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Organic Applications Of Carbon-13 And Deuterium Nmr Spectroscopy

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ORGANIC APPLICATIONS OF ^{13}C AND ^{2}H NMR SPECTROSCOPY

by

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ABSTRACT

The characteristic effects produced in ^{13}C spectra by ^{2}H substitution offer a straightforward means for identifying the location of the ^{2}H while integration provides a quantitative assessment of ^{2}H content at individual carbons. In addition to the ^{2}H-induced splitting and isotope shift exhibited by the signal for the carbon bearing ^{2}H, the geminal carbons also experience a readily resolved isotope shift while vicinal carbons are spin coupled to the ^{2}H. Examples in which these features have been utilized for signal assignments are presented. The application of these features as a mechanistic probe for the quantitative investigation of ^{2}H incorporation via homoenolization in several ketones are illustrated. The advantages of the ^{13}C NMR technique over other, more familar, physical methods are discussed. The utilization of ^{2}H NMR and lanthanide shift reagents as a tool for the quantitative investigation of ^{2}H incorporation in several ketones are described and the particular advantage of the ^{2}H NMR over ^{13}C NMR methods are illustrated.

One of the most important and interesting features of ^{13}C nuclear shieldings is their remarkable sensitivity to stereochemical environment. In order to understand more about ^{13}C shieldings and its applications, several series of model compounds were chosen and prepared and their ^{13}C spectra examined.

A series of bicyclic ketones, embracing eight skeletal types was selected for ^{13}C examination. Their carbonyl shieldings have led to an interpretation of the variation of carbonyl shieldings in the cycloalkanones (C_4 - C_{17}) in terms of their preferred conformations.

The ^{13}C spectra of several β,γ unsaturated polycyclic ketones have been recorded to examine the shielding difference for all carbons relative

to those for their saturated analogs and the parent olefins. The variations of the sp^2 carbon shieldings provide qualitative evidence for the existence of homoconjugative interactions between the olefinic and carbonyl groups in the ground state. Similar evidence of interaction between γ,δ double bonds and the carbonyl groups was found from spectra for a few examples.

The ^{13}C spectra of 21 methyl substituted cyclohexanones and 15 methylcyclopentanones have been examined. These series were chosen as model systems for the study of steric and conformation effects on ^{13}C shieldings. Each of the cyclohexanones exist preferentially in chair conformations although there is evidence of ring distortion in the tetramethyl derivatives. The cyclopentanones apparently strongly favor half-chair forms with maximum puckering at C_3 and C_4.

The ^{13}C spectra of a series of 34 norbornyl derivatives have been recorded to examine the variation of ^{13}C shieldings with molecular geometry. Since it is well-established that nonbonded interactions between vicinal carbon nuclei lead to pronounced upfield shifts, the so-called γ effects, series of methyl-substituted norbornanes, norbornenes, and norbornan-2-one were prepared as model systems having a variety of γ interactions between vicinal methyl groups. The observed shifts of these methyl carbons are considered in terms of the dihedral angle relating the vicinal nuclei.

The ^{13}C spectra of a series of 16 bicyclo(2.2.2)octenones and -octanones have been determined to examine the variation of ^{13}C shieldings with methyl substitution. The well-defined effects arising from 1,4-nonbonded interactions are apparent and are useful to stereochemical assignments. The ^{13}C shieldings observed for 1,5,8,8-tetramethylbicyclo(2.2.2)oct-5-en-2-one and the isomeric saturated bicyclooctanones obtained therefrom

established their structures.

The ^{13}C spectra of a series of 37 bicyclic ketones have been recorded to examine the variations in ^{13}C shieldings with structure and the methyl substitution. The observed trends associated with methylsubstitution follow well-defined patterns and offer further support for the application of ^{13}C shieldings as aids for stereochemical assignments.

The ^{13}C spectra of a series of 42 methylsubstituted norbornanols and 32 bicyclo(2.2.2)octyl derivatives have been determined to gain further insight into the nature of stereochemical effects on the shieldings of carbons having close substitutents. The relatively rigid bicyclic skeletons permit examination of a variety of orientations of substituents separated by three and four bonds, the γ and δ interactions, respectively. While methyl carbons close to γ substituents exhibit upfield shifts, as is well-established, methyl carbons close to δ substituents are significantly deshielded. Even more striking shifts are found for the carbon bearing these closely lying groups. The penultimate carbons in a fragment having a δ interaction between terminal groups show deviations of up to +11 ppm from shielding predicted by simple additivity. For fragments having a corresponding γ interaction, the penultimate carbons absorb as much as -10 ppm from the values expected by additivity. These deviations have considerable potential for stereochemical assignments and offer a challenge for theoretical interpretation.

The ^{13}C spectra of some phenanthrene and fluorene derivatives have been examined. The results show that 1,6 Me - Me interactions (ε effect) can be either shielding or deshielding.

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CHAPTER 1

GENERAL INTRODUCTION

The first actual observation of nuclear magnetic resonance was made by Rabi and his co-workers (1) in 1939, but such studies were performed only in molecular beams under vacuum. The original discoveries of the nuclear magnetic resonance phenomenon in bulk matter (solids and liquids) did not occur until 1945 when Purcell and his colleagues (2) at Harvard found nuclear magnetic resonance absorption in paraffin wax, while Bloch et al. (3) at Stanford reported resonance in water; Purcell and Bloch shared the 1952 Nobel prize for their discoveries. In 1951, separate absorption bands were resolved for chemically different protons in the same molecule (4). This finding led to the term "chemical shift" to describe the differences in resonance conditions required for the same isotope in different chemical environments. With this development, nuclear magnetic resonance became tremendously exciting for chemists as a new method for the study of molecular structure and over the past 24 years, nuclear magnetic resonance has become firmly established as one of the major tools in several branches of chemistry and chemical physics. Due to the high sensitivity and natural abundance, ^{1}H and ^{19}F nuclear magnetic resonance (NMR) methods have been well established and are used routinely by chemists. The early work with nuclei of low inherent sensitivity and natural abundance was restricted to relatively few laboratories and the potential of these nuclei was not exploited entensively. With the

development of new stable spectrometers and pulse techniques the major difficulties were overcome and now it is clear that NMR studies of the less sensitive nuclei are extremely useful.

Nuclear magnetic resonance of carbon (^{13}C) and hydrogen (^{1}H) nuclei share some characteristics but differ in an important aspect. The most abundant isotope of carbon, atomic weight 12, has no nuclear spin and is not observable in NMR experiments. The ^{13}C isotope has a nuclear spin of 1/2 (as does ^{1}H), however, and a natural abundance of 1.1%. This natural abundance is low enough to make ^{13}C-^{13}C spin-spin coupling interactions unlikely in unenriched compounds and thus renders ^{13}C spectra simple. Another factor further lowers the effective sensitivity of a ^{13}C NMR experiment. The magnetic moment μ of ^{13}C nuclei is about 1/4 that of ^{1}H nuclei. Since the sensitivity of a nucleus in a magnetic resonance experiment is proportional to μ^3, ^{13}C nuclei give rise to $(1/4)^3$ or 1/64 the signal that proton nuclei would yield on excitation. The result of the 1.1% natural isotopic abundance and lower μ is a lowering of the sensitivity in a ^{13}C NMR experiment by a factor of ca. 5700 relative to that for protons. In 1957, the first NMR observations of ^{13}C nuclei were individually reported by Lauterbur and by Holm (5). The difficulty of the experiments, coupled with poor spectral resolution and the requirement of working with liquids or highly soluble solids of low molecular weight, severly restricted the early publications of ^{13}C NMR spectroscopy. Nevertheless, by mid 1960, several research groups (6) had succeeded in studying many classes of organic compounds with ^{13}C NMR techniques. These studies indicated that direct observations of carbon nuclei had many

advantages over the equivalent proton studies and had great potential. Recently, pulsed Fourier transform NMR techniques have been introduced (7) and ^{13}C spectroscopy has become a routine method. Three important monographs (8, 9, 10) and several review articles (11 - 24) provide a basis for further progress and will assist the development of new applications.

Tracer techniques using ^{13}C NMR methods are very attractive for investigations of reaction mechanisms and biosynthetic paths. The key advantage is the elimation of stepwise degradation of the enriched materials which is required to locate specifically labeled radioactive centers. Several applications of ^{13}C NMR in biosynthetic and reaction mechanism studies using enriched ^{13}C labeled materials have been reported and reviewed (8, 22, 23, 24c).

Another way in which ^{13}C techniques may be employed in tracer studies is the use of ^{13}C spectra to follow the incorporation and to determine the distribution of deuterium atoms in suitable systems. One part of my research work was to examine the use of ^{2}H labels and ^{13}C NMR analysis for mechanistic investigation. The characteristic effects produced by ^{2}H - labeled centers in ^{13}C spectra afforded a straightforward monitor for deuterium exchange studies in several polycyclic ketones (see chapter 3). Futhermore these characteristic effects have also been employed for signal assignments (see chapter 2). Recently, our NMR spectrometer was modified to perform ^{2}H experiments in the Fourier transform mode. The direct examination of deuterated samples by ^{2}H NMR offers distinct advantages over the ^{13}C approach (see chapter 3). It is somewhat surprising that

^{2}H NMR has not been exploited extensively by organic chemists (25) especically since deuterium containing materials can be synthesized with relative ease (26) and the price of the deuterated compounds is relatively low. Deuterium has a relatively low nuclear moment and natural abundance which combine to make it ca. 100 times less sensitive than ^{13}C. With current multinuclear spectrometers, however, ^{2}H NMR spectra for simple molecules can be determined in natural abundance. Some natural abundance ^{2}H NMR spectra have been recently reported by Randall and his co-workers (27) to demonstrate that it is useful for deriving chemical shifts for use in the analysis of the corresponding ^{1}H spectrum. Deuterium NMR has been employed in the study of biological problems such as molecular mobility and order within biological membranes (28).

In ^{1}H NMR, three types of spectra information --- chemical shifts, coupling constants, peak area measurements --- are of value for organic structure determinations. Although the same types of information are available in ^{13}C NMR, their relative importance and use differ. In ^{13}C NMR, chemical shifts generally are the most useful parameter. Carbon nuclei in neutral organic compounds appears over a range of ca. 250 ppm while if one includes carbonium ions and highly halogenated species (namely CI_4), the known shielding range is ca. 600 ppm. Thus, there is a much greater shift dispersion than in ^{1}H spectra. For example the spectra of steroids (29) generally have few, if any, overlapping signals for nonequivalent carbons. Consequently, ^{13}C spectra are potentially rich sources of shielding (chemical shift) information.

One of the most interesting and useful results is the general finding that ^{13}C shieldings in related series tend to follow additive relationships. Thus one is able to estimate the shieldings for many compounds with remarkable precision. For linear hydrocarbons, only five parameters are required to define the shieldings and these factors --- labeled α, β, γ, δ and ε --- are the effects produced along an alkyl chain by replacing a hydrogen atom with a methyl group, i.e., the methyl substituent effects at the α, β, γ, δ, and ε positions. Similar factors can be deduced for other substituents by a comparison of the shieldings for RX with those for RH. In general, α and β effects are deshielding and the γ is shielding. This γ effect has been empirically linked to a 1,4 steric repulsion and has served as a useful guideline in making assignments and in conformational analysis. Grant and Cheney (30, 31) have rationalized the γ effects in terms of a model of steric interactions between neighboring CH moieties. According to their proposal, the C-H bonds of the intereacting hydrogens suffer steric polarization such that the electron density at the carbons is changed because of the bonded repulsion between hydrogens on γ-carbons in gauche or eclipsed orientations. The existence of the γ effect has been verified in a wide variety of hydrocarbon systems, and the qualitative theoretical model described above for a steric origin has been widely accepted. This concept has also been extended to substituent moieties other than the methyl group (e.g. hydroxyl and halogens). (32 - 39). The effects arising from interactions of more remote nuclei tend to be much smaller and variable. Theoretical

treatments of ^{13}C chemical shifts have been attempted using several methods (23, 31, 40 - 42). These treatments have not been entirely successful even for some simple molecules. Therefore, the applications of ^{13}C shieldings, are for the most part, based on empirical correlations of ^{13}C shieldings and molecular geometry. To understand more about the dependence of ^{13}C shieldings on molecular geometry, several series of relatively rigid model compounds were prepared and their ^{13}C spectra examined. The results exhibited several interesting trends which can be useful for signal assignments in complex spectra and for stereochemical assignments for groups within a molecule.

The main purpose of my work was to apply ^{13}C and ^{2}H NMR methods to some organic problems. It can be divided into two parts:

(1) Deuterium labeling as a probe for signal assignments and mechanistic studies by ^{13}C and ^{2}H NMR.

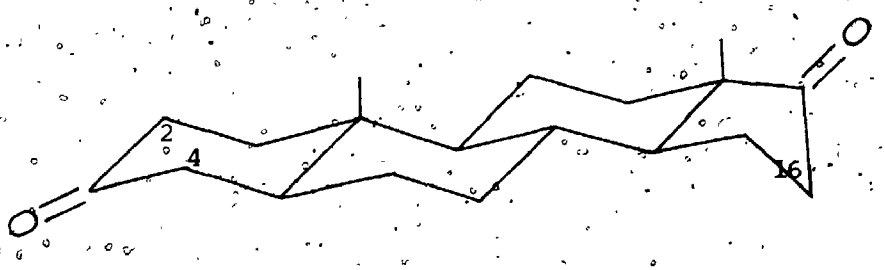
(2) To study and apply ^{13}C shieldings to structural, stereochemical and conformational problems.

CHAPTER 2

DEUTERIUM LABELING AS A PROBE FOR SIGNAL ASSIGNMENTS BY ^{13}C NMR

(A) INTRODUCTION

In some of the earliest ^{13}C NMR studies of substituted benzenes (43), deuterium labeled compounds were utilized to obtain unequivocal signal assignments. Although the ^{13}C resonance of a ring carbon directly bonded to a deuterium nucleus (I = 1) may be expected to show triplet splitting and quadrupolar broadening these signals were not observed, thereby identifying the deuterated carbons. The effect of deuterium substitution is to increase the relaxation time, T_1, of the carbon nucleus (44) to which it is attached such that the carbons were saturated by the large radio-frequency, H_1, power demanded by the technique employed. Later, Roberts and his co-workers (29) obtained signal assignments for a variety of steroids by comparison of the spectra of deuterium exchanged material with those of unlabeled compounds. For example, after base-catalyzed deuteration of the 2-, 4-, and 16- positions of androstanedione (1),



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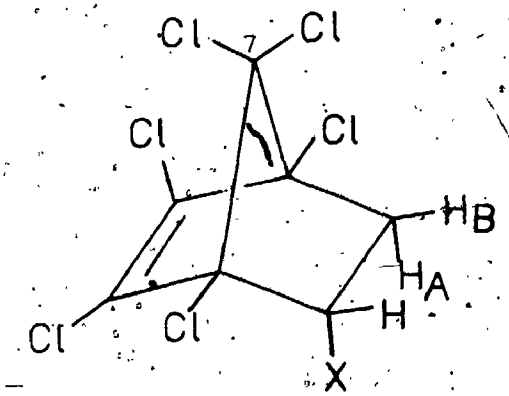
the resonances of these carbons were unobservable at the attainable signal-to-noise ratios with continuous wave (CW) operating and proton-noise decoupling because of quadrupole broadening, spin-spin splitting, and decreased Overhauser enhancement. Specifically labeled benzenes were also used to simplify the analysis of the coupled ^{13}C spectrum of benzene (45). Under the conditions employed for these early studies (29, 43, 45), however, the effects of the deuterium nucleus were only detected in the absorption of the carbon bearing deuterium. If the absorption was resolved, two parameters were observed, the ^{13}C-D spin-spin coupling (20 - 40) Hz) and isotope shift (~0.5 ppm). With slow-passage, CW operation, effects at the geminal carbons were first recognized (46a-d) namely the existence of a geminal isotope shift. These isotope effects operative through two bonds shield the geminal carbon by approximately 0.1 ppm. In the earliest work, using rapid-passage techniques the resolution was insufficient to show the geminal isotope shift. Recently, in monodeuteriobenzene, Bell and his co-workers have observed the following upfield "isotope shifts" relative to benzene: $^{13}C_{\alpha}$-D (0.289 ppm), $^{13}C_{\beta}$-C-D$_{ortho}$ (0.110 ppm) and $^{13}C_{\alpha}$-C-C-D$_{meta}$ (0.011 ppm) (46b). Monosubstituted benzene derivatives specially labeled with deuterium in the ortho, meta, or para positions also show similar isotope shifts (46c, 47). Similar effects for a number of other organic compounds such as long-chain aliphatic compounds (48), steroids (49), polyaromatic hydrogens (50) and sugars (51) have also been reported.

With Fourier transform operation and proton-noise decoupling, the ^{13}C-D spin coupling interactions are unaffected because the

deuterium resonance frequency is 15.4 MHz at the field (23.5 kgauss) at which ^{13}C absorbs at 25.2 MHz and ^{1}H at 100.1 MHz and the coupling may be readily discerned if $J_{CD} > 1$ Hz. Of course, the detection of small J values depends on the spectrometer resolution which may be computer-limited. Since $J_{CD} = (\gamma_D/\gamma_H)J_{CH}$, the ^{13}C-D coupling constants are smaller than the corresponding ^{13}C-H interactions by a factor of 6.51. In general, geminal C-H coupling constants tend to be small (0.4 to 6.4 Hz) except in aldehydes, acetylenes and a few olefins (28 - 66 Hz) (8). The even smaller C-C-D splittings (J_{CCD} <1 Hz) are generally unresolved and the geminal carbon signals are usually characterized by the isotope shift only. In general it is found that J_{CCCH}, the vicinal coupling constant, is larger than J_{CCH} and it may be expected to exhibit a stereochemical dependency by analogy with the well-established trends for H-H spin interactions. Preliminary results (52) for some 5-endo-substituted hexachlorobicyclo(2.2.1)heptenes confirm this notion since the coupling of C-7 with the endo- and exo-3-protons (A & B in 2) are 9 and 0 Hz, respectively, and the



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dihedral angles relating these nuclei are approximately 150° and 90°, respectively. This has been demonstrated for several other systems (17) for which it is found that J_{CCCH} is maximal if $\phi \approx 0^{\circ}$ or 180° and minimal if $\phi \approx 90^{\circ}$. The trend from these few examples may be utilized to gain information on the stereochemistry of deuterium atoms in labeled compounds. Since ^{13}C-D coupling is not affected by proton decoupling, one can expect to resolve vicinal C-D interactions in favorable cases. Hence the ^{13}C spectrum of a deuterated material can provided information not only for the carbon bearing the label but also for the geminal and vicinal carbons. In this chapter, the ^{13}C spectra of a few deuterium-labeled compounds are described and their applications for signal assignments and stereochemical elucidations as well as for a variety of mechanistic studies are illustrated.

(B) RESULTS AND DISCUSSION

With Fourier transform operation and proton decoupling, the ^{13}C spectra of camphor, camphor-3-exo-d and camphor-3,3-d_2 were recorded and are reproduced in Fig. 2.1. The assignments for all the carbon signals in camphor will be discussed in chapter 4. In the spectrum of camphor-exo-3-d, the effects of the deuterium atom are readily detected not only for the labeled carbon but also for the carbons geminal and vicinal to the deuterated center. It is clear that the pattern for C-3 consists of a triplet arising from ^{13}C-D coupling which is shifted upfield by ca. 0.5 ppm relative to the absorption signal of non-deuterated C-3. The signals for the

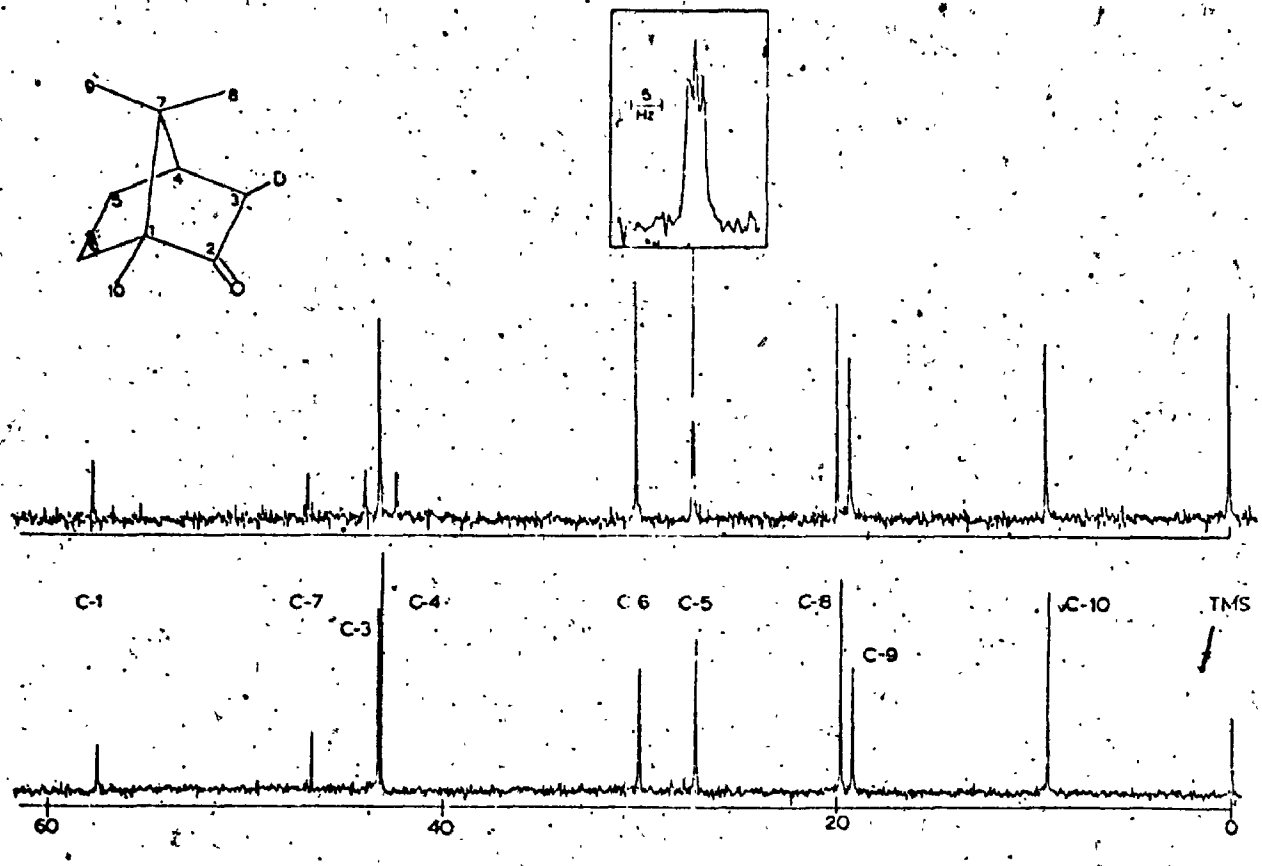


Figure 2.1a. High field regions of the 25.2 MHz ^{13}C spectra of camphor (lower) and camphor-3-exo-d_1 (upper) in $CDCl_3$. The inset is a four-fold expansion of the C-5 absorption for the 3-exo-d_1 derivative.

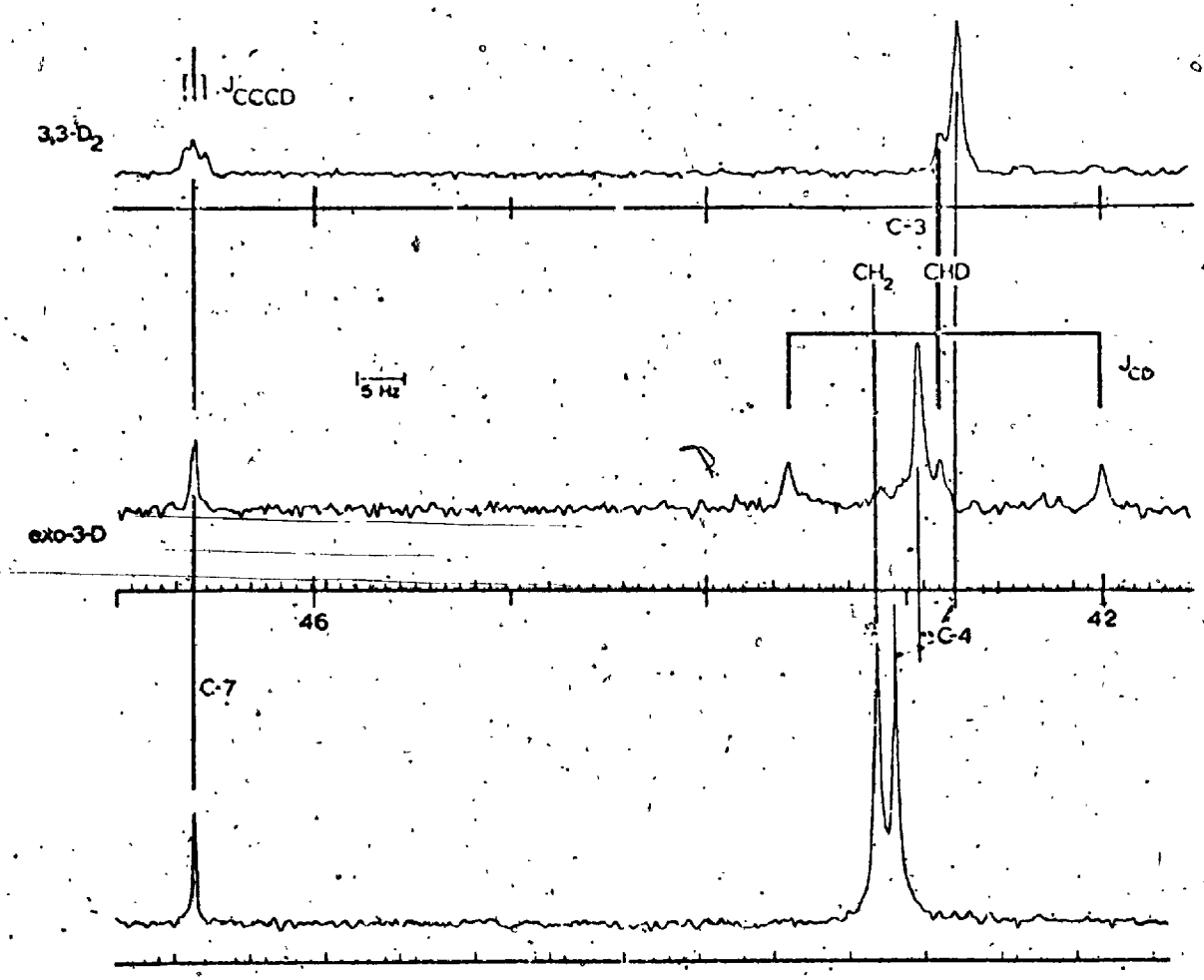
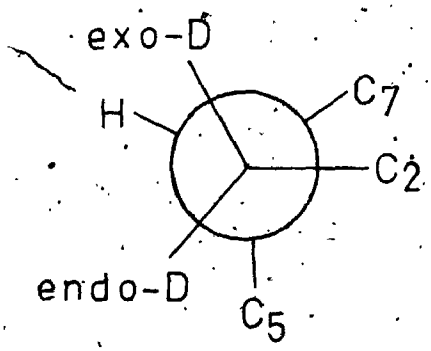


Figure 2.1b. The C-3, -4 and -7 signals for camphor (lower), camphor-3-exo-d_1 (middle) and camphor-3,3-d_2 (upper) obtained at 25.2 MHz. With this S/N, the absorption for CD_2 is not observed because of the small Overhauser effect and the multiplicity.

carbons geminal to deuterium exhibit isotope shifts of 0.12 ± 0.04 ppm, upfield for the sp^3 - carbon (C-4) but downfield for the carbonyl carbon. As expected, the signal for C-5 appears as a triplet while the C-7 signal is essentially the same as that in the spectrum of normal camphor. For camphor-3,3-d_2, however, the C-7 signal is a triplet, clearly demonstrating a significant vicinal coupling with the 3-endo-deuterium nucleus. a Newman projection along the C-3 — C-4 bond, (3), shows that the 3-exo-deuterium is anti-periplanar to C-5 as is the 3-endo-deuterium to C-7, whereas the dihedral angle for the 3-exo-deuterium and C-7 is close to 90°. Thus the vicinal interaction displays the expected stereo-dependence.



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The utility of ^2H-labeling for spectral assignment may also be illustrated by the results for the four 5,6-dimethylnorcamphors. While most of the assignments for these four ketones were straightforward (see chapter 4), the C-4, C-5, and C-6 signals could not be unambiguously assigned without additional information. For this purpose, the ketones were subjected to base-catalyzed deuterium exchange at the 3-position and the spectra of the deuterated ketones

were compared with those of the normal materials. In each case the mono-deuterated ketones exhibited a 0.1 ppm upfield shift for one of the unassigned methine signals and a significantly broadened band for another, while the third was unaffected. Thus, the assignments for C-4, -5, and -6, respectively, were completed unequivocally.

To illustrate these effects, the spectra for endo-5-exo-6-dimethylnorcamphor and its exo-3-d_1 derivative are shown in Fig. 2.2. In these spectra, it was readily shown by off-resonance decoupling that the four lower field signals arise from methine carbons with the most deshielded one from C-1; but specific assignments for C-4, -5, and -6 are difficult without additional information. In the expended spectrum shown at the top of this figure, the differences in the C-4, -5, and -6 absorptions are apparent. The small spike on the low field side of the main C-4 absorption corresponds exactly to the C-4 absorption in the normal material indicating that deuteration was not complete. Clearer evidence of this is given by the pattern for C-3 which consists of a triplet arising from ^{13}C-D coupling which is shifted upfield from the residual CH_2 signal by ca. 0.5 ppm. The marked broadening of the C-5 signal relative to the C-6 peak readily identifies each (the relatively small memory core of the system used for these spectra somewhat limited the attainable resolution with the sweep width required (ca. ±0.5 Hz) nevertheless the perturbations caused by deuterium were readily detected); thus the assignments for C-4, -5, and -6, respectively, were completed. This

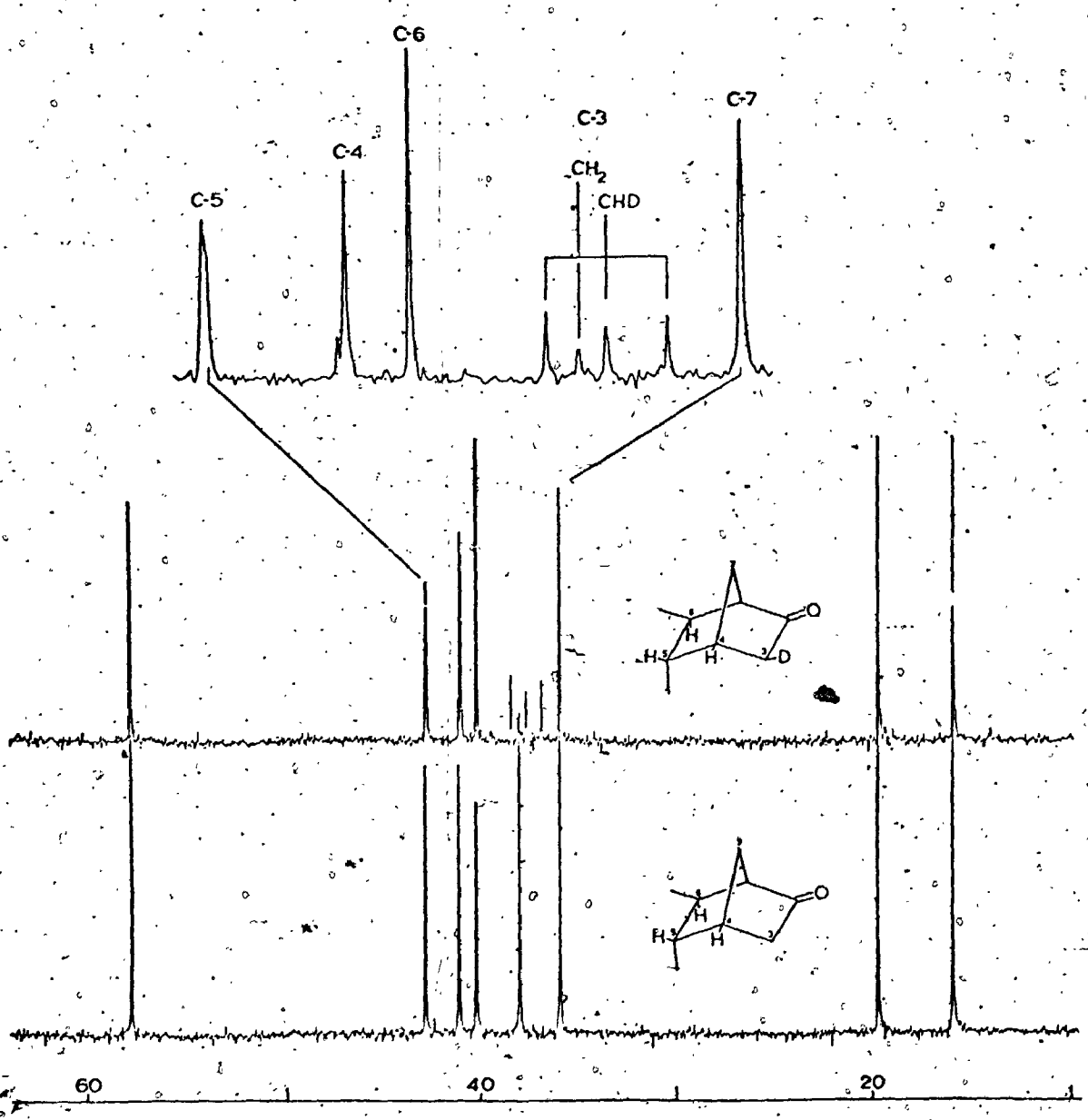


Figure 2.2. The high field region of the ^{13}C spectra of endo-5-exo-6-dimethylnorcamphor and its exo-3-d_1 derivative (shielding scale in ppm from TMS). The upper inset is a fourfold expansion of the central portion to illustrate the effects of deuterium substitution.

technique has been employed for signal assignments in several other compounds (see chapter 4).

In addition to these qualitative features, experiments show that the total integrated intensities of partially deuterated methyl and / or methylene carbons are equal to those for the non-deuterated materials. While the decrease in intensity for the residual CH absorption of a partially deuterated methine carbon gives a direct measure of the extent of deuteration. The ^{13}C-D induced triplets for $-CH_2D$ and $-CHD-$ do not overlap the residual $-CH_3$ and $-CH_2-$ absorptions because of the substantial isotope shifts (0.5 ppm) and J_{C-D} values of 20-40 Hz. With careful selection of operating parameters, it is relatively straightforward to obtain quantitative data. The quantitative results for individual carbons may be summed and compared with mass spectrometric data for total ^2H content as a check. The application of these features as a mechanistic probe for the investigation of homoenolization of several ketones will be discussed in the following chapter.

(C) CONCLUSION

The introduction of a single deuterium atom significantly affects the absorption of the neighboring carbons in addition to that at the site of substitution. The ^{13}C spectra of deuterium-labeled materials offer an informative means for monitoring these tracers, both qualitatively and quantitatively.

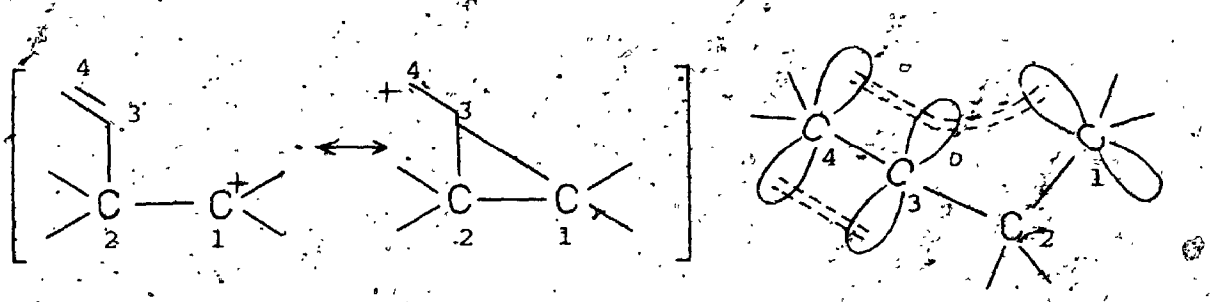
CHAPTER 3

DEUTERIUM LABELING AS A PROBE FOR MECHANISTIC STUDIES BY ^{13}C AND ^{2}H NMR ---- HOMOENOLIZATION

(A) INTRODUCTION

(a) HOMOENOLIZATION

The ability of π-electron systems to stabilize positive charges by conjugation (orbital overlap between contiguous atoms) and by homoconjugation (orbital overlap between noncontiguous atoms) is well documented (53). The idea behind the homoallyl designation is that a methylene group (C-2) is a poor insulator of conjugation if the proper rotational positions about the C-1 — C-2 and C-2 — C-3 bonds are assumed (Scheme 3.1). With proper rotational positions, there can be appreciable 1,3-orbital overlap of a type intermediate



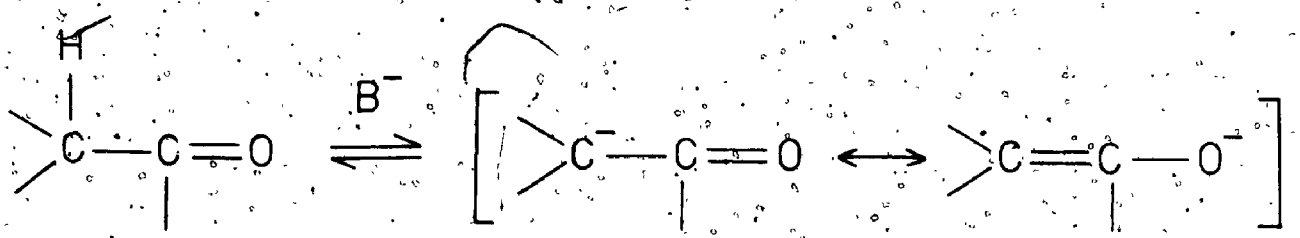
Scheme 3.1

between σ and π bonds. Semi-empirical molecular orbital calculations suggest substantial stabilization from electron delocalization (54, 55). On this basis, one may say that a homoallyl cation is homoconjugatively

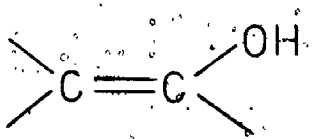
stabilized. In conjugation there is electron delocalization over adjacent carbon atoms. Homoconjugation involves electron delocalization through space across one or possibly more carbon atoms.

Delocalization of negative charge by conjugation is also common, enolate anions represent important examples of this class. In an enolate anion the charge is shared (unequally) by the α-carbon and the carbonyl oxygen, and reversible proton capture at either site provide a mechanism for base-catalyzed interconversion of keto and enol tautomers (Scheme 3.2). A carbonyl group could activate a more remote hydrogen sufficiently to allow conversion to an anion stabilized by homoconjugation which was first proposed and illustrated by Nickon and Lambert (55). In 1962, they found that optically active (+)-camphenilone (4) with no ordinarily enolizable hydrogen atoms had been racemized with potassium t-butoxide in t-butanol under fairly vigorous conditions (4 hr at 250°). Under similar conditions using deuterated solvent, in each run the percentage racemization corresponded closely with the percentage of molecules having deuterium. After 48 hr at 185°, up to three deuteriums were introduced. After 266 hr recovered camphenilone contained 1% $\underline{d}_0$ 7% $\underline{d}_1$, 26% $\underline{d}_2$, 38% $\underline{d}_3$, 21% $\underline{d}_4$, 6% $\underline{d}_5$ and 1% $\underline{d}_6$. With higher temperatures and longer reaction times, even more deuterium could be introduced (56). Hydrogen-deuterium exchange only occurred at the C-1, C-6 and methyl positions (57) as was unequivocally established by a combination of techniques including nuclear magnetic resonance (proton) and infrared spectroscopy and the examination of specifically labeled substrates. The suggestion was then made that

SCHEME 3.2

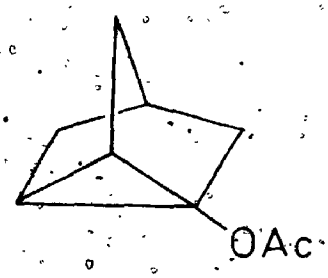


ENOLATE ANION



ENOL

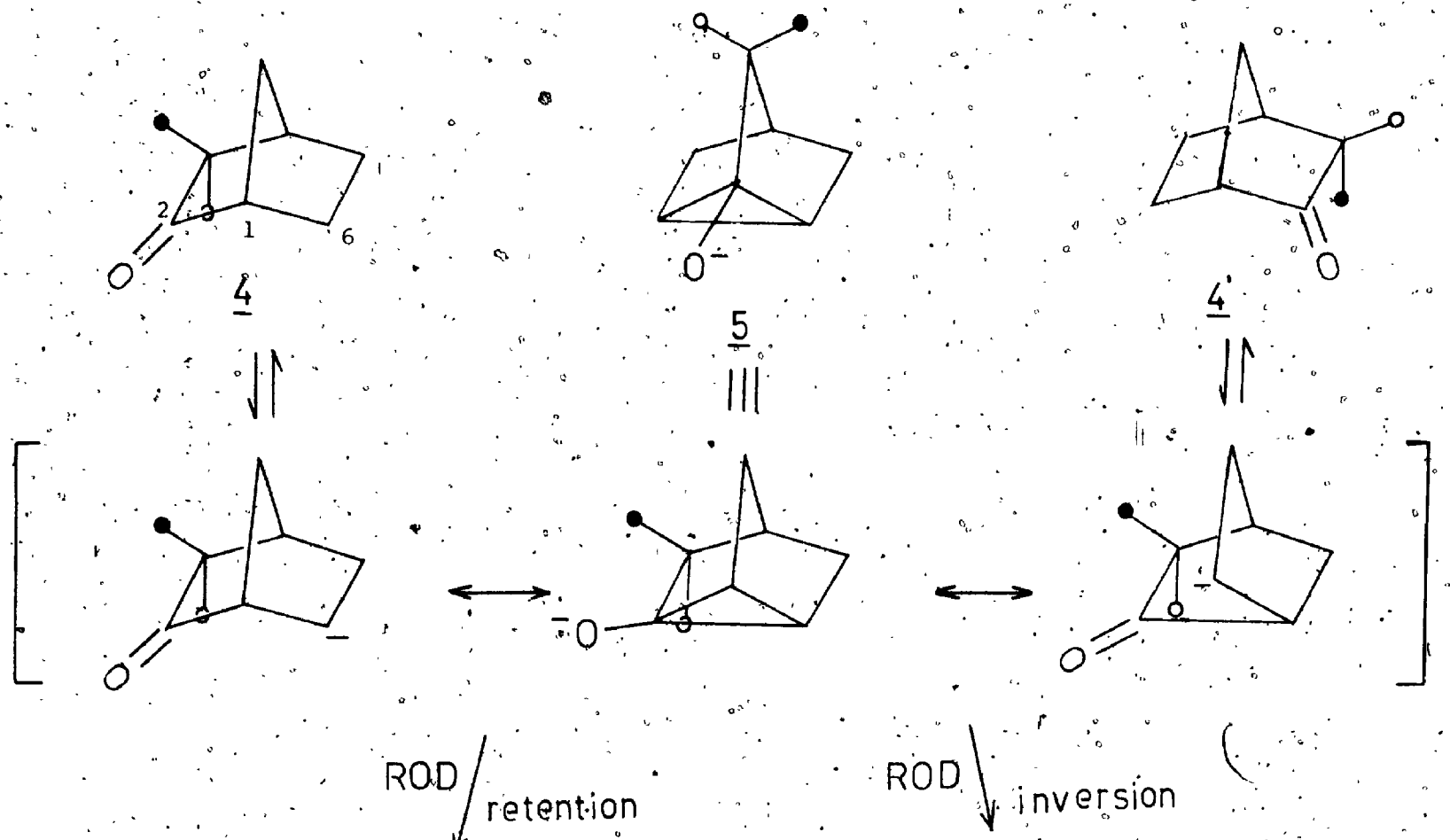
the homoenolate anion 5 was involved (Scheme 3.3). It is clear that reaction through the symmetric homoenolate anion 5 leads to deuterium incorporation at C-1 and C-6, which are equivalent in 5, and serves to racemize camphenilone (Scheme 3.3), thereby rendering the methyl groups equivalent and thus masking any stereoselectivity which may be involved in the exchange at the exo- and endo-methyl positions. To examine the stereochemistry of exchange at C-6 the reverse reaction, homoketonization of 1-acetoxynortricyclene (6), was studied (58). It was found that in alkaline media protonation occured with high stereoselectivity, favoring inversion of configuration, i.e. exo-protonation (94.5%).

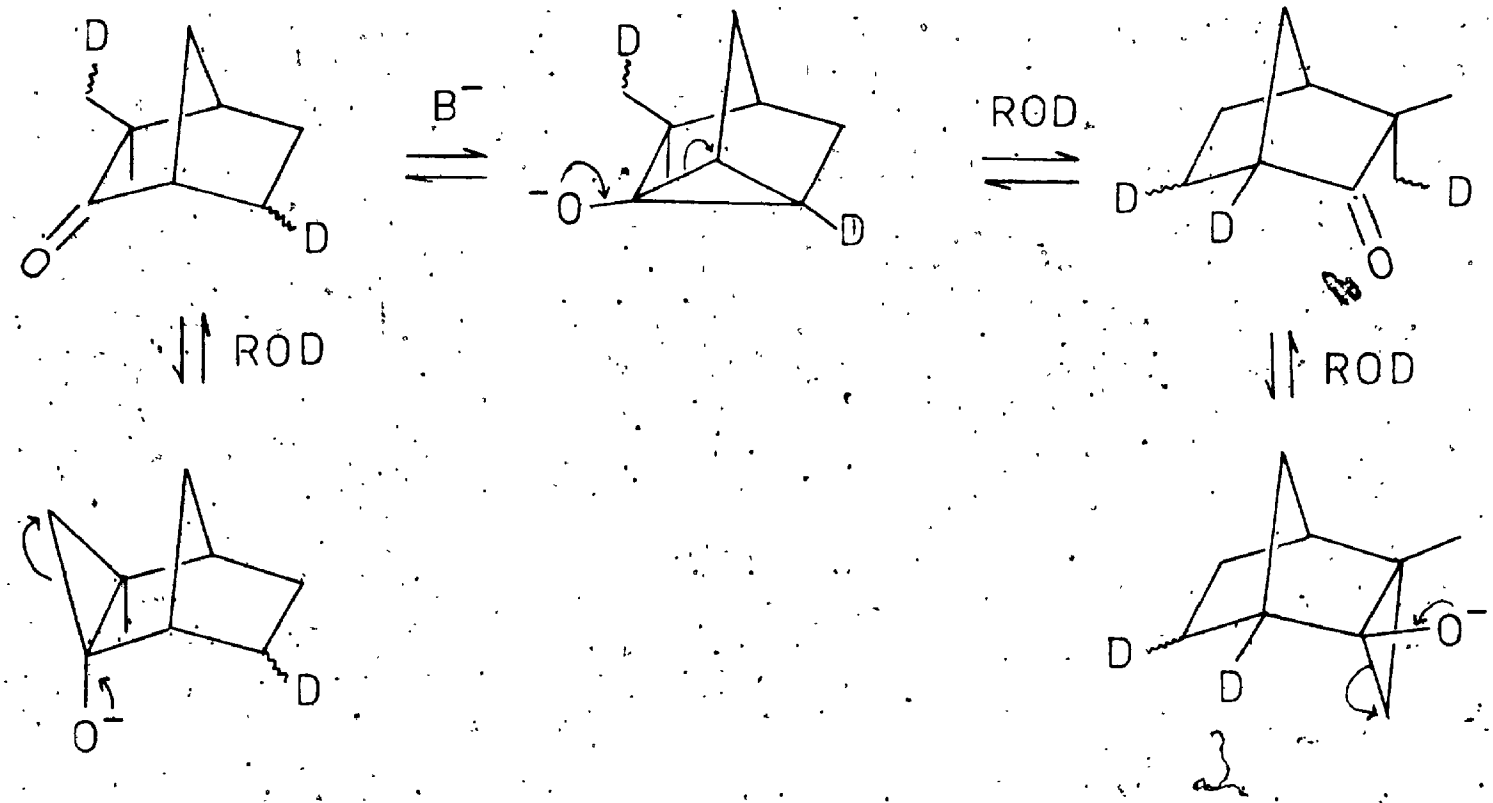


6

Homoenolization was then defined by Nickon and Lambert (57) as base-catalyzed hydrogen abstraction from the β- or more remote positions of a carbonyl compound. They have proposed the general case as shown in Scheme 3.4. The presence of an appropriately oriented carbonyl group could lead to a homoconjugated anion whose charater can be described in term of two contributing structures. The relative importance of each contributor should depend upon the detailed structure of the molecule involved. The intervention of the closed structure provides an opportunity for cyclization and

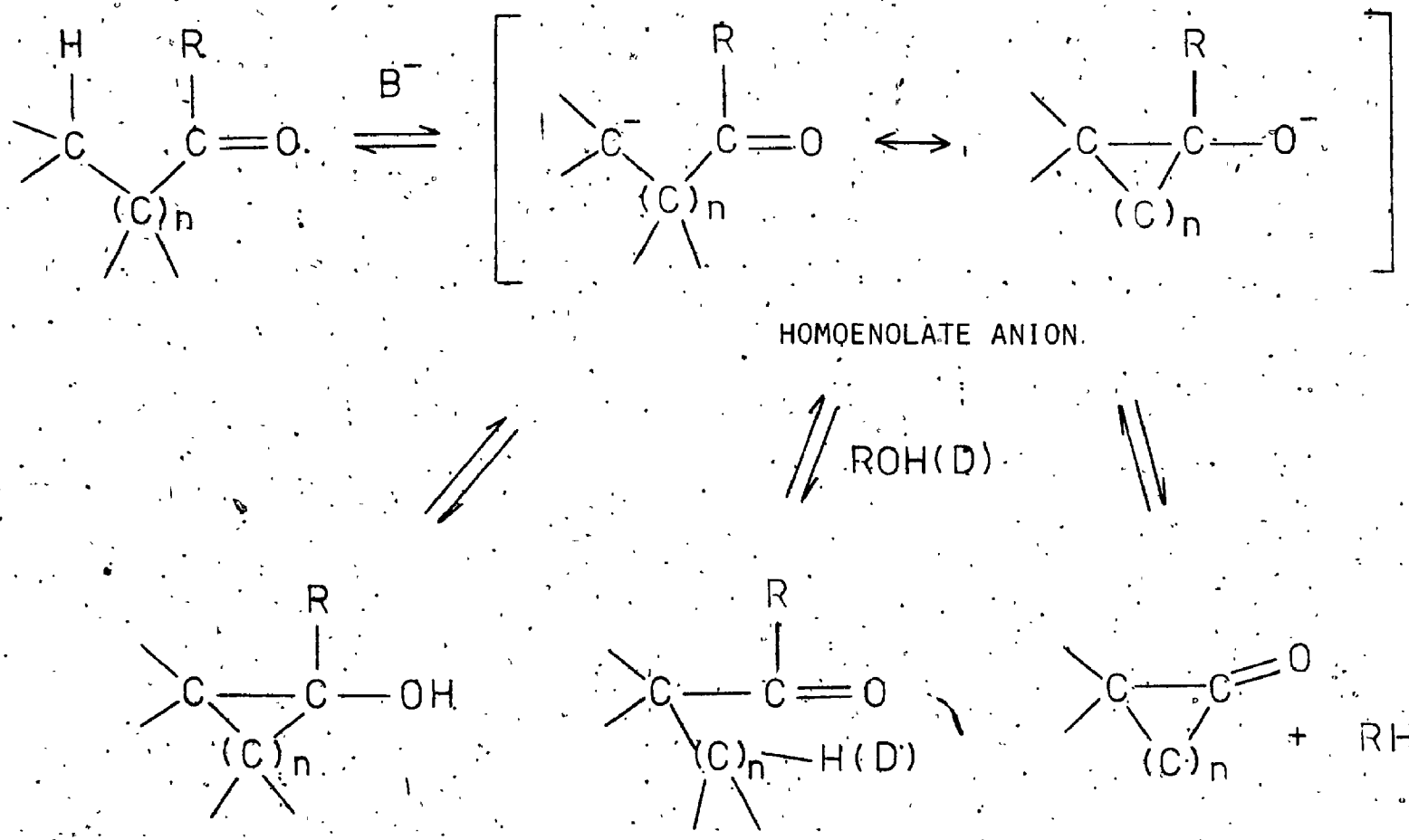
SCHEME 3.3





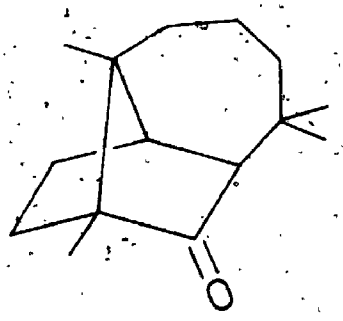
SCHEME 3.3'

SCHEME 3.4

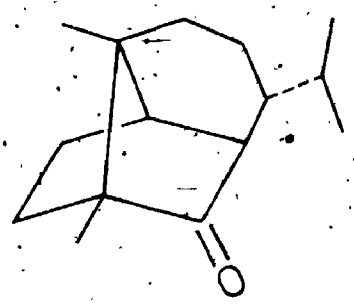


rearrangement as well as for isotopic exchange. It is worth noting that a second rearrangement (or cleavage) is also possible. Stothers and his co-workers have suggested that a more general term to specify the reaction site may be appropriate (59). For example, "β-enolization" and "γ-enolization" would refer to proton removal for β- and γ-carbons, respectively. Therefore in this chapter, the terms "β-enolization" and "γ-enolization" will also be used.

The synthetic potential of skeletal rearrangement via β-enolate anions to generate systems which would otherwise be difficult to obtain was also demonstrated in the initial investigations of β-enolization of Nickon et al. (60). Treatment of brexan-2-one (7) with t-butoxide in t-butanol at 185° gave a 60% yield of brendan-2-one (8). A similar rearrangement of longicamphenilone (9) was employed by Coates and Chen (61) to generate the endo-bridged system 10 as a structural proof for one of the solvolysis products of longicamphenilyl tosylate. Further information on β-enolization in polycyclic systems was provided by Arigoni and co-workers (62) who examined deuterium exchange in longicamphor (11) and copacamphor (12) under β-enolization conditions. While 11 was found to incorporate up to three atoms of



11



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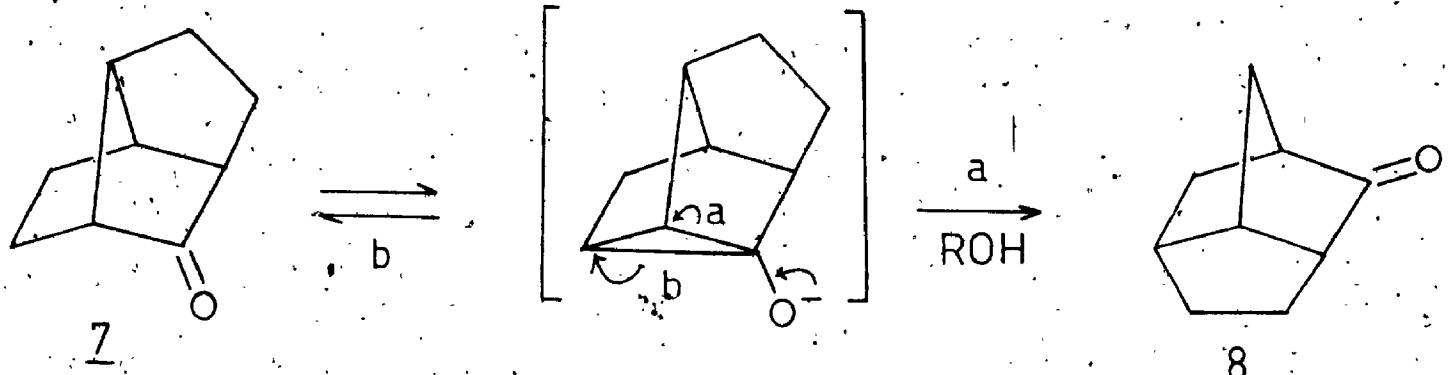
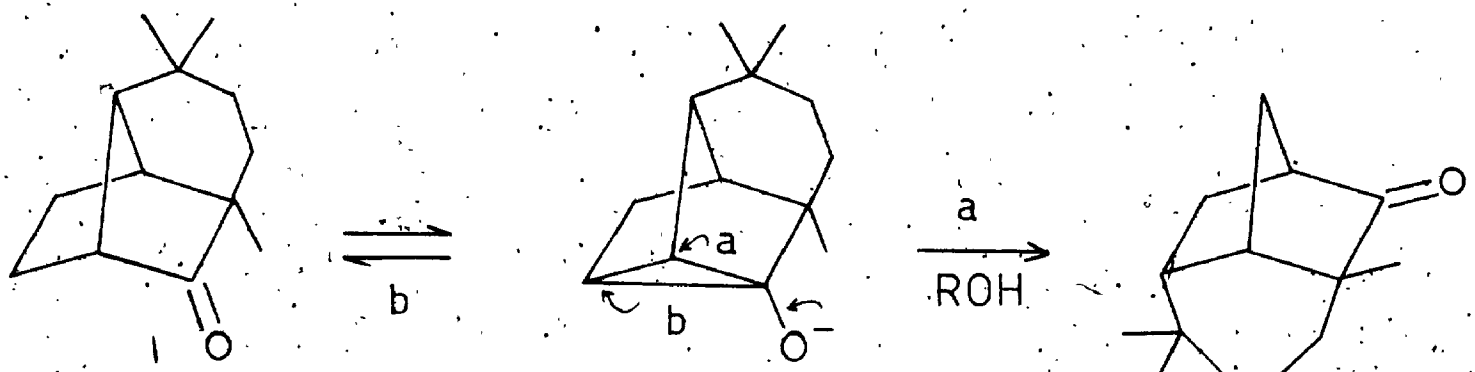
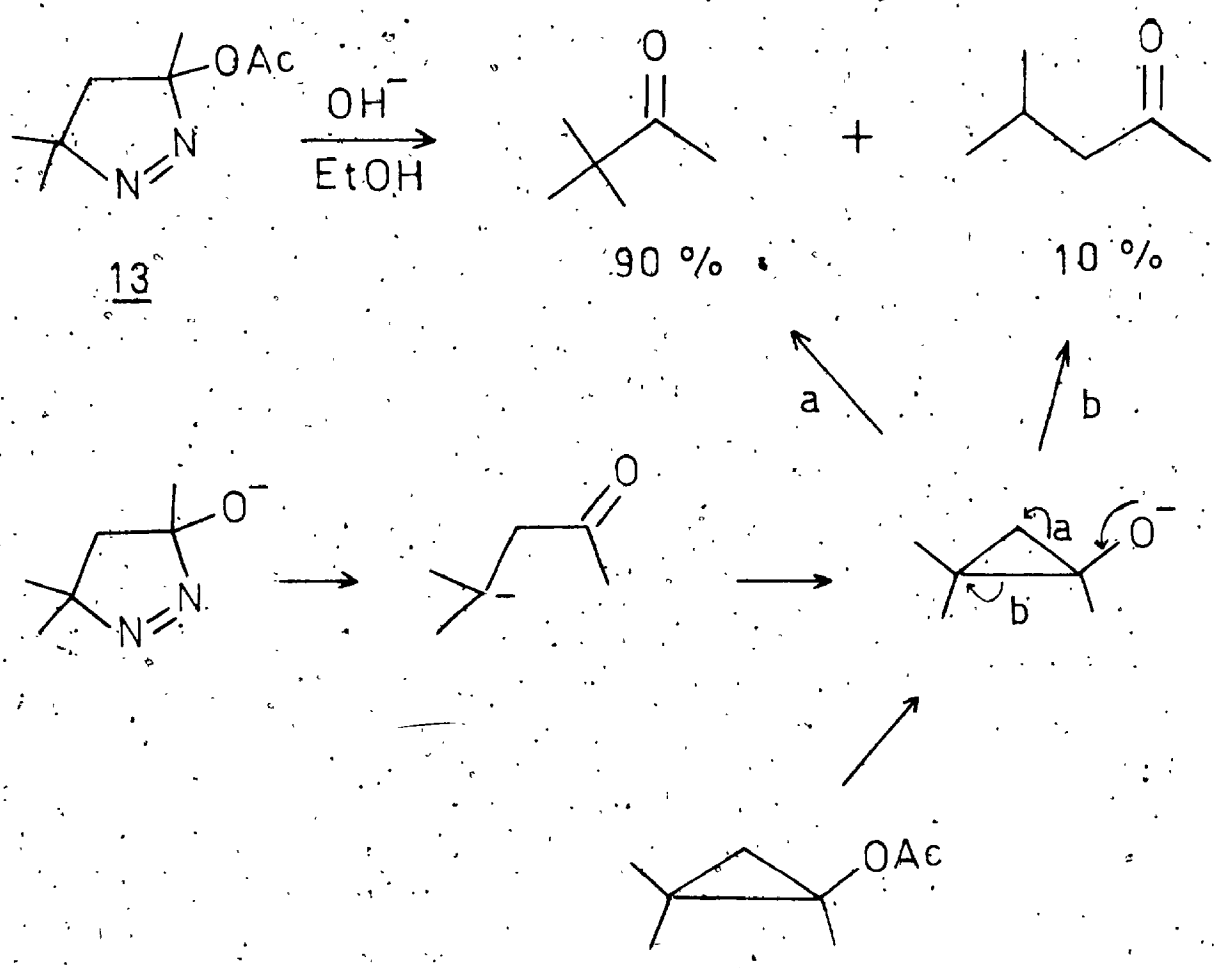


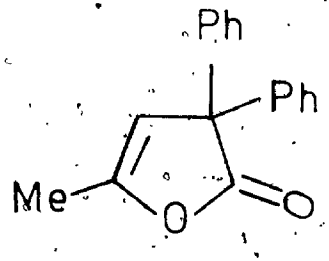
7 8



9 10

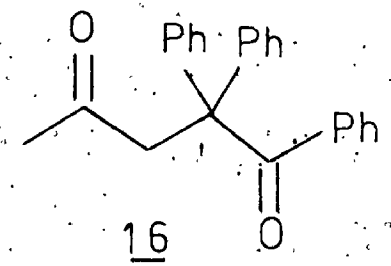
deuterium, only mono-deuteration was observed for 12, exclusively at the α-position. Clearly the additional deuterium incorporation in 11 shows that β-enolization has occurred. The lack of more remote exchange in 12 was attributed to the additional strain imposed by the three-membered ring in the bicyclo(2.2.1)heptane system but it seems somewhat surprising that 12 failed to β-enolize in view of the brexan-2-one ⟶ brendan-2-one conversion; perhaps more vigorous conditions and / or a longer reaction time would cause more extensive deuterium exchange. In addition to these polycyclic examples, β-enolization has been invoked to account for the results in two monocyclic examples. Alkaline hydrolysis of 3,5,5-trimethyl-3-acetoxyl-Δ-pyrazoline (13) yielded pinacolone as the major product (90%) and methyl isobutyl ketone as the minor product (10%) (63). These results can be interpreted in term of a β-enolate intermediate which is formed faster than the open chain anion is captured by solvent. The same product distribution was observed upon hydrolysis of 1,2,2-trimethyl-1-acetoxy-cyclopropane (14) (63). Reaction of 4-hydroxy-2,2-diphenyl-3-pentenoic acid lactone (15) with phenyllithium (64) leads to the formation of three open chain ketones: 1,2,2-triphenyl-1,4-pentadione (16), 1,3,3-triphenyl-1,4-pentadione (17), and 3,3-diphenylpropiophenone (18). This rearrangement has been rationalized as occurring through two consecutive β-enolate anions (19a, b) and ^{13}C labeling experiments afforded evidence for a pathway involving two β-enolate ions (65). It was demonstrated that reaction of C-3 labeled 4-hydroxy-2,2,4-triphenyl-3-butenoic acid lactone (20) with


OAc
OH⁻
EtOH
O
O
+
90 %
10 %
13
a
b
O⁻
O
N
N
a
b
O⁻
OAc
14

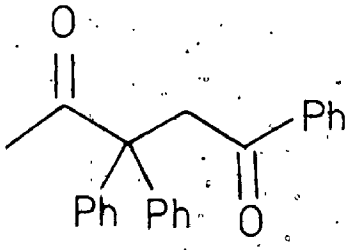


15

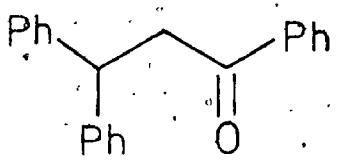
① PhLi
② H_2O



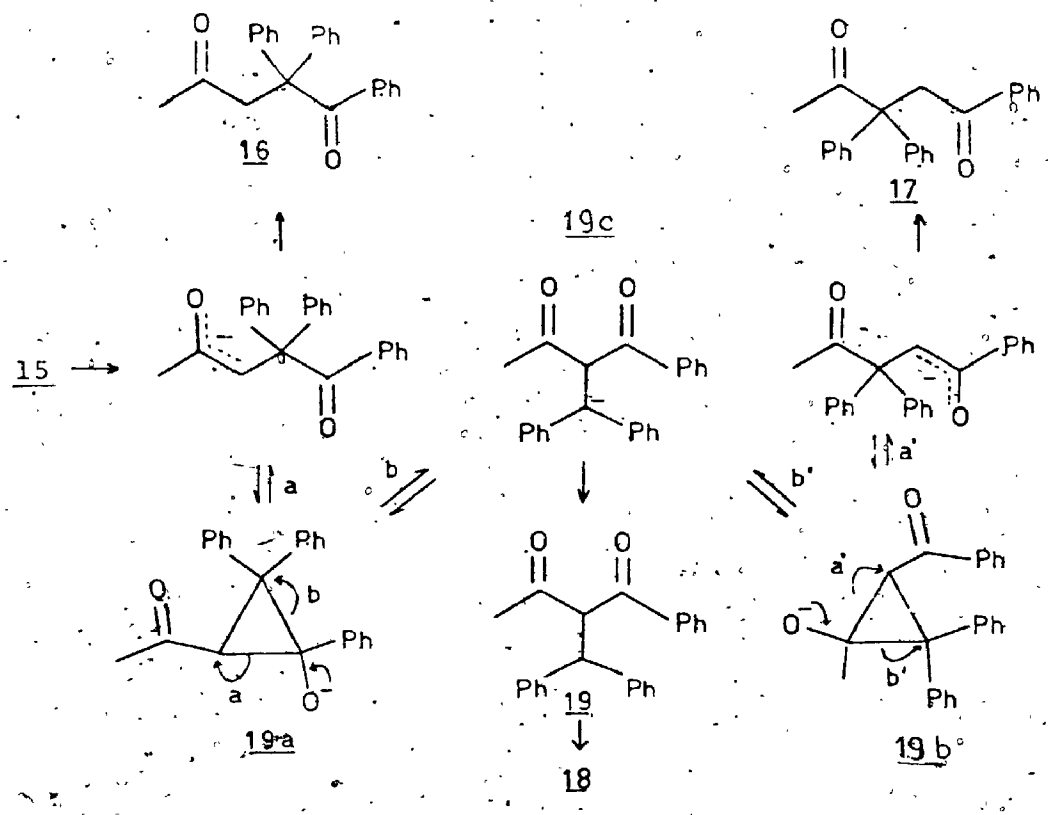
16 42 %



17 4 %



18 6 %


16
17
19c
15
a
b
a'
b'
19a
19
18
19b

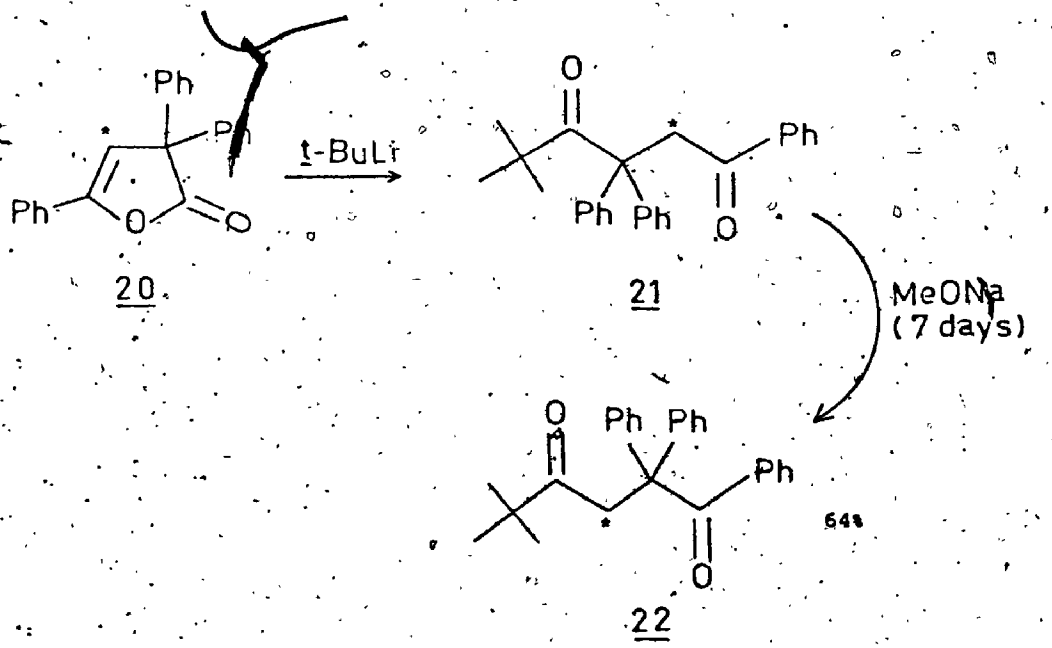
t-butyllithium gave 21 labeled at C-2 and rearrangement of labeled 21 with sodium methoxide gave labeled 22. The formation of 18 can most readily explained in terms of the formation of 19c, which in the protic medium is protonated to give 19d which in turn undergoes methanolysis to give 18.

Recently, Stothers and Rampersad (66) have found that 5,5,7,7-tetramethylundecan-6-one (23) rearranges to 5,5,8-trimethyldodecan-6-one (24), under homoenolization conditions. Under the same conditions no rearrangement product was detected for 5,5,7-trimethylundecan-6-one.

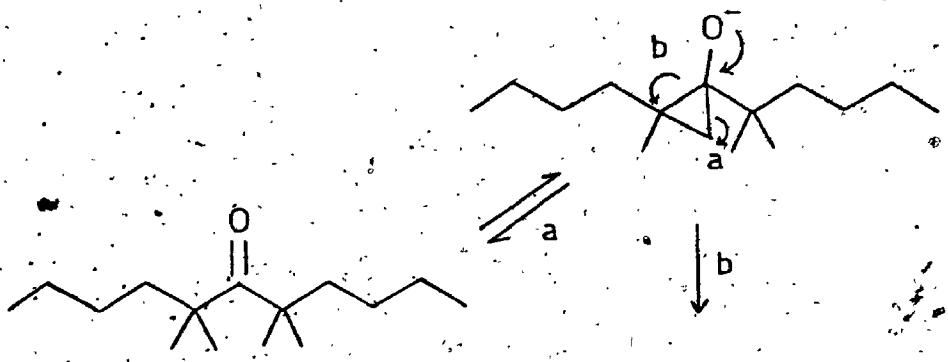
Evidence that β-enolization can occur concurrently with α-enolization in bridgehead ketones containing an α-methylene group was recently presented (67). The endo and exo-isocamphanones (25a and b, respectively) are interconvertible via a common β-enolate ion 26 which could also lead to camphor (25c). The interconversion of 25a ⇌ 25b gave further evidence for preferential exo-protonation of 26. Since 25a gave only 1.5% 25b whereas, under comparable conditions, 25b gave 42% 25a; in these experiments the relative yields of camphor were 58% and 22%, respectively.

Each of the foregoing examples involved proton abstraction from a β-position of the ketone but more remote abstraction should also be possible and has in fact been observed at the syn-methyl of camphor (68). The half-cage ketone 27, also undergoes γ-enolization and rearranges to 28 (69). Homoketoniztion of the bird-cage alcohol 29, the expected intermediate alkoxide species, gave the same mixture of 27 and 28, heavily favoring the latter (69).

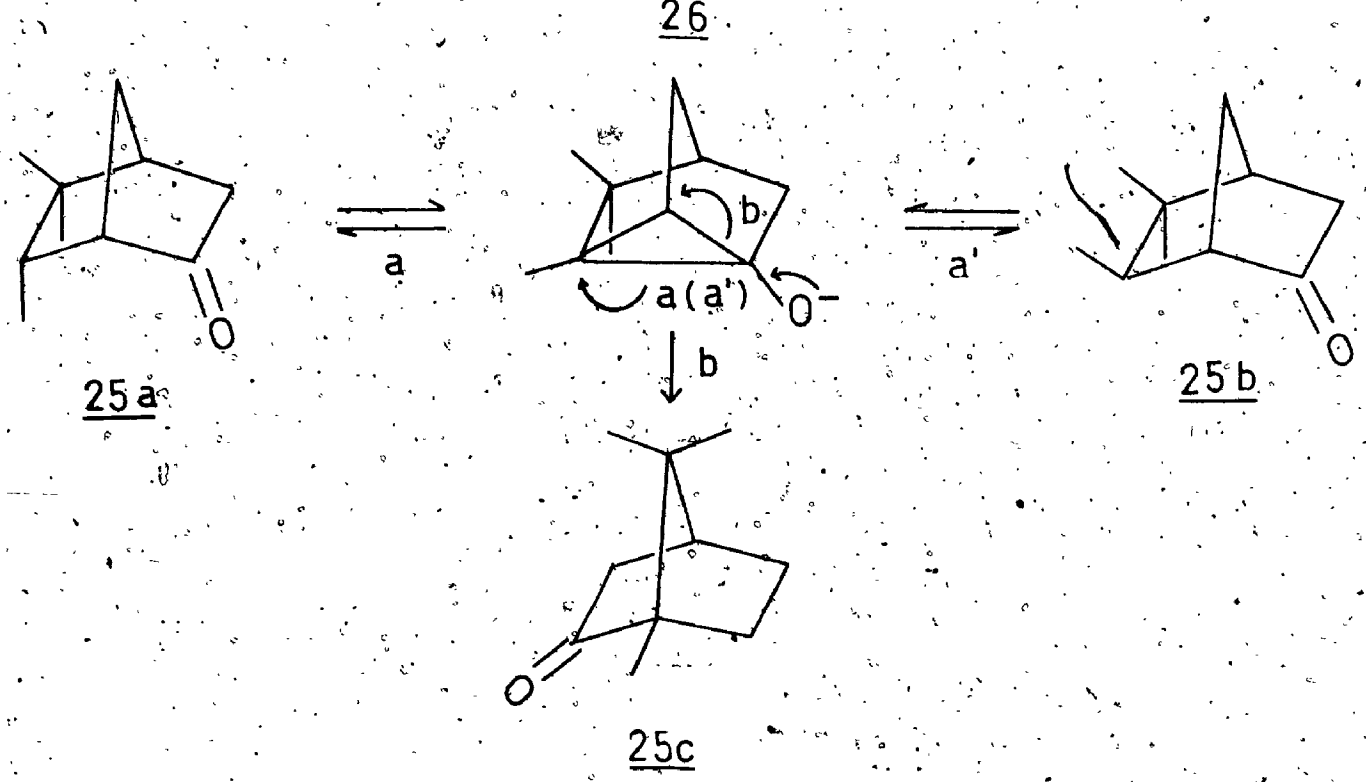
Stothers and his co-workers recently have reported the first



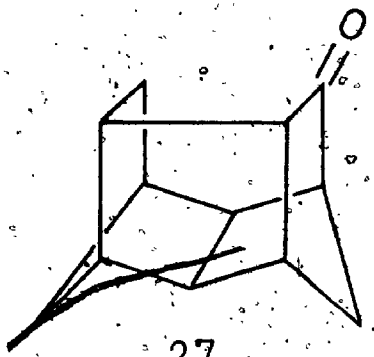
20 21 22



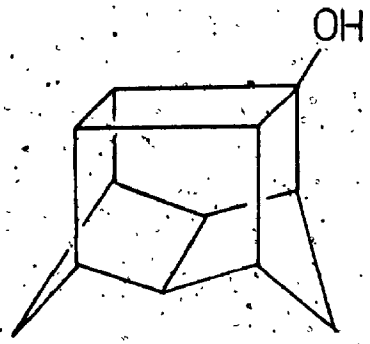
23 24



25a 25c 25b



27



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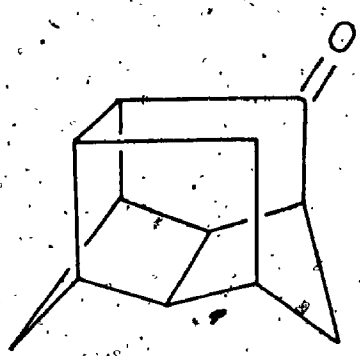
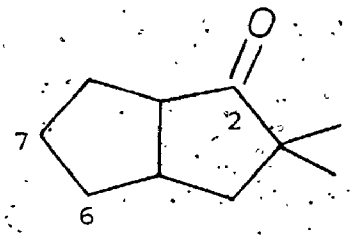


28

example of γ-enolization in a relatively flexible carbon skeleton, i.e. 3,3-dimethylbicyclo(3.3.0)octan-2-one (30) (59). Under homoenolization conditions, deuterium exchange occurred at six carbons (nine sites) in 30: H-1, H-6, H-7 and H-8 and the methyls. The presence of deuterium at C-6 and C-7 clearly implies that γ-enolates are intermediates.

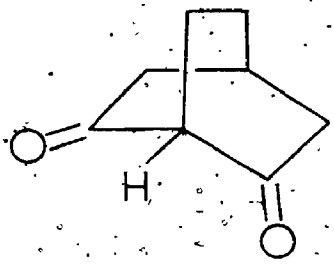


30

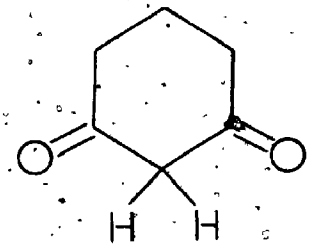
(b) α-ENOLIZATION

The contribution of the carbonyl function to carbanion stability has normally been thought to result from delocalization of the electron pair onto the more electronegative oxygen if the enolate were planar or near planar, at least when free of restrictions of ring systems (70). Deformation from the planar state in response to steric, solvation, or ring constraint effects will completely destroy the conjugative effect only in the extreme case in which a dihedral angle of 90° is enforced between the plane of the carbanion and that of the carbonyl group. A good example of the loss of acidity of a carbon acid due to steric inhibition of resonance of its conjugate base is found in the work of Bartlett and Woods (71). These authors found that the bicyclic diketone 31 is much less acidic than its monocyclic analog 32.

The pair of electrons of the bridgehead anion of the bicyclic system are held in a sp^3 orbital whose angular disposition makes overlap with

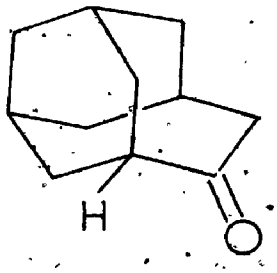


31



32

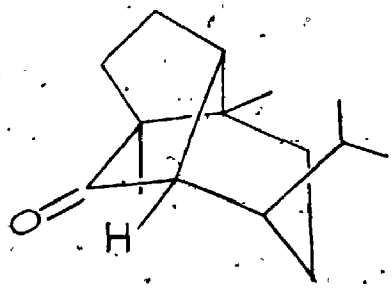
the p-orbitals of the carbonyl group minimal. The anion from homoadamantan-4-one (33) on the bridgehead side is, however, evidently too restrained to form even under severe enolization conditions such as t-butoxide in t-butanol-d at reflux (72).



33

While delocalization of charge to the more electronegative atom is undoubtedly the major factor in the stabilization of a carbanion adjacent to a carbonyl function, there is some question as to the extent to which a carbonyl function can stabilize an adjacent carbanion in other ways. A carbonyl group would be expected to provide inductive stabilization for an adjacent negative charge. Although orbital overlap has been recognized as the principal factor in acidifying α-hydrogens, the experimental conditions which are required to effect abstraction of α-hydrogens

in the absence of any orbital overlap factor have been reported. Gassman and Zeler have demonstrated (73) that a carbonyl group, through its inductive effect alone, could acidify α-hydrogens sufficently to permit proton abstraction by potassium t-butoxide at temperatures in the vicinity of 200°. For example, bicyclo(2.2.1)heptan-7-one incorporates up to 25% of deuterium per bridgehead carbon after treatment at high temperature with potassium t-butoxide in t-butyl-O-d. Also, in copacamphor (12) and ent-17-norkauran-16-one (34), the indicated bridgeheads undergo exchange in the presence of t-butoxide at high temperatures (185° for 12 (62) and 172° for 34 (74)). The bridgehead enolates in each of these ketones involves a transoid double bond in a seven-membered ring. Recently, Nickon and his co-workers (76) have reported that a remarkably easy bridgehead exchange occurs at C-3 in brendan-2-one (8) in which the corresponding



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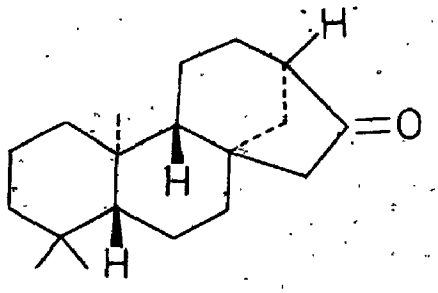

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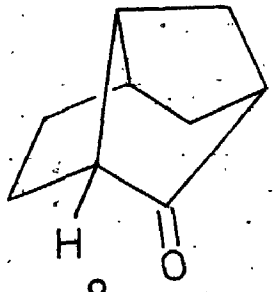


8

anti-Bredt enolate also contains a transoid olefin in a seven-membered ring.

(c) NMR TECHNIQUE

In the earlier work on homoenolization, a variety of techniques was employed to establish the course of deuterium exchange through homoenolate anions. For example, the details of camphenilone homoenolization were elucidated through a combination of ^{1}H NMR, infrared and mass spectra, together with separate synthesis of deuterated analogs (57). In some cases, deuterium tracers may often be monitored successfully by proton NMR spectroscopy. But this approach is impractical for cases in which several pairs of sites in the same system undergo exchange. In many such systems the proton spectra are not easy to analyse. Despite the recent availability of lanthanide shift reagents to simplify the spectral analysis (76), precise measurement of the lightly deuterated sites is still difficult. In this chapter, homoenolization studies of several ketones serve to illustrate how similar information can be obtained much more easily by ^{13}C and ^{2}H NMR studies. Reaction mechanisms studied by ^{13}C NMR techniques have been reviewed recently (23).

(i) ^{13}C NMR

Carbon resonances of organic compounds are found over a chemical shift range of 600 ppm, compared with under 20 ppm for proton nuclei. With modern instrumental methods, it is also possible to have narrower resonance lines in ^{13}C NMR than for ^{1}H spectra because ^{1}H spectra are extensively spin-coupled, leading to broadened resonance bands for most protons. Thus it is not unusual in ^{13}C NMR to be able to identify individual resonances for each carbon in a compound whose molecular

weight is 300 - 500. In effect this readily permits one to follow the fate of an individual center throughout a reaction or reaction sequence by isotopic enrichment (23).

The characteristic effects produced by a deuterium atom in the absorption of its neighbouring carbons because of isotope shifts and spin-spin coupling are readily detectable in natural abundance ^{13}C spectra obtained by Fourier transform operation (see chapter 2). Comparison of the ^{13}C spectrum of the labeled material with that of the unlabeled compound immediately reveals the site(s) of deuterium incorporation and integrated intensity data provide a measure of the deuterium content at the individual carbons. In practice, however, meaningful intensity data from ^{13}C spectra require careful selection of the optimum operating conditions, because of variations in relaxation times and in nuclear Overhauser enhancements (NOE) of nonequivalent carbons, and calibration data from spectra of the natural abundance material are required. Since the observed NOE produced by proton decoupling for a specific protonated carbon is independent of the number of directly bonded hydrogens (78), carbons bearing both hydrogen and deuterium should exhibit total intensities equal to those observed for the corresponding nuclei in unlabeled materials, if both samples are examined under identical operating conditions. For instance, the relative intensities of the $-CH_2-$ singlet and -CHD- triplet for a methylene carbon provide a direct assay of the deuterium content. Similarly, the corresponding assay for partially deuterated methyl carbons can be performed. For methine carbons, however, ^2H substitution renders the same comparison meaningless since the -CH- signal can experience a complete nuclear Overhauser effect, but the -CD- absorption cannot (the contribution of neighbour protons is

generally small). For the case of 50% deuterium exchange of a methine (-CH-) center having a maximum nuclear Overhauser effect, each component of the -CD- triplet could be only 11% as intense as the -CH- signal (i.e. the relative intensities of the -CH- and -CD- absorptions will differ by a factor of 3). Thus, without a precise determination of the nuclear Overhauser effect for this centre, the deuterium content cannot be measured by comparison of the two sets of signals. Furthermore, T_1 for the -CD- carbon will be longer than T_1 for the -CH- carbon. Thus, unless very long pulse intervals are used, the -CD- intensity will be reduced by partial saturation. The difference in individual -CD- and -CH- signal strengths of about an order of magnitude demands a high signal and noise ratio spectrum. These difficulties are obviated, however, by a determination of the decrease in relative intensity of the -CH- signal with respect to those of undeuterated carbons and the calibration data for an unlabeled sample.

Since the total deuterium content in a sample may be readily and precisely determined by mass spectrometry. A comparison of this value with the sum of the deuterium contents for individual centers within the molecule as assayed by ^{13}C NMR provides a check for the latter measurements. In our experience, the precision of quantitative assessment of the deuterium content at individual center is, at best, 3 - 5% and, thus, lightly labeled centers can be missed. Another deficiency of the ^{13}C method concerns exchange at methylene carbons bearing nonequivalent hydrogens. In general, The ^{13}C absorption

pattern will be the same regardless of which hydrogen undergoes exchange. Hence, information on the stereochemistry of exchange at such methylene carbons is unavailable from the ^{13}C spectrum.

(ii) ^{2}H NMR

The chemical shift range of ^{2}H nuclei is essentially the same in parts per million as that of ^{1}H. Due to the low gyromagnetic ratio of ^{2}H, a 10 ppm range is only 154 Hz for a magnetic field of 23 KG. However, with reasonable linewidths, this is quite sufficient to allow distinction between chemical environments that are only slightly different when the samples are ^{1}H-decoupled. In contrast, ^{2}H spin-spin coupling constants are substantially smaller than ^{1}H coupling constants. In systems differing only in terms of isotopic substitution, $J_{DD} = J_{HH} / (6.51)^2$, $J_{HD} = J_{HH} / 6.51$. These simple considerations alone and the usefulness of lanthanide shift reagents to simplify the spectral analysis by increasing the shift dispersion suggest a host of possible applications of ^{2}H NMR for mechanistic studies.

In the present case, the use of ^{2}H spectra of the labeled compounds neatly overcomes the major deficiencies of the ^{13}C method. Since magnetic relaxation of ^{2}H nuclei is induced entirely by an intramolecular quadrupole mechanism (79) there is no Overhauser enhancement accompanying proton-decoupling. In addition, ^{2}H relaxation times are relatively short (80) which minimizes the possibilty of partial saturation. These two features circumvent the major pitfalls associated with ^{13}C spectra and render integrations of ^{2}H spectra more favorable. Another advantage of ^{2}H NMR spectroscopy accrues

from the low natural abundance of ^2H, 0.015%. Thus, even at low incorporation levels of ca. 1%, the NMR signals of ^2H labels will be about two orders of magnitude more intense than the natural abundance signals and one can readily monitor lightly deuterated centers. With ^1H decoupling and the absence of other magnetic nuclei, ^2H spectra consist of relatively narrow singlets having half-widths of ca. 1 Hz for each nonequivalent site. Although the shieldings for ^1H and ^2H in identical environments are the same, on a ppm scale, for observations at the same magnetic field (25), the shift range for ^2H nuclei is reduced by a factor of 6.5 because of the lower magnetogyric ratio and the spectra of compounds containing similar but nonequivalent ^2H nuclei may have heavily overlapping signals. In many cases, this inconvenience may be reduced through the use of lanthanide shift reagents to obtain greater shift dispersion (76). Even with overlapping signals, however, precise integrated intensities may be obtained by computer line-shape fitting rather than the usual electronic integration. Our experience indicates that the line-shape fitting technique permits precision of the order 1 - 2%. The major deficiency of the ^2H NMR technique is that spectra for complicated systems lacking a complexing center for interaction with a shift reagent are not easy to analyze because the ^2H signals overlap severly; but, ^{13}C NMR spectra may help to solve some of these problems.

(d) PURPOSE

The main purpose of the present work is to examine the use of ^2H labels and ^{13}C and / or ^2H NMR analysis for mechanistic investigations. Furthermore, we have also continued to explore the mechanistic features and synthetic scope of the homoenolization of polycyclic ketones.

The results of a detailed examination of the behavior of fenchone, 3,3-dimethylbicyclo(2.2.2)octan-2-one, 7,7-dimethylbicyclo(3.2.1)oct-

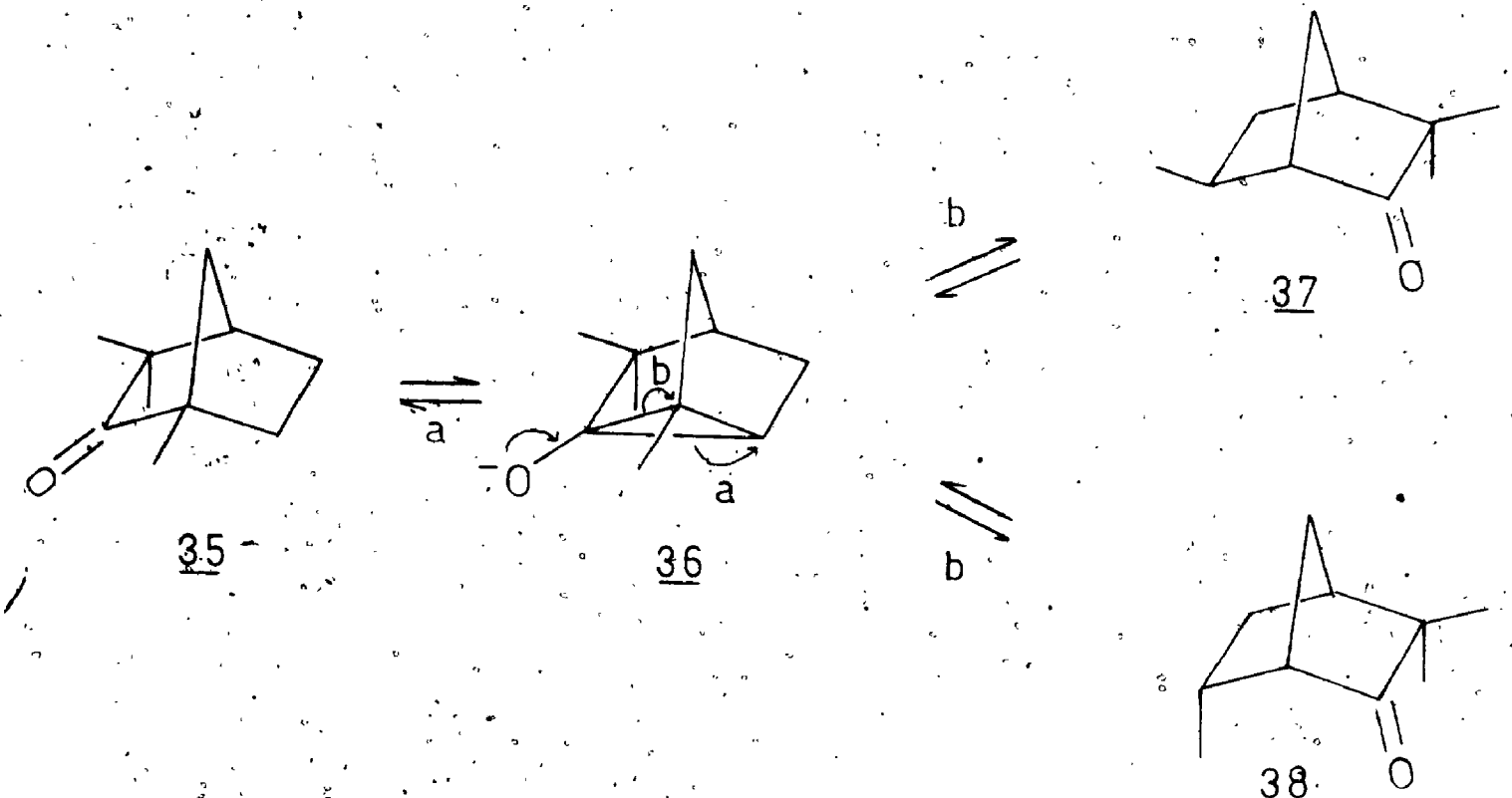
an-6-one, adamantanone, 2,2,5,5-tetramethylcyclopentanone, 2,2,6,6-tetramethylcyclohexanone, 2,2,7,7-tetramethylcycloheptanone amd 2,2,8,8-tetramethylcyclooctanone under homoenolization conditions, namely at 185° in t-butoxide / t-butyl-O-d are presented in this chapter.

