] however a semiempirical valence bond approach of Barfield and Grant[18] met with more success. Although in each method there are grounds for dissatisfaction with the theory,[6] the molecular orbital approach appears to account for the trends caused by substituents or changing hybridization. It predicts the following effects on geminal coupling constants:

(a) withdrawal of electrons from orbitals symmetric between hydrogen atoms (generally inductive effects) should lead to a positive change in J.

(b) withdrawal of electrons from orbitals antisymmetric between hydrogen atoms (generally hyperconjugative effects) should lead to a negative change in J. Exactly analogous but opposite predictions apply to electron donation.

(c) the hyperconjugative effect varies with the orientation of the substituent with respect to the methylene hydrogen.

Cookson and co-workers[19] arrived at similar conclusions by examining a large number of geminal coupling constants reported in the literature up to 1966. In two more recent works[20] they have attempted to explain any apparent anomalies that have arisen as well as pointing out examples that comply with the general rules outlined above.

Various trends in geminal coupling constants have been observed in numerous series of compounds. Substitution of an electronegative group in the *alpha* position leads to a positive change in J in accordance with the inductive removal of electrons from the symmetric CH_2 orbital. This has been shown in a series of substituted methanes[21].

Substitution of an electronegative group in the beta position leads to a negative change in J in accordance with the hyperconjugative removal of electrons from the antisymmetric CH_2 orbital. This has been shown in a series of bicycloheptenes,[22] 1,1-dichlorocyclopropyl compounds,[23] epoxides[23] and alkyl tetrahydropyranyl ethers[24]. However the change in J produced by the beta substituent depends on the projected angle between the CH_2 group and C-X bond and on the C-C-X bond angles and lengths. If the C-C-X plane bisects the HH axis, electrons will be drawn from the symmetric CH_2 orbital and a slight positive change in J is observed (Figure 2). On the other hand, if the C-C-X plane is parallel to the HH axis electrons will be drawn from the antisymmetric CH_2 orbital and a negative change in J is observed. The staggered and eclipsed conformations c and d in Figure 2 are sufficiently close to the parallel arrangement that this effect predominates. In a freely rotating group the latter effect out-

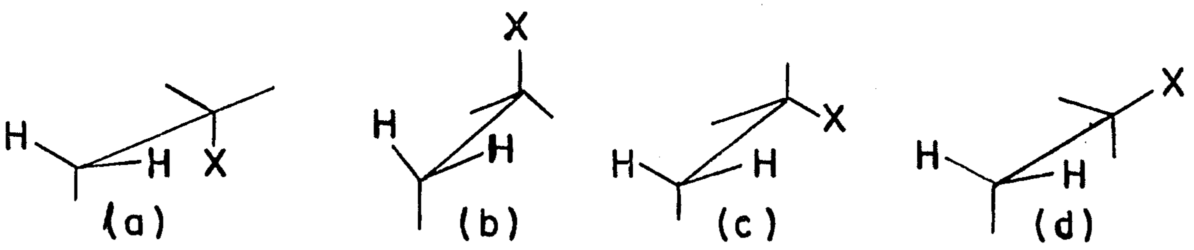

Figure 2. Orientations of a BETA Substituent.

weighs the former and a negative change in J is observed[6]. In general for tetrahedral groups <u>beta</u> substitution has a small effect on J.[19]

The largest change in J is produced by hyperconjugation of the CH_2 group with an adjacent pi-bond[17,18,25] which removes electrons from the antisymmetric CH_2 orbital. Here the change in J is sensitive to the angle between the HH axis and the nodal plane of the conjugating system. For a freely rotating methyl group an adjacent pi-bond produces a change in J of about -1.5 Hz, the effect being additive up to the maximum of four increments[17,25].

However for a cyclic CH_2 group of fixed conformation or for a system in which one conformer is more prevalent the pi-bond contribution to J can range from 0 to -4.5 Hz. The maximum change in J occurs when the HH axis of the CH_2 group is parallel to the pi-orbital of the adjacent sp^2 carbon atom[17,18,25] (Figure 3). The theoretical curves describing this effect as calculated from molecular orbital theory[14] and modified molecular orbital theory[15] are also shown in Figure 3.

The actual value of J (neglecting all other contributions) is obtained by adding the pi-bond contribution to J to -12.4 Hz the value for methane[26] or cyclohexane[27] taken as the ideal in the absence of hyperconjugation (assuming that the inductive effect of the unsaturated group is negligible).

Cookson and co-workers[19] have plotted ΔJ versus ϕ for a large number of compounds containing CH_2 groups in five-, six- and rigid seven-membered rings flanked by one pi-bond.

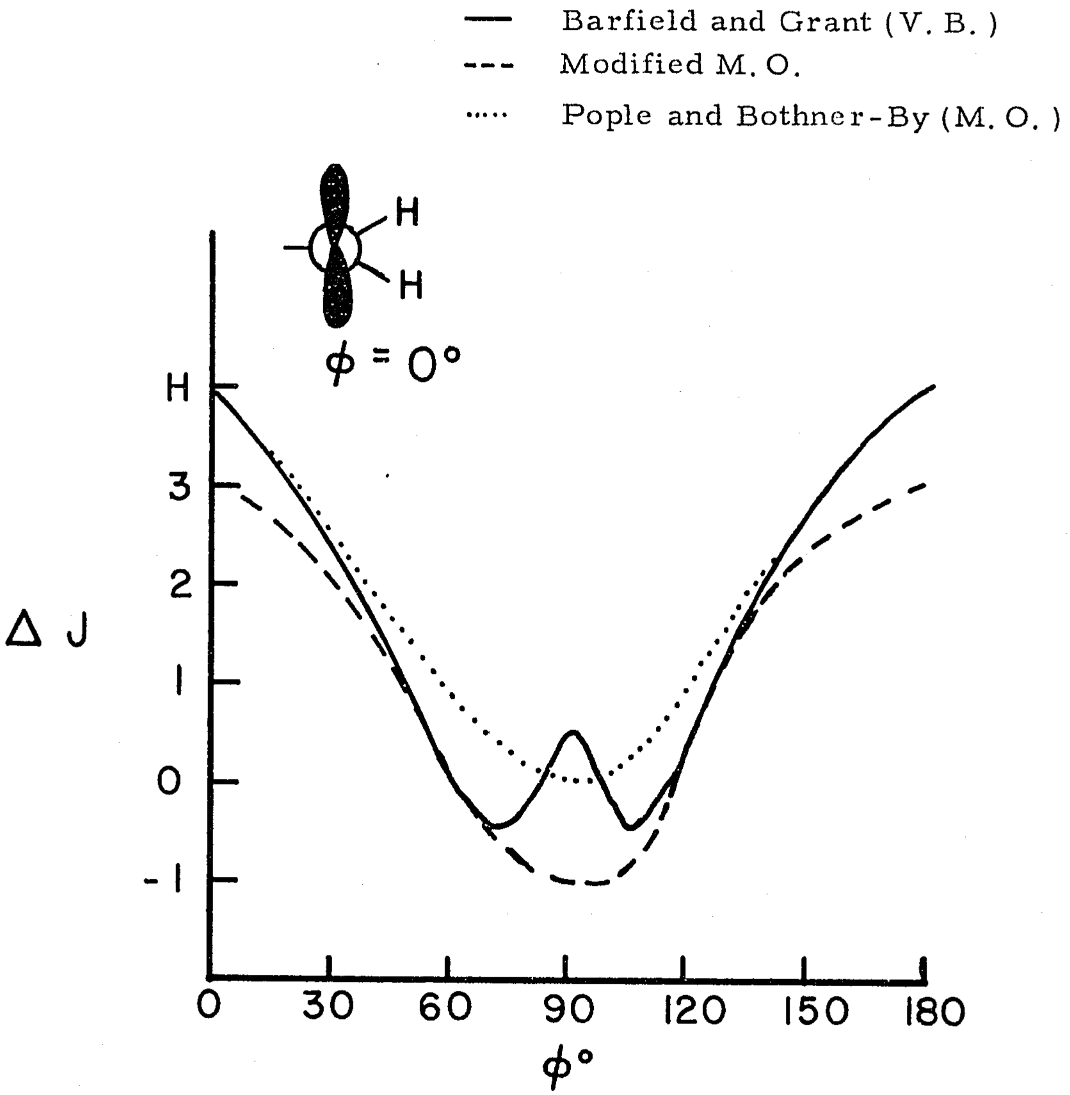

Figure 3. pi-bond contribution to J as a function of ϕ the dihedral angle between the methylene group and the adjacent pi-bond.

They found that J does depend on ϕ^* in the general way predicted by the Barfield-Grant valence bond curve and the molecular orbital curves although there was no sign of the minor minimum at 90° present in the valence bond curve.

Geminal coupling constants in the benzylic CH_2 group of a series of para-substituted 2-benzyloxytetrahydropyrans have been examined by two groups[24, 28]. The phenyl substituents were observed to cause a shift in the value of J, the direction of which was found to agree with the prediction regarding hyperconjugation. The value of J was found to correlate with σ_p, the Hammett substituent constant. The slope of the line, ρ (the rho value) was -1.5^{**}. In a series of para-substituted benzyl phenyl sulfoxides a similar correlation had $\rho = 0^{**}$. The difference in slopes of these correlations has been attributed to the relative orientation of the benzylic protons with respect to the benzene ring. It was suggested that the tetrahydropyranyl ethers possess a dominant conformation in which $\phi = 0°$ while in the sulfoxides $\phi = 90°$. It was proposed that ρ was conformationally dependent and should be proportional to $\cos^2 \phi$.[24]

In a study on para-substituted N-benzyl-2-methylpiperidines a similar correlation between J and σ_p was observed with $\rho = -1.4^{\ddagger}$. A dominant conformation having $\phi = 0°^{+}$ was proposed[29].

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[*] ϕ covered the range from 30° to 120° with no gap greater than 10°. ϕ was either calculated or usually measured from Dreiding models.

[**] Measured in $CDCl_3$.

[+] ϕ is taken as 0° when the HH axis is perpendicular to the nodal plane of the benzene ring.

[‡] Measured in CCl_4.

Correlations between J and σ_p have been observed in three series of para-substituted benzyl derivatives where the benzylic CH_2 groups are restricted to a definite orientation with respect to the adjacent benzene ring[30]. In a series of 1-phenylphthalans, 2-methyl-1-phenylisoindolines ($\phi = 0^\circ$) and dibenzo [a,d]cycloheptene-10,11-oxides ($\phi = 72^\circ$), ρ was found to be -1.9, -1.7 and +0.2 respectively*. These results strengthen the proposal that ρ is a conformationally dependent parameter and shows, qualitatively, a $\cos^2\phi$ relationship.

There have been numerous attempts to extend the Hammett equation to physical properties which are a function of substituent effects[31]. In n.m.r. spectroscopy, along with the above correlation between J and σ_p, there have been numerous reports of correlations between chemical shifts or chemical shift differences and Hammett substituent constants[32,33]. Where resonance effects do not enter in and inductive effects are important, correlations have been observed between chemical shifts and σ^*, the Taft substituent constant[34]. In addition other correlations between chemical shifts and substituent electronegativities have been reported[22,23].

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*All three series measured in $CDCl_3$.

AB SPECTRA

The chemical shift between two magnetically non-equivalent nuclei is a measure of the difference in the magnetic environments of the two nuclei and the coupling constant between them reflects their bonding character.

The AB non-equivalence quartet has been discussed in numerous places[35-37]. The simplest system in which the effects of chemical shift and spin coupling are intermingled consists of two non-equivalent nuclei (spin 1/2) of the same species isolated from the effects of any other nuclei. The general appearance of the spectrum depends only on the absolute value of $J/\Delta\nu$ where $\Delta\nu$ represents the difference in the chemical shift in cycles per second of the nuclei A and B. As the ratio of $J/\Delta\nu$ increases from a small value, the spectrum changes from two simple doublets into a symmetrical group of four lines, the inner lines being stronger than the outer. Eventually the two central lines degenerate into a single line and the outer lines disappear so that only a single signal is observed corresponding in the limit to the grouping A_2 (Figure 4).

The numerical analysis is straightforward. The separation between either the right hand pair or the left hand pair of lines is equal to $|J|$. The separation between the inner lines is $2C-|J|$ and between the outer lines $2C+|J|$ where C is defined as:

$$2C = [J^2 + (\Delta\nu)^2]^{1/2} \qquad (1)$$

From this relation the chemical shift of the two nuclei A and B can be obtained. The intensity of the inner and outer lines are given by:

$$\text{Intensity of inner lines} = 1 + \frac{|J|}{2C} \qquad (2)$$

$$\text{Intensity of outer lines} = 1 - \frac{|J|}{2C} \qquad (3)$$

However it is not possible to determine the sign of J from the analysis of an AB spectra.

