CARBON-13 NUCLEAR MAGNETIC RESONANCE SPECTRA OF HETEROCYCLIC COMPOUNDS

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By

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A Thesis
Submitted to the Faculty of Graduate Studies
in Partial Fulfilment of the Requirements
for the Degree
Master of Science

McMaster University
August 1973

MASTER OF SCIENCE (1973)
(Chemistry)

McMaster University
HAMILTON, Ontario

TITLE: Carbon-13 Nuclear Magnetic Resonance Spectra of Heterocyclic Compounds

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SUPERVISOR: Professor R. A. Bell

NUMBER OF PAGES: vi , 91

SCOPE AND CONTENTS:

Experimental carbon-13 nuclear magnetic resonance chemical shifts are given for substituted 1,3-dioxanes, tetrahydrofurans, dihydro-2-furanones and succinic anhydrides. The experimental data are used to improve and extend the carbon-13 chemical shift prediction parameters which allow one to estimate with considerable accuracy unknown chemical shift values.

ACKNOWLEDGEMENTS

The author wishes to express her gratitude to all those who had made this thesis possible.

I am particularly indepted to Dr. R. A. Bell (Research Director) for his advice and encouragement throughout this work; Dr. M. Mazet of the University of Limoges, France, for samples of 1,3-dioxanes used in this research; and Mr. B. Sayer for his cooperation.

The Department of Chemistry, McMaster University, provided the financial support. For this I am grateful.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. INTRODUCTION

1.1 General

Although natural abundance carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were first reported in 1957, practical difficulties restricted activities to relatively few laboratories. The low natural abundance (1.11%) and poor nmr sensitivity of ^{13}C have in the past hindered the use of this potentially very useful nucleus. With the development of field frequency controlled spectrometers, however, these difficulties have to a large extent, been overcome and ^{13}C capability is now available to many more workers. Presently the high resolution nmr spectroscopy of ^{13}C in natural abundance is developing very rapidly. The work reported in this thesis involves an investigation of carbon-13 nmr data in 2,5-substituted-1,3-dioxans and in alkyl tetrahydrofurans, lactones and anhydrides. Substituents effects are calculated and differences between real and predicted chemical shifts are discussed.

1.2 Theory of nmr

All atomic nuclei have charge and mass, and many possess angular momentum. As a result, the latter behave as spinning bodies and possess non-zero magnetic moments. Nuclei with odd mass numbers have spins whose value, I, is an odd-integral multiple of 1/2. Nuclei with even mass are spinless if the nuclear charge is even, or have integral spin if the charge is odd. The maximum observable component of the angular momentum is $Ih/2\pi$ where I is the spin quantum number, and the permitted values of the vector moment along any specific axis are given, in terms of the magnetic quantum number m (in units of $\hbar$) as a species:

$$m = I, (I-1), (I-2), \ldots, -I$$

There are a total of (2I + 1) angular momentum states available. Since the magnetic moment μ of a nucleus is directly related to the angular momentum p by,

$$\mu = \gamma p$$

where γ is the magnetogyric ratio, there will also be (2I + 1) magnetic moment states, and the maximum allowed value of μ can be expressed as:

$$\mu = \gamma I \hbar \qquad \hbar = h/2\pi$$

The (2I + 1) states are degenerated in the absence of a magnetic field, but in the presence of an applied field they correspond to different potential energy levels. The detection and measurement of transitions between these spin states constitute nmr spectroscopy. For a spinning nucleus, in a magnetic field H_o, the magnetic moment μ lies at an angle θ with respect to the field (Z-axis). The interaction of H_o and μ causes a torque L which tips μ toward H_o, but its spinning causes the nucleus to precess about the Z axis and θ does not change.

These parameters are interrelated as:

$$L = \mu \times H_o$$

Thus

$$d\mu/dt = \gamma\mu \times H_o = w_o \times \mu$$

where w_o is the angular velocity. The precessional (or Larmor) frequency ν_o is given by the Larmor equation,

$$\nu_o = (\gamma/2\pi)H_o$$

and is independent of θ. The energy of the system, however, depends on θ

since

$$E = -\mu\ H_o = -\mu\ H_o\ \cos\theta$$

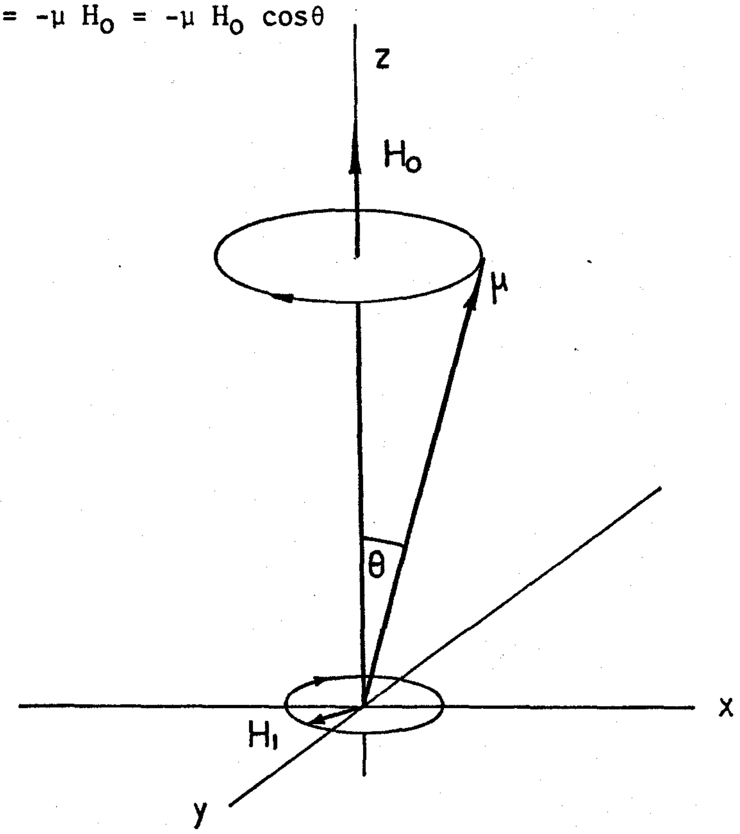


Figure 1. Schematic representation of Larmor precession.

If a small rotating field H_1 is generated orthogonal to H_o, μ would experience the combined effects of H_o and H_1, but it would only interact strongly with H_1 if the angular frequency of H_1 approached the Larmor precession frequency ν_o. In this way energy can be exchanged between the nuclear spin and the rotating field (Figure 1).

Suitable rotating H_1 fields are readily generated by passing an oscillating radio-frequency (rf) signal through a coil whose axis is orthogonal to the H_o axis. This signal generates two equal, but contrarotating fields in the xy plane, one of which moves in the same direction as the precessing nucleus and can be brought into resonance while the other, moving in the opposite direction, can be ignored.

The quantum mechanical treatment of the interaction of H_o and μ leads to the same expression for the precessional frequency as the classical approach:

$$h\nu = \gamma H_o \hbar = \Delta E$$

where ΔE is the energy separation between adjacent nuclear spin states as shown in Figure 2.

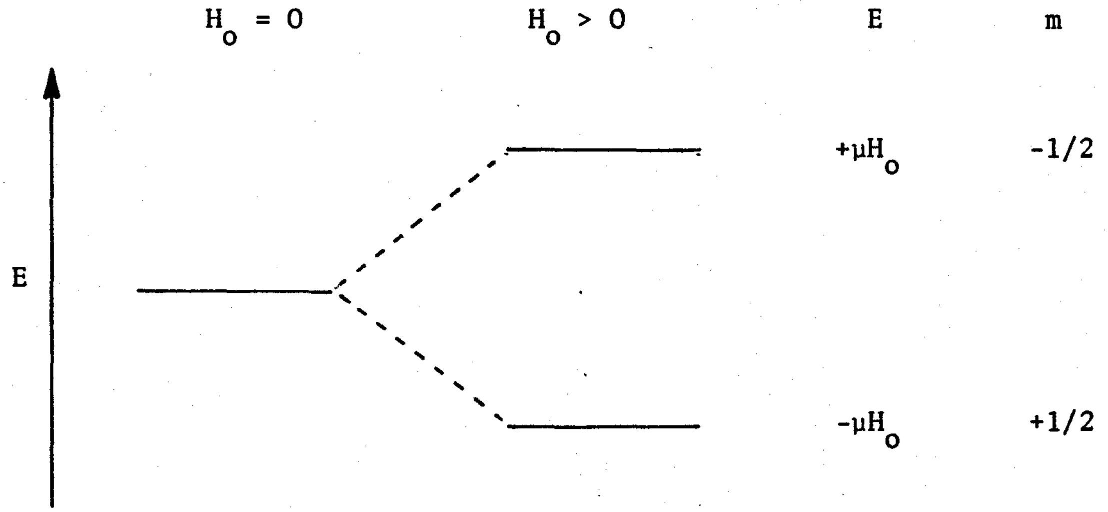


Figure 2. Energy levels for a spin 1/2 nucleus in a magnetic field.

For spin 1/2 nuclei, only 2 states are possible whose separation is $2\mu H_o$. Their relative population is given by the Boltzmann equation as

$$N_+/N_- = \exp(-\Delta E/kT)$$

where N_+ and N_- are the populations of the upper and lower states, respectively.

The probabilities of transitions are proportional to the populations of the energy levels, thus the probability of an upward transition is slightly higher than the probability of a downward transition. If the H_1 irradiation passes through a resonance line very rapidly, then perturbation of the populations in the two energy levels for that nucleus does not become a significant factor. However, in most nmr experiments a relatively slow sweep rate is used and therefore while the excitation is occurring the energy level populations may equalize if the magnitude of H_1 is too large. In this situation absorption is observed and the sample is said to be saturated. There are a number of physical processes which allow the nuclei to establish a Boltzmann population distribution. They are generally termed spin-lattice relaxation processes and are measured by an exponential time constant, T_1. The quantity T_1 can be conveniently understood as either representing the lifetime of nuclei in either the upper or lower spin state, or alternatively as being the time constant for the nuclear spins to exponentially return towards a Boltzmann distribution after the spin system has been perturbed(1). The experimentally observed values of T_1 range from milli-seconds to hundreds of seconds.

A spectrum may be recorded by varying either the frequency ν or the applied field H_0 as a function of time. In the first case, the experiment is referred to as a frequency sweep experiment and in the second case as a field sweep experiment.

1.3 Techniques of carbon-13 nmr

Carbon nuclear magnetic resonance studies are confined to the ^{13}C nucleus since ^{12}C has no magnetic moment. The problem with ^{13}C and many other interesting nuclei like ^{15}N is that they have small intrinsic magnetic moments and consequently small values of ΔE. Thus the difference in populations for the two energy levels is even smaller for these nuclei than for protons, leading to much lower sensitivities. In addition, the isotopes have low natural abundance, making the problem of detection even more difficult by a factor of over one hundred.

Each carbon resonance in an organic molecule is spin-coupled not only to directly attached protons (coupling constant $J_{C-H} > 125$ H_Z) but also to protons 2-4 bonds distant ($J < 20$ H_Z). Thus in the absence of ^1H decoupling, early carbon nmr spectra appeared as multiplets with unresolved long-range coupling broadening each peak. Most of the effort concerning J_{CH} has been devoted to ^{13}C - ^1H coupling constants between directly bound carbon and hydrogen atoms. The great interest in these parameters is due, of course, to the known relation between their magnitude and the nature of the bonding-carbon orbitals(2). Several mathematical procedures with different levels of approximation have been used in quantum mechanical calculations of ^{13}C - ^1H coupling constants(3).

For pure ^{13}C spectra, it is useful to decouple or reduce the effective coupling of all protons from ^{13}C in an organic molecule. This is effected by double resonance techniques which have a very important place in magnetic resonance in general and in the study of nuclei of low sensitivity in particular. For those nuclei of spin 1/2, not only is an increase in signal to noise obtained because of coalescence of multiplets but also because of nuclear Overhauser effect enhancements (see below). If the sample is irradiated at two frequencies ν_1 and ν_2 instead of one, the resonance condition will be satisfied for two values of the field H_0 and two signals will result if both ν_1 and ν_2 are detected. This defines an interval $\nu_1 - \nu_2$ in the spectrum, which may be used for spectral calibration. New effects occur if two transitions are excited simultaneously by ν_1 and ν_2, for then ν_2 may have an effect on the signal detected at ν_1. The power may be regarded as defining a spread of frequency, α, around ν_2. α may be obtained by inserting the value of the magnetic field associated with ν_2 in the resonance equation. If nucleus 1 and nucleus 2 with Larmor frequencies ν_1 and ν_2 have their spins coupled (coupling interaction energy termed J) then weak power levels at ν_2 cause perturbations to the line intensities and positions of nucleus 1. However, at higher power levels, $\gamma H_2/2\pi >> J$, the coupling interaction is removed and nucleus 1 appears as a single resonance line. If we use extremely high levels of α, then all the nuclei in one region can be simultaneously irradiated and the process is referred to a broad-band decoupling. Additionally ν_2 may be varied rapidly and randomly to give what is termed noise decoupling. At lower power levels, noise decoupling irradiation can cause broadening of all carbon resonances coupled to protons. The effect is to leave only quarternary carbon atoms with significant intensity so that they may be identified. This process is known as off-resonance decoupling(4).

The Nuclear Overhauser effect is a by-product of proton irradiation in ^1H decoupled ^{13}C nmr experiments (notation: $^{13}C\{^1H\}$). The ^{13}C nuclei depend chiefly on the ^1H nuclei for spin-lattice relaxation via a simple magnetic dipole interaction. The carbon nuclei react to the equalization of the ^1H energy level populations by changing their own energy level populations. This results in an equilibrium excess of nuclei in the lower ^{13}C energy level relative to that required for a Boltzmann distribution. Experimentally, this means that more rf energy will be absorbed by the ^{13}C nuclei as a result of the larger population in the lower energy level. In a $^{13}C\{^1H\}$ nmr experiment, the theoretical nuclear Overhauser enhancement is 2.988. This means that if the NOE is fully operative, each carbon resonance will have a peak area 2.988 times the total resonance signal area in the absence of H irradiation.

With the advent of field-frequency control, signal enhancement through the technique of repetitive scanning and time averaging became possible. In this method, the digitized output of each scan is fed into the memory of a small computer such that successive scans are collected in the same channels. The signal intensity increases directly with the number of scans, n, while the rate of noise increase is $(n)^{1/2}$; thus the signal:noise (S/N) enhancement is $(n)^{1/2}$. The combination of time averaging and proton decoupling as well as the use of larger samples, permits one to obtain high resolution ^{13}C spectra for a vast array of compounds containing ^{13}C in natural abundance (see Fig. 3 for a block diagram of a typical frequency swept spectrometer).

Can these n experiments be conducted simultaneously to gain the same information more rapidly? One possible but expensive way is to have N sepctrometers operating at the same time, each with a swept ν_1 frequency. A more practical method is to use N fixed ν_1 frequencies in the same spectrometer simultaneously. For this n channel transmitter one requires an n channel receiver, each channel tuned to a particular value of ν_1. n should be large enough to cover the whole spectrum and the individual values of the frequencies should be close. Such an n channel transmitter can be simulated by pulsing ν_1; that is, by applying ν_1 for a very short time period (microseconds) but at a very high power level. The sample is magnetized by the pulse, all spectral lines being excited at the same time, and after the pulse is switched off these magnetizations decay. The time variation of the

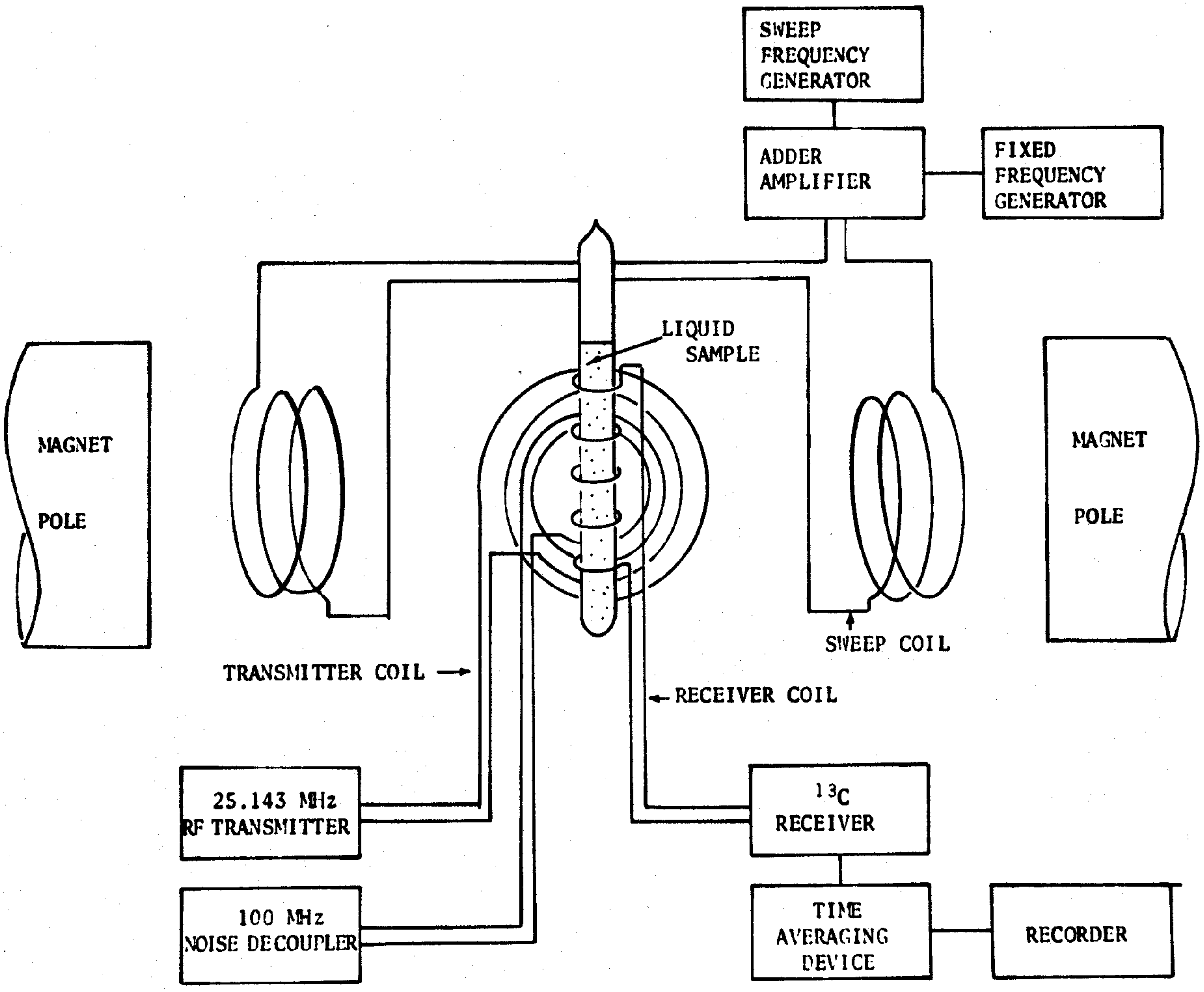


FIGURE 3. BLOCK DIAGRAM OF A FREQUENCY-SWEEP NMR SPECTROMETER

decay contains all the normal spectral information, but in a different form from the normal spectrum: each point of the decay contains some information from every part of the spectrum. The time decay and the normal spectrum are related as Fourier transforms, so that Fourier transformations of the output of the pulse experiment give the normal frequency spectrum(5). The initial experiments on Fourier transform nmr were carried out in 1966, and since that time rapid technological advances have been made and a range of commercial pulse spectrometers are available.

Early ^{13}C nmr studies reference ^{13}C chemical shifts to an external capillary of ^{13}C enriched CS_2. According to that convention, positive chemical shifts are upfield from CS_2. Most nmr spectroscopists now favor TMS. Shifts downfield from TMS are stated as positive in analogy with the proton scale. With internal ^{13}C-lock instruments, it is common practice to employ the decoupled solvent signal as the lock; benzene, dioxane, and cyclohexane are particularly well suited for this purpose since they contain equivalent carbons, each of which is bonded to hydrogen. The chemical shifts of those secondary standards are adjusted to the TMS scale and in our case: δ dioxane 67.4 ppm, δ cyclohexane 26.9 ppm, δ benzene 128.6 ppm are values used throughout this work.

1.4 Carbon-13 chemical shifts

For almost all organic molecules, complete ^{13}C spectra appear between low-field carbonyl groups and high-field methyl groups in a range of just over 200 ppm (Table 1). To date the ^{13}C spectra of a reasonably wide variety of compounds have been determined and the shielding effects of an assortment of substituents in aliphatic and aromatic systems have been characterized.

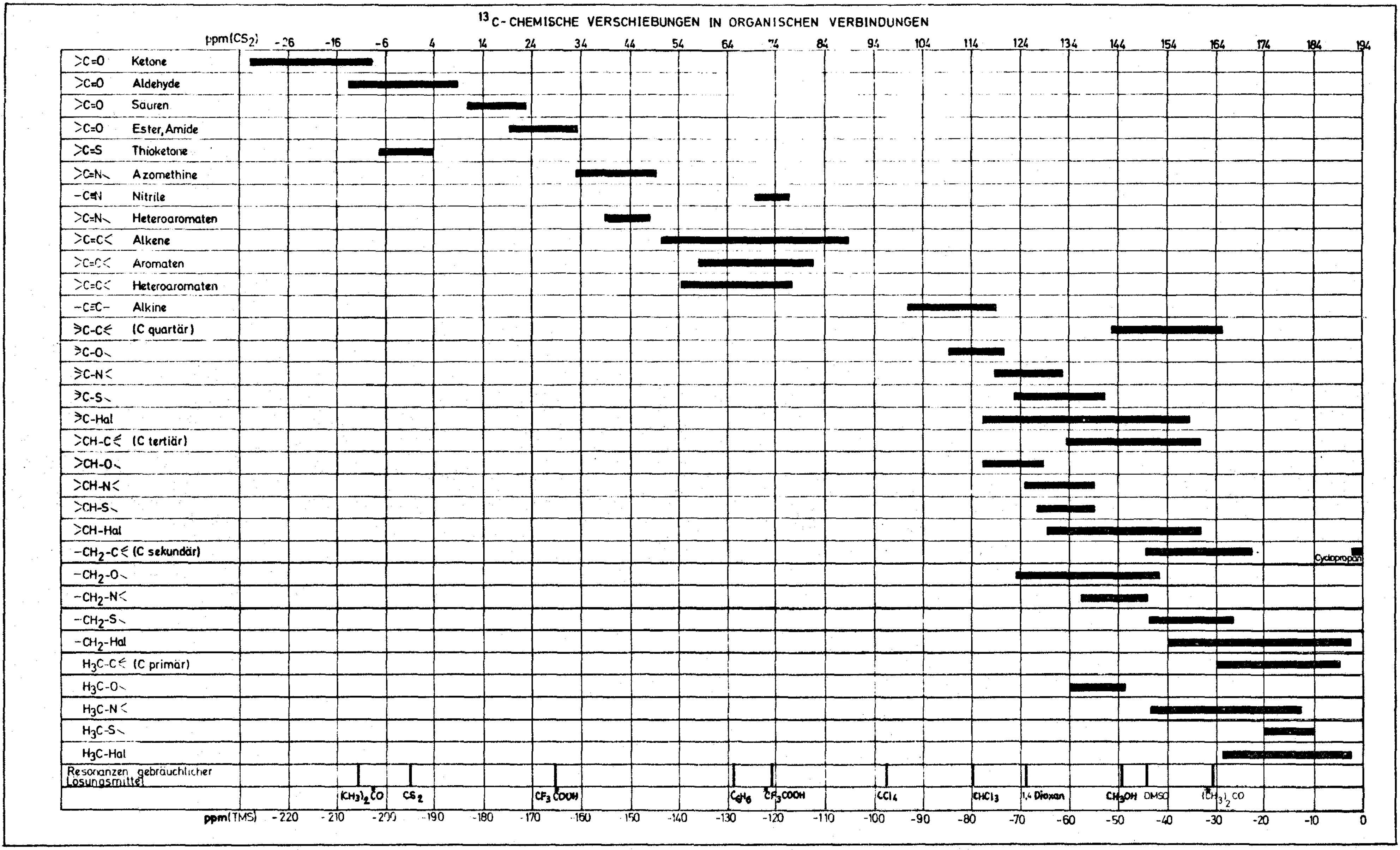
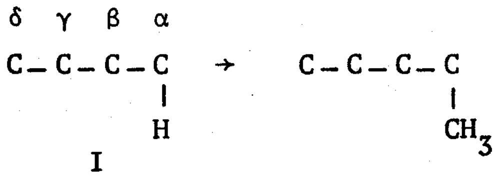


Table 1. Carbon-13 Chemical Shifts for Organic Molecules.