(B) FENCHONE

(a) RESULTS

(i) ^{13}C NMR ASSESSMENT OF DEUTERIUM INCORPORATION

Fenchone differs structurally from camphenilone only by the replacement of the C-1 bridgehead hydrogen in camphenilone with a methyl group in fenchone. Fenchone (35) therefore has a total of fourteen protons on carbons β to the carbonyl plus two protons on C-5, γ to the carbonyl. Analogous behavior to that of camphenilone (4) was expected but the unsymmetrical homoenolate ion (36), in contrast to camphenilone, could lead to rearranged products 37 and 38. It could also reveal stereoselectively of exchange at the exo and endo-methyl carbons, C-8 and C-9. In the first set of experiments, the progress of deuterium incorporation in fenchone was monitored with ^{13}C NMR and mass spectrometry (67). To make the story systematic and complete, I would like to use these results to illustrate first how one ^{13}C NMR spectral analysis can provide directly the content of deuterium at the individual sites of exchange. From the ^{13}C spectra, the specific carbons undergoing exchange were readily revealed because of the distinctive spectral change produced



35 36 37 38

by deuterium incorporation (see chapter 2); spectra of two samples after treatment with t-BuO / t-BuOD at 185° are reproduced in Figure 3.1. After 60 hr the characteristic 1:1:1 triplet is evident for C-6, while the absorption of C-5 and C-1 contain an isotope-shifted component indicative of one geminal deuterium. After 400 hr, the $-CH_2-$ signal for C-6 was very much reduced and the C-5 and C-1 absorption contained two isotope-shifted components indicative of molecules with one and with two geminal atoms. In addition, a 1:1:1 triplet for C-8 was apparent. Careful integration of the ^{13}C absorption for all protonated and partially protonated carbons gave a measure of the ^2H content at C-6 and the exo-methyl group. For example, the C-6 absorption consisted of a singlet identical to that in normal fenchone and a -CHD- triplet, the relative intensity of the latter provides a measure of the extent of monodeuteration at this center. From the intensities of the non-deuterated carbons, a "standard" intensity for a single carbon for each sample was obtained as the average. The difference between this "standard" value and the sum of the $-CH_2-$ and -CHD- intensities gave the relative concentration of the $-CD_2-$ species. As a check on the ^2H assay by ^{13}C NMR, each sample was analyzed by mass spectrometry to obtain precise data on the ^2H content. These data for samples which were allowed to react for various times are listed in Table 3.1. The agreement between the total atoms ^2H / molecule obtained by mass spectrometry and ^{13}C NMR was gratifyingly good, even though the estimated error for the measurement of ^2H at individual carbons by ^{13}C NMR is ca. 5%.

To try to maximize the ^2H content in fenchone, one sample recovered

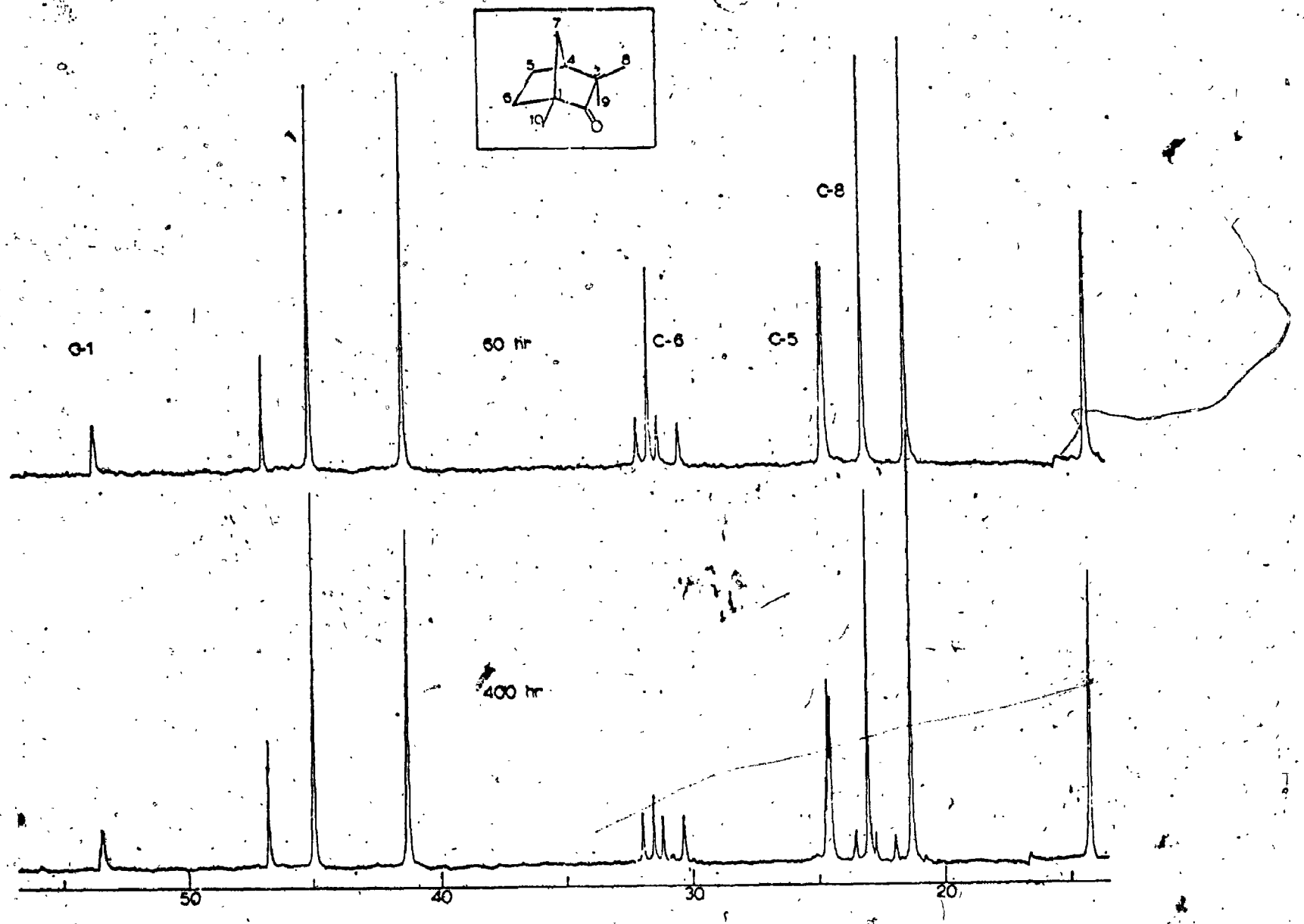


Figure 3.1. ^{13}C spectra of fenchone after treatment with t-BuOD/t-BuO$^-$ at 185° for the time indicated. The scale is in ppm from TMS.

Table 3.1

Deuteration in Fenchone at 185°

Time (hr)	^2H content by mass spectrometry[a]							^2H assay by ^{13}C nmr[b]			
	1D	2D	3D	4D	5D	6D	Total atoms ^2H	CHD	CD_2	CH_2D	Total atom ^2H
60	0.468	0.071					0.61	0.42	0.07		0.56
140	0.589	0.188	0.015				1.01	0.59	0.19	0.07	1.04
272	0.381	0.387	0.111	0.015			1.55	0.44	0.42	0.17	1.45
400	0.342	0.404	0.143	0.022	0.005		1.69	0.36	0.50	0.25	1.61
400[c]	0.278	0.497	0.144	0.035	0.009		1.86	0.33	0.68	0.27	1.96
800[d]	0.206	0.457	0.238	0.055	0.009	0.001	2×10^6	[e]	[e]	0.40	--

[a] Atoms ^2H, ± 0.001

[b] Atoms ^2H, ± 0.05

[c] Fenchone-d_x from a 140 hr run was treated with fresh t-BuO⁻/t-BuOD for 250 hr.

[d] Fenchone-d_x from a 400 hr run was treated with fresh base for an additional 400 hr.

[e] The C-6 absorption was too complex for precise integration (see text).

after 140 hr was treated again with a fresh deuterium pool for 260 hr and a sample from a 400 hr run was reacted with fresh base for an additional 400 hr. From the latter experiment it was apparent that up to 6 deuterium atoms were incorporated into fenchone under homo-enolization conditions; this result is in complete accord with some preliminary data obtained by Lambert (68) several years ago. The ^{13}C spectrum of this sample very clearly served to point up some of the deficiencies in the ^{13}C NMR method for ^{2}H analysis. The presence of species containing more than five ^{2}H nuclei demands that exchange has occurred at centers in addition to C-6 and C-8. But the ^{2}H content at the lightly deuterated centers was not observable from the ^{13}C spectrum. In addition the exchange was so extensive at C-6 that the intensity of the "quintet" possibly a triplet of triplets, for the $-CD_2-$ containing molecules precluded precise integrations of the $-CH_2-$ and -CHD- absorptions. The intensity of the quintet is not meaningful for comparison with the intensities of the signals from protonated carbons, since the former absorption lacks the significant Overhauser enhancement produced by proton decoupling. Another weakness of the ^{13}C analysis is the fact that it is not possible to distinguish between exo and endo deuteration at C-6, only the total ^{2}H incorporation at this carbon can be assayed.

Notwithstanding these deficiencies, however, ^{13}C spectra can be valuable for quantitative analysis of deuterium incorporation in a host of systems. In the present case, the major result of the exchange was clearly apparent from the ^{13}C spectra and the total deuterium content was readily assayed for C-6 and C-8.

(ii) Identification of Rearrangement Products

Examination of the recovered material from each run by gas chromatography (g.c.) on SE 30 columns showed an additional peak, comprising 6-7% of the total product, having a longer retention time than that of fenchone (93 - 94% of the isolated product). Column chromatography on alumina of the total product decreased the second fraction to ca. 5% of the product obtained from the longer runs. Since the g.c. retention time corresponded to that of fenchol, there was apparently some reduction (~1%) of the fenchone, presumably by undissolved potassium metal. Some larger scale runs provided larger samples of the second fraction and, after removal of the alcohol, g.c. analysis of these on a DEGS column showed the minor fraction to contain two components in the ratio of ca. 1:3, although the peaks were not completely resolved.

Infrared and ^{13}C NMR spectra confirmed that these were ketonic and isomeric with fenchone since each contained three methyl, two methylene, three methine and one quaternary carbon signal in the high field region of the ^{13}C spectrum, besides a typical carbonyl carbon signal near 220 ppm (8). The positions of the individual resonances corresponded well for those expected for ketones 37 and 38, the 3,3,6-trimethyl-norcamphors which could arise from homoenolate 38 by cleavage of the bond between the original carbonyl carbon and C-1 in fenchone. The assignments are discussed later in conjunction with a ^{13}C study of several methyl substituted norcamphors (see chapter 4). For additional confirmation of the structure of these rearranged ketones, the mixture was reduced to the corresponding endo-alcohols with $LiAlH(OMe)_3$. The ^{13}C shieldings of these two alcohols also accorded well with those

expected for the endo-alcohols, corresponding to 37 and 38. These assignments will be discussed in Chapter 5. Thus it can be concluded that the homoenolate ion 36 opened in the two possible modes to produce fenchone or a mixture of 37 and 38. Since the concentration of the minor products never exceeded 7% even in the longest runs, this appears to be the equilibrium amount.

A sample of the mixture of rearranged ketones (37 and 38 in a ratio of 1 : 3) was treated with t-BuO$^-$ / t-BuOH at 185^o for 200 hr. The isolated product was examined by g.c.. It was found that the ratio of ketones was 20 : 5 : 75 for 37, 38, and 35, respectively, thus 38 is the more reactive of the rearranged ketones.

(iii) ^{2}H NMR Assessment of Deuterium Incorporation in Fenchone

A number of developments suggested that a second examination of fenchone homoenolization might be valuable. After obtaining the results discussed above; we extended our study of homoenolization to other cyclic and bicyclic systems and had some difficulty obtaining reproducible rates of deuterium incorporation. We found that a modified drying procedure of t-butyl alcohol-O-d$_1$ eliminated this problem. All subsequent work was done with t-butyl alcohol which tested for <0.005 M in water by Karl Fischer titration. The rate-depressing effect of water on t-BuO$^-$ / t-BuOH has been discussed by Cram et al. (81). It may be noted that the general precautions regarding the use of t-BuO$^-$ have been discussed recently (82); these problems have been circumented in the present work by generation of the base in situ. Since the NMR spectrometer had been modified to perform ^{2}H experiments in the Fourier transform mode, the direct examination of deuterated samples by ^{2}H NMR offered distinct advantages over the ^{13}C approach as

noted in the Introduction. Consequently, a second set of experiments was carried out for fenchone under homoenolization conditions.

A prime reason for this re-examination was to follow the rates of deuterium incorporation at the exo- and endo-6-position and to check for small extents of incorporation in the remaining two methyl groups (C-9 and C-10): features which could not be discerned by ^{13}C NMR. The ^{2}H spectra of samples of 35-d_x recovered after treatment with t-BuO$^-$ / t-BuOD consisted of three distinct absorptions at 5.79, 5.98 and 6.32 ppm upfield from the absorption of $CDCl_3$. These signals were tentatively assigned to the 6-exo-, 6-endo-, and C-8-methyl deuterons, respectively. In the ^{1}H spectrum of 35, the C-10 methyl group absorbs at 6.22 while the C-8 and C-9 protons are equivalent at 6.32 ppm upfield from $CHCl_3$ in $CHCl_3/C_6F_6$ (4:1) solution. Thus, this medium was inappropriate for the desired measurements, since the ^{2}H signals had line widths of 1.0 - 1.2 Hz (0.06 - 0.08 ppm). To increase the separation of the deuterium resonances as well as to obtain unequivocal proof for the assignments of the C-6 signals, spectra were obtained using Eu(fod)$_3$ and Pr(fod)$_3$ as shift reagents. The results with the latter reagent seemed better for our purposes and the shifts produced in its presence were examined in detail.

Upon addition of Pr(fod)$_3$ to solutions of 35-d_x in $CHCl_3/C_6F_6$ (4:1; v/v), each of the three signals noted above shifted to higher field with the central peak exhibiting the greatest relative shift. These shifts over the range of 0 - 0.36 equiv. of Pr(fod)$_3$ are plotted in Figure 3.2, together with the corresponding shifts for the remaining methyl protons as observed in the ^{1}H spectra. Decoupling experiments in

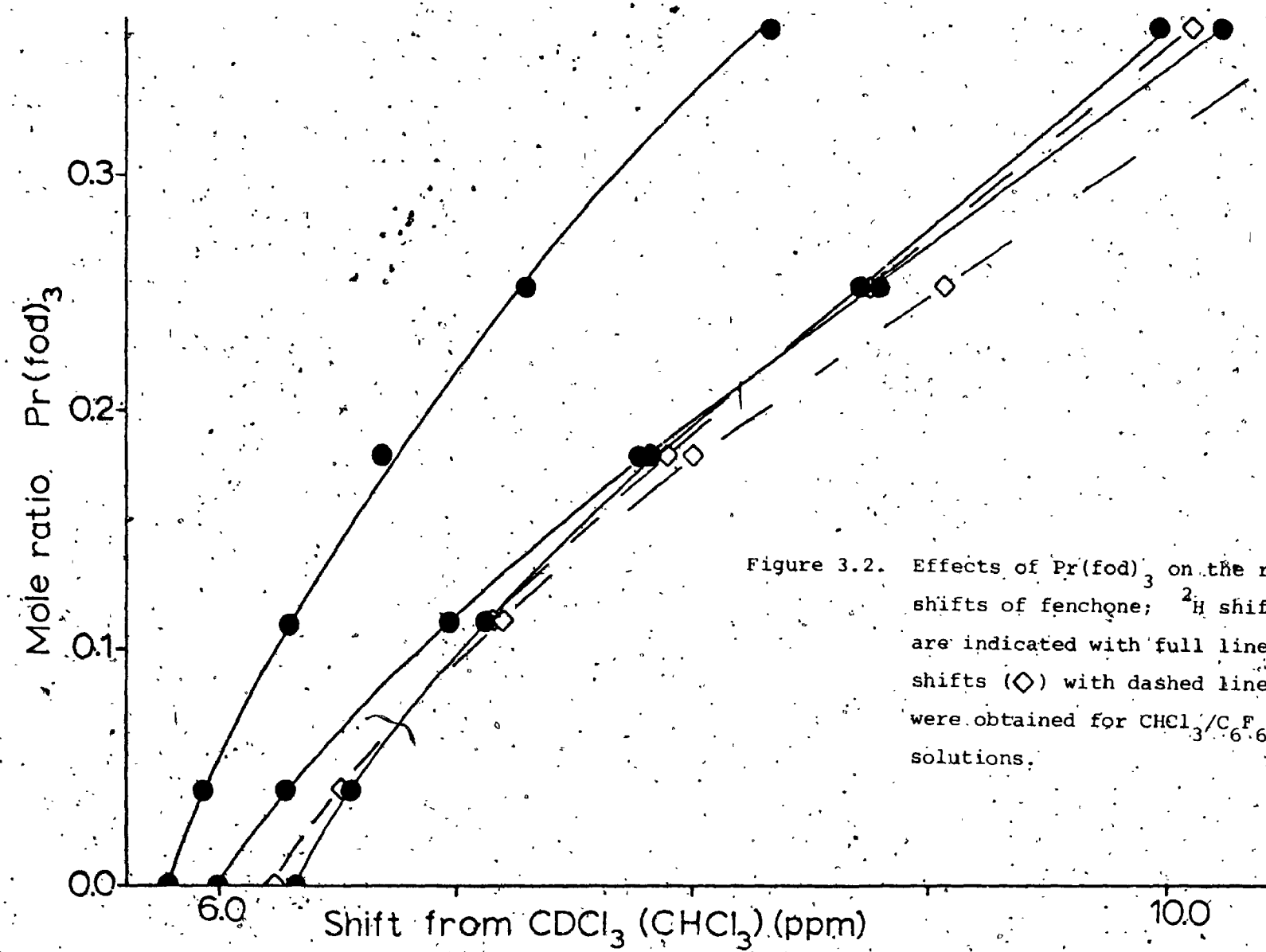


Figure 3.2. Effects of $Pr(fod)_3$ on the relative shifts of fenchone; ^2H shifts (●) are indicated with full lines, ^1H shifts (◇) with dashed lines. Spectra were obtained for $CHCl_3/C_6F_6$ (4:1; v/v) solutions.

the ^1H spectra confirmed the tentative assignments noted for the 6-deuterons. In the more dispersed spectra the methylene proton absorption at highest field was essentially a six-line pattern with repeated spacings of 13, 7 and 2 Hz correspondingly, in a first-order analysis, to the couplings with the exo-6, endo-5 and exo-5 protons, respectively. Double irradiation at the position of the exo-6 proton, as found from the ^2H spectrum, eliminated the larger of these splittings in the high field methylene proton pattern, confirming the assignments for the exo- and endo-6-deuterium nuclei. For the 35-d_x samples isolated after reaction with the base for relatively short times, ^2H spectra for solutions containing about 0.05 equiv. of $Pr(fod)_3$ were recorded and the relative intensities of the three absorption signals measured by line-shape fitting. An example is shown in Figure 3.3. These data, together with the total ^2H content determined for each sample by mass spectrometry, provided a measure of the relative extent of deuteration at the three positions.

From Figure 3.2, it is apparent that the three types of methyl protons show different shifts with added $Pr(fod)_3$ reagent so that, in principle, the ^2H spectra of heavily doped samples should permit the detection of deuterium at C-9 and C-10. In practice, however, the increased line broadening which accompanied the increased shifts produced by the lanthanide reagent gave spectra with insufficient resolution of the close-lying absorptions for good integrations, although it was apparent for the 40, 100, and 300 hr samples that some deuteration had occurred at C-9 and C-10. At somewhat lower concentrations of 35 in $CHCl_3/C_6F_6$ (1:4; v/v), the relative shifts are larger for comparable

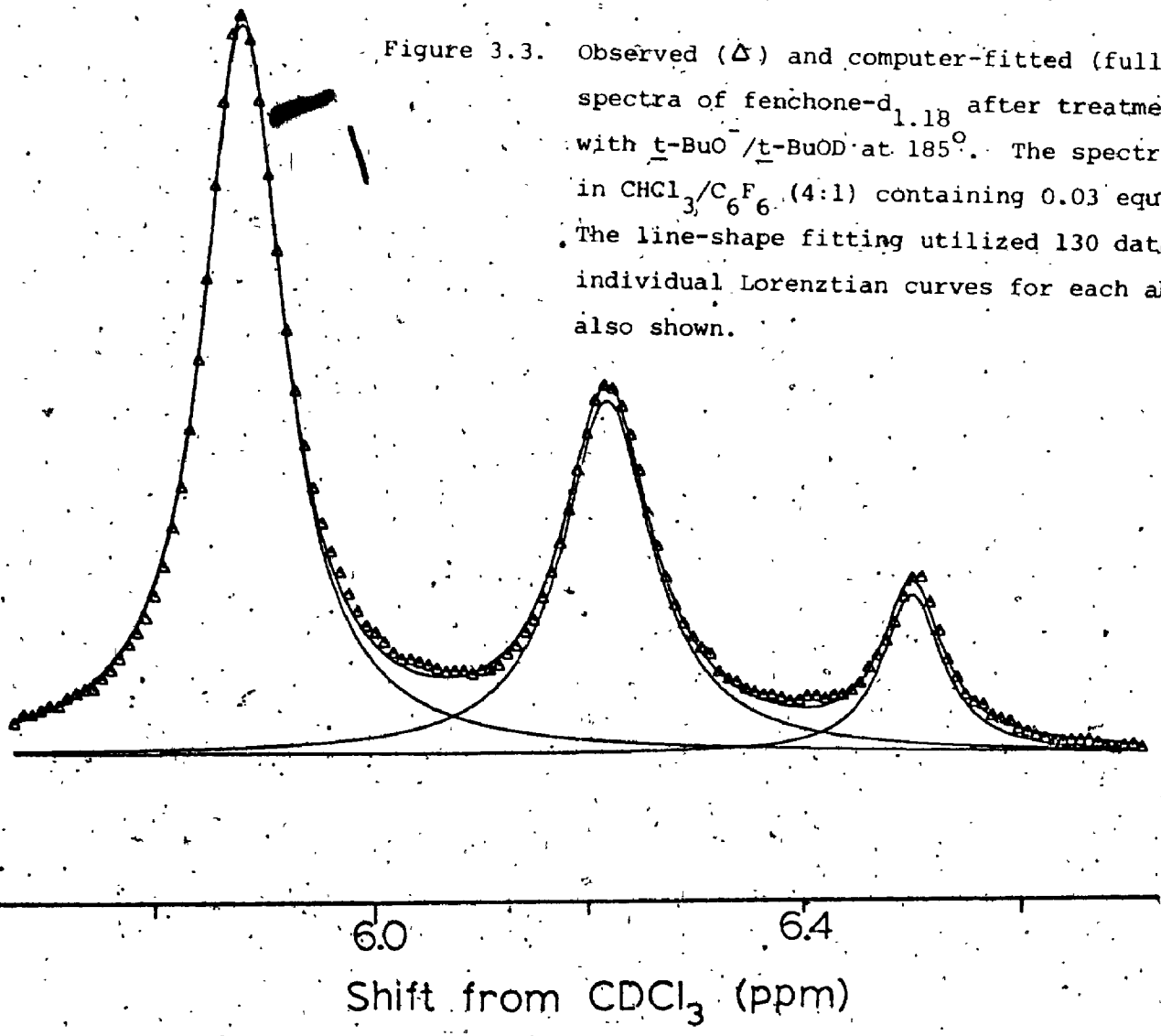


Figure 3.3. Observed (Δ) and computer-fitted (full line) ^2H spectra of fenchone-$d_{1.18}$ after treatment for 40 hr. with t-BuO^-/t-BuOD at 185°. The spectrum was obtained in $CHCl_3/C_6F_6$ (4:1) containing 0.03 equiv. of $Pr(fod)_3$. The line-shape fitting utilized 130 data points; the individual Lorenztian curves for each absorption are also shown.

amounts of added $Pr(fod)_3$; this solvent change was serendipitous. With 0.25 equiv. of $Pr(fod)_3$ five resonances were apparent in the ^2H spectrum of the 300 hr sample at 8.76, 10.66, 10.82, 11.04 and 11.50 ppm upfield from $CDCl_3$. From the relative intensities and the known effects of added $Pr(fod)_3$ these signals could be assigned to the exo-6, C-8, C-9 (or 10), endo-6, and C-10 (or 9) deuterons. It remained to distinguish unequivocally between the C-9 and C-10 signals. Since the assignments for the ^{13}C signals for each of the methyl carbons were known (see chapter 4). ^{13}C spectra of fenchone were recorded with added shift reagent $Pr(fod)_3$ to determine the relative shifts for each. These results are shown in Figure 3.4 from which it is apparent that the order of the methyl shieldings is unchanged with added shift reagent. In the ^1H spectrum of solutions containing 0.313 equiv. of $Pr(fod)_3$, the methyl protons absorbed at 10.95, 11.08, and 11.93 ppm upfield from $CHCl_3$. Selective proton decoupling at the highest field methyl protons gave a ^{13}C spectrum in which only the highest field carbon signal was decoupled; selective irradiation at the lowest field methyl protons decoupled only the third highest field ^{13}C signal. Thus, the shieldings of the methyl signals are in the same order in both ^1H and ^{13}C spectra, namely, C-8 < C-9 < C-10, and the assignments were completed for the ^2H spectra.

With the greater relative shift dispersion obtained in $CHCl_3/C_6F_6$ (1:4) solutions, ^2H spectra for 40, 100, and 300 hr samples were recorded and the extent of deuteration at C-6, C-8, C-9, and C-10 determined by line-shape fitting; the spectrum of a 300 hr sample is reproduced in Figure 3.5. The deuterium incorporation data for several samples from this second set of homoenolization experiments are listed in Table 3.2.

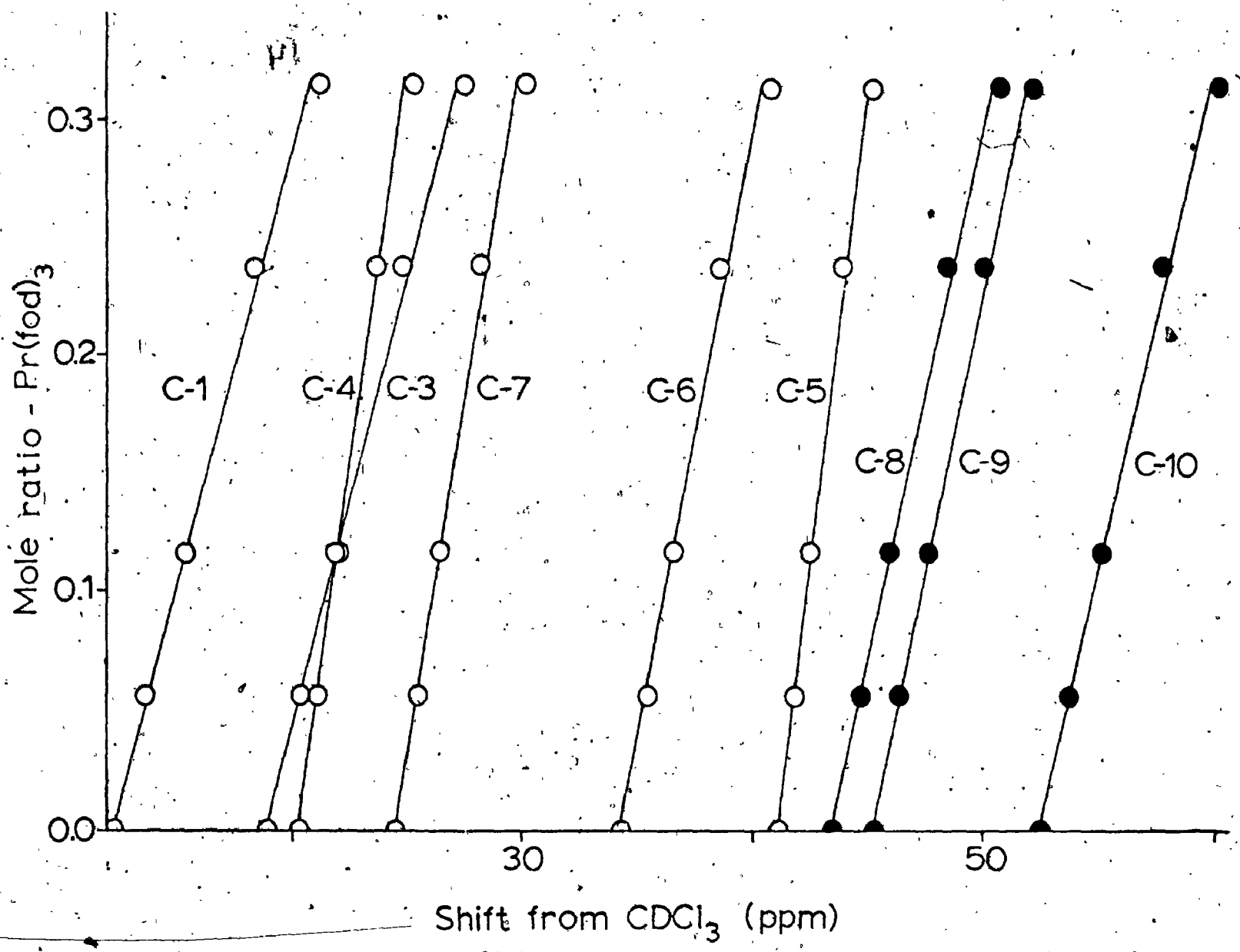


Figure 3.4. Effects of $Pr(fod)_3$ on the ^{13}C shieldings of fenchone. Spectra were obtained for $CDCl_3/C_6F_6$ (1:4; v/v) solutions.

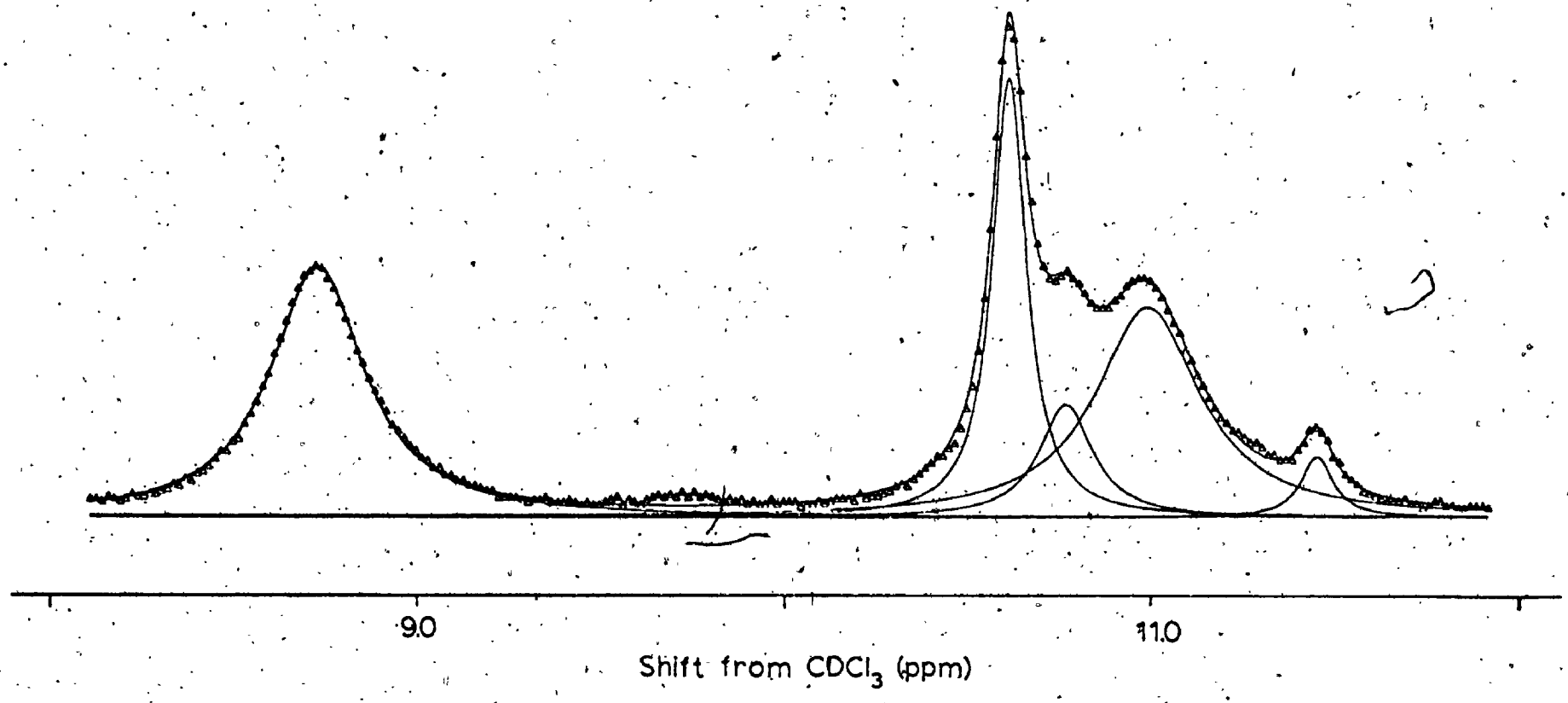


Figure 3.5. Experimental (Δ) and computer-fitted (full line) ^2H spectra of fenchone-$\underline{d}_{1.94}$ after treatment with $\underline{t}$-BuO$^-$/$\underline{t}$-BuOD at 185° for 300 hr. The spectrum was obtained in $CHCl_3/C_6F_6$ (1:4) containing 0.26 equiv. of Pr(fod)$_3$. The line-shape fitting was done with 472 data points but, for clarity, every second point is plotted. The individual Lorentzian curves for each signal are also shown.

Table 3.2

Deuterium Incorporation in Fenchone at 185°

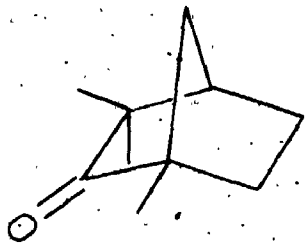
Time (hr)	^2H content by mass spectrometry[a]							^2H assay by ^2H nmr[b]					
	1D	2D	3D	4D	5D	6D	Total ^2H atoms	C-6		CH_3			
								exo	endo	Total	exo	endo	bridge
10	0.311	0.025					0.36	0.26	0.08	0.01_8			
20	0.399	0.040					0.48	0.34	0.12	0.02_5			
40	0.551	0.273	0.030				1.18	0.70	0.38	0.10	0.09		0.01
100	0.352	0.444	0.117	0.017			1.66	0.75	0.58	0.33	0.26	0.05	0.01_8
200	0.328	0.433	0.137	0.027	0.007		1.75	0.68	0.68	0.39			
300	0.286	0.370	0.190	0.059	0.014	0.005	1.94	0.65	0.64	0.65	0.42	0.16	0.06

[a] Atoms ^2H, ± 0.001.

[b] Atoms ^2H, ± 0.02.

(b) DISCUSSION

Fenchone (35) differs structurally from the camphenilone (4) system



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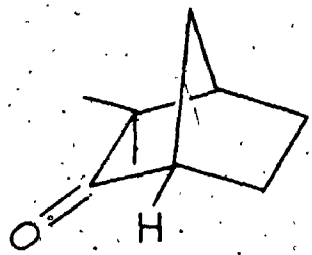
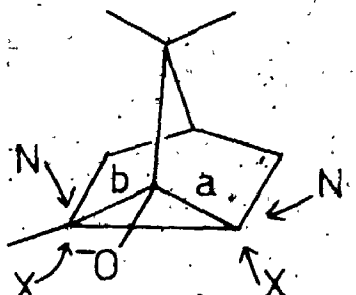


4

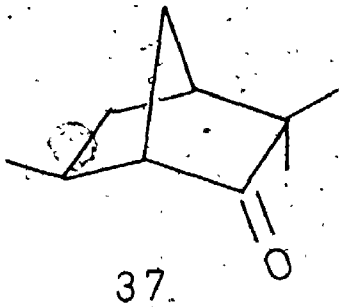
only in the replacement of the C-1 bridgehead hydrogen in camphenilone with a methyl group in fenchone. By analogy with camphenilone, the mechanism for deuterium exchange involves homoenolate intermediates, and the protons at C-6 were expected to be the most readily exchanged. Because of the asymmetry introduced by the C-1 methyl substituent, the fenchone homoenolate ion 36 cannot become symmetrical, and therefore rearrangement products are expected. Clearly, there are four ways in



36

which the ring opening in 36 can occur to give ketones. Cleavage of bond a with retention or inversion at C-6 produces endo-6-deuterio-35 or exo-6-deuterio-35, respectively (arrow N and X indicate endo- and exo-deuteration). Similarly, cleavage of bond b leads to the exo-

methyl derivative 37 (arrow N) or its endo-isomer 38 (arrow X). From



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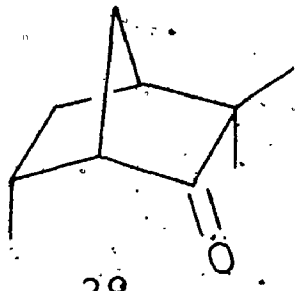


38

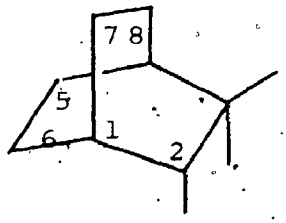
the results in Table 3.2, for the samples from the shorter times, according to the equation 1, one can estimate the pseudo first order

$$k = 2.303 / t \log (H)_o/(H)_t \quad \text{------} \quad 1$$

where $(H)_o$ is the hydrogen concentration at time zero and $(H)_t$ is the hydrogen concentration at time t.

rate constants for deuteration at the exo-6, endo-6, and exo-methyl positions as $\sim 7 \times 10^{-6}$, $\sim 2 \times 10^{-6}$, and $\sim 2 \times 10^{-7}$ sec^{-1} per hydrogen, respectively. From the rate constants, it is apparent that the bond a cleavage is favored by ca. 20 : 1, with exo-deuterium attack, i.e. inversion at C-6, favored over endo-deuteration by a factor of ca. 3.5. Since endo-3,3,6-trimethylnorboran-2-one is the more abundant of the two rearrangement products, inversion at the methyl bearing center with cleavage of bond b is also the favored pathway. Apparently, the realtive rates of endo and exo attack are similar for modes of cleavage a or b, since endo-6- (38) and exo-6,3,3-trimethylnorbornan-2-one (37) were formed in a ratio of ca. 3 : 1. Since exo-deuteration is favored

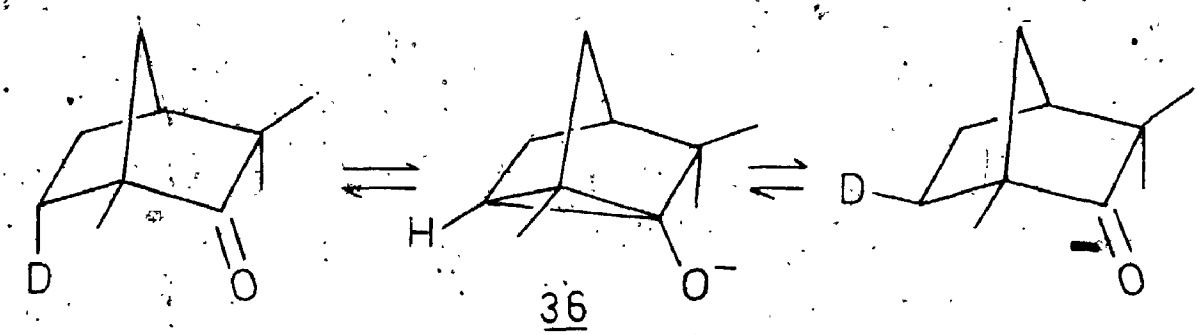
the product was analyzed by g.c. (20% SE 30 column) and showed two peaks, i.e. one is starting material and one is rearranged product. After 400 hr, the mixture contained 30% of rearrangement product and 70% of starting material (see Table 3.8). The structure of the rearrangement product was confirmed by comparison of its physical properties with an authetic sample of 45 prepared by the methylation of bicyclo(3.2.1)octan-6-one. Samples of 42-d_x isolated by preparative g.c., were examined by mass spectrometry and ^{13}C NMR. Although the ^{13}C NMR spectrum of 42 was attractively simple, by symmetry, the signals of interest unfortunately were not ideally separated for ^{2}H assay (Figure 3.6). Thus samples of 42-d_x were reduced to the corresponding alcohol 46,



46

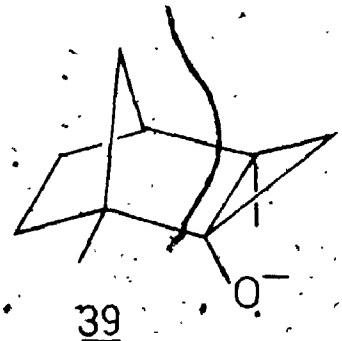
because the well known γ-effect of the hydroxyl group produces a large shielding difference between the methyl and the C-6 and -7 in 46 rendering better integration. Therefore their ^{13}C spectra were used for ^{2}H assay. From these ^{13}C spectra, the ^{2}H content at C-6, -7 and the methyl carbons were measured as described previously. Spectra of three samples are reproduced in Figure 3.7. The triplet characteristic of -CHD- groups was apparent only for the C-6 and -7 absorptions while isotope shifts for C-1, -5 and -8 were also

pathways avilable for deuterium exchange in the shorter reaction times



36

can be viewed as shown in Scheme 3.5 with two homoenolate ions 36 and 39 and the rate equations for this Scheme were numerically



39

integrated using the MIMIC simulation language of the CDC computer neglecting secondary kinetic isotope effects. The observed and computed ^2H concentrations at the three sites for 10, 20, and 40 hr runs are listed in Table 3.3 as obtained using $k_X : k_N : k_M$ of 3.5 : 1.0 : 0.085. Inclusion of a primary isotope effect of 4 - 5 for the inversion reactions, $k_{N'}$ and $k_{X'}$, led to consistently poorer agreement with experiment indicating that the isotope effect is <2. Effectively this partitions the homoenolate ion according to the relative rate constants $k_{X'}$ and $k_{N'}$, modified by the isotope effect of deuterium abstraction. Since the standard free energies of formation of endo- and exo-6-deuterio-35 are nearly equal, $k_{X'} = k_{N'}$ and assuming the isotope effects for exo

Scheme 3.5

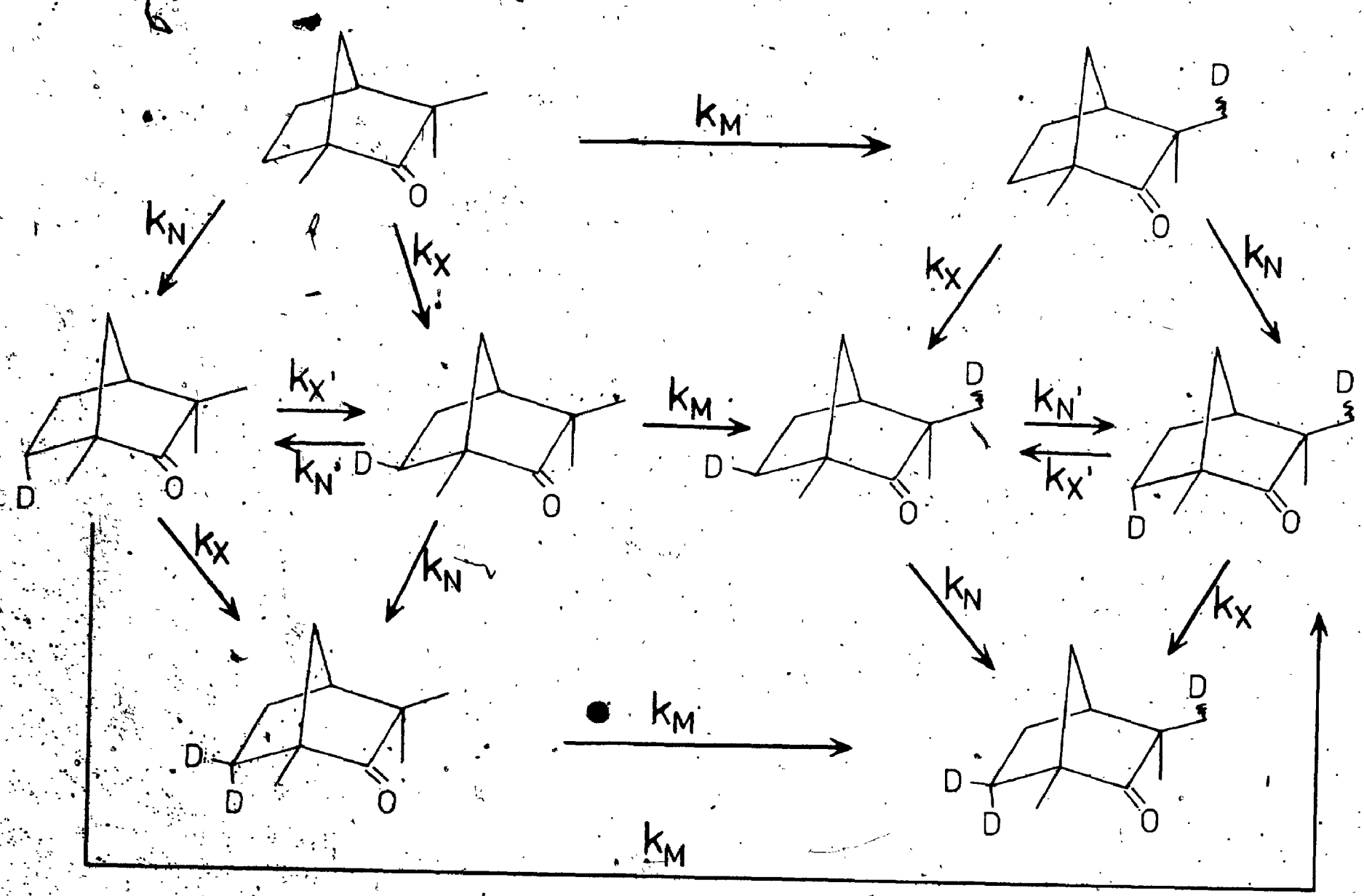


Table 3.3

Observed and Computed ^2H Incorporation[a] in Fenchone

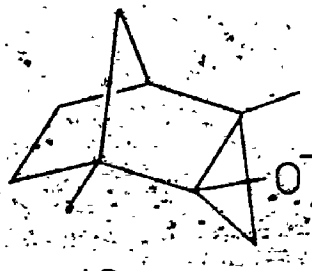
Time (hr)	Observed			Computed[b]		
	C-6		C-8	C-6		C-8
	exo	endo		exo	endo	
10	0.26	0.08	0.006	0.24	0.08	0.007
20	0.34	0.12	0.008	0.33	0.12	0.010
40	0.70	0.38	0.033	0.70	0.38	0.032

[a] Given as % ^2H / exchangeable hydrogen.

[b] For Scheme 3.1, using $k_N = 1.0$, $k_X = 3.5$; $k_{N'} = k_{X'} = 0.78$, $k_M = 0.085$.

and endo-deuterium abstraction to be equal it follows that $k_{X'} = k_X k_N / (k_X + k_N)$. $k_D/K_H = k_{N'}$.

For the samples from the longer reaction times (Table 3.2) it is apparent that the ^2H content at C-6 passes through a maximum and approaches an equilibrium value because of dilution of the deuterium pool by exchanged protons. The progressive increases in ^2H concentration at C-9 and C-10, therefore, can only provide lower limits for the estimated rates of exchange at these centers. It appears, however, that endo-methyl exchange (C-9) is ca. twice as fast as bridgehead methyl exchange (C-10) and approximately 25% as fast as exchange at the exo-methyl carbon. In any event, the stereoselectivity of methyl exchange is a new observation for homoenolization reactions. From the relative rates, $k^{C-8} \simeq 4k^{C-9} \simeq 10k^{C-10}$, the activation energies differ by ca. 1 kcal/mole. The fact that the rates are different for the three methyl carbons provides evidence for the intermediacy of homoenolate ions (39, 40 & 41) since the inductive effect of the carbonyl group, as an activating influence for proton abstraction, would be



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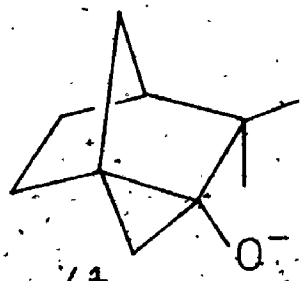


41

comparable at each methyl carbon. In principle, species such as 39, 40, and 41 could lead to ring expanded products but none was isolated or detected. This was not unexpected since cyclopropanols open in base

to give the product derived from the more stable carbanion (83) hence 39, 40, or 41 ---> 36 are the favored paths. The alternative ring opening of 39, 40, and 41 would lead to an enolizable ketone which could undergo condensation reactions. The stereoselectivity of methyl exchange as observed for fenchone could be useful for preparing selectively deuterated derivatives for other tracer studies.

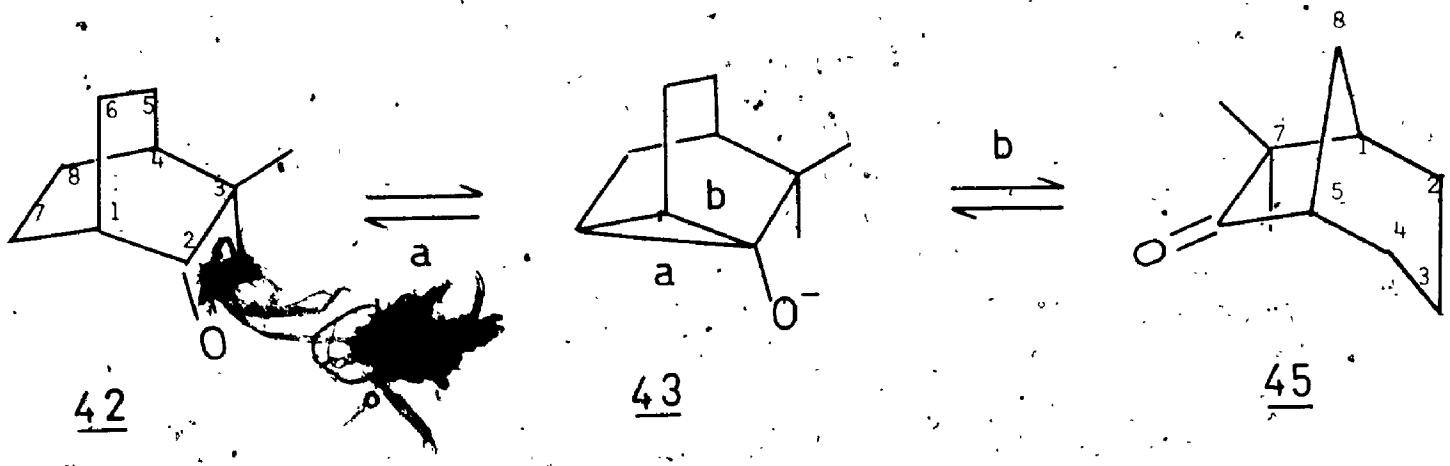
(C) 3,3-DIMETHYLBICYCLO(2.2.2)OCTAN-2-ONE (42) and 7,7-DIMETHYL-BICYCLO(3.2.1)OCTAN-6-ONE (45)

(a) INTRODUCTION

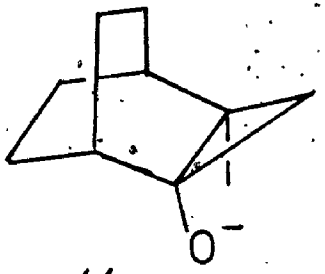
On the basis of previous studies of the formation of homoenolate anions from bicyclic ketones, 3,3-dimethylbicyclo(2.2.2)octan-2-one (42), in principle, could be expected to homoenolize at C-6, C-7 and the two methyl groups. Therefore, two different unsymmetrical homoenolate anions 43 and 44 could be expected to lead to rearranged products: 7,7-dimethylbicyclo(3.2.1)octan-6-one (45) and 4-methyl-bicyclo(3.2.2)nonan-2-one, respectively. Since homoenolate anion 43 is an intermediate between 42 and 45, they are interconvertible. Similarly, 45, in principle, could be expected to homoenolize at C-4, C-8 and the exo- and endo-methyls. Since bridgehead exchange had been reported for copacamphor (12) (62) and ent-17-norkauran-16-one (34) (74) under homoenolization conditions, bridgehead exchange could also be expected for 45. Deuterium exchange at C-1 had been detected in bicyclo(2.2.1)heptan-7-one (73) under homoenolization conditions which indicated that bridgehead exchange in 42 would be possible as well.

(b) RESULTS

To a solution of t-BuOK (1 M) in t-BuOD (99% deuterated and <0.005 M in water), prepared by dissolving potassium metal in the dry alcohol, was added 42 (0.2 M). Aliquots were sealed in thick-walled glass tubes under vacuum after degassing. The mixture in the glass tubes was heated in an oven for various times at 185 ± 3°. After recovery of the product by pentane extraction (70 - 80% yields)

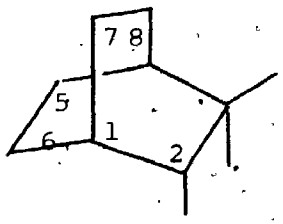


42 43 45



44

the product was analyzed by g.c. (20% SE 30 column) and showed two peaks, i.e. one is starting material and one is rearranged product. After 400 hr, the mixture contained 30% of rearrangement product and 70% of starting material (see Table 3.8). The structure of the rearrangement product was confirmed by comparison of its physical properties with an authetic sample of 45 prepared by the methylation of bicyclo(3.2.1)oct-an-6-one. Samples of 42-d_x isolated by preparative g.c., were examined by mass spectrometry and ^{13}C NMR. Although the ^{13}C NMR spectrum of 42 was attractively simple, by symmetry, the signals of interest unfortunately were not ideally separated for ^{2}H assay (Figure 3.6). Thus samples of 42-d_x were reduced to the corresponding alcohol 46,



46

because the well known γ-effect of the hydroxyl group produces a large shielding difference between the methyl and the C-6 and -7 in 46 rendering better integration. Therefore their ^{13}C spectra were used for ^{2}H assay. From these ^{13}C spectra, the ^{2}H content at C-6, -7 and the methyl carbons were measured as described previously. Spectra of three samples are reproduced in Figure 3.7. The triplet characteristic of -CHD- groups was apparent only for the C-6 and -7 absorptions while isotope shifts for C-1, -5 and -8 were also

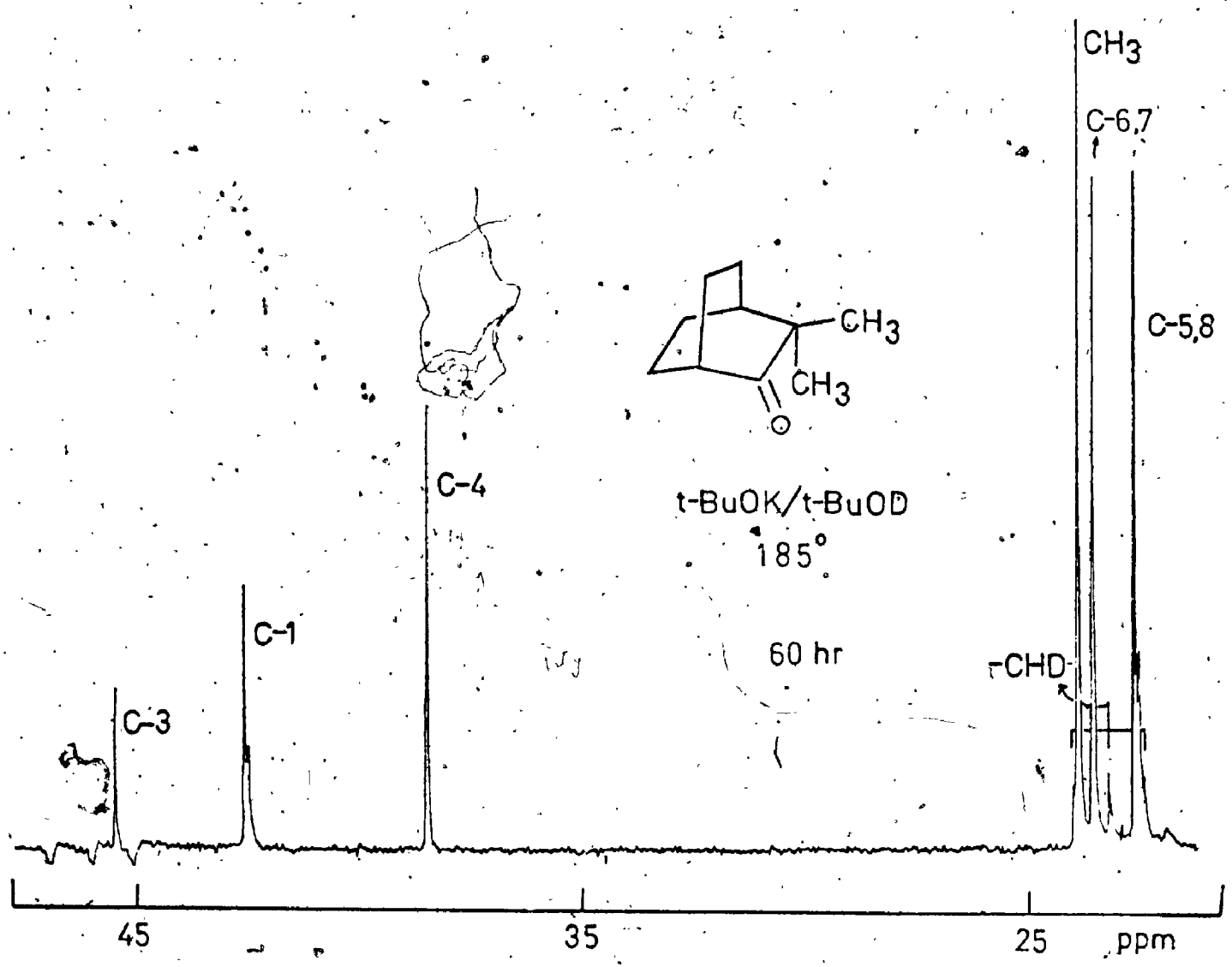


Figure 3.6. Proton-decoupled ^{13}C spectrum (in C_6D_6) of 3,3-dimethylbicyclo(2.2.2)octan-2-one (42) after treatment with t-BuO^-/t-BuOD at 185° for 60 hr.

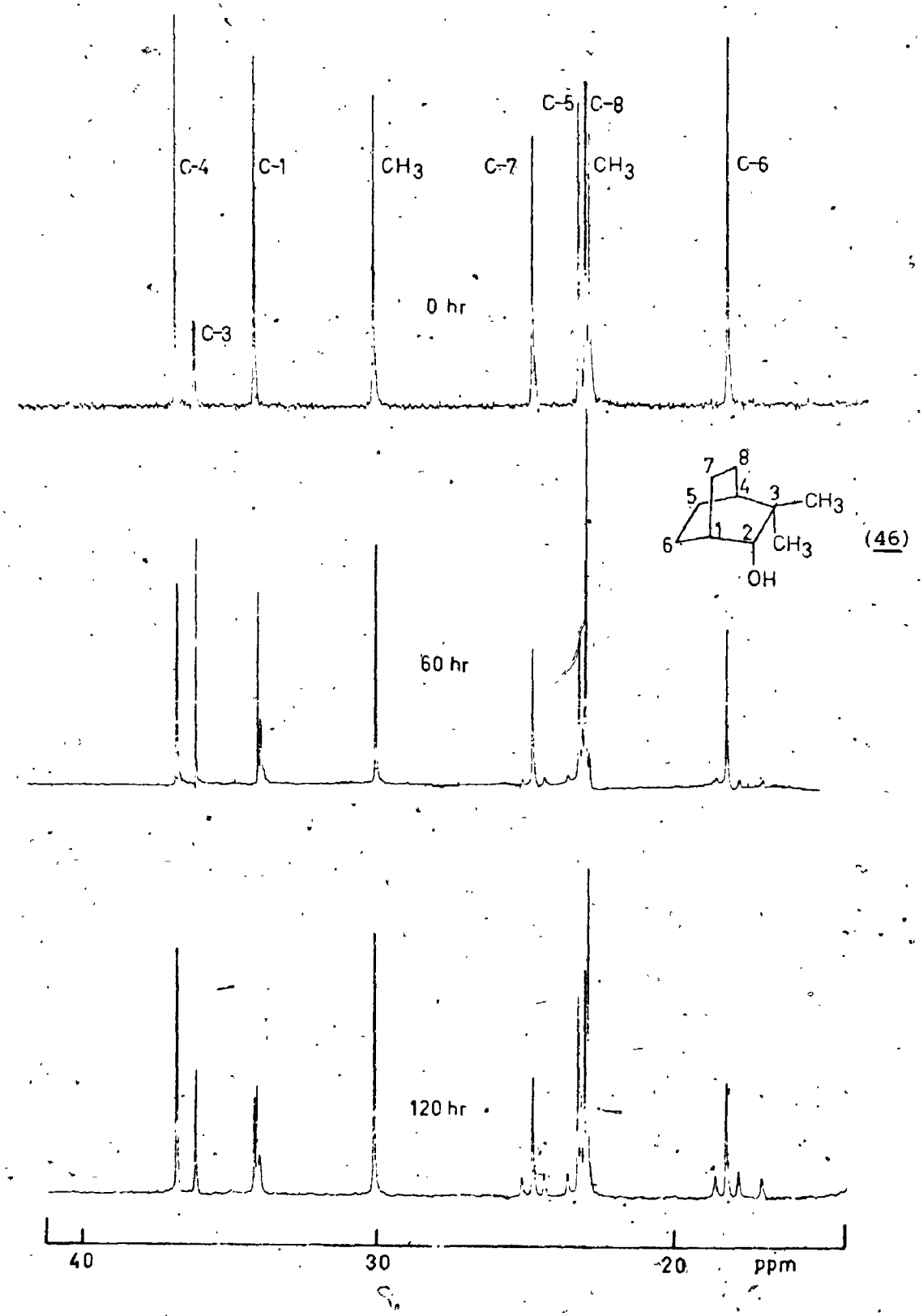


Figure 3.7. Proton-decoupled ^{13}C spectra of 3,3-dimethylbicyclo(2.2.2)-octan-2-ol (46) and two deuterated samples. The deuterated samples were prepared from 42-d_x after treatment with t-BuO$^-$/ t-BuOD at 185° for 60 and 120 hr, followed by $LiAlH_4$ reduction.

observed. After 240 hr, ^2H was detected at both methyl groups but not at the other centers. The ^{13}C NMR and mass spectral data are collected in Table 3.4.

Similarly from the homoenolization studies of 7,7-dimethylbicyclo-(3.2.1)octan-6-one (45), samples of 45-d_x were isolated by g.c. and the ^2H content determined by mass spectrometry and ^{13}C NMR spectra. ^{13}C spectra of two samples of 45-d_x are shown in Figure 3.8. Triplets characteristic of -CD- and $-CH_2D$ were apparent for the C-5 and exo-methyl absorptions. The quintet from $-CHD_2$ group was found in the exo-methyl absorption after the longer reaction time. The difference between the "standard value" and the sum of the $-CH_3$, $-CH_2D$ and $-CHD_2$ intensities gave the relative concentration of the $-CD_3$ species. All assays are listed in Table 3.4.

After 400 hr, 45 gave 14% of 42 (see Table 3.8). Clearly, equilibrium was not attained and the lack of detectable ^2H at C-4 in 45 showed that its homoenolization is very slow indeed. The ^{13}C spectrum of the rearrangement product 45-d_x from 42 isolated from the longer reaction times revealed that C-3, C-4 and C-5 and the two methyl carbons undergo exchange (Figure 3.9). The C-4 absorption consisted of two $-CH_2-$ singlets and two triplets characteristic of -CHD-. This implies that the high field singlet and triplet arise from a geminal ^2H isotope shift caused by neighboring ^2H at C-3 and C-5. There seems no doubt that the ^2H found at C-3 and the endo-methyl arise from direct exchange of starting material before conversion to 45 because no ^2H was detected at these centers in the homoenolization

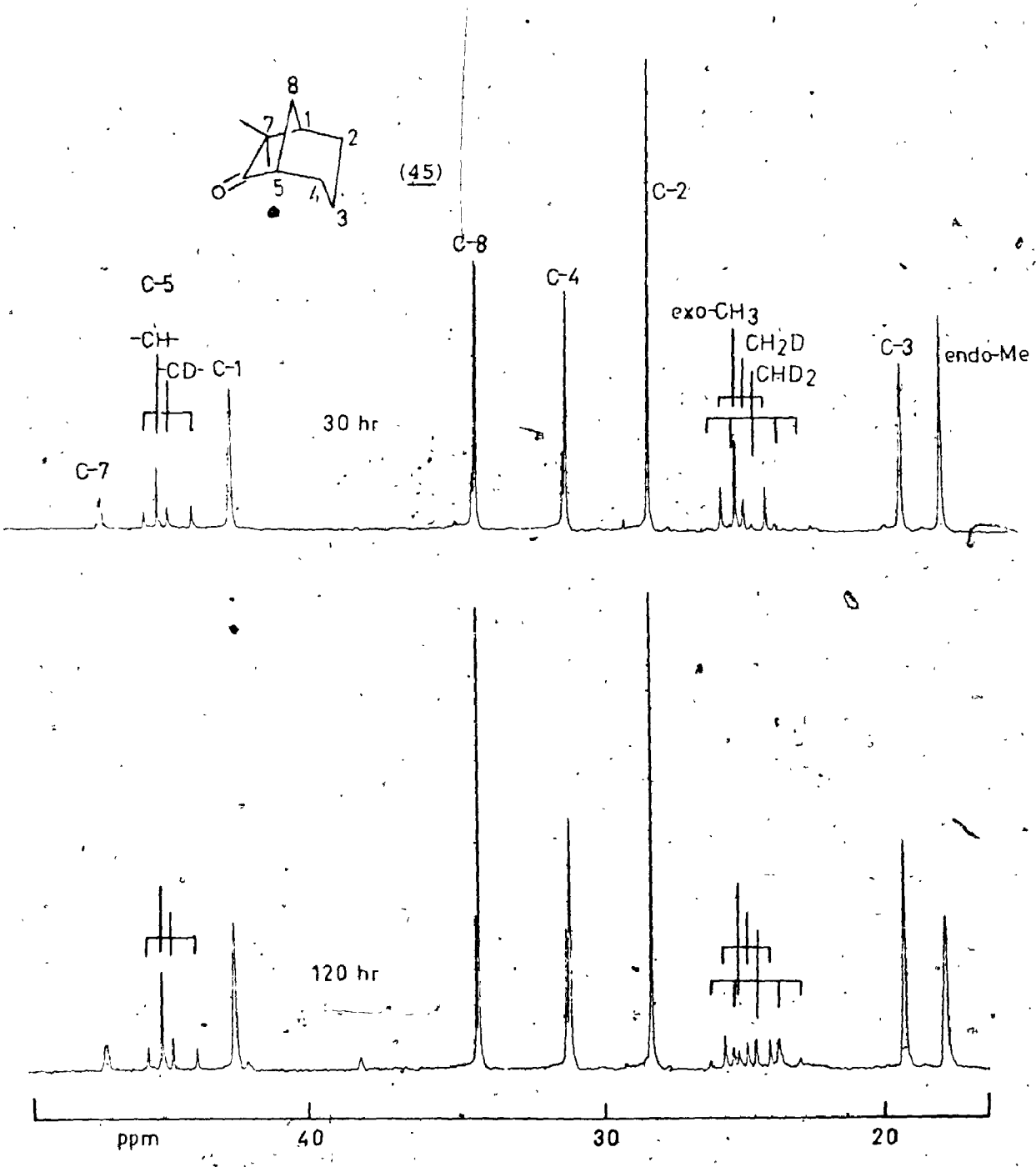
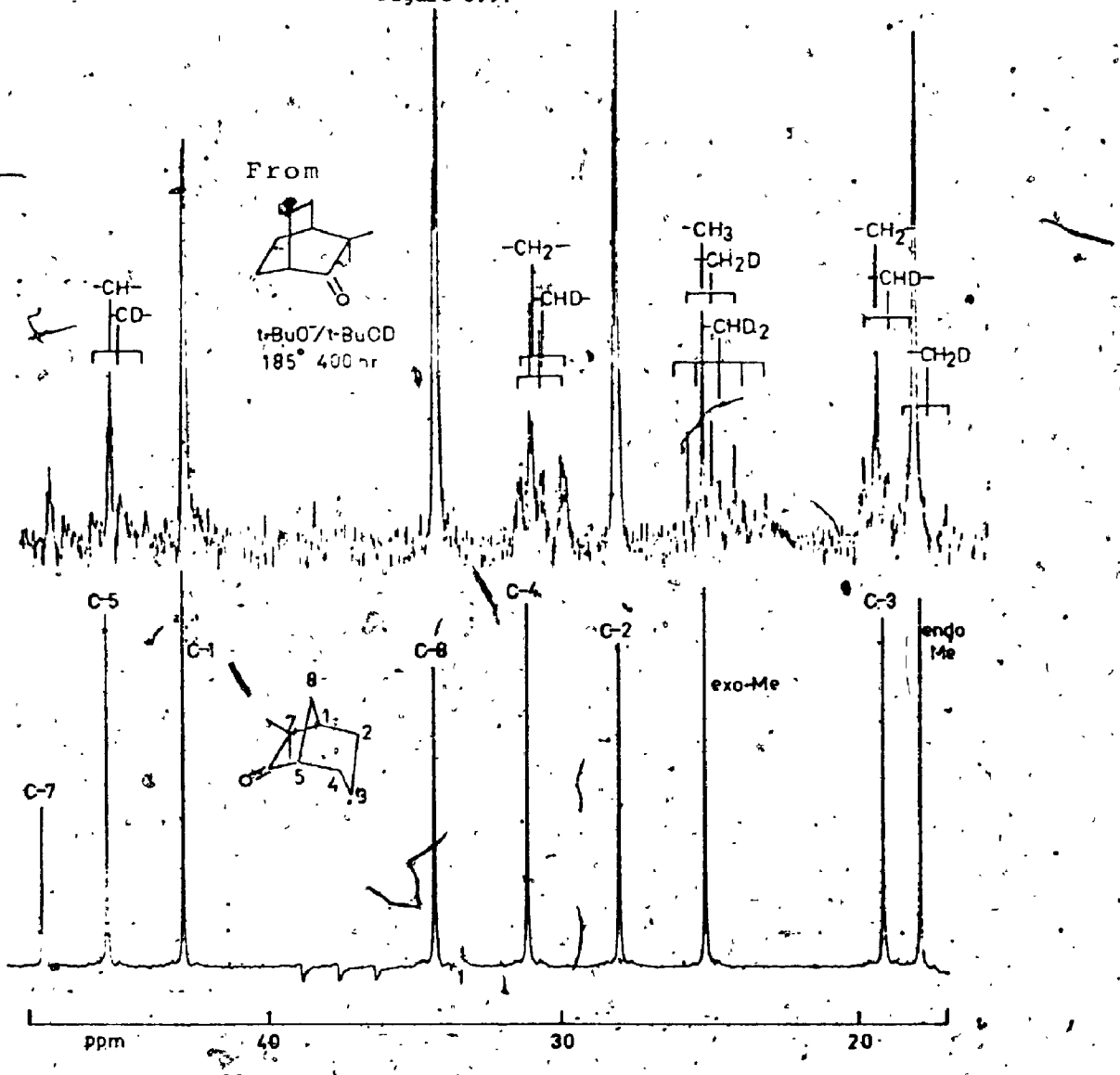


Figure 3.8. Proton-decoupled ^{13}C spectra (in C_6D_6) of 7,7-dimethyl-bicyclo(3.2.1)octan-6-one (45) after treatment with t-BuO$^-$ / t-BuOD at 185° for 30 and 120 hr .

Figure 3.9.



Proton-decoupled ^{13}C spectra (in C_6D_6) of the rearrangement product 7,7-dimethylbicyclo(3.2.1)octan-6-one (45-d_x) formed from 3,3-dimethylbicyclo(2.2.2)-octan-2-one (42) after treatment with t-BuO⁻/t-BuOD at 185° for 400 hr (upper spectrum) and 7,7-dimethylbicyclo(3.2.1)octan-6-one (lower spectrum).

Table 3.4

Deuterium Incorporation in 3,3-Dimethylbicyclo(2.2.2)octan-2-one (42) and 7,7-Dimethylbicyclo-(3.2.1)octan-6-one (45) at 185°

Time	42					45					
	C-6,7[a]		Methyl[a]	Atoms ^2H		C-5[a]	Methyl[a]			Atoms ^2H	
	CHD	CD_2	CH_2D	^{13}C	M.S.[b]	CD	CH_2D	CHD_2	CD_3	^{13}C	M.S.[b]
30						88	34	29		1.80	1.72
60	32			0.64	0.61	83	34	21	34	2.61	2.39
120	36	10	8	1.28	1.08	79	19	21	55	3.05	2.78
240	56	18	18	2.20	2.25	72	16	25	56	3.06	2.89
400	46	28	27	2.58	2.47	63	17	23	56	2.94	2.92

[a] Percentage ^2H determined by integration of ^{13}C spectra (see text); estimated precision ± 5 %.

[b] Mass spectral data obtained with a Varian M-66 spectrometer at 30 eV ionization voltage.

studies of 45. Most of the ^2H incorporated at C-4 is accounted for through cleavage of the C-1 and C-2 bond of the homoenolate intermediate, followed by the abstraction of a deuteron from the solvent.

After the NMR spectrometer was modified to perform ^2H experiments in the Fourier transform mode, the direct examination of deuterated samples by ^2H NMR offered distinct advantages over the ^{13}C approach as noted before. Consequently, all samples of 42-d_x and 45-d_x from the above studies were re-examined by ^2H NMR.

The ^2H spectra of the samples of 42-d_x consisted of two distinct absorptions at 5.44 and 6.20 ppm upfield from the absorption of $CDCl_3$. The high field signal was assigned to the methyl groups and the lower field signal was assigned to the methylene deuterons at C-6 (and C-7). To increase the separation of the ^2H resonances as well as to obtain unequivocal proof for the assignments of the ^2H signals, spectra were obtained using $Pr(fod)_3$ as shift reagent. Upon addition of $Pr(fod)_3$ to a solution of 42 in $CHCl_3/C_6F_6$ (1 : 4; v/v), the four signals were resolved (exo-H-6 and -7, endo-H-6 and -7, methyls and H-1), shifted to higher field and all of the absorption peaks were well separated. Decoupling experiments in the ^1H spectrum confirmed the assignments. Shift reagent studies over the range of 0.0 - 0.2 equiv. of $Pr(fod)_3$ are plotted in Figure 3.10. ^2H Spectra of the 42-d_x samples containing about .0.2 equiv. of $Pr(fod)_3$ were recorded and the relative intensities of the three major absorption signals measured by line-shape fitting. The smallest peak near 10 ppm arising from the bridgehead deuteron was too small for reliable line-shape fitting. Two

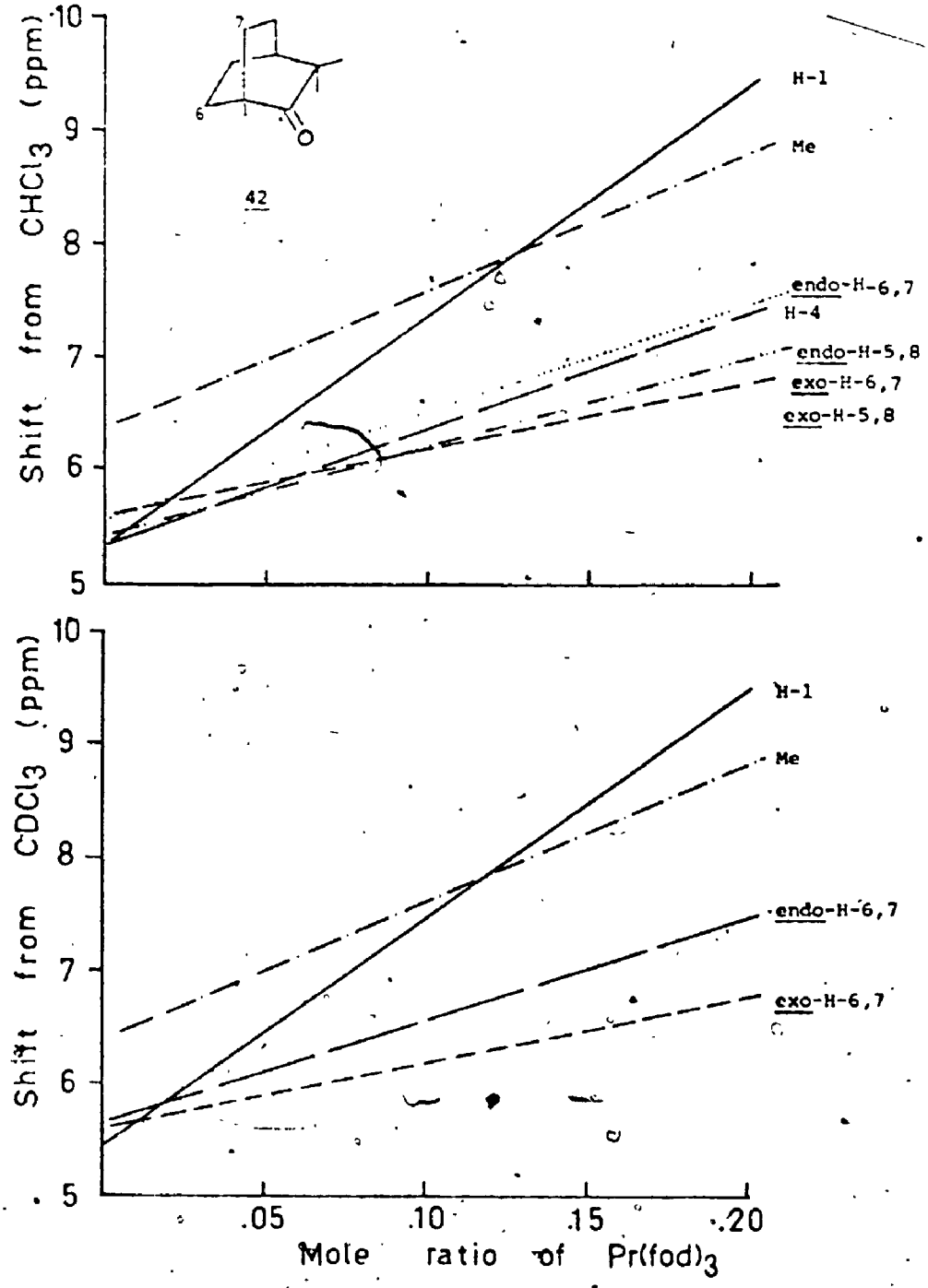


Figure 3.10. Effects of $Pr(fod)_3$ on the relative shifts of 42; ^1H (top) and ^2H shifts (bottom). Spectra were obtained for $CHCl_3/C_6F_6$ (4:1; v/v) solutions.

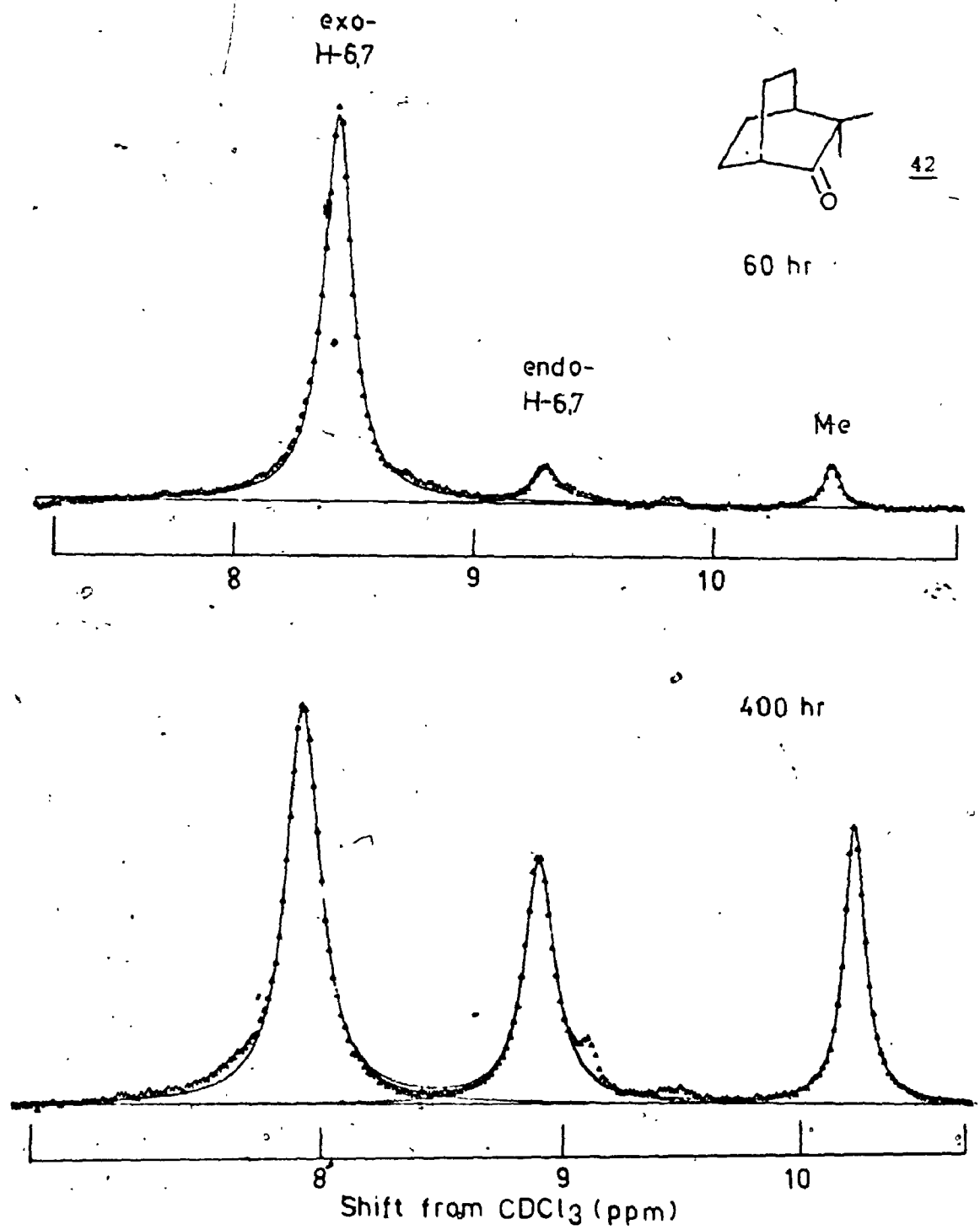


Figure 3.11. Observed (Δ) and computed fitted (full-line) ^2H spectra of 42-d_x after treatment for 60 hr and 400 hr with t-BuO^-/ t-BuOD at 185°. The spectra were obtained in $CHCl_3$/ C_6F_6 (1:4) containing 0.14 and 0.18 equiv. of $Pr(fod)_3$ for 60 and 400 hr samples, respectively.

examples of 42-d_x spectra are shown in Figure 3.11. These data together with the total ^2H content determined for each sample by mass spectrometry, provided a measure of the relative extent of deuteration at the other three positions (Table 3.5)

Incorporation of ^2H in 45 from 42 was determined from ^2H NMR spectra. The ^2H assignments were confirmed by comparison of ^1H and ^2H spectra of 45 containing $Pr(fod)_3$. With 0.6 equiv. of $Pr(fod)_3$ all twelve ^1H shifts could be determined using spin-decoupling to establish the individual assignments. The shifts over the range of 0.0-0.72 equiv. of $Pr(fod)_3$ are plotted in Figure 3.12. The results for 45-d_x from 42 are listed in Table 3.6. Five ^2H signals were resolved revealing exchange of exo-H-3, exo-H-4, exo- and endo-methyl and H-5 (Figure 3.13). Incorporation of ^2H in 45 results from exchange in 42 before conversion to 45 and from exchange after its formation. To examine the latter processes separately, samples of 45 were treated with base at 185°. The ^2H spectra of the recovered 45-d_x samples differed significantly from those for 45-d_x generated from 42. Four ^2H signals were resolved revealing exchange of exo-H-4, exo- and endo-methyl and H-5 (Figure 3.14). The ^2H incorporation data for several samples are listed in Table 3.7.

(c) DISCUSSION

From the results for the samples from the shorter times (Table 3.5), one can estimate the first-order rate constants for deuteration of 42 at the exo-6 (or -7), endo-6 (or -7) and methyl positions as $\sim 14 \times 10^{-7}$, $\sim 1.8 \times 10^{-7}$ and $\sim 0.5 \times 10^{-7}$ sec^{-1}, respectively. For homoenolate anion

Table 3.5

Deuterium Incorporation in 3,3-Dimethylbicyclo(2.2.2)octan-2-one (42) at 185°

Time (hr)	^{2}H content by mass spectrometry[a]							^{2}H assay by ^{2}H nmr[b]		
	1D	2D	3D	4D	5D	6D	Total Atoms ^{2}H	C-6,7 exo	C-6,7 endo	CH_3
60	0.412	0.094	0.004				0.61	0.54	0.05	0.03
120	0.486	0.249	0.032				1.08	0.89	0.11	0.07
240	0.212	0.400	0.259	0.090	0.021		2.25	1.56	0.35	0.34
400	0.175	0.320	0.275	0.136	0.044	0.011	2.47	1.32	0.60	0.57

[a] using a Varian M-66 spectrometer at 30 ev ionization voltage.

[b] Spectra obtained by FT operation of a Varial XL-100-15 at 15.4 MHz with noise decoupling at 100 MHz and integrated by line-shape fitting. Sample were examined as 10% in $CHCl_3$ / C_6F_6 (1:4) containing $Pr(fod)_3$.

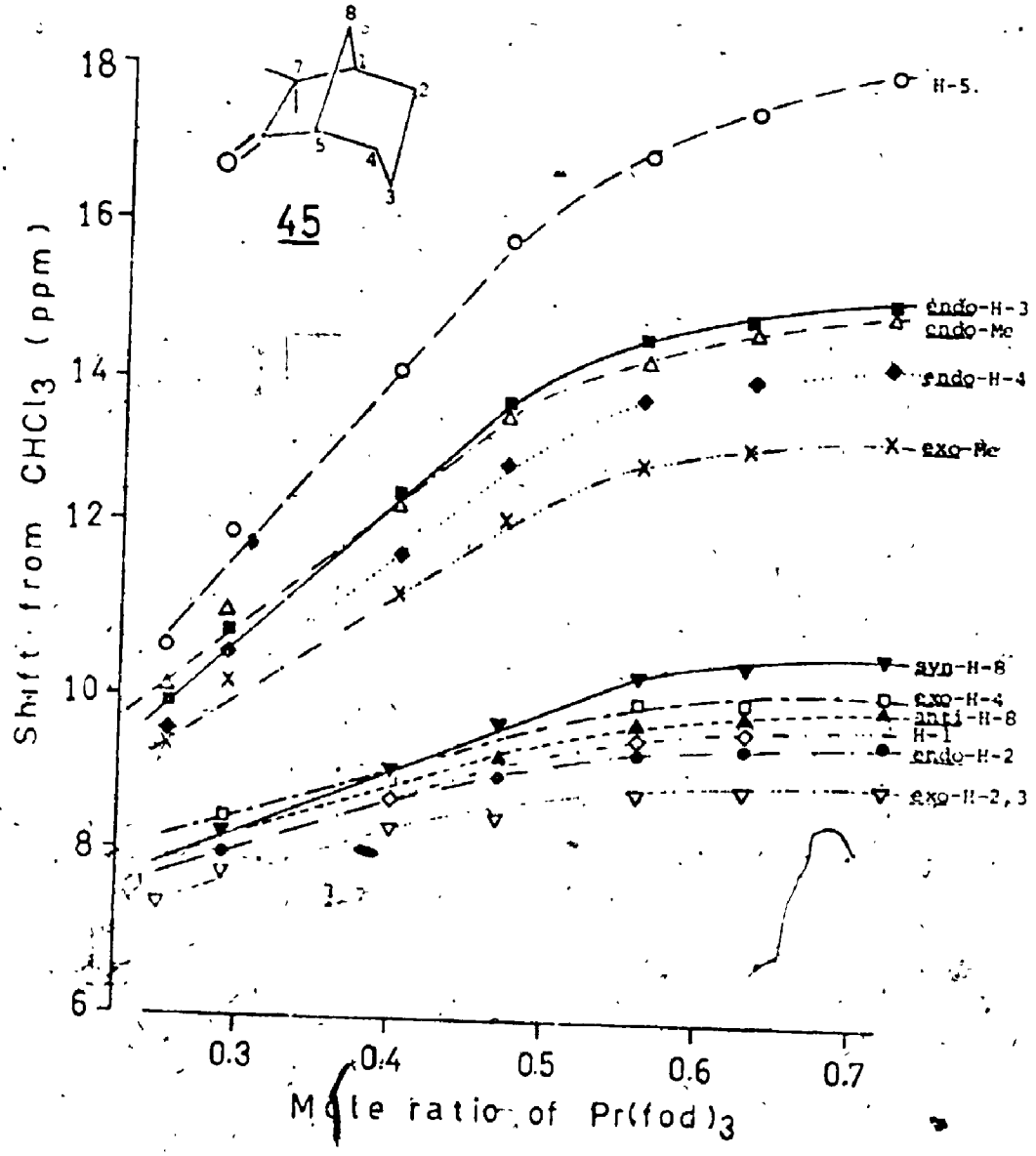


Figure 3.11. Plot of ^1H Chemical Shift vs. Mole Ratio of $Pr(fod)_3$ for in $CHCl_3$/ C_6H_6 (1:4) solutions

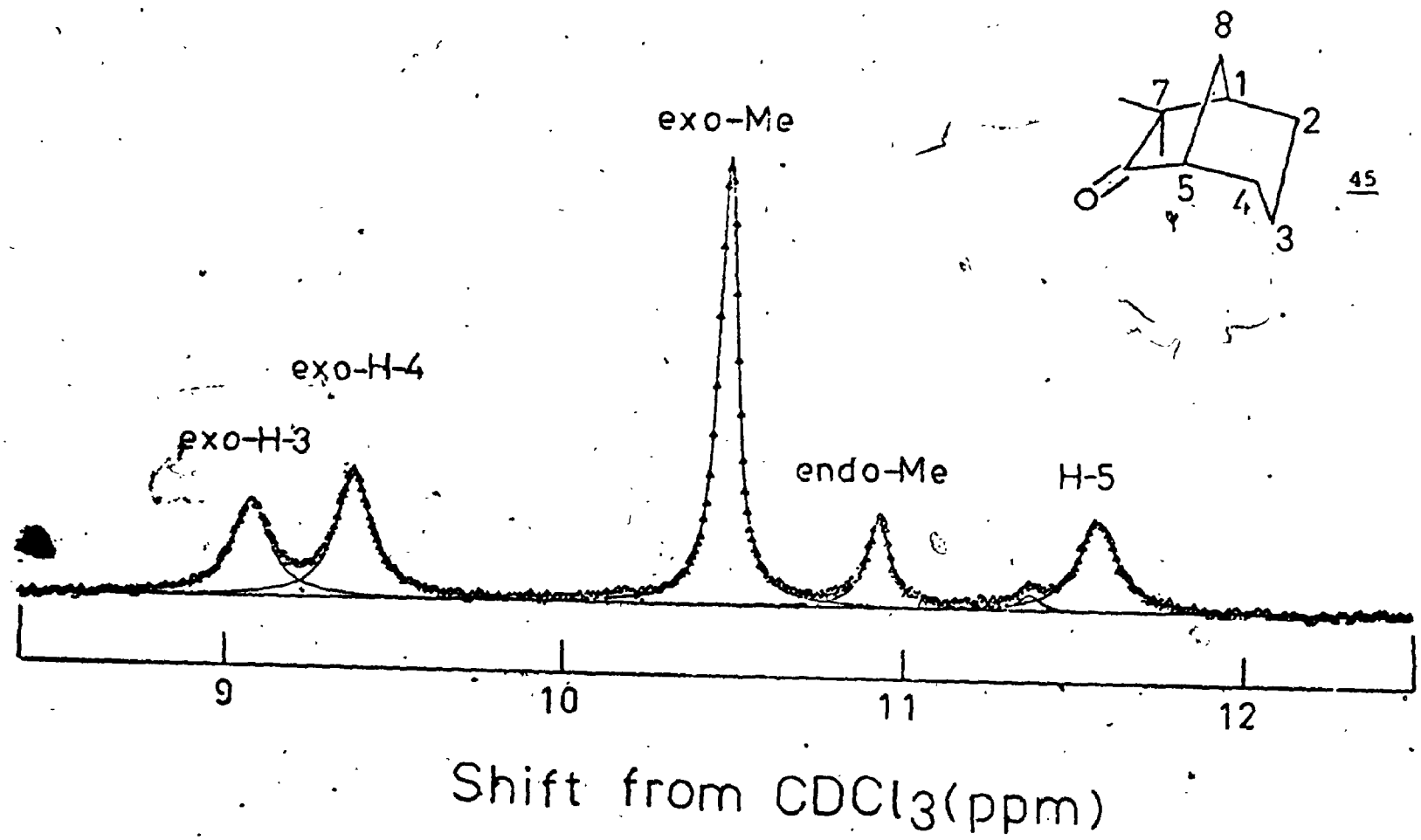


Figure 3.13. Observed (Δ) and computer fitted (full-line) ^2H spectrum of the rearrangement product 45 from 42 after treatment for 400 hr with t-BuO^-/t-BuOD at 185°. The spectrum wa. obtained in $CHCl_3/C_6F_6$ (1:4; v/v) containing 0.33 equiv. of $Pr(fod)_3$.