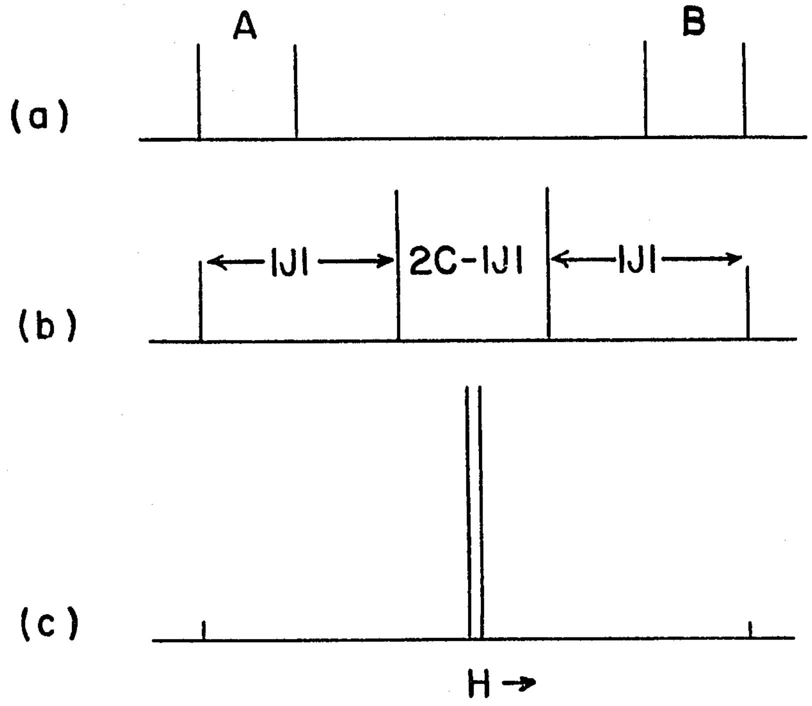


Figure 4. Typical spectra for two nuclei AB. (a) $\Delta\nu > J$, (b) $\Delta\nu \approx J$, (c) $\Delta\nu < J$.

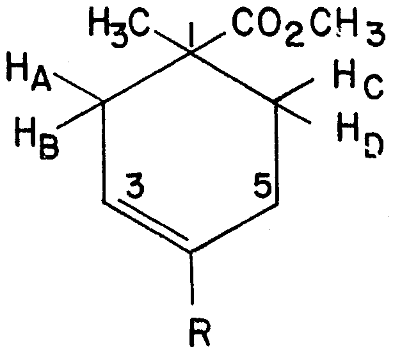
Geminal nuclei occupying geometrically non-equivalent sites in a molecule may be magnetically non-equivalent and thus have different chemical shifts. For these diastereotopic nuclei to be magnetically non-equivalent there must be some source of asymmetry in the molecule and usually a difference in conformer populations[38-40]. Non-equivalence may also arise from intrinsic asymmetry[41-43] or from dissymmetry as in the case of hindered and bridged biphenyls[44]. The relative importance of intrinsic asymmetry as a cause of magnetic non-equivalence has been discussed several times and is normally negligible[40-43].

The magnitude of the chemical shift difference depends on the nature of the centre of asymmetry and upon the distance by which the diastereotopic nuclei are removed from it. The difference usually decreases as the distance is increased[39, 40].

AIM

It was the aim of this project to study the substituent effect on the geminal coupling constant in the allylic CH_2 group in a series of 4-substituted methyl 1-methylcyclohex-3-ene-1-carboxylates, 1. This substituted cyclohexene contains a centre of asymmetry and should have different chemical shifts for the hydrogens designated H_A and H_B as well as H_C and H_D. An electron-withdrawing substituent should cause a negative shift in J on the basis of hyperconjugative effects. Some correlation between J and a substituent parameter may also be observed. Should the slope, ρ, exhibit conformational dependence, it could serve as a useful method for conformational analysis in freely rotating allylic systems.

The substituted cyclohexenes should be readily synthesized from methyl 1-methyl-4-ketocyclohexanecarboxylate which is known[45]. Cyclohexenes, 1, synthesized from the ketone deuterated in the 3, 3', 5, 5' positions should give simple n.m.r. spectra from which J_{AB} and J_{CD} could be obtained directly.



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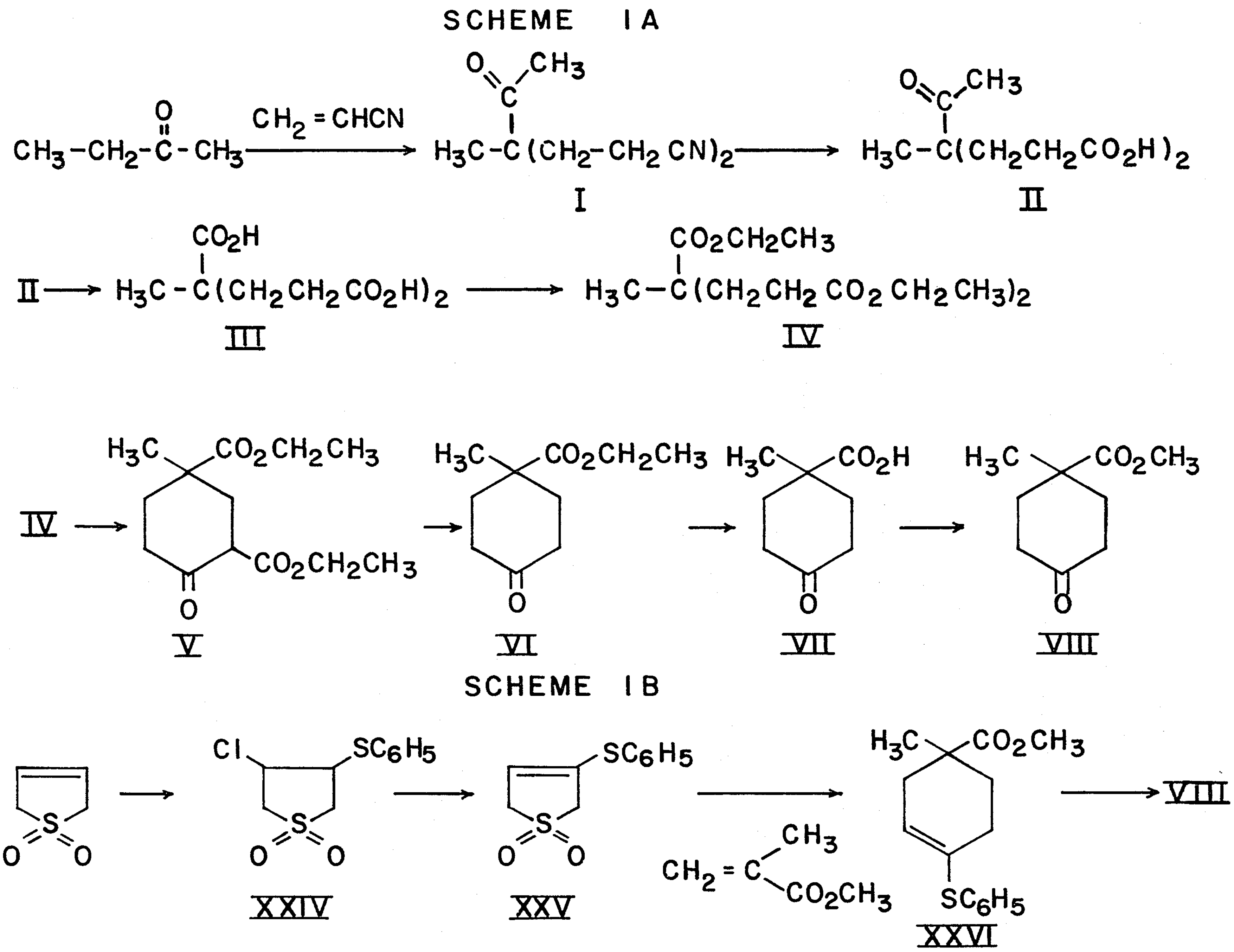
RESULTS and DISCUSSION

SYNTHESIS

The starting material, methyl 1-methyl-4-ketocyclohexanecarboxylate, VIII, was synthesized with only minor changes according to the procedure of Rubin and Wishinsky[45] (Scheme 1A). They obtained the free acid, VII, as the product of decarboxylation of V; however by using a ten-fold excess of the solvent (acetic acid) the ester VI was obtained. This eliminated the difficulties encountered in trying to distill a solid. Alkaline hydrolysis of VI gave VII. In addition, hydrolysis of VI in NaOD/D_2O gave 3, 3', 5, 5'-tetradeutero - VII which was the starting material for the deuterated series of compounds. Esterification of VII was carried out using the usual method of methanol-sulphuric acid and by reaction with silver oxide-methyl iodide. The latter method proved more satisfactory and easily adaptable to small scale preparations. It was used to prepare 3, 3', 5, 5'-tetradeutero - VIII.

Compound VIII was also synthesized by an alternative route starting from butadiene sulphone which is commercially available (Scheme 1B). The addition of benzenesulfenyl chloride to butadiene sulphone and the elimination of hydrogen chloride to give XXV proceeded smoothly as described by Gunderman and Holtman[82]. The elimination of sulphur dioxide and the Diels-Alder reaction between the resultant 2-thiophenyl-1, 3-butadiene and methyl methacrylate were carried out in one step and gave XXVI in 58% yield.



Synthesis of methyl 1-methyl-4-ketocyclohexanecarboxylate

In a Diels-Alder reaction between an unsymmetrical diene and an unsymmetrical dienophile, two structural isomers are theoretically possible (Figure 5). However it has been shown that 2-methoxy-1, 3-butadiene (or 2-ethoxy-1, 3-butadiene) with acrolein gives rise to only one product[46], that corresponding to structure I in Figure 5. Free-radical and ionic mechanisms have been proposed for the Diels-Alder reaction[47]. In the case of unsymmetrical reactants, both mechanisms predict one product (that being structure I in Figure 5). On this basis and from steric considerations the product obtained should be XXVI. The structure of this compound was proven by n.m.r. and by hydrolysis to the corresponding ketone which was found to be identical to compound VIII. No trace of the isomer corresponding to structure II was observed by n.m.r.