One of the most detailed studies of the ^{13}C spectra of a family of compounds which appeared in 1964 is that of Grant and Paul(6) in which a series of saturated hydrocarbons containing up to 10 carbon atoms was examined, including both linear and branched chain species. 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.

Normally, substituent effects are discussed in terms of replacement of hydrogen atoms by a carbon. That is in molecule I:



$$\overset{\delta}{C}-\overset{\gamma}{C}-\overset{\beta}{C}-\underset{\substack{|\\ H}}{\overset{\alpha}{C}} \rightarrow C-C-C-\underset{\substack{|\\ CH_3}}{C}$$

I

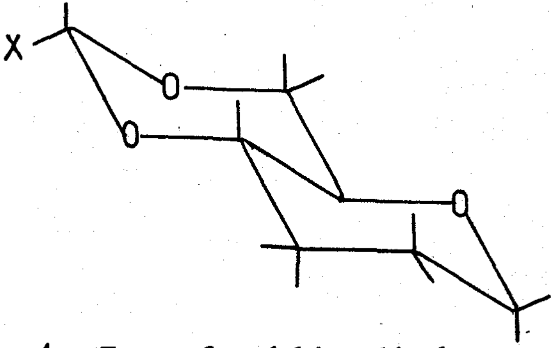
The structural change, -C-H → C-Me, causes a deshielding effect. This has been termed the "α effect" and appears to be general for all classes of compounds although its magnitude differs in various families. A similar trend is apparent for the substitution of a β-hydrogen by a methyl. The β effect is, surprisingly, comparable to the α effect. The γ effect is a shielding effect in most cases. Exceptions are found in heterocyclic five-membered rings. The γ effect is probably the most interesting of these trends for the organic chemist, since it appears to be primarily operative through space rather than through the bonds of the molecule. The current feeling is that the α effect is largely inductive with some steric contribution while the β effect has not been satisfactorily explained. More remote replacements of hydrogen atoms with methyl groups have little effect on the carbon shifts.

Carbon-13 nmr of non-aromatic heterocyclic systems

In most of the cyclic systems so far investigated, the hetero-atom has been a nitrogen atom. The results for the N-phenyl derivatives of aziridine, pyrrolidine and piperidine were reported by Nash and Maciel(7). Later, Maciel and Javitsky(8) published ^{13}C data for the series $X(CH_2)_n$ where n = 2-5 for X = O and S, and n = 2-6 for X = N - Me. Pehk and Lippmaa(9) have reported the shieldings for piperidine and its 2,2,6,6-tetramethyl derivative. The data for the former permit an examination of the effect of methyl substitution on the ring carbon shieldings, showing a pronounced downfield shift of the β carbons. Further evidence of the similarity of methyl substituent effects in the piperidine and cyclohexane systems has recently been presented by Duch(10) from the ^{13}C spectra of piperidine and its monomethyl derivatives. Recently a ^{13}C nmr study of poly-substituted pyridines has been reported by M. L. Cotter(11).

In 1971, two studies were carried out on 1,3-dioxans. G. M. Kellie and K. G. Riddell(12) demonstrated the occurrence of the non-chair conformations of 2,4,6-substituted dioxans and A. J. Jones et al.(13) published the results of a ^{13}C nmr study on t-butyl-1,3-dioxans.

Several ^{13}C examinations of various types of natural products have been reported over the past two years. The structural study of trans-fused bicyclic hexopyranoside (Fig. 4) derivatives have established the general utility of the technique(14).



X = Me

X = ϕ

Figure 4. Trans-fused bicyclic hexopyranoside.

Very recently, Johnson and Jankowski(15) published among 500 spectra, the ^{13}C nmr data of 2-methyl and 3-methyl tetrahydrofurans.

Carbon-13 nmr of anhydrides and lactones

A series of lactones have been examined by both Overton and Stothers(16) and Christl *et al.*(17) These authors have studied the variation in the carbonyl carbon shieldings with ring size. The same investigation has been carried out by Nelson(18) in acylic and cyclic anhydrides. There is considerable evidence in the literature that ^{13}C chemical shifts are sensitive to steric interactions and this fact has been demonstrated by Storm and Koshland(19) with endohydroxybicyclo[2.2.1] heptane-*endo*-carboxylic acid lactones (Fig. 5).

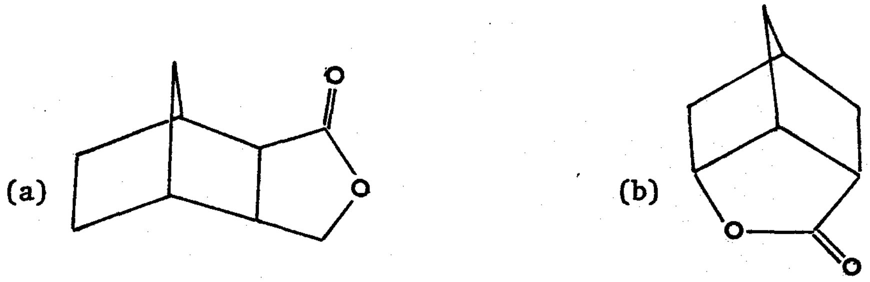


Figure 5. (a) 6-*endo*-hydroxybicyclo[2.2.1]heptane-2-*endo*-carboxylic acid lactone.
(b) 2-*endo*-hydroxybicyclo[2.2.1]heptane-3-*endo*-carboxylic acid lactone.

Among a series of natural products, Easton and Bell have established the stereochemistry of labdane derivatives (Fig. 6).(20)

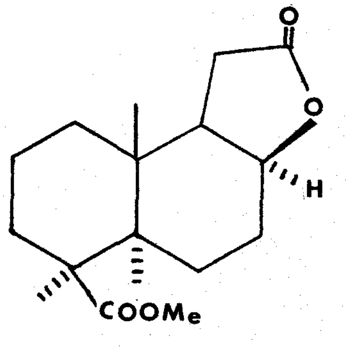


Figure 6. 8 β-hydroxy-(13 → 17)-pentanorlabdan-12,19-dioic acid 19-methyl ester 12 → 8 lactone.

1.5. Objectives

The objective of this work was to determine the shift parameters as a function of position, orientation, and nature of the substituents on five and six-membered rings. The results have lead to the determination of steric interaction shifts and have provided information on the conformational requirements of the substituents.

The first part is concerned with substituted 1,3-dioxans, the second part with the five-membered oxygen heterocycles: the tetrahydrofurans, the third part with methyldihydrofuranones and the last part with methyl anhydrides.

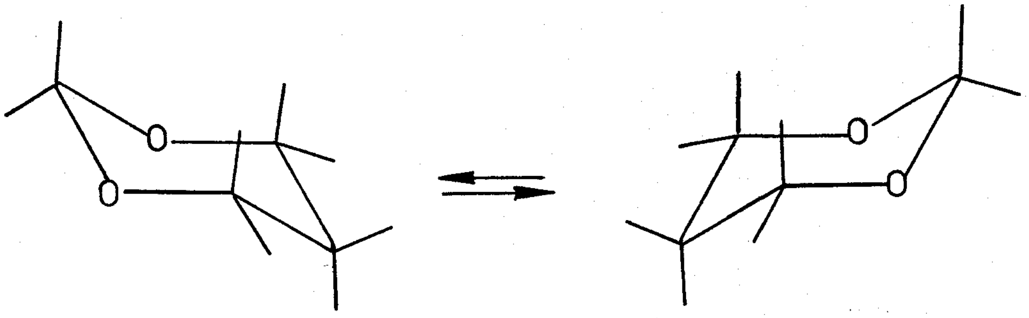
2. 1,3-DIOXANES

2.1. Stereochemistry of 1,3-Dioxans

The variety of cyclic structures is astronomical and it is very important to realize the limitations of the applicability of data obtained from model compounds. Nevertheless, nmr spectroscopy affords information that has proved to be of value, particularly in the quantitative description of group interactions and the conformational equilibria of organic molecules.

When hetero atoms are included in the ring, the situation with respect to a detailed approach is more difficult. It is true that there are many overall similarities in the preferred conformations assumed by homocyclic and heterocyclic ring structures. This is especially the case with the six-membered rings, where, as a rule, the chair form appears to be preferred. On the other hand, significant differences exist between the forces that determine the exact geometry and the conformational equilibrium of heterocyclic and homocyclic compounds.

In the past ten years, the conformational behaviour of 1,3-dioxan and its derivatives has been extensively investigated and is now well understood(21-69). The 1,3-dioxan ring exists in chair conformations which are substantially more stable than any of the boat forms.



The original estimate of the free energy difference between the boat and chair forms of 2.2 Kcal/mole(24a) has been continually revised upwards, to over 3 Kcal/mole(21d). Large energy differences (> 2 Kcal/mole) between the axial and equatorial positions exist for 2-, 4-, and 6-substituents, but 5-alkyl groups have an axial-equatorial energy difference(24c,56,57) of about 1 Kcal/mole (1.5 to 1.9 Kcal/mole for a 5-t-butyl group.)(24b,c,21c)

Since the C-O bond is shorter than a C-C bond, carbon atom 2 will be forced towards carbon atoms 4 and 6. This effect will increase 1,3-diaxal interactions between these positions and is responsible for the large conformational energy differences for 2-, 4-, and 6-substituents(56,57).

On the basis of models, it was concluded that the ring is a "puckered chair" in the O_1-C_2-O_3 region and a "flattened chair" in the C_4-C_5-C_6 region. It is now generally accepted that in 2 monosubstituted 1,3-dioxans, the C_2 substituent occupies the equatorial position(70).

Recently, ^{13}C nmr has been applied for stereochemical purposes and substituent shift information in two series of 1,3-dioxanes(12,13). From new data, it has been concluded that the substituent shift correlations for the ring carbons of cyclohexanes and 1,3-dioxanes are comparable but differ in magnitude. The purpose of this thesis is to investigate and extend the substituent shift parameters as a function of position, orientation and nature in a series of linear and cyclic substituted 1,3-dioxanes.

2.2. ^{13}C chemical shift results for 1,3-dioxanes.

Throughout the discussion, the conventional labelling system for the 1,3-dioxan ring is employed. Carbon atoms in substituents are labelled C_{na}, C_{nb}, C_{nc},.... n represents the position of the substituent on the ring, a, b, b',... indicate the attached carbons in the substituent chain, a', b' refer to the equatorial substituent (Fig. 7). Because of the gradual substitution in C_2, it has been possible to identify and assign all the signals of the carbons in the alkyl substituents on the dioxane ring. In the case of monosubstituted mixtures of cis and trans isomers, assignments have been aided by the fact that the intensity of each peak in the C_2 substituent is approximately 2 times greater than the intensity of the C_5 substituent signals. This is further evidence of the equatorially favoured position of C_2 substituents$^{(70)}$ (Fig. 8).

The results are summarized in Tables 2 and 3.

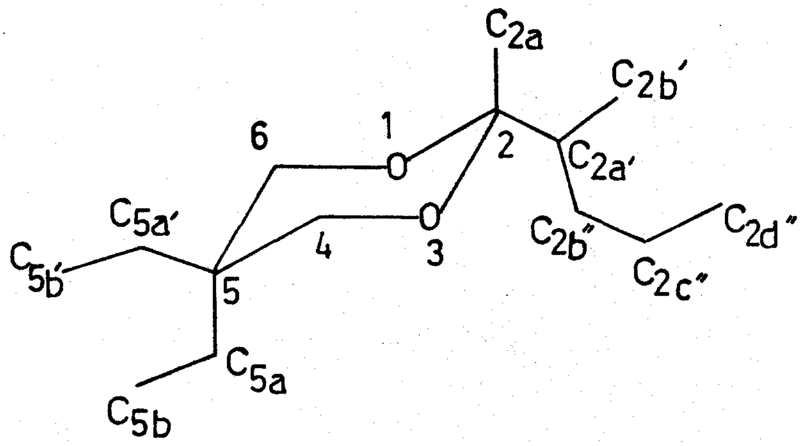


Figure 7. Labelling system employed for the 1,3-dioxanes.

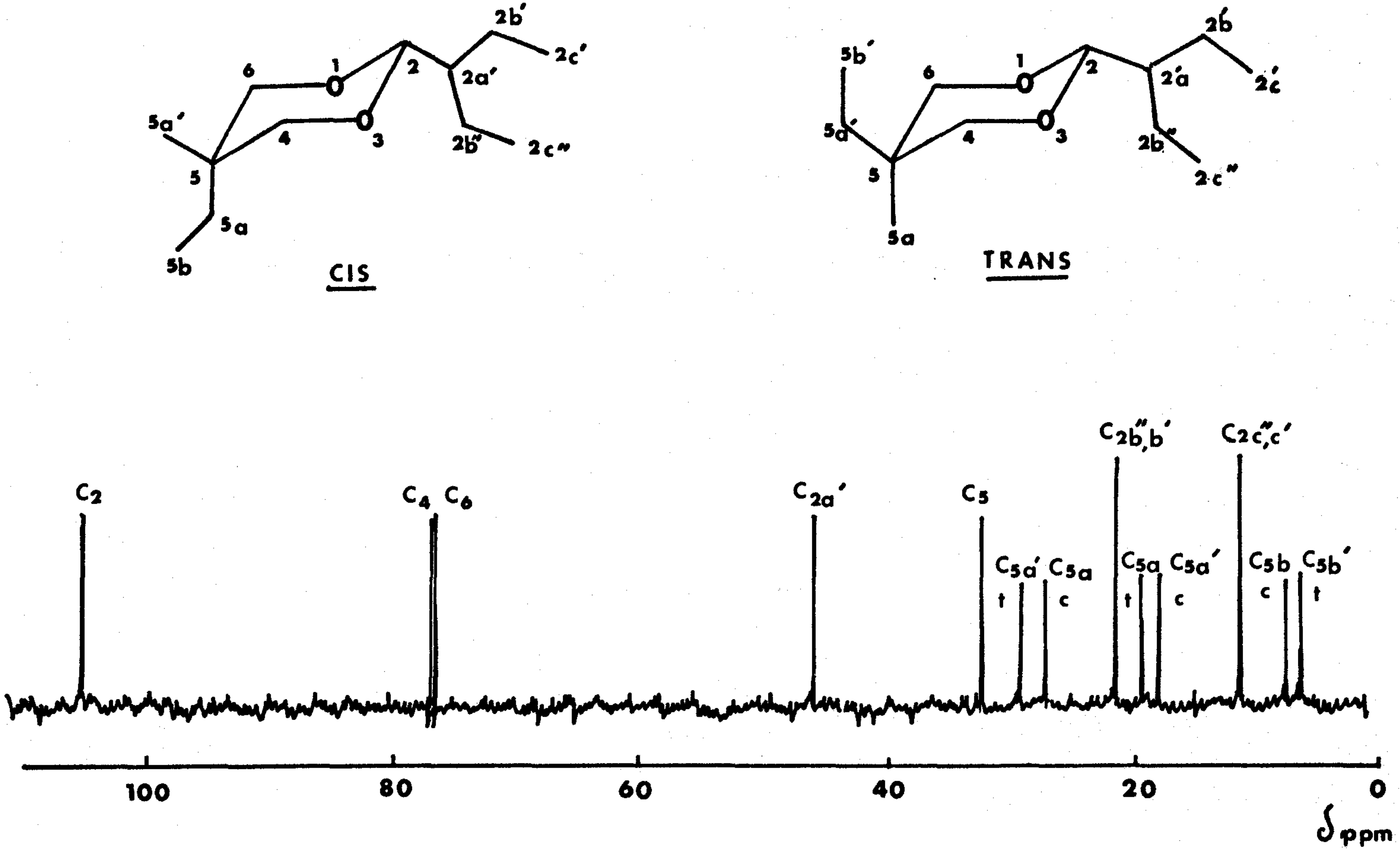


Figure 8. ^{13}C nmr spectra of <u>cis</u> and <u>trans</u> 2-(3-pentyl)-5-methyl-5-ethyl-1,3-dioxane.

Table 2. ^{13}C Shieldings of Substituted 1,3-dioxanes

1,3-Dioxane	Compound	C_2	$C_{4,6}$	C_5	C_{5a}	C'_{5a}	C_{5b}	C'_{5b}	C_{5c}	C'_{5c}	C_{2a}	C'_{2a}	C_{2b}	C'_{2b}	C'_{2c}	C''_{2b}	C''_{2c}
2-Me	<u>1</u>	99.55	66.8	25.8								20.95					
5,5-Me_2	<u>2</u>	94.3	77.3	30.6	22.2	22.2											
2,5,5-Me_3	<u>3</u>	99.7	77.3	29.7	22.9	21.6						20.7					
2-iPr-5,5-Me_2	<u>4</u>	106.1	77.3	30.0	22.8	21.4						32.8		16.6		16.6	
2-(2-butyl)-5,5-Me_2	<u>5</u>	105.5	77.5	29.9	22.8	21.4						39.3		13.1		24.1	11.1
cis 2-sec-bu-5-Me-5-Et	<u>6</u>	105.6	75.5	32.4	26.85	17.8	7.45					39.4		13.1		24.1	
trans		105.6	76.6	32.4	19.2	28.75		6.4				39.4		13.1		24.1	11.1
cis 2-(3-pent.)5-,e-5-Et	<u>7</u>	104.7	75.6	32.35	26.9	17.8	7.45					45.7		21.1	11.35	21.1	11.3
trans		104.7	76.7	32.35	19.3	28.8		6.3				45.7		21.1	11.35	21.1	11.3
cis 2-(2-pent.)5-Me-5-Et	<u>8</u>	105.7	75.5	32.25	26.9	17.9	7.4					37.40		14.0		33.7	20.1
trans		105.7	76.55	32.25	19.3	28.8		6.40				37.40		14.0		33.7	20.1
cis 2-Et-2-iPr-5-Me-5-Et	<u>9</u>	102.1	68.3	31.8	27.6	18.7	6.9				20.9	30.1	6.74	16.0		16.0	
trans		102.1	68.6	31.8	19.0	28.25		6.75			20.9	30.1	6.74	16.0		16.0	
2-Me-2(2-pent.)-5,5-Et_2	<u>10</u>	101.7	67.25	34.7	24.6 23.7		6.92	6.63			15.70	39.35		14.15		33.25	21.0
cis 2-(3-hex.)-5-Me-5-Pr	<u>11</u>	104.9	76.0	32.45	37.0	18.5	16.8		14.65			43.9		21.65	11.45	30.95	20.4
*trans		104.9	76.9	32.3	19.95	39.1		15.7		14.65		43.9		21.65	11.45	30.95	20.4
#cis-2-(2-hex.)-5-Me-5Pr	<u>12</u>	105.7	75.9	32.45	37.1	18.5	16.70		14.6			37.8		13.65		31.2	29.0
cis 2-Et-5-Me-5ϕ	<u>13</u>	103.7	75.9	36.5	22.7							27.8		7.8			
**trans			76.6	36.48								27.97					
2-Et-5-Me-5-hydroxy-Me	<u>14</u>	103.6	73.0	34.7	65.0	16.6						27.85		7.7			
cis 2-Et-5-Me-5-Allyl	<u>15</u>	103.7	75.4	32.6	38.9	18.0	134.9		118.0			27.9		7.6			
trans		103.7	76.3	32.4	20.1	41.0		134.9		118.0		27.9		7.6			
2-Et-5,5-diallyl	<u>16</u>	103.8	74.15	35.2	36.05	37.2	134.7	134.7	118.1	118.1		27.9		7.6			
2-Et-5,5-dipropargyl	<u>17</u>	104.1	73.0	34.8	22.25	22.5	72.3	71.9	81.3	78.3		27.75		7.7			

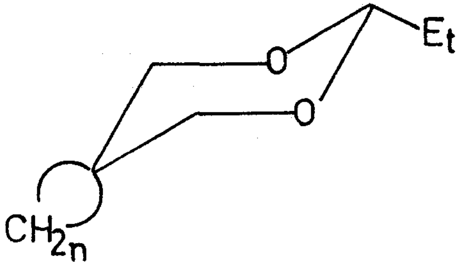
---

*cis and trans isomers separated.

**cis and trans isomers unassigned. $C_{5aa'}$: 144.3, 144.4; Co, Cm: 128.3, 128.9, 127.6, 125.4; Cp: 126.2, 129.9.

#compound <u>12</u>, C''_{2e} 13.65.

Table 3. ^{13}C Shieldings of Some Dioxaspiroalkanes

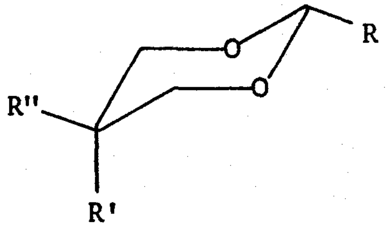


n	name	N°	C_2	$C_{4,6}$	C_5	$C_{5a'}^{a,}$	$C_{5b'}^{b,}$	C_{5c}	$C_{2a'}$	$C_{2b'}$
2	6-Et-5,7-dioxaspiro[2,5] octane	<u>18</u>	103.8	80.0	17.5	4.05 13.1			27.95	7.7
3	7-Et-6,8-dioxaspiro[3,5] nonane	<u>19</u>	103.3	75.5	36.9	24.95 30.4	15.12		27.9	7.8
4	8-Et-7,9-dioxaspiro[4,5] decane	<u>20</u>	103.45	75.95	39.05	30.9 33.3	24.6 25.15		27.7	7.8
5	3-Et-2,9-dioxaspiro[5,5] undecane	<u>21</u>	104.05	75.5	32.1	30.8 31.8	21.3 21.5	26.8	27.9	7.7

2.3. Substituent effects on 1,3-dioxanes

Consideration was first given to the effects of substitution of an alkyl group in the equatorial position on carbon-2 (Table 4).

Table 4. Substituent effects in the alkyl group of 2-substituted dioxanes.

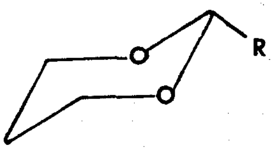


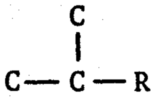
R	α	β	γ
Et	7.2	4.0*	
iPr	4.9	8.9, -2.5*	
2-bu.	7.5	6.5	-3.5,-0.7*
2-pent.	8.9	9.6	-2.0
2-hex.	9.2	9.4	-2.5
3-pent.	8.0	6.3	-3.0,-0.9*
3-hex.	9.0	9.8	-1.9

*Referred to C_2.

R' and R'' are alkyl groups.

Recently, Lindeman and Adams(71) extending the work of Grant and Paul(72) have studied 56 linear and branched chain alkanes. We have compared their data with the present results and conclude that a correlation between the chemical shifts exists but there is a difference in the magnitude of the substituent effects. This difference is found more particularly on the C_2 atom itself (Table 4) and comparing the 1,3-dioxan system with the isopropyl





$$\overset{\displaystyle C}{\overset{|}{C-C-R}}$$

structure we can deduce that the substituent effects are slightly smaller in the dioxan series than in the alkane series (Table 5). The only exception is when R = isopropyl and this is certainly due to 1,2-methyl-methyl interactions as are observed to be present in the hydrocarbon 2,3-dimethyl butane.