Table 3.6

Deuterium Incorporation in 7,7-Dimethylbicyclo(3.2.1)octan-6-one[a] (45)

Time (hr)	^2H content by mass spectrometry[b]								^2H assay by ^2H nmr[c]				
	1D	2D	3D	4D	5D	6D	7D	Total Atoms ^2H	H-3 exo	H-4 exo	H-5	CH_3 exo	CH_3 endo
400	0.057	0.165	0.272	0.266	0.154	0.049	0.008	3.39	0.56	0.69	0.53	1.31	0.32
500	0.043	0.169	0.281	0.277	0.159	0.050	0.008	3.49	0.60	0.68	0.54	1.34	0.32

[a] Rearrangement product from 3,3-dimethylbicyclo(2.2.2)octan-2-one.

[b] Atom ^2H, ± 0.001.

[c] Atom ^2H, ± 0.02.

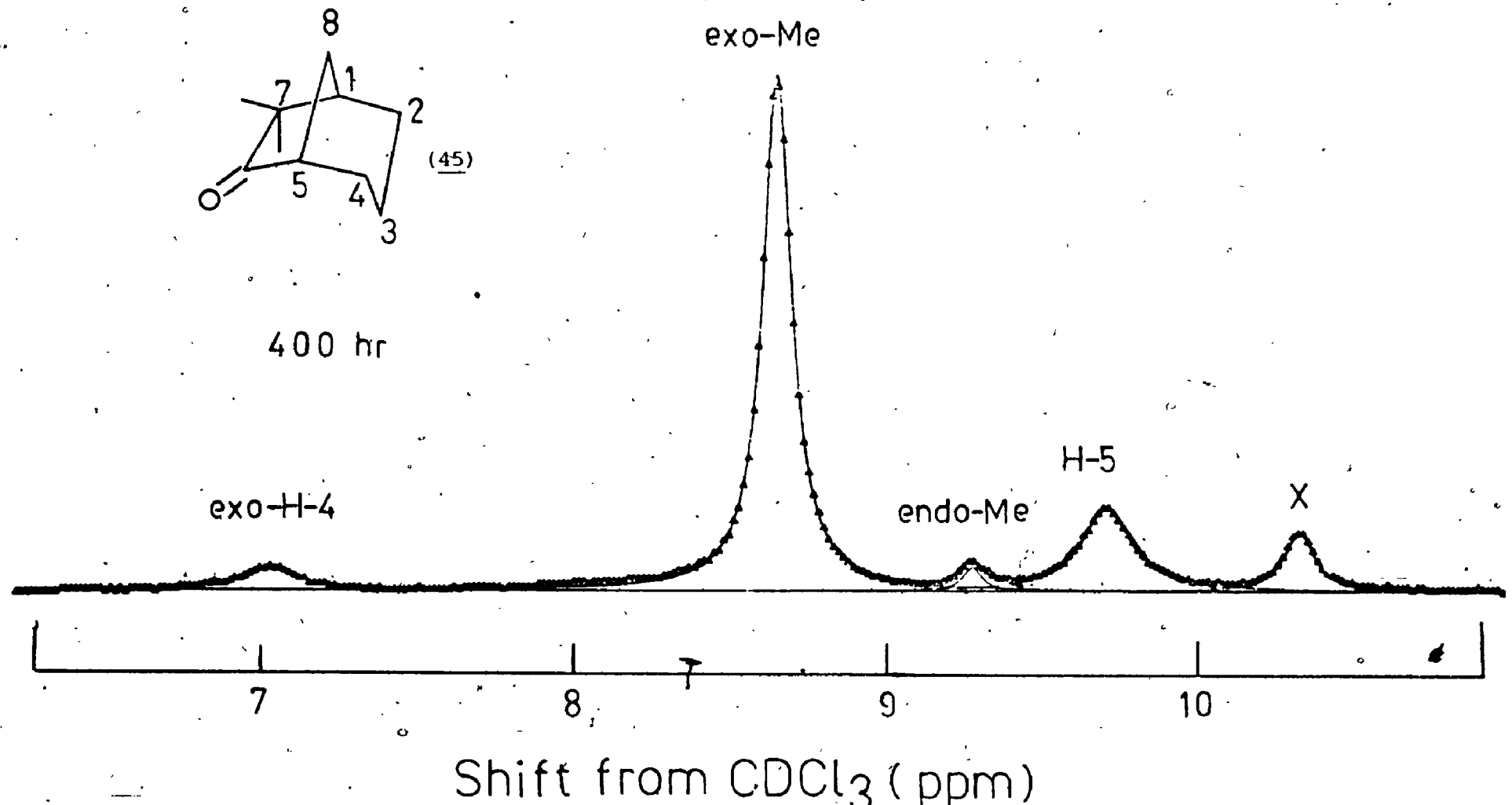


Figure 3.14. Observed (△) and computer fitted (full line) ^2H spectrum of 45-d_x (400 hr sample). The spectrum was obtained in $CHCl_3/C_6F_6$ (4:1; v/v) containing 0.32 equiv. of $Pr(fod)_3$. Peak X is impurity.

Table 3.7

Deuterium Incorporation in 7,7-Dimethylbicyclo(3.2.1)octan-6-one (45)

Time (hr)	^2H content by mass spectrometry[a]								^2H assay by ^2H nmr[b]			
	1D	2D	3D	4D	5D	6D	7D	Total Atoms ^2H	H-4 exo	H-5	CH_3 exo	CH_3 endo
30	0.375	0.411	0.147	0.018	0.002			1.72		0.85	0.87	
60	0.154	0.374	0.338	0.104	0.007	0.004		2.39	0.06	0.76	1.56	0.01_0
120	0.086	0.288	0.388	0.199	0.024	0.007		2.78	0.10	0.73	1.92	0.03_1
240	0.078	0.256	0.379	0.231	0.036	0.009		2.89	0.11	0.65	2.07_5	0.04_6
400	0.085	0.258	0.360	0.217	0.047	0.017	0.005	2.92	0.24	0.58	2.08_4	0.06_5

[a] Atom ^2H, ± 0.001.

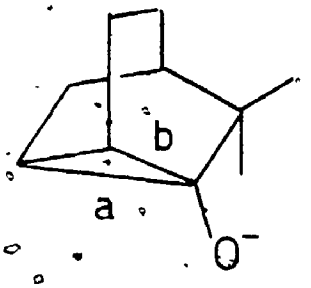
[b] Atom ^2H, ± 0.02.

Table 3.8

% Rearrangement Product from 42 and 45 in t-BuOK / t-BuOD at 185°

Time (hr)	42	45
60	7.5	6.5
120	11.1	9.7
240	16.2	10.9
400	30.2	14.3
600	31.0	

43, formed by abstraction of a C-6 or C-7 proton from 42, there are four ways in which the ring opening can occur to give ketones. Cleavage of bond a with retention or inversion at C-6 or C-7 produces endo-6 or -7-deuterio-42 or exo-6- or -7-deuterio-42, respectively. Similarly, cleavage of bond b with retention or inversion at C-1 leads to the exo-4 or endo-4-deuterio-45, respectively. From the results



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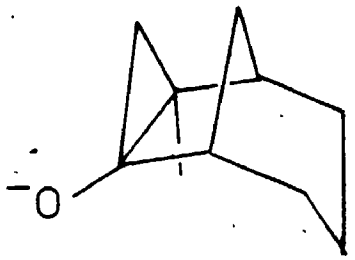
it is apparent that bond a cleavage is favored by ca. 2.3 : 1, with exo-deuterium attack, i.e. inversion at C-6 or C-7, favored over endo-deuteration by a factor of ca. 7. With cleavage of bond b, inversion at C-1 is favored over retention. ^2H spectral analysis of 45-d_x isolated from 42 indicated that the ^2H at C-4 is mainly exo. Incorporation of ^2H at C-3 in 45 from 42 results from exchange in 42 before conversion to 45. But ^2H incorporation at the exo- and endo-methyl groups can result from exchange in 42 before conversion to 45 as well as by exchange after its formation. To examine the latter processes separately and the conversion between 42 and 45, samples of 45 were treated with t-BuOK / t-BuOD at 185°. From the results for the shorter times in Table 3.7, the first-order rate

constant for deuteration at H-5, exo-H-4 and exo- and endo-methyl position were found to be >1800 x 10^{-7}, ~2.7 x 10^{-7} and ~30 x 10^{-7} and ~0.2 x 10^{-7} sec^{-1}, respectively. The rate of the bridgehead exchange is fast under the homoenolization conditions therefore one can only obtain a lower limit for the estimated rate of exchange at this center.

It is interesting that methyl exchange was also preferentially exo. This process occurred at a faster rate than β-enolization at C-4 and the endo-methyl group. There are two ways in which the exo- and endo-methyls can incorporate deuterium. One of the ways it can occur would be by the rearrangement of 42 (rearrangement from 45) which already has ^2H incorporation at the methyl groups. In this transformation, one of the methyls would become the exo-methyl of 45. The other would become the endo-methyl of 45. A second path for deuteration of the methyls involves the formation of a three-membered ring with opening to form the deuterated methyl. It seem likely that exo-methyl exchange will mainly involve 45 because the rate of ^2H exchange of an exo-methyl in 45 is 60 times faster than that in 42.

In principle, species such as 44 and 47 could lead to ring-expanded products but none was isolated or detected. This was not unexpected since cyclopropanols open in base to give the product derived from the more stable carbanion (83) hence the formation of the starting material is the favored path. From the results of the formation of rearrangement products from 42 and 45 (Table 3.8), it is clear that equilibrium was not attained and the slow exchange rate at C-4 in 45 showed that its homoenolization is very slow indeed.



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(D) ADAMANTANONE: STEREOCHEMISTRY OF ITS HOMOENOLIZATION AS SHOWN BY ^2H NUCLEAR MAGNETIC RESONANCE

(a) INTRODUCTION

Several examples of homoenolization in polycyclic ketones have been reported. But, somewhat surprisingly Nordlander and his co-workers (84) reported that adamantanone (48) showed no exchange under homoenolization conditions, although the separation of β-carbon atoms from the carbonyl group is not greatly different in 48 from that in a variety of bicyclo(2.2.1)heptanone derivatives known to exhibit β-proton exchange. Also, α-hydrogen exchange would be possible because α-hydrogen exchange in bicyclo(2.2.1)heptan-7-one (73) and some bicyclo(3.2.1)octanones (85) has been detected under homoenolization conditions. Therefore re-examination of the homoenolization of 48 seemed warranted.

(b) RESULTS

To a solution of t-BuOK in t-BuOD (99% deuterated, $<H_2O$ 0.005 M) prepared by dissolving potassium metal in the alcohol, was added 48 to produce a solution 0.2 M in ketone and 1 M in base. Aliquots were sealed in thick-walled glass tubes under vacuum after degasssing and heated for various times at 185°. After recovery of 48 by pentane extraction (90% yields), the recovered material was examined by mass spectrometry and ^2H NMR spectrometry. The results for four samples are listed in the Table 3.9. It is apparent that up to five ^2H atoms have been incorporated under these conditions.

Because of its high symmetry, 48 has only five types of nonequivalent

Table 3.9

Deuterium Incorporation in Adamantanone (48) at 185°

Time (hr)	^2H content by mass spectrometry[a]						^2H assay by ^2H nmr[b]		
	1D	2D	3D	4D	5D	Total Atom ^2H	H-1(3)	H-4(8,9,10) endo	H-4(8,9,10) exo
127	0.267	0.038	0.004			0.35_6	0.050	0.016	0.29
213	0.373	0.105	0.015			0.62_6	0.103	0.028	0.494
318	0.390	0.130	0.019	0.001_4		0.71_3	0.118	0.038	0.557
407	0.398	0.163	0.033	0.007_3	0.004_8	0.87_6	0.169	0.040	0.667

[a] Using a Varian M-66 spectrometer at 30 ev ionization voltage; atom ^2H ± 0.001.

[b] Spectra obtained in the Fourier transform mode with a Varian XL-100-15 system operating at 15.4 MHz with noise decoupling at 100 MHz. Samples were examined as 15% solutions in $CHCl_3/C_6F_6$ (4:1). Atom ^2H, ± 0.02.

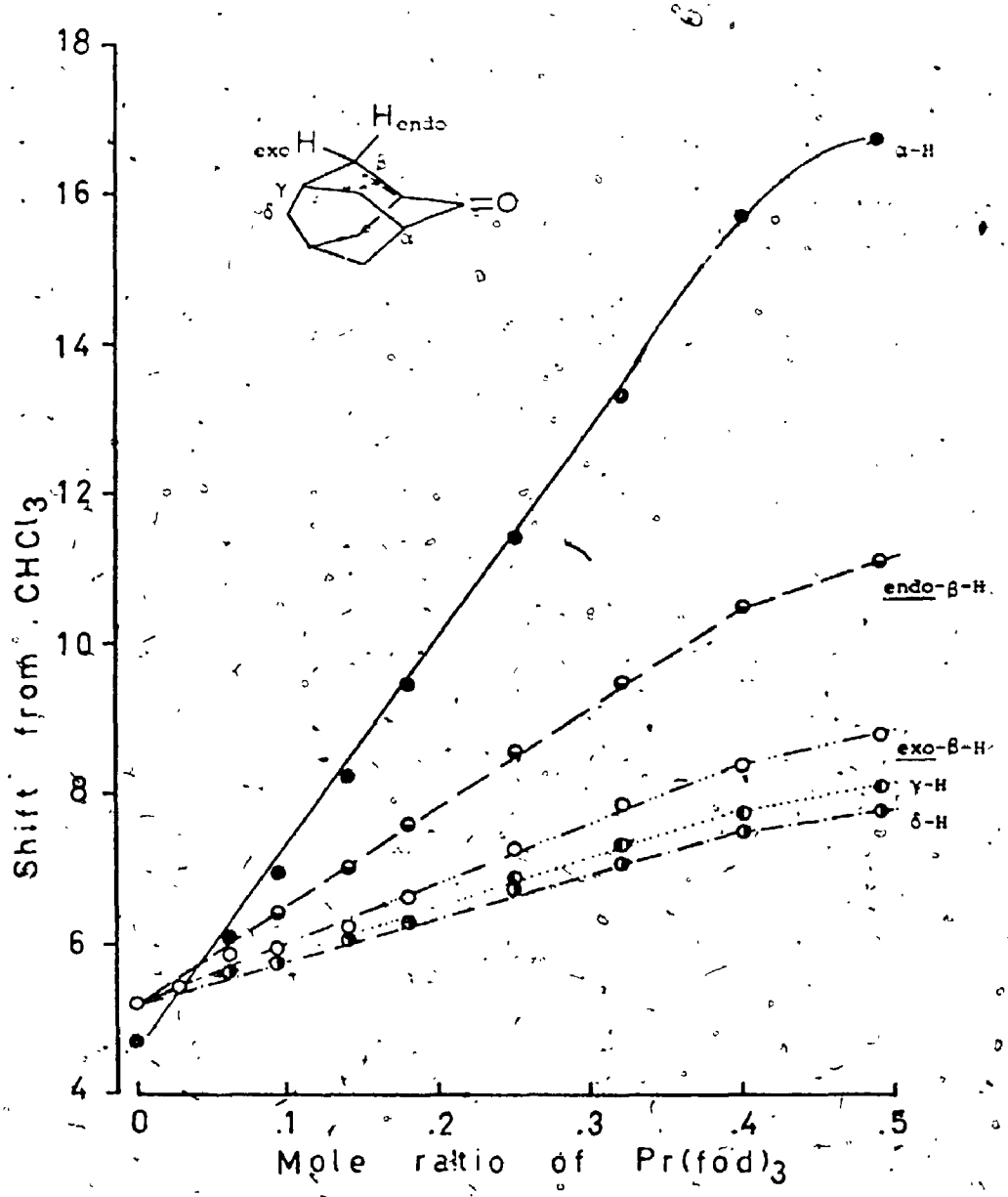


Figure 3.15. Plot of ^1H chemical shift vs. mole ratio of $Pr(fod)_3$ for 48 in $CHCl_3/C_6F_6$ (4:1) solutions.

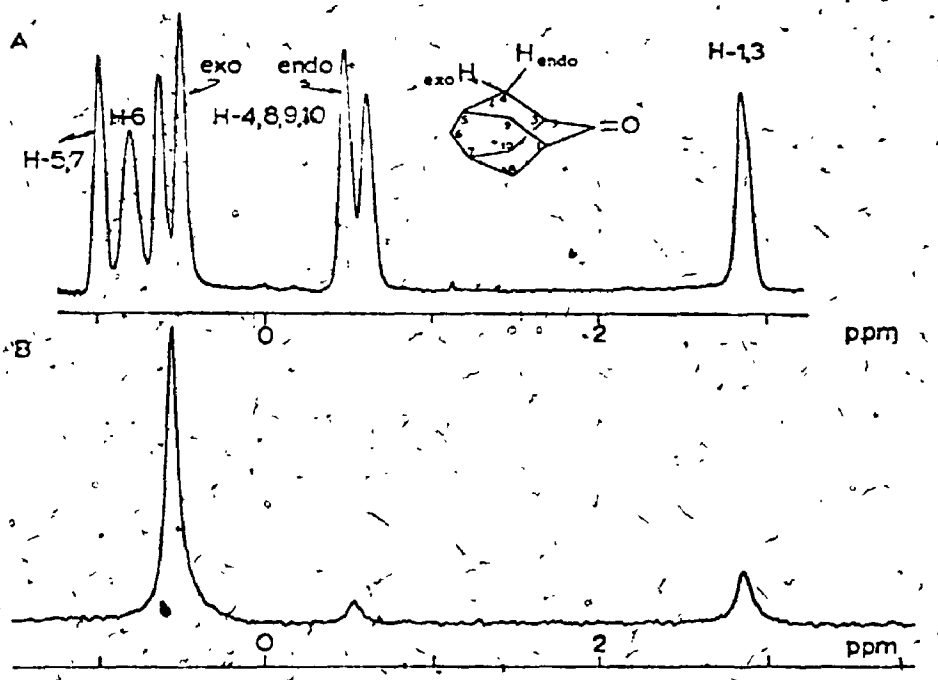


Figure 3.16. (A) 100 MHz ^{1}H n.m.r. spectrum of adamantanone (48); (B) 15.4 MHz ^{2}H n.m.r. spectrum of 48-d_2 (213 hr sample). Both spectra obtained for $CHCl_3/C_6F_6$ (4:1;v/v) solution containing 0.17 equiv. of Pr(fod)$_3$, the scale is relative to TMS.

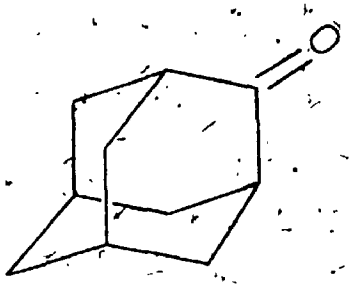
protons, two of which are at β-positions (C-4, -8, -9 and -10), exo and endo with respect to the carbonyl group. Since the chemical shifts of ^2H nuclei are the same as those of the corresponding ^1H nuclei, on a ppm scale (74), the ^2H NMR spectra of the deuterated materials were readily assignable. The spectra are simple with a single line for each non-equivalent deuteron. To increase the separation of the ^2H resonances as well as to obtain unequivocal proof for the assignment of the ^2H signals, spectra were obtained using $Pr(fod)_3$ as shift reagent. The ^1H shifts of 48 over the range of 0 - 0.5 equiv. of $Pr(fod)_3$ are plotted in Figure 3.15. Typical spectra of 48 and 48-d_x are shown in Figure 3.16 from which it can be seen that the endo-β-hydrogens were readily distinguished from exo-β-hydrogens by their greater upfield shift in the presence of $Pr(fod)_3$ and the α-hydrogens exhibit even larger shifts. Integration of the spectra of the deuterated samples by line-shape fitting, together with the total ^2H content measured by mass spectrometry allowed the relative extents of ^2H incorporation to be calculated for these three sites of exchange (Table 3.9).

(c) DISCUSSION

From the results, one can roughly estimate the first-order rate constants per hydrogen for deuteration at the α-carbons, exo-β-carbons and endo-β-carbons positions as $\sim 0.63 \times 10^{-7}$, $\sim 0.1 \times 10^{-7}$, and $\sim 1.5 \times 10^{-7}$ sec^{-1}, respectively. In other words, exo-β-hydrogen exchange occurred ca. 15 times faster than endo-β-hydrogen exchange and approximately twice as fast as bridgehead exchange. The stereoselectivity of homo-enolization in this system, therefore, is the same as the other bicyclic

systems. From homoenolate 49, formed by abstraction of a β-hydrogen in 48, there are six ways in which ring opening can occur to give ketones. But, only cleavage of bond 1 was observed which with retention or inversion at β-carbons produces endo-β-deuterio-48 or exo-β-deuterio-48 respectively. Cleavage of bonds 2 or 3 would lead to rearranged ketones but none was detected.

A comparison of the rate of ^{2}H incorporation at the exo-β-positions in 48 with that for homoenolization of fenchone indicates that the former process is ca. 100 times slower.



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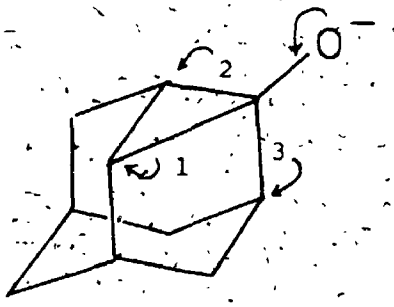

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(E) α,α,α',α'-TETRAMETHYL CYCLOALKANONES

(a) INTRODUCTION

The reversible formation of homoenolates from monocyclic ketones by remote proton abstraction with strong base has not received any attention since the discovery and detailed characterization of β-enolization of camphenilone by Nickon and his co-workers (55-58). At present, homoenolization has only been observed for several polcyclic and a few cyclic systems but it was expected that monocyclic ketones could also undergo this reaction. Therefore, four α,α,α',α'-tetramethyl monocyclic ketones (C_5 - C_8) were prepared and their behavior under the homoenolization conditions examined.

In principle, these four ketones could be expected to β-enolize at the four equivalent methyl groups and at the two equivalent β-carbons. Furthermore, γ enolization could also occur although only two examples were available (59, 69). In principle, rearrangement could follow if the β-enolates formed.

(b) RESULTS AND DISCUSSION

The ketone was dissolved in t-BuOK/t-BuOD (1M) to furnish a 0.2 M solution. Aliquots were sealed in glass tubes under vacuum after degassing and heated at 185° for various times. Gas chromatographic analysis of the six-, seven-, and eight-membered ring ketones recovered from the reaction mixture (pentane extraction, ~90% yields), revealed the presence of a new component having a retention time different from the starting material. In each case these new components constituted less than 2% of the amount of recovered ketones and no attempts were made to isolate these components. No rearrangement occurred for the five-

-membered ring ketones. A pure sample of each of the four ketones w isolated by preparative g.c. ^2H NMR and mass spectrometry were employed to follow ^2H incorporation. The results for the deuterated ketones isolated after various reaction times are listed in Table 3.10. Deuterium exchange only occurred at the methyl groups in 2,2,5,5-tetramethylcyclopentanone and 2,2,8,8-tetramethylcyclooctanone. Somewhat susprisingly, β- and δ-enolization were not observed for the eight-membered ring ketone. From the shift reagent studies, the relatively large induced shift for the δ-protons in the eight-membered ring ketones indicated a relatively short transannular separation between the δ protons and the carbonyl group (Figure 3.17) but, in fact, ^2H was not detected at the δ-carbon even after 375 hr. Deuterium exchange occurred at the methyl groups and the β-carbons in 2,2,6,6-tetramethylcyclohexanone and 2,2,7,7-tetramethylcycloheptanone but methylene exchange occurred at a much slower rate than that in the methyl carbons. From the results in Table 3.10, one can roughly estimate the first-order rate constants per hydrogen for deuteration at the methyl group in 5-, 6-, 7- and 8-membered ketones as $\sim 4.1 \times 10^{-7}$, $\sim 0.5 \times 10^{-7}$, $\sim 0.5 \times 10^{-7}$ and $\sim 0.6 \times 10^{-7}$ sec^{-1}, respectively. A comparison of the rate of deuteration incorporation at the methyl group in 2,2,5,5-tetramethylcyclopentanone with that for homoenolization of fenchone at the exo-methyl position indicates that the former process is ca. 2 times faster.

Table 3.10

Deuterium in Monocyclic Ketones $(CH_2)_{n-3}C(Me)_2C{=}O$ at 185°

n	Time (hr)	^2H content by mass spectrometry[a] 1D	2D	3D	4D	5D	6D	7D	Total atom ^2H
5	60	0.392	0.204	0.062	0.013	0.004			1.05
	99[b]	0.345	0.280	0.134	0.042	0.008			1.51
	120	0.251	0.295	0.209	0.102	0.033	0.009		2.10
	120[c]	0.106	0.208	0.251	0.208	0.123	0.061	0.020	3.22
6	60	0.064							0.06
	99[b]	0.161	0.018						0.20
	120	0.290	0.063						0.42
	375[c]	0.363	0.247	0.105	0.028	0.010			1.34
7	99[b]	0.118	0.035						0.19
	399	0.247	0.052	0.011					0.39
	255[c]	0.375	0.207	0.066					0.99
8	99[b]	0.172	0.028						0.23
	375	0.376	0.181	0.066					0.94

[a] Atom ^2H, ± 0.001.

[b] Using same batch of base, same oven and the same reaction time.

[c] At 215° for the first 12 hr.

Table 4.1

^{13}C Carbonyl Shieldings[a] in Several Bicyclic Ketones

Item	Skeleton	Substitution	δ_C
	(3.2.1)	3-oxo	211.9
	(4.4.0)[b]	1-oxo	211.9
		2-oxo	210.5
		2-oxo-10-Me	211.2
		3-oxo-10-Me	210.6
		4-oxo-10-Me	210.9
52	cyclohexanone		212.0
50	(2.1.1)	2-oxo	214.0
51	(3.1.1)	2-oxo-6,6-Me_2	214.3
59	(3.2.1)	2-oxo	214.0
56	(2.2.1)	2-oxo	217.4
57	(2.2.2)	2-oxo	216.7
58	(3.2.2)	6-oxo	216.2
54	(3.2.1)	6-oxo	221.4
55	(3.3.0)	2-oxo	223.0
53	cyclopentanone		220.5

[a] In ppm from internal TMS in $CDCl_3$ solutions.

[b] Reference (88).

(F) CONCLUSIONS:

In an exploration of the mechanistic features and synthetic scope of homoenolization of cyclic and polycyclic ketones, the behavior of eight different ketones has been examined. These studies demonstrate the utility of ^{13}C and ^{2}H NMR spectroscopic methods for mechanistic investigation. The use of ^{2}H labels with ^{13}C and ^{2}H NMR assays readily provides mechanistic formation that is either difficult or impossible to obtain by other physical methods.

It was found that fenchone, 3,3-dimethylbicyclo(2.2.2)octan-2-one, 7,7-dimethylbicyclo(3.2.1)octan-6-one and a few monocyclic ketones do rearrange but the results indicate that either the equilibrium between the starting material and the rearranged products strongly favours the starting material or that the formation of homoenolate anions is very slow. The estimated first-order rate constants at the different sites of exchange for all of these ketones are summarized in Table 3.11. From these data it is clear that exchange at the β-carbon in these systems is stereoselective with exo-proton exchange consistently faster than endo- exchange, i.e. the homoenolate ions open with preference in inversion. The rate constants for exchange at the three different bridgehead carbons may presumably be due to the orientation of the carbonyl group with respect to the α-hydrogen and/or its ring size.

It is interesting that in the cyclic system the methyl deuterium incorporation in cyclopentanone is eight times faster than six-, seven-, and eight-membered ring ketones. In the bicyclic systems, exo-methyl deuterium incorporation are faster than endo-methyl. It is presumably the homoenolate anion intermediate for exo-methyl exchange that seems

less sterically hindered than the homoenolate anion intermediate for endo-methyl exchange.

Table 3.11

Estimated First Order Rate Constant (x 10^{-8} sec^{-1} per hydrogen)

Compound		
2,2,5,5-tetramethylcyclopentanone	40	(Me)
2,2,6,6-tetramethylcyclohexanone	5	(Me)
2,2,7,7-tetramethylcycloheptanone	5	(Me)
2,2,8,8-tetramethylcyclooctanone	6	(Me)
1,3,3-trimethylbicyclo(2.2.1)heptan-2-one	>2.	(Me-1)
	>20	(exo-Me-3)
	> 5	(endo-Me-3)
	750	(exo-H-6)
	220	(endo-H-6)
3,3-dimethylbicyclo(2.2.2)octan-2-one	5	(Me)
	140	(exo-H-6,7)
	20	(endo-H-6,7)
7,7-dimethylbicyclo(3.2.1)octan-6-one	300	(exo-Me)
	2	(endo-Me)
	27	(exo-H-4)
	> 1800	(H-5)
Adamantanone	6	(H-1,3)
	15	(exo-H-4,8,9,10)
	1	(endo-H-4,8,9,10)

CHAPTER FOUR

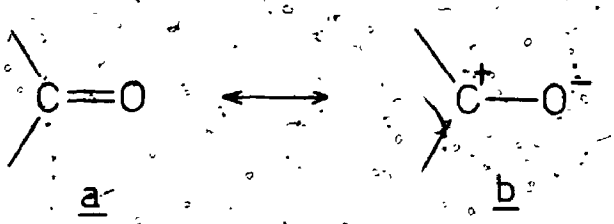
^{13}C NMR STUDIES OF SEVERAL SERIES OF MONOCYCLIC AND POLYCYCLIC KETONES

(A) ^{13}C CARBONYL CARBON SHIELDINGS IN MONOCYCLIC AND BICYCLIC KETONES

-----BOND ECLIPSING INTERACTION

(a) INTRODUCTION

^{13}C NMR spectroscopy is one of the best tools available for the study of the carbonyl group since the carbonyl carbon shieldings are strikingly dependent on the structure of the molecule. These resonances occur over a total range of 70 ppm in the lower field region of the ^{13}C spectrum. The carbonyl signals of aldehydes and ketones are appreciably downfield (186 - 226 ppm) from the region in which olefinic carbons absorb. Presumably this is primarily because of polarization of the bond a toward oxygen i.e. the contribution of form b to the overall electronic distribution.



a b

A detailed study of the ^{13}C resonance position of the carbonyl nuclei in a variety of carbonyl derivatives (86) was reported in 1964 and the avaflable data were reviewed recently (87). It is interesting that a marked variation in the chemical shift of the carbonyl carbon of the cycloalkanones (cyclobutanone to cycloheptadecanone) was noted eleven years ago (86). At that time, no satisfactory explanation was

put forward although a conformational origin might be suspected. To understand this feature, a series of bicyclic ketones was prepared for ^{13}C NMR examination. The relative rigidity of the bicyclic skeletons, however, provides a means whereby potential conformational contributions can be controlled and tested. The carbonyl shieldings for this series has led to an interpretation of the variation of carbonyl shieldings in cycloalkanones (C_4 - C_{17}) in terms of their preferred conformations. This feature has potential application for stereochemical elucidation.

(b) RESULTS AND DISCUSSION

The carbonyl carbon signals were readily assigned from their characteristic low field positions and the shielding data for this series of ketones are collected in Table 4.1. The complete assignments for all of these ketones will be discussed in section (E).

The variation in the shieldings in this series of bicyclic ketones seems particularly interesting, since the values span a range of 13 ppm δ_C 210.5 - 223.0 for the parent ketones. There appears to be a trend which may account for the well-known but unexplained variations in the monocyclic series (86). The remarkable sensitivity of this shielding to ring size has only been attributed to conformational factors in the most general terms. Although most of these bicyclic ketones can be regarded as either substituted cyclohexanones or cyclopentanones, the observed carbonyl shieldings seem to depend primarily on features other than ring size. For the simple five- and six-membered rings the carbonyl shieldings differ by 8.5 ppm, 220.5 and 212.0 ppm, respectively, in $CDCl_3$, but in bicyclo(2.1.1)hexan-2-one (50) and 6,6-dimethylbicyclo(3.1.1)heptan-2-one

Table 4.1

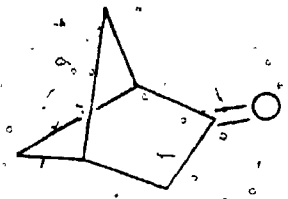
^{13}C Carbonyl Shieldings[a] in Several Bicyclic Ketones

Item	Skeleton	Substitution	δ_C
	(3.2.1)	3-oxo	211.9
	(4.4.0)[b]	1-oxo	211.9
		2-oxo	210.5
		2-oxo-10-Me	211.2
		3-oxo-10-Me	210.6
		4-oxo-10-Me	210.9
52	cyclohexanone		212.0
50	(2.1.1)	2-oxo	214.0
51	(3.1.1)	2-oxo-6,6-Me_2	214.3
59	(3.2.1)	2-oxo	214.0
56	(2.2.1)	2-oxo	217.4
57	(2.2.2)	2-oxo	216.7
58	(3.2.2)	6-oxo	216.2
54	(3.2.1)	6-oxo	221.4
55	(3.3.0)	2-oxo	223.0
53	cyclopentanone		220.5

[a] In ppm from internal TMS in $CDCl_3$ solutions.

[b] Reference (88).

(51) this absorption is near 214 ppm, even though their carbonyl groups are in different sized rings. As a possible explanation, it can be suggested that the number of α-bond eclipsing interactions present in each case is the most important feature. Cyclohexanone (52) has two bond eclipsing interactions, while 50 and 51 have one and cyclopentanone (53) can be viewed as lacking such interactions, since its favored conformation is the half-chair (C_2) (89). Inspection of



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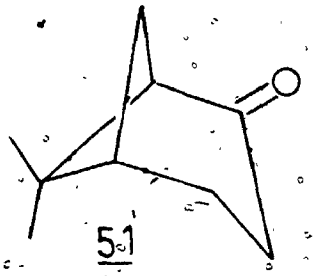

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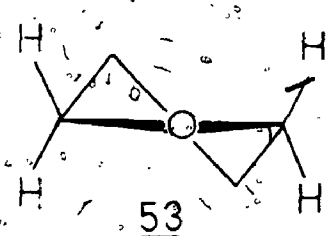

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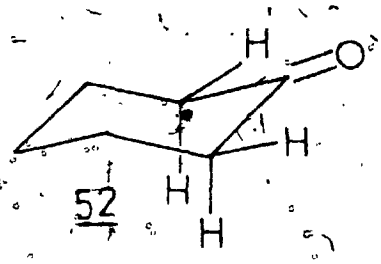

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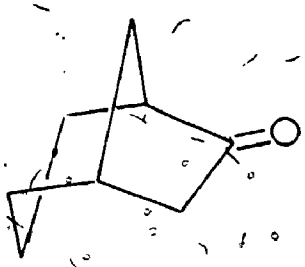
molecular models indicates that α-bond eclipsing interactions should be minimal in bicyclo(3.2.1)octan-6-one (54) and bicyclo(3.3.0)octan-2-one (55) and their carbonyl shieldings of 221.4 and 223.0 ppm, respectively, are comparable to the cyclopentanone value. The carbonyl shielding for bicyclo(3.2.1)octan-3-one and five decalones (see Table 4.1) are essentially the same as that of cyclohexanone and each of these has comparable bond eclipsing interactions. The carbonyl shieldings of norcamphor (56), bicyclo(2.2.2)octan-2-one (57) and bicyclo(3.2.2)nonan-6-one (58) are



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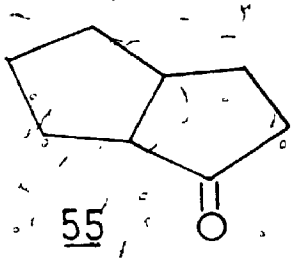

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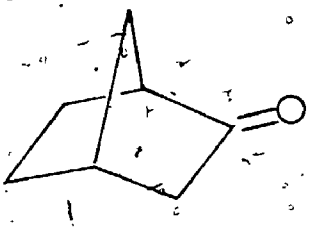

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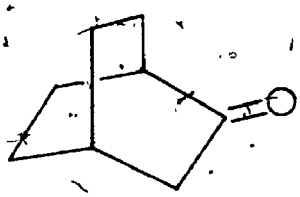

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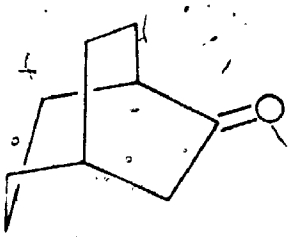

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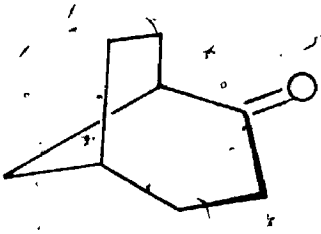

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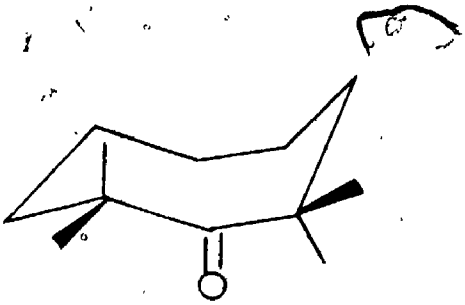

BC-3

60

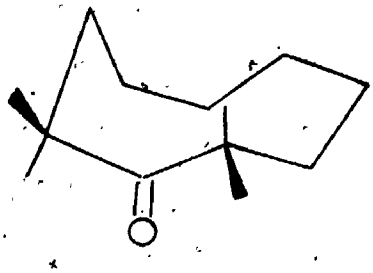

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Table 4.2

^{13}C Shieldings[a] of Some Cycloalkanones

Ring	C=O		α-CH_2								ω-CH_2
	CS_2[b]										
4		209.1	47.7								9.7
5	217.2	220.5	38.3	23.3							
		219.4	38.1	23.2	(2.5 M)						
		220.5	38.3	23.3	(0.5 M)						
6	208.9	212.0	42.0	27.1							25.1
		211.5	41.9	27.1	(2.0 M)						25.0
		212.0	42.0	27.1	(0.5 M)						25.1
7	211.6	215.2	43.9	30.5	24.4						
8	214.6	218.1	42.0	27.3	25.7						24.8
9	214.5	218.1	43.6	27.0	25.1	24.4					
10	211.7	214.7	42.1	25.0	24.9	23.5					25.2
11	213.1	214.3	42.0	26.1	25.0	24.5	22.6				
12	209.4	212.7	40.4	24.8	24.7	24.3	22.6				22.5
13	209.5	212.7	42.0	26.6	25.9	25.8	24.6	23.3			
14	208.1	211.9	40.9	26.1	25.9	25.4	25.3	23.0			24.5
15	208.9	212.6	42.2	27.7	26.8_3	26.8_5	26.6	26.4	23.5		
16	208.6	212.2	42.1	27.7	27.3	27.1	26.6_2	26.5_7	23.5		26.6
17	208.5	212.1	42.4	28.3	27.9	27.7	27.2_4	27.2_6	27.0	23.9_8	

[a] In ppm from internal TMS in $CDCl_3$ solutions (~1 M). [b] Data taken from ref. (86) for CS_2 solutions and corrected to the TMS scale with the factor 192.8 ppm.

217.4, 216.7, and 216.2 ppm, respectively, which on the basis of the present proposal suggests that the carbonyl group has a single bond eclipsing interaction somewhat smaller than that in the more rigid bicyclo(2.1.1)hexan-one (50) skeleton. Again, molecular models indicate that this is a reasonable interpretation. On similar grounds, carbonyl absorption at 214.0 ppm for bicyclo(3.2.1)octan-2-one can be interpreted in term of 59 as the favored conformation having the 3-carbon bridge nearly planar.

Since the variation in the carbonyl shieldings in these bicyclic systems are explicable in terms of the number of bond eclipsing interactions it seems reasonable to re-examine the trends found several years ago for the monocyclic ketones (86). The data for 1-M solutions in $CDCl_3$ are listed in Table 4.2 and the effects of concentration for two compounds are also included. The carbonyl positions for this series in $CDCl_3$ and CS_2 are shown in Figure 4.1. The trends are almost identical with the carbonyl carbons deshielded by ca. 3 ppm in $CDCl_3$ presumably because of hydrogen bonding (8). Varying the concentration from 0.5 to 2.5 M does not change the carbon shieldings very much. From the Figure, it is apparent that the carbonyl carbons in 8- and 9-membered rings are appreciably deshielded relative to cyclohexanone, while those in the 7-, 10-, and 11-membered rings are slightly deshielded. For the larger rings the carbonyl values are essentially the same as that for cyclohexanone. On the basis of bond eclipsing contributions to the carbonyl shieldings, the observed values for cyclooctanone and cyclononanone indicate that these favor conformations with one eclipsing interaction as in 60 and 61, respectively. These are boat-chair (BC-3) conformations, somewhat distorted to relieve bond opposition strain to

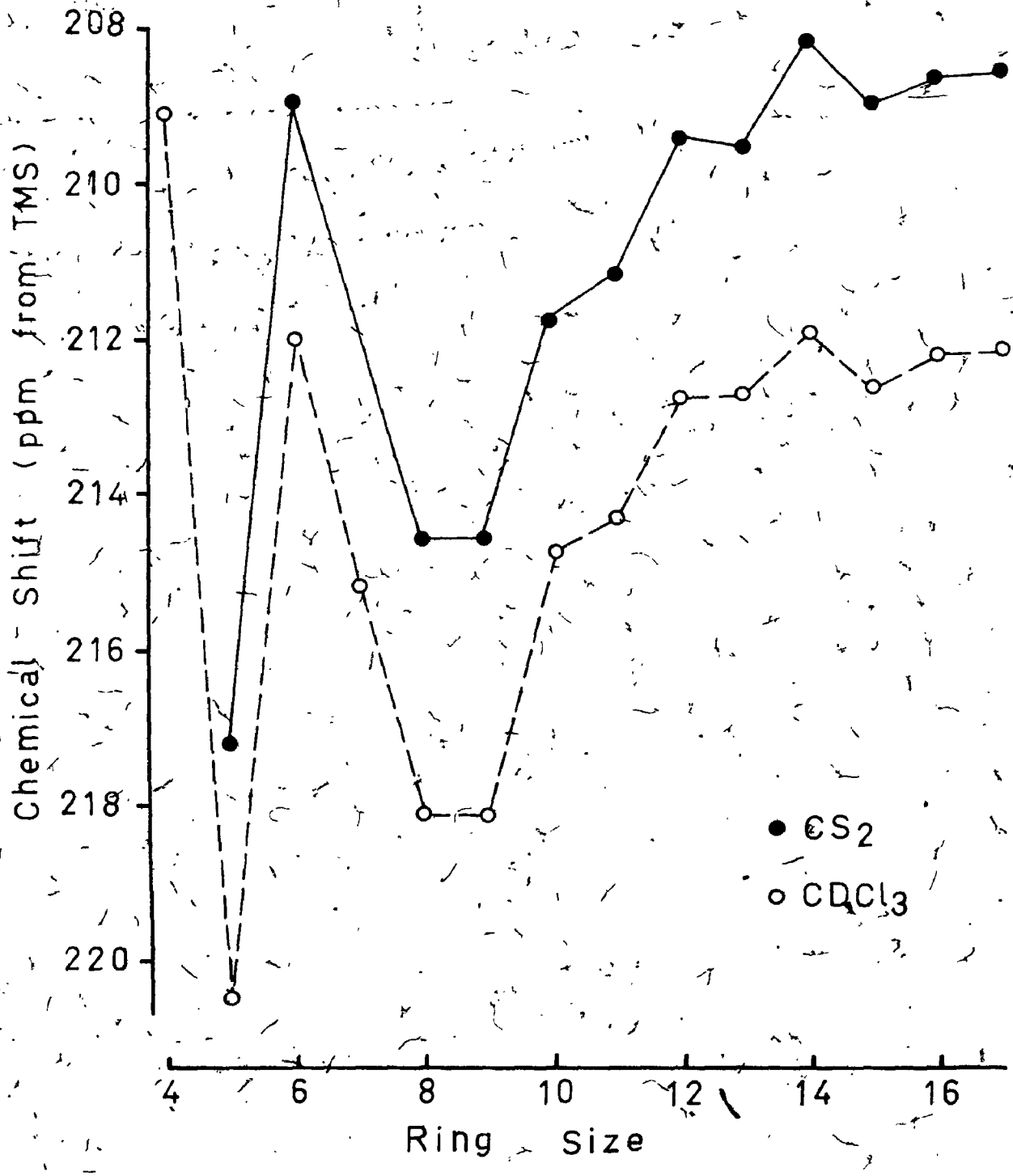
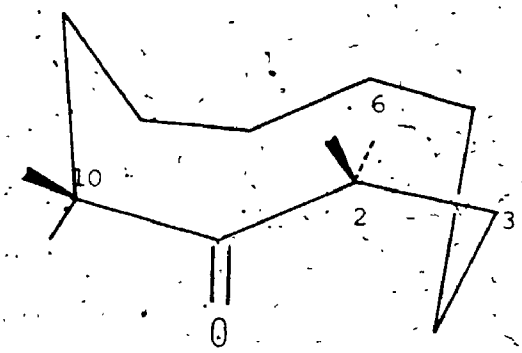


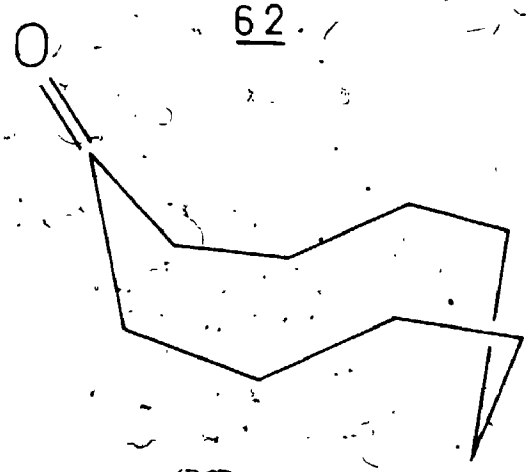
Figure 4.1. Variation of Carbonyl Carbon Chemical Shifts of Cycloalkanones in $CDCl_3$ and CS_2 (86) with Ring Size.

C-3 and C-4. Anet and his co-workers have established that 60 is the favored conformation for cyclooctanone (90) and have shown that cyclononanone very likely exists in a single conformation of the same symmetry (91). For cyclodecanone, two of the possible boat-chair-boat (BCB) conformations are BCB-3, 62 and BCB-1, 63. If BCB-1 were favored, one could anticipate a carbonyl shielding essentially the same as that for cyclohexanone whereas in BCB-3 transannular interactions tend to maximize the separation between closely approaching hydrogens (e.g. on C-2 and C-6 in 62) thereby reducing the bond eclipsing interactions of the carbonyl group (i.e. with the $C_2 - C_3$ bond and one of the α-hydrogens at C-10) and decreasing the carbonyl shielding. The observed shielding of 214.7 ppm is significantly less than the cyclohexanone value of 212.0 ppm. The remaining BCB-2 conformation for cyclodecanone has the carbonyl group in an environment very similar to that for cyclohexanone, always eclipsed with two hydrogens on the α and α' carbons. Thus the carbonyl shielding results favor BCB-3 as the preferred conformation. Anet et al. (91) have recently presented evidence that cyclodecanone strongly favors 62 (BCB-3) over the BCB-2 conformer and their results clearly eliminate BCB-1 as a major contributor. Since the carbonyl shielding of cycloundecanone (214.3 ppm) is close to that for cyclodecanone, a similar preferred conformation is indicated and it has been shown that the 11-membered ring ketone probably exists as a single conformer in solution (91). The conformation of the crystalline state has recently been established (92). Anet et al. have also shown that cyclododecanone, a "square" D_4 form 64, is represented by 65 with the carbonyl group at a nonecorner position (91). This conformation



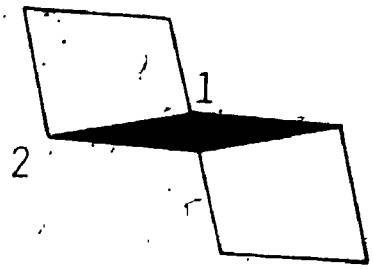
(BCB - 3)

62



(BCB - 1)

63



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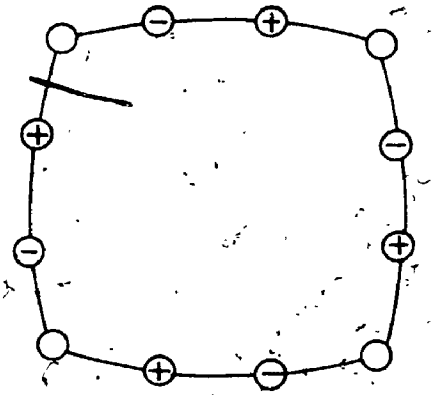
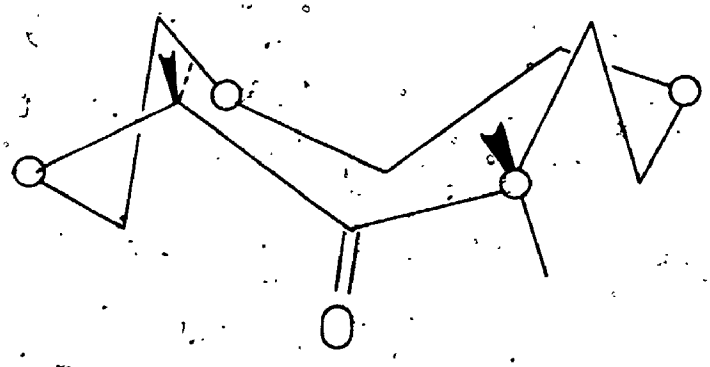


64



65

has two bond eclipsing interactions for the carbonyl group and the observed shielding of 212.7 ppm fits very well with the present interpretation. For cycloheptanone, Allinger et at (93) have calculated that there are small differences between the four possible twist-chair conformations of cycloheptanone. The 2-substituted twist-chair conformer was found to be the lowest in energy, with the 1-substituted twist-chair conformer only 0.25 kcal/mole higher, indicating that a conformational mixture of 1- and 2-substituted twist-chair conformers exists at room temperature. This suggestion agrees with the carbonyl shielding observed. From models, the bond eclipsing for the carbonyl group at C-1 and C-2 in the twist-chair 66 would appear to be less than that for cyclohexanone, and the observing shielding of 215.2 ppm seems reasonable.

Although the notion that bond eclipsing interactions are important factors governing carbonyl shieldings is speculative, the favored conformations indicated by the observed shieldings for the cycloalkanones are in excellent agreement with those deduced on the basis of much more rigorous information. This indicates that carbonyl shielding data may be helpful for conformation assignments in a variety of systems.

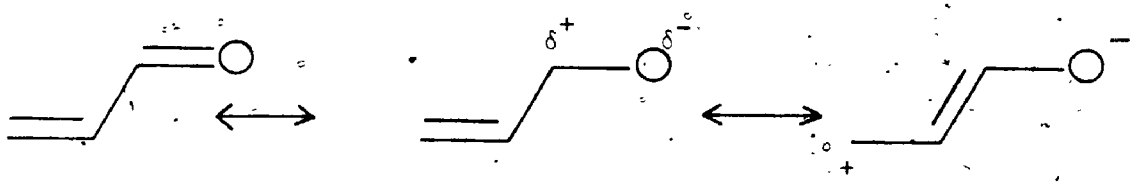
(c) SUMMARY

The variation in the ^{13}C shieldings of the carbonyl carbons in this series of bicyclic ketones suggested that bond eclipsing interactions have an important influence on this parameter. With this notion, the heretofore puzzling variations observed for the cycloalkanones (C_4 - C_{17}) are readily interpretable in terms of their favored conformations. Therefore, carbonyl shielding data may be helpful for conformational assignments in a variety of systems.

(B) THE ^{13}C SPECTRA OF SOME β,γ AND γ,δ UNSATURATED POLYCYCLIC KETONES ------ HOMOCONJUGATION

(a) INTRODUCTION

One important factor contributing to the carbonyl chemical shift is conjugation. A significant shielding effect is found for conjugated systems in which either an olefinic bond (94) or an aryl ring (95) is in the α position to the carbonyl group. This change is typically 10 - 12 ppm by comparison with the corresponding saturated system. The results have been rationalized in terms of a decreased electron deficiency at the carbonyl carbon because of electron release from the conjugated π system, i.e. e tends to offset the effect of d with regard to the electron density at the carbonyl carbon.



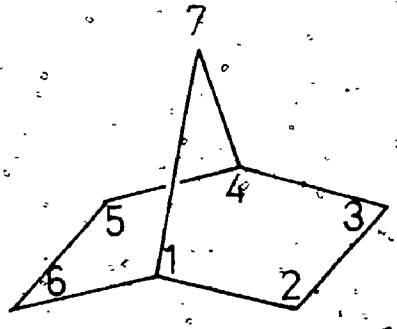
c d e

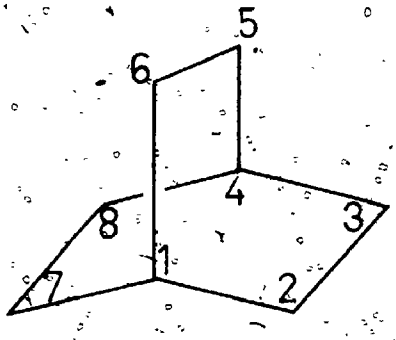
In view of the pronounced effect of an adjacent conjugated π-bond on carbonyl carbon shieldings it seems reasonable to expect that any factor tending to increase the local electron density could be expected to shift the carbonyl absorption to higher field. One such factor is a homoconjugative interaction between a carbonyl group and a more remote olefinic bond which can adopt a geometry to permit overlap of the π systems. The extent of interaction should be reflected in the observed carbonyl ^{13}C shielding. In 1969, Gurudata and Stothers found that the carbonyl

shieldings for a number of β,γ -unsaturated ketones were increased relative to the absorption positions for the saturated analogs. The magnitude of the shift in the β,γ-unsaturated systems depended on the relative orientation of the double bond and the carbonyl group. At that time instrumental limitations precluded definitive detection and assignments for the remaining carbon signals. In principle, however, evidence should be provided by the variations in the shieldings of the olefinic carbons and other closely neighboring centers. For this purpose, several β,γ-unsaturated polycyclic ketones and the corresponding saturated ketones, olefins and hydrocarbons were prepared. The ^{13}C shielding data for the β,γ-unsaturated ketones were compared with those for the corresponding olefins and saturated ketones. The results tend to support the original conclusions (96) but only in a qualitative fashion. A detailed examination of the shielding variation clearly showed that factors in addition to charge density must make significant contributions. The results for some ketones containing γ,δ-double bonds were assessed in a similar fashion.

(b) RESULTS

The ^{13}C shielding data for the polycyclic ketones, olefins and hydrocarbons are collected in Table 4.3. The assignments for norborn-5-en 2-one, norbornan-2-one, norborn-2-ene and norbornane (68, 56, 69 and 67, respectively) and bicyclo(2.2.2)oct-5-en-2-one, -an-2-one, -5-ene and -ane (73, 57, 74 and 72, respectively) will be discussed in the next section. In each case, the carbonyl signals were readily identified. Off-resonance decoupling experiments readily distinguished methylene and methine sp^3 carbons and the latter were easily assignable





56 2-oxo

68 2-oxo-Δ^5

69 Δ^5

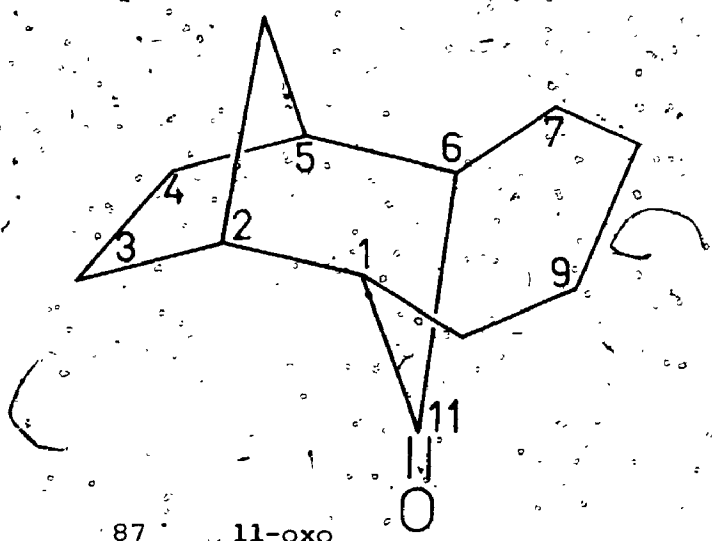
70 7-oxo-Δ^5

71 7-oxo

57 2-oxo

73 2-oxo-Δ^5

74 Δ^5

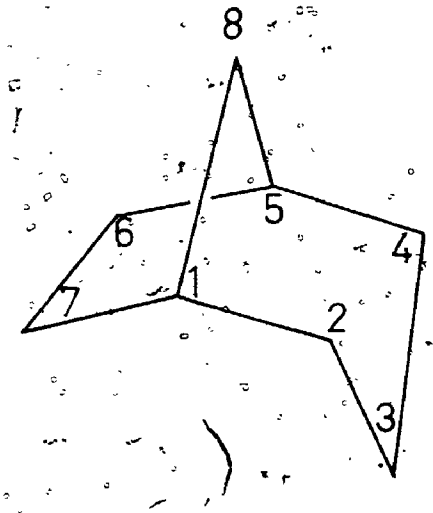


87 11-oxo

88 11-oxo-Δ^3

89 11-oxo-Δ^7,Δ^9

90 11-oxo-Δ^3,Δ^7,Δ^9



59	2-oxo	82	3-oxo	91	3-Br-Δ^3,Δ^6
76	2-oxo-Δ^3	54	6-oxo	92	2-oxo-3-Br-Δ^3,Δ^6
77	2-oxo-Δ^3,Δ^6	83	6-oxo-Δ^3	93	exo-2-OH-3-Br-Δ^3,Δ^6
78	Δ^3,Δ^6	84	Δ^3	94	endo-2-OH-3-Br-Δ^3,Δ^6
79	2-oxo-Δ^6	85	8-oxo-Δ^3	95	exo-2-OH-Δ^3,Δ^6
80	Δ^6	86	8-oxo	96	endo-2-OH-Δ^3,Δ^6
81	3-oxo-Δ^6			97	3-Br-Δ^3

Table 4.3

^{13}C Shieldings[a] of Several Polycyclic Derivatives

Compound	Skeleton	Substitution[b]	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-10	C-11
67	(2.2.1)	Nil	36.3	29.6	29.6	36.3	29.6	29.6	38.3			
56		2-oxo	49.7	217.4	45.1	35.3	27.1	24.2	37.6			
			(49.8)	(214.8)	(45.0)	(35.4)	(27.3)	(24.3)	(37.5)			
68		2-oxo-Δ^5	55.8	214.7	37.1	40.0	142.7	130.4	50.8			
			(57.7)	(212.7)	(37.1)	(40.3)	(142.7)	(131.0)	(50.8)			
69		"Δ^5"	41.8	24.6	24.6	41.8	135.2	135.2	48.5			
70		"7-oxo-Δ^5"	45.3	21.0	21.0	45.3	133.2	133.2	205.3			
			(45.6)	(21.1)	(21.1)	(45.6)	(133.6)	(133.6)	(204.1)			
71		7-oxo	37.8	24.2	24.2	37.8	24.2	24.2	216.8			
			(38.0)	(24.4)	(24.4)	(38.0)	(24.4)	(24.4)	(214.5)			
72	(2.2.2)	Nil	24.0	26.1	26.1	24.0	26.1	26.1	26.1	28.1		
57		2-oxo	42.3	216.7	44.6	27.9	24.8	23.4	23.4	24.8		
73		2-oxo-Δ^5	48.6	212.4	40.4	32.4	136.8	128.3	22.5	24.3		
74		"Δ^5"	29.5	25.8	25.8	29.5	134.1	134.1	25.8	25.8		
75	(3.2.1)	Nil	35.2	32.8	19.1	32.8	35.2	28.9	28.9	39.7		
59		2-oxo	51.2	214.0	34.7	32.1	34.1	28.1	28.0	38.3		
76		2-oxo-Δ^3	50.6	203.2	127.2[c]	156.5[c]	37.4	29.4	24.5	40.2		
77		2-oxo-Δ^3,Δ^6	57.1	198.8	123.6[c]	154.9[c]	42.1	143.3[c]	131.8[c]	52.0		
78		Δ^3,Δ^6	38.7	28.7	123.8	134.1	38.5	139.7[c]	130.2[c]	40.7		
79		2-oxo-Δ^6	55.9	210.0	34.5	25.2	38.7	137.8[c]	131.7[c]	42.1		
80		Δ^6	39.5	25.2	18.7	25.2	39.5	132.1	132.1	45.1		
81		3-oxo-Δ^6	38.3	46.4	210.1	46.4	38.3	135.3	135.3	42.8		
82		3-oxo	35.8	50.3	211.9	50.3	35.3	29.3	29.3	37.8		
54		6-oxo	32.2	30.5	18.9	30.7	46.2	221.4	43.5	37.2		
			(32.3)	(30.5)	(19.0)	(30.8)	(45.9)	(218.2)	(43.3)	(37.2)		
83		6-oxo-Δ^3	30.2	31.9	128.0[d]	126.0[d]	46.7	212.4	43.7	34.3		
84		"Δ^3"	33.6	37.5	123.8[c]	134.7[c]	35.6	35.5	30.6	35.5		
85		"8-oxo-Δ^3"	42.5	43.1	125.5[c]	132.7[c]	45.2	30.2	25.6	217.9		
			(42.6)	(43.0)	(126.9)	(133.2)	(45.2)	(30.3)	(25.7)	(216.0)		
86		8-oxo	44.8	37.0	17.4	37.0	44.8	22.7	22.7	222.3		
			(44.9)	(36.8)	(17.5)	(36.8)	(44.9)	(22.8)	(22.8)	(219.2)		
87	(4.4.1.$1^{2,5}$)	11-oxo	57.3	42.2	29.2	29.2	42.2	57.3	28.4	28.2	216.5	30.2
88		11-oxo-Δ^3	52.8	45.1	137.0	137.0	45.1	52.8	28.9	27.1	213.2	33.9
89		11-oxo-Δ^7,Δ^9	62.1	45.2	30.0	30.0	45.2	62.1	127.3	126.3	210.9	29.4
90		11-oxo-Δ^3,Δ^7,Δ^9	57.9	48.7	135.4	135.4	48.7	57.9	128.3	126.2	208.0	33.3

[a] In ppm from internal TMS for $CDCl_3$ abd C_6D_6 solutions; the latter values are given in parentheses. Values underlined may be interchanged.

[b] For ease of comparisons within the table, some of the monoolefinic compounds are numbered in an unconventional manner: bicyclo(2.2.1)hept-5-ene, bicyclo(2.2.1)hept-5-en-7-one, bicyclo(2.2.2)oct-5-ene, bicyclo(3.2.1)oct-3-ene and bicyclo-(3.2.1)oct-3-en-8-one; the substitution as listed in quotation marks.

[c] Assigned by selective proton decoupling (see text). Example (see Table 4.6 and Figure 4.3).

[d] Assigned by selective proton decoupling of solutions containing Eu(fod)$_3$ (see text).

since, in the unsymmetrical cases, the methine carbon lying closer to the carbonyl group is the more deshielded of the pair in each spectrum. The methylene assignments for 7-oxo-norborn-2-ene (70) and 7-oxo-norbornane (71) as well as bicyclo(3.2.1)oct-6-ene (80), bicyclo-(3.2.1)oct-6-en-3-one (81) and bicyclo(3.2.1)octan-3-one (82) were straightforward from the relative intensities and the strong deshielding effect exerted by the carbonyl group at the α-carbons. The sp^3 assignments forbicyclo(3.2.1)octa-3,6-dien-2-one (77) were also straightforward and led to the assignments for the corresponding diene. For most of the remaining (3.2.1) derivatives, however, the methylene assignments are not unequivocal but a consistent set was obtained by comparison within the series and with the results for the synthetic precursors 91 - 97 whose data are listed in Table 4.4.

The results for bicyclo(3.2.1)octa-3,6-dien-2-one (77), bicyclo-(3.2.1)octa-3,6-diene (78), 3-bromo-bicyclo(3.2.1)octa-3,6-diene (91), and 3-bromo-bicyclo(3.2.1)octa-3,6-dien-2-one show that C-8 is only slightly affected by the 3-bromo group whereas C-2 in 91 is shielded by ca. 10 ppm relative to 78. The data for 93 - 96 indicate that an exo-2-hydroxyl shields C-8 while its endo counterpart deshields C-8 relative to hydrocarbon 78 and its 3-bromo derivative 91. The lone methylene signal in 92 - 96 renders this assignment unambiguous. The methylene shieldings on bicyclo(3.2.1)oct-3-ene (84) and its 3-bromo derivative 97 together with the data for 78 and 91 indicated that the most deshielded methylene carbon is C-2; thus, C-8 was assigned the value near 35 ppm for bicyclo(3.2.1)oct-3-ene and 3-bromo-bicyclo-(3.2.1)oct-3-ene. The two strong methylene signals for bicyclo(3.2.1)-

Table 4.4

^{13}C Shieldings[a] of Some Bicyclo(3.2.1)octane Derivatives

Compound	Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
91	3-Br-Δ^3,Δ^6	(40.6)	38.5	120.1	134.3	(40.1)	139.2	130.8	40.3
92	2-oxo-3-Br-Δ^3,Δ^6	56.8	206.4	118.2	154.6	44.4	143.2	131.7	51.4
93	exo-2-OH-3-Br-Δ^3,Δ^6	46.8	71.9	123.7	144.1	41.6	139.5	130.5	37.6
94	endo-2-OH-3-Br-Δ^3,Δ^6	47.3	71.9	124.8	143.6	41.6	138.7	130.5	44.3
95	exo-2-OH-Δ^3,Δ^6	46.0	66.2	126.3	144.5	39.5	138.2	130.3	37.9
96	endo-2-OH-Δ^3,Δ^6	47.2	67.1	127.1	144.1	38.9	137.1	129.8	44.7
97	3-Br-Δ^3	35.2	46.9	120.6	135.6	37.5	34.8	30.2	34.8

[a] In ppm from internal TMS for $CDCl_3$ solutions. Values in parentheses may be interchanged.

octane (75), the parent hydrocarbon were also most appropriately assigned as 32.8 (C-2, -4) and 28.9 ppm (C-6, -7) by comparison with the corresponding centers in bicyclo(3.2.1)oct-3-one. From this it appeared that C-6 would be deshielded relative to C-7 in 84 and 97 because introduction of the double bond at C-3, -4 eliminates a steric interaction between the endo protons at C-4 and C-6 in bicyclo-(3.2.1)octane. From these assignments for bicyclo(3.2.1)octane and bicyclo(3.2.1)oct-3-ene the more intense methylene signals in bicyclo-(3.2.1)octan-8-one were assigned and those for the methylene signals of bicyclo(3.2.1)oct-3-en-8-one (85) followed on the same basis. From the data for bicyclo(3.2.1)oct-6-ene (80) and the expected α effect of the carbonyl group, the methylene assignments for bicyclo(3.2.1)oct-6-en-2-one (79) were made. By comparison with bicyclo(3.2.1)octane, the signal near 43.5 ppm was assigned to C-7 in each of bicyclo(3.2.1)-octan-6-one (54) and bicyclo(3.2.1)oct-3-en-6-one (83), while those near 30.5 ppm for 54 were assigned to C-2 and C-4 and that at 32.0 ppm for 83 was ascribed to C-2. These assignments for 54 agree with those made on the basis of the data for the 7-methyl and 7,7-dimethyl derivatives (see section F). The exo-3-methyl and 3,3-dimethyl derivatives of bicyclo(3.2.1)octan-2-one were also available from another project (section, F) and the assignment in Table 4.3 was made by comparison with these data. Finally the methylene assignments listed for bicyclo(3.2.1)oct-3-en-2-one appear to agree best with the trends found throughtout the series. For ketones 87 - 90, the assignments are essentially straightforward with the exception of those for C-7 (-10) and C-8 (-9) which were not unequivocally distinguished.

Individual assignments for the olefinic carbons in the symmetrical unsaturated compounds 76 - 79 and 83 - 85 were obtained by selectively irradiating each olefinic multiplet at its ^{1}H resonance frequency to determine the specific carbon associated therewith. If a given ^{1}H resonance can be identified in an ^{1}H NMR spectrum, it is possible to irradiate only those protons at low radio-frequency power. The result observed in the ^{13}C spectrum is the collapse of one carbon signal to a sharp singlet while the other carbon signals retain some C--H coupling. To determine the appropriate, ^{1}H resonance frequencies, spectra were obtained with a Varian HA-100 spectrometer and the individual proton assignments followed readily from the observed splitting patterns together with proton-proton spin-decoupling experiments. In most cases the bridgehead proton signals were distinct and double irradiation at these positions uniquely defined the nearer of the two olefinic protons on a given double bond. Decoupling was not essential for the bicyclo(3.2.1)oct-3-ene derivatives since the vicinal coupling of H-4 with the bridgehead proton is relatively large, ~ 6.5 Hz, and therefore characteristic. In one case, bicyclo(3.2.1)oct-3-en-6-one (83), the olefinic protons are nearly equivalent giving rise to a deceptively simple pattern and consequently solutions containing the shift reagent, $Eu(fod)_3$, were employed to enchance their nonequivalence. In the presence of 0.185 equiv. of $Eu(fod)_3$, the olefinic proton shieldings differed by 0.56 ppm, and the coupling patterns readily identified each center whereupon selective decoupling readily distinguished the olefinic carbons bonded to each of the protons. Both carbons, however, absorbed downfield from the signals for the solution without $Eu(fod)_3$ and it

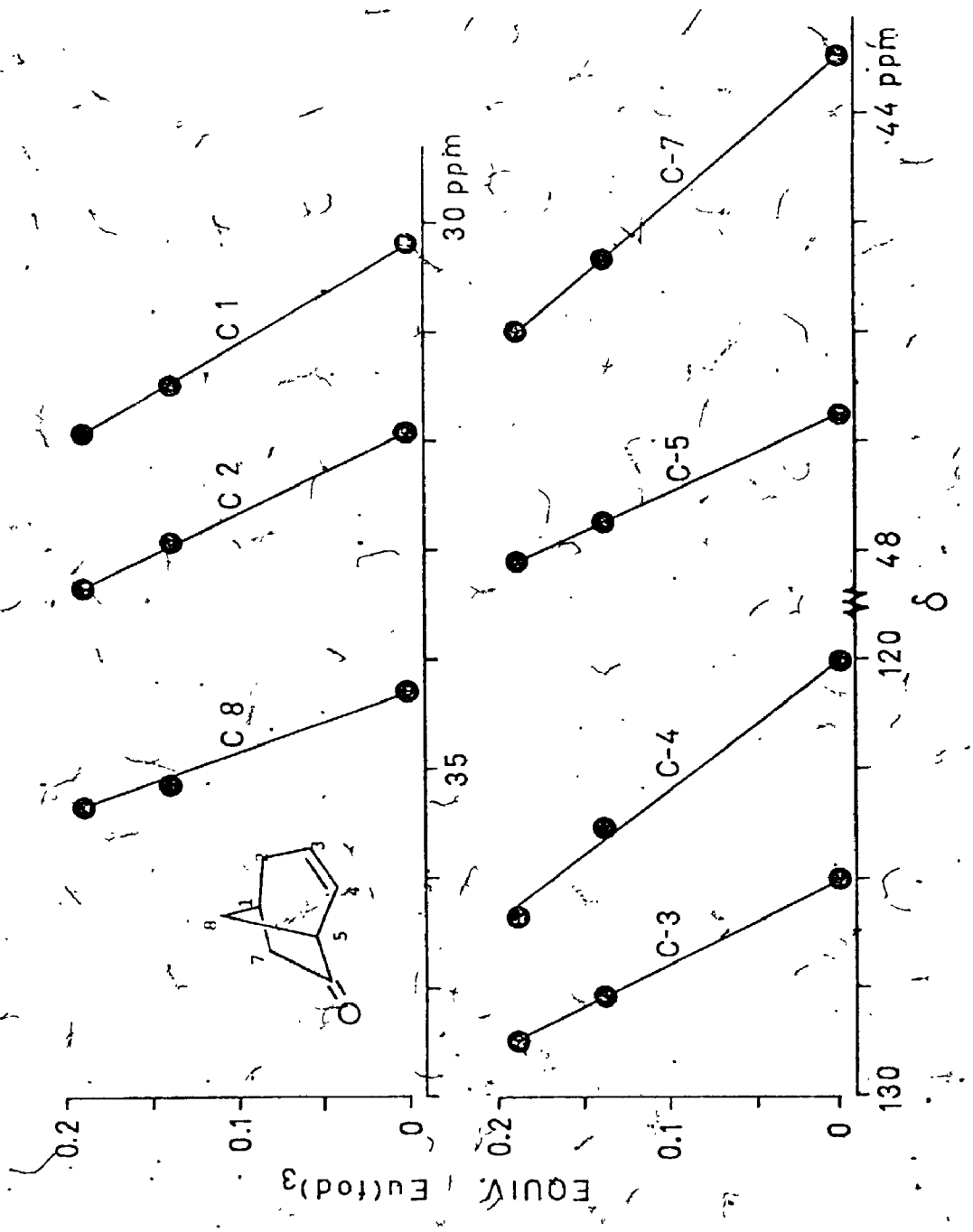


Figure 4.2. Effect of the addition of $Eu(fod)_3$ to $CDCl_3$ solutions of bicyclo(3.2.1)oct-3-en-6-one (83). The olefinic carbons were assigned by selective proton decoupling.

Table 4.5

Olefinic proton shieldings[a] in some bicyclo(3.2.1)octenones

Compound	3-H	4-H	6-H	7-H
76	5.81	7.25		
77	5.41	7.32	6.66	6.15
78	5.21	6.03	6.23	5.71
79			6.21	6.00
80			5.82	5.82
81			6.01	6.01
83	~5.65[b]	~5.75[b]		
	6.35[c]	6.91[c]		
84	5.34	5.86		
85	5.55	5.86		

[a] In ppm from internal TMS for $CDCl_3$ solutions.

[b] Assignments uncertain (see text).

[c] Solution containing 0.2 equiv. $Eu(fod)_3$.

Table 4.6

Proton parameters[a] for skeletal protons of $\Delta^3\Delta^6$-bicyclo(3.2.1)octan-2-one (77)

	1	3	4	5	6	7	syn-8[b]	anti-8[b]
1	3.33	2.0				3.2		
3		5.40_8	10.0	0.8				
4			7.31_9	6.5	3.0			
5				3.19				
6					6.65_6	5.3		
7						6.14_7		
syn-8							2.51_8	9.4
anti-8								2.58_8

[a] The values on the diagonal are the chemical shifts in ppm from internal TMS, ± 0.005 ppm, while the off-diagonal values are the coupling constants in Hz, ± 0.05 Hz.

[b] Syn and anti with respect to the carbonyl group.

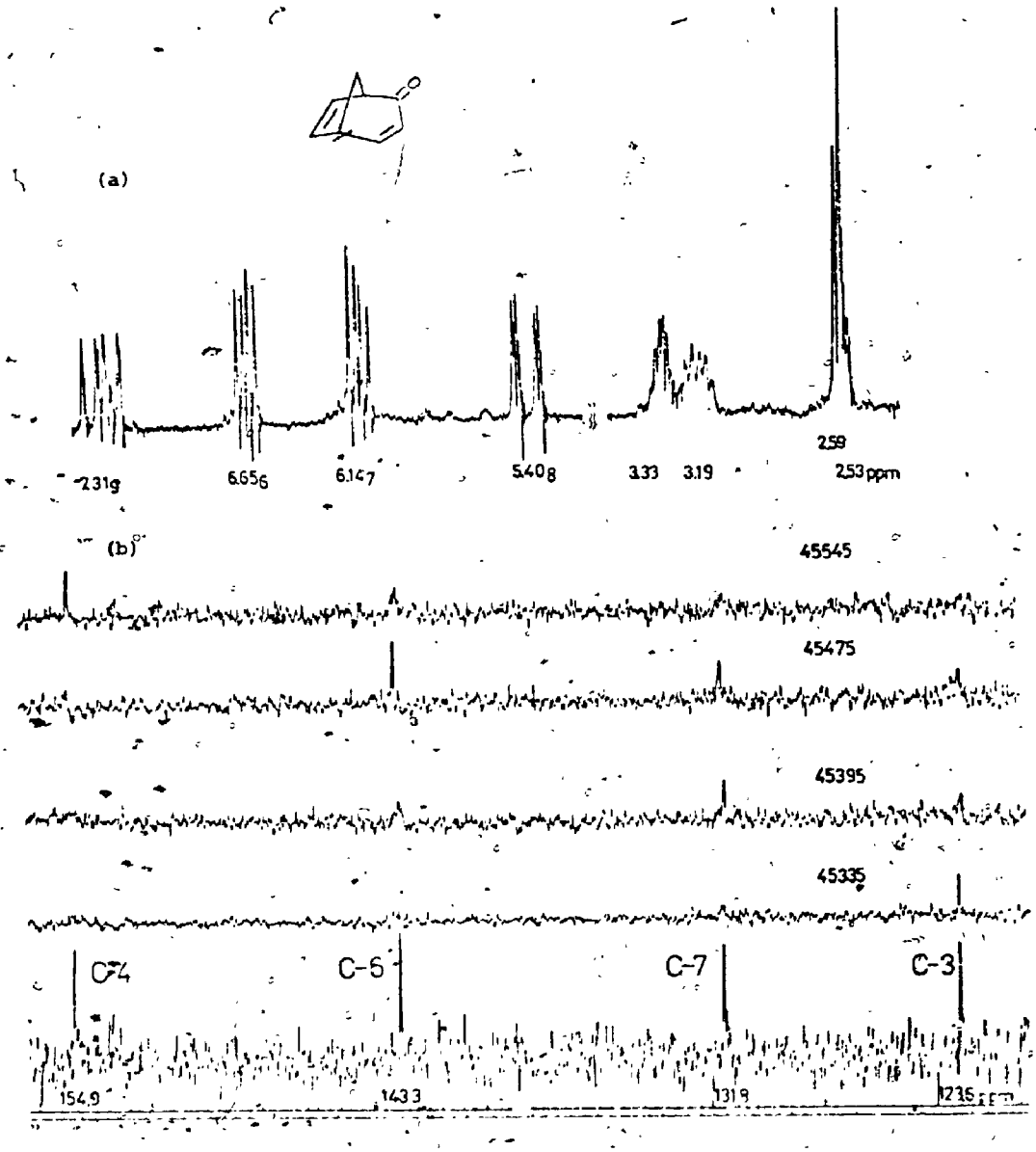


Figure 4.3. (a) ^{1}H nmr spectrum of bicyclo(3.2.1)octa-3,6-dien-2-one.
(b) ^{13}C nmr spectrum of bicyclo(3.2.1)octa-3,6-dien-2-one. The lower field region with wide-band ^{1}H decoupling (lower) and selective decoupling with irradiation at the different olefinic positions.

was necessary to record the ^{13}C spectrum of a solution containing 0.135 equivalent of $Eu(fod)_3$ to identify the specific olefinic carbons. This was accomplished by plotting the observed shieldings vs. $\{Eu(fod)_3\}$; Figure 4.2 shows that the individual assignments followed readily.

(c) DISCUSSION

In the earlier study of homoconjugated bicyclic ketones (96), attention was focussed entirely on the carbonyl shieldings for which it was found that β,γ unsaturation tended to increase the carbonyl shielding relative to that observed for the saturated analog. The present data, summaried in Table 4.7, show that this trend is general and that bicyclo(2.2.2)oct-5-en-2-one isnot anomalous as originally found. Previously the value for bicyclo(2.2.2)oct-5-en-2-one was compared with that reported for the corresponding saturated ketone (97) but apparently the solvent difference masked the shift, now found to be −4.3 ppm in $CDCl_3$. A brief examination of solvent effects for a few examples showed that the shieldings are lower in $CDCl_3$ than in C_6D_6 (Table 4.3) presumably because of hydrogen bonding in the former, a feature known to deshield carbonyl carbons (98). It is interesting that the $\Delta\Delta_C$ values in Table 4.7 are somewhat less for C_6D_6 solutions. The magnitude of the shift caused by the β,γ double bond depends on the relative orientation of the olefinic and carbonyl bonds, ranging from -2.7 to -11.5 ppm (in $CDCl_3$) for this series. The larger shifts for bicyclo(2.2.1)hept-5-en-2-one (68) and bicyclo(3.2.1)oct-3-en-6-one (83) are comparable to those found for conjugated systems (94, 95), as illustrated by the one bicyclic example, bicyclo(3.2.1)oct-3-en-2-one

Table 4.7

^{13}C Carbonyl Shieldings[a] in Several Polycyclic Ketones

Compound	Skeleton	Carbonyl position	δ_C	Compound	Double bond(s)	δ_C	$\Delta\delta_C$[b]
56	(2.2.1)	2	217.4(214.8)	68	Δ^5	214.7(212.7)	-2.7(-2.1)
71		7	216.8(214.5)	70	Δ^2	205.3(204.1)	-11.5(-10.4)
57	(2.2.2)	2	216.7	73	Δ^5	212.4	-4.3
59	(3.2.1)	2	214.0	76	Δ^3	203.2	
				77	Δ^9,Δ^6	198.8	-4.4
				79	Δ^6	210.0	-4.0
82		3	211.9	81	Δ^6	210.1	-1.8[c]
54		6	221.4(218.2)	83	Δ^3	212.4	-9.0
86		8	222.0(219.0)	85	Δ^3	217.9(216.0)	-4.1(-3.0)
87	(4.4.1.$1^{2,5}$)	11	216.5	88	Δ^3	213.2	-3.3[c]
				89	Δ^7,Δ^9	210.9	-5.6
				90	$\Delta^3,\Delta^7,\Delta^9$	208.0	-2.9[c,d]

[a] In ppm from internal TMS. Measured in $CDCl_3$ and C_6D_6; the latter values given in parentheses.

[b] The effect of a β,γ double bond unless otherwise indicated.

[c] The effect of the γ,δ double bond.

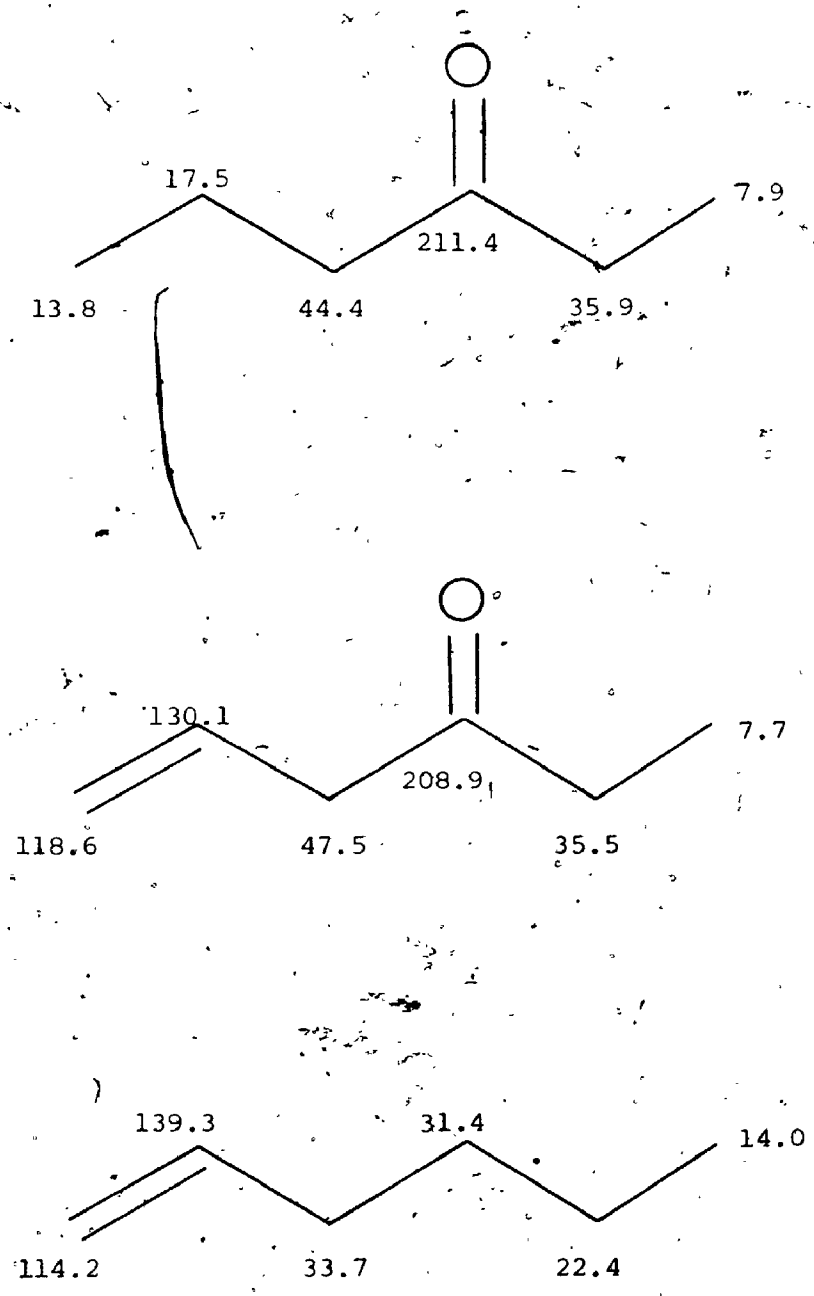
[d] 90 relative to 89.

(76), included in this series, for which $\Delta\delta_C$ = -10.8 ppm relative to bicyclo(3.2.1)octan-2-one (59). For α,β conjugated systems, a maximum interaction is expected if the nodal planes of the two π-bonds are coplanar so that $2p\pi$ overlap is at a maximum. For β,γ-unsaturation, however, a different realtionship is to be expected (96). Although the marked effect of the β,γ olefinic bond in bicyclo(2.2.1)hept-2-en-7-one was well known (96, 97) it seemed somewhat surprising that bicyclo(3.2.1)oct-3-en-6-one (83) exhibited a shift of -9.0 ppm. since bicyclo(2.2.2)oct-5-en-2-one (73), bicyclo(3.2.1)oct-6-en-2-one (79) and bicyclo(3.2.1)oct-3-en-8-one show shifts near -4 ppm although all four ketones appear from molecular models to be very closely related in terms of the relative orientations of their olefinic and carbonyl bonds. On the basis of the carbonyl shifts for these homoconjugated ketones relative to their saturated analogs, the extent of homoconjugative interaction between the π systems appears to decrease in the order: bicyclo(2.2.1)oct-2-en-7-one > bicyclo(3.2.1)oct-3-en-6-one (83) > bicyclo(2.2.2)oct-5-en-2-one (73) ~ bicyclo(3.2.1)oct-2-en-8-one (85) ~ bicyclo(3.2.1)oct-6-en-2-one (79) > bicyclo(2.2.1)hept-5-en-2-one (68)

A comparison of tricyclo(4.4.1.$1^{2,5}$)dodeca-7,9-dien-11-one (89) with tricyclo(4.4.1.$1^{2,5}$)dodecan-11-one (87) indicates that the homoconjugated diene system in 89 shields the carbonyl carbon by -5.6 ppm. It is also interesting that the carbonyl shift for bicyclo-(3.2.1)octa-3,6-dien-2-one vs. bicyclo(3.2.1)oct-3-en-2-one, -4.4 ppm, is comparable to that for bicyclo(3.2.1)oct-6-en-2-one vs. bicyclo(3.2.1)octan-2-one, -4.0 ppm indicating that the 6,7-double bond is homoconjugated with the carbonyl group in each. The increased

carbonyl shielding of bicyclo(3.2.1)octa-3,6-dien-2-one relative to bicyclo(3.2.1)oct-3-en-2-one is analogous to that found for a number of cross-conjugated ketones (96). Additional evidence for a homoconjugative interaction in bicyclo(3.2.1)octa-dien-2-one is provided by the olefinic shieldings since C-6 is shifted 4.6 ppm downfield from its position in bicyclo(3.2.1)octa-3,6-diene and C-3 is essentially the same in both. The latter observation indicates a significant reduction in the α effect of the carbonyl group bicyclo(3.2.1)octa-3,6-dien-2-one relative to that, for example, found for bicyclo(3.2.1)oct-3-en-2-one. Similarly, acyclic β,γ ketones also show the same shielding effect compared with the corresponding saturated ketone, as illustrated by one example in Figure 4.4.

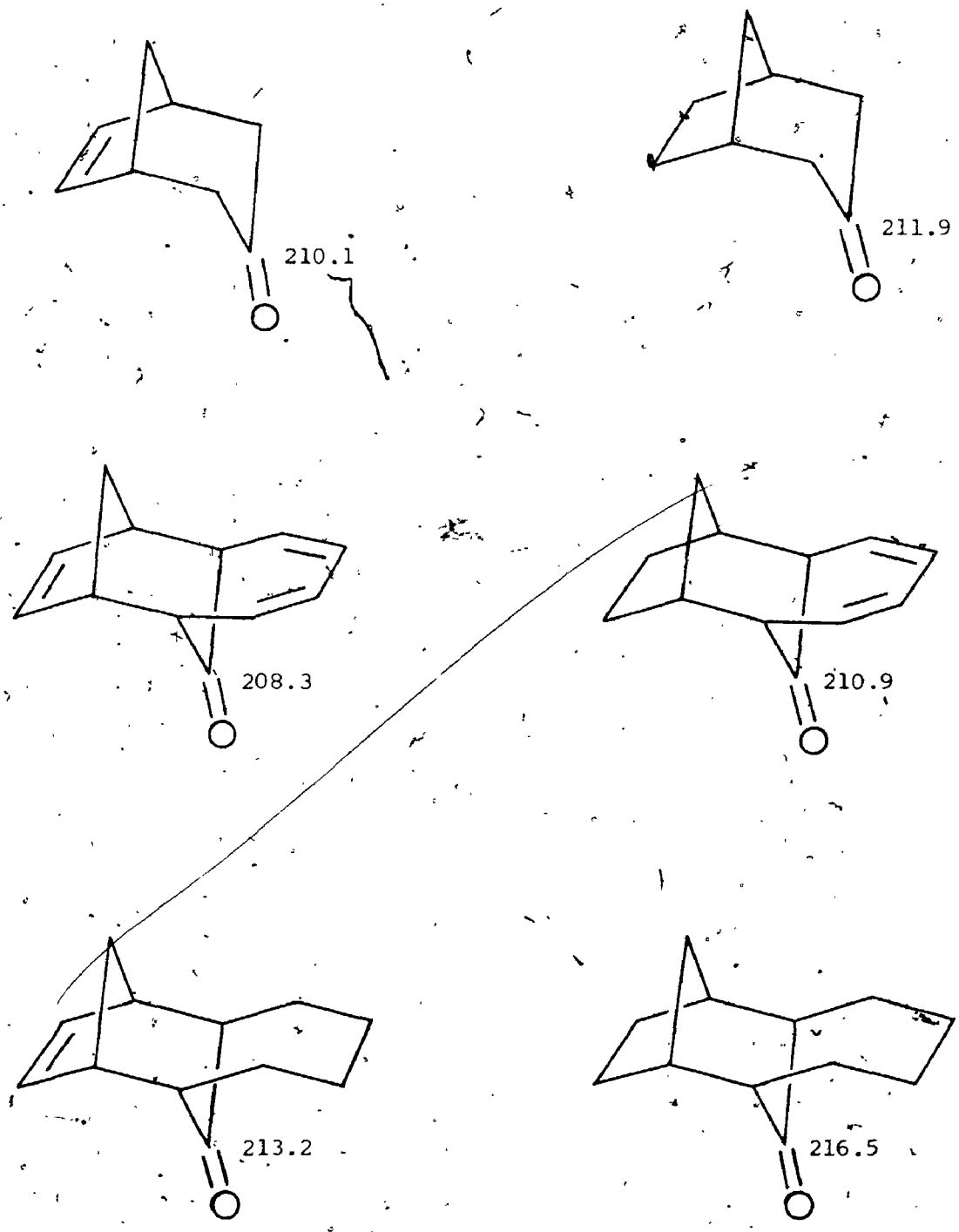
A few ketones having γ,δ -double bonds were included in this series (Figure 4.5) and the results indicate that there is an interaction between the olefinic and carbonyl groups which is dependent on geometry. For bicyclo(3.2.1)oct-6-en-3-one vs. bicyclo(3.2.1)oct-6-ene the carbonyl shift is -1.8 ppm while for tricyclo(4.4.1.$1^{2,5}$)dodec-3-en-11-one (88) vs. tricyclo(4.4.1.$1^{2,5}$)dodecan-11-one (87) the change is -3.3 ppm. In bicyclo(3.2.1)oct-6-en-3-one and 88 the relative orientations of the carbonyl and olefinic bonds must be similar since substitution of a tetramethylene chain between C-2 and C-4 in bicyclo(3.2.1)oct-6-en-3-one gives 88. The additional ring, however, must reduce the flexibility of 88 in the neighborhood of the carbonyl group and serve to hold the latter somewhat closer to the γ,δ double bond as the carbonyl shielding data indicate. Since $\Delta\delta_C$ for 90 vs. 89 is -2.9 ppm, which is comparable to that for 88 vs. 87 the effect of the γ,δ olefinic



[a] In ppm from internal TMS in $CDCl_3$ solutions.