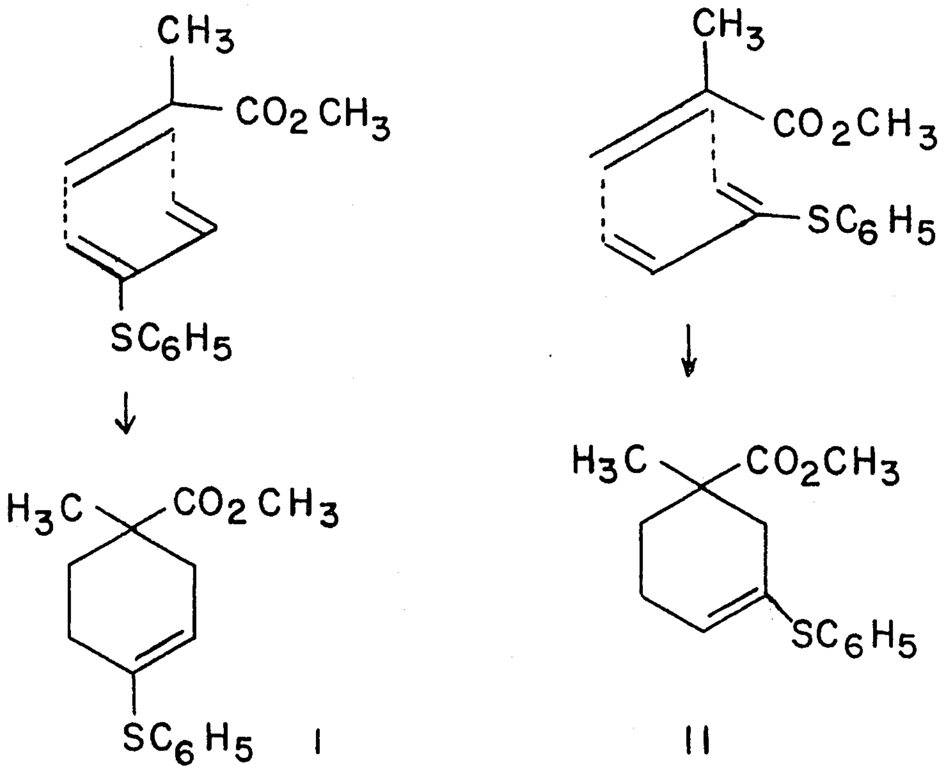
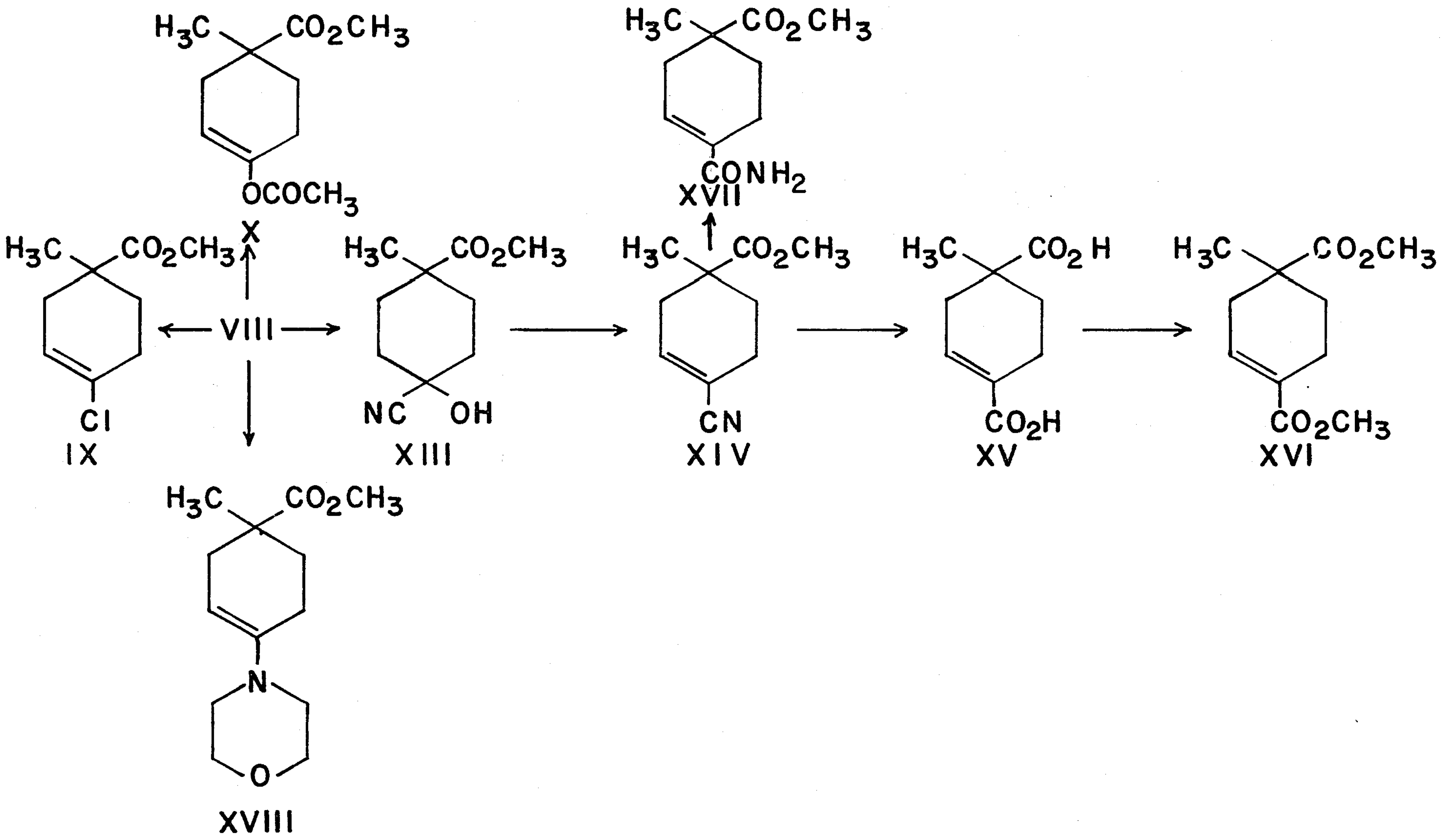


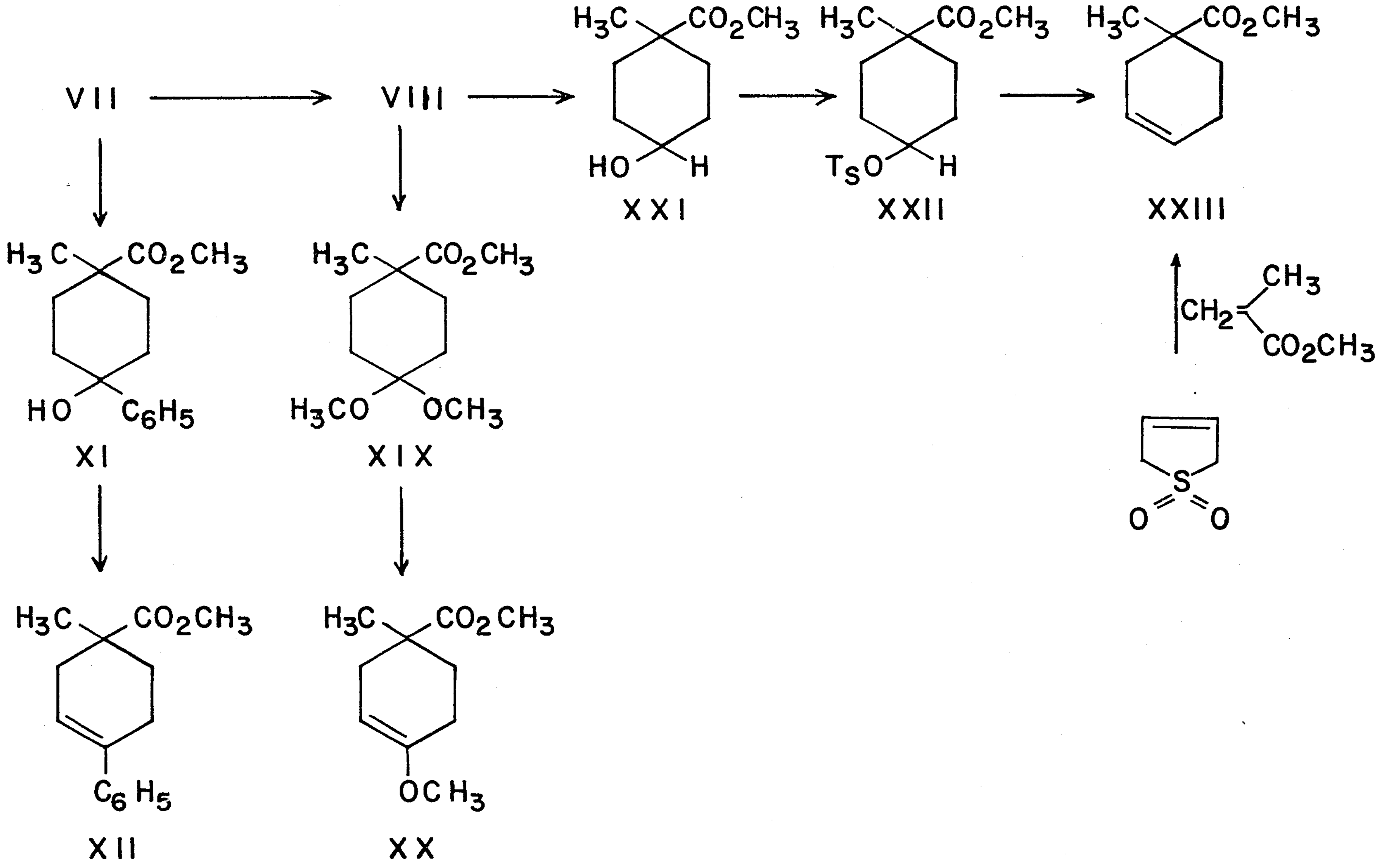
Figure 5. Possible products of the reaction of 2-thiophenyl-1, 3-butadiene with methyl methacrylate.

SCHEME 2A



Synthesis of 4-substituted methyl 1-methylcyclohex-3-ene-1-carboxylates

SCHEME 2 B



so XXIII was also synthesized from VIII. Reduction of VIII with sodium borohydride gave XXI. Dehydration of XXI using standard procedures such as thionyl chloride/pyridine gave a mixture of the olefin, the 4-chloride and the lactone, 3, resulting from attack of the carbomethoxy group on C_4. The monochloride and olefin could not be separated by chromatography. A more facile route using the tosylate, XXII, was successfully employed.

CONFORMATIONAL and SPECTRAL ASPECTS

The conformation of the cyclohexene ring has been discussed in numerous places[48, 49]. The geometry of the cyclohexene ring is essentially defined by the double bond with its two sp^2-hybridized carbon atoms. The two carbon atoms adjacent to the double bond are forced to be co-planar with the carbon atoms of the double bond. This prevents the ring from adopting the chair conformation commonly assumed by cyclohexanes. To accommodate this coplanarity the cyclohexene ring can adopt either a boat conformation or a half-chair conformation. For cyclohexene the boat conformation is energetically less favoured than the half-chair conformation by 2.7 kcal/mole[50]. In an n.m.r. study on cyclohexene no evidence for an equilibrium mixture of boat and half-chair forms was found for temperatures as low as -170°. Thermodynamic calculations have shown that the proportion of the boat form present at -170° is too small to be measured by n.m.r.[50].

In half-chair cyclohexene the homoallylic protons are attached to carbon atoms which are normally staggered and hence occupy equatorial and axial positions. However the allylic protons are attached to carbon atoms which are imperfectly staggered and therefore occupy pseudoequatorial and pseudoaxial positions[48, 49]. Substituents in the equatorial (e) and pseudoequatorial (e') position have been shown to be more stable than those in the axial (a) and pseudoaxial (a') positions[48, 49, 52]. The pseudoaxial hydrogen in cyclohexene is better disposed for pi-orbital overlap than a pseudoequatorial one since the plane of the double bond does not bisect the $H_{a'}$-C-$H_{e'}$ angle but is more nearly (though not quite) perpendicular to the C-$H_{a'}$ bond (Figure 6). The angles from the plane of the double bond to the $H_{a'}$ and $H_{e'}$ bonds have been calculated as 67° and 53° respectively[53]. However a Dreiding model gives angles closer to 75° and 45°.

The n.m.r. analysis of several substituted cyclohexenes have yielded coupling constants which are consistent with a half-chair conformation either as one single conformation or as two rapidly inverting conformations[54-57].

In cyclic systems that undergo rapid conformational inversion the observed n.m.r. spectrum is time averaged and represents a statistical average of all the conformational species

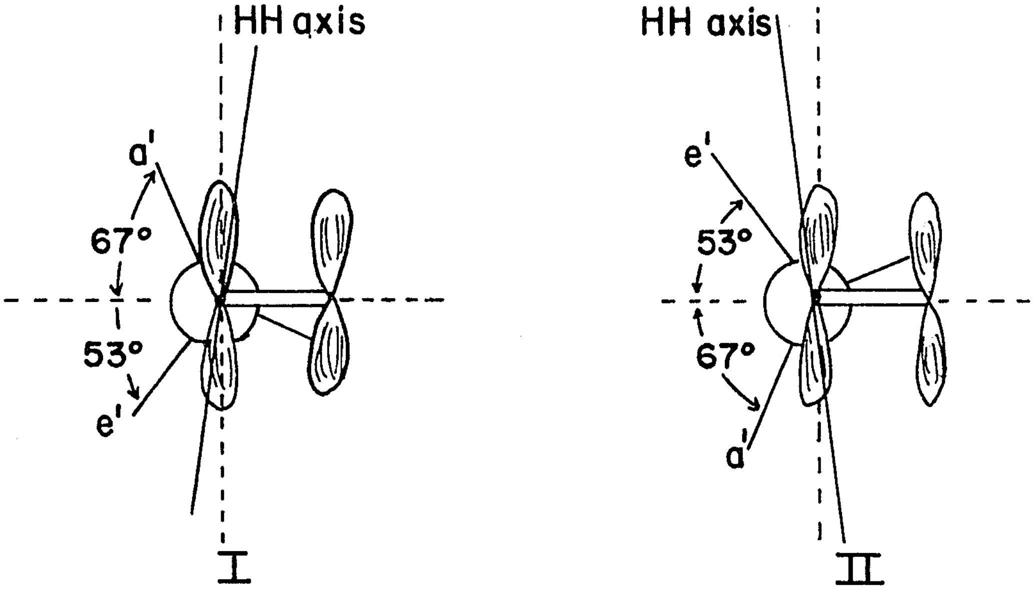


Figure 6. Projection of the allylic CH_2 protons on the adjacent pi-orbital in cyclohexene systems.

participating in the inversion cycle. If the cyclic system bears substituents which are arranged such that one conformational species is more favoured energetically than any other, then the observed conformation will approximate to that of the favoured species. Contributions of the other less favoured species to the observed spectrum are proportional to their mole fractions. Thus chemical shifts and coupling constants should represent the time-weighted averages for all the conformations present, provided interconversion is rapid on the n.m.r. time scale[2].