The substituent effects change slowly with the extent of substitution at C-2, and when R = 2-butyl, more remote replacement of hydrogen atoms by methyl groups leads to substituent effects that are little different than those observed for the alkanes (see Table 6).

Table 6. Substituent effects in linear series:

(a) In the 2-equatorial alkyl group of 1,3-dioxanes.

(b) In the alkane series (J. B. Stothers, p. 58).

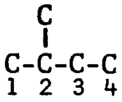
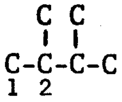
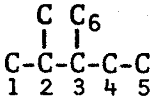
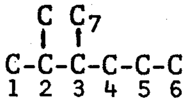
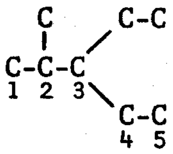
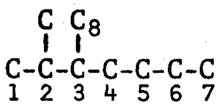
	(a)	(b)
α	9.1 ± 0.1 ppm	9.1 ± 0.1 ppm
β	9.6 ± 0.2 ppm	9.4 ± 0.1 ppm
γ	2.65 ± 0.15 ppm	2.5 ± 0.1 ppm

A similar pattern is evident in the chemical shifts observed for C-2 as the side chain is increased in size and length and this is graphically illustrated in Fig. 9. The value for t-butyl in Fig. 9 is taken from the work of Jones et al.(13), and it is of interest to note that for the longer chains, R = 2-pentyl, and 2-hexyl, the shift of C_2 is 105.65 ± 0.15 ppm and for R = 3-pentyl, and 3-hexyl, the shift is 104.8 ± 0.1 ppm. Not surprisingly,

Table 5. ^{13}Chemical Shifts and Shielding Values for C_5 to C_9 Paraffins

TMS = 0, CS_2 = +192.8

Original data from Lindeman and Adams(71)

		R	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
C_5H_{12}		Et	21.9	22.2	31.6	11.5				
				29.9						
C_6H_{14}		iPr	19.2	34.0						
				(β,4.1)	(α,2.4)	(β,7.7)				
C_7H_{16}		2-Bu	20.0	31.9	40.6	26.8	11.6	14.5		
			17.7	(γ;2.1)	(β,6.6)	(α,7.6)				
C_8H_{18}		2-pent	17.8	32.8	38.5	36.7	30.7	14.0	15.1	
			20.0		(γ;2.1)	(β,9.9)	(α,9.1)			
		3-pent	19.0	29.1	47.6	22.6	11.8			
				(γ;2.8)	(β,7.0)	(α,8.1)				
C_9H_{20}		2-hex	20.1	32.2	38.8	34.0	30.0	23.1	13.8	15.2
			17.9			(γ;2.7)	(β,9.3)	(α,9.1)		

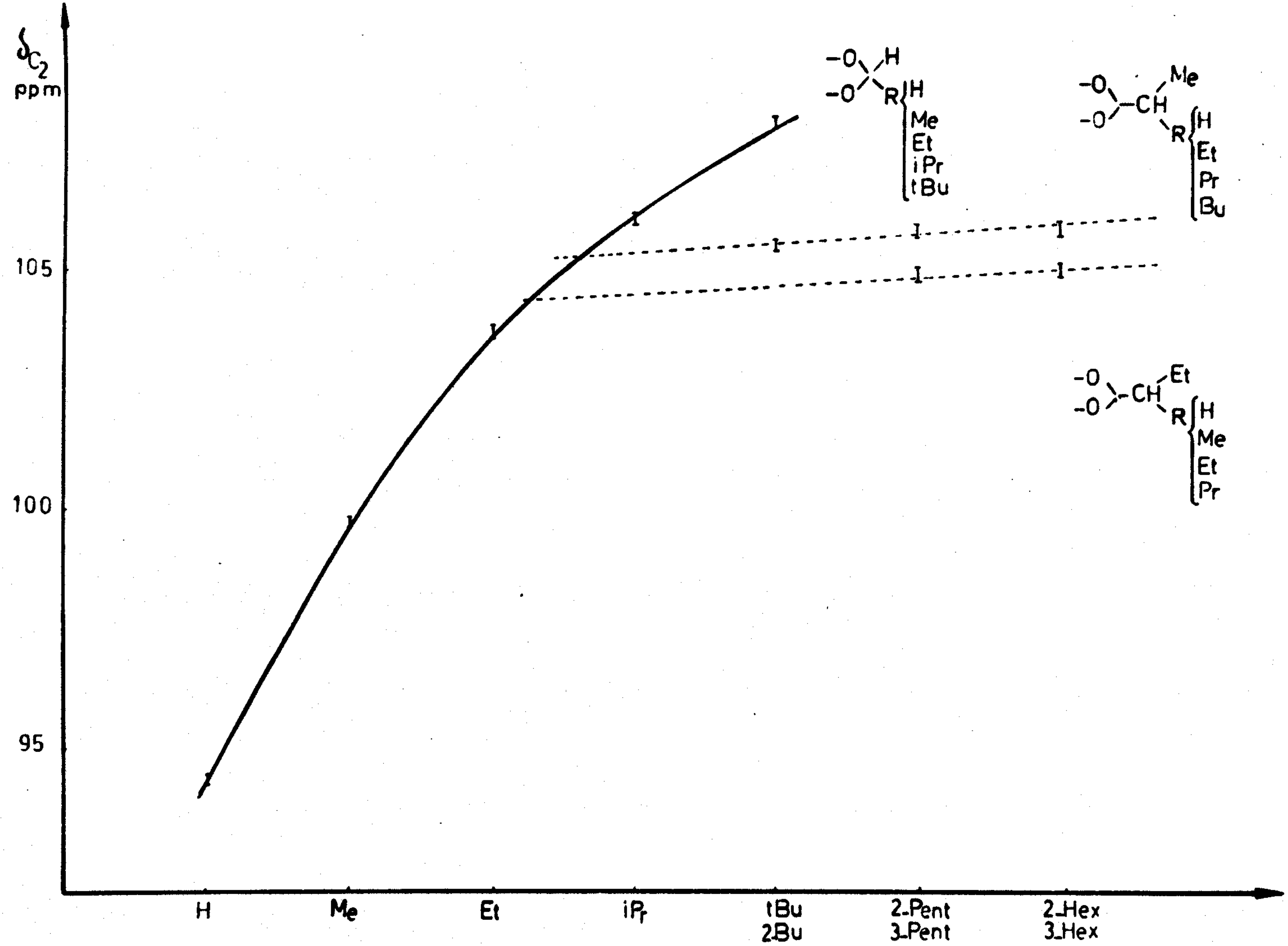
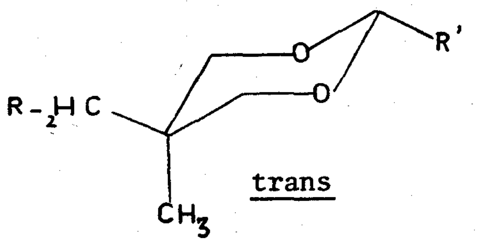


Figure 9. ^{13}C shieldings in the C-2 alkyl substituents of 1,3-dioxanes.

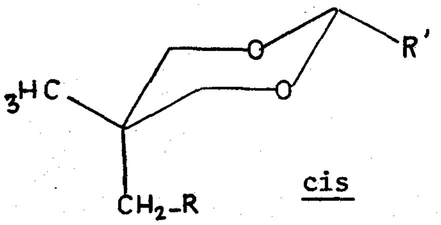
the C_2 substituents from R = Me upwards show no influence on the other dioxane ring carbons (C_4, C_5 and C_6) and this shows that none of the molecules, even with the longest chain substituents, undergo any significant conformational coiling, at least not in the solvents used in this work. The γ effect is probably the most interesting since it appears to be much smaller on the C-2 carbon than on the alkyl chain.

The effects of a variety of substituents on carbon-5 of the dioxane ring were also determined. The shieldings upon successive substitution of one hydrogen of a C_5 methyl group by a methyl, ethyl, vinyl, and hydroxyl are shown in Table 7.

Table 7. Substituent effects on carbon-5 in 1,3-dioxane .



trans



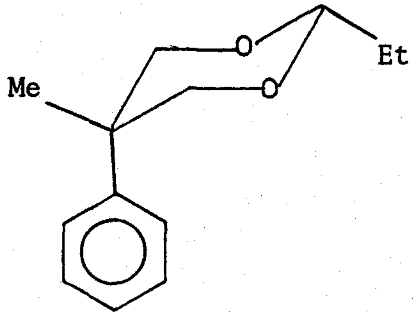
cis

R' = Me or Et

R	Compound	α		β	γ		$C_{4,6}$	
		cis	trans		cis	trans	cis	trans
CH_3-	6	4.0	7.15	3.5	-3.6	-3.7	-1.8	-0.7
CH_3-CH_2-	11	14.2	17.6	2.6	-3.0	-3.1	-1.3	-0.4
CH_2=CH_2-	15	16.1	19.5	2.7	-2.7	-3.5	-1.9	-1.0
OH-	14	42.2		4.9	-4.9		-4.3	

Replacement of a hydrogen of an axial methyl group C_{5a} by an hydroxyl group leads to a normal deshielding effect of 42.2 ppm. Unfortunately the trans isomer was not available for comparison, but of the remaining isomer pairs, a substituted axial carbon (C_{5a}) appears to show a highfield shift relative to an equatorial $C_{5a'}$ carbon. The shifts of these carbons are therefore useful in stereochemical assignment whereas the ring carbon C_5 showed no significant changes in chemical shift in proceeding from an axial to an equatorial isomer. The behaviour of the C_5 methyl group in the series of compounds in Table 7 is interesting since these methyls showed a reversal of the behaviour of the substituted carbons above; that is, the axial methyls resonated at lowfield relative to the equatorial methyls. The shifts are useful in being additional evidence for stereochemical assignment and comment is made on the possible origin of these shift differences in Section 2.3.

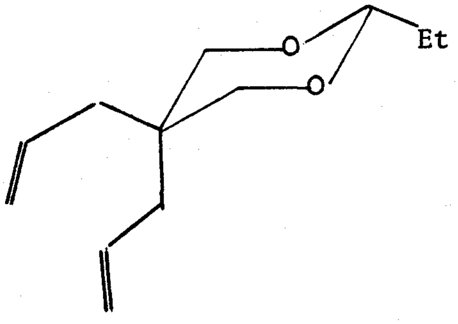
In only one instance in this work, where one of the 5-methyls was replaced by a phenyl group (compound 13), it was not possible to assign the



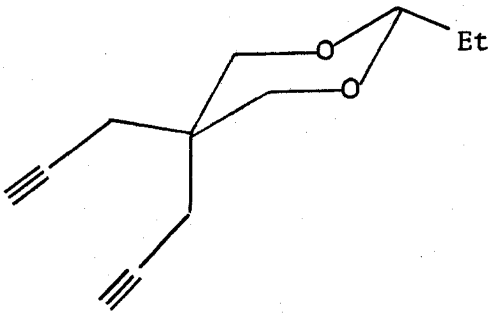
13 (cis)

cis and trans isomers, because curiously enough the C_5 axial and equatorial methyls showed identical chemical shifts. The origin of this chemical shift equivalence must lie in the presence of the phenyl group but it is not clear how the effect might operate.

If we consider the 5,5-dipropargyl dioxan 17 and 5,5-diallyl dioxan 16, the vinyl group has a very important average deshielding effect (+14.35



16



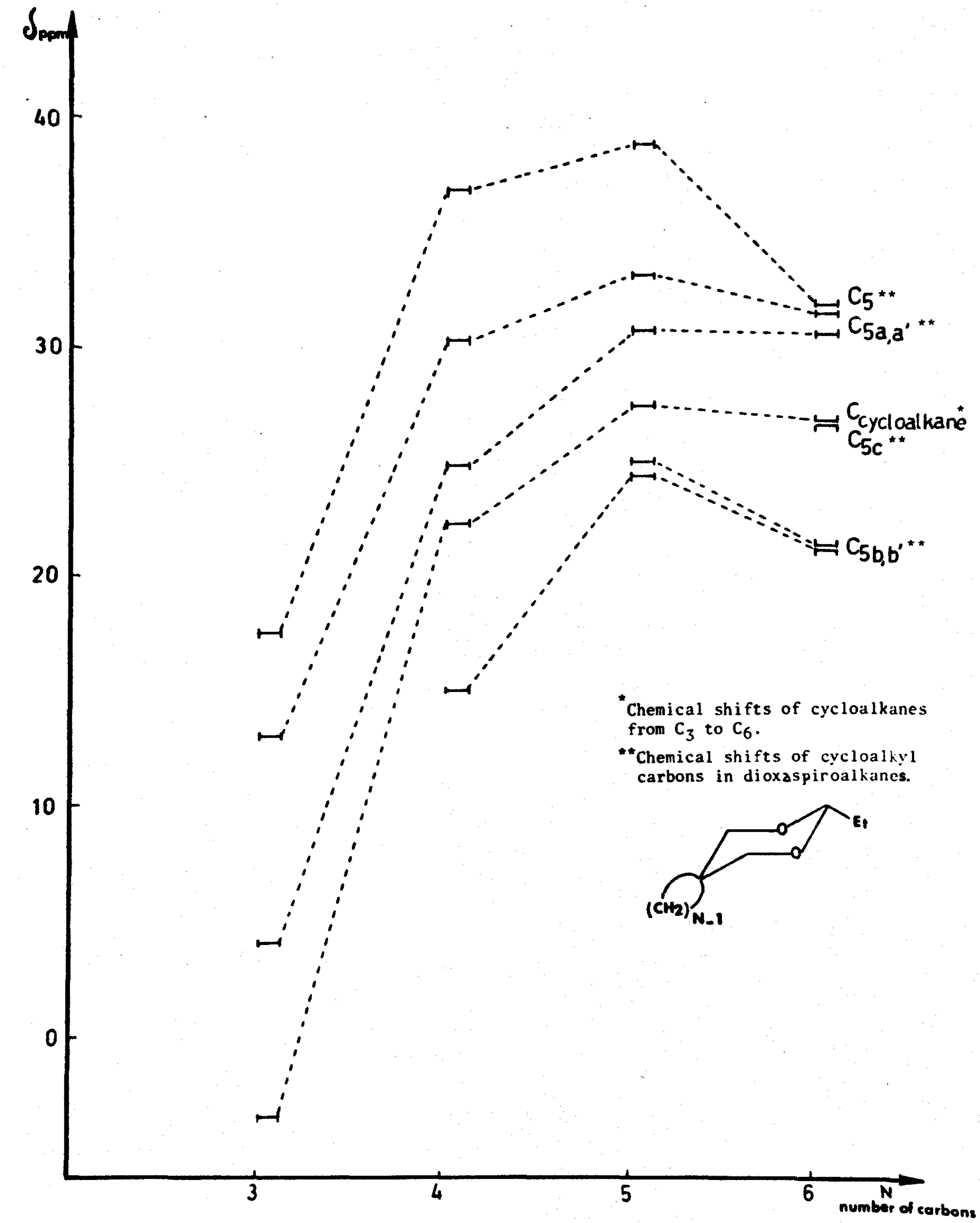
17

ppm) on the C_{5a} and $C_{5a'}$ carbons, whereas the ethynyl group has a very small effect (-0.4, -0.65 ppm). There are only small differences in chemical shift between the axial and equatorial positions C_{5a} and $C_{5a'}$ for 16 and 17, but the axial carbon remains at slightly higher field than the equatorial carbon.

The γ substituent effects experienced at C_4 and C_6 for compounds 6, 11 and 15 in table 7 as well as the dipropargyl and diallyl compounds 16 and 17 are all remarkably small. The lower than normal values (e.g., -0.7 ppm for trans 6 (equatorial R group) and -1.8 ppm for cis 6 (axial R group))are consistent with the current picture of a 1,3-dioxan ring where carbons 4, 5 and 6 are more flattened than in a normal chair.

2.4. Dioxaspiroalkanes

The chemical shifts for cycloalkanes through C_{10} have been studied by Burke and Lauterbur(73) (Table 8). In the present thesis a number of dioxaspiroalkanes have been studied (see Table 3). Interesting differences were found upon comparison of the substituent effect in cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl systems (see Fig.10 for graphical repre-



*Chemical shifts of cycloalkanes from C_3 to C_6.

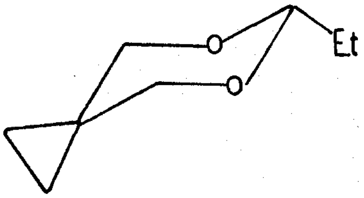
**Chemical shifts of cycloalkyl carbons in dioxaspiroalkanes.

Figure 10. Plot of chemical shift versus number of carbon atoms for cycloalkanes and dioxaspiroalkanes.

Table 8. Chemical Shifts of Some Cycloalkanes.

		C_1	$C_{2,6}$	$C_{3,5}$	C_4
cyclopropane	22	-3.5			
cyclobutane	23	+22.4			
cyclopentane	24	+25.6			
cyclohexane	25	+26.9			
1,1-Me_2 cyclopentane	26	39.3	41.5	25.1	
1,1-Me_2 cyclohexane	27	29.85	39.65	22.42	26.51

sentation.) In 2-ethyl-5,7-dioxaspiro(2,5)octane, 18, the carbons of the cyclopropyl ring were found at very high field in analogy with the proton shifts in cyclopropanes. For all the cycloalkanes studied, the successive replacement of two geminal hydrogens by the dioxane ring produces low field shifts of the tetrasubstituted carbon and of the two nearest neighbours. These shifts decrease when the size of the ring increases being +21.1 ppm for the dioxaspiro(2,5)octane, 18, +14.5 ppm for the dioxaspiro(3,5)nonane, 19, +13.3 ppm for the dioxaspiro(4,5)decane, 20, and +5.2 ppm for the dioxaspiro(5,5)undecane, 21. A similar deshielding of +13.6 ppm of the quarternary carbon has been noted for 1,1-dimethylcyclopentane 26 (Table 8) while in

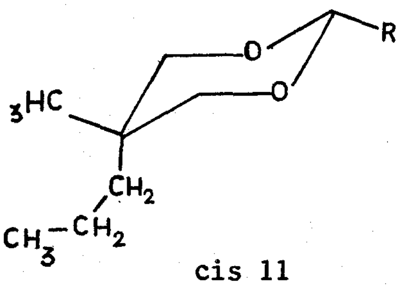


18

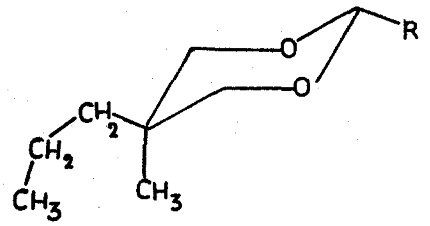
1,1-dimethylcyclohexane, the deshielding has been found to be only +2.95 ppm$^{(74)}$.

One other feature of the results is the shift difference between the carbons C_{5a} and $C_{5a'}$. For these axial and equatorial carbons, the difference in their chemical shifts changes with the size of the ring. This may be partly caused by a decrease in the angle in the cycloalkyl ring which also results in a slight opening of the C_4-C_5-C_6 angle of the dioxan ring. When comparison is made between the C_{5a}, $C_{5a'}$ carbons in the 5,5-spiro systems with the corresponding carbons in cis and trans 6,7,8,9,11 (see Table 9), it is evident that the shift difference between the axial and

Table 9. Changes in chemical shifts for the C_5 side chains of cis and trans isomers 6. 7, 8, 9, 11.



cis 11



trans 11

R= -CH(Et$_2$)

cis	⟶	trans
5a'-Me		+1.45 ± 0.05
$5a$-CH_2		+1.8 ± 0.2
5b-Me or $-CH_2$		-1.15 ± 0.05
5c-Me or $5c$-CH_2		0
C_4,C_6		1.0 ± 0.1

equatorial carbons is smaller for the non-cyclic substituent than for any of the spiro system Indeed it is only in the most strained of the spiro systems, the 5,7-dioxaspiro[2,5]octane (18) and 6,8-dioxaspiro[3,5]nonane (19) that the axial-equatorial shift differences approach those observed for methyl groups in the simple cyclohexane, 1,1,3-trimethylcyclohexane, where Dalling and Grant(75) found a difference of 8.8 ppm, the axial methyl being at higher field. The deshielding of the axial C_{5a} carbon, which for a simple methyl group reaches the point where the axial methyl is at lower field than the equatorial methyl (see Section 2.2), has been attributed by Jones et al.(13) to the presence of the two 1,3-ring oxygen atoms. These authors suggest that the deshielding is a result of a lowered steric interaction between the C_{5a} carbon and the oxygen atoms in comparison with the steric compression presented by the 1,3-hydrogen atoms in cyclohexane. Whilst this suggestion appears reasonable, it is difficult to rationalize the behaviour of the dioxaspiro[2,5]octane, 18, and dioxaspiro[3,5]nonane, 19, compounds where the bond angle changes at C_5 cause the axial C_{5a} carbons to move away from the oxygen atom, and yet the axial-equatorial shift differences are close to that in cyclohexanes. A possible alternative or contributing explanation is that the electrons on the oxygen atoms are able to interact in a U-fashion (Fig. 11) with the C_5-C_{5a} bonding electrons(75a) generating two new delocalized orbitals, one of lower energy and one of higher energy. The mean excitation energy for promotion of an electron from occupied to unoccupied orbitals should therefore decrease, and the chemical shifts of the C_5 and C_{5a} carbon atoms should show an increased paramagnetic or downfield shift. According to this suggestion then, any decrease in the axial nature of the C_5-C_{5a} bond, as in the spirocyclopropyl dioxane, 18, should show a decrease

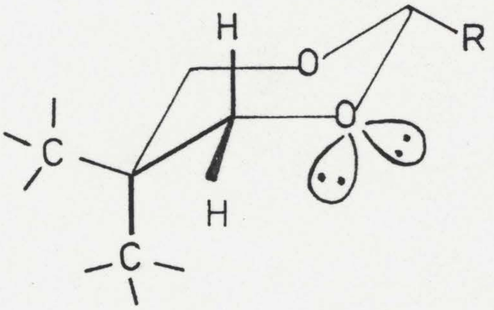


Fig. 11. Model arrangement of orbital lobes and intervening σ bonds.

in interaction with the oxygen n electrons and therefore an upfield shift, as is observed.

The effect of the alkane rings on the neighbouring carbons (β carbons C_4 and C_6) are large only for the cyclopropyl substituent (+13.2 ppm) and decrease to +8.7 ± 0.5 ppm for the remaining spiro-rings. The β effects of simple C_5 dimethyl substitution (e.g., 3, 4 or 5) are 10.5 ppm and are only marginally smaller than those found in 1,1-dimethyl cyclopentane, 26, (+15.8 ppm) and in 1,1-dimethylcyclohexane, 27, (+12.7 ppm)$^{(75)}$. The γ effects experienced by the C_{5b} and $C_{5b'}$ carbons in the dioxaspiro[4,5]-decane (20) and dioxaspiro[5,5]undecane, 21, are near normal and require no comment. The C_{5b} carbon of dioxaspiro[3,5]nonane, 19, is however strongly shielded by -7.28 ppm. Unfortunately the chemical shifts of 1,1-dimethylcyclobutane were not available for comparison.

The small difference between axial and equatorial chemical shifts of C_5 substituents decreases in the case of disubstitution at C_2. In the axial and equatorial positions, for 5-methyl and 5-methylene carbons, the differences are 0.3 and 0.8 ppm respectively, and for a C_{5b} methyl carbons 0.25 ± 0.5 ppm (Table 9). The introduction of a methyl or ethyl group in the C_2 axial position results in C_2 experiencing a downfield shift of 4.1 ppm. This is similar to the results obtained by Jones *et al*.(13) They also noted a downfield shift of 5.1 to 5.4 ppm on introducing an equatorial methyl group into the C_2 position.