Figure 4.4 ^{13}C Shieldings [a] of 3-Heptanone, 5-Hept-1-enone and Hept-1-ene.

Figure 4.5. ^{13}C Carbonyl Carbon Shieldings [a] in some γ,δ-Unsaturated Ketones



[a] In ppm from internal TMS in $CDCl_3$ solutions.

bond appears to be approximately additive.

Homoconjugation between a double bond and a carbonyl group would be expected to alter the polarization of the olefinic carbons and, therefore, to be reflected in their ^{13}C shieldings relative to the values exhibited by the corresponding olefins. This appears to be the case and the appropriate data are collected in Table 4.8 including the proton shieldings. In each unsymmetrical β,γ unsaturated ketone the γ olefinic carbon absorbs downfield from its position in the olefin whereas the β carbons are generally shielded. A similar trend emerges for the β and γ olefinic protons. Thus the observed trends for the olefinic centers are qualitatively consistent with the carbonyl shifts but the relative magnitudes of the shielding changes would suggest a quite different order for the relative extents of homoconjugation throughout this series from that indicated by the carbonyl data, namely, 68 > 79 > 83 > 73 > 85. Another trend could be anticipated to emerge from the shielding variations for the α carbons since homoconjugative interaction of an olefinic bond with a carbonyl group may be expected to reduce its inductive effect, thereby reducing the deshielding effect of the carbonyl carbon at the α positions. The appropriate data are listed in Table 4.8 to show that the expected trend is found for α-methylene carbons in the β,γ unsaturated cases but the opposite tendency is exhibited by the α-methine (bridgehead) carbons. Clearly, interpretation of the observed trends simply in terms of polarization changes arising from homoconjugative interactions is inadequate.

Recently, the shielding differences observed for olefinic carbons in a series of acyclic unsaturated esters have been ascribed to through-

Table 4.8

Shielding effects[a] of the carbonyl group at the olefinic and α-carbon positions in unsaturated bicyclic ketones

			Olefinic nuclei				α-Carbons	
Skeleton	A	B	β-C	γ-C	β-H	γ-H	CH_2	CH
(2.2.1)	67	56					15.5	13.4
		71					--	1.5
	69	68	-4.8	+7.5	-0.03	+0.43	12.5	14.0
		70	-2.0[b]	-2.0[b]	+0.48[b]	+0.48[b]	--	3.5
(2.2.2)	72	57					18.5	18.3
	74	73	-5.8	+2.7	-0.07	+0.22	14.6	19.1
(3.2.1)	75	54					14.6	11.0
	84	83	-8.7	+4.2	-0.10	+0.31	13.1	11.1
	75	59					15.6	16.0
	80	79	-0.4	+5.7	+0.18	+0.39	15.8	16.4
	75	82					17.5	--
	80	81	--	+3.2	--	+0.19	21.2	--
	75	86					--	9.6
	84	85	-2.0	+1.7	0.0	+0.21	--	9.6, 8.9
	84	76	+21.8[c]		+1.91[c]		--	17.0
	78	77	+20.8[c]	+3.6	+1.29[c]	+0.43	--	18.4
			+ 1.6		+0.44			

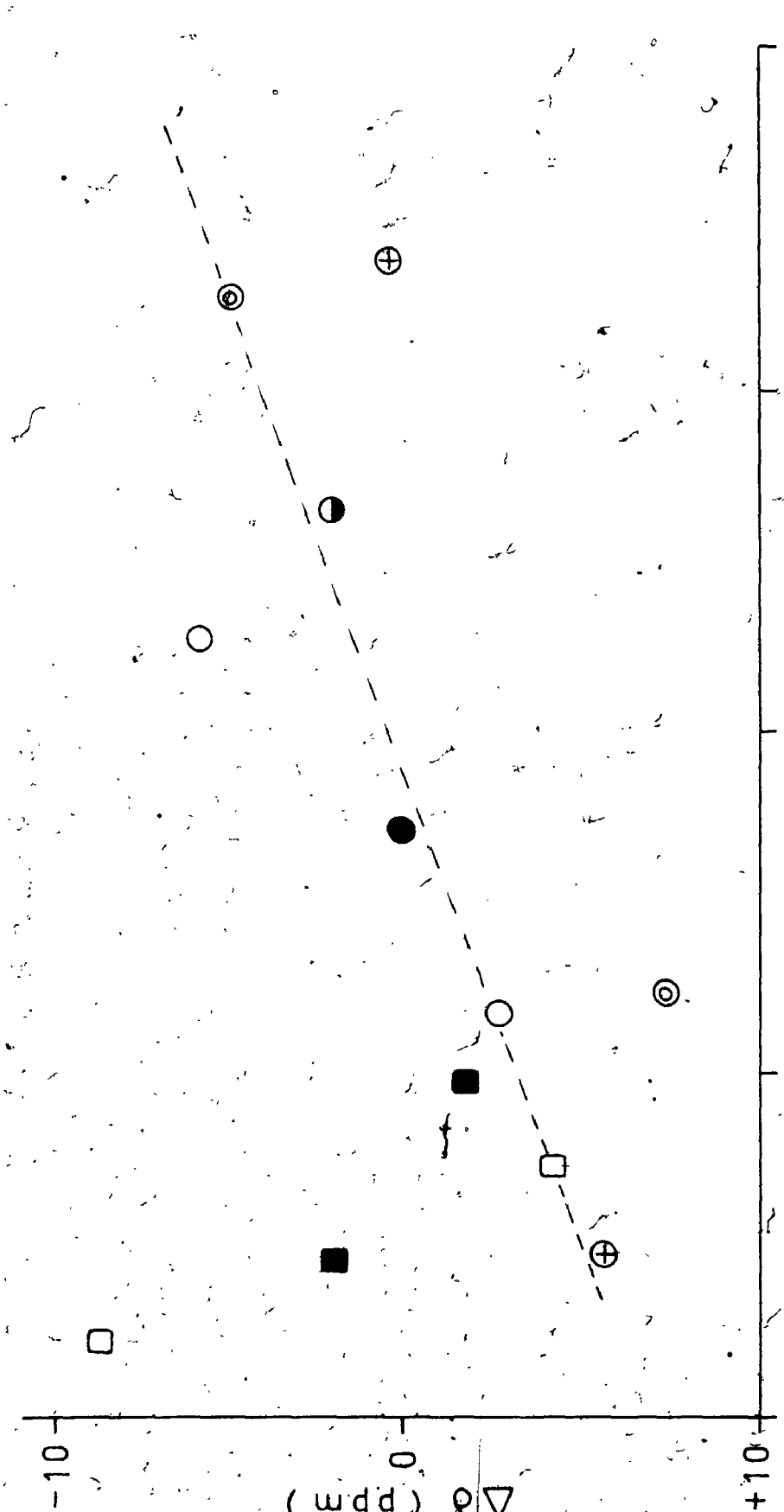
[a] The individual values represent ($\delta^{B}_{C} - \delta^{A}_{C}$) for the compounds listed in columns 2 and 3 .

[b] Because of the symmetry of 70 these positions are both β and γ with respect to the carbonyl group.

[c] β-position on the conjugated double bond, i.e. C-4.

space polarization arising from an electric field effect of the carbonyl group (99). As a test for this sort of contribution to the olefinic shieldings of the bicyclic β,γ-unsaturated ketones some model '4-31G' *ab initio* molecular orbital calculations (100) were carried out. To simulate the bicyclic ketone system, the polarization of an ethylene double bond by an electric dipole field of a carbonyl group, defined by point charges 1.20 Å apart having the charges adjusted to simulate the dipole moment of a carbonyl group, was examined. Using the COORD program (101), the positions of the constituent atoms of a specific ketone were determined. With the point charges placed at the geometrical coordinates of the carbonyl carbon and oxygen, the net charges at the olefinic carbons, represented by ethylene, were calculated using a carbonyl dipole moment of 2.84 D, the value for acetone. In this way the net charges on the olefinic carbons in bicyclo(2.2.1)hept-5-en-2-one (68), bicyclo(2.2.1)hept-2-en-7-one (70), bicyclo(2.2.2)oct-5-en-2-one (73), bicyclo(3.2.1)oct-6-en-2-one (79), bicyclo(3.2.1)oct-3-en-6-one (83) and bicyclo(3.2.1)oct-2-en-8-one (85) were computed and the results are shown in Figure 4.6. The calculated net charges are plotted against $\Delta\delta$ values representing the ^{13}C shielding difference for the olefinic carbons in the β,γ unsaturated ketone and the parent olefin. For those systems having the olefinic carbons in a two-carbon bridge there appears to be a roughly linear trend having a slope of *ca.* -300 ppm per unit charge but the β carbon in the ketones having the olefinic bond in a three-carbon bridge, bicyclo(3.2.1)oct-3-en-6-one and bicyclo(3.2.1)oct-2-en-8-one, are significantly shielded relative to their counterparts in two-carbon bridges. Clearly the notion of a dominant shielding contribution arising

Figure 4.6. A Plot of the Net Charge on Olefinic Carbons as Given by "4 - 31G" MO Calculations For some β,γ unsaturated Ketones *vs.* the Observed Shifts (Δδ) Relative to the Corresponding Bicyclic Olefins: 68 (◎), 70 (◓), 73 (○), 79 (⊗), 83 (□) and 85 (■).


-0.35
-0.33
-0.31
Net Charge
-10
0
+10
Δδ (ppm)

from through-space polarization by the carbonyl electric dipole field is inadequate to account for the observed trends. It may be noted that, for the present series, the separation between the olefinic bond and the carbonyl group is very much less than that in the acyclic esters for which the electric field effect contributions appeared to dominate the shielding variations (99).

The basic assumption inherent in an interpretation of the shielding differences in these unsaturated ketones in terms of homoconjugative interactions is that the observed shieldings are dominated by variations in electron density. While electron density is a major factor, it is not the sole contributor, and it has been shown that variations in bonding parameters can make major contributions. These bicyclic systems undoubtedly differ in strain energy and therefore in the nature of the bonding parameters associated with the constituent carbons. Grant and his co-workers (102) have recently demonstrated for some simple systems that the bonding contribution to ^{13}C shieldings depends strongly on the σ and π character of the orbitals, their orientation, symmetry properties, and the energy gap between ground and excited states. From the variations observed in the present systems it would appear, therefore, that while the trends for the sp^2 carbons are qualitatively in accord with the existence of a homoconjugate polarization, interpretation solely in terms of charge density variations is a grossly over simplified and inadequate view. These results underscore the dangers associated with such a simple interpretation and re-emphasize the fact ^{13}C shieldings are dependent on additional factors. We conclude that homoconjugative interactions are observable by ^{13}C shielding variations

but quantitative assessments of the relative extent of these interactions must await further theoretical developments.

(d) SUMMARY

In this study, the variations of the sp^2 carbon shieldings in several β,γ unsaturated ketones provide qualitative evidence for the existence of homoconjugative interaction between the olefinic and carbonyl groups in the ground state. Similar evidence of interaction between γ,δ double bonds and carbonyl groups has also been found from ^{13}C spectra for a few examples. The charge-density calculation showed that a simple interpretation of the shielding trends entirely in terms of charge density variations arising from through-space polarization is shown to be inadequate thereby emphasizing the existence of other major shielding contributions.

(C) THE ^{13}C SPECTRA OF SEVERAL METHYLCYCLOPENTANONES AND METHYLCYCLOHEXANONES ----- STERIC AND CONFORMATIONAL EFFECTS ON ^{13}C SHIELDINGS

(a) INTRODUCTION

The results of ^{13}C NMR studies of a variety of cyclic systems have established that ^{13}C spectroscopy is a powerful method for stereochemical assignments and conformational analysis (8, 9, 10, 17). Several six-membered ring systems, both mono- and polycyclic, have been examined in detail. In general it is found that axial substituents tend to shield the neighboring carbons (C-1, -2, -3, -5 and -6 in a monosubstituted cyclohexane) relative to their positions in the spectrum of the equatorial analogs. The variation of carbon shieldings with substitution in simple five-membered ring derivatives has received much less attention. Apart from studies of a variety of norbornyl derivatives (34, 38) the only detailed examinations of cyclopentane derivatives is that of Christl et al. (35) in which several methylcyclopentanes, methylcyclopentanols, and methylcyclopentyl acetates were studied. Methyl substituent effects in cycloheptane systems have been studied by the examination of several di- and trimethyl derivatives as well as the corresponding alcohols, acetates and ketones (103). In general, the results were in good agreement with predictions based on the twist-chair form which according to force-field calculations is the most stable conformation. As an extension of our investigation of the effects of molecular geometry and stereochemistry on ^{13}C shieldings, we chose to study the effects of methyl substitution in rings containing a trigonal carbon and to compare the trends observed for the 5- and 6-membered rings. A series of 21 methylcyclohexanones and 16 methylcyclopentanones were selected for ^{13}C NMR examination.

Some pairs of cis-trans dimethyl derivatives were included to illustrate the shielding differences arising from geometrical isomerism and to demonstrate the utility of ^{13}C NMR for stereochemical assignments.

(b) RESULTS AND DISCUSSION

The ^{13}C shieldings for the methylcyclohexanones examined are listed in Table 4.9 and the data for the methylcyclopentanones are given in Table 4.10. While the results for cyclohexanone, its monomethyl derivatives and cyclopentanone and its 3,5-dimethyl derivatives have been reported previously (36), these were re-examined to obtain a set of data for the entire series in a common solvent at comparable concentrations.

(i) Methylcyclohexanones: sp^3 - carbon shieldings

The microwave spectrum of cyclohexanone has recently been reported (104) but many assumptions regarding geometry had to be made before reaching structural conclusions. The authors did conclude, however, that cyclohexanone exists primarily in the chair form. It is not very different from that of cyclohexane but probably slightly flattened owing to two facts: the greater normal valence angle C--C(O)--C (117°) and the shorter bond length C--C(O) (1.51 Å) compared to the values found in n-alkanes (112.4° and 1.53 Å) (105). Allinger and his co-workers have recently calculated (89c) that the conformational energy* of the twist boat (C_2) conformation is 2.72 kcal/mole and

* Conformational energy has been defined as the excess energy of a given conformation over that of the conformation of minimum energy of the same molecule.

the C_1 boat and C_s boat are 3.77 and 5.33 kcal/mole, respectively (Figure 4.7). The chair form therefore predominates for most substituted cyclohexanones, but the energies of the boat forms are relatively low, as is the barrier to inversion (calculated, 3.9 kcal/mole), and sterio interactions can easily affect the chair-boat equilibrium (106). Recently, Anet and his co-workers (107) using ^1H NMR at 251 MHz, succeeded in observing a spectral change near -183° for cyclohexanone-3,3,4,5,5-d_5 and determined, a $\Delta G^{\#}$ value of 4 kcal/mole for the free energy of activation of the inversion process of cyclohexanone. The reason for the low barrier to inversion of cyclohexanone derivatives relative to their cyclohexane analogues ($\Delta G^{\#} = \sim 10$ kcal/mole) is mainly a result of the much lower barrier to rotation about the $C_{sp^2} - C_{sp^3}$ bond compared to that for the $C_{sp^3} - C_{sp^3}$ moiety.

For the parent ketone and its monosubstituted derivatives the ^{13}C signal assignments were straightforward (36). Since the methylcyclohexanones can be assumed to exist predominantly in chair conformations having equatorial methyl groups, a comparison of the individual shieldings for specific carbons with those for the corresponding carbons in cyclohexanone furnished a set of substituent effects for equatorial methyl group in this system. These values may be compared with those for methyl substitutions in cyclohexane (108) as shown in Table 4.11. From the values for equatorial 2- and 3-methyl groups, the shieldings for cis-2,6-, cis-3,5- and trans-2,5-dimethylcyclohexanone were estimated and compared with those observed as a test of the additivity of these substituent effects. For the 11 possible comparisons the average deviation between the predicted and observed values is 0.4 ppm

Table 4.9

^{13}C Shieldings[a] of Some Cyclohexanones

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	Me
Nil	211.5	41.9	27.1	25.0	27.1	41.9	
4-Me	211.4	40.6	34.7	31.1	34.7	40.6	20.9
4-t-Bu	211.5	41.2	27.6	46.7	27.6	41.2	27.6[b]
3-Me	211.0	49.9	34.1	33.3	25.3	41.0	22.0
cis-3,5-Me_2	210.4	49.3	33.2	42.7	33.2	49.3	22.3
trans-3,5-Me_2	211.0	48.7	29.6	39.6	29.6	48.7	20.8
3,3,5-Me_3	210.5	53.9	35.1	47.2	29.5	49.0	22.4(5-Me);25.7(ax-3-Me);32.0(eq-3-Me)
3,3,5,5-Me_4	212.0	53.8	36.0	51.5	36.0	53.8	31.3
2-Me	212.9	45.3	36.2	25.2	28.0	41.8	14.7
2-Me-4-t-Bu	213.3	44.5	37.3	47.2	28.7	41.3	14.7(2-Me);27.7(Me_3)[b]
cis-2,5-Me_2	213.0	44.5	31.3	30.1	32.8	47.5	15.3(2-Me);19.8(5-Me)
trans-2,5-Me_2	211.6	44.3	35.2	34.2	35.6	50.2	14.4(2-Me);22.4(5-Me)
cis-2,6-Me_2	213.6	45.3	37.3	25.6	37.3	45.3	14.6
trans-2,6-Me_2	216.2	42.7	34.8	20.3	34.8	42.7	16.0
cis-2,6-Me_2-4-t-Bu		44.4	38.2	47.1	38.2	44.4	14.7(2,6-Me_2);27.7(Me_3)[c]
2,2-Me_2	215.0	45.1	41.1	21.5	27.6	38.2	25.2
2,2-Me_2-4-t-Bu	216.3	44.4	42.2	42.5	28.2	37.8	25.8,25.7,27.6(Me_3)[d]
2,2,6-Me_3	216.4	45.0	41.8	21.6	36.7	40.6	15.0(6-Me);25.2,25.6
2,2,6-Me_3-4-t-Bu	216.8	44.3	43.0	42.4	37.8	40.0	15.0(6-Me);26.0(ax-2-Me); 26.0(eq-2-Me);27.5(Me_3)[e]
2,2,6,6-Me_4	220.0	44.4	40.2	18.1	40.2	44.4	27.6
2,2,6,6-Me_4-4-t-Bu	220.1	44.1	41.6	38.8	41.6	44.1	27.4(Me_3)[f];27.9 eq-2,6-Me_2; 28.4(ax-2,6-Me_2)

[a] In ppm from internal TMS in $CDCl_3$ solutions.

[b] Quaternary carbon, 32.4 ppm.

[c] Quaternary carbon, 32.3 ppm.

[d] Quaternary carbon, 32.1 ppm.

[e] Quaternary carbon, 32.0 ppm.

[f] Quaternary carbon, 31.8 ppm.

Table 4.10

^{13}C Shieldings[a] of Some Cyclopentanones

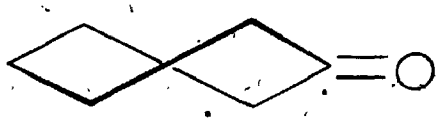
Substitution	C-1	C-2	C-3	C-4	C-5	Me
Nil	219.4	38.1	23.2	23.2	38.1	
3-Me	218.6	46.7	31.8	31.4	38.5	20.3
cis-3,4-Me_2	218.6	45.5	34.1	34.1	45.5	15.0
trans-3,4-Me_2	217.3	47.3	39.2	39.2	47.3	18.1
2-Me	220.9	43.9	31.9	20.7	37.5	14.2
cis-2,3-Me_2	220.9	48.0	34.4	28.1	35.2	9.5 (2-Me), 14.8 (3-Me)
trans-2,3-Me_2	220.3	51.8	39.8	29.6	37.5	12.0 (2-Me), 19.1 (3-Me)
cis-2,4-Me_2	220.0	45.6	40.9	29.6	46.1	14.0 (2-Me), 20.3 (4-Me)
trans-2,4-Me_2	221.0	41.5	39.1	28.0	45.9	15.3 (2-Me), 20.8 (4-Me)
2,4,4-Me_3	220.2	42.7	46.1	33.8	52.5	14.9 (2-Me), 27.9, 29.8
cis-2,5-Me_2	222.7	42.5	28.9	28.9	42.5	15.3
trans-2,5-Me_2	222.3	43.6	30.1	30.1	43.6	14.7
2,2,4-Me_3	222.0	46.5	47.5	27.5	45.8	20.5 (4-Me), 24.3, 24.4
2,2,4,4-Me_4	222.5	45.2	52.3	33.1	52.6	27.4 (2-Me), 30.1 (4-Me)
2,2,5-Me_3	224.1	44.7	36.6	28.0	43.1	15.2 (5-Me), 24.8, 24.1
2,2,5,5-Me_4	226.4	45.2	34.9	34.9	45.2	24.9

[a] In ppm from internal TMS in $CDCl_3$ solutions.

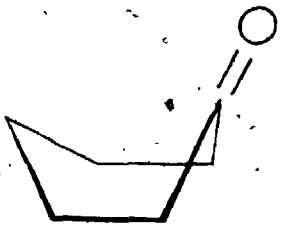
Figure 4.7

Calculated Conformational Energies[a] of Several Different Conformers of Cyclohexanone

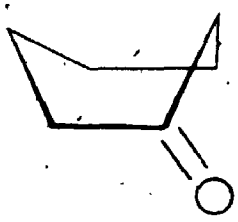
CHAIR
(0.00)



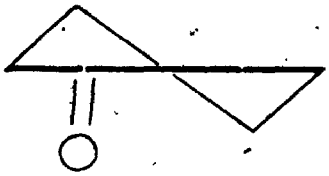
TWIST-BOAT(C_2)
(2.72)



BOAT(C_s)
(5.33)



BOAT(C_1)
(3.77)



6 - 1 - 2 - 3 - PLAN AR
(TRANSITION STATE)
(3.86)

[a] From ref. (96) Values are in kcal/mole.

Table 4.11

Methyl Substitution Effects on sp^3 Carbons in Cyclohexane and Cyclohexanone[a]

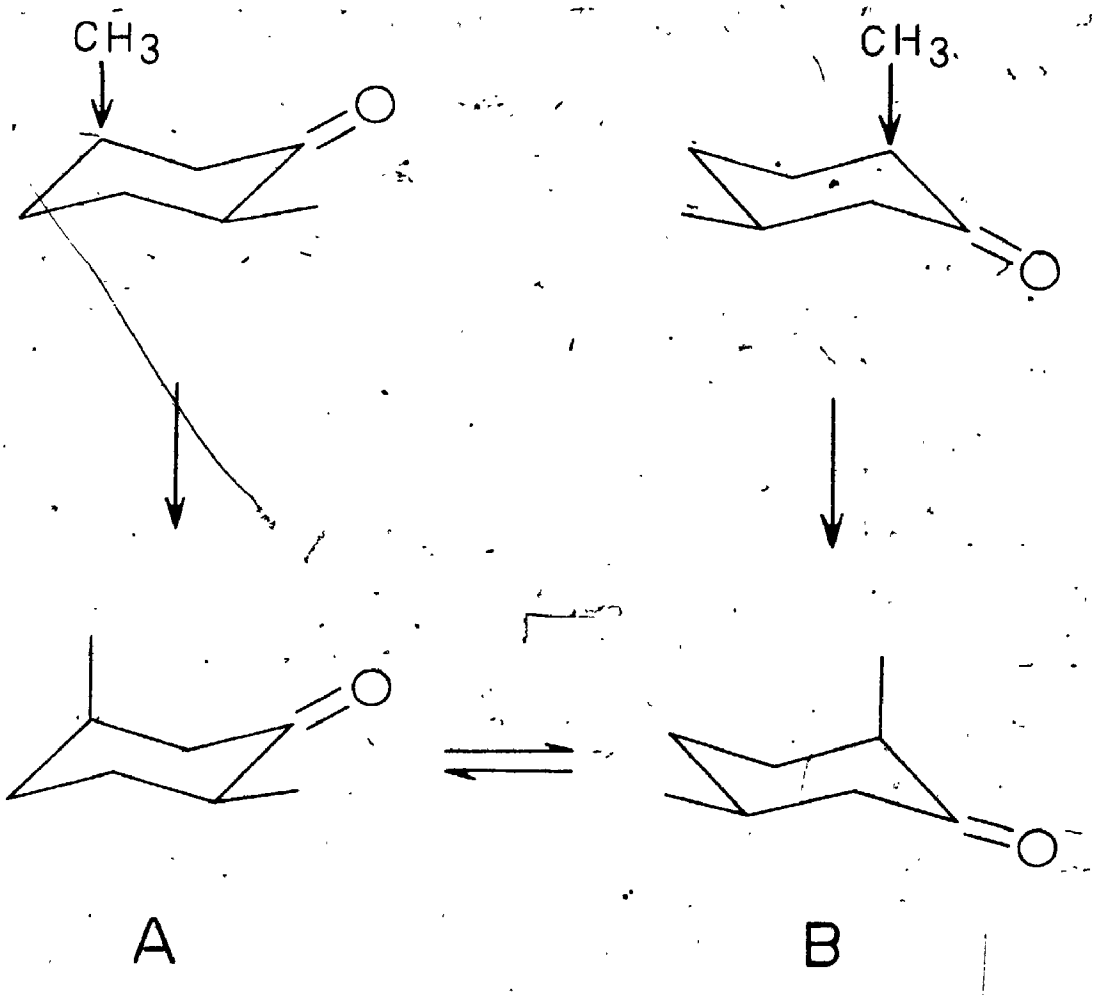
Parent	Substitution	α	β	γ	δ
Cyclohexane[b]	eq-Me	6.0	9.0	0.1	-0.2
	ax-Me	1.4	5.4	-6.4	-0.1
	gem-Me_2	-3.8	-1.3	2.0	
Cyclohexanone	eq-2-Me	3.4	9.1	0.2(C-4) -0.1(C-6)	0.9
	ax-2-Me	3.6	6.0	-6.2(C-4) -6.0(C-6)	-0.5
	eq-3-Me	7.0	8.0(C-2) 8.3(C-4)	-1.8	-0.9
	ax-3-Me	5.7	5.9	-5.7	-0.3
	eq-4-Me	6.1	7.6	-1.3	
	ax-4-Me	3.6	6.7	-3.8	

[a] In ppm. [b] Results from ref. (36).

with a maximum deviation of 1.1 ppm. To obtain an estimate of the substituent effects of an axial 3-methyl group, the shieldings of the cis-3,5-dimethyl and 3,3,5-trimethyl derivatives were compared and the differences adjusted for the known attenuation of the α, β, and γ effects caused by geminal methyl substitution (108b). These results are listed in Table 4.11. With these effects and the observed shieldings for 3-methylcyclohexanone the shieldings for trans-3,5-dimethylcyclohexanone were estimated and found to be in good agreement with experiment; the predicted and observed values, in parentheses, are C-2,6, 48.3 (48.7); C-3,5, 29.7 (29.6); and C-4, 39.1 (39.6) ppm. In a similar manner, substituent effects were found for an axial 2-methyl group by comparing the data for 2-methylcyclohexanone and 2,2-dimethylcyclohexanone and their 4-t-butyl derivatives and for the cis-2,6-dimethyl and 2,2,6-trimethyl derivatives; these results are included in Table 4.11.

As a test of the utility of these effects, the estimated shieldings for trans-2,6-dimethylcyclohexanone may be compared with those observed; C-2,6, 42.3 (42.7); C-3,5, 34.9 (34.8); and C-4, 19.3 (20.3) ppm. As a further test of these axial methyl effects, the individual shieldings for the two conformers of cis-2,5-dimethylcyclohexanone were predicted from the results for 2-methylcyclohexanone with the axial 3-methyl effects operative at C-5 and for 3-methylcyclohexanone with the axial 2-methyl effects operative at C-6 as illustrated in Scheme 4.1. Assuming a 1:1 mixture of the two conformers at equilibrium, the predicted shieldings for cis-2,5-dimethylcyclohexanone were obtained

SCHEME 4.1



from the averaged values for each carbon in the two conformers: C-2, 44.8 (44.5); C-3, 30.9 (31.3); C-4, 29.3 (30.1); C-5, 33.7 (32.8); and C-6, 45.7 (47.5) ppm, the observed shieldings are given in parentheses. Since an axial methyl at C-5 has only one **syn**-axial interaction, it is reasonable that conformer A (Scheme 4.1) will predominate. For a 4 : 1 mixture of A : B the predicted shieldings become: C-2, 44.9; C-3, 30.7; C-4, 30.4; C-5, 33.7; and C-6, 46.9 ppm, which fit somewhat better with those observed. Thus, this sort of analysis provides a crude indication of the equilibrium mixture but, as shown below, the methyl shieldings seem to give a better indication of the relative proportions of conformers. To obtain an estimate of the substituent effects of an axial 4-methyl group, the shieldings of the 4-methyl and 4,4-dimethyl derivatives from Roberts et al (36) were compared; these results are included in Table 4.11.

From Table 4.11 it is apparent that the differences in substituent effects for axial and equatorial methyl groups are similar for both cyclohexane and cyclohexanone. The attenuation of the α effects of 2-methyl groups in the latter system may be due to the concomitant γ interaction between the methyl group and the carbonyl oxygen. A comparison of the individual effects for the axial methyl with those for the corresponding equatorial methyl groups reveals consistent shielding trends associated with γ interactions between the methyl groups and syn-axial ring protons, i.e. those at C-4 and C-6 in the case of an axial 2-methyl group. Although the number of model compounds from which these individual methyl substituent effects were derived is very restricted, the results of the tests for additivity described above indicate that the data in

Table 4.11 may be useful for estimations of shieldings in related systems.

An additional examination of substituent effects is interesting, namely, the perturbations produced by the 4-t-butyl group in the six examples included in this study. Comparison of their shieldings with those for the corresponding ketones lacking the 4-t-butyl group shows the following effects: α, 21.3 ± 0.5; β, 1.0 ± 0.3; γ, −0.5 ± 0.2 ppm. These are closely similar to the effects found for t-butylcyclohexane and trans-1,4-di-t-butylcyclohexane (33), namely, 21.3, 0.5, and 0.1 ppm, respectively. The close agreement indicates that each of the 4-t-butyl substituted cyclohexanones exists preferentially in a chair conformation rather than a twist form for which one would expect somewhat different substituent effects. This is certainly not unexpected for 4-t-butylcyclohexanone and its 2,2,6-trimethyl derivative but is particularly interesting for the 2,2,6,6-tetramethyl isomer for which the syn-axial interaction of the axial methyl groups tends to increase the energy of the chair conformer. It may be noted that a variety of similarly substituted heterocyclic systems (17, 109, 110) have been shown to favor twist conformations and the ring carbon shieldings exhibit substantial derivations from those predicted by assuming additivity of substituent effects.

The results for the ring carbon shieldings in the tetramethylcyclohexanones can also be compared with those predicted from the data for less highly substituted derivatives and the substituent effects listed in Table 4.11. For example, the shieldings of the 2,2,6,6-tetramethyl derivative may be estimated from the results for cis-2,6-dimethyl-

and 2,2,6-trimethyl-cyclohexanone. These estimates together with the corresponding predictions for the 3,3,5,5-tetramethyl isomer are given in Table 4.12. There is good agreement between the estimated and predicted values for all except the carbons bearing the methyl groups suggesting that a major conformational change does not occur for either tetramethyl system. Evidence confirming the chair conformation for 3,3,5,5-tetramethyl ketone has been presented by St. Jacques et al (111).

The variation in the methyl carbon shieldings also appear to provide conformational information. Equatorial 3-methyl carbons absorb near 22.3 ppm from the results for cis-3,5-dimethylcyclohexanone and the 5-methyl in the 3,3,5-trimethyl derivative. These were selected as models in preference to the 3-methyl derivative since the latter exists to a small extent in a conformation having an axial methyl group. The slightly greater methyl shielding of 3-methylcyclohexanone may be ascribed to those feature. Equatorial 2-methyl carbons are significantly shielded relative to the 3-methyl nuclei, appearing near 14.6 ppm. The 7.7 ppm upfield shift presumably arises from the γ interactions of the 2- methyl group with the carbonyl oxygen. From the results for the trans-3,5- and trans-2,6-dimethyl isomers shieldings for axial 3- and 2-methyl carbons can be estimated as 19.3 and 17.4 ppm, respectively, since the observed shielding represent averaged values for axial and equatorial environments. The axial 3-methyl carbon is shielded relative to its equatorial counterpart as expected because of the syn-axial interaction with the axial 5-proton. The observed 3 ppm upfield shift is approximately half that exhibited by an axial methyl on a cyclohexane ring (112) which is entirely consistent

systems (Chapter 5) suggests that the presence of appreciable ring distortion tending to decrease the syn-axial interactions.

(ii) Carbonyl Carbons

The carbonyl carbon shieldings are most affected by axial α-methyl substitution while equatorial α-methyl groups produce smaller downfield shifts. Presumably this difference arises from the differences in steric interactions of α-methyl groups with the carbonyl oxygen for the two orientations. More remote methyl substitution on the cyclohexanone ring has little affect on the carbonyl absorption. Thus, cyclohexanone carbonyl absorptions are readily distinguished from those of cyclopentanones with the exception of the α-tetramethyl cases in the former systems. With increasing methyl substitution at the α positions, the cyclopentanone carbonyls also exhibit a pronounced downfield shift such that the 226.4 ppm shielding of 2,2,5,5-tetramethylcyclopentanone is the most deshielded carbonyl carbon yet reported (8).

(iii) Methylcyclopentanones: sp^3-Carbon Shieldings

Cyclopentanone has been found to exist predominantly in the half-chair conformation in the gas phase (89) with no envelope conformation detected. Allinger and his co-workers have calculated (89c) the energy difference between the half-chair (99) and envelope forms (98) of cyclopentanone to be 3.22 kcal/mole, in excellent agreement with the experimental results. This number is to be contrasted to the very low energy difference between the two forms of cyclopentane itself (~ 0 kcal/mole) (115). The experimental angle of twist (Γ = the angle between the

with the difference in syn-axial interactions between the two systems, since in the hydrocarbon an axial methyl is syn-axial with respect to two protons. It may be noted that the methyl shielding for 3-methylcyclohexanone, therefore, indicated the presence of about 10% of the axial methyl conformer which agrees very nicely with an expected $-\Delta G^{\circ}$ of 1.3 kcal/mole (113). In contrast to the behavior of the 3-methyl group, an axial 2-methyl carbon is apparently deshielded relative to its equatorial counterpart, indicating that the interaction of an equatorial methyl with the carbonyl group has a greater shielding effect than the two syn-axial interactions of an axial 2-methyl group.

The methyl shieldings for trans-2,5-dimethylcyclohexanone are essentially the same as the characteractic values for equatorial 2- and 3-methyl groups as noted above as is expected for the diequatorial conformer which this molecule must adopt almost exclusively. For the cis-2,5-dimethyl isomer, however, two conformers are in equilibrium but the observed methyl shieldings of 15.3 and 19.8 ppm differ substantially from the values predicted for a 1:1 mixture, 16.0 and 20.8 ppm. In fact, the observed values are close to those predicted for a 4:1 mixture of A : B (Scheme 4.1) favoring the conformer having an axial 5-methyl, namely, 15.2 and 19.9 ppm. Clearly, however, these ^{13}C data donot permit a precise quantitative assessment of the equilibrium populations but do indicate thebias of the system.

In those ketones having gem-dimethyl substitution, the gem-methyl carbons are deshielded by the mutual β effects of each other (8, 9, 10, 17). In methylcyclohexanes, this shift is 10.4 ppm (108b). Thus, the

equatorial 3-methyl carbon in the 3,3,5-trimethyl derivative is readily assigned to the 32.0 ppm signal while the remaining methyl signal at 25.7 ppm must arise from the axial 3-methyl group. For the 2,2,6-trimethyl derivative it is not possible to specifically assign the gem-methyl signals at 25.2 and 25.6 ppm. In both of the tetramethyl isomers which undergo rapid interconversion between equivalent conformers only a single methyl signal is observed which represents the averaged shielding for axial and equatorial environments. In each case the observed signal is at lower field than that calculated by simply averaging the gem-dimethyl shieldings of the trimethyl derivatives. For example, if there were no additional perturbation on the gem-dimethyl shieldings the values for the 3,3,5-trimethyl derivative lead to a prediction of 28.9 ppm for the averaged methyl shieldings in the 3,3,5,5-tetramethyl derivatives but the observed value is 31.3 ppm. For the 2,2,6-trimethyl and 2,2,6,6-tetramethyl cases, the corresponding values are 25.4 and 27.6 ppm. In each case there is a difference of ca. 2.3 ppm. Initially this finding seemed particularly surprising in view of the general tendency for sterically crowded carbons to exhibit upfield shifts. This generalization, however, refers specifically to γ nuclei separated by three bonds whereas these syn-axial interactions are γ effects involving nuclei separated by four bonds. At the time of our first observations of these shifts, we were also examining a variety of other systems which contained similar spatial arrangements of methyl groups relative to hydroxyl and to other methyl groups. The general finding for syn-axial orientations, either Me --- OH or Me --- Me, is a downfield shift in striking contrast to the trends for eclipsed or

gauche γ interactions. A detailed discussion of the δ effect is given in chapter 5. For the tetramethylcyclohexanones it is not possible to estimate the magitude of the syn-axial δ effects since it is known that both geminal methyl carbons are deshielded by the syn-axial interaction of one (see Chapter 5). The ^{13}C chemical shifts of 1,1,3-trimethyl- (108) and 1,1,3,3-tetramethyl-cyclohexane (114) have been reported and the latter was measured at -78° in which the conformation of this compound is frozen. For comparison with our results, the original data were converted to the TMS scale using the factor 129.4 ppm (8) and 192.8 ppm (8), respectively. The ^{13}C chemical shifts of the equatorial and axial methyls in 1,1,3,3-tetramethylcyclohexane are close to those in the corresponding 5-t-butyl derivative (Figure 4.8) which was recorded in $CDCl_3$. A comparison of the methyl shieldings for 1,1,3-trimethylcyclohexane and 1,1,3,3-tetramethylcyclohexane reveals comparable differences between the axial and equatorial methyl carbons. It is interesting that both geminal methyl carbons are deshielded by 2.1 ppm. For 2,2,6-trimethyl- and 2,2,6,6-tetramethyl-4-t-butylcyclohexanone, the axial and equatorial methyls of the gem-dimethyl pairs are deshielded by 2.4 and 1.9 ppm, respectively. It is interesting that the α-methyl shieldings of the 4-t-butyl-2,2,6,6-tetramethyl derivative, which is essentially a single conformer, give an averaged shielding of 28.2 ppm which is slightly lower than that observed for 2,2,6,6-tetramethylcyclohexanone, 27.6 ppm. This may arise from slightly different distortions of the ring in the two cases but, seems too small to indicate a departure from a chair conformation. The fact that the deshielding of the syn-axial methyl carbons appears to be smaller than those found for more rigid

their trans isomers. The ring carbons of the cis isomers are shielded relative to those in the trans isomers, reflecting the greater steric crowding of the vicinal methyls as well as the shielding effects associated with axial methyl groups. The results, therefore, are readily interpreted in terms of the half-chair conformation of the cyclopentanone ring such that the trans-2,3- and trans-3,4-dimethyl isomers are equatorial and the cis isomers are equilibrium mixtures of axial-equatorial conformers.

(c) SUMMARY

These series of ketones were chosen as model systems for the study of steric and conformation effects on ^{13}C shieldings. Complete assignments of the individual signals were accomplished by intercomparison of the shielding data within each series and the trends observed are readily interpreted in conformational terms. Each of the cyclohexanones exists preferentially in chair conformations although there is evidence of ring distortion in the tetramethyl derivatives. The cyclopentanones apparently strongly favor half-chair forms with maximum puckering at C-3 and C-4. In general, shielding differences between cis and trans isomers are pronounced and the assignment of stereochemistry for some cis - trans dimethyl derivatives has been illustrated.

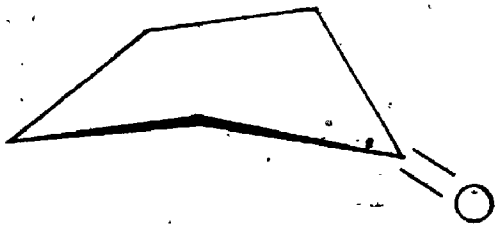
systems (Chapter 5) suggests that the presence of appreciable ring distortion tending to decrease the syn-axial interactions.

(ii) Carbonyl Carbons

The carbonyl carbon shieldings are most affected by axial α-methyl substitution while equatorial α-methyl groups produce smaller downfield shifts. Presumably this difference arises from the differences in steric interactions of α-methyl groups with the carbonyl oxygen for the two orientations. More remote methyl substitution on the cyclohexanone ring has little affect on the carbonyl absorption. Thus, cyclohexanone carbonyl absorptions are readily distinguished from those of cyclopentanones with the exception of the α-tetramethyl cases in the former systems. With increasing methyl substitution at the α positions, the cyclopentanone carbonyls also exhibit a pronounced downfield shift such that the 226.4 ppm shielding of 2,2,5,5-tetramethylcyclopentanone is the most deshielded carbonyl carbon yet reported (8).

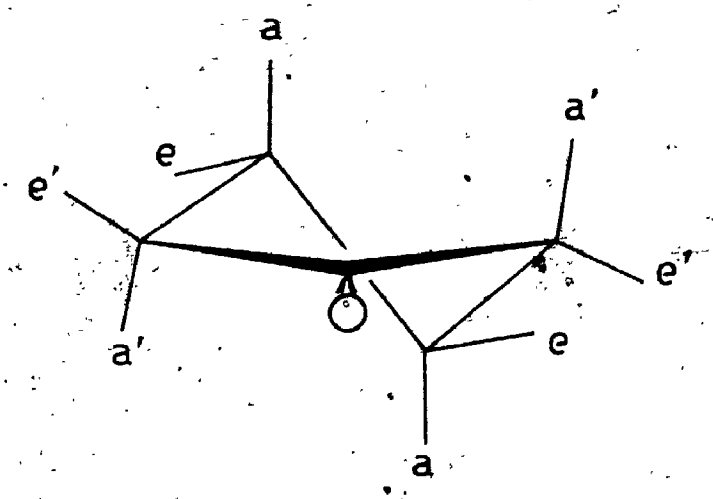
(iii) Methylcyclopentanones: sp^3-Carbon Shieldings

Cyclopentanone has been found to exist predominantly in the half-chair conformation in the gas phase (89) with no envelope conformation detected. Allinger and his co-workers have calculated (89c) the energy difference between the half-chair (99) and envelope forms (98) of cyclopentanone to be 3.22 kcal/mole, in excellent agreement with the experimental results. This number is to be contrasted to the very low energy difference between the two forms of cyclopentane itself (∿ 0 kcal/mole) (115). The experimental angle of twist (Γ = the angle between the



ENVELOPE (C_S)

98



HALF-CHAIR (C_2)

99

C_5-C_1-C_2 plane and the C_3-C_4 bond) in cyclopentanone is reported (89) as 22.1 and 23.6°. Allinger's calculation (89c) for Γ is 24.1°. The higher energy of the envelope conformer is the result of increased Van der Waals (~ 1.2 kcal) and torsional (1.3 kcal) energies associated with the eclipsing of the C_2-C_3-C_4-C_5 butane unit in the former. In the cyclopentanone envelope, the same degree of eclipsing is present, but very little is gained upon pseudorotation to the half-chair conformer, since there is a high degree of eclipsing in this conformer as well. From calculations (89c), these two different (C_2 and C_s) conformations seem to be all there are for the ketone. Other envelope and half-chair conformations which had the carbonyl off the C_2 axis or C_s plane did not correspond to minima. Hence, the cyclopentanone ring exists in the half-chair form 99 with maximum puckering at C-3 and C-4 and consequently there are two orientations for methyl groups at either of the α and β positions which, for convenience, are denoted axial (a') and equatorial (e') although these orientations are not strictly comparable to those in cyclohexane systems. Although little is known about the relative energies of the conformation available to the methylcyclopentanones, the ^{13}C results give some qualitative indications of the preferred conformers in a variety of cases. The methyl shieldings appear to be the more informative in this regard. With the assumption that conformations having axial methyls are less stable than their equatorial counterparts, some consistent trends emerge. The shielding for the β-methyl carbon in the 3-methyl, cis-2,4-dimethyl, and 2,2,4-trimethyl derivatives is 20.4 ± 0.1 ppm, while the α-methyl shielding in the 2-methyl, trans-2,5-, and cis-2,4-dimethyl derivatives averages 14.3 ppm.

With these values representive of equatorial and pseudo-equatorial groups, respectively, it is apparent that the shielding influence of the carbonyl group at the α-methyl carbon is less than that found for the cyclohexanones. This is consistent with the larger dihedral angle between the carbonyl and the α-C-CH_3 bonds in cyclopentanones relative to that in cyclohexanones in which these bonds are nearly eclipsed. The similarity of the methyl shieldings for cis-2,4-dimethylcyclopentanone with respect to the two monomethyl derivatives indicates that this dimethyl derivative is essentially diequatorial. The same conclusion results from a comparison of the ring shieldings with those predicted by additivity of the substituent effects for each of the methyl groups; the latter were obtained by comparison of the shieldings of the monomethyl derivatives with those of cyclopentanone itself. For cis-2,4-dimethylcyclopentanone the predicted (and observed) shieldings are: C-2, 44.3 (45.6); C-3, 40.1 (40.3); C-4, 29.3 (29.6); and C-5, 46.1 (46.1) ppm. The general trend toward higher field for all ring carbons in the trans-2,4-dimethyl derivative is consistent with the presence of an axial methyl group. Similar results obtained from the corresponding comparison for the 2,5-dimethyl isomers indicated that the trans isomers is essentially diequatorial. It is interesting that the α-methyl shieldings for cis-2,5- and trans-2,4-dimethylcyclopentanones are the same, 15.3 ppm, deshielded by 4 ppm relative to their pseudo-equatorial counterparts. This trend toward lower field for axial α-methyl carbons is consistent with the cyclohexanone series.

A comparison of the geminal methyl shieldings in the tri- and tetramethylcyclopentanones reveals the same trend noted earlier for the cyclo-

hexanones, namely, the downfield shift exhibited by syn-axial methyl carbons. The 2,2- and 4,4-dimethyl carbons have averaged shieldings of 27.4 and 30.1 ppm in 2,2,4,4-tetramethylcyclopentanone, both of which are significantly downfield from the geminal methyl absorptions in the 2,2,4- and 2,2,5-trimethyl derivatives, respectively. It may be noted that the remaining methyl shielding in each of the latter compounds is similar to that for an equatorial methyl group indicating that each favors a specific conformation. For 2,2,5,5-tetramethylcyclopentanone the averaged methyl shielding, 24.9 ppm, is close to the α-methyl shieldings in the 2,2,4- and 2,2,5-trimethyl derivatives, in sharp contrast to the situation for the cyclohexanone systems lacking syn-axial arrangements of methyls separated by four bonds.

An additional feature illustrated by the results for the cyclopentanone series concerns the trends exhibited by the vicinal methyl substituents in the 2,3- and 3,4-dimethyl derivatives. It is well-established that closely neighboring vicinal methyl groups exhibit upfield shifts which increase with decreasing separation (8, 107). The magnitude of the shift is inversely proportional to the dihedral angle relating the two methyl carbons; this feature is examined in detail in next section. As a consequence of the puckered nature of the half-chair conformation of cyclopentanone, the dihedral angles relating vicinal substituents differ markedly for equatorial-equatorial and axial-equatorial arrangements. The dihedral angle is significantly smaller for the latter. This difference accounts nicely for the more shielded methyl carbons in the cis-2,3- and cis-3,4-dimethyl isomers relative to

their trans isomers. The ring carbons of the cis isomers are shielded relative to those in the trans isomers, reflecting the greater steric crowding of the vicinal methyls as well as the shielding effects associated with axial methyl groups. The results, therefore, are readily interpreted in terms of the half-chair conformation of the cyclopentanone ring such that the trans-2,3- and trans-3,4-dimethyl isomers are equatorial and the cis isomers are equilibrium mixtures of axial-equatorial conformers.

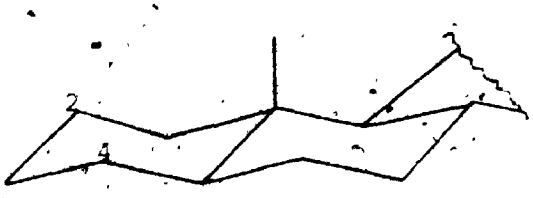
(c) SUMMARY

These series of ketones were chosen as model systems for the study of steric and conformation effects on ^{13}C shieldings. Complete assignments of the individual signals were accomplished by intercomparison of the shielding data within each series and the trends observed are readily interpreted in conformational terms. Each of the cyclohexanones exists preferentially in chair conformations although there is evidence of ring distortion in the tetramethyl derivatives. The cyclopentanones apparently strongly favor half-chair forms with maximum puckering at C-3 and C-4. In general, shielding differences between cis and trans isomers are pronounced and the assignment of stereochemistry for some cis - trans dimethyl derivatives has been illustrated.

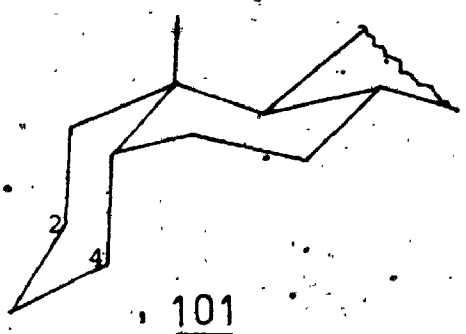
(b) THE ^{13}C SPECTRA OF SEVERAL NORBORNYL DERIVATIVES —— 1,4-NONBONDED INTERACTION

(a) INTRODUCTION

From the results of some of the earliest systematic studies of ^{13}C shielding trends within various families of compounds it was established that ^{13}C shieldings are remarkably sensitive to molecular geometry (8, 9, 10, 17). In particular, the relative orientation of vicinal carbons, or of a carbon vicinal to a heteroatom, has a marked effect on their observed shieldings which has been attributed to 1,4-nonbonded interactions. These shifts, termed γ effects, are consistently to higher field with increased steric crowding and, consequently, provide a new method for the assignment of stereochemistry in a variety of systems. The relative magnitudes of the shifts are well characterized for cyclohexane derivatives (107, 112) in which, for example, an axial methyl carbon absorbs ca. 6 ppm upfield from its equatorial counterpart. The axial methyl experiences γ gauche interactions with C-3 and -5 while the equatorial methyl is anti to these ring carbons. An even larger difference (ca. 12 ppm) is found (37, 116) for C-19 angular methyl carbons in 5α- and 5β- steroids (100 and 101, respectively) for

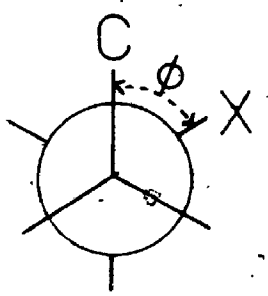


100



101

which there is also a difference of two gauche interactions (with C-2 and -4 in the 5,1-series). Clearly the shielding of these methyl carbons depends strikingly on the dihedral angle (ø) relating the γ nuclei but these alicyclic derivatives provide examples for only two such angles the gauche (102) and anti (103) arrangements. The



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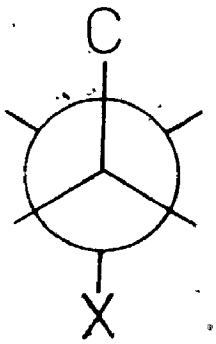

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relatively rigid and well-defined norbornyl skeleton, however, offers a framework with which a variety of dihedral angles between γ nuclei can be examined. A series of methyl-substituted norbornyl derivatives were prepared and examined to investigate the effect of different γ vicinal orientations on the observed shieldings. While the ^{13}C spectra of a number of compounds included in this series have been reported previously (34, 38, 117 - 119), these were re-examined to obtain data for the entire series under comparable conditions, namely 10 - 20% in $CDCl_3$, for internal consistency. The earlier operation necessitated the use of highly concentrated solutions. Furthermore, a variety of referencing methods was employed which renders difficult detailed comparison of the results from different laboratories. In the present study, all data were measured relative to internal tetramethylsilane (TMS) which has become the reference of general choice.

In most instances the assignment of signals to specific carbons was straightforward on the basis of the earlier results, together with off-resonance decoupled, spectra and the general additivity of substituent effects on shieldings. For four of the derivatives, however, an unambiguous assignment was only achieved through the examination of specifically deuterated materials. The details of this technique were discussed in chapter 2.

(b) RESULTS

The ^{13}C shieldings for the norbornanes and norbornenes examined in this study are listed in Table 4.13. Each of the parent compounds and their monomethyl derivatives have been examined previously (34, 38) and, in general, the agreement between the various sets of data is reasonable in view of the different referencing methods employed. For comparison with our results, those reported relative to CS_2 (34) were converted to the TMS scale using the factor 192.8 ppm (8). Although the present results tend toward higher field than the earlier data by approximately 0.5 ppm, the observed shieldings for the methyl carbons differ by only 0.0 - 0.2 ppm in the three set of results indicating the existence of small but significant solvent effects rather than arising from calibration differences. In norbornene, the differences between our data and those of the Roberts' and Lippmaas groups are 0.8 ppm. The assignments for C-5 and -6 in exo-2-methylnorbornane and for C-3 and -7 in endo-3-methylnorbornane are similar to those of Lippmaa's group but reversed from those of Roberts' group. The substituent effects for exo- and endo-methyl groups in norbornane were obtained

Table 4.13

^{13}C Shieldings[a] for some Methyl- and Dimethylnorbornanes and -norbornenes

Parent	Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	Me
Norbornane	Nil	36.3	29.6	29.6	36.3	29.6	29.6	38.3	
	exo-2-Me	43.0	36.4	39.8	36.9	28.7	30.0	34.8	22.3
	endo-2-Me	41.7	34.0	38.4	37.7	30.2	22.1	40.2	17.4
	exo-2-exo-3-Me_2	44.5	39.9	39.9	44.5	29.7	29.7	31.9	15.7
		(0.9)	(-6.6)	(-6.6)	(0.9)	(0.6)	(0.6)	(0.6)	
	endo-2-exo-3-Me_2	42.4	44.0	45.2	38.4	30.3	21.2	36.9	15.9(2-Me);21.1(3-Me)
		(0.1)	(-0.2)	(0.8)	(0.0)	(-0.3)	(0.0)	(0.2)	
	endo-2-endo-3-Me_2	43.1	34.8	34.8	43.1	21.8	21.8	39.7	11.8
		(0.0)	(-8.0)	(-8.0)	(0.0)	(-0.9)	(-0.9)	(-2.4)	
Norbornene	Nil	41.8	135.2	135.2	41.8	24.6	24.6	48.5	
	exo-5-Me	42.3	135.9	137.0	48.3	32.5	34.6	44.8	21.6
	endo-5-Me	43.1	136.7	132.1	47.2	32.5	33.7	50.1	19.3
	exo-5-exo-6-Me_2	43.5	136.8	136.8	49.5	34.5	34.5	41.8	16.7
		(0.7)	(-0.9)	(-0.9)	(0.7)	(-8.0)	(-8.0)	(0.7)	
	endo-5-exo-6-Me_2	43.4	137.9	138.0	48.1	42.5	41.5	46.9	18.6(5-Me);20.2(6-Me)
		(-1.2)	(-0.6)	(-0.2)	(0.4)	(0.0)	(-0.2)	(0.3)	
	endo-5-endo-6-Me_2	43.1	135.0	138.0	49.1	35.7	35.7	48.3	14.4
		(0.6)	(1.4)	(1.4)	(0.6)	(-5.9)	(-5.9)	(-2.2)	

[a] In ppm from internal TMS in $CDCl_3$ solutions. Values in parentheses are $(\delta_C^{obs.} - \delta_C^{Calcd.})$, where $\delta_C^{Calcd.}$ were calculated by assuming simple additivity of substituent effects.

Table 4.14

Substitution Effects[a] of Methyl Groups on the Skeletal Shieldings of Norbornyl Systems.

Substitution	Orientation	α	β	γ	δ
2-Me	exo	6.8	6.7(C-1)	0.6(C-4)	-0.9
			10.2(C-3)	0.4(C-6)	
				-3.5(C-7)	
	endo	4.4	5.4(C-1)	1.4(C-4)	0.6
			8.8(C-3)	-7.5(C-6)	
				1.9(C-7)	
1-Me[b]		7.3	7.0(C-2,6)	1.5	1.4
			6.9(C-7)		
7-Me[b]		5.6	4.2	-2.9(C-2,3)[c]	
Δ^2-5-Me	exo	7.9	6.5(C-4)	0.5(C-1)	0.7
			10.0(C-6)	1.8(C-3)	
				-3.7(C-7)	
	endo	7.9	5.4(C-4)	1.3(C-1)	1.5
			9.1(C-6)	-3.1(C-3)	
				-1.5(C-7)	

[a] $\Delta^{Me} = \delta_C^{RMe} - \delta_C^{RH}$, where RH = hydrocarbon, in ppm. Positive values indicate downfield shifts.
[b] Ref. (38). [c] Syn with respect to the 7-methyl.

by comparison of the data for the methylnorbornanes and norbornane itself. The results are shown in Table 4.14. The methyl substituent effects from our data were used for predicting the carbon shieldings of other norbornyl derivatives (see Chapter 5) and were found to give better agreement with experiment than Roberts' data.

From the methyl results for the exo- and endo-monomethyl derivatives in each series it is apparent that the endo-methyl carbons are shielded relative to their exo-counterparts. On this basis the assignment of the methyl signals in the trans-dimethyl derivatives is straightforward. The remaining signals for the trans-dimethyl compounds were assigned by comparison of the observed shieldings with those expected on the basis of additivity of the individual substituent effects of each methyl group. Apart from the consistent upfield shift of each skeletal carbon (0.3 - 0.6 ppm), our assignments agree well with those of Lippmaa et al.[36] except for the reversal of the C-5 and -6 signals for trans-2,6-dimethylnorbornene. The assignments for each of the four cis-dimethyl derivatives were readily accomplished, again by comparison of the observed shieldings with those predicted assuming additivity of methyl substituent effects. Major deviation occur only for the methine carbons bearing methyl groups as expected from the general behavior of [illegible] having appreciable γ interactions. In these cases, the methyl groups are eclipsed, or nearly so, and the pronounced upfield shifts found for the methyl and methine carbons seem unexceptional. These shifts are considered in more detail in the discussion.

Table 4.15

^{13}C Shieldings for Some Methyl-substituted Norcamphors[a]

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	Me	
Nil	49.7	217.4	45.1	35.3	27.1	24.2	37.6		
1-Me	53.6	218.4	45.5	34.3	28.9	31.5	44.1	13.8	
exo-3-Me	49.4	221.0	48.2	41.5	29.0	23.8	34.4	14.1	
endo-3-Me	50.2	219.8	48.2	40.4	20.9	25.4	37.2	10.7	
4-Me[b]	51.6	214.6	51.0	42.8	34.2	25.7	41.6	20.8	
exo-5-Me	50.5	216.1	45.4	41.8	34.5	33.3	44.2	22.0	
endo-5-Me	51.1	217.6	39.0	40.3	32.4	33.1	38.7	17.1	
exo-6-Me	56.6	216.4	44.2	36.0	37.3	31.0	34.2	20.8	
endo-6-Me	55.8	216.7	45.6	35.5	35.8	32.3	38.7	18.7	
1-anti-7-Me_2	55.6	218.5	46.1	39.0	26.4	27.8	46.6	11.5(1-Me), 10.5(7-Me)	
1-syn-7-Me_2	56.2	218.7	41.0	36.7	28.2	31.9	47.7	21.8(1-Me), 20.9(7-Me)	
exo-5-exo-6-Me_2	57.9	217.4	45.5	43.2	38.1	33.9	31.6	14.9(6-Me), 15.7(5-Me)	
exo-5-endo-6-Me_2	57.9	216.8	48.1	41.0	43.4	41.8	35.6	17.2(6-Me), 21.0(5-Me)	
endo-5-exo-6-Me_2	57.7	217.1	46.1	41.2	42.9	40.2	36.0	15.9(5-Me), 19.7(6-Me)	
endo-5-endo-6-Me_2	57.6	216.9	39.4	41.2	34.4	33.3	37.9	11.9(5-Me), 13.6(6-Me)	
7,7-Me_2	56.1	217.5	44.1	43.3	29.6	29.3	45.2	20.7(anti), 21.6(syn)	
3,3-Me_2	50.0	222.0	44.8	44.1	33.3	24.5	34.9	21.4(endo), 23.2(exo)	
6,6-Me_2	61.7	216.6	44.1	35.9	43.8	35.8	36.8	28.2(endo), 29.7(exo)	
1,3,3-Me_3	53.8	222.6	47.1	41.3	24.9	32.8	41.5	14.6(1-Me), 23.6(endo), 23.3(exo)	
3,3-exo-6-Me_3	57.1	221.7	46.0	41.9	33.5	31.5	31.7	21.0(6-Me), 21.9(endo), 23.2(exo)	
3,3-endo-6-Me_3	56.2	219.3	47.7	40.8	30.6	33.4	36.3	10.1(6-Me), 20.6(endo), 23.9(exo)	
1,7,7-Me_3	57.5	218.7	43.2	43.1	29.1	29.9	46.6	9.2(1-Me), 19.1(anti), 19.8(syn)	
1-endo-3,7,7-Me_3	56.[illegible]	221.4	43.9	40.2	19.9	31.0	45.8	9.0(1-Me), 11.7(3-Me), 19.3, 19.4	

[a] In ppm from external TMS in $CDCl_3$ solutions.

[b] Data taken from ref. [illegible] for C_6D_6 solutions and corrected to the TMS scale with the factor 192.9 ppm.

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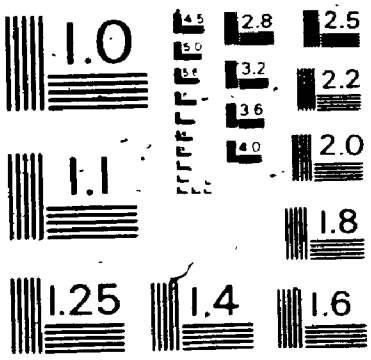

MICROCOPY RESOLUTION TEST CHART
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The ^{13}C NMR data of the norcamphors are collected in Table 4.15. The assignments for the carbonyl, bridgehead, α-carbon (C-3), and the methyl signals presented no problems on the basis of the observed shieldings and the off-resonance decoupled spectra. For the 5- and 6-methyl derivatives, the methine carbon bearing methyl was readily identified by off-resonance decoupling. The remaining methylene signals were assigned by comparison of the observed shieldings with those predicted assuming that the introduction of a methyl group causes changes similar to those found for norbornane, using the values for norcamphor as the base. For an unequivocal assignment of the C-5 and C-6 signals in norcamphor, the spectrum of norcamphor-3-exo-d_1 was recorded. The methylene signal at 27.1 ppm showed the characteristic broadening caused by vicinal coupling with the exo-deuterium (see Chapter 2) while that at 24.2 ppm was unaffected; thus these signals arise from C-5 and -6, respectively. The opposite assignment had been reported by one group (117). Although from additivity C-5 and -7 in endo-6-methylnorcamphor are predicted to be equivalent, the lower field signal of the two remaining methylene signals (38.7 and 35.8 ppm) was assigned to C-7 since there is no precedent for an endo-methyl group to shield C-7 by 2 ppm; our assignment for these positions is reversed from those in an earlier report (34) but off-resonance decoupling supports the present identification.

Of the remaining ketones in Table 4.15, the 3,3- and 6,6-dimethyl as well as the 1,3,3- and 1,7,7-trimethyl derivatives have been reported previously (34, 38, 117-119) and the agreement between the

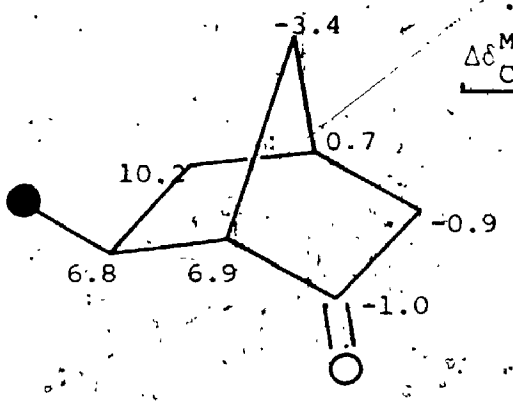
various sets of results is satisfactory. It may be noted that our assignment for the 7-methyl carbons in camphor followed from the spectrum of the endo-3,9,9,9-tetradeuterio derivative (121). An earlier report using a similar test surprisingly reached the opposite conclusion (117) while results of selective-decoupling experiments (38) agree with the present assignment . The complete assignments for the four 5,6-dimethylnorcamphors were discussed in Chapter 2. The assignments for the 1,7-dimethylnorcamphors followed directly from the available data for the corresponding hydrocarbons (38) and monomethyl ketones (34). Since the 1- and 7-methyl carbons are gauche the upfield shift relative to their positions in the monomethyl ketones is expected to be comparable for both. On this basis, the more shielded methyl signal was assigned to the 7-methyl carbon in each case. The methyl assignments for 7,7-dimethylnorcamphor were based on the relative shieldings for the corresponding carbons in camphor discussed above. The comparison of the data for endo-3-methylcamphor with those for camphor leads readily to the assignments listed.

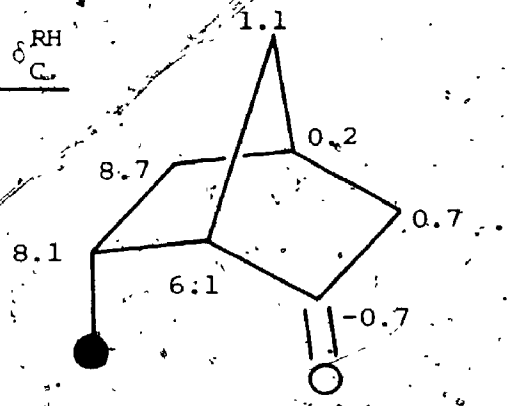
The 3,3,6-trimethylnorcamphors were isolated as the minor rearrangement products arising from homoenolization of fenchone (see Chapter 3). The assignments given in Table 4.15 were obtained by the comparison of the observed shieldings with those estimated by combining the data for the 6-methylnorcamphors and camphenilone (Figure 4.9). For each carbon in 3,3-exo-6-trimethylnorcamphor, the agreement is within $\sim$ 0.2 ppm, while the deviations for the endo-isomer are larger, especically for the C-5, -6, and methyl carbons. An interpretation of these deviations is considered in the Discussion.

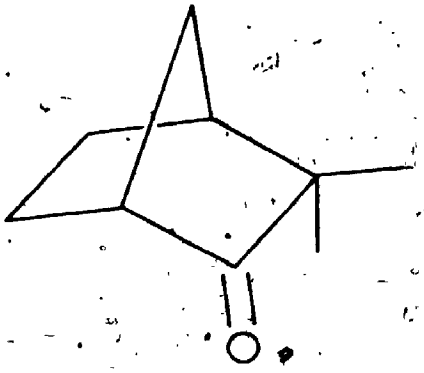
Figure 4.9

Difference[a] Between Observed and Estimated Shieldings in 3,3,6-Trimethylnorcamphors

$$\Delta\delta_C^{Me} = \delta_C^{RMe} - \delta_C^{RH}$$







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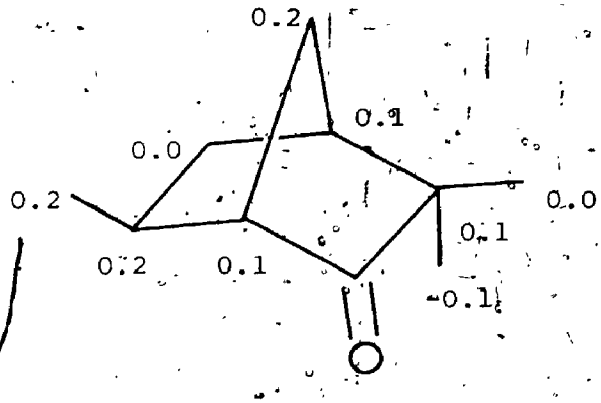
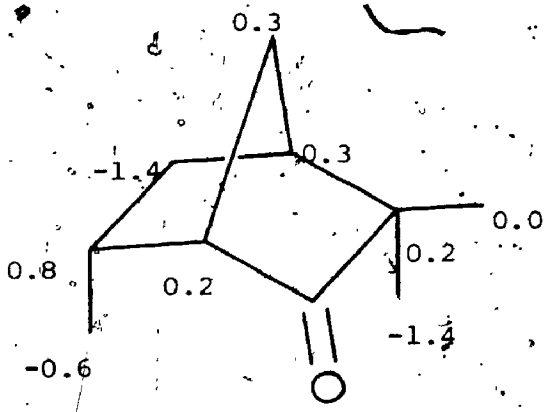




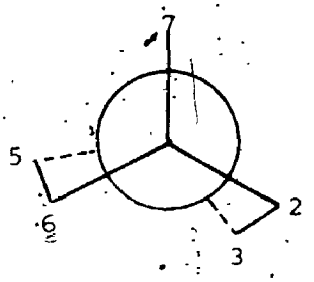
[a] Values in 3,3,6-trimethylnorcamphors are ($\delta_C^{obs.} - \delta_C^{calcd.}$) in ppm where $\delta_C^{calcd.} = \delta_C^{b} + \Delta\delta_C^{Me}$

[b] 3,3-dimethylnorcamphor.

(c) DISCUSSION

The shielding trends exhibited by the skeletal carbons in many of these compounds have been considered in detail previously (8, 9, 17, 34, 38). The ^{13}C chemical shifts are very sensitive to changes in molecular geometry. In particular the differences between the ^{13}C chemical shifts of endo- and exo-isomers are analytically significant. For example, an exo-2-methyl group shields C-7 while its endo counterpart shields C-6. Similarly a 7-methyl group exerts different effects at the syn and anti carbons. The methyl substituent effects of the methyl group in the norbornane system were obtained by comparison of the methylnorbornanes with norbornane itself. The results are listed in Table 4.14 which could be used to estimate the carbon shieldings of other norbornyl derivatives. In general, the estimated values agree quite well with the observing shieldings (see Table 4.13). But it is hardly surprising that the C-5 and -6 nuclei in cis-5,6-dimethyl-norcamphor and cis-5,6-dimethylnorborn-2-ene and C-2 (C-3) in the cis-2,3-dimethylnorbornanes are upfield from the positions predicted by simple additivity since the eclipsing interaction of the vicinal methyls increases the shieldings of the ethano-bridge carbons. Therefore additional parameters for vic-substituted carbon atoms are needed. It is interesting that the β-effect of the methyl group differs at secondary and tertiary carbons, with the latter less shielded. The β effect also has a geometric dependence. A carbon involved in a gauche or eclipsed 1,4-nonbonded interaction is more strongly shielded than its counterpart in an anti orientation ($^{\gamma}$ effect). In general

the magnitude of the shifts depends on the degree of crowding between two γ nuclei. It seems reasonable to conclude from the available data that steric interactions are the principal factor governing these geometrical effects. The following discussion is centered primarily on the methyl absorptions and their variation with structure and substituent orientation. The present series afforded a number of comparisons of these interactions as a function of the dihedral angle relating the γ-nuclei. The dihedral angle offers, at the least, a relative measure of the degree of crowding. Although a detailed analysis will require a more complete description of molecular geometry, relatively little geometric information is available for these systems, but it has been shown that the norbornyl skeleton may be twisted from C_{2v} symmetry by as much as 14° (122). The experimental torsional angles of the parent compound are summarized in Table 4.16.



"Synchro" - Twist

As a reference point for considering the methyl shieldings in these systems, the data for exo-2-methylnorbornane, exo-5-methylnorborn-2-ene, and exo-5-methylnorcamphor have been selected because the latter may be expected to be least affected by the carbonyl and olefinic functions. This gives a base value of 22.0 ± 0.4 ppm. It is interesting that this

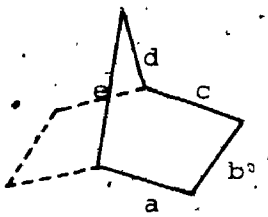
Table 4.16

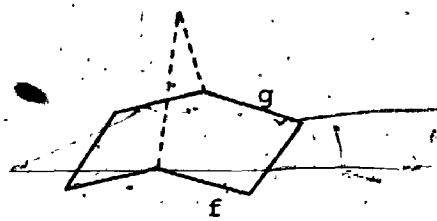
Experimental Torsional Angles in Norbornane[a]

[b]	ø (°)
a = c	34.6
b	0
d = e	55.3
f = g	71.8

[a] From electron diffraction (122).

[b] Definition of torsional angle in norbornane skeleton.





lies midway between the methyl shieldings for methyl cyclohexane (107) and methylcyclopentane (35), but it is difficult to rationalize the trend. Endo-2-methylnorbornane and endo-5-methylnorcamphor have comparable methyl shieldings, 17.4 and 17.1 ppm, respectively. The upfield shift of ca. 4.7 ppm is consistent with the smaller dihedral angle (ϕ) between these endo-methyl carbons and the γ-carbons (C-6 and -3, respectively). For the latter, $\phi \sim 45^{\circ}$ whereas $\phi \sim 90^{\circ}$ for the exo-methyl groups relative to C-7 since the synchro twist occurring in exo-2-methylnorbornane (122) tends to increase ϕ from the value of $\sim 85^{\circ}$ for a symmetric skeleton. It is interesting that $\phi \sim 65^{\circ}$ for a 7-methyl carbon relative to both carbons in the nearer ethano bridge and the observed shielding of 12.7 ppm represents a shift of 9.3 ppm upfield from the base value which is essentially twice the shift exhibited by the endo-methyl as one would expect. These may be compared with the 1.3 ± 0.2 ppm upfield shifts found for the 2- and 5-methyl carbons upon trans-vicinal methyl substitution, i.e. trans-5,6-dimethylnorcamphor, for which $\phi \sim 120^{\circ}$. Although the 6-methyl shieldings in the monomethylnorcamphors differ from those found for the 5-methyl derivatives the effect of a trans-vicinal methyl group is comparable for both. While the orientation of the endo-6-methyl relative to C-2 is similar to that of the endo-5-methyl and C-3, the smaller shift of -2.1 ppm for the former presumably results from the absence of an endo-2-hydrogen. Similarly, the methyl carbon in endo-5-methylnorborn-2-ene is only 2.2 ppm more shielded than its exo-counterpart. The increased shielding for the exo-6-methyl relative to the exo-5-methyl may be due in part to a long-range shielding effect of the carbonyl group (C-4 in cyclohexanone is shielded relative to cyclohexane) or may

result from a difference in the degree of twist of the skeleton. An indication that the latter feature may contribute is the fact that 5- and 6-methyl carbons in the norbornenones are nearly equivalent (0.5 ppm) and this skeleton is less flexible (122).

The 1-methyl shieldings for the α- and β-santenones (1,7-dimethyl-norcamphors) compared with that for 1-methyl norcamphor showed an upfield shift of 2.2 ± 0.2 ppm. Although this seems smaller than may have been anticipated since $\phi \sim 60^{\circ}$, the methyl carbons in the santenones are further separated becasue of the small bridge angle of ca. 96° (123). A comparable shift is found for the 7-methyl carbons by comparison with the data for the 7-methylnorcamphors (34).

For the cis-vicinal dimethyl groups, ϕ lies in the range $0 - 15^{\circ}$, and as expected the upfield shifts relative to the monomethyl derivatives are largest. For the norbornanes and norcamphors the cis-exo-methyls are shielded by -6.3 ± 0.3 ppm. Perhaps the difference is indicative of different degrees of twisting since the shifts for both exo- and endo-dimethyl carbons in the less flexible 5,6-dimethylnorborn-2-enes are equal, -4.9 ppm.

The 1-methyl shieldings for exo- and endo-1,2-dimethylnorbornane (38) compared with that for 1-methylnorbornane show an upfield shift of 3.2 and 1.5 ppm, respectively. Clearly the former has the smaller dihedral angle ($\sim 35^{\circ}$) and the latter has $\phi \sim 85^{\circ}$. From this series of model compounds plus others, we can make a plot of the methyl carbon shielding changes ($\Delta\delta$) arising from the γ interactions vs the dihedral angle between vicinal methyl groups as shown in Figure 4.10.

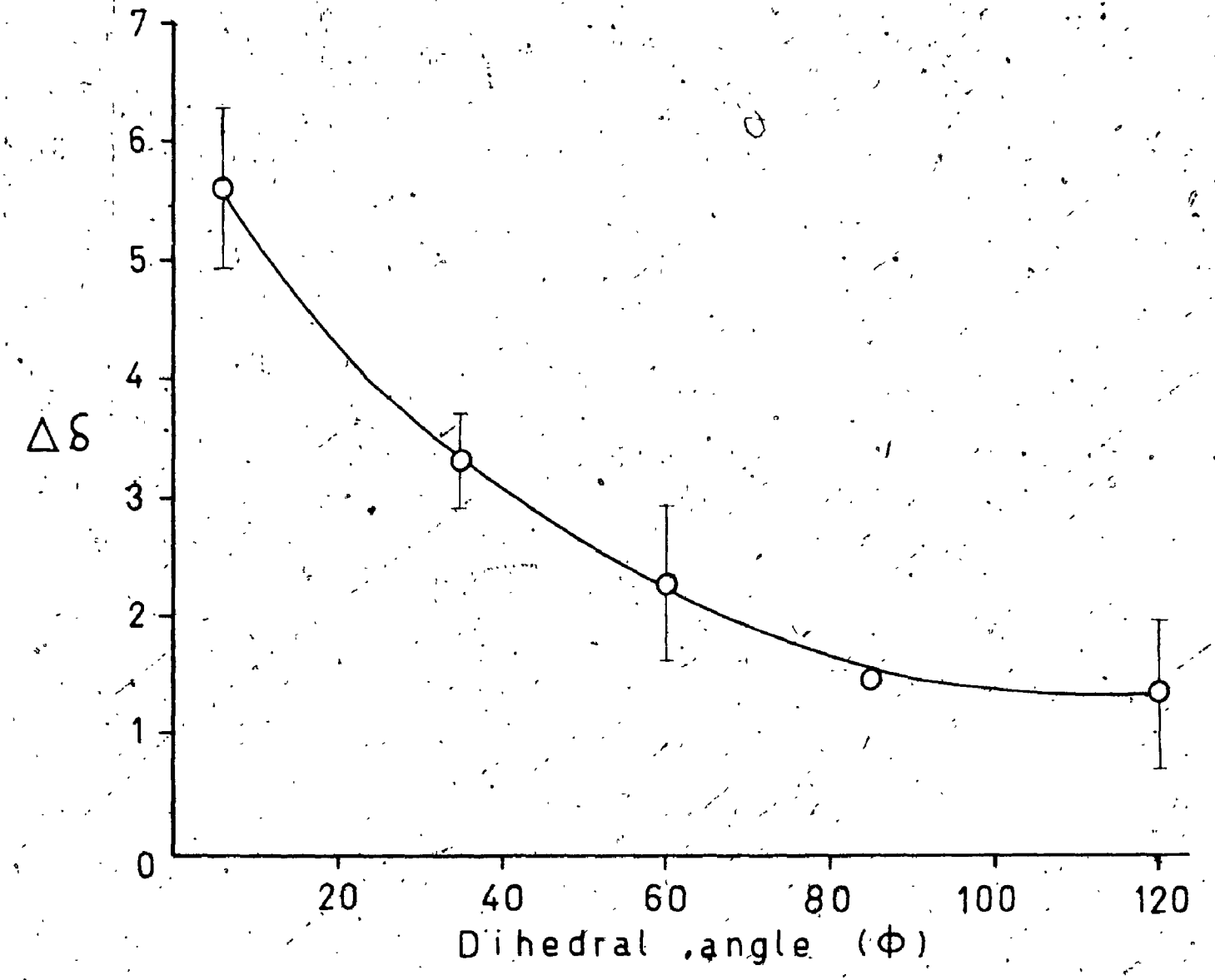


Figure. 4.10 Plot of the Methyl Carbon Shielding Change ($\Delta\delta = \delta_C^{RMe}{}_2 - \delta_C^{RMe}$) arising from γ Interaction vs Dihedral Angle (ø) Between Two Vicinal Methyl Groups.

It is clear that as the dihedral angle ϕ becomes smaller, γ becomes larger, i.e. the methyl carbon signal is shifted considerably to higher field. These results have been employed for stereochemical assignments of some pair of cis / trans dimethylated compounds (see previous section).

The remaining monomethyl ketones are those with methyl carbons vicinal to the carbonyl oxygen and it is apparent that these are substantially shielded. Since as exo-3-methyl is shifted by -8.2 ppm and an endo-3-methyl by -6.7 ppm, it can be suggested that the dihedral angle between the C-Me and C=O bonds is smaller for the former because of skeletal twist. Interestingly, the difference of 1.5 ppm between the methyl carbons in 6,6-dimethylnorcamphor is comparable to the 1.8 ppm difference found for 3,3-dimethylnorcamphor. For 3-endo-6-trimethylnorcamphor, however, the 3-methyl carbons differ by 3.9 ppm with the endo-carbon substantially shielded relative to the other 3,3-dimethyl derivatives. Since the endo-6-methyl is not nearly so greatly affected, it follows that the difference for the α-methyls may arise from a change in either orientation relative to the carbonyl bond such that the endo-methyl is closer to the carbonyl oxygen and exo-methyl further from it than is the case for the other 3,3-dimethyl derivatives.

It is interesting that the non-equivalence of 0.8 ± 0.1 ppm for the 7-methyl carbons in 7,7-dimethylnorcamphor and camphor is essentially the same as that for the 7-methylnorcamphors (34). While these carbons differ by 0.4 ppm in the santenones and only 0.1 ppm in endo-3-methylcamphor. Perhaps these variations arise from slight

differences in skeletal twist, a notion which is supported by the 1 ppm downfield shift found for the 3-methyl group in the latter derivative relative to the methyl shielding in endo-3-methylnorcamphor.

Previously it had been pointed out (34, 38) that 1,4-interactions are not reciprocal in that skeletal carbons exhibit larger shifts with crowding than methyl carbons. This comparison, however, may not be valid because different sorts of nuclei are affected. The present results permit comparison of methyl with methyl and it is apparent that these are similarly affected. It seems hardly surprising that methyl, methylene, and methine exhibit different sensitivities to γ gauche interactions and it emphasizes one of the difficulties in developing a satisfactory theortical basis for these shifts. The problems associated with deriving a simple prescription to account for the effect of steric crowding of γ nuclei have been discussed by Dalling and Grant (108).

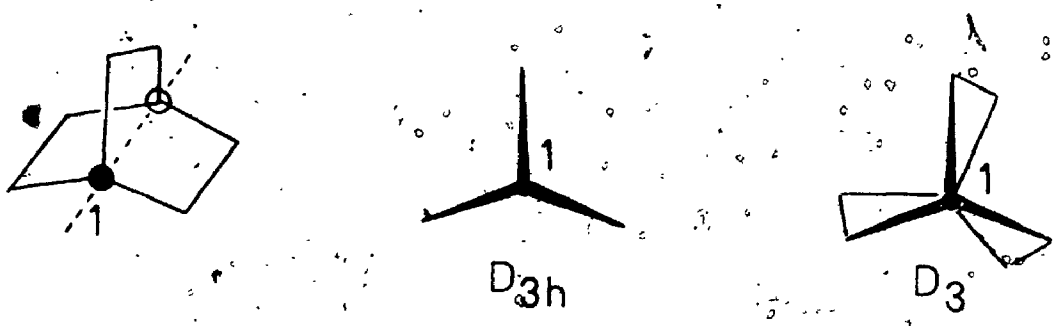
(d) SUMMARY

The variation of the ^{13}C shieldings for methyl and carbonyl carbons vicinal to other carbons or substituents depend on the dihedral angle relating the two groups. As the dihedral angle becomes smaller, the vicinal carbon signal is shifted considerably to higher field. These results can be applied for stereochemical assignments of a variety of systems.

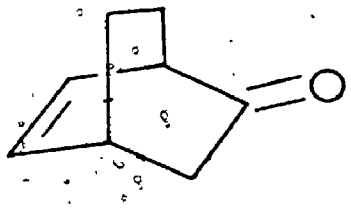
(E) ^{13}C NMR STUDIES OF SOME BICYCLO(2.2.2)OCTANONES ——— CHARACTERIZATION OF THE ISOMERIC 1,5,5,8-TETRAMETHYL-BICYCLO(2.2.2)OCTAN-2-ONES

(a) INTRODUCTION

As an extension of our investigation of the effects of molecular geometry and stereochemistry on ^{13}C shieldings, a number of methyl substituted bicyclo(2.2.2)octanones and octenones were prepared and their ^{13}C NMR spectra examined. Bicyclo(2.2.2)octane and -octene have been investigated by means of gas-phase electron diffraction (124). Bicyclo(2.2.2)octane may be regarded as having "quasi" - D_{3h} symmetry and may be twisted as much as 13° (124) while bicyclo(2.2.2)octene was found to have C_{2v} symmetry (125). Because of the closely defined



skeletal framework the orientations of substituents with respect to the ring carbons are constrained within relatively narrow limits, thereby permitting an assessment of geometrical effects on the observed shieldings for comparison with those found in cyclohexane and norbornane systems (34, 38, 108, 126). In this study, two isomeric 1,5,5,8-tetramethylbicyclo(2.2.2)octan-2-ones were prepared and their ^{13}C spectra



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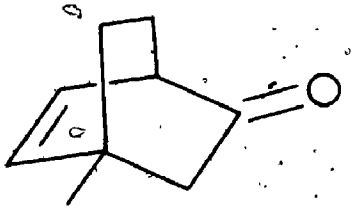

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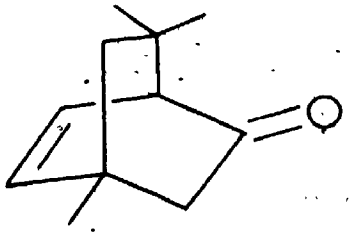

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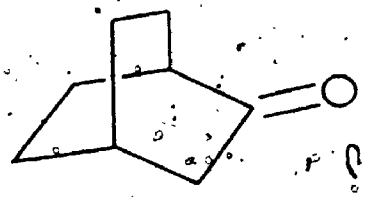

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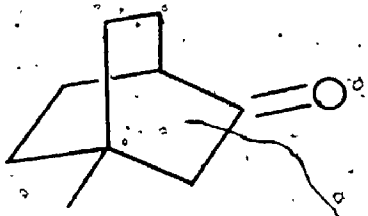

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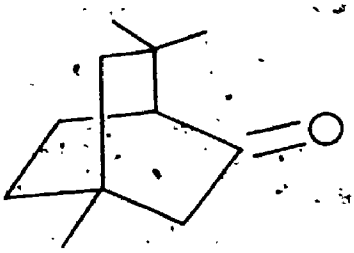

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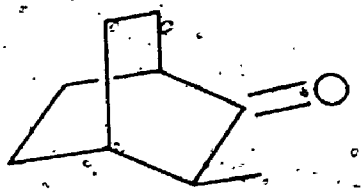

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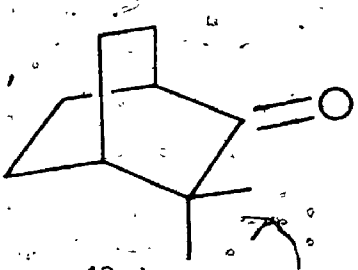

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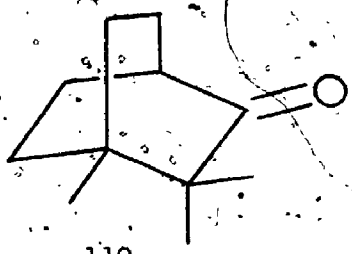

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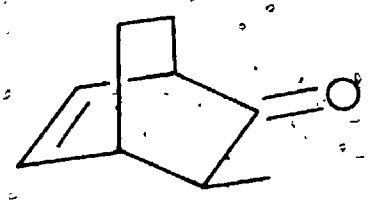

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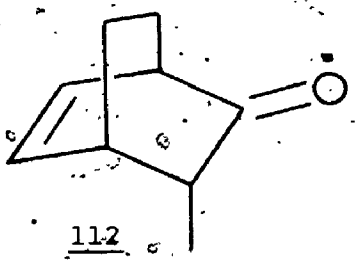

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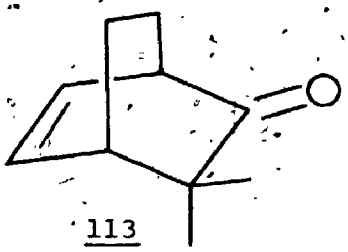

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Table 4-17

^{13}C Shieldings[a] of Some Bicyclo(2.2.2)oct-5-en-2-ones and octan-2-ones

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Me
Bicyclooctane	24.0	26.1	26.1	24.0	26.1	26.1	26.1	26.1	
Bicyclooctene	29.5	134.1	134.1	29.5	25.8	25.8	25.8	25.8	
Δ^5-2-one	48.6	212.4	40.4	32.4	136.8	128.3	22.5	24.3	
Δ^5-4-Me-2-one	48.7	212.1	47.0	37.4	141.5	127.7	23.8	32.1	24.1
Δ^5-4,7,7-Me_3-2-one	61.6	211.6	45.4	37.9	140.6	127.8	35.7	48.8	24.0(4-Me); 29.4; 30.8
4-Me-2-one	42.1	216.6	50.5	32.6	31.9	23.7	23.7	31.9	27.0
2-one	42.3	216.7	44.6	27.9	24.8	23.4	23.4	24.8	
4,6,6-Me_3-2-one	54.1	216.3	49.1	33.7	48.8	31.2	19.7	30.8	26.9(4-Me); 31.9(syn); 28.8(anti)
3-Me-2-one	42.3	220.1	47.2	33.9	20.2[b]	24.2	22.7	26.1	13.5
3,4-Me_2-2-one	42.3	219.9	48.7	36.7	26.8[b]	24.2	22.8	34.1	10.4(3-Me); 24.7(4-Me)
3,3-Me_2-2-one	42.7	221.9	45.9	38.5	22.4	23.5	23.5	22.4	23.7
3,3,4-Me_3-2-one	42.3	222.2	48.7	36.7	30.0	23.4	23.4	30.0	20.3(3-Me); 21.3(4-Me)
Δ^5-3-exo-Me-2-one	48.4	215.1	42.5	38.2	136.0	128.1	23.1	18.6	14.4
Δ^5-3-endo-Me-2-one	48.4	214.1	44.4	39.1	136.0	127.2	21.9	24.8	17.5
Δ^5-3,3-Me_2-2-one	48.8	216.7	43.8	44.1	138.6	126.1	21.8	20.7	24.3(exo); 27.5(endo)

[a] In ppm from internal TMS in $CDCl_3$ solutions. [b] Carbon syn relative to the 3-methyl group.

revealed that sterically crowded δ-carbons exhibit downfield shifts in striking constrast to the behavior of γ (vicinal) carbons. Although significant downfield shifts of sterically crowded δ-carbons were indicated by earlier results for some acyclic systems (127), data from studies of a variety of model cyclic compounds has now confirmed that deshielding effects occur for syn-axial arrangements of δ nuclei presumably via 1,5-nonbonded interactions (see Chapter 5).