The two half-chair conformations for the cyclohexene system under study are represented in Figure 7. The free energy differences between the equatorial and axial positions for methyl and carbomethoxy are 1.7 and 1.1 kcal/mole* respectively[49]. The

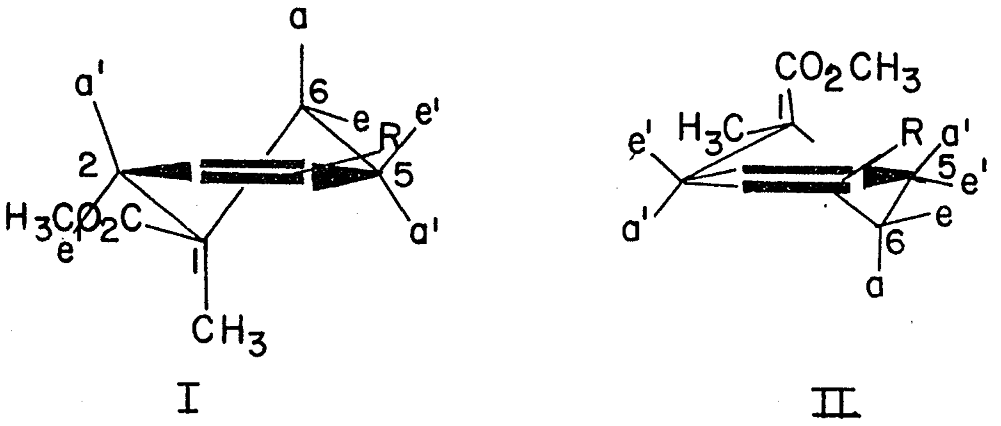


Figure 7. Half-chair inversion in 4-substituted methyl 1-methyl-cyclohex-3-ene-1-carboxylates.

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*The free energy differences are equal to twice the interaction energy between the substituent and an axial hydrogen in cyclohexane since in the axial conformation there are two such interactions. In cyclohexene there is only one such interaction and the A values are halved such that $|\Delta F| = 0.3$ kcal/mole.

equilibrium constant for the half-chair inversion can be calculated as 1.64*. The percent ratio of the more stable conformer (II) is therefore 62%. Only the two conformers shown in Figure 7 contribute significantly to the observed time-averaged conformation. Other energetically less favoured conformers (including intermediates in the inversion cycle) can be neglected[51]. Since the inversion from I to II and II to I is very fast on the n.m.r. time scale**, the n.m.r. spectra of the substituted cyclohexenes under study will be a weighted average (ratio approximately 2/3) of the two half-chair conformers I and II. It is assumed that the shape of the ring is not altered on changing the substituent R, as any deformation of the ring as a result of substitution will alter dihedral angles and consequently lead to undesired variances in coupling constants.

The 100 MHz spectra of compound XIV (R = CN) are shown in Figures 8 and 9. The overall features of the spectra (such as those due to methyl, carbomethoxy and vinyl protons) are readily assigned from consideration of chemical shifts and relative intensities.

The chemical shift of the olefinic proton was found to vary with different substituents (Table I). Sternhell has developed a method for estimating the chemical shifts of olefinic protons using additive increments[58]. Assuming the additivity of substituent effects+ on the chemical shifts of olefinic protons, the following

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[*] From the relation $\Delta F = -RT \ln K$.

[**] The barrier to inversion for cyclohexene is 5.3 kcal/mole[51].

[+] Strict additivity of substituent effects in ethylene derivatives is not to be expected on general grounds[59].

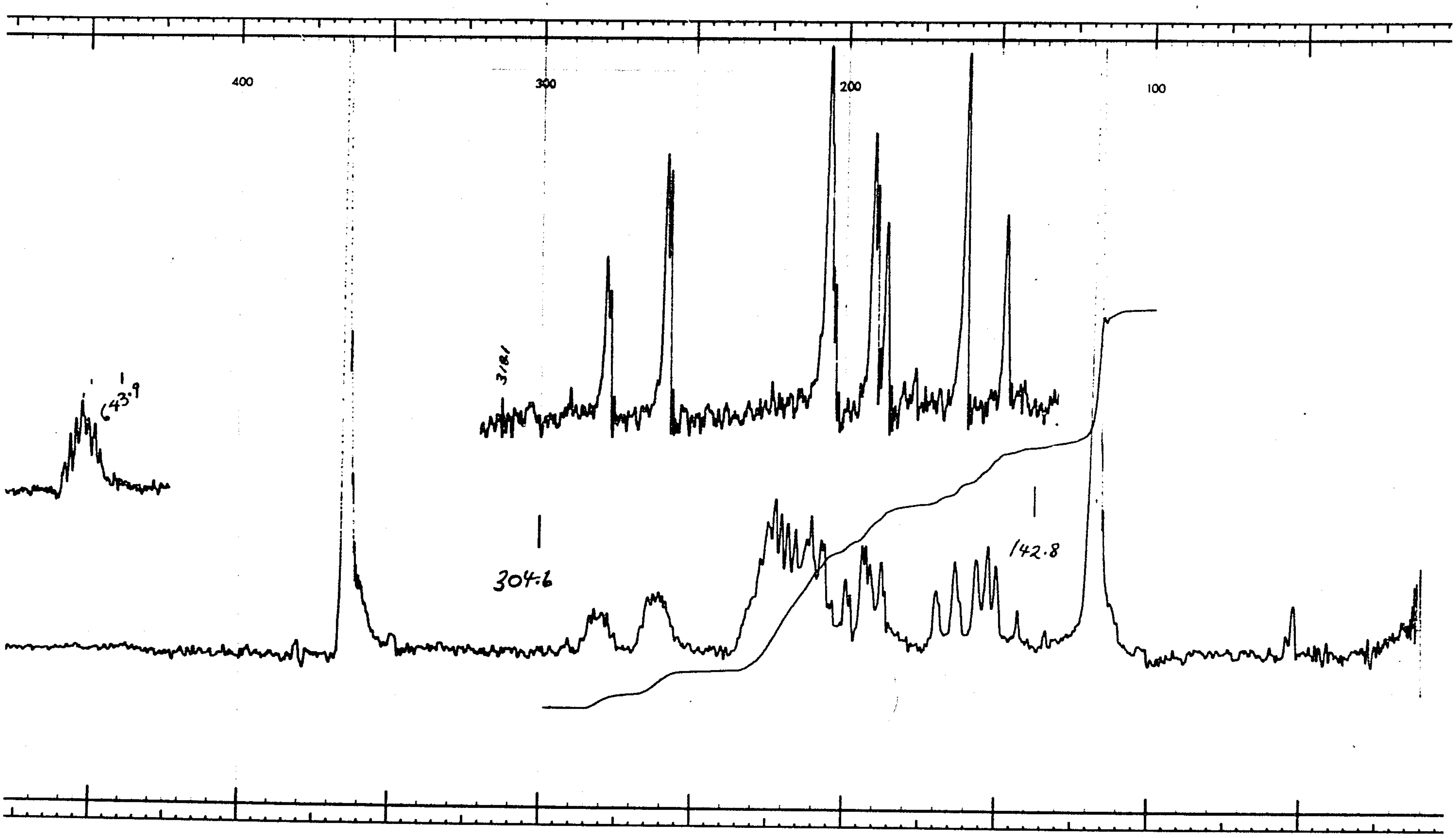


Figure 8. N.M.R. spectrum of compound XIV (R=CN) at 500 Hz sweep width. Insert-N.M.R. spectrum of protons H_A, H_B, H_C and H_D of 3,5,5'-trideutero-XIV at 500 Hz sweep width.

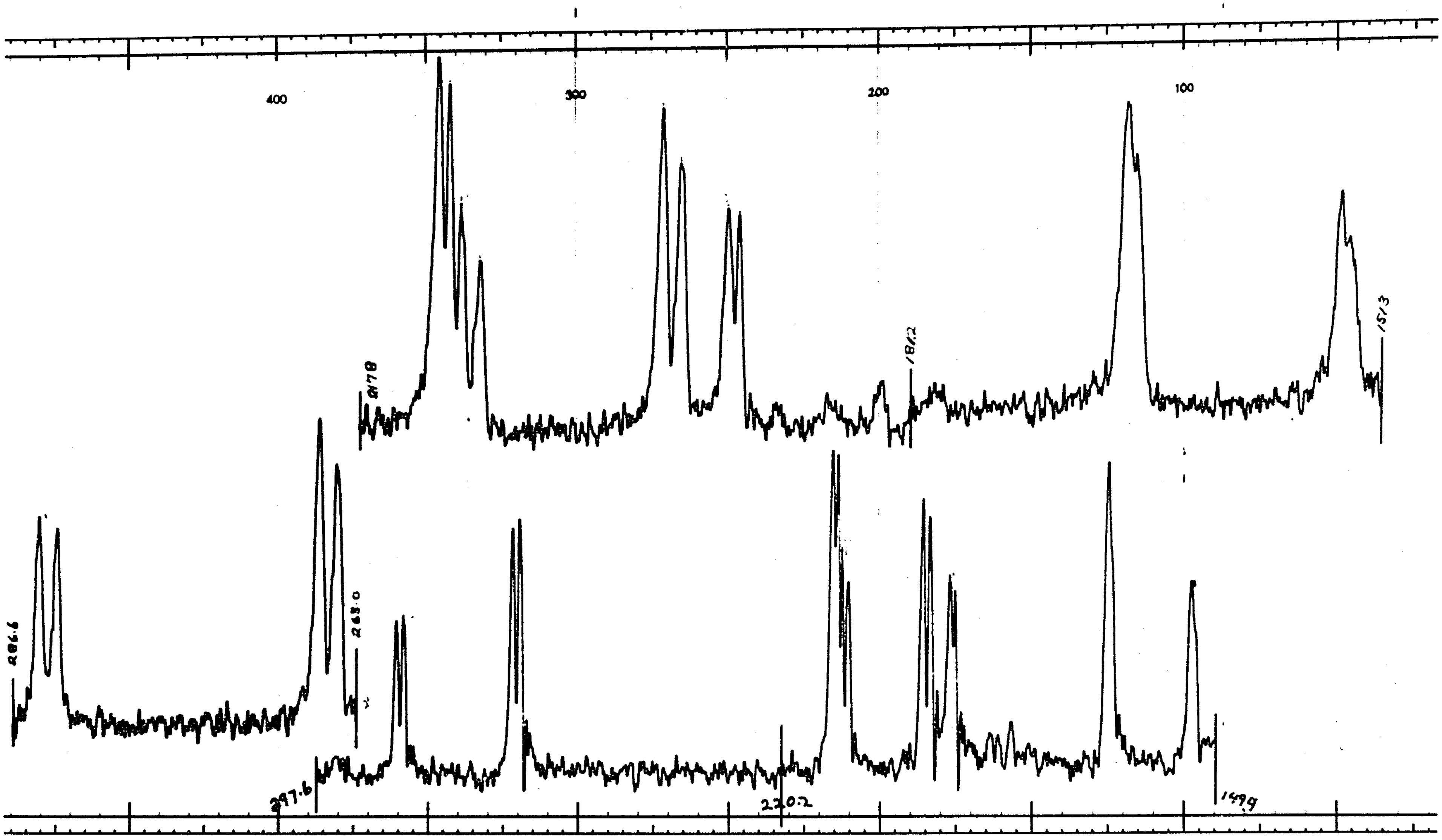
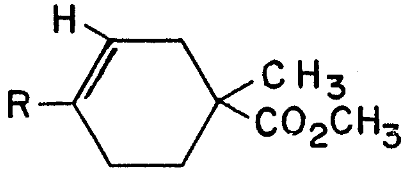
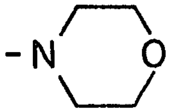


Figure 9. N.M.R. spectrum of the protons H_A, H_B, H_C and H_D of 3, 5, 5'-trideutero-XIV at 250 and 100 Hz sweep width.

TABLE I

Calculated and Experimental Chemical Shifts for the Olefinic Proton in



Compound	R	Z_{cis}[a]	τ_{cal}	τ_{exp}
IX	-Cl	0.18	4.20	4.28
X	$-OCOCH_3$	-0.35	4.73	4.73
XII	$-C_6H_5$	0.36	4.02	3.94
XIV	-CN	0.75	3.63	3.44
XVI	$-CO_2CH_3$	1.01	3.37	3.08
XVII	$-CONH_2$	0.98	3.42	3.39
XX	$-OCH_3$	-1.07	5.45	5.49
XXVI	$-SC_6H_5$	b		3.99
XVIII	 -N O	-1.26[c]	5.64	5.42

[a] Z_{cis} values from ref. 58.

[b] no value quoted.

[c] value for -N-R, R aliphatic.

expression may be written for the chemical shift of any olefinic proton:

$$\delta = \text{base value} + \sum_i Zi \qquad (4)$$

where Zi are the respective shielding increments for substituents Ri in the gem, cis and trans relationships to the proton. The base value is taken as the calculated value for ethylene, 5.25 δ , such that the shielding increment for H is zero. The equations for the substituted and unsubstituted cyclohexenes under study become:

$$\delta_{\text{parent}} = 5.25 + Z_{\text{gem}} + Z_{\text{trans}} + (Z_{\text{cis}} = 0) \qquad (5)$$

$$\delta_R = 5.25 + Z_{\text{gem}} + Z_{\text{trans}} + Z_{\text{cis}} \qquad (6)$$

however since $(Z_{\text{gem}} + Z_{\text{trans}})_{\text{parent}} = (Z_{\text{gem}} + Z_{\text{trans}})_R$ then

$$\delta_R = \delta_{\text{parent}} + Z_{\text{cis}} \qquad (7)$$

or

$$\tau_R = \tau_{\text{parent}} - Z_{\text{cis}} \qquad (8)$$

With $\tau_{\text{parent}} = 4.38$ and the Z_{cis} substituent increments of Sternhell, the chemical shifts of the olefinic proton of the substituted cyclohexenes may be calculated by equation (8) and compared to the experimental values. The agreement between calculated and experimental values (Table I) is very good*.