3. TETRAHYDROFURANS

3.1. Stereochemistry of five-membered rings

The conformational analysis of nonplanar five-membered ring compounds is considerably more complicated than that of six-membered rings. The latter, thanks to their relative rigidity (high resistance to deformation by bulky groups) are easily characterized by the orientation of substituents, equatorial or axial, and by a well-defined geometry for each conformation. The nonplanarity of cyclopentane has been demonstrated by its thermodynamic and spectroscopic properties. It does not exist in any stable or rigid forms analogous to the chair form of cyclohexane. The deformation of the cyclopentane ring is exceedingly facile and results in a motional behaviour termed pseudorotation; here the ring goes through an series of conformations (Fig. 13) in which the energy minima are all equal. Two of these conformations have an element of symmetry; the C_s or envelope form and the C_2 or half chair form (see Fig. 12).

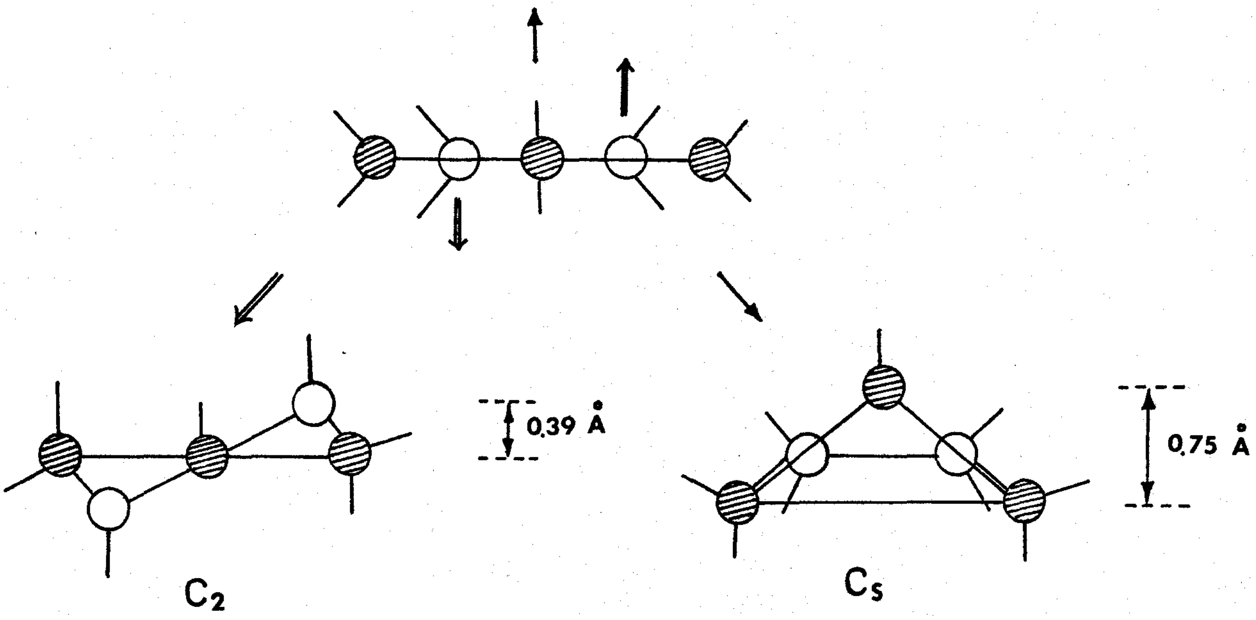


Figure 12. Deformations of the cyclopentane ring.

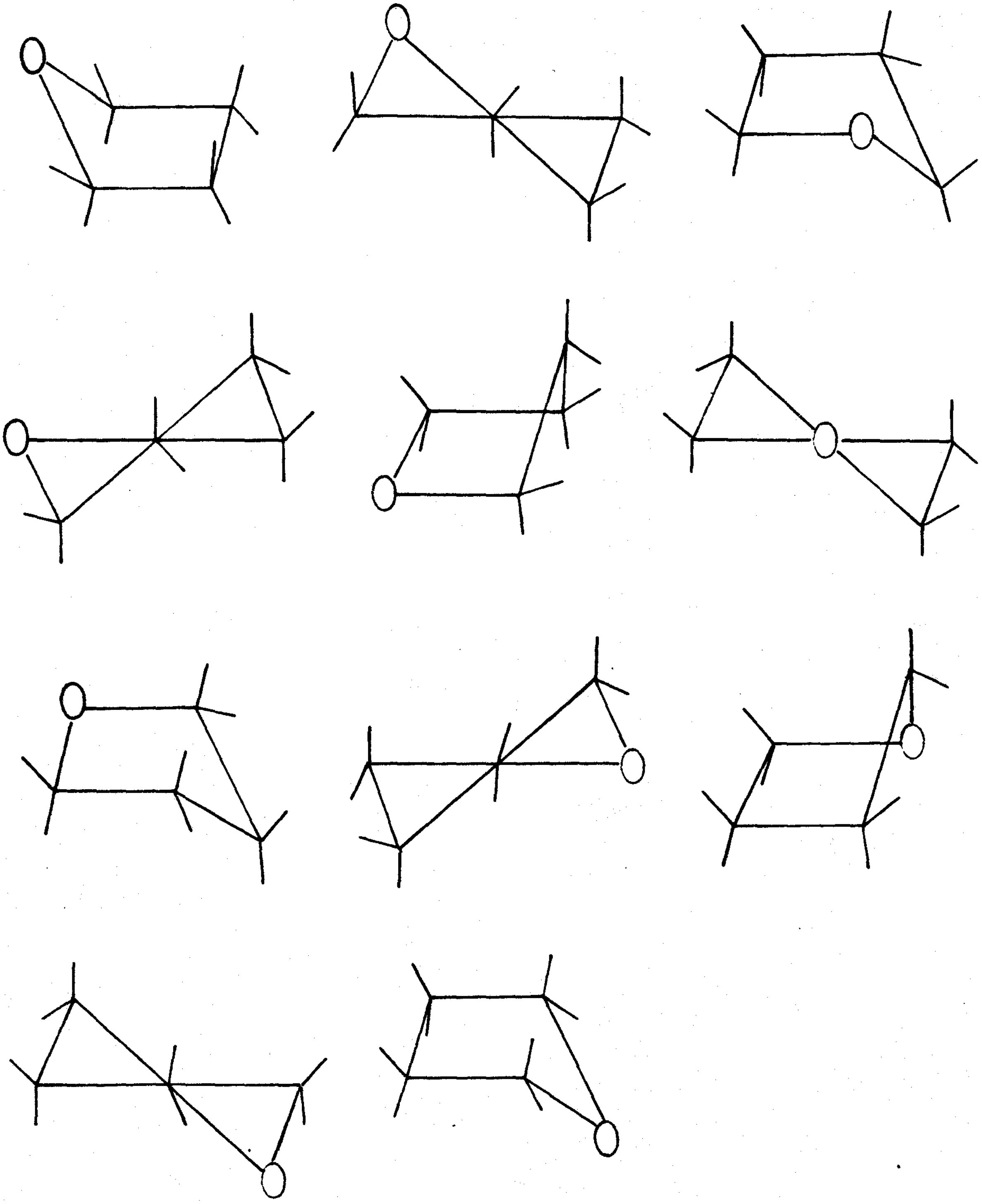


Figure 13. Eleven of the 20 possible conformations of Tetrahydrofuran representing one part of the pseudorotation circuit.

Until recently it had been considered that the "envelope" or "half-chair" forms were adequate models for a description of the conformation of a given five-membered ring system (76,77,78), since these two forms were postulated as the most stable forms in much of the pioneering work on five-membered rings (79,80). It is now becoming clear that the true geometry is usually somewhere "in between", neither C_2 nor C_s.

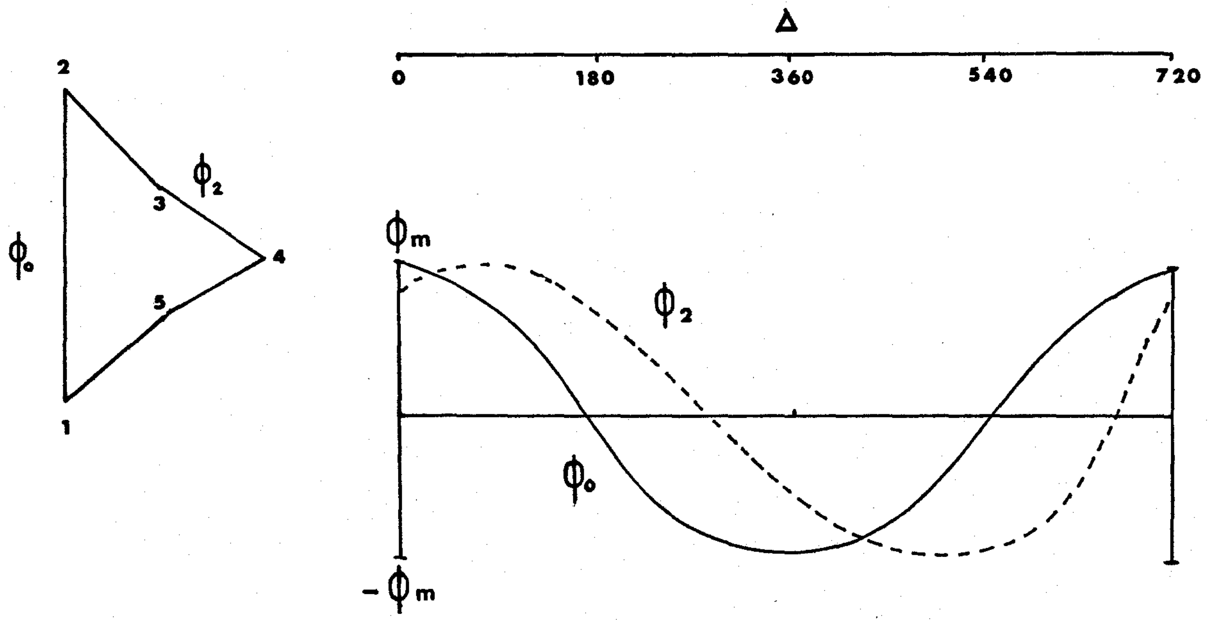


Figure 14. Amplitude and phase angle of pseudorotation of a five-membered ring.

Consider the half-chair form, where the torsional angle ϕ_o about the 1-2 bond is taken equal to ϕ_m (amplitude of puckering) with positive sign (Figure 14). Along the pseudorotation itinerary, ϕ_o decreases until at $\Delta = 360°$ (Δ is the phase angle of pseudorotation), the mirror image of the original structure is obtained: $\phi_o = -\phi_m$. A rotation over $\Delta = 720°$ restores the original conformation . Mathematically, the relation between the angles can be expressed by

$$\phi_j = \phi_m(\cos \frac{1}{2}\Delta - \frac{4}{5}\pi j) \qquad (j = 0,1,2,3,4)$$

Along the pseudorotation circuit, as Δ varies from 0 to 720°, ten envelope (C_s) and ten half-chair (C_2) forms are met (Fig. 13). It has been calculated(81) that there is little if any energy difference between the envelope and half-chair conformers in cyclopentane. Internal substitution of the five-membered ring with a hetero atom seems to introduce a small energy barrier (0.05 - 0.3 Kcal/mole) in the pseudorotation circuit(79,76,82). External substitution of a five-membered ring has a similar effect(83). Presumably, one or two small substituents while preventing complete pseudorotation may still permit a wide conformational oscillation about rather flat energy minima. As the substituents become larger or more numerous, however, their own steric requirements seem to confine the ring to certain defined conformations with distinct minima(83). The position of their minima in the pseudorotation circuit of the ring is now dictated by the steric requirements of the substituents rather than any ring properties. Quantitative information regarding preferred conformations of five-membered ring systems is limited largely to cyclopentane derivatives. The work in the heterocyclic area was confined largely to NMR spectroscopy(84-86), although certain systems had been investigated by X-ray diffraction(87,89), dipole moment studies(90,91) and infrared and Raman spectroscopy(90,92,93). Few free-energy differences between diastereoisomeric five-membered ring systems have been measured with precision(94-98).

Some substituted tetrahydrofurans (THFs) have been investigated by proton NMR(99-110), but simple alkyl substituted THFs have received little attention(111,112). It was anticipated that the present investigation would lead to a better understanding of the conformations of five-membered rings in general. Some methyl cyclopentanes have been studied recently(74), and will permit interesting comparisons. In view of the occurrence of THF rings in many natural products, it will be demonstrated in this thesis that ^{13}C spectroscopy has great potential application as a new tool in the assignment of stereochemistry in these systems.

3.2. Chemical Shifts of THFs: Results and Discussion

(a) Ring Carbons

The chemical shifts of 33 methyl and ethyl substituted tetrahydrofurans are summarized in Table 10. The usual analysis for the discussion of substituent effects will again be followed here as for the 1,3-dioxanes above. Table 11 shows the α, β, γ, and δ substituent effects observed for mono and dimethyl substitution on the THF ring. For comparison purposes the corresponding substituent effects of the mono and dimethyl cyclopentanes(74) are included in brackets. It is clear from Table 11 that the oxygen atom of the THF ring has had a distinct diamagnetic or shielding effect on all the α and β parameters with the exception of 3,3-dimethyl THF, 32, which has a larger α effect (7.4 ppm) at C_3 than the corresponding 1,1-dimethylcyclopentane (4.3 ppm). Apart from the influence of the oxygen atom, the α and β effects appear to follow the same general trends as in the cyclopentane series. The ring carbons which are γ or δ to the substituting methyl, all show small effects but their signs are frequently at variance with the cyclopentane cases.

As has been noted above in this thesis, the tetrahydrofuran ring is a very flexible ring, and although in the main C_s and C_2 conformers there are alternating axial and equatorial type bonds, the rapid interconversion of the conformers leads to an averaging of the axial and equatorial effects. This is

Table 10. Carbon-13 Shieldings in Substituted THFs

NO.	THF Substituents	C_2	C_3	C_4	C_5	$C_2{}^{a}_{a'}$	$C_3{}^{a}_{a'}$	$C_4{}^{a}_{a'}$	$C_5{}^{a}_{a'}$	$C_2{}^{b}_{b'}$	$C_5{}^{b}_{b'}$
28	Nil	67.75	25.65								
29	2-Me	75.15	33.2	25.8	67.4	20.5					
30	3-Me	74.95	33.8	34.5	67.7		17.4				
31	2,2-Me_2	80.1	38.3	26.05	67.0	27.6					
32	3,3-Me_2	80.5	41.2	43.6	67.6		25.65				
33a	cis-2,3-Me_2	77.25	36.3	34.0	66.0	15.5	13.95				
33b	trans-2,3-Me_2	82.1	41.35	35.0	66.35	18.8	16.3				
34a	cis-2,4-Me_2	75.2	41.8	33.4	74.6	21.05		17.6			
34b	trans-2,4-Me_2	76.1	43.1	34.7	74.7	20.9		17.95			
35a	cis-2,5-Me_2	75.4	33.3			21.3					
35b	trans-2,5-Me_2	74.4	34.2			21.3					
36a	cis-3,4-Me_2	74.1	36.7				12.0				
36b	trans-3,4-Me_2	75.3	41.4				15.5				
37	2,2,3-Me_3	81.6	42.8	34.2	64.5	21.4 27.1	14.3				
38	2,2,4-Me_3	80.65	47.9	34.5	74.2	28.2 28.9		17.3			
39	2,2,5-Me_3	80.3	39.1	34.0	74.4	27.9 29.4			21.7		
40	2,2,3,3-Me_4	83.4	42.6	40.6	63.1	23.8	22.9				
41	2,2,4,4-Me_4	81.0	54.4	40.5	79.1	29.0		27.2			
42	2,2,5,5-Me_4	80.9	39.0			29.6					
43	3,3,4,4-Me_4	76.2	42.5				22.25				
44	2,2,3,5,5-Me_5	82.7	43.6	47.7	78.0	23.3 28.9	13.9		30.1 30.75		
45	2,2,3,3,5-Me_5	83.9	43.6	49.15	70.75	25.2 24.65	24.2 23.1		22.9		
46	2,2,3,3,4-Me_5	84.9	43.95	42.25	71.3	23.15 24.45	21.7 17.75	11.35			
47	2,2,3,3,5,5-Me_6	84.6	44.2	54.3	76.9	25.2	25.0		31.7		
48	2,2,3,3,4,4-Me_6	85.15	45.8	44.2	77.4	26.55	21.9	24.05			
49	2-Et	80.8	31.05	25.7	67.55	28.6				10.0	
50	2-Me,2-Et	82.6	36.5	26.1	67.05	a 24.8 a'33.6				b' 8.2	
51	2,2-Et_2	85.2	34.2	26.3	67.4	30.5				8.1	
52	2,2-Et_2,3-Me	84.2	39.5	34.75	65.2	28.7 25.3	14.4			7.6 7.8	
53	2,2-Et_2,5-Me	85.5	34.6	34.1	74.6	31.0 31.4			21.1	7.9	
54	2,2-Et_2,4,4-Me_2	86.6	50.8	39.95	79.2	30.3		27.7		8.2	
55	2,2,5-Et_3,5-Me	85.9	35.1	36.7	83.1	31.4			a 26.3 a'34.6	8.15	b'8.5
56	3,4-Cl_2 trans	74.4	63.4								

Table 11. Chemical shift substituent parameters (in ppm) produced by methyl groups on tetrahydrofuran[a]

No.	THF	Substituting methyl	α	β	γ	δ
29	2-Me	2-Me	7.4 (9.3)[c]	7.55 (9.3)	0.15 (-0.1)	-0.35
30	3-Me	3-Me	8.15	7.2(C_2) 8.85(C_4)	-0.05	
33a	cis-2,3-Me_2	3-Me	3.1	2.1(C_2) 8.2(C_4)	-1.4 -5.0[b]	
		2-Me	2.3	2.5	-0.5 -3.5[b]	-1.7
33b	trans-2,3-Me_2	3-Me	8.2	7.0(C_2) 9.2(C_4)	-1.1 -1.7[b]	
		2-Me	7.2	7.6	0.5 -1.1[b]	-1.4
34a	cis-2,4-Me_2	2-Me	7.5	7.3	-0.4	-0.35 0.2[b]
		4-Me	7.6	8.6(C_3) 6.2(C_5)	0.05	0.5[b]
34b	trans-2,4-Me_2	2-Me	8.4	8.6	0.9	-0.25 0.55[b]
		4-Me	8.9	9.9(C_3) 7.3(C_5)	1.0	0.4[b]
35a	cis-2,5-Me_2	5-Me	8.0 (10.0)	7.5 (10.2,8.9)	0.1 (-1.3,0.4)	0.25 0.8[b]
35b	trans-2,5-Me_2	5-Me	7.0 (8.1)	8.4 (8.9,9.8)	1.0 (0.6-0.5)	-0.8 0.8[b]
36a	cis-3,4-Me_2	4-Me	2.2 (2.8)	2.9(C_3) 6.4(C_5) (2.8,7.8)	-0.9 -5.4[b] (-1.6,-2.2) (-5.4)[b]	
36b	trans-3,4-Me_2	4-Me	6.9 (7.9)	7.6(C_3) 7.6(C_5) (7.9,9.6)	0.35 -1.9[b] (0.2,-2.1) -1.7[b]	
31	2,2-Me_2	2-Me	4.95	5.1,7.1[b]	0.3	-0.4
32	3,3-Me_2	3-Me	7.4 (4.3)	5.6(C_2) 9.1(C_4) (6.5,8.6[b])	-0.1 (-0.5)	

[a] The substituent parameters were obtained by taking the shifts of the compound and subtracting the shifts for the species containing one less methyl group (indicated as the substituting methyl).

[b] Parameters for a methyl group.

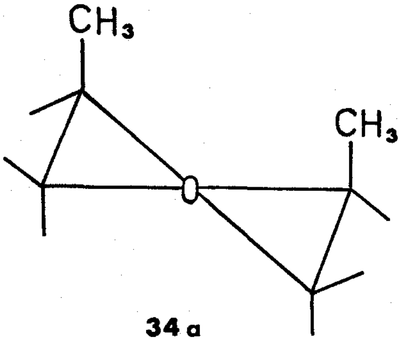
[c] Values in parentheses are the substituent effects obtained by Roberts *et al.* (74) for the corresponding substituted cyclopentanes.

in contrast to cyclohexane rings where distinct axial and equatorial substituent shifts are observable for all α, β, γ, and δ carbons(75a,b). However, because most of the more substituted THFs are also averaging between a number of conformations, it was not unreasonable to expect the shift parameters of Table 11 to be useful in the prediction of the chemical shifts of these polysubstituted rings. In the event a straightforward additivity relationship between the shift parameters was found to give chemical shifts in excellent agreement with observed values for all but the most sterically congested molecules (see Appendix I for typical computations of predicted shifts). Such a relationship has the additional advantage of enabling rapid shift assignments to be made for many-carbon THFs, and the particular value of showing up molecules possessing subtle steric and conformational properties which would otherwise not be evident. Since a self-consistent set of assignments has been carried out for the compounds in Table 10, the majority of the remaining discussion will centre on molecules with shifts which diverge significantly (> 2.0 ppm) from their predicted values, or on molecules with shifts which are affected by their conformational or steric properties.

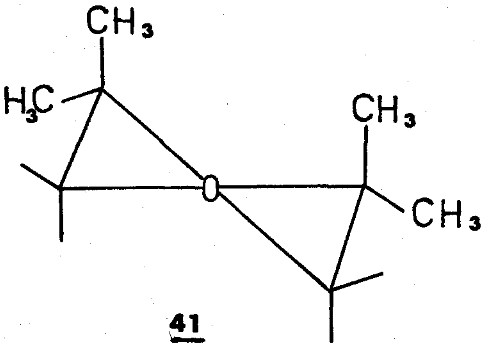
The chemical-shift effects produced by methyl substitution are largely different in the case of cis-1,2- and trans-1,2-dimethyl substituted compounds. In the cis compounds (33a and 36a), the α and β effects are small (2 to 3 ppm) while in the trans compounds (33b and 36b), the α and β effects vary between 7 and 9.6 ppm. Although the origin of the α and β effects do not seem well understood, they seem to have at least partly a steric origin. The α effect in the cis-1,3-dimethyl cyclopentane is more important than the α effect of the trans compound (Table 11). The same result is found for the THF ring where the α effect in cis-2,5-dimethyl THF is 8 ppm and 7 ppm in the trans compound.

In all cases, the cis isomers are thermodynamically favoured over the corresponding trans isomers. This has been explained on the basis of an unfavourable steric interaction of a pseudoaxial substituent at C_2 with a pseudoaxial hydrogen at C_5 (envelope conformation) in the trans isomer.(168) In the cis-2,5-dimethyl THF , the molecule must be in the envelope form with 2 methyls in the equatorial position.

