A THESIS ENTITLED

"STUDIES IN NATURAL PRODUCT CHEMISTRY"

SUBMITTED TO THE

UNIVERSITY OF GLASGOW

FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

IN THE FACULTY OF SCIENCE

BY

GORDON A. LINDSAY, B.Sc.

Chemistry Department   October, 1969.

TO SANDRA

SUMMARY OF THESIS

ENTITLED

STUDIES IN NAURAL PRODUCT CHEMISTRY

Section 1. The correlation between the infra-red carbonyl

frequency and conformation of δ -lactones was based on the

study of a limited number of examples. To substantiate

the correlation, a pair of epimeric δ -lactones were synthesised

by degradation of the sesquiterpene drimenol. One of the pair

was forced to adopt a half-chair conformation and had an infra-

red carbonyl frequency of 1740 cm^{-1}. The other δ -lactone was

forced to adopt the half-boat conformation and had an infra-red

carbonyl frequency of 1755 cm^{-1}.

The preferred conformation of simple unstrained δ -lactones

has not previously been determined. The n.m.r., infra-red and

circular dichroism spectra of the lactone of 5 - hydroxy - 5 -

t - butyl - pentanoic - acid could be best interpreted in terms

of it existing as an equilibrium mixture of half-boat and half-chair

conformers with the latter predominating.

The circular dichroism and optical rotatory dispersion curves

of a number of δ -lactones were examined and the signs of their

Cotton effects found to be best interpreted in terms of the rule

which correlates sign with the chirality of the lactone ring.

Investigation of the n.m.r. spectra of columbin, isocolumbin

and decarboxy columbin confirmed that the conformation of the first

two δ -lactones was the same in solution as in the solid state

as determined by X-ray crystallography.

Section 2. The conformation of medium ring lactones have not

previously been examined. The n.m.r. spectrum of cycloheptanolide

at 173°K was consistent with it adopting a boat-chair conformation

with the lactone group occupying one side of the molecule.
The n.m.r. spectra of cyclononanolide and derivatives at
different temperatures and in different solvents were
consistent with cyclononanolide adopting a boat—chair—boat
conformation similar to that preferred by cyclodecane. In
addition the conformational inversion processes occuring
in these two molecules are discussed. The free energy of activation
of cycloheptanolide was found to be 8.9 ± 2.0 K cal mole^{-1}
and for cyclononanolide 9.2 ± 1.0 K cal mole^{-1}.

ACKNOWLEDGEMENTS

CONTENTS

SECTION 1

SECTION 2

An explanation in molecular orbital terms would be
that the lactone group is placed, that this is the most
effective overlap of the π orbital system the carbonyl
the p orbital of the alkyl oxygen can occur. If this
is postulated to explain the higher energy of the π^*
orbital as compared to that of the β-lactone and
saturated on the β-lactone region of ultraviolet data
is shown in (1), it is seen that the effect could even
raise the energy of the π^* orbital as compared to both

CHAPTER 1

THE CONFORMATION AND INFRA RED SPECTRA OF δ-LACTONES

It has been deduced[1,2,3] from the results of X-ray analysis that the lactone group C — C — O — C is planar. To account for this it is suggested[4] that the lactone group is a resonance hybrid of the canonical forms (1) and (2).
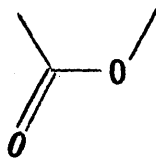
1   2
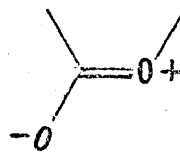
An explanation in molecular orbital terms would be to say that when the lactone group is planar, then this is the condition that maximum overlap of the π orbital system of the carbonyl group and the p — orbital of the alkyl oxygen can occur. Overlap of this kind is postulated to explain the higher energy of the $n \rightarrow \pi^*$ transition of esters as compared to ketones. An approximate energy level diagram[5] for the π electron system of ester (and lactone) groups is shown in (3). It is seen that the effect of π overlap is to raise the energy of the π^* orbital as compared to ketones, thus causing a blue shift of the $n \rightarrow \pi^*$ transition.

3
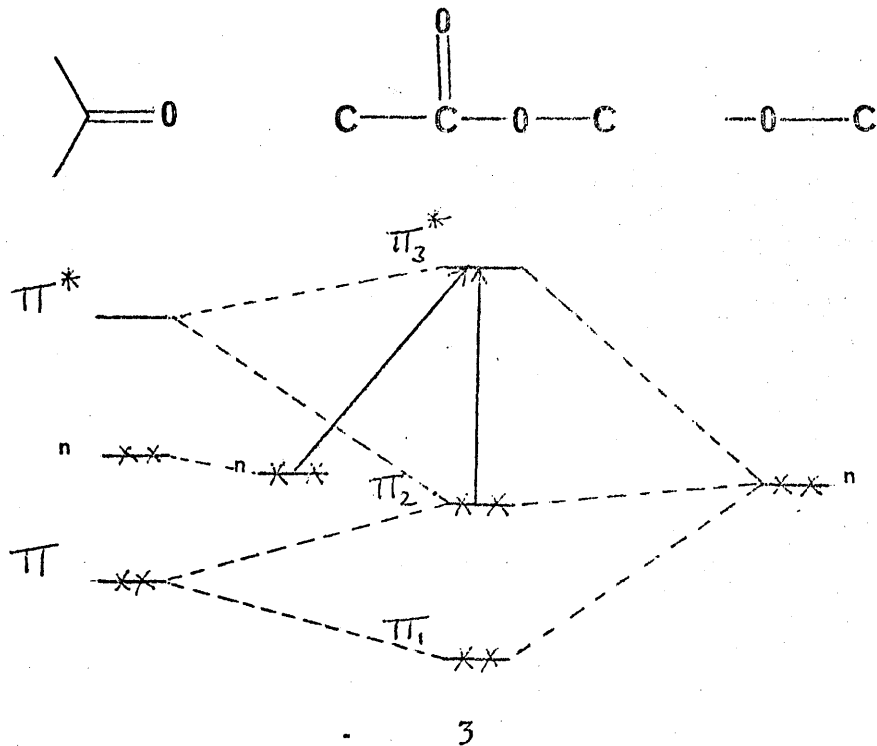
In a δ-lactone the planarity of the lactone group leads to two possible extreme conformation of the ring[3]. These are the half-boat (4) and the half-chair (5). In (4) the carbon atoms A and B of the lactone ring are displaced to the same side of the plane containing the lactone group, whereas in (5) they are on opposite sides of the plane.
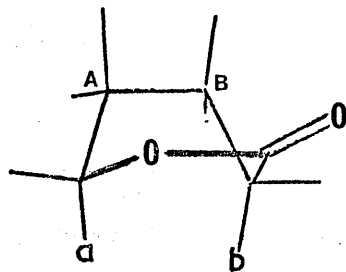
4
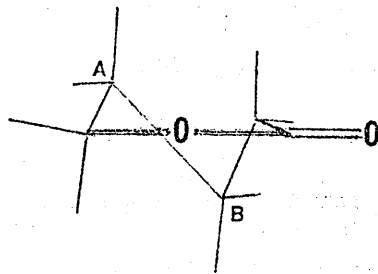
5

Mathieson[6] originally concluded from the x-ray analysis of a limited number of examples that the half-boat was the preferred conformer of δ-lactones. He suggested that a six membered ring (6) could be considered as two parts a and b each consisting of four atoms. The terminal atoms of each group are common and the planar group b is defined by its dimensions. a, however, is flexible and has an extra degree of freedom through variation of the torsion angle about bond BC.

6
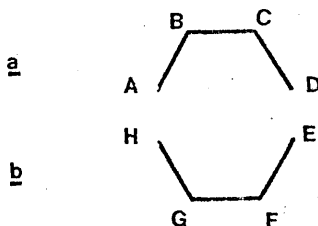
In a δ-lactone the distance HE is such that group a must minimise AD which results in ABCD being in one plane. On the other hand when b has FG a carbon-carbon double bond then HE is greater and consequently AD increases by adjustment of the torsion angle about BC. This argument over simplifies the problem since the conformation a molecule adopts depends on the minimisation of strain arising from bond angle bending, deviation from preferred torsion angles, non bonded repulsions and bond compression and stretching. This point is discussed at greater length in the discussion.

In 1965 Overton and his co workers[3] noted a number of structures

determined by X-ray crystallography in which δ-lactones preferred to adopt a half-chair (5) conformation. In addition they argued that the half-chair is the preferred conformer and that the half-boat (4) only arises in response to special circumstances. As examples they cite iridomyrmecin (7), isoiridomyrmecin (8) and lactone (A) of limonin (9), all of which have the lactone ring cis fused at its β and γ carbon atoms to a five membered ring. In isocolumbin (10), the boat conformation removes the non bonded interaction between the C – 9 methyl group and the C – 12 furyl group which would arise in the half-chair. Overton quotes three structures, simarolide (11), glaucarubin (12) and swietenine (13) which contain δ-lactones in the half-chair conformation.

More recent work has tended to support Overton's conclusions. Sheppard and Turner[7] have on the basis of n.m.r. studies of substituted steroidal lactones of types (14) and (15) concluded that the lactone is present as a half-chair. In (14) and (15) the conformation also manifested itself in the chemical properties of the acetate group. The acetate group in (14) on treatment with base underwent hydrolysis but in (15) under the same conditions it was smoothly eliminated.

This is rationalised by the C – 10 axial proton and the C – 17 acetate being anti-periplanar a situation which can only arise if the lactone ring in (15) is in the half-chair.

The n.m.r., spectra of the twelve isomeric gem-dimethyl-phenyl valerolactones[8] have been examined by Johnson and Riggs and found to be consistent with the lactone ring being a half-chair.

The opposite point of view has been taken by Wolf[9], and Legrand and Bucourt[10], who have proposed that the stable conformation of δ-lactones is the half-boat. Wolf argues that the half-boat is preferred unless the following constraints are imposed in which case the ring reverts to a half-chair. The constraints are:

a) if the 2 or 4 axial positions are substituted i.e. if a or b in (4) are substituents.

b) if the carbon atoms A and B in (4) are fused to a six membered ring in the chair conformation.

c) if the lactone ring is fused to two other rings which force it to adopt a half-chair.

Using these rules, Wolf correlated the signs of the Cotton effects of a number of δ-lactones with their conformation. Legrand and Bucourt have deduced a similar correlation.

Wolf gives no reasons for his initial assertion that the stable conformer is the half-boat and Legrand and Bucourt base their proposals on some unpublished calculations by Bucourt and Hainaut[10]. At present conformational energy calculations on systems other than alkanes are not well developed and any predictions arising from them must be treated with care.

The compounds studied by Sheppard and Turner and shown to have a flattened half-chair conformation are 15 - oxa - 16 oxo steroids with an angular methyl at C - 13. Yet, according to the generalisations of Wolf, Legrand and Bucourt these compounds are expected to take up a boat conformation.

The proposals and results of Wolf, Legrand and Bucourt will be discussed in greater detail in chapter 3.

Consideration of the conformation of δ-lactones and their infra-red spectra led Overton to the interesting correlation between conformation and frequency of the infra-red carbonyl bands of δ-lactones. They observed that those compounds, which in the crystal have δ-lactones in the half-chair conformation, are assosiated with carbonyl absorption within the range normally accepted for δ-lactones ($V_{max}(CCl_4)$ 1730 - 1750 cm.$^{-1}$). The compounds which in the crystal have δ-lactones in the half-boat conformation, however, have carbonyl absorption frequencies lying in a higher range ($V_{max}(CCl_4)$ 1758 - 1765 cm.$^{-1}$) (see Table 1).[3]

TABLE 1

	Conformation	Displacement in A from		$V_{c=c}$ [a]	Solvent
		lactone	plane		
		A	B	Cm^{-1}	
Iridomyrmecin	(4)	+1.15	+1.07	1758	CCl_4
Isoiridomyrmecin	(4)	+1.12	+1.14	1761	CCl_4
Isocolumbin	(4)	+1.22	+1.25	1761	CCl_4
Limonin (A lactone)	(4)	+0.77	+0.39	1758	$CHCl_3$ [b]
		+1.11	+0.87		
Swietenine	(5)	+0.33	−0.48	1732	$CHCl_3$ [b]
Simarolide	(5)	+0.17	−0.54	1727	$CHCl_3$ [b]
Glaucarubin	(5)	+0.43	−0.30	1753 [c]	CCl_4

(a) I.r. spectra refer where appropriate to derivatives in which the obscuring effect of other carbonyl functions has been removed. The compounds used for I.R. measurement are given in reference 3.

(b) Insoluble in CCl_4. Solvent shifts $(CHCl_3 \rightarrow CCl_4)$ for δ -lactones are +10 to 15 cm^{-1}.

(c) α -Methoxy -δ- lactone.

In line with the above predictions, the lactone of 4 - hydroxycyclohexanecarboxylic acid (16) (conformation 4) has $V_{max}(CCl_4)$ 1768 cm^{-1} and α -campholide (17) (conformation 5).

$V_{max}(CCl_4)$ 1744cm^{-1}. The carbonyl frequencies of the lactones studied by Sheppard and Turner and Johnson and Riggs, which are all half-chair δ-lactones, fall into the lower range.

It is pertinent here to examine the factors which affect the frequency of carbonyl bands. These factors can conveniently be divided into two[11].

First of all inductive and resonance effects are considered. In general carbonyl frequencies which are higher than those of acetone in a given solvent can be regarded as examples of carbonyl groups where inductive effects outweigh resonance effects whereas the reverse is true for those exhibiting lower frequencies. This is explained by considering the carbonyl group as a resonance hybrid (18), from which it can be seen that if an electron withdrawing group X is attached to the carbonyl carbon (19) the polar resonance form becomes destabilized and hence the carbonyl possesses more double bond character. This results in a higher force constant and thus a higher frequency.

18

19
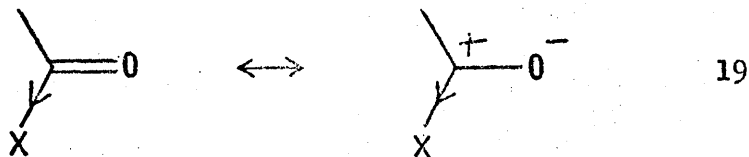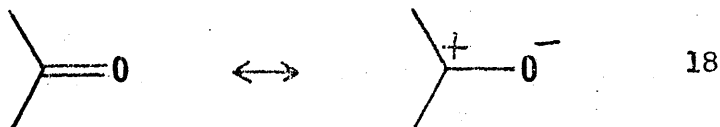
On the other hand, if the group X can participate in the
resonance hybrid (20), then the resulting delocalization of electrons
will lead to the carbonyl group having more single bond character, a
lower force constant and thus a lower frequency.
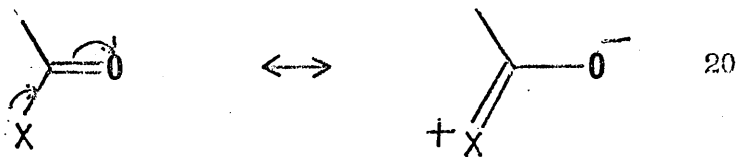
In esters and lactones since the carbonyl frequency is higher
than in acetone it must be assumed that the first effect predominates.

The other effect which must be considered is the simple physical one
of changing the bond angle. An example of this is the change in
carbonyl frequency as the size of the ring is altered. Two different
reasons have been advanced for this phenomenon.

One explanation is that frequency shifts of the above kind can
be interpretated in terms of hybridization changes. This is largely
based on the relation of the inter-orbital angle to the degree of
hybridization. Contraction of the XCX angle from 120° is said to
cause an increase in p-character of the ring bonds and a corresponding
increase in the s -character of the C = O bond. Since an increase
in s-character of a bond strengthens it, then a higher force constant
and thus a higher frequency will result. Thus the increase in
frequency as the ring size of the cyclic ketones falls. There is
experimental evidence for the above view, notably the work of Hall

and Zbinden[12] who have tabulated extensive data on cyclic systems from which they conclude that the observed frequencies show a fair correlation with hydrolysis rates and that hybridization changes are a major factor in frequency changes.

Calculations by a number of workers[13,14,15], however, indicate that the change in carbonyl frequency with ring size can be wholly accounted for by changes in bond angles. Futhermore, these calculations showed that little change occurred in force constants which is necessarily implied by the hybridization approach.

Brauman and Lawrie[16] have described the carbonyl vibration in terms of a simple model (21), which illustrates this physical explanation. The carbonyl vibration involves not only $C = 0$ stretching but also bending of the XCX angle and compression of the CX bonds. (21) is a model of the $X - \underset{O}{C} - X$ system which can for $C = 0$ stretching be represented by (22). In (22) the CX bonds have been replaced by their resultant in the direction of $C = 0$ and their resultant force constant, denoted by $K'_{xx'}$, is equal to $2K_{cx}\cos\theta/2$.
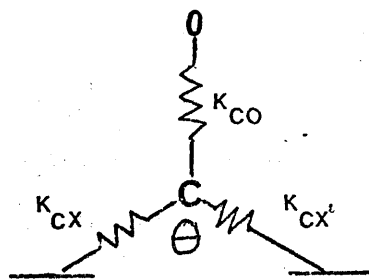
21
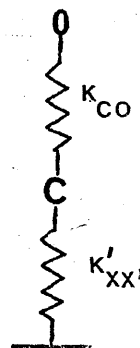
22

It is assumed for the purposes of this argument that the rest of the molecule is held rigid.

Thus the effect of decreasing the bond angle will be to increase K'_{xx} and therefore raise the frequency of the carbonyl vibration. This model also predicts that hybridization effects should tend to cancel, for although $C = O$ is strengthened, the CX bonds are correspondingly weakened. Calculations based on this model account quantitatively for the changes in carbonyl frequency with bond angle.

In this short review it has been shown that at least two different conformations of δ-lactones can exist. As regards preferred conformation, evidence is presented which shows that the majority of δ-lactones whose conformations have been determined prefer to exist as half-chairs. The review also discusses Overton's observations which were based on a limited number of examples that the half-chair conformation of δ-lactones is associated with an infra red carbonyl frequency in the range $(V_{max}(CCl_4)\ 1730 - 1750 cm^{-1})$ whereas the half-boat conformation has a carbonyl frequency in a higher range $(V_{max}(CCl_4)\ 1758 - 1765 cm^{-1})$
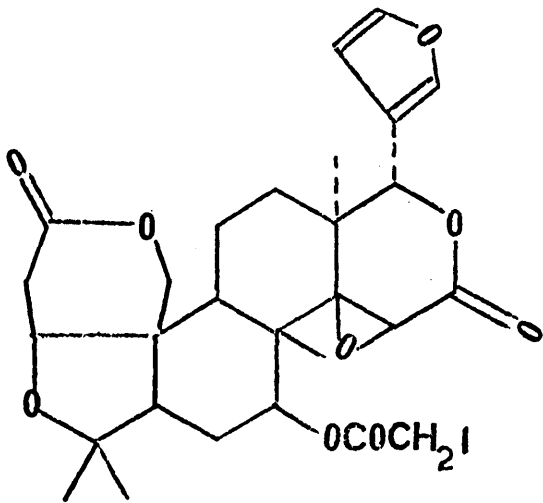
In the work which follows, further examples of δ-lactones which obey Overton's rules are produced and in addition it is hoped to obtain further evidence that the preferred conformation of δ-lactones is indeed the half-chair.
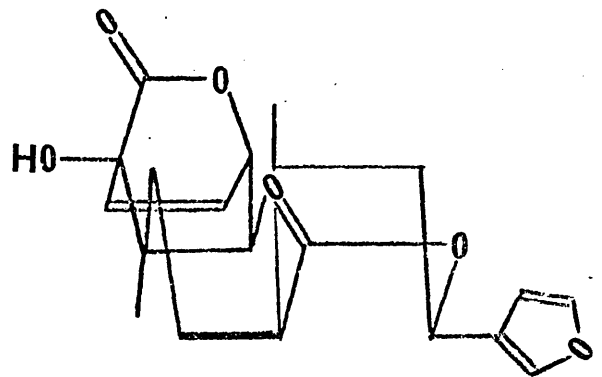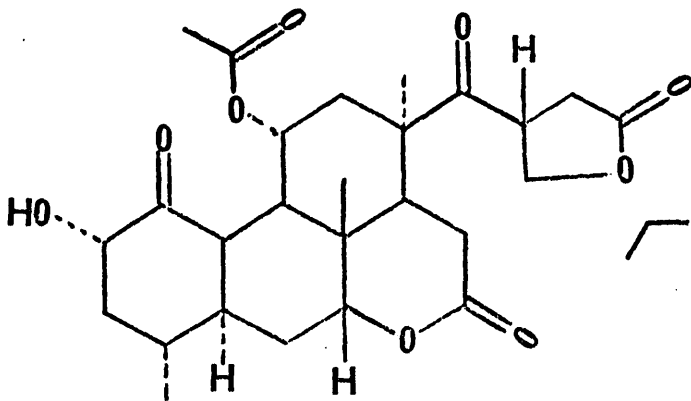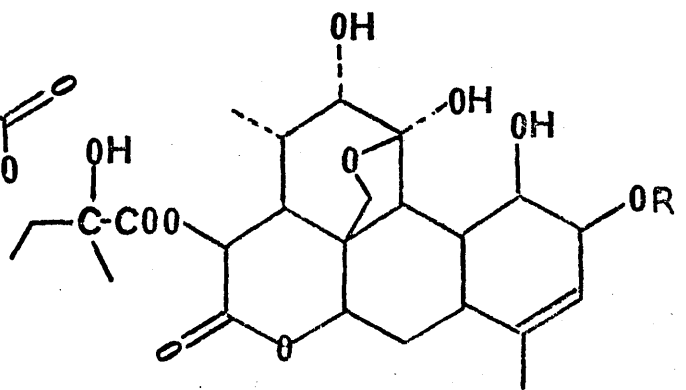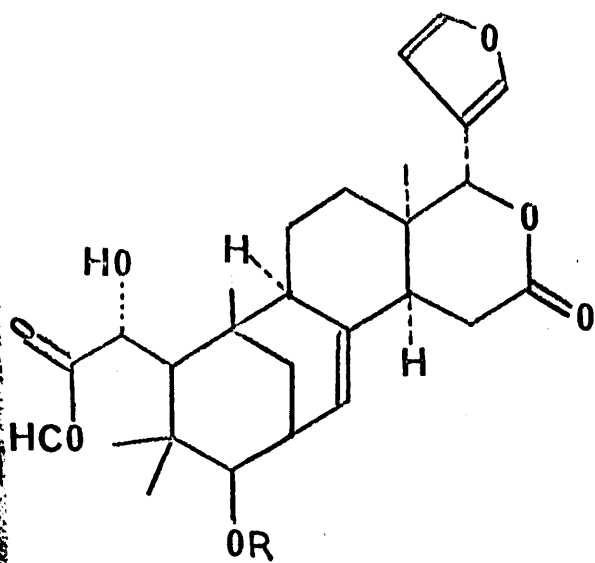
7

8

9

10

11

12

13
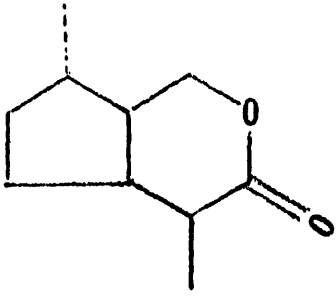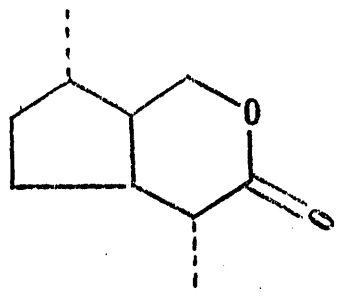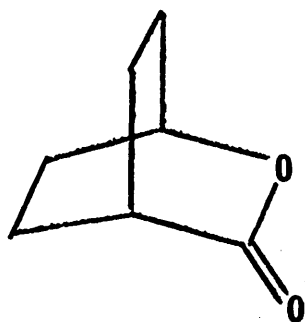
14 R₁= OCOCH₃, R₂=H
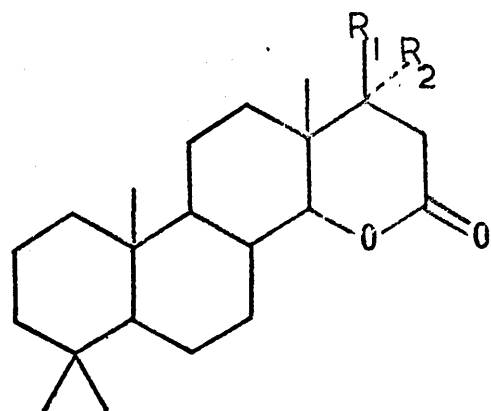
$14\ R_1= OCOCH_3,\ R_2=H$

$15\ R_1=H,\ R_2=OCOCH_3$

16
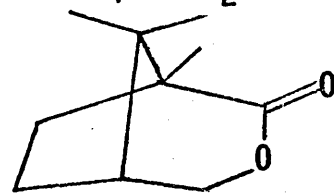
17

CHAPTER 2.

PART 1 DISCUSSION

When this work was initiated, the correlation between lactone carbonyl frequency and conformation[3] was based on a limited number of examples and subsequent work by two groups[7,8] has confirmed the observation that the half-chair conformer is associated with carbonyl frequencies in the lower range - V_{max} (CCl_4) 1730 - 1750 cm^{-1}. However, no further examples of half-boat δ-lactones have been brought to our notice. To establish Overton's correlations beyond doubt, more examples of δ-lactones of known conformation are required and especially lactones adopting the half-boat conformation. The advantage of this correlation is that it provides an extremely simple and rapid method of determining the conformation of δ-lactones, which are important in the interpretation of their Cotton effects, about which there is some controversy.

The first question which must be resolved is whether it is reasonable to expect the carbonyl frequency of a half-boat δ-lactone to be higher than that of a half-chair. A satisfactory answer to this question can be obtained in terms of changes in bond angle, the effect of which is discussed in the review.

The distance[17] r between two carbon atoms separated by three carbon-carbon single bonds is given by:-

$$r = a(3 - 4\cos\theta + \cos^2\theta - \sin^2\theta\cos\omega)^{\frac{1}{2}}$$

where a is the carbon-carbon bond length, $\ominus$ is the C - C - C angle and ω is the torsion angle as denoted in (18).

18

Thus as ω increases the distance r increases.

In a δ-lactone r is the distance between the C - 2 and C - 5 carbon atoms, (19) and (20). In the half-chair (19) the torsion angle about bond C - 3 —— C - 4 is greater than the same torsion angle in the half-boat (20). Therefore to accomodate the greater distance between C - 2 and C - 5 in (19), the C - CO - O and C - O -C bonds must expand.
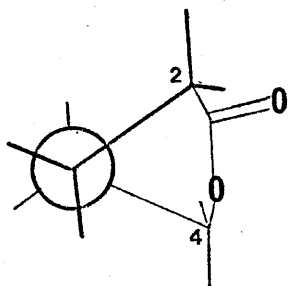
19
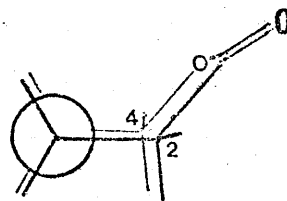
20

This analysis is borne out by bond angles obtained from the X-ray crystal structures of compounds containing δ-lactones. The bond angles of the lactone rings in swietenine[18], a half-chair

δ-lactone and isocolumbin[19], a half-boat δ-lactone are shown in (21) and (22) respectively.
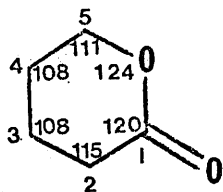
21
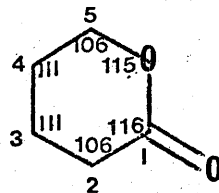
22

The C - CO - O and C - O - C angles in the half-chair δ-lactone (21) are both greater than the corresponding angles in the half-boat δ-lactone (22). To distribute the angle strain evenly the $C_2C_3C_4$ and $C_3C_4C_5$ angles in (21) are smaller than in (22) thus reducing the C - 2 -- C - 5 distance in (21).

Thus the increase in carbonyl frequency on changing from a half-chair to a half-boat δ-lactone can most probably be ascribed to the decrease in bond angle discussed above.

Examination of the carbonyl frequencies of δ-lactones mentioned in the literature revealed that the majority have

frequencies lying in the lower range quoted by Overton et al.

One exception is the 6 - Oxa - 5β - cholestan - 7 - on steroidal δ-lactone[20] which has $V_{max}(CHCl_3)$ 1739 cm^{-1}. The corresponding 5α - epimer has $V_{max}(CHCl_3)$ 1727 cm^{-1}. Since the shift in frequency[21] on going from chloroform to carbon tetrachloride is about + 15 cm^{-1} then this puts the carbonyl frequency of the 5β epimer near the higher range ($V_{max}(CCl_4)$ 1758 - 1763 cm^{-1}) proposed by Overton, thus indicating a half-boat conformation for the δ - lactone.

The 5α epimer will adopt the conformation shown in (23) with the δ-lactone fixed in a half-chair conformation. In the 5β epimer, however, the δ-lactone can adopt either the half-chair (24) or the half-boat (25) conformation. (24) will be destabilised by the non bonded interactions between the axial protons on C - 2 and C - 4 with C - 9. Furthermore, the δ-lactone ring has pseudo-axial groups on C - 5 and C - 10 whereas (25) has only one pseudo-axial group at C - 10. Thus it appears reasonable that the δ-lactone ring in 6 Oxa - 5β cholestan - 7 - on will be a half-boat since this removes the destabilising interactions indicated. This then provides another example which fits Overton's correlations.

To furnish a further example of a pair of δ-lactones, one of which would be a half-chair and one a half-boat, it was decided to synthesise (26) and (27). (26) with an 8α - methyl group would adopt a half-chair conformation (28), with the 8 methyl equatorial.

(27), on the other hand, should adopt a half-boat conformation, (29), with the 8β - methyl group equatorial. (27), in the alternative half-chair conformation would have severe destabilising interactions between the 8β - methyl which would be axial and the 10 - methyl group. The position of the carbonyl bands in the infra - red spectra of (26) and (27) will therefore enable a further check to be made on Overton's correlations.

The projected synthesis of (26) and (27) envisaged starting from the sesquiterpene drimanol (30), which was available in these laboratories. A number of routes are possible but they all involve similar problems. These are removal of the CH_2OR grouping and cleavage of the double bond. The first route which suggested itself involved cleavage of the $\triangle^{7,8}$ double bond of (31), followed by removal of C - 11 to afford the keto-ester (32). It was felt that C - 11 could be removed by a retro-aldol type of reaction (35) which was feasible because of the C - 8 keto group which would be present in any cleavage product.

35
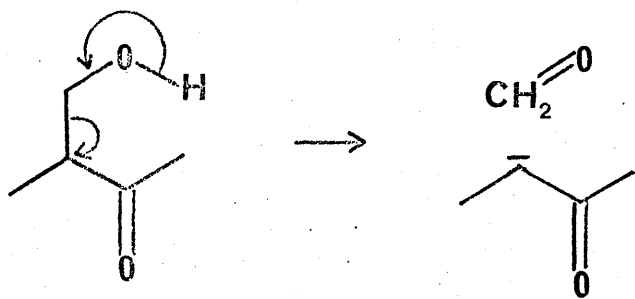
From (32) it would be possible to reduce the keto group giving the epimeric alcohols (33) which could be separated and degraded in stages to (26) and (27).

Alternatively (32) could be degraded to the nor-ester (34) and the 8 - keto group reduced at this stage. Separation of the resulting epimeric alcohols and hydrolysis could lead to (26) and (27).

Examination of the reactions of drimanol[22] pointed to a further route. It is known that drimanol (30) on treatment with sulphuric acid - potassium dichromate oxidising mixtures affords in reasonable yield (80%) and $\alpha\beta$ - unsaturated ketone nordrimenone (37) in which the 11-carbon atom has been removed. This would then allow reduction of the $\Delta^{8,9}$ double bond to (38) followed by Baeyer Villiger oxidation to the epimeric ε -lactones (39), which could be transformed into (26) and (27) by the route previously described.

Examination of the n.m.r. spectrum of nordrimenone at 100 M Hz indicated three tertiary methyl groups, an allylic methyl group which showed a small coupling of 2 Hz, two allylic protons which showed up as a broad singlet ($W_{\frac{1}{2}}$ = 14 Hz) at T 7.80 and a broad singlet ($W_{\frac{1}{2}}$ = 8 Hz) at T 3.44 which was assigned to the olefinic proton. Double irradiation at the frequency of the allylic methyl resonance caused the T 3.44 singlet to sharpen up to a

triplet (1 : 2 : 1) (J = 4 Hz). Futhermore, double irradiation
at the frequency of the olefinic proton resonance caused the
broad peak at T 7.80 to sharpen up to a poorly resolved doublet
(J = 7 Hz) and irradiation at the frequency of the two allylic
proton resonances at T 7.80 sharpened up the broad peak at
T 3.44 to a singlet (J = 4 Hz).

The n.m.r. data cannot be accomodated by the proposed structure of
nordrimenone (37) in which the olefinic proton has no near
neighbours with which it can couple. However, the data does
fit the alternative structure (40) in which the double bond is
in the 7 - 8 position. In this structure the olefinic proton couples
with the allylic protons on C - 6 as well as with the allylic
methyl group. Removal of the long range coupling of the methyl group
by double irradiation causes the olefinic proton to show up as a triplet.

(40) was confirmed by mass spectroscopy which showed the presence
of the ion (m/e 82, 100%). This ion is considered to arise via the
fragmentation shown in (41) which cannot take place in the alternative
structure.

This discovery halted further work on this route and it was
decided to concentrate on the cleavage of the $\Delta^{7,8}$ double bond in
drimanol. Studies by Johnston[23] showed that treatment of drimenyl
acetate (31) with osmium tetroxide in ether and pyridine afforded the
isomeric 7ξ, 8ξ - dihydroxy - 11 - acetoxy - drimanes (42) and (43)
in 80% yield. (42) and (43) were separated by p.t.l.c., whence

it was found that (42) was formed twice as fast as (43). Johnstone[24]

also determined the configurations of the hydroxyl groups in (42)

and (43) by oxidation with N - bromosuccinimide to the isomeric

7 - oxo - 8 hydroxy - 11 - acetoxy - drimanes (48) and (49).

(48) and (49) were also obtained by oxidation of the corresponding

trans - diols (46) and (47) which in turn were prepared by acid

catalysed ring opening of the known β and α epoxy acetates[22]

(44) and (45).

Diol (42) showed bands in the infra-red at 1753, 1737 and 1724cm^{-1}.

These bands were assigned to the acetate carbonyl which in addition

to free acetate at 1737cm^{-1}, shows acetate bonded at the ether

oxygen to the 8 - hydroxyl group (1753cm^{-1}) and acetate bonded at

the carbonyl oxygen to the 8 - hydroxyl group (1724cm^{-1}). In addition,

the hydroxyl stretching region shows four bands at 3635, 3584, 3563

and 3460cm^{-1}, which can be accounted for by free secondary hydroxyl

stretching (3635cm^{-1}), hydroxyl bonded to hydroxyl stretching and

hydroxyl bonded to the ether and carbonyl oxygens of the acetate

group.

The observed hydrogen bonding data can be explained if (42)

is considered to adopt conformation (50) in which it is possible to form

the bonds described above. In addition the n.m.r. spectrum shows

the C - 7 proton as a narrow multiplet (W = 4 Hz) which is expected

since it is equatorial and lies between the dihedral angle enclosed
by the two protons on C - 6.

(43) shows two hydroxyl peaks, at 3630 cm^{-1} due to free
secondary hydroxyl stretching and 3582 cm^{-1} which is probably
due to hydroxyl bonded to hydroxyl since the acetate carbonyl
at 1741 cm^{-1} shows no signs of splitting. In addition the C - 7
proton at T 6.72 shows up as four lines (J = 12 Hz, 5 Hz) due to
coupling with the C - 6 protons. The magnitude of the splitting
indicates a large diaxial and a smaller axial-equatorial coupling.
This is in accord with conformation (51). Presumably hydrogen
bonding to the acetate group is hindered by non bonded repulsive
interactions between it and the C - 10 methyl (52).

The isomeric cis - dihydroxy drimanes (42) and (43) were
cleaved with sodium metaperiodate to the keto-aldehyde (53). (53)
showed bands at 2714 cm^{-1} (aldyhde C - H stretch) and 1717 cm^{-1}
(carbonyl absorption). N.m.r. showed a narrow doublet at T 0.2
due to the aldehyde proton and a sharp singlet at T 8.06 due to
the methyl ketone.

Since (53) decomposed on standing, it was oxidised with
Jones reagent[25] to the corresponding acid (54) which was characterised
by infra-red, n.m.r. and analysis, as its methyl-ester (55). The
overall yield of (55) from drimanol was 50%.

A better procedure which was suitable for large scale work
involved oxidising

drimenyl acetate (51) with potassium periodate in aqueous solution containing a catalytic amount of potassium permanganate. This is a modification of the procedure developed by Rudloff and Lemieux [26] in that much more concentrated solutions of the reagents were used. (55) was obtained in 65% yield in just one stage.

The main by product of this oxidation was the keto-acetate (57) which was characterised as the ketol (58) obtained by hydrolysis of (57). The α-ketol showed a characteristic sharp bonded hydroxyl band at 3490 cm^{-1}, and a ketonic carbonyl band at 1697 cm^{-1}. The 11-protons showed an AB quartet with J_{AB} = 18 Hz and δ_{AB} = 0.13 p.p.m.

The next obstacle was the removal of the one carbon side chain on C - 9. It was felt that this could be achieved by a retro-aldol reaction induced by either acid or base treatment of (55).

However, as was feared the major product in most base catalysed hydrolysis procedures was the enone (59), which was easily recognised by its mobility on t.l.c. as compared to (55) and by infra-red bands due to ester (1740 cm^{-1}) and enone (1689 cm^{-1}) carbonyls and the double bond of the $\alpha\beta$-unsaturated ketone (1606 cm^{-1}). The olefinic protons showed as a doublet at T 4.24 (two lines separated by 0.09 p.p.m. and the characteristic doublet (T 4.24, J 6 Hz) and triplet (T 7.39) of the CH - CH_2 - CO system.

Mild acid (1% concentrated sulphuric acid in methanol)
treatment of (55) afforded the hydroxy-ketone (56) in good yield
with the enone (59) and the ϵ-lactone (60) as by products. The
ϵ-lactone was identified by mass spectra, MW 224, and n.m.r. which
showed the protons on C - 8 and C - 9 as an ABX system with
$J_{AB} = -14$ Hz, $J_{AX} = 4.7$ Hz, and $J_{BX} = 0.8$ Hz. The protons
on C - 5 and C - 6 appeared as an A_3 singlet in deuterochloroform
but in benzene as a complex ABC system. The C - 5 proton at T 7.45
is deshielded as compared with other systems in this series;
cf. T 8.40 for (68); T 8.25 for (66); T 8.00 for (65). The infra-
red spectrum showed two carbonyl peaks at 1759 and 1728 cm^{-1}. These
values are abnormally high for the types of carbonyl functions in
this molecule.

It is suggested that (60) adopts the chair-conformation (61) where
the   proton on C - 9 lies within the dihedral angle enclosed
by the two protons on C - 8, thus accounting for the small coupling
constants observed. The C - 5 proton is most probably deshielded
by the ketonic carbonyl group which is oriented as shown thus causing
the C - 5 proton to fall within its deshielding region[52].

The C.D. curve of this molecule shows a negative Cotton effect,
$(\Theta)_{219}$ (isooctane) = - 3,150, due to the lactone n→π^* transition.
This is the same sign and magnitude as the Cotton effect obtained

for the chair ϵ-lactone (69) and strongly supports the conformation (61). In addition both the Klyne and Snatzke[61,62] sector rules predict a negative Cotton effect for this conformation. The Cotton effect of the methyl ketone is positive, $(\Theta)_{293}$ (iso-octane) = + 2,210 and application of the octant rule to the conformation (61) predicts a positive Cotton effect. (61a) shows that most substituents lie in the back upper left octant. The effects of substituents in the front lower and upper left octants will cancel.

Explanation of the high carbonyl frequencies is difficult although it may involve twisting of the system to relieve the interaction between the axial C - 9 methyl ketone and the axial protons at C - 1 and C - 5. An alternative explanation is that there is some kind of intramolecular field effect between the carbonyl dipoles. This has been observed in certain 1, 4 - dicarbonyl compounds by Sondheimer[76]. The result of such an effect, the exact mechanism of which is not clear, is to raise the carbonyl frequency.

Vigorous acid hydrolysis afforded only the enone (59), together with unidentified by-products. The keto-alcohol (56) was heated in a pyrolysis furnace at 500°C, but again the enone (59) together with unidentified by-products were obtained.

The side chain was finally removed by oxidising the primary alcohol group of (56) with Jones[25] reagent followed by oxidation of the resulting aldehyde (62) with refluxing basic silver oxide[22]

solution. The major product of this reaction was the acid (63), which was characterised as its methyl ester (64). (64) had a molecular weight of 252 by mass spectoscopy and showed no O - H stretching in the infra-red. The carbonyl region showed bands at $1739cm^{-1}$ due to the ester carbonyl and $1709cm^{-1}$, due to the ketonic carbonyl. N.m.r. showed at 2H doublet at T 7.67 (J = 4 Hz) which was shown by double irradiation to be coupled to a 1H triplet at T 8.12. This indicates retention of the $CH - CH_2 - CO$ grouping. The 2H singlet at T 7.65 and 3H singlet at 7.87 are attributed to the $CH_2 - CO - CH_3$ grouping. (63) must arise by oxidation of the aldehyde (62) to the corresponding acid which decarboxylates in presence of base.

At this stage it was possible to transform (64) into its ethylene-ketal and degrade it by the Barbier-Wieland procedure. Alternatively the keto group of (64) could be reduced and the degradation carried out on the resulting epimeric hydroxy-esters (65) and (66).

Sodium borohydride reduction[27] of (64) afforded three products which were separable by p.t.l.c. The most mobile product (33%) was nicely crystalline and showed a strong carbonyl band at 1738 cm^{-1}, but no hydroxyl stretching in the infra-red. The mass spectrum indicated a molecular weight of 224 and the molecular formula from micro analysis was $C_{14}H_{24}O_2$. N.m.r. showed a secondary methyl, a 1H low field multiplet at T 5.50 and a 2H multiplet between T 7 - 8.

This compound could also be formed by base hydrolysis and acidification
of the least mobile reduction product which was obtained in only
14% yield. The least mobile product $(C_{15}H_{28}O_3)$ showed non bonded
secondary hydroxyl stretching at 3625 cm^{-1}, and an ester carbonyl
at 1740 cm^{-1}, in the infra-red. N.m.r. showed a secondary methyl
at T 8.85, a low field multiplet at T 6.0 and the characteristic
1H triplet and 2H doublet of the CH $-$ CH$_2$ $-$ CO system. The evidence
indicates that the least mobile compound is one of the expected
hydroxy-esters and the more mobile non-hydroxylic compound, the
corresponding ϵ-lactone.

The third reduction product showed infra-red and n.m.r. spectra
similar to those of the above hydroxy-ester with the exception that
there was intra-bonded hydroxyl stretching at 3523 cm^{-1} and the frequency
of the ester carbonyl group was lowered to 1727 cm^{-1} by hydrogen
bonding. This compound on base hydrolysis and acidification afforded
acidic material. However, refluxing in benzene with a catalytic
amount of para-toluene sulphonic acid[28] resulted in formation of
a neutral product which was of the same mobility on t.l.c. and
had similar infra-red and n.m.r. spectra as the previously described
ϵ-lactone. This compound was formulated as the epimeric ϵ-lactone
which was found to be extremely unstable, existing as an equilibrium
mixture of the lactone and acidic material.

The multiplets between T 7 - 8 in the n.m.r. spectra of the ϵ -lactones were recognised as arising from the two protons α to the carbonyl group and were the AB parts of the ABX systems formed by the protons on C - 5 and C - 6. The coupling constants were calculated (see page 103) the stable lactone having $J_{AX} = 0.5$ Hz, $J_{BX} = 10.5$ Hz and $J_{AB} = -14$ Hz (in CCl_4 solution) while the unstable lactone had $J_{AX} = J_{BX} = 8$ Hz and $J_{AB} = -17.0$ Hz. First order analysis of the lowfield multiplet at T 5.50 due to the C - 8 proton in the stable ϵ -lactone indicated the presence of a large coupling (J = 8 Hz) and a smaller coupling (J = 1 Hz) in addition to the coupling with the methyl group (see page 103).

If the stable ϵ -lactone is formulated as (68) with the C - 8 methyl α, then it can adopt a chair like conformation (69) where the C - 8 methyl is equatorial. H_B and H_X are almost anti-periplanar while the torsion angle between H_A and H_X is almost 90°. This will result in the observed large J_{BX} and small J_{AX} which is in accord with the familiar Karplus equation[29,30]. For the same reason C - 8 proton is also expected to have a large diaxial and a smaller axial-equatorial coupling, which is as observed. The observation that the C - 6 axial proton is at lower field than the C - 6 equatorial proton is also explained in terms of the shielding properties of the carbonyl group (see page 105).

The observed negative Cotton effect, $(\Theta)_{224} = -2,795$, confirms the conformation (69) since application of both the Klyne[61] and

62

Snatzke sector rules predict the correct sign.

On the other hand the unstable ϵ-lactone which is epimeric at C - 8 must be formulated as (67) and will adopt a conformation like (70) where the C - 8 methyl is equatorial and H_X lies outside the dihedral angle enclosed by the AB protons at C - 6, in order that the two coupling constants J_{AX} and J_{BX} should have such high values[31].

This means that the least mobile hydroxy-ester has structure (66) and the more mobile hydroxy-ester is (65).

Treatment of the epimeric hydroxy-esters and lactones with phenyl magnesium bromide[32] followed by dehydration with acetic anhydride afforded products which reflect the assignments shown above. The hydroxy-ester (65) on reaction with the above reagents, afforded the expected diphenyl ethylene acetate (71). However, on identical treatment both the hydroxy-ester (66) and the lactone (68) yielded the cyclic enol-ether (72).

(72) must be formed by dehydration of the hemi-ketal (73) which is sufficiently stable to prevent further reaction of the molecule with phenyl magnesium bromide. The hemi-ketal from (65) would have an axial methyl at C - 8 which would destabilise the stable chair like conformation shown for (73) and as a result a substantial proportion of the open form would be present which would react with the phenyl magnesium bromide to form (71).

(71) was easily recognised by n.m.r. which showed the presence of the CH – CH = grouping as an AX quartet (J = 11 Hz) and the ten protons of the two phenyl groups as a broad singlet at T 2.72. The enol ether was very mobile on t.l.c. in ethyl acetate, petroleum ether (1:20) as eluant. The infra-red spectrum showed no carbonyl absorption but had strong C – O stretching bands at 1063 and 1120 cm^{-1}. N.m.r. showed the CH – CH = grouping as an AX quartet (J = 6 Hz) while the aromatic protons between T 2 and T 3 integrated for five protons.

Initially degradation of (71) was attempted by the usual ozonolysis procedure[32]. However, the required acid as its methyl-ester (74) was only obtained in low yield (14%), the major product (20%) being (75) in which one of the phenyl groups had been oxidised. A substantial amount of poymeric gums were obtained in this reaction together with unreacted starting material (50%).

(75) was identified by mass spectra, the parent ion at m/e 386 being absent, owing to ease of loss of acetic acid to give the first peak at m/e 326. N.m.r. confirmed the five aromatic protons at T 2.70 and the CH – CH= group which showed as an AX system (J = 12 Hz). Infra-red showed two carbonyl bands at 1740 cm^{-1} (acetate) and 1720 cm^{-1} ($\alpha\beta$ – unsaturated ester).