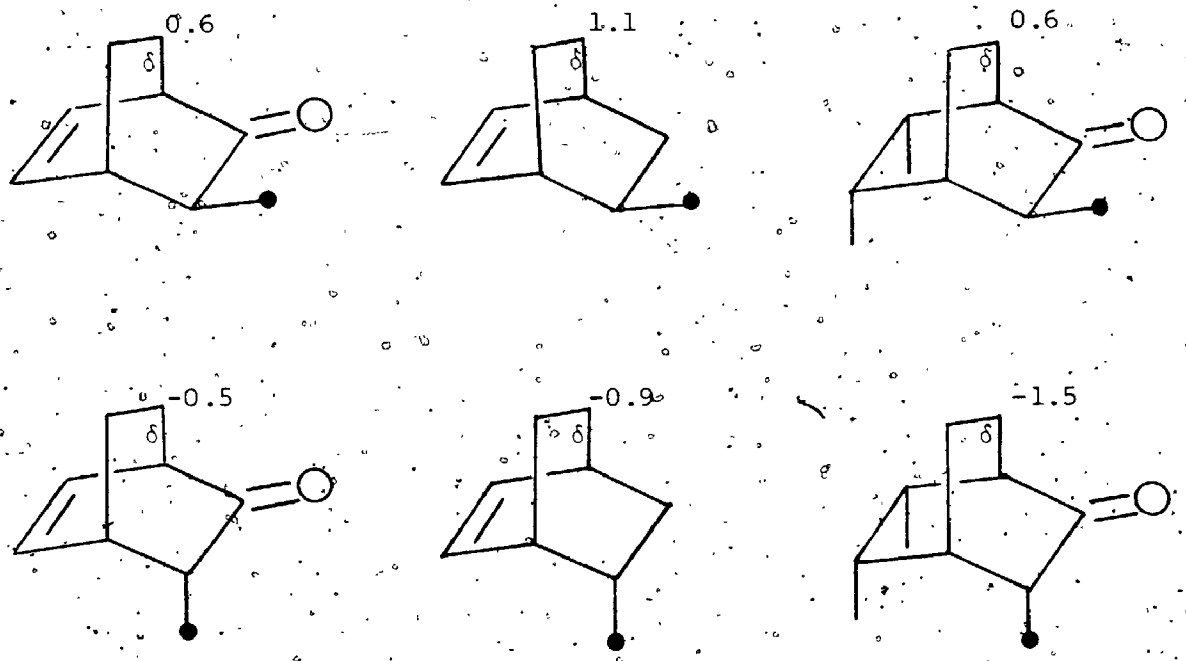
(b) RESULTS

The proton-noise decoupled ^{13}C spectra of ketones 42, 57, 73, and 104 - 113 were recorded and the shielding values are listed in Table 4.17, together with those of the parent hydrocarbons. The carbonyl and olefinic signals were readily identified by their low and intermediate field positions, respectively, and the olefinic assignments for bicyclo(2.2.2)oct-5-en-2-one (73), from follow the results for 4-methylbicyclo(2.2.2)oct-5-en-2-one (104). Introduction of a methyl group at C-4 is expected to deshield C-5 and shield C-6 since this is the typical behavior in olefinic systems (8, 9, 10). On this basis, the olefinic assignments for 4,7,7-trimethylbicyclo(2.2.2)oct-5-en-2-one (105) and the methylated bicyclo(2.2.2)oct-5-en-2-ones 111 - 113 were completed. For the high field region of these spectra, off-resonance decoupling permitted the straightforward identification of quaternary, methine, methylene and methyl signals, which can be considered in turn. The assignments for the two quaternary carbons in 105 and 4,6,6-trimethylbicyclo(2.2.2)octan-2-one (107) followed from the single quaternary

value for 104 and 4-methylbicyclo(2.2.2)octan-2-one (106), respectively, since methyl substitution at C-7 should have little effect at C-4 in each case. The two quaternary centers in 3,3,4-trimethylbicyclo(2.2.2)-octan-2-one (110) were assigned by comparison with the results for 3,4-dimethylbicyclo(2.2.2)octan-2-one (109) and 3,3-dimethylbicyclo-(2.2.2)octan-2-one (42). Of the signals arising from methine carbons those for C-1 were readily assigned for 73, 104 and 111 - 113 to the 48.6 ± 0.2 ppm signal because it is uniquely defined in 104 and is not expected to be affected by methyl substitution at C-3 or C-4. The characteristic β-effects of the geminal methyls are clear for C-1 in 105 for which this assignment is unequivocal. Similarly the C-1 signal for 42, 57, 106, and 108 - 110 must be that near 42.3 ppm while the C-1 absorption for 107 is uniquely defined by off-resonance decoupling. The remaining methine signal in the spectra 42, 73, 106, and 113 must arise from C-4 and in 109 from C-3. Each of 108, 111 and 112 exhibit a pair of methine signals, in addition to that for C-1. The lower field member of each pair must arise from C-3 since methyl substitution deshields the α and β carbons and the higher field signal of each pair lies at <40 ppm i.e. at higher field than C-3 in the parent ketones. The individual assignments for the methylene carbons are more difficult but a consistent assignment was possible as listed in Table 4.17 from the values for 106, the analysis of which has been described (see Chapter 2) and was confirmed by the data for 57- and 106-3,3-d_2. For the latter compound, obtained by base-catalyzed exchange, the effects of vicinal ^{13}C - D couplings are evident in only one of

the remaining methylene signals, that at 24.8 ppm, which must therefore arise from C-5 and C-8. It may be noted that the expected γ effect of the exo-3-methyl group at C-8 is clearly apparent in 111 and 113 compared to 73. In contrast to the trend in the norbornene derivatives (see Section D) an endo-3-methyl group appreciably deshields the anti γ carbon (C-8). Similar trends attend the variations in the saturated ketones since the 3-methyl group shields the syn γ carbon (C-5 in 108 and 109) while deshielding the anti γ carbon (C-8 in 108 and 109). It follows that the syn arrangement leads to a shielding of 4 - 5 ppm while the anti arrangement produces a downfield shift of 1 - 2 ppm. Supporting evidence for the upfield shift of a methylene carbon syn to a γ methyl group was provided by the spectrum of 108-3-d_1, obtained by base-catalyzed deuterium exchange. In this spectrum the effects of vicinal ^{13}C - D coupling were clearly apparent in the 20.2 ppm methylene signal indicating that the dihedral angle resulting C-5 and the deuterium atom is close to 180° while the 26.1 ppm signal was slightly broadened and arises therefore, from C-8. Thus, the signals for methylene carbons γ to geminal methyls such as C-8 in 42, 110 and 113 and C-7 in 107 lie 2 - 4 ppm upfield from their positions for the parent ketones. Interestingly, δ methylene carbons syn to the methyl group are shifted downfield while their anti counterparts are shifted upfield. This may be regarded as δ effect and the deshielding effects for syn arrangements of δ nuclei may be ascribed to 1,5-nonbonded interactions. Several examples are described later. The above considerations led to the complete assignments of the signals

for the skeletal carbons.



The assignments for the various methyl carbons are unequivocal for 104, 57, 108, 42, 110 - 112 while those for 109 follow from the values for 57 and 108. In 109 the vicinal methyls are gauche and both exhibit the expected upfield shifts (2.7 ± 0.4 ppm) relative to their positions in the corresponding monomethyl derivatives. From the differences for the exo- and endo-methyl carbons in 111 and 112, the methyl assignments for 113 follow directly. Because the difference in shielding of the geminal methyls in 107 is comparable to that in 113 the higher field signal has been assigned to the methyl carbon anti to the carbonyl group. Presumably there is greater steric crowding between sp^3 - carbons than between sp^2 and sp^3 carbons as evidenced by the results for 111 and 112. The downfield shifts for geminal methyl carbons relative to

the monomethyl derivatives (i.e. 110 vs. 108; 110 vs. 109) are typical (8, 9) and arise from the usual β-effect of methyl substitution.

On the basis of the foregoing results, the ^{13}C spectra of 114 and 118 led to the assigned structures; the shieldings are collected in Table 4.18. The absence of a methyl signal near 24 ppm for the unsaturated ketone indicates that the Diels-Alder Adduct from the reaction of α-acetoxyl-acrylonitrile with cyclohexadiene (115) (Scheme 4.2) (129), is 116 rather than 117 since alkaline hydrolysis of the latter would yield 119 having a methyl signal equivalent to the bridgehead methyl absorptions of 104 and 105. It was expected that the formation of 117 would be hindered because of steric interference between the dienophile and the closer of the two geminal methyl groups. Furthermore, the geminal methyl signals at 28.6 and 31.1 ppm are consistent with 114 rather than 119 on the basis of the geminal methyl shieldings for 105. From the off-resonance decoupled spectrum, the methylene signals were identified at 36.4 and 46.8 ppm. The more shielded of these strongly indicates a methylene carbon experiencing the γ gauche effect of a neighbor methyl group which is consistent only with 114. The upfield shift of 4 ppm relative to the C-3 absorption of 73 agrees entirely with that found for a variety of methylene carbons γ to geminal methyls as noted above. The sp^3 - methine signal at 49.8 ppm is consistent only with 114 since the corresponding signal in 105 appears at 61.1 ppm. The appearance of a quaternary signal at 49.8 ppm is also consistent only with structure 114 since the quaternary bridgehead carbon in 119 would absorb near 38 ppm on the basis of the value for 105. Thus, these five pieces of evidence establish the

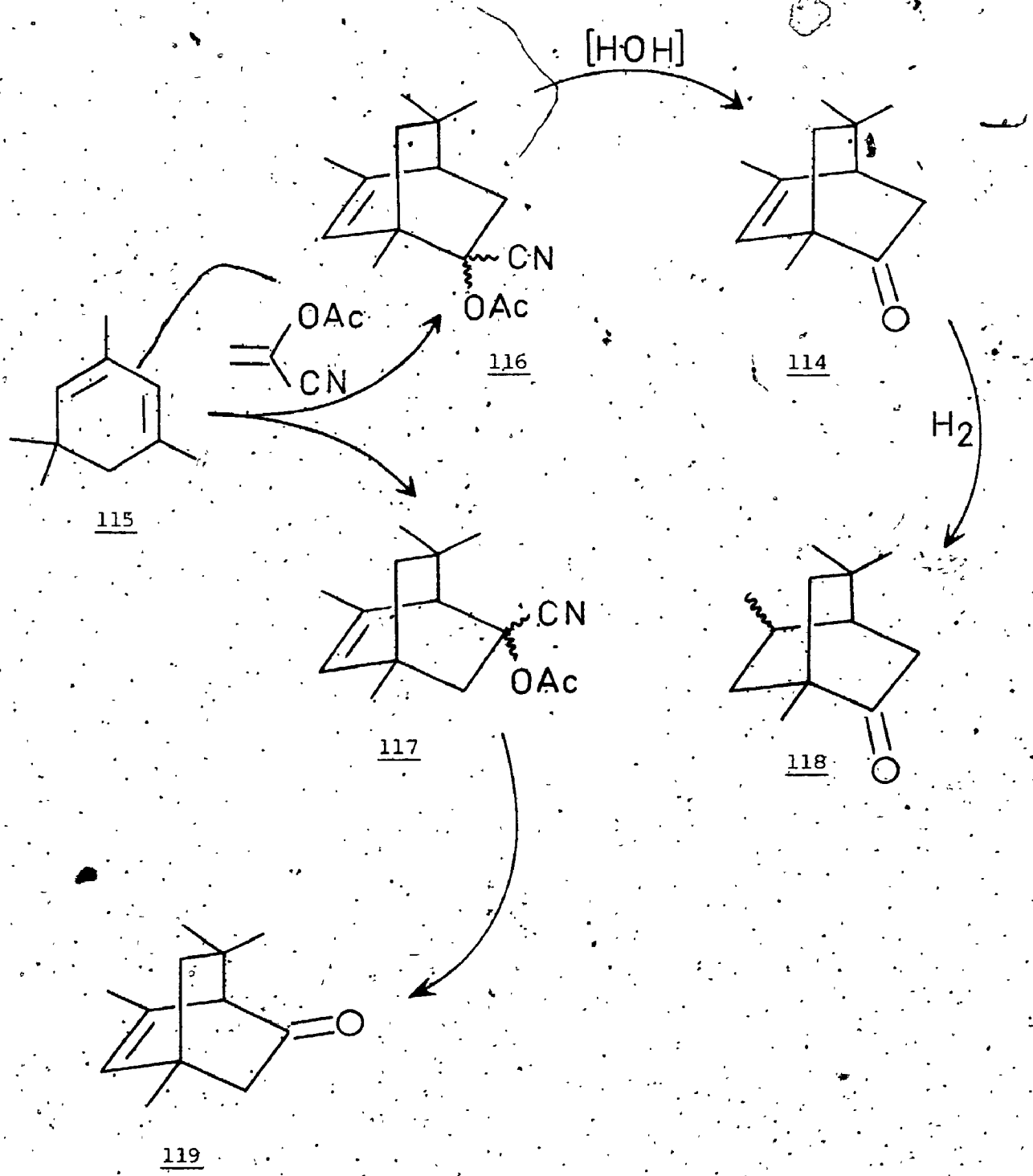
Table 4.18

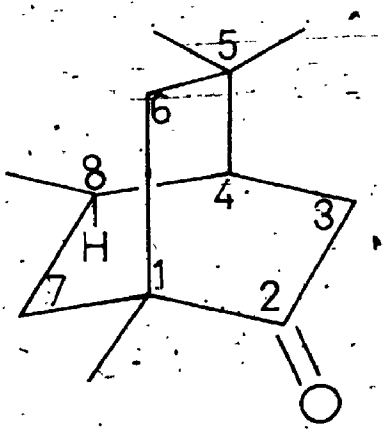
^{13}C Shieldings[a] of Ketones

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Me
114	49.8	213.1	36.4	49.8	147.1	124.1	46.8	35.0	17.1(1-Me) 21.9(5-Me) 28.6(exo-8-Me) 31.1(endo-8-Me)
a	44.8	217.2	44.8	45.3	32.5	47.3	38.6	34.4	20.1(1-Me) 32.3, 32.8(5,5-Me_2)
118									22.6(8-Me)
b	45.0	217.7	35.8	45.4	32.3	47.3	39.3	25.4	20.1(1-Me) 29.5(5,5-Me_2) 20.6(8-Me)

[a] In ppm from internal TMS in $CDCl_3$ solutions.

SCHEME 4.2





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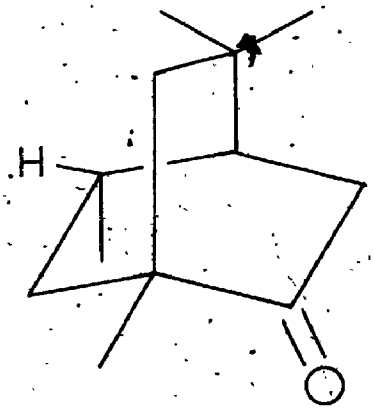
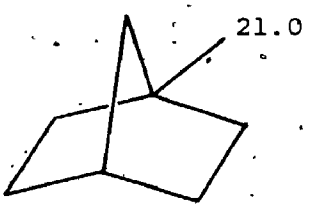


b

118

unsaturated ketone to be 114. Since it is known that methyl carbons gauche to, or eclipsed with, a carbonyl group experience an upfield shift of 6 - 7 ppm, the 17.7 ppm signal was assigned to the bridgehead methyl carbon. Supporting data for this assignment are provided by the methyl shieldings in 120 vs. 121 (34, 38), 122 vs. 123 (38, 130) and 124 vs. 125. The remaining assignments for 114 were straightforward.

Catalytic hydrogenation of 114 proceeded slowly to give a 4 : 1 mixture of two saturated bicyclooctanones. From earlier work with related materials (129), hydrogenation was expected to occur primarily, if not exclusively, on the side of the olefinic bond away from the geminal methyls, i.e. syn with respect to the carbonyl group. On this basis, 118a should represent the major product and 118b the minor. The ^{13}C data are entirely consistent with expectations. Only three nonequivalent methyl signals were observed in the spectrum of the minor product at 20.1, 20.6 and 29.5 ppm in the ratio 1 : 1 : 2, while four separate methyl signals were found for the major isomer: 20.1, 22.6, 32.3 and 32.8 ppm. For each ketone, the 20.1 ppm signal was assigned to the bridgehead methyl since the 7 ppm upfield shift relative to 57 and 107 is expected because of the vicinal carbonyl bond. Of the two structures, equivalent geminal methyl carbons can only arise in 118b. Since the syn-8-methyl in 118a lies in close proximity to one of the geminal methyls the steric pertubation will render the latter nonequivalent. The surprising feature is the fact that these methyl carbons are deshielded relative to their unhindered conterparts. This trend is discussed in the next Chapter. To complete the assignments



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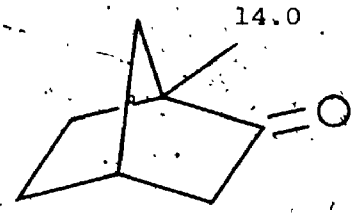

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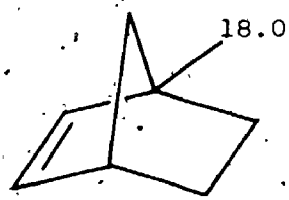

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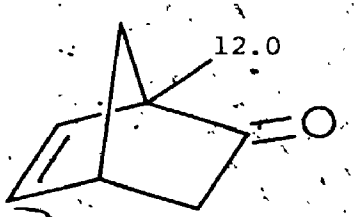

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125

for 118a and 118b, each was subjected to base-catalyzed deuterium exchange and the ^{13}C spectra of the 3,3-dideuterio derivatives were recorded. From these spectra the signals for C-3, C-4, C-5 and C-8 were unequivocally distinguished by the characteristic effects of deuterium through 1, 2, and 3 bonds, respectively (see Chapter 2). The C-4 methine signals exhibited geminal isotope shifts of ca. 0.1 ppm while the C-5 and C-8 signals were appreciably broadened due to vicinal $^{13}C - D$ coupling. Because deuteration was essentially complete the C-3 signals were not observed in these spectra. The relative shieldings of C-3 in 118a and 118b established that the latter has a γ gauche interaction with the 8-methyl group. The remaining two methylene signals for each isomer were readily assigned since the lower field signal must arise from that adjacent to the gem-dimethyl group.

(c) DISCUSSION

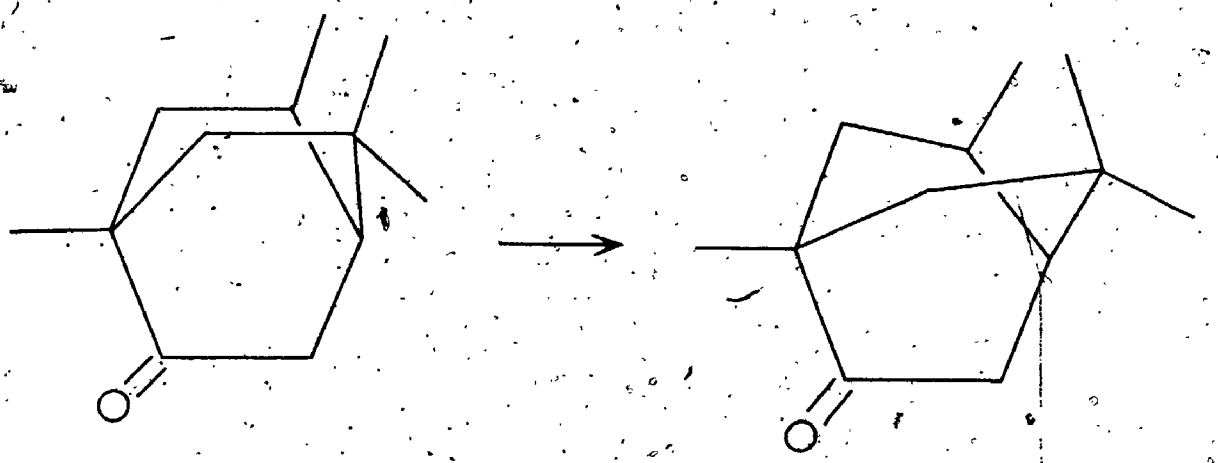
The carbonyl shieldings in this series reveal some interesting trends. Perhaps the most striking of which is the consistent difference observed between pairs of saturated and unsaturated ketones with the same substitution pattern, e.g. 106 vs. 73, 57 vs. 104 etc. In each case, the β, γ unsaturated ketone exhibits its carbonyl absorption 4.6 ± 0.5 ppm upfield from that in its saturated counterpart. This shift was attributed to homoconjugation which has been discussed in detail in Section B. Homoconjugative interaction between the double bond and carbonyl group may be expected to reduce the electron withdraw-

ing influence of the carbonyl at C-3 and the relatively higher shielding of C-3 in the unsaturated ketone of each pair is consistent with this notion. As expected methyl substitution at C-3 tends to deshield the carbonyl carbon significantly while more remote methyl substitution has little effect. It is interesting that a 1-methyl group has a smaller deshielding effect than a 3-methyl to judge from the results for 114 and 118 relative to 73 and 106, respectively. Perhaps a steric interaction between the 1-methyl hydrogens and the carbonyl oxygen tends to diminish the deshielding effect since the dihedral angle between the C-Me and C=O bonds is appreciably smaller than that for a 3-methyl group.

Several instances of upfield shifts arising from 1,4 nonbonded interaction between neighboring γ nuclei have been cited in the discussion of individual assignments in the previous section. A comparison of some of these with other systems seems warranted. The shielding differences between exo- and endo-methyl groups in 111 - 113 are appreciably larger than those in the corresponding norbornenones (130). In the present system, the exo-methyl lies closer to C-8 than an exo-methyl relative to C-7 in the norbornenones which will account for the observations. In a similar manner, the larger difference between geminal methyls in 107 relative to that for camphor or 7,7-dimethylnorcamphor (see Section D) seems attributable to the closer approach of the anti-methyl to C-7 in 107 than the corresponding interaction of the anti-methyl with C-5, C-6 in the camphor series. It should be noted that a specific assignment of the geminal methyls in 105 has not been indicated in Table 4.17. By comparison with the results for 107, however, it

may be suggested that the lower field signal of the geminal methyl pair in 105 arises from the exo-6-methyl carbon. The geminal assignments for 107 were based on the fact that the anti-methyl suffers the greater steric crowding with the methylene carbon than the syn-methyl with the carbonyl group. For each of 105 and 107, the least shielded methyl signal was most strongly affected by the addition of the shift reagent, $Eu(fod)_3$, supporting the above assignments.

As discussed in the preceding section, the geminal methyl signals in the 118 isomers provided a clear distinction between the two unsaturated ketones since equivalent gem-dimethyl carbons are only expected for the minor isomer, 118b. The other evidence substantiating this conclusion has been discussed above. Intially it seemed surprising that the geminal methyl carbons are deshielded in 118a in which there must be steric interference with the 8-methyl group because it was well-established that steric crowding causes upfield shifts between γ nuclei (8, 9, 10). Steric crowding of δ nuclei, however, appears to have the opposite effect. Moreover both gem-dimethyl carbons are deshielded relative to the corresponding carbons in 118b. The relative orientation of the neighboring methyls in 118a is close to syn-axial with the flexibility of the ring system permitting some distortion to maximize the separation as depicted in 126. Concurrent with this work, a variety of bicyclic alcohols had been examined and their trends are similar. In each case having a syn-axial arrangement of hydroxyl and methyl groups the methyl carbon exhibited a downfield shift relative to its shielding for a less hindered environment (see



126

Chapter 5). On the basis of the upfield shifts consistently observed for γ nuclei, there has been a developing tendency to associate steric crowding in general with increased shieldings. Unfortunately it seems that this generalization is somewhat premature.

(d) SUMMARY

The well-defined effects arising from 1,4-nonbonded interactions (γ effects) are apparent and are useful for stereochemical assignments. Evidence is presented to show that closely neighboring δ carbons experience deshielding effects, in sharp constrast to the influence of steric crowding on γ carbons. The ^{13}C shieldings observed for 1,5,8,8-tetramethylbicyclo(2.2.2)oct-5-en-2-one and the isomeric saturated bicyclooctanones obtained therefrom established their structures.

(F) ^{13}C SPECTRA OF A VARIETY OF BICYCLIC KETONES —— METHYL AND CARBONYL SUBSTITUENT EFFECTS

(a) INTRODUCTION

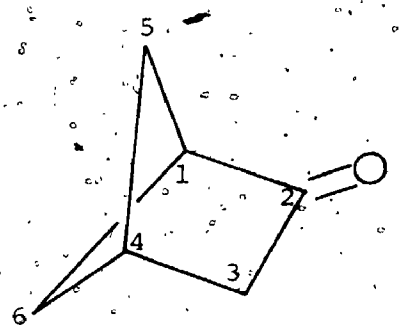
In one of the first systematic studies of substituent effects in alicyclic systems, Dalling and Grant (108) showed the remarkable reproducibility and stereochemical dependence of the effects of methyl groups on the shieldings of cyclohexane ring carbons. Similar results were subsequently obtained for the norbornane system by Roberts and co-workers (34) and also in this study, as described in the preceding sections of this chapter. In each case, the carbons γ to the site of substitution are significantly shielded if gauche to the methyl group and tend to be deshielded slightly, if anti. As an extension of the investigation of the effects of molecular geometry and stereochemistry on ^{13}C shieldings, a variety of methyl-substituted bicyclic ketones were prepared and examined. Several examples of six skeletal types were included: bicyclo(4.4.0)decanones, bicyclo(4.1.0)heptanones, bicyclo-(3.1.0)hexanones, bicyclo(3.2.2)nonanones, bicyclo(3.2.1)- and -(3.3.0)octanones as well as bicyclo(2.1.1)hexanone, nopinone (6,6-dimethylbicyclo(3.1.1)heptan-2-one) and two methyl derivatives of the latter. The observed trends associated with methyl substitution follow well-defined patterns and offer further support for the application of ^{13}C shieldings as aids for stereochemical assignments especially through the well known γ effects.

(b) RESULTS

The shielding data for this series of ketones are collected in Table 4.19. In each case, both noise and off-resonance decoupled spectra were obtained to distinguish between carbon types, the first step for the assignments. The carbonyl carbons were readily assigned from their characteristic low field positions (8, 9) and in the parent systems, the nonequivalent bridgehead carbons could be distinguished readily since that closer to the carbonyl is consistently less shielded. For the symmetrical compounds, the relative intensities led to straightforward assignments. From these features, the assignments for bicyclo-(3.2.1)octan-2-one, bicyclo(2.1.1)hexan-2-one and bicyclo(3.1.0)hexan-3-one were completed.

The bicyclo(3.1.0)hexan-2-one derivatives each have three methylene carbons which were distinguished in the monomethyl derivatives by deuterium exchange of the α-methylene protons. In the spectra of the dideuterated derivatives, one methylene signal essentially disappeared, one was shifted to higher field by ~0.2 ppm, by the geminal isotope effect, while the third was unaffected, establishing these as the C-3, C-4 and C-6 signals, respectively (see Chapter 2). From the methyl shieldings for the monomethyl derivatives, it followed that the more shielded methyl signal for the 1,5-dimethyl derivatives was due to the 1-methyl carbon. In a similar manner, the assignments for the bicyclo-(4.1.0)heptan-2-one derivatives were completed, again, utilizing the results for the 3,3-dideuterio monomethyl isomers to identify the different methylene signals.

To aid the assignments for nopinone and its derivatives, the ^{13}C



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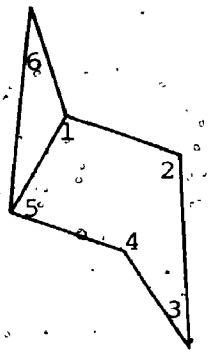

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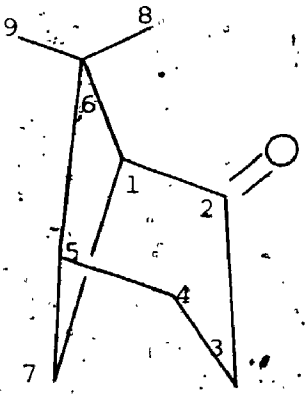

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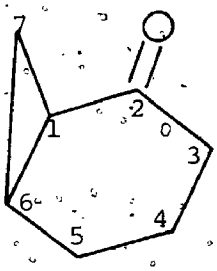

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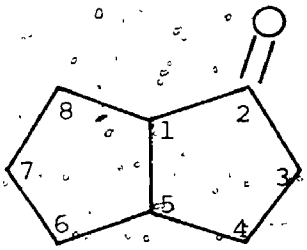

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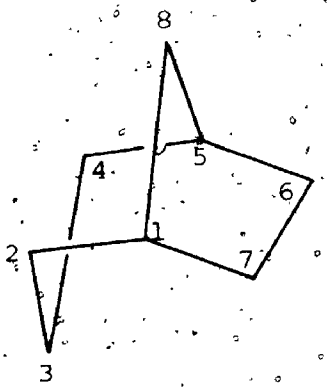

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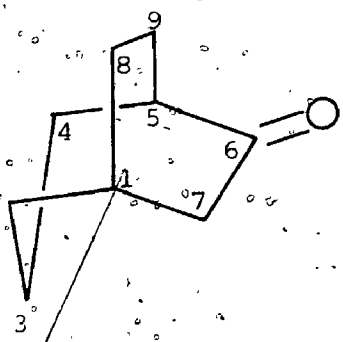

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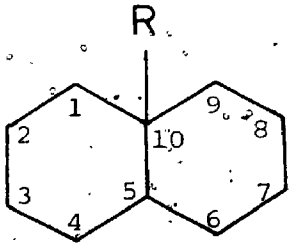

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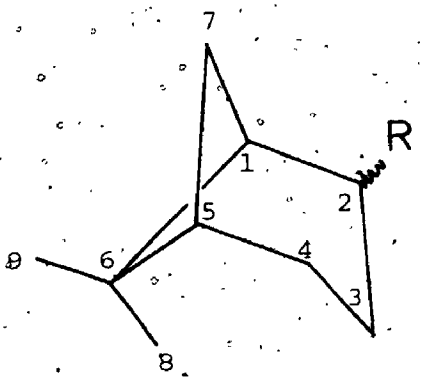

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Table 4.22

Carbonyl Substituent Effects[a]

Skeleton	Substituent	α-C		β-C		γ-C
		CH	CH_2	CH	CH_2	
(2.2.2)	2-oxo	18.3	18.5	3.9	-2.7(C-6,7)	-1.3(C-5,8)
(3.2.2)	6-oxo	17.9	18.4	-0.5	-3.8(C-4)	-1.6(C-2)
					-2.7(C-9)	-0.6(C-3)
						-1.5(C-8)
(2.2.1)	2-oxo	13.4	15.5	-1.6	-5.4(C-6)	-2.5(C-5)
					-0.7(C-7)	
(3.2.1)	6-oxo	11.0	14.6	-3.9	-2.1(C-4)	-2.3(C-2)
					-3.5(C-8)	-0.2(C-3)
	2-oxo	16.0	15.6		-0.7(C-4)	-1.1(C-5)
					-0.9(C-7)	-0.8(C-6)
					-1.4(C-8)	
	3-oxo		17.5	0.1		0.4(C-6,7)
						-1.9(C-8)
(4.4.0)	1-oxo	11.2	14.7	1.2	-1.5(C-3)	-1.3(C-4)
					-7.8(C-9)	0.0(C-6)
						-1.1(C-8)
	2-oxo		14.2(C-1)	-0.4	-1.6	-2.1(C-5)
			14.5(C-3)			-0.7(C-9)
Cyclohexanone			15.0		-0.1	-1.9
cyclopentanone			12.4		-2.6	
Cycloheptanone			15.5		-4.0	2.1

[a] In ppm. Positive values denote deshielding effects.

Table 4.20

^{13}C Shieldings[a] of Some bicyclic Hydrocarbons and Alcohols

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
apopinane(127a)	41.1	25.4	22.4	25.4	41.1	39.1	26.7	20.5	26.8	
cis-pinane(127b)	48.1	36.0	33.9	23.9	41.4	38.7	26.6	(22.9)	28.3	(23.2)
α-nopinol(127c)	47.9	73.1	28.3	24.8	41.0	37.4	25.5	22.4	27.3	
β-nopinol(127d)	48.0	69.4	23.3	22.7	40.5	39.4	25.7	20.0	26.7	
bicyclo(3.2.1) -octane	35.2	32.8	19.1	32.8	35.2	28.9	28.9	39.7		
bicyclo(3.2.2) -nonane	29.0	35.7	22.2	35.7	29.0	25.9	25.9	25.9	25.9	
trans-decalin[b]	34.3	26.9	26.9	34.3	43.7	34.3	26.9	26.9	34.3	43.7
10-methyl-trans -decalin[c]	42.1	22.1	27.2	29.3	45.8	29.3	27.2	22.1	42.1	33.9

[a] In ppm from internal TMS. Measured for 5-15% (w/v) solutions in $CDCl_3$.
[b] From ref. (131) [c] From ref. (132), the methyl shielding is 15.7 ppm.

spectra of apopinane (127a), cis-pinane (127b) and the nopinols (127c, 127d) were also recorded; these data appear in Table 4.20. For apopinane, the C-1, -2, -4, -5 and -6 assignments were straightforward and it remained to distinguish the C-3 from the C-7 signal and the gem-dimethyl resonances. The consistent appearance of a methylene signal near 26 ppm in all spectra of the (3.1.1) series led to its assignments as C-7 since C-2 substitution is expected to have little effect at this position. Since C-8 is essentially axial with respect to the six-membered rings and C-9 is equatorial, it was expected that C-8 would be the more shielded of the gem-dimethyl carbons. This was supported by an examination of the relative shifts in nopinone upon addition of $Eu(fod)_3$, since the higher field methyl signal exhibited a greater downfield shift. With two methyl signals near 23 ppm for nopinol (127c) the assignments of C-8 and C-10 are uncertain and for 3,3,6,6-tetramethylbicyclo(3.1.1)heptan-2-one, the methyl assignments may not be correct; the present assignments are discussed more fully later.

3,3-Dimethyl-cis-bicyclo(3.3.0)octan-2-one was obtained by homoenolization of 3,3-dimethylbicyclo(3.2.1)octan-2-one (59). Deuterium exchange under homoenolization conditions, coupled with ^2H NMR examination, permitted unequivocal identification of C-6, -7 and -8 (59) in the ^{13}C spectrum and completed the assignments, from which those for bicyclo(3.3.0)octan-2-one and its trimethyl derivative followed readily.

In the (3.2.1) series, the parent hydrocarbon is included (Table 4.20). For the 2-exo compounds, the spectra of the 3,3-dideuterio, 3-deuterio-3-methyl and 1,7,7,9,10-pentadeuterio-3,3-dimethyl derivatives were also determined; the latter isomer was obtained from

homoenolization experiments(59). With these data the assignments for the 2-exo-derivatives were readily completed. For the 3-exo derivatives, the well-separated methine signals permitted straightforward assignments while the C-6 and -7 methylene resonances were identified on the basis of an expected shielding influence of an endo-2-methyl at C-7 but for the exo-2-methyl isomer these methylene signals were not so readily assigned. By analogy with exo-3-methylnorcamphor, however, one may predict that the exo-2-methyl group would tend to deshield C-7 slightly and, on this basis, the C-6 and C-7 signals were taken to be those at 28.5 and 30.1 ppm, respectively. A comparison of the data for the 6-exo series with that for the parent hydrocarbon led to the assignments given in Table 4.19 for these four derivatives. A sample of 7,7-dimethyl-bicyclo(3.2.1)octan-6-one containing deuterium at C-3, -4, -5 and -9 was available from homoenolization studies (see Chapter 3) to confirm the assignments and to provide supporting evidence for those of the other derivatives.

For the bicyclo(3.2.2)nonan-6-ones, the spectra of the 7,7-dideuterio, 7-deuterio-7-exo-methyl and 7-deuterio-7-endo-methyl derivatives as well as the parent hydrocarbon (Table 4.20) were also recorded. This permitted a ready distinction between the methine signals for the monomethyl cases. Since one signal was essentially eliminated, one was shifted upfield by 0.1 ppm while the third methine signal was unaffected in the spectra of the deuterated compounds, these arose from C-7, C-1 and C-5, respectively. In addition, one of the methylene signals in each was significantly broadened, identifying the vicinal methylene carbon anti to the deuterium. Of the remaining methylene peaks, the highest field signal, ~21 ppm, was

assigned to C-3 in the four ketones because of its similarity with C-3 in the hydrocarbon and the fact that it should be little affected by 7-substitution. All four ketones exhibited methylene absorption near 31 ppm which was assigned to C-4 since this carbon should be little affected by 7-substitution. Supporting this assignment, the spectrum for 7,7-dideuteriobicyclo(3.2.2)octan-6-one showed broadening due to vicinal C-D coupling for the 24.4 and 34.1 ppm resonances. Thus it also followed that C-9 gave rise to the signal near 23 ppm in the four ketones.

(c) DISCUSSION

From the earlier studies of aliphatic and alicyclic ketones it was found that the ^{13}C shieldings of carbonyl carbons are not nearly so sensitive to alkyl substitution as saturated carbons in hydrocarbons (8, 9, 10). For the latter, it is established that the replacement of an α- or β-hydrogen by a methyl group deshields the carbon nucleus by ~9 ppm. With the carbonyl compounds, this effect is attenuated to ca. -5 ppm for α-substitution, e.g. $RCHO \longrightarrow RCOCH_3$ and the effects of more remote substitutions are much smaller. To examine the trends for methyl substitution in the present ring systems, some pertinent data are given in Table 4.21 which contains the shifts observedfor the skeletal carbons in the monomethyl derivatives from their positions for the parent ketones. The first seven entries have the carbonyl in a two-carbon bridge with the α-methyl gauche, or approximately so, to either a one or two-carbon bridge. It is apparent

Table 4.21

Methyl Substituent Effects[a] in Some Bicyclic Ketones and Cyclohexanone

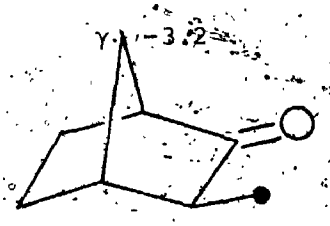
Skeleton	Substitution	Substituent-effects					
		α	β		γ		
			C=O	$CH(CH_2)$	gauche	anti	CH[b]
(2.2.1)	2-oxo-3-exo-Me	3.1	2.6	6.2	-3.2	0.9	-0.3
(3.2.1)	6-oxo-7-exo-Me	3.4	2.8	7.2	-2.8	0.9	0.5
(3.2.1)	6-oxo-7-exo-Me	3.2	2.7	6.7	-4.3	1.3	0.0
(2.2.2)	2-oxo-3-Me	2.6	3.4	6.0	-4.6	1.3	0.0
(2.2.1)	2-oxo-3-endo-Me	3.1	2.4	5.1	-6.2	-0.4	0.5
(3.2.1)	6-oxo-7-endo-Me	4.9	2.0	4.6	-4.4	-0.8	-0.5
(3.2.2)	6-oxo-7-endo-Me	2.2	1.8	5.6	-5.0	1.5	-0.4
(3.2.1)	2-oxo-3-exo-Me	3.6	0.7	10.4		-0.1(C-1)	
						0.7(C-5)	
	3-oxo-2-endo-Me	1.1	1.1	7.4	-5.0(C-7)	-0.5(C-4)	
						2.0(C-8)	
$C_6H_{10}O$[c]	2-Me(equatorial)	3.4	1.0	9.1		0.2(C-4)	
						-0.1(C-6)	
$C_6H_{10}O$[c]	2-Me(axial)	3.6	3.6	6.0	-5.9(C-4)		
					-6.2(C-6)		
(3.2.1)	3-oxo-2-exo-Me	2.8	6.2	6.3	-2.6(C-4)	0.8(C-7)	
					-5.7(C-8)		
(4.4.0)	1-oxo-10-Me	-6.6	3.7	1.2(C-5)	-4.2(C-2)		
				6.0(C-9)	-5.3(C-4)		
					-6.3(C-6)		
					-4.4(C-8)		
	2-oxo-10-Me	-5.7		8.3(C-1)	0.7(C=O)		
				2.1(C-5)	-4.7(C-4)		
				8.0(C-9)	-4.8(C-6)		
					-4.5(C-8)		
	3-oxo-10-Me	-8.5		7.6(C-1)	-3.3(C-2)		
				1.3(C-5)	-3.7(C-4)		
				6.8(C-9)	-4.6(C-6)		
					-4.5(C-8)		
	4-oxo-10-Me	-5.3		7.8(C-1)	-4.9(C-2)		
				2.7(C-5)	-1.0(C=O)		
				7.0(C-9)	-3.9(C-6)		
					-3.9(C-8)		

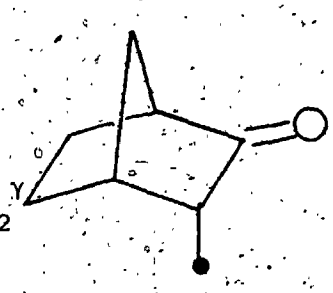
[a] In ppm. Positive values denote deshielding effects.

[b] Bridgehead carbon; C-1 in (2.2.1) and (2.2.2) ketones; C-5 in (3.2.1) and (3.2.2) series.

[c] Cyclohexanone, data from Chapter 4.

that a γ-carbon gauche to the methyl group in the latter arrangement produces the larger upfield shift, as might be expected because of the smaller dihedral angle between the two γ-centers. The relative shieldings of the methyl carbons exhibit the same trend. For example, the upfield shift of C-6 in endo-3-methylnorcamphor is larger than that for C-7 in exo-3-methylnorcamphor. The exo-methyl shows somewhat larger shift





(3.4 ppm) than the endo-methyl. As expected, α-methylation shifts the carbonyl absorption downfield but the magnitude of the shift depends on the position of substitution. For example, a 3-methyl group in norcamphor causes a somewhat larger shift (2.5 ppm) than a 1-methyl group (~1 ppm). Since methyl substitution of an α-hydrogen places the methyl carbon γ to the carbonyl oxygen it is conceivable that the normal β-effect of the methyl group at the carbonyl carbon is reduced by the γ interaction with the oxygen atom. Since the dihedral angle between the C—Me and C=O bonds is less for a bridgehead methyl than for a 3-methyl group, the differences in the observed shifts may be rationalized. The smallest shifts caused by an α-methyl group occur in exo-3-methylbicyclo(3.2.1)octan-2-one, endo-2-methylbicyclo(3.2.1)-octan-3-one and 2-methylcyclohexanone having the methyl group in an

equatorial orientation in a six-membered ring and almost eclipsing the carbonyl oxygen thereby, leading to a reduced β-substituent effect. In constrast, the carbonyl carbon for the last two entries having axial methyls is apparently deshielded relative to that in the equatorial counterparts. It is clear that the dihedral angle between the carbonyl group and the methyl group is greater. Similarly the methyl carbon shieldings also exhibit the same trend. For example, an equatorial α-methyl carbon in a cyclohexanone is significantly shielded (-7.8 ppm) relative to an equatorial methyl carbon in cyclohexane. Also, an axial 2-methyl carbon in cyclohexanone is shielded by -1.8 ppm relative to an axial methyl in cyclohexane (107).

For each exo / endo pair, the β effects are somewhat diminished in the isomer having the greater upfield γ shift. For example, exo-3-methylbicyclo(3.2.1)octan-2-one, endo-2-methylbicyclo(3.2.1)octan-3-one and equatorial-2-methylcyclohexanone have an equatorial α-methyl nearly eclipsed with the carbonyl group; but only one has an additional gauche γ interaction, which presumably accounts for the attenuated β effect at the adjacent bridgehead carbon. It has been generally found that the shieldings of all carbons in the gauche fragment are upfield from those in the corresponding arrangement-lacking the gauche interaction (8, 9). From Table 4.21, it is apparent that methyl substitution at the ring junction in the (3.1.0) and (4.1.0) systems does not produce distinctive upfield shifts for the carbons. This is consistent with the relatively large dihedral angles, ~120°, relating these centers. The γ shielding interactions between the nearly eclipsed

methyls in the dimethyl derivatives, however, are clearly evident from the methyl carbon shieldings.

To examine the effect of the carbonyl group on the shieldings of the neighboring carbons, the relevant data are listed in Table 4.22, obtained by comparison of the results for the unsubstituted ketones with those for the parent hydrocarbons. In general, the α-methylene carbons are more strongly deshielded in the bicyclic systems than in cyclopentanone. It is also interesting that the carbonyl group tends to shield the γ carbons in all cases. There seems to be no ready explanation for either of these trends. The upfield shifts exhibited by the β-methylene carbons, however, are consistent with γ interactions involving the carbonyl oxygen. The effects are larger with small dihedral angles such that a trend is discernible. The maximum upfield shifts are found for the decalones having the carbonyl group at either C-1 or C-4, in which case the carbonyl oxygen must be nearly eclipsed with C-9 or C-6, respectievly. The smallest shifts occur in the systems for which the carbonyl oxygen and β-methylene carbon are separated by relatively large dihedral angles, ~120°. Presumably the interaction producing these upfield shifts involves the hydrogen bonded to the affected carbon. For the β-bridgehead carbons, the bridgehead hydrogen and carbonyl oxygen are much too far apart to interact and there is no apparent trend in these data.

The observed trends in this series offer further support for the application of ^{13}C shieldings as aids for stereochemical assignments especially through the well known γ effects.

Table 4.22

Carbonyl Substituent Effects[a]

Skeleton	Substitutent	α-C		β-C		γ-C
		CH	CH_2	CH	CH_2	
(2.2.2)	2-oxo	18.3	18.5	3.9	-2.7(C-6,7)	-1.3(C-5,8)
(3.2.2)	6-oxo	17.9	18.4	-0.5	-3.8(C-4)	-1.6(C-2)
					-2.7(C-9)	-0.6(C-3)
						-1.5(C-8)
(2.2.1)	2-oxo	13.4	15.5	-1.6	-5.4(C-6)	-2.5(C-5)
					-0.7(C-7)	
(3.2.1)	6-oxo	11.0	14.6	-3.9	-2.1(C-4)	-2.3(C-2)
					-2.5(C-8)	-0.2(C-3)
	2-oxo	16.0	15.6		-0.7(C-4)	-1.1(C-5)
					-0.9(C-7)	-0.8(C-6)
					-1.4(C-8)	
	3-oxo		17.5	0.1		0.4(C-6,7)
						-1.9(C-8)
(4.4.0)	1-oxo	11.2	14.7	1.2	-1.5(C-3)	-1.3(C-4)
					-7.8(C-9)	0.0(C-6)
						-1.1(C-8)
	2-oxo		14.2(C-1)	-0.4	-1.6	-2.1(C-5)
			14.5(C-3)			-0.7(C-9)
Cyclohexanone			15.0		-0.1	-1.9
cyclopentanone			12.4		-2.6	
Cycloheptanone			15.5		-4.0	2.1

[a] In ppm. Positive values denote deshielding effects.

(d) SUMMARY

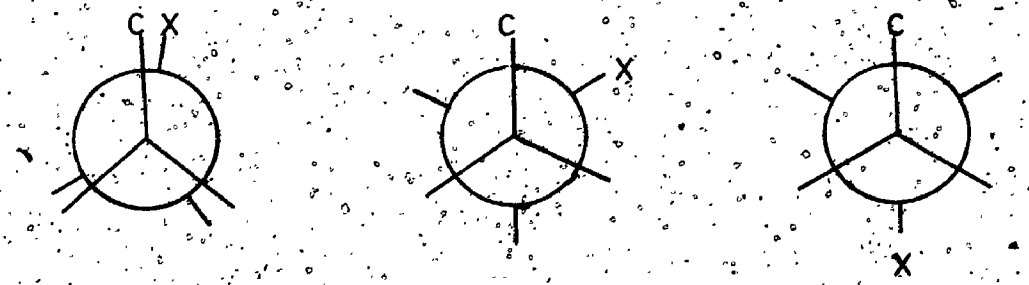
The ^{13}C NMR spectra of a series of ketones showed that the observed trends associated with methyl substitution follow well-defined patterns and offer further support for the application of ^{13}C shieldings as aids for stereochemical assignments especially through the well-known γ effects. In each case, the carbons γ to the site of substitution are significantly shielded slightly if gauche to the methyl group and tend to be deshielded, if anti. The effect of the carbonyl group on the shieldings of the neighboring carbons are obtained by comparison of the results for the unsubstituted ketones with those for the parent hydrocarbons. The carbonyl group tends to deshield the α-carbons and shield the γ-carbons in all cases.

CHAPTER 5

EXAMINATION OF THE LONG-RANGE SHIELDING EFFECTS OF METHYL AND HYDROXYL GROUPS IN ALICYCLIC, BICYCLIC AND AROMATIC SYSTEMS — δ AND ε EFFECTS

(A) INTRODUCTION

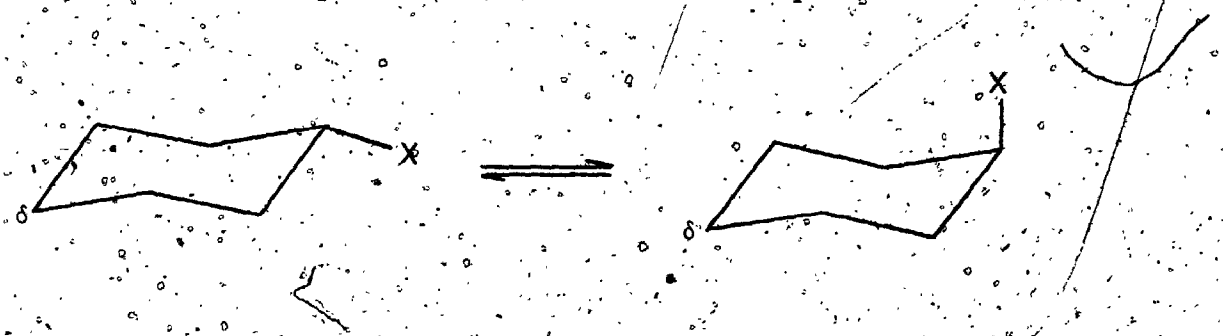
Carbon-13 magnetic resonance is generally recognized as one of the most useful spectroscopic techniques available for stereochemical assignment and the elucidation of structure. These applications are, for the most part, based on empirical correlations of ^{13}C shieldings with molecular geometry (17). The marked sensitivity of ^{13}C shieldings to molecular geometry is well known and certain trends are sufficiently well defined that even relatively small shielding differences often offer valuable assistance for signal assignments and may lead to definite stereochemical assignments. Perhaps the most distinctive of these trends is the variation in shielding of a carbon as a function of its orientation with respect to a nucleus other than hydrogen in the γ position. Invariably the γ gauche or eclipsed arrangement produces an upfield shift of the signal relative to the shielding of a corresponding carbon in the anti form. This γ effect has been empirically linked to



Eclipsed Gauche Anti

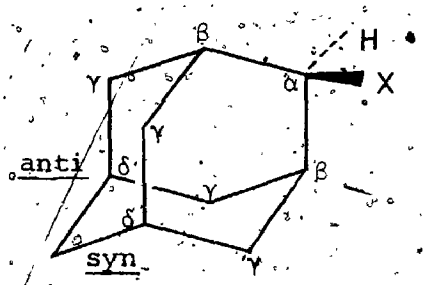
a 1,4 steric repulsion and has served as a useful guideline in making peak assignments and in conformational analysis (8). Grant and Cheney (30, 31) have rationalized the γ effect in terms of a model of steric interactions between neighboring CH moieties. In this model, the hydrogen atoms experience strong nonbonded interactions of such a nature that the electronic distribution on the carbons is altered — that is, a steric polarization of the valence electrons of the carbon atom of interest.

In general the small δ effects of substituents in acyclic systems are not readily interpretable. These effects tend to be larger in cyclic systems and, in some instances, appear capable of providing stereochemical information. Lippmaa and his co-workers have recently reported the ^{13}C shieldings for an extensive series of monosubstituted cyclohexanes (133) and adamantanes (134) which shed light on the behavior of δ effects. In the former series, the δ-carbon (C-4) is consistently shielded, relative to cyclohexane, for a wide variety of substituents,



and the upfield shift is as large as 2 ppm. Although the monosubstituted cyclohexanes are equilibrium mixtures of two chair conformations, the major species is the equatorial conformer. Consequently the substituent is at a maximum separation from the δ-carbon much of the time and it seemed unlikely that δ effects have any steric component. Supporting

evidence for this was given by the data for 2-chloro- and 2-hydroxy-adamantane (128), each of which has two carbons in the δ position but



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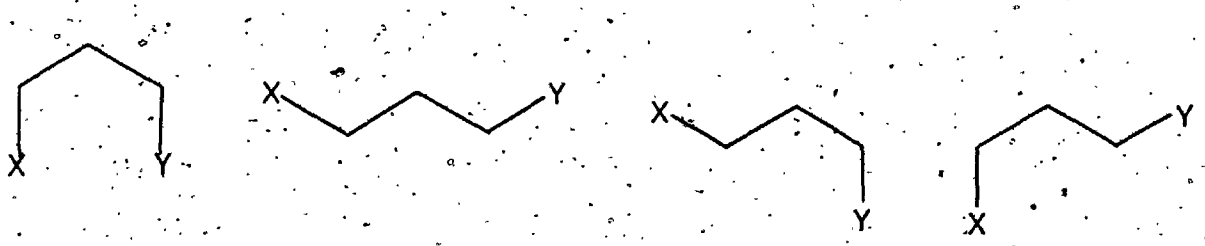
each is oriented differently with respect to the substituent. The two orientations are exactly analogous to those for C-4 in axial and equatorial monosubstituted cyclohexanes. In each of these 2-adamantane derivatives, the δ-carbons have identical shieldings tending to confirm the absence of a significant steric contribution. In fact, nuclei separated by four bonds can exist in orientations in which the nonbonded internuclear distances are comparable to or shorter than those for the γ gauche rearrangement. In general, substituent effects operative through one, two, and three bonds (the α, β and γ effects) dominate but the overwhelming majority of the model systems either lack cases in which syn-axial interactions occur or, in acyclic systems, these represent minor contributions to the observed δ effects because more favorable orientations are available. Notable exceptions to the latter were examined in the first ^{13}C study of molecular asymmetry effects (127), these results indicated that the downfield shift exhibited by one of the methyl carbons in a series of isopropylcarbinols was due to a 1,5 $CH_3—CH_3$ interaction, a δ effect. A systematic study, therefore,

seemed warranted to include examples having different orientations of neighboring δ-nuclei. Cyclic and bicyclic systems are intrinsically better models to establish the existence of such effects, since compounds incapable of conformational interconversion may be selected. To this end, a series of monocyclic and bicyclic compounds were chosen and prepared to determine the variation of methyl carbon shieldings for different orientations of a δ-CH_3 or -OH group. In general, two groups separated by four bonds can adopt a variety of orientations; four possibilities can be drawn, 129 - 132. Of these, the syn-axial



129 130 131 132

129 with either or both X and Y = C is particularly interesting since the separation of X and Y is comparable to that of γ gauche interactions. The results demonstrated that the syn-axial orientation 129 of neighboring δ-nuclei produces appreciable downfield shifts (δ effect) as large as 6.6 ppm. This finding is in striking contrast to the general trend for gauche interactions and clearly violates the general premise which associate steric crowding with upfield shifts.

The shielding and deshielding effects arising from the nonbonded interactions between two nuclei may depend on the number of bonds between them. It seems that there may be an alternation along an alkyl chain

such that a ε steric interaction is a shielding effect and a γ interaction is deshielding. To test this hypothesis, some model compounds were prepared which have ε steric interactions between the two methyl groups. The results show that ε interactions can be either shielding or deshielding. This unusual trend shows that interpretations of the ^{13}C spectra of complex systems in which small shielding differences occur must be approached cautiously. Particular care will be needed in the study of conformational changes in large molecules such as biopolymers.

(B) THE ^{13}C SPECTRA OF SEVERAL BICYCLO(2.2.1)HEPTANOLS AND THEIR ACETATES

(a) RESULTS

The ^{13}C shieldings for some mono-, di- and tri-methylnorbornanols examined in this study are listed in Tables 5.1 and 5.2. The parent norbornan-2-ols, 1-methyl- and 3-methyl-norbornan-2-ols, borneol, isoborneol and endo-fenchol have been examined previously (34, 38, 118, 134, 135). In general, the agreement between the various sets of data is reasonable in view of the different referencing methods employed. For comparison with our results, those reported relative to CS_2 (34) were converted to the TMS scale using the factor of 192.8 ppm. The present results tend toward higher field than the earlier data, by approximately 0.5 ppm, indicating the existence of small but significant solvent effects rather than arising from calibration differences. One exception is the methyl carbon shielding for exo-3-methyl-exo-2-norbornanol reported by Roberts' group at 6.5 ppm lower field than our result. There is little doubt that the value reported earlier is incorrect because the hydroxyl group is almost eclipsed with the methyl group and should shift this methyl carbon upfield relative to the methyl carbon (17.4 ppm) in exo-2-methylnorbornane. Our assignments for the norbornanols agree well with those of Lippmaa et al.(38) except for the reversal of the C-3 and -7 signals for endo-2-norbornanol. The hydroxyl substituent effects in the norbornyl skeleton obtained from these assignments may be used for predicting the carbon shieldings of other norbornanol derivatives and the estimated shieldings agree well with the experimetnal results.

Assignments for the other methylnorbornanol derivatives followed from the results from off-resonance decoupled spectra together with the

Table 5.1

^{13}C Shieldings[a] of Some Monomethylnorbornanols

Substitution		C-1	C-2	C-3	C-4	C-5	C-6	C-7	Me
Me	2-OH								
--	exo	44.2	74.7	42.2	35.4	28.1	24.4	34.4	
--	endo	42.5	72.9	37.4	37.2	29.9	20.0	37.6	
1	exo	47.4	77.3	43.1	35.9	30.0	33.1	40.1	16.1
		(-4.1)	(-4.4)	(-3.6)	(-0.9)	(0.7)	(1.7)	(-1.2)	
1	endo	47.8	77.6	40.6	36.8	31.3	26.9	44.4	18.4
		(-2.0)	(-2.3)	(-0.3)	(-1.8)	(-0.1)	(-0.1)	(-0.1)	
endo-3	exo	45.4	81.5	46.6	40.9	21.0	25.0	36.5	15.0
		(-0.2)	(-1.0)	(0.0)	(0.1)	(0.4)	(0.0)	(0.2)	
exo-3	endo	43.2	81.8	45.8	43.8	30.1	19.4	34.4	20.1
		(0.1)	(-1.2)	(-0.4)	(-0.1)	(-0.2)	(0.3)	(0.3)	
exo-3	exo	44.8	76.5	43.2	42.8	29.2	24.6	31.9	13.4
		(0.0)	(-8.4)	(-5.8)	(0.7)	(0.7)	(1.1)	(1.0)	
endo-3	endo	43.5	72.2	36.5	42.2	21.8	19.7	36.7	10.2
		(-0.4)	(-9.5)	(-7.3)	(-0.4)	(-0.6)	(-0.9)	(-2.8)	
exo-5	exo	44.8	74.1	42.5	42.0	34.9	34.3	30.7	21.9
		(0.0)	(0.3)	(-0.1)	(-0.1)	(0.0)	(-0.3)	(-0.2)	
endo-5	exo	45.5	74.6	34.8	40.7	32.4	33.3	36.2	16.9
		(-0.1)	(0.7)	(0.4)	(-0.1)	(-0.1)	(0.1)	(-0.1)	
exo-6	exo	51.1	74.6	41.3	35.7	38.1	31.3	31.2	21.4
		(0.2)	(-0.5)	(0.0)	(-0.3)	(-0.2)	(0.1)	(0.3)	
endo-6	exo	49.4	69.0	42.9	36.8	36.8	31.5	36.5	16.9
		(-0.2)	(1.8)	(0.1)	(0.0)	(-0.1)	(2.7)	(0.2)	
exo-5	endo	43.0	72.1	40.3	43.5	36.3	30.2	34.1	22.4
		(-0.1)	(0.1)	(0.5)	(-0.4)	(-0.4)	(0.0)	(0.0)	
endo-5	endo	43.7	73.3	31.5	42.7	34.3	27.6	39.5	16.3
		(-0.2)	(-0.2)	(-0.4)	(0.1)	(0.0)	(-1.2)	(-1.6)	
exo-6	endo	49.2	72.8	38.5	37.8	40.0	25.3	34.3	21.8
		(0.0)	(-0.5)	(0.0)	(0.1)	(-0.1)	(-1.5)	(0.2)	
endo-6	endo	47.0	76.4	39.4	39.1	37.9	35.4	40.0	19.4
		(-0.9)	(11.0)	(-8.6)	(0.5)	(-0.8)	(11.0)	(0.7)	
anti-7	exo[b]	48.5	75.4	43.4	39.5	25.3	22.2	39.6	11.9
		(0.1)	(-0.2)	(0.3)	(-0.1)	(0.1)	(0.7)	(-0.4)	
syn-7	exo[b]	48.1	76.1	37.2	39.9	28.8	26.6	43.8	13.7
		(-0.3)	(4.3)	(-2.2)	(0.3)	(-0.2)	(1.3)	(3.8)	
endo-2	exo	49.3	77.9	48.7	37.0	27.9	24.0	37.4	25.8
		(-0.3)	(-1.2)	(-3.3)	(0.2)	(-0.8)	(7.1)	(1.1)	
exo-2	endo	48.4	77.2	47.0	37.3	28.3	22.0	38.7	30.4
		(-0.8)	(-2.5)	(-2.6)	(-0.5)	(-0.7)	(1.6)	(4.6)	

[a] In ppm. from internal TMS in $CDCl_3$ solutions. Values in parentheses are $(\delta_C^{obsd.} - \delta_C^{calc.})$, where $\delta_C^{calc.}$ were obtained by assuming simple additivity of substituent effects (see text).

[b] From ref. (130).

Table 5.2

^{13}C Shielding[a] of Some Di- and Trimethylnorbornanols

Substitution		C-1	C-2	C-3	C-4	C-5	C-6	C-7	Me	
Me	2-O-								5-Me	6-Me
exo-5-exo-6	exo	52.9	74.8	42.5	43.5	38.5	34.5	28.4	(15.4)	(15.3)
		(0.5)	(0.0)	(0.2)	(-0.1)	(0.1)	(0.2)	(-0.4)		
	endo	50.7	72.7	40.2	45.2	40.2	28.9	31.6	(15.8)	(15.2)
		(0.0)	(0.3)	(0.7)	(-0.2)	(0.0)	(-1.4)	(0.4)		
endo-5-exo-6	exo	52.4	74.8	34.3	(11.5)	(42.7)	(40.7)	33.4	15.5	20.2
		(0.1)	(0.6)	(0.5)	(0.0)	(-0.2)	(0.7)	(0.4)		
	endo	50.2	73.2	30.9	43.5	44.6	33.4	36.4	14.8	20.6
		(0.4)	(0.4)	(0.1)	(0.2)	(0.3)	(-2.2)	(0.2)		
exo-5-endo-6	exo	50.5	69.0	43.4	(43.4)	(43.9)	(41.7)	33.2	20.9	15.5
		(0.2)	(2.7)	(0.5)	(0.1)	(0.2)	(2.9)	(0.2)		
	endo	47.9	75.8	40.8	(45.2)	(45.8)	(44.3)	36.2	21.2	17.7
		(-0.7)	(11.3)	(0.7)	(0.1)	(0.3)	(9.9)	(0.0)		
endo-5-endo-6	exo	51.2	69.0	35.2	42.4	33.3	33.3	35.9	(11.8)	(11.3)
		(0.2)	(2.1)	(0.8)	(0.2)	(0.0)	(3.7)	(0.1)		
	endo	48.2	76.2	31.1	43.8	(35.1)	(35.5)	38.8	11.6	14.2
		(-1.1)	(11.1)	(0.5)	(0.2)	(0.0)	(10.3)	(-0.2)		
									1-Me	7-Me
1-anti-7[b]	exo	48.6	78.3	42.2	40.4	30.4	27.4	42.3	13.8	10.0
		(-3.0)	(-4.3)	(0.5)	(-0.2)	(0.6)	(-0.2)	(1.1)		
	endo	49.4	78.5	40.2	41.6	28.5	24.0	46.6	16.1	10.5
		(-0.5)	(-2.4)	(1.3)	(0.8)	(-3.1)	(0.8)	(0.0)		
1-syn-7[b]	exo	48.1	78.3	40.6	41.1	28.6	35.3	47.3	14.1	11.4
		(-3.2)	(0.4)	(-3.3)	(0.5)	(1.0)	(2.9)	(3.9)		
	endo	48.4	76.1	38.3	41.2	29.7	28.6	49.5	16.2	10.1
		(-1.5)	(0.0)	(-2.8)	(-1.2)	(0.3)	(0.6)	(2.9)		
7,7	exo	51.4	77.6	41.9	44.4	27.5	25.7	45.7		22.2
										22.4
1,7,7	exo	46.3	79.7	40.5	45.1	27.3	34.0	48.9	11.4	20.2(syn)
										20.5(anti)
	endo	49.5	77.2	39.0	45.2	28.3	26.0	48.0	13.3	18.7(syn)
										20.2(anti)
										3-Me
3,3[b]	exo	46.3	83.9	42.8	48.0	25.1	23.9	35.2		23.2(exo)
		(0.1)	(-7.9)	(-6.2)	(1.3)	(2.1)	(0.9)	(0.9)		26.2(endo)
	endo	44.1	80.5	38.0	48.4	24.7	18.3	33.9		30.6(exo)
		(-0.4)	(-9.5)	(-8.2)	(-0.1)	(-0.1)	(-0.3)	(-3.6)		20.2(endo)
1,3,3	exo	49.1	86.2	43.5	48.4	25.6	33.8	40.9	17.1	23.1(exo)
										26.3(endo)
	endo	49.2	83.1	39.1	48.0	26.2	25.2	41.1	19.5	30.8(exo)
										20.2(endo)
									6-Me	
3,3-exo-6	endo	51.1	80.6	37.4	49.3	34.8	24.1	29.7	21.7	30.6(exo)
										19.7(endo)
3,3-endo-6	endo	48.6	83.9	37.4	49.5	33.2	31.8	35.6	18.9	31.1(exo)
										20.0(endo)
6,6	endo	52.7	76.1	37.1	38.3	47.8	33.2	37.2	33.2(exo)	
									28.8(endo)	

[a] In ppm from internal TMS in $CDCl_3$ solutions. Values in parentheses are ($\delta_C^{obsd.} - \delta_C^{calc.}$), where $\delta_C^{calc.}$ was obtained by assuming simple additivity of substituent effects (see text).

[b] From ref. (133)

expected trends for methyl and hydroxyl substitution in the norbornyl skeleton (see Table 5.3). In this way, consistent assignments were obtained for the whole series. Differences between the estimated and observed ring carbon shieldings for most of the methyl substituted norbornanols were listed in Tables 5.1 and 5.2. Major deviations occur only for the methine and quaternary carbons bearing substituent groups which have steric interactions with other substituents. For example, if the methyl group is eclipsed or nearly so with another vicinal substituent i.e. a γ interaction, pronounced upfield shifts are found for the carbons attached to the substituent groups. If two substituents separated by four bonds have a syn-axial orientation, the carbons attached to these substituents exhibit pronounced down-field shifts.

The 3,3,6-trimethyl-endo-2-norbornanols were obtained by the reduction of the 3,3,6-trimethylnorcamphors with $LiAlH(OMe)_3$. The assignments given in Table 5.2 were obtained by a comparison of the observed shieldings with those estimated by combining the data for the 6-methyl-endo-2-norbornanols and 3,3-dimethyl-endo-2-norbornanol (130) (Figure 5.1). For each carbon in 3,3-exo-6-trimethyl-endo-2-norbornanol, the agreement is good while the deviations for the endo-6-methyl isomer are larger especially for C-3, -4, -5, -6 and the methyl carbons.

The assignments for norborneol and isonorborneol have been unequivocally determined by shift reagent studies (136, 137).

A series of norbornyl acetates was also included in this study and their ^{13}C shieldings are shown in Table 5.4. These are useful not only for aiding the signal assignments for some of norbornanol derivatives but these also provide interesting substituent effects (see Table 5.5)

Table 5.3

Substituent Effects[a] of Methyl and Hydroxyl Groups on the Skeletal Shielding of Bicyclo(2.2.1) Systems

Substituent	Orientation	α	β		γ			δ	Ref.
		C-2	C-1	C-3	C-4	C-6	C-7	C-5	
2-Methyl	exo	6.8	6.7	10.2	0.6	0.4	-3.5	-0.9	
	endo	4.4	5.4	8.8	1.4	-7.5	1.9	0.6	
2,2-Dimethyl		6.8	11.3	17.1	2.0	-5.1	-0.1	-1.4	
2-Hydroxyl	exo	45.1	7.9	12.6	-0.9	-5.2	-3.9	-1.5	
	endo	43.3	6.2	9.8	0.9	-9.6	-0.7	0.3	

	C-1	C-2	C-7	C-3	C-4
1-Methyl	7.3	7.0	6.9	1.5	1.4

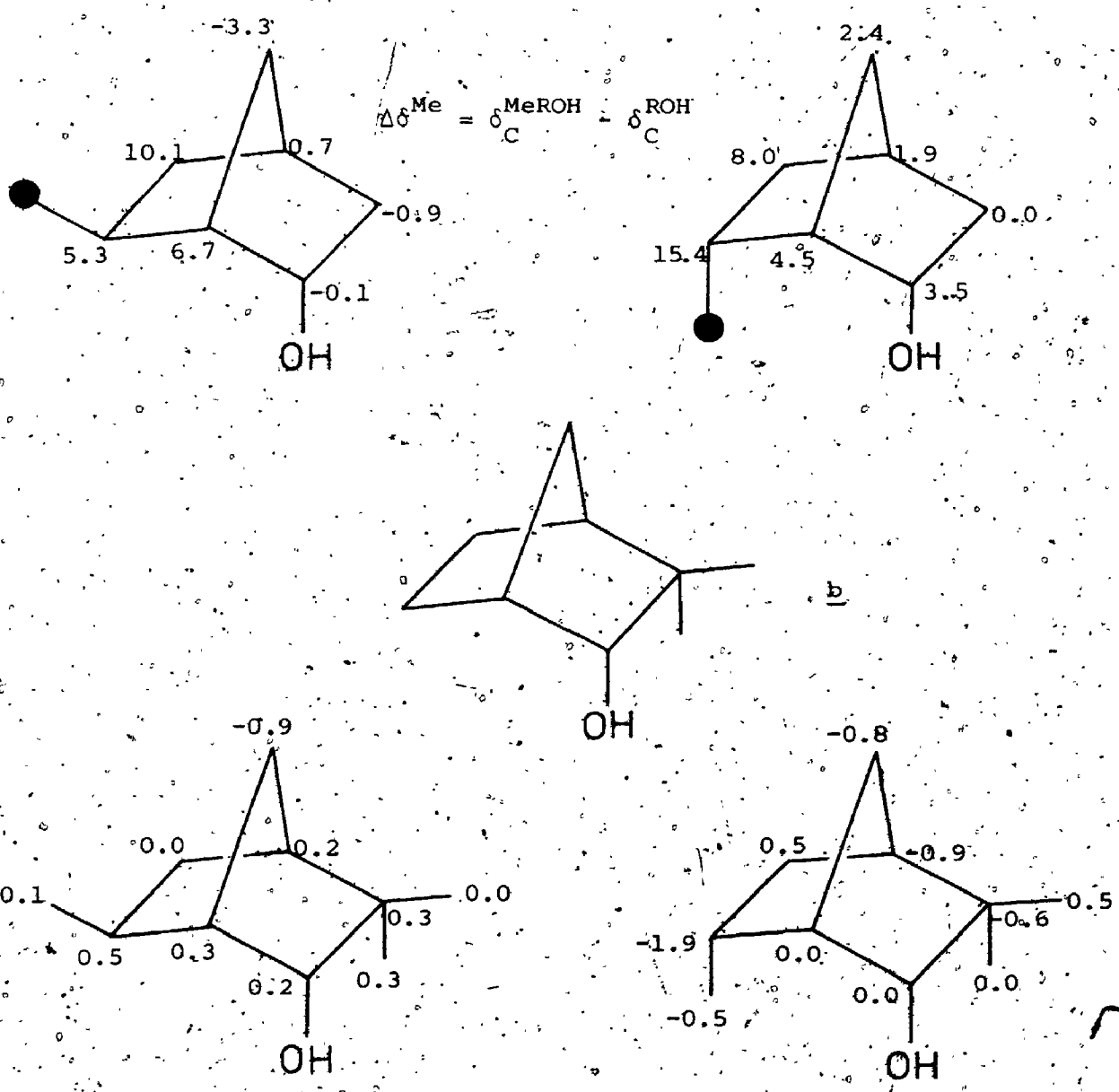
	C-7	C-1	C-2,3	C-5,6
7-Methyl	5.6	4.2	-2.9[b]	0.9[c]

	C-1	C-7	C-2	C-4	C-6	C-3	C-5
1,7-Dimethyl	7.4	9.0	3.2[b]	5.2	8.0[c]	1.7[b]	-0.5[c]

[a] $\Delta\delta^X = \delta_C^{RX} - \delta_C^{RH}$, where RH = hydrocarbon, in ppm. Positive values indicate downfield shifts.
[b] *syn* with respect to the 7-methyl. [c] *anti* with respect to the 7-methyl.

Figure 5.1

Difference[a] Between Observed and Estimated ^{13}C Shieldings in 3,3,6-Trimethyl-endo-2-norbornanols.



[a] Values in 3,3,6-trimethyl-endo-2-norbornanols are ($\delta_C^{obs.} - \delta_C^{calcd.}$) in ppm where $\delta_C^{calcd.} = \delta_C^{b} + \Delta\delta_C^{Me}$.

[b] endo-3,3-dimethyl-norbornan-2-ol.

Table 5.4

^{13}C Shieldings[a] of Some Bicyclo(2.2.1)heptyl acetates

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	Me	OAc-	
									Me	C=O
exo-2-OAc	41.6	77.5	39.7	35.5	28.3	24.4	35.3		21.2	
exo-5-Me-exo-2-OAc	41.8	76.9	39.8	41.9	34.6	34.1	31.6	21.8	21.3	
exo-6-Me-exo-2-OAc	48.0	77.3	38.7	35.8	38.2	31.2	31.9	21.3	21.3	
endo-5-Me-exo-2-OAc	42.8	77.5	32.7	40.8	32.3	33.3	37.0	16.9	21.3	170.5
endo-6-Me-exo-2-OAc	46.7	73.3	40.5	36.8	36.8	31.7	37.3	16.9	21.4	170.4
exo-5-endo-6-Me_2-exo-2-OAc	47.7	73.2	40.8	43.2	44.1	41.7	34.0	20.9 15.5	21.4	170.8
endo-2-OAc	40.4	75.7	(37.1)	36.7	29.5	21.0	(37.0)		21.0	
exo-5-Me-endo-2-OAc	40.7	75.6	37.5	42.8	35.9	31.1	33.8	22.2	21.1	
exo-6-Me-endo-2-OAc	46.7	75.4	35.9	37.1	39.5	26.3	33.8	21.6	21.1	

[a] In ppm from internal TMS in $CDCl_3$ solutions.

Table 5.5

Substituent Effects[a] of the Acetyl Group in Norbornyl Acetates

Substitution	β	γ		δ			ε	
	C-2	C-1	C-3	C-4	C-6	C-7	C-5	Me
exo-2-OAc	2.8	-2.6	-2.5	0.1	0.0	0.9	0.2	
exo-5-Me-exo-2-OAc	2.8	-1.9	-2.7	0.1	-0.2	0.9	0.0	-0.1
exo-6-Me-exo-2-OAc	2.7	-3.1	-2.6	0.1	0.1	0.7	0.1	-0.1
endo-5-Me-exo-2-OAc	2.9	-2.7	-2.1	0.1	0.0	0.8	-0.1	0.0
endo-6-Me-exo-2-OAc	4.3	-2.7	-2.4	0.0	0.2	0.8	0.0	0.0
exo-5-endo-6-Me_2-exo-2-OAc	4.2	-2.8	-2.6	-0.2	0.0	0.8	0.2	0.0
								0.0
endo-5-exo-6-Me_2-exo-2-OAc	2.7	-3.1	-2.6	0.0	-0.2	0.7	0.3	0.0
								-0.1
endo-2-OAc	2.8	-2.1	-2.3	-0.5	1.0	-0.6	-0.4	
exo-5-Me-endo-2-OAc	3.5	-2.3	-2.8	-0.7	0.9	-0.3	-0.4	-0.2
exo-6-Me-endo-2-OAc	2.6	-2.5	-2.6	-0.8	1.0	-0.5	-0.5	-0.2

[a] $\Delta\delta = \delta_C^{ROCOMe} - \delta_C^{ROH}$, in ppm. Positive values indicate downfield shifts.

and could be used for stereochemical assignments.

(b) DISCUSSION

Several acyclic (33, 138, 139) and alicyclic alcohols (33, 140-142) have been examined to determine the influence of the hydroxyl group on the alkyl carbon shieldings. The trends permitted both stereochemical and signal assignments for related systems. In general, the hydroxyl group deshields the carbon to which it is bonded and its immediate neighbors; these have been termed α and β effects, respectively. Carbons three and four bonds removed from the oxygen atom tend to experience upfield shifts. With the most pronounced effects found for gauche γ carbons. More remote carbons are expected to be little affected by the hydroxyl group and this feature has been characterized in a series of trans-decanols and steroids (131).

By comparison of the ^{13}C shieldings of the parent norbornanols with the corresponding hydrocarbons, a set of hydroxyl substituent effects was obtained. These values and those for methyl substituent effects in the norbornyl skeleton are listed in Table 5.3. It is interesting that the β effects differ at the tertiary C-1 and secondary C-3 centers and also depend on the geometry of the hydroxyl group. A series of methyl substituted norbornyl derivatives having a variety of γ interactions between vicinal methyl groups has been discussed in detail in Chapter 4. The observed shifts for the methyl carbons were considered in terms of the dihedral angle relating the vicinal nuclei. The methyl shieldings for the norbornanol series display the same trend; the results are summarized in Table 5.6.

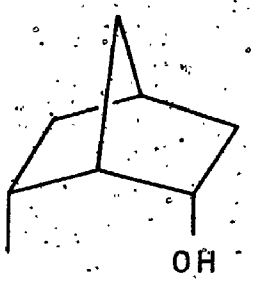
Table 5.6

γ Methyl Substitution Effect Between Vicinal Methyl Groups in Norbornanols

Substitution		$\Delta\delta$[a]		
Me	2-OH	0-15°	~120°	~60°
endo-5-endo-6	endo	-4.7(5-Me)		
		-5.2(6-Me)		
	exo	-5.1(5-Me)		
		-5.6(6-Me)		
endo-5-exo-6	endo		-1.5(5-Me)	
			-1.6(6-Me)	
	exo		-1.4(5-Me)	
			-1.2(6-Me)	
exo-5-endo-6	endo		-1.2(5-Me)	
			-1.2(6-Me)	
	exo		-1.0(5-Me)	
			-1.4(6-Me)	
exo-5-exo-6	endo	-6.6(5-Me)		
		-6.6(6-Me)		
	exo	-6.5(5-Me)		
		-6.1(6-Me)		
1-syn-7	endo			-2.2(1-Me)
	exo			-2.0(1-Me)
				-2.3(7-Me)
1-anti-7	endo			-2.3(1-Me)
	exo			-2.2(1-Me)
				-1.9(7-Me)

[a] $\Delta\delta = \delta_C^{Me}(RMe_2) - \delta_C^{Me}(RMe)$, in ppm. Negative values indicate upfield shifts. Dihedral angles between vicinal methyl groups are estimated from ref. (123).

Furthermore, this series also permits characterization of the interactions between hydroxyl and methyl groups separated by four bonds. Four different arrangements occur in this series of compounds. These various δ effects, $\delta_c^{Me}(ROH) - \delta_c^{Me}(RH)$, are listed in the Table 5.7. Of these only the syn-axial interaction would be expected to have a significant steric component and it is clear that a syn-axial hydroxyl group deshields a methyl carbon appreciably (1.0 to 2.4 ppm). For example, endo-6-methyl-endo-2-norbornanol (133) which has an syn-axial arrangement of the CH_3 and OH groups exhibits a 2.0 ppm downfield shift of the methyl absorption relative to that of endo-2-methylnorbornane. It is interesting that both methyl carbons in 6,6-dimethyl-endo-2-norbornanol (134) exhibit a 1.6 ppm



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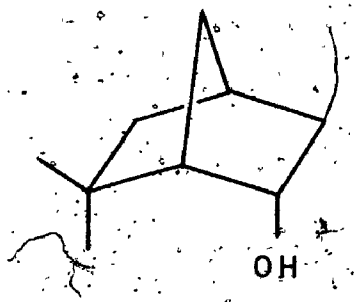

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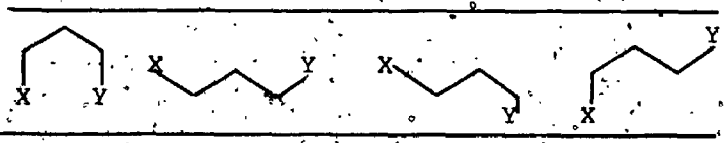
downfield shift relative to those in 2,2-dimethylnorbornane (34). The carbinyl carbon and the methine carbon bonded to the methyl group in norbornanols having a syn-axial CH_3 —— OH interaction experience appreciable downfield shifts of 2.2 - 5.4 ppm downfield shifts relative to their absorptions in the corresponding compounds lacking this arrangement.

Similarly, the syn-7-methyl carbon in syn-7-methyl-exo-2-norbornanol (135), syn-1,7-dimethyl-, 1,7,7-trimethyl- and 7,7-dimethyl-exo-2-

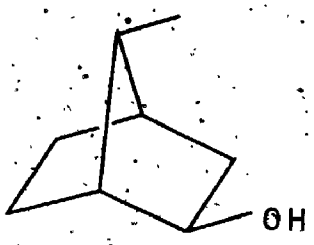
Table 5.7

δ Hydroxyl Substituent Effect[a] Between Methyl and Hydroxyl Groups

Substitution X	Substitution Y	$\Delta\delta_C$ 
Me	2-OH	
endo-6	endo	2.0
exo-6	exo	-0.9
exo-6	endo	-0.5
endo-6	exo	-0.5
endo-5-endo-6	endo	2.4
exo-5-endo-6	endo	1.8
exo-5-exo-6	exo	-0.4
endo-5-exo-6	exo	-0.9
exo-5-exo-6	endo	-0.5
endo-5-exo-6	endo	-0.5
endo-5-endo-6	exo	-0.5
exo-5-endo-6	endo	-0.4
3,3-endo-6[b]	endo	1.5
3,3-exo-6[b]	endo	-0.6
6,6	endo	1.6 (endo)
		1.6 (exo)

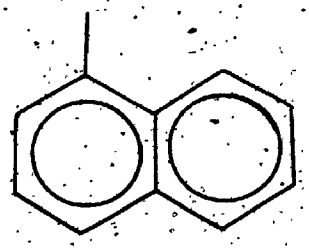
a $\delta_C^{Me}(ROH) - \delta_C^{Me}(RH)$, in ppm. Positive values denote downfield shifts.

b $\delta_C^{Me}(ROH) - \delta_C^{Me}$(2-methylnorbornanes).

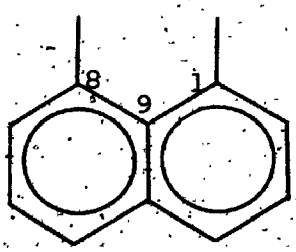


135

norbornanol exhibit a downfield shift of ca. 1 ppm relative to the shieldings in the corresponding hydrocarbons or ketones. These δ effects are smaller (see Table 5.8) than those found for syn-axial interactions between endo-6-methyl and endo-2-hydroxyl groups presumably because the distance between the endo-6-methyl and endo-2-hydroxyl is smaller than those between a syn-7-methyl and a exo-2-hydroxyl group. It is of interest to examine the methyl shieldings in a more rigid system and one may predict from the foregoing results that the deshielding effect will be enhanced. This was substantiated by the methyl shieldings for 1-methylnapthalene (δ_c 19.2) (136) and 1,8-dimethylnapthalene (δ_c 25.8) (137). The introduction of the second methyl in the peri position (δ)



136



137

causes a 6.6 ppm downfield shift. Recently the x-ray crystal structure of 1,8-dimethylnaphthalene has been published (143). The molecule is

Table 5.8

δ Hydroxyl Substitution Effects[a] Between Methyl and Hydroxyl Groups

Substitution		Δδ[a]			
X	y				
Me	2-OH				
syn-7	exo	1.0			
anti-7	exo				-0.8
1-syn-7	exo	0.7			
1-anti-7	endo		-0.2		
1-syn-7	endo			-0.6	
1-anti-7	exo				-0.7
7,7[b]	exo	1.0			
		1.2			
1,7,7-	exo	1.0(syn)			
		1.3(anti)			
1,7,7	endo			-0.5(syn)	
				1.0(anti)	

[a] $\delta_C^{Me}(ROH) - \delta_C^{Me}(RH)$, in ppm. Positive values denote downfield shifts.

[b] $\delta_C^{Me}(ROH) - \delta_C^{Me}$(7,7-dimethylnorcamphor).

planar, but steric interactions between the methyl groups cause considerable angular distortion i.e. the $C_1 - C_9 - C_8$ angle is 125.2°, and the $C_1 - C_8$ internuclear distance is 2.92 Å.

It is interesting that exo-6-methyl-exo-2-norbornanol, which has the trans-trans arrangement 130 with the CH_3 and OH groups at a maximum separation, exhibits an upfield shift of the methyl absorption (-0.9 ppm) relative to exo-2-methylnorbornane. Similarly, the exo-6-methyl carbons in exo,exo-5,6-dimethyl- and endo,exo-5,6-dimethyl-exo-2-norbornanol show the same trend.

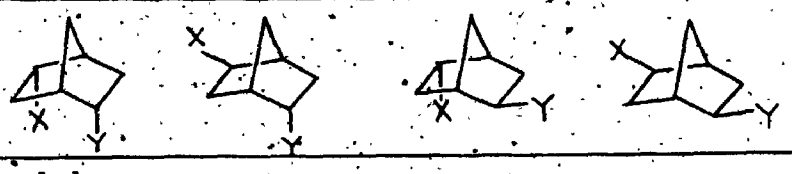
In any event, syn-axial effects are largest and most distinct. This deshielding influence is in direct contrast to the trend normally associated with sterically crowded carbons and of the possible arrangements 129 - 132 for δ groups these are closest in 129. Clearly, the interpretation relating steric crowding with upfield shifts through steric polarization of the bonds of the interacting nuclei is inadequate to account for these syn-axial effects.

The results in Table 5.9 show that even more remote methyl carbons are slightly affected by a hydroxyl group. It seems reasonable to attribute this ε effect to slight geometrical alterations of the norbornyl skeleton. In two examples having the geometry in which the methyl and hydroxyl groups are syn to each other and separated by five bonds, the methyl carbon exhibits an upfield shift of ca. 1.1 ppm relative to that for the corresponding hydrocarbons.

Carbons near hydroxyl groups can be readily identified from the shielding change attendant upon acetylation. This approach has been used by Roberts et al (29) for the assignments of carbons near the hydroxyl

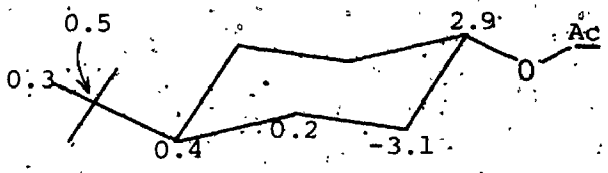
Table 5.9

ε Hydroxyl Substitution Effect[a] Between Methyl and Hydroxyl Groups

Substitution X	Substitution Y	Δδ 
Me	2-OH	
endo-5	endo	-1.1
exo-5	endo	0.1
endo-5	exo	-0.5
exo-5	exo	-0.4
endo-5-endo-6	endo	-0.2
endo-5-exo-6	endo	-1.1
exo-5-exo-6	endo	0.1
exo-5-endo-6	endo	0.1
endo-5-endo-6	exo	0.0
endo-5-exo-6	exo	-0.4
exo-5-exo-6	exo	-0.3
exo-5-endo-6	exo	-0.2

[a] $\delta_C^{Me}(ROH) - \delta_C^{Me}(RH)$, in ppm. Positive values denote downfield shifts.

center in a series of steroids. The characteristic shifts of the acetoxyl group through the cyclohexane skeleton (138 & 139) are shown below.



138

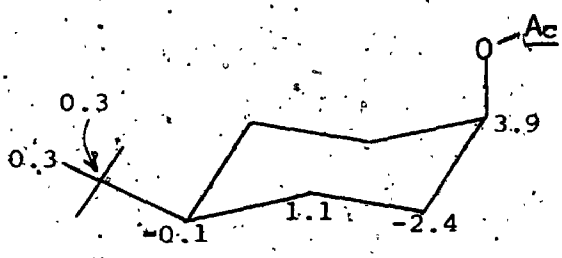


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Table 5.5 lists the shifts which occur on acetylation of the exo- and endo-2-norbornanol derivatives. The downfield shift of the carbinol carbon may be the result of the greater electron-withdrawing power of the acetoxyl group while the upfield shift of C-1 and -3 result from γ interactions with the acetoxyl group. It is interesting that exo- and endo-acetoxyl groups deshield the C-7 and -6 carbon, respectively, by ca. 1 ppm, which can be regarded as a δ effect. Steric perturbations due to a 2-acetoxyl group can be expected at C-6 by an endo group and at C-7 by an exo-group. Although the magnitude of these δ-effects is small, it may be helpful for stereochemical assignments.

(C) THE ^{13}C SPECTRA OF SEVERAL BICYCLO(2.2.2)OCTANE DERIVATIVES

(a) INTRODUCTION

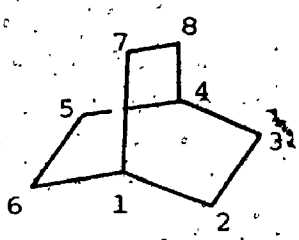
As an extension of our examination of the effects of molecular geometry on ^{13}C shieldings we have obtained the spectra of a series of bicyclo(2.2.2)octane derivatives for comparison with the results for other bicyclic systems (see Chapter 4 and Chapter 5). In earlier parts of this series, we have examined in some detail the shielding variations produced by γ and δ interactions between two substituents in several bicyclo(2.2.1)heptanes. In these systems, however, it is conceivable that ring strain may contribute to the observed shifts. Since the bicyclo(2.2.2)octane skeleton is less strained, by 4-6 kcal/mole according to molecular mechanics (144) a comparison of the corresponding interactions could reveal differences ascribed to strain effects. The bicyclo(2.2.2)octane skeleton permits the examination of three different vicinal interactions having dihedral angles of 0°, 60°, and 120°; assuming D_{3h} symmetry. Substituted bicyclooctanes, of course, may assume D_3 symmetry, to reduce vicinal interactions but it is difficult to estimate the maximum degree of twist. For the parent hydrocarbon, molecular mechanics and spectroscopic data point to the higher symmetry (145), while an electron diffraction study indicated that the twisting point of 13° in terms of the twist angle (124). It was concluded that the potential probably has a low hump at the D_{3h} position so the molecule was described as "quasi-D_{3h}". Possibly in substituted cases, skeletal twist can exceed that for disubstitutednorbornanes, which may be as large as 14° (122), but it seems reasonable to assume that vicinal substituents at C-2 and C-3 would have similar mutual orientations in

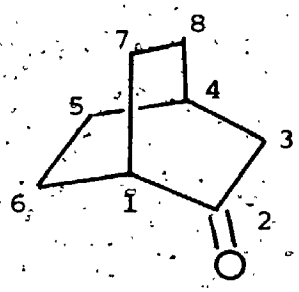
each of these bicyclic systems. Thus, several 2,3-disubstituted examples have been prepared for comparison. Also, a number of systems having syn-axial (129) arrangements of 2,6-substituents were synthesized. These compounds provide several examples of methyl-methyl and methyl-hydroxyl interactions for substituents separated by three and four bonds for all of these compounds, therefore, allow detailed comparisons for an array of substitution patterns in the bicyclo(2.2.2)octane and norbornone systems.

(b) RESULTS

The ^{13}C shielding data for this series of model compounds 140 - 173 are collected in Tables 5.10, 5.11 and 5.12. In each case, both noise and off-resonance decoupled spectra were obtained to distinguish between carbon types, the first step for the assignments. The assignments for the carbonyl, olefinic and carbinyl carbons presented no problems on the basis of the observed shieldings. The assignments for two olefinic carbons in 144 and 145 followed from the results for 74, 147 and 148. The shielding difference between the C-6 carbon in exo-2-OH-167 and endo-2-OH-168 is ca. 3 ppm. On this basis, the olefinic carbon assignments for 162 - 166 were completed.