As noticed before in the case of 2,4 and 2,5 polysubstituted THF, the predicted values agree with the observed values (<1 ppm). Nevertheless in the case of cis-2,4-dimethyl THF, one can observe an upfield shift of the ring carbon C_3 (-1.3 ppm), compared to the trans compound. The same upfield shift of a ring carbon placed between two substituted methylcarbons is also seen in the case of cis-1,3-dimethylpentane(74). Because steric hindrance generally results in upfield shifts, we can conclude that β shifts are influenced by steric hindrance. This is confirmed in 2,2,4,4-tetrasubstituted THF, <u>41</u> and <u>54</u>. Two of the substituents have to be in pseudo-axial positions, the steric effect is more important and result for the carbon 3 in an upfield shift (1.8 ppm) of the real value compared to the predicted one. The chemical shift of the carbon 4 in both cases agrees with the predicted value. In 2,2,4-trimethyl THF (<u>38</u>), our data would rather suggest that in the predominant conformation the substituent in C_4 is pseudoaxial. The C_2 methyl which is axial at a given instant does not interact strongly with the hydrogen in C_4. There is only a 1,3-Me-Me interaction and the real shifts of carbons 4 and 2 agree with the predicted one. In contrast, in 2 cases (2,3,3-trimethyl THF <u>37</u> and 2,2,3,3-tetramethyl THF <u>40</u>) there is a 1,3-diaxal methyl-hydrogen interaction. The carbon 5 is shifted upfield (respectively by 3 ppm and 4.5 ppm). The same effect has been observed in cyclohexane. In a 1,3-diaxal Me-H inter-



34a



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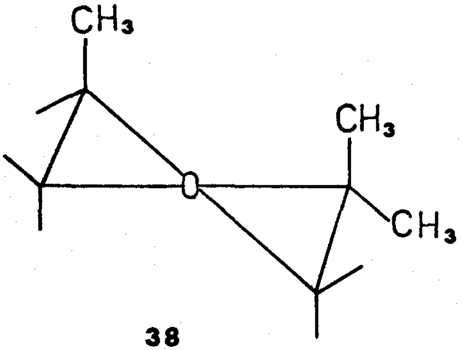

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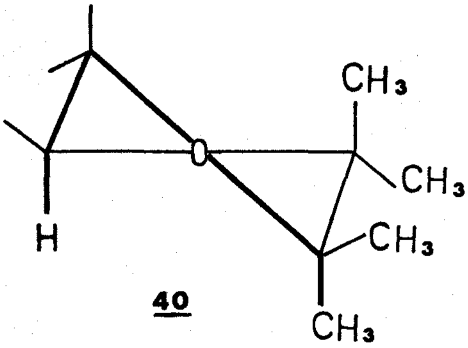

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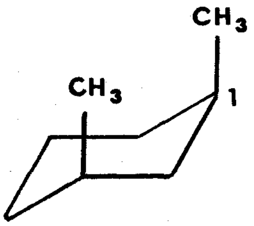
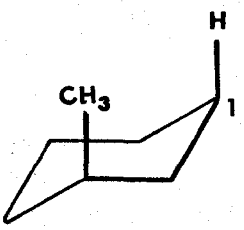
action, the normal steric γ effect of an axial methyl on C_1 as in (b) is + 4 ppm considering what it is with a corresponding 1,3-diaxial methyl-methyl



(a)

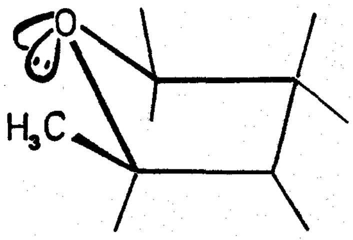


(b)

interaction (a). The explanation given by Roberts et al.(74) is that the steric effect on C_1 in (a) is not seen on the ^{13}C chemical shift because there is no directly attached hydrogen.(155) In the case of polysubstitutions on 2 adjacent carbon atoms, the predicted values were consistently higher than the experimental results. The differences can be greater than 10 ppm in the most substituted THF 44, 45, 46, 47, and 48, due to mutual steric interactions between methyl groups.

(b) Methyl Carbons

The shielding values of methyl groups are very typical of the steric environment in the molecule. A 1,3-methyl-methyl interaction through the oxygen (compound 39) shifts the methyl carbon by +2 ppm. The same 1,3-methyl-methyl interaction through the carbon atom (compound 38) shifts the methyl carbon in C_2 by 1.4 ppm and the methyl carbon in C_4 by 1.55 ppm. The C-O bond is shorter than the C-C bond and this might explain the smallest shift in the second case. In the case of 1,3-methyl-methyl substitution , the δ effects of one methyl on the other one is slightly positive and vary from 0.2 to 0.8 ppm. The δ effect increases suddenly on tri and tetrasubstitution and the chemical shieldings of methyl groups are shifted downfield. It is certain that there is an interaction through space between the methyl groups but this interaction which is small cannot explain this particular downfield shift. An additional repulsion energy may result from the interactions and the steric strain contributes to ring bond angle changes. But even this does not explain satisfactorily why in the trisubstituted THF (39) one of the methyls at C_2 is shifted by 0.3 ppm while the other moves by 1.8 ppm. One of the methyls must interact with the oxygen n electrons and therefore be shifted downfield.



In contrast, for 1,2-methyl-methyl interactions, the steric hindrance results in an upfield shift of the methyl carbons. In compound 36 (3,4-dimethyl THF) the cis methyls are shifted upfield (+ 3.5 ppm) compared to the trans methyls. The same difference (+ 3.6 ppm) has been observed between cis and trans methyl groups in 1,2-dimethyl cyclopentane(74).

The same conclusions can be extended to the ethyl substituted tetrahydrofurans. An examination of the shifts produced by ethyl substitution reveals some general trends in alkyl substituted THF's.

The substitution of hydrogen atoms by chlorine atoms causes a shielding value of +38.1 ppm on carbons 3 and 4, and a shielding value of +7.35 ppm on carbons 2 and 5. The same shielding values have been observed by Perlin and Rock(113) in the trans-1,2-dichlorocyclohexane (α effect: +38.3 ppm; β effect: +8.9 ppm). The similarity in those shielding values can be explained by the fact that chlorine predominates in the axial positions on the THF ring(90) as well as on the cyclohexane ring.

4. DIHYDRO-2-FURANONES

4.1. Stereochemistry of Dihydro-2-furanones

Until recently, the γ-lactones were, by their names (4-hydroxybutanoic acid γ-lactones), considered as acid derivatives. In a new nomenclature, they have been called dihydrofuranones. This will enable us to introduce a comparison--by the way of ^{13}C NMR shifts--between the methyl derivatives of tetrahydrofuranes and dihydrofuranones. In the last ten years, differently substituted γ-lactones have been studied by proton nmr(114-122) and Johnson et al.(115) have interpreted the values of vicinal ^{1}H coupling constants in terms of an envelope conformation, possibly slightly distorted, in which ϕ, the cis dihedral angle for vicinal protons (2,3- or 3,4-) is 35-40° (see Fig. 15).

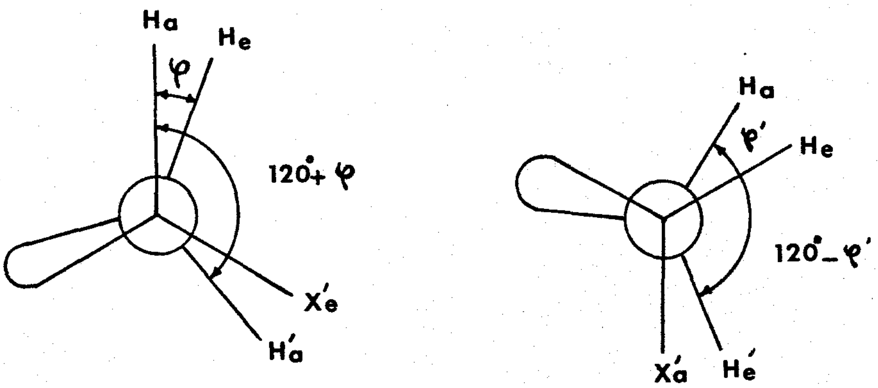


Figure 15. Two "envelope" conformations of dihydro-2-furanone.

The same two types of "envelope" conformations have been observed in crystalline γ-lactones(123). The lactone group $-\mathrm{O}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-$ appears to be planar(124) but deviations from planarity may occur in ring systems which are more highly strained.

4.2. Chemical Shifts of Dihydro-2-furanones; Results and Discussion

(a) Ring Carbons

The chemical shifts of 22 methyl dihydro-2-furanones are summarized in Table 12. By comparing ^{13}C shieldings of dihydro-2-furanone and tetrahydrofuran , one can observe an upfield shift of carbon 4 (3.2 ppm) while carbons 3 and 5 are shifted downfield (2.1 ppm, 1.85 ppm). For the carbon 2, a general trend is apparent (Fig. 16): the carbonyl signal is appreciably down field from the region in which the carbon 2 of THF absorbs (+111.55 ppm between C_2 THF 28 and the C_2 of dihydrofuranone 57). The same calculations as for tetrahydrofurans have been carried out and the substituent effects are shown in Table 13. In general, the α and β effects appear to follow the same general trends as in cyclopentane and tetrahydrofuran derivatives. The parameters of Table 13 have been used to predict chemical shifts of polysubstituted dihydrofuranones. As expected the additivity relation between the shift parameters has been found to be good for non-sterically congested ring systems, 69, 71 (see Appendix 2).

For most substituted dihydrofuranones, the real values are always at higher field compared to the predicted ones, exactly as in the tetrahydrofuran ring systems. Nevertheless, there is an exception for the C_2 carbon atom. The predicted values are generally closer to the real ones (see Appendix 3) and the difference is only 3 to 4 ppm in the most congested molecules 73, 74, 75.

It is apparent that substituent effects on C_2 are always smaller than on other carbons of the ring. That is, the carbonyl shift is not very sensitive to the effect of methyl substitution. Savitsky *et al*.(125a) after studying a series of cyclic carbonyl compounds by ^{13}C nmr indicate that the low-field shifts of sp_2 carbons in five-membered rings are common to all carbonyl carbons. This has been explained by Pople and Karplus(125b) in terms of a paramagnetic effect.

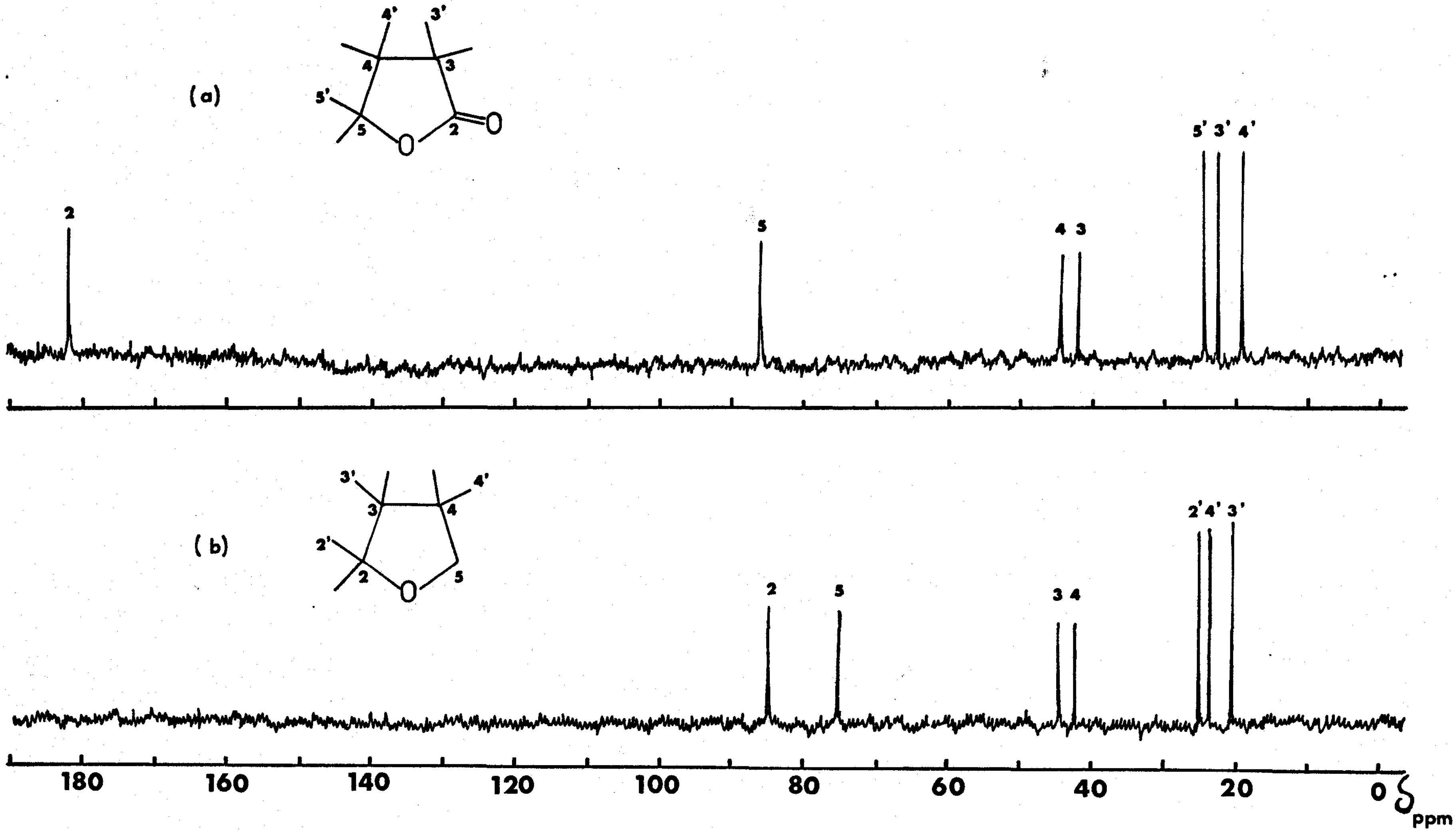
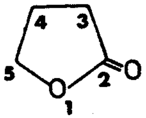


figure.16. ^{13}C NMR SPECTRA OF (a) 3,3,4,4,5,5-hexamethyldihydro-2-furanone.

(b) 2,2,3,3,4,4-hexamethyl THF.

Table 12. Carbon-13 Shieldings in Dihydro-2-furanones



No.	Substituents	C$_3$	C$_4$	C$_5$	3-Me	4-Me	5-Me	C$_2$
57	Nil	27.4	22.1	68.9				178.1
58	3-Me	34.0	30.6	66.7	14.8			180.4
59	4-Me	35.9	30.3	75.1		17.35		177.6
60	5-Me	28.75	29.5	77.4			20.7	177.2
61	3,3-Me$_2$	38.35	36.9	64.9	24.0			182.4
62	4,4-Me$_2$	43.0	36.5	79.7		25.4		176.7
63	5,5-Me$_2$	29.05	34.5	84.25			27.45	176.15
64a	cis-3,4-Me$_2$	37.9	33.75	73.1	9.4	12.85		179.05(d)
64b	trans-3,4-Me$_2$	41.45	38.65	72.5	12.75	14.9		179.3
65a	cis-3,5-Me$_2$	36.8	33.8	75.0	15.3		20.6	179.2
65b	trans-3,5-Me$_2$	39.05	36.2	75.2	14.75		20.5	179.55
66a	cis-4,5-Me$_2$	33.45	37.0	80.0		13.25	14.8	177.0
66b	trans-4,5-Me$_2$	37.25	38.4	83.9		16.05	18.6	176.65
67	3,3,4-Me$_3$	40.4	41.0	71.15	17.75 23.05	11.0		181.2
68	4,5,5-Me$_3$	36.55	39.8	86.4		13.75	21.25 26.75	175.05
69	3,3,5-Me$_3$	40.7	45.25	73.3	24.15 25.1		21.0	181.7
70	3,3,4,4-Me$_4$	45.1	41.1	77.15	19.25	21.4		181.7
71	3,3,5,5-Me$_4$	41.7	50.15	80.45	27.35		29.8	181.55
72	4,4,5,5-Me$_4$	41.0	43.9	88.5		22.8	23.15	175.2
73	3,3,4,5,5-Me$_5$	43.0	50.8	84.2	20.75 23.15	9.1	26.55 29.3	181.9
74	3,4,4,5,5-Me$_5$	43.85	44.6	86	8.55	18.65 20.9	22.15 23.35	179.6
75	3,3,4,4,5,5-Me$_6$	44.3	45.9	87.0	23.5	21.5	25.85	181.9

(d) doublet

Table 13. Chemical Shift Substituent Parameters (in ppm) produced by Methyl Groups on dihydro-2-furanone

No.	dihydro-2-furanone	substituting methyl	α	β	γ	δ
58	3-Me	3-Me	6.6	8.5 2.4a	-2.2	
59	4-Me	4-Me	8.2	8.5(C_3) 6.2(C_5)	-0.5 a	
60	5-Me	5-Me	8.5	7.4	1.35	-0.9a
61	3,3-Me_2	3-Me	4.35	6.3 2.0a 9.2b	-1.8	
62	4,4-Me_2	4-Me	6.2	7.1(C_3) 4.6(C_5) 8.05	-0.9a	
63	5,5-Me_2	5-Me	6.85	5.0 6.75b	0.3	-1.1a
64a	cis-3,4-Me_2	4-Me	3.15	3.9(C_3) 6.4(C_5)	-1.45a -5.4b	
		3-Me	2.0	3.45 1.45a	-2.0 -4.5b	
64b	trans-3,4-Me_2	4-Me	8.05	7.45(C_3) 5.8(C_5)	-1.2a -2.05b	
		3-Me	5.55	8.35 1.7a	-2.6 -2.45b	
65a	cis-3,5-Me_2	5-Me	8.3	3.2	2.8	-0.95a 0.5b
		3-Me	8.15	4.3 2.55a	-2.4	-0.1b
65b	trans-3,5-Me_2	5-Me	8.5	5.6	5.05	-0.95a -0.05b
		3-Me	10.3	6.7 2.9a	-2.2	-0.2b
66a	cis-4,5-Me_2	5-Me	4.9	6.7	-2.45 -4.1b	-0.6a
		4-Me	7.5	4.7(C_3) 2.6(C_5)	-5.9b 0.35a	
66b	trans-4,5-Me_2	5-Me	8.8	8.1	1.35 -1.3b	-0.95a
		4-Me	8.9	8.5(C_3) 6.5(C_5)	-2.1b 0a	

a Parameters for the carbonyl group.
b Parameters for a methyl group.

Table 13a. Predicted Chemical Shifts for dihydro-2-furanones

No.	Substituents		C_3	C_4	C_5	C_2
69	3,3,5-Me_3	predicted	39.7	44.3	73.2	181.6
		observed	40.7	45.25	73.3	181.7
71	3,3,5,5-Me_4	predicted	40.0	49.3	80.25	180.6
		observed	41.7	50.15	80.45	181.55

Table 13b. Observed and Predicted Chemical Shifts of the Carbonyl Group in dihydrofuranones

No.	Substituents	C_2 observed	C_2 predicted
67	3,3,4-Me_3	181.2	182.0
68	4,5,5-Me_3	175.05	175.6
69	3,3,5-Me_3	181.7	181.6
70	3,3,4,4-Me_4	178.8	181.1
71	3,3,5,5-Me_4	181.55	180.6
72	4,4,5,5-Me_4	175.2	174.7
73	3,3,4,5,5-Me_5	181.9	180.0
74	3,4,4,5,5-Me_5	179.6	177.1
75	3,3,4,4,5,5-Me_6	181.9	179.1

Savitsky et al (125a) suggested that unusually low or high carbonyl chemical shifts in homologous compounds may be explained in terms of their electronic excitation energies ΔE and established a correlation between the carbonyl shifts and the $n \rightarrow \pi^*$ transition energies. A low excitation energy leads to a low-field shift and vice-versa. The five-membered cyclic ketones and butyrolactones have a low $n \rightarrow \pi^*$ transition energy(169,170) and therefore the paramagnetic contribution to the chemical shift is very large and other factors will be small in comparison.

(b) Methyl Carbons

The presence of the carbonyl group causes some differences between the chemical shifts of differently substituting methyl carbons. By comparing the data with the THF's one, an upfield shift is observed for methyl substitutions at C_3 while substituting methyls in C_4 or C_5 do not show any significant change. The ring is inverting very rapidly between the alternative envelope conformations with one pseudoaxial and one pseudoequatorial substituent. This invertion of conformation is very rapid; we see only one signal for each of the gem-dimethyl groups, 61, 62, 63, 70, 71, 72. The introduction of an odd number of methyl groups favours the existence of one conformation to the detriment of the other one and the molecule should stay on average longer in the privileged conformation, at room temperature, 67, 68, 69, 73, 74.

The same general trends in the methyl chemical shifts are noted in both the tetrahydrofurans and dihydrofuranones. Thus a cis 1,2-methyl-methyl interactions shifts the methyls upfield by 4.1 to 5.9 ppm, while a trans 1,2-methyl-methyl interaction causes only a 1.3 to 2.45 ppm shift.

It is interesting to note here that the upfield shifts of the trans methyls in the dihydrofuranones are much larger than the upfield shifts of the corresponding trans methyls in the tetrahydrofurans (1.1 to 1.9 ppm). This suggests that the less preferred conformers in the dihydrofuranone series are more populated than the less preferred conformers in the dihydrofuran series. In contrast to the 1,2-methyls, the methyl interactions cause a downfield shift < 2 ppm which is again mirrored by the tetrahydrofurans.

5. SUCCINIC ANHYDRIDES

5.1. Stereochemistry of Succinic Anhydrides

The last series of five-membered ring systems which concern us are the methyl succinic anhydrides. Quantitative studies using molecular polarizability(126), infrared(127,128) or proton nuclear magnetic resonance(129,130) spectroscopy have been applied for structural purposes to succinic anhydrides. It appears now reasonably well established that the ring is approximately planar(126,131, 132,133) (Fig. 17).

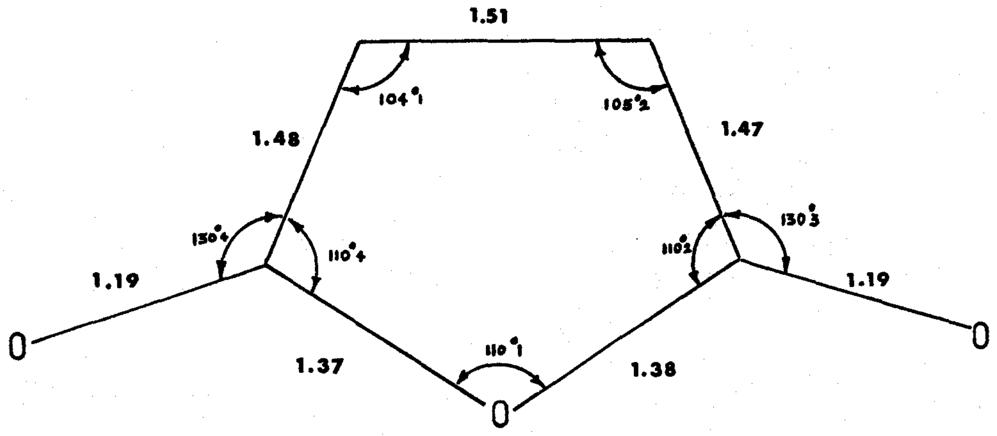
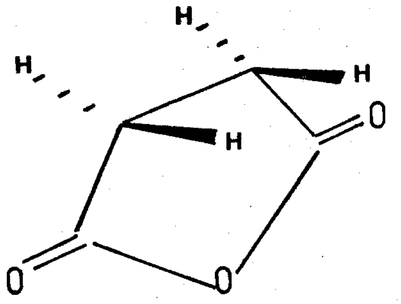


Figure 17. Crystal structure of succinic anhydride. Bond distances, Å, and angles, ° (131).

In its ground state, succinic anhydride <u>76</u> itself must possess considerable conformational strain, since the planar or nearly planar ring structure forces two pairs of C-H bonds to be eclipsed or nearly so. Moreover, the planarity of the ring causes an unfavourable conformational situation with respect to the CH_2-C-O bond, in that two C-H bonds are forced out of the favoured conformation of this bonding arrangement (which has eclipsing C-H and C=O bonds)(134).



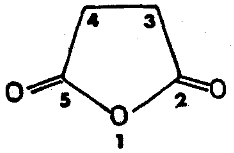
76

5.2. Chemical Shifts of Succinic Anhydrides: Results and Discussion

The chemical shifts of methyl succinic anhydrides are summarized in Table 14, and the substituent parameters in Table 15. Despite the fact that succinic anhydride ring is not as flexible a ring as the THF and dihydrofuranone rings, the α, β and γ effects appear to follow the same general trends with the exception of the carbonyl groups C_2 and C_5. For the 2 carbons, the substituent effects are always lower than those of carbons 3 and 4; the same low values have been noted for the C_2 of dihydro-2-furanones and have been explained above in terms of a paramagnetic effect. A downfield shift of the carbonyl group is observed in the case of 3,3,4,4-tetramethylsuccinic anhydride, 80. This is certainly related to the conformation of 80. This last compound is surprisingly more stable than the corresponding diacid derivative, while for all the other succinic anhydrides, the stability is reversed.