The chemical shifts of the other ring protons could not be extracted from the n.m.r. spectra of the non-deuterated

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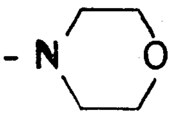
*Sternhell found that in 94% of the cases studied $\Delta\delta$ (or $\Delta\tau$) was within 0.3 ppm[58].

compounds. However, in the spectra of the cyclohexenes containing deuterium in the 3, 5, 5' positions, the remaining ring protons H_A, H_B, H_C and H_D of C_2 and C_6 appeared as two AB quartets from which the chemical shifts of the respective protons could be obtained by use of equation (1). The results are summarized in Table II.

TABLE II

Chemical Shifts of Protons H_A, H_B, H_C and H_D

Chemical Shifts (τ value)[a]

Compound	R	H_A	H_B	H_C	H_D
IX	-Cl	7.33	7.97	7.93	8.33
X	$-OCOCH_3$	7.38	7.97	7.95	8.30
XII	$-C_6H_5$	7.27	7.90	7.90	8.27
XIV	-CN	7.26	7.97	7.98	8.39
XVI	$-CO_2CH_3$	7.27	7.95	8.02	8.40
XVII	$-CONH_2$	7.27	7.95	7.97	8.37
XX	$-OCH_3$	7.41	8.04	7.97	8.34
XXIII	-H	7.46	8.14	8.07	8.44
XVIII		7.41	8.03	7.99	8.37

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[a] Chemical shifts were obtained from the spectra by use of equation (1). Spectra were recorded at 250 Hz sweep width with simultaneous irradiation at the deuterium decoupling frequency.

The chemical shifts of the two diastereotopic protons at C_2 (H_A and H_B) show a different sensitivity to the substituent R. The low field proton H_A, shows the larger variation with the slope or rho value of a τ versus σ_p plot being -0.134. Proton H_B has a rho value of -0.076*. The protons H_A and H_B have been tentatively assigned as being cis and trans to the carbomethoxy group at C_1 ‡. Proton H_A spends approximately 60% of the time in the pseudoequatorial position (conformer II, Figure 7). Protons H_C and H_D, also assigned as being cis and trans to the carbomethoxy group at C_1, show little substituent effect.

The line parameters of the Hammett relation, and in particular rho, should have some meaning. The magnitude of rho might be expected to vary systematically although such a variance was not observed in an extensive study of substituted benzylic systems[32]. It was concluded that rho values make no traditional sense. Apart from the fact that the majority of correlations do not satisfy the basic requirement of being precise (i.e. $r > 0.9$[31]) the theoretical significance of acceptable correlations is usually obscure. Indeed a large number of effects on or contributions to SCS (effect of substituents on the chemical shift) have been noted, e.g. conformation, solvent, anisotropy, charge density, ring currents, etc.

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[*] The correlation coefficient (r) and standard deviation (s) for the Hammett correlations are 0.641 and 0.067 for H_A and 0.455 and 0.062 for H_B. For a precise correlation r should be greater than 0.90[31]. However since ρ decreases as r decreases s is often more meaningful. Values of 0.067 and 0.062 indicate only a mediocre correlation. The sigma constants were taken from refs. 71 and 72.

[‡] This assignment will be further justified by long-range coupling constants. The equatorial proton in cyclohexene has been tentatively assigned to the low field position[51].

These effects have not been entirely identified or isolated. It would seem that in seeking a systematic variance of rho, such effects should not only be identifiable but also quantitatively separable.

The mechanism by which a substituent exerts its effect in benzylic systems is also a subject of some contention. It is usually assumed that the substituent alters the electron density of the aromatic ring by both inductive and resonance interactions and that this effect is relayed to the protons on the ring or in the side chain by polarization of the intervening sigma electrons[33]. An alternative explanation involving field and mesomeric effects has also been put forward[60].

Several explanations for limited sets of rho values have appeared[32]. In several series of para-substituted toluenes bearing different groups in the alpha position Hammett correlations between the chemical shift of the benzylic protons and the σ value of the para-substituent were interpreted as being based on the probable conformation of the benzylic protons with respect to the aromatic ring. It was suggested that ρ is a conformationally dependent parameter and that substituent effects are maximal when the benzylic C-H bond is colinear with the adjacent pi-orbital and minimal when perpendicular to it. This explanation accounted for the observed effects in para-substituted benzyl phenyl sulphoxides where the benzylic protons are diastereotopic and show a different sensitivity to the para-substituent (rho valuesof -0.20 and +0.01 were observed). A hyperconjugative interaction between the benzylic protons and the pi-system of the aromatic ring was suggested as being responsible for the variations in chemical shifts[33].

In the allylic system under study, such an explanation should give a larger SCS with the proton trans to the carbomethoxy group which is axial 60% of the time (assigned the high field proton, H_B) and better disposed for pi-orbital overlap then the proton cis to the carbomethoxy group (assigned the low field proton, H_A). However, this is opposite to the observed effects. It appears that other factors must dominate in this case at least.

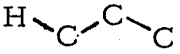
It is generally agreed that the p.m.r. chemical shifts at any point in a molecule are in some sense related to the rest of the molecule and its environment. In the parent compound, XXIII, the chemical shift difference between H_A-H_B and H_C-H_D are 0.68 and 0.37 τ respectively. The difference in the chemical shift of axial-equatorial protons in cyclohexene has been estimated as 0.4 ± 0.03 τ [51]. It appears that the net effect of the methyl and carbomethoxy groups at C_1 on the chemical shift difference of H_C-H_D is negligible. Assuming that the net effect is also negligible on H_A-H_B, the chemical shift difference of the pseudoaxial-pseudoequatorial protons may be estimated as 0.7 τ.

The ring protons of the non-deuterated compounds appear to be extensively coupled to each other giving rise to a complex spectrum (Figure 8). The low field half of the H_AH_B AB quartet is shifted to lower field than the other ring protons but appears as very broad adsorptions. The H_AH_B protons are probably coupled to the olefinic proton, the allylic protons at C_5 (homoallylic coupling) and the homoallylic protons at C_6 (long-range coupling). The olefinic proton appears to be a triplet of triplets (Figure 8) being coupled more or less equally to each of the protons at C_2 and C_5 respectively as a result of time averaging. The protons at C_5 will also be coupled to those at C_6 (vicinal coupling).

When the 3, 5, 5'-trideutero derivatives are irradiated at the deuterium decoupling frequency the two geminal couplings J_{AB} and J_{CD} and the two long-range couplings between $H_A H_B$ and $H_C H_D$ are readily obtained from the four proton spectrum.

The magnitude of coupling over four single bonds has been shown to depend on the conformation taken up by the bonds between the interacting nuclei and is given by the equation:

$$ {}^{4}J_{HH} = \cos^2\phi_1 + \cos^2\phi_2 - 0.8\ \text{Hz} \qquad (9) $$

where ϕ_1 and ϕ_2 are the two  dihedral angles. The maximum positive coupling is always found to exist between protons in a coplanar **W** arrangement[1]. In the cyclohexene system under study the pseudoequatorial and equatorial protons H_A and H_C in conformation II appear to adopt this arrangement.

In the spectra of these substituted cyclohexenes the low field protons ($H_A H_C$) and the high field protons ($H_B H_D$) of the two AB patterns appear to be coupled to each other (Figure 8). The magnitude of the couplings are 1.2 and 0.8 Hz* respectively. The results for the series are presented in Table III. On this basis H_A and H_C are assigned as being <u>cis</u> to the carbomethoxy group (i.e. in the pseudoequatorial position 60% of the time).

In a cyclic system rapidly inverting, the coupling constants as well as the chemical shifts are time averaged. If the

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* ${}^{4}J_{AC}$ and ${}^{4}J_{BD}$ are the averages for all nine compounds.

mole fraction of the two conformers in Figure 7 are (1-x) and x respectively, then it follows that:

$$\langle {}^{4}J_{AC} \rangle = xJee'_{II} + (1-x)\,Jaa'_{I} = 1.2 \text{ Hz} \qquad (10)$$

$$\langle {}^{4}J_{BD} \rangle = (1-x)Jee'_{I} + xJaa'_{II} = 0.8 \text{ Hz} \qquad (11)$$

Assuming that $Jee'_{I} = Jee'_{II}$ and $Jaa'_{I} = Jaa'_{II}$ and x and (1-x) are 0.6 and 0.4 respectively (from thc estimated free energy differences), then Jee' may be calculated as 2.0 Hz and Jaa' as 0.0 Hz. These values are in reasonable agreement with the theoretical values of +1.2 Hz and -0.2 Hz for Jee' and Jaa' respectively[1]. The value of +1.2 Hz for Jee' as calculated by equation (9) is probably too small. Indeed, enhanced values of Jee' (and Jee in saturated systems) have been noted in several compounds[61].

Theoretical couplings between J_{AD} and J_{BC} are predicted by equation (9) and time averaging effects to be approximately 0.5 Hz (Je'a and Ja'e are calculated as 0.6 and 0.4 Hz respectively). In addition coupling over four bonds has been shown to be important in compounds containing tertiary methyl groups. The coupling is maximal for an axial methyl group where the **W** rule is followed to a greater extent than for an equatorial methyl group. The magnitude of the coupling to H_A and H_C may be estimated as $0.6 \left\{1/3(Jaa+2Jea)\right\} + 0.4 \left\{1/3(Jee + 2Jea)\right\}$ or approximately +0.4 Hz. Similarly the magnitude of the coupling to H_B and H_D may be estimated as $0.6 \left\{1/3(Jaa + 2Jea)\right\} +0.4 \left\{1/3(Jaa + 2Jea)\right\}$ or approximately +0.2 Hz. Due to this type of coupling line widths at half height (W_H) are generally significantly greater for axial methyl resonances[62-64].

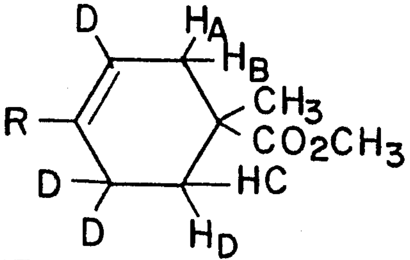
The spectra were not recorded with sufficient precision to accurately determine couplings equal to or less than 0.5 Hz. In view of the uncertainties in obtaining complete deuterium decoupling, such experiments were not attempted. However, the presence of these smaller long-range couplings cannot be denied.

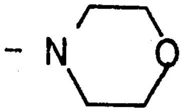
The geminal coupling constants J_{AB} and J_{CD} are presented in Table III. It can be seen that J_{CD} shows very little substituent effect as predicted by theory[18,19]. However J_{AB} shows a 3 Hz variation in going from R = OCH_3 to R = CN the value of $|J|$ going from 16.4 Hz to 19.3 Hz. Assuming that the contributions to J_{CD} from the <u>beta</u> carbomethoxy and <u>beta</u> methyl groups are the same to J_{AB} then the contribution of the pi-bond to J_{AB} may be estimated as 17.5 - 13.2 or 4.3 Hz from compound XXIII. The HH axis of $H_A H_B$ is inclined at an angle of about 80° to the plane of the double bond (or 10° from colinearity with the pi-orbital of the double bond) in both conformation I and II as shown in Figure 6, almost the condition for maximum hyperconjugative interaction. The observed value of J_{AB} agrees well with theory which predicts a contribution to $|J|$ of about 4.5 Hz[14,15,17,25].

In certain examples in the literature which approximate the cyclohexene system under study, the values of $|J|$ for the allylic protons were found to range from 17 to 19 Hz[65-68]. It is interesting to note that for a cyclohexene ring locked in a boat conformation by <u>trans</u> fusion, $|J|$ for the allylic protons was found to be 15.0 to 15.1 Hz for three examples[69]. This supports the assumption that only the half-chair conformation of the substituted cyclohexene need be considered in this study.

TABLE III

Coupling Constants (Hz) for



Compound	R	$-J_{AB}$[a]	$-J_{CD}$[a]	J_{AC}[b]	J_{BD}[b]
IX	-Cl	17.4	13.3	1.24	0.88
X	$-OCOCH_3$	17.3	13.3	1.07	0.87
XII	$-C_6H_5$	18.1	13.2	1.11	0.92
XIV	-CN	19.3	13.4	1.23	0.73
XVI	$-CO_2CH_3$	19.2	13.3	1.11	0.85
XVII	$-CONH_2$	18.8	13.4	1.20	0.79
XX	$-OCH_3$	16.4	13.2	1.25	0.79
XXIII	-H	17.5	13.2	1.06	0.84
XXVI	$-SC_6H_5$	17.2	-	-	-
XVIII		16.8	13.0	1.17	0.86

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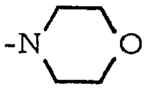
[a] J_{AB} and J_{CD} were measured from both the low and high field halfs of the AB quartet. Values are the average of at least twelve measurements. Spectra were recorded at 250 Hz sweep width. Maximum uncertainty is ±0.1 Hz (except $-SC_6H_5$ ± 0.2 Hz).