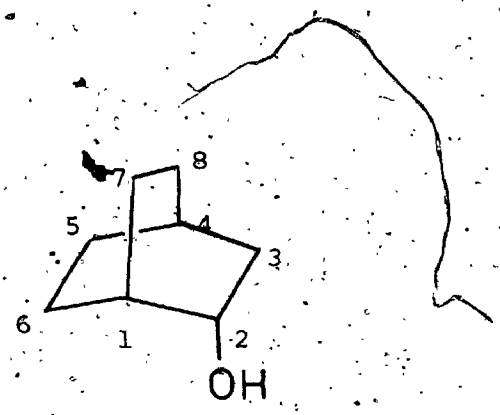
The methine carbons in 144 - 146, 162 and 163 were readily identified because the lower field signals are deshielded by the nearby methyl or hydroxyl group, i.e. α and β-substituent effects of methyl and hydroxyl groups are the deshielding effect (8-10). The methylene signals were assigned by the expected trends arising from methyl and hydroxyl substitution. From the carbon shieldings of the 2-methylbicyclo-

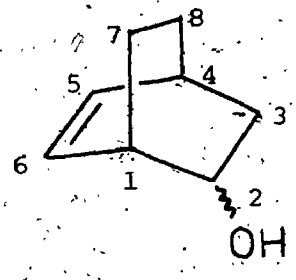




72	Nil
140	2-Me
141	2,2-Me_2
142	cis-2,3-Me_2
143	trans-2,3-Me_2
74	Δ^2
144	Δ^2-exo-5-Me
145	Δ^2-endo-5-Me
146	Δ^2-5,5-Me_2
147	Δ^2-trans-5,6-Me_2
148	Δ^2-endo,endo-5,6-Me_2

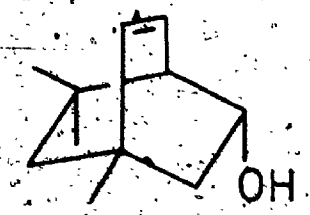
108	3-Me
42	3,3-Me_2
149	endo,endo-5,6-Me_2
150	anti-3-endo,cis-5,6-Me_3
151	syn-3-endo,cis-5,6-Me_3
152	3,3-endo,cis-5,6-Me_4



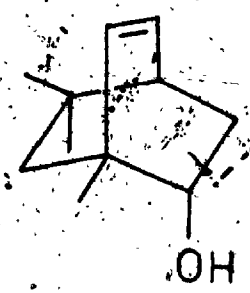


153	Nil	162	exo-2-OH
154	4-Me	163	endo-2-OH
155	cis-3-Me	164	3,3-Me_2-exo-2-OH
156	trans-3-Me	165	3,3-Me_2-endo-2-OH
46	3,3-Me_2		
157 *	syn,cis-5,6-Me_2		
158 *	anti,cis-5,6-Me_2		
159	trans-3-syn,cis-5,6-Me_3		
160	3,3-syn,cis-5,6-Me_4		
161 *	4,6,6-Me_3		

* The author wish to thank Dr. A. K. Cheng for a sample of 146 and K. R. Stephens for samples 154, 157, 158, 161, and 166.



166



167

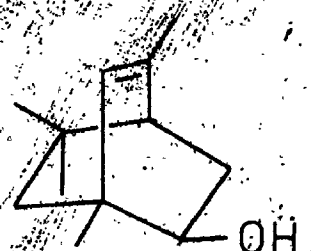


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Table 5.10

^{13}C Shieldings[a] of Some Methyl-substituted Bicyclo(2.2.2)octanes and octenes

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Me
Nil	24.0	26.1	26.1	24.0	26.1	26.1	26.1	26.1	
2-Me	30.4	30.4	35.8	25.2	26.2	20.1[b]	27.5	25.2	21.2
cis-2,3-Me_2	31.8	33.3	33.3	31.8	20.3[b]	20.3[b]	27.4	27.4	15.2
	(0.2)	(-6.8)	(-6.8)	(0.2)	(-0.2)	(-0.2)	(0.8)	(0.8)	
trans-2,3-Me_2	31.5	40.1	40.1	31.5	27.5	20.2[b]	27.5	20.2[b]	19.2
	(-0.1)	(0.0)	(0.0)	(-0.1)	(0.4)	(0.7)	(0.7)	(0.4)	
2,2-Me_2	35.1	30.6	42.7	26.5	25.1	23.4	23.4	25.1	30.9
	(-1.7)	(-4.1)	(-2.8)	(0.1)	(-0.7)	(4.4)	4.4)	(-0.2)	
Δ^2	29.5	134.1	134.1	29.5	25.8	25.8	25.8	25.8	
Δ^2 -exo-5-Me	30.8	132.9	136.4	36.0	30.4	34.9	26.4	18.9	20.5
Δ^2 -endo-5-Me	30.5	134.1	132.0	36.8	32.2	36.0	24.3	26.6	23.0
Δ^2 -endo-5-endo-6-Me_2	38.5	132.9	132.9	38.5	36.6	36.6	26.0	26.0	17.1
	(0.7)	(0.9)	(0.9)	(0.7)	(-5.8)	(-5.8)	(0.9)	(0.9)	
Δ^2 -exo-5-endo-6-Me_2	37.4	131.5	136.3	36.6	40.8	41.5	27.0	17.7	18.6(5-Me); 22.2(endo)
	(-0.7)	(0.9)	(-0.1)	(-0.4)	(0.2)	(0.2)	(-0.2)	(0.3)	
Δ^2-5,5-Me_2	35.1	131.9	136.0	41.7	33.3	42.8	23.7	21.8	30.1(exo); 32.1(endo)
	(-0.3)	(-1.0)	(1.7)	(-1.6)	(-3.5)	(-2.3)	(-1.2)	(2.1)	

[a] In ppm from internal TMS in $CDCl_3$ solutions. Values in parentheses are ($\delta_C^{obs.} - \delta_C^{calcd.}$), where $\delta_C^{calcd.}$ were calculated by assuming simple additivity of substituent effects. [b] Taken syn with respect to the Me group.

Table 5.11

^{13}C Shieldings[a] of Some Bicyclo(2.2.2)octan-2-ones

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Me
endo-5-endo-6-Me_2	50.7	216.8	39.8	35.5	32.7	34.6	23.5	26.3	14.9(5-Me)
									16.4(6-Me)
exo-3-endo-5-endo-6-	51.0	219.6	(42.0)	(41.2)	33.5	34.1	24.6	21.8	13.1(3-Me)
-Me_3 (150)	(0.3)	(-0.6)	(-0.4)	(-0.3)	(-0.5)	(0.2)	(0.3)	(0.1)	14.9(5-Me)
									16.8(6-Me)
endo-3-endo-5-endo-	50.2	220.3	47.6	41.7	34.5	36.3	22.6	29.2	15.4(3-Me)
6-Me_3 (151)	(-0.5)	(0.1)	(5.2)	(0.2)	(6.4)	(0.9)	(-0.2)	(1.6)	16.9(5-Me)
									16.3(6-Me)
3,3-endo-5-endo-6-	51.1	221.3	46.1	46.1	36.1	35.5	23.0	26.0	25.6(exo-3-Me)
Me_4 (152)	(0.1)	(-0.7)	(5.0)	(0.0)	(5.8)	(0.8)	(-0.6)	(2.1)	27.3(endo-3-Me)
									18.2(5-Me)
									16.8(6-Me)

[a] In ppm from internal TMS in $CDCl_3$ solutions. Values in parentheses are ($\delta_C^{obs.} - \delta_C^{calcd.}$), where $\delta_C^{calcd.}$ were calculated by assuming simple addivity of methyl substituent effects (see text).

Table 5.12

^{13}C Shieldings[a] of Several Methyl-substituted Bicyclo(2.2.2)octan-2-ols

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Me
2-OH	31.7	69.5	37.5	24.8	25.6	18.6[b]	23.8	24.5	
4-Me-2-OH	31.7	69.8	44.5	28.6	32.8	19.4[b]	24.2	32.0	28.0
cis-3-Me-2-OH	31.8	70.9	35.8	31.3	20.2	18.6[b]	23.7	26.5	12.8
trans-3-Me-2-OH	32.9	78.1	41.8	31.3	27.1	18.4[b]	24.1	19.7	18.6
3,3-Me_2-2-OH	33.7	77.9	35.9	36.5	(22.7)	17.7[b]	24.4	(22.5)	22.4; 29.9
endo-5-endo-6-Me_2-exo-2-OH	40.1	65.0	32.3	(33.1)	(32.9)	(32.7)	19.9	27.1	15.4(5-Me) 14.6(6-Me)
endo-5-endo-6-Me_2-endo-2-OH	39.1	71.4	31.6	(32.7)	(33.1)	(33.3)	25.8	26.4	14.8(5-Me) 17.7(6-Me)
exo-3-endo-5-endo-6-Me_3-endo-2-OH	40.2	79.6	(34.9)	39.7	(34.0)	(33.5)	26.8	21.0	18.3(3-Me) 14.5(5-Me) 17.6(6-Me)
3,3-endo-5-endo-6-Me_4-endo-2-OH	40.6	80.2	37.1	43.9	36.2	32.8	26.8	25.8	25.0(3-Me) 32.8(3-Me) 18.6(5-Me) 17.5(6-Me)
4,6,6-Me_2-endo-2-OH	43.0	72.8	43.4	31.0	50.1	30.7	22.5	30.6	27.9(4-Me) 32.3; 32.5

a In ppm from internal TMS in $CDCl_3$ solutions. b Carbon syn relative to the hydroxyl group.

(2.2.2)octane, 5-methylbicyclo(2.2.2)oct-2-enes and 2-hydroxyl derivatives 153, 162 and 163 relative to those for the corresponding hydrocarbons, and olefins, substituent effects at the various skeletal carbons were obtained as listed in Table 5.13. With these substituent effects, one can predict the shieldings for the array of methylbicyclo(2.2.2)octanes and -octanols. For many of these compounds, the signals were readily assigned from the expected substituent effects but for those having closely neighboring substituents there are pronounced differences between the observed and predicted shieldings. The differences $\delta_C^{obsd.} - \delta_C^{calc.}$ are given in parentheses in Tables 5.10, 5.11 and 5.12. There is a distinct pattern for the compounds having large deviations from additivity; these are discussed later. For the bicyclo(2.2.2)octanones, in the spectrum of 3,3-dideuterio-149 one methylene signal (C-3) essentially disappeared and one (C-8) was significantly broadened due to vicinal C-D coupling while the third was unaffected, establishing these to be the C-3, C-8 and C-7 signals, respectively. The bridgehead carbon, C-1 could be distinguished readily since the carbonyl group renders it consistently less shielded. Of the remaining methine signals, one was shifted to higher field by ca. 0.2 ppm by the geminal isotope effect, one was significantly broadened due to vicinal C-D coupling while the third was unaffected, establishing these as the C-4, C-5 and C-6 signals, respectively. According to the methyl carbon shieldings in the 149 derivatives, it is clear that the more deshielded methyl signal for 149 was due to the 6-methyl carbon. The assignments for the 149 derivatives were established by comparison of the observing shieldings with those estimated by assuming simple additivity of methyl substituent effects at C-3 in 149 (i.e. 169 - 171)

Table 5.13

^{13}C Shieldings[a] of Some Bicyclo(2.2.2)oct-5-en-2-ols

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Me[b]
exo-2-OH	37.6	68.8	35.4	30.1	135.2	132.0	17.3	26,1	
endo-2-OH	37.6	70.2	38.9	30.1	135,9	129.9	22.1	24.1	
3,3-Me_2-exo-2-OH	39.2	76.7	35.1	42.6	136.4	130.1	14.9	21.9	22.7(x); 32.5(n)
3,3-Me_2-endo-2-OH	39.9	79.9	40.1	43.3	138.7	127.9	20.9	21.7	29.7(x); 24.5(n)
4,7,7-Me_3-exo-2-OH	49.9	72.9	40.5	35.4	136.8	133.4	34.7	51.5	25.0(4-Me) 31.8(anti) 33.3(syn)
1,4,8,8-Me_4-exo-2-OH	40.3	73.3	32.2	48.2	145.3	127.6	41.2	34.5	21.8; 21.9 28.3(anti) 31.5(syn)
1,4,8,8-Me_4-endo-2-OH	41.0	74.6	35.7	48.3	145.6	124.6	47.9	34.3	21.6; 21.9 29.3(anti) 30.9(syn)

[a] In ppm from internal TMS in $CDCl_3$ solutions.

[b] Syn and anti with respect to the double bond.

Table 5.14

Substituent Effects of Methyl and Hydroxyl Groups on the Skeletal Shieldings of Bicyclo(2.2.2)systems[a]

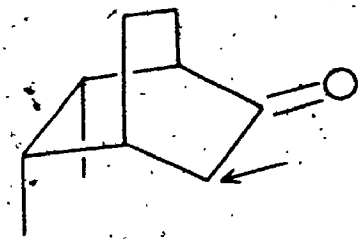
Substitution	Orientation	α	β		γ			δ	
		C-2	C-1	C-3	C-4	C-6	C-7	C-5	C-8
2-Me		4.3	6.4	9.7	1.2	-5.7[b]	1.4[c]	0.0	-0.9[c]
1-Me[d]		3.8(C-1)		7.3(C-2)		0.5(C-3)		0.0(C-4)	
2-OH		43.4	7.7	11.4	0.8	-7.5[b]	-2.3[c]	-0.5[b]	-1.6
Δ^5-2-Me	exo	4.6	6.5	9.1	1.3	2.3	-6.9	-1.2	0.6
	endo	6.4	7.3	10.2	1.0	-2.1	0.8	0.0	-1.5
Δ^5-2-OH	exo	43.0	8.1	9.6	-0.6	-2.1	-8.5	1.1	0.3
	endo	44.4	8.1	13.1	-0.6	-4.2	-3.7	1.8	-1.7
2-oxo-3-Me[e]		2.6(C-3)	6.0(C-4)		0.0(C-1)		-4.6(C-5)[b]	0.8(C-6)[b]	
							-1.3(C-8)[c]	-0.7(C-7)[c]	
2-oxo-3,3-Me_2[e]		1.3(C-3)	10.6(C-4)		0.3(C-1)		-2.4(C-5,8)	0.1(C-6,7)	

[a] $\pm \Delta\delta^X = \delta_C^{RX} - \delta_C^{RH}$, where RH = hydrocarbon, in ppm. Positive values indicate downfield shifts.

[b] Syn with respect to substituent. [c] Anti with respect to the substituent.

[d] $\Delta\delta^{Me} = \delta_C^{4\text{-Me-bicyclo(2.2.2)octan2-ol}} - \delta_C^{\text{bicyclo(2.2.2)octan2-ol}}$ [e] RH = bicyclo(2.2.2)octan-2-one.

169



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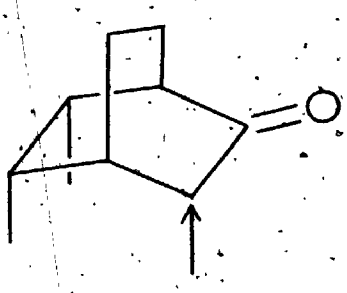

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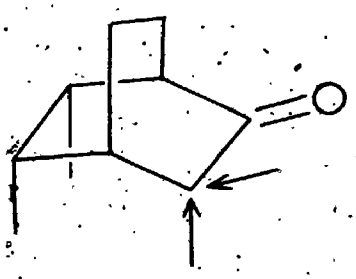


(c) DISCUSSION

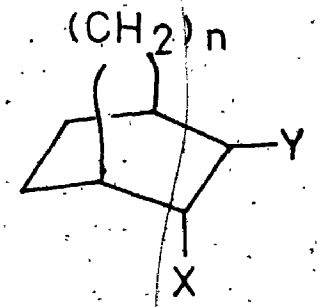
The present series provides further examples of two different arrangements involving methyl and hydroxyl groups and supports the results from the previous section. As the first set, one can consider the various orientations of vicinal substituents while the second set consists of those having two methyls or a methyl and a hydroxyl group separated by four bonds.

To examine the effect of the vicinal methyl and hydroxyl groups, the methyl carbon shieldings may be compared with those for the corresponding centers in the appropriate hydrocarbons or olefins. For the simplest cases, 142, 143, 147, and 148, there are two different dihedral angles relating the two methyl carbons, 0° and 120°. For 142, with $\phi \sim 0^\circ$, the methyl carbons are shielded by 0.6 ppm relative to the values for the corresponding methylbicyclo(2.2.2)octane; for 143, with $\phi \sim 120^\circ$, the upfield shift is 2.0 ppm. In the bicyclo(2.2.2)oct-2-ene derivatives 148 and 147, comparable shifts are found for the methyl carbons: $\phi \sim 0^\circ$, -5.9 ppm; $\phi \sim 120^\circ$, -1.9 ppm (for

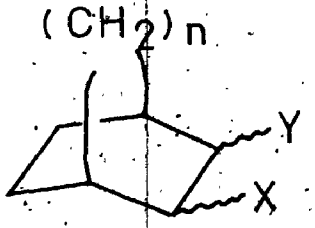
exo-Me in 147) and +0.8 ppm (for endo-Me in 147). For the bicyclo(2.2.2)-octan-2-ol derivative, 155 with $\phi \sim 0^{\circ}$, the methyl carbon is shielded by 8.4 ppm relative to the value for 2-methylbicyclo(2.2.2)octane; for 156, with $\phi \sim 120^{\circ}$, the upfield shift is -2.6 ppm. To compare the γ effect between vicinal methyl groups and that between vicinal methyl and hydroxyl groups the results for several norbornanols (from the previous section) and bicyclo(2.2.2)octanols, are collected in Table 5.15. The γ effect for the bicyclo(2.2.2)octane derivatives are comparable to the values found for the corresponding bicyclo(2.2.2)heptane system indicating that "ring strain" has little effect on these shieldings. In fact, the methyl substituted effects in these two bicyclic systems are closely similar, comparing the observed shifts for the carbons in the 6-membered ring in the bicycloheptanes with those for the cyclooctanes. It is interesting, however, that γ gauche effects of a 2-methyl and a 2-hydroxyl group at C-6 are somewhat more shielding by $\sim$ -2 ppm in the bicycloheptane cases. Also these substituents tend to deshield the more remote olefinic carbon in the bicycloheptenes more strongly than in the bicyclooctenes. Otherwise, the methyl and hydroxyl substituent effects are comparable for both bicyclic systems with shifts generally < 1 ppm for the corresponding carbons. Clearly there is a distinct sensitivity of the methyl shielding to ϕ, but it may be noted that there is a variation of nearly 2 ppm within each group perhaps due to different degrees of skeletal twist which alter the dihedral angle between the substituents. In the 3,3-dimethyl derivatives 46, 157 and 165, one of the geminal methyls is eclipsed or nearly so, with the hydroxyl group while the other has $\phi \sim 120^{\circ}$ and the upfield shifts average 7.8

Table 5.15

γ Methyl and Hydroxyl Substituent Effect Between Vicinal Methyl groups or Vicinal Methyl and Hydroxyl groups

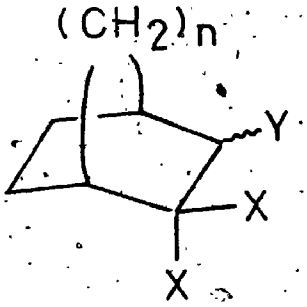


n	X	Y	Δ	Δδ[a] exo	endo
1	Me	Me		-1.2	-1.5
2	Me	Me		-2.0	-2.0
1	Me	Me	5	-0.9	-0.7
2	Me	Me	5	-1.9	0.8
1	Me	OH			-2.4
2	Me	OH			-2.6
1[b]	Me	OH	5		-1.2
1	OH	Me		-2.2	
1[b]	OH	Me	5	-2.2	



1	exo-Me	exo-Me		-6.6	
2	exo-Me	exo-Me		-6.0	
1	exo-Me	exo-Me	5	-4.9	
1	exo-Me	exo-OH		-8.9	
2	exo-Me	exo-OH		-8.4	
1[b]	exo-Me	exo-OH	5	-6.8	
1	endo-Me	endo-Me			-5.6
1	endo-Me	endo-Me	5		-4.9
2	endo-Me	endo-Me	5		-5.9
1	endo-Me	endo-OH			-7.2
1[b]	endo-Me	endo-OH	5		-6.2

Table 5.15 (Cont.)



n	X	Y	Δ	exo	endo
1[b]	Me	exo-OH		-8.4	-1.0
2	Me	exo-OH		-8.5	-1.0
2	Me	exo-OH	5	-7.4	0.4
1[b]	Me	endo-OH		-1.0	-7.0
2	Me	endo-OH	5	-0.4	-7.6

[a] In ppm, a negative value indicates a upfield shifts.

$\Delta\delta = (\delta_C^{RMe_2} - \delta_C^{RMe})$, $(\delta_C^{RMeOH} - \delta_C^{Me})$ or $(\delta_C^{RMe_2OH} - \delta_C^{RMe_2})$

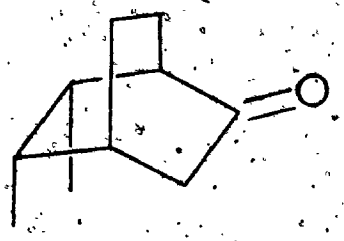
[b] From ref. (130).

and 0.3 ppm, respectively, for the two different orientations.

In this series, there are several examples having a variety of different orientations of two methyl groups or the methyl and hydroxyl groups separated by four bonds. This array of δ interactions have been subdivided into four basic types, 129 - 132 in the Introduction. The methyl shift and the values of the effect of methyl and hydroxyl groups in two different series of compounds were shown in Figure 5.2 and 5.3. The methyl carbons are slightly shielded if well-separated from the hydroxyl group or the methyl group but are deshielded if the two groups are close neighbors as in 129. For example, in 151 having the 129 arrangement the methyl groups at C-3 and C-5 are deshielded by 1.9 and 2.0 ppm, respectively. For the gem-dimethyl derivatives 152 and 160 having the same arrangement the methyl carbons are deshielded by as much as 4.1 ppm, possibly reflecting the effect of a more severe interaction between the substituents. It is interesting that in 152 and 160 the exo-3-methyls are deshielded by 1.9 and 2.9 ppm, respectively. although these methyl group experience no severe steric interaction. Examples having syn-axial interactions between methyl and hydroxyl groups include 157, 161 and 168 for which the methyl carbons are deshielded from 1.4 to 2.5 ppm; also both geminal methyls in 161 and 168 are deshielded. It appears that the interaction of substituents in syn-axial, or equivalent, orientations tend, in general, to deshield the terminal carbons in a δ fragment and the present series allows further definition of the effects accompanying these steric perturbations.

Closer inspection of the data for the compounds having γ interactions reveals a much more striking trend. The differences between the

Figure 5.2. δ Methyl substituent effect between syn-axial dimethyl groups, in ppm.



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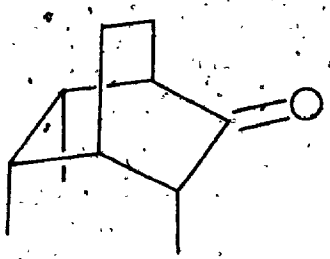

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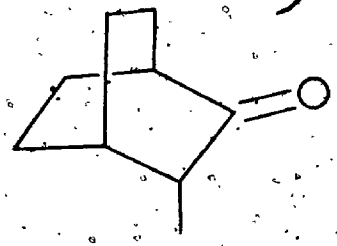

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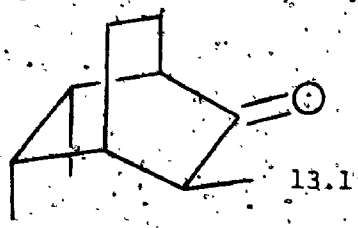

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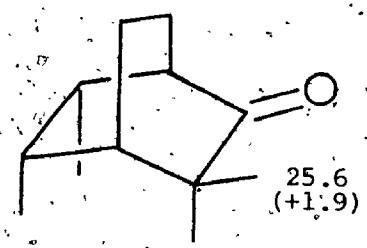

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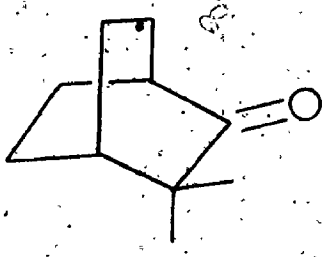
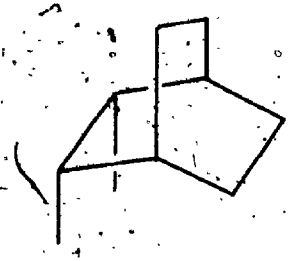


42

Figure 5.3. δ methyl and hydroxyl substituent effects between Me and Me or Me and OH groups, in ppm.



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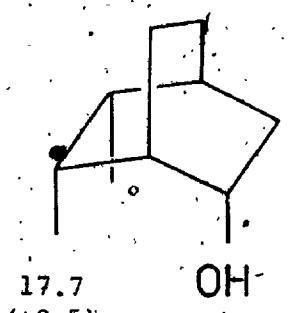
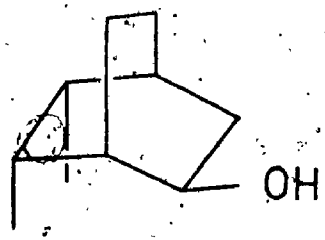


157



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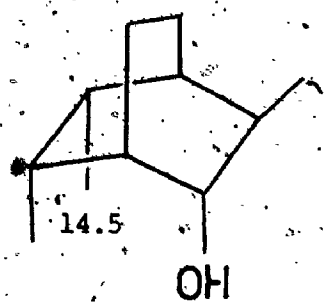

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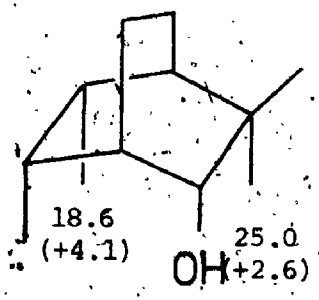

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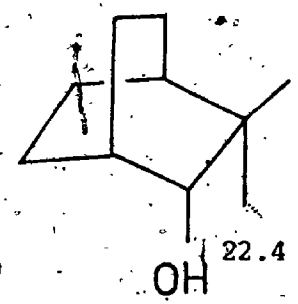

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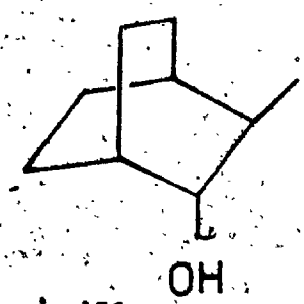

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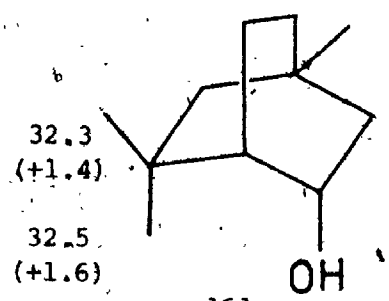

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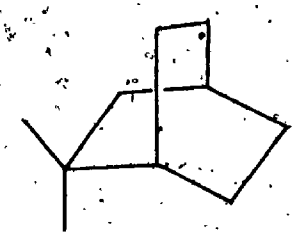


141

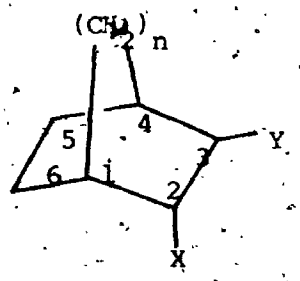
observed shieldings and those estimated by additivity for the skeletal carbons are particularly large for the carbons bearing the terminal nuclei in the crowded γ fragment. The derivations from additivity for the carbons bearing closely neighboring γ substituents are negative, i.e. these carbons are more shielded by the γ interaction than predicted by simple additivity (Table 5.16). Examples having eclipsed vicinal substituents at C-2 and C-3 include 142, 148 and 155 for which the substituted carbons show deviations of 5.8 - 8.2 ppm, upfield from the predictdd values. For the trans isomers, in which the substituents are oriented at a dihedral angle of $\sim 120^{\circ}$, simple additivity of the individual substituent effects gave good estimates of the shieldings with the exception of the methyl carbons or the terminal nuclei of the γ fragment.

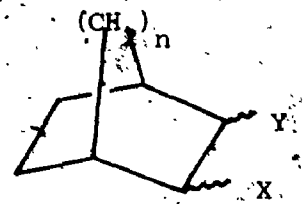
In contrast to the effects of closely neighboring γ substituents, the deviations from additivity for the carbons bearing closely neighboring δ substituents are positive, i.e. these carbons are much less shielded than predicted by simple additivity. To illustrate the contrast, the deviations from additivity for several bicyclo(2.2.2)octyl and norbornanol derivatives having syn-axial substituents are collected in Table 5.17. It is clear that carbons bearing the substituents exhibit the largest deviations from simple additivity and these deviations are most striking, 5 - 11 ppm, if the substituents are in a syn-axial or equivalent orientation. In contrast, the shieldings for the remaining carbons agree well with those predicted by simple additivity.

From the data for these two sets of compounds, it is apparent that very significant shielding variations are exhibited by carbons bearing

Table 5.16

A Comparison of Observed and Predicted ^{13}C Shieldings ($\Delta\delta$) in Some Bicyclic Systems





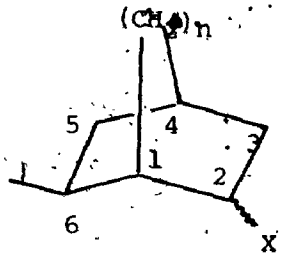
n	X	Y	$\Delta\delta$[a]							
			CH_3	C-3	C-2	C-1	C-4	C-5	C-6	C-7	C-8
1	OH	Me	-2.2	-0.4	-1.2	0.1	-0.1	-0.2	0.3	0.3	
2			-2.6	0.0	-1.1	0.0	0.1	0.1	0.7	0.3	0.9
1	Me	Me	-1.2[b]	0.0	-0.2	0.1	0.0	-0.3	0.0	0.2	
2			-2.0	0.0	0.0	-0.1	-0.1	-0.4	0.7	0.4	0.7
1	Me	OH	-2.4	0.0	-1.0	-0.2	0.1	0.4	0.0	0.2	
1	exo-OH	exo-Me	-8.9	-5.8	-8.4	0.0	0.7	0.7	1.1	1.0	
2			-8.4	-6.0	-8.2	-1.1	0.1	0.6	0.8	0.0	0.3
1	exo-Me	exo-Me	-6.6	-6.6	-6.6	0.9	0.9	0.6	0.6	0.6	
2			-6.0	-6.8	-6.8	0.2	0.2	0.8	0.8	-0.2	-0.2
1	endo-OH	endo-Me	-7.2	-7.3	-9.5	-0.4	-0.4	-0.6	-0.9	-2.8	
1	endo-Me	endo-Me	-5.6	-8.0	-8.0	0.0	0.0	-0.9	-0.9	-2.4	

[a] In ppm, a negative value denotes higher shielding than that predicted by simple additivity.

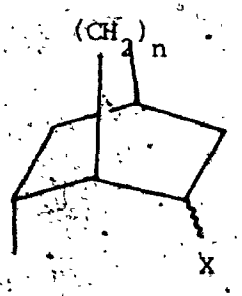
[b] For endo-Me, $\Delta\delta$ = -1.5 ppm.

Table 5.17

A Comparison of Observed and Predicted ^{13}C Shieldings ($\Delta\delta$) in Some Bicyclic Systems



n	X	$\Delta\delta$[a] Me	C-6	C-1	C-2	C-3	C-4	C-5	C-7	C-8
1	exo-OH	-0.9	0.1	0.2	-0.5	0.0	-0.3	-0.2	0.3	
1	endo-OH	-0.5	-1.5	0.0	-0.5	0.0	0.1	-0.1	0.2	



	exo									
1	OH	-0.5	2.7	-0.2	1.8	0.1	0.0	-0.1	0.2	
2	OH	-0.6	1.9	0.6	1.3	0.6	0.1	0.3	0.0	0.2
2	Me	0.0[b]	-0.5	-0.3	-0.4	-0.6	0.3	0.2	0.1	0.3
	endo									
1	OH	2.0	11.0	-0.9	11.0	-0.6	0.5	-0.8	0.7	
2	OH	2.5	7.5	-0.4	7.7	-0.1	0.1	0.3	0.7	0.6
2	Me	2.0[c]	6.4	0.2	5.2	0.1	-0.5	0.9	1.6	-0.2

[a] In ppm, a negative value indicates a higher shielding than predicted by simple additivity.

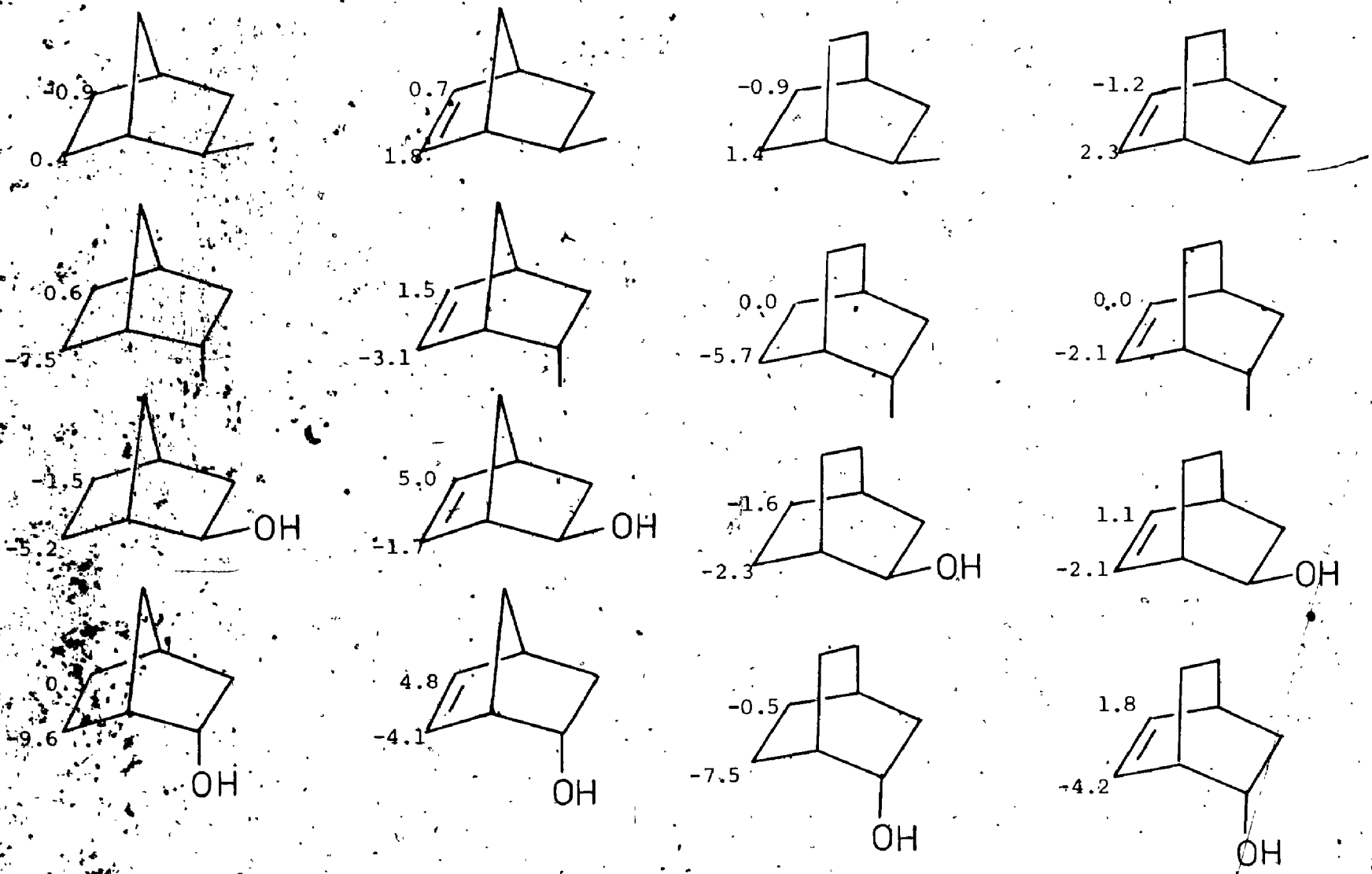
[b] For X = Me, $\Delta\delta$ = -0.4. [c] For X = Me, $\Delta\delta$ = 1.9.

closely neighboring substituents and the shifts are in opposite directions depending on the number of bonds between the substituents. It is clear that in highly substituted systems the simple additivity approach for ^{13}C shielding estimations requires additional parameters. While it is clear that the steric polarization model, originally proposed to account for the shifts arising from γ interactions (30, 31) cannot be appropriate for δ interactions, any theoretical interpretation of the latter must account for the pronounced shifts exhibited by the penultimate carbons in the δ fragment. Their magnitude, however, may allow empirical stereochemical interpretations for shieldings observed in complex systems.

Systematic studies of the olefinic carbon shieldings in some simple systems were undertaken with the primary aim of examining both the effects of polar substituents and the influence of the stereochemistry of vicinal groups on these values (147 - 153). But detailed studies for the long-range substituent effects at the olefinic carbons such as γ and δ effects are lacking. Some of the models in this series allowed an examination of the hydroxyl and methyl substituent effects at γ- and δ-olefinic carbons. By comparing the shieldings of a monosubstituted compound with those for the parent hydrocarbon one can obtain the substituent effects of interest. To understand the substituent effects at the olefinic carbons, the substituent effects at the corresponding sp^3 carbons were needed and these results are shown in Figure 5.4. These results indicated that the methyl and hydroxyl effects at the γ olefinic carbon are precisely as expected, i.e., similar to those for the corresponding saturated compounds. Although the δ olefinic carbons have no severe steric interactions, these are deshielded by as much as 6.5 ppm by hydroxyls but the methyl group does not affect the δ olefinic carbons

Figure 5.4

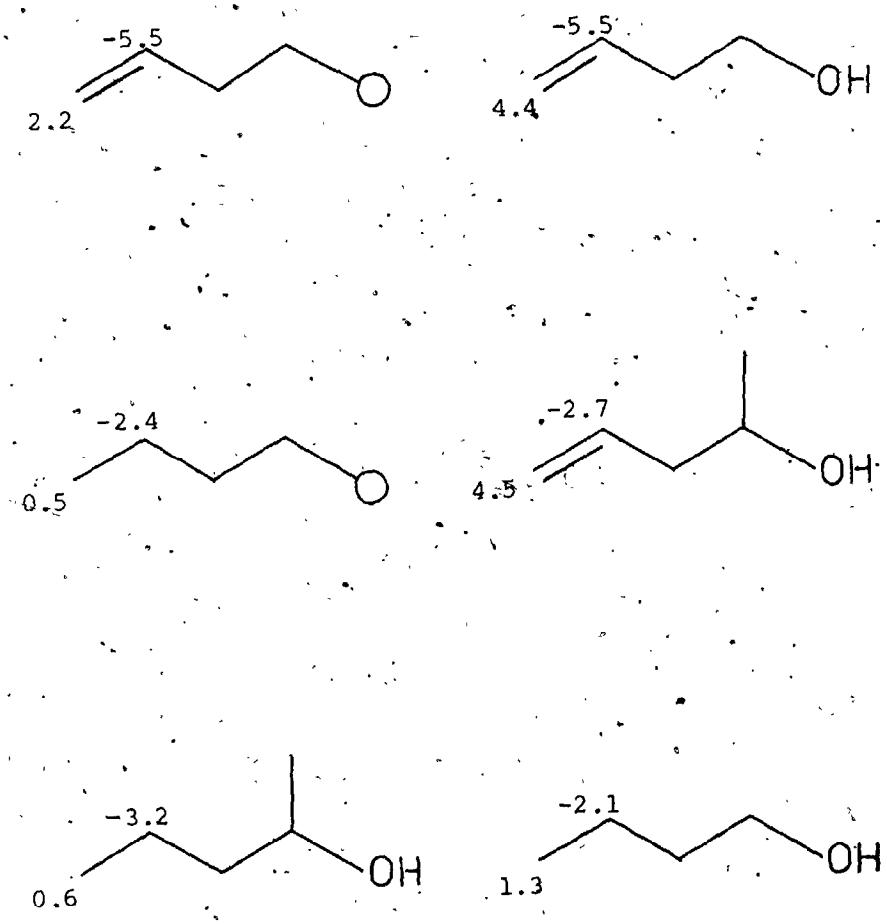
γ and δ Methyl and Hydroxyl Substituent Effects in Bicyclic Systems[a]



[a] In ppm, a negative value indicates upfield shift. $\Delta\delta = (\delta_C^{RX} - \delta_C^{RH})$.

Figure 5.4a

γ and δ-Methyl and Hydroxyl Substituent Effects in Aliphatic Systems[a]



[a] In ppm, a negative value indicate upfield shift. $\Delta\delta = (\delta_C^{RX} - \delta_X^{RH})$

markedly. This δ hydroxyl effect appears to be independent of the geometry of the hydroxyl group but rather, depends on the carbon skeleton. For example, the δ olefinic carbons in the bicyclo(2.2.1)hept-5-en-2-ols are deshielded by ca. 4.9 ppm but in the bicyclo(2.2.2)oct-5-en-2-ols, the olefinic carbons are only deshielded by ca. 1.5 ppm. Clearly further studies are required to define the origin of these results.

In summary, the marked shielding effects apparently arising from steric interactions of closely neighboring substituents in syn-axial orientations are similar in the bicyclo(2.2.1)heptane and bicyclo(2.2.2)-octane systems, although for the latter the effects are slightly smaller. The most striking differences are found for the carbons bearing the δ substituents while significant, but much smaller, downfield shifts are found for the terminal carbons in a syn-axial δ fragment. This trend contrast directly with those found for closely neighboring vicinal substituents for which each carbon in the δ fragment is appreciably shielded, but again the shifts are comparable in both ring systems, indicating that ring strain has little effect on these shieldings. The distinctive shifts exhibited by syn-axial arrangements should be helpful in the interpretation of spectra of more complex systems, since the trends appear to be general.

(D) THE ^{13}C SPECTRA OF SEVERAL METHYLCYCLOHEXANOLS

(a) INTRODUCTION

A potentially valuable application of ^{13}C spectroscopy concerns the examination of conformationally mobile systems for which the observed shieldings are averaged on the NMR time scale because of rapid interconversion between two (or more) nonequivalent forms. In view of the pronounced dependence of ^{13}C shieldings on molecular geometry, it follows that ^{13}C results could provide a new approach to conformational analysis which complements and extends the scope of the well-established proton NMR methods. In ^{13}C NMR spectra it is generally found that various substituents exert shielding effects which are additive within families of compounds. As a result, the positions of ^{13}C signals for closely related materials may often be predicted with good precision in a wide variety of systems (8 - 10, 17 and previous sections and Chapter 4). Therefore the substituent effects are not only useful for signal and stereochemical assignments but also for conformational analysis (17).

The earlier work on oxygenated cyclohexane derivatives was restricted to the measurement of the carbinyl carbon shieldings which were used for conformational analysis (140, 141). Recently, a number of methyl cyclohexanols has been studied by Roberts and his co-workers (33). In general, many of these involve equilibria between two chair conformations, one with an alkyl group equatorial and the hydroxyl equatorial. Roberts and his co-workers tried to simplify their analysis and assumed in all cases that the conformational preference for equatorial alkyl over equatorial hydroxyl will be sufficiently great that there will be no substantial contribution from the conformer with axial alkyl and equatorial hydroxyl groups. In fact, in some cases, the equilibrium mixture will contain up

to 25% of the conformer with an equatorial hydroxyl group (155).

The ^{13}C NMR spectra of 19 methyl substituted cyclohexanols have been determined. These were chosen as model systems for the study of steric and conformational effects on ^{13}C shieldings. Further examples of marked deshielding trends associated with sterically crowded δ nuclei in syn-axial arrangements are described.

(b) RESULTS AND DISCUSSION

The ^{13}C shieldings for the methylcyclohexanols examined in this study are listed in Table 5.18. While the results for cyclohexanol and its monomethyl derivatives had been reported previously (33), some were re-examined to obtain a set of data in a common solvent at comparable concentrations.

To estimate reliable substituent effects for the hydroxyl group in the cyclohexane ring system, two pairs of t-butyl cyclohexanol derivatives were adopted as the base cases. The ^{13}C shieldings of t-butylcyclohexane were compared with those for the 4-t-butylcyclohexanols and the 3-t-butyl cyclohexanols, from which the substituent effects of the equatorial and axial hydroxyl group in the cyclohexane ring system were obtained. The results are listed in Table 5.19. It is apparent that the differences for γ-carbons (C-3 and -5) between the axial and equatorial hydroxyl substituent effects is 4.7 ppm which is smaller than found for the methyl in methylcyclohexane (6.3 ppm). If these shielding differences mainly arise from steric interactions, the results imply that the methyl group is larger than the hydroxyl group as is in fact the case (156). As a test of the utility of these hydroxyl and methyl substituent effects

(108), the estimated shieldings of the possible chair conformations of methylcyclohexanols were calculated. The observed shieldings of cis-3-methyl-, cis,cis-3,5-dimethyl-, trans,trans-3-5-dimethyl-, cis-3,3,5-trimethyl, trans-4-methyl- cyclohexanols agree well with these estimated values for the stable conformer expected. For the 30 possible comparisons, the average deviation between predicted and observed values is 0.3 ppm. Since cyclohexanol and some methyl cyclohexanol derivatives exist as a mixture of two chair conformations, the conformational free energies of these cyclohexanol derivatives can be estimated by using the set of substituent effects in Table 5.19. This sort of analysis is the same as that described for the methylcyclohexanones. For cyclohexanol, it seems surprising that the observed shieldings are very close to the estimated values for equatorial cyclohexanol. This implies that cyclohexanol in deuterio-chloroform at room temperature exists almost entirely in the equatorial form. This result is quite different from the generally accepted conclusion that cyclohexanol contains 20% of the axial conformer in its equilibrium mixture in $CDCl_3$ (157). As a further test of these substituent effects, the individual shieldings for the two conformers of cis-4-methylcyclohexanol were estimated. Several different ratios for the mixture of conformers at equilibrium were assumed so that the predicted shieldings for cis-4-methylcyclohexanol were obtained from the average values for each carbon from the contribution of each conformer. The results are listed in Table 5.20. For a mixture of 172 and 173 (3:1) the predicted shieldings for each carbon fit somewhat better with those observed. The variation of the methyl carbon has also been used to provide conformational information on methylcyclohexanones. Similar conclusions

Table 5.18

^{13}C Shieldings[a] of Some Cyclohexanols

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	Me
Nil	70.0	35.6	24.2	25.6	24.2	35.6	
trans-2-Me	76.1	40.1	33.7	25.7	25.2	35.4	18.6
cis-2-Me[b]	71.4	36.1	29.6	24.5	21.8	32.1	16.5
2,2-Me_2	77.0	38.3	38.3	21.6	24.3	30.6	19.4(ax); 28.3(eq)
trans-2,2,6-Me_3	83.5	35.8	40.0	21.6	34.7	34.7	18.4(ax-2-Me); 29.6(eq-2-Me) 19.3(eq-6-Me)
cis-2,2,6-Me_3	78.9	35.2	32.5	21.8	27.5	31.8	24.5(ax-2-Me); 28.5(eq-2-Me) 18.9(eq-6-Me)
2,2,6,6-Me_4	83.9	35.9	40.2	18.6	40.2	35.9	19.9(ax); 32.0(eq)
2,2,6,6-Me_4-4-t-Bu	84.3	36.2	41.4	39.0	41.4	36.2	20.2(ax); 32.5(eq); 27.6(Me_3C)[c]
trans-3-Me[b]	66.8	41.5	26.9	34.7	20.5	33.1	20.5
trans-3-t-Bu	67.1	33.7	40.8	27.2	20.6	32.7	27.3(Me_3C)[d]
cis-3-Me	70.6	44.6	31.4	34.1	24.2	35.4	22.3
cis-3-t-Bu	71.4	37.1	46.7	26.3	24.4	35.7	27.5(Me_3C)[e]
cis-3-cis-5-Me_2	70.0	44.0	30.8	43.3	30.8	44.0	22.3
trans-3-cis-5-Me_2	66.9	40.8	28.2	40.0	25.9	44.8	19.2(3-Me); 22.5(5-Me)
trans-3-trans-5-Me_2	66.1	41.2	26.1	44.0	26.1	41.2	22.5
3,3-cis-5-Me_3	67.5	49.0	32.1	47.5	27.2	44.4	25.6(ax-3-Me); 33.0(eq-3-Me) 22.3(eq-5-Me)
3,3,5,5-Me_4	65.7	48.6	32.5	51.4	32.5	48.6	27.7(ax); 35.1(eq)
trans-4-Me	71.0	35.5	33.3	31.7	33.3	35.5	21.9
trans-4-t-Bu	70.9	36.0	25.6	47.2	25.6	36.0	27.6(Me_3C)[e]
cis-4-Me	67.0	32.1	29.0	29.5	29.0	32.1	21.6
cis-4-t-Bu	65.7	33.4	20.9	46.1	20.9	33.4	27.5(Me_3C)[e]
Cyclohexane	27.0	27.0	27.0	27.0	27.0	27.0	
t-Bu-cyclohexane	49.9	28.2	27.8	27.2	27.8	28.2	

[a] In ppm from internal TMS in $CDCl_3$ solutions.

[b] From ref. (33)

[c] Quaternary carbon, 31.8 ppm. [d] Quaternary carbon, 32.1 ppm. [e] Quaternary carbons, 32.2 ppm.

Table 5.19

Hydroxyl Substituent Effects in Cyclohexane[a]

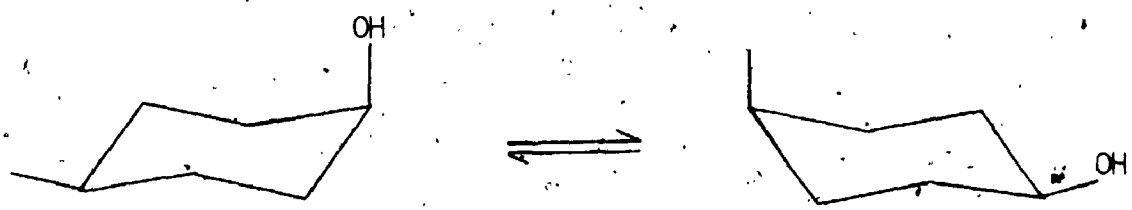
	α	β	γ	δ
axial-OH	38.9	5.6	-7.5	-0.9
equatorial -OH	43.7	8.5	-2.8	-1.8

[a] In ppm, negative sign denotes to upfield shift.

Table 5.20

Estimated ^{13}C Shieldings of cis-4-methylcyclohexanol at the Different Ratio of the Mixture of Two Chair Conformers

cis-axial-4-Me : cis-equatorial-4-Me	C-1	C-2	C-3	C-4	C-5	C-6
0 : 10	65.7	32.7	28.5	32.1	28.5	32.7
1 : 9	66.2	32.3	28.6	31.6	28.6	32.3
2 : 8	66.7	32.0	28.7	31.0	28.7	32.0
2.5: 7.5	66.9	31.8	28.8	30.7	28.8	31.8
2.7: 7.3	67.0	31.7	28.8	30.6	28.8	31.7
3 : 7	67.2	31.6	28.8	30.5	28.8	31.6
10 : 0	70.6	29.1	29.6	26.6	29.6	29.1
Observed	67.0	32.1	29.0	29.5	29.0	32.1

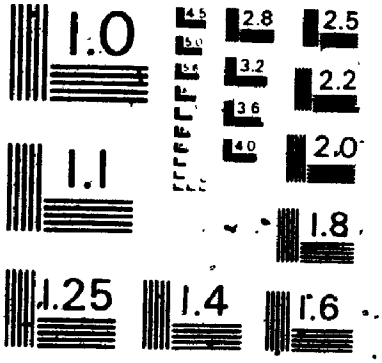


172 173

follow from the analysis of the methyl shielding of cis-4-methylcyclohexanol. Equatorial methyl carbons absorb near 22.4 ± 0.1 ppm from the results of cis-3-methyl-, cis-3,5-dimethyl-, trans,trans-3,5-dimethyl, cis-3,3,5-trimethyl- and trans,cis-3,5-dimethylcyclohexanols. From the trans,cis-3,5-dimethylcyclohexanol, axial methyl carbons can be assumed to absorb at 19.2 ppm. In fact, the observed value for cis-4-methylcyclohexanol is similar to that predicted for a 3 : 1 mixture favoring the conformer having an axial hydroxyl group. From equilibration studies for cis-4-methylcyclohexanol, the relative amount of 172 is ca. 85%. The conformational free energy of cyclohexanol has been studied extensively and values ranging from 0.20 to 1.25 kcal/mole have been tabulated (155), with the best values taken as (157) 0.52 kcal/mole in aprotic solvents and 0.87 kcal/mole in protic solvents. The equilibrium is also concentration dependent. As the concentration changed from 0.015 to 2.0 M in cyclohexane ΔG° varied from 0.61 to 0.85 kcal/mole (157). In any event the conformational energies from the ^{13}C data are much different from those from other studies. Clearly, this ^{13}C approach does not permit a precise quantitative assessment of the equilibrium population but may indicate the bias of the system in a very approximate fashion.

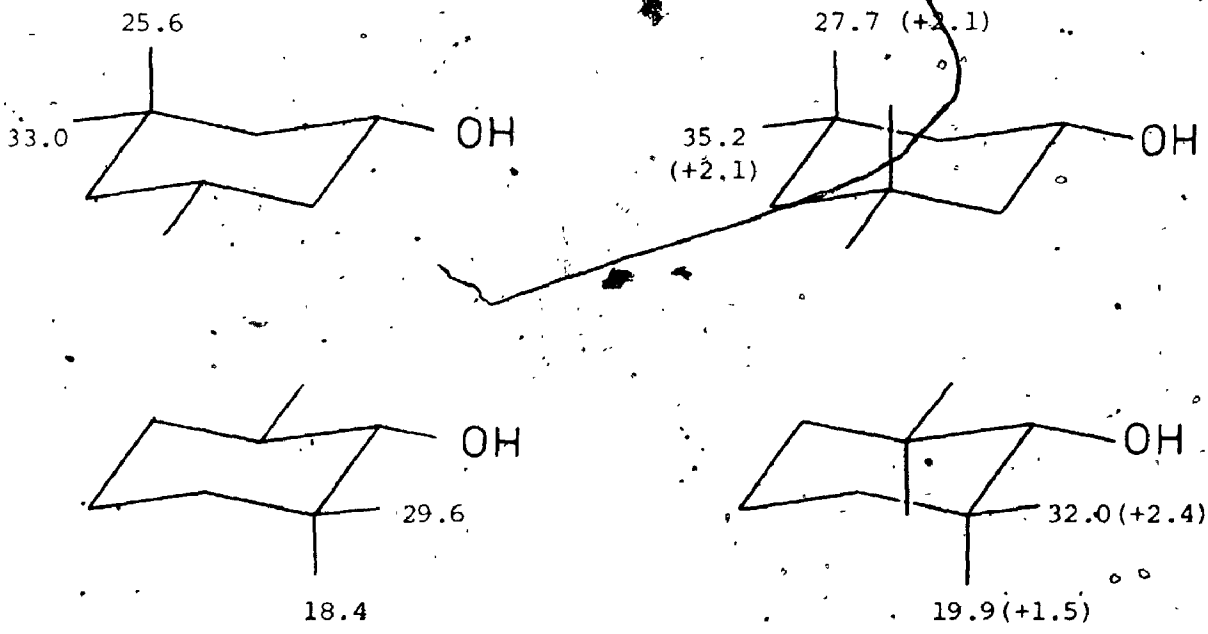
4 5

OF/DE



Further examples of the marked deshielding trend associated with sterically crowded δ nuclei in syn-axial 1,5-Me — Me arrangements can be found in this series of compounds. A comparison of the methyl shieldings for 3,3,5-trimethylcyclohexanol and 3,3,5,5-trimethylcyclohexanol reveal comparable differences for the axial methyl carbons. The single axial methyl in cis-3,3,5-trimethylcyclohexanol absorbs at δ_C 25.6 while the pair of axial methyl carbons in 3,3,5,5-tetramethylcyclohexanol appear at 27.7 indicating a syn-axial effect for 1,5-methyl groups of 2.1 ppm. A similar difference is found for the equatorial methyl carbons.

For the 2,2,6-trimethyl and 2,2,6,6-tetramethyl cases, the δ deshielding effect of the axial methyl carbon is 1.5 ppm but the equatorial methyl carbons are deshielded ca. 2.4 ppm. This difference may arise



from slightly different distortions of the ring skeleton in the 2,2,6-trimethyl and 2,2,6,6-tetramethyl derivatives.

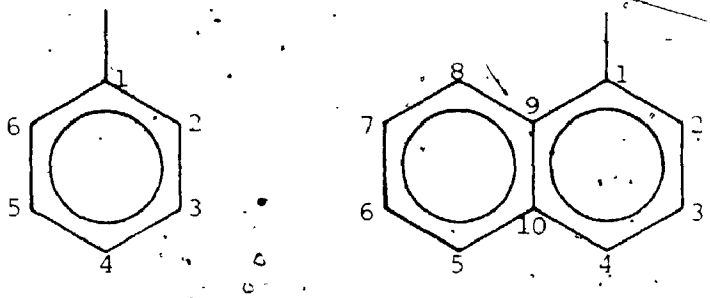
(E) THE ^{13}C NMR SPECTRA OF SOME AROMATIC COMPOUNDS ---- γ, δ and ε EFFECTS

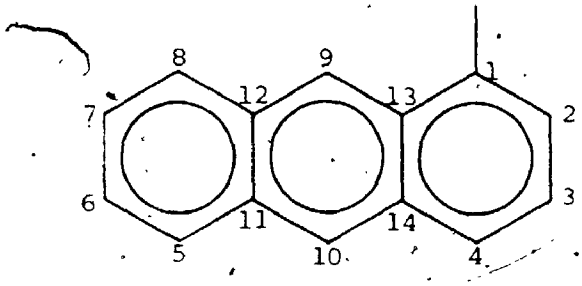
(a) INTRODUCTION

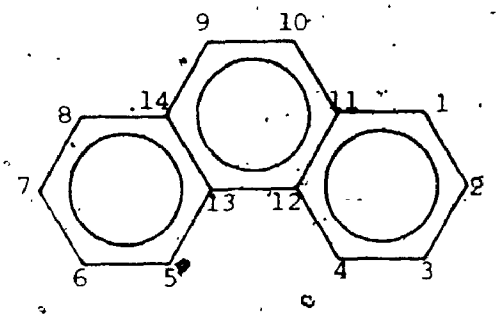
To aid the understanding of ^{13}C shieldings in aryl systems and as a preliminary study for the investigation of carcinogenic methylated polycyclic aryl hydrocarbons, series of methylnaphthalenes (158, 159) and methylanthracenes (160) had been examined in these laboratories. These compounds included several examples having δ interactions between peri-methyls and in each case the methyl carbons were significantly deshielded. It was of interest therefore, to examine the trends produced by methyl groups separated by five bonds and to this end series of 4- and 4,5-methylated phenanthrenes, fluorenes and fluorenones were prepared. While the results for toluene, the xylenes (161) and phenanthrene (50c) had been reported previously, these were re-examined to obtain a set of data for the entire series in a common solvent at comparable concentrations.

(b) RESULTS AND DISCUSSION

The numbering schemes and structures for the aromatic compounds included in the present study are shown in Figure 5.5. The ^{1}H and ^{13}C shielding data for several aromatic hydrocarbons and their mono- and dimethyl derivatives are given in Figures 5.6, 5.7, 5.8, 5.9 and 5.10. Assignments of ^{13}C resonance positions were accomplished using a variety of techniques. Initially resonances for the quaternary carbons could be separated from those for carbons bearing hydrogen by their reduced intensities and their singlet structure in off-resonance decoupling experiments. The signals for the quaternary carbons in the phenanthrenes







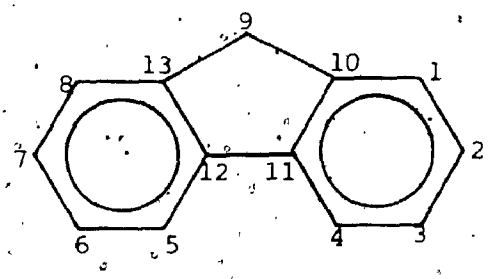


Figure 5.5. Numbering scheme for polynuclear hydrocarbons.

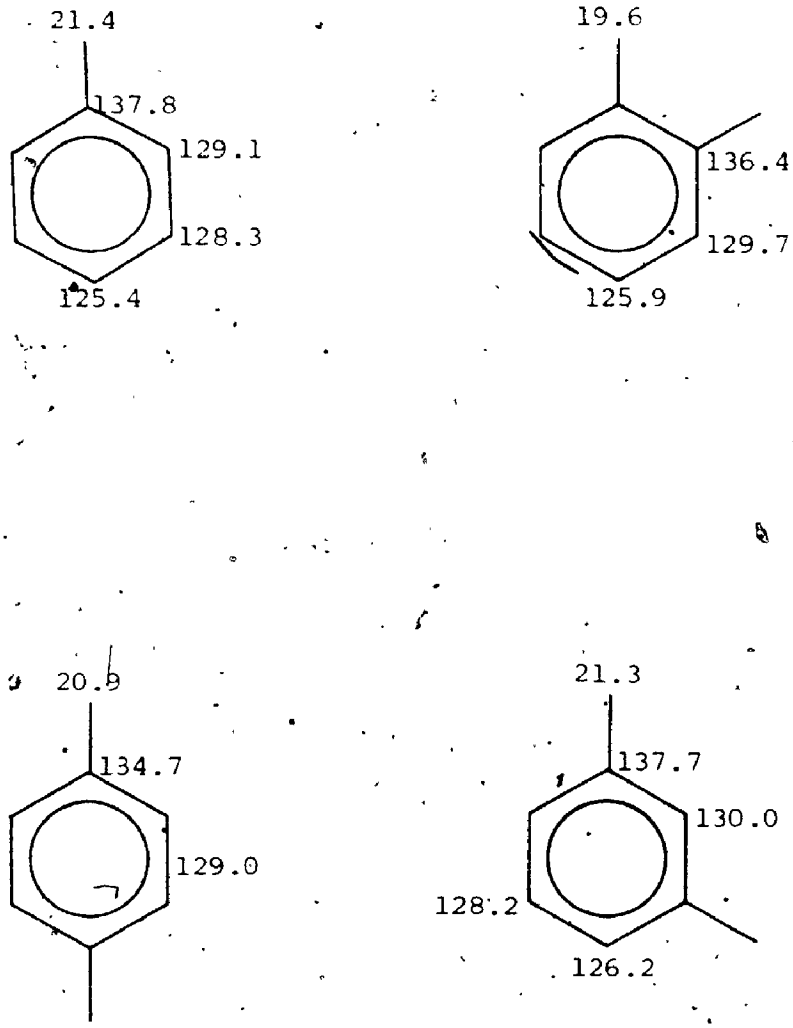
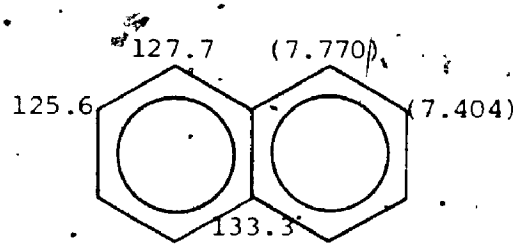
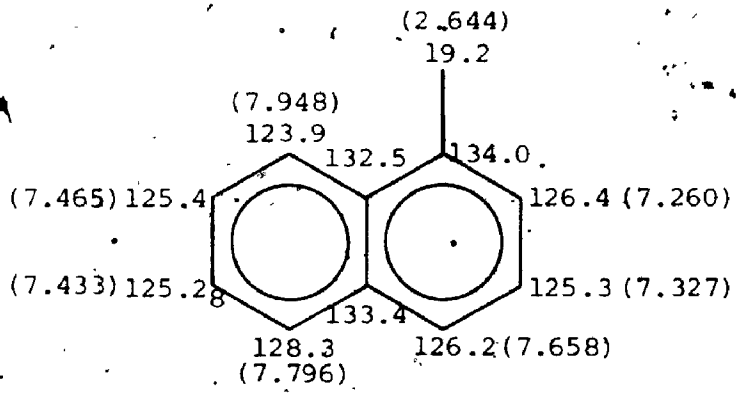


Figure 5.6. ^{13}C Shieldings of Toluene and Xylenes, (in ppm from internal TMS in $CDCl_3$ solution).

Figure 5.7. ^{1}H and ^{13}C Shieldings of naphthalene, 1-methyl and 1,8-dimethyl naphthalene. (In ppm from internal TMS in $CDCl_3$ solution. The values in parentheses are ^{1}H chemical shifts). From ref. (159)





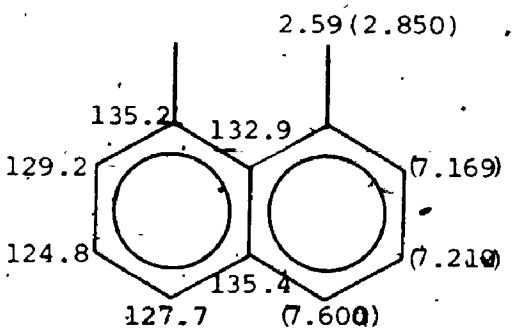
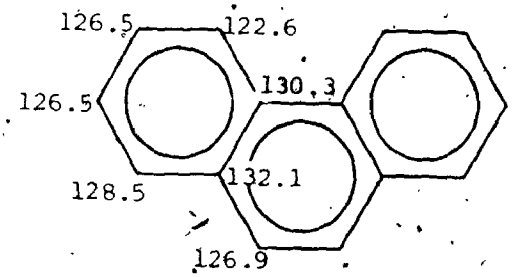
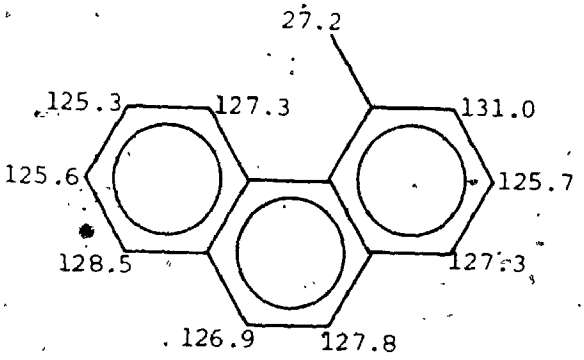


Figure 5.8a ^{13}C Shieldings of some phenanthrenes. (In ppm from internal TMS in $CDCl_3$ solution).





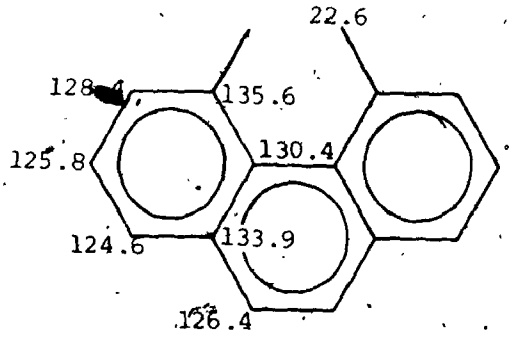
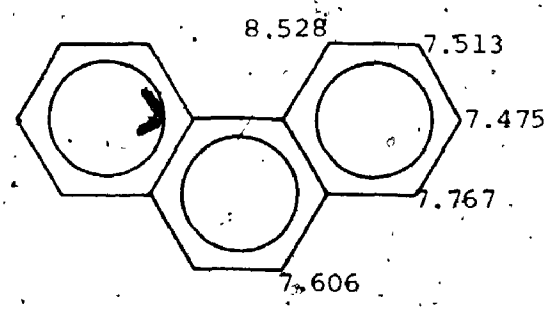
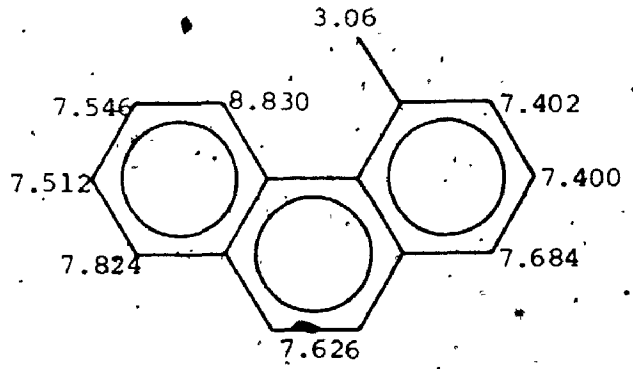


Figure 5.8b ^1H shieldings of some phenanthrenes. (In ppm from internal TMS in $CDCl_3$ solution).





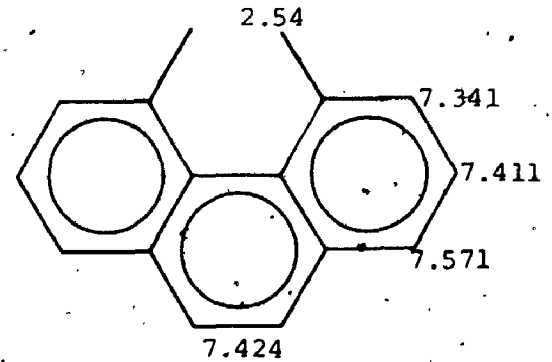
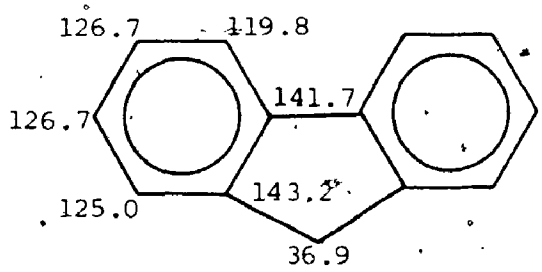
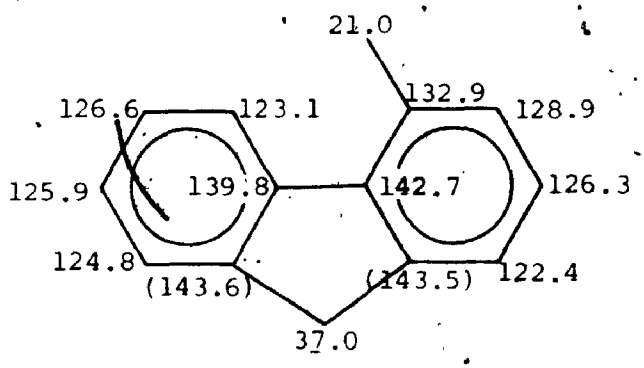


Figure 5.9a ^{13}C shieldings of some methyl fluorenes. (In ppm from internal TMS solutions. Assignments for similar values in parentheses may be reversed.)





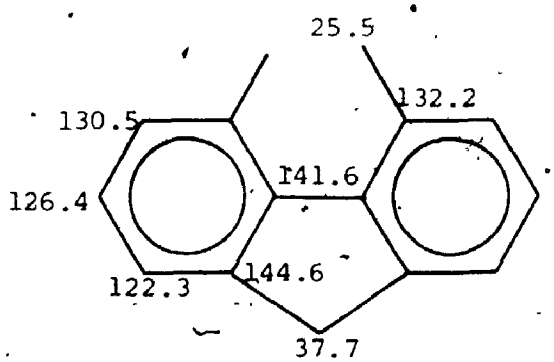
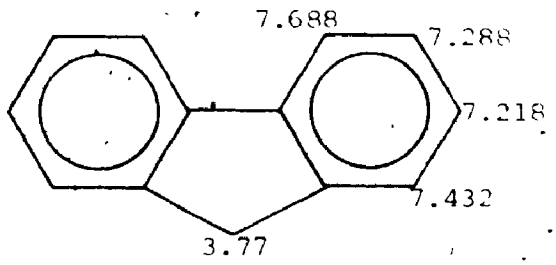
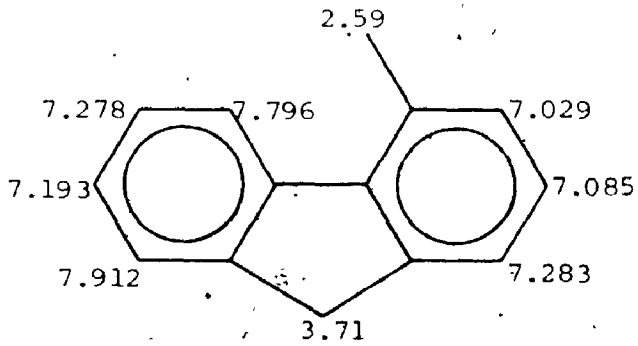


Figure 5.9b $^{1}_{H}$ shieldings of some methyl fluorenes. (In ppm from internal TMS in $CDCl_3$ solutions).





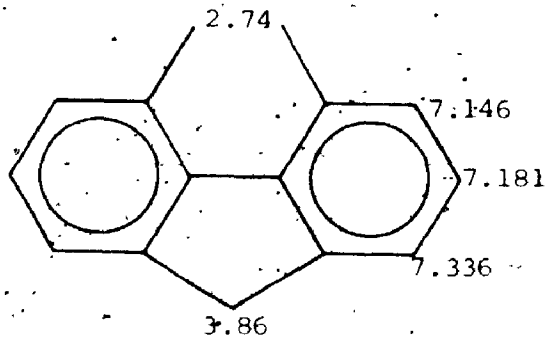
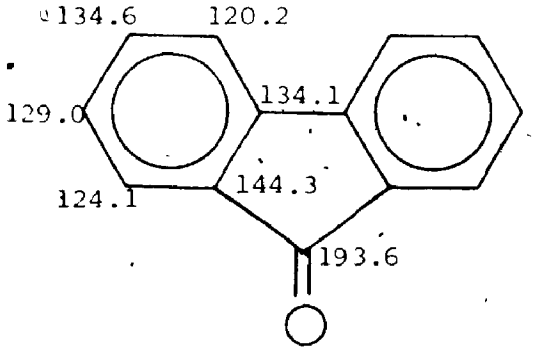
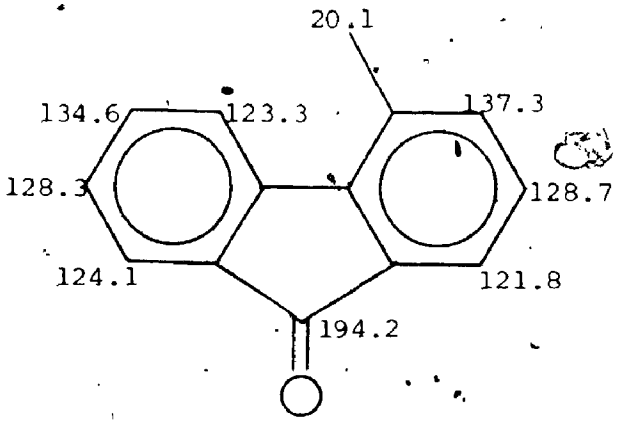
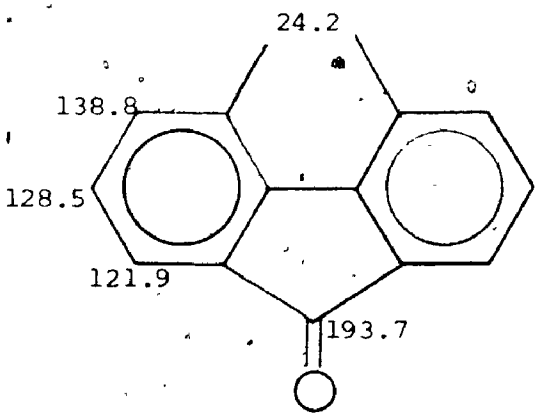


Figure 5.10a. ^{13}C shieldings of some methyl fluorenones. (In ppm from internal TMS in $CDCl_3$ solutions).



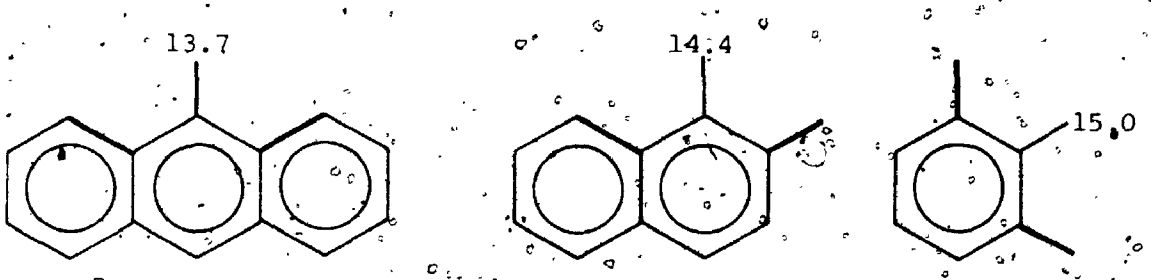


QC
145.2
142.1
134.5
134.4
133.6

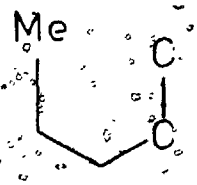


QC
144.5
135.9
132.7

These shifts to higher field are precisely as expected since it is well-established that closely-lying carbons separated by three bonds (γ interactions) absorb at higher fields than their less crowded counterparts. The environment of one of the methyl carbons in 9-methylanthracene (160), 1,2-dimethylnaphthalene (159) and 1,2,3-trimethylbenzene (161) which have two γ C-C bonds results in increased shielding to 13.7, 14.4 and 15.0 ppm, respectively. This arrangement, of course, is the most extreme example of interacting γ -carbons in aromatic systems.



In contrast, the methyl carbons in 1,8-dimethylnaphthalene, 4-methylphenanthrene, 4-methylfluorene and 4-methylfluorenone having a syn-axial orientations of the methyl carbon and a C-C bond (174) leads to pronounced downfield shifts varying from 0.9 to 8.0 ppm. The changes



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presumably depend on the extent of the steric interaction. This "δ" steric effect has been recently recognized (131, 164). More examples can

and fluorenes were assigned with the assumption of approximately equal spin-lattice relaxation times with predominant dipolar relaxation. Thus, the relative intensities of the quaternary carbon signals reflect their relative nuclear Overhauser enhancements (NOE), those with the closest neighboring protons having the largest NOE. For the fluorenones, this approach failed to give assignments which seemed consistent with the observed shieldings. However, if one assumes that another relaxation mechanism is operative for the quaternary carbons ortho to the carbonyl groups, e.g. a chemical shift anisotropy contribution, a consistent set of assignmetas was obtained as shown in Figure 5.10.

Analysis of the ^{1}H NMR spectra allowed unequivocal assignments of the resonances of the proton-bearing carbons by selective proton decoupling. Proton spectra were examined with the methyl protons or (and) methylene protons decoupled and with other protons decoupled as appropriate to obtain more accurate line positions by removal of line broadening due to small long-range couplings. These spectra were then analyzed with the aid of the iterative spectral fitting program LAOCN$_3$*. After measuring the individual aryl carbon shieldings from noise-decoupled spectra, definitive assignments were obtained for the protonated carbons by single frequency decoupling at relatively low power, with the decoupler frequency set at the appropriate value for each individual proton resonance in sequence. In some cases, the coupled spectrum was used to confirm the the assignments (162).

From the measured effects of the methyl substituents on the ^{13}C shieldings, a set of parameters describing these effects at all aryl

* The author is indebted to Dr. Nancy K. Wilson for these analyses.

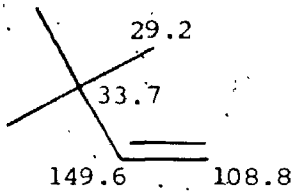
Table 5.21. Methyl Substitution Effects[a] on Several Aromatic Compounds

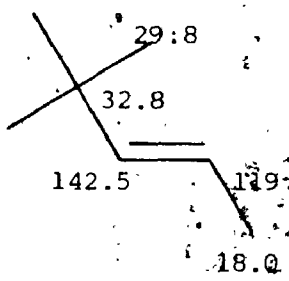
Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14
Toluene	9.3	0.6	-0.2	-3.1	-0.2	0.6								
Napthalene[b]														
1-Me-	6.2	0.8	-0.3	-1.6	0.6	-0.3	-0.2	-3.8	-0.8	0.2				
2-Me-	-1.0	9.6	2.3	-0.6	-0.2	-0.8	0.1	-0.3	0.2	-1.8				
Anthracene[c]														
1-Me-	5.8	0.3	-0.2	-1.5	-0.2	0.0	0.0	0.4	-3.6	0.5	-0.4	0.0	-0.1	-0.3
2-Me-	-1.5	9.6	2.9	0.0	0.2	-0.3	0.0	0.1	-1.0	0.0	0.4	-1.2	-0.4	0.2
9-Me-	-3.6	-0.2	-0.6	0.8	-0.8	-0.6	-0.2	-3.6	3.7	-1.7	-1.6	-0.3	-0.3	-1.6
Phenanthrene														
4-Me-	-1.2	-0.8	4.5	12.7	4.7	-1.2	-0.9	0.0	0.0	0.9	1.2	-0.4	1.2	1.5
Fluorene														
4-Me-	-2.6	-0.4	2.2	13.1	3.3	-0.1	-0.8	-0.2	0.1	0.3	1.0	-1.9	0.4	
Fluorenone														
4-Me-	-2.3	-0.3	2.7	13.4	3.1	0.0	-0.7	0.0	0.6	-2.2	0.4	0.3	0.9	

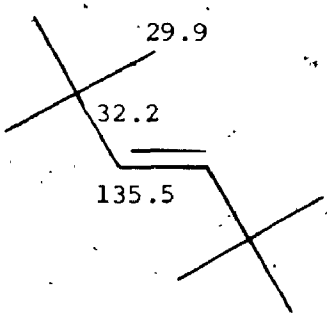
[a] In ppm; positive values denote downfield shifts. [b] Ref. (159). [c] Ref. (160).

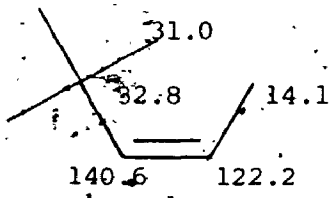
Figure 5.11

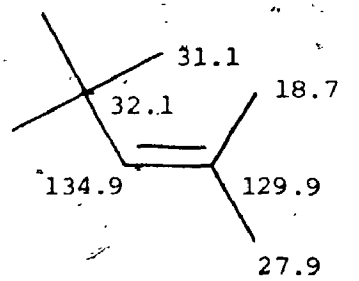
^{13}C Shieldings of Several Olefins











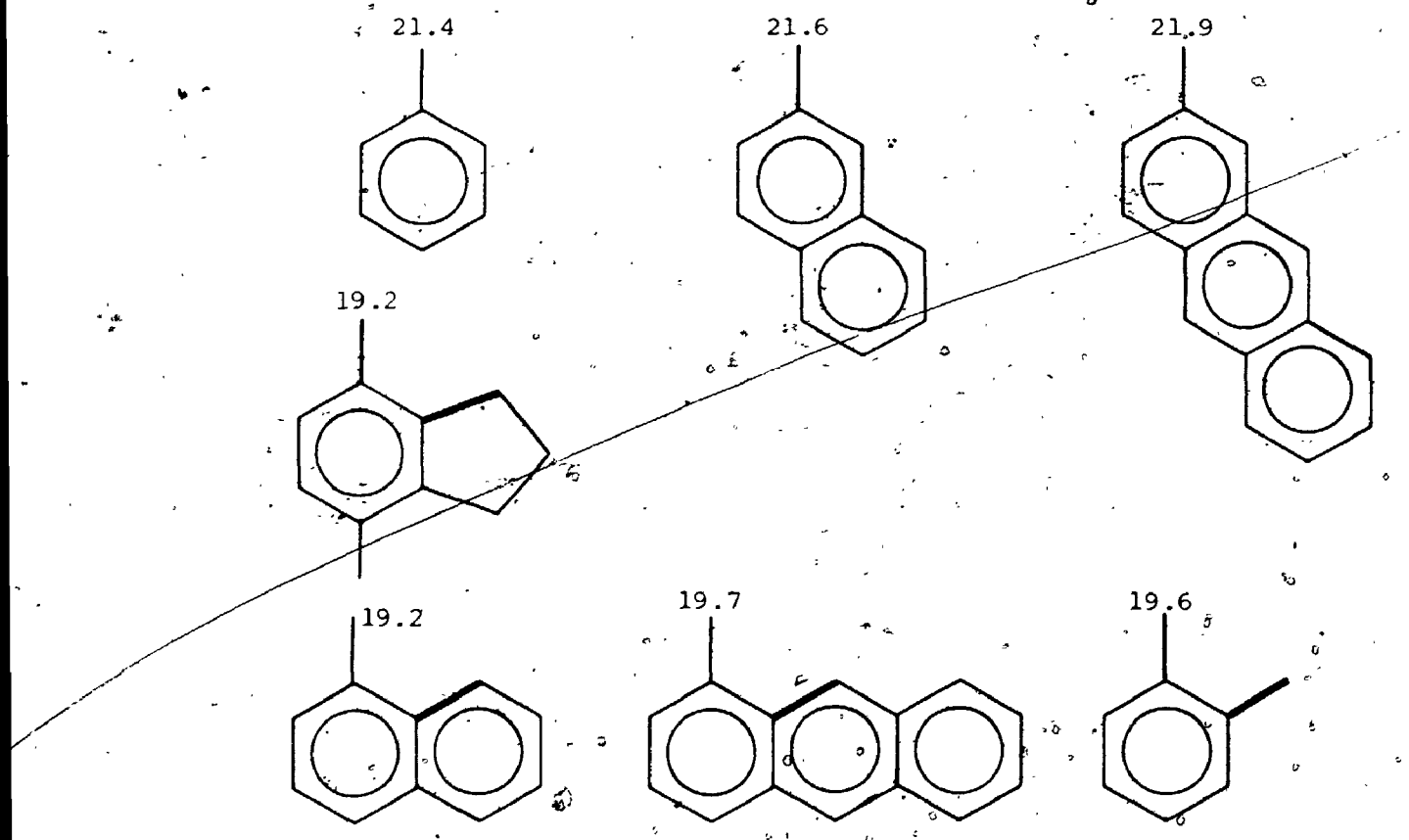
In ppm from internal TMS in $CDCl_3$ solutions.

carbons was derived (Table 5.21).

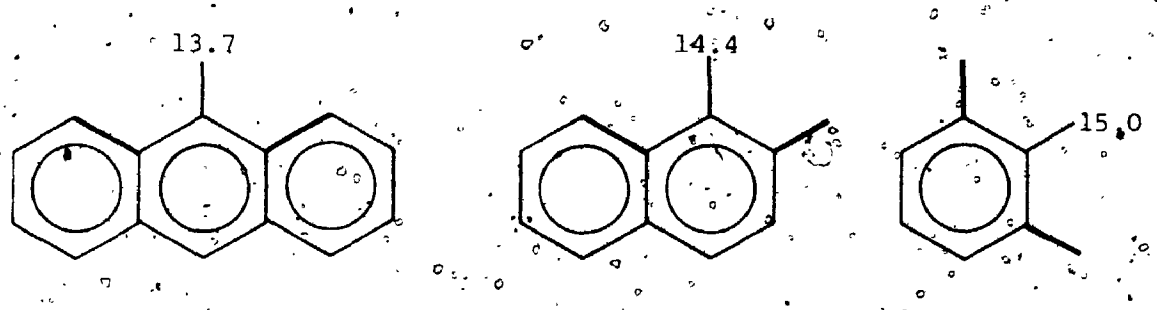
The ^{13}C shielding data of five t-butyl olefins are collected in Figure 5.11.

(i) Methyl Carbon Shieldings

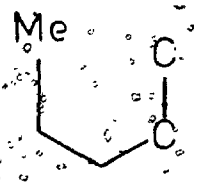
It is interesting that the methyl carbons in toluene, 2-methylnaphthalene and 2-methylanthracene (160) absorb at 21.6 ± 0.3 ppm although these have different aromatic ring systems. But, the methyl carbons in o-xylene, 1-methylnaphthalene, 1-methylanthracene (159) and methyl indene (163) exhibit a significant upfield shift relative to the former cases with an average value of 19.4 ± 0.3 ppm.



These shifts to higher field are precisely as expected since it is well-established that closely-lying carbons separated by three bonds (γ interactions) absorb at higher fields than their less crowded counterparts. The environment of one of the methyl carbons in 9-methylanthracene (160), 1,2-dimethylnaphthalene (159) and 1,2,3-trimethylbenzene (161) which have two γ C-C bonds results in increased shielding to 13.7, 14.4 and 15.0 ppm, respectively. This arrangement, of course, is the most extreme example of interacting γ -carbons in aromatic systems.

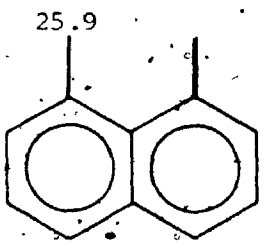


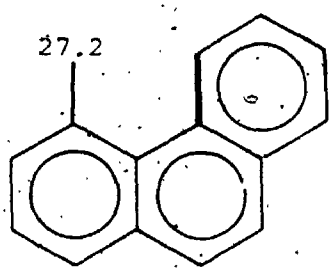
In contrast, the methyl carbons in 1,8-dimethylnaphthalene, 4-methylphenanthrene, 4-methylfluorene and 4-methylfluorenone having a syn-axial orientations of the methyl carbon and a C-C bond (174) leads to pronounced downfield shifts varying from 0.9 to 8.0 ppm. The changes

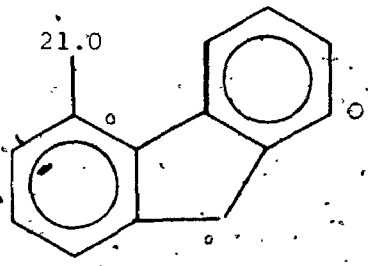


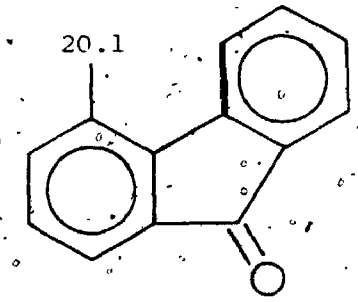
174

presumably depend on the extent of the steric interaction. This "δ" steric effect has been recently recognized (131, 164). More examples can

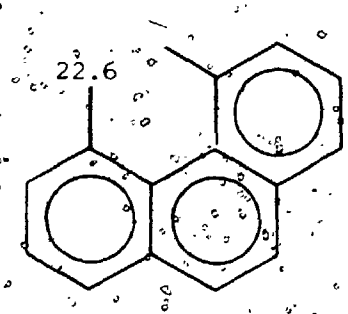


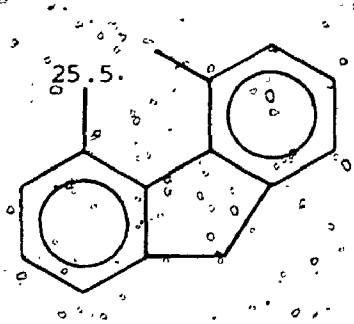


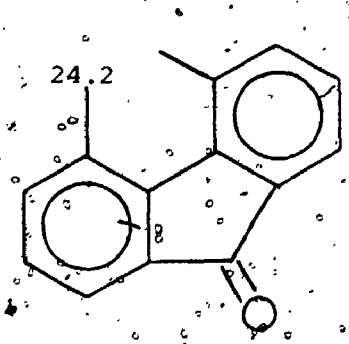




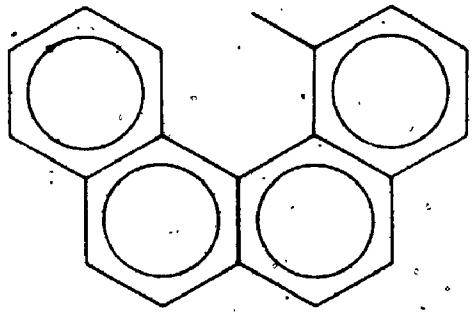
be found in the previous studies. Thus, syn-axial interactions lead to appreciable deshielding shifts which are directly opposite to those for gauche or eclipsed γ nuclei although the nonbonded internuclear distances are comparable for both arrangements. It is desirable to understand the steric effect for the carbon nuclei separated by more than four bonds. Although simple models for the carbon nuclei having steric interactions over more than four bonds are rare, a few examples exhibiting 1,6 Me - Me effects are cited. A shielding δ effect of 4.6 ppm was







found for 4,5-dimethylphenanthrene. In contrast, a deshielding effect of ca. 4.3 ppm was found in the corresponding dimethylfluorene and fluorenone. It thus appears that steric interactions can be either shielding or deshielding. Two pairs of interesting model compounds: 1-methyl- (175), 1,12-dimethyl-benzo[c]phenanthrene (176), 1-methylhexahelicene (177) and 1,16-dimethylhexahelicene (178) which have 1,7 and 1,8 Me - Me interactions, are known (165, 166) and it would be interesting to examine their ^{13}C spectra; unfortunately, these compounds were not in hand.