The upfield shift of the methyl groups in the case of 3,4-dimethylsuccinic anhydride 79 is more important in the cis compound (5.2 ppm) than in the trans compound (2.3 ppm). This appears to be a general rule for cyclic derivatives and is due to steric interaction between 2 methyl groups placed on 2 adjacent carbons (Fig. 18).

Table 14. ^{13}C Shieldings of Methyl-Substituted Succinic Anhydrides



Substituents	No.	C_3	C_4	3-Me	C_2	C_5
Nil	76	28.95			173.25	
3-Me	77	35.70	35.75	15.3	176.2	171.65
3,3-Me_2	78	42.0	42.45	24.8	177.95	170.1
cis-3,4-Me_2	79a	38.4		10.1	174.85d	
trans-3,4-Me_2	79b	42.7		13.0	175.05	
3,3,4,4-Me_4	80	48.2		21.2	184.3	

d: doublet

Table 15. Chemical Shift Substituent Parameters (in ppm) produced by Methyl Groups on Succinic Anhydride.

No.	Succinic Anhydride	Substituting methyl	α	β	γ	δ
77	3-Me	3-Me	6.75	6.8(C_4) 2.95(C_2)	-1.6	
78	3,3-Me_2	3-Me	6.3	6.7(C_4) 1.75(C_2) 9.5b	-1.55	
79a	cis-3,4-Me_2	4-Me	2.65	2.7(C_4) 3.2(C_5)	-1.35 -5.2b	
79b	trans-3,4-Me_2	4-Me	6.95	7.0(C_4) 3.4(C_5)	-1.15 -2.3b	

b: parameters of methyl group.

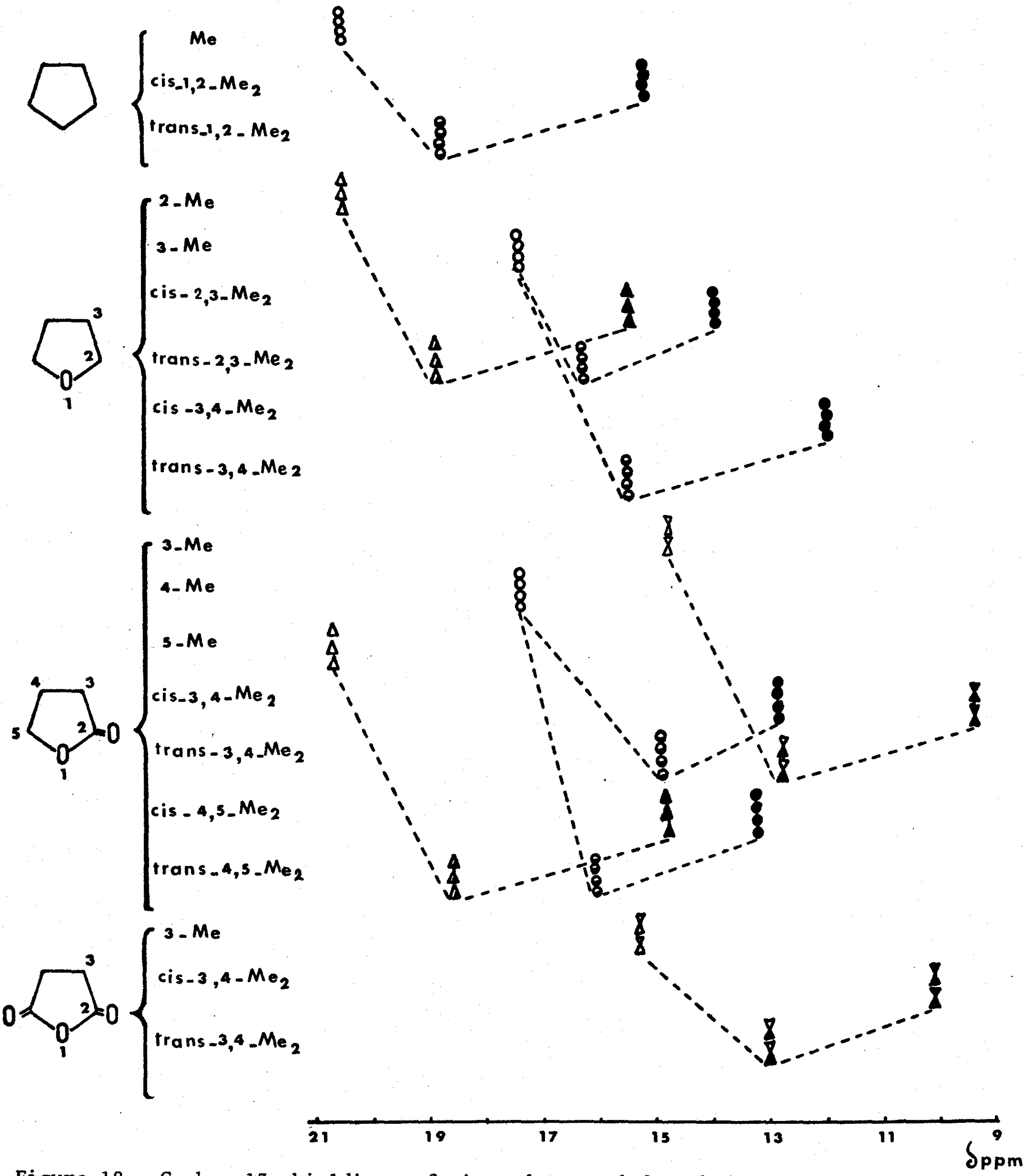


Figure 18. Carbon-13 shieldings of <u>cis</u> and <u>trans</u>-1,2-methyl groups in five-membered rings.

○ △ ⧖ Me
◒ △ ⧖ cis-Me$_2$
● ▲ ⧗ trans-Me$_2$
○ Carbon adjacent to two carbon atoms.
△ Carbon adjacent to a carbon atom and an oxygen atom.
⧖ Carbon adjacent to a carbon atom and a carboxy group.

6. EXPERIMENTAL

Apparatus, Methods and Materials

Spectra were recorded with a Varian Associates HA 100 spectrometer at 23.5 KG and 25.1 MHz. The operating probe temperature was 55°. Field-frequency stability was achieved by use of an external (1.5 mm capillary) $^{13}CS_2$ lock and chemical shift measurements were made initially relative to internal dioxan (67.4 ppm), benzene (128.6 ppm) or cyclohexane (26.9 ppm) and then adjusted to tetramethylsilane (TMS). A sample volume of 0.2 - 0.3 ml was used in a 5 mm o.d. sample tube. Normally a signal accululation of 4-100 scans with a Varian Associates C-1024 time averaging computer was sufficient to give an adequate signal-to-noise enhancement. Proton decoupling was carried out using a Varian Associates V-3512-1 noise decoupler. Quaternary carbon atom assignments were accomplished by examination of off-resonance decoupled spectra which were obtained by an accumulation of 4-100 scans. Calculations of the chemical shifts were carried out using a simple FORTRAN program run on a CDC 6400 computer.

The separation of cis and trans isomers were carried out on an AUTO annular Teflon$^{(R)}$ spinning band distillation column (Nester/Faust Manufacturing Corporation). The infrared spectra were recorded between salt plates on a Beckman model IR_5. Proton spectra were recorded with a Varian T-60 or an HA-100 spectrometer. Chemical shifts are expressed in parts per million (δ ppm) from tetramethylsilane as internal standard.

6.1. Preparation of 1,3-dioxans

The 1,3-dioxans were prepared by the Rondesved method(135) (compounds 2, 3, 4) or isolated from the dehydration of 1-3 diols in the presence of

H_2SO_4(136) (compounds 5, 7, 8, 10, 11, 12). A typical experimental procedure is as follows: A mixture of 0.025 mole of 1,3-diol and 0.05 mole of aldehyde or ketone, with 0.1 g of p-toluenesulfonic acid and 50 ml of benzene, were refluxed 5 hrs using an azeotropic head to remove water as it was formed. During this time, 0.9 ml of water was collected. The benzene was removed by distillation and the 1,3-dioxan collected. Dioxans were purified by reflux over Na metal and then distilled. The purity was ascertained to be 99% by gas chromatography (Varian Aerograph 1520 B, polymethyl siloxane column SE 30).

Some diols were commercially available compounds (2,2-dimethyl, 2-methyl-2-propyl, 2-methyl, 2-ethyl, 2,2-diethyl-1-3 diols). Gemdihydroxymethylcycloalkanes were prepared following the method of Cason and Allen(137). 5-Methyl-5-allyl-1,3-diol, 5,5-diallyl-1,3-diol and 5,5-dipropargyl-1,3-diol (mp 82°C) were prepared by classical malonic ester synthesis.

6.2. Preparation of tetrahydrofurans, dihydrofuranones and succinic anhydrides

Tetrahydrofuran (THF), 28, 2-methyl THF, 29, 3-methyl THF, 30, 2,5-dimethyl THF, 35, 2,2,4,4-tetramethyl THF, 42, dihydro-2-furanone, 57, 3-methyl-dihydro-2-furanone, 58, 5-methyl-dihydro-2-furanone, 60, and succinic anhydride, 76, were commercial compounds (Aldrich Chemical Company).

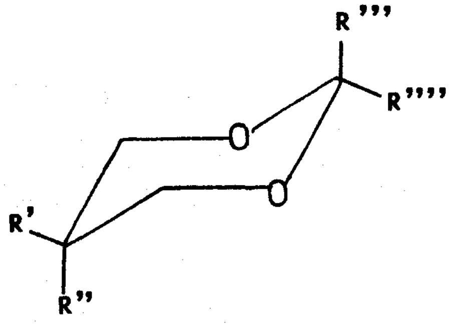
2,5-dimethyl THF (cis 35a and trans 35b)

The commercially available mixture was separated using a spinning band column. The cis configuration has been assigned(101,138) to the isomeric cyclic ether of lower boiling point, shorter gas-chromatographic retention time, and lower refractive index.

35a: b.p. 90-91°, n_D^{21} 1.4030; pmr, δ, 1.20 (d, 6H, J = 6Hz, $2CH_3$), 1.68 (m, 4H), 3.86 ppm (m, 2H, J = 6Hz).

35b: b.p. 93-94°; n_D^{21} 1.4050; pmr, δ, 1.12 (d, 6H, J = 6Hz, $2CH_3$), 1.72 (m, 4H), 4.0 ppm (m, 2H, J = 6Hz).

Table 16. Physical constants in some substituted 1,3-dioxans



No.	R'	R''	R'''	R''''	b.p., °C (mm)	n_D^{22}	i.r. (cm^{-1})
6	Me	Et	H	(Me,Et)CH	79-80°	1.4361	1035, 1117
6	Et	Me	H	(Me,Et)CH	(10)		
9	Me	Et	Et	iPr	98-100	1.4441	1110
9	Et	Me	Et	iPr	(15)		
11	Me	Pr	H	(Et,Pr)CH	142(35)	1.4440	1113
11	Pr	Me	H	(Et,Pr)CH	146(35)	1.4460	1113
13	ϕ	Me	H	Et		15110	1030, 1100, 1160
13	Me	ϕ	H	Et			
14	Me	CH_2OH	H	Et	130 (20)	1.4533	1040, 1100, 1165
15	Me	CH_2=CH-CH_2	H	Et	74-76	1.4449	1035, 1105, 1125, 1163, 1630
15	CH_2=CH-CH_2	Me	H	Et	(12)		
16	CH_2=CH-CH_2	CH_2=CH-CH_2	H	Et	100 (12)	1.4615	1030, 1125, 1162
17	CH≡C-CH_2	CH≡C-CH_2	H	Et	118 (13)	1.4740	1087, 1150, 3027

Table 16 (cont'd.)

No.	R'+ R''	R'''	R''''	b.p.,°C	n_D^{22}	i.r. (cm^{-1})
18	$(CH_2)_2$	H	Et	60 (15)	1.4450	1018, 1100, 1115
19	$(CH_2)_3$	H	Et	86 (32)	1.4487	1025, 1087, 1163
20	$(CH_2)_4$	H	Et	88 (13)	1.4563	1025, 1087, 1163
21	$(CH_2)_5$	H	Et	102 (12)	1.4645	1028, 1100, 1160

cis-3,4-Dimethyl THF (36a)

To a solution of 2,3-dimethylmaleic anhydride in 80 ml ethanol was added 0.5 g of Pd/C and the whole hydrogenated during 12 hrs. After filtration and evaporation of the solvent, 6.5 g of 2,3-dimethylmonoethyl succinate was obtained. Without any further purification this compound was added to a solution of diazomethane in ether to give 2,3-dimethyl methyl ethyl succinate. Reduction with $LiAlH_4$ in ether gave 4 g of 2,3-dimethyl butane diol-1,4; pmr δ 0.8 (d, 6H, J = 6Hz, $2CH_3$), 1.5-1.95 (m, 2H), 3.5 (br, 4H), 5.33 ppm (br, 2H). The diol, 4 g, and 60 ml of DMSO were heated for 17 hrs at 170°(139) and the THF was collected immediately by distillation as it was formed; yield 2 g (60% of 36a); b.p. 106°(112); pmr, δ, 0.95 (d, 6H, J = 6Hz, $2CH_3$), 2.2 (m, 2H), 3.36 (m, 2H), 3.9 ppm (m, 2H).

3,4-Dimethyl THF (mixture of cis and trans isomers, 36a, 36b)

Five grams of 2,3-dimethylsuccinic acid (mixture of dl and meso) were added to a solution of diazomethane in ether to give 2,3-dimethyl methylsuccinate (6 g); pmr, δ, 1.1 (d, 6H, J = 6Hz, $2CH_3$), 2.55, 2.95 (m, 2H), 3.6 ppm (s, 6H, $2CH_3$). To 6 g of 2,3-dimethyl methylsuccinate in ether were added 2 g of $LiAlH_4$. Work up afforded 2,3-dimethyl-1,4-butanediol (4 g); pmr, δ, 0.8 (d, 6H, J = 6Hz, $2CH_3$), 1.0 (d, 6H, J = 6Hz, $2CH_3$), 1.5-2.2 (m, 4H), 3.5-3.7 (m, 8H), 4.85 ppm (s, 4H). A solution of 4 g of the above diol was refluxed with 60 ml of DMSO at 170° during 17 hrs. The mixture of cis and trans 3,4-dimethyl THF was collected immediately it was formed by distillation giving 3.0 ml: b.p., 105-109°; pmr, δ, 1.0 (d, 6H, J = 6Hz, $2CH_3$), 1.65 (m, 2H), 3.2 (m, 2H), 3.85 ppm (m, 2H); lit.(140) 36b, b.p.$_{760}$ 108.4-108.8°; n_D^{20} 1.4183.

2,3-Dimethyl THF (mixture of cis and trans isomers, 33a, 33b)

A mixture of 26 g of methylacetoacetate (0.22 mole) and 13 ml of MeI (0.21 mole) were added dropwise to 10 g of NaH in 200 ml of dioxan at 0°C. The mixture was then refluxed for one hour and after cooling, poured onto ice, acidified with dilute HCl and extracted with ether for 3 days on a continuous extraction apparatus. After evaporation of the solvent, 19 g of methyl-α-methylacetoacetate was obtained by distillation; b.p.$_{10}$ 89-90°, pmr, δ, 1.25 (d, 3H, CH_3), 2.2 (s, 3H, CH_3), 3.5-3.7 (q, 1H), 3.75 ppm (s, 3H, CH_3).

A mixture of 19 g of the above compound (0.146 mole) and 25 g of ethylbromoacetate was added dropwise to a refluxing suspension of 8 g of NaH in 200 ml of dioxane. The mixture was then refluxed for 12 hours. After cooling, the mixture was poured into ice, acidified, extracted with ether and hydrolyzed by heating for 8 hrs with 5 volumes of dilute HCl (1:2). The solution obtained was then evaporated to dryness. The dry residue was extracted with ether and yielded 5 g of 3-methyllevulinic acid, 81, b.p.$_4$ 119.5°. Reduction with $LiAlH_4$ in ether gave 4 g of 3,5-dimethyl-1,4-pentanediol. The diol was dehydrated with p-toluenesulfonic acid in benzene to yield 2 ml of 2,3-dimethyltetrahydrofuran (mixture of cis and trans isomers); b.p.$_{756}$ 93-94°, n_D^{20} 1.4160; pmr, δ, 33a, 0.89 (d, 3H, J = 6.8 Hz, CH_3), 1.07 (d, 3H, J = 6.8 Hz, CH_3), 1.35-2.3 (m, 3H), 4-4.5 (m,3H); 33b, 0.99 (d,3H, J = 6Hz, CH_3), 1.18 (d,3H, J = 6Hz, CH_3), 1.3-2.4 (m,3H), 3.25-3.55 ppm (m,3H); mass spectrum (80 eV), m/e 100 (M^+ calcd. for $C_6H_{12}O$: 100.0888; found: 100.0889); ν_{max} 109 cm^{-1}

2,4-Dimethyl THF (mixture of cis and trans isomers, 34a, 34b)

Methylacetoacetate, 23.2 g (0.2 mole) and ethyl-α-bromopropionate, 38.0 g (0.21 mole) were added dropwise to a refluxing suspension of NaH, 10 g

(0.21 mole) in dioxane (200 ml). The mixture was refluxed 12 hrs, cooled, poured onto ice, acidified with dilute HCl and extracted with ether for 3 days. The product obtained was hydrolyzed by heating for 9 hours with 5 volumes of dilute HCl (1:2). The solution obtained was then evaporated to dryness and α-methyllevulinic acid, <u>82</u>, is extracted with ether and distilled giving 10 g of the mixed acids; b.p.$_3$, 120°C. Eight g of α-methyllevulinic acid was reduced with $LiAlH_4$ in dry THF to give 6 g of 2-methyl pentanediol 1-4 which was dehydrated without any further purification in a Dean Stark apparatus with p-toluenesulfonic acid in benzene. After removal of excess of benzene with a spinning band column, 2.0 g of 2,4-dimethyl THF, <u>34a</u> and <u>34b</u>, was obtained; b.p.$_{750}$ 97.8°; n_D^{24} 1.4110; δ, <u>34a</u>, 1.0 (d, 3H, J = 6.8 Hz, CH_3), 1.18 (d, 3H, J = 6.8 Hz, CH_3), 1.60 (t, 2H, J = 6.8 Hz, H_3, $H_{3'}$), 1.83 (m, 1H, H_4), 3.22 (q, 1H, H_5), 3.65-4.2 (m, 2H, $1H_2$, $1H_5$); <u>34b</u>, 1.03 (d, 3H, J = 6.2 Hz, CH_3), 1.23 (d, 3H, J = 6.2 Hz, CH_3), 2-2.5 (m, 2H), 3.36 (q, 1H, H_5), 3.65-4.2 ppm, (m, 2H, $1H_2$, $1H_5$); lit.(141,112).

Alternative preparation of 2,4-Dimethyl THF (34a, 34b)

The method of Mihailovic *et al.*(142) was used. Bromine (0.1 mole) was added to a stirred suspension of 0.05 mole of 4-methyl penta-2-ol, 0.105 mole of silver carbonate in 150 ml of pentane at room temperature. The reaction is carried out in dark, with a red light as the only illumination, with an average reaction time of 0.5 hr. The resulting mixture was filtered and the filtrate was washed successively with aqueous $Na_2S_2O_3$, $NaHCO_3$ and H_2O. After drying, the reaction products were distilled. The 2,4-dimethyl THF obtained by this method was mixed with another compound of very close boiling point(143).

2,2-Dimethyl THF (31)

γ-Butyrolactone (dihydro-2-furanone 57) 5 g (0.058 mole) was added dropwise to an ethereal solution of MeMgI (2.1 moles for 1 mole of γ-butyrolactone) in dry ether. The reaction mixture was refluxed for 3 hrs, then cooled and hydrolyzed with NH_4Cl. The ether layer was dried on anhydrous magnesium sulfate after neutralization with potassium carbonate. The ether was removed in vacuo and the diol used without any further purification. Dehydration was effected in benzene with p-toluenesulfonic acid. After removal of the benzene on a spinning band column, the THF was distilled; b.p.$_{760}$ 92.5°, n_D^{20} 1.4075; pmr, δ, 1.13 (s, 6H, $2CH_3$), 1.5-2.1 (m, 4H,), 3.6 - 4.0 ppm (m, 2H, $H_{5,5'}$).

2,2-Diethyl THF (51)

The same procedure as used above for the 2,2-dimethyl THF was used here with an ethereal solution of EtMgBr (1.22 moles) and γ-butyrolactone (5 g, 0.058 mole). Normal work up gave 6 g (80%) of 51: b.p. 144-145°, n_D^{20} 1.4317; pmr, δ, 0.86 (t, 6H, J = 7.8 Hz, $2CH_3$), 1.4-1.7 (m, 6H, $2CH_2$(Et), H_3, $H_{3'}$), 1.56 (m, 2H, H_4, $H_{4'}$), 3.80 ppm (t, 2H, J = 6.2 Hz, H_5, $H_{5'}$).

3,3-Dimethyl THF (32)

The procedure of Bates et al.(144) was used. A sample of 5 g of 3,3-dimethylsuccinic acid (Aldrich Chemical Company) was placed in a soxhlet cup and the soxhlet extractor mounted above a three-necked flask containing 2 g of $LiAlH_4$ in 150 ml of ether. The ether was heated at reflux until all the diacid had dissolved. The reaction flask was then cooled to 0° and successively, 2 ml of H_2O, 2 ml of NaOH (15%) and 6 ml of H_2O were added slowly with stirring. The ether solution was decanted and then used to extract the solid residue for 24 hr in a soxhlet apparatus. The solvent was removed by distillation at atmospheric pressure. The diol was then dehydrated by heating for 16 hrs with DMSO (45 ml) at 160°. The material boiling below 110° was distilled out, dried and redistilled to give 2.5 g of 3,3-dimethyl THF; b.p.$_{756}$ 97°, pmr, δ, 1.1 (s, 6H, $2CH_3$), 1.65 (t, 2H, J = 7.2 Hz, H_4, $H_{4'}$), 3.4 (s, 2H, H_2, $H_{2'}$), 3.8 ppm (t, 2H, J = 7.2 Hz, H_5, $H_{5'}$); lit.$^{(110)}$.

2,2,3-Trimethyl THF (37)

To an ethereal solution of MeMgI (0.1 mole) in ether was added dropwise 5 g (0.05 mole) of 3-methyl dihydrofuranone, 58 (Aldrich Chemical Company). The diol (b.p.$_{10}$ 79°) obtained was dehydrated with p-toluenesulfonic acid in benzene to yield 3 g (0.026 mole) of 37; b.p.$_{756}$ 108°; $n_D^{19.5}$ 1.4180; pmr, δ, 0.88 (d, 3H, J = 6H), 0.98 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.4-2.2 (m, 3H, H_3, H_4, $H_{4'}$), 3.6-3.9 (m, 2H, H_5, $H_{5'}$); mass spectrum (80 eV), m/e, 99 (M^+-CH_3; calcd. for $C_6H_{11}O$: 99.0809; found: 99.0813); lit. (145).

2,2-Diethyl-3-methyl THF (51)

This diethyl derivative was prepared analogously to the Trimethyl THF 37 above using 5 g (0.05 mole) of 3-methyldihydrofuranone, 58, with 0.1 mole of EtMgBr in ether. A yield of 4 g (0.028 mole) of 51 was obtained; b.p.$_{756}$ 149°; n_D^{20} 1.4380; ν_{max} 1050 cm^{-1}; pmr, δ 0.75-0.95(t, 6H, $2CH_3$), 0.97 (d, 3H, J = 6.6 Hz, CH_3), 1.2-2.3 (m, 5H), 1.87-2.2 (m, 2H), 3.55-3.9 ppm (m, 2H, H_5, $H_{5'}$); mass spectrum (80 eV), m/e, 113 (M^+-C_2H_5; calcd. for $C_7H_{13}O$: 113.0966; found: 113.09711).