[b] J_{AC} and J_{BD} are the average of at least ten measurements. Spectra were recorded at 100 Hz sweep width. Maximum uncertainty is ±0.07 Hz.

The substituent effect of R on J_{AB} is clearly evident in Table III. A plot of J_{AB} versus σ_p (Figure 10) gave the results in row one of Table IV. The correlation cannot be termed precise. A slightly better correlation can be obtained by dropping the point for the enamine (compound XVIII) for which σ_p is not definitely known (σ_p for $-N(CH_3)_2$ was used as an approximate value for the morpholino group, but even this value is not precisely known nor does the substituent give consistent behaviour[31, 71]).

Both field effects (pure field and inductive effects) and resonance effects are assumed to contribute to the substituent effect on J_{AB}. All the substituents R exhibit electron-withdrawing ability for their field effects (-I groups) and should lead to enhanced J_{AB} values. Some of the substituents exhibit electron-withdrawing ability for their resonance effects (-R groups), others exhibit electron-donating ability (+R groups). The -R groups include $-C\equiv N$, $-CO_2CH_3$, $-CONH_2$. The +R groups include $-OCH_3$, $-OCOCH_3$, -Cl,  , $-C_6H_5$ and $-SC_6H_5$[70]. The resonance interactions of these groups are represented in Figure 11. From Figure 11 it might be expected that -R groups should give enhanced values of J_{AB} as a result of increased electron withdrawal from the antisymmetric CH_2 orbital. On the other hand, +R groups should give decreased values of J_{AB} as a result of electron donation to the antisymmetric CH_2 orbital. These differing resonance effects may be one factor leading to the scatter in the points.

One of the problems that arises is the relative importance of resonance effects to non-resonance effects. Similar situations have led to the great abundance of alternate sets of σ values that

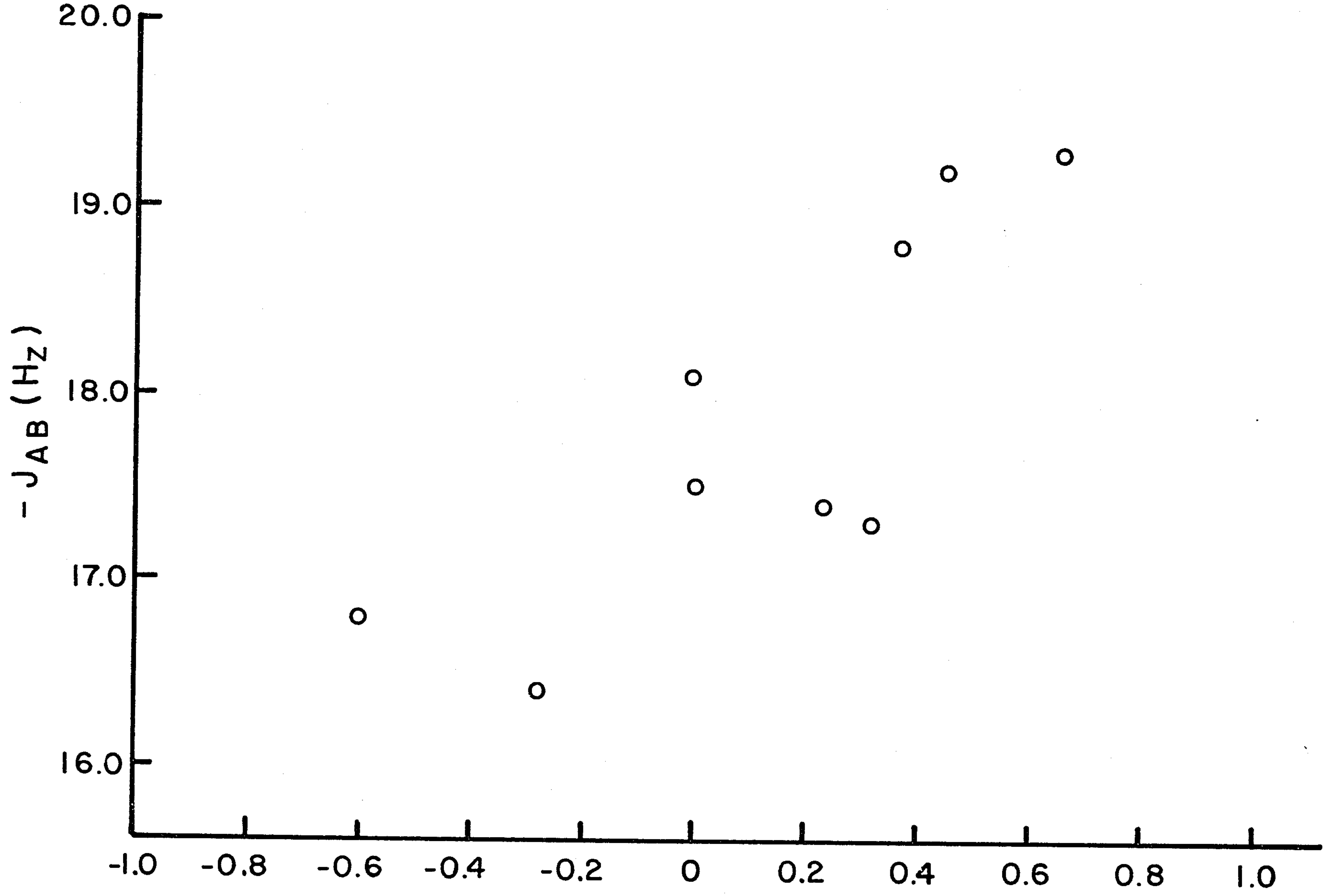
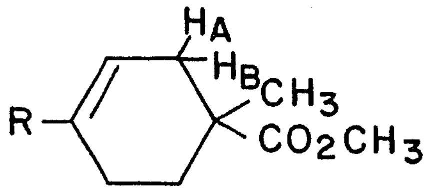


Figure 10. Plot of J_{AB} versus σ_p, the Hammett substituent constant.

TABLE IV

Rho Values for Hammett Plots for



	ρ^a	r^a	s^a	n^b
σ_p^c	2.2	0.811	0.653	9
σ_p^d	2.9	0.823	0.632	8
$(F + R)^e$	1.8	0.710	0.816	7
(F + 9R)	0.45	0.905	0.492	7
(F + 9.4R)	0.43	0.906	0.492	7
(F + 9.6R)	0.42	0.905	0.492	7
(F + 10R)	0.37	0.903	0.497	7

[a] ρ, r and s represent the slope in ppm/σ, the correlation coefficient and the standard deviation as derived from a least squares treatment of the data[31].

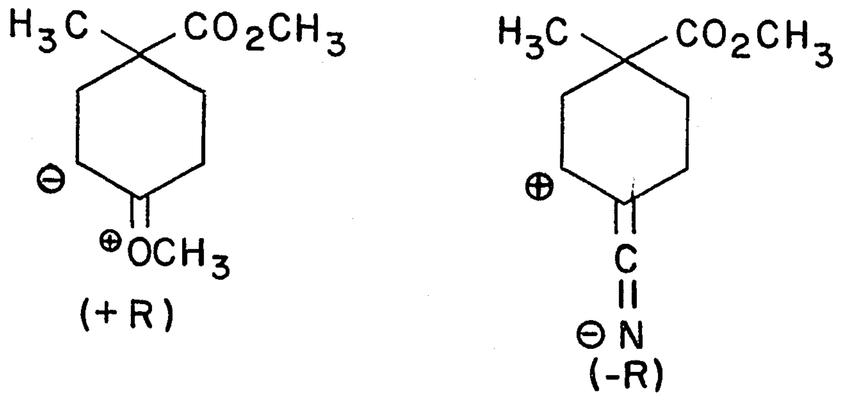
[b] n is the number of compounds used in the plot.

[c] σ_p values from McDaniel and Brown[71]. σ_p for $-CONH_2$ from Charton[72]. σ_p for $-N\bigcirc O$ taken as the value for $-N(CH_3)_2$ from Jaffe[31]. No σ_p value reported for $-SC_6H_5$.

[d] The point for the morpholino group left out.

[e] F and R values from Swain and Lupton[73]. Values used for CO_2CH_3 are the values for $CO_2CH_2CH_3$. No values quoted for $-CONH_2$, $-N\bigcirc O$ or $-SC_6H_5$.

Figure 11. Resonance interactions of +R and -R groups in the cyclohexene system.



emphasize non-resonance capability, resonance capability or some mixture of both for a particular system. This condition comes from the fact that the σ_p and σ_m values do not resolve the observed effects into their basic field and resonance effects*. In the cyclohexene system under study where a hyperconjugative interaction is predominately responsible for the effects on J_{AB}, it might be expected that resonance effects are more important than field effects.

Swain and Lupton[73] have attempted to resolve field effects and resonance effects for any given substituent, the σ constant for the substituent being written as:

$$\sigma = fF + rR \tag{12}$$

where F and R are field and resonance effects different for each substituent and f and r are empirical sensitivities or weighting factors independent of substituent but different for each set of

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* σ_m and σ_p have been calculated as being 53% and 22% sensitive to field effects respectively[73].

substituent constants. It was assumed that all substituent constants for a given substituent R may be written as a linear combination of any two others for the same substituent.

The Hammett equation correlating J and σ may be written as

$$J = \rho^{1}(F + \alpha R) \qquad (13)$$

where σ has been resolved into Field and Resonance effects, F and R respectively. The slope or rho value is now equal to ρ^{1}. The results of plotting J_{AB} versus (F + αR) for various values of α are shown in Table IV. The correlation coefficient reaches a maximum value when α is 9.4 clearly indicating the dominance of resonance effects over inductive effects in this system.

As was mentioned earlier, it has been proposed that ρ is conformationally dependent and should be proportional to $\cos^{2}\phi$ [24], where ϕ is the dihedral angle between the HH axis and the adjacent pi-orbital. In benzylic systems where the dominant conformation has been proposed as having ϕ equal to 0° (the condition for maximum hyperconjugative interaction) a large negative slope or rho value was observed (ρ varied from -1.4 to -1.9 for five systems studied)[24, 28, 29, 30]. Where the dominant conformation has been proposed as having ϕ equal to 90° a rho value of zero was observed[24, 30]. The variation in rho values for ϕ equal to 0° have been attributed mainly to deviations from planarity (i.e. ϕ is not exactly 0°). Other effects due to changes in internal bond angles or bond hybridizations resulting from a change in the electronegativity of the atom attached to the CH_2 group are small. Similarly changes in J due to solvent effects are small and the solvent effect on ρ negligible[30].

In plotting J_{AB} versus σ_p a rho value of -2.9 was obtained with a correlation coefficient of 0.823 (row 2 Table IV). Although no such correlations have been carried out in allylic systems, the large negative rho value is in qualitative agreement with those found in benzylic systems. Since the pi-electrons of a double bond are more easily perturbed than the pi-system in an aromatic ring, substituent effects should be larger. The substituent effects on J in the allylic case are approximately twice those in the benzylic case where the systems are of similar geometry. This could account for the rho value of -2.9 as compared to rho values of approximately -1.7.

Although this is the first such study in an allylic system, the results agree qualitatively with the conformational dependence of ρ proposed for the benzylic systems. In freely rotating systems ρ offers the potential ability to determine the time average of all existing conformations and to provide an indication of the predominant conformation. Further studies on allylic systems are obviously required.

EXPERIMENTAL

All boiling and melting points are uncorrected. The precise n.m.r. spectra were recorded on a Varian HA-100 spectrometer equipped with an N.M.R. Specialties SD-100 Decoupler. A Varian T-60 spectrometer was used for routine spectral measurements. All n.m.r. spectra, unless otherwise noted, were taken as 0.1M solutions in deutereochloroform. The peak positions are recorded in parts per million relative to T.M.S. using the τ scale. The I.R. spectra were measured using a Beckman I.R.-20 spectrometer. The I.R. spectra of solid compounds were taken as potassium bromide dispersions. All I.R. spectra of liquids were taken neat. The absorptions are recorded in units of cm^{-1}. The mass spectral analyses were performed using an Hitachi-Perkin-Elmer RMU-6Dspectrometer. Microanalyses were carried out at Scandinavian Mikroanalytical Laboratory, Herlev, Denmark.