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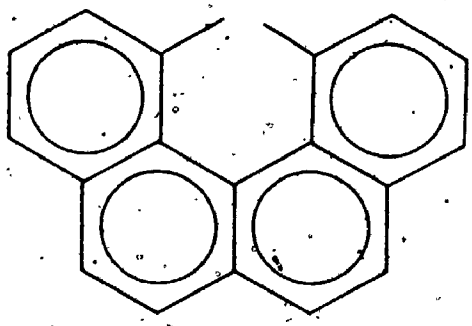

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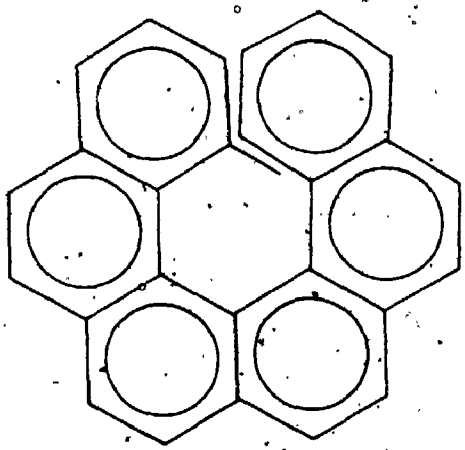

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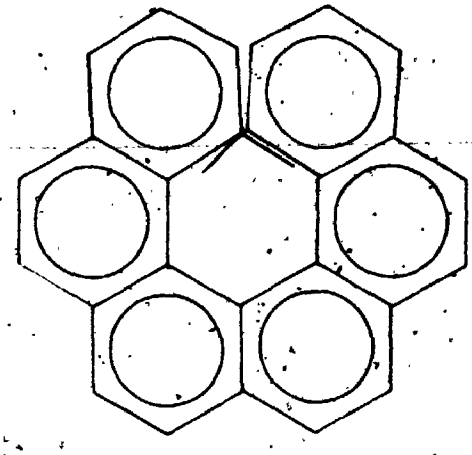

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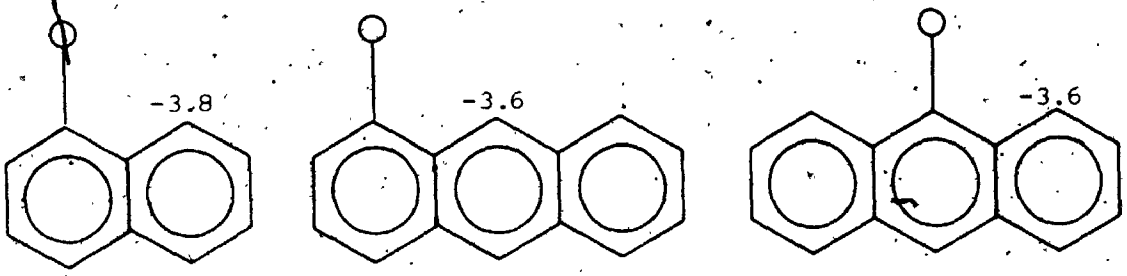
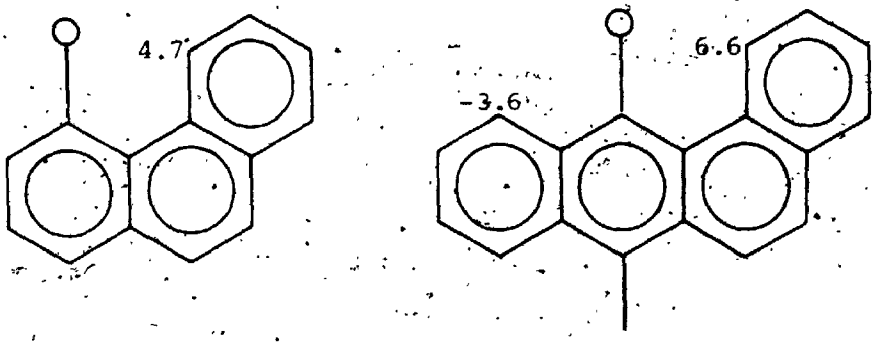
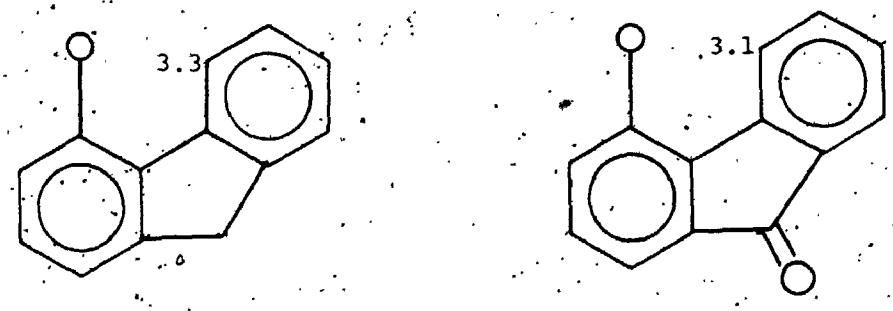
(ii) Ring Carbon Shieldings

In 1-methylnaphthalene, 1-methylanthracene, 9-methylanthracene (160) and 7,12-dimethylbenz(a)anthracene (50c), the γ aryl carbons are shielded by the methyl group by ca. 3.6 ppm. In contrast, in 4-methylphenanthrene, 4-methylfluorene, 4-methylfluorenone and 7,12-dimethylbenz(a)anthracene, the aryl carbons were deshielded by the methyl group by 4.7, 3.3, 3.1 and 6.6 ppm, respectively, each of which has a "δ" steric interaction between them.







(F) SUMMARY

The ^{13}C spectra of a series of cyclic and bicyclic compounds have been determined to gain further insight into the nature of stereochemical effects on the shieldings of carbons having closely neighboring substituents. The relatively rigid skeleton in these molecules permits examination of a variety of orientations of substituents separated by three and four bonds, the γ and δ interactions, respectively. The chemical shifts for the carbons three and four bonds from the site of the substituent depend strongly on their orientation with respect to the substituent group. Methyl carbons close to γ substituents exhibit upfield shifts and the shielding variations are a function of the mutual orientation. For small dihedral angles, 0 - 60°, as in eclipsed and gauche arrangements, there is a pronounced upfield shift relative to the shielding for the 120° orientation. A complementary trend is exhibited by the carbons bearing the γ nuclei, i.e. all carbons in the γ fragment are more shielded in orientations having relatively small dihedral angles. The penultimate carbons absorb as much as -10 ppm from the values expected by additivity. Carbons closely neighboring δ nuclei (other than hydrogen) are deshielded relative to those for gauche or eclipsed γ nuclei although the nonbonded internuclear distances are comparable for both arrangements. The penultimate carbons in a fragment having a δ interaction between terminal groups show deviations of up to +11 ppm from the shieldings predicted by simple additivity. These deviations have considerable potential for stereochemical assignments and also offer a challenge for theoretical interpretation.

The methyl carbon shieldings for a series of methylated phenanthrenes,

fluorenes and fluorenones reveal that 1,6 Me - Me interactions (ε effects) produce both deshielding and shielding effects.

Thus, steric crowding of carbon nuclei may lead to downfield shifts (syn-axial δ and ε effects) or upfield shifts (the well-known γ gauche effects and ε effect). These unusual trends could render detailed interpretations of the ^{13}C spectra of complex system difficult.

CHAPTER 6

EXPERIMENTAL

As the experimental methods engaged in this work are by themselves unique and may be of interest to those working with organic synthesis, the experimental parts of the preceding chapters have been left out where they should be and put together here in this chapter.

(A) GENERAL

Melting points were obtained on a Reichert melting point apparatus and are uncorrected. Gas chromatographic (g.c.) analyses were performed with columns on an Aerograph series 1400 instrument, using nitrogen as carrier gas and a hydrogen flame detector. The following columns were used: 10% SE 30 on 60/80 Chromosorb W (1/8" x 14'), 15% DEGS on 80/100 Chromosorb P (1/8" x 7') and 10% Carbowax 4000 on 60/80 Chromosorb W (1/8" x 10'). Preparative g.c. separations were accomplished with an Aerograph Dual Column gas chromatograph with thermal conductivity detectors and using helium as the carrier gas. The following columns were used: 20% SE 30 on 60/80 Chromosorb W (3/8" x 25'), 20% DEGS on 80/100 Chromosorb P (3/8" x 27'), 20% Carbowax 4000 on 80/100 Chromosorb P (3/8" x 11') and 15% FFAP on 80/100 Chromosorb (1/4" x 12'). Infrared spectra were obtained on a Beckman IR-10 spectrophotometer. Routine proton spectra (for following reactions and checking purity) were obtained on a Varian T-60 NMR spectrometer.

Distillations of mixtures of isomers with close boiling points were carried out on a Nester / Faust 46 cm platinum spinning band column. For

the purification of liquids of ca. 1 gm containing essentially only one isomer, bulb-to-bulb distillation apparatus constructed by H. Brouwer was used.

No attempts was made to maximize the yields of the reactions since the object of the preparative work was merely to obtain the compounds of interest. Purity of the final products, as determined by g.c. and/or NMR was at least 95% except for some pairs of isomers which were difficult to separate.

The structures of most of the compounds studied were known. The structure determination of new compounds was based on the structure of the starting material, the reaction used and analysis of the spectral data. In most cases, an elemental analysis or precise mass determination was obtained on the compound. Precise mass data were obtained on a Varian M-66 mass spectrometer. Elemental analyses were done by Chemalytics Inc., Tempe, Arizona.

(B) NMR SPECTRA

Proton NMR spectra were recorded with either a Varian T-60, or HA-100 spectrometer while ^{13}C spectra were obtained using a Varian XL-100-15 system operating in the Fourier transform mode. Solutions (5 - 15 % w/v) in deuteriochloroform or hexadeuteriobenzene containing a few drops of TMS as an internal standard were examined in 5 mm tubes using a 5 mm receiver insert. All peak positions were measured relative to TMS and the shieldings have precisions greater than 0.1 ppm. In general, 2000 transients were accumulated for each compound except for samples of less than 15 mg) for which longer runs were required. Off-resonance decoupling was employed to confirm the assignments for methyl, methylene, methine,

and quaternary carbons. Selective decoupling experiments were utilized to assign some carbon signals for which the ^{1}H resonances could be identified in an ^{1}H NMR spectrum. In these experiments the decoupler was operated at low power (108 - 112 dB) and carefully adjusted to the resonance frequency of an individual proton to cause the specific signal of the carbon attached to that proton to collapse to a sharp singlet while other protonated carbon signals retain some C-H coupling. Thus it is possible to relate ^{1}H and ^{13}C spectral lines directly. A gated decoupling technique was employed to aid the assignments for some aromatic carbons as described originally by Günther (102). Specifically deuterated materials were examined in some cases to distinguish the signals for carbons near the deuterated center (see Chapter 2). In a few cases, shift reagents were also used for signal assignments.

(C) EXPERIMENTAL FOR CHAPTER 2

MATERIALS

The samples of camphor-3-exo-d_1 and camphor-3,3-d_2 were kindly supplied by Prof. E.W.Warnhoff and Dr. G.C.Joshi. The preparation of four 5,6-dimethylnorcamphors will be described in Section E. The four exo-3-deuterio-5,6-dimethylnorcamphors were prepared by base-catalyzed exchange of enolizable hydrogen atoms with MeOD/ MeOK.

Approximately 150 mg of a ketone was refluxed in 10 ml of 0.4N MeOK / MeOD under a nitrogen atmosphere for 20 hr. The mixture was cooled, diluted with 20 ml of distilled water and extracted twice with pentane. The extract was washed with water, then dried with anhydrous magnesium sulfate. Evaporation of the solvent afforded ~ 120 mg of deuterated-

ketone.

(D) EXPERIMENTAL FOR CHAPTER 3

(a) MATERIALS.

Commercial fenchone and adamantanone were employed for these studies. Adamantanone was used without further purification. Initially, the camphor present as an impurity in fenchone (~ 5%) was not removed before use but in the later stages this impurity was removed by reaction with 2,4-dinitrophenylhydrazone or preparative gas chromatography on a 20% SE-30 column. Other starting materials were prepared as described below.

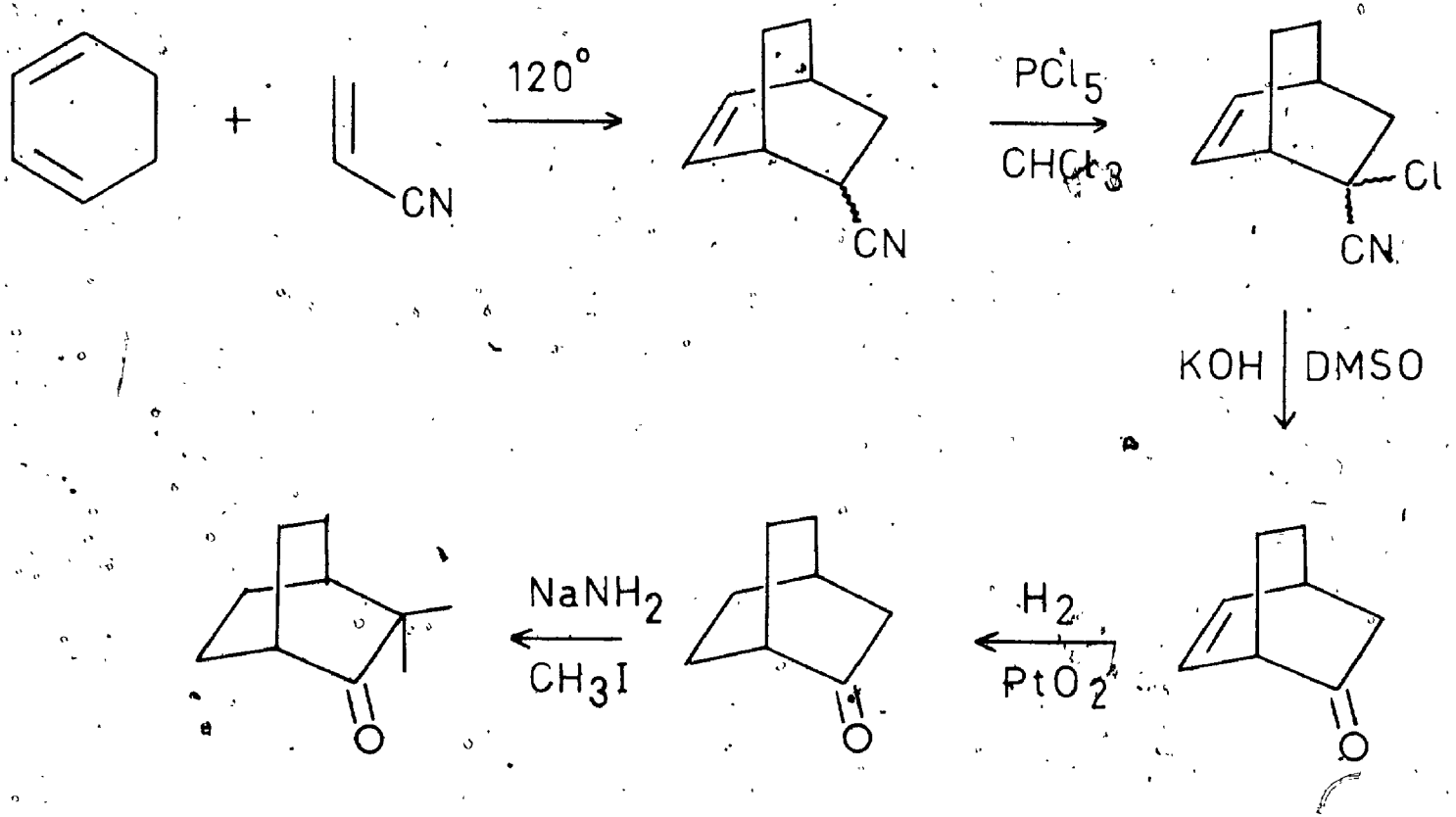
(i) Synthesis of 3,3-dimethylbicyclo(2.2.2)octan-2-one (42)

A seven stage synthesis was used to obtain this compound (Scheme 6.1). The precursor, bicyclo(2.2.2)oct-5-en-2-one (167) was prepared by Diel-Alder addition of acrylonitrile to 1,3-cyclohexadiene, chlorination of the nitrile adduct with phosphorous pentachloride, followed by hydrolysis of the resulting α-chloronitrile with potassium hydroxide in aqueous dimethyl sulfoxide. The desired ketone was obtained by catalytic hydrogenation of the unsaturated ketone over platinum oxide in ether, followed by methylation using $NaNH_2/CH_3I$ (168).

1,2-Dibromocyclohexane

In a three-necked flask, fitted with a 500 ml separatory funnel, a mechanical stirrer and a thermometer, was placed a solution of 123 g (1.5 mole) of cyclohexene in a mixture of 300 ml of CCl_4 and 15 ml of absolute alcohol. The flask was surrounded by a dry ice and isopropyl alcohol bath (-30°). A solution of 210 g of bromine in 145 ml of CCl_4 was added from

Figure 6.1. Preparation of 3,3-Dimethylbicyclo(2.2.2)octan-2-one



the separatory funnel at such a rate that the temperature of the reaction mixture did not exceed -1°. After the reaction was complete, the excess cyclohexene, CCl_4 and alcohol was removed by simple distillation. Finally, the product was distilled at 99-103° / 16 mm (lit. 115° - 117° / 28 mm (169)) and the yield was 93% (295 g).

1,3-Cyclohexadiene

A modification of the method of Schaefe, Endres and Moran (170) was used to prepare 1,3-cyclohexadiene.

In a three-necked flask, fitted with a mechanical stirrer, a dropping funnel and a Claisen column, was placed potassium hydroxide (88 g) and triglyme (340 ml). The flask was heated in an oil bath at 150° and the contents stirred until the potassium hydroxide dissolved. To the Claisen column was connected a condenser and a vacuum receiver adapter with a dry-ice-acetone receiver. Maintaining the temperature at 150°, the pressure was reduced to approximately 200 mm and 1,2-dibromocyclohexane (121 g), was added slowly, the rate of addition was kept equal to the rate of distillation. Upon completion of the distillation, the distillate was washed with saturated sodium chloride solution, dried with anhydrous $MgSO_4$ and fractionally distilled to give 22.2 g (55.5%) of 1,3-cyclohexadiene, bp 80° (lit. 80.5° (170)).

2-Cyano-bicyclo(2.2.2)oct-5-ene

A solution of 1,3-cyclohexadiene (50 g) and freshly distilled acrylonitrile (36 g) was placed in four pyrex thick-walled tubes, which were then cooled with a dry-ice-acetone bath and sealed under vacuum. The tubes were heated at 120° for 16 hr. The tubes were be opened carefully and excess acrylonitrile was removed by distillation. Pure 2-cyano-bicyclo-

(2.2.2)oct-5-ene (73.9 g; 88.9%) was distilled through the spinning-band column (bp 92°/12 mm, lit.104 - 106°/12 mm (171)). The liquid which solidified in the receiver immediately had the following physical properties: mp 57 - 63° (lit. 58°; (171)), IR(CCl_4): $\nu_{C\equiv N}$ 2245 cm^{-1}, $\nu_{C=C}$ 1620 cm^{-1}.

5-chloro-5-cyanobicyclo(2.2.2)oct-2-ene

5-Cyanobicyclo(2.2.2)oct-2-ene (73.9 g) was added slowly with stirring to a solution of pyridine (104.5 g) and phosphorous pentachloride (200 g) in 1500 ml of dry chloroform (distilled from phosphorous pentachloride). After refluxing for 24 hr, the mixture was poured onto 2 kg of ice. After the ice had melted, the layers were separated and the aqueous phase was washed three times with ether. The organic extracts were combined and washed once with 10% aqueous sodium carbonate, once with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation gave 64.8 g (69.7%) of the chloronitrile, mp 88 - 93° (lit. 88 - 90° (167)) (recrystallized from ethanol-water); the IR spectrum showed absorption at 2230, 1620 cm^{-1}.

Bicyclo(2.2.2)oct-2-en-5-one

A hot solution of 100 g of 85% potassium hydroxide was added to a solution of 60 g of the chloronitrile in 500 ml of dimethyl sulfoxide. There was a gradual darkening of colour from yellow to black and a mild increase in temperature from 50° to 65°. After standing for 24 hr, the reaction mixture was poured into 1 kg of ice-water and extracted five times with petroleum ether (bp 30 - 60°). Drying over magnesium sulfate and removal of the solvent left a semisolid mass which was sublimed to give 25.5 g (43.7%) of the desired ketone, which had the following physical properties: mp 89 - 90.5° (lit. 84 - 86° (167)), IR(CCl_4):

$\nu_{C=O}$ 1730 cm^{-1}, $\nu_{C=C}$ 1610 cm^{-1}.

Bicyclo(2.2.2)octanone

Hydrogenation of the unsaturated ketone in ether using platinum oxide as the catalyst in the Parr hydrogenator at 50 psi gave bicyclo(2.2.2)-octanone having the following physical properties: mp 170 - 171° (lit. 172 - 173° (172)), IR($CHCl_3$): $\nu_{C=O}$ 1710 cm^{-1}; ^1H NMR(CCl_4); 1.77 ppm (bs, 8H), 2.17 ppm (bs, 4H).

3,3-Dimethylbicyclo(2.2.2)octan-2-one

To a stirred suspension of 4.71 g of freshly powdered sodium amide in 300 ml of ether under a nitrogen atmosphere was added in one portion a solution of 5 g of bicyclo(2.2.2)octanone in 25 ml of dry ether. The mixture was agitated vigorously with a powerful stirrer for 20 hr. The resulting mixture was treated with 60 g of freshly distilled methyl iodide in one portion and stirred for 5 hr. Excess sodium amide was hydrolyzed by water and the product isolated by ether extraction. The ether extracts were washed with water, saturated sodium chloride solution and then dried over anhydrous magnesium sulfate. The solvent was removed by distillation and the residue was retreated with sodium amide in ether and the methylation procedure repeated. The resulting product was chromatographed on an alumina column (eluted first with pentane, then 10% ether in pentane) to give 4.73 g (77%) of the dimethylketone which was shown to be 99% pure by g.c. After sublimation, this ketone was used for the homoenolization studies. Gas chromatography was used to obtain the analytical sample which had the following properties: $\nu_{max}^{CCl_4}$ 1705 cm^{-1}; ^1H NMR 1.08 (s, Me); mp 102 - 103° (sealed capilliary tube).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59.

Found : C, 79.05; H, 10.81.

(ii) Preparation of 7,7-dimethylbicyclo(3.2.1)octan-6-one (45)

3-Bromobicyclo(3.2.1)oct-3-en-6-yl formate was prepared by the procedure of Saucers et al.(173) in which dibromocarbene is added to norbornadiene, followed by lithium aluminium hydride reduction and the addition of formic acid (173). Hydrogenation using palladium on carbon in basic solution led to the reduction of the double bond, hydrogenolysis of the bromine, and hydrolysis of the formate group, giving exo-bicyclo-(3.2.1)octan-6-ol. Oxidation with chromic acid gave bicyclo(3.2.1)octan-6-one. Methylation of this ketone with $NaNH_2/CH_3I$ gave 7,7-dimethyl-bicyclo(3.2.1)octan-6-one.

Addition of dibromocarbene to norbornadiene

A solution of 236 g of freshly distilled bromoform in an equal volume of pentane was added dropwise with stirring to a mixture of 86.3 g of potassium t-butoxide and 85 g of bicyclo(2.2.1)heptadiene in 300 ml of pentane maintained at 0°. Stirring was continued for 30 min after the addition was completed. Then, after the mixture had warmed to room temperature, water was added. The pentane extract was washed with water and dried with anhydrous magnesium sulfate. Solvent and unreacted starting material were removed by distillation under reduced pressure and 87.3 g of a pale yellow liquid distilled at 95 - 97° / 0.3 mm (lit 77° / 0.05 mm (174)).

3-Bromobicyclo(3.2.1)octadiene

The mixture (87.3 g) of three bromides from the addition of dibromo-carbene to norbornadiene was added dropwise to a stirred mixture of 12 g

of lithium aluminum hydride in 1.5 l of anhydrous ether. After the addition was completed, refluxing was continued for 40 hr, then the mixture was worked up in the usual way. Distillation gave 39.8 g of 3-bromobicyclo(3.2.1)-octadiene, bp 68 - 75° / 5 mm (lit. 63°/ 5 mm (174)).

exo-3-Bromobicyclo(3.2.1)oct-2-en-7-yl formate

A 15% solution (by wt) of 34.7 g (0.246 mole) of 3-bromobicyclo(3.2.1)-octadiene in 231 g of 98% formic acid was placed in a flask and stirred for 72 hr at room temperature. The resulting dark solution was diluted with three times its volume of water and neutralized with solid sodium carbonate. The mixture was extracted three times with 500 ml of ether. After drying, distillation gave 34.5 g (80%) of the bromoformate (lit. 90 - 105°/ 0.05 - 0.1 mm (173)).

Bicyclo(3.2.1)octan-6-ol

A mixture of 40 g (0.175 mole) of 3-bromobicyclo(3.2.1)oct-2-en-yl formate, 160 ml of tetrahydrofuran, 212 ml of 2N NaOH solution, and 10 g of 5% palladium on charcoal was treated with hydrogen using a Parr apparatus until no more hydrogen was taken up. The solution was filtered and the filtrate was diluted with 900 ml of water and acidified with 1N HCl solution. The mixture was extracted with three portions of ether (300 ml). After drying, removal of the solvent by distillation gave 19.7 g (90%) of a brown solid which could be used without further purification. A small amount of the alcohol was sublimed, further purified by g.c. and was found to have the following physical properties: mp 144 - 145° (lit. 147 - 149° (174)); IR(CCl_4) ν_{OH} 3630; ^1H NMR ($CDCl_3$): δ 1.1 - 2.6 (13H), 4.13 (dddd, CHOH).

Bicyclo(3.2.1)octan-6-one

To a stirred solution of 15 g (0.12 mole) of the crude bicyclo(3.2.1)-octan-6-ol in 58 ml of acetone was added dropwise a solution of 23 g of chromium trioxide in 17 ml of conc. sulfuric acid diluted to a total volume of 80 ml with water. The temperature was kept between 20 - 30° using an ice-water bath. The chromic acid solution was added until the orange-brown color persisted. The mixture was allowed to stand overnight at room temperature. Sodium bisulfite was then added until the green colour persisted. The liquid was decanted from the green sludge, and the residue was washed three times with ether. After drying over anhydrous potassium carbonate, the acetone was removed by distillation and the residue was sublimed giving 12 g (81%) of the ketone, mp 145 - 151°. A small amount of the ketone was further purified by g.c. and had mp 157 - 159° (lit. 155 - 157°).

7,7-Dimethylbicyclo(3.2.1)octan-6-one (45)

Following the method described previously (p.297), methylation of bicyclo(3.2.1)octan-6-one using sodamide and methyl iodide afforded 56% of 7,7-dimethylbicyclo(3.2.1)octan-6-one. The pure sample was isolated by preparative gas chromatography(using a SE-30 column)which had the following properties; $\nu_{max}^{CDCl_3}$ 1715 cm^{-1}; ^1H NMR: δ 1.07 (s, Me), 1.11 (s, Me); low melting solid, 2,4-dinitrophenylhydrazone, mp 165.0 - 165.5°.

Mol. wt. Calcd. for $C_{10}H_{16}O$: 152.1200. Found (m/e): 152.1199.

(iii) Preparation of the $\alpha, \alpha, \alpha', \alpha'$ - tetramethyl-monocyclic ketones

The preparation of these ketones was accomplished using a modification of the procedure described by Corey et al (168). The modification

consisted of the use of a large excess of sodium amide and the slow addition of methyl iodide to the reaction mixture without removal of excess sodium amide. In this way the methylation of cyclopentanone, 2,5-dimethylcyclopentanone and cyclohexanone (for which the methylation procedure was repeated twice) produced the appropriate tetramethylated ketone as the sole product. But the methylation of cyclopentanone and cyclooctanone gave trimethylated ketones. Presumably the formation of the enolate of the trimethylated ketone is very slow under these reaction conditions. The synthesis of 2,2,7,7-tetramethylcycloheptanone and 2,2,8,8-tetramethylcyclooctanone was achieved using base, less solvent and longer reaction times. The physical properties of these methylated ketones are summarized in Table 6.1 and 6.2.

Procedure

To a stirred suspension of 10.5 g (0.269 mole) of freshly powdered sodium amide in 800 ml of anhydrous ether under a nitrogen atmosphere was added in one portion a solution of 10 g (0.089 mole) of cycloheptanone in 25 ml of dry ether. The mixture was agitated very vigorously with a powerful stirrer for 4 hr at room temperature. Then, 127 g (0.89 mole) of methyl iodide was added slowly and the stirring continued for another 20 hr. Excess sodium amide was hydrolyzed by the addition of water and the product isolated by ether extraction. The ether extracts were washed with water, saturated sodium chloride solution and then dried over anhydrous magnesium sulfate. The solvent was removed by distillation and the residue was treated with sodium amide in ether and the methylation procedure repeated. One further cycle gave the pure product which was isolated by fractional distillation under reduced pressure. The physical properties and elemental analyses of the new ketones are listed in Table 6.1 and 6.2.

Table 6.1

Physical Properties of Several Methylated Cyclic Ketones

Compound	% Yield	bp (°C)	IR(CCl_4) cm^{-1}	pmr($CDCl_3$): (ppm)	e/m
2,2,5,5-Me_4-cyclopentanone	72[a]	165 (lit.156 (175))	1730	1.03 (s, 12 H) 1.78 (s, 4 H)	140.1
2,2,6,6-Me_4-cyclohexanone	67[b]	120-122/80 mm (lit.185 (176))	1700	1.08 (s, 12 H) 1.70 (m, 6 H)	154.1
2,2,7,7-Me_4-cycloheptanone	61[c]	95/18 mm	1695	1.16 (s, 12 H) 1.63 (s, 8 H)	168.1
2,2,8,8-Me_4-cyclooctanone	87[d]	97/7 mm	1690	1.17 (s, 12 H) 1.17-1.22 (m)	182.1
2,2,6-Me_3-cyclohexanone	from g.c.		1720	1.00 (d, 6.5 Hz) 1.04 (s) 1.20 (s)	140.0
2,2,7-Me_3-cycloheptanone	50[e]	110-112/40 mm	1710	1.0 (d, 8 Hz) 1.05 (s)	154.0
2,2,8-Me_3-cyclooctanone	90[f]	88-90?11 mm	1715	1.0 (d, 8 Hz) 1.03 (s)	168.0

[a] From 2,5-Me_2-cyclopentanone (2 methylations).

[b] From cyclohexanone (3 methylations).

[c] From 2,2,7-Me_2-cycloheptanone (2 methylations).

[d] From 2,2,8-Me_3-cyclooctanone (1 methylation).

[e] From cycloheptanone (3 methylations).

[f] From cyclooctanone (1 methylation).

Table 6.2

Elemental Analyses of Some Methylated Cyclic Ketones

Compound	Calculated		Found	
	% C	% H	% C	% H
2,2,7-Me_3-cycloheptanone	77.87	11.76	77.66	11.81
2,2,7,7-Me_4-cycloheptanone	78.51	11.98	78.62	12.03
2,2,8-Me_3-cyclooctanone	78.51	11.98	78.78	11.99
2,2,8,8-Me_4-cyclooctanone	79.06	12.17	79.08	12.28

(b) HOMOENOLIZATION EXPERIMENTS

t-Butyl alcohol-O-d_1 was prepared according to the procedure of Young and Guthrie (177). After the initial hydrolysis of the borate ester, a small amount of potassium metal was added to the wet alcohol and the alcohol was distilled. This was repeated and a third distillation from molecular sieves gave t-butyl alcohol-O-d_1 which was < 0.005 M in water by Karl Fischer titration. t-Butyl alcohol was dried by refluxing with calcium hydride and distilled.

The general procedure followed for the homoenolization studies was essentially as described by Nickon et al. (56, 57). In general, the ketone was added to the base, prepared by refluxing freshly cut potassium in t-butanol under nitrogen for 24 hr (until the potassium dissolved), to give a solution containing ketone / t-BuO$^-$ / t-BuOH(D) in a mole ratio of 1:4:40. Aliquots were placed in glass tubes which were already filled out with nitrogen gas. The tubes were sealed under vacuum after being degassed with nitrogen at least three times. After heating at 185 ± 3° for varying periods of time, the tubes were opened and the ketonic products isolated by pentane extraction in average yields of 80%. The total product composition was determined by g.c. on 20% SE-30; 10% FFAP or 20% DEGS columns. In each case, the starting material and the rearrangment product(s) were isolated by preparative g.c. on SE-30 columns.

(c) NMR ASSAYS OF THE ^{2}H DISTRIBUTION.

^{13}C spectra were obtained with a Varian XL-100-15 system operating in the Fourier transform mode. To optimize operating conditions for measuring the integrated signal intensities in the ^{13}C spectra, samples in

$CDCl_3$ or C_6D_6 solutions were run under a variety of conditions varying the pulse width and repetition rate using sweep "windows" of 1 KHz or less. Under conditions which gave essentially equal integrals for each nonequivalent protonated carbon in the normal sample, the deuterated samples at similar concentrations were examined and the relative intensities of the absorptions for each carbon were measured. As a check on these results, mass spectral data were obtained using a Varian M-66 instrument to determine the relative concentrations of the various deuterated species in each sample. The estimates of the deuterium content at the individual carbons by ^{13}C NMR were judged to be within ±5% and comparison of the total ^2H content with that from the mass spectra support this.

Deuterium spectra were obtained at 15.4 MHz with a Varian XL-100-15 system operating in the Fourier transform mode. A solvent mixture of C_6F_6 and $CHCl_3$ (1:4 or 4:1 v/v) was used and the instrument was locked to the ^{19}F signal with noise modulated proton decoupling. Because of the relatively small ^2H shift range, on a frequency scale, and the fact that the signals are ~ 1 Hz wide, the individual signals of similar deuterium nuclei are heavily overlapped. Greater shift dispersion was obtained through the use of the $Pr(fod)_3$ shift reagent but line broadening accompanied the increased dispersion. Consequently, line-shape fitting by computer, assuming Lorentzian line shapes, was employed to obtain the relative areas of the individual absorption signals. For this purpose a modified version of the BMDX85 program (178) was used. With the total deuterium content, as measured by mass spectrometry, the relative concentrations of deuterium at the individual centers was readily calculated and these data are judged to have precisions of 1%. Shift reagent studies of

the proton spectra of non-deuterated samples, using a Varian HA-100 instrument, were also carried out to confirm the assignments in the ^2H spectra.

(E) EXPERIMENTAL FOR CHAPTERS 4 AND 5

(a) PREPARATION OF THE BICYCLO(2.2.1)HEPTANE DERIVATIVES

The (2.2.1) ring skeleton was obtained in all cases via a Diels-Alder reaction involving freshly distilled cyclopentadiene and dienophiles such as maleic anhydride (179), crotonic acid (180), acrylonitrile (181) and methyl acrylate (182), followed by the appropriate chemical transformations required. One example is summarized in Figure 6.2.

The Diels-Alder reaction of methyl acrylate with cyclopentadiene at $0^{\circ}C$ produced a 3:1 mixture of 2-endo and 2-exo-methoxycarbonyl-5-norbornene. The mixture of esters was converted to the corresponding acids with alkaline hydrolysis, followed by the iodo-lactone procedure (181) to separate the exo- and endo- isomers. Since only the endo-acid has the required orientation to form a lactone, the exo-acid is recovered by separation of the neutral material from the acid salt and regenerated by acidification. The iodolactone was reconverted to the unsaturated endo-acid by treatment with zinc in acetic acid. The exo-acid could also be prepared from the Diels-Alder reaction of acrylonitrile with cyclopentadiene followed by conversion to 2-norbornen--5-exo-carboxamide in the presence of sodamide and liquid ammonia which was saponified readily to the mainly exo-acid with aqueous sodium hydroxide (181).

The exo- and endo-acid could be converted to the corresponding alcohol by means of lithium aluminum hydride reduction. Their tosylates were treated with lithium aluminum hydride in anhydrous ether to afford the

Figure 6.2. Preparation of trans-5,6-Dimethylnorbornyl Derivatives

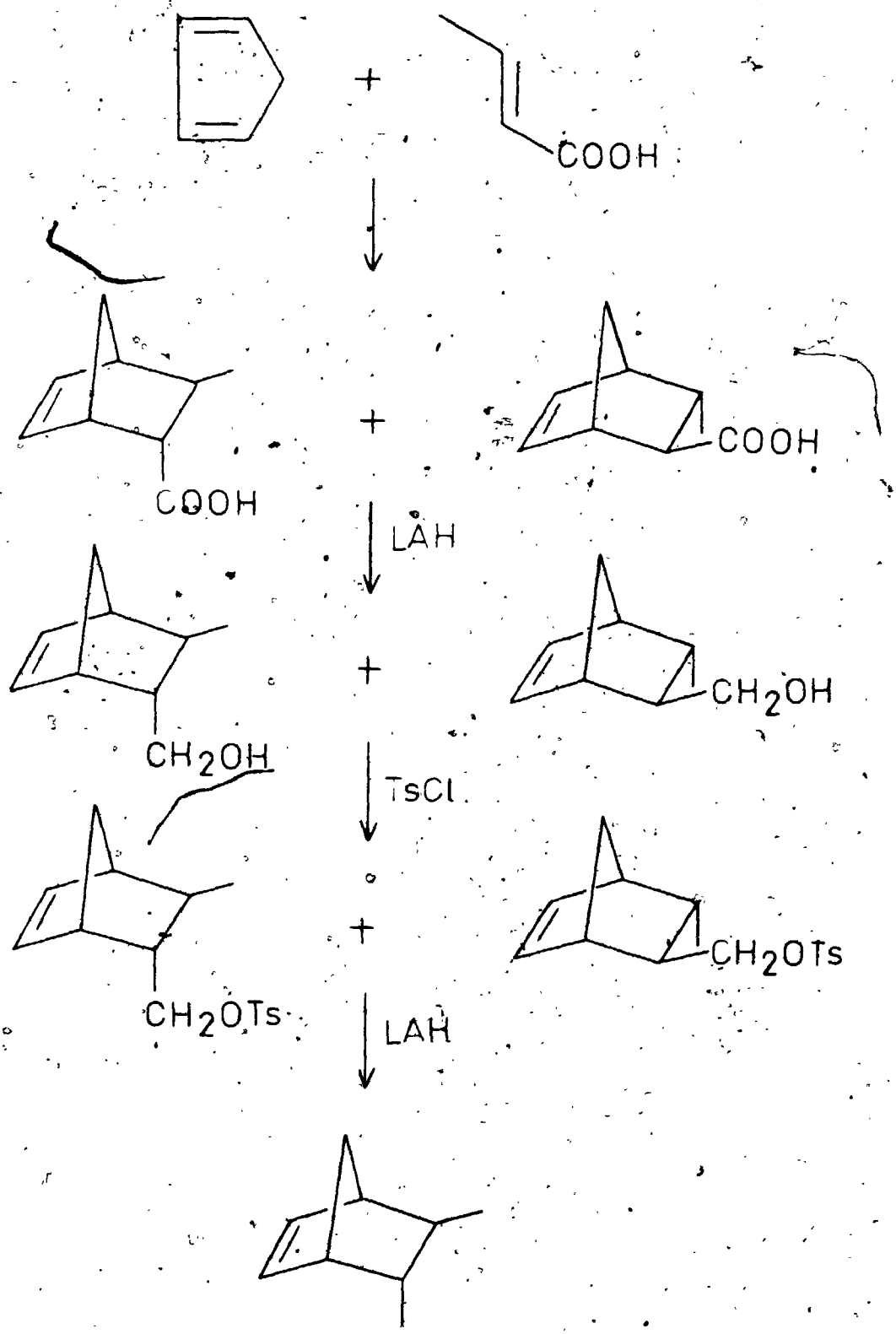
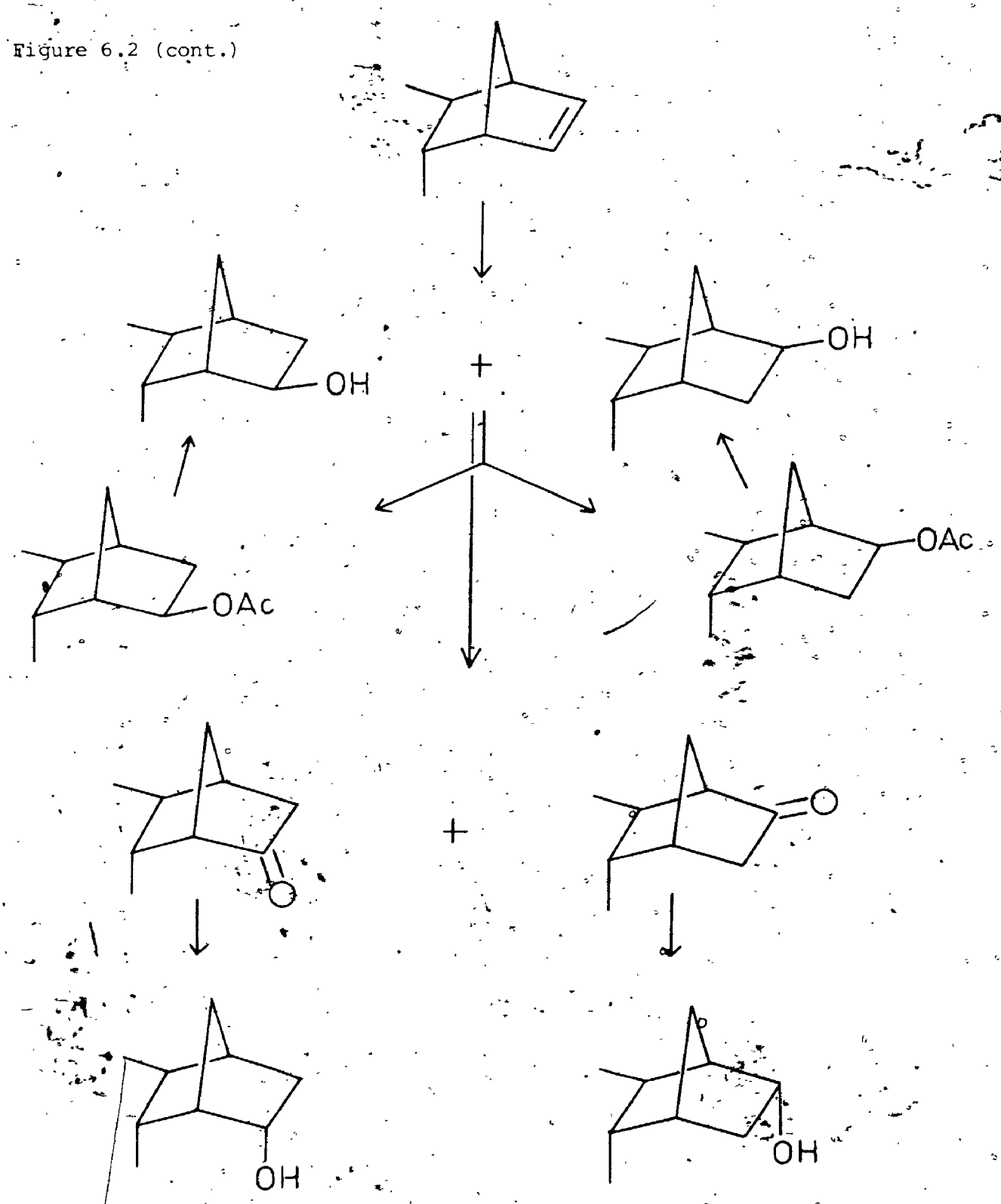


Figure 6.2 (cont.)



corresponding exo-5 and endo-5-methylnorborn-2-enes.

The addition of maleic anhydride to cyclopentadiene proceeds smoothly in ethyl acetate and ligroin solution at 0° to give exclusively the endo-anhydride (179) adduct. The endo-anhydride adduct was thermally isomerized to the exo-form at 190° by the method of Crag (183). The pure exo-anhydride was obtained by several recrystallizations from benzene followed by two recrystallizations of the corresponding diacid. Condensation of cyclopentadiene and crotonic acid yielded a mixture of trans-acids (180). The two isomeric anhydrides and the mixture of trans-acids were converted to three isomeric 5,6-dimethylnorborn-2-enes by the chemical transformations shown in Figure 6.2. Since the anhydrides are only sparingly soluble in ether and because the esters are more easily reduced than the anhydrides, the anhydrides were then converted to diethyl esters by refluxing with absolute ethanol, triethylorthoformate and concentrated sulfuric acid. Reduction of the diesters and of the mixture of acids with lithium aluminum hydride afforded the corresponding diols and alcohols. The ditosylate and the mixture of tosylates prepared from the corresponding diols and the mixture of alcohols were reduced by lithium aluminum hydride to 5,6-dimethylnorborn-2-ene in the manner described by Russell and co-workers (184). The physical properties of the olefins are summarized in Table 6.3. The ^{1}H NMR spectra of three 5,6-dimethylnorborn-2-ene are shown in Figure 6.3. Hydrogenation of the norbornenes in anhydrous diethyl ether using platinum oxide as catalyst in the Parr hydrogenator at 50 psi gave the saturated hydrocarbons (Table 6.4).

Hydroboration of endo, endo-5,6- and exo,exo-5,6-dimethylnorborn-2-ene gave the epimerically pure exo-alcohols. Hydroboration of exo-5-,

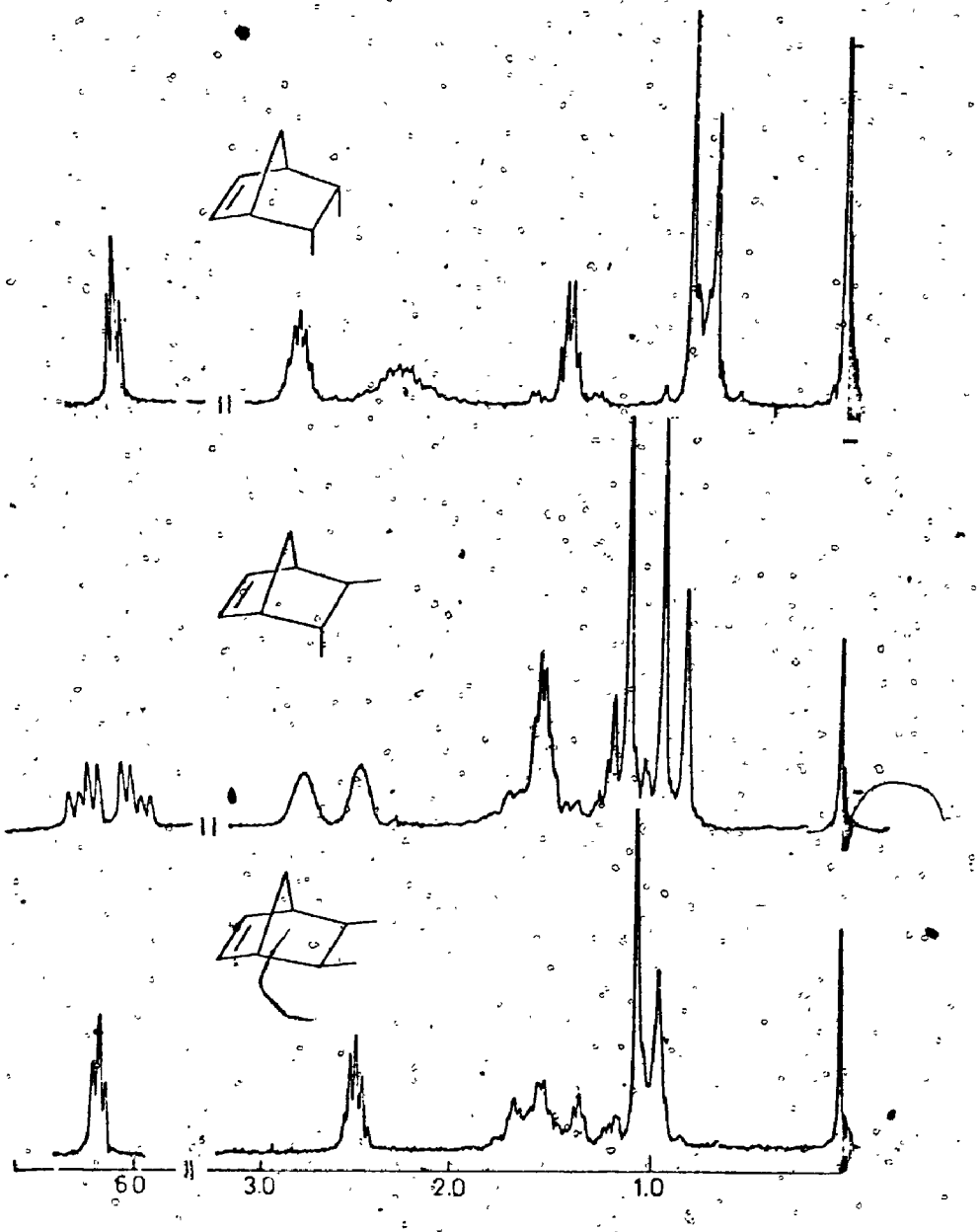


Figure 6.3. The 60 MHz spectra of 5,6-dimethylnorborn-2-enes

endo-5-methylnorborn-2-ene and trans-5,6-dimethylnorborn-2-ene led to a pair of exo-alcohols in the ratio of ca. 1 : 1. Although preparative separation by g.c. of these alcohols is difficult, the corresponding acetates are readily separable by preparative gas chromatography. In this way six isomeric exo-alcohols are obtained in a pure form from the corresponding esters by lithium aluminum hydride reduction. Oxidation of the alcohols with chromium trioxide-pyridine in methylene chloride gave the corresponding ketones. In most cases, in which mixtures of two ketones were obtained from the oxidation of the alcohols, the individual isomers were isolated by gas chromatography using a 20% SE 30 column.

Reduction of rigid bicyclic ketones like bicyclo(2.2.1)heptan-2-one with complex metal hydrides has been found to proceed by hydride transfer to the less hindered exo side of the carbonyl group to give the endo alcohol as the chief product (185). The use of lithium trimethoxy aluminum hydride in tetrahydrofuran decreased the proportion of the exo-alcohol to 0.5% from norcamphor (185). By analogy, the eight alcohols obtained from the complex metal hydride reduction of the corresponding ketones had the endo- configuration. The NMR spectra of the exo- and endo- alcohols were also consistent with the assigned configuration. Musher has noted that for the bicyclo(2.2.1)heptan-2-ols the endo protons are upfield from the exo protons by 0.3 to 0.5 ppm (186). A similar chemical shift situation was also observed for the eight pairs of exo- and endo- alcohols in Table 6.9. The physical constants of the diols, alcohols, ketones and hydrocarbons are listed in Tables 6.3 to 6.9.

2-Cyano-norborn-5-ene

Freshly distilled cyclopentadiene was added to an equimolar amount of

cooled acrylonitrile (ca. 0°C) with stirring. Stirring was continued for 3 hr. at 0°C and 19 hr at room temperature. The product was distilled under reduced pressure to give 2-cyano-5-norbornene as a colorless oil in 80% yield: bp 87 - 95°/ 20 mm (lit. 98 - 101°/ 37 mm (182)). G.c. analysis of the mixture indicated the presence of about 40% of exo-2-cyano-norborn-5-ene and 60% of its endo-2-cyano epimer.

5-Norbornene-2-carboxamide

2-Cyano-norborn-5-ene (81 g) was added slowly to a stirred suspension of sodamide (26.2 g) in 650 ml of liquid ammonia. Dry toluene (100 ml) was added and the ammonia was allowed to evaporate spontaneously. The residue was decomposed carefully with water and acidified with 10% hydrochloric acid. The aqueous phase was drawn off, washed with toluene and saponified by refluxing for 0.5 hr in 20% sodium hydroxide solution. Recrystallization of the crude product from water gave 47 g (50.4%) of 5-norbornene-2-carboxamide.

5-Norbornene-2-exo-carboxylic acid

5-Norbornene-2-carboxamide (25 g) was refluxed with 200 ml of 20% sodium hydroxide solution for 24 hr. The cooled solution was washed with ether, acidified with hydrochloric acid and the precipitated product was extracted with ether. The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure giving 24 g of acids: bp 127 - 129°. The distillate upon further purification via the iodolactonization method (189) and by recrystallization from pentane, gave 21.6 g of the exo-acid: mp 44 - 45° (lit. 44 - 45° (181)).

Endo-norbornene-cis-5,6-dicarboxylic anhydride

To a solution of maleic anhydride (98.1 g, 1 mole) in 440 ml of ethyl

acetate and ligroin (1 : 1 v/v) was added freshly distilled cyclopentadiene (72.6 g, 1.1 mole) over a period of 0.5 hr. During the period of addition, the flask was cooled periodically in ice. After standing for a few minutes at room temperature, the crystalline material which had separated from the solution was collected. The filtrate was concentrated to a smaller volume to yield a second crop of crystals. The crude product was recrystallized from 1 ; 1 ethyl acetate and ligroin to give 159.5 g (97%) of the anhydride having the following physical properties: mp 164 - 165° (lit. 165°(183)); IR(CCl_4): ν_{max} 1790, 1875 cm^{-1}; ^1H NMR($CDCl_3$): δ 1.60 (H_{7s}), 1.74 (H_{7a}), 3.47($H_{2,3}$), 3.57 ($H_{1,4}$) and 6.29 ($H_{5,6}$, t).

Exo-norbornene-cis-5,6-dicarboxylic anhydride

The endo-anhydride (120.9 g) was heated under a nitrogen atmosphere in an Erlenmeyer flask immersed in an oil-bath. The temperature was held at 190° for about 1.5 hr. The crude product was analyzed by NMR spectrum. The NMR integrals of the α-hydrogen absorption of exo-anhydride at 3.0 ppm and the combined exo- and endo-olefinic absorption at ca. 6.37 ppm were measured using Varian T-60 spectrometer. The ratio of the integrals indicated the presence of 54% of the isomer in the crude product. In benzene, the exo- and endo-olefinic absorptions were well-separated by ca. 12 Hz.

The integration gave the same result. The product was crystallized from benzene. A first recryatallization gave 31.5 g of 85% exo-anhydride. After five recrystallization, ca. 5% of the endo-isomer was still present. The purest sample of exo-anhydride was prepared by hydrolysis in boiling water and the resulting diacid crystallized three times from water. The diacid was dried, suspended in dry benzene and refluxed in a Soxhlet

apparatus containing $CaSO_4$ as a drying agent. After about 12 hr all the diacid had reacted and dissolved. The cool solution was further dried with magnesium sulfate, and partly evaporated to crystallize the exo-anhydride.

The benzene mother liquours were combined and the solvent evaporated. The residue was heated at 190° for 1.5 hr and the product crystallized from benzene as before to provide more exo-anhydride. The cycle was repeated three times to give a total yield of 65%. The exo-anhydride had the following physical properties: mp 142 - 143° (lit. 140 - 142° (183)); IR(CCl_4): ν_{max} 1790, 1880 cm^{-1}; ^1H NMR($CDCl_3$) δ1.45(H_{7s}, J = 10 Hz), 1.65(H_{7a}), 3.0($H_{2,3}$, d, 1.5 Hz), 3.43($H_{1,4}$), 6.43($H_{5,6}$, t, 2 hz).

General Procedure for Tosylation

The alcohol was dissolved in dry pyridine and cooled in an ice-bath for 20 min. Then an equal molar amount of p-toluenesulfonyl chloride was added slowly to the solution. The temperature was maintained below 0° during the addition. After heat was no longer evolved, the solution was stored in the refrigerator for 1 day. The reaction mixture was poured over crushed ice and water and allowed to stand for 1 - 2 hr. If the tosylate or ditosylate precipitated, the crude product was obtained by filtration, otherwise the tosylate was extracted with ether. The ether extract was washed with 10% hydrochloric acid until the solution was free of pyridine, followed by 10% sodium bicarbonate and saturated sodium chloride solution. The solution was dried over anhydrous magnesium sulfate and the solvent was removed by evaporation on a rotary evaporator. The crude product so obtained was used without further purification. Normally, the ^1H NMR spectrum showed that the product was very pure.

Preparation of methyl-substituted norbornenes from the corresponding tosylate or ditosylate

The tosylate or ditosylate was added slowly with stirring to a suspension of lithium aluminium hydride in anhydrous ether. The mixture was stirred under reflux for two or three days. After cooling in an ice water bath, a minimum amount of water was added with caution until all the grey powder turned white in color. The ether was filtered and the white powder was washed with ether two or three times. The combined ether extract was dried and concentrated by careful distillation to furnish the crude hydrocarbon. Fractional distillation on a spinning band column yielded fairly pure methylated norbornene which was shown by g.c. (20% SE 30 column) to contain 90% of the norbornene and 10% norbornane. Analytical samples were obtained by preparative g.c.

Hydroboration

A solution of 15 g of trans-5,6-dimethylnorborn-2-ene in 30 ml of tetrahydrofuran (dried with lithium aluminium hydride) was added dropwise to 130 ml of 1.0 M borane in tetrahydrofuran at 0°. After the addition was completed, the reaction mixture was allowed to stir at 0° for an additional three hours. Water was added cautiously to hydrolyze the excess borane. The mixture was oxidized by the addition of a cold solution made from 30 ml of 30% hydrogen peroxide and 45 ml of 3 N sodium hydroxide. The oxidant was added at such a rate and with sufficient cooling to keep the temperature at 0°. Following the addition of the oxidant, the reaction mixture was stirred for 2 hrs at 0° and then saturated with sodium chloride. The organic layer was separated and dried over anhydrous magnesium sulfate. Careful concentration yielded the crude alcohol

mixture which was inseparable by preparative g.c. Acetylation of the alcohol mixture with acetyl chloride at 0° gave a mixture of acetates (bp 113 / 17 mm). G.c. showed two well-separated peaks in the ratio of ca. 1 : 1 on a 20% DEGS column. The first fraction of the hydroboration mixture was colorless liquid acetate. Exo,endo-5,6-dimethylnorbornan-2-ol was obtained from its acetate by reduction with lithium aluminium hydride in the usual manner. Bulb-to-bulb distillation at reduced pressure produced an oily liquid. The p-nitrobenzoate of this alcohol, recrystalization from methanol yielded white cryatals, mp 96 - 97°. Endo,exo-5,6-dimethylnorbornyl acetate, the component of longer retention time from the hydroboration of trans-5,6-dimethylnorborn-2-ene was a liquid acetate. Endo,exo-5,6-dimethylnorbornan-2-ol was obtained from the acetate by reduction with lithium aluminium hydride. After bulb-to-bulb distillation, it was an oily liquid. The p-nitrobenzoate derivative recryatallized from methanol yielded white cryatals, mp 71 - 73°.

In the same manner, hydroboration of the other norbornenes also gave exo-alcohols. Their physical properties are summarized in Table 6.7.

Oxidation of norbornan-2-ols

A mixture of trans-5,6-dimethylnorbornan-2-ol (exo) was oxidized with chromium trioxide-pyridine (190) in methylene chloride to yield a pair of ketones which could be preparatively separated on a 20% SE 30 column.

Chromium trioxide 6.0 g (60 mmole) was added to a magnetically stirred solution of 9.49 g (120 mmole) of pyridine in 150 ml of methylene chloride. The deep burgundy solution was stirred for 15 min at room temperature. At the end of this period, a solution of the alcohol (10 mmole) in a small volume of methylene chloride was added in portions. A tarry

black deposit separated immediately. After stirring for an additional 15 min at room temperature, the solution was decanted from the residue, which was washed with 200 ml of ether. The combined organic solutions were washed with three 100 ml portions of 5% aqueous sodium hydroxide solution, two 100 ml portions of 5% hydrochloric acid, 100 ml of 5% sodium bicarbonate solution, 100 ml of saturated aqueous sodium chloride solution, and were dried over anhydrous magnesium sulfate. Evaporation of the solvent by simple distillation afforded the crude mixture of ketones which showed two peaks on g.c. on a 20% SE 30 column in the ratio ca. 1 : 1. Therefore, a pair of ketones could be separated with a SE 30 column. For exo,endo-5,6-dimethylnorbornan-2-one, the first fraction was a clear oily liquid. A characteristic infrared absorption was found at 1720 cm^{-1} (C=O); ^1H NMR spectrum: δ 0.95 (Me, doublet, J = 7 Hz) and 1.125 (Me, multiplet). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.20. Found: C, 78.44; H, 10.16. The second fraction, endo,exo-5,6-dimethylnorbornan-2-one, was also liquid. The 2,4-dinitrophenylhydrazone of the ketone was obtained as orange platelets, mp 172 - 173° (absolute alcohol). A characteristic infrared absorption was found at 1720 cm^{-1} (C=O); ^1H NMR spectrum, δ 0.99 (Me, doublet, J = 7 Hz) and 1.06 (Me, doublet, J = 6.5 Hz). Anal. Calcd. for $C_{9,14}O$: C, 78.21; H, 10.21. Found: C, 78.74; H, 10.45.

Reduction of norcamphor

Method A --- $NaBH_4$

To a solution of the ketone (0.5 g) in methanol (5 ml) was added a solution of sodium borohydride in 1 ml of water. The reaction temperature was maintained at 0° for 1 hr. After 8 ml of 10% aqueous sodium

hydroxide was added, the borate ester was hydrolyzed by refluxing for 1 hr. Water was added and the aqueous solution extracted with ether. The ether extract was dried and most of the solvent was removed by distillation. The remaining solvent was removed under vacuum. The alcohol was obtained by bulb-to-bulb distillation under reduced pressure.

Method B -- $LiAlH(OR)_3$

Methanol (1.26 g, 0.04 mole) or t-butanol (2.92 g, 0.04 mole) was slowly added to a cold solution of 500 mg of lithium aluminium hydride (0.013 mole) in 30 ml of dry THF. Norcamphor (500 mg) in 20 ml of THF was slowly added to the cold solution and the reaction mixture was stirred at 0° for 0.5 hr and at room temperature for an additional hour. The hydride was hydrolyzed with a minimum quantity of water. The white precipitate was removed by gravity filtration and the residue was washed twice with THF, The THF solution was dried and distilled. The pure alcohol was obtained by bulb-tobulb distillation under reduced pressure.

Table 6.3

Preparation[a] and Properties of Methyl Substituted Norborn-2-ene Derivatives

Substitution	% yield[b]	bp (°)	^{1}H NMR[c]	
			δ_{Me}	Olefinic proton
endo-5-Me	58	114 - 118	1.075 (d, 6 Hz)	6.11 (m, H-2)
		(115 - 116.5 (187))		5.92 (m, H-3)
exo-5-Me	48	117 - 118	0.79 (d, 7.5 Hz)	5.99 (m, H-2)
		(116 - 116.7 (187))		6.09 (m, H-3)
endo,endo-5,6-Me$_2$	60	42 / 16 mm	0.68 (d, 7 Hz)	6.085 (t)
		(143.3 (188))		
endo,exo-5,6-Me$_2$	52	32 - 33 / 20 mm	0.80 (d, 7 Hz)	5.94 (m, H-3)
		(144.0 (188))	1.04 (m)	6.19 (m, H-2)
exo,exo-5,6-Me$_2$	57	52 - 54 / 40 mm	0.935 (d, 7 Hz)	6.08 (t)
		(132.5 (188))		

[a] From the reduction of the corresponding mono- or di-tosylate with lithium aluminum hydride in anhydrous ether.

[b] The product contained ca. 10% of the corresponding norbornane.

[c] In ppm from internal TMS in $CDCl_3$ solutions.

Table 6.4

Preparation[a] and Properties of some Mono- and Di methylolnorborn-5-enes

substitution	% yield	mp or bp (°)	$\nu_{max}^{CCl_4}$
exo-2-CH_2OH	98[b]		
endo-2-CH_2OH	65[c]		
exo,exo-2,3-$(CH_2OH)_2$	70[c]	bp 114 - 116 / 0.8 mm (lit 132 - 136 / 3 mm (188))	3620
exo,endo-2,3-$(CH_2OH)_2$	~90[c]		3625
endo,endo-2,3-$(CH_2OH)_2$	66[d]	mp 84 - 86 (lit 84.5 - 86.2 (188))	3620
trans-3-Me-2-CH_2OH	78[a]	bp 98 - 100 / 10 mm	

[a] Reagent: $LiAlH_4$ in anhydrous ether.

[b] From the corresponding acid.

[c] From the corresponding diethyl ester.

[d] From the corresponding anhydride.

Table 6.5

Methyl Protons Chemical Shifts in Some Methyl Norbornane Derivatives

Substitution	δ_{Me} [a]
endo-2-Me	0.95 (d, 6 Hz)
exo-2-Me	0.86 (d, 6.5 Hz)
endo,endo-2,3-Me_2	0.79_5 (d, 7 Hz)
endo,exo-2,3-Me_2	0.69_5 (m)
	0.90_5 (d, 7 Hz)
exo, exo-2,3-Me_2	0.80 (d, 7 Hz)

[a] In ppm from internal TMS in $CDCl_3$ solutions.

Table 6.6

Preparation[a] and Properties of some Methyl Norcamphors

Substitution	% yield	mp or bp (°)	$\nu_{max}^{CDCl_3}$ (cm^{-1})	^1H NMR[b] δ_{Me}	m/e
endo-5-Me	74[c]	liq 2,4-DNP 149-150 (151.0-151.5 (191))	1745	1.0 (d, 7 Hz)	124.1
endo-6-Me		mp 45.0-45.5 DNP 125-128 (mp 45.5-47.0 (191)) (DNP 129.4-130.0 (191))	1742	0.96$_5$ (d, 7 Hz)	124.1
exo-5-Me exo-6-Me	80	liquid	1745	0.94$_5$ (d, 7 Hz) 1.07 (d, 7 Hz)	
endo,endo-5,6-Me_2	66	mp 62-64 (mp 65-65.5 (192))	1725	0.79 (d, 7 Hz) 0.90 (d, 7 Hz)	
endo,exo-5,6-Me_2	82[c]	DNP 172-173	1720	0.99 (d, 7 Hz) 1.06 (d, 6.5 Hz)	138.1
exo,endo-5,6-Me_2		liquid	1720	0.95 (d, 7 Hz) 1.12$_5$ (m)	138.1
exo,exo-5,6-Me_2	82	liquid[e]	1725	0.96 (d, 7 Hz) 0.97 (d, 7 Hz)	138.1

[a] From the oxidation of the corresponding exo-alcohol(s) using chromium trioxide-pyridine complex in methylene chloride (190)

[b] In ppm from internal TMS in $CDCl_3$ solutions.

[c] Separated from preparative g.c. using 20% SE-30 columns.

[d] See text.

[e] Anal. Calcd. for $C_9H_{14}O$ C, 78.21; H, 10.20. Found: C, 78.67; H, 10.30

Table 6.7

Preparation[a] and Properties of some Methyl exo-2-norbornanol Derivatives

Starting material norborn-2-ene	Product(s) exo-2-norbornanol	% yield	mp or bp (°C)	$\nu_{max}^{CCl_4}$	m/e [c]
endo-5-Me-	endo-5-Me-	89	PNB 58-59 (56.5-57.0 (191))	3620	126.1
	endo-6-Me-		PNB 107-108 (108-109 (191))	3620	126.1052
exo-5-Me-	exo-5-Me-	70	liquid	3610	126.1058
	exo-6-Me-		liquid	3600	126.1055
endo,endo-5,6-Me_2-	endo,endo-5,6-Me_2-	77	mp 48-49	3620	140.1205
endo,exo-5,6-Me_2-	endo,exo-5,6-Me_2-	83	PNB 71-73	3620	140.1203
	exo,endo-5,6-Me_2-		PNB 96-97	3620	140.1205
exo,exo-5,6-Me_2-	exo,exo-5,6-Me_2-	82	bp 120-122/20 mm PNB 93-95	3620	140.1203

[a] Hydroboration

[b] PNB — p-nitrobenzoate derivative.

[c] Calculated precise mass for monomethylnorbornanol is 126.1044 and for dimethylnorbornanol is 140.1200.

Table . 6.8

Preparation and Properties of some Methyl-endo-2-norbornanols

Starting Material (Norcamphor)	Reducing Agent	% endo isomer	mp (°C)	$\nu_{max}^{CCl_4}$ (cm^{-1})	m/e
nil	$LiAlH(O\text{-}t\text{-}Bu)_3$	93			
endo-5-Me-	$LiAlH(OMe)_3$	> 99	PNB 92 - 93	3620	126.1050
endo-6-Me-	$LiAlH_4$	> 99	54 - 55	3640	126.1054
exo-5-Me-	$LiAlH(OMe)_3$	> 98	PNB 73 - 75	3630	126.1054
exo-6-Me-			PNB 89 - 90	3620	126.1057
endo,endo-5,6-Me_2-	$LiAlH_4$	> 99	67 - 68	3640	140.1205
endo,exo-5,6-Me_2-	$NaBH_4$	74	liquid	3620	140.1203
exo,endo-5,6-Me_2-	$NaBH_4$	> 99	47 - 47.5	3640	140.1206
exo,exo-5,6-Me_2-	$LiAlH(OMe)_3$	> 98	PNB 93 - 95	3620	140.1203
7,7-Me_2-	$LiAlH_4$	< 5		3620	140.
6,6-Me_2-	$LiAlH_4$	> 99			

Table 6.9

Proton Chemical Shifts in Some Methyl-substituted Norbornanols

Substitution Me	2-OH	δ_{CH_3}	δ_{CHOH}
exo-5-	exo	0.88_5 (d, 6.5 Hz)	3.73_5 (bd)
	endo	0.90 ((d, 6.0 Hz)	4.18 (m)
endo-5-	exo	0.84_5 (d, 6.5 Hz)	3.64_5 (bd)
	endo	1.02 (d, 6.5 Hz)	4.20 (m)
exo-6-	exo	0.92_5 (d, 6.0 Hz)	3.74 (bd)
	endo	0.93 (d, 7.0 Hz)	4.20 (tt)
endo-6-	exo	0.94_5 (d, 6.5 Hz)	4.10 (bd)
	endo	1.31 (m)	4.37 (m)
exo,exo-5,6-	exo	0.80 (d, 7.0 Hz)	3.65 (dd)
		0.83 (d, 7.0 Hz)	
	endo	0.83 (d, 7.5 Hz)	4.19 (tt)
		0.85 (d, 7.5 Hz)	
exo,endo-5,6-	exo	0.88 (m)	4.07 (bd)
		0.92 (d, 7.0 Hz)	
	endo	0.94 (d, 6.5 Hz)	4.35 (m)
		1.28 (d, 6.0 Hz)	
endo,exo-5,6-	exo	0.83 (d, 6.0 Hz)	3.65 (bd)
		0.93 (d, 6.0 Hz)	
	endo	0.94 (d, 7.0 Hz)	4.21 (tt)
endo,endo-5,6-	exo	0.73 (d, 7.0 Hz)	4.00 (m)
		0.80 (d, 7.0 Hz)	
	endo	0.98 (d, 6.5 Hz)	4.04 (m)
		1.15 (d, 6.5 Hz)	
7,7-Me	exo	0.94 (s)	3.82 (dd)
		1.21 (s)	

(b) PREPARATION OF THE BICYCLO(2.2.2)OCTANE DERIVATIVES

The skeleton of the bicyclo(2.2.2)octyl derivatives was constructed by the Diels-Alder reactions of 1,3-cyclohexadiene and three different dienophiles: maleic anhydride (184), acrylonitrile (167) and crotonic acid (193). Endo,endo-5,6-dimethylbicyclo(2.2.2)oct-2-ene obtained from the endo-anhydride adduct by the methods of Russell and his co-workers (184) was hydrogenated over platinium oxide to yield the corresponding cis-2,3-dimethylbicyclo(2.2.2)octane. The trans-5,6-dimethylbicyclo-(2.2.2)oct-2-ene was prepared by a similar sequence from the trans-5,6-dicarboxylic acid formed by epimerization of endo,endo-5,6-bicyclo(2.2.2)-octyl diethyl ester with base, followed by saponification in aqueous base. The monomethyl derivatives were prepared in a similar manner from the corresponding carboxylic acids. The parent hydrocarbon and olefin were prepared by Wolff-Kishner reduction of the corresponding ketones. Ketones 57, 73, and 149 were prepared by published procedures (184, 167) and 4-methylbicyclo(2.2.2)oct-5-en-2-one, 4-methylbicyclo(2,2.2)octan-2-one and 4,7,7-trimethylbicyclo(2.2.2)oct-5-en-2-one were prepared by Stephens (129). Methylation of 57, 73, 106 and 149 using the sodamide method of Corey et al. (168) furnished mixtures of the mono- and di-methyl derivatives. In each case the mixtures were separated by gas chromatography using 20% SE 30 column. The results are summarized in Table 6.10.

Physical data for the products prepared from methylation of some bicyclo(2.2.2)octan-2-one and -oct-5-en-2-one are :

3-methylbicyclo(2.2.2)octan-2-one(193): $\nu_{max}^{CCl_4}$ 1708 cm^{-1}; ^1H NMR, δ 1.05 (d, 7 Hz).

3,4-dimethylbicyclo(2.2.2)octan-2-one: $\nu_{max}^{CCl_4}$ 1710 cm^{-1}; ^1H NMR, δ

0.89$_5$ (s), 1.065 (d, 7.5 Hz); Calcd. for $C_9H_{16}O$, 152.1200; m/e, 152.1211; mp 36.0 - 36.5°.

3,3,4-trimethylbicyclo(2.2.2)octan-2-one: $\nu_{max}^{CCl_4}$ 1707 cm^{-1}; ^1H NMR, δ 0.83 (s), 1.05 (s); Calcd. for $C_{11}H_{18}O$, 166.1357; m/e, 166.1355; mp 90 - 91°.

endo,endo-5,6-dimethylbicyclo(2.2.2)octan-2-one: $\nu_{max}^{CHCl_3}$ 1720 cm^{-1}; ^1H NMR δ 0.87$_5$ (d, 7 Hz), 0.95$_5$ (d, 7 Hz); mp 68.0 - 68.5° (lit. 67.5 - 68.5° (184)).

exo,endo,endo-3,5,6-trimethylbicyclo(2.2.2)octan-2-one: $\nu_{max}^{CCl_4}$ 1710 cm^{-1}; ^1H NMR, δ 0.87 (d, 7 Hz), 1.01 (d, 7 Hz), 1.11 (d, 7 Hz); 2,4-dinitrophenylhydrazone, mp 171.0 - 172.0°; m/e, 166.1; Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.24; H, 11.00.

endo,endo,endo-3,5,6-trimethylbicyclo(2.2.2)octan-2-one: $\nu_{max}^{CCl_4}$ 1715 cm^{-1}; ^1H NMR, δ 0.91 (d, 7 Hz), 0.99 (d, 7.5 Hz), 1.23 (d, 7 Hz); liquid; Calcd. for $C_{11}H_{18}O$, 166.1356; m/e, 166.1363.

3,3-endo,endo-5,6-tetramethylbicyclo(2.2.2)octan-2-one: $\nu_{max}^{CCl_4}$ 1725 cm^{-1}; ^1H NMR, δ 0.92 (d, 7.5 Hz), 1.12 (d, 7 Hz), 1.20 (s); low melting solid; Calcd. for $C_{12}H_{20}O$, 180.1513; m/e, 180.1511.

3-methylbicyclo(2.2.2)oct-5-en-2-one: $\nu_{max}^{CCl_4}$ 1717 (C=O) and 1615 cm^{-1} (C=C); ^1H NMR, δ 1.04 (d, 7 Hz, endo-Me), 1.08 (d, 7.5 Hz, exo-Me); Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88; Found: C, 79.50; H, 9.01.

3,3-dimethylbicyclo(2,2.2)oct-5-en-2-one: $\nu_{max}^{CCl_4}$ 1710 (C=O) and 1610 cm^{-1} (C=C); ^1H NMR δ 1.05 (s), 1.09 (s); mp 89 - 90°; Calcd. for $C_{10}H_{14}O$, 150.1044; m/e, 150.1039.

Most of the alcohols were obtained by reduction of the corresponding ketones with lithium aluminum hydride in ether. The preparation and

properties of the alcohols are summarized in Tables 6.11 and 6.12. The procedures for the reduction, tosylation, hydroboration and oxidation have been described in the previous section. Also, the physical properties of several methyl bicyclo(2.2.2)octanes and bicyclo(2.2.2)-octenes are summarized in Tables 6.13 and 6.14.

Table 6.10

Methylation[a] of some Bicyclo(2.2.2)octanones and -octenone

Starting Material (SM)	% Products[b] SM	Mono- exo	Mono- endo	Di-
bicyclo(2.2.2)octan-2-one	21	24		55
4-methylbicyclo(2.2.2)octan-2-one	31	40		29
endo,endo-5,6-Me_2-bicyclo(2.2.2)octan-2-one	14	47	3	37
bicyclo(2.2.2)oct-5-en-2-one	20	18[c]	36[c]	26

[a] Following the method described by Corey et al. (168).

[b] The product was analyzed by gas chromatography using 20% SE 30 column.

[c] Estimated from the ^{13}C NMR spectrum.

Table 6.11

Preparation[a] and Properties of Some Bicyclo(2.2.2)octanol and -octenols

Starting Material	Product(s)	m.p.(°)	$\nu_{max}^{CCl_4}$ (cm^{-1})	m/e[b]
bicyclo(2.2.2)octan-2-one	153	205 - 206	3590	
		(lit. 205 - 212.5°).		
3-methylbicyclo(2.2.2)oct-5-en-2-one[c]	[illegible]	[illegible]	3630	
3,3-dimethylbicyclo(2.2.2)octan-2-one	155	[illegible]	3620	154.1353
				(154.1355)
endo,endo-5,6-dimethylbicyclo(2.2.2)octan-2-one	[illegible]	[illegible]	3590	
anti-3-endo,cis-5,6-trimethyl-bicyclo(2.2.2)octan-2-one	[illegible]	[illegible]	3580	168.1522
				(168.1513)
3,3-endo,cis-5,6-tetramethyl-bicyclo(2.2.2)octan-2-one	169	59 - 59.5	3650	182.1672
				(182.1670)
bicyclo(2.2.2)oct-5-en-2-one	162(exo) : 163(endo) 1 : 2		3625	
3,3-dimethylbicyclo(2.2.2)oct-5-en-2-one	164(exo) : 165(endo) 4 : 6		3640 ; 1620 3610 ; 1605	152.1198 (152.1201)

a. Reagent: $LiAlH_4$ in anhydrous ether. b. Values in parentheses are calculated precise mass.

c. Reduction with $LiAlH_4$ followed by hydrogenation in ether using a Pt/C catalyst furnished a mixture.

Table 6.12

Proton Chemical Shifts[a] of Some Bicyclo(2.2.2)octanols and -octenols

Compound	δ_{Me}	δ_{CHOH}
Bicyclo(2.2.2)octan-2-ol		3.83 (m)
cis-3-Me-	1.26 (m)	3.82 (d, 5 Hz)
trans-3-Me-	1.02 (d, 8 Hz)	3.40 (dd, 9.5, 3 Hz)
3,3-Me_2-	1.03 (s)	3.45 (d, 2 Hz)
anti,cis-5,6-Me_2-	0.88 (d, 7 Hz)	4.14 (m)
	0.96 (d, 7 Hz)	
syn, cis-5,6-Me_2-	1.03 (d, 7 Hz)	3.95 (m)
	1.13 (d, 7 Hz)	
trans-3-syn,cis-5,6-Me_3-	1.00 (d, 7 Hz)	3.37 (d, 7 Hz)
	1.04 (d, 7 Hz)	
	1.10 (d, 7.5 Hz)	
3,3-syn,cis-5,6-Me_4-	1.04 (s)	3.55 (d, 2.5 Hz)
	1.15 (s)	
	1.13 (d, 7.5 Hz)	
	1.16 (d, 8 Hz)	
Bicyclo(2.2.2)oct-2-en-5-ol		3.9 (m)
3,3-Me_2-exo-	0.90 (s)	3.31 (d, 3 Hz)
	0.99 (s)	
3,3-Me_2-endo	0.89 (s)	3.42 (d, 3 Hz)
	1.06 (s)	

[a] In ppm from internal TMS in $CDCl_3$ solutions.

Table 6.13

Physical Properties of some Mono- and Di-methyl bicyclo(2.2.2)octanes

Substitution	mp or bp	^{1}H NMR[a] (δ_{Me})	m/e[b]
Nil	mp 168 - 169		110.22
	(lit. 169.5-170.5 (195)		
2-Me	bp 175	0.97 (d, 7 Hz)	124.1252
	(lit. mp 32 - 33 (196)		(124.1251)
cis-2,3-Me_2 (197)		0.93 (d, 7 Hz)	138.1404
			(138.1408)
trans-2,3-Me_2 (197)		0.94 (m)	138.1409
			(138.1408)

[a] In ppm from internal Tms in $CDCl_3$ solutions.

[b] Values in parenthese are calculated precise mass.

Table 6.14

Physical Properties of Some Mono- and Di-methyl Bicyclo(2,2.2)oct-2-enes

Substitution	mp or bp	$\nu_{max}^{CCl_4}$ (cm^{-1})	^1H NMR[a]	m/e[b]
Nil	mp 112,5 - 113.5°		6.22 (m)	108.24
	(lit. 113 - 114 (198))			
endo-5-Me[c]		1610	0.77 (d, 7 Hz),	122.1094
		3040	6.29 (dd); 6.39 (dd)	(122.1095)
exo-5-Me[c]		1635	1.01 (d, 7 Hz)	
		3040	6.31 (m)	
endo,endo-5,6-Me_2	bp 149 - 150°	1615	0.76 (d, 7 Hz)	136.1256
	(lit. 145 - 148 (197))	3040	6.16 (m)	(136.1251)
endo,exo-5,6-Me_2	bp 164°	1615	0.79 (d, 5.5 Hz)	136.1245
	(lit. 164 (197))	3040	6.06 (t); 6.34 (m)	(136.1251)
			0.99 (m)	

[a] In ppm from internal TMS in $CDCl_3$ solutions.

[b] Values in parentheses are calculated precise mass.

[c] Endo-5-methylbicyclo(2.2.2)oct-2-ene is in pure form but exo-5-methylbicyclo(2.2.2)oct-2-ene is in the mixture of the endo- and exo-isomers.

(c) PREPARATION OF THE BICYCLO(3.2.1)OCTANE DERIVATIVES

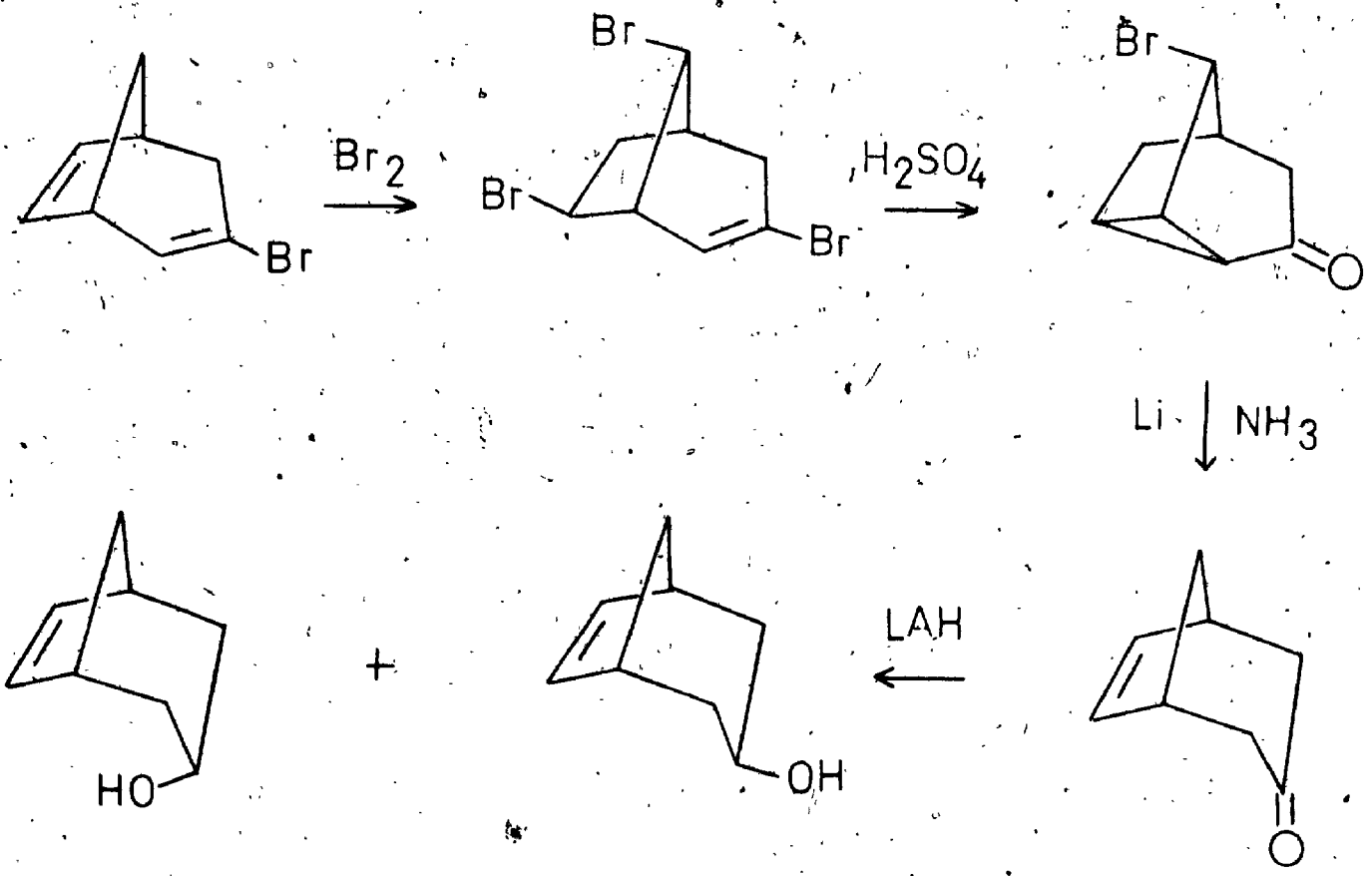
(i) Preparation of Bicyclo(3.2.1)oct-6-en-3-one

Bromination of 3-bromobicyclo(3.2.1)oct-2,5-diene in ether at -10° led to a high yield of a sharp melting, crystalline tribromide for which the structure was either exo,anti-3,6,8-tribromobicyclo(3.2.1)oct-2-ene or exo,anti-3,7,8-tribromobicyclo(3.2.1)oct-2-ene. Hydrolysis of the tribromide in aqueous ethanol containing sulfuric acid furnished the bromo ketone, anti-8-bromotricyclo(3.2.1.$0^{2,7}$)octan-3-one (201). Reduction of this bromoketone with lithium in ammonia afforded bicyclo-(3.2.1)oct-6-en-3-one (202). Reduction of this unsaturated ketone with lithium aluminium hydride in ether gave a mixture of the exo and endo alcohols in the ratio of 3 : 2 (202) (see Figure 6.4).

3,7,8-Tribromobicyclo(3.2.1)oct-2-ene

A solution of 10 g (0.057 mole) of 3-bromobicyclo(3.2.1)oct-2,5-diene in 150 ml of ether was cooled to -10° to -15°, and a solution of 9 g (0.056 mole) of bromine in 10 ml of carbon tetrachloride was added with stirring. When the addition was completed, the flask was allowed to warm to room temperature. The contents were transfered to a separatory funnel and additional ether was added. The ether layer was shaken four times with a saturated sodium bisulfite solution, washed with water, dried, and concentrated. Crystallization of the residue from a mixture of ether and pentane afforded 14.8 g (80%) of white crystals, mp $99 - 101^{\circ}$ (lit. $100 - 101^{\circ}$ (201)). ^{13}C NMR ($CDCl_3$), δ 132.7 (C-2), 122.0 (C-3), 53.2 (2 CH), 47.4 (CH), 46.2 (CH), 45.6 (CH_2), 42.6 (CH_2).

Figure 6.4. Preparation of Bicyclo(3.2.1)oct-6-en-3-one and its alcohols



of white crystals, mp 199 - 200° (lit. 200.2 - 201.0 (203)), $\nu_{max}^{CCl_4}$ 3620 (O-H); ^{1}H NMR, 3.99 ppm (CH-OH).

Preparation of exo-bicyclo(3.2.1)octan-8-ol

This alcohol was prepared by acetolysis of endo-bicyclo(3.2.1)octyl-8-tosylate. The tosylate was prepared in the usual way, mp 75 - 76° (lit. 75.7 - 76.1 (303)).

To a solution of 28 g of potassium acetate in 25 ml of acetic acid was added 1.5 g of endo-bicyclo(3.2.1)octyl-8-tosylate. The solution was refluxed for 4 hr, then cooled and poured into water. The solution was extracted with pentane. The extracts were washed with water, dried and the solvent was removed. Gas chromatographic analysis (20% SE 30) showed that the residue contained at least four products. The major component (∿50%) was exo-8-bicyclo(3.2.1)octyl acetate which was isolated by column chromatography. Exo-bicyclo(3.2.1)octan-8-ol was obtained from its acetate by reduction with lithium aluminium hydride in the usual manner. After sublimation in vacuum, the exo-alcohol had mp 190 - 192° (lit. 192.2 - 192.5° (203)); $\nu_{max}^{CCl_4}$ 3640 cm^{-1}; ^{1}H NMR, δ 3.70 ppm (m).

Reduction of bicyclo(3.2.1)oct-2-en-8-one

(a) Sodium borohydride in methanol

A solution of 125 mg of the ketone in 5 ml of methanol was cooled to 10°, and 0.5 g of $NaBH_4$ was added. The mixture was stirred at 10° for 1 hr. Hydrolysis was effected by the addition of 8 ml of 10% aqueous sodium hydroxide and refluxing for 1 hr. After dilution with water, the aqueous solution was extracted with ether. The ether extracts were washed and dried. Evaporation of the solvent afforded ca. 100 mg of product. The ^{13}C spectrum showed that the product was mainly the endo isomer.

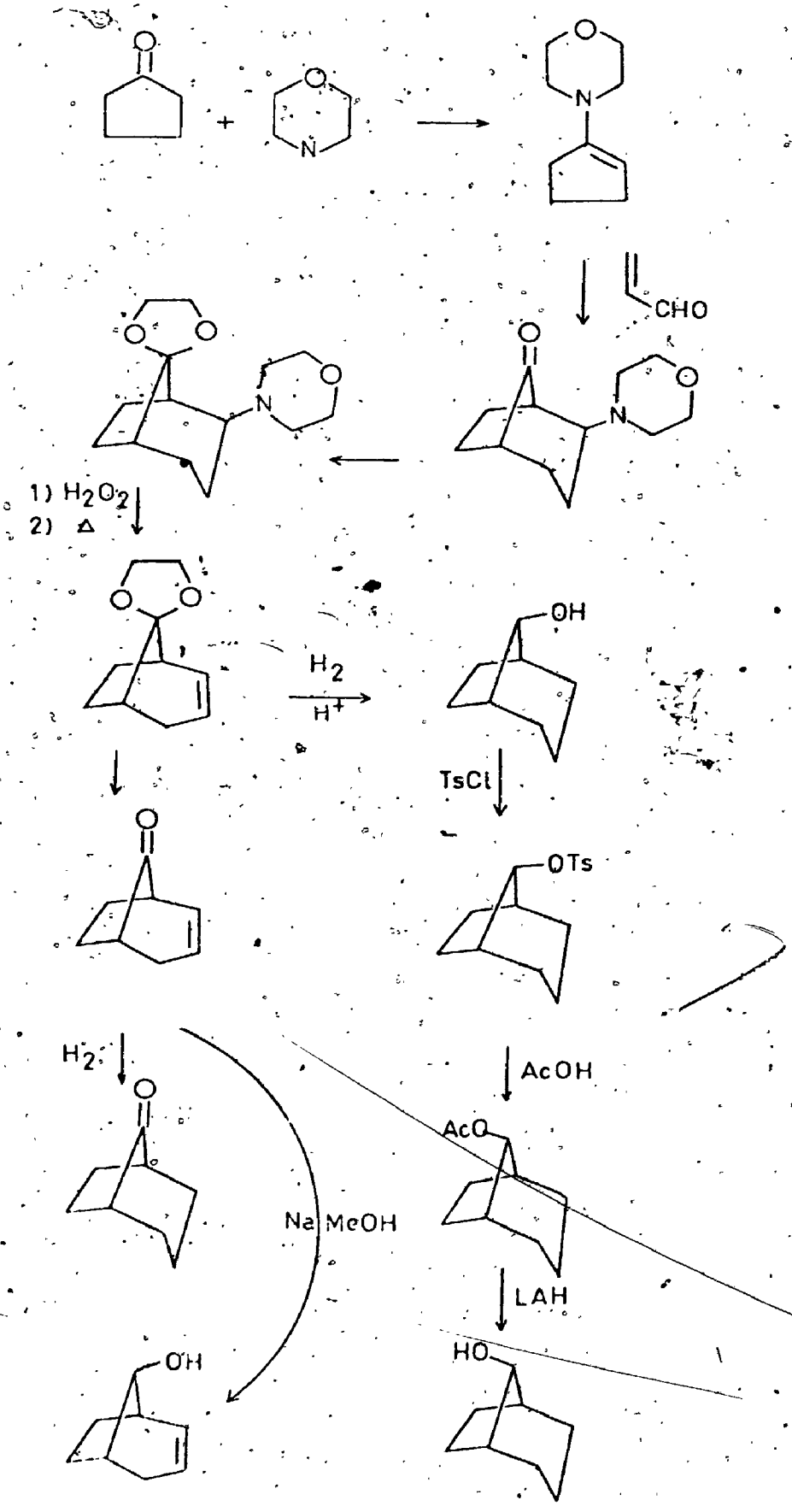
Reduction of Bicyclo(3.2.1)oct-6-en-3-one with $NaBH_4$

A solution of 0.3 g of bicyclo(3.2.1)oct-6-en-3-one in 5 ml of methanol was stirred at room temperature and 200 mg of sodium borohydride was added. Stirring was continued for 5 hr. Work-up consisted of dilution with water, followed by continuous extraction with pentane. The pentane extract was washed with water and dried ($MgSO_4$). After concentration 0.27 g of a mixture containing 35% exo- and 65% endo-alcohol was obtained. The proton NMR spectrum of this mixture showed that the carbinyl protons of these two isomers are equivalent but the olefinic protons for the exo- and endo-alcohols were found at 5.73 (bs) and 6.13 ppm, respectively. The infrared spectrum showed $\nu_{max}^{CCl_4}$ 3580, 3050 cm^{-1}.