2,2,4-Trimethyl THF (38)

To a solution of 5 g of citraconic anhydride in 50 ml of ethyl acetate was added 0.5 g of 5% Pd/C and the whole hydrogenated in Parr apparatus at 3 atm. and room temperature. At the end of 24 hrs, the consumption of hydrogen had ceased and methylsuccinic anhydride, 77, was obtained after evaporation of the solvent; b.p.$_9$ 114°; pmr, δ, 1.44 (d, 3H, J = 6.8 Hz, CH_3), 2.45-3.65 ppm (m, 3H).

The method of Bloomfield and Lee$^{(146)}$ was used: A 500 ml 3-necked round-bottom flask was fitted with a reflux condenser, a Hersberg addition funnel and a stirrer with an inlet for maintaining a slight positive pressure of dry, oxygen-free nitrogen. To 200 ml of THF, which was freshly distilled from $LiAlH_4$, was added 2.2 g of $LiAlH_4$ and the mixture stirred under reflux for 30 min. The condenser was removed and replaced by a low temperature thermometer and the mixture was cooled with stirring to -55° (dry ice and acetone bath). Then 0.1 mole of the above anhydride, dissolved in 150 ml of THF, was added at a rate to maintain the temperature at -55±5° (usually 30 min.). When the anhydride had all been added the solution was allowed to warm to 0° over 90 min, stirred at 0° for 10-20 min (ice bath), then cooled to -15° (dry ice and acetone bath) and 40 ml of 6N HCl was added over 5-15 min. After the cold bath had been removed, stirring was continued for 20 min. At this point the mixture was allowed to stand several hours and then the layers were separated and the aqueous layer extracted with ether and dried with Na_2SO_4. The solvent was evaporated and the residue distilled to give a mixture, 6 g (60%), of 3- and 4-methyl dihydrofuranones (58 and 59) in the ratio 1:2.2; b.p.$_{23}$ 95-98°; pmr, δ, 58, 1.2 (d, 3H, J = 6.5 Hz, CH_3), 1.45-2.0 (m, 1H), 2.0-2.85 (m, 2H), 4.0-4.45 (m, 2H, H_5, $H_{5'}$); 59, 1.15 (d, 3H, J = 6.5 Hz, CH_3), 2.22 (2 d, 1H, J = 9.5 Hz, H_3), 2.2-3.0 (m, 2H, H_3, H_4), 3.9 (2 d, 1H, J = 6 Hz, H_5), 4.1-4.5 ppm (m, 1H, $H_{5'}$). The mixture of 6 g of 3- and 4-dihydro-2-furanones was added slowly to a solution of MeMgI (0.15 mole) in ether. After normal work up, the diols were dehydrated with p-toluenesulfonic acid in benzene to yield 3 g (25%) of the mixture of 37 and 38; b.p.$_{756}$ 112-115°; pmr, δ, 38, 0.97 (d, 3H, J = 6Hz, CH_3), 1.15 (s, 3H), 1.19 (s, 3H), 1.6-2.2 (m, 2H), 2.1-2.6 (m, 1H), 3.25 (t, 1H, J = 7.9 Hz, H_5), 3.9 ppm (m, 1H, $H_{5'}$); lit. (147, 112).

2,2,5-Trimethyl THF (39)

A sample of 5 g of 5-methyl-dihydro-2-furanone, 60 (0.05 mole) was added dropwise to a solution of MeMgI (0.125 mole) in ether. The 2-methyl-2,5-hexanediol obtained was dehydrated with p-toluenesulfonic acid in benzene and gave 2 g of 2,2,5-trimethyl THF; b.p. 102-103°; n_D^{25} 1.4019; pmr, δ, 1.18 (d, 3H, J = 6Hz, CH_3), 1.27 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.65 (m, 2H), 2.0 (m. 1H), 4.0 ppm (m, 1H).

2,2-Diethyl-5-methyl THF (53)

Analogously to the above, 5 g of valerolactone (0.05 mole) were added dropwise to a solution of EtMgBr (0.12 mole) in ether. 4 g of 2,2-diethyl-5-methyl THF, 53, was obtained; b.p.$_{755}$ 142°; n_D^{20} 1.4275; ν_{max} 1080 cm^{-1}; pmr, δ, 0.87 (t, 6H, J = 7Hz, $2CH_3$), 1.20 (d, 3H, J = 6Hz, CH_3), 1.30-2.0 (m, 8H), 4.01 ppm (m, 1H); mass spectrum (80 eV), m/e 142 (M^+ calcd. for $C_9H_{18}O$: 142.1357; found: 142.1350).

2,2,3,3-Tetramethyl THF (40)

The method of Baas et al.(149) was used. A mixture of 8.6 g (0.1 mole) of dihydro-2-furanone and 40.0 g (0.28 mole) of MeI was added in 1.5 hr with stirring to a refluxing suspension of 12.0 g (0.25 mole) NaH (in oil) in 100 ml dioxane. After one hour more boiling, the mixture was poured into ice, acidified with dilute HCl, and extracted with ether for 3 days. After evaporation of the solvent, the 3,3-dimethyldihydro-2-furanone, 61, was distilled giving 8 g (70%); b.p.$_{12}$ 79°; n_D^{20} 1.4330; pmr, δ, 1.18 (s, 6H), 2.12 (t, 2H, J = 6.8 Hz, H_4, $H_{4'}$), 4.24 ppm (t, 2H, J = 6.8 Hz, H_5, $H_{5'}$), ν_{max} 1760 cm^{-1} (C=O), 1100 cm^{-1} (C-O-C); lit. (149).

The above product (8 g) was added to a solution of MeMgI (0.15 mole) in ether. The diol obtained was dehydrated with p-toluenesulfonic acid in benzene, yielding 4 g of <u>40</u>; b.p.$_{758}$ 132°; m.p. 25-27°; n_D^{20} 1.4160; pmr, δ, 0.96 (s, 6H, $2CH_3$), 1.07 (s, 6H, $2CH_3$), 1.79 (t, 2H, J = 7.3 Hz, H_4, $H_{4'}$), 3.77 ppm (t, 2H, J = 7.3 Hz, H_5, $H_{5'}$); ν_{max} 1160 cm^{-1}, 1040 cm^{-1} (C-O-C); mass spectrum (80 eV), m/e, 128 (M^+-CH_3, calcd. for $C_7H_{13}O$: 113.0966; found: 113.0960); lit. (148).

<u>2,2,5,5-Tetramethyl THF (42)</u>

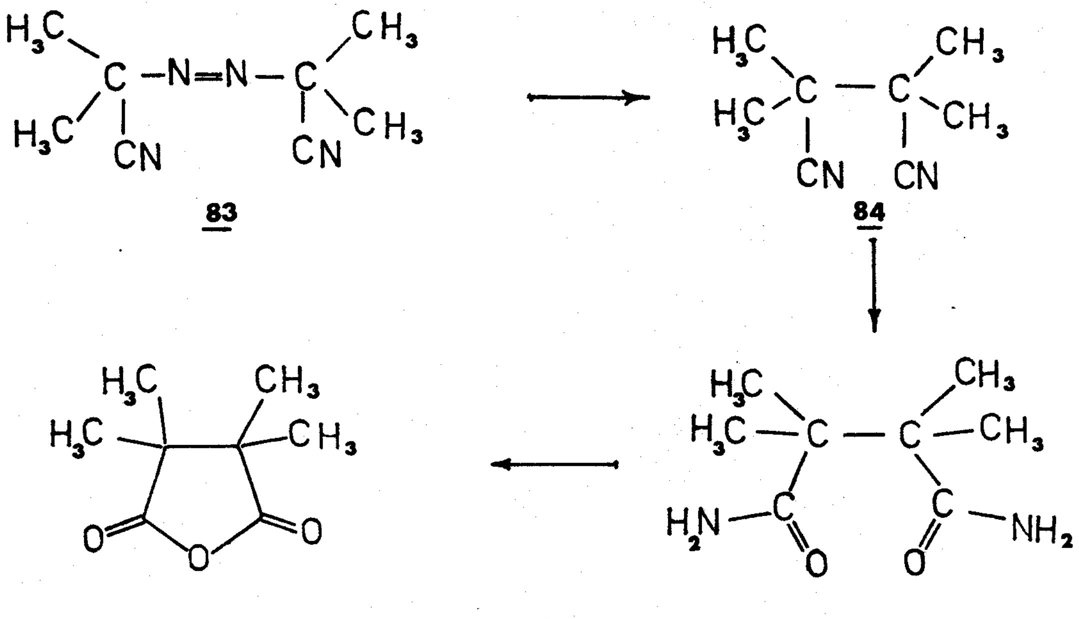
A sample of 7.2 g (0.05 mole) of ethyl levulinate was added dropwise to a solution of MeMgI (3 moles for 1 mole) in ether. The diol formed was dehydrated by refluxing 16 hrs at 166° in DMSO and the material boiling below 130° was distilled out, dried and redistilled, yielding 2.5 g (45%), <u>42</u>; b.p.$_{758}$ 115-117°; n_D^{20} 1.4014; pmr, δ, 1.15 (s, 12H), 1.82 (s, 4H); lit. (150).

<u>2,2,5-Triethyl-5-methyl THF (55)</u>

An analogous reaction to the above was carried out with 7.2 g of ethyllevulinate and EtMgBr (0.2 mole) in ether. The diol (8.5 g, 90%, b.p. 179°) was dehydrated with p-toluenesulfonic acid in benzene, yielding 5 g of <u>55</u>; b.p.$_6$ 60°; n_D^{20} 1.4450; ν_{max} 1120 cm^{-1}; mass spectrum 80 eV, m/e, 141 (M^+-C_2H_5; calcd. for $C_9H_{17}O$: 141.1279; found: 141.1277; pmr, δ, 0.75-1.12 (m, 9H, $3CH_3$), 1.14 (s, 3H, CH_3), 1.27-1.33 (m, 6H, $2CH_2$, H_3, $H_{3'}$), 1.33-1.35 (m, 2H, CH_2), 1.42 ppm (m, 2H, H_4, $H_{4'}$).

<u>3,3,4,4-Tetramethyl THF (43)</u>

The following reaction intermediates were used in the preparation of <u>43</u>.



83 84 80 85

The azo-compound, 83 (pmr, δ, 1.75 ppm (s)), 10 g (0.06 mole) was dissolved in 50 ml of toluene and the solution heated in such a manner as to produce a regular evolution of nitrogen. When the main reaction was finished (2 hrs) the solution was refluxed for 2 more hrs and then subjected to fractional distillation. The fraction, b.p. 215-235°, was recrystallized from ethanol and yielded 7 g (80%) of pure tetramethylsuccinonitrile, 84, m.p. 167°, pmr, δ, 1.62 ppm (s). A sample of 7 g of 84 was mixed with a solution of 28 g NaOH in 30 ml of EtOH and 140 ml of H_2O, and the whole was refluxed 24 hrs. After acidification, the solution was extracted with ether and yielded 7 g of tetramethylsuccinamide, 80, pmr, δ, 1.18 (s, 12H), 3.5-3.9 ppm (m, 4H). A sample of 7 g of 80 was refluxed with 70 ml of 60% H_2SO_4 for 3 hrs in order to convert the succinamide into the succinic anhydride 85. After extraction with ether, a yield of 6 g of 85 was obtained, m.p. 152°; pmr, δ, 1.2 ppm (s);

lit. (151). A solution of 6 g of 87 in 200 ml of THF was added to a stirred solution of 3 g of $LiAlH_4$ in 200 ml of THF. After 16 hr at reflux, 3 ml of water, 3 ml of 15% NaOH and 9 ml of water, were added dropwise. The liquid was decanted and the solids were rinsed with ether. Evaporation gave 3 g of crude 2,2,3,3-tetramethylbutanediol-1,4; pmr, δ, 1.09 (s, 12H), 3.24 (s, 4H), 8.2 ppm (b.s, 2H); lit. (144, 112). The cyclodehydration of the above diol was carried out by heating in the presence of p-toluenesulfonic acid (1 g) under 16 mm pressure; the receiving flask was cooled in liquid nitrogen. The 3,3,4,4-tetramethyl THF was obtained as a colourless solid, m.p. 110°; pmr, δ, 0.9 (s, 12H), 3.5 ppm (s, 4H); lit. (144, 112).

2,2,3,5,5-Pentamethyl THF (44)

Methylsuccinic acid (6 g) (0.045 mole) was added to a solution of diazomethane in ether and after evaporation of the ether afforded methyl-α-methyl succinate. The diester was added dropwise to a solution of MeMgI in dry ether (0.25 mole). After classical work up the diol obtained was dehydrated with p-toluenesulfonic acid in benzene to yield 1 g (20%) of 44; b.p. 135°; n_D^{21} 1.4185; ν_{max} 998, 1155 cm^{-1} (C-O-C); pmr, δ, 0.915 (d, 3H, J = 6.8 Hz, CH_3), 0.98 (s, 3H), 1.165 (s, 3H), 1.20 (s, 3H), 1.25 (s, 3H), 1.755 (m, 2H), 2.075 ppm (m, 1H); mass spectrum (80 eV), m/e, 127 (M^+-15, calcd. for $C_8H_{15}O$: 127.1123; found: 127.1112).

2,2,3,3,5,5-Hexamethyl THF (57)

The same procedure as recorded above was used with 6 g of 2,2-dimethylsuccinic acid to yield 3 g (76%) of 57, b.p.$_{756}$ 139°; n_D^{20} 1.4296; pmr, δ, 1.0 (s, 6H), 1.12 (s, 2H), 1.28 (s, 6H), 1.83 ppm (s, 2H) ν_{max} 985, 1105, 1170 cm^{-1}; mass spectrum (80 eV), m/e, 156 (M^+, calcd. for $C_{10}H_{20}O$: 156.1514; found: 156.1511).

2,2,3,3,4-Pentamethyl THF (46)

The method of Baas *et al.*(149) was used. An analogous reaction to the above 40 was carried out with 5 g of the mixture of 3- and 4-methyl dihydrofuranones, 58 and 59, 0.14 mole of MeI and 6.0 g (0.125 mole) NaH in 100 ml dioxane, yielding 5 g (78%) of the mixture of 3,3-dimethyldihydro-2-furanone, 61, and 3,3,4-trimethyldihydro-2-furanone, 67, b.p.$_8$ 68-72°; pmr, δ, 67, 1.0 (d, 3H, J = 6Hz, CH_3), 1.03 (s, 3H), 1.15 (s, 3H), 1.9-2.6 (m, 1H, H_4), 3.85 (t, 1H, J = 9Hz), 4.25-4.55 ppm (m, 1H); lit. (152).

A solution of 5 g of 61 and 67 was added to a stirred suspension of MeMgI (0.1 mole) in ether and yielded 4.5 g (70%) of the mixture of 2,3,3,4-tetramethylpentanediol-1,4- and 3,3,4-trimethylpentanediol-1,4. The above diols were dehydrated with p-toluenesulfonic acid in benzene, yielding 2 g of 40 and 46, b.p.$_{100}$ 80°; $n_D^{22.5}$ 1.4331; pmr, δ 46, 0.74 (s, 3H), 0.82 (s, 3H), 0.82 (d, 3H, J = 6.8Hz), 1.05 (s, 3H), 1.09 (s, 3H), 2.24 (m, 1H), 3.34 (2d, 1H, J = 8Hz), 3.93 ppm (t, 1H, J = 8.5 Hz); mass spectrum (80 eV), m/e, 142 (M^+, calcd. for $C_9H_{18}O$: 142.1357, found: 141.1394).

2,2,3,3,5-Pentamethyl THF (45)

The method of Baas *et al.*(149) was used. An analogous reaction to the above, 46 and 40, was carried out with 5 g of 5-methyldihydro-2-furanone, 60, 0.14 mole of MeI and 6.0 g (0.125 mole) NaH in 100 ml dioxane, yielding 2 g (32%) of 3,3,5-trimethyldihydro-2-furanone, 69, b.p.$_{18}$ 89-91°C, m.p. 43°; pmr, δ, 1.27 (s, 3H), 1.4 (d, 3H, J = 6Hz), 1.45-2.5 (m, 2H), 4.68 ppm (m, 1H); lit. (153). A solution of 2 g of the above 69 was added to a stirred suspension of MeMgI (0.03 mole) in ether and yielded 1 g of 2,2,3,3,5-pentamethyl THF, 45, b.p.$_{136}$ 90°; n_D^{24} 1.4255; pmr, δ, 0.98 (s, 6H, $2CH_3$), 1.10 (s, 3H), 1.11 (s, 3H), 1.22 (d, 3H, J = 6Hz), 1.71 (oct, 2H, J = 7Hz), 4.11 (m, 1H);

mass spectrum (80 eV), m/e, 142 (M^+, calcd. for $C_9H_{18}O$: 142.1357; found: 142.1391).

2,2,3,3,4,4-Hexamethyl THF (48)

A solution of 12 g of 2,2-dimethylsuccinic acid (0.082 mole) in 77 ml of acetic anhydride were refluxed 4 hr. After distillation 10 g (95%) of 2,2-dimethylsuccinic anhydride 78 were obtained; b.p.$_{10}$ 101°, b.p.$_{23}$ 123°; pmr, δ,1.45 (s, 6H), 2.95 (s, 2H). The succinic anhydride was reduced with 2 g of $LiAlH_4$ at -55° according to the procedure of Bloomfield and Lee(146) and gave, after work up, only 4,4-dimethyldihydro-2-furanone, 62 (6 g), b.p.$_{10}$ 80°; pmr, δ,1.16 (s, 6H), 2.32 (s, 2H), 3.98 ppm (s, 2H); n_D^{20} 1.4400; ν_{max} 1770 cm^{-1} (C=O), 1020, 1165 cm^{-1} (C-O-C).

The 3,3,4,4-tetramethyldihydro-2-furanone, 70, 4 g (53%) is obtained according to the procedure of Baas *et al.*(149). M.p. 44°, pmr, δ 1.08 (s, 6H), 1.12 (s, 6H), 4.0 (s, 2H); lit. (154). A solution of 4 g of the above 70 was added to a stirred suspension of MeMgI (0.07 mole) in ether and yielded 4.5 g (90%) of 2,2,3,3,4-pentamethylpentanediol-1,4. The diol was dehydrated with p-toluenesulfonic acid in benzene, yielding 2 g of 2,2,3,3,4,4-hexamethyl THF, 48, b.p.$_6$ 55°; n_D^{23} 1.4452; pmr, δ,0.88 (s, 6H), 0.99 (s, 6H), 1.18 (s, 6H), 3.52 (s, 2H); mass spectrum (80 eV), m/e, 141 (M^+-15, calcd. for $C_9H_{17}O$: 141.1279; found: 141.1354); ν_{max} 1065 cm^{-1}.

2-Ethyl THF (49)

To a suspension of finely divided, freshly prepared silver oxide (0.105 mole) and hexanol (0.05 mole) in pentane (150 ml) was added bromine (0.1 mole) over a period of 3 hr and stirring was continued for another 1.5 hr. The resulting mixture was filtered, and the filtrate was washed successively with aqueous $Na_2S_2O_3$, $NaHCO_3$ and water. After drying, the reaction products were separated by fractional distillation through a spinning band column to yield 1.5 g (30%) of 49, b.p. 107°; n_D^{20} 1.4169; pmr, δ, 0.9 (t, 3H), 1.25-2.15 (m, 6H), 3.3-4.3 ppm (m, 3H); lit. (142).

2,2-Diethyl-4,4-dimethyl THF (54)

A solution of 4,4-dimethyldihydro-2-furanone, 62 (2 g) was added to a solution of 0.05 mole of EtMgBr in dry ether and the diol formed dehydrated with p-toluenesulfonic acid in benzene to give 1.5 g (55%) of 54, b.p.$_{756}$ 162°, n_D^{21} 1.4302; ν_{max} 1060 cm^{-1}; mass spectrum (80 eV), m/e, 127 ($M^+-C_2H_5$, calcd. for $C_8H_{15}O$: 127.1123; found: 127.1119); pmr, δ, 0.84 (t, 6H, J = 7.5Hz, $2CH_3$), 1.09 (s, 6H, $2CH_3$), 1.52 (s, 2H), 1.4-1.6 (m, 4H), 3.46 ppm (s, 2H).

2-Methyl-2-Ethyl THF (50)

2-Acetylbytyrolactone, 8 g (0.062 mole), was added dropwise over 3 hr to a refluxing solution of HBr, 20 ml (48%), and 9 ml of H_2O in a flask surmounted by a Dean-Stark trap. The product was collected in the trap during the course of the reaction. The oily layer of the distillate was washed with H_2O, filtered through $MgSO_4$, and distilled, giving 4 g (39%) of 5-bromopentan-2-one, b.p.$_7$ 66°, lit. (156). The above bromo-ketone was added to a cooled solution of Et and stirred for one hour. After hydrolysis with NH_4Cl, the ether layer was evaporated and the compound distilled to give 2 g (72%) of 50, b.p. 119°; pmr, δ, 0.93 (t, 3H, J = 6Hz, CH_3), 1.13 (s, 3H), 1.4-2.1 (m, 6H), 3.6-3.95 ppm (m, 2H); lit. (157).

3,4-Dichloro THF (56)

A solution of 10 g of dihydrofuran in 15 ml of ether was cooled in a dry ice-acetone bath and stirred vigorously whilst chlorine and dry nitrogen were passed into the reaction vessel during 45 min. Removal of the solvent and distillation gave 5 g of trans-3,4-dichloro THF, 56, b.p.$_{20}$ 46°, b.p.$_{756}$ 155-156°; n_D^{20} 1.4380; ν_{max}, 1075, 1218 cm^{-1}; pmr, δ, 4.0 (q, 2H, J = 3.8 Hz), 4.4 (q, 2H, J = 3.8Hz), 4.45 ppm (s,2H); mass spectrum (80 eV), m/e, 141 (M^+, calcd. for $C_4H_6Cl_2O$: 141.9766; found: 141.9780); lit. (90, 158).

5,5-Dimethyl-dihydro-2-furanone (63)

The method of Bayer has been used$^{(159)}$. A solution of levulinic acid (10 g, 0.0865 mole) in 80 ml of absolute ether was added to 0.1 mole of MeMgI in ether over 1 hr, the solution stirred 2 hrs, 50 ml of H_2O were added with cooling followed by 10 ml of acetic acid in 50 ml of H_2O and the water layer extracted with ether to yield 2 g of 5,5-methyldihydro-2-furanone 63, b.p.$_{20}$ 95°; pmr, δ, 1.37 (s, 6H), 1.9-2.2 (m, 2H), 2.4-2.75 ppm (m, 2H); n_D^{24} 1.4306

3,4-Dimethyldihydro-2-furanone (mixture of cis and trans isomers 64a and 64b)

A solution of 5 g of 2,3-dimethylsuccinic acid (mixture of dl and meso) in 35 ml of acetic anhydride were refluxed 4 hrs. After distillation 4.0 g (90%) of 2,3-dimethyl succinic anhydrides 79a and 79b were obtained, m.p. 66°; pmr, δ, 79a, 1.4 (d, 6H), 3.25 (m, 2H); 79b , 1.45 (d, 6H, J = 6 Hz, 2CH_3), 2.75 ppm (m, 2H); lit. (130). The method of Bloomfield and Lee$^{(146)}$ was used. The anhydrides 79a and 79b (4.5 g) were reduced with $LiAlH_4$ (1.3 g) in 100 ml of THF, yielding 2 g (55%) of 3,4-dimethyldihydro-2-furanones (mixture of cis and trans isomers 64a and 64b), b.p.$_4$ 72-75°; n_D^{23} 1.4316; pmr, δ, 64a, 1.01 (d, 3H, J = 7Hz, CH_3), 1.21 (d, 3H, J = 7Hz, CH_3), 2.65 (m, 2H), 3.9 (m, 2H); 64b, 1.15 (d, 3H, J = 7Hz), 1.23 (d, 3H, J = 7Hz, CH_3), 2.15 (m, 2H), 3.72 (m, 1H), 4.33 ppm (m, 1H).