γ-Acetyl-γ-Methylpimelonitrile (I)[74]

Cyanoethylation of 192 g (2.64 mole) of methyl ethyl ketone with 212 g (4.0 mole) of acrylonitrile according to the procedure of Bruson and Riener[74] gave 320 g (90%) of I. After recrystallization from benzene the product melted at 66°-67°. [Lit. m.p. 67° [74]].

γ-Acetyl-γ-Methylpimelic Acid (II)[74]

Alkaline hydrolysis of 100 g (0.58 mole) of I gave after recrystallization from ethylene dichloride 97 g (80%) of II, m.p. 123°-124°. [Lit. m.p. 125° [74]].

γ-Methyl-γ-Carboxypimelic Acid (III)[74]

In a 2 litre flask equipped with a dropping funnel and a mechanical stirrer were placed 160 g (4 mole) of sodium hydroxide and 800 ml of water. The flask was cooled in an ice/water bath. Then 191.8 g (1.2 mole) of bromine was added dropwise to the stirred solution at such a rate that the temperature did not exceed 10°. Next 86.4 g (0.4 mole) of II dissolved in a 30% solution of dioxane in water was added slowly keeping the temperature below 10°. Following the addition, the mixture was stirred for an additional hr and allowed to come to room temperature. The mixture was concentrated to a small volume. Sodium metabisulfite (20 g) was added to destroy excess oxidizing agent and the mixture acidified with 50% hydrochloric acid. After evaporating the mixture to dryness, the residue was extracted with hot acetone. Removal of the acetone left a viscous syrup which crystallized on chilling. The product was recrystallized from nitromethane to give 60 g (69%) of III, m.p. 110°-111°. [Lit. m.p. 111° [74]].

Ethyl-γ-Methyl-γ-Carbethoxypimelate (IV)[45]

Esterification of 109 g (0.5 mole) of III by heating with 230 g of 99% ethanol, 400 ml of dry benzene and 30 ml of concentrated sulphuric acid for 30 hr gave 118 g (78%) of IV, b.p. 141°-143° (0.25 mm). [Lit. b.p. 128°-131° (0.1 mm)[45]].

Ethyl 1-Methyl-3-Carbethoxy-4-ketocyclohexanecarboxylate (V)[45]

Dieckmann cyclization[45, 74] of 100 g (0.33 mole) of IV gave 76 g (89%) of V, b.p. 105°-109° (0.1 mm). [Lit. b.p. 125°-130° (0.2 mm)[45]].

Ethyl 1-Methyl-4-Ketocyclohexanecarboxylate (VI)

A mixture of 20 g (78 mmole) of V, 400 ml of glacial acetic acid, 10 ml of concentrated hydrochloric acid and 6 ml of water were refluxed for 8 hr. Distillation at atmospheric pressure left the product as a residue which on distillation under reduced pressure gave 12 g (83%) of VI. b.p. 70°-73° (0.1 mm).

I.R.: 1720 (ester C=O and ketone).
N.M.R. (100 MHz): 5.79 quartet (2H), 2.7-8.5 (8H),
8.72 singlet, 8.73 triplet (total 6H).
Mass Spec.: m/e 184.

If the reaction was carried out in 40 ml of glacial acetic acid (other quantities remaining unchanged) 1-methyl-4-ketocyclohexanecarboxylic acid was obtained as the product. The acid on distillation crystallized rapidly in the receiver, b.p. 130°-135° (0.05 mm)[45].

1-Methyl-4-Ketocyclohexanecarboxylic Acid (VII)[45]

Alkaline hydrolysis of 12 g (69 mmole) of VI gave after recrystallization from benzene/petroleum ether (30°-60°), 9.3 g (86%) of VII, m.p. 77.5°-79°. [Lit. m.p. 78°-79° [45]].

Methyl 1-Methyl-4-Ketocyclohexanecarboxylate (VIII)[45]

Method A

Esterification of 2.1 g (14 mmole) of VII using methanol and concentrated sulphuric acid gave, after bulb to bulb distillation, 2 g (85%) of VIII, b.p. 53°-57° (0.08 mm). [Lit. b.p. 80°-83° (0.2 mm)[45]].

Method B

A mixture of 1.0 g (6.4 mmole) of VII, 2.1 g of silver oxide and 30 ml of anhydrous ether was stirred and heated to reflux. Excess methyl iodide was added and refluxing continued for 2 hr. The mixture was cooled, filtered and the ether removed under vacuum. Bulb to bulb distillation gave 1 g (90%) of VIII.

Methyl 1-Methyl-4-Chlorocyclohex-3-ene-1-Carboxylate (IX)

Treatment of 2.6 g (15 mmole) of VIII with 3.3 g (16 mmole) of phosphorus pentachloride according to the procedure of Braude and Coles[76] gave the desired vinyl chloride along with a compound tentatively identified by mass spectral analysis as methyl 1-methyl-4, 4'-dichlorocyclohexanecarboxylate. These compounds were not separable by distillation or by chromatography on silica.

The mixture was then treated with sodium methoxide in dimethylsulfoxide at 40°-50° for approximately 3 hr, poured into dilute acid and extracted several times with pentane. The combined pentane fractions were washed with water and dried over anhydrous magnesium sulphate. The pentane was removed under vacuum and the residue chromatographed on silica using cyclohexane-ethyl acetate (7:3) as eluant. Bulb to bulb distillation gave 0.8 g (27%) of IX, b.p. 33°-35° (0.06 mm).

Anal. Calcd. for $C_9H_{13}O_2Cl$: C, 57.30; H, 6.95; Cl, 18.79.
Found: C, 57.60; H, 6.97; Cl, 19.01.
I.R.: 1720 (ester C=O), 1648 (C=C).

N.M.R. (100 MHz): 4.28 multiplet (1H), 6.33 singlet
(3H), 7.1-8.6 (6H), 8.79 single (3H).
Mass Spec.: m/e 188, 190.

Methyl 1-Methyl-4-Acetoxycyclohex-3-ene-1-Carboxylate (X)

The enol acetate was prepared according to the general procedure of Barton[77] as outlined in Fieser and Fieser[78].

A mixture of 1.8 g (11 mmole) of VIII, 60 ml of carbon tetrachloride, 8.5 ml acetic anhydride and 5 drops of perchloric acid (70%) was stirred at room temperature for 3.5 hr. The resulting dark coloured solution was treated with decolourizing carbon, filtered, and the solvent removed under vacuum. The crude product was chromatographed on silica using cyclohexane-ethyl acetate (7:3) as eluant. Bulb to bulb distillation gave 1.7 g (73%) of X, b.p. 63°-65° (0.06 mm).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.24, H, 7.59.
Found: C, 62.26; H, 7.63.
I.R.: 1748 (acetate C=O), 1725 (ester C=O), 1690 (C=C).
N.M.R. (100 MHz): 4.73 multiplet (1H), 6.33 single (3H),
7.91 singlet, 7.1-8.6 (total 9H),
8.75 singlet (3H).
Mass Spec.: m/e 212.

Methyl 1-Methyl-4-Hydroxy-4-Phenylcyclohexanecarboxylate (XI)

Phenyl magnesium bromide was prepared from 0.4 g (16 mmole) of magnesium and 2.6 g of bromobenzene in 25 ml of anhydrous ether.

In a 250 ml 3-necked flask equipped with a nitrogen inlet and a condenser protected by a calcium chloride tube was placed 1.2 g (7.7 mmole) of VII dissolved in 100 ml anhydrous ether. The Grignard reagent prepared above was added dropwise by means of a syringe to the rapidly stirred solution. After refluxing for 8 hr, dilute sulphuric acid was added, the ether layer separated and the aqueous layer extracted several times with ether. The combined ether extracts were washed with 5% sodium hydroxide solution. The aqueous layer was carefully acidified with dilute hydrochloric acid and extracted with chloroform. Evaporation of the chloroform left a thick viscous residue which was taken up in ether and treated with an ethereal solution of diazomethane. After 4 hr the ether was removed under vacuum and the residue distilled bulb to bulb to give 440 mg (23%) of XI, b.p. 96°-105° (0.05 mm).

I.R.: 3500 (-OH), 1725, 1710 (ester C=O), 755, 698 (monosubstituted benzene).

N.M.R. (100 MHz): 2.6 multiplet (5H), 6.31 singlet (3H), 7.6-8.6 (9H), 8.75, 8.77 singlets (total 3H), D_2O exchange 7.6-8.6 (8H).

Methyl 1-Methyl-4-Phenylcyclohex-3-ene-1-Carboxylate (XII)

The dehydration of XI was effected using the procedure of Sarett[79].

To 230 mg (0.93 mmole) of XI dissolved in 4 ml of pyridine (dried over sodium hydroxide) was added 0.25 ml of phosphorus oxychloride. The mixture was refluxed for 3 hr, cooled and poured into cold, dilute hydrochloric acid and extracted several times with ether. After washing with dilute acid, water and drying over anhydrous magnesium sulphate the ether was removed under vacuum. The residue was chromatographed on silica using cyclohexane-ethyl acetate (7:3) as eluant. Bulb to bulb distillation gave 151 mg (74%) of XII, b.p. 76°-80° (0.06 mm).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.22; H, 7.89.
Found: C, 78.30; H, 7.93.
I.R.: 1726 (ester C=O), 1640 (C=C), 755, 692 (mono-substituted benzene).
N.M.R. (100 MHz): 2.7 multiplet (5H), 3.94 multiplet (1H), 6.33 singlet (3H), 6.9-8.5 (6H), 8.75 singlet (3H).
Mass Spec.: m/e 230.

Methyl 1-Methyl-4-Cyano-4-Hydroxycyclohexanecarboxylate (XIII)

In a 100 ml stoppered flask were placed 2.0 g (12 mmole) of VIII, 30 ml of dry methanol and 2.3 g of potassium cyanide. The mixture was stirred and cooled to 0°-5° in an ice/water bath. Then 14 ml of glacial acetic acid was added dropwise over a period of 20 min. After standing at 0°-5° for an additional 2 hr, the mixture was poured into excess sodium bicarbonate solution and extracted several times with ether. The combined ether extracts were washed once with water and dried over anhydrous magnesium sulphate. After removing the ether under vacuum the residue was distilled bulb to bulb to give 1.9 g (80%) of XIII, b.p. 90°-96° (0.08 mm).

I.R.: 3430 (-OH), 2220 ($-C\equiv N$), 1725, 1708 (ester C=O)
N.M.R. (100 MHz): 6.31 singlet (3H), 6.8-8.5 (9H), 8.79, 8.81 singlets (total 3H). D_2O exchange 6.8-8.5 (8H).

Methyl 1-Methyl-4-Cyanocyclohex-3-ene-1-Carboxylate (XIV)

Dehydration of 1.1 g (5.6 mmole) of XIII was performed in the usual fashion[79] in 10 ml of pyridine (dried over sodium hydroxide) with 1.2 ml of phosphorus oxychloride. Following workup and chromatography on silica using cyclohexane-ethyl acetate (7:3) as eluant, bulb to bulb distillation gave 750 mg (75%) of XIV, b.p. 53°-55° (0.08 mm).

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.04; H, 7.31; N, 7.81.
Found: C, 67.09; H, 7.31; N, 7.80.
I.R.: 2200 ($-C\equiv N$), 1722 (ester C=O), 1635 (C=C).
N.M.R. (100 MHz): 3.44 multiplet (1H), 6.31 singlet (3H), 7.1-8.6 (6H), 8.78 singlet(3H).
Mass Spec.: m/e 179.

1-Methylcyclohex-3-ene-1,4-Dicarboxylic Acid (XV)

A solution of 550 mg (3 mmole) of XIV in 20 ml of 1N sodium hydroxide was refluxed for 4 hr. After cooling and acidification with hydrochloric acid, the product precipitated out of solution and was filtered off. After air drying and recrystallization from acetone, 420 mg (76%) of XV was obtained m.p. 247°-249°.

I.R.: 3500-2200 very broad (-OH), 1670 broad (C=O), 1640 (C=C).
N.M.R. (trifluoroacetic acid, 100 MHz): 2.68 multiplet (1H), 6.8-8.4 (6H), 8.64 singlet (3H).

Dimethyl 1-Methylcyclohex-3-ene-1,4-Dicarboxylate (XVI)

A mixture of 300 mg (1.6 mmole) of XV, 1.6 g of silver oxide and 30 ml of 1,2-dimethoxyethane was stirred and

and heated at 45°-50°. Excess methyl iodide was added and heating continued for 3 hr. The mixture was cooled, filtered and the solvent removed under vacuum. After chromatography on silica using cyclohexane-ethyl acetate (8:2) as eluant, bulb to bulb distillation gave 280 mg (83%) of XVI, b.p. 61°-63° (0.06 mm).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.24; H, 7.59.
Found: C, 62.19; H, 7.62.
I.R.: 1712 (ester C=O), 1640 (C=C).
N.M.R. (100 MHz): 3.08 multiplet (1H), 6.29 singlet (3H), 6.34 singlet (3H), 7.1-8.6 (6H), 8.79 singlet (3H).
Mass Spec.: m/e 212.