The required degradation product, the acetate-ester (74), was obtained in better yield (50%) using the periodate catalysed ruthenium dioxide

procedure[32]. (74) showed a peak in the mass spectrum at m/e 224 corresponding to loss of acetic acid while n.m.r. showed a sharp singlet at T 7.90 owing to the methine proton at C – 5.

(74) is the precursor of one of the required δ-lactones (27). To obtain the other δ-lactone (26), attention was once more directed towards the enol ether (72). Reference to the literature indicated that cleavage of the double bond could probably be achieved by ozonolysis [33] or by reaction with meta-chloroperbenzoic acid[34]. Ozonolysis at room temperature had little effect but action of m – chloroperbenzoic acid resulted in formation of a complex mixture.

However, osmium tetroxide was found to react rapidly with (72) and after a few days, decomposition of the osmate complex with hydrogen sulphide afforded a mixture of three compounds as judged by t.l.c. The major product was the benzoate (76) with the ketol (77) occuring as a minor product. The third product which occured in very low yields was not characterised.

(76) showed bands in the infra-red at 2738 cm^{-1} (aldehyde C – H stretch), 1717 cm^{-1} (aldehyde and benzoate carbonyl stretching) and at 1275 and 1110 cm^{-1} due to the C – O – C assymetric and symmetric stretching of the benzoate. N.m.r. showed the presence of the aldehyde proton at T –0.74 as a doublet (J = 6 Hz) owing to coupling with the C – 5 methine proton which showed as a doublet at T 8.17. The aromatic protons of the benzoate showed up as two groups, the o – and p – protons between T 2–2.7 and the m-protons between T1.6 – 2.

(77) and the third product which were separated by p.t.l.c.

showed up as two spots of similar polarity on t.l.c. The infra-red

spectrum of (77) showed non bonded secondary hydroxyl stretching at

3620 cm^{-1}, bonded hydroxyl stretching at 3455 cm^{-1} and a carbonyl band

at 1702 cm^{-1}. N.m.r. showed a secondary methyl and a multiplet at

T 6.50 due to the proton on C - 8 coupling with the secondary

methyl and methylene protons on C - 9. The protons on C - 5 and

C - 6 were singlets ($W_{\frac{1}{2}}$ = 2 Hz) at T 7.45 and T 4.89. Small coupling

between them was indicated by double irradiation. The singlet at

T 4.89 sharpened considerably on addition of D_2O due to removal of the

coupling between it and the hydroxyl proton.

Both (76) and (77) are visualized as being formed from the

initially formed osmate by a cyclic fragmentation reaction.

The aldehyde-benzoate (76) resisted attempts to oxidise it

to the acid by both Jones reagent and refluxing silver oxide in

ethanol. However, by allowing it to stand in air, an acidic product

was obtained which on methylation was shown by infra-red and n.m.r. to

be the ester (78).

Although (78) is a precursor of the required $\int$ -lactone (26),

(26) was obtained via the ethylene ketal (79). (79) was formed by

refluxing (64) with ethylene glycol and p - toluene sulphonic acid.

(79) was transformed into the diphenyl ethylene ketone (80) by

treatment with phenyl magnesium bromide followed by dehydration

by refluxing with acetic acid and water[35]. (80) showed bands in the

infra-red at 1710 cm^{-1} (ketonic carbonyl) and the typical AX quartet

$(J, 12 \text{ Hz})$ of the CH – CH = system.

Degradation of (80) was accomplished once more by the ruthenium dioxide catalysed potassium periodate method. The nor-keto-ester (81) obtained by methylation of the oxidation product was analysed as $C_{14}H_{24}O_3$ by high resolution mass spectrometry. (81) showed bands in the infra-red at 1734 and 1705 cm^{-1} due to ester and ketonic carbonyl absorptions. N.m.r. showed a singlet at T 7.57 due to the methine proton at C – 5.

Sodium borohydride reduction of (81) afforded two less mobile products as shown by t.l.c. Careful p.t.l.c. afforded two hydroxy-esters (82) and (83). (82) was acetylated and the acetate was shown to be identical by t.l.c., g.l.c., and I.R. with the acetate-ester (74) obtained by degradation of (71). (83) was similarly shown to be identical with the hydroxy-ester obtained by mild hydrolysis of the benzoate (78).

In addition the infra-red spectra of (82) and (83) differed in that (82) showed substantial bonding of the hydroxyl to the keto group of the methyl-ester as evidenced by the presence of a bonded hydroxyl stretching bond at 3565 cm^{-1} and a bonded carbonyl bond, as a low intensity peak at 1700 cm^{-1}. (83) on the other hand showed a sharp band at 3615 cm^{-1} and no bonded hydroxyl bands. Explanation of these observations is difficult owing to the hydrogen bond being part of a highly substituted eight membered ring.

(82) and (85) were hydrolysed with methanolic potassium hydroxide solution and on acidification the required epimeric δ - lactones (27) and (26) were obtained.

The spectral details of the δ -lactones (26) and (27) are shown in Figures 1 and 2 and in Tables II, III, IV and V.

The mass spectra of both lactones, the principal peaks of which are shown in table II, show parent ions at m/e 210. The base peak at m/e 127 is the same in both cases, and results from the fragmentation shown in (84). The ion at m/e 109 is pictured as being formed by elimination of water from the ion of m/e 127 as shown in (85). The spectrum of lactone (26) was measured on a high resolution mass spectrometer and metastable ions at 107.22, 93.55 and 76.8 were observed. The metastables at 76.8 and 93.55 arise from the fragmentations shown in (84) and (85) respectively.

The n.m.r. spectra of (26) and (27) are shown in figures 1 and 2 respectively. Inspection of the n.m.r. spectrum of (26) shows a doublet at T 8.67 (J = 6 Hz) due to the secondary methyl group, a singlet at T 8.06 due to the methine proton at C - 5 and a multiplet at T 5.40 due to the C - 8 proton. On irradiation at T 5.40, the secondary methyl doublet collapses to a singlet and the four lines, marked with ticks, just above the base line, collapse to a doublet with J = 13 Hz. These four lines are assigned to one of the two C - 9 protons which constitute the AB part of the ABXM$_3$ system formed by the protons on C - 8, C - 9 and the C - 8 methyl group. Since

J_{AM} and J_{BM} are approximately zero, the two C - 9 protons approximate to the AB part of an ABX system. The four lines marked in Figure 1 originate from the B proton and since the four lines expected from the A proton could not be located, it is presumed that they are hidden under the methyl signals at higher field. The magnitude of the splitting in the B part (J = 13 Hz, 5 Hz) implies that it is probably an equatorial proton. This is confirmed by examination of the T 5.40 multiplet structure, which is accounted for by the signal from the C - 8 proton being split into a 1:3:3:1 quartet (J = 6 Hz), which is further split by a large (J_{AX} = 12 Hz) and a smaller (J = 5 Hz) coupling. This is consistent with the conformation (86) for (26) in which the C - 8 proton is coupled to the C - 8 methyl (J = 6 Hz), the C - 9 axial proton (J = 12 Hz) and the C - 9 equatorial proton (J = 5 Hz). The alternative conformation for (26) in which the lactone ring is in the half-boat would lead to very small (J = 1 to 3 Hz) coupling constants between the C - 8 and C - 9 protons, (see for example ⋉ -campholide page 110). This would not be consistent with the observed n.m.r. spectrum.

Inspection of the n.m.r. spectrum of (27), Figure 2, shows a doublet (J = 6 Hz) at T 8.69 due to the secondary methyl group, a singlet at T 7.83 due to the C - 5 methine proton and multiplet at T 5.57 due to the C - 8 proton. On irradiation at T 5.57 the secondary

methyl doublet collapses to a singlet and the signals due to the
protons on C - 9 are observed to change. The C - 9 protons
as in (26) form the AB part of an ABXM$_3$ system and as before it
is possible to consider them as the AB part of an ABX system.
Double irradiation at T 5.57 locates six of the eight lines which
constitute the AB part. The two lines which cannot be observed are
easily positioned since all of the four lines which constitute the B
part and the two most intense lines of the A part are visible.
The positions of the eight lines are marked with ticks just above
the base line in Figure 2. Sub-spectral analysis (see page 103)
furnishes approximate values of J_{AB} = -14 Hz, J_{AX} = 12 Hz, J_{BX} = 4 Hz
and $(\delta_A - \delta_B)$ = 30 Hz. These values of J_{AX} and J_{BX} are confirmed
by analysis of the multiplet structure of the C - 8 proton at T 5.57.
This is consistent with the conformation (87) for (27) in which the
C - 8 proton couples to the methyl group (J = 6 Hz), to the C - 9
axial proton (J = 12 Hz) and to the C - 9 equatorial proton (J = 4 Hz).
Were (27) in the alternative conformation in which the lactone ring is
a half-chair then the coupling between the C - 8 and C - 9 protons
would be very small (J = 1 - 3 Hz) (see for example α-campholide
page 110) and thus would be inconsistent with the above data.

The n.m.r. spectra of (26) and (27) confirm that the preferred
conformations are (86) and (87) which were predicted on the basis
of stereochemical arguments (see page 15). Furthermore the observed
carbonyl frequencies of (26) and (27), 1740 and 1755 cm^{-1} respectively,

fully support Overton's correlation[3]. This correlation is now supported by a reasonable number of examples and must therefore be considered to be a good criterion from which the conformation of δ-lactones can be deduced.

The optical rotatory dispersion and circular dichroism data are presented in tables IV and V and will be discussed fully in chapter 5.

TABLE II

Principal ions in mass spectra of δ-lactones (26) and (27).

δ-lactone (26)		δ-lactone (27)	
m/e	% Abundance	m/e	% Abundance
210	85	210	23
167	21	167	17
151	27	151	17
150	43	150	33
127	100	127	100
109	41	109	61
95	37	95	45
94	34	94	21
83	20	83	36
82	82	82	50
81	22	81	34
107.22	metastable		
93.55	metastable		
76.8	metastable		

TABLE III

Positions of infra red absorption maxima in carbon tetrachloride solution of the δ-lactones (26) and (27).

δ-lactone (26) V_{max} cm^{-1}	δ-lactone (27) V_{max} cm^{-1}
1740 (S)[*]	1755 (S)
1382	1382
1233	1225
1214	1204
1128 (S)	1172
1064	1118 (S)
	1098
	1070

* (S) indicates bands of highest intensity.

TABLE IV

Optical rotatory dispersion data for δ-lactones (26)
and (27) in methanol.

Compound	First Extremum $[\phi] \; \lambda_{nm}$		Lowest Wavelength $[\phi] \; \lambda_{nm}$		Sign of Cotton Effect
δ-lactone (26)	+1620	239	−4320	217	+
δ-lactone (27)	+6520	236	−10400	212	+

TABLE V

Circular dichroism data for δ-lactones (26) and (27)
in ethanol

Compound	Molecular Ellipticity $[\theta] \times 10^{-3}$	λ (nm.)
δ-lactone (26)	+4.60	225
δ-lactone (27)	+9.17	223

23

24

25

33

34

36

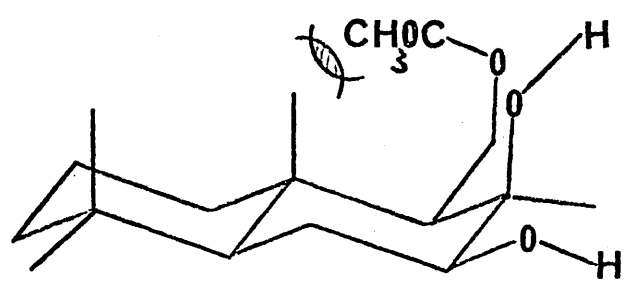**37**

38

39

40

41
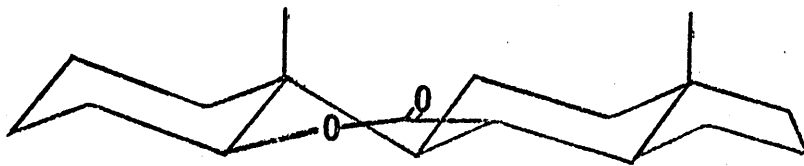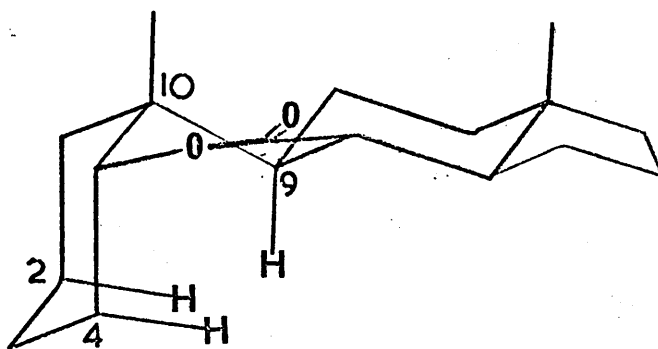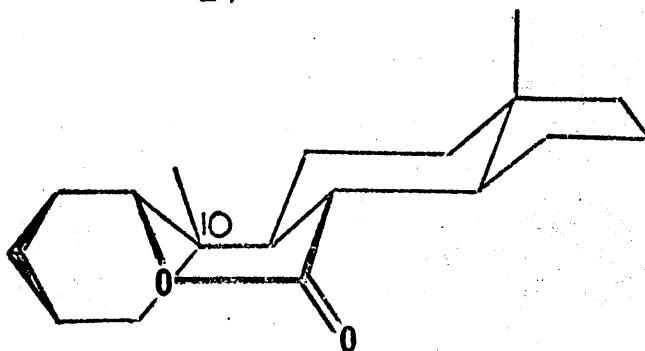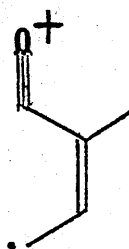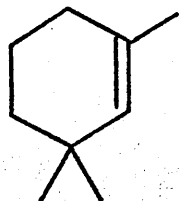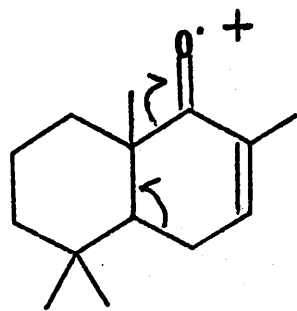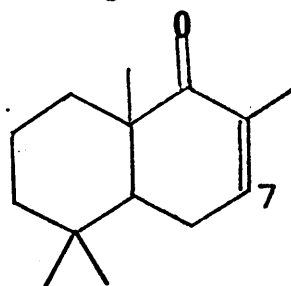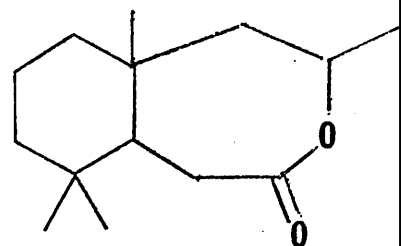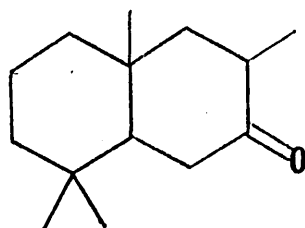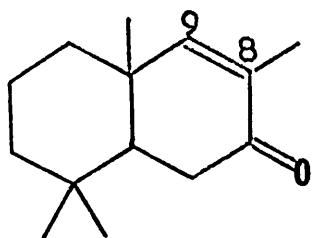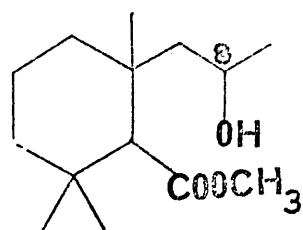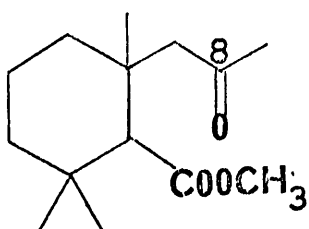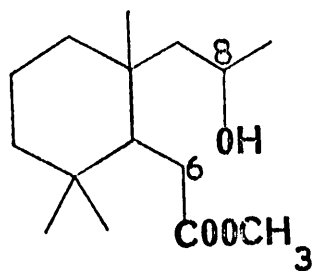
m/e 82 (100%)
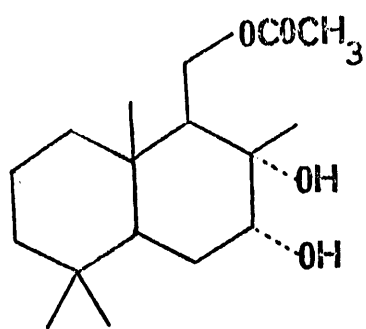
42
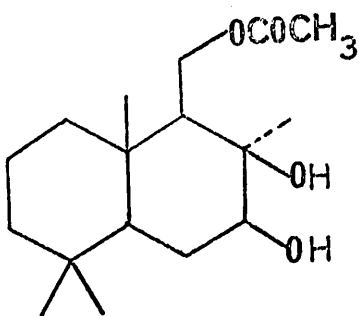
43
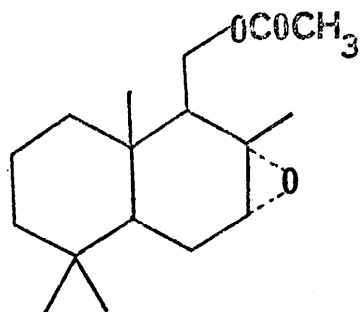
45

44

46

47

48

49

50
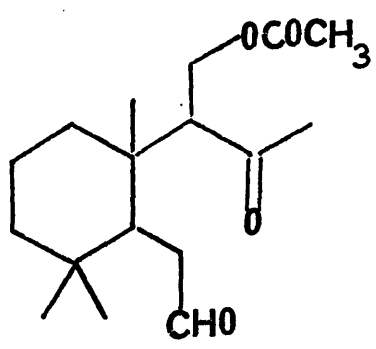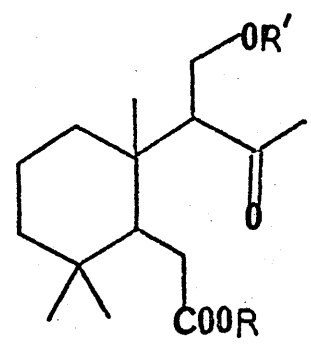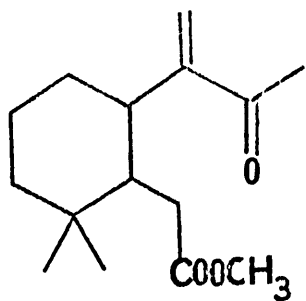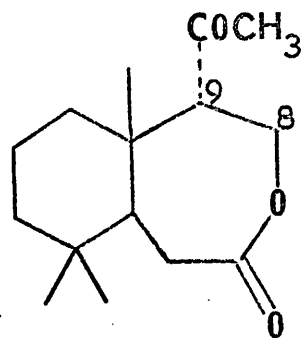
51

52
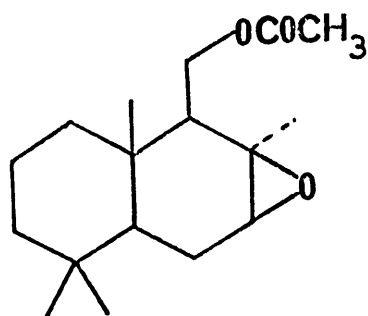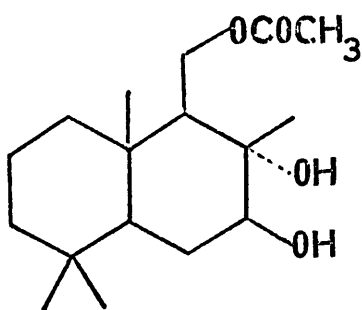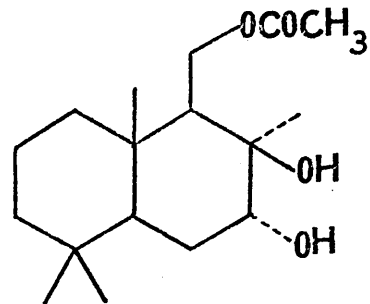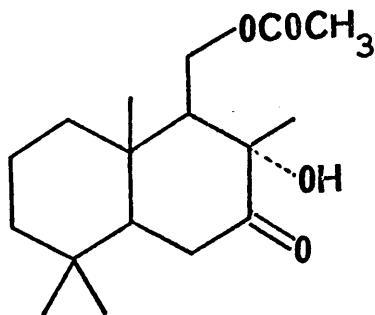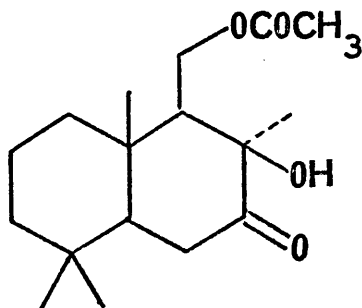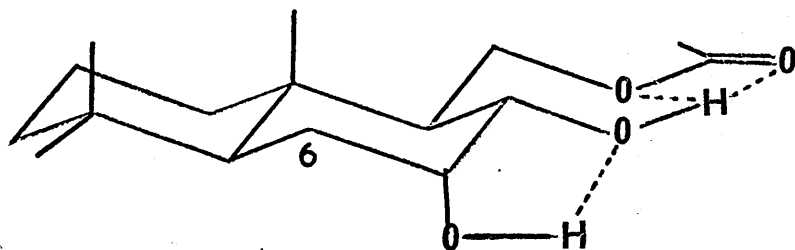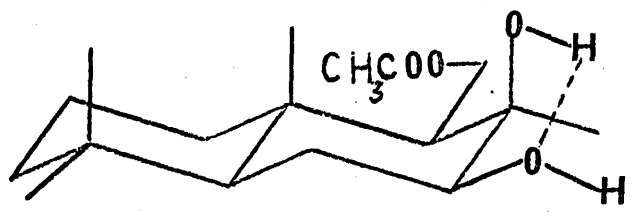
53

54 R=H R′=COCH₃

55 R= CH₃ R′=COCH₃

56 R= CH₃ R′= H
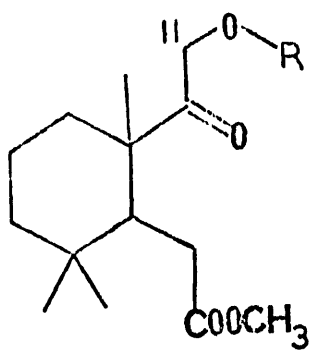
57 R = COCH₃
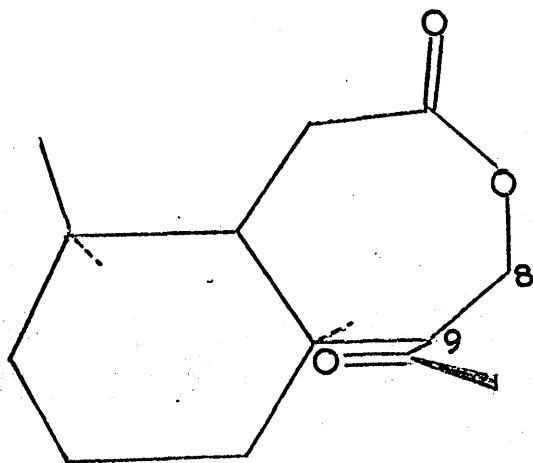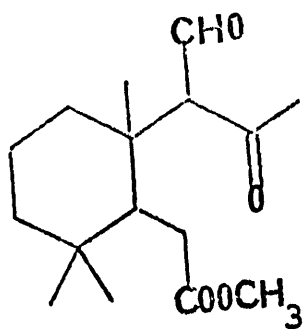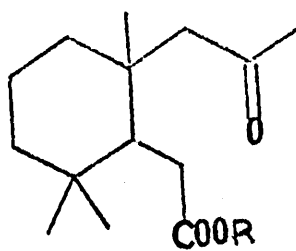
58 R = H

59

60
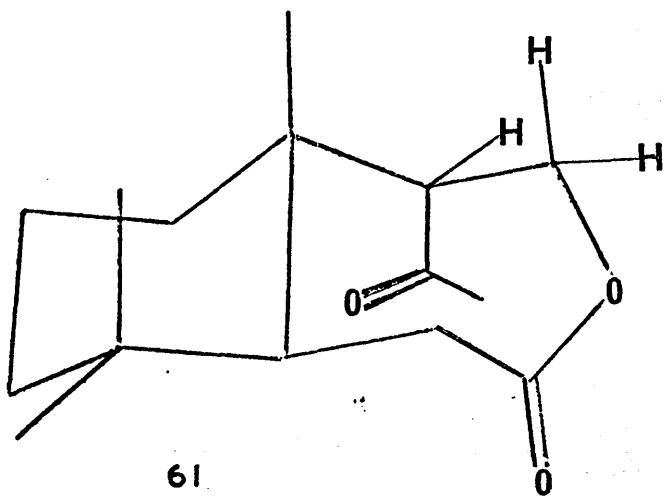
61

61a

62

63 R=H

64 R=CH₃
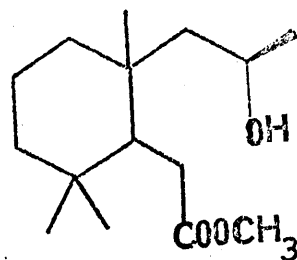
65
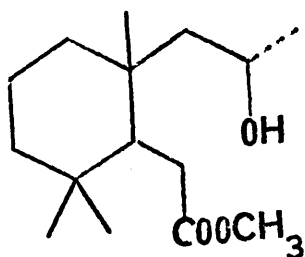
66
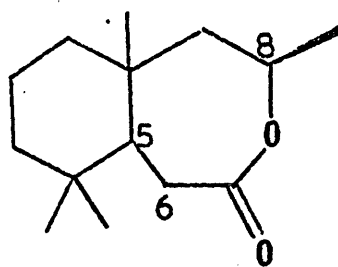
67
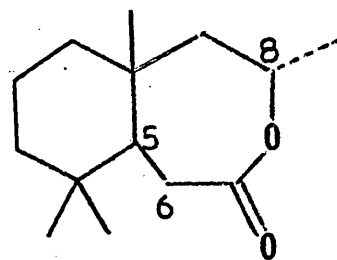
68
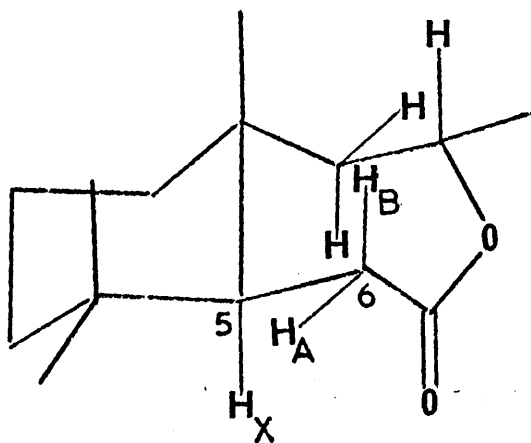
69
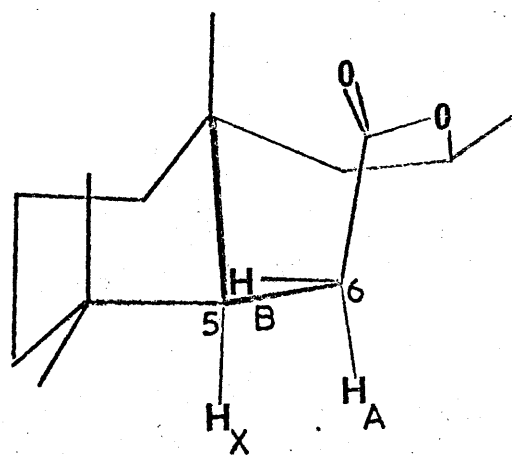
70
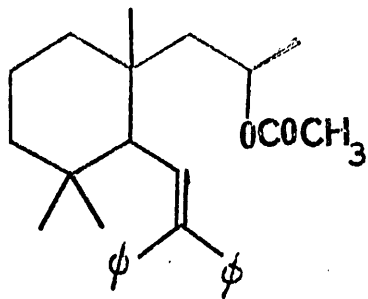
71
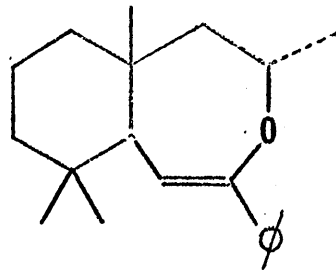
72
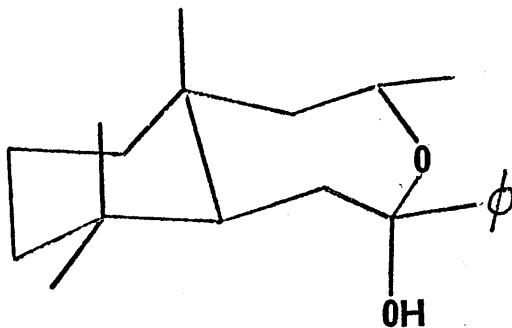
73
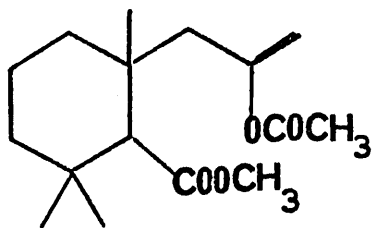
74
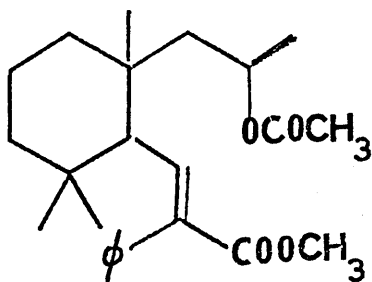
75
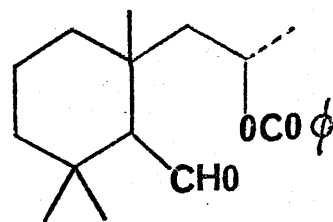
76

77

78

79

80

81

82

83

84

85

87

86
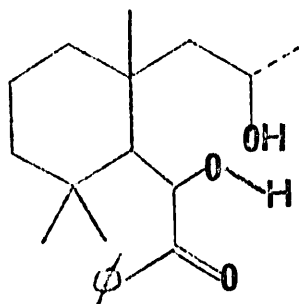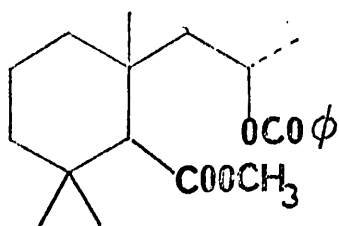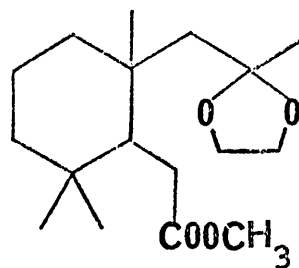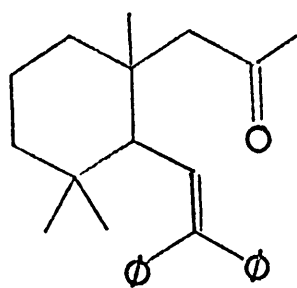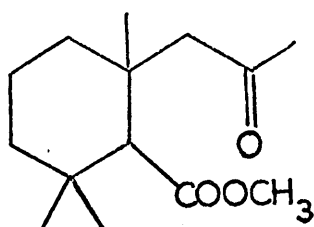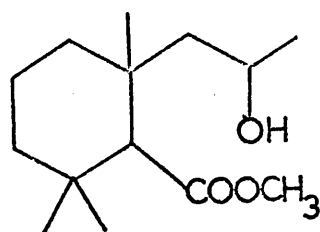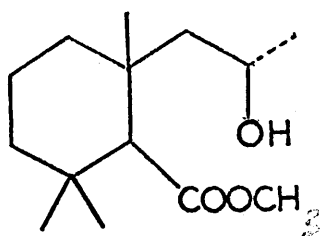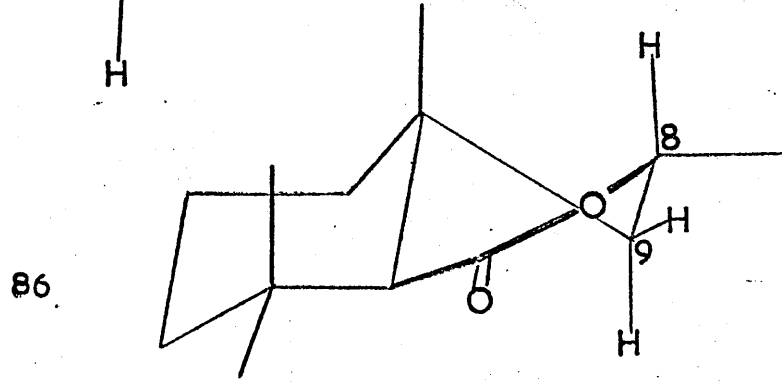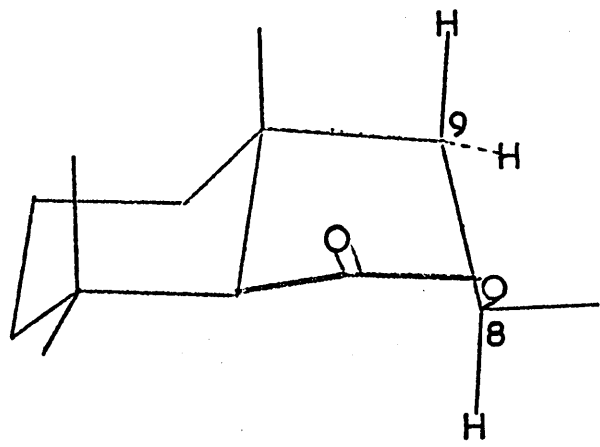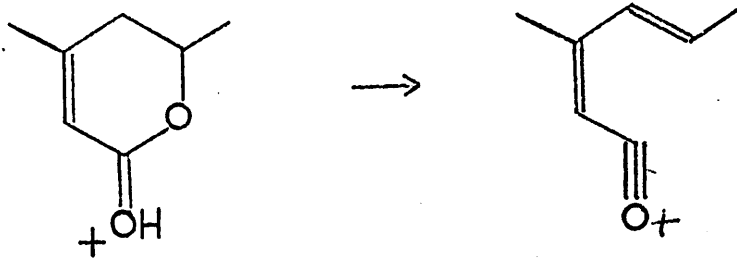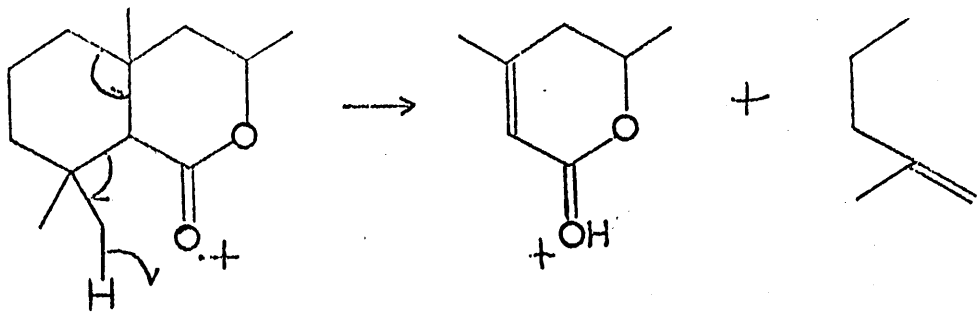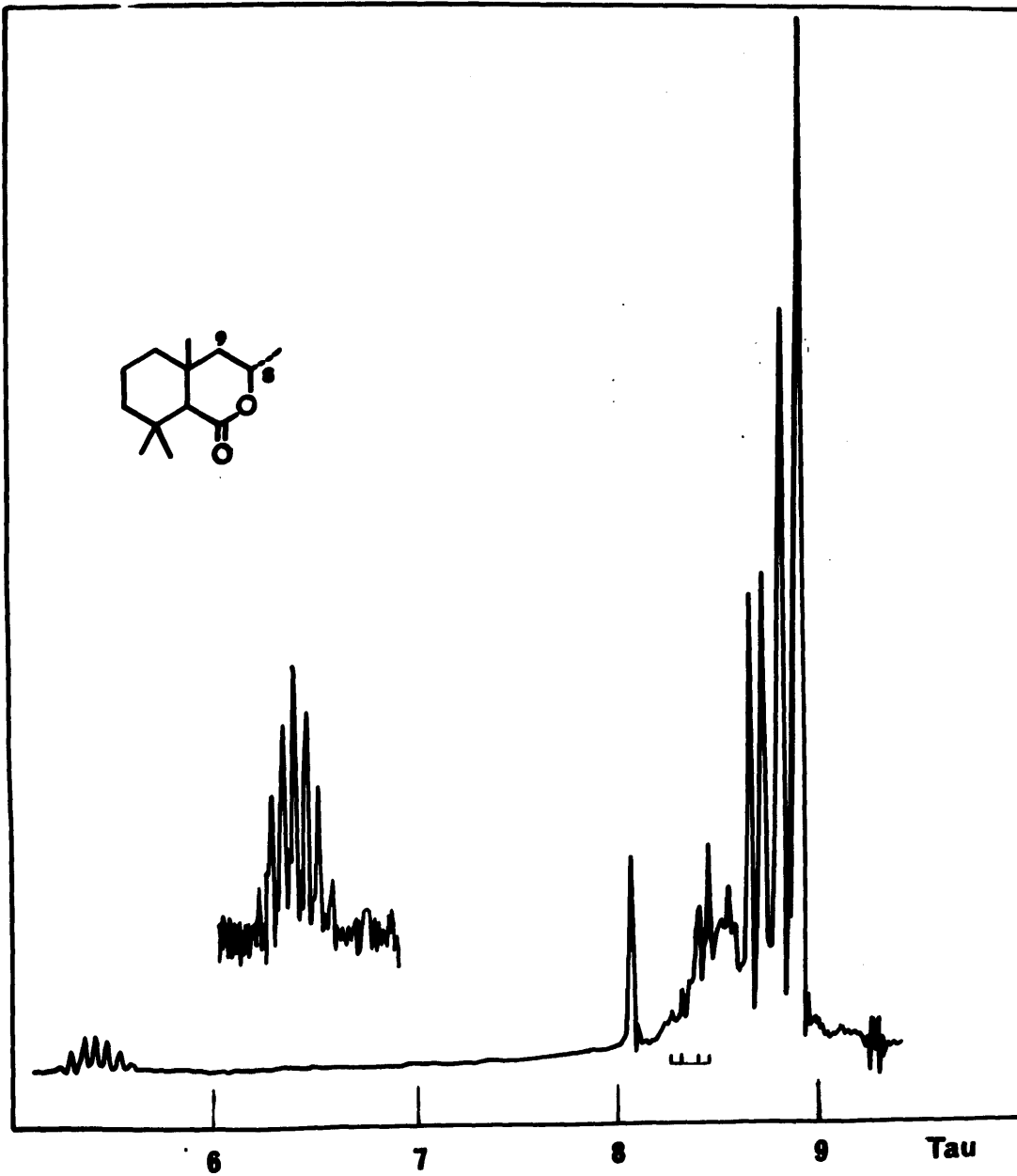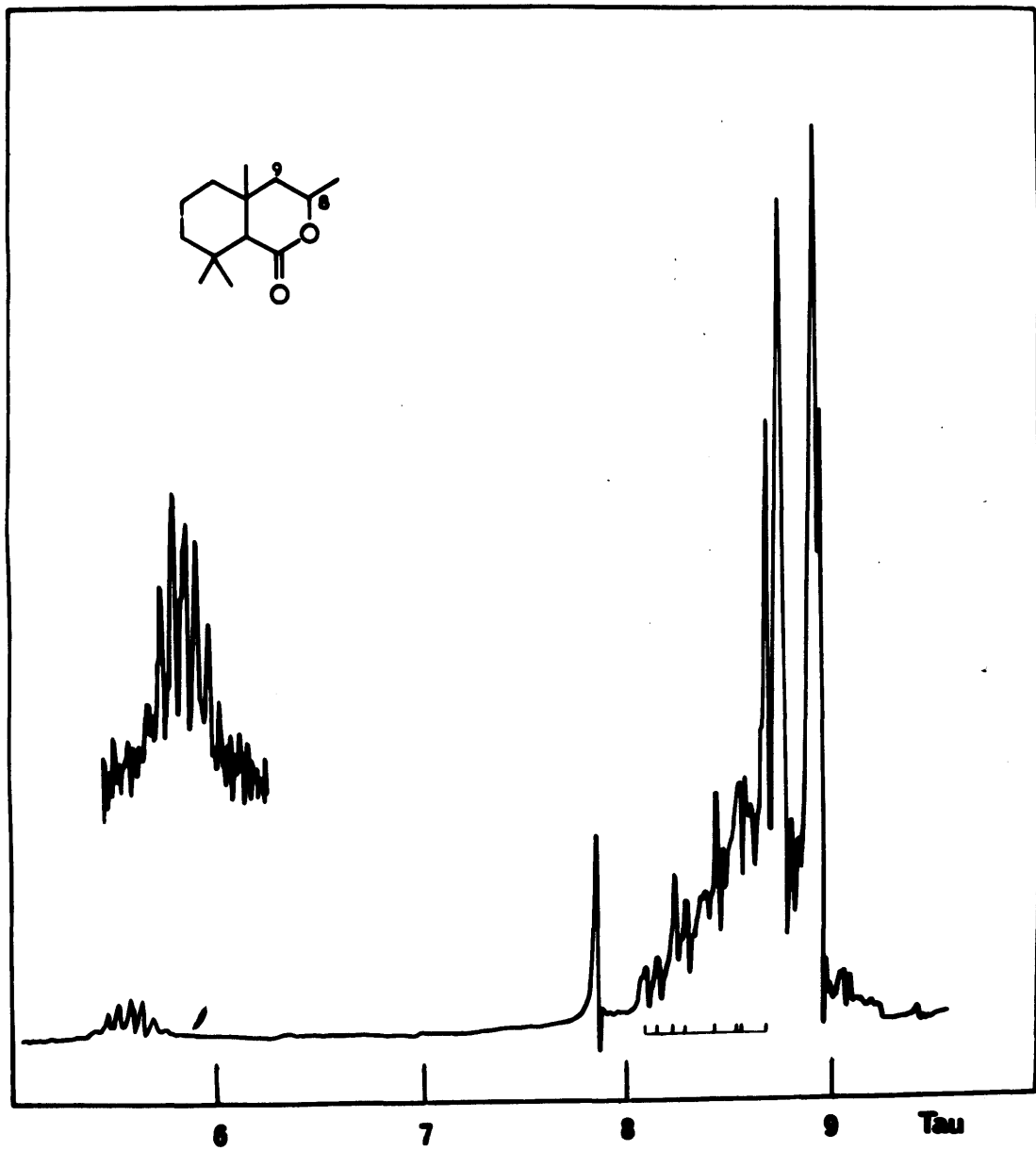
Figure I

Figure 2

EXPERIMENTAL

General Experimental

All melting points were obtained on a Kofler Block and are uncorrected.

Infra-red solution spectra (I.R.) were recorded linearly in cm^{-1} (V_{max}) as percentage transmission by Mrs. P. Lawrie and Mrs. A. M. MacNiven on a Unicam S.P. 100 or a Perkin-Elmer 225 double beam spectrophotometer. Other solution spectra and thin film spectra were obtained on a Perkin Elmer 237 and a Unicam S.P. 200 spectrophotometer respectively. Only the major peaks or peaks of diagnostic value are quoted.

Nuclear magnetic resonance (n.m.r.) spectra were recorded in $CDCl_3$ solution using T.M.S. as an internal standard on a Perkin Elmer R 10, 60 M Hz spectrometer or a Varian H.A. 100, 100 M Hz, spectrometer. The n.m.r. data is recorded on the Tau (T) scale and only signals of diagnostic value are quoted. The Tau (T) values are those obtained from the 60 M Hz spectrum or from the 100 M Hz spectrum after calibration with a Hewlett Packard electronic counter (5212A) and double resonance experiments were performed with a Muirhead Oscillator (D-890-A) on the H.A. 100 spectrometer.

Mass spectra were obtained on an L.K.B. 900 G.C.M.S. or an A.E.I. M.S.9. or M.S.12 spectrometer.

Micro-analysis were performed by Mr. J.M.L. Cameron and his staff.

Gas chromatography (g.l.c.) was performed on Pye Argon gas chromatographs using 4m. x 4mm. I.D. packed glass columns. Other g.l.c. was carried out on a Perkin Elmer F.11. gas chromatograph.

Merk Kieselgel G silica was used for analytical thin layer chromatography (t.l.c.) and preparative thin layer chromatography (p.t.l.c.).

Petroleum ether (pet-ether) refers to the fraction which boils between $60 - 80^{\circ}C$ unless otherwise stated.

All solutions were dried over anhydrous magnesium sulphate or anhydrous sodium sulphate.

Optical rotatory dispersion (O.R.D.) and Circular Dichroism curves (C.D.) were kindly run by Professor W. Klyne and Professor G. Snatzke respectively.

Drimenyl Acetate (31)

Drimanol (9 g.) was dissolved in dry pyridine (60 ml.) and "Analar" acetic anhydride (60 ml.) added. After standing overnight, the solvents were removed under reduced pressure and a red oil (11 g.) was obtained which showed one main spot on t.l.c. (ethyl acetate, petroleum ether 1:9 as eluant.) The oil was chromatographed on silica (300 g.) and drimenyl acetate (31) (8 g.) was eluted with benzene/petroleum ether as a colourless oil.

V_{max}(film) 1735, 1240cm^{-1}

The Isomeric 7ξ, 8ξ – Dihydroxy – 11 Acetoxy – Drimanes (42) and (43)[23].

Drimenyl acetate (0.586 g.) in dry ether (10 ml.) was added to osmium tetroxide (0.5 g.) in dry ether (10 ml.) and pyridine (0.5 ml.). Brown crystals of the osmate complex formed after a few minutes. After 24 hours at room temperature, the ether was removed under vacuum, the osmate taken up in benzene and hydrogen sulphide bubbled through the solution for several minutes. On filtering off the black osmium sulphide and evaporation of the benzene, the crude isomeric 7ξ, 8ξ –dihydroxy – 11 acetoxy drimanes (0.603 g.) were obtained as a brown semi solid. (42) and (43) were separated by p.t.l.c. (ethyl acetate, petroleum ether 1:1 as eluant).

The major product (0.256 g.) was the least mobile diol (42); m.p. 136.5 - 137.5°C (prisms from pet-ether/chloroform); $(\alpha)_D$ - 46.5 (c = 1.46, chf.).

$V_{max}(CCl_4)$ 3635, 3584, 3565, 3460, 1753, 1737, 1724, 1241 cm^{-1}; n.m.r. showed 3H singlets at T9.21, 9.16, 9.13; 3H singlets at T8.00 and T8.87; IH singlets at T7.06 and 6.46 (disappear on D_2O exchange); IH multiplet at T6.44 and a 2H multiplet at T5.80.

(Found: C, 68.57; H, 10.47; $C_{17}H_{30}O_4$ requires C, 68.42; H, 10.13%).

The minor product (0.148 g.) was the more mobile diol (43). m.p. 122.5 - 123.5°C (needles from pet-ether/chloroform); $(\alpha)_D$ + 29 (c = 0.62 chf.); $V_{max}(CCl_4)$ 3582, 3630, 1741, 1233, 1017 cm^{-1}; n.m.r. showed 3H singlets at T9.17, 9.12, and 9.04; 3H singlets at T 8.76 and T 8.02; IH singlets at T 7.88 and 7.72 (disappear on D_2O exchange); IH quartet at T 6.72 (J 12 Hz, 5 Hz); 2H multiplet at T 5.74.