(ii) Bicyclo(3.2.1)oct-2-en-8-one and its derivatives

A convenient route to bicyclo(3.2.1)oct-2-en-8-one and its derivatives (Figure 6.5) was developed from the aminoketones which are readily made in good yield by condensation of the enamine derived from cyclopentanone with acrolein (203). The aminoketone was converted to the N-oxide of the corresponding ethylene ketal and pyrolyzed to yield bicyclo(3.2.1)oct-2-en-8-ethylene ketal. This ketal was hydrolyzed to the unsaturated ketone. Reduction of bicyclo(3.2.1)octan-8-one with lithium aluminium hydride in ether gave endo-bicyclo(3.2.1)octan-8-ol, uncontaminated by the exo isomer. Acetolysis of endo-bicyclo(3.2.1)octyl-8-tosylate was found to give satisfactory yields of the exo-acetate (~ 50%) which could be reduced to give exo-bicyclo(3.2.1)octan-8-ol. Reduction of bicyclo-(3.2.1)oct-2-en-8-one with sodium borohydride in methanol gave mainly the endo-unsaturated alcohol. But reduction with sodium in methanol gave a mixture of exo- and endo-unsaturated alcohols which contained about 24%

Figure 6.5. Preparation of Bicyclo(3.2.1)oct-2-en-8-one and its Corresponding Derivatives



of the exo isomer.

Preparation of the morpholine enamine of cyclopentanone

Morpholine (135 g) and cyclopentanone (126 g) were dissolved in 560 ml of benzene and a few crystals of p-toluenesulphonic acid were 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. The benzene was distilled off at atmospheric pressure and the product was distilled in vacuum, bp 94 - 96°/8 mm yielded 186.9 g of enamine (85%).

Preparation of 2-N-morpholinobicyclo(3.2.1)octan-8-one

The amino-ketone was prepared by the addition of 61.8 g acrolein to 180 g 1-N-morpholine-cyclopentanone in 180 ml dioxane at 0°. The reaction mixture was stirred at room temperature for 12 hr. After the solvent had been removed, the residue was distilled, yielding 110 g of the amino-ketone, bp 185 - 194 / 1 mm (lit. bp 127 - 140°/ 0.2 mm (203).

Preparation of the ethylene ketal of the amino-ketone

The amino-ketone, 25 g (0.128 mole), was dissolved in 92.3 g (1.28 mole) of ethylene glycol, and 26.8 g (1.41 mole) of toluenesulfonic acid monohydrate were added. The solution was heated to 80° for 14 hr, then cooled and poured into a well-stirred solution of 32.7 g KOH in 300 ml ice water. The suspension was diluted with water to 600 ml and extracted three times with ether. The ether extracts were washed with water and with saturated sodium chloride solution, and then the solvent was evaporated. The residue was distilled, yielding 24.2 g of the pure ketal, bp 141 - 153°/ 1 mm (lit. 114 - 122°/ 0.2 mm (203)). The methylene protons of the ketal function appear as a singlet at 4.23 ppm (in $CDCl_3$).

Preparation of Δ^2-bicyclo(3.2.1)octen-8-ethylene ketal

The aminoketal (50 g) was dissolved in 50 ml of methanol to which 23 g of 30% H_2O_2 were added. The solution was refluxed until it became neutral to pH 6 - 8 indicator paper (15 hr). After the reaction had cooled, platinum black was added to decompose excess peroxide and the solution stirred for 2 days and filtered. After removal of solvent and most of the water, the residue, the crystalline N-oxide, was pyrolyzed at 180° and 1 mm. The product which had distilled into a Dry-ice-cooled trap was dissolved in ether and extracted with 6N HCl, 10% aqueous Na_2CO_3, water and with saturated NaCl solution. After the solvent had been removed, the residue was distilled, yielding 10.2 g (29%) Δ^2-bicyclo-(3.2.1)octen-8-ethylene ketal, bp 128 - 134°/ 1 mm (lit. 97 - 102°/0.12 mm (203)).

Preparation of endo-bicyclo(3.2.1)octan-8-ol

Δ^2-Bicyclo(3.2.1)octen-8-ethylene ketal (5 g) was dissolved in 25 ml of acetic acid containing 5 ml of water and 2 drops of conc. HCl. The mixture was hydrogenated on a Parr apparatus at 55 psi. After 3 hr, the solution was filtered, poured into 200 ml water and extracted with pentane. The extract was washed with 10% sodium bicarbonate solution and distilled through a short Vigreux column. The residue was dissolved in 30 ml of methanol with 3 g of KOH. The solution was refluxed for 1 hr to saponify any acetate. The reaction mixture was then cooled, poured into water, and extracted with pentane. The pentane extracts were washed with water, saturated NaCl solution, and dried over magnesium sulfate. The pentane was removed by distillation and the residue solidified upon cooling. The crude product was recrystallized from pentane to give 3.1 g

of white crystals, mp 199 - 200° (lit. 200.2 - 201.0 (203)), $\nu_{max}^{CCl_4}$ 3620 (O-H); ^{1}H NMR, 3.99 ppm (CH-OH).

Preparation of exo-bicyclo(3.2.1)octan-8-ol

This alcohol was prepared by acetolysis of endo-bicyclo(3.2.1)octyl-8-tosylate. The tosylate was prepared in the usual way, mp 75 - 76° (lit. 75.7 - 76.1 (303)).

To a solution of 28 g of potassium acetate in 25 ml of acetic acid was added 1.5 g of endo-bicyclo(3.2.1)octyl-8-tosylate. The solution was refluxed for 4 hr, then cooled and poured into water. The solution was extracted with pentane. The extracts were washed with water, dried and the solvent was removed. Gas chromatographic analysis (20% SE 30) showed that the residue contained at least four products. The major component (~50%) was exo-8-bicyclo(3.2.1)octyl acetate which was isolated by column chromatography. Exo-bicyclo(3.2.1)octan-8-ol was obtained from its acetate by reduction with lithium aluminium hydride in the usual manner. After sublimation in vacuum, the exo-alcohol had mp 190 - 192° (lit. 192.2 - 192.5° (203)); $\nu_{max}^{CCl_4}$ 3640 cm^{-1}; ^{1}H NMR, δ 3.70 ppm (m).

Reduction of bicyclo(3.2.1)oct-2-en-8-one

(a) Sodium borohydride in methanol

A solution of 125 mg of the ketone in 5 ml of methanol was cooled to 10°, and 0.5 g of $NaBH_4$ was added. The mixture was stirred at 10° for 1 hr. Hydrolysis was effected by the addition of 8 ml of 10% aqueous sodium hydroxide and refluxing for 1 hr. After dilution with water, the aqueous solution was extracted with ether. The ether extracts were washed and dried. Evaporation of the solvent afforded ca. 100 mg of product. The ^{13}C spectrum showed that the product was mainly the endo isomer.

After purification, the endo alcohol had mp 113 - 116° (lit. 117 - 118° (204)); $\nu_{max}^{CCl_4}$ 3580 (OH), 1640 cm^{-1} (C=C); ^1H NMR δ 4.02 (t), 5.69 (m).

(b) Sodium in methanol

To a solution of 250 mg of the ketone in 8 ml of methanol was added, over 20 min, sodium metal (0.4 g) in small pieces. When all the sodium had reacted, the mixture was allowed to reflux for 12 hr. Water was added and the mixture was extracted with ether. The extracts were washed with water and dried. After the solvent had been removed, the residue was purified by column chromatography. The ^{13}C spectrum showed that the mixture (∿150 mg) contained 76% endo- and 24% exo-bicyclo(3.2.1)oct-2-en-8-ol.

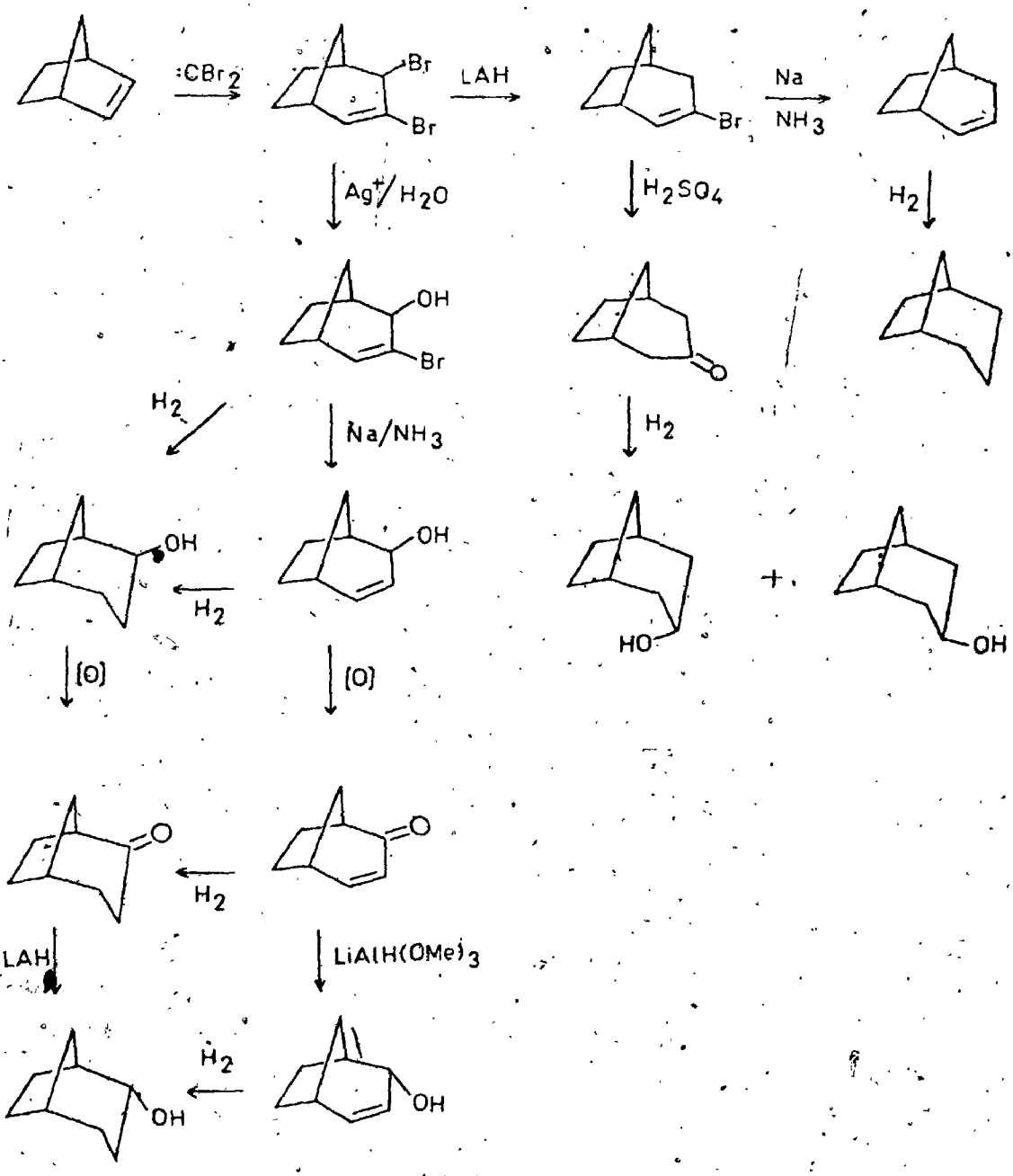
(iii) Bicyclo(3.2.1)oct-3-en-2-one and its corresponding derivatives

The reaction of bromoform with potassium t-butoxide in the presence of norbornene in pentane at -10° gave 3,4-dibromobicyclo(3.2.1)-oct-2-ene (205). Hydrolysis of the crude product in 60% aqueous acetone containing silver nitrate afforded 3-bromo-exo-bicyclo(3.2.1)oct-2-en-4-ol (206). Reduction of this exo-alcohol with sodium in liquid ammonia provided exo-bicyclo(3.2.1)oct-3-en-2-ol. Oxidation with chromium trioxide-pyridine complex in methylene chloride (190) gave bicyclo(3.2.1)-oct-en-2-one. Hydrogenation of 3-bromo-exo-bicyclo(3.2.1)oct-2-en-4-ol using palladium on carbon in basic solution led to the reduction of the double bond, and hydrogenolysis of the bromine, leading to exo-bicyclo-(3.2.1)octan-2-ol. Oxidation with chromium trioxide-pyridine complex in methylene chloride gave the corresponding ketone. Reduction of 3,4-dibromobicyclo(3.2.1)oct-2-ene with lithium aluminium hydride gave 3-bromobicyclo(3.2.1)oct-2-ene which was further reduced with sodium in liquid ammonia to bicyclo(3.2.1)oct-2-ene (205). Hydrogenation of bicyclo(3.2.1)oct-2-ene in ether in the presence of platinium oxide gave the very volatile solid, bicyclo(3.2.1)octane. The hydrolysis of 3-bromo-bicyclo(3.2.1)oct-2-ene with aqueous sulfuric acid gave moderate yields of bicyclo(3.2.1)octan-3-one. Reduction of bicyclo(3.2.1)oct-3-en-2-one with lithium aluminium hydride trimethoxide gave the corresponding endo-alcohol (Figure 6.6).

exo-3,4-dibromobicyclo(3.2.1)oct-2-ene

A solution of 258 g of freshly distilled bromoform was added dropwise with stirring to a mixture of 88.7 g of potassium t-butoxide and 84 g of norbornene in 500 ml of pentane maintained at 10°. After

Figure 6.6. Preparation of Bicyclo[3.2.1]octan-2- and -3-one and its Derivatives



the addition was completed the mixture was stirred for 30 min. The mixture was then allowed to warm to room temperature. Water was added to hydrolyse the excess potassium t-butoxide. The pentane layer was washed with water and dried. Short-path distillation at 74 - 76° / 0.05 mm (lit. 80° / 0.2 mm (205)) gave 61.8 g (25.8%) of exo-3,4-dibromobicyclo(3.2.1)oct-2-ene which had the following physical properties: $\nu_{max}^{CCl_4}$ 1610 (C=C) cm^{-1}; ^1H NMR($CDCl_3$): δ 2.60(m, H-1), 2.82 (m, H-5), 4.53 (m, H-4, J_{45} = 3 Hz), 6.31 (dd, H-2, J_{12} = 7 Hz; J = 1.5 Hz) and the complex pattern between 1.2 and 2.5 ppm (6 protons).

3-bromobicyclo(3.2.1)oct-2-ene

The dibromide (20 g) was added dropwise to a stirred mixture of 4.2 g of lithium aluminium hydride in 600 ml of anhydrous ether. After the addition was completed, the mixture was allowed to reflux for two days. The excess hydride was destroyed with water and the mixture was worked-up in the usual way. Short-path distillation gave 7.7 g (54.6 %) of 3-bromobicyclo(3.2.1)oct-2-ene, bp 94 - 96° / 15 mm. The infrared spectrum showed $\nu_{max}^{CCl_4}$ 1625 cm^{-1}.

bicyclo(3.2.1)oct-2-ene

The required amount of liquid ammonia (50 ml) was distilled into the reaction flask and sodium (3 g-atom per mole of bromide to be dehalogenated) was added in several pieces. When the sodium had dissolved, the bromide (2 g) diluted with one to two volumes of anhydrous ether was added dropwise to the stirred sodium solution. After the addition was complete , the mixture was stirred an addition hour.

The excess sodium and the sodium amide formed during the reaction were neutralized with solid ammonium chloride added gradually from the

side-neck of the flask. The cooling bath was removed, ammonia was allowed to evaporate at room temperature. Water was added until all the salts were dissolved. The aqueous layer was extracted three times with ether. The combined ether extracts were washed with saturated aqueous sodium chloride solution, dried and concentrated. Yield of the product from short-path distillation was about 80% (205).

Bicyclo(3.2.1)octane

A mixture of 85 mg of bicyclo(3.2.1)oct-2-ene, 20 ml of anhydrous ether and small amount of platinium oxide was treated with hydrogen at approximately 51 psi on a Parr apparatus for 5 hr. The catalyst was filtered off and the filtrate was dried and concentrated to give ca. 80mg of a very volatile white solid, mp 134 - 135° (sealed capillary) (lit. 133 - 135° (205)). The proton NMR spectrum showed a broad singlet at 2.13 ppm (H-1 and H-4) and a multiplet around 1.23 ppm (12 H).

Bicyclo(3.2.1)octan-3-one

Vinyl bromide (5 g) was added to 250 ml of concentrated sulfuric acid. The mixture was then stirred at room temperature for 1 hr. Then the mixture was poured into ice-water and extracted with ether. The ether extracts were dried and concentrated. The residue was chromatographed on an alumina column with pentane and the crude product so obtained was sublimed under vacuum to give 1.32 g of a waxy crystalline solid (34.3 %). An analytical sample was obtained by g.c., mp 136 - 138° (lit. 137 - 139° (205)).

3-Bromobicyclo(3.2.1)oct-2-en-4-exo-ol

15 ml of silver nitrate solution (9.5 g in 100 ml of water and 75 ml of acetone) was added dropwise to a stirred mixture of the dibromide (10 g) in 10 ml of acetone. A precipitate of silver bromide formed instantaneously. The mixture was stirred another four hours at room temperature. The product was extracted with three portions of ether. The combined ether extracts were washed with water, then with saturated aqueous sodium chloride solution, dried and the solvent was evaporated. Gas chromatographic analysis showed that the residue contained two major components (74 % exo-alcohol and 26 % exo-nitrate) which were easily separated by column chromatography. The crude product was chromatographed through a column of 100 g of alumina and eluted first with pentane, then with ether and the mixture of ether and methanol (1 : 1). The first fraction from pentane was exo-4-nitrate-3-bromobicyclo(3.2.1)oct-2-ene which had the following physical properties: liquid; IR $\nu_{max}^{CCl_4}$ 1265, 1630 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.70 (m, 8H), 5.14 (d, J = 3 Hz, H-4), 5.62 (d, J = 7Hz, H-2). The second fraction, from the ether-methanol mixture, was 3-bromobicyclo(3.2.1)oct-2-en-exo-4-ol which had the following physical properties: mp 72 - 73° (recrystallized from pentane) (lit. 72 - 73° (206)); IR $\nu_{max}^{CCl_4}$ 3575, 3450, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.55 (m, two bridgehead protons), 3.8 (d, J = # Hz, H-2), 6.25 (dd, J = 7, 2 Hz, H-4).

The exo-nitrate was easily converted to exo-alcohol by refluxing in water and acetone for 22 hr. Overall yield of exo-alcohol was ca. 70%.

exo-Bicyclo(3.2.1)oct-3-en-2-ol

Reduction of 3-bromobicyclo(3.2.1)oct-2-en-exo-4-ol (6 g) with excess sodium (2.3 g) in liquid ammonia (150 ml) in six hours, followed by the usual work-up gave 3.5 g of crude product. The product was purified by vacuum sublimation, mp 85 - 87° (lit. 87.2 - 88.2° (207)). Characteristic infrared absorptions were found at 3640 and 1640 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.735 (dd, J = 3.5, 2.5 Hz, H-2), 5.470 (dddd, J = 10, 4 and 2 Hz, H-3), 6.06 (dddd, J = 10, 6.5 and ca. 1 Hz, H-4).

Bicyclo(3.2.1)oct-3-en-2-one

Exo-Bicyclo(3.2.1)oct-3-en-2-ol was oxidized to the ketone in 70% yield using the procedure of R. Ratcliff et al. (190). The crude product was purified by vacuum distillation, bp 95° / 15 mm (lit. 76° / 7 mm (207)). The infrared spectrum showed $\nu_{max}^{CCl_4}$ 1670 cm^{-1}.

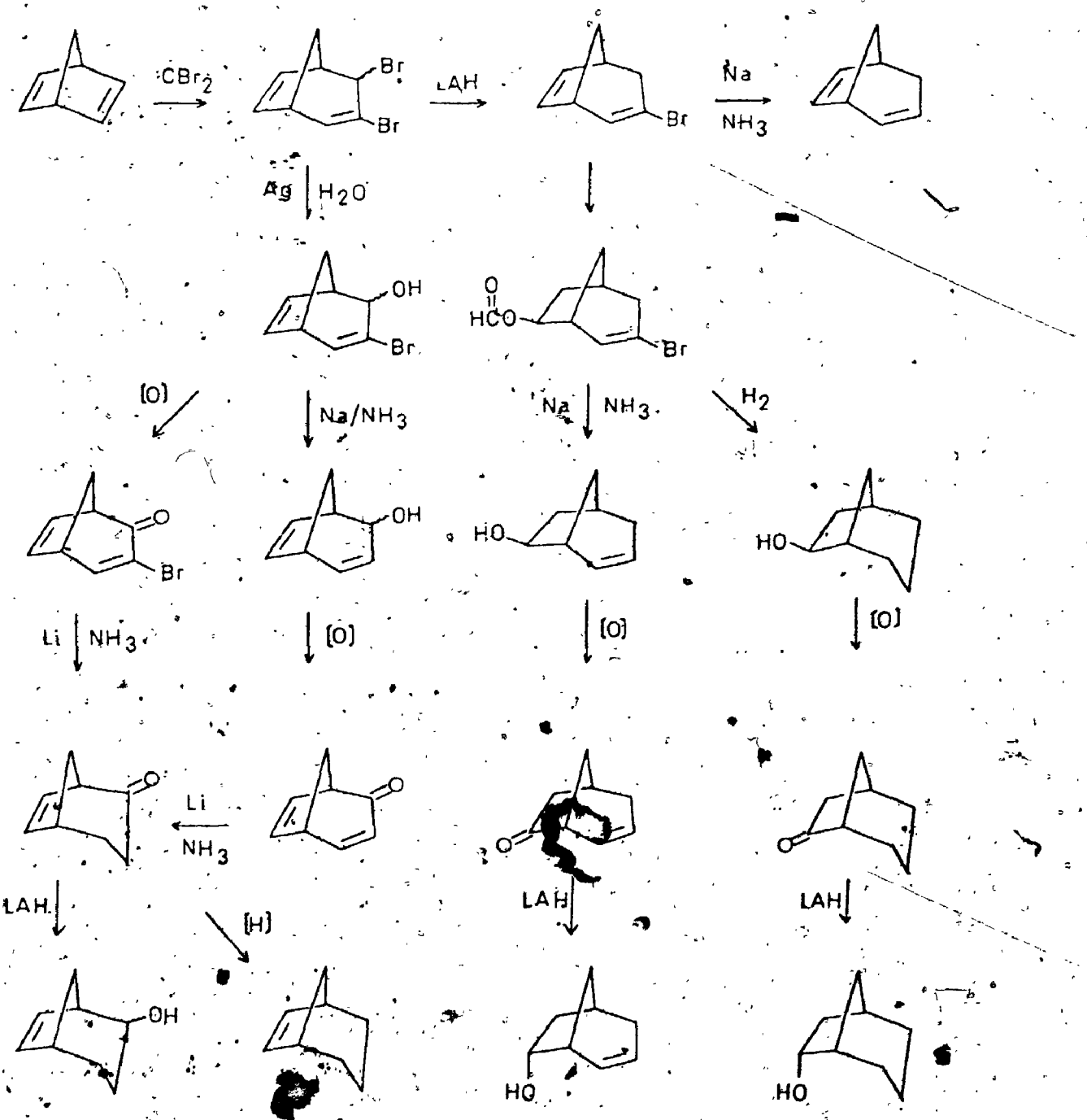
endo-Bicyclo(3.2.1)oct-3-en-2-ol

The $LiAlH(OMe)_3$ in THF reduction of bicyclo(3.2.1)oct-3-en-2-one was carried out by the method described earlier. The crude product was isolated in 85% yield. The melting point after sublimation was 78 - 79° (lit. 77.5 - 80.5° (207)). The infrared spectrum showed characteristic absorptions at 3610 and 1670 cm^{-1}; ^1H NMR ($CDCl_3$), δ 4.53 (bd, J = 10 Hz, H-2), 5.30 (tt, J = 10, 4 and 2.5 Hz, H-3), 6.10 (m, J = 10, 8 and ca. 1 Hz, H-4).

exo-2-Bicyclo(3.2.1)octanol

A solution of 15 g of exo-3-bromobicyclo(3.2.1)oct-2-en-4-ol, 40 ml of THF, 70 ml of 2N NaOH and 3 g of 5% Pd / C was treated with hydrogen gas using a Parr apparatus at room temperature and 55 psi. After 17 hr, no more hydrogen was taken up. The catalyst was removed

Figure 6.7. Preparation of Bicyclo(3.2.1)oct-3-en-6-one and Bicyclo(3.2.1)octa-3,6-dien-2-one and their Corresponding Derivatives

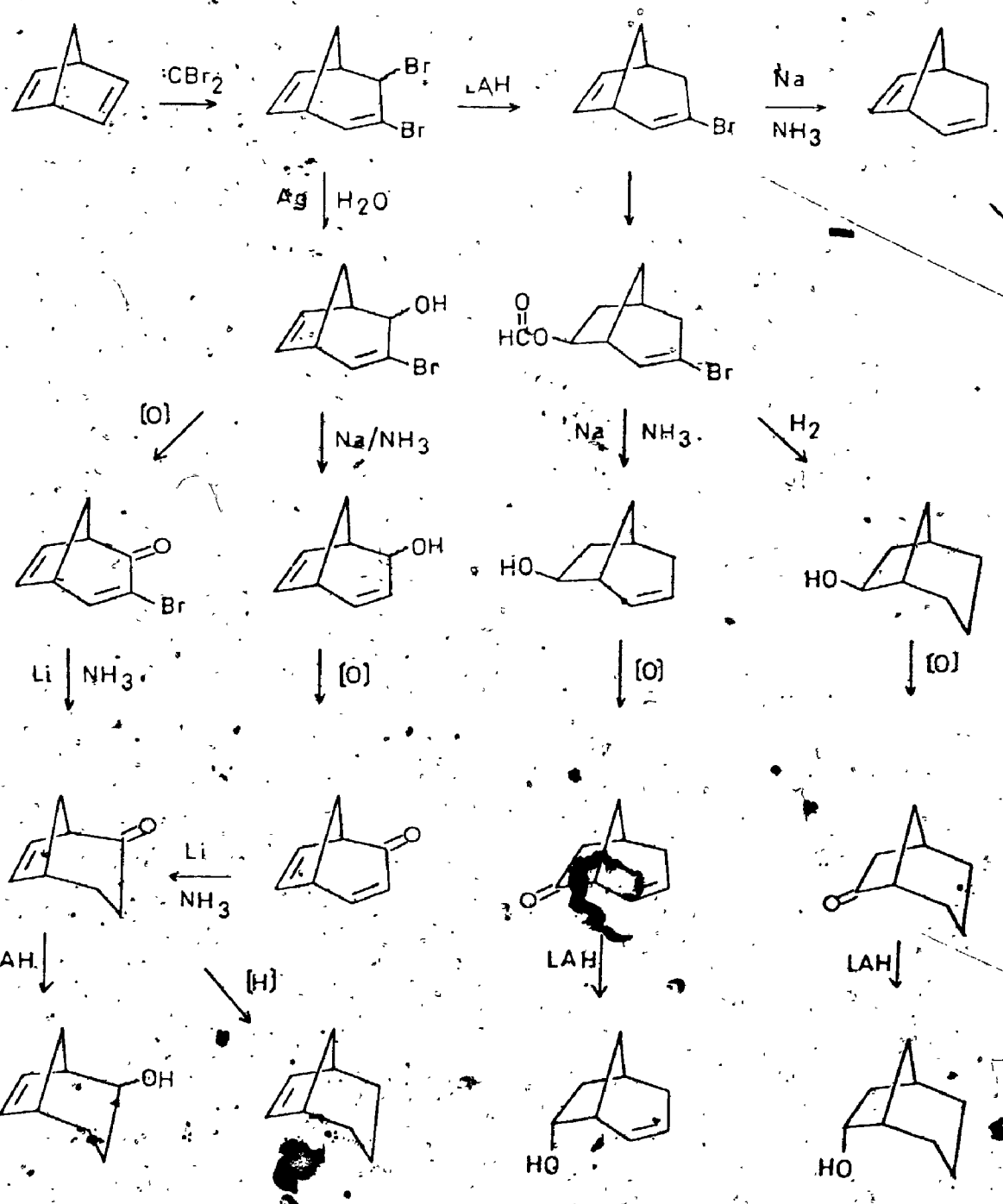


(iv) Bicyclo(3.2.1)oct-3-en-6-one; bicyclo(3.2.1)oct-3,6-dien-2-one and their corresponding derivatives

The addition of dibromocarbene to norbornadiene gave a mixture of dibromides (174). Reduction of the mixture with lithium aluminium hydride gave an apparently isomer-free 3-bromobicyclo(3.2.1)oct-2,6-diene (174). Reduction of this bromide with sodium in liquid ammonia gave bicyclo(3.2.1)oct-2,6-diene (174). Addition of formic acid to 3-bromobicyclo(3.2.1)oct-2,6-diene gave 3-bromobicyclo(3.2.1)oct-3-en-yl formate (174). Hydrogenation using palladium on carbon in basic solution led to the reduction of the double bond, hydrogenolysis of the bromine, and hydrolysis of the formate group leading to exo-bicyclo-(3.2.1)octan-6-ol (174). Oxidation with chromium trioxide-pyridine complex in methylene chloride (190) gave bicyclo(3.2.1)octan-6-one (see Section B). Reduction of 3-bromobicyclo(3.2.1)oct-3-en-yl formate with sodium in liquid ammonia gave exo-bicyclo(3.2.1)oct-3-en-6-ol (209). Oxidation this alcohol with chromium trioxide-pyridine complex in methylene chloride gave bicyclo(3.2.1)oct-3-en-6-one. Reduction of bicyclo(3.2.1)octan-6-one and bicyclo(3.2.1)oct-3-en-6-one with $LiAlH(OMe)_3$ gave mainly endo-alcohol.

The exo- and endo-3-bromobicyclo(3.2.1)oct-3,6-dien-2-ols were obtained by the Ag^+ (210) promoted hydrolysis of the dibromide. Reduction of the vinyl bromide in this mixture with sodium in liquid ammonia gave the mixture of exo- and endo-bicyclo(3.2.1)oct-3,6-dien-2-ols. Oxidation of this mixture of alcohols with chromium trioxide-pyridine in methylene chloride gave bicyclo(3.2.1)oct-3,6-dien-2-one. Reduction with lithium in liquid ammonia in the presence of a small

Figure 6.7. Preparation of Bicyclo(3.2.1)oct-3-en-6-one and Bicyclo(3.2.1)octa-3,6-dien-2-one and their Corresponding Derivatives



amount of t-butanol gave a mixture of bicyclo(3.2.1)oct-6-en-2-one and endo-bicyclo(3.2.1)oct-6-en-2-ol. Wolff-Kishner reduction of bicyclo-(3.2.1)oct-6-en-2-one gave bicyclo(3.2.1)oct-6-ene.(see Figure 6.7).

Bicyclo(3.2.1)oct-2,6-diene

Reduction of 3-bromobicyclo(3.2.1)oct-3,6-diene with excess sodium in liquid ammonia gave bicyclo(3.2.1)oct-2,6-diene in about 41% yield, liquid (lit. bp 50° / 120 mm (205)); IR, $\nu_{max}^{CCl_4}$ 1603 cm^{-1}.

3-Bromobicyclo(3.2.1)oct-3,6-dien-2-ol

Silver nitrate (4.7 g) in 30 ml of acetone and 60 ml of water was added dropwise to a stirred mixture of the dibromide in 10 ml of 50% aqueous acetone. Silver bromide precipitated immediately. After the addition was completed, the reaction mixture was allowed to stir for 12 hr at room temperature. The product was extracted with three portions of ether and the combined extracts were washed with water, saturated aqueous sodium chloride solution and dried over magnesium sulfate. After concentration, the residue was purified by column chromatography. Examination of this mixture by ^1H NMR showed two doublets at 3.90 ppm, J = 2 Hz (exo-alcohol) and 4.84 ppm, J = 5.5 Hz (endo-alcohol) and the multiplet pattern for olefinic protons between 5.9 to 6.9 ppm. The integral from the two doublets gave the ratio of exo : endo alcohols as 1 : 1. Before purification, the ratio of the exo and endo mixture was 2 : 1. The mixture had the following properties: IR, $\nu_{max}^{CCl_4}$ 3580 (O-H), 1600 (C=C) cm^{-1}; Calcd. for C_8H_9OBr, 199.9836; m/e, 199.9824.

Bicyclo(3.2.1)oct-3,6-dien-2-ol

Reduction of the crude 3-bromobicyclo(3.2.1)oct-3,6-dien-2-ol (10 g) with 6.9 g of sodium in 600 ml of ammonia gave 5.1 g of crude

product. Short-path distillation gave 4.3 g of bicycli(3.2.1)oct-3,6-dien-2-ol (211), bp 110 - 115° / 20 mm. ^{1}H NMR showed absorption at 3.9 ppm (d, J = 2 Hz) with an integrated area corresponding to 78% exo-alcohol and at 4.34 (d, J = 5 Hz) indicating the presence of 22% endo-alcohol. The infrared spectrum showed bands at $\nu_{max}^{CCl_4}$ 3640, 3350 and 1625 cm^{-1}.

Bicyclo(3.2.1)octa-3,6-dien-2-one

Oxidation of bicyclo(3.2.1)oct-3,6-dien-2-ol with chromium trioxide-pyridine in methylene chloride (190) gave bicyclo(3.2.1)oct-3,6-dien-2-one in 80% yield, bp 110°/ 25 mm (212). The infrared spectrum contained a strong carbonyl peak at 1680 cm^{-1}.

3-Bromobicyclo(3.2.1)oct-3,6-dien-2-one

3-Bromobicyclo(3.2.1)oct-3,6-dien-2-ol was oxidized to 3-bromo-bicyclo(3.2.1)oct-3,6-dien-2-one in 83% yield using the procedure of R. Ratcliffe and R. Rodehorst. The infrared spectrum (CCl_4) contained a strong carbonyl peak at 1710 cm^{-1} and the C=C stretching at 1640 cm^{-1}. Examination of this compound by ^{1}H NMR in $CDCl_3$ showed two multiplets at 3.31 (H-5) and 3.60 (H-1); 6.12 (dd, J = 5 and 3 Hz, H-7), 6.74 (dd, J = 5 and 3 Hz, H-6), 7.73 (dd, J = 6.5 and 1 Hz, H-4) and a complex pattern between 1.5 and 2.8 ppm.

endo-Bicyclo(3.2.1)oct-6-en-2-ol and Bicyclo(3.2.1)oct-6-en-2-one

A solution of 1.5 g of lithium in 250 ml of liquid ammonia was treated with a solution of 1.12 g of the bicyclo(3.2.1)oct-3,6-dien-2-one and 5.4 ml of t-butanol in 15 ml of diethyl ether. After the resulting blue solution had been stirred for 3 min, solid ammonium chloride was added to consume the excess lithium and the ammonia was

allowed to evaporate. The residue was dissolved in ether and water. The organic layer was washed with saturated sodium chloride solution, dried and concentrated. Removal of the solvent afforded 800 mg of a mixture of ketone and alcohol which was separated by column chromatography. The pure endo-alcohol was obtained by vacuum sublimation and had the following properties: IR, $\nu_{max}^{CCl_4}$ 3610 (O-H), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$), δ 3.62 (m, CHOH), 5.94 (m, olefinic protons); mp 129 - 130°.

An analytical sample of bicyclo(3.2.1)oct-6-en-2-one was collected by g.c. and had the following properties: IR, $\nu_{max}^{CCl_4}$ 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$), δ 2.8 (m, H-4), 2.99 (m, H-1), 6.00 (m, H-7), 6.21 (m, H-6) ppm; m/e, 122.0; mp 83 - 85° (lit. 65 - 81° (213)).

Bicyclo(3.2.1)oct-6-en-2-one with $LiAlH_4$

To a suspension of 100 mg of lithium aluminium hydride in 20 ml of dry ether was slowly added a solution of 100 mg of bicyclo(3.2.1)oct-6-en-2-one in 5 ml of dry ether. The mixture was stirred overnight and worked up in the usual way. This reaction afforded 90 mg of a mixture containing 77% of endo- and 23% of exo-alcohol.

exo-Bicyclo(3.2.1)oct-3-en-6-ol

A solution of 3.15 g of sodium was dissolved in 300 ml of ammonia. A Dry Ice condenser was used to prevent evaporation. Exo-3-Bromobicyclo-(3.2.1)oct-2-en-7-yl formate (10.5 g) was added in one portion and the mixture was stirred for 6 hr. Solid ammonium chloride was added and the ammonia was then allowed to evaporate and the residue was covered with ether and water. The aqueous phase was extracted further with ether. The combined extracts was washed with water, dried over magnesium

sulfate and concentrated. The crude product was purified by column chromatography and distillation gave 2.4 g of a waxy solid, bp 84° / 13 mm (lit. mp 45.0 - 46.5° (209)); IR, $\nu_{max}^{CCl_4}$ 3610 (O-H), 1625 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$), δ 4.19 (dd, J = 5.5 and 2 Hz), 5.75 (m) and 5.39 (m) ppm.

Bicyclo(3.2.1)oct-3-en-6-one

Exo-Bicyclo(3.2.1)oct-3-en-6-ol was oxidized to the ketone in 80% yield using the procedure of R. Ratcliff and R. Rodehorst (190). It had the following physical properties: IR, $\nu_{max}^{CCl_4}$ 1708 (C=O) and 1607 (C=C) cm^{-1}; m/e, 122.1; liquid; 2,4-dinitrophenylhydrazone, 121 - 125° (lit. 146° (214)).

endo-Bicyclo(3.2.1)oct-3-en-6-ol

Reduction of bicyclo(3.2.1)oct-3-en-6-one with lithium aluminum hydride in ether gave 92% of endo-bicyclo(3.2.1)oct-3-en-6-ol which had the following properties: IR, $\nu_{max}^{CCl_4}$ 3590 (O-H) and 1630 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$), δ 4.37 (m) and 5.76 (m) ppm; mp 89 - 91°.

endo-Bicyclo(3.2.1)octan-6-ol

Bicyclo(3.2.1)octan-6-one was reduced with the excess of lithium aluminum hydride in refluxing ether. The product was isolated in the usual way and recrystallized from pentane to yield pure endo-bicyclo-(3.2.1)octan-6-ol, mp 192 - 194° (lit. 192 - 194° (215)); IR, $\nu_{max}^{CCl_4}$ 3620 (O-H) cm^{-1}; ^1H NMR ($CDCl_3$), δ 4.42 (m, CHOH) ppm.

(d) PREPARATION OF OTHERS BICYCLIC COMPOUNDS

Professors R. R. Fraser and J. L. Charlton kindly provided samples of bicyclo(3.2.2)nonan-6-one and bicyclo(2.1.1)hexan-2-one, respectively. 3,3-Dimethylbicyclo(3.3.0)octan-2-one was isolated as the rearrangement product obtained by homoenolization of 3,3-dimethylbicyclo(3.2.1)octan-2-one (59). Several samples were available from earlier work in this laboratory: the bicyclo(3.1.0)hexanones (216) and the bicyclo(4.1.0)-heptan-2-ones (131).

Ring expansion of norcamphor with diazoethane furnished endo-2-methylbicyclo(3.2.1)octan-3-one (217) which upon equilibration with trifluoroacetic acid gave a mixture of the exo and endo isomers (37 : 63). This ring expansion also gave exo-3-methylbicyclo(3.2.1)-octan-2-one but, contrary to the original report, attempted epimerization with sodium methoxide failed to produce detectable amounts of the endo-3-methyl isomer. To confirm enolate formation under these conditions, an experiment with MeO^- / MeOD was carried out giving only the endo-3-deuterio-exo-3-methyl isomer in high yield. The remaining examples were obtained by methylation of 6,6-dimethylbicyclo(3.1.1)heptan-2-one, bicyclo(3.2.1)octan-6-one and bicyclo(3.2.2)nonan-6-one using the sodamide methyl iodide procedure (168). The mono- and dimethyl derivatives were, in most cases, readily separated by g.c. on SE 30 column. Norcamphor also served as the starting material for 2,2-dimethylbicyclo(3.2.1)octan-3-one which was generated from the 2-methyl-2-chloromethyl derivatives (218a) By reduction with $t\text{-BuO}^-$ / t-BuOH followed by CrO_3 oxidation to furnish the desired ketone identical to that reported by another route, (218b).

The preparation of tricyclo(4.4.1.$1^{2,5}$)dodec-3-en-11-one and tricyclo(4.4.1.$1^{2,5}$)dodeca-3,7,9-trien-11-one has been described by Haywood-Farmer et al.(218c), who kindly provided us with samples of each of these ketones. Catalytic hydrogenation of these furnished samples of tricyclo(4.4.1.$1^{2,5}$)dodecan-11-one and tricyclo(4.4.1.$1^{2,5}$)-dodeca-7,9-dien-11-one, respectively.

Ring Expansion of Norcamphor

To a solution of 2.0 g (18.2 mole) of norcamphor in 10 ml of 3% methanolic potassiumcarbonate was added 8.7 g (59.6 mole) of N-ethyl-N-nitrosourethane (217) at such a rate so as to maintain the temperature of the reaction mixture between 20 and 25°. The reaction mixture was concentrated and the residue chromatographed on neutral alumina with pentane to yield 2 g of an oily liquid. The g.c. analysis indicated three components which were collected individually and identified as follows (15% DEGS, 15' x 3/8", T = 160°, 30 psi): Fraction 1 (46%; retention 56 min) was identified as the starting material. Fraction 2 (29% retention time 87 min) was mainly endo-2-methylbicyclo(3.2.1)octan-3-one having the following physical properties: IR(neat), ν_{max} 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$), δ 1.03 (d, 7 Hz, Me) ppm. Its ^{13}C NMR spectrum showed that this fraction contained a small amount of exo-2-methylbicyclo(3.2.1)octan-3-one. Fraction 3 (24%, retention time 98 min) was identified as exo-3-methylbicyclo(3.2.1)octan-2-one which had the following physical properties: IR, $\nu_{max}^{CCl_4}$ 1705 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$), δ 1.0 (d, 6.5 Hz, Me)ppm; 2,4-dinitrophenylhydrazone, mp 150 - 150.5° (lit. 146 - 147° (217)). Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.34;

H, 5.73; N, 17.26.

Methylation of Bicyclo(3.2.1)octan-2-one

Following the method described by Corey et al (168) the sodio derivative of the ketone was generated using sodamide in ether under a nitrogen atmosphere and methylated with freshly distilled methyl iodide. After the usual work-up, the product was analyzed by g.c. (20% SE 30) and found to contain 33.2% of starting material, 49.3% of exo-3-methylbicyclo(3.2.1)octan-2-one and 17.4% of 3,3-dimethylbicyclo(3.2.1)-octan-2-one. The dimethyl derivative had the following physical properties: IR, $\nu_{max}^{CCl_4}$ 1700 cm^{-1}; ^1H NMR ($CDCl_3$), δ 1.08 (s, Me), 1.17 (s, Me), 2.46 (m, 1H), 2.77 (m, 1H); mass spectrum (70 ev), m/e 152.0; liquid; 2,4-dinitrophenylhydrazone, mp 157 - 158°. Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59; Found: C, 79.11; H, 10.41.

Equilibration of exo-3-Methylbicyclo(3.2.1)octan-2-one

A 85 mg sample of exo-3-methylbicyclo(3.2.1)octan-2-one was dissolved in 3 ml of 3% sodium methoxide in methanol and the solution was heated under reflux in a nitrogen atmosphere for 26 hr. The solution was cooled and diluted with 15 ml of water, extracted with pentane, washed with water, dried and concentrated using a Vigreux column. The residue was analyzed by g.c. (20% SE 30 & 15% DEGS), ^1H and ^{13}C NMR spectra. No new component was detected. Three repeated experiments showed the same result. In order to confirm enolate formation under these conditions, an experiment with MeO^- / MeOD was carried out giving only the endo-3-deuterio-exo-3-methyl isomer in high yield.

Isomerization of endo-2-Methylbicyclo(3.2.1)octan-3-one

A 100.4 mg of sample of endo-2-methylbicyclo(3.2.1)octan-3-one was

heated to 110° in 2 ml trifluoroacetic acid for 24 hr under nitrogen atmosphere. The mixture was diluted with water, neutralized with solid sodium bicarbonate, extracted with ether, dried (anhydrous $MgSO_4$), and concentrated. ^1H NMR Spectrum analysis showed a 37 : 64 mixture of exo-2-methyl and endo-2-methylbicyclo(3.2.1)octan-3-one, respectively (integration of the two methyl absorptions. 1.03 (d, J = 7 Hz, endo-Me), and 1.20 (d, J = 6.5 Hz, exo-Me) ppm).

3,6,6-Trimethyl- and 3,3,6,6-Tetramethylbicyclo(3.1.1)heptan-2-one

Methylation of nopinine using sodamide and methyl iodide (168) afforded a mixture of four ketones. Gas chromatographic analysis and separation on SE 30 columns showed the mixture to contain nopinone (52%), 3-methyl derivatives (34%), and the desired 3,3-dimethylnopinone (14%). The 3,6,6-trimethylbicyclo(3.1.1)heptan-2-one, however, could not be separated but the mixture gave signals in its ^1H NMR spectrum at 1.32 (s), 1.15 (d, J = 6.5 Hz), and 0.70 (s) for the exo-3-methyl derivative and 1.34 (s), 1.30 (d) and 0.88 (s) for the endo-3-methyl isomer. These two isomers exhibited the same ^1H NMR data as those reported (218d). Integration of the highest field methyl signals indicated that the two ketones were present in a 7 : 3 (exo : endo) ratio. IR, $\nu_{max}^{CCl_4}$ 1710 (C=O) cm^{-1}.

Mol wt. Calcd. for $C_{10}H_{16}O$: 152.1200. Found (m/e): 152.1199.

A sample of 3,3,6,6-tetramethylbicyclo(3.1.1)heptan-2-one had the following properties: $\nu_{max}^{CCl_4}$ 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$), δ 0.84 (s, Me), 1.24 (s, Me), 1.31 (s, Me), 1.33 (s, Me) ppm; liquid, 2,4-dinitrophenylhydrazone: mp 211.5 - 218.5°.

Mol. wt. Calcd. for $C_{11}H_{18}O$: 166.1357. Found (m/e): 166.1359.

7-Methyl- and 7,7-Dimethylbicyclo(3.2.2)nonan-6-ones

Methylation of bicyclo(3.2.2)nonan-6-one using sodamide and methyl iodide (168) gave a mixture containing unreacted starting material (20%), the monomethyl ketones (43%), and 7,7-dimethylbicyclo(3.2.2)nonan-6-one (37%). The latter was isolated by preparative g.c. on a SE 30 column and found to have the following properties: IR, $\nu_{max}^{CCl_4}$ 1711 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$), δ 1.14 (s, two methyls); mp 89 - 90°;

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91; Found: C, 79.56; H, 10.78.

The 7-methylbicyclo(3.2.2)nonan-6-ones, however, could not be separated but the mixture gave methyl signals in its ^1H NMR spectrum at 1.16 (d, J = 7.5 Hz) and 1.13 (d, J = 6.5 Hz) ppm assigned to the exo and endo isomers on the basis of the ^{13}C NMR spectrum (see Chapter 4) which indicated that the two ketones were present in a 2 : 3 (exo : endo) ratio.

Anal. Calcd. For $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.85; H, 10.64.

Methylation of Bicyclo(3.2.1)octan-6-one

Methylation of bicyclo(3.2.1)octan-6-one using sodamide and methyl iodide (168) gave a mixture containing unreacted starting material (16%), exo-7-methylbicyclo(3.2.1)octan-6-one (17%), endo-7-methylbicyclo(3.2.1)-octan-6-one (4%), and 7,7-dimethylbicyclo(3.2.1)octan-6-one (63%). The major monomethyl derivative was found to be identical to that described by Kubota et al (219) and sebsequently shown to be the 7-exo-methyl isomer which had the following physical properties: IR, $\nu_{max}^{CDCl_3}$ 1710, (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.11 (d, J = 7.5 Hz) ppm; m/e 138.1;

liquid; 2,4-dinitrophenylhydrazone, mp 182 - 186° (lit. 180 - 186° (219)).

A sample of exo-7-methylbicyclo(3.2.1)octan-6-one (400 mg) was dissolved in 10 ml of 3% sodium methoxide in methanol and the solution refluxed for 7 hr in a nitrogen atmosphere. After dilution with 15 ml of ice water, the ketone product was isolated by pentane extraction. Gas chromatographic analysis on 20% Carbowax 4000 showed that the mixture contained 45% of the exo-7-methyl isomer and 55% of the desired endo-7-methylbicyclo(3.2.1)octan-6-one. Separation by preparative g.c. gave a sample of the latter having the following properties: IR, $\nu_{max}^{CCl_4}$ 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$), δ 1.10 (d, J = 7 Hz) ppm; liquid, 2,4-dinitrophenylhydrazone, mp 203.5 - 204.6°.

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.63; H, 5.88; N, 17.42.

(e) Preparation of 4-Methylphenanthrene

4-Methylphenanthrene was prepared by the reported procedure (figure 6.8) (220). The condensation of napthalene with succinic anhydride in the presence of anhydrous aluminium trichloride in nitrobenzene gave β-1-napthoyl-propionic acid and β-2-napthoylpropionic acid. A pure β-2-napthoylpropionic acid was isolated and reduced by Clemmenson s method to the corresponding γ-napthoylbutyric acid which were converted into 4-keto-1,2,3,4-tetrahydrophenanthrene by the action of 85% sulfuric acid at 100°. 4-Methylphenanthrene were obtained by condensing 4-keto-1,2,3,4-tetrahydrophenanthrene with methyl magnesium iodide in ethereal solution and the resulting carbinol lost water readily, yielding a mixture of hydrocarbons which on treatment with 5% Pd / C in cumene (221) gave 4-methylphenanthrene.

(f) Preparation of 4,5-Dimethylphenanthrene

4,5-Dimethylphenanthrene was prepared acoording to the literature method (222). Ozonolysis of pyrene (223) gave 4-formyl phenanthrene-5-carboxylic acid. Esterification of the acid with methanolic hydrogen chloride gave the corresponding esten. Reduction of this ester with lithium aluminium hydride furnished 4,5-bishydroxylmethylphenanthrene in excellent yield. The corresponding bisbromomethyl compound was obtained by action of phosphorous tribromide on the diol. Reduction of this bromide gave the cyclic ether. 4,5-Dimethylphenanthrene was prepared in low yield by fission of the cyclic ether with phosphorous and hydroiodidic acid at 165° for 24 hr (224) (Figure 6.9).

(g) Preparation of 4-Methyl fluorene and fluorenone

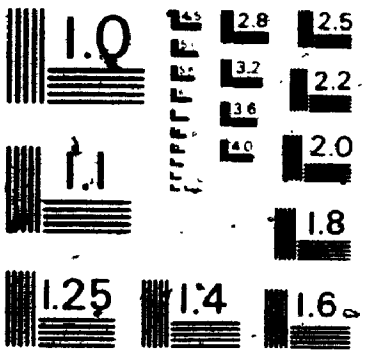
Fluorene-4-carboxylic acid was obtained by the Clemmenson s reduction from fluorenone-4-carboxylic acid. Reduction with lithium aluminium hydride yielded fluoren-4-yl-methanol. Treatment with phosphorous tribromide in benzene gave fluoren-4-yl methyl bromide which on reduction with lithium aluminium hydride afforded 4-methylfluorene. Oxidation of 4-methylfluorene with potassium permanganate in 1% sodium hydroxide gave 4-methylfluorenone (Figure 6.10) (225, 226).

(h) Preparation of 4,5-Dimethylfluorene and -fluorenone

2-Amino-3-methyl benzoic acid was converted via the diazonium salt into 6,6 -dimethyldiphenic acid (227). 4,5-Dimethylfluorenone was obtained by heating 6,6 -dimethyldiphenic acid at 360° under N_2 atmosphere for 1 hr. Wolff Kishner s reduction of 4,5-dimethyl-fluorenone gave 4,5-dimethylfluorene (Figure 6.11) (228, 229).

5 5

OF/DE



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Preparation of 4-Methylphenanthrene Figure 6.8.

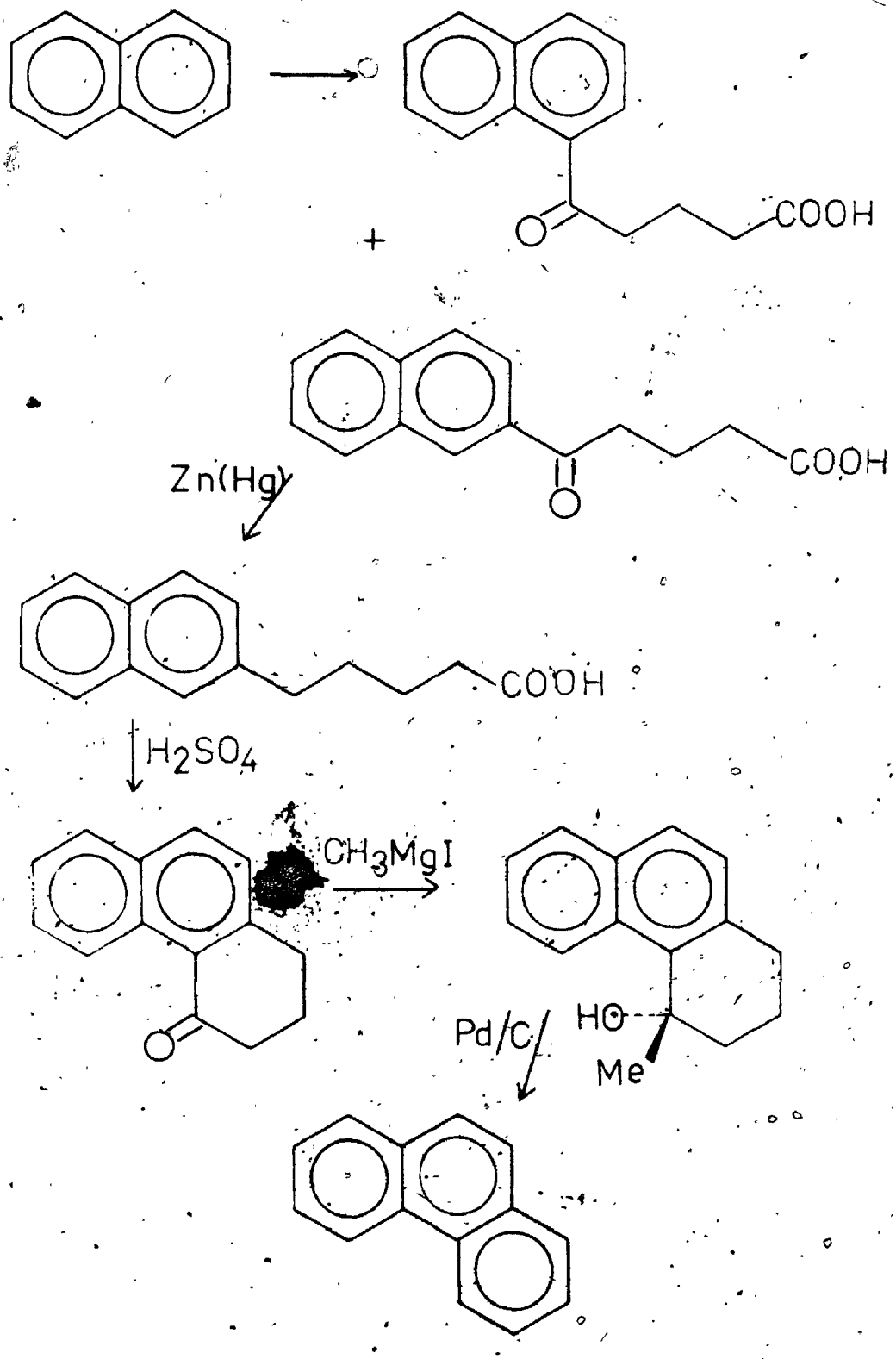


Figure 6.9. Preparation of 4,5-Dimethylphenanthrene

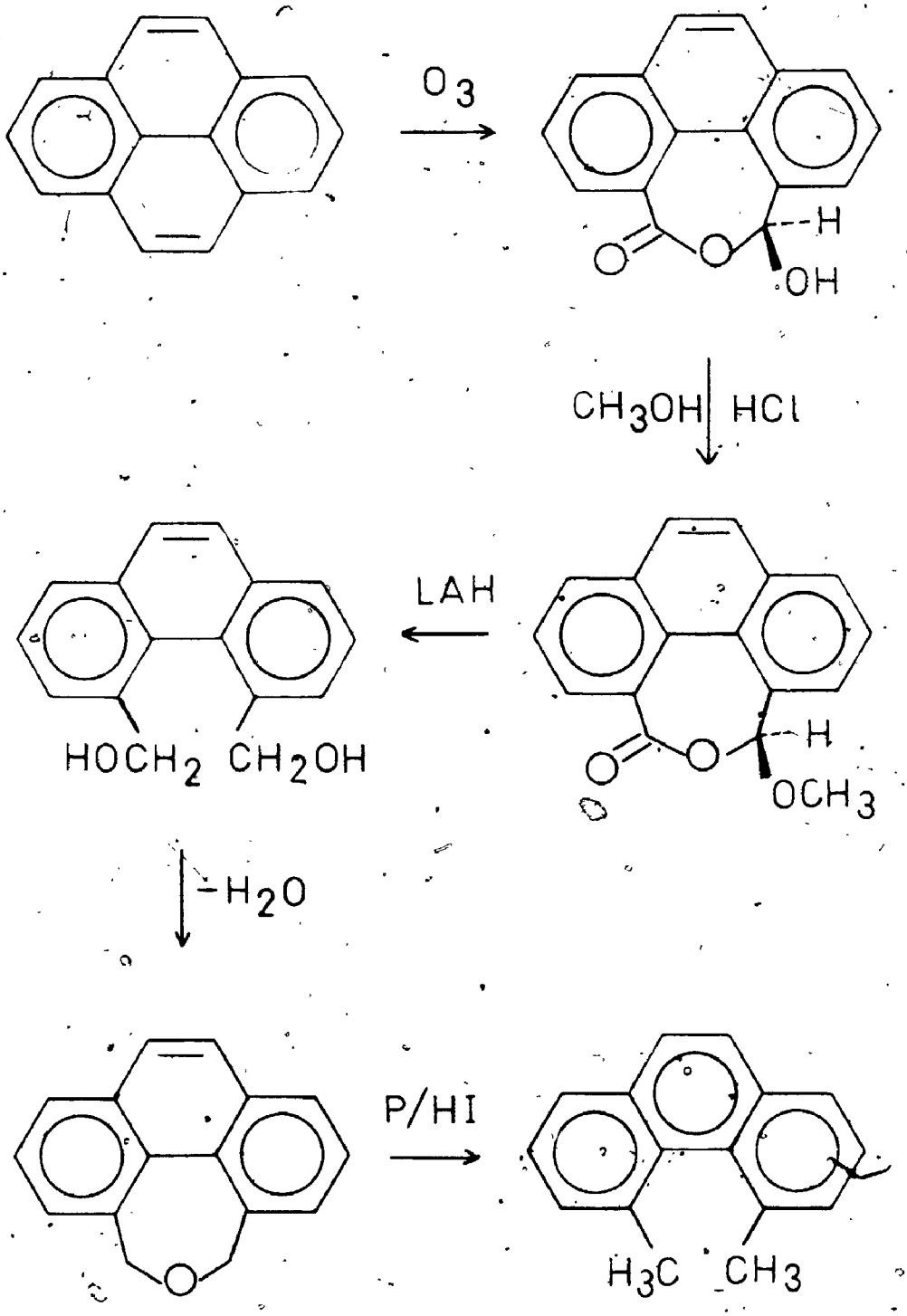


Figure 6.10. Preparation of 4-Methyl fluorene and -fluorenone

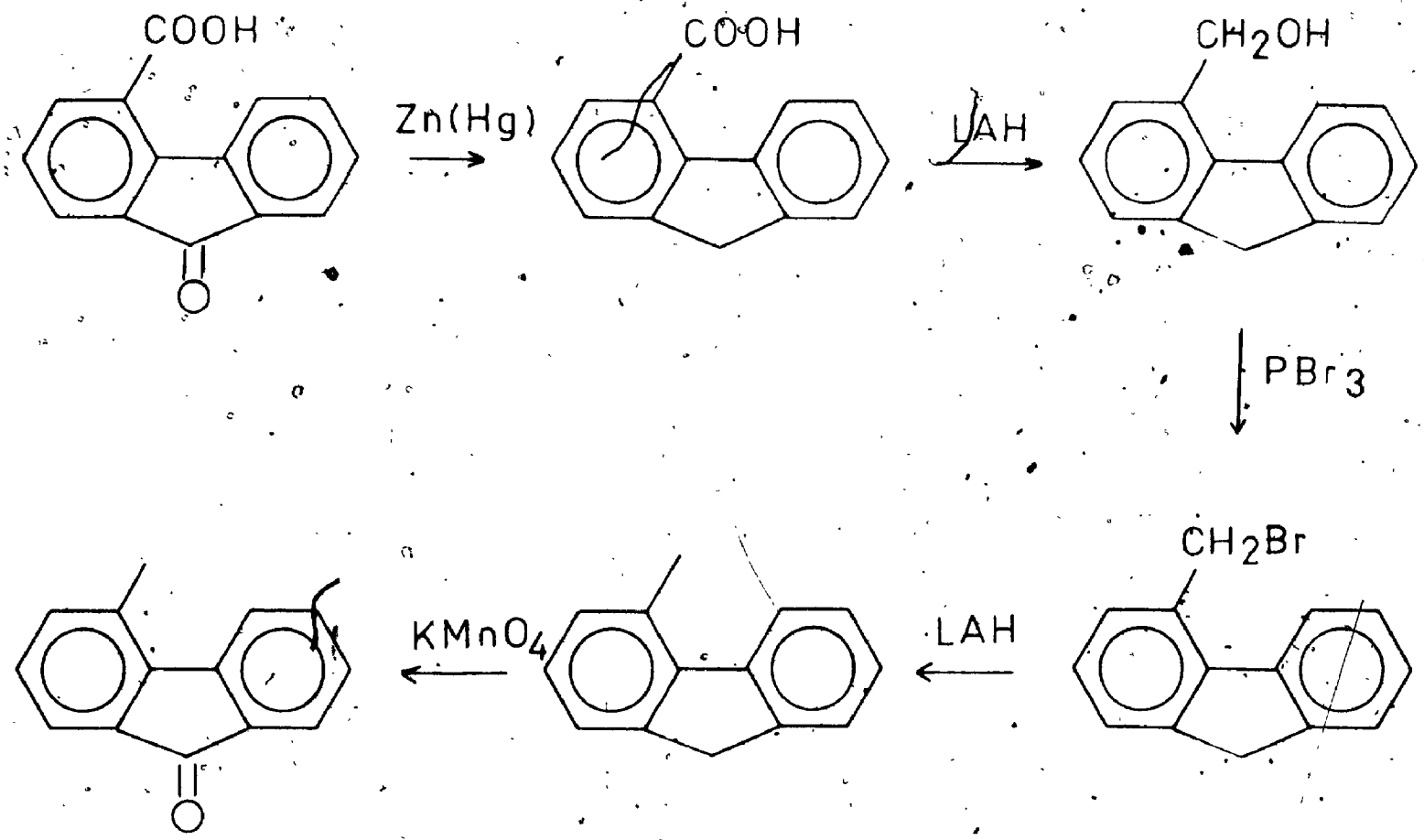
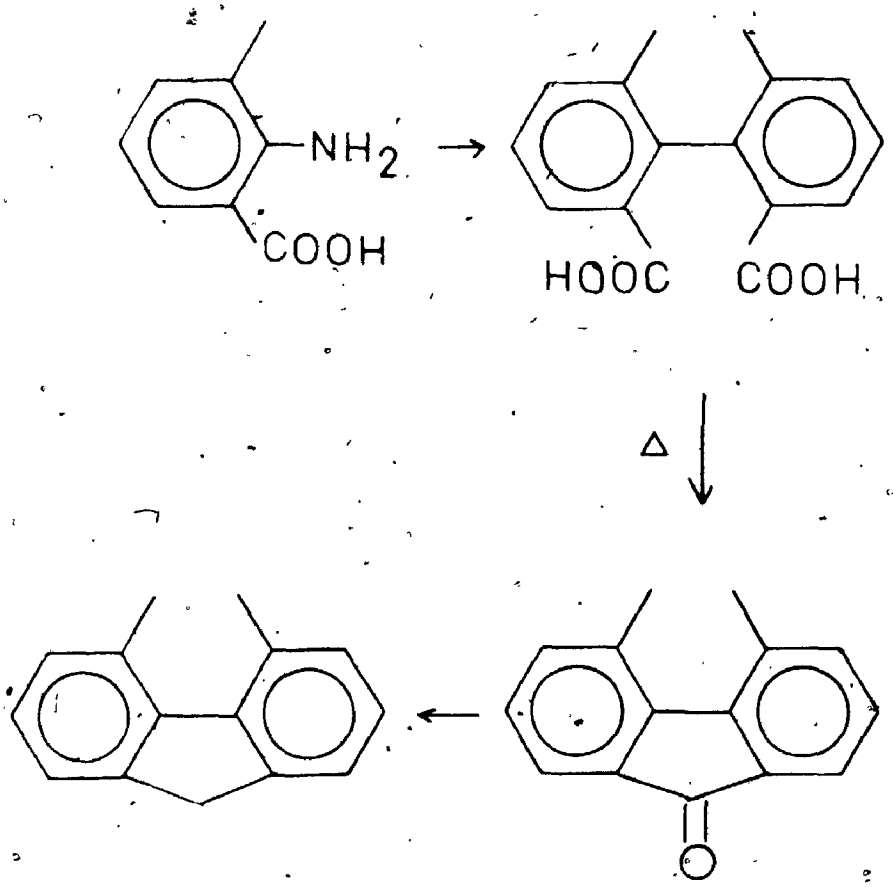


Figure 6.11. Preparation of 4,5-Dimethyl-fluorene and -fluorenone



APPENDIX --- TABLES

^{13}C SHIELDINGS OF SEVERAL SERIES OF ORGANIC COMPOUNDS

Table A.1

^{13}C Shieldings[a] of some Cycloalkanols

Ring	α-C	β-C	γ-C							ω-C	C_nH_{2n}[b]
4	67.0	33.6								12.0	22.5
5	74.0	35.5	23.4								25.9[a]
6	70.0	35.6	24.2							25.6	27.0[a]
7	72.8	37.6	22.7	28.2							28.4[a]
8	72.2	34.8	22.8	27.5						25.3	26.8[a]
9	72.1	33.7	21.7	27.3	24.9						26.1
10	71.2	33.2	22.0	24.2	25.3					25.3	25.3
11	71.6	35.2	22.9	26.0	26.2	26.5					25.8
12	69.1	32.5	21.1	23.4	23.5	24.3				23.9	23.6
13	70.7	34.9	23.0	25.9	26.0	26.1	26.5				25.6
14	69.5	33.7	22.0	25.4	24.8	24.9	25.4			25.6	25.0
15	70.6	35.3	23.3	26.7_6	26.8_1	26.9	27.2	27.2			26.8
16	70.5	35.1	23.4	26.7	26.7	26.7	27.0	27.1		26.6	26.9
17	70.8	35.8	23.8	27.5	27.5	27.6	27.6	27.7	27.7		27.1

[a] 1 M solutions in $CDCl_3$ solutions. In ppm from internal TMS.

[b] Data taken from ref. (86) for neat liquids or CS_2 solutions and corrected to the TMS scale with the factor 193.7 ppm.

Table A.2

^{13}C Shieldings[a] of Several Bicyclic Alcohols

Skeleton	Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
(2.1.1)	2-OH	46.2	72.0	39.2	38.8	38.2	34.9			
(2.2.1)	exo-2-OH	44.2	74.7	42.4	35.4	28.1	24.4	34.4		
	endo-2-OH	42.5	72.9	39.4	37.2	29.9	20.0	37.6		
	7-OH	40.4	26.8[b]	26.8[b]	40.4	26.9	26.9	79.5		
(2.2.2)	2-OH	31.7	69.5	37.5	24.8	25.6[b]	18.6[b]	23.8	24.5	
(3.2.1)	exo-2-OH	41.7	71.3	(26.8)	(26.9)	34.3	28.4	(26.5)	32.1	
	endo-2-OH	42.7	72.5	(28.3)	30.7	33.7	(28.5)	23.3	37.3	
	exo-3-OH	34.9	42.3	66.2	42.3	34.9	29.1	29.1	39.1	
	endo-3-OH	33.9	40.9	66.6	40.9	33.9	28.8	28.8	38.6	
	exo-6-OH	35.8	31.4	19.5	29.8	44.6	76.0	41.2	36.2	
	endo-6-OH	34.2	32.6	19.4	26.8	39.3	74.8	37.8	37.8	
	exo-8-OH	42.2	31.3	17.0	31.3	42.2	26.2	26.2	82.1	
	endo-8-OH	37.7	24.6	17.8	24.6	37.7	25.3	25.3	74.6	
(3.2.2)	endo-6-OH	30.2	36.7	21.8	26.6	36.8	70.0	38.3	24.4	23.7
(3.3.0)	endo-2-OH	47.5	75.1	35.1	27.8	42.6	34.0	26.6	29.4	
(4.1.0)	2-OH	17.7	67.1	29.8	23.1	21.0	12.7	7.6		

[a] In ppm from internal TMS in $CDCl_3$ solutions.

[b] Carbons syn with respect to the hydroxyl group.

Table A.9. ^{13}C Shieldings[a] of Some Cycloheptanones

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	Me
Nil[b]	215.2	43.9	24.4	30.5	30.5	24.4	43.9	
	212.6	43.6	24.4	30.6	30.6	24.4	43.6	
2-Me	213.6	46.5	33.8	29.2	30.4	24.9	42.8	17.6
2,2-Me_2	215.4	47.6	39.7	25.5	31.2	27.0	40.2	26.1
2,2,7-Me_3[b]	218.9	47.4	38.9	24.6	30.2	35.6	41.7	27.7 (2-Me)
								23.4 (2-Me)
								17.9 (7-Me)
2,2,7,7-Me_4[b]	218.9	48.7	38.9	25.6	25.6	38.9	48.7	27.7
3-Me	211.4	52.0	31.7	39.8	29.2	24.8	44.3	23.8
3,3-Me_2	210.6	56.2	32.9	45.3	24.8	25.6	44.2	29.8
4-Me	212.6	42.6	32.9	37.2	39.4	23.7	44.1	23.7
4,4-Me_2	212.3	39.6	36.8	33.8	43.9	20.4	43.9	29.1
cis-3,5-Me_2	211.7	52.5	31.5	49.1	36.7	33.3	43.3	24.8 ; 24.8

[a] In ppm from TMS. Original data (103) converted using the value $\delta_C^{CS_2}$ 193.7.

[b] In ppm from internal TMS in $CDCl_3$ solutions.

Table A.4

^{13}C Shieldings[a] of Several Unsaturated Bicyclic Alcohols

Skeleton	Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
(2.2.1)	Δ^2	41.8	24.6	24.6	41.8	135.2	135.2	48.5	
	Δ^2-exo-2-OH	50.1	72.3	36.9	40.7	140.2	133.5	45.6	
	Δ^2-endo-2-OH	48.2	72.3	37.6	42.9	140.0	131.1	48.2	
	Δ^2-syn -7-OH	47.4	22.2	22.2	47.4	131.9	131.9	86.9	
	Δ^2-anti-7-OH	45.6	21.4	21.4	45.6	134.3	134.3	82.0	
(2.2.2)	Δ^2	29.5	25.8	25.8	29.5	134.1	134.1	25.8	25.8
	Δ^2-exo-2-OH	37.6	68.6	35.4	30.1	135.2	132.0	17.3	26.1
	Δ^2-endo-2-OH	37.6	70.2	38.9	30.1	135.9	129.0	22.1	24.1
(3.2.1)	Δ^3	33.6	37.5	123.8	134.7	35.6	35.5	30.6	35.5
	Δ^3-exo-2-OH	40.5	72.1	125.2	137.9	35.6	(30.8)	24.8	(31.0)
	Δ^3-endo-2-OH	41.8	73.7	127.1	135.9	35.2	32.5	21.3	37.5
	Δ^3-exo-6-OH	33.3	36.4	125.9	130.2	44.0	78.0	42.7	31.4
	Δ^3-endo-6-OH	32.7	37.9	128.1	129.4	40.0	80.5	40.8	32.7
	Δ^3-syn-8-OH	35.7	31.5	126.6	129.9	39.8	32.2	28.4	73.5
	Δ^3-anti-8-OH	40.7	37.5	124.2	132.6	42.3	32.6	28.3	78.1
	Δ^5	39.5	25.2	18.7	25.2	39.5	132.1	132.1	45.1
	Δ^5-exo-2-OH	46.4	66.1	27.4	21.9	39.2	134.8	132.9	37.3
	Δ^5-endo-2-OH	46.8	68.5	28.5	23.3	38.4	134.3	130.1	42.5
	Δ^5-exo-3-OH	39.1	35.2	67.4	35.2	39.1	132.6	132.6	44.9
	Δ^5-endo-3-OH	38.1	36.8	67.1	36.8	38.1	138.3	138.3	44.7
	Δ^3,Δ^5	(38.3)	28.7	123.8	134.1	(38.7)	139.7	130.2	40.7
	Δ^3,Δ^5-exo-2-OH	45.7	66.0	126.0	144.3	39.5	138.0	130.2	37.6
	Δ^3,Δ^5-endo-2-OH	47.0	66.9	126.8	143.9	38.7	137.0	129.6	44.5

[a] In ppm from internal TMS in $CDCl_3$ solutions. Assignments for similar values in parenthese may be reversed.

Table A.5

Substitution Effects of the Hydroxyl Group in Some Unsaturated Bicyclic Alcohols[a]

Skeleton	Substitution	α	β		γ			δ
		CH	CH_2	CH	CH	CH_2 (gauche)	CH_2 (anti)	CH_2
(2.2.1)	Δ^5-exo-2-OH	47.7	8.3	12.3	-1.1	-2.9		
	Δ^5-endo-2-OH	47.7	6.4	13.0	1.1		-0.3	
	Δ^5-syn-7-OH	38.4	5.6				-2.4	
	Δ^5-anti-7-OH	33.5	3.8			-3.2		
(2.2.2)	Δ^5-exo-2-OH	42.8	8.1	9.6	0.6	-9.5		0.3
	Δ^5-endo-2-OH	44.4	8.1	13.1	0.6		-3.7	-1.7
(3.2.1)	Δ^3-exo-2-OH	34.6	6.9			-4.5	-5.8	-4.7(C-6)
								0.0(C-5)
	Δ^3-endo-2-OH	36.2	8.2			-9.3	2.0	-3.0(C-6)
								-0.4(C-5)
	Δ^3-exo-6-OH	42.5	8.4	12.1	-0.3	-4.1		-1.1
	Δ^3-endo-6-OH	45.0	4.4	10.2	-0.9		-2.8	0.4
	Δ^3-syn-8-OH	38.0	2.1(C-1)			-6.0	-3.3(C-6)	
			4.2(C-5)				-2.2(C-7)	
	Δ^3-anti-8-OH	42.6	7.1(C-1)			-2.9(C-6)	0.0(C-2)	
			6.7(C-5)			-2.3(C-7)		
	Δ^4-exo-2-OH	40.9	6.9	8.7		-7.8(C-8)	-3.3(C-4)	-0.3
	Δ^4-endo-2-OH	43.3	7.3	9.8		-7.9(C-4)	-2.6(C-8)	-1.1
	Δ^4-exo-3-OH	48.7		10.2	-0.4			-0.2
	Δ^4-endo-3-OH	48.4		11.6	-1.4			-0.4
	Δ^3,Δ^4-exo-2-OH	37.3	7.4			-3.1		0.8
	Δ^3,Δ^4-endo-2-OH	38.2	8.7				3.8	0.0

[a] $\Delta\delta = \delta_C^{ROH} - \delta_{CH}^{RH}$, where RH = olefins, in ppm; positive values indicate downfield shifts.

Table A.6. ^{13}C Shieldings[a] of Some Bicyclo(3.2.1)octane acetates

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Me	C=O
exo-2-OAc	38.7	74.0	23.8	27.1	34.1	28.9	26.8	32.9	21.4	170.2
endo-2-OAc	39.7	75.2	24.7	30.6	33.9	28.4	24.2	37.2	21.3	170.0
exo-3-OAc	34.7	38.1	69.4	38.7	34.7	28.6	28.6	38.9	21.3	171.0
endo-3-OAc	33.7	37.7	69.4	37.7	33.7	28.5	28.5	38.5	21.5	170.3
exo-8-OAc	39.6	31.2	17.1	31.2	39.6	26.5	26.5	84.8	21.4	

[a] In ppm from internal TMS in $CDCl_3$ solutions.

Table A.7. ^{13}C Shieldings[a] of Several Monomethylol and Dimethylol Bicyclic Derivatives

Skeleton	Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	CH_2	Me
(2.2.1)	exo-2-CH_2OH	38.2	44.9	34.1	36.2	29.0	29.9	36.2		66.8	
	exo-3-Me-exo-2-CH_2OH	39.5	48.6	39.4	44.5	29.8	29.6	32.6		63.2	15.0
	endo-3-Me-exo-2-CH_2OH	39.3	53.4	36.7	41.7	21.7	30.0	37.2		66.2	16.5
	exo,exo-2,3-$(CH_2OH)_2$	40.5	48.6	48.6	40.5	29.7	29.7	34.7		63.4	
	exo,endo-2,3-$(CH_2OH)_2$	39.4	50.7	49.1	39.2	22.8	30.4	37.7		66.0(x)	
										64.2(n)	
	endo,endo-2,3-$(CH_2OH)_2$	40.9	43.3	43.3	40.9	22.8	22.8	40.2		61.8	
	endo-3-Me-endo-2-CH_2OH	39.4	43.0	34.2	43.0	21.8	22.0	35.6		61.2	11.2
	exo-3-Me-endo-2-CH_2OH	38.4	52.5	40.7	43.3	30.0	21.7	36.4		63.9	21.7
	endo-2-CH_2OH	37.9	42.5	33.7	36.7	29.9	22.6	39.8		64.8	
(2.2.2)	2-CH_2OH	24.4	38.3	30.2	24.8	26.1	20.7[b]	27.0	25.5	65.9	
	trans-3-Me-2-CH_2OH	25.6	41.2	34.5	30.9	27.3	20.4[b]	26.9	20.2	64.8	20.0
	trans-2,3-$(CH_2OH)_2$	26.7	45.0	45.0	26.7	27.2	21.1[b]	27.2	21.2[b]	66.6	
	cis-2,3-$(CH_2OH)_2$	28.3	41.2	41.2	28.3	21.2[b]	21.2[b]	26.9	26.9	64.3	
Δ^2-(2.2.1)	exo-2-CH_2OH	49.3	41.5	29.5	41.8	136.5	136.3	44.9		67.2	
	exo-3-Me-exo-2-CH_2OH	43.6	43.4	34.2	49.4	137.2	136.7	42.1		64.6	16.1
	endo-3-Me-exo-2-CH_2OH	44.5	50.5	37.6	47.2	134.0	137.3	46.8		66.6	19.1
	exo,exo-2,3-$(CH_2OH)_2$	45.7	43.4	43.4	45.7	137.3	137.3	43.8		64.6	
	exo,endo-2,3-$(CH_2OH)_2$	44.5	46.9	47.9	44.6	133.5	138.0	47.1		66.4(x)	
	endo,endo-2,3-$(CH_2OH)_2$	46.4	45.0	45.0	46.4	134.6	134.6	49.8		63.1	
	endo-3-Me-endo-2-CH_2OH	45.5	44.5	35.4	49.3	135.7	134.8	49.0		63.3	13.9
	exo-3-Me-endo-2-CH_2OH	44.2	51.3	36.8	48.7	138.2	132.7	46.1		66.2	21.0
	endo-2-CH_2OH	43.6	41.6	28.8	42.1	137.1	132.0	49.4		66.2	
Δ^5-(2.2.2)	exo-CH_2OH	31.3	38.9	29.7	30.4	135.8	134.1	19.3	24.9	65.7	
	endo-3-Me-exo-2-CH_2OH	30.8	48.7	38.9	36.9	132.4	135.2	18.1	26.4	64.4	22.7
	exo-3-Me-endo-2-CH_2OH	32.1	49.5	36.0	35.0	136.4	131.0	26.1	18.4	66.9	19.4
	exo,endo-2,3-$(CH_2OH)_2$	(32.3)	44.6	46.9	(32.0)	132.0	135.7	19.3	25.9	66.0	
										67.5	
	endo,endo-2,3-$(CH_2OH)_2$	34.5	45.6	45.6	34.5	133.0	133.0	25.5	25.5	65.0	
	endo-2-CH_2OH	31.3	40.5	30.2	29.8	134.8	131.7	26.0	24.8	67.2	

[a] In ppm from internal TMS in $CDCl_3$ solutions. Assignments for similar values in parentheses may be reversed.

[b] Syn with respect to the CH_2OH.

Table A.8. ^{13}C Shieldings[a] of Some Bicyclo(2.2.2)octyl Carboxylic Acid Derivatives

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Me	C=O
2-COOH	27.5	41.9	28.9	23.7	(25.3)	21.9[b]	26.3	(25.1)		183.0
trans-3-Me-2-COOH	28.6	51.0	32.8	30.3	(26.6)	21.4	(26.4)	19.8	20.2	181.4
Δ^5-exo-2-COOH	32.4	42.7	28.1	29.4	135.2	133.8	21.1	25.1		181.2
Δ^5-endo-2-COOH	32.4	42.8	29.7	29.4	135.3	131.5	24.4	25.4		181.2
Δ^5-endo-3-Me-exo-2-COOH	33.0	51.7	34.9	36.5	133.1	133.1	19.8	25.7	22.6	181.6
Δ^5-exo-3-Me-endo-2-COOH	32.8	51.4	(35.6)	(35.8)	135.3	130.8	25.8	17.7	19.7	180.8

[a] In ppm from internal TMS in $CDCl_3$ solutions. Assignments for similar values in parentheses may be reversed.

[b] Syn with respect to the acid group.

Table A.9. ^{13}C Shieldings[a] of Some Cycloheptanones

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	Me
Nil[b]	215.2	43.9	24.4	30.5	30.5	24.4	43.9	
	212.6	43.6	24.4	30.6	30.6	24.4	43.8	
2-Me	213.6	46.5	33.8	29.2	30.4	24.9	42.8	17.6
$2,2\text{-Me}_2$	215.4	47.6	39.7	25.5	31.2	27.0	40.2	26.1
$2,2,7\text{-Me}_3$[b]	218.9	47.4	38.9	24.6	30.2	35.6	41.7	27.7 (2-Me)
								23.4 (2-Me)
								17.9 (7-Me)
$2,2,7,7\text{-Me}_4$[b]	218.9	48.7	38.9	25.6	25.6	38.9	48.7	27.7
3-Me	211.4	52.0	31.7	39.8	29.2	24.8	44.3	23.8
$3,3\text{-Me}_2$	210.6	56.2	32.9	45.3	24.8	25.6	44.2	29.8
4-Me	212.6	42.6	32.9	37.2	39.4	23.7	44.1	23.7
$4,4\text{-Me}_2$	212.3	39.6	36.8	33.8	43.9	20.4	43.9	29.1
cis-$3,5\text{-Me}_2$	211.7	52.5	31.5	49.1	36.7	33.3	43.3	24.8 ; 24.8

[a] In ppm from TMS. Original data (103) converted using the value $\delta_C^{CS_2}$ 193.7.

[b] In ppm from internal TMS in $CDCl_3$ solutions.

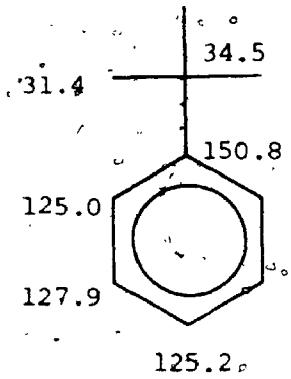
Table A.10. ^{13}C Shieldings[a] of Some Cyclooctanones.

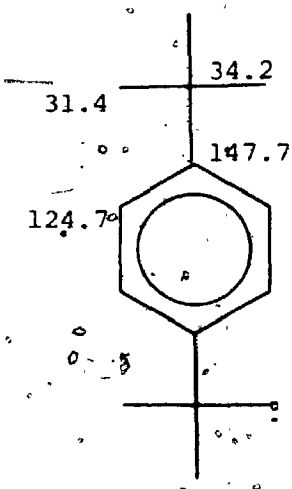
Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Me
Nil	218.1	42.0	25.7	27.3	24.8	27.3	25.7	42.0	
2,2,8-Me_3	223.0	46.8	39.3	25.3[b]	23.8	25.4[b]	35.6	39.1	27.2 20.5 19.7
2,2,8,8-Me_4	221.3	48.8	40.0	24.5	22.0	24.5	40.0	48.8	28.4

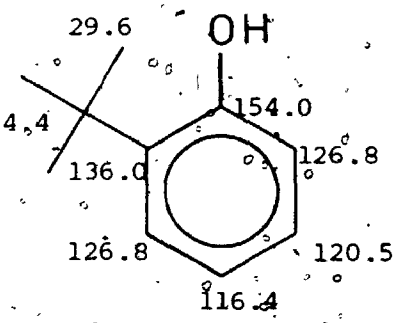
[a] In ppm from internal TMS in $CDCl_3$ solutions.

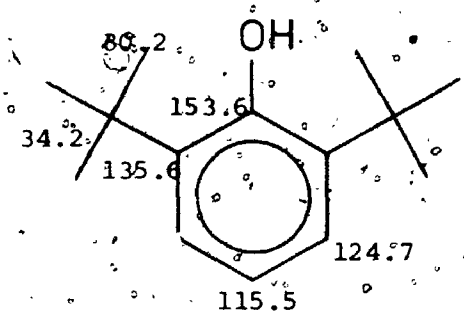
[b] Assignments uncertain.

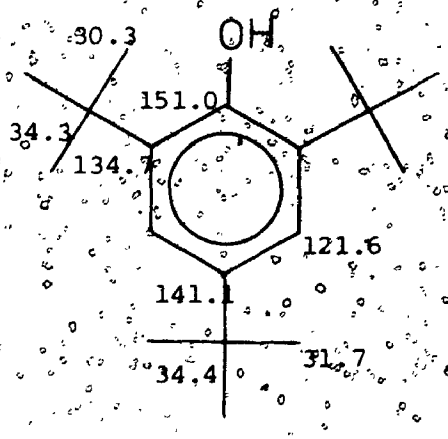
Table A.11. ^{13}C Shieldings[a] of Some Phenols

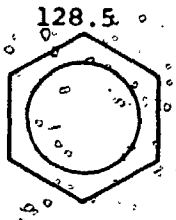






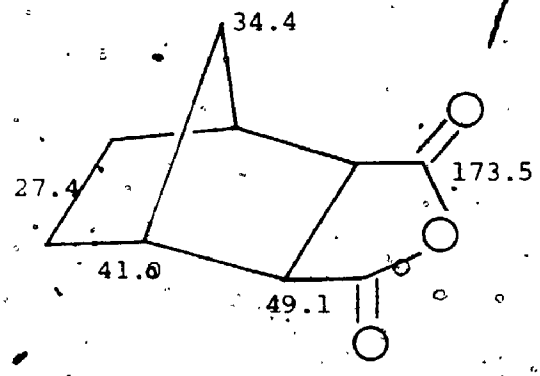


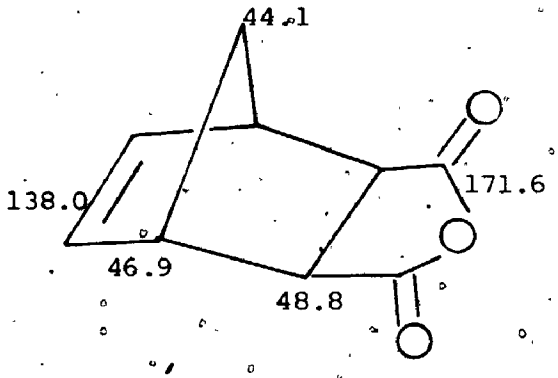


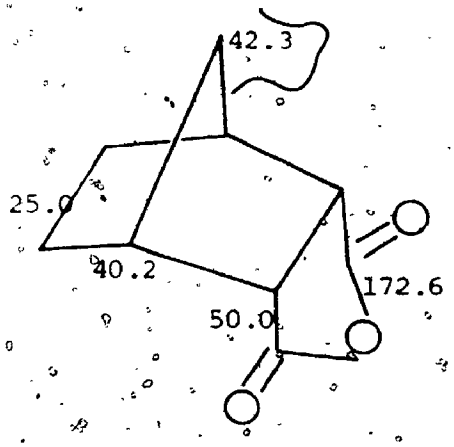


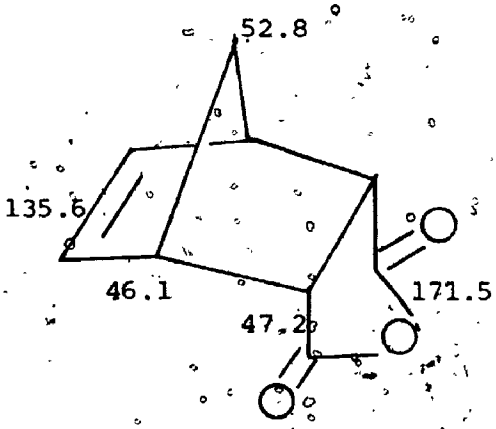
[a] In ppm from internal TMS in $CDCl_3$ solutions.

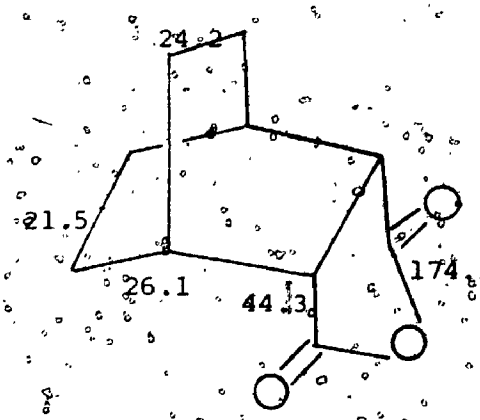
Table A.12. ^{13}C Shieldings[a] of Some Bicyclic Anhydrides

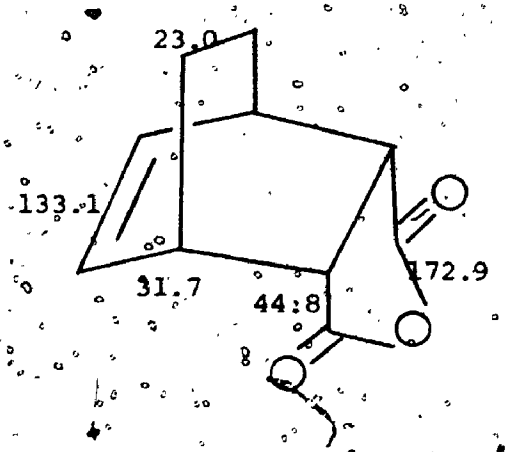












[a] In ppm from internal TMS in $CDCl_3$ solutions.

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