Methyl 1-Methyl-4-Carboxamidocyclohex-3-ene-1-Carboxylate (XVII)

A mixture of 165 mg (0.92 mmole) of XIV in 10 ml of 1N sodium hydroxide containing 15 ml of 30% hydrogen peroxide (w/v) was stirred at 30° for 10 min. The alkaline solution was extracted with chloroform. The chloroform extracts were washed once with water and filtered through anhydrous magnesium sulphate. Removal of the chloroform under vacuum left a white solid which after two recrystallizations from carbon tetrachloride weighed 78 mg (43%) and melted at 120°-121°.

Anal. Calcd. for $C_{10}H_{15}O_3N$: C, 60.87; H, 7.69, N, 7.11.
Found: C, 60.95; H, 7.63; N, 7.10.
I.R.: 3365, 3160 (N-H), 1710 (ester C=O), 1665 (amide C=O), 1638 (C=C), 1600 (N-H).
N.M.R. (100 MHz): 3.42 multiplet (1H), 4.5 broad (2H), 6.34 singlet (3H), 7.0-8.6 (6H), 8.78 singlet (3H).
Mass Spec.: m/e 197.

Methyl 1-Methyl-4-(1'-Morpholino)-Cyclohex-3-ene-1-Carboxylate (XVIII)

The enamine was prepared according to the general procedure described in "Advances in Organic Chemistry".[80]

A solution of 300 mg (1.7 mmole) of VIII in 20 ml of benzene was treated with a 10 fold excess of morpholine. To this was added a catalytic amount of p-toluenesulphonic acid. The mixture was refluxed for 8 hr in a Soxhlet extractor containing calcium carbide. The solvents were removed under vacuum and the residue distilled bulb to bulb to give a 70-80% yield of XVIII, b.p. 85°-90° (0.08 mm). The product contained a small amount of unreacted ketone and rapidly underwent hydrolysis to the ketone on exposure to the atmosphere. For this reason analysis was not attempted.

I.R.: 1720 (ester (C=O), 1638 (C=C).
N.M.R. (100 MHz): 5.42 multiplet (1H), 6.30 triplet,
6.34 singlet (total 7H), 7.24 triplet,
7.2-8.6 (total 10H), 8.81 singlet (3H).
Mass Spec.: m/e 239.

Methyl 1-Methyl-4,4'-Dimethoxycyclohexanecarboxylate (XIX)

To 284 mg (1.7 mmole) of VIII in 20 ml of dry methanol was added 2 ml of glacial acetic acid. After standing overnight at room temperature, the mixture was added dropwise to a rapidly stirred solution of sodium bicarbonate. The aqueous solution was extracted with chloroform, the chloroform removed under vacuum and the residue chromatographed on alumina (activity I) using cyclohexane-ethyl acetate (9:1) as eluant. Bulb to bulb distillation gave 268 mg (77%) of XIX, b.p. 45°-50° (0.08 mm).

I.R.: 1715 (ester C=O).

N.M.R. (100 MHz): 6.32 singlet (3H), 6.84 singlet,
6.86 singlet (total 6H), 7.7-8.7 (6H),
8.83 singlet (3H).

Methyl 1-Methyl-4-Methoxycyclohex-3-ene-1-Carboxylate (XX)

The ketal XIX was converted to the enol ether XX using the procedure described by Eppenberger[81].

To 200 mg (0.92 mmole) of XIX dissolved in 1 ml of pyridine (dried over sodium hydroxide) was added 0.18 ml of phosphorus oxychloride. The mixture was refluxed for 2 hr. The temperature was then raised to 140°-150° whereupon the volatile components were distilled off. After cooling, the dark coloured residue was added dropwise to a solution of sodium bicarbonate. After extraction with chloroform and removal of the chloroform under vacuum the residue was chromatographed on alumina (activity 1) using cyclohexane-ethyl acetate (9:1) as eluant. Bulb to bulb distillation gave 110 mg (65%) of XX, b.p. 80°-85° (5 mm).

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.25; H, 8.69.
Found: C, 65.07; H, 8.70.

I.R.: 1715 (ester C=O), 1655 (C=C).

N.M.R. (100 MHz): 5.49 multiplet (1H), 6.35 singlet (3H),
6.53 singlet (3H), 7.2-8.6 (6H), 8.80
singlet (3H).

Mass Spec.: m/e 184.

Methyl 1-Methyl-4-Hydroxycyclohexanecarboxylate (XXI)

A solution of 800 mg (4.7 mmole) of VIII in 10 ml of dry methanol was reduced to XXI using 500 mg of sodium borohydride. The mixture was stirred for 2 hr at 10°-15°, poured into dilute hydrochloric acid and extracted with chloroform. The chloroform extracts were washed once with water and after filtering through anhydrous magnesium sulphate the chloroform was removed under vacuum. The residue was chromatographed on silica using cyclohexane-ethyl acetate (7:3) as eluant. Prior to elution of the alcohol 75 mg of unreacted ketone were recovered. Bulb to bulb distillation of the major fraction gave 580 mg (79% based on reacted ketone) of XXI, b.p. 68°-73° (0.06 mm).

I.R.: 3400 broad (-OH), 1720 broad (ester C=O).

N.M.R. (100 MHz): 6.36 singlet, 6.4 multiplet (total 4H), 7.5-8.8 (9H), 8.84 singlet, 8.86 singlet (total 3H).

D_2O exchange 7.5-8.8 (8H).

Methyl 1-Methyl-4-Tosyloxycyclohexanecarboxylate (XXII)

A solution of 570 mg (0.33 mmole) of XXII in 10 ml of pyridine (dried over sodium hydroxide) was converted to XXIII using 1.3 g of p-toluenesulfonyl chloride. After standing for 5 days at -20° the mixture was added dropwise to 40-50 g of an ice/water mixture. The tosylate which oiled out at first, gradually solidified and was filtered off. The product was washed several times with water and dried under vacuum. After two recrystallizations from petroleum ether (30°-60°), the product melted at 83°-87°. The yield was 945 mg (88%).

I. R.: 1720 (ester C=O), 1345, 1170 (S=O).
N. M. R. (100 MHz): 2.2 doublet (2H), 2.9 doublet (2H),
5.5 multiplet (1H), 6.36 singlet (3H),
7.59 singlet, 7.6-8.8 (total 11H),
8.96 singlet, 8.99 singlet (total 3H).

Methyl 1-Methylcyclohex-3-ene-1-Carboxylate (XXIII)

Method A

A solution of 700 mg (2.2 mmole) of XXII in 20 ml of 0.5M potassium tertiary butoxide was refluxed for 2 hr. After adding 5 ml of water, refluxing was continued for an additional 1/2 hr. After cooling, the basic solution was extracted once with chloroform to remove any non-acidic material, made acid with dilute hydrochloric acid and extracted again with chloroform. Removal of the chloroform under vacuum left the free acid as a white solid. Esterification using silver oxide-methyl iodide and chromatography on silica using cyclohexane-ethyl acetate (9.5:0.5) as eluant gave XXIII in 20-25% yield.

Method B

A mixture of 1.0 g (8.5 mmole) of butadiene sulfone, 10 ml of dry toluene, 4.3 g of methyl methacrylate and a few mg of hydroquinone was placed in a sealed tube and heated at 130° for 30 hr. After cooling, the solvents were removed under vacuum and the residue passed through 20 g of silica using cyclohexane-ethyl acetate (3:2) as eluant. Polymethylmethacrylate found in the reaction remained on the column. Bulb to bulb distillation gave 770 mg (59%) of XXIII, b.p. 53°-55° (5 mm).

An analytical sample was prepared by additional chromatography on silica using cyclohexane-ethyl acetate (8.5:1.5) as eluant and bulb to bulb distillation.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.12; H, 9.15.
Found: C, 70.06; H, 9.17.
I.R.: 1725 (ester C=O), 1645 (C=C).
N.M.R. (100 MHz): 4.38 multiplet (2H), 6.25 singlet (3H), 7.4-8.7 (6H), 8.70 singlet (3H).
Mass Spec.: m/e 154.

Benzenesulfenyl Chloride

A mixture of 22 g (0.2 mole) of thiophenol in 100 ml of carbon tetrachloride was stirred and cooled to 0^o-5^o in an ice/water bath. Then 14.2 g of chlorine in 200 ml of carbon tetrachloride was added dropwise. After an additional 2 hr the solvent was removed under vacuum leaving the crude benzenesulfenyl chloride in 80-90% yield. No further purification was carried out.

3-Phenylthio-4-Chlorothiolane-1,1-Dioxide (XXIV)[82]

To the above benzenesulfenyl chloride in 100 ml of methylene chloride was added 23.6 g (0.2 mole) of butadiene sulfone in 100 ml of the same solvent. Recrystallization from ethanol gave 42.5 g (81%) of XXIV, m.p. 79^o-80^o. [Lit. m.p. 81^o [82]].

3-Phenylthio-Δ^3-Thiolene-1,1-Dioxide (XXV)[82]

Dehydrohalogenation of 30 g (0.11 mole) of XXIV using triethylamine and dimethylsulfoxide gave, after recrystallization from methanol 21.2 g (82%) of XXV m.p. 58^o-59^o. No physical constants were reported for this compound[82].

I. R.: 1300, 1124 (sulfone), 735, 690 (monosubstituted benzene).

N. M. R. (100 MHz): 2.5 singlet (5H), 4.3 multiplet (1H), 6.18 multiplet (2H), 6.31 quartet (2H).

Methyl 1-Methyl-4-Thiophenylcyclohex-3-ene-1-Carboxylate (XXVI)

In a 250 ml flask were placed 20 g (88 mmole) of XXV, 120 ml of toluene (dried and distilled over sodium) and 30 g of methyl methacrylate. The mixture was heated at 125° for 20 hr. After cooling and removal of the solvents under vacuum, the residue was distilled to give 13.4 g (58%) of XXVI, b.p. 94°-96° (0.08 mm). An analytical sample was prepared by chromatography on silica using cyclohexane-ethyl acetate (8:2) as eluant and bulb to bulb distillation.

Anal. Calcd. for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.93, S, 12.21.
Found: C, 68.72; H, 6.92; S, 12.17.

I. R.: 1725 (ester C=O), 1630 (C=C), 746, 690 (monosubstituted benzene).

N. M. R. (100 MHz): 2.37 singlet (5H), 3.99 multiplet (1H), 6.34 singlet (3H), 7.0-8.6 (6H), 8.79 singlet (3H).

Mass Spec.: m/e 262.

Methyl 1-Methyl-4-Ketocyclohexanecarboxylate (VIII)

The procedure of Corey and Shulman[83] was used to convert the vinyl sulphide to the corresponding ketone.

To 4.6 g (18 mmole) of XXVI in 90 ml of acetonitrile-water (3:1) was added a solution of 9.7 g of mercuric chloride in 90 ml of the same solvent. The mixture was stirred at approximately

80° for 35 hr. The mixture was cooled, filtered and the precipitate washed thoroughly with ether. After further extraction of the filtrate with ether, the combined ether extracts were washed with sodium bicarbonate, water and then dried over anhydrous magnesium sulphate. After removing the ether, distillation of the crude residue gave 1.4 g (45%) of VIII.

1-Methyl-3, 3', 5, 5'-Tetradeutero-4-Ketocyclohexanecarboxylic Acid (VII-d$_4$)

Hydrolysis of 4.5 g (24 mmole) of VI in 100 ml of D_2O (99.5% D) reacted with 4 g of sodium gave 3 g (78%) of VII-d$_4$.

Methyl 1-Methyl-3, 3', 5, 5'-Tetradeutero-4-Ketocyclohexane-1-Carboxylate (VIII-d$_4$)

A sample of VII-d$_4$ was converted to the methyl ester VIII-d$_4$ using silver oxide and methyl iodide as described for VIII, Method B.

The deuterated analogues of compounds IX through XXIII were prepared from VIII-d$_4$ (or VII-d$_4$) in an identical manner to that used for the non-deuterated compounds. Where proton exchange may have occurred during reaction, deuterated reagents were used. These included acetic acid-O-d, methanol-O-d, morpholine-N-d and sodium borodeuteride. Deuterated compounds were characterized by their respective melting or boiling points, I.R. and n.m.r. spectra. All the deuterated compounds were found to contain greater than 95% deuterium in each of the 3, 5 and 5' positions by n.m.r. and mass spectral analysis (X and XVIII greater than 85% deuterium incorporation).

CLAIMS TO ORIGINAL WORK

1. Ten new substituted cyclohexene compounds were synthesized. Nine selectively deuterated analogues of these compounds were also prepared.

2. The chemical shifts and coupling constants for the allylic methylene protons were obtained from analysis of the n.m.r. spectra of the deuterated analogues.

3. The olefinic substituent was found to have a rather large effect on the magnitude of the allylic geminal coupling constant. A plot of J versus σ_p had a slope of -2.9.

4. Resonance effects were shown to be much more predominant than inductive effects in influencing J.

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