(Found: C, 68.39; H, 10.08; $C_{17}H_{30}O_4$ requires C, 68.42; H, 10,13%.)

The Keto-aldehyde (53) and the keto-ester (55)[24].

The isomeric diols (42) and (43) (89 mg.) in methanol (10 ml.) were mixed with sodium metaperiodate (114 mg.) in water (10 ml.) and the solution left at room temperature for 20 hours. The methanol was removed under reduced pressure and water (10 ml.) added. Extraction with ethyl acetate followed by washing with brine and drying afforded

the keto-aldehyde (53) (84 mg.) as a white crystalline solid. m.p. 139.5 - 140.5;

$V_{max}(CCl_4)$ 2714, 1717, 1746, 1225, 1020 cm^{-1}; n.m.r. showed 9H singlet at T 9.1; 3H singlets at T 8.06 and T 7.88.

(53) (53 mg.) was dissolved in acetone (5 ml.) and Jones reagent added dropwise with shaking and cooling until the brown colour persisted. After a few minutes, water (50 ml.) was added and ether extraction afforded a white solid (49 mg.). The white solid was taken up in ether and the ethereal solution extracted with sodium bicarbonate solution. After acidification and ether extraction a white solid (30 mg.) was recovered which showed characteristic acid streaking on t.l.c. The material was methylated with ethereal diazomethane to give the keto-ester (55). m.p. 75 - 76°C, (needles from pet-ether). $V_{max}(CCl_4)$ 1742, 1717, 1233, 1014 cm^{-1}; n.m.r. showed 3H singlets at T 9.07, 9.12, 9.03, 8.00, 7.78 and 6.30; 2H doublet at T 7.60; 1H quartet at T 7.05 and a 2H multiplet at T 5.55.

(Found: C, 66.19; H, 9.05; $C_{18}H_{30}O_5$ requires C, 66.23; H, 9.26%.)

The keto-ester (55) by oxidation of Drimenyl Acetate with potassium permanganate and potassium periodate.

Drimenyl acetate (8 g.) was oxidised in (2 g.) batches in order that proper mixing of the reagents occured.

Drimenyl acetate (2 g.) was dissolved in "Analar" dioxan (80 ml.) and added to a solution of potassium permanganate (0.5 g.) in water (1300 ml.) containing potassium periodate (26.4 g.). The pH of

the solution was adjusted to 8.0 by addition of potassium carbonate.
The mixture was stirred vigorously for two days and then worked up
by acidification with concentrated hydrochloric acid and then
thorough extraction with ether. The ethereal extract was concentrated,
washed with brine and dried. The four batches yielded a pale green
oil (9.5 g.) which crystallised on standing. This material was
dissolved in ether (100 ml.) and thoroughly extracted with 20% sodium
carbonate solution (4 x 30 ml.). The alkaline solution was acidified
and thoroughly extracted with ether. After washing with brine and drying,
the ether was removed under reduced pressure to yield a brown semi
solid (7.32 g.) which showed characteristic acid streaking on t.l.c.

The neutral material a brown oil (2.0 g.) was checked by t.l.c.
to ensure that all the drimenol acetate had been oxidised.

The acidic material was carefully methylated with ethereal
diazomethane. T.l.c., (ethyl acetate, pet-ether 3:10 as eluant)
showed mainly one spot with a small amount of more mobile material.
G.l.c. (1% SE30, 150°C) showed two peaks, retention times 20.6 minutes
and 11.2 minutes, relative areas 10:1. The components were separated
by p.t.l.c. and the major component was shown to be identical
(g.l.c., t.l.c., I.R. and mixed m.p.) with the keto-ester (55).

The minor component, the keto-acetate (57) was characterised
as the ketol (58) obtained by mild acid hydrolysis (1% concentrated
sulphuric acid in methanol at room temperature overnight.) of the acetate
(57). The ketol was purified by sublimation (80°C at 0.5 mm Hg) and
had m.p. 51 - 53°C (needles). $V_{max}(CCl_4)$ 3490, 3380, 1740, 1697cm^{-1};

n.m.r. showed a 6H singlet at T 9.11.; 3H singlets at T 8.80 and T 6.42; 3H multiplet at T 7.40 – 8.20; 2H quartet at T 5.59 and a 1H broad singlet at T 7.15 which disappeared on addition of D_2O.

(Found: C, 65.75; H, 9.30; $C_{14}H_{24}O_4$ requires C, 65.59; H, 9.44%)

The Hydroxy-Ketone (56).

The keto–ester (55),(9 g.) was dissolved in methanol (2400 ml.) containing 1% concentrated sulphuric acid and allowed to stand overnight at room temperature. The excess sulphuric acid was neutralised with sodium carbonate and the methanol removed under reduced pressure. Brine was added and the solution thoroughly extracted with ether. After washing with brine and drying, the ether was removed under reduced pressure and a pale green oil (7.3 g.) which crystallised on standing was recovered.

V_{max}(film) 3600, 1740, 1670 (shoulder) cm^{-1}.

T.l.c. (ethyle acetate, pet-ether 6:10 as eluant) showed one major spot with two minor ones. The major component, the hydroxy-ketone (56), (5.5 g.) was obtained by crystallisation from pet-ether (40 – 60). The minor components were separated by p.t.l.c.

(56) had m.p. $87°C$ (plates from 40 – 60 pet-ether), $(\alpha)_D$ – $52°$ (c = 1.0, chf.); $V_{max}(CCl_4)$ 3638, 3580, 3515 (unchanged on dilution), 1737, 1715 cm^{-1}; n.m.r. 3H singlets at 9.11, 7.73, and T 6.31; 6H singlet at T 9.05; 1H triplet at T 8.05; 2H doublet at T 7.61; 1H quartet at T 7.23; 2H multiplet at T 6.10.

(Found: C, 67.35; H, 9.64; $C_{16}H_{28}O_4$ requires C, 67.57; H, 9.93%.)

The minor products were the least mobile ϵ -lactone (60);
m.p. 143 - 145°C (needles from 40 - 60 pet-ether);

V_{max} (CCl$_4$) 1759, 1728cm^{-1}; n.m.r. showed 3H singlets at
T 9.23, 9.02, 8.92 and T 7.80; 1H doublet (J 4 Hz) at T 7.57;
3H multiplet at T 7.4 and a 2H multiplet at T 5.52. CD (ethanol);
$(\theta)_{293}$ + 2,210 $(\theta)_{219}$ - 3,150.

(Found: C, 71.32; H, 9.33; C$_{15}$H$_{24}$O$_3$ requires C, 71.39;
H, 9.59%).

The other minor product was the very mobile enone (59); $(\alpha)_D$
- 33° (C = 0.9, chf.); which was microdistilled, (80°C at 0.5 mm. Hg)

V_{max} (CCl$_4$) 3010, 1740, 1689, 1606 cm^{-1}; n.m.r. showed 3H
singlets at T 9.17, 9.06, 8. 91, 7.69 and T 6.43; 2H multiplet at
T 7.77; 1H triplet at T 7.39 and a 2H doublet at T 4.24.

Mass spec. M.W. 266, C$_{16}$H$_{26}$O$_3$ requires 266.

(Found: C, 71.83; H, 9.94; C$_{16}$H$_{26}$O$_3$ requires C, 72.14; H, 9.94%.)

Attempted retroaldol reaction on Keto-ester (55) and hydroxy-ketone (56).

The keto-ester (55) was treated under a variety of acidic and
basic conditions. Generally mild acidic conditions afforded the
hydroxy-ketone (56) while more vigorous conditions; e.g. refluxing
sulphuric acid in dioxan yielded the enone (59) as well as unidentified
products. Basic conditions, even sodium carbonate in methanol,
tended to yield high proportions of the enone (59).

Pyrolysis of the hydroxy-ketone (56) in a furnace at 500°C
yielded the enone (59) and unidentified products.

The Keto-Aldehyde (62).

(i)   The hydroxy-ketone (56) (25 mg. 0.1 m mole), D.M.S.O. (0.33 ml.), dry benzene (0.33 ml.), dicyclohexylcarbodiimide (0.062 g.), dry pyridine (0.008 ml.) and trifluoroacetic acid (0.005 ml.) were stirred overnight at room temperature. Benzene (2 ml.) was added and the dicyclohexylurea produced in the reaction filtered off. The benzene solution was washed with water and dried. T.l.c. showed partial formation of a more mobile product, adjudged to be the keto-aldehyde (62), but although the conditions were varied; Jones oxidation was found to be faster and more convenient.

(ii)   The hydroxy-ketone (56) (9 g.) was dissolved in "Analar" acetone (1.2 l.). Jones reagent (16 ml.) was added slowly with stirring and cooling in ice. The solution was stirred at room temperature for six minutes and methanol added to destroy excess Jones reagent. The reaction mixture was diluted with brine (4 l.) and thoroughly extracted with ether (6 l.). The ethereal extracts were concentrated, washed with brine and dried. Removal of the ether under reduced pressure afforded a pale green oil (8.7 g.). T.l.c. showed one major spot of similar R.F. as that obtained by the D.C.C. oxidation (i)

V_{max} (film) 1730, 1700 cm^{-1}; λ_{max} (C_2H_5OH) 212 nm.; (C_2H_5OH + NaOH) 295 nm. and increase in ε.

(62) decomposed rapidly on standing and was used without delay for the next stage.

The Keto-ester (64).

(i) The crude keto-aldehyde (62) (4 g.) was dissolved in ethanol (300 ml.) and added dropwise with stirring to an aqueous solution of 20% sodium hydroxide (50 ml.) and silver nitrate solution (silver nitrate (3.8 g.) in water (50 ml.)). The resulting solution was stirred over a steam bath for $1\frac{1}{2}$ hours. A silver mirror formed on the sides of the flask during the reaction. The solution was diluted with water (100 ml.) and filtered through a celite pad. The basic solution was carefully acidified with concentrated hydrochloric acid and thoroughly extracted with ether. The ether solution was washed with brine and dried. Removal of the ether under reduced pressure afforded a crystalline product (3.5 g.) which showed characteristic acid streaking on t.l.c. The material was carefully methylated with ethereal diazomethane and a pale green oil (3.5 g.) was obtained. T.l.c. (ethyl acetate, pet-ether 3:7) showed one main spot. G.l.c. (1% SE30, 125°C) showed one main component as 85% of the mixture.

A sample was purified by p.t.l.c. and microdistillation (75°C at 0.04 mm. Hg) and had $(\alpha)_D$ + 40 (c = 1.0); V_{max}(CCl$_4$) 1739, 1709, 1161 cm^{-1}; n.m.r. showed 3H singlets at T 9.13, 9.10, 8.97, 7.87 and T 6.31; 1H triplet (J, 4 Hz) at T 8.12; 2H singlet at T 7.65; 2H doublet (J, 4 Hz) at T 7.67.

Mass spec. M.W. 240 $C_{15}H_{26}O_3$ requires 240.

(Found: C, 70.06; H, 11.10; $C_{15}H_{26}O_3$ requires C, 70.27; H, 11.01%.)

(ii)   The hydroxy-ketone (56) (21 mg.) was dissolved in "Analar"
acetic acid (0.5 ml.). Beckmanns mixture (0.5 ml.) was added
dropwise with stirring and the solution was stirred overnight at
room temperature.   Water (5 ml.) was added and the solution extracted
with ether.   The ether solution was washed with brine and dried.
Removal of the solvent under reduced pressure afforded a pale yellow
oil (12 mg.) which was purified by p.t.l.c. The keto-ester (64) (7 mg.)
was obtained.

Sodium Borohydride Reduction of the Keto-ester. (64).

The keto-ester (64) (2.35 g., 0.01 mole) was dissolved in
ethanol (45 ml.). Sodium borohydride (200 mg. 0.005 mole) was added
and the reaction mixture stirred overnight at room temperature. The
excess sodium borohydride was destroyed by careful addition of dilute
hydrochloric acid to pH 3. The ethanol was removed under reduced
pressure and a few ml. of brine added. The solution was thoroughly
extracted with ether which was washed with brine and dried. Removal
of the ether under reduced pressure afforded a pale green oil (2.2 g.).
T.l.c. showed three products slightly less mobile than starting material.
   V_{max} (film) 3400, 1740 cm^{-1}.

The mixture was separated by multiple running p.t.l.c. on
five (100 x 20 x 0.05 mm.) plates. (ethyl acetate, petroleum ether

2:8 as eluant).

The most mobile product was the ϵ-lactone (68) (769 mg.),

m.p. 117°C (plates from pet-ether 40 -60);

V_{max} (CCl$_4$) 1738, 1273, 1117 cm^{-1}; n.m.r. showed 3H singlets at

T 9.11, 8.94 and T 8.93; 3H doublet (J, 6 Hz) at T 8.63; 2H multiplet

at T 7.4 and a 1H multiplet at T 5.35.

C.D. (isooctane) $(\theta)_{224}$ -2,795 ; Mass spec. M.W. 224,

$C_4 H_{24} O_2$ requires M.W. 224.

(Found: C, 75.15; H, 11.14; $C_{14}H_{24}O_2$ requires C, 74.95; H, 10.78%).

The least mobile product was the hydroxy-ester (66) which was

microdistilled (80°C at 0.03 mm. Hg);

V_{max}(CCl$_4$) 3623, 3400 - 3550 (broad weak band), 1740 cm^{-1};

n.m.r. showed 3H singlets at T 9.18, 9.12, 9.06 and T 6.36;

3H doublets (J 6 Hz) at T 8.85; 1H triplet (J 5 Hz) at T 8.26;

2H doublet (J 5 Hz) at T 7.72 and a 1H multiplet at T 5.92.

(Found: C, 7.06; H, 11.26; $C_{15}H_{28}O_3$ requires C, 70.27; H, 11.01%).

The third component was the hydroxy-ester (65) (773 mg.) which

was microdistilled (80°C at 0.03 mm. Hg) $(\alpha)_D$ -31° (C = 0.8 chf.);

V_{max}(CCl$_4$) 3623, 3523, 1727, (1739 shoulder) cm^{-1}; n.m.r. showed

3H singlets at T 9.25, 9.15, 8.97 and T 6.30; 3H doublet (J, 6 Hz)

at T 8.80; 1H triplet (J, 6 Hz) at T 8.04; 2H doublet (J, 6 Hz)

at T 7.63 and a 1H multiplet at T 5.92.

(Found: C, 70.06; H, 11.10; $C_{15}H_{28}O_3$ requires C, 70.27; H, 11.01%).

The hydroxy-ester (66) decomposed to the ϵ-lactone (68) on standing.

The ϵ-Lactone (67).

The hydroxy-ester (65) (30 mg.) was heated under reflux with 2% potassium hydroxide in aqueous methanol for two hours. The solution was acidified with dilute hydrochloric acid and allowed to stand for a few minutes. The aqueous solution was thoroughly extracted with ether and after washing with brine and drying, a colourless oil (28 mg.) was recovered which showed characteristic acid streaking on t.l.c.

The acidic material was taken up in dry benzene (25 ml.) and refluxed with p - toluene sulphonic acid (15 mg.) under a Dean and Stark for 10 minutes. The benzene solution was cooled in ice, washed with sodium bicarbonate solution, brine and dried. A colourless oil (19 mg.) which crystallised on standing was recovered. T.l.c. showed one spot together with a small amount of acidic material on the base line. This acidic material increased on standing or if attempts were made to purify the lactone by p.t.l.c. or crystallization. However, although satisfactory analysis could not be obtained the ϵ-lactone (67) was sufficiently pure to obtain infra-red and n.m.r. spectra.

V_{max} (CCl$_4$) 1750, 1275, 1190, 1142 cm^{-1}; n.m.r. showed 3H singlets at T 8.9, 9.1 and 9.2; 3H doublet (J = 6 Hz) at T 8.75; 2H multiplet at T 7.4. and 1H multiplet at T 5.45.

The Diphenyl Ethylene Acetate (71).

The hydroxy-ester (65) (600 mg.) was dissolved in ether (16 ml.) and added with stirring during 10 minutes to a solution of phenyl magnesium bromide prepared from magnesium turnings (640 mg.) and bromobenzene (4.5 ml.) in ether (32 ml.). The mixture was refluxed for two hours and stirred overnight at room temperature under nitrogen. The carbinol was liberated by dropwise addition of saturated ammonium chloride solution (10 ml.). The ether layer was decanted and the precipitated ammonium salts washed with ether by decantation. The ether solution was washed with brine and dried. A pale green oil (1.5 g.) was obtained. T.l.c. showed a mixture with one spot predominating.

V_{max} (film) 3400 (broad), 3050, 2910, 1590, 740, 690 cm^{-1}.

The oil was not purified but was dissolved in glacial acetic acid (12 ml.) and acetic anhydride (24 ml.) and refluxed for four hours. All the solvent was removed under reduced pressure and the residue (1.5 g.) was chromatographed on silica (100 g.) The fraction rich in diphenyl ethylene acetate (71) was eluted with benzene/pet-ether (40 - 60). (71) crystallised as white needles (400 mg.) from pet - ether (40 - 60); m.p. 117 - 118°C, $(\alpha)_D$ + 86° (c = 0.6 chf.);

V_{max} (CCl$_4$) 3084, 2930, 1744, 1606, 1250 cm^{-1}; n.m.r. showed 3H singlet at τ 9.19; 6H singlet at τ 8.9; 3H doublet (J 6 Hz)

at T 8.87; 1H doublet (J 11 Hz) at T 8.17; 3H singlet T 8.06;
1H multiplet at T 5.0; 1H doublet (J 11 Hz) at T 3.80; and a 10H
multiplet at T 2.72.

(Found: C, 82.96; H, 8.92; $C_{28}H_{38}O_2$ requires C, 83.12; H, 8.97%.)

Further elution with ether/benzene afforded a crystalline
compound (200 mg.) which had $V_{max}(CCl_4)$ 1744, 1705, 1240;
n.m.r. showed 3H singlet at T 9.27; 6H singlet at T 9.06; 3H doublet
(J 6 Hz) at T 9.93; 3H singlet at T 8.03; 1H multiplet at T 4.95;
3H multiplet at T 2.6 and a 2H multiplet at T 2.0.

The Enol-ether (72).

(i) The ϵ -lactone (68) (200 mg.) was dissolved in ether
(5 ml.) and added with stirring during 5 minutes to a solution of
phenyl magnesium bromide prepared from magnesium (220 mg.) and
bromobenzene (1.5 ml.) in dry ether (10 ml.). The mixture was
refluxed for four hours under nitrogen and the carbinol liberated
by dropwise addition of a solution of saturated ammonium chloride (4 ml.).
A pale green oil (533 mg.) contaminated with biphenyl (a by product
of the Grignard reaction) was obtained after the usual work up.

V_{max} (film) 3400, 3050, 2950, 1680, 1590, 1570, 740, 700cm^{-1}.

The green oil was dehydrated by dissolving in acetic acid (3 ml.)
and acetic anhydride (6 ml.) and refluxing for four hours. The
solvents were removed under reduced pressure and some of the

biphenyl removed by adding water and azeotroping with benzene. Finally a brown oil (512 mg.) was obtained which showed one main spot on t.l.c. (ethyl acetate, pet-ether 1:9) which was much more mobile than the diphenyl ethylene acetate (71).

The major product, the enol-ether (72) (200 mg.) was isolated by p.t.l.c. and an analytical sample prepared by microdistillation. (80°C at 0.03 mm. Hg .).

V_{max} (CCl$_4$) 3080, 2933, 1648, 1496, 1380, 1118, 1063, 1038 cm^{-1}; n.m.r. showed 6H singlet at T 9.07; 3H singlet at T 8.97; 3H doublet (J 6 Hz) at T 8.65; 1H doublet (J 6 Hz) at T 7.75; 1H multiplet at T 6.10; 1H doublet (J 6 Hz) at T 4.37 and 5H multiplet at T 2.5.

(Found: C, 84.07, H, 10.15; $C_{20}H_{28}O$ requires C, 84.45; H, 9.92%.)

(ii) The hydroxy-ester (66) was reacted with phenyl magnesium bromide as in (i). The major product was the enol-ether (72) as shown by t.l.c. and I.R.

Ozonolysis of the Diphenyl Ethylene Acetate (71).

(71) (500 mg.) was dissolved in "Analar" ethyl acetate (250 ml.). Ozone (100 ml./min.) was bubbled through the solution for five hours at room temperature. Acetic acid (50 ml.) and 30% hydrogen peroxide (5 ml.) were added to the solution and left at room temperature overnight. The solvents were removed under reduced pressure and the

residue taken up in ether. The ether solution was extracted with aqueous sodium carbonate solution which on acidification and ether extraction afforded a pale green oil (200 mg.). Continous ether extraction of the sodium carbonate solution yielded a further (60 mg.) of material. The acidic material was carefully methylated with ethereal diazomethane and the two major products separated by p.t.l.c. (ethyl acetate, pet-ether 2:8).

The most mobile band was the acetate (74) (50 mg.). (74) showed one peak on g.l.c. (1% QF - 1, 100°C, 1% SE 30, 100°C). (74) was microdistilled and the oil had $(\alpha)_D$ + 19 (C = 1.1); V_{max} (CCl$_4$) 1735, 1239, 1158 cm^{-1}; n.m.r. showed 3H singlets at T 9.09, 8.90, 8.85, 8.00 and T 6.35; 3H doublet (J 6 Hz) at T 8.82; 1H singlet at T 7.90; and a 1H multiplet at T 4.90.

(Found: C, 67.82; H, 9.90; $C_{16}H_{28}O_4$ requires C, 67.57; H, 9.93%).

The less mobile product was the crystalline acetate (75) (70 mg.); m.p. 108 - 109°C (plates from pet-ether); V_{max} (CCl$_4$) 3040, 2930, 1736, 1720, 1240, .700 cm^{-1}. n.m.r. showed 3H singlet at T 9.24; 6H singlet at T 8.95; 3H doublet (J 6 Hz) at T 8.84; 1H doublet (J 12 Hz) at T 8.24; 3H singlet at T 6.27; 1H multiplet at T 5.0; 1H doublet (J 12 Hz) at T 2.79; 5H multiplet at T 2.70 and a 3H singlet at T 8.06.

(Found; C, 74.71; H, 8.88; $C_{24}H_{34}O_4$ requires C, 74.57; H, 8.87%).

Unreacted starting material (500 mg.) was recovered.

Oxidation of the Diphenyl Ethylene Acetate (71) with Ruthenium Tetroxide.

Ruthenium dioxide (12 mg.) was added to a stirred 5% aqueous solution of sodium periodate (1.3 ml.). The diphenyl ethylene acetate (71) (60 mg.) in acetone (5 ml.) was added to the stirred solution. After 15 minutes the solution turned black and the yellow colour was regenerated by addition of sodium periodate (100 mg.). This was repeated twice during the ensuing 24 hours. The excess ruthenium tetroxide was destroyed by addition of isopropanol (1 ml.) and the solvent removed under reduced pressure. The residue was taken up in ethyl acetate (10 ml.) and washed with brine. The ethyl acetate was dried and removed under reduced pressure to yield a black oil (50 mg.) which showed characteristic acid streaking on t.l.c. The black oil was dissolved in ethyl acetate and thoroughly extracted with saturated sodium carbonate solution. The carbonate solution was acidified with concentrated hydrochloric acid, saturated with sodium chloride and thoroughly extracted with ethyl acetate. After washing with brine and drying, removal of the ethyl acetate under reduced pressure afforded a colourless oil (32 mg.) $V_{max}(CCl_4)$ 3400 – 2400, 1757, 1703, 1240 cm^{-1}.

The acid was methylated with ethereal diazomethane and the resulting ester shown by t.l.c., g.l.c. and I.R. comparison to be identical with the acetate (74)

Attempted ozonolysis of the Enol-ether (72).

The enol-ether (72) (25 mg.) was dissolved in absolute
ethanol (10 ml.) and a stream of ozone bubbled through the solution
for 1.5 hours at $0^{o}C$. The ethanol was removed under reduced pressure
and 30% hydrogen peroxide (0.5 ml.) and acetic acid (2.5 ml.) added
to the oily residue. The solution was left overnight at room
temperature and the solvents removed under reduced pressure. T.l.c.
showed mainly unchanged starting material together with a small
amount of acidic material.

Reaction of the Enol-ether (72) with Osmium Tetroxide.

The enol-ether (72) (200 mg.) in dry ether (5 ml.) was added
to a solution of osmium tetroxide (220 mg.) and pyridine (0.25 ml.)
in ether (5 ml.). After a few minutes the solution turned brown.
The reaction mixture was left in a stoppered flask in the dark at room
temperature for 3 days. The ether was blown off with a stream of
nitrogen and the brown residue dissolved in benzene (10 ml.).
Hydrogen sulphide gas was bubbled through the benzene solution for
two minutes. The black precipitate of osmium disulphide was removed
by filtration through a celite pad. A clear oil (208 mg.) was
obtained. T.l.c. showed some starting material together with three
less mobile products. The products were isolated by p.t.l.c. (ethyl
acetate, pet-ether 2:8) Unreacted starting material (61 mg.) was

recovered. The two least mobile products were recovered as crystalline material (26 mg.) which were separated by multiple running on p.t.l.c. (ethyl acetate, pet-ether 2:8). The minor product (3 mg.) was not examined any further but the major band afforded the ketol (77) (20 mg.) which had m.p. 107 – 108°C (plates from pet-ether); $V_{max}(CCl_4)$ 3620, 3455, 1702 cm^{-1}; n.m.r. showed 3H doublet (J 6 Hz) at T 9.33; 6H singlet at T 8.98; 3H singlet at T 8.90; 1H singlet (sharpens on irradiation at T 4.89) at T 7.45; 1H multiplet at T 6.50; 1H singlet at T 4.89 (sharpens on irradiation at T 7.45 and on addition of D_2O); 5H broad singlet at T 2.65.

(Found: C, 75.42; H, 9.48; $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50%).

The third product from p.t.l.c. was the aldehyde (76) (67 mg.) which was obtained as a colourless oil.

$V_{max}(CCl_4)$ 3460 (weak, carbonyl overtone), 3060, 3015, 2840, 2740, 1730 ($\epsilon \sim 600$), 1275, 1110 cm^{-1}; n.m.r. showed 3H singlets at T 9.04, 8.81, 8.75; 3H doublet (J 6 Hz) at T 8.68; 1H doublet (J 6 Hz) at T 8.17; 1H multiplet at T 4.52; 2H quartet at T 1.89; 3H multiplet at T 2.48 and a 1H doublet (J 6 Hz) at T – 0.74.

The aldehyde (76) (60 mg.) on standing in air was oxidised to acidic material which on extraction with sodium carbonate solution, acidification and the usual work up afforded an oil which on methylation with ethereal diazomethane afforded the benzoate (78) (30 mg.) as a colourless oil. The benzoate was purified by p.t.l.c. (ethyl acetate, pet-ether 2:8) and microdistilled (80°C at 0.05 mm.

Hg.) $(\alpha)_D$ + 51 (C = 1.26 chf.);

$V_{max}(CCl_4)$ 3060, 2930, 1736, 1718, 1270 cm^{-1}; n.m.r. showed 3H singlets at T 9.09, 8.88, 8.82; 3H doublet (J 6 Hz) at 8.71; 1H singlet at T 7.81; 3H singlet at T 6.34; 1H multiplet at T 4.60; 3H multiplet at T 2.49 and a 2H multiplet at T 1.97.

(Found: C, 72.69; H, 8.75; $C_{21}H_{30}O_4$ requires C, 72.80; H, 8.73%.)

Attempted oxidation of the aldehyde (76).

(i) The aldehyde (76) (20 mg.) in acetone (10 ml.) was stirred with Jones reagent (two drops) for ten minutes at room temperature. The excess oxidising reagent was destroyed by addition of methanol and the solvents removed under reduced pressure. Dilution with brine and ether extraction afforded an oil (16 mg.) which was unchanged starting material as adjudged by t.l.c.

b) The aldehyde (76) (16 mg.) in ethanol (5 ml.) was treated with silver nitrate solution (silver nitrate (50 mg.) in water (1 ml.)) and 20% aqueous sodium hydroxide (1 ml.) on a steam bath for one hour. The solution was diluted with water and filtered through a celite pad. Acidification with hydrochloric acid followed by ether extraction afforded a colourless oil (10 mg.) which showed a number of spots on t.l.c. together with a small amount of acidic material.

The Ethylene Ketal (79).

The keto-ester (64) (750 mg) in benzene (50 ml.) was refluxed together with ethylene glycol (2g.) and p – toluene sulphonic acid (15 mg.) under a Dean and Stark water separator. The reaction was monitored by t.l.c. and after 24 hours the conversion of starting material to a product of slightly greater mobility was complete. The benzene solution was washed with sodium bicarbonate solution (3 x 20 ml.), water (2 x 20 ml.) and brine (2 x 20 ml.) After drying the solvents were removed under reduced pressure to yield the ethylene ketal (79) as a colourless oil (800 mg.). G.l.c. showed one peak, (1% SE-30 at 140°C) of retention time 24.7 minutes. (64) under the same conditions has a retention time of 10.0 minutes.

V_{max} (film) 1740, 1200, 1100, 1045 cm^{-1}; n.m.r. showed 3H singlets at T 9.2, 9.1, 9.0 and T 8.68; 4H multiplet at T 6.33; 3H singlet at T 6.1 and a 3H multiplet at T 7.7.

The ketal was used without further purification for the next stage.

The Diphenyl Ethylene Ketone (80).

The ethylene ketal (79) (670 mg.) was dissolved in ether (35 ml.) and added with stirring during 10 minutes to a solution of phenyl

magnesium bromide prepared from magnesium (630 mg.) and bromobenzene (3.5 ml.) in ether (17 ml.). The mixture was refluxed for three hours and stirred overnight at room temperature. The carbinol was liberated by dropwise addition of saturated ammonium chloride solution (10 ml.) The ether layer was decanted and the precipitated ammonium salts washed with ether. After work up in the usual way a pale green oil (2.1 g.) was obtained. T.l.c. showed a mixture with two spots predominating.

V_{max} (film) 3400, 3050, 2920, 1590, 730, 695 cm^{-1}.

The oil was dissolved in glacial acetic acid (100 ml.) and water (25 ml.) and refluxed for five hours. The solvents were removed under reduced pressure and a pale green oil (1 g.) was obtained.

V_{max} (film) 3400, 3050, 2910, 1740, 1700, 1595, 1450, 1370, 1240, 735, 700 cm $^{-1}$.

The crude product (1 g.) was chromatographed on silica (80 g.). The first product a colourless oil (121 mg.) was eluted with benzene, pet-ether (2:98); V_{max} (film) 3050, 2910, 1670, 1595, 740, 690 cm^{-1}. This compound was not examined any further.

The diphenyl ethylene ketone (80) (270 mg.) was eluted with benzene, pet-ether (2:8). A sample was microdistilled for analysis (100°C at 0.05 mm. Hg.).

$V_{max}(CCl_4)$ 3070, 3050, 3010, 2940, 2920, 1710, 1595, 695 cm^{-1}; n.m.r. showed 3H singlets at T 9.14, 8.93, 8.80 and T 8.01; 1H doublet (J 14 Hz) at T 7.39; 1H doublet (J 14 Hz) at T 3.80 and 10 H multiplet at T 2.7.

(Found: C, 86.64; H, 9.18; $C_{26}H_{32}O$ requires C, 86.61; H, 8.95%.)

The Nor-Keto-ester (81).

Ruthenium dioxide (60 mg.) was added to a stirred 5% aqueous solution of sodium periodate. The diphenyl ethylene ketone (200 mg.) in acetone (30 ml.) was added to the stirred solution. After a few minutes the solution turned black and the yellow colour was regenerated by addition of sodium periodate (200 mg.). This was repeated several times during the ensuing 24 hours after which the excess ruthenium tetroxide was destroyed by the addition of iso-propanol (1 ml.). The black colloidal solution was filtered through glass filter paper and the residue washed well with acetone. The filtrate, which was still slightly cloudy owing to the presence of colloidal ruthenium dioxide, was evaporated to dryness. The black oil was taken up in ether and washed thoroughly with brine. After drying the ether was removed under reduced pressure and a pale green oil (150 mg.) was recovered. Continuous extraction of the residues afforded no further material. T.l.c. showed typical acid streaking.

V_{max} (film) 3500 -- 2500, 3050, 2910, 1720, 1690, 1650, 700 cm^{-1}.

The oil was taken up in chloroform which was extracted with sodium carbonate solution. The basic extract was acidified with concentrated hydrochloric acid, saturated with sodium chloride and thoroughly extracted with chloroform. The chloroform extract was washed with brine and dried. Removal of the solvent under reduced pressure afforded a pale green oil (70 mg.). The material was carefully methylated with ethereal diazomethane and t.l.c. (ethyl-acetate, pet-ether 2:8) showed one main spot. The oil was purified by p.t.l.c. to yield the nor keto-ester (81) as a colourless oil (52 mg.). An analytical sample was prepared by microdistillation (80°C at 0.1 mm. Hg.); $(\alpha)_D$ + 37° (C = 0.46 chf.).

V_{max}(CCl$_4$) 2920, 1734, 1705 (1734 band almost twice as intense as band at 1705 cm^{-1}.), 1140, 1158 cm^{-1}, n.m.r. showed 3H singlets at T 9.10, 8.90, 8.80, 7.92, and T 6.37; 2H singlet at T 7.66; 1H singlet at T 7.57.

(Analysis by Mass Spec: found M.W. 240.1723 ; $C_{14}H_{24}O_3$ requires 240.1725.)

The Isomeric Hydroxy -esters (82) and (83).

The nor keto-ester (81) was taken up in ethanol (4 ml.) and sodium borohydride (10 mg.) added. The solution was stirred for six hours at room temperature and the excess sodium borohydride

destroyed by addition of dilute hydrochloric acid to pH 3. The
solvents were removed under reduced pressure and the residues
taken up in ether. The ether solution was washed with brine
and dried. Removal of the ether under reduced pressure afforded
a pale green oil (70 mg.). T.l.c. (ethyl acetate, pet ether 4:6)
showed formation of two products of similar mobility but more
polar than the starting ketone. The epimeric hydroxy-esters (82) and
(83) were separated on p.t.l.c. by multiple running (ethyl acetate,
pet-ether 1:9). The hydroxy-ester (82) (18 mg.), the more mobile
epimer was acetylated and the acetate shown to be identical to the
acetate (74) by t.l.c. and I.R.

(82) showed: V_{max} (CCl$_4$) 3612, 3565, 1732, 1715 (shoulder),
1700 (lower intensity that 1732 band), 1136 cm^{-1}; n.m.r. showed
3H singlets at T 9.13, 8.90 and T 8.92; 3H doublet (J 6 Hz) at
T 8.88; 1H singlet at T 8.20 (disappears on addition of D$_2$O); 1H singlet
at T 7.76; 3H singlet at T 6.39 and a 1H multiplet at T 6.05.

The least mobile epimer, the hydroxy-ester (83) (18 mg.) was
shown to be identical with the hydroxy-ester formed by mild
hydrolysis of the benzoate (78) by t.l.c. and I.R. (83) showed:
V_{max} (CCl$_4$) 3615, 1733, 1715 (small shoulder), 1136 cm^{-1}; n.m.r.
showed 3H singlets at T 9.11, 8.88 and 8.81; 3H doublet (J 6 Hz)
at T 8.87; 1H broad singlet at T 7.5 (disappears on addition of
D$_2$O), 1H singlet at T 7.84; 3H singlet at T 6.39 and a 1H multiplet at
T 6.00.

The δ-lactone (26).

The hydroxy-ester (83) (18 mg.) in 2% potassium hydroxide in methanol (20 ml.) was refluxed for three hours. The methanol solution was acidified and the solvents removed under reduced pressure. The residue was taken up in brine which was thoroughly extracted with ethyl acetate. The ethyl acetate solution was washed with brine and dried. Removal of the solvents afforded a pale green oil (15 mg.) which was purified by p.t.l.c. (ethyl acetate, pet-ether 2:8) and microdistilled to yield a colourless oil (9 mg.) which was one peak on g.l.c., 1% SE – 30, 1% P.F.G.A., 10% APL. V_{max} (CCl$_4$) 1740, 1128 cm^{-1}; n.m.r. showed 3H singlets at T 8.87, 8.87 and 8.78; 1H singlet at T 8.06, 3H doublet (J 6 Hz) at T 8.67 and 1H multiplet (W 36 Hz) at T 5.40.

(found: Mass spec. M.W. 210.16186; $C_{13}H_{22}O_2$ requires 210.16197.)

The δ-lactone (27).

The acetate-ester (74) (30 mg.) was hydrolysed by refluxing with 2% potassium hydroxide in methanol (30 ml.). On acidification and the usual work up, a colourless oil (20 mg.) was obtained. The δ-lactone (27) (15 mg.) was isolated by p.t.l.c. and sublimation. (27) was a semi solid mp. 36 – 38°C; g.l.c. one peak (1% SE –30, 1% P.F.G.A., 5% APL); V_{max} (CCl$_4$) 1755, 1118 cm^{-1}; n.m.r. showed 3H singlets at T 8.92, 8.89 and 8.74; 3H doublet (J 6 Hz) at T 8.69;

1H singlet at T 7.83 and a 1H multiplet at T 5.57 (W 36 Hz).

Mass spec. M.W. 210 $C_{13}H_{22}O_2$ requires 210.

(Found: C, 74.06; H, 10.62; $C_{13}H_{22}O_2$ requires C, 74.24;
H. 10.54%.)

CHAPTER 2

DISCUSSION PART 2

As discussed in chapter 1, there is disagreement as to the preferred conformation of δ-lactone rings. The controversy arises mainly over supposedly unstrained δ-lactones such as (88) and (89). According to Overton[3] lactones such as these prefer to adopt the half-chair conformation (91) whereas, Wolf[9], and Legrand and Bucourt[10] suggest that they should adopt a half-boat conformation (90).

To try and resolve the above differences of opinon, the simple unstrained δ-lactone (92) has been synthesised and efforts made to determine its conformation by n.m.r. and by using the well established correlation between infra-red carbonyl frequency and conformation (see chapters 1 and 2 (part 1)). In chapter 5, the chiroptical properties of (92) in relation to its conformation are discussed.

First of all, however, we wish to present the results of some calculations of the relative conformational energies of the half-boat (90) and half-chair (91) conformations of δ-valerolactone. This has been done in order to see if it was possible to reproduce Bucourt[10] results.

Since we did not have the necessary computer programme, it

was not possible to carry out a strain energy minimisation
calculation of the type developed by Wiberg[36]. Instead
the geometries of the minimum energy forms of the half-chair
and half-boat were obtained from the X-ray data of the appropriate
molecules. The bond lengths which were finally used are shown
in table VI and the bond angles in figure 3 (half-chair) and
figure 4 (half-boat).

Table VI. Bond lengths used in the calculation of the
conformational energies of the half-chair and half-boat
δ-valerolactones.

Bond	Bond length Å
C_{sp^3} — C_{sp^3}	1.53
C_{sp^2} — C_{sp^3}	1.49
C_{sp^3} — O	1.49
C_{sp^2} — O	1.37
C_{sp^3} — H	1.09

The C – C – H and H – C – H angles were calculated as described by Hendricksen[37] and the torsion angles calculated to fit the assigned bond-lengths and bond-angles. An attempt was made to minimise the energy of the half-boat conformation (figure 4) by adjusting the bond angles so as to minimise the strain due to the H_2 – – – H_8 non bonded interaction. In both conformations the C – O – C – C group was kept planar.
                                                            ‖
                                                            O

Once the geometry of the systems had been assigned it was a simple matter to calculate their conformational energies. The expressions used to evaluate the contributions from torsional strain (E_t), bond angle deformations (E_Θ) and non-bonded inter-actions (E_v) were taken from Allingers and Hendricksons[38,39] papers and are summarised in table VII. Also listed in tables VIII, IX and X are the values of the parameters used in these equations. These are the equilibrium values of the different bond angles (table VIII), the constants used in the expression for E_v (table IX) and the torsional constants (table X). These parameters are again taken mainly from Allingers papers[40,41].

Table VII. Expressions for E_t, E_θ and E_v.

$$E_t \quad = \quad 0.5\,K_t\,(1 + \cos 3\omega)$$

K_t = torsional constant

ω = torsion angle

$$E_\theta \quad = \quad K_\theta\,(\Delta\theta)^2$$

K_θ = bonding force constant

$\Delta\theta$ = deformation from

equilibrium bond angle.

$$E_v \quad = \quad -2.25\,\epsilon\,(d^*/r)^6 + 8.28 \times 10^5\,(\epsilon)\,\exp\,(-r/0.0736\,d^*)$$

r = internuclear distance

d^* and ϵ are empirically

determined parameters

characteristic of each

atom.

Table VIII. Constants used in calculating bond angle strain

Angle	Equilibrium bond angle	K_θ K cal mole^{-1} rad^{-2}
H - C - H	107.1	23.0
H - C - C	109.4	39.6
C - C - C	112.0	57.5
H - C - O	109.5	36.0
$C_{sp}3 - C_{sp}3 - 0$	111.0	70.5
$C_{sp}3 - C_{sp}2 - 0$	(a)	79.3
$C_{sp}3 - C_{sp}2 = 0$	(a)	45.8
$0 - C = 0$	(a)	50.0
$C_{sp}3 - 0 - C_{sp}2$	(a)	70.0
$C_{sp}3 - C_{sp}3 - C_{sp}2$	111.0	79.3

(a) see text.

Table IX. Parameters used in calculating E_v.

Atom	r^* $(d^* = 2r^*)$	ϵ
$C_{sp}3$	1.65	0.040
$C_{sp}2$	1.85	0.020
H	1.45	0.100
0	1.54	0.070

Table X. Torsional constants.

Angle	K_t k cal mole^{-1}
$H - C_{sp}3 - C_{sp}3 - H$	0.55
$C_{sp}3 - C_{sp}3 - C_{sp}3 - H$	0.98
$C_{sp}3 - C_{sp}3 - C_{sp}3 - C_{sp}3$	0.49
$0 - C_{sp}3 - C_{sp}3 - C_{sp}3$	1.00
$C_{sp}2 - C_{sp}3 - C_{sp}3 - C_{sp}3$	0.49
$0 - C_{sp}2 - C_{sp}3 - C_{sp}3$	1.00
$C_{sp}2 - 0 - C_{sp}3 - C_{sp}3$	1.00[b]

(b) estimated from barrier in ethyl formate[42].

Some difficulty was encountered in choosing an equilibrium

value for the C - O - C and C - CO - O bond angles. Values for open

chain esters are not very good because of the difference in

conformation between them and lactones (i.e. esters are s - trans

while lactones are s - cis). The C - CO - O angle in open chain

esters is around 113° [4] which is close to the value obtained for

the half-boat. In addition examination of molecular models

suggests that the angle strain in the half-boat is low. Accordingly

a calculation was carried out assuming that the C - CO - O and

C - O - C bond angles in the half-boat were completely unstrained.

The energies of the two conformations are shown in table XI. As

can be seen the difference in conformational energy between the

two forms is only 0.4 k cal mole^{-1}.

Table XI. Strain energies of a half-chair and half-boat δ-valerolactone.

Conformation	E_{θ}	E_t	E_v	E_{total}
half-chair	3.656	2.033	2.327	8.006
half-boat	0.264	1.804	6.305	8.373

E_Θ is very sensitive to the equilibrium bond angles chosen for C - O - C and C - CO - O and if for example these values are changed by 2° and 1° respectively in favour of the half-chair then the energies are as shown in table XII.

Table XII. Strain energies of a half-chair and half-boat δ-valerolactone.

Conformation	E_Θ	E_t	E_v	E_{total}
half-chair	2.609	2.023	2.327	6.959
half-boat	0.403	1.804	6.305	8.512

From tables XI and XII it can be seen that most of the strain in the half-chair is due to angle strain while in the half-boat, non-bonded interactions account for the bulk of the total strain. Owing to difficulties in obtaining reasonable values for some of the parameters used in the calculation and because of the small difference in total energy content between the two conformations, any predictions as to the most stable conformer based on a calculation of the above type must be treated with caution.

However, it does seem that the difference in energy between the two conformations is small and as a result equilibrium mixtures of the two conformations cannot be ruled out in certain situations.

During the course of this work, Sheppard and Turner[7] published evidence which was consistent with the δ-lactone ring in (93), (94) and (95) being a flattened half-chair (96). This conclusion was based on the magnitude of the coupling constants between the C 17 and C 17a protons and on the deshielding effect of an axial acetate group on the C 14 proton. Their results are summarised in table XIII.

Table XIII.   N.m.r. and I.R. data from reference 7.

Lactone	τ, C 14 - H	J(C 17 - H C 17a - H)	$V_{c=o}$ (cm^{-1})
93	5.92	6.0, 1.5	1723 $(CHCl_3)$
94	6.01	6.5, 1.3	1743 (CCl_4)
95	6.47	8.0, 8.7	1751 (CCl_4)

While agreeing with Sheppard and Turner that these results can be explained by the lactone ring being in conformation (96), an alternative and equally valid explanation is that the lactone ring

is a rapidly inverting equilibrium mixture of half-chair and half-boat conformers with the former predominating (see also page 86). This of course results in the average conformation on the n.m.r. time scale being a slightly flattened half-chair.

The conformation of (92) can be determined by application of Overton's correlation[3] between infra-red carbonyl frequency and conformation. However, to act as a check, it was decided to try and determine the conformation by n.m.r. To achieve this end, the trideutero-lactone (97) was synthesised and n.m.r. spectra of it obtained at 220 M Hz. It was hoped that it would be possible to assign the conformation of (97) by fitting a calculated spectrum to the observed one. It was felt that calculated spectra based on parameters appropriate to the two possible conformers would differ considerably because of the difference between the coupling constants expected for a half-chair conformation of (92) and those expected for a half-boat. Thus in the half-chair (97a) there are one large and three small vicinal coupling constants while in the half-boat (97b) there are two large and two small vicinal coupling constants.

(92) was easily synthesised by a Baeyer Villiger oxidation[43,44] of the t - butyl - cyclopentanone (99) which was obtained by reacting lithium dimethyl copper[45] in ether solution with the

known 2 - isopropylidene cyclopentanone[48] (98). (92) was characterised by n.m.r. which showed a 1H quartet (J = 12 Hz, 3 Hz) at T 6.05 due to the C 5 proton, a 9H singlet at T 9.05 due to the t-butyl group and multiplets between T 7 - 9 due to the other protons. The infra-red carbonyl frequency in carbon tetrachloride solution was 1745 cm^{-1} which is within the range characteristic of half-chair δ-lactones.

To obtain the trideutero-lactone (97), the t-butyl ketone (99) was refluxed in methanol-OD and deuterium oxide containing sodium and the product oxidised with buffered peroxytrifluoroacetic acid[43]. (97) showed no signals in the n.m.r. below T 8.0 and the deuterium content by mass spectroscopy was d_3 80%, d_2 20%.

The n.m.r. spectrum of (97) in deuterochloroform solution at 220 M Hz is shown in figure 5. Spectra were obtained in number of different solvents, (benzene d_6, pyridine d_5, DMSO d_6, acetone d_6) but the one shown in figure 5 proved to be the most informative. The spectrum was initially divided into four groups of multiplets A, B, C, D, (figure 5). Because of the signal width, D is assigned to an axial proton. C which partly overlaps B can tentatively be assigned to the other axial proton. The splitting of the multiplet C suggests coupling of the order of J = 6 Hz and J = 14 Hz. It seemed from preliminary computer calculations based on the limited parameters that could be extracted from the 220 M Hz

spectrum of (97), that a distinction could be made in favour of the half-chair conformation. However it was felt that as many of the unknown parameters as possible should be determined and this was attempted as follows.

In order to assign the multiplets in figure 5 to the protons in (97) decoupling experiments on the lactone (92) were carried out at 220 M Hz. Irradiation at the multiplet in the 220 M Hz n.m.r. spectrum of (92), corresponding to the multiplet D in figure 5 collapsed the large coupling (J = 12 Hz) in the C 5 – H quartet. This confirms that the multiplet D in figure 5 is due to the axial proton on C 4. Irradiation at the multiplet corresponding to A in the 220 M Hz spectrum of (92) removed the small coupling (J = 3 Hz) in the C 5 – H quartet. Thus the multiplet A in figure 5 is due to the C 4 equatorial proton.

In order to obtain the chemical shift and geminal coupling constant between the C 3 protons, the tetra-deutero lactone (100) was synthesised. It was planned to obtain (100) via the keto-ester (102), which in turn was obtained by Jones oxidation of the methyl ester (101) of the hydroxy-acid formed by base hydrolysis and methylation of the lactone (92). Unfortunately, deuteration of (102) was hindered owing to hydrolysis of the methyl ester to the carboxylic acid which in basic solution formed the carboxylate anion. The carboxylate anion is of course not a strong enough electron

withdrawing group to allow exchange of the protons on the carbon atom α to it. However, this problem was circumvented by hydrolysing the trideutero-lactone (97) with KOD/D_2O to the corresponding hydroxy acid which was methylated with diazomethane to give the trideutero – hydroxy – ester (103). (103) was oxidised with deuterated Jones[25] reagent (CrO_3, D_2SO_4, D_2O) to give the dideutero-keto-ester (104). (104) was easily converted into the tetradeutero-keto-ester (105) by refluxing in methanol – OD and deuterium oxide containing sodium followed by methylation with ethereal diazomethane. (105) had identical chromatographic properties to (102) but the n.m.r. spectrum showed a 9H singlet at T 8.87 due to the t-butyl group, a 3H singlet at T 6.33 due to the methyl ester and a broad singlet ($W_{\frac{1}{2}} = 6$ Hz) at T 8.17 due to the methylene protons. The mass spectrum indicated (70% d_4, 30% d_3).

Sodium borohydride[27] reduction of (105) afforded the tetradeutero-hydroxy-ester (106) which on hydrolysis with methanol-OD and deuterium oxide containing sodium, followed by acidification gave (100) in good yield. (100) had identical chromatographic properties to (92) and its n.m.r. spectrum showed in addition to the singlet due to the t-butyl group, an AB quartet centred at T 8.17 due to the C 3 methylene protons and a 1H triplet (J = 1.8 Hz)

at T 6.08 due to the C 5 proton coupling with an axial deuterium
atom. The mass spectrum showed 70% d_4, 17% d_3, 7% d_2, 6% d_1.

The principal mass spectral fragmentation modes of the
keto-ester (102) and the lactone (92) are shown in schemes 1 and
2. These are of interest because they illustrate the influence
of the t-butyl group on the direction of fragmentation. The
rearrangement which accounts for the formation of the ion m/e 55
is detected by deuterium labelling at C 2 whereupon m/e 55 moves
up to m/e 56. This rearrangement has been observed by Djerassi[46]
in lactams and by Millard[47] in ζ-lactones. The other fragmentations
are self explanatory and the ions show the predicted shifts on
introduction of deuterium.

The spectrum of the C 3 methylene protons of (100) is shown
in figure 6. The lines are broadened by deuterium coupling but
the two outer lines at T 8.32 and T 8.01 are clearly visible.
Because of the deuterium coupling it was only possible to estimate
the chemical shift difference and coupling constant between the two
protons. The geminal coupling constant between the two protons
was estimated to be 14 $\pm$ 0.4 Hz and the chemical shift difference
0.109 $\pm$ 0.010 p.p.m. The high field lines can be assigned to the
C 3 axial proton on the basis of their width, which is about
twice that of those at low field. In addition, the width of
the high field lines ($W_{\frac{1}{2}}$ = 9 Hz) is about right for a proton

having two large diaxial and two smaller axial-equatorial
deuterium couplings as adjudged by comparison with the band
width of the C 5 axial proton in (100) ($W_{\frac{1}{2}} = 5$ Hz). The
chemical shift of the high field proton corresponded to the
multiplet C and the chemical shift of the low field proton to
multiplet B in figure 5.

The C 3 and C 4 protons in the half-chair (107) and
half-boat (108) conformations of (97) are labelled H_1, H_2, H_3
and H_4. From the foregoing evidence, the multiplets A,B,C,D
can be assigned to protons H_1, H_2, H_3, H_4 respectively. The
approximate chemical shifts of H_3 and H_2 relative to H_4 are
63 Hz and 84 Hz respectively. The coupling constants between
H_2 and H_3 (14 Hz) and H_1 and H_3 (6 Hz) can be estimated from the
n.m.r. spectrum of (100) and from the splitting in the multiplet
C in figure 5 respectively. By symmetry $J_{H_1 H_4} \sim$ 14 Hz and
$J_{H_2 H_4} \sim$ 6 Hz. The chemical shift of H_1 was estimated to be
88 Hz relative to H_4 and values of $J_{H_3 H_4}$ and $J_{H_1 H_2}$ appropriate
to either (107) or (108) were assigned. The above data was then
used to compute spectra assuming either a half-chair (107) or a
half-boat (108) conformation.

Unfortunately, calculated spectra using data appropriate to
(107) did not differ markedly from calculated spectra using data

appropriate to (108).   It had been hoped that it

would be impossible to reproduce the distinctive features of figure 5

with one set of data.   Accurate line matching was of course

impossible because of the deuterium coupling in figure 5.   This was a

disappointment   because it implied that the conformation of (97)

could not be directly assigned by n.m.r.

It is worth noting one further point which arises out of

examination of the n.m.r. spectrum (figure 5) of (97).   This is

the magnitude of the coupling between H_1 and H_3.   The value of

6 Hz is large compared to the magnitude of similar coupling

constants observed in half-chair lactones by Riggs[8].   Thus

Riggs observed J_{1M} = 3.5 Hz in (109).   In other similar compounds,

the axial-equatorial coupling constant did not differ significantly

from the above value.   An explanation of the high value of

$J_{H_1H_3}$ in (97) may be that (97) is an equilibrating mixture of

(107) and (108) with (107) predominating or that (97) exists as a

slightly flattened half-chair (110) in which the dihedral angle

between H_1 and H_3 is about 30 to 40°.   The dihedral angle between H_1

and H_3 in the half-boat (108) is 120° which according to the Karplus

equation [29,30] gives coupling constants of the order of 3 - 4 Hz.

Flattening (108) (moving C 3 down towards the lactone plane) would

move the dihedral angle between H_1 and H_3 towards 90° and thus reduce

$J_{H_1H_3}$ still further.   Thus the observed value of $J_{H_1H_3}$ is consistent

with an equilibrium mixture of (107) and (108) with the former predominating or alternatively a slightly flattened half-chair (110) as the conformation of (97) (see also Sheppard's lactones).

The infra-red carbonyl frequency in carbon tetrachloride solution of the lactone (92) is 1745 cm^{-1}. This is consistent with its being in the half-chair conformation. However, if there were a small amount (10 - 20%) of the half-boat conformer present then this would not be detected because the half-band width of the carbonyl band ($\Delta V_{\frac{1}{2}} = 23$ cm^{-1}) is so large. For example, a 9:1 mixture of the half-chair and half-boat δ-lactones (26) and (27) (see part 1) respectively, shows $V_{c=o}$ (CCl_4) (1740 cm^{-1}) and $\Delta V_{\frac{1}{2}}$ (18 cm^{-1}). However a 3:1 mixture of (26) and (27) shows a shoulder on the high frequency side of the carbonyl band due to the half-boat conformer and for this mixture $V_{c=o}$ (CCl_4) is 1744 cm^{-1} and $\Delta V_{\frac{1}{2}}$ is 24 cm^{-1}.

The above discussion indicates that it may be possible to establish if a conformational equilibrium between the half-chair and half-boat exists by comparison of the observed carbonyl half-band widths with standard values for the half-chair and half-boat. These values can be obtained by examination of the half-band widths of δ-lactones which have been shown to adopt or are constrained to adopt the half-chair (table XIV) or half-boat (table XV) conformations.

Table XIV. Half-band width $(\Delta v_{\frac{1}{2}})$ and $V_{c=o}(CCl_4)$ for half-chair δ-lactones.
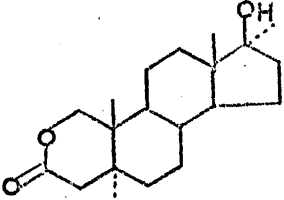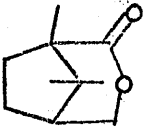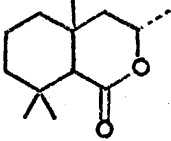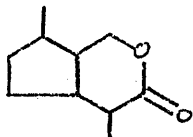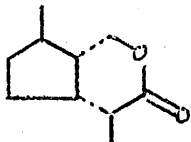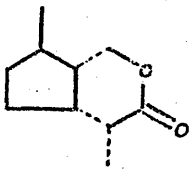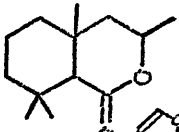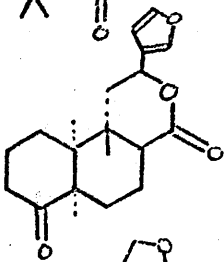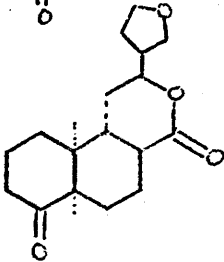
Compound	$V_{c=o}(cm^{-1})$	$\Delta v_{\frac{1}{2}} (cm^{-1})$
	1745	18
	1745	16
	1740	18

<u>Table XV.</u> Half–band width $(\Delta V_{\frac{1}{2}})$ and $V_{c=o}(CCl_4)$ for half–boat δ-lactones.

Compound	$V_{c=o}(cm^{-1})$	$\Delta V_{\frac{1}{2}}(cm^{-1})$
	1755	14
	1756	14
	1758	14
	1755	14
	1760	14
	1758	18
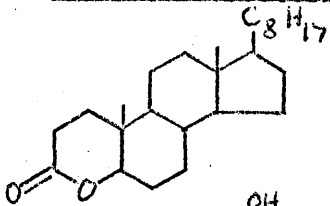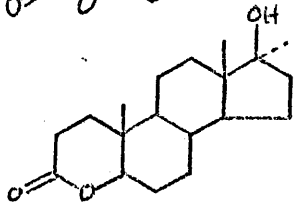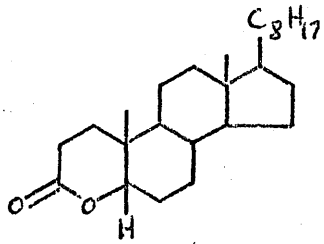
Although not many examples are available it does seem that those compounds which are almost pure half-chair or half-boat conformers have carbonyl half-band widths less than 20 cm^{-1}. However, if the half-band width of the carbonyl band is greater than 20 cm^{-1} then the possibility of there being a mixture of conformers must be considered. This of course arises from the fact that $\Delta V_{c=o}$ for half-chair and half-boat lactones is about 15 cm^{-1}.

The predominant conformer in the equilibrium mixture will be that indicated by the position of $V_{c=o}$ max.

Applying the above reasoning to (92) ($\Delta V_{\frac{1}{2}} = 23 \ cm^{-1}$) suggests that it is mainly in the half-chair with a small amount of the half-boat conformation present. The possibility of broadening due to Fermi resonance is discounted because the tri-deuterated lactone (97) has the same half-band width.

The carbonyl frequencies and half-band widths for the $\measuredangle$ -lactones shown in table XVI refer to compounds which, according to Wolf[9] are predominantly in the half-boat conformation.

Table XVI. The half-band width ($\Delta V_{\frac{1}{2}}$) and $V_{c=o}$ (CCl_4) for some δ-lactones.

Compound		$V_{c=o}$ (cm^{-1})	$\Delta V_{\frac{1}{2}}$ (cm^{-1})
C_8H_{17}	(1)	1746	21
OH	(2)	1746	25
C_8H_{17} H	(3)	1743 1750	32

The first two δ-lactones in table XVI appear to be mainly in the half-chair conformation with some half-boat present to account for the slight broadening of the absorption bands. The δ-lactone (3) shows a very broad band which has the appearance of two overlapping bands, one at high frequency $(V_{max} \sim 1755 \text{cm}^{-1})$ and

one at lower frequency (approximately 1740 cm^{-1}). The relative weights of the two bands suggests that there is about 40% of the half-boat conformation in the equilibrium mixture.

Examination of molecular models suggests a possible explanation for the high percentage of the half-boat conformer in 4 - Oxa - 5 β - cholestan - 3 one (3 in table XVI). Thus, in the half-chair conformer (111a) there are three serious non-bonded H - - - H interactions while in the half-boat (111b) there are only two. This will favour the half-boat and will thus account for the slightly higher proportion of it in the equilibrium mixture than in the other two δ-lactones.

More convincing evidence in support of the presence of equilibrium mixtures of conformational isomers in δ-lactones is presented in Chapter 5.
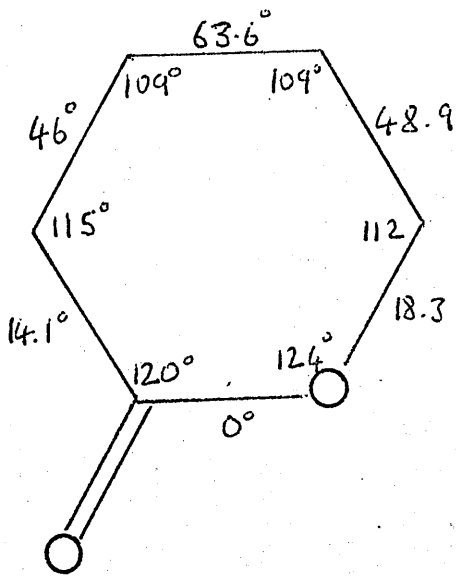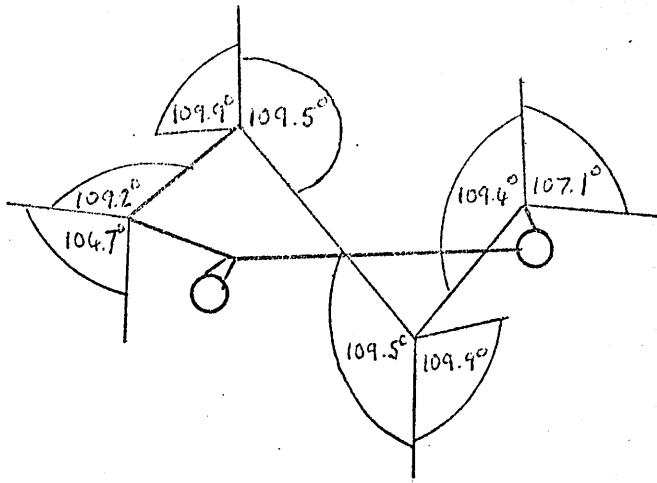
Figure 3
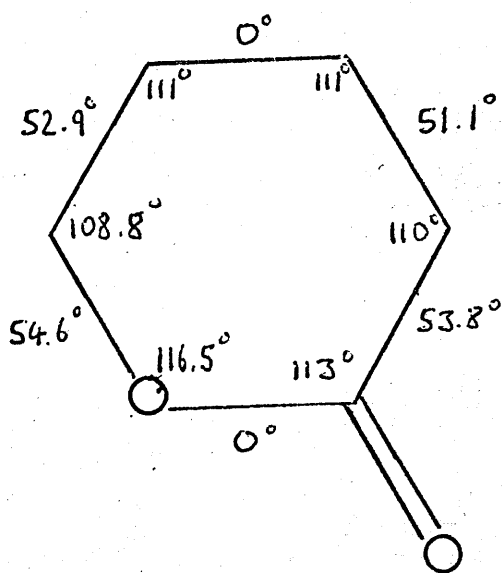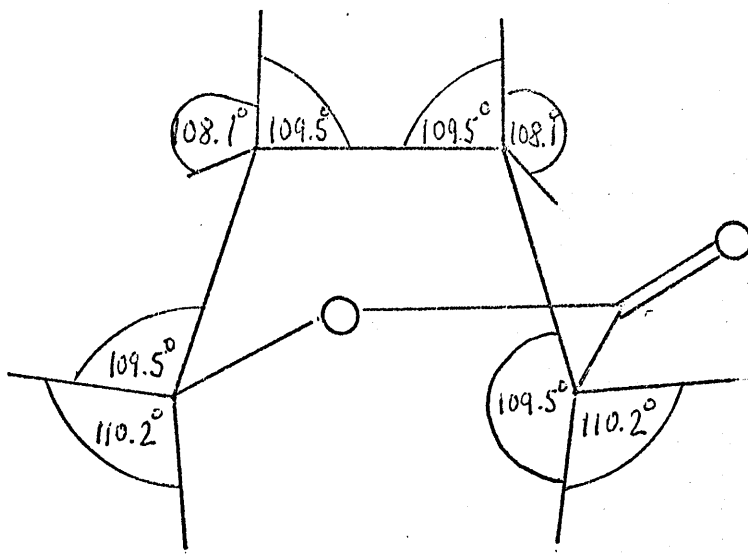
Figure 4
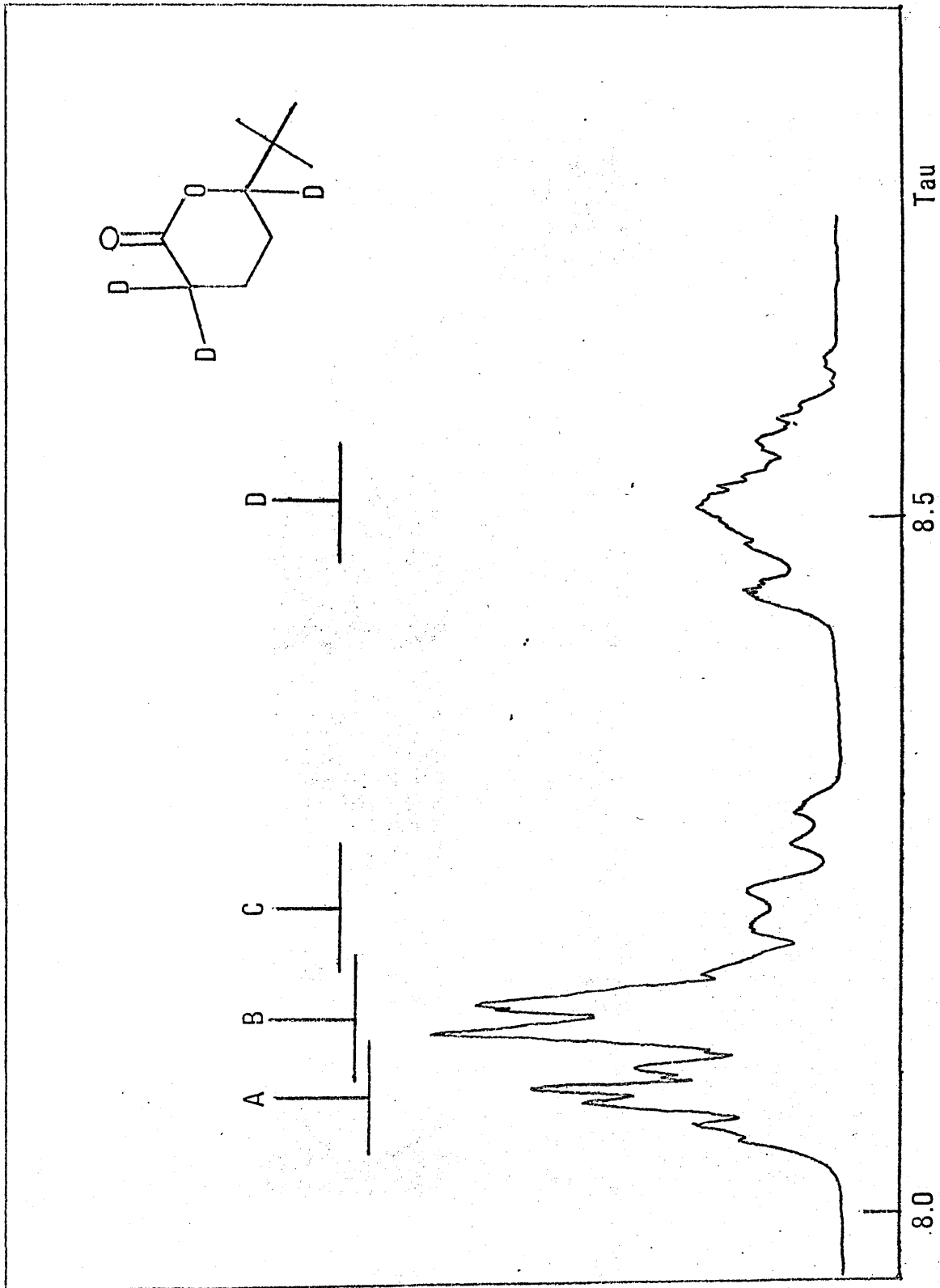
Figure 5
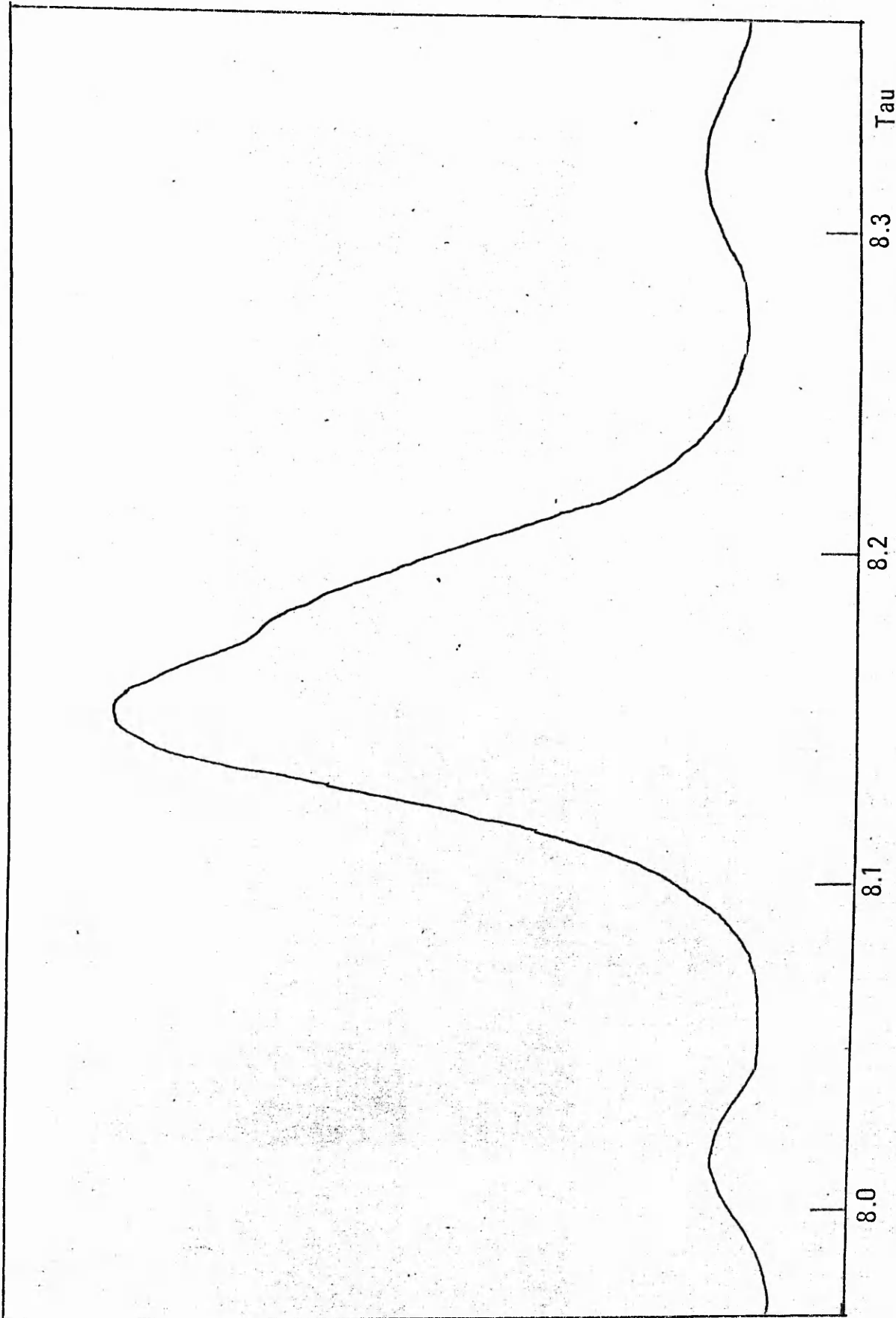
Figure 6
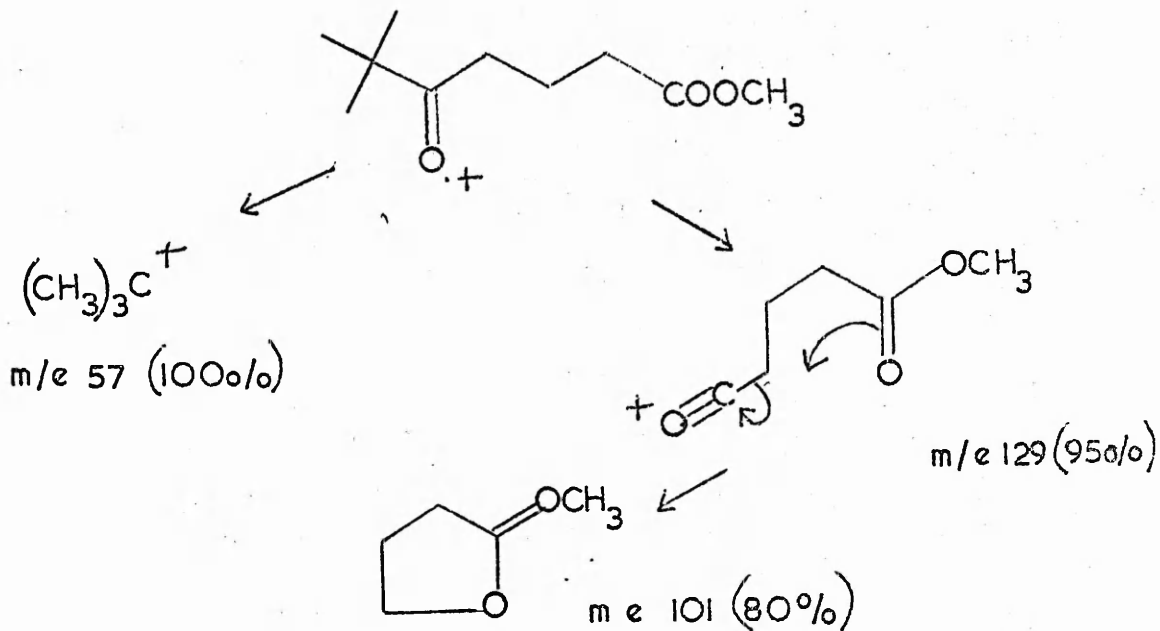
Scheme 1
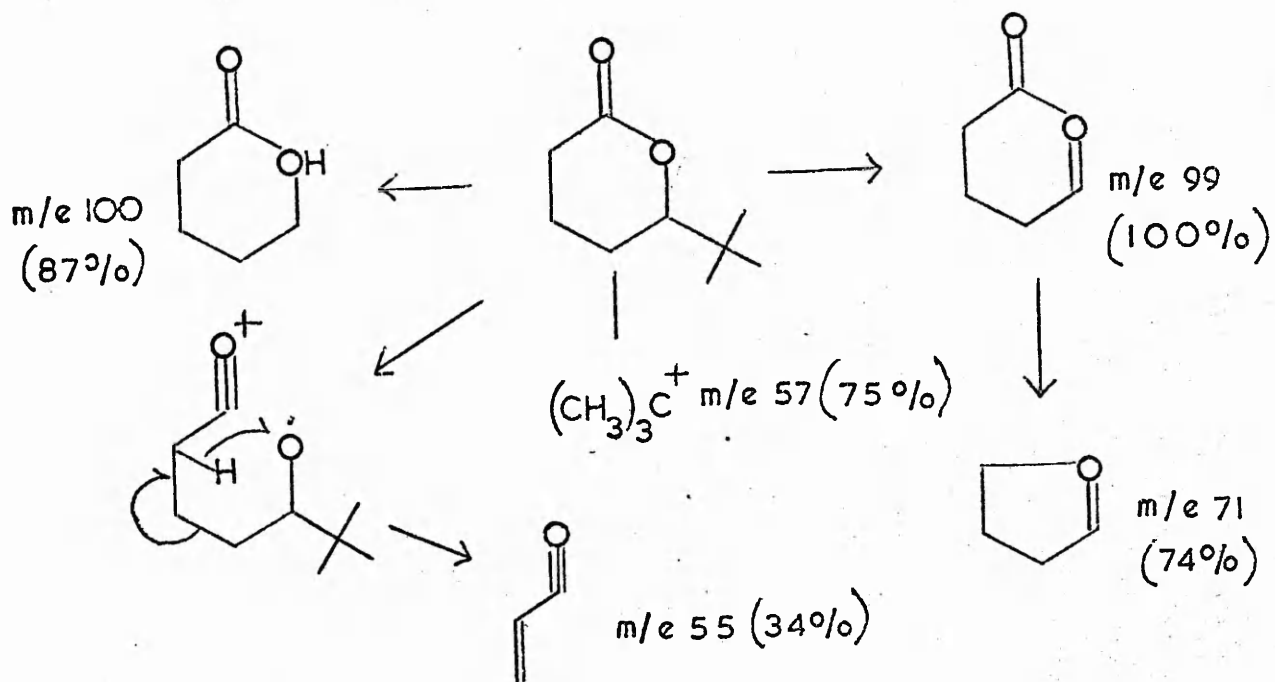
Scheme 2
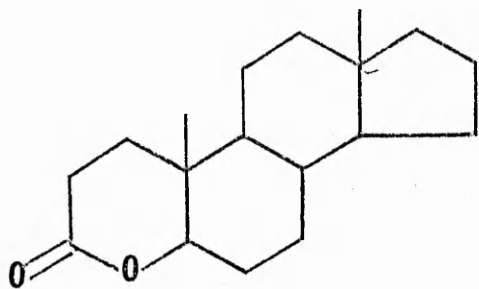
88
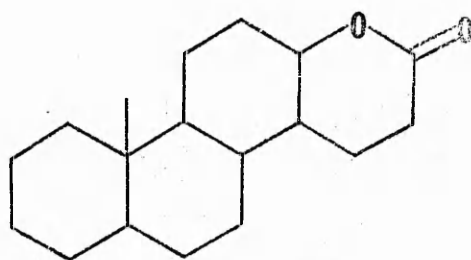
89
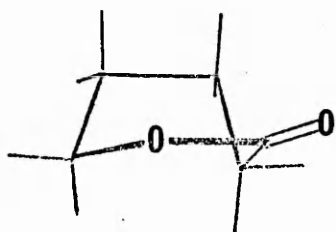
90
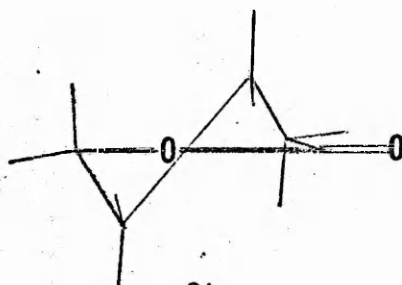
91
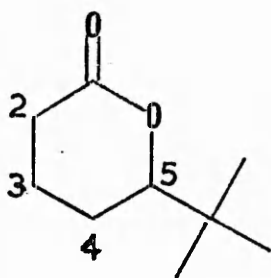
92
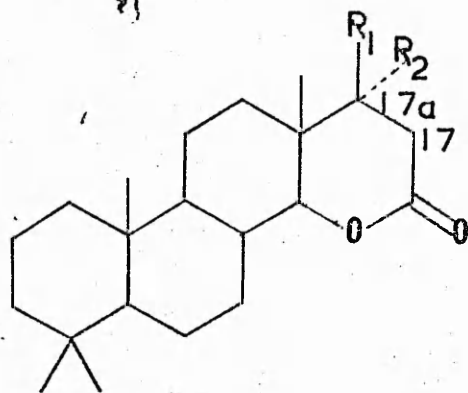
93   $R_1 = H$, $R_2 = OH$

94   $R_1 = H$, $R_2 = OCOCH_3$

95   $R_1 = OCOCH_3$, $R_2 = H$

96

97

97a

97b
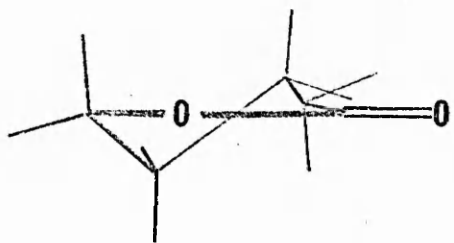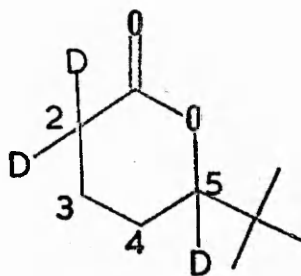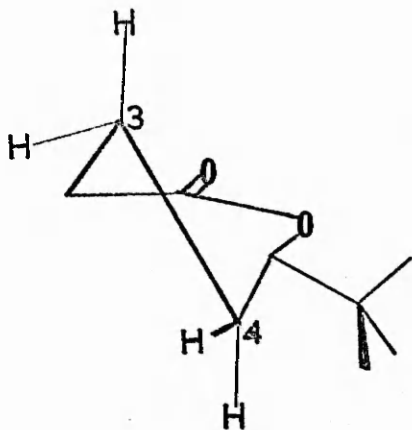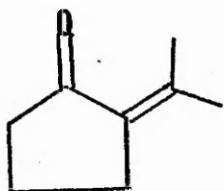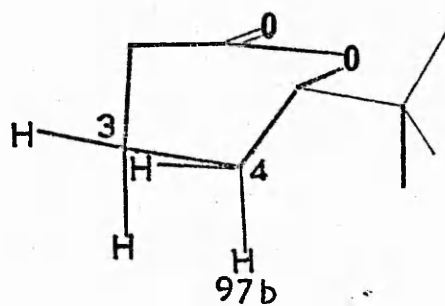
98
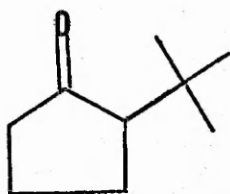
99
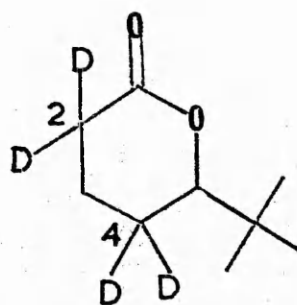
100
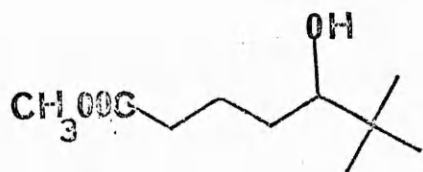
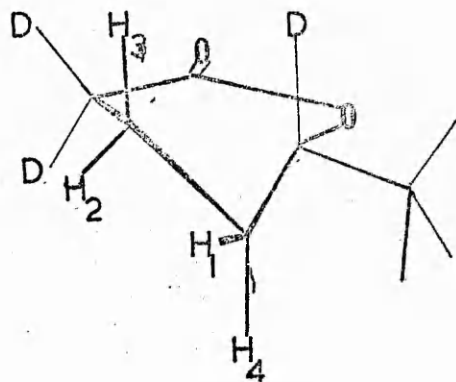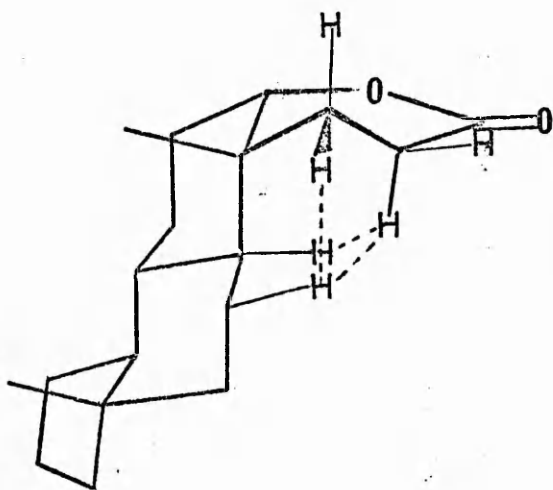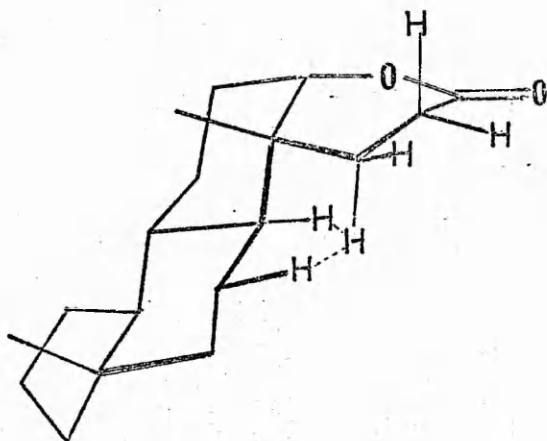101
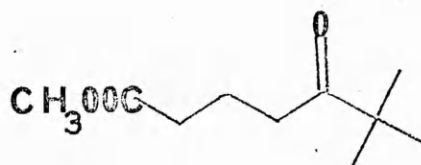
102
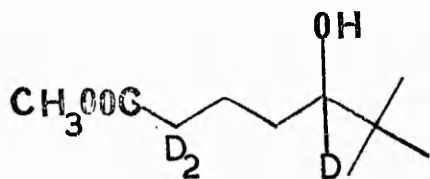
103
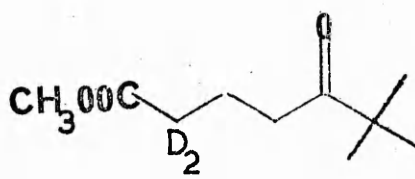
104
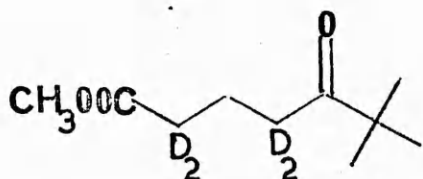
105

106

107

108

109

110

IIIa
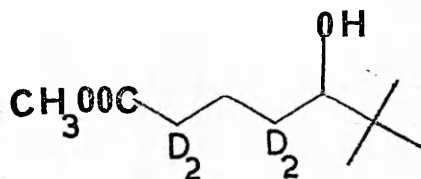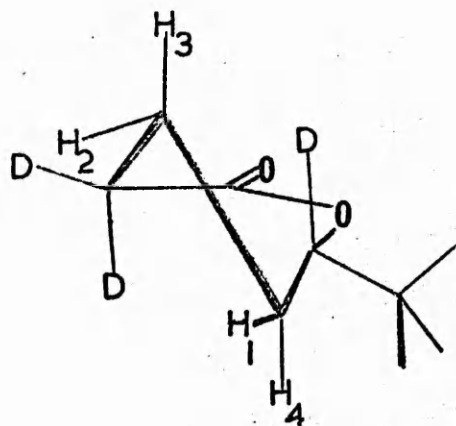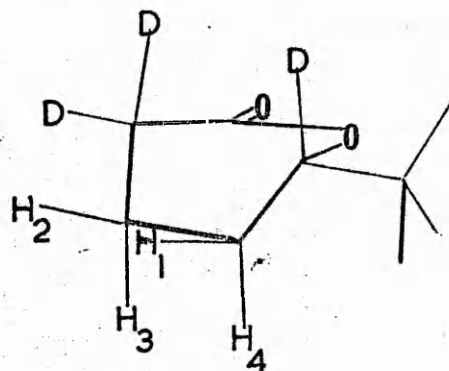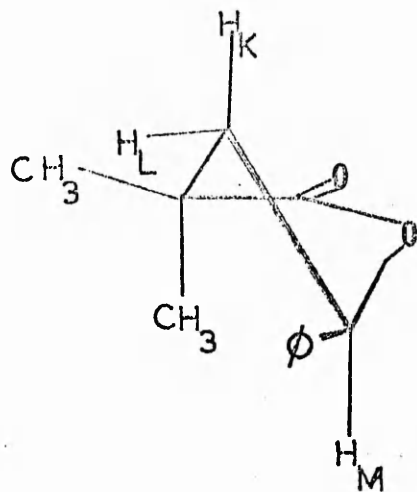
IIIb

EXPERIMENTAL PART 2.

General experimental

220 M Hz n.m.r. spectra were very kindly recorded by Dr. J. K. Becconsall of I.C.I. Petrochemical and Polymers Laboratory, Runcorn and by Professor N.H. Bhacca at Varian Associates, Pao Alto , California on a Varian H.A. 220 spectrometer. All 220 M Hz spectra were recorded at 500 Hz sweep width over 500 sec. and were run at different spinning rates to check for spinning side bands. T.M.S. was used as an internal standard and all spectra were recorded at a probe temperature of about $30^{\circ}C$.

The ABCD spectra were calculated on an English Electric KDF 9 computer using the programme FREQUINT IVa (translated from FORTRAN by R. Kaptein and extensively modified by D.A. Morton-Blake).

2 - Isopropylidene Cyclopentanone[48] (98).

A solution of "Analar" acetone (300 g.), cyclopentanone (102 g.),
sodium hydroxide solution (1N) (780 ml.) and methanol (180 ml.)
was magnetically stirred for two days at room temperature in
a stoppered flask. The sodium hydroxide was neutralized with
acetic acid and the solution diluted with brine (600 ml.). The
solution was thoroughly extracted with benzene which was washed
with brine and dried. Removal of solvents under reduced pressure
left a brown oil (150 g.).

V_{max}(film) 1700, 1630 cm^{-1}.

The oil was distilled using a short fractionating column
and the fraction distilling between 88 - 95°C (12 mm. Hg.)
(48 g.) contained greater than 95% of (98) as judged by g.l.c.
(10% APL, 100°C).

V_{max}(CCl$_4$) 1710, 1633, 1262, 1182 cm^{-1}.

The red 2,4 - dinitrophenylhydrazone of (98) was
recrystallised from methanol and had m.p. 229°C (needles).
Literature[49] value 226 - 227°C.

2 - Tertiary Butyl Cyclopentanone (99).

An approximately 1 molar solution of methyl lithium in

ether[44] was prepared by adding lithium (15 g. 2.2 moles; small pieces) to ether (500 ml.) under an atmosphere of nitrogen. Methyl iodide (150 g., 1.05 moles) in ether (500 ml.) was added slowly (over 30 minutes) to the stirred solution, (care — reaction very vigorous). After the initial reaction had subsided, the mixture was refluxed for one hour, allowed to cool and filtered under nitrogen pressure into a flask which was kept stoppered in a fridge.

The lithium dimethyl copper complex[45] was prepared by adding methyl lithium solution (300 ml., 0.3 moles) dropwise to a vigorously stirred slurry of cuprous iodide (28 g., 0.15 moles) in ether (250 ml.) at $0^{\circ}C$. The reaction flask was flushed with a steady stream of nitrogen throughout the addition and subsequent reaction. The initially formed complex is bright yellow in colour but as more methyl lithium is added, the yellow colour changes to a pale brown. Care was taken to ensure that no more than the correct amount of methyl lithium was added and in general it was usual to add less that the calculated amount.

2 — isopropylidene cyclopentanone (98) (6 g., 0.5 moles) in ether (500 ml.) was added dropwise to the above solution with stirring and cooling in an ice salt bath. The addition of the unsaturated ketone resulted in the yellow colour being regenerated.

The solution was stirred under nitrogen for six hours at ice-salt temperature and then poured on to a rapidly stirred saturated aqueous solution of ammonium chloride. The organic layer was separated and combined with the ethereal extract of the aqueous phase and washed with brine. After drying and removal of the solvents under reduced pressure, a pale green oil (6.0 g.) containing 90% of the conjugate addition product (99), as judged by g.l.c. (10% APL, 100°C), was obtained. The oil was distilled under reduced pressure and the fraction distilling between 65 – 70°C (11 mm. Hg.) (4 g.) was collected.

(99) had $V_{max}(CCl_4)$ 2955, 2865, 1737, 1365, 1143 cm^{-1}, n.m.r. showed 9H singlet at T 9.0; 7H multiplet between T 7.6 – 8.4.

The 2,4 – dinitrophenylhydrazone of (99) was recrystallised from ethanol and had m.p. 156.5 – 158°C (needles). N.m.r. showed 9H singlet at T 8.90, 7H multiplet between T 7 and 8.7. 3 multiplets at T 2.2., 1.7 and 1.05 of the ABX system of the aromatic protons.

(Found: C, 56.40, H, 6.21, N, 17.40; $C_{15}H_{20}O_4N_4$ requires C, 56.24; H, 6.29; N, 17.49%.)

The Lactone (92) of 5 – Hydroxy – 5-t-Butyl – n – Pentanoic Acid.

(I) Trifluoroacetic anhydride (10.5 ml., 0.072 mole)[43] added over 30 minutes from a chilled pressure equilibrated dropping funnel to a stirred suspension of 90% H_2O_2 (1.64 ml., 0.06 moles) in dry methylene chloride (10 ml.) cooled in ice. The solution was stirred at ice temperature for 30 minutes. The above solution of peroxytrifluoroacetic acid was added over 1 hour from a chilled dropping funnel to a stirred suspension of anhydrous disodium hydrogen phosphate (16 g.) in dry methylene chloride (40 ml.) containing the t – butyl ketone (99) (2.5 g., 0.018 moles). The reaction was cooled to $0^{\circ}C$ during the addition and was stirred for 4 hours at $0^{\circ}C$ and 2 hours at room temperature.

Water (30 ml.) was added and the organic layer separated and combined with the methylene chloride extract of the aqueous phase. The methylene chloride solution was washed with saturated sodium carbonate solution (2 x 10 ml.) and brine (2 x 10 ml.). After drying and removal of solvents under reduced pressure, a colourless oil (2.5 g.) which contained 95% of (92) as judged by g.l.c. (10% APL, $125^{\circ}C$; 5% QF – 1, $100^{\circ}C$).

A sample of (92) was purified for analysis by p.t.l.c. (ethyl acetate, pet-ether 30:70) and microdistillation. ($50^{\circ}C$ at 0.5 mm. Hg.).

$V_{max}(CCl_4)$ 1746, 1369, 1241, 1180, 1057 cm^{-1};

n.m.r. showed 9H singlet at T 9.05; 4H multiplet at T 8.2;

2H multiplet at T 7.5 and a 1H quartet $(J = 12 Hz, J = 2 Hz)$

at T 6.10.

Mass spec M.W. 156 $C_9H_{16}O_2$ requires 156.

(Found: C, 69.00; H, 10.29; $C_9H_{16}O_2$ requires C, 69.19; H, 10.32%.)

(II)   2 - t - butyl cyclopentanone (99) (440 mg. 3.1 m moles)

in chloroform (1.5 ml.) was added to m - chloro - perbenzoic acid

(900 mg. 5.3 m moles)[45] in chloroform (4.5 ml.). The solution

was left in the dark for two days at room temperature. A further

portion of M.C.P.B.A. (900 mg.) in chloroform (1 ml.) was then

added. After a further 24 hours the chloroform solution was

washed with potassium iodide solution, aqueous sodium thiosulphate,

saturated sodium bicarbonate solution and finally brine. After

drying and removal of solvents under reduced pressure, a pale green

oil (420 mg.) was recovered. The major product (80%), as judged

by g.l.c. (10% APL, 125°C; 5% QF - 1, 100°C), was the required t -

butyl lactone (92). The material was purified by p.t.l.c.

(ethyl acetate, pet-ether 30:70) to yield (92) (250 mg.).

The Trideuterated Lactone (97).

2 - t - butyl cyclopentanone (99) (4 g.) in methanol - OD
(prepared according to Djerassi[77]) (10 ml.) was added to
deuterium oxide (10 ml.) and methanol - OD (10 ml.) containing
sodium (100 mg.). The solution was refluxed for 2 hours under
an atmosphere of nitrogen and allowed to stand overnight at
room temperature. Most of the methanol - OD was removed on a
rotary evaporator and the remaining solution diluted with deuterium
oxide (20 ml.). The solution was saturated with "Analar" sodium
chloride and thoroughly extracted with ether. The ethereal extract
was washed with brine and dried. Removal of solvent under reduced
pressure afforded a pale green oil (2.5 g.) which showed one peak
on g.l.c. (10%, APL, 100°C) of identical retention time as (99).

$V_{max}(CCl_4)$ 2220, 2100, 1735, 1736 cm^{-1}.

The crude trideutero-t-butyl ketone (2.5 g.) was oxidised
with peroxtrofluoroacetic acid exactly as described for the
oxidation of (99).

The crude trideutero-t-butyl lactone (2.5 g.) was obtained as
a colourless oil which showed one peak on g.l.c. (10% APL, 125°C;
5% QF - 1, 100°C) of identical retention time as (92) by cross
injection. (97) was purified by p.t.l.c. and microdistillation
(50°C at 0.5 mm. Hg.).

$V_{max}(CCl_4)$ 2141, 2090, 1745, 1369 cm^{-1}.

N.m.r. showed 9H singlet at T 9.05 and no signals below T 8.0.

The mass spectrum showed 80% d_3, 20% d_2.

The Keto - ester (102).

The lactone (92) (500 mg.) was heated on a steam bath with water (50 ml.) containing "Analar" potassium hydroxide (900 mg.). After 1 hour the solution was washed with ether (25 ml.) and titrated to pH 5.5 using acetate buffer solution (pH 4.9) and a pH meter. The solution was saturated with sodium chloride and thoroughly extracted with ether. The ether solution was washed with brine and methylated with ethereal diazomethane. After drying the solvents were removed under reduced pressure and the hydroxy - ester (101)(450 mg.) was obtained as a pale green oil which contained 5% of the lactone (92) as judged by g.l.c. (5% QF - 1, 100°C) and t.l.c. (ethyl acetate, benzene 14:86.).

$V_{max}(CCl_4)$ 3635, 3608, 3530, 3460, 1740 cm^{-1}.
(101) was fully characterised as the crystalline ester of etienic acid (153b)(see page 155).

The crude hydroxy-ester (101) (450 mg.) was taken up in "Analar" acetone (50 ml.) and cooled in ice. Jones reagent (1 ml.) was added dropwise with shaking and cooling in ice. After 15 - 20 minutes

at ice temperature, methanol (1 ml.) was added to destroy excess
Jones reagent. The low boiling solvents were removed under
reduced pressure with a minimum of heating and the residue
taken up in brine (10 ml.). The resulting solution was extracted
thoroughly with ether which was washed with brine and dried.
Removal of the ether under reduced pressure afforded an oil
(415 mg.), which showed one main product of greater mobility
than starting material by t.l.c. (ethyl acetate, pet-ether
20:80), G.l.c. (5% QF - 1, 80°C) showed one major peak of
r.t. 11.2 min. (101) has r.t. 10.2 min. under identical
conditions. The oil was purified by p.t.l.c. to yield the
keto-ester (102) (314 mg.).

V_{max}(CCl$_4$) 1743, 1710, 1368 cm^{-1}. n.m.r. showed 9H singlet
at T 8.87; a 2H multiplet at T 8.15 overlapping a 4H multiplet
centred at T 7.54 and a 3H singlet at T 6.33.

Mass spec. M.W. 186 $C_{10}H_{18}O_3$ requires 186.

(Found: C, 64.21; H, 9.50; $C_{10}H_{18}O_3$ requires C, 64.49; H, 9.74%.)

Attempted Deuteration of the Keto-ester (102).

(102) (50 mg.) in methanol - OD (5 ml.) was added to methanol
- OD (5 ml.) containing sodium (100 mg.). The solution was
refluxed for five hours under an atmosphere of nitrogen. After

allowing to cool, the solution was acidified with D_2SO_4/D_2O and the methanol removed under reduced pressure.

The aqueous solution was thoroughly extracted with ether and the ethereal extracts washed with brine. After drying, the ether was removed under reduced pressure to yield an oil (40 mg.) which showed characteristic acid streaking on t.l.c. The oil was methylated with ethereal diazomethane and the resulting methyl ester showed one peak with the same retention time as (102) on g.l.c. The methyl ester showed one main spot on t.l.c. of identical mobility to authentic keto-ester (102).

The oil was purified by p.t.l.c. and n.m.r. showed 9H singlet at T 8.87; a 2H broad singlet at T 8.15; a 1H multiplet at T 7.7 and a 3H singlet at T 6.33.

The 1H multiplet at T 7.7 due to protons adjacent to the carbomethoxy group indicated incomplete deuteration.

The Dideuterated Keto-ester (104).

Potassium hydroxide (2 g.) was dissolved in deuterium oxide (10 ml.) which was distilled off. The residue was taken up in a further 10 ml. of deuterium oxide and the process repeated twice. The residue, which was presumed to be potassium deuteroxide, was

taken up in deuterium oxide (60 ml.) and added to the trideuterated

lactone (97) (2.4 g.). The solution was kept just below reflux

temperature for one hour under an atmosphere of nitrogen. After

cooling, the solution was rapidly titrated with pH 4.9 acetate

buffer solution, using a pH meter, to pH 5. The aqueous solution

was saturated with salt and thoroughly extracted with ether

which was washed with brine. The ether extracts were methylated

with ethereal diazomethane, dried and the solvents removed under

reduced pressure. The crude trideuterated hydroxy-ester (103)

(2.3 g.) was obtained as an oil which showed one major peak on

g.l.c. (5% QF - 1, 100°C) of r.t. identical to that of (101).

$$V_{max}(CCl_4) \; 3630, 3500, 1740 \; cm^{-1}.$$

Crude (103) (2.2 g.) was dissolved in "Analar" acetone

(200 ml.) and cooled in ice. Deuterated Jones reagent was

prepared from chromium trioxide (2.67 g.), D_2SO_4 (2.30 ml.)

and made up to 10 ml. with deuterium oxide. The deuterated

Jones reagent (5 ml.) was added dropwise with shaking and cooling

to the hydroxy-ester solution. After 15 - 20 minutes the

excess Jones reagent was destroyed by adding methanol - OD (4 ml.).

The low boiling solvents were removed under reduced pressure

and the residue taken up in deuterium oxide (30 ml.). Ether

extraction afforded crude dideuterated keto-ester (104)as an oil

(2.3 g.). G.l.c. showed one major peak of r.t. identical to that

of authentic (102). T.l.c. showed one main spot which had the same mobility as (102). The crude material was purified by p.t.l.c. (ethyl acetate, pet-ether 20:80).

$V_{max}(CCl_4)$ 1743, 1710 cm^{-1}

The mass spectrum showed 82% d_2, 18% d_1.

The Tetradeuterated Keto-ester (105).

The dideuterated keto-ester (104) (600 mg.) in methanol — OD (10 ml.) was added to methanol — OD (10 ml.) and deuterium oxide containing sodium (100 mg.). The solution was refluxed under nitrogen for two hours and allowed to stand overnight at room temperature. Most of the methanol — OD was removed under reduced pressure and the solution acidified with D_2O/D_2SO_4 and ether extracted to give an oil (510 mg.) which showed characteristic acid streaking on t.l.c.

The oil was methylated with ethereal diazomethane and the resulting methyl ester (500 mg.) showed one main spot on t.l.c. of identical mobility to the keto-ester (102). The oil was purified by p.t.l.c. (ethyl acetate, pet-ether 20:80) to afford the tetradeuterated keto-ester (105) as an oil (330 mg.) which was identical by t.l.c. and g.l.c. to the keto-ester (102).

$V_{max}(CCl_4)$ 1740, 1705, 1130 cm^{-1}; n.m.r. showed 9H singlet at

T 8.87; 2H broad singlet $(W_{\frac{1}{2}} = 6$ Hz) at T 8.17; 3H singlet at

T 6.33 and 0.33 H between T 7 and 8.

The mass spectrum showed 70% d_4 and 30% d_3.

The Tetradeuterated Hydroxy-ester (106).

The tetradeuterated keto-ester (105) (190 mg. 1 m mole) was

dissolved in methanol - OD (6 ml.). The solution was cooled

in ice and sodium borohydride (24 mg. 0.63 m mole)[27] added.

The reaction was stirred at ice temperature for 45 minutes. Deuter-

ium oxide (10 ml.) was added and the methanol removed under

reduced pressure. Extraction with ether afforded an oil (160 mg.)

which was identical to the hydroxy ester (101) by g.l.c. and t.l.c.

$V_{max}(CCl_4)$ 3630, 3500, 1740, 1705 (shoulder) cm^{-1}; n.m.r.

showed 9H singlet at T 9.2; 3H between T 8 - 8.5; 1H broad singlet

$(W_{\frac{1}{2}} = 9$ Hz) at T 6.82 and a 3H singlet at T 6.33; one of the

protons between T 8 - 8.5 disappeared on addition of D_2O.

The Tetradeuterated Lactone (100).

The tetradeuterated hydroxy-ester (106) (130 mg.) was

dissolved in methanol - OD (10 ml.) containing sodium (200 mg.).

Deuterium oxide was added until the solution became cloudy

(approx. 10 ml.). The solution was refluxed under nitrogen

for 3 hours and acidified with D_2SO_4/D_2O and allowed to stand for a few minutes. Extraction with ether afforded an oil (40 mg.) which was purified by p.t.l.c. (ethyl acetate, benzene 14:86) to yield the tetradeuterated lactone (100) (30 mg.) which was identical by g.l.c. and t.l.c. to the δ-lactone (92).

$V_{max}(CCl_4)$ 2230, 2130, 1745, 1369. N.m.r. showed 9H singlet at T 9.03; 2H AB quartet centred at T 8.17; 1H triplet (J = 1.8 Hz) at T 6.08.

The mass spectrum showed 70% d_4, 17% d_3, 7% d_2 and 6% d_1.

CHAPTER 3

THE N.M.R. SPECTRA OF SOME COMPOUNDS

CONTAINING LACTONE RINGS.

During the synthesis of the δ-lactone (26) and (27) the epimeric ϵ-lactones (67) and (68) were isolated. The evidence for the proposed stereochemistry of the latter pair of compounds was obtained from examination of their n.m.r. spectra which have been segregated here for the sake of clarity. In addition the n.m.r. spectra of isocolumbin (112), decarboxy-columbin (114), columbin (115) and α-campholide (118) have been examined in some detail and provide firm evidence that the conformations adopted by the δ-lactone rings in solution are the same as those in the crystal. In addition it was necessary to know the order of magnitude of coupling constants between protons in δ-lactone rings to assist in the understanding of other n.m.r. spectra in this thesis.

All of the compounds discussed in this chapter with the exception of α-campholide contain ABX systems and in each case the magnitude of J_{AX} and J_{BX} serves to determine the conformation of the lactone ring. In all the examples J_{AB} is a geminal coupling constant and is assumed to be negative. On the other

hand J_{AX} and J_{BX} are vicinal coupling constants and are assumed to be positive.

The actual J values for the systems were derived as follows. J_{AB} was obtained by direct inspection and J_{AX} and J_{BX} were calculated by sub spectral analysis[50]. Essentially this involves taking the two symmetrical quartets which constitute the AB part of an ABX system and considering each of them as two AB sub spectra (ab and a'b'), each characterised by $M_X = \pm \frac{1}{2}$. Then by making use of the following relationships

$$V_a = V_A + \tfrac{1}{2} J_{AX}$$

$$V_b = V_B + \tfrac{1}{2} J_{BX}$$

$$V_{a'} = V_A - \tfrac{1}{2} J_{AX}$$

$$V_{b'} = V_B - \tfrac{1}{2} J_{BX}$$

values of J_{AX} and J_{BX} can be obtained. The advantage of this approach is that it is only necessary to observe the AB part of the ABX system. When the X part is visible it serves as a check on the above assignments.

The energy and number of each transition was calculated using the expressions on page 360 of reference 51. In all the examples H_A is the higher field proton of the AB part.

The 100 M Hz n.m.r. spectrum (Figure 7) of (67), run in

carbon tetrachloride solution, shows an eight line multiplet
(also shown at 250 Hz sweep width) centred at T 7.4. This
is the AB part of the ABX system formed by the protons on
C - 5 and C - 6. The X part due to the methine proton on
C - 5 is lost among the higher field signals. Analysis of the
AB part gives $J_{AB} = - 17.0$ Hz; $J_{AX} = J_{BX} = 8.0$ Hz. As
discussed on page these coupling constants are consistent
with a conformation (70) for (67).

Inspection of the 100 M Hz n.m.r. spectrum (Figure 8) of
(68), run in carbon tetrachloride solution, shows the protons
on C - 6 as an eight line multiplet (also shown at 250 Hz
sweep width) centred at T 7.6. These form the AB part of an
ABX system in which the X part, due to the C - 5 proton, is lost
among the high field signals. The coupling constants and
chemical shifts are $J_{AB} = -14$ Hz; $J_{AX} = 0.5$ Hz; $J_{BX} = 10.5$ Hz;
$\delta_A = T\ 7.90$ and $\delta_B = T\ 7.66$. From the magnitude of J_{BX}, H_B
is assigned to the C - 6 axial proton and H_A to the C - 6
equatorial proton in (69). The lower field resonance position
of the C - 6 axial proton is explained by its being within
or close to the deshielding region[52] of the carbonyl group as depicted
in (110).
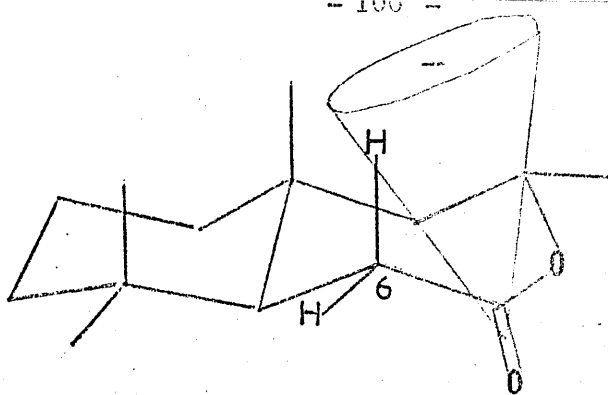
110,

In benzene solution the coupling constants and chemical
shifts become J_{AB} = -14.6 Hz; J_{AX} = 11.2 Hz; J_{BX} = 0.4 Hz;
δ_A = T 7.70; and δ_B = T 7.51. It can be seen that H_A is
the C 6 axial proton this time, and has thus been moved to a
higher field than the C 6 equatorial proton.

The solvent shifts for some of the protons of (68) on
changing from carbon tetrachloride to benzene solution are
shown in (III). The magnitude of the shifts are in agreement
with the rule of Connolly and McCrindle[53], whereby if the
protons are behind a reference plane (A) drawn through the
carbonyl group at right angles to the carbon oxygen bond, then
they suffer an upfield shift as does the C 6 axial proton, the
C 8 axial proton and the C 8-methyl group. Protons in or close
to the plane suffer very small shifts while those in front move
downfield. The C 6 - equatorial proton experiences a small
downfield shift (- 0.04 p.p.m.) since it is just in the plane.

−0.04 p.p.m. H

H +0.39 p.p.m.

H +0.58 p.p.m.

CH$_3$ +0.25 p.p.m.
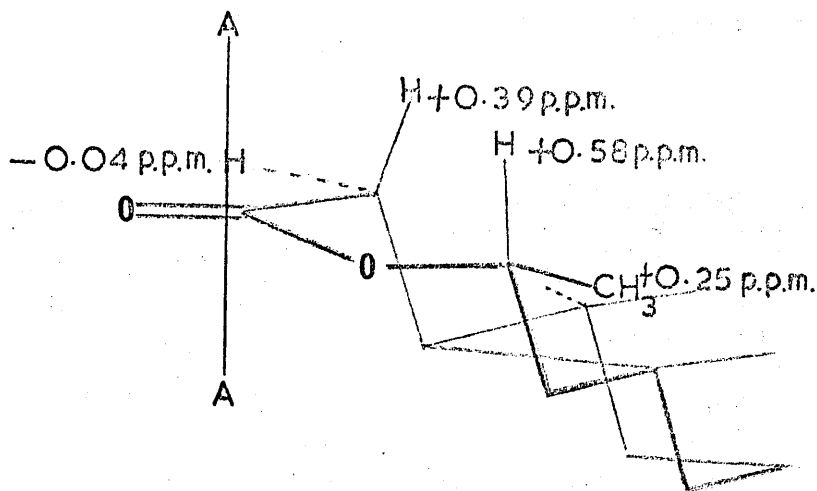
III

The structure of the multiplet at T 5.50, due to the C − 8 proton, shows little change on changing the solvent from carbon tetrachloride to benzene. The multiplicity can be accounted for if the C − 8 methyl splits the signal from the C − 8 proton into a 1:3:3:1 quartet (J = 6 Hz) which is further split by a large (J = 8 Hz) coupling and a smaller (J = 0 − 1 Hz) coupling. This is consistent with the conformation (69) in which the dihedral angles between the C − 8 proton and the C − 9 axial and equatorial protons are approximately 150° and 90° respectively and according to the Karplus equation[30] should therefore have coupling constants of the above magnitude.

The n.m.r. spectrum at 100 M Hz of isocolumbin (112) is shown in Figure 9. Simple inspection shows the following familiar features: two α furanic protons (two 1 H diffuse singlets at T 2.48 and T 2.54); one β furanic proton overlapping two olefinic protons (3 H multiplet at T 3.54); 1 H quartet at T 4.64; 1 H quartet at T 4.85; one hydroxyl proton (1H singlet at T 6.48); two tertiary methyl groups (3 H singlets at T 8.77 and T 8.90).

Irradiation at the quartet centred at T 4.85 collapsed the eight lines of the olefinic protons at T 3.54 to an AB quartet $(\delta_A - \delta_B) = 12.7$ Hz; $J_{AB} = 8$ Hz). This identifies this quartet as being due to H_1. The other quartet centred at T 4.64 is due to H_{12} and forms the X part of the ABX system where H_A and H_B are H_{11} and H_{11}. The eight lines of the AB part are in the high field signals between T 7.5 and T 8.5. Irradiation at H_{12} causes the lines due to the H_{11} protons to change their positions. In this way it was possible to pick out the eight lines of the AB part.

The numbered transitions of the X part on an expanded scale are shown inset in Figure 9. The numbered transitions of the AB part on an expanded scale are shown in Figure 10. The coupling constants of the ABX system formed by the H_{12} and H_{11} protons are $J_{AB} = -14.0$ Hz; $J_{AX} = 12.0$ Hz; $J_{BX} = 3.5$ Hz. The values of J_{AX} and J_{BX} obtained by a first order analysis of the X part are $J_{AX} = 10.5$ Hz; $J_{BX} = 5.0$ Hz.

The conformation of isocolumbin as determined by X-ray crystallography is shown in (113)[19]. In the crystal, the ring C δ-lactone is in the half-boat conformation in which the steric arrangement of the C_{11} and C_{12} protons is such that according to the Karplus equation[30] one large diaxial and one smaller axial equatorial coupling, would be expected. The n.m.r. spectrum of (112) in $CDCl_3$ confirms that the ring - C δ-lactone is in the half-boat conformation, since the coupling constants between the C_{11} and C_{12} protons are consistent with a large diaxial $(J=12.0 \text{ Hz})$ and a smaller axial-equatorial $(J = 3.5 \text{ Hz})$ coupling.

The n.m.r. spectra of columbin (115) and decarboxy-columbin (114) at 60 MHz and 100 MHz were examined. The n.m.r. spectra of columbin showed the H_{12} proton as a quarted at T 4.60 which did not change significantly on running the spectra at two different field strengths. This justifies first order analysis which gives $J_{AX} = 11.5 \text{ Hz}$ and $J_{BX} = 4.5 \text{ Hz}$ from the spectrum at 100 MHz for the ABX system formed by the H_{11} and H_{12} protons.

The conformation of columbin as determined by X-ray crystallography is shown in (116)[18]. It can be seen that the coupling constants between the H_{11} and H_{12} protons are consistent with the half-chair conformation for the ring - C δ-lactone. Thus, the ring - C lactone in columbin is in the half-chair conformation in $CDCl_3$ solution as well as in the crystal.

A full analysis was made of the ABX system formed by the

C_{11} and C_{12} protons in decarboxycolumbin $(114)^{56}$. The n.m.r. spectrum at 100 M Hz of (114) is shown in Figure 11 with the quartet due to the H_{12} proton shown inset on an expanded scale. As in isocolumbin, the AB part was picked out by irradiation at H_{12} and observing the lines which collapse in the T 6.5 to T 8.5 region. The lines due to the AB part are shown in Figure 12. The coupling constants and chemical shift between the two H_{11} protons are J_{AB} = 14.4 Hz; J_{AX} = 12.8 Hz; J_{BX} = 3.7 Hz; $\delta_A - \delta_B$ = 46.4 Hz. First order analysis of the X part alone gives J_{AX} = 12.1 Hz; J_{BX} = 4.4 Hz.

The above coupling constants are consistent with decarboxy-columbin being in the conformation (117) in which the δ-lactone is in the half-chair conformation.

The n.m.r. spectrum of α-campholide in benzene solution at 100 M Hz is shown in Figure 13. The protons H_1 and H_2 form the AB part of an approximately ABMX system due to the protons H_1 (B); H_2 (A); H_3 (M); H_4 (X). Irradiation at H_3 (Figure13) removes the small coupling (J = 1 Hz) in H_2 and the larger coupling (J = 3 Hz) in H_1. Irradiation at H_4 removes the small coupling (J = 1 Hz) in H_1.

From the n.m.r. spectrum (Figure 13) by first order analysis the following coupling constants are obtained:

$J_{H_1H_2} = 11$ Hz; $\quad J_{H_1H_3} = 3$ Hz; $\quad J_{H_2H_3} = 1$ Hz; $\quad J_{H_1H_4} = 1$ Hz.

H_1 is deshielded relative to H_2 which is in accordance with the shielding region of the carbonyl group being as is shown in (119).

Both H_1 and H_2 suffer a solvent shift of + 0.44 p.p.m. on changing from denterochloroform to benzene solution in accord with the rule of Connolly and McCrindle[53].

The n.m.r. spectra of columbin and isocolumbin confirm that the conformation of the ring - C δ-lactone is the same in the crystal as in solution. From the spectra of the columbin and isocolumbin compounds it is found that in the ring C δ-lactones $J_{diaxial}$ and $J_{axial-equatorial}$ are of the order of 12 Hz and 4 Hz respectively. $J_{geminal}$ in these compounds is of the order of - 14 Hz. The above vicinal coupling constants contrast with those found in α-campholide in which values of 1 Hz and 3 Hz are found. In cases where applied it was found that shielding predictions based on the carbonyl shielding regions by Karabatsos[52] gave the correct result.

EXPERIMENTAL

The n.m.r. spectra were recorded as previously described.
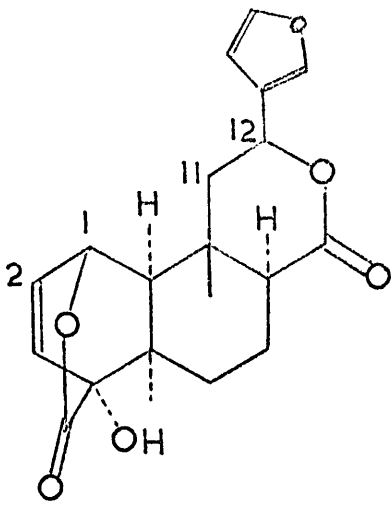
112
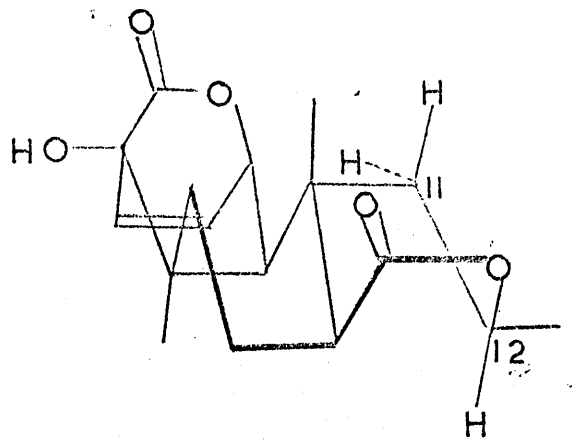
113
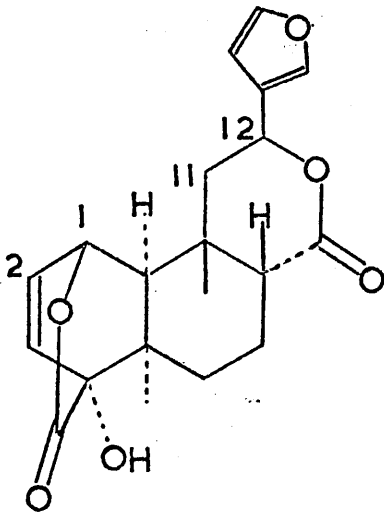
115
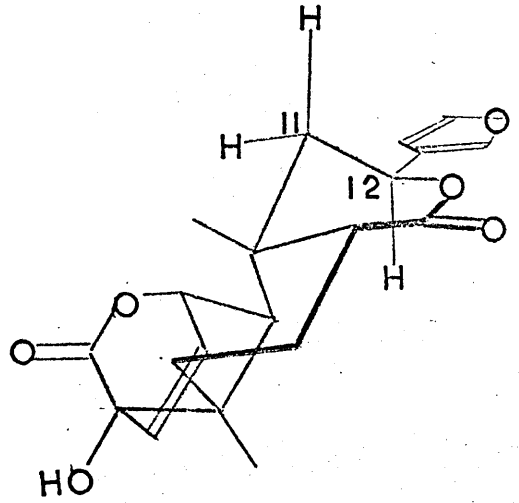
116
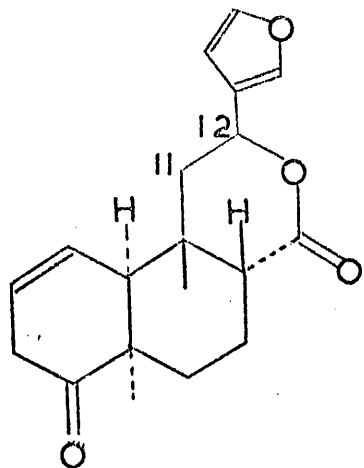
114
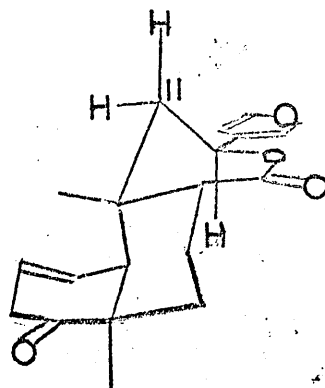
117
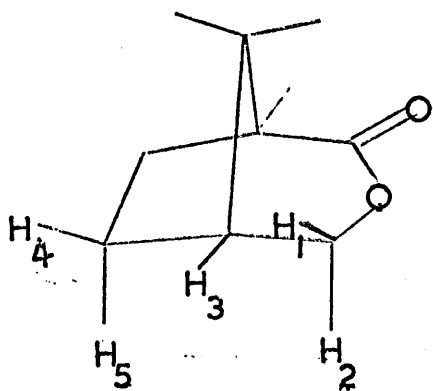
118
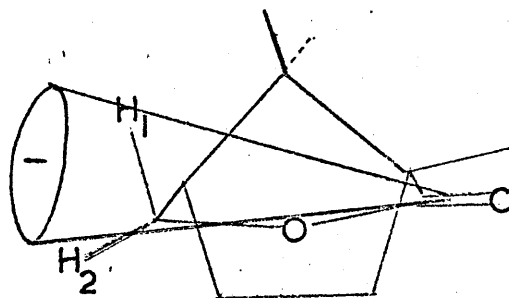
119
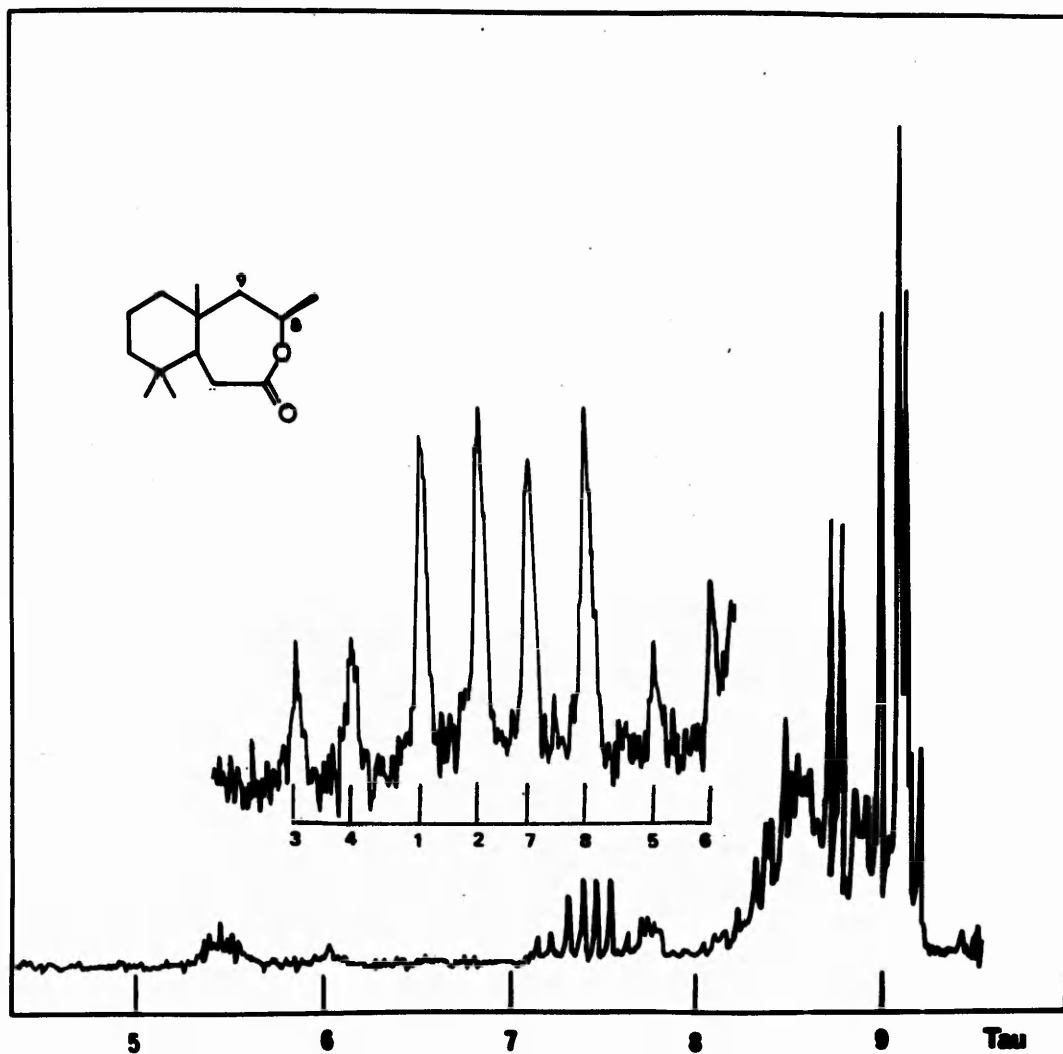
Figure 7

Figure 8

Figure 9

REGION FROM T 7 — 6.5
AT 250 MHz SWEEP WIDTH
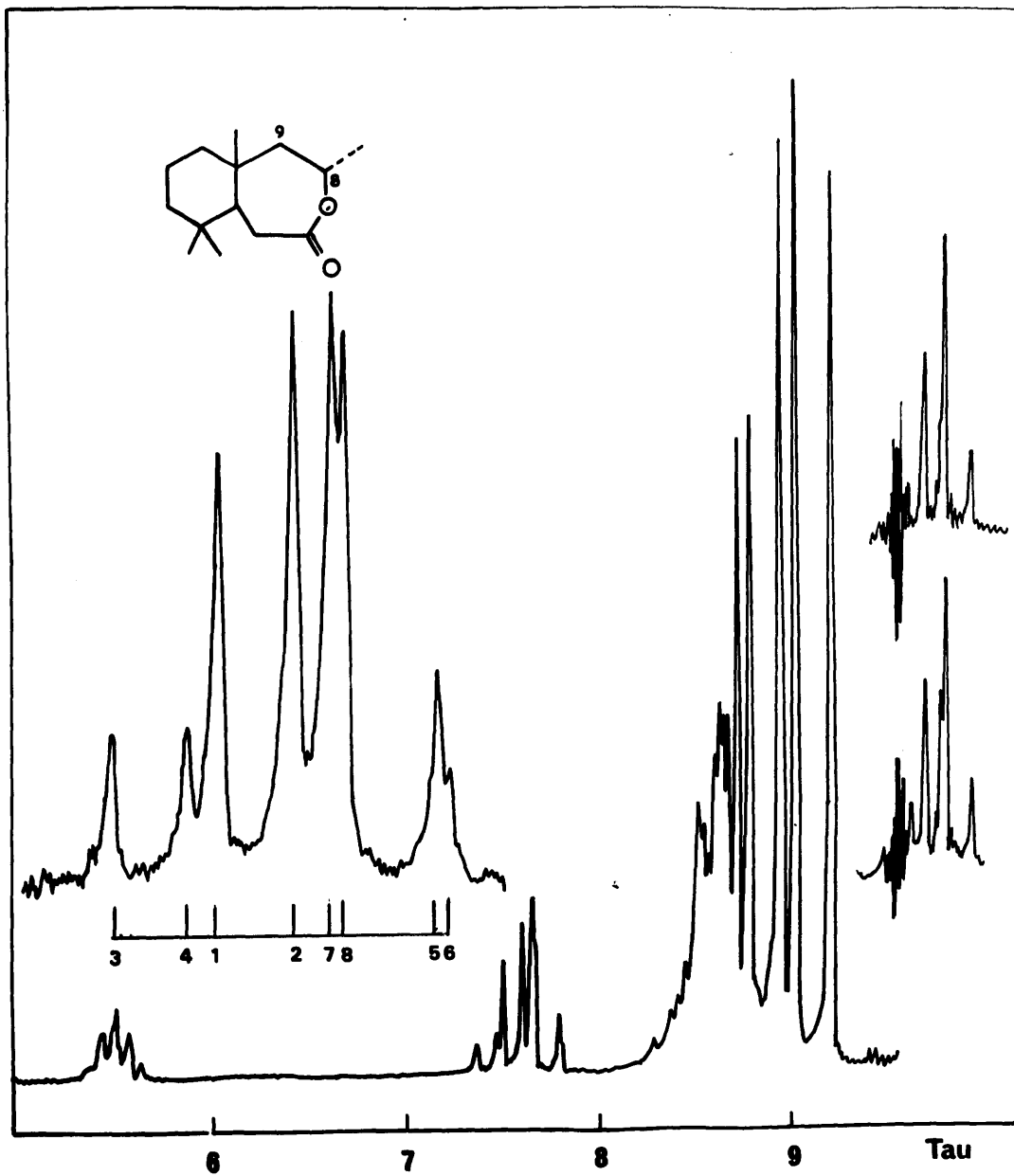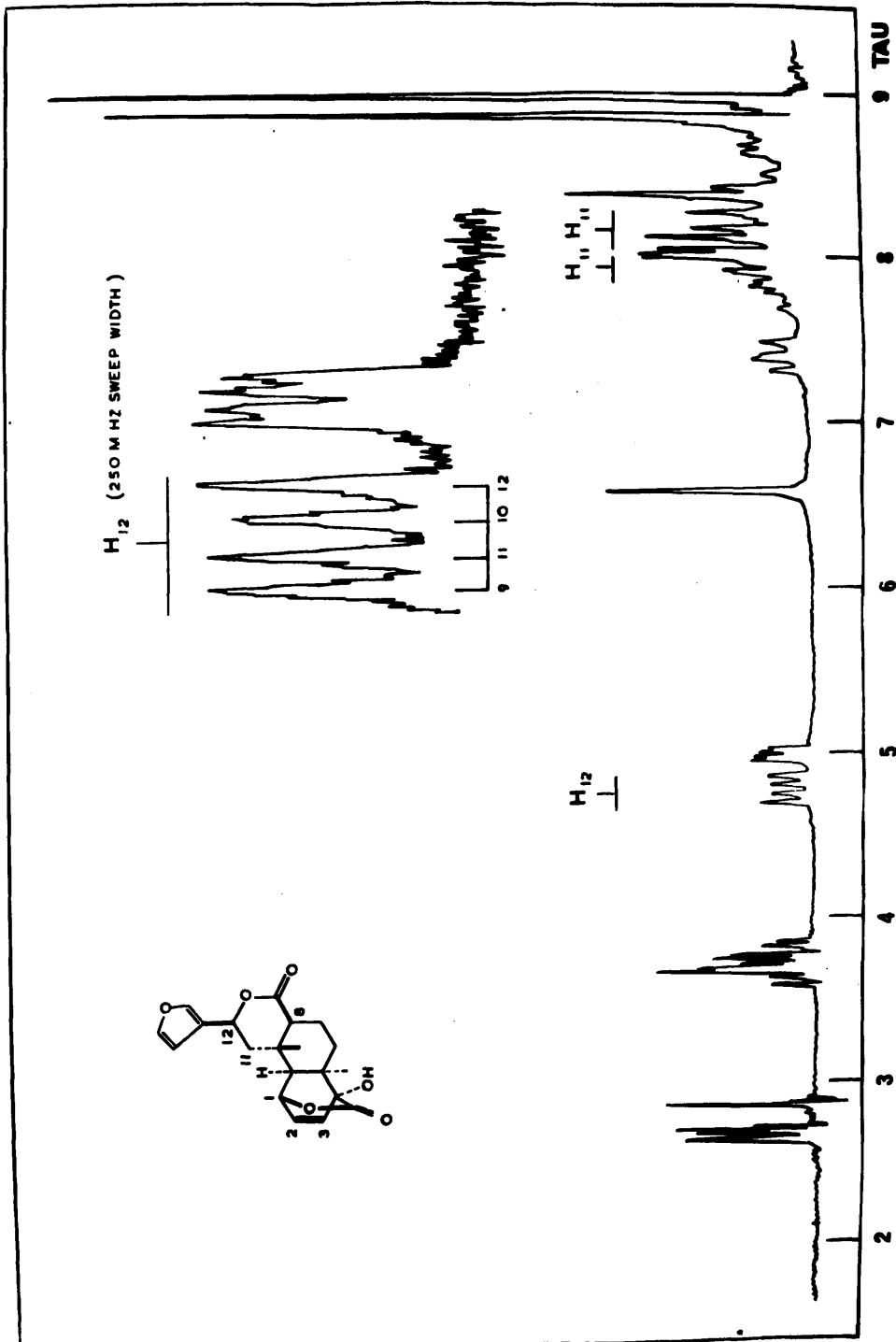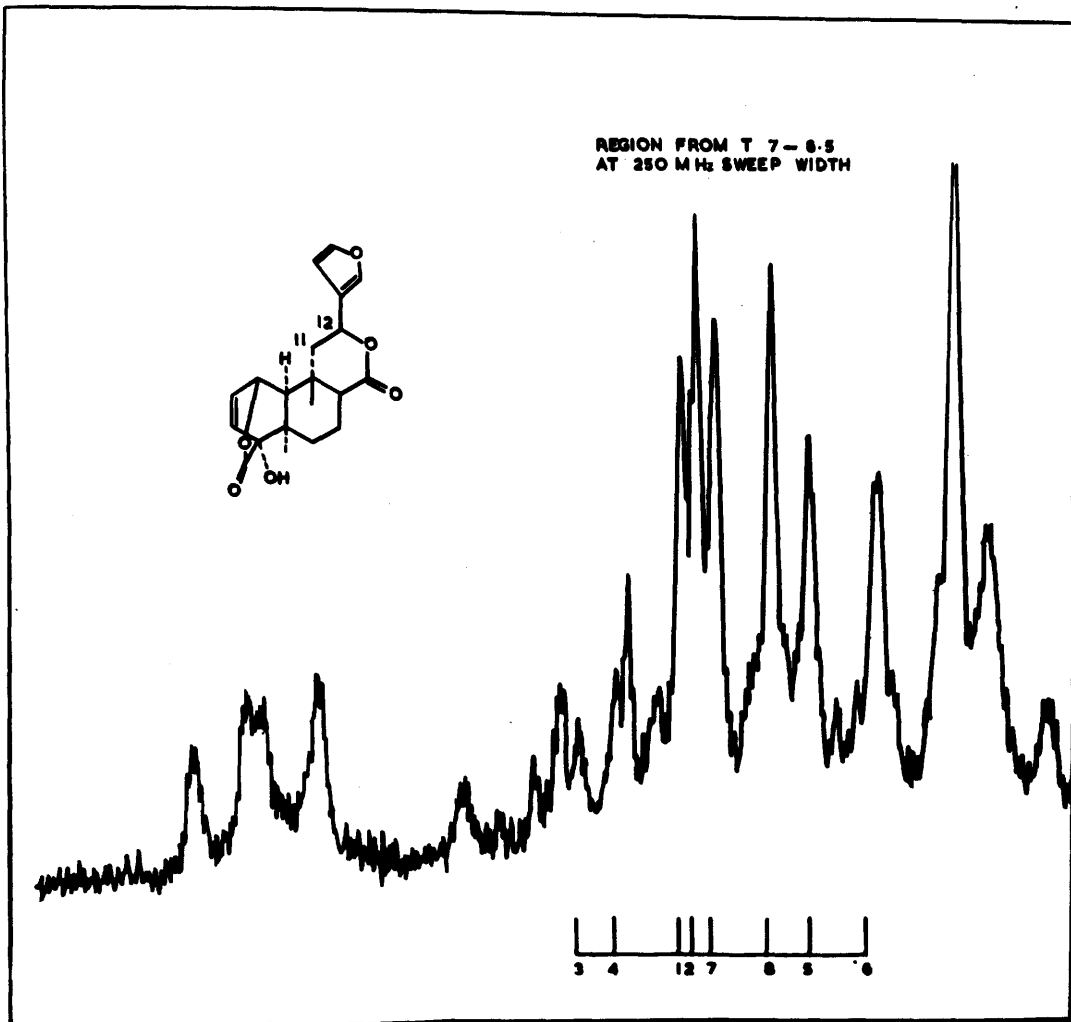
Figure 10

Figure 11

Figure 12

DECARBOXYCOLUBIN REGION FROM τ 6·5 TO τ 8·5
AT 250 HZ SWEEP WIDTH

H_{11}

H_{11}
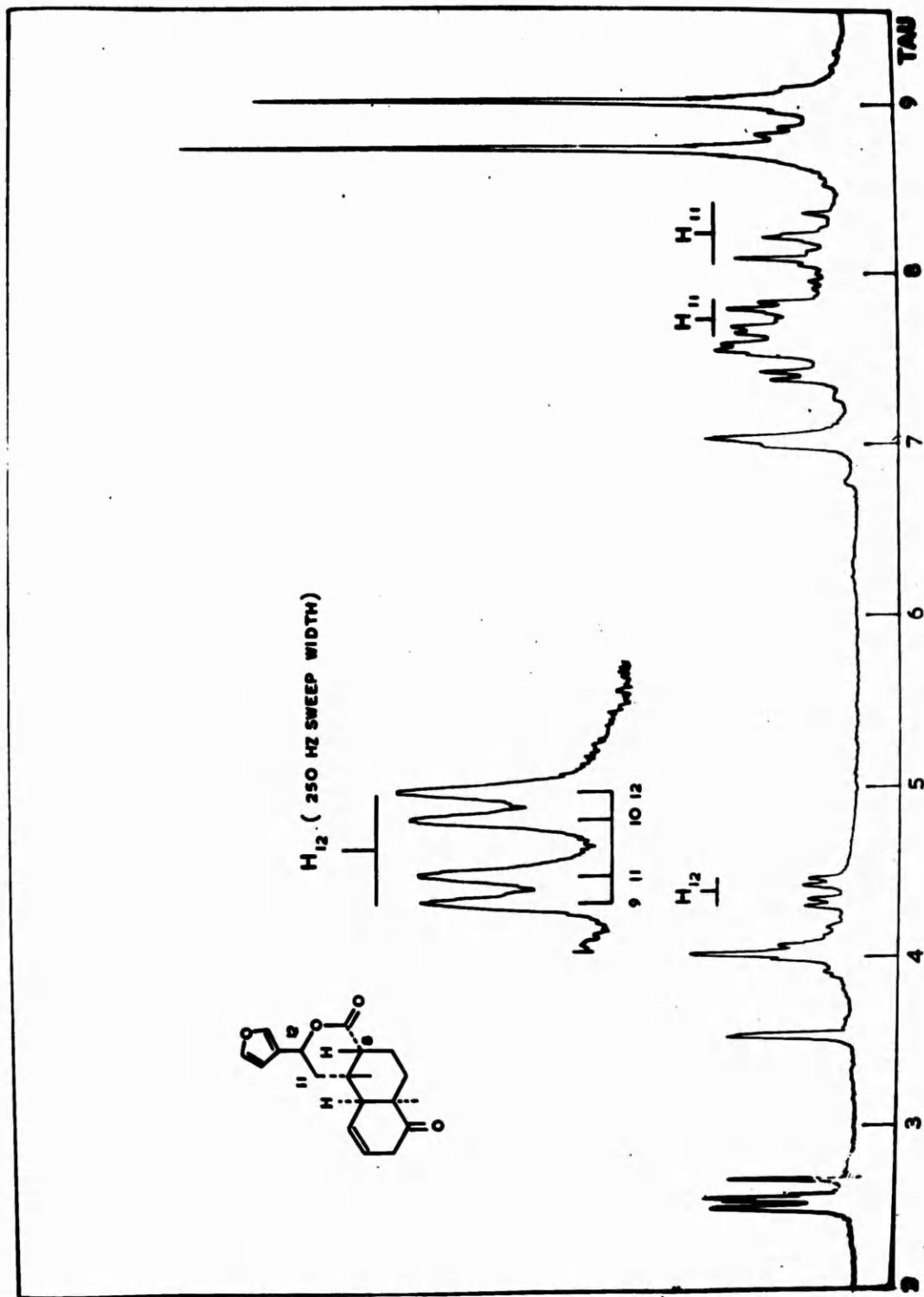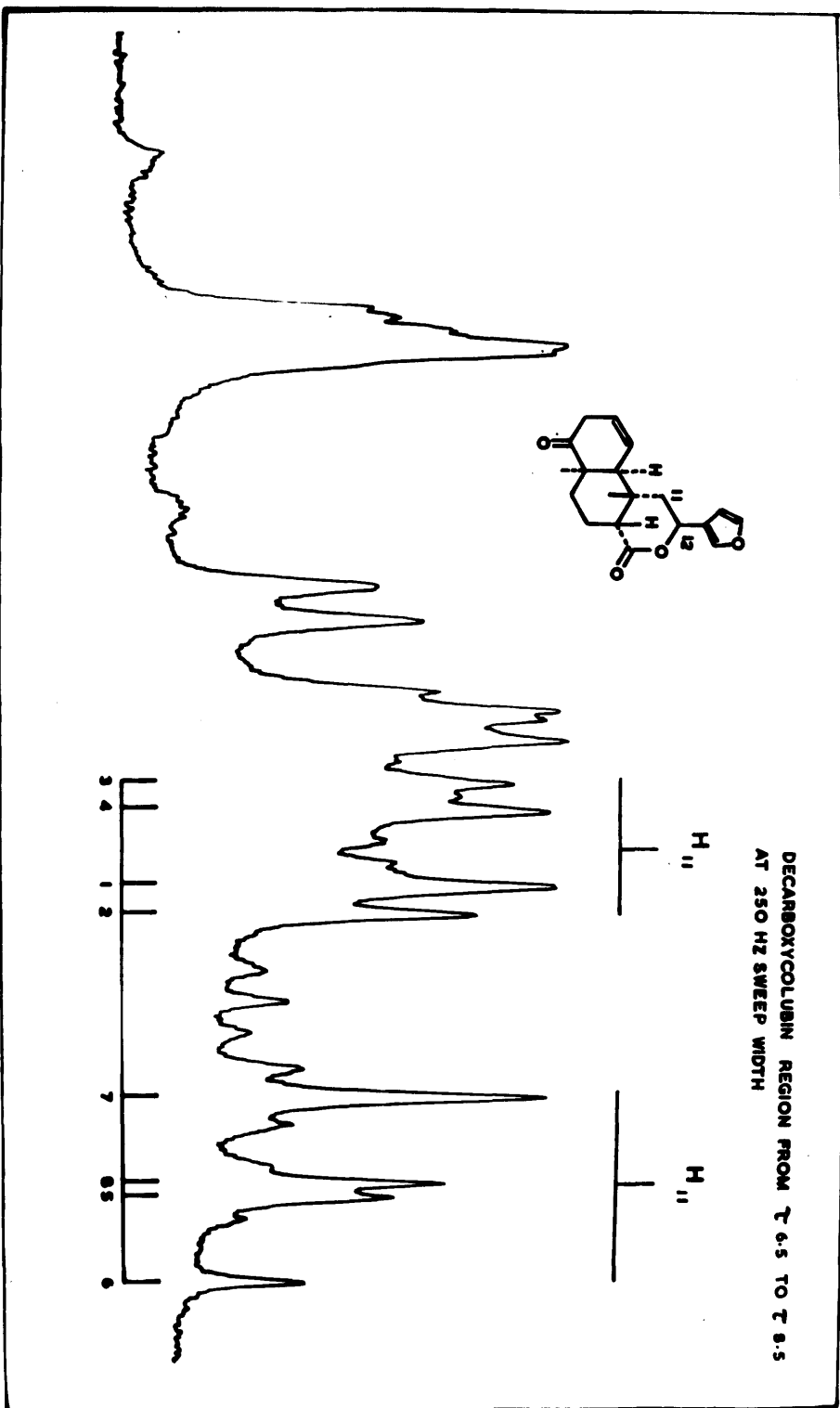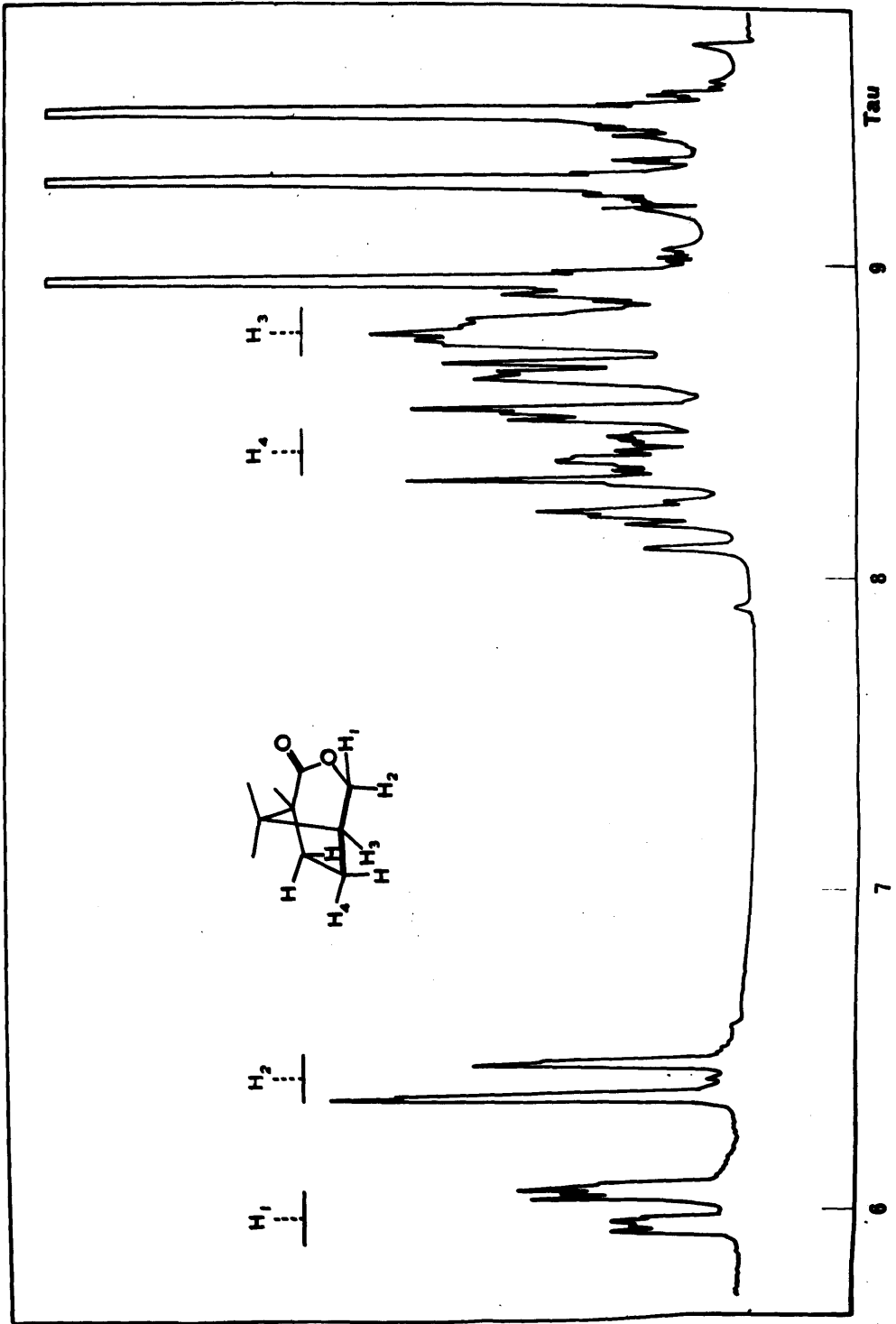
Figure 13

CHAPTER 4

THE CHIROPTICAL PROPERTIES OF δ-LACTONES.

The change in optical rotation of chiral substances
is called optical rotatory dispersion. Optical rotation or
circular birefringence is caused by the different velocities
of propagation of the right and left circularly polarized
waves which constitute plane polarized light. The associated
phenomenon, circular dichroism is caused by the differential
absorption of the right and left circularly polarized waves which
leads to elliptical polarization of the plane polarized light.
The net effect of differential absorption of right and left
components of the plane polarized light and different velocities
of propagation of the two components is to rotate the major
axis of the ellipse traced out by the head of the resultant
vector of the two components.

Optical rotatory dispersion (O.R.D.) curves are obtained
by plotting the molecular rotation ($\bar{\Phi}$) (4.1) against wavelength.

$$(\bar{\Phi}) \quad = \quad \frac{(\alpha) \times MW}{100} \quad - - - - - - (4.1)$$

The corresponding circular dichroism (C.D.) curves are
obtained by plotting the molecular ellipticity (θ) against

wavelength. (θ) is related to the difference in molecular

extinction coefficients, $\triangle \epsilon$, of the right and left circularly

polarized waves by (4.2).

$$(\theta) = 3500 \triangle \epsilon \quad - - - - - - - - (4.2)$$

If the compound is devoid of a chromophore within the

spectral range under investigation then a plain O.R.D.curve

(i.e. a curve with no maximum or minimum), results. However,

if the compound under investigation has an "optically active

chromophore" then there results an anomalous O.R.D. curve.

These curves exhibit a maximum or minimum or both. Cotton

observed this phenomenon at the end of the last century and

anomalous curves are called Cotton effect curves.

An "optically active chromophore" is one which shows

an anomalous O.R.D. or C.D. maximum at the position of the

ultra-violet λ_{max} for the particular chromophore. For example,

the carbonyl group in saturated ketones has a λ_{max} at around

290 nm., due to an $n \rightarrow \pi^*$ transition involving orbitals of

roughly the type depicted in (130)[57].

130
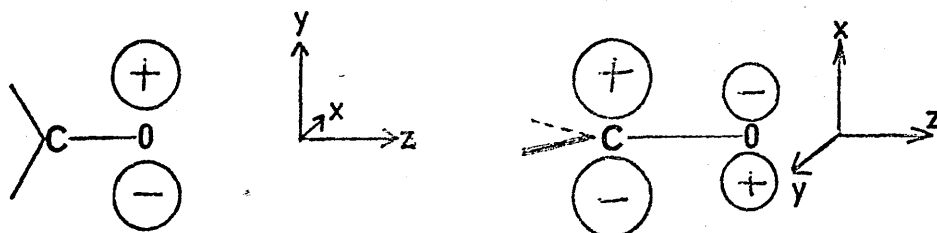
To a first approximation these orbitals may be represented as

$$n = 2_{p_{y,0}}$$

$$\pi^* = A2_{p_{x,0}} + B2_{p_{x,C}}$$

where the subsripts 0 and C designate oxygen and carbon respectively, and A and B are constants. If the two orthogonal symmetry planes of the carbonyl group are also symmetry planes of the entire molecule, as in, say formaldehyde, then on symmetry grounds the transition is electric dipole forbidden, magnetic dipole allowed, i.e.,

$$(n |M_e|\pi^*) = 0$$
$$(n |M_m|\pi^*) \neq 0$$

so that the rotational strength for the transition, R_1, which is proportional to $(n |M_e|\pi^*) \cdot (\pi^*|M_m|n)$ is zero.

According to Moscowitz[57], however, when the carbonyl group is placed in an asymmetric molecular enviroment, then it experiences a disymmetric perturbing potential V due to the presence of neighbouring incompletely shielded nuclei. The effect of V is to cause a mixing in to the π^* orbital of higher atomic orbitals

which lowers the symmetry of the resulting π'^* orbital such that it is neither symmetric nor antisymmetric with respect to the carbonyl planes. This then gives a non vanishing component of the electric dipole transition moment along the direction of $(n \, |M_m| \pi^*)$. Using this type of arguement Moscowitz was able to calculate rotatory strengths which were of the same order of magnitude as those observed for certain cyclohexanone derivatives.

More recently Pao and Santry[58] have carried out LCAO MO calculations on cyclohexanone and its derivatives. They have confirmed the assumptions made by Moscowitz that the n and π^* orbitals are localized mainly on the carbonyl group and that the change in rotatory strengths between different molecules is due mainly to changes in the induced electric dipole moment.

The optically active chromophore which concerns us in the study of the chiroptical properties of lactones is the carboxyl group. This group is in itself symmetric but when placed in a chiral environment gives rise to a Cotton effect at around 220 nm owing to the $n \rightarrow \pi^*$ transition of the carboxyl group (see page 1).

According to the theory of Moscowitz[57], the sign of the Cotton effect will depend on the perturbing effect of the incompletely shielded nuclei in the enviroment of the chromophore. Thus the sign and magnitude of the Cotton effect can be used to

obtain information concerning the configuration and conformation
of the molecule in the neighbourhood of the chromophore. In
ketones this has been facilitated by the development of the Octant
Rule[59], which relates the sign of the Cotton effect to the
substitution pattern around the keto group. Recently there
have been a number of rules proposed by different workers to relate
the sign of the Cotton effect of lactones to the stereochemistry
of the immediate enviroment of the group.

Okuda, Marigaya and Kiyomoto[60] studied the O.R.D. curves
of a series of γ-lactones derived from sugars. They found
that the sign of the Cotton effect was given by the sign of the
quadrant (based on the octant rule) in which the 2 - hydroxyl
group is situated.
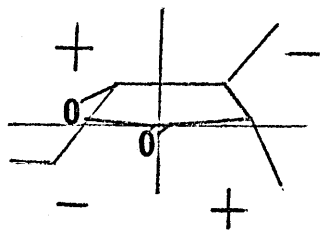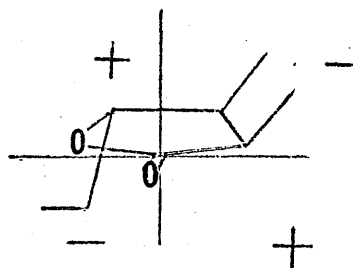
131   132

For example if the two lactones (131) and (132) are divided
into eight octants by three planes (A) (B) and (C) where:-

(A) is a vertical plane passing through O, C - 1 and
    bisecting the C - 3 ——— C - 4 bond.

(B) is a horizontal plane passing through the

O - CO - C2 atoms.

(C) is a vertical plane passing through the

mid-point of the carbonyl bond and perpendicular

to (A).

then the signs of (131) and (132) are the signs of the back-

octants as given by the octant rule. Thus in (131) the 2 - hydroxyl

is in a positive octant and the sign of the O.R.D. curve is positive

while in (132) the 2 - hydroxyl is in a negative octant and the

sign of the O.R.D. curve is negative. Theoretically the octant rule

is not strictly applicable, since the electronic structure of the

lactone group is different from that of a ketone.

The first interpretation which took account of the different

electronic structure of lactones was the sector rule proposed by

Klyne[61]. In this approach Klyne considered the lactone group to

be a resonance hybrid where the two C - O bonds are equivalent

(see page 1). Each carbon-oxygen bond is then regarded in turn

as a double bond and the signs of the contributions made by atoms

in different octants are allocated according to the ketone octant

rule, (133) and (134).
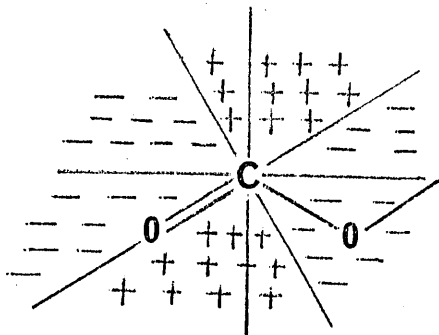
133
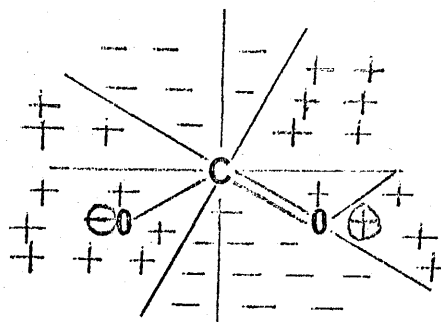
134

If these diagrams are superposed then the signs in some sectors
cancel while in other sectors they reinforce (135). This gives
on balance a positive contribution in the back upper sector
(E) and a negative contribution in the back upper left sector
(B) in accordance with empirical observations. Of course in
view of the uncertainty regarding the correct orbital treatment
of the lactone group the boundaries of these sectors are provisional
and even without this proviso, atoms near a sector boundary will
have small but significant contributions.
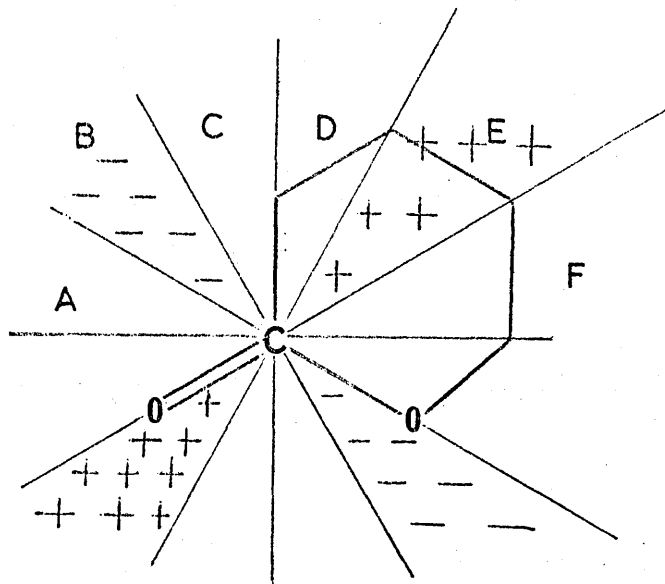
135

To apply the sector rule it is necessary to consider two views of the molecule. These are the view along the bisectrix of the O - C - O angle and the view from above projected on to the plane of the lactone ring. For example if we consider the steroidal δ-lactone 4 - oxa - 5α - androstan - 3 - one (136) which when viewed along the bisectrix of the O-C-O angle as in (137) and viewed from above is as in (138).
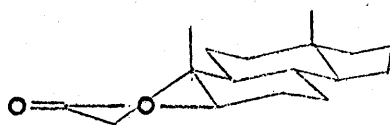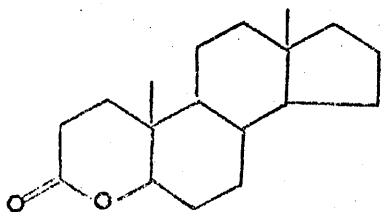
136

137
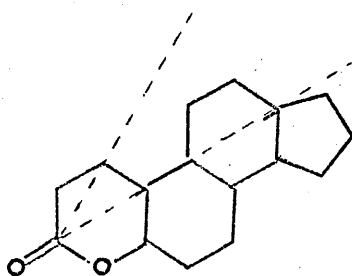
138

All the atoms in the sector indicated lie above the plane and therefore make positive contributions. The sector rule predicts a positive Cotton effect which is indeed observed.

While the sector rule stresses the similarity between the two oxygen atoms an alternative sector rule proposed by Snatzke[62] treats the two atoms as being different. Snatzke considers the orbital picture of the lactone chromophore as shown in (139) and (140). If the nodal planes of these orbitals are

then drawn in and combined as in (141) then one has the
nodal surfaces for Snatzke's sector rule. The signs are
derived empirically.

139   140

141
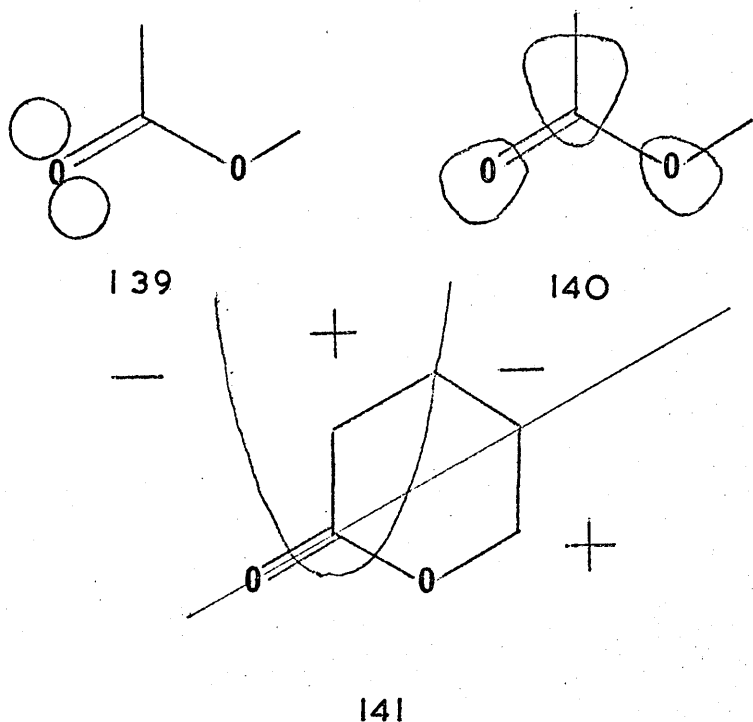
Snatzke's sector rule is applied in a similar way to Klyne's.
It is of interest to note that the sector E in Klyne's rule is
positive contributing yet in Snatzke's rule, groups in this
sector make a negative contribution. A further point of interest
is that the nodal surfaces of the sectors in both rules pass
through all the atoms in the ring (135) and (141), (there is of

course a nodal plane in the plane of the lactone group).
This latter observation implies that the atoms in the ring
will make little or no contribution to the rotatory strength
of the transition.

The rules of Klyne and Snatzke are based on an approach
which is similar to the octant rule. However, a different
approach is due to Wolf[9], and Legrand and Bucourt[10] who take
the view that the chirality of the lactone ring is sign
determining. Thus the above workers propose that the sign of
the $n \rightarrow \pi^*$ Cotton effect in δ-lactones is determined by the
location of the β-carbon atom relative to the lactone plane.

According to Wolf[9], δ-lactones which exist in conformations
(142) and (143) are assosiated with a positive Cotton effect
while (144) and (145) are assosiated with a negative Cotton
effect. (143) and (145) are half-boat while (142) and (144)
half-chair δ-lactones.
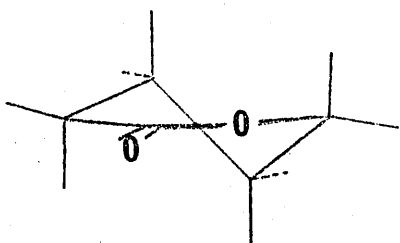
142
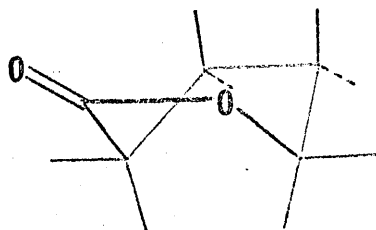
143
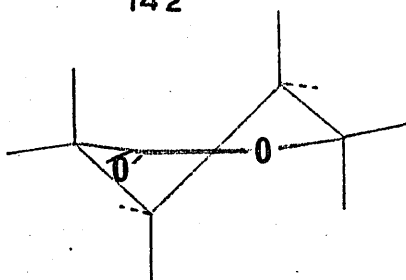
144
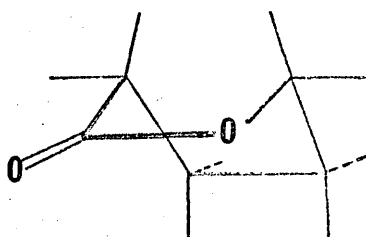
145

Legrand[10] has generalised Wolf's rule, above, and proposes that the sign of the Cotton effect of any lactone is opposite to the sign of the C_β – C – CO – O dihedral angle as defined below.

Positive

Negative

Snatzke postulates that the nearest sphere to the chromophore, which becomes dissymmetric, determines the sign and to a great extent also the magnitude of the Cotton effect. Thus in a δ-lactone, the ring containing the δ-lactone is dissymmetric and therefore it would be expected, according to the above idea, that the chirality of the lactone ring determines the sign of the Cotton effect.

As discussed earlier (pages 76, 83), the assertion that the half-boat is the preferred conformation of δ-lactones is open to question. The work of Sheppard and Turner[7] indicates that in lactones of type (147), the δ-lactone adopts a half-chair (or slightly flattened half-chair) conformation which contradicts Wolf and Legrands predictions. Klyne[64] has discussed the O.R.D. curves of lactones of type (147) and has concluded that they can be satisfactorily explained by application of his sector rule.
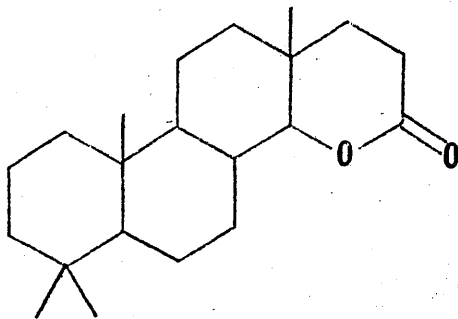

147

Care must be exercised in interpreting O.R.D. curves of
δ-lactones since the n→π^* and π→π^* transitions have
very similar energies and occasionally the two dispersion
curves overlap and the sign of the n→π^* dispersion curve
becomes masked by the much stronger π→π^* one. This
effect[65] has been observed in the case of 3 - hydroxy - 17a - oxa -
D - homo - 5α - androstan - 17 - one (148) which has a strongly
negative O.R.D. but a positive C.D. curve.

At first sight application of Klynes sector rule to (148)
predicts a negative Cotton effect since all the atoms lie
within a negative sector (148) and (149). Klyne[64] has explained
the observed positive Cotton effect by suggesting that the
C - 13 methyl projects into a positive region and since it is
very close to the chromophore, it cancels the effect of the more
distant negative contributing rings.
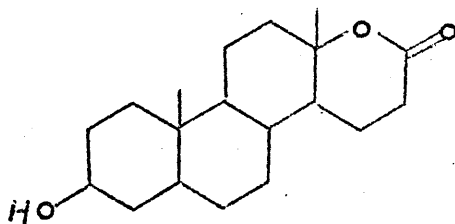
148
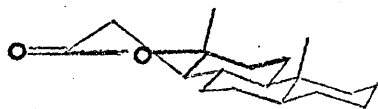
149
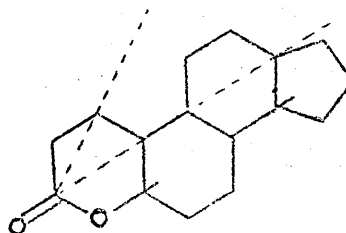
150

In this brief review the different attempts to correlate
the sign of the Cotton effects of δ-lactones with their
structure and conformation have been discussed. It is noted
that there is a difference of opinion as regards the influence
of the conformation of the lactone ring on their chiroptical
properties.

TABLE XVII

δ-Lactone	Conformation/ Chirality (According to Wolf)	Cotton effect
1) 17a-Oxa-18-nor-13χ, 14χ-androstan-17-one	143	positive
2) 17-a-Oxa-13α, 14α androstan-17-one	144	negative
3) 14χ- Bromo-17a-Oxa-13χ-androstan-17-one	144	negative
4) 17a-Oxa-18-nor-13β,14χ-androstan-17-one	145	negative
5) 17a-Oxa-13β, 14χ-androstan-17-one	142	positive
6) 17a-Oxa-13β,14β-androstan-17-one	144	negative
7) 4-Oxa-5α-cholestan-3-one	143	positive
8) 4-Oxa-5β-cholestan-3-one	145	negative
9) 6-Oxa-5β-cholestan-7-one	143	positive
10) 3β-Acetoxy-6-oxa-5α-cholestan-7-one	142	positive
11) 6-Oxa-5χ-cholestan-3,7-dione	142	positive

TABLE XVII (CONTINUED)

12) 2-Oxa-5ᴁ-cholestan-3-one	142	positive
13) 3-Oxa-5ᴁ-cholestan-2-one	142	positive
14) Ambrenolide	144	negative
15) L-(-)Lactid	145	negative
16) Verrucarino-lactone	143	positive

CHAPTER 5

DISCUSSION

In chapter 4 it was shown that there is a proliferation of rules which correlate the sign of the Cotton effect of δ-lactones with their immediate environment. These rules can be divided into two groups. There are those which use an octant rule approach and predict that the sign of the Cotton effect of δ-lactones is determined by the sectors in which the atoms of the molecule are placed while the other approach considers the sign of the Cotton effect to be determined by the chirality of the lactone ring. The work which is discussed in the following pages is an attempt to clarify the position.

To investigate the effect of conformation on the sign of the Cotton effect, the simple δ-lactone (92) whose conformation is discussed in chapter 3 (part 2) has been resolved and its C.D. curve obtained. In addition the C.D. and O.R.D. curves of a number of other δ-lactones have been obtained and studied.

(92) was resolved by forming the diastereoisomeric esters (153a and 153b) and separating them by p.t.l.c. Etienic acid (151) was prepared by the method of Staunton and Eisebraun[66]. (151) was converted into its acid chloride (152) and reacted with the racemic hydroxy ester (101) as described by Djerassi[67]. The resulting diastereoisomeric etienates (153a and b) were separated by

careful p.t.l.c. and the etienate (153b) was obtained as white

a)

needles (m.p. 94 – 95°C, $(\alpha)_D$ – 46°). The other etienate (153a)

amount of (153b).

The next problem was to obtain the required optically

active δ-lactone from the etienate (153b). It was thought

that base hydrolysis of the etienate would yield the sodium salt

of the hydroxy acid (101a) which on acidification would cyclise

to the required optically active δ-lactone. However, refluxing

(153a) in basic solution followed by acidification and methylation

with diazomethane afforded the hydroxy–etienate (154). Steric

hindrance by the C 18 methyl was thought to be responsible for

the absence of reaction at C 20.

Djerassi, however, has shown that etienates of type (153)

can be reduced with lithium aluminium hydride which results in

cleavage of the C 20 – 0 bond. Unfortunately this will result in

reduction of the carbomethoxy group to yield the diol (155). In

anticipation of this reaction, model experiments were carried out

to convert (155) into the δ-lactone (92). The diol (155)

required for these trial experiments was obtained by lithium

aluminium hydride reduction of (92).

It was found that (155) could be transformed into (92) in

low yields by stirring overnight with a large excess of active

manganese dioxide[54] in very dry methylene chloride. The reaction was found to be dependent on solvent systems, since use of acetonitrile[69] resulted in formation of a complex mixture of products while D.M.F. gave no reaction whatsoever. The low yields were caused by irreversible adsorption of (155) on to the surface of the manganese dioxide. Other oxidation methods, Jones[25], Snatzke[55] and Sarrett[68] gave complex mixtures with only very small amounts of the required lactone being formed.

Reduction of the etienate (155b) gave two products as judged by t.l.c. The less mobile had the same retention factor as the diol (155), but because of streaking from the more mobile component, it could not be isolated by p.t.l.c. Separation was achieved by acetylation of the above product mixture followed by p.t.l.c. which gave the optically active diacetate (158) ($(\alpha)_D$ - 15.5^o). (158) was reduced with lithium aluminium hydride to give the optically active diol (157) ($(\alpha)_D$ - 30°).

The absolute configuration of the diol (157) was determined by Horeau's method according to Herz[70]. T.l.c. was used to check that the diol (157) was completely esterified with α-phenyl ethyl butyric anhydride. On this basis the esterification yield was taken to be 100% and the optical yield of the α-phenyl butyric anhydride was 11% (-). According to Horeau[71] this indicates an (S) configuration for the carbon atom which carries the t-butyl group.

The optically active diol (157) was oxidised with manganese
dioxide in dry methylene chloride solution to give the optically
active δ-lactone (159). Confirmation of the absolute stereochemistry
was obtained from the C.D. curve, which was almost the mirror image,
of the known dihydro-parasorbic acid (160)[72]. The C.D. data for
(159) and (160) are shown in table XVIII.

Table XVIII. C.D. data for the lactone (159) and dihydro-
parasorbic acid (160).

Compound	Solvent	Circular Dichroism Molecular Ellipticity (Θ)	
(159)	Isooctane	$(\Theta)_{242}$ -363;	$(\Theta)_{213}$ +264.
	Ethanol	$(\Theta)_{238}$ -198;	$(\Theta)_{213}$ +462.
(160)	Isooctane	$(\Theta)_{243}$ +957;	$(\Theta)_{214}$ -626.
	Ethanol	$(\Theta)_{238}$ +264;	$(\Theta)_{211}$ -924.

Before discussing the C.D. curves of (159) and (160) it is
of interest to examine other lactones which show two oppositely

signed Cotton effects. The C.D. data for these lactones (161) to (164) taken from Wolf[9,65] is shown in table XIX. Unfortunately Wolf only gives C.D. data for the longer wavelength bands. However, Klyne[64] has published O.R.D. data for compounds (163) and (164) from which it is possible to obtain information on the sign and magnitude of the shorter wavelength (approximately 215 nm.) band. The O.R.D. data for (163), (164) and some of their derivatives are shown in table XX.

Table XIX. C.D. data for the longer wavelenth band of δ-lactones which show two oppositely signed Cotton effects[9,65].

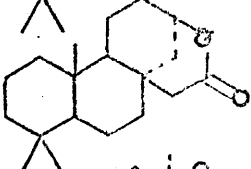| Compound	Solvent	Circular Dichroism Molecular Ellipticity (θ)
(161)	Methanol	$(\theta)_{248}$ −180
(162)	Methanol	$(\theta)_{243}$ +250
(163)	Methanol	$(\theta)_{248}$ −120
	Isooctane	$(\theta)_{215}$ +3700 $(\theta)_{250}$ −200
(164)	Methanol	$(\theta)_{243}$ +300

Table XX. O.R.D. data for some δ-lactones[64].

(all measured in methanol)

Compound	(ϕ) at first extremum	(ϕ) at lowest wavelength	
(163) 4-Oxa-5α-cholestan-3-one.	+8150 pk 227	+4800	208
17β-Hydroxy-4-oxa-5α-androstan-3-one.	+6250 pk 226	+3520	211
17β-Hydroxy-17α-methyl-4-oxa-5αandrostan-3-one.	+4670 pk 227	+4200	220
(164) 4-Oxa-5β-cholestan-3-one.	−1400 tr 225	−800	212
17 -Hydroxy-4-oxa-5β-androstan-3-one.	−1400 tr 230	−885	218
17β-Hydroxy-17α-methyl-4oxa-5β-androstan-3-one.	−3240 tr 225	−2530	213

From the data shown in tables XIX and XX it can be seen that the short wavelength (ca. 215 nm.) band in the C.D. is considerably more intense than the longer wavelength (ca. 240 nm.) band. In fact the longer wavelength bands are not visible in the O.R.D. curves of (163) and (164).

Wolf[9] has proposed that the double humps in the C.D. curves of (161) to (164) are caused by a conformational equilibrium between the half-chair and half-boat δ-lactones. He also assumed that the short wavelength (ca. 215 nm.) band is due to the half-boat conformer and the longer wavelength band to the half-chair. Since the short wavelength band is the more intense, Wolf[9] concluded that the preferred conformer was the half-boat. This of course directly contradicts predictions made in chapter 2 (part 2, page 88) based on I.R. evidence that the preferred conformation of the lactone rings in (163) and (164) is the half-chair.

Because of this conflict of evidence it was decided to check the assumption that the C.D. maxima for half-boat δ-lactones occur at shorter wavelengths than the maxima for the half-chairs. Tables XXI and XXII show C.D. data for a number of δ-lactones both from this thesis and from the literature. The U.V. data for some lactones is shown in table XXIII. It is assumed that δ-lactones such as ambreinolide and the 17a - oxa - androstan - 17 - ones shown in table XXI are in the half-chair conformation (see reference 9).

Table XXI. C.D. data for some half-chair δ-lactones.
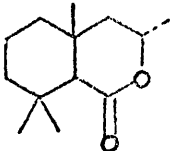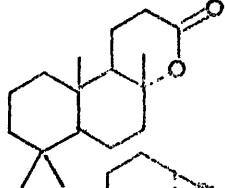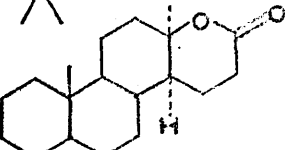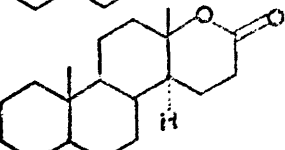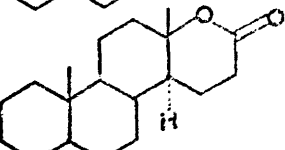
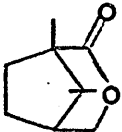| Compound	Solvent	Circular Dichroism Molecular Ellipticity (θ)	Reference
	EtOH	$(\theta)_{226}$ +4600	This work.
	EtOH	$(\theta)_{234}$ -825	This work
	i-octane	$(\theta)_{239}$ -1420	
	EtOH	$(\theta)_{255}$ +2210	This work.
	i-octane	$(\theta)_{235}$ -2000	(65)
	i-octane	$(\theta)_{237}$ +2000	(65).

Table XXII. C.D. data for some half-boat δ-lactones.
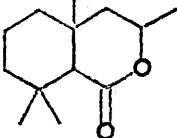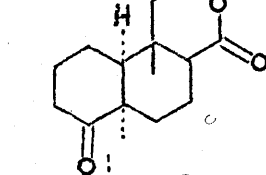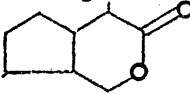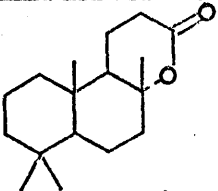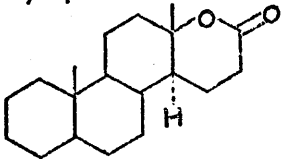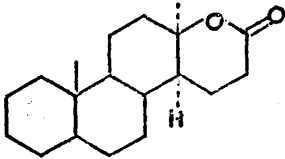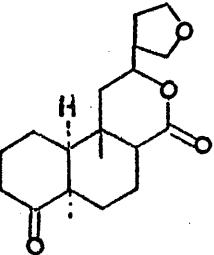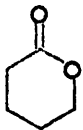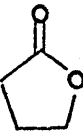
Compound	Solvent	Circular Dichroism Molecular Ellipticity (Θ)		Reference
	EtOH	$(\Theta)_{223}$	+9160	This work.
	EtOH	$(\Theta)_{217}$ $(\Theta)_{297}$	+13,200 +6,470	This work
	MeOH	$(\Theta)_{215}$	−16,300	(73)

Table XXIII. U.V. data for some δ-lactones.

Compound	n-hexane or isooctane		ethanol	
	U.V.$_{max}$ nm.	ϵ	U.V.$_{max}$ nm.	ϵ
	223	48	213	59
	222	ref. 65		
	222	ref. 65		
	220	96	216	96
			no maxima ϵ = 130 at 220 nm.	

Table XXIII (Continued).

Compound	U.V._{max} nm.	ϵ	U.V._{max} nm.	ϵ
	222	40		
	214	41		

The tables above show that even after taking into account the hypsochromic shift due to ethanol as solvent that the C.D. maxima for half-boats appear at shorter wavelength which confirms Wolfs assumption. This shift is proabably caused by the smaller C − CO −O bond angle in the half-boat as compared to the half-chair since a similar shift is observed on going from δ-valerolactone to γ-butyrolactone in which such an angle decrease is more pronounced (see page 12).

The magnitude of the hypsochromic shift on going from a half-chair to a half-boat δ-lactone is difficult to estimate because

the C.D. maxima in some of the lactones are altered by the presence of strong bands of opposite sign below 200 nm. However, it seems probable that the shift is of the order of 3 to 10 nm.

Another point which arises out of tables XXI and XXIII is that δ-lactones in the half-boat conformation have much stronger Cotton effects than those in the half-chair.

A possible answer to the seemingly conflicting evidence (noted on page 136) lies in the calculations of Djerassi and Moscowitz[74] who have investigated complex C.D. curves of the type obtained for (161) to (164). They have shown that C.D. curves with two oppositely signed extrema separated by 30 nm. arise whenever two Cotton effects of opposite sign are superposed with their individual maxima separated by 1 to 20 nm. Some of the results of their calculations are shown in table XXIV.

Table XXIV. Original separate C.D. curves of species 1 and 2 (A) and double Cotton effect resulting from superposition of C.D. curves 1 and 2 (B).

(A)
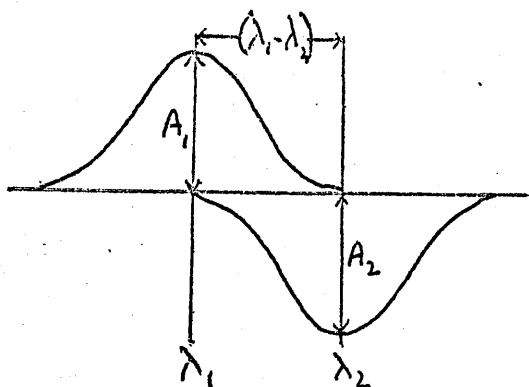
	λ_1^{nm}	λ_2^{nm}	$(\lambda_2 - \lambda_1)^{nm}$	A_1	A_2
			A		
i)	300	302	2	+1.000	−1.000
ii)	300	304	4	+1.000	−1.000
iii)	300	308	8	+1.000	−1.000
iv)	300	302	2	+1.000	−0.500
v)	300	304	4	+1.000	−0.500
vi)	300	308	8	+1.000	−0.500

(B)
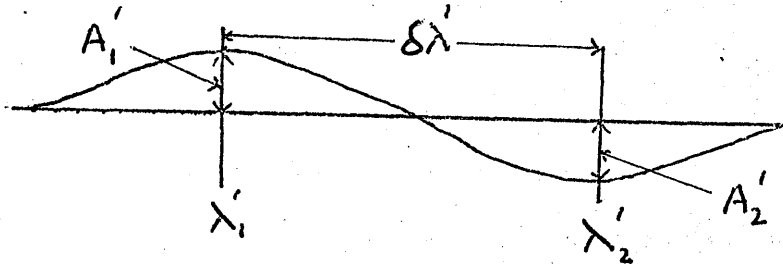
λ'_{1} nm.	λ'_{2} nm.	B A'_{1}	A'_{2}	$\delta\lambda'$ nm.
i) 286.8	315.2	0.0856	−0.0856	28
ii) 287.8	316.2	0.1704	−0.1704	28
iii) 289.6	318.4	0.3341	−0.3341	29
iv) 298.2	0.0	0.5097	0.0	−
v) 296.8	0.0	0.5355	0.0	−
vi) 295.6	329.3	0.6123	−0.0459	34

The C.D. data for (163) (table XIX) shows two oppositely signed extrema separated by 35 nm. and of relative amplitudes 3.7 and -0.2. Although we do not have the full C.D. data for (163), it does appear that there is a strongly positive Cotton effect below 200 nm. (see reference 65) which may accentuate the short wavelength band, thus causing it to be more intense than it really is. Examination of table XXIV shows that the above amplitudes resemble those of the resultant curve (vi). The relative amplitudes of the resultant curve in (vi) are 3.7 and -0.3 and the separation between the two extrema is 34 nm. and it is shown that this curve is formed by two strongly overlapping Cotton effects of relative amplitudes 1.0 to -0.5 with their extrema separated by 8 nm.

In addition to the conformational equilibrium which is undoubtedly present the possibility of a solvational equilibrium must not be neglected. This will of course intensify the shorter wavelength band (ca. 215 nm.) since the $n \rightarrow \pi^*$ transition for the solvated chromophore is close to 215 nm. For example, in table XXIII it can be seen that the U.V. maximum is shifted to shorter wavelengths in the more strongly solvating solvent.

The above discussion shows that the actual Cotton effect attributable to the half-chair conformation in (163) is much stronger than would appear at first. This together with the observation

that the Cotton effects of δ-lactones in the half-boat conformation
are stronger than those of δ-lactones in the half-chair conformation
makes it very difficult to predict what the preferred conformation of
(163) is from its C.D. curve alone. In order to be able to do this
it would be necessary to know the amplitudes of the Cotton effects
of the two species in the equilibrium mixture together with
rotational strengths of the pure half-chair and half-boat conformers.

Although we do not have the full C.D. data for the other
δ-lactones (161), (162), and (164) it seems probable that Wolf has
underestimated the contribution made to the C.D. curves by the
half-chair conformers. In conclusion, it is felt that there is no
reason to doubt the conclusions reached in chapter 2 (part 2) that
(163) is a mixture of conformers with the half-chair predominating
and that (164) has about 40% of the half-boat in the equilibrium
mixture.

As Wolf[9] has suggested, studies of the C.D. curves at
different temperatures will give some information about the
conformational equilibrium which is present. However, care
will have to be taken in interpreting the results because of the
presence of solvational equilibria.

Returning now to the C.D. curves of the lactones (159) and (160),
(table XVIII) it seems that the best explanation of the double
hump is that a half-chair half-boat equilibrium exists. This was
indicated for the t-butyl lactone (159) by n.m.r. and I.R. For
(159) the longer wavelength (ca. 240 nm.) band will be due to

the half-chair (165) which in accordance with the Wolf[9] and Legrand[10] rules gives negative Cotton effect. The short wavelength (ca. 214 nm.) band is therefore due to the half-boat (166) which again gives the sign expected by both Wolf and Legrand. Since the Cotton effect of the half-boat is stronger than that of the half-chair then in isooctane the half-chair is the predominant conformer. The increase in intensity of the shorter wavelength band on changing to ethanol as solvent must be due to either a change in the proportions of the two conformers in the equilibrium mixture or more probably to formation of a higher proportion of the solvated lactone which has its C.D. maximum at lower wavelength. In accord with Djerassi and Moscowitz[74], the amplitudes of the constituent Cotton effects will be much greater than those shown in table XVIII and their extrema will be much closer together. A similar discussion applies to the lactone of dihydro-parasorbic acid (160).

As can be seen from (167), application of Snatzkes sector rule[62] to the half-chair conformer of (159) predicts a positive Cotton effect which is opposite to that found.

All of the other lactones whose O.R.D. and C.D. curves have been obtained for this thesis (see tables XXI and XXII) obey the rules of Wolf and Legrand. Some of the more interesting cases are discussed below.

Hexahydrodecarboxyisocolumbin (168) shows positive Cotton effects at 297 nm. due to the $n \rightarrow \pi^*$ transition of the keto group and at 217 nm. due to the lactone $n \rightarrow \pi^*$ transition, (see table XXII). (168a) shows that the lactone Cotton effect obeys the rules of Wolf[9] and Legrand[10]. (168b) shows the C - 5 methyl projecting into a positive octant which is close to the carbonyl chromophore and therefore a positive Cotton effect is predicted and found for the ketone Cotton effect (see also reference 63, chapter 9).

α-Campholide (169) has a strongly positive Cotton effect, $(\Theta)_{226} = 3,880$ (iso-octane), which is of the opposite sign to that predicted by applying the rules of Wolf and Legrand to the δ-lactone ring. Beecham[75], however, has observed that in γ-lactones of type (170) the sign is opposite to that predicted by applying Legrands rule to the γ-lactone ring. This suggests that in bicyclic lactones which have two β carbon atoms, then the sign of the Cotton effect is determined by the largest O - CO - C - C_β dihedral angle. Thus in (169) and (170), O - CO - C - $C_{\beta'}$ is the largest dihedral angle and according to Legrands rule the Cotton effects will be positive which is indeed found.

The other bicyclic lactone studied, is the 17 - norphylloclada

- 13, 14 - lactone (171) which does not have two β carbon atoms and hence the normal rule applies. Thus (171) has a positive Cotton effect (see table XXII) which is as predicted by the Wolf and Legrand rules.

The two ϵ -lactones (67) and (68) (see chapter 2 part 1) have negative Cotton effects. Both of them obey Legrand's rule as shown in (172) and (173).

Table XXV shows the sign of the Cotton effect at wavelengths below 200 nm. for a number of δ-lactones. This effect is probably due to a $\pi \rightarrow \pi^{*}$ transition and accounts for the very strong background in many O.R.D. curves of δ-lactones.
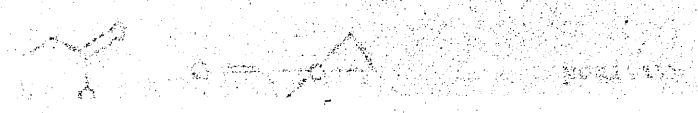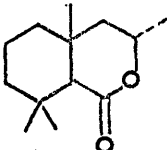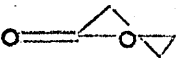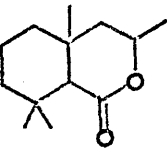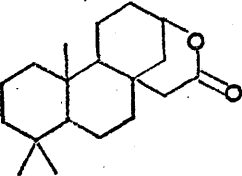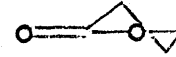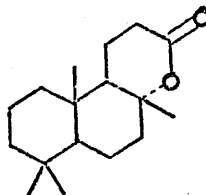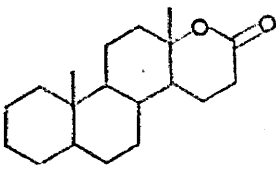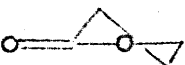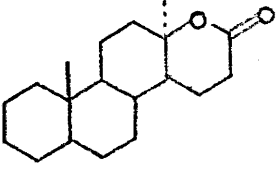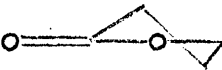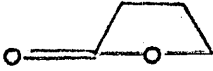
Table XXV. The signs of the $\pi \rightarrow \pi^*$ Cotton effect for some

　　　　　δ-lactones.

Compound	Conformation of δ-lactone ring.	Sign of $\pi \rightarrow \pi^*$ Cotton effect	Reference
		negative	This work
		negative	This work
		negative	This work
		positive	This work

Compound	Conformation of δ-lactone ring	Sign of $\pi \rightarrow \pi^*$ Cotton effect	Reference
		negative	65
		positive	65

As can be seen the sign of the $\pi \rightarrow \pi^*$ Cotton effect is opposite to that of the $n \rightarrow \pi^*$ Cotton effect in all cases. This suggests that the sign of the $\pi \rightarrow \pi^*$ transition is related to the chirality of the lactone ring as shown in table XXVI.

Table XXVI. Relationship between sign of $\pi \to \pi^*$ Cotton effect and chirality of δ-lactones.

	Chirality	Sign
(a)		negative
(b)		negative
(c)		positive
(d)		positive

It is of interest to note that the lactone (163) has a strongly positive $\pi \to \pi^*$ Cotton effect[65] which is of the same sign as its $n \to \pi^*$ Cotton effect, (this is the only δ-lactone we have data on which has both the $n \to \pi^*$ and $\pi \to \pi^*$ Cotton effects with the same sign). The sign of the $\pi \to \pi^*$ effect, suggests that (163) is predominantly in the half-chair conformation, (c) in table XXVI, which is in agreement with predictions based on examination of its I.R. spectrum (see page 83). As pointed out earlier in this

discussion (page 145), there is doubt about Wolfs conclusion that (163) is predominantly in the half-boat conformation, hence, it may be that the sign of the $\pi \longrightarrow \pi^*$ Cotton effect (or the sign of the background in the O.R.D. curves) of δ-lactones is a better guide to their conformation than the sign of the $n \longrightarrow \pi^*$ effect.

The conclusions summarised in table XXVI are necessarily tentative as not much data is available, but, the correlation observed in the few results so far (table XXV) is encouraging.

In this part of the thesis the optically active δ-lactone (159) has been synthesised and its C.D. curve has been shown to be best interpreted in terms of the rules of Legrand and Wolf as being a conformational mixture of the half-boat and half-chair forms with the latter predominating. C.D. and O.R.D. curves of a number of δ-lactones have provided further evidence in support of the rules of Legrand and Wolf. The C.D. data for the lactone (163), which Wolf suggested is preferentially a half-boat δ-lactone, has been examined and it has been concluded that in this case it is extremely difficult to predict the conformation from the C.D. curve.
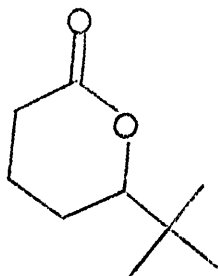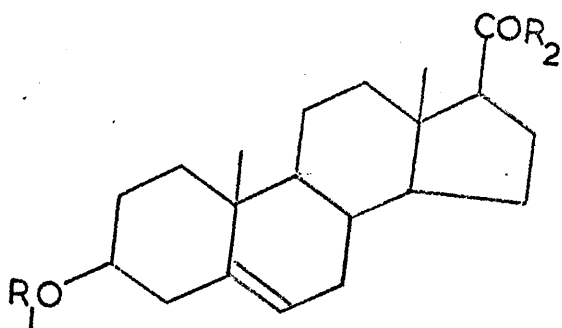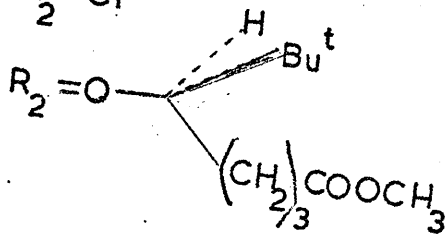
92
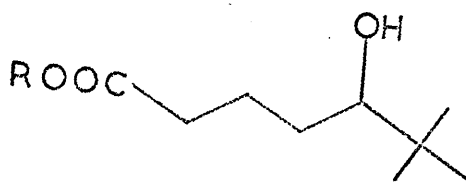
101 R = CH$_3$

101a R = H

151 R$_1$ = COCH$_3$ R$_2$ = OH

152 R$_1$ = COCH$_3$ R$_2$ = Cl

153a R$_1$ = COCH$_3$ R$_2$ = O

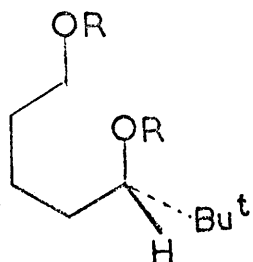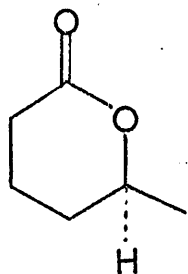**153b** R$_1$ = COCH$_3$ R$_2$ = O
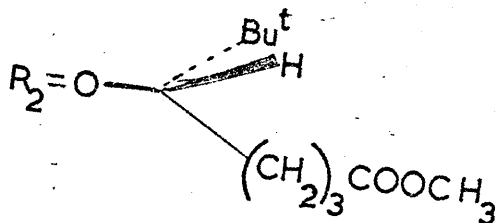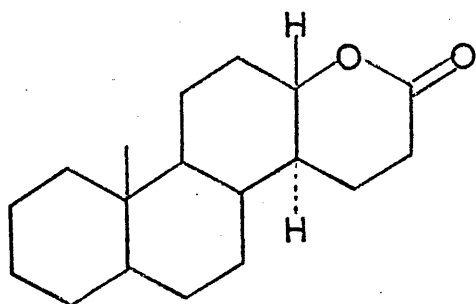
154 R$_1$ = H
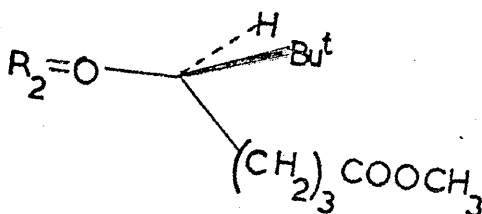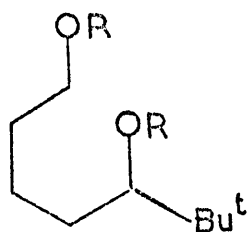
155 R = H
156 R = COCH$_3$

157 R = H
158 R = COCH$_3$
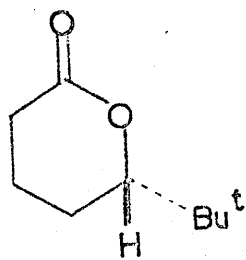
159

160
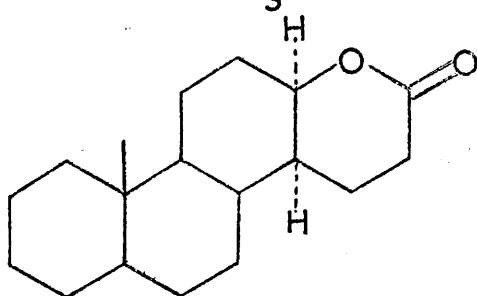
161

162
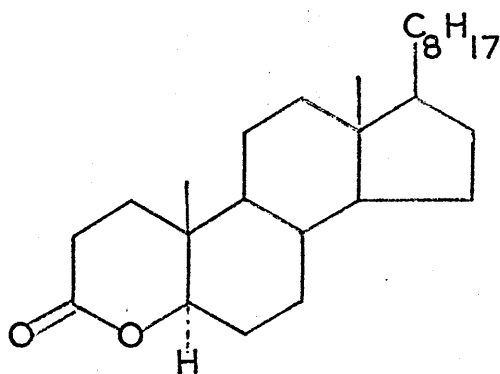
163
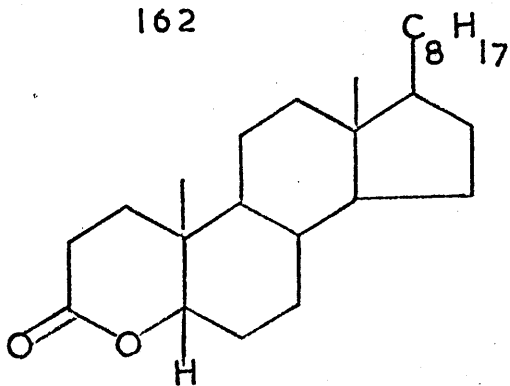
164
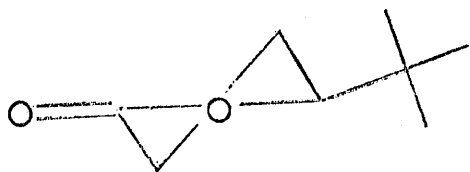
165
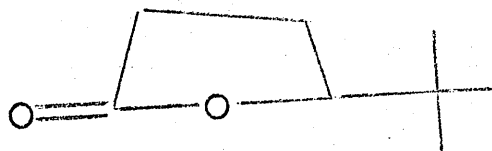
166
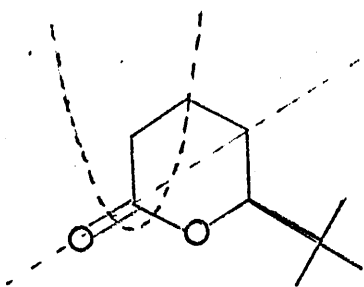
167
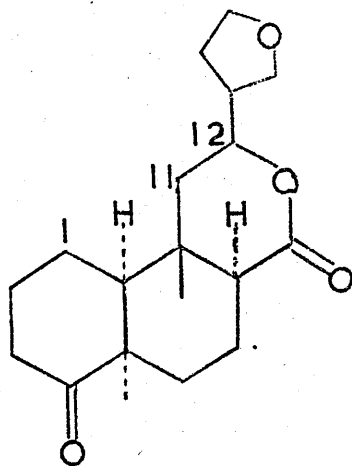
168
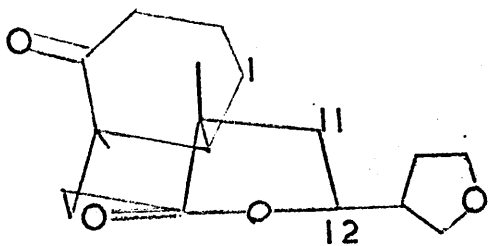
168a
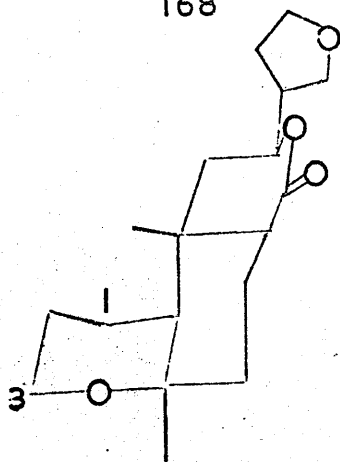
168b
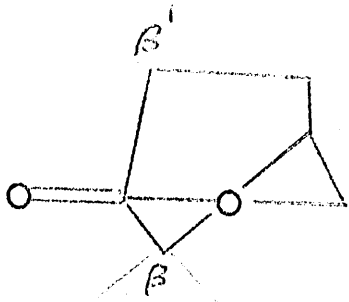
169
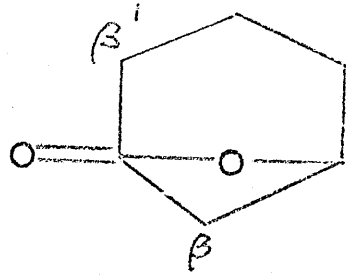
170
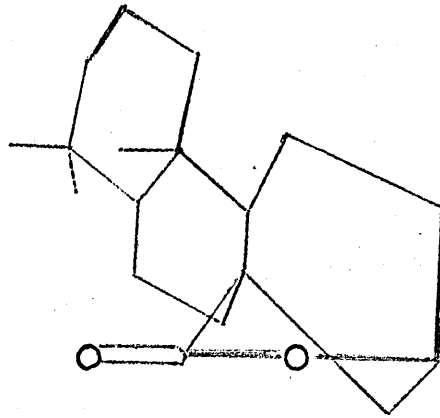
171
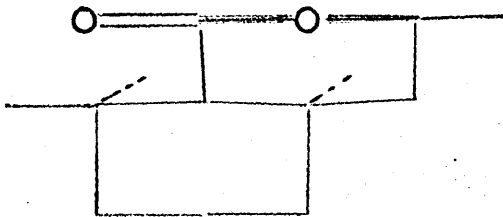
172
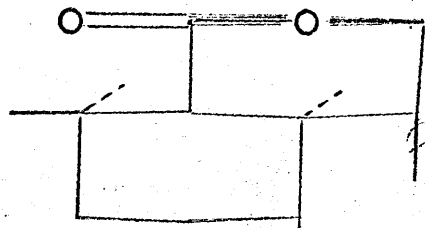
173

EXPERIMENTAL

Preparation and Separation of the Diastereoisomeric Etienates (153).

The lactone (92) (500 mg.) was added to water (50 ml.) containing potassium hydroxide "Analar" (1.061 g.). The solution was heated under nitrogen on a steam bath for thirty minutes and the base carefully neutralised to p H 6 with a calculated amount of .1 N hydrochloric acid "Analar". The solution was immediately extracted with ether, which was washed with brine and then methylated with ethereal diazomethane. The excess diazomethane was neutralized with acetic acid. After drying the ether was removed under reduced pressure and the hydroxy-ester (101) was recovered as a pale green oil (500 mg.) It showed one peak on g.l.c. (5% QF - 1, 100°C) of retention time 8.6 min. as against the lactone which under the same conditions has a retention time of 22.4 minutes. T.l.c. (ethyl acetate, pet-ether 50:50) showed one spot a little more mobile than starting material.

$V_{max}(CCl_4)$ 3635, 3608, 3530, 3460, 1740, 1160 cm^{-1}.

This material relactonised on standing or on heating and was used straight away for the next stage.

3β - Acetoxy - Δ^5 - etienic acid (1.2 g.) (151)[66], benzene (12 ml.) and oxalyl chloride (2.0 g.) were left at room temperature for 48 hours, the relatively insoluble acid

gradually dissolving during the course of the reaction. The

benzene and excess oxalyl chloride were removed under reduced

pressure and a white crystalline residue was obtained[67].

V_{max} (nujol) 1790, 1730, 1240 cm^{-1}.

Dry pyridine (10 ml.) was added to the residual acid

chloride followed by a solution of the hydroxy-ester (101),

prepared as above, in dry pyridine (2 ml). The mixture was

stirred for 72 hours at room temperature and the reddish violet

suspension poured on to 3 M hydrochloric acid (30 ml.) cooled

in ice. The white precipitate was filtered off and the aqueous

solution extracted with ether. The precipitate was dissolved

in ether and filtered to remove excess etienic acid. After

drying and evaporation of solvents, the crude diastereoisomeric

etienates (153) were obtained as a pale green oil (950 mg.).

V_{max} (film) 1730, 1240 cm^{-1}.

T.l.c. (run eight times in ethyl acetate, benzene 1:99)

showed two major spots of very similar r.f. The green oil

(900 mg.) was purified by p.t.l.c. (eighteen 100 x 20 x 0.05 cm

plates run eight times in ethyl acetate, benzene 1:99, visualized

by iodine). The broad band was cut into three parts, the centre

band rechromatographed and the resulting broad band divided into two.

The most mobile band (364 mg.) was a pale green oil which could not be induced to crystallise probably because of contamination by the less mobile component. The less mobile component (335 mg.) crystallised as white needles from pet-ether and was the pure diastereoisomeric etienate (153b); m.p. 94 - 95°C; $(\alpha)_D$ - 46° (C = 1.0 chf);

$V_{max}(CCl_4)$ 1730, 1240, 1100 cm^{-1}; n.m.r. showed 3H singlets at T 9.24 and T 8.97; 9H singlet at T 9.11; 3H singlet at T 7.97; 3H singlet at T 6.35; multiplet at T 5.3 and a multiplet at 4.7.

(Found: C, 72.96; H, 9.52; $C_{32}H_{50}O_6$ requires C, 72.41; H, 9.50%)

Base Catalysed Hydrolysis of the non Crystalline Etienate (153a).

The diastereoisomeric etienate (153a) which failed to crystallise (34 mg.) was dissolved in 50% methanol/water (25 ml.) containing potassium hydroxide (500 mg.). The solution was refluxed for 24 hours, acidified and extracted with ether. After washing the ethereal extracts with brine and drying, the solvents were removed under reduced pressure and a white solid (40 mg.)

was obtained. T.l.c. showed that no t-butyl lactone (92) was present. The solid was methylated with ethereal diazomethane and a colourless oil (40 mg.) recovered. T.l.c. (ethyl acetate, pet-ether 3:7) showed one spot which was less mobile than starting material. The methyl ester (154) showed:

$V_{max}(CCl_4)$ 3610, 3580, 1735, 1150 cm^{-1}; n.m.r. showed 3H singlets at T 9.25, 9.0 and 6.35; 9H singlet at T 9.12; 1H multiplets at T 6.0 and 5.3 and a 1H doublet at T 4.7.

The Racemic Diol (155) and Racemic Diacetate (156).

The lactone (92) (400 mg, 2.6 m moles) in dry ether (10 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (200 mg., 10.4 m moles) in dry ether (30 ml.). The solution was refluxed for one and a half hours and then the excess lithium aluminium hydride destroyed by dropwise addition of water. The white granular precipitate was filtered off and washed several times with ether. The ethereal solutions were combined and the ether removed under reduced pressure. A colourless oil (365 mg.) was obtained which showed one spot on t.l.c. less mobile than starting material. This was the racemic diol (155);

V_{max}(film) 3400, 2950, 1080 cm^{-1}; n.m.r. showed 9H singlet at T 9.15; 6H multiplet at T 8 - 9; 1H multiplet at T 6.8 and a

2H triplet at T 6.4. The broad singlet at T 8.0 (1H) disappeared on D$_2$O exchange.

The racemic diol was characterised as the racemic diacetate (156) which was prepared by dissolving the diol (60 mg.) in pyridine (1 ml.) and adding acetic anhydride (1 ml.). The solution was allowed to stand overnight at room temperature and the pyridine and excess acetic anhydride removed under reduced pressure. A pale green oil (58 mg.) was obtained which showed one spot on t.l.c. (ethyl acetate, pet-ether 2:8). An analytical sample of (156) was prepared by p.t.l.c. and microdistillation. (40° C at 0.4 mm Hg.).

V$_{max}$(CCl$_4$) 1744, 1240 cm^{-1}; n.m.r. showed 9H singlet at T 9.1.; 3H singlets at T 7.95 and 7.98; a 2H multiplet at T 5.9 and a 1H multiplet at T 5.3.

(Found: C, 63.79; H, 9.93; C$_{13}$H$_{24}$O$_4$ requires C, 63.90; H, 9.90%)

Lithium Aluminium Hydride Reduction of the Racemic Diacetate (156).

The racemic diacetate (156) (60 mg., 0.25 m mole) in ether (2 ml.) was added to a stirred solution of lithium aluminium hydride (40 mg., 1 m mole) in ether (2 ml.). The solution was refluxed for one hour and the excess hydride destroyed by careful addition of water. The white granular precipitate was removed by

filtration and the precipitate washed several times with ether.
Removal of solvent under reduced pressure afforded the racemic
diol (155) as shown by I.R. and t.l.c. comparison with authentic
material.

Sarrett[68] Oxidation of the Racemic Diol (155).

Chromium trioxide (300 mg.) was added to a solution of
diol (155) (60 mg.) in pyridine (15 ml.) The solution was kept in
the dark at room temperature for 24 hours and then poured on to
ice cold water (60 ml.). The aqueous solution was thoroughly
extracted with ether which was washed with brine and dried. Evaporat-
ion of solvents under reduced pressure afforded a colourless oil.
The lactone (92) (15 mg.) was obtained by p.t.l.c. (ethyl acetate,
pet-ether 6:4) and was shown by t.l.c. and I.R. to be identical
to authentic (92).

Manganese Dioxide Oxidation[69] of the Racemic Diol (155).

The diol (30 mg.) in methylene chloride (freshly distilled
from phosphorous pentoxide) was stirred overnight with manganese
dioxide (1 g.). The manganese dioxide was filtered off and
continuously extracted with ethyl acetate for 24 hours. The

methylene chloride filtrate and the ethyl acetate extract
were combined and removal of solvents under reduced pressure
afforded a clear oil (17 mg.). The lactone (92) (8 mg.)
(I.R. and t.l.c. comparison with authentic (92)) was obtained
by p.t.l.c.

Lithium Aluminium Hydride Reduction of the Crystalline Etienate (153b).

The crystalline etienate (153b) (320 mg.) in dry ether
(13 ml.) was treated with lithium aluminium hydride (320 mg.)[67].
The mixture was refluxed for 45 minutes and stirred at room
temperature for a further 45 minutes. The excess hydride was
destroyed by careful addition of water and the white crystalline
precipitate filtered off. The precipitate was washed with
chloroform which was combined with the filtrate. The solvents
were removed under reduced pressure to afford a white crystalline
solid (329 mg.) T.l.c. showed two spots, the less mobile corres-
ponding to that of the diol (155). Because of "streaking" from
the more mobile component the product was acetylated by dissolving
it in pyridine (4 ml.) and acetic anhydride (4 ml.) and allowing
to stand overnight at room temperature. The solvents were removed
under reduced pressure and a colourless oil (312 mg.) was recovered
which contained two components as judged by t.l.c. (ethyl acetate,
benzene 4:96). The less mobile spot, which corresponded to the

diacetate (156), was isolated as a colourless oil (120 mg.)
by p.t.l.c. In order to remove a small amount of the other
component the material was rechromatographed. The optically
active diacetate (158) (111 mg.) (as shown by I.R. and t.l.c.
comparison with authentic (156)) had $(\alpha)_D = -15.5$ (C = 1.11 chf.).

(158) was carefully reduced with lithium aluminium hydride
as previously described to afford the diol (157) (72 mg.) as
a colourless oil which showed one spot on t.l.c. corresponding
to racemic diol (155). (157) had $(\alpha)_D = -30^o$ (C = 0.984 chf).

Determination of the Absolute Configuration[70] of the Optically Active Diol (157).

The optically active diol (157) (12 mg., 0.075 m moles)
and α-phenyl - butyric - anhydride (96 mg., 0.290 m moles) in
pyridine (1 ml.) were allowed to stand overnight at room
temperature. Water (1 ml.) was added and the solution kept for
six hours at room temperature. Ether (5 ml.) was added and t.l.c.
showed that most of the diol had been esterified. The ether solution
was washed with water (5 ml.), 5% sodium bicarbonate solution
(3 x 5 ml.) and water (2 x 5 ml.). The combined aqueous extracts
were washed once with chloroform (20 ml.) and acidified with
hydrochloric acid and finally extracted with chloroform (3 x 10 ml.)

which was washed with brine (15 ml.) and dried over magnesium

sulphate. Removal of the solvents under reduced pressure

afforded an oil (70 mg.) which showed typical acid streaking

on t.l.c. The acidic material was taken up in benzene (2 ml.)

and its rotation measured; $(\alpha)_D = -2.1^\circ$ (benzene). This

corresponds to an optical yield of (11.3%) as calculated by

the method described in reference 70.

The Optically Active Lactone (159).

The optically active diol (157) (55 mg.) was oxidised with

manganese dioxide as described previously. The optically active

lactone (159) (11 mg.), which was purified by p.t.l.c., had

identical t.l.c. and I.R. properties to the racemic lactone

(92). $(\alpha)_D = +33.1$ (C = 1.1 chf).

C.D.; (isooctane) $(\theta)_{241} - 376;$ $(\theta)_{212} + 267;$ (ethanol)

$(\theta)_{238} - 188;$ $(\theta)_{213} + 472.$

REFERENCES

1. J. F. McConnell, A. McL. Mathieson and B.P. Schoenborn,

    Tetrahedron Letters, 1962, 445.

2. A. McL. Mathieson and J.C. Taylor,

    Tetrahedron Letters, 1961, 590.

3. K.K. Cheung, K.H. Overton and G.A. Sim,

    Chem. Comms., 1965, 634.

4. J.D. Asher and G.A. Sim,

    J. Chem. Soc., 1965, 1584.

5. W.D. Closson and P. Haug,

    J. Amer. Chem. Soc., 1964, __86__, 2384

6. A.McL. Mathieson,

    Tetrahedron Letters, 1963, 81.

7. R.C. Sheppard and S. Turner,

    Chem. Comms., 1968, 77.

8. R.N. Johnson and N.V. Riggs,

    Tetrahedron Letters, 1967, 5119.

9. H. Wolf,

    Tetrahedron Letters, 1966, 5151.

10. M. Legrand and R. Bucourt,

    Bull. Soc. Chim. France, 1967, 2241

11.   L.J. Bellamy, "Advances in Infra-red Group Frequencies"
p. 136, Methuen, 1968.

12.   Hall and Zbinden,
J. Amer. Chem. Soc., 1958, 80, 6428.

13.   Bratoz and Besnainou,
Compt. Rendu., 1959, 248, 546.

14.   J.O. Halford,
J. Chem. Phys., 1956, 24, 230.

15.   J. Overend and J.R. Scherer,
Spectrochimica. Acta., 1960, 16, 773.

16.   J.I. Brauman and V.W. Lawrie,
Tetrahedron, 1968, 24, 2595.

17.   J.B. Hendrickson,
J. Amer. Chem. Soc., 1961, 83, 4537.

18.   A.T. McPhail and G.A. Sim,
J. Chem. Soc (B), 1966, 318.

19.   K.K. Cheung,
Ph.D Thesis, Glasgow.

20.   N. Atwater,
J. Amer. Chem. Soc. 1961, 83, 3071.

21.   E.M. Graham,
B.Sc. Thesis, Glasgow, 1960.

22.   K.H. Overton and C.W.J. Brooks,
J. Chem. Soc., 1959, 32.

23. J.P. Johnston ,

    B.Sc. Thesis, Glasgow, 1966.

24. J.P. Johnston and K.H. Overton,

    Unpublished Results.

25. A. Bowers, T.G. Halsall, E.R.H. Jones and A.J. Lemin,

    J. Chem. Soc., 1953, 2548.

26. R.U. Lemieux and E. von Rudloff,

    Can. J.Chem., 1955, 33, 1701.

27. H.O. House et al.,

    J. Org. Chem., 1962, 27, 4141.

28. W.S. Johnson et al.,

    J. Amer. Chem. Soc., 1961, 83, 606.

29. S. Sternhall,

    Quart. Revs. 1969, 23, 236.

30. M. Karplus,

    J. Amer. Chem. Soc., 1964, 85, 2870.

31. R. J. Abraham,

    J. Chem. Soc., 1963, 806.

32. J. Roberts,

    Ph.D. Thesis, Glasgow.

33. Schmidt and Grafen,

    Ann., 1962, 97, 656.

34. I.J. Borowitz, G.J. Williams, L. Gross and R.Rapp,

    J. Org. Chem., 1968, 33, 2013.

35. G. Stork et al.,

J. Amer. Chem. Soc., 1963, 85, 3419.

36. K.B. Wiberg,

J. Amer. Chem. Soc., 1965, 87, 1070.

37. J.B. Hendricksen,

J. Amer. Chem. Soc., 1967, 89, 7036.

38. N.L. Allinger,

J. Amer. Chem. Soc., 1967, 89, 4345.

39. J.B. Hendricksen,

J. Amer. Chem. Soc., 1961, 83, 4537.

40. N.L. Allinger,

J. Amer. Chem. Soc., 1968, 90, 1199.

41. N.L. Allinger,

J.Amer. Chem. Soc., 1969, 91, 337.

42. J.M. Riveros and E. Bright Wilson, Jr.,

J. Chem. Phys., 1967, 47, 4605.

43. E.E. Smissman, J.F. Muren and N.A. Dahle,

J. Org. Chem., 1964, 29, 3517.

44. J. Meinwald, J.J. Tufariello, J.J. Hurst,

J. Org. Chem., 1964, 29, 2914.

45. H. O'House, W.L. Respass, and George M. Whitesides,

J. Org. Chem., 1966, 31, 3128.

46. A.M. Duffield, H. Budzikiewicz and C. Djerassi,

J. Amer. Chem. Soc., 1965, 87, 2913.

47. B.J. Millard,

Org. Mass Spectrometry, 1968, 1, 279.

48. J.M. Conia and J.P. Sandre,

Bull. Soc. Chim., 1963, 744.

49. M.F. Ansell and S.S. Brown,

J. Chem. Soc., 1958, 2955.

50. P. Diehl, R.K. Harris and R.G. Jones in "Progress in N.M.R.

Spectroscopy", ed., by J.W. Emsley, J. Feeney and L.H. Sutcliffe,

Pergamon, 1967, 3, Chapter 1.

51. J.W. Emsley, J. Feeney and L.H. Sutcliffe, "High Resolution

Nuclear Magnetic Resonance Spectroscopy", Volume 1, Pergamon, 1965,

Chapter 8.

52. G. J. Karabatsos, G.C. Sonnichsen, N. Hsi and D.J. Fenoglio,

J. Amer. Chem. Soc., 1967, 89, 5067.

53. J.D. Connolly and R. McCrindle,

Chem. and Ind., 1965, 2066.

54. J. Attenburrow et al.,

J. Chem. Soc., 1952, 1094.

55. G. Snatzke,

Ber., 1961, 94, 729.

56. K.H. Overton, N.G. Weir and A. Wylie,

J. Chem. Soc., (C), 1966, 1482.

57. A. Moscowitz,

Advan. Chem. Phys., 1962, 4, 97.

58.   Yoh-Han Pao and D.P. Santry,

J. Amer. Chem. Soc., 1966, 88, 4157.

59.   W. Moffitt, R.B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi,

J. Amer. Chem. Soc., 1961, 83, 4013.

60.   T. Okuda, S. Marigaya and A. Kiyomoto,

Chem. and Pharm. Bull. (Japan), 1964, 12, 504.

61.   J.P. Jennings, W. Klyne and P.M. Scopes,

J. Chem. Soc., 1965, 7211.

62.   G. Snatzke, H. Ripperger, Chr. Horstmann and K Schreiber,

Tetrahedron, 1966, 22, 3103.

63.   G. Snatzke in "Optical Rotatory Dispersion and Circular Dichroism

in Organic Chemistry", ed. by G. Snatzke, Heyden, London, 1967,

Chapter 13.

64.   W. Klyne, P.M. Scopes, R.C. Sheppard and S. Turner,

J. Chem. Soc. (C), 1968, 1954.

65.   H. Wolf,

Tetrahedron Letters, 1965, 1075.

66.   J. Staunton and E.J. Eisenbraun,

Org. Syn., 1962, 42, 4.

67.   C. Djerassi, P.A. Hart and E.J. Warawa,

J. Amer. Chem. Soc., 1964, 86, 78.

68.   G.I. Poos, G.E. Arth, R.E. Beyler and L.H. Sarrett,

J. Amer. Chem. Soc., 1953, 75, 422.

69.   P. Johnston, R.C. Sheppard, C.E. Stehr and S. Turner,

J. Chem. Soc. (C), 1966, 1847.

70. W. Herz and H. B. Kagan,

J. Org. Chem., 1967, 32, 216.

71. A. Horeau and H.B. Kagan,

Tetrahedron, 1964, 20, 2431.

72. Personal communication from Professor G. Snatzke.

73. A.F. Beecham,

Tetrahedron Letters, 1968, 2355.

74. K.M. Wellman, P.H.A. Laur, W.S. Briggs, A. Moscowitz and

C. Djerassi,

J. Amer. Chem. Soc., 1965, 87, 66.

75. A. F. Beecham,

Tetrahedron Letters, 1968, 3591.

76. Y. Mazur and F. Sonheimer,

Experientia, 1960, 16, 181.

SECTION 2

CHAPTER 1

THE CONFORMATION OF MEDIUM RING LACTONES

Having considered the conformation of δ-lactones in some detail, it was felt that investigation of lactones of ring size greater than six would prove interesting. In particular we wished to investigate two problems. Firstly what are the preferred conformations of these lactones and secondly how does the placing of the lactone group (C - O - C - C) in these rings alter its configuration and properties. This chapter will consist of a review of what is already known about medium ring lactones and since it is relevant, a brief review of the conformations of medium ring cycloalkanes and cycloolefins.

Huisgen and Ott[1] have reported the only systematic study of the variation of certain properties of the lactones ((1) n = 5 to n = 16). They investigated the change in dipole moment, boiling point, infra-red spectrum and rate of hydrolysis of the lactone group as the ring size was increased. It was concluded that in lactones with n = 5, 6 and 7 the lactone group is plannar and s - cis (2), whereas when n = 10 or more it is planar and s - trans (3). When n = 8 and 9 the lactone group was considered to exist as an equilibrium mixture of (2) and (3).

This conclusion was based on the observation that the dipole moments of the smaller rings ((1) n = 5,6 and 7) were in the region of 4 D and in the larger rings ((1) n = 13,14 and 16), in the region of 1.8 D. In the smaller rings, the lactone group is s - cis (2) and the C = 0 and C - 0 dipoles point in the same direction to give a resultant dipole moment of 4 D. In the larger rings the lactone group can exist in the more stable s - trans configuration[19], which is adopted by open chain esters and here the C = 0 and C - 0 dipoles point in opposite directions to give a resultant dipole moment of about 1.8 D. The dipole moments of the 8,9 and 10 membered rings are 3.70, 2.25 and 2.01 D respectively and since these values are intermediate between the extremes quoted above, Huisgen and Ott concluded that there must be an equilibrium mixture of the two forms (2) and (3) in these compounds.

The infra-red spectra of the lactones ((1) n = 5 - 16) showed no systematic variation with ring size. This is surprising since the carbonyl frequency of cyclic ketones has been shown to fall regularly with increasing ring size[2]. Similarly the cyclic amides show a regular decrease in $V_{C=0}$ with increasing ring size (Figure 1)[3], but with a break at the nine membered ring which shows two carbonyl peaks. This has been attributed to the presence of a conformational mixture in the 9 membered-lactam and it is suggested that the higher

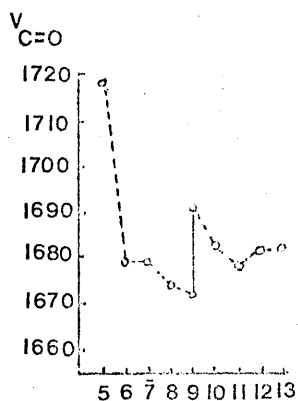frequency band is due to the amide group being twisted or skewed.

$V_{C=O}$

1720
1710
1700
1690
1680
1670
1660

5 6 7 8 9 10 11 12 13

Figure 1. Plot of $V_{C=O}$ of lactams in dilute

CCl_4 soln. against ring size.

Huisgen and Ott confined their discussion to the configuration

of the lactone group since at that time very little was known

concerning the conformation of rings larger than cyclohexane.

The last decade, however, has seen a considerable accumulation of

information on the conformations of rings larger than cyclohexane.

A number of X-ray cystallographic studies have been carried out

and in certain cases the preferred conformations are well established.

In cases where no X-ray data is available, strain energy minimization

calculations furnish the required information[4]. The conformations

of the medium rings (8 - 12 membered rings) have recently been

discussed in detail in an excellent review by Dunitz[5].

Since the lactone group $(C - O - \underset{\overset{\|}{O}}{C} - C)$ has been shown to

be planar[6], then it is to be expected that it will have similar

stereochemical requirements to the olefinic double bond. This

analogy has certain reservations attached to it, however, since

the preferred torsion angles about the two groups are different.

Thus, the preferred $C - C - C = C$ torsion angle about the single

bond adjacent to the double bond is close to 120°, corresponding

to eclipsing of one of the hydrogen atoms of the α-methylene

group with the double bond[5]. In lactones, on the other hand, the

preferred torsion angles are illustrated in (4) and (5). In (4)

the hydrogen atom on the adjacent α-carbon atom eclipses the

carbonyl group while in (5) the $O - C_{sp}2$ bond is staggered with

respect to the two $C - H$ bonds on the adjacent carbon

atom. The barrier to rotation of the methyl group in acetaldehyde[7]

and methyl formate[8] is about 1 K cal mole^{-1}. A further difference

between olefins and lactones in the degree of rigidity of the

double bond as compared to the lactone group. The barrier to

rotation about a $C = C$ double bond is about 60 K cal mole^{-1} (5)

while about the $C_{sp}2 - O$ bond in a lactone group, it is probably

around 5 - 10 K cal mole^{-1}. Bearing the above points in mind it is

possible to make meaningful comparisons between the conformations

of cycloolefins and lactones. This is necessary since little is

known concerning the preferred conformations of medium ring
lactones while a considerable amount of information has been
accumulated on the conformational preferences of cycloolefins.

The relative stabilities of cis- and trans-olefins can be
estimated from their heats of hydrogenation. Table (1), for example,
shows that the trans-cycloolefins are more strained that the cis
isomers in eight-, nine-, and 10- membered rings[5]. For smaller
rings the trans-olefins are apparently too unstable to exist but
for larger rings they are more stable than the cis isomers as shown
by equilibration studies[5]. This is of interest since according
to Huisgen and Ott, the s - trans lactones are preferred in the
nine and ten membered rings. As will be shown later this probably
reflects the different torsional requirements of the olefinic
double bond and the lactone group.

Table 1. Heat of hydrogenation, $-\Delta H$ (K cal mole^{-1}) of
cycloalkanes in acetic acid at 25°C.

	$-\Delta H_{trans}$	$-\Delta H_{cis}$
Cyclohexene	—	27.1
Cycloheptene	—	25.9
Cyclooctane	32.2	23.0
Cyclononene	26.5	23.6
Cyclodecene	24.0	20.7

Cyclohexanolide

Strictly speaking cyclohexanolide is not a medium ring lactone but it is included here for the sake of completeness.

Hendricksen[9] has applied his method of calculating conformational energies to cycloheptane and of the four conformers discussed:-the chair (6); twist-chair (7); boat (8); twist-boat (9); it is concluded that the twist-chair is the most stable by about 2 K cal mole^{-1}.

The low temperature n.m.r. spectrum of 5, 5 difluorocycloheptene shows an AB quartet at low temperatures[10]. On this evidence, Roberts proposes the chair conformation (10) as being the most stable. However, the boat conformer (11) would also give an AB quartet at low temperatures. The alternative twist conformer (12) is ruled out, since the two fluorine atoms are equivalent because of the two fold symmetry axis which passes through C - 5 and the mid-point of the C - C double bond.

By analogy with cycloheptene, there are three possible conformations of cyclohexanolide which maintain the planarity of the lactone group. These are the chair (13), boat (14) and twist-chair (15). Overberger and Kaye[11] have studied the O.R.D. curves of the optically active cyclohexanolides (16), (17), (18) and (19). The signs of the Cotton effects were all accounted for by considering the cyclohexanolides to be in the chair conformation. However, examination of Overberger's results indicates that the twist

conformer of (16) and (18) is equally compatible with the observed Cotton effects. Thus application of Snatzke's sector rule[12] to (16) shows that in the twist conformer, the observed positive Cotton effect would be predicted, since, the 3 - methyl group is in a positive sector (20) and (21). A similar argument can be applied to (18).

Thus as yet there is no definite evidence which points to one particular conformation of cyclohexanolide as being the most stable.

Cycloheptanolide

Apart from the work of Huisgen and Ott there have been no conformational studies on cycloheptanolide at all. However, X-ray crystallography[5] has established the preferred conformation of cyclooctane as being a boat-chair (22). Anet[13] has investigated the low temperature n.m.r. spectra of deuterated cyclooctanes and his results are consistent with conformation (22).

Trans-cyclooctene is very highly strained as is evidenced by its high heat of hydrogenation (table 1) compared to cis-cyclooctene. Trans-cyclooctene has been resolved into two stable optically active forms[14] and the barrier to recemization has been shown to be 35.6 K cal mole^{-1} (15). No X-ray studies have been carried out on trans-cyclooctene although the nature of the molecule points to

it having one of two possible conformation (23) or (24)[20], both of which are extremely rigid. Dunitz[5] has suggested that the torsion angle about the double bond in trans-cyclooctene will deviate considerably from $180°$ which would explain the very high heat of hydrogenation.

No X-ray data is available on the preferred conformers of cis-cyclooctene. However, the constraints on the ring geometry introducted by a cis fused three membered ring are similar to that of a cis-double bond and X-ray analysis[5] of cis - 9, 9 - dimethyl - 9 - azoniabicyclo (6.1.0) nonane furnishes the conformation (25).

On the grounds that cycloheptanolide has a dipole moment of 3.70 D which is intermediate between the values for cyclohexanolide (4.45 D) and cycloundecanolide (1.86 D), Huisgen and Ott proposed that an equilibrium mixture of s - cis and s - trans lactone groups are present with the s - cis predominating. From the highly strained nature of the double bond in trans-cyclooctene, it is unlikely that a planar s - trans lactone group can exist in cycloheptanolide. A more plausible explanation for the lower dipole moment is that the lactone group is twisted from the planar cisoid form, as for example in (26). This conformer (26) would probably be preferred over the alternative chair-boat (27) where the torsion angles about the $C_{sp}3 - 0$ bond are such that the C7 - H bond eclipses the $C_{sp}2 - 0$ bond.

Cyclooctanolide.

The conformation of cyclononane, as shown by the cystal-structure analysis of cyclononylamine hydrobromide[5], is depicted in (28). Apart from this example, information concerning the preferred conformation of nine-membered rings is lacking in the literature.

Trans -cyclononene is slightly less stable than cis-cyclononene as shown by their heats of hydrogenation (table 1). A rather unstable optically active trans-cyclononene has been isolated[16] and the barrier to interconversion determined to be 20 K cal mole^{-1}. This, when compared to the barrier of 36 K cal mole^{-1} for racemization of trans-cyclooctene shows that trans-cyclononene is less rigid.

The dipole moment of cycloctanolide is 2.25 D, which is slightly higher than 1.86 D, the value associated with fully s – trans lactone groups. Huisgen and Ott propose that this is due to the presence of an equilibrium mixture of s – cis and s – trans lactone groups with the latter predominating. This is a possible explanation although again the possibility of a twisted lactone group cannot be overlooked.

Cyclononanolide

A number of cyclodecane derivatives have been analysed by X-ray crystallography and the conformation depicted in (29) is

recognised as being the energetically stable one[5]. Because of the approximate C_{2h} symmetry of the ring skeleton, there are three types of carbon atoms labelled I, II and III. Assosiated with these three types of carbon atoms are six different kinds of hydrogen atoms, two of which are intra-annular and four extra-annular. Because of the overcrowding of the intra-annular hydrogen atoms, replacement of a hydrogen atom by a larger substituent will occur preferentially at the extra-annular positions. On the other hand, conversion of a tetrahedral into a trigonal atom will be accompanied by a substantial release of strain energy for a type I or type III atom (but not for a type II atom). For type I or type III, the change from tetrahedral to trigonal is assosiated with the removal of an intra-annular hydrogen atom and therefore with erasure of two of the six transannular interactions. Accurate X-ray measurements[5] indicate that the most serious interactions are between the intra-annular hydrogen atoms attached to type III carbon atoms and so it is found that trigonal atoms occur preferentially at type III atoms as is exemplified by the observed cystal structure of cyclodecane - 1, 6 - dione (30)[5].

Similar reasoning to the above predicts that the preferred conformation of cyclononanolide should be (31) which has favourable torsion angles about the lactone group (see (4) and (5)). The crystal structure analysis of cyclononanolide itself, has not been carried out but an accurate analysis has been made of the recently

synthesised 6 - ketononalide[17], which has been shown to have

the conformation (32) in the crystal[5]. This conformation is particularly

favoured in this compound since three type III carbon atoms

have been replaced by two trigonal carbon atoms and an oxygen

atom. The torsion angle about the $C_{sp}2 - 0$ bond is 174^{0} which

confirms the planarity of the lactone group. A point of interest

is the extremely short $0 \cdots\cdots C = 0$ distance $(2.85 \overset{o}{A})$, which is

much smaller than the sum of the van der Waals radii $(3.1 \overset{o}{A})$.

Dunitz suggests that there may well be a weak interaction between

the intra-annular lone pair and the partial positive charge on

the carbonyl group.

The conformation (32) found for the 6 - ketononanolide is

to be contrasted with the conformation (33) found for the

$AgNO_3$ adduct of trans-cyclodecene[18]. The skeleton has distorted

to accomodate the favoured torsion angles about the double bond (page 172).

The conformation of the $AgNO_3$ adduct of cis-cyclodecene is shown in

$(34)^{5}$. The torsion angle about the cis-double bond is close to 180^{0}

while about the trans double bond it is 140^{0}. This observation is

discussed more fully by Dunitz in his review[5].

By analogy with cis-cyclodecene(34), cyclononanolide, in which

the lactone group is s - cis, would adopt a conformation like (35).

However, in this conformer the oxygen and the trigonal carbon atom

only replace one type III carbon atom and hence it would not be as favourable as (31) in which two type III carbon atoms have been replaced. It is probable that the slightly higher dipole moment (2.01 D) observed by Huisgen and Ott for this compound is explained by slight distortion of the lactone group from planarity rather than by an equilibrium between the s – cis and s - trans forms.

In this review, possible conformations of seven to ten- membered lactone rings have been discussed in light of dipole moment studies by Huisgen and Ott[1] and on the basis of conformational preferences of cycloalkanes and cycloolefins.

CHAPTER 2

DISCUSSION 1

During their investigation into the configuration of the lactone group in the ring systems, ((1) n = 5 - 16), Huisgen and Ott[1] showed that when n = 5 to 7, the lactone group is s - cis (2), while when n = 10 and over it is s - trans. For the intermediate rings, n = 8 and 9, it was proposed that an equilibrium existed. In chapter 1 the possibility of there being non-planar lactone groups was raised and in this part of the thesis it is proposed to investigate this possibility and in addition, examine the lactones ((1) n = 5 to 10 and 16), to observe what the effect of changing the configuration of the lactone group has on their spectral properties.

The lactones (1) n = 6 to 10 were synthesised by Baeyer Villiger oxidation of the corresponding ketones using buffered peroxytrifluoroacetic acid according to the method of Smissman[21].

It was felt that if twisted lactone groups existed, then they might be detected by examination of their infra-red spectra. This is because it is to be expected that if the lactone group is twisted out of planarity, then overlap of the p - orbital of the ether oxygen with the π - electrons of the carbonyl group will be diminished and thus, the carbonyl frequency will increase (see page 9). Hence, it could be argued that higher frequency bands might appear

in the 8 or 9 membered ring lactones as in the 9 membered
ring lactam (see page 171).

The infra-red spectra, obtained in carbon tetrachloride
solution of the lactones ((1) n = 5 to 10 and 16) are very
complex and the C = O stretching vibrations are the only ones
which can be assigned with certainty. However, the lactones
((1) n = 5 to 10), all had spectra in which the bands were sharp
and well defined whereas in exaltolide, ((1) n = 16), the
bands were broad and poorly resolved. This is presumably because
the smaller ring lactones are conformationally rigid while the
larger ones are "floppy".

The carbonyl frequencies in carbon tetrachloride and chloroform
solution are shown in table 2 together with the solvent shifts
$\triangle$ ($CHCl_3 \rightarrow CCl_4$). The integrated intensities of the carbonyl
band in carbon tetrachloride solution are shown in the last column.
For comparison the data for two open chain esters are included at the
bottom of the table.

Table 2. Frequencies and integrated intensities of the

carbonyl group in some lactones and esters.

Compound	$V(CCl_4)$ (cm^{-1})	$V(CHCl_3)$ (cm^{-1})	Δ (CHCl$_3$ CCl$_4$) (cm^{-1})	$A(CCl_4)$ (1 x 10^4 1 mole^{-1}cm^{-1})
γ-butyrolactone	1783.0 1794.5	1772.5	16.5	1.66
cyclopentanolide	1750.0	1730.0	20.0	1.58
cyclohexanolide	1743.0 1748.5	1728.5	17.5	1.57
cycloheptanolide	1742.5	1724.0	18.5	1.37
cyclooctanolide	1738.5	1729.5	9.0	1.24
cyclononanolide	1731.0	1721.5	9.5	1.30
exaltolide	1734.0	1723.5	10.5	1.32
ethyl propionate[22]	1739	1728	11	1.27
ethyl isobutyrate[22]	1736	1725	11	1.25

Several points of interest arise from table 2. First of all it
is observed that in carbon tetrachloride solution, there is a gradual
decrease in carbonyl frequency similar to that found in cycloalkanones[2].
This is probably due to widening of the carbonyl bond angle with increasing

ring size (see page 9). The effect reaches a maximum around the 10 to 12 membered rings as in the cyclic ketones.

The carbonyl frequencies of the lactones which are mainly s - cis show different solvent shifts from those which are mainly s - trans. In addition the integrated intensities of the carbonyl bands of s - cis lactones are consistently higher than those of the s - trans. The value for cyclooctanolide is intermediate between the two ranges. This pattern of behaviour is mirrored in the $\alpha\beta$ unsaturated ketones where it is found[23] that the integrated intensities of the s - cis ketones (36) are less than those of the s - trans ketones (37). The solvent shift behaviour is also mirrored in that it is found that the frequency of the s - cis ketones (36) are less shifted in chloroform solution from their position in carbon tetrachloride solution than are the s - trans ketones (37).

It has been suggested[23] that this is because in the s - cis ketones the C = O and C = C vibrations are strongly coupled whereas in the s - trans ketones they are more isolated. The $CHCl_3$ solvent molecules act in both cases on the carbonyl group by forming a weak hydrogen bond with it, but in s - cis ketones the effect on the carbonyl vibration is also transmitted to the stretching vibration of the C = C bond. To explain the lower intensity of the s - cis

carbonyl band it is suggested that the total intensity of the

$C = O$ and $C = C$ bands are "smeared" over both bands with the

result that the former loses while the latter gains in intensity.

Such an effect may be operating in the lactone group where

it is probable that there is coupling between the $C - O$ and

$C = O$ stretching vibrations just as between the $C = C$ and $C = O$

vibrations above. Thus in the s - trans lactone (3) the

vibrations are strongly coupled while in the s - cis (2) they

are more isolated. Thus the effect of bonding of the solvent

molecules is transmitted partly to the $C - O$ vibration more in

the s - trans than in the s - cis lactone group. As in the

s - cis ketones the s - trans lactone carbonyls have a lower

intensity since part of the intensity has been "smeared" out over the

$C = O$ and $C - O$ vibrations. While it is possible to observe the

expected changes in the $C = C$ vibrations of $\alpha\beta -$ unsaturated

ketones it is not very easy to do the same for the $C - O$

vibrations of the lactone group since these vibrations occur

in the $1100 - 1200$ cm^{-1} region of the spectrum which is generally

very complex. Thus although the above explanation of the solvent

effects and intensity changes in table 2 sounds plausible, further

work is necessary in order to confirm it.

If the lactone group is twisted then it bears a closer

resemblence to a keto group since delocalization of the oxygen

p-electrons is reduced. The integrated intensity of ketone carbonyl bands is less than that of esters and lactones hence, it is to be expected that if the lactone group is twisted then the integrated intensity will move towards that of a ketone. Thus the intermediate value of A found for cycloheptanolide could be due to a twisted lactone group.

Another technique which would be expected to show the presence of a twisted chromophore is Ultra Violet spectroscopy. If the lactone group is twisted, then the interaction between the p - orbital of the ether oxygen and the π orbitals of the carbonyl group is diminished and hence the π^* orbital is expected to be lowered in energy (see page 2). Thus the $n \longrightarrow \pi^*$ transition will move to longer wavelength.

The absorption maxima and the extinction coefficients of the $n \longrightarrow \pi^*$ transition of the lactones (1) are shown in table 3.

Table 5. U.V. absorption maxima of the lactones (1) in n - hexane.

Compound	λ_{max}, nm.	ε_{max}
propiolactone[24]	207	-
γ-butyrolactone	214	41
cyclopentanolide	222	40
cyclohexanolide	221	46
cycloheptanolide	220	89
cyclooctanolide	211	149
cyclononanolide	216	69
exaltolide	213	77
n-propyl acetate[24]	210	56
methyl propionate[24]	211	61

Closson and Haug[24] have suggested that the (lone-pair)-(lone-pair) electon repulsions in the s - cis conformation may lead to a lowering of the $n \rightarrow \pi^*$ transition energy relative to the strain free s - trans conformation. This is confirmed by the observed absorption maxima from which it can be seen that those lactones which take up the s - cis configuration, cyclopentanolide, cyclohexanolide and cycloheptanolide all have lower $n \rightarrow \pi^*$ transition energies than the corresponding s - trans

lactones. The values for propiolactone and γ-butyrolactone
are abnormal because of ring strain. According to Closson and Haug
this is because of the reduction in bond angles which leads to
an increase in s - character of the σ-bond of the carbonyl group
which in turn leads to the shortening of both the σ- and π- bonds
and thus raises the π^* level.

The absorption maxima of cycloheptanolide and cyclooctanolide
are both perfectly normal in that the former has the value
expected for an s - cis lactone while the latter has that expected
for an unstrained s - trans lactone. The extinction coefficients
for both these compounds are higher than the others, but it is
difficult to place any significance on this.

Thus the infra-red and ultra-violet spectra of the lactones
((1) n = 5 - 10 and 16) show nothing untoward about the medium ring
lactones, cycloheptanolide and cyclooctanolide. It is possible that
the lactone groups in these compounds are twisted a little out
of planarity which would explain their intermediate dipole moments,
the intermediate integrated carbonyl intensity of cyclooctanolide
and may in some way account for their high U.V. extinction coefficients.
However, it is certain that there is no appreciable twisting of the
lactone group since this would show up in the carbonyl frequency
and in the U.V. (see for example I.R. and U.V. of twisted lactams

reference 36). On the other hand, an equilibrium mixture of
s – cis and s – trans would account for some of the abnormal
properties of cycloheptanolide and cyclooctanolide.

DISCUSSION 2

In this part of the thesis an attempt has been made to determine the preferred conformations of cycloheptanolide and cyclononanolide in solution. To achieve this aim, the n.m.r. spectra of the above compounds and some of their derivatives have been studied at various temperatures.

At room temperature all of the lactones (1) (n = 6 to 10) show n.m.r. spectra which are similar in form to that of cyclononanolide shown in figure 3. The triplet in the region of T 5.7 is due to the two protons on the carbon atom adjacent to the ether oxygen while the higher field triplet between T 7.5. and 8 is due to the protons on C - 2 of the lactones. These methylene protons show up as triplets because of rapid conformational equilibration which averages the proton chemical shifts. The high field signals between T 8 and 9 are due to the remaining methylene protons. Because of the conformational mobility of these systems, their n.m.r. spectra at room temperature provided little information as to their preferred conformations.

However, as the temperature is lowered the conformational motion is slowed down and in two of the lactones, cycloheptanolide and cyclononanolide, bands corresponding to discrete protons begin to appear within the temperature range being investigated. The

n.m.r. spectra of these lactones in $CFCl_3$ solution at $173^{\circ}K$ are shown in figures 2 and 7 and are dramatically different from the spectra obtained at room temperature.

At the lowest temperatures we were able to reach $(173^{\circ}K)$, these were the only two lactones in which it was possible to arrest conformational motion sufficiently to be able to observe the n.m.r. spectra of the "frozen out" conformers.

Cycloheptanolide

The 100 M Hz spectrum of cycloheptanolide in $CFCl_3$ solution at room temperature consists of a 2H triplet at T 5.72, a 2H triplet at T 7.62 and a broad 8H multiplet between T 8 and 9. As the temperature is lowered to $203^{\circ}K$, the low field triplets begin to collapse and form broad singlets, which split into discrete bands as cooling is continued. At $173^{\circ}K$ the signal at lowest field has split into a triplet $(J \sim 12 \text{ Hz})$ at T 5.59 and a doublet $(J \sim 12 \text{ Hz})$ at T 5.90 which partly overlaps the triplet (see figure 2). At the same temperature the signal between T 7 and 8 has become a broadened triplet $(J \sim 12 \text{ Hz})$ at T 7.30 and a doublet $(J \sim 12 \text{ Hz})$ at T 7.81 (see figure 2). The coalescence temperature, T_c, determined for the peaks at T 7.30 and T 7.81 is $183^{\circ} \pm 5^{\circ}K$.

This type of behaviour is characteristic of systems having

protons which may be transferred between non equivalent sites in an intermediate rate process. At the coalescence temperature the rate constant for interconversion k' can be obtained from Gutowsky and Holms expression[25,26]:

$$k' = \pi \Delta v (\sqrt{2})^{-1}$$

This equation has been widely used in its simplified form, which holds for two states having equal populations and lifetimes. The signal width must also be small in comparison to the signal separation Δv[26,27]. In the present calculation these conditions are assumed to hold.

An estimate of $\Delta G^{\ddagger}$ for the barrier to inversion can be obtained from the Eyring equation[23] by assuming a transmission coefficient $K = 1$:

$$k' = \frac{k\,kt}{h} \exp\left(-\frac{\Delta G^{\ddagger}}{RT}\right)$$

which can be written in the more convenient form:

$$\Delta G^{\ddagger} = 2.303\,R\,T_c\,(10.319 - \log_{10} k' + \log_{10} T_c)$$

When the data for cycloheptanolide, $\Delta v = 50$ Hz and $T_c = 183^{\circ}$K are substituted in the above equation, then $k' = 111$ sec^{-1} and $\Delta G^{\ddagger} = 8.9 \pm 2.0$ k cal mole^{-1} are obtained for the conformational process which exchanges the C 2 methylene protons.

Consideration of the possible conformers of cyclooctane (see for example reference 29) and constraining the lactone group to a planar or slightly twisted s − cis configuration leads to

seven different possibilities; (38a and b),(39a and b), (40),
(41) and (42) for the conformation of cycloheptanolide. For
simplicity the conformations (38b) and (39b) will not be considered
at present. Although the various C H bonds cannot be labelled
as equatorial or axial with the same meaning as these terms are
used in cyclohexane systems, it is nevertheless convenient to
label those bonds in the general plane of the molecule as
"equatorial" and the others are then "axial". Each of the five
possible conformers then has six "equatorial" protons (e) and
six "axial" protons (a).

The triplets in the n.m.r. spectrum of cycloheptanolide at
173° K (figure 2) are consistent with the protons associated
with them being coupled to the neighbouring protons with two
large $(J \sim 12 \text{ Hz})$ and one small $(J \sim 3 \text{ Hz})$ coupling constants.
The doublets on the other hand are consistent with the protons
associated with them being coupled to the neighbouring protons with
one large $(J \sim 12 \text{ Hz})$ and two small $(J \sim 3 \text{ Hz})$ coupling constants.
The above coupling constants can be accounted for if the protons
on C 2 and C 3, and C 6 and C 7 are geometrically related as
shown in (43) where H_a has a large diaxial coupling, $(J \sim 12 \text{ Hz})$
with $H_{a'}$, a large geminal coupling, $(J \sim 12 \text{ Hz})$, with H_e and
a smaller axial-equatorial coupling, $(J \sim 3 \text{ Hz})$ with $H_{e'}$. H_e
on the other hand has a large geminal coupling, $(J \sim 12 \text{ Hz})$ with

H_a and two smaller couplings $(J \sim 3 \text{ Hz})$, with $H_{e'}$ and $H_{a'}$. Thus H_a protons give rise to the triplets and H_e protons to the doublets.

The conformations which best fit the above data are (38a) and (39a) both of which have the protons on C 2 and C 3, and C 6 and C 7, in the geometrical relationship shown in (43). Thus the triplets at T 5.59 and T 7.30 are due to the H_a protons on C 2 and C 7 respectively while the doublets at T 5.90 and T 7.81 are due to the H_e protons on C 2 and C 7.

The lower field positions of C 2 H_a and C 7 H_a relative to C 2 H_e and C 7 H_e are consistent with conformation (38a). The deshielding region of the carbonyl group[30] in (38a) as shown in (44) predicts that C 2 H_a and C 7 H_a should be deshielded relative to C 2 H_e and C 7 H_e respectively. In conformation (39a), however, the deshielding region of the carbonyl group, as shown in (45), predicts that C 2 H_a and C 7 H_e would be deshielded relative to C 2 H_e and C 7 H_a respectively. Shielding predictions based on the above arguement have been shown to hold in the lactones on page 106.

(38a) resembles the conformation found in cyclooctane itself (22) and for cyclooctane cis-fused to a three-membered ring (25). The lactone group in this conformation is of necessity twisted in order to relieve the serious non-bonded interaction

between C 2 H_a and C 7 H_a. This would account for the low
dipole moment observed for cycloheptanolide by Huisgen and
Ott[1].

As mentioned earlier, consideration of the possible conformations
(38b) and (39b) was omitted. However, conformation (38b) fits the
n.m.r. evidence just as well. It is difficult to predict whether
(38a) or (38b) will be preferred. The lack of fine structure
in the region between T 8 and 9 at 173° K (figure 2) may indicate
that there is still substantial conformational motion in the ring
methylene protons. A possible process is illustrated in scheme - 1
which interconverts (38a) and (38b) via a chair like intermediate.
This process only involves flipping of the C 4 and C 5 methylene
protons and should require very little activation energy. A
mixture of (38a) and 38b) would be expected to give an n.m.r.
spectrum similar to that for (38a) or (38b) alone. A further
process which requires little activation energy involves inter-
conversion of the boat-chair (38a) with a saddle conformation
(scheme 2) by flipping the C 6 methylene group. However, the n.m.r.
evidence suggests that there is very little of the saddle conformation
(39) in the equilibrium mixture.

The above processes only interconvert the species (38a),
(38b), (39a) (39b) and as a result the C 2 H_a and H_e, and C 7 H_a

and H_e protons are not exchanged. To exchange these protons it
is necessary to go through some sequence such as scheme - 3, which
involves converting the boat to a twist like conformation which
then reverts to the enantiomeric boat chair. The barrier to
conformational inversion of this type is 9 K cal mole^{-1} which is
in the same range as the barrier for cyclooctane itself[31].
Anet[35] has reported the low temperature n.m.r. spectrum of cis-
cyclooctene which shows changes in the region of 173 to 153°K.
The spectrum is rather ill defined though and no information
regarding the conformational processes which take place was
obtained.

The above results are consistent with cycloheptanolide
being in the chair boat conformation (38a) or (38b) or a mixture
of (38a) and (38b). Since little is known concerning the
barrier to rotation about the $C_{sp}2 - 0$ bond it is difficult
to make any predictions about the actual inversion processes which may
be occuring.

Cyclononanolide

The 100 M Hz n.m.r. spectrum of cyclononanolide in freon
at room temperature is shown in figure 3. It consists of 2 H triplets
at T 5.80 and T 7.73, and a broad 12 H multiplet betwen T 8 and 9.
As the temperature is lowered the triplets begin to collapse and a signal

begins to appear out of the highfield end of the methylene protons
(figure 4). As the temperature is further lowered the two lowfield
signals form broad singlets, (217° K for the T 5.80 signal and
204° K for the T 7.73 signal). The signal at T 5.80 begins to
split into two separate signals below 195°K (see figures 5 and 6)
and at 173°K (figure 7) it has become a broad doublet (J = 11 Hz)
at T5.27 and a broad triplet (J = 11 Hz) at T 6.24. At 173° K
the signal at T 7.73 has become a poorly resolved quartet
(J $\sim$ 12 Hz, 5 Hz) centred at T 7.52 and a poorly resolved, distorted,
triplet (J = 12 Hz) at T 7.90 (figure 7). The changes in the
low field multiplet as the temperature is lowered are illustrated
in figure 8. The coalescence temperature T_c determined for the
peaks at T 5.27 and T 6.24 is 195 $\pm$ 3° K, (see figure 5 for
spectrum at T_c).

The activation parameters for the conformational process
which exchanges the methylene protons on C 9 were calculated as
for cycloheptanolide and were found to be:

$\triangle$ G = 9.2 $\pm$ 1 Kal mole^{-1} and K$'$ = 228.5 sec^{-1} at T_c.

Examination of molecular models shows that if the lactone
group is kept planar and s − trans, then the possible conformations
of cyclononanolide fall into two groups; those in which the
two four atom chains, $C_2 - C_1 - O - C_9$ and $C_4 - C_5 - C_6 - C_7$ are

parallel: (46), (47), (48), (49) and those in which the two chains are not parallel: (50), (51), (52), (53). The protons are labelled (a) and (e) as in cycloheptanolide.

By an analogous argument to that used for cycloheptanolide, the triplets at T 6.24 and T 7.90 are assigned to C 2 H_a and C 9 H_a protons respectively and the doublet at T 5.27 and quartet at T 7.52 to the C 2 H_e and C 9 H_e protons respectively. Molecular models show that the protons on C 2 and C 3, and C 8 and C 9 are in the geometric relationship shown in (43) in all of the conformations (46) to (53) and therefore the multiplet structures do not distinguish between the different conformations.

(54) and (55) show the two possible conformations of the – CH_2 – CO – O part of cyclononanolide found in the above conformations with the carbonyl deshielding region drawn in[30]. In (54) it is predicted that C 2 H_e will be deshielded relative to C 2 H_a since it projects closer to the deshielding zone of the carbonyl group. The opposite is true in (55), however, where it is predicted that C 2 H_a will be deshielded relative to C 2 H_e. Now it is known that C 2 H_e is deshielded relative to C 2 H_a, hence the partial conformation (54) is consistent with the observed shielding predictions. The partial conformer (54) is found in conformations (46), (48), (50) and (53).

In an effort to pin down the preferred conformation of cyclononanolide, it was decided to synthesise some substituted derivatives which would be expected to have the same conformation as cyclononanolide itself. The 6 - hydroxy and 6 - acetoxynonanolides (56) and (57) were synthesised to obtain information about coupling constants and therefore conformation of the C 5 - C 6 - C 7 part of the molecule. It was expected that the band width of the C 6 proton in (56) and (57) would indicate whether a conformation of type (46) or (48) was present. In (46) the steric relationship of the neighbouring protons to C 6 H_a resembles the relationship of the neighbouring protons to C 4 H in (67). Thus the C 6 Ha in (46) and C 4 H in (67) should have similar band widths.

In (48) on the other hand the dihedral angles between the C 6 Ha and the C 7 protons are 120° and therefore the coupling constants between C 6 H_a and the C 7 protons are expected to be small and as a result the band width will also be smaller.

Using a similar approach it was hoped to be able to distinguish between conformations of type (46) and (47) by studying the coupling constants and band widths of the C 5 proton in (58) and (59)

(56) and (57) were readily synthesised from the 6 - keto - nonanolide (60) which has been previously prepared by Borowitz et al[17].

(56) was obtained by sodium borohydride reduction of (60).
The reduction went rapidly and was stopped before going to completion
as the sodium borohydride attacked the lactone group in a side
reaction. (57) was readily obtained by acetylation of (56).

Following the ease of conversion of (60) to (56) it was
planned to obtain (58) and (59) from the 5 - keto - nonanolide (61).
(61) was readily obtained by the following sequence. The acetoxy
ketone (62) was obtained by condensation of 4-bromo-butyl acetate
the pyrollidine enamine of cyclopentanone. (62) was hydrolysed
to the hydroxy ketone (63) which was cyclised and dehydrated
to the enol ether (64) by refluxing with p - toluene sulphonic
acid in benzene under a water separator[33]. (64) was a very volatile
oil which had a strong band in the infra-red at 1649 cm^{-1} due to
the C = C stretching vibration. The mass spectrum showed a
molecular ion of 138 (90%) with a strong peak at 110 (100%)
corresponding to loss of carbon monoxide. (64) was smoothly
cleaved to the required 5 - ketononanolide with m- chloroperbenzoic
acid in methylene chloride according to the method of Borowitz[17].
(61) had a similar infra-red spectrum to (60), with two carbonyl
bands at 1747 cm^{-1}, (lactone) and 1713 cm^{-1} (ketone), the former
band being almost twice as intense as the latter.

Unfortunately the reactivity of the carbonyl groups in (61)
was different from that of (60). The required 5 - hydroxy -

nonanolide (58) could not be obtained by treatment of (61)
with sodium borohydride or lithium aluminium t-butoxide.
Catalytic hydrogenation of (61) in acetic acid solution afforded
a product which had hydroxyl bands at 3630, 3520 and 3460 cm^{-1}
and strong C - O stretching bands at 1050 and 1090 cm^{-1}. The
n.m.r. was not helpful, showing a complex multiplet at T 4.5.
and methylene protons at T 8.6. Owing to lack of time it was
not possible to investigate this compound any further.

The infra-red spectrum of (56) showed a doublet in the free
hydroxyl stretching region at 3624 and 3605 cm^{-1}. It is unlikely that
the low frequency band is caused by hydrogen bonding. A possible
explanation is that it is due to a rotamer of the hydroxyl group.
No intra molecular H - bonding was observed which suggests that
the hydroxyl group is pointing away out from the ring.

The n.m.r. spectrum of (56) at room temperature showed a 1 H
diffuse doublet (J ~ 11 Hz) at T 5.3 and a 1 H diffuse triplet
at T 6.10 overlapping a 1 H broad singlet a T 6.0. On cooling to
213° K the spectrum sharpened up considerably and the doublet
and triplet showed up at T 5.23 (J = 11 Hz) and T 6.20 (J = 11 Hz)
respectively. The singlet was centred at T 5.86 and partially
overlapped the triplet, however, its band width was estimated to
be about 36 Hz. The positions of the doublet and triplet were

almost identical to the equivalent signals in the spectrum of cyclononanolide at 173° K. This is an indication that the conformations of the substituted and unsubstituted cyclononanolides are the same and that the hydroxyl is acting as group which fixes the conformation.

The n.m.r. spectrum of (57) is similar to that of (56), except that the C 6 proton has been pulled downfield by the acetate group, to T 4.71 where it shows up as a broad singlet (W = 33 Hz) at 233° K in $CDCl_3$. At -50° C the doublet and triplet due to the C 9 protons show up at T 5.29 and T 6.16 which is close to where they are in (56) and cyclononanolide. The C 2 H_e proton in (57) appears as a well defined quartet (J =13 Hz, 5 Hz) centred at T 7.36. This is consistent with it having one large geminal coupling (13 Hz) and two smaller equatorial-axial and equatorial-equatorial couplings (J = 5 Hz and J $\sim$ 2 Hz). The C 2 H_a proton was further upfield under the signal due to the acetate protons at T 7.90.

The benzene induced solvent shifts of the C 9 H_e, C 9 H_a protons are shown in table 3 for (56) and (57)

Table 3. Benzene induced solvent shifts in p.p.m. measured at room temperature.

Compound	Proton		
	C 9 H_e	C 9 H_a	C 6 H
(56)	+0.20	+0.47	+0.2
(57)	+0.20	+0.47	−0.2

If we consider the two partial structures (65) and (66) and draw a reference plane (A) through the carbonyl group at right angles to the carbon oxygen bond such that it divides the space around the carbonyl group into two regions, that behind the group and that in front of it. According to Connolly and McCrindle[32] protons behind this plane suffer an upfield shift and those in front a downfield shift. Protons in or close to the plane suffer a small shift in either direction. This predicts that in (65) the proton H_a will suffer a larger upfield shift than proton H_e while in (66) the reverse in true. From table 3 it can be seen that H_a suffers a larger upfield shift than H_e, hence the partial structure (65) is representative of cyclononanolide. Partial structure (65) is found in the probable conformers (46), (47), (50) and (51).

Thus, only two conformations (46) and (50) are consistent with all the n.m.r. evidence so far. In addition the observed band width of C 4 H in (67) is 30 Hz[34] which is close to the band width found for C 6 H_a in (57) i.e. 33 Hz. This suggests that C 6 H in (57) has two large diaxial and two smaller axial-equatorial couplings a situation which can only occur in conformations (46) and (50).

Of the two conformations (46) and (50), (46) is of the type which has been found for most cyclodecane derivatives so far (29).

It is also the conformation which has been found for the
6 - ketononanolide (52). In line with this it seems probable
that (46) is therefore the preferred conformation of cyclononanolide.
The discussion below shows that cyclononanolide cannot be a
equilibrating mixture of the two conformers (46) and (50).

Roberts[20] has discussed the conformational processes
which occur in the deuterated trans - cyclodecene (68) (shown
in this conformation for ease of discussion only). He suggests
that there are three different processes occuring. These are
flipping of the C 4 and C 9 methylene groups, rotation of the
C 1 - C 2 segment through the loop formed by the other atoms
and rotation of the C 6 - C 7 segment through a similar loop.
He concluded that the flipping of the C 4 and C 9 methylene
groups required a low activation energy and that this process
took place even at low temperatures. This implies that (68) is
a mixture of the conformers formed by flipping the C 4 and C 9 methylene
protons. To account for the observation that the high field signals
due to the C 5 - C 6 - C 7 - C 8 methylene protons began to broaden
at a higher temperature than the allylic protons, Roberts proposed
that rotation of the C 6 - C 7 segment required a higher activation
energy than rotation of the C 1 - C 2 segment. In the region of
slow exchange the allylic protons formed an AB quartet. In order
that the axial and equatorial allylic protons be exchanged it is

necessary that both methylene flipping and rotation of the C 1 – C 2 segment should occur. By computing line shapes of the AB quartet due to the allylic protons at different temperatures, Roberts was able to obtain the activation energy for rotation of the C 1 – C 2 segment.

By analogy with trans–cyclodecene, it is expected that similar processes occur in cyclononanolide, assuming that the lactone group remains planar. These are flipping of the C 3 and C 8 methylene groups and rotation of the C 1 – 0 and C 5 – C 6 segments through the loops formed by the other atoms. The first process interconverts the conformers 46, 47, 48, 49, and 50, 51, 52, 53 respectively. however, in cyclononanolide 47, 48, 49, and 51, 52, 53 do not contribute substantially to the equilibrium mixture, as inferred above.

In order that the C 2 and C 9 axial and equatorial protons may be exchanged it is necessary to invoke at least one of the rotation processes together with methylene flipping. The above protons may be exchanged by the process shown in scheme – 4, in which a conformer of type (i) is interconverted with a conformer of type (iii). This is sufficient to exchange the protons on C 2 and C 9. Scheme – 4 also shows how an equilibrating mixture of the conformers of type (46) and (50) could arise and a equilibrating mixture of this type is consistent with the spectrum of cyclononanolide at

173° K (figure 7). Interconversion of (iii) and (iv)(scheme - 4) only requires rotation of the C 5 - C 6 segment.

Similar changes in the n.m.r. spectra of cyclononanolide and of the deuterated trans - cyclodecene occur as they are cooled. The T 8 - 9 region in cyclononanolide begins to broaden 10 - 15° higher than the C 2 and C 9 methylene signals. This can be seen in figure - 4 which shows how a high field peak has started to appear out of the high field methylene protons. This is probably due to a slowing down of the conformational mobility in the C 4 - C 5 - C 6 - C 7 fragment. The signals due to the C 5, C 6, C 7, C 8, methylene protons in (68) pattern the above behaviour. The signals due to the C 2 and C 9 protons in cyclononanalide change as shown in figure 8, and again pattern the behaviour of the allylic protons in (68). The energy barrier to exchange of the C 2, and the C 9 axial and equatorial methylene protons, as calculated by determining the coalescence temperature, will be a measure of the barrier to rotation of the C 1 - 0 segment through the loop. The free energy of activation for this process is 9.2 K cal mole^{-1} and for the analagous process in trans cyclodecene, the energy of activation is 11.2 K cal mole^{-1} which compares favourably.

If the above explanation of the changes which take place in the n.m.r. spectrum of cyclononanolide as it is cooled is correct, then this implies that the process which exchanges the axial and equatorial protons on C 2 and C 9 involves methylene flipping

and rotation of at least one of the segments, C 1 – O or C 5 – C 6. Now, if a hydroxyl or acetoxy group is placed on C 6 as in (56) and (57), then the rotation of the C 5 – C 6 segment will become an unfavourable process, since it would involve forcing a bulky (relative to H) group into the centre of an already overcrowded ring. Rotation of the C 1 – O segment through the loop will still be possible though and as shown in scheme – 4 this will enable the axial and equatorial protons on the C 2 and C 9 methylene groups to be exchanged. However, in the n.m.r. spectra of (56) and (57) even at room temperature, the signals due to these protons occur as multiplets corresponding to the H_a and H_e protons on C 2 and C 9. This implies that analogously these protons are not being exchanged and therefore that one of the conformations, either (46) or (50) is present in a high proportion.

All the evidence therefore points to cyclononanolide adopting one preferred conformation which is most probably (46). The variation of the n.m.r. spectrum with temperature suggests that similar rate processes occur in cyclononanolide and in trans cyclodecene.

1

2

3

4

5

6

7

8

9

10
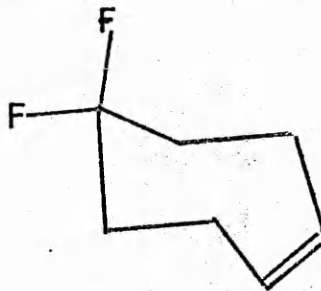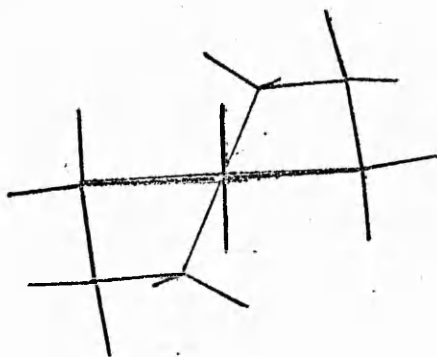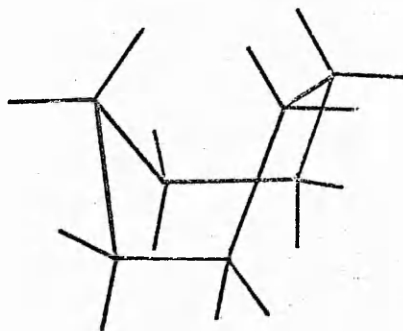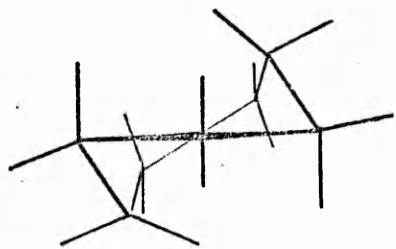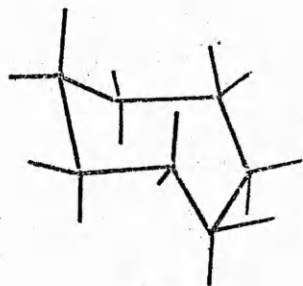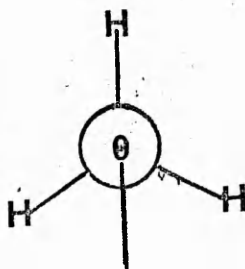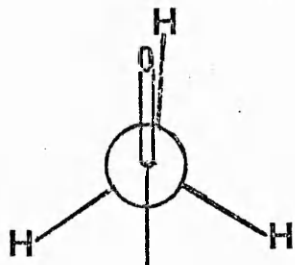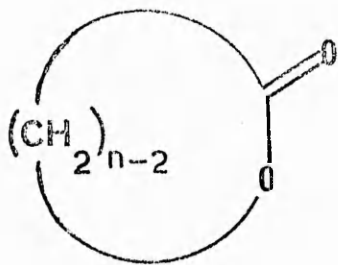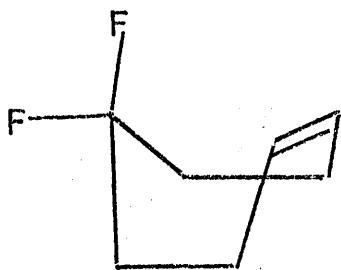
11
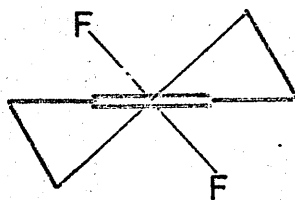
12
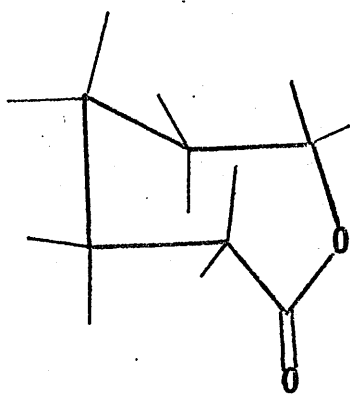
13
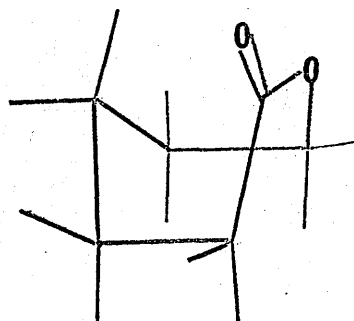
14
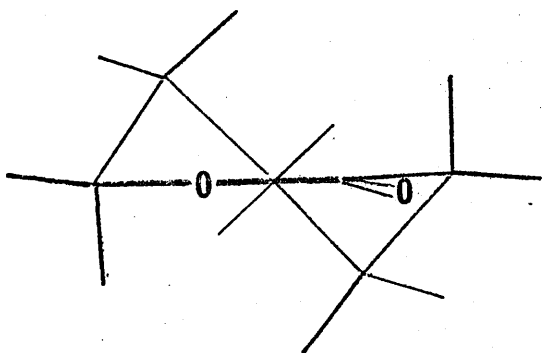
15
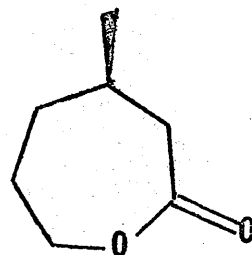
16
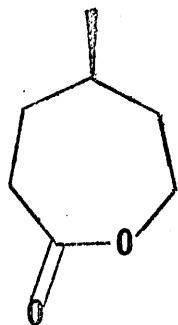
17
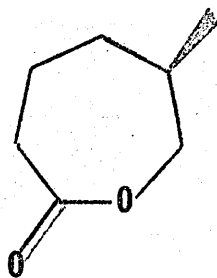
18
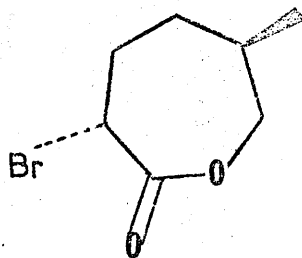
19
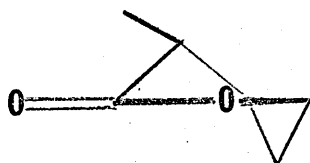
20
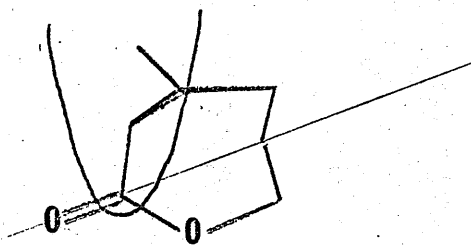
21
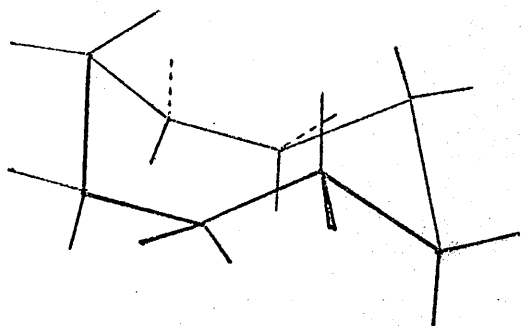
22
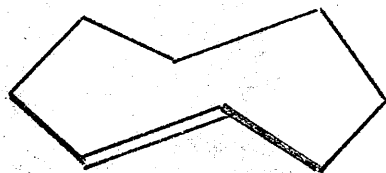
23
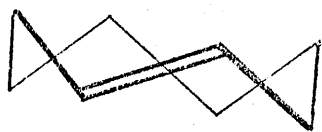
24
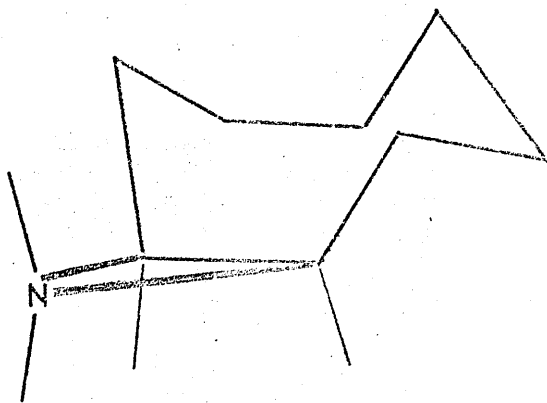
25
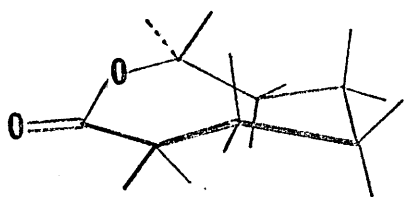
26
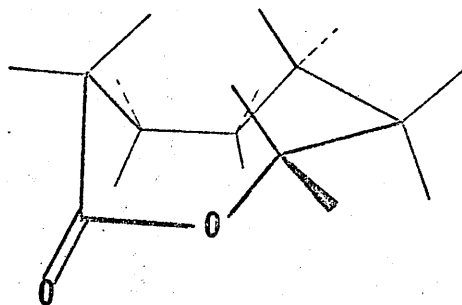
27
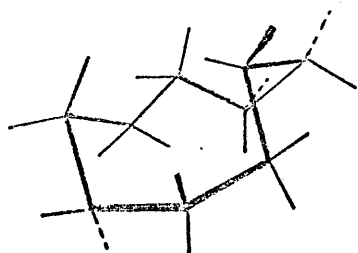
28
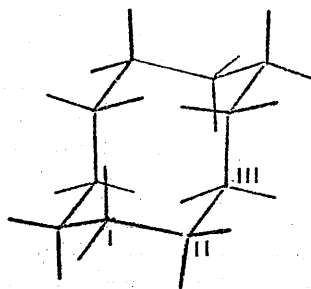
29
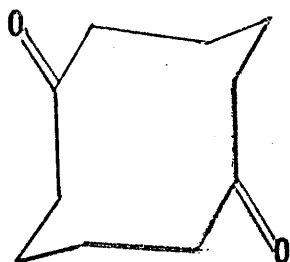
30

31

32

33

34

35

36

37

38a

38b

39a

39b

40

41

42

43

44

45
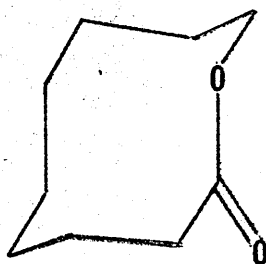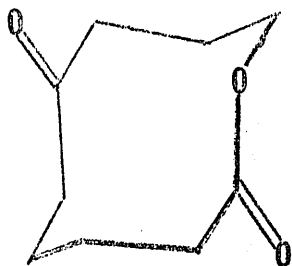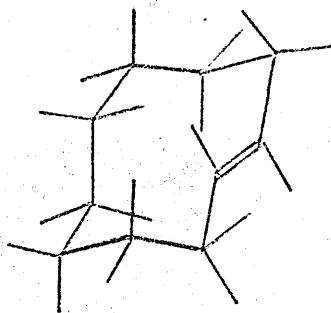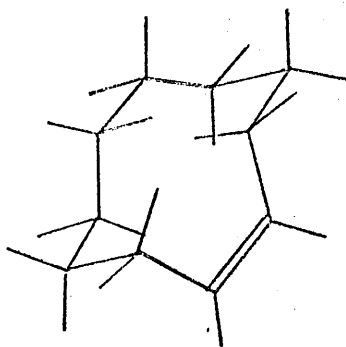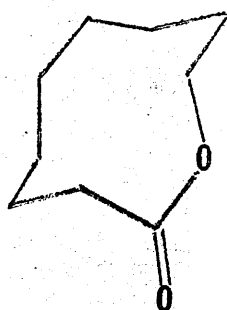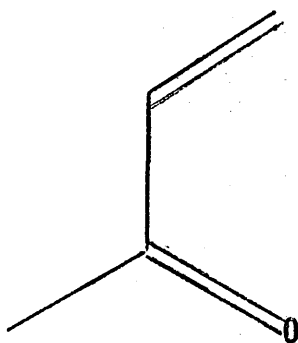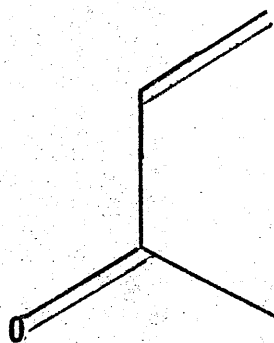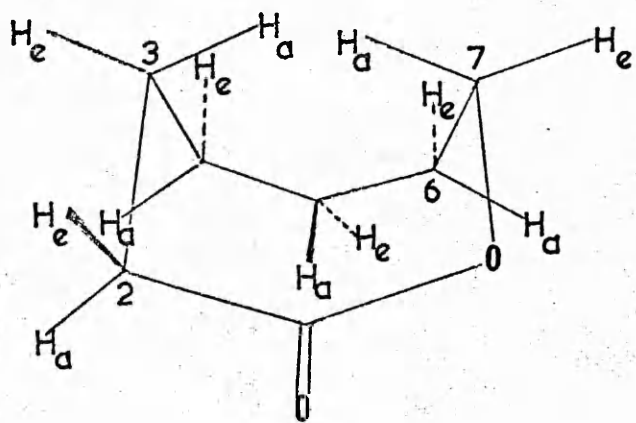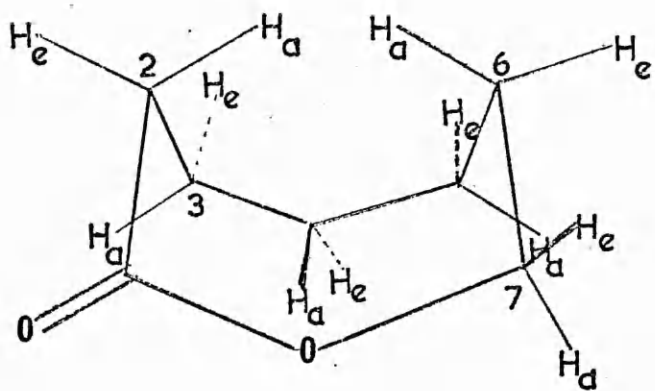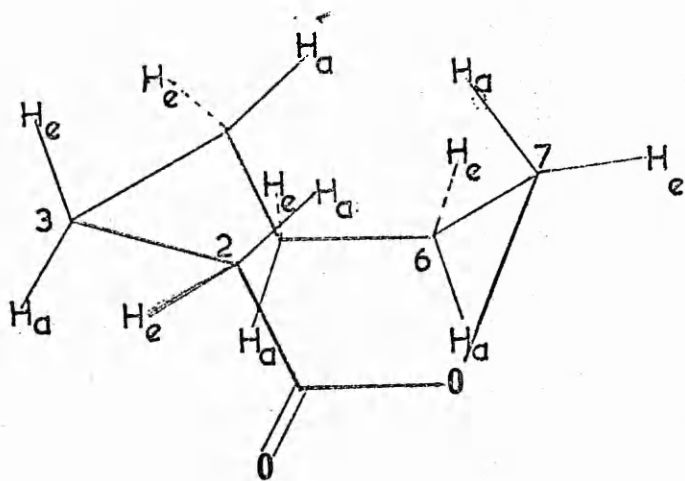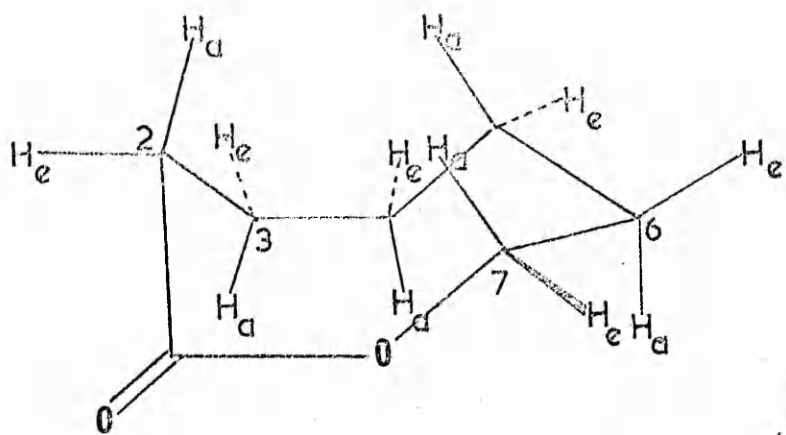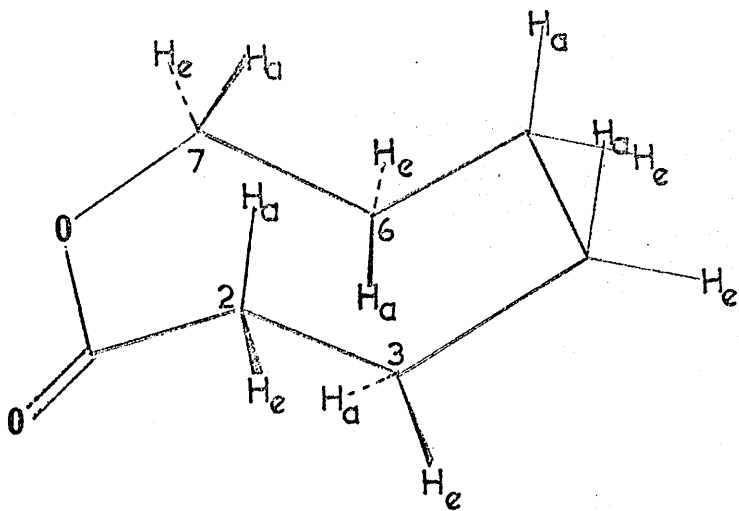