3,5-Dimethyldihydro-2-furanone (mixture of cis and trans isomers 65a and 65b)

To a solution of 2-methyllevulinic acid (2 g), 82, in 5 ml of ether was added 0.05 g of PtO_2 and the whole hydrogenated during 48 hrs(160). After filtration and evaporation of the solvent, 1.5 g (87%) of 3,5-dimethyl-2-furanones were obtained, b.p.$_{12}$ 77-83°; pmr, δ, 65a, 1.25 (d, 3H, J = 7.5 Hz, CH_3), 1.36 (d, 3H, J = 7.5 Hz,CH_3), 1.5-1.75 (m, 1H), 2.4-2.9 (m, 2H), 4.3-4.7 (m, 1H); 65b, 1.24 (d, 3H, J = 7.8 Hz, CH_3), 1.39 (d, 3H, J = 6.3 Hz, CH_3), 1.95-2.15 (m, 1H), 2.4-2.9 (m, 2H), 4.3-4.7 ppm (m,1H); lit. (161).

4,5-Dimethyl-2-furanone (mixture of cis and trans isomers 66a and 66b)

The same procedure as used above for the 3,5-dimethyldihydro-2-furanones 65a and 65b was used here with a solution of 1 g of 3-methyllevulinic acid, 81, in 3 ml of ether and 0.04 g of PtO_2 yielding 0.6 g of 4,5-dimethyl-2-furanones; pmr, δ, 65a, 0.97 (d, 3H, J = 6.5Hz, CH_3), 1.25 (d, 3H, J = 6.5 Hz, CH_3), 2-2.75 (m, 3H), 4.45-4.75 (m, 1H); 65b, 1.1 (d, 3H, J = 6Hz, CH_3), 1.35 (d, 3H, J = 6Hz, CH_3), 2-2.75 (m, 3H), 4-4.17 ppm (m,1H); lit. (116,162). b.p.$_{10}$ 85-92°(163); n_D^{20} 1.4287 (65a); b.p.$_5$ 86-86.5°; n_D^{20} 1.4333 (65b).

4,4,5,5-Tetramethyldihydro-2-furanone (72)

The method of Korotkov *et al.*(148) has been used. 2,2,3,3-tetramethyl THF 40 (1.9 g) was oxidized by an aqueous solution of MnO_4K (3.3 g) for 3 hrs. The oxidation was carried out in a 50 ml flask fitted with stirrer and reflux condenser. When the rate decreased markedly (after 2.5 hrs), 0.50 ml of H_2SO_4 was added to the reaction mixture. The reaction products were extracted by ether from the acidic solution, the recovered material, 2.0 g (95%), was dissolved in a small excess of hot 50% NaOH, the solution was boiled down, and the residue was dried and washed with ether. The lactone freed from salt by acidification was dissolved in ether, the solution was dried with anhydrous SO_4Na_2 and ether distilled out, m.p. 75°; pmr, δ, 1.1 (s, 6H), 1.33 (s, 6H), 2.4 ppm (s, 2H); lit. (164).

3,3,5,5-Tetramethyldihydro-2-furanone (71)

The same procedure as used above for the 4,4,5,5-tetramethyldihydro-2-furanone 72 was used here with 2 g of 2,2,4,4-tetramethyl THF 41 and 3.5 g of MnO$_4$K yielding 1.2 g of 68, m.p. 38°; pmr, δ, 1.38 (s, 6H), 1.52 (s, 3H), 2.16 ppm (s, 2H); lit. (164).

4,5,5-Trimethyldihydro-2-furanone (68)

An analogous reaction to the above was carried out with 14.5 g of 2,2,3-trimethyl THF 37, and 25.4 g of MnO$_4$K yielding 8 g (50%) of 4,5,5-trimethyldihydro-2-furanone 68, b.p.$_{12}$ 91°; pmr, δ, 1.09 (d, 3H, J = 6Hz, CH$_3$), 1.21 (s, 3H), 1.44 (s, 3H), 2.0-2.8 ppm (m,3H); lit. (159).

3,3,4,5,5-Pentamethyldihydro-2-furanone (73)

The method of Baas et al.(149) was used. A solution of 8 g of the above 68 and 13 ml of MeI were added to 10 g of NaH in 200 ml of dioxane, yielding 4 g of 3,3,4,5,5-pentamethyldihydro-2-furanone 73, m.p. 46°; pmr, δ, 0.98 (d, 3H, J = 7.4Hz), 1.15 (s, 3H), 1.21 (s, 3H), 1.30 (s, 3H), 1.41 (s,3H), 2.07 ppm (q, 1H, J = 7.4 Hz); lit. (165), m.p. 55-56°; ν_{max} 1.775 cm^{-1} (C=O); pmr, δ 0.94 (d, 3H, J = 7.5 Hz), 1.03 (s, 3H), 1.01 (s, 3H), 1.22 (s, 3H), 1.33 (s, 3H), 2.00 ppm (q, 1H, J = 7.5 Hz); m/e 156.

3,4,4,5,5-Pentamethyldihydro-2-furanone (74)

The method of Korotkov et al.(148) has been used. 2,2,3,3,4-pentamethyl THF 46 (4 g) was oxidized by an aqueous solution of MnO$_4$K (6.2 g) for 3 hrs, yielding 0.5 g of 74, m.p. 62°; pmr, δ 0.96 (d, 3H, J = 6 Hz, CH$_3$), 1.06 (s, 3H), 1.1 (s, 3H), 1.33 (s, 6H, 2CH$_3$), 2.70 ppm (q, 1H, J = 6Hz); lit. (166), m.p. 65°.

3,3,4,4,5,5-Hexamethyldihydro-2-furanone (75)

The same procedure as used above for the 3,4,4,5,5-pentamethyldihydro-2-furanone, 74, was used here with 3 g of 2,2,3,3,4,4-hexamethyl THF 48 and 4.5 g of MnO$_4$K, yielding 2 g (60% of 75), m.p. 47°; pmr, δ,0.96 (s, 6H), 1.16 (s, 6H), 1.33 ppm (s, 6H); lit. (167), m.p. 59-60°.

The 18 mass spectra were determined on a C.E.C. 21-110B double-focusing mass spectrometer. Spectra are plotted in terms of relative abundance, with the most intense peak (base peak) taken as 100%. Only those peaks with an intensity equal to or greater than 3% of the most intense peak above 40 have been recorded.

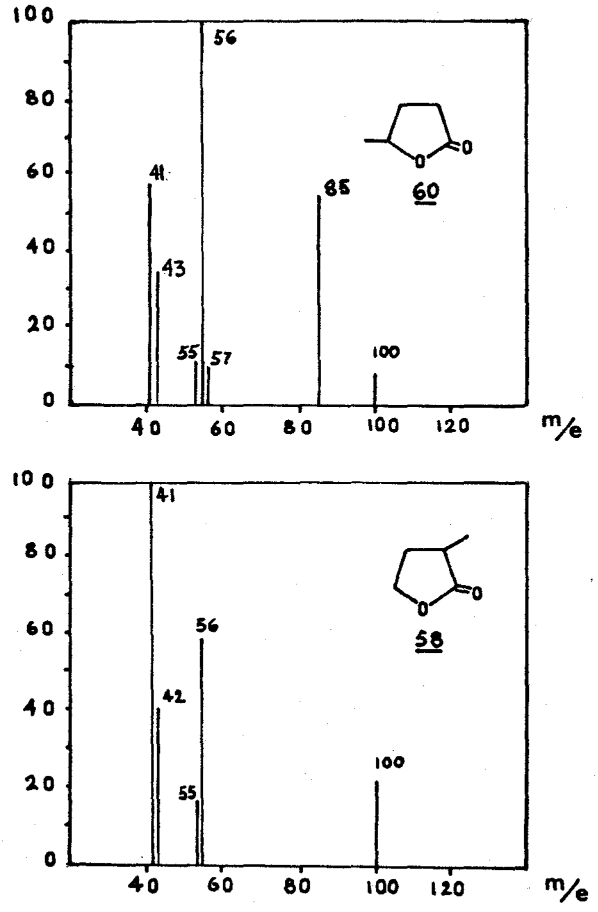
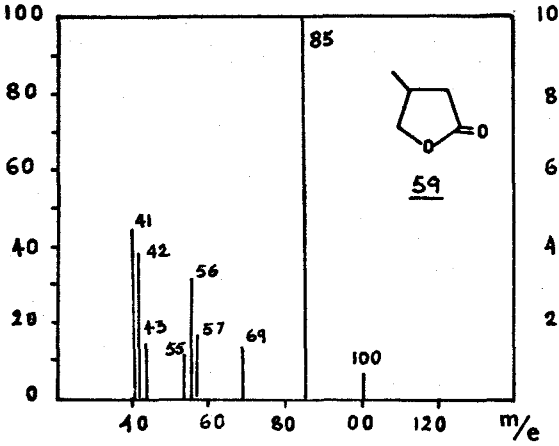
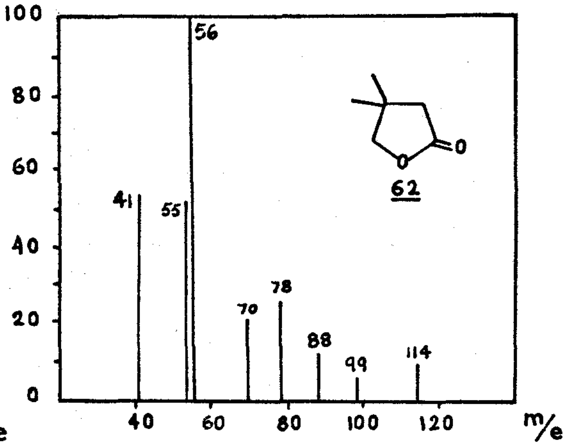


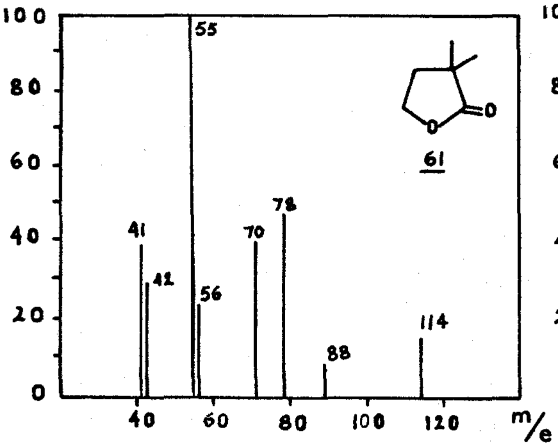
Figure 19. Mass spectra of dihydro-2-furanones. (cont'd. pages 80,81)



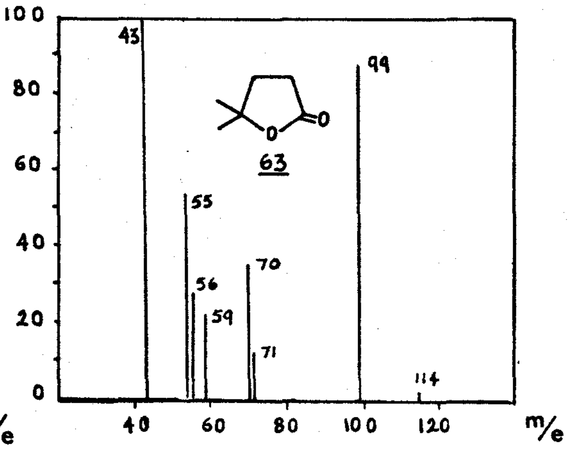
59



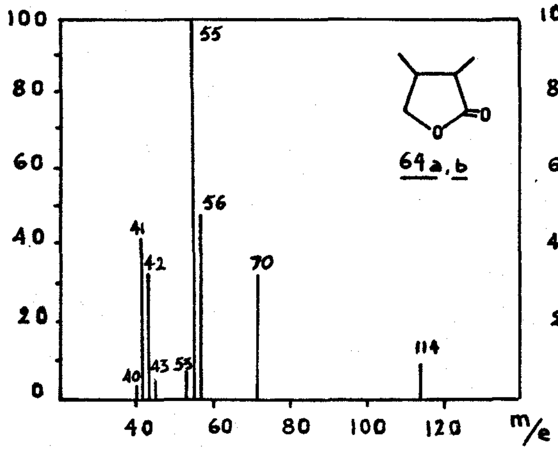
62



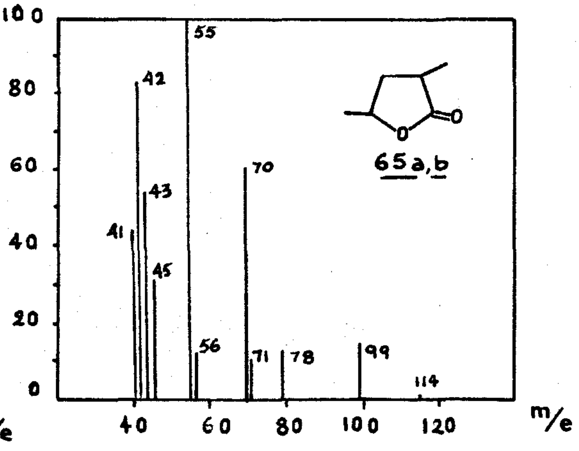
61



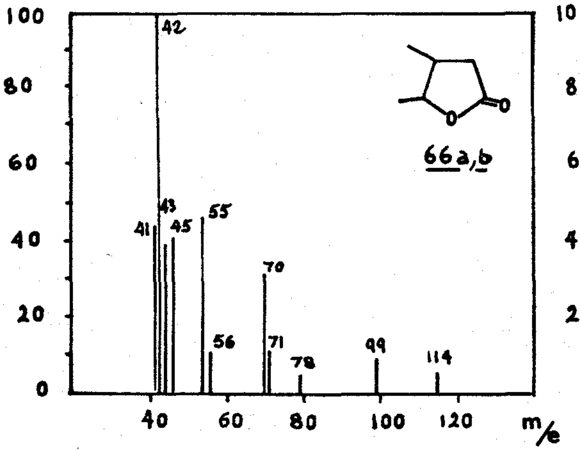
63



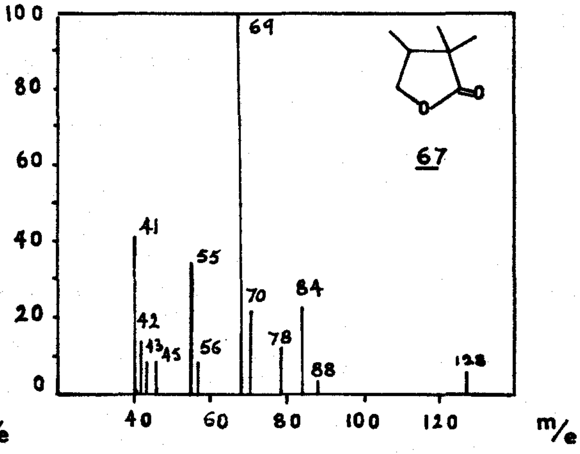
64a,b



65a,b



66a,b



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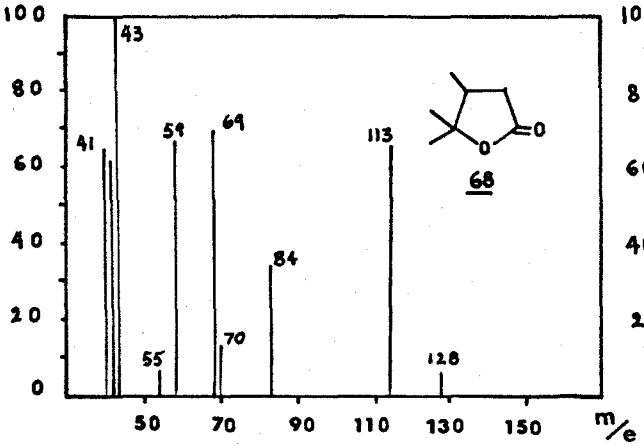
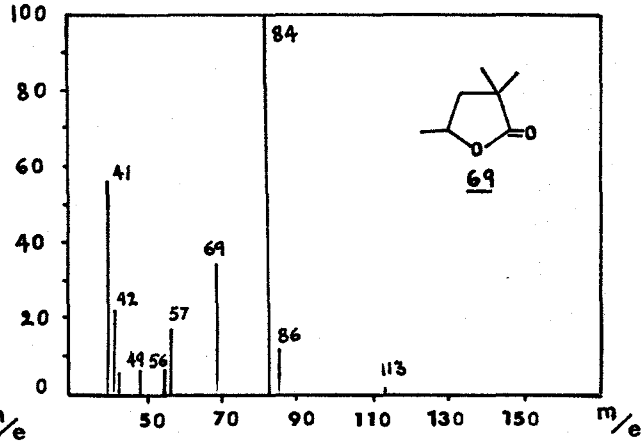
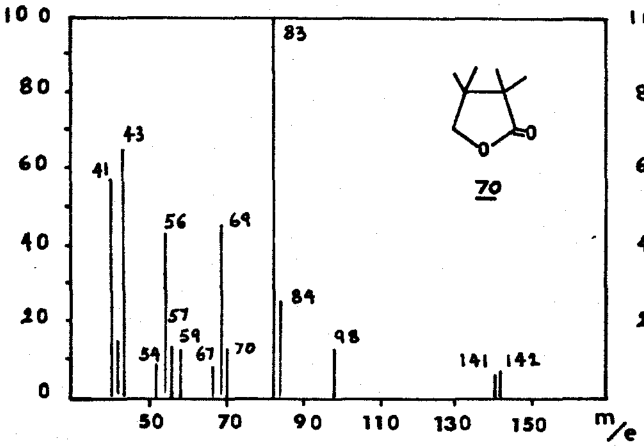


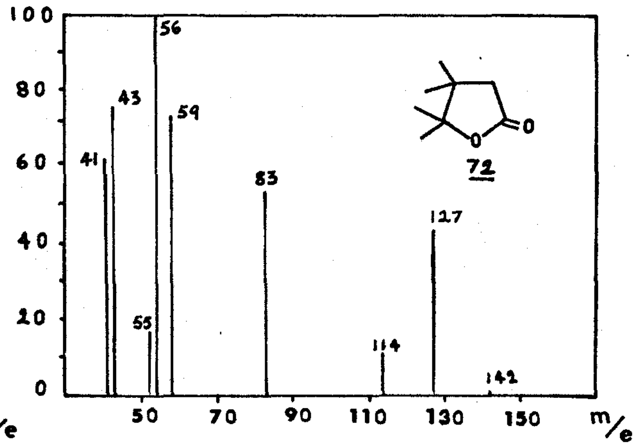
68



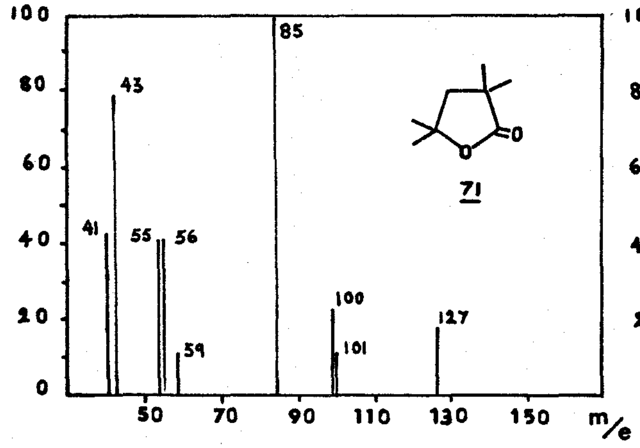
69



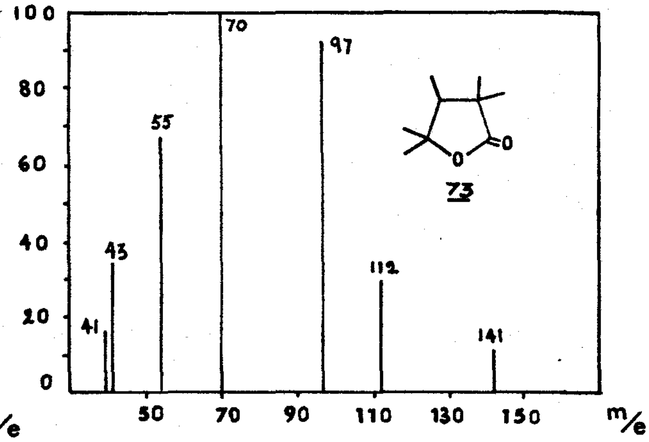
70



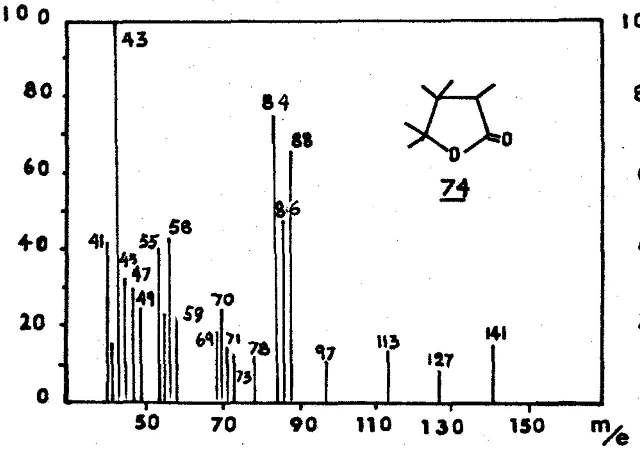
72



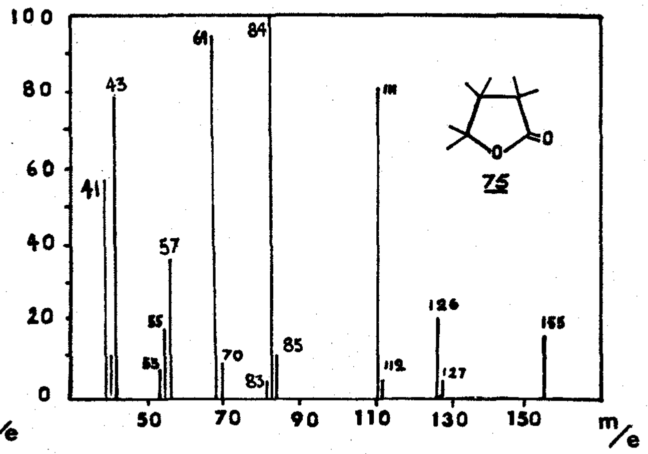
71



73



74



75

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APPENDIX I

Calculations of Chemical Shifts from Substituent Effects

A typical calculation of the chemical shifts of the ring carbons of 2,2,4-trimethyl tetrahydrofuran from the substituent effect parameters of Table 11 is shown below.

Carbon 2.	Base value	67.75
	First α Me	7.4
	Second α Me	4.9
	γ Me (at C_4)	0.05
	Total shift	80.15
	Observed shift	80.65
Carbon 3.	Base value	25.65
	First β Me (at C_2)	7.55
	Second β Me (at C_2)	5.1
	β Me (at C_4)	8.85
	Total shift	47.15
	Observed shift	47.9
Carbon 4.	Base value	25.65
	First α Me	8.15
	First γ Me (at C_2)	0.15
	Second γ Me (at C_2)	0.3
	Total shift	34.25
	Observed shift	34.5
Carbon 5.	Base value	67.75
	β Me (at C_4)	7.2
	First δ Me (at C_2)	-0.35
	Second δ Me (at C_2)	-0.4
	Total shift	74.2
	Observed shift	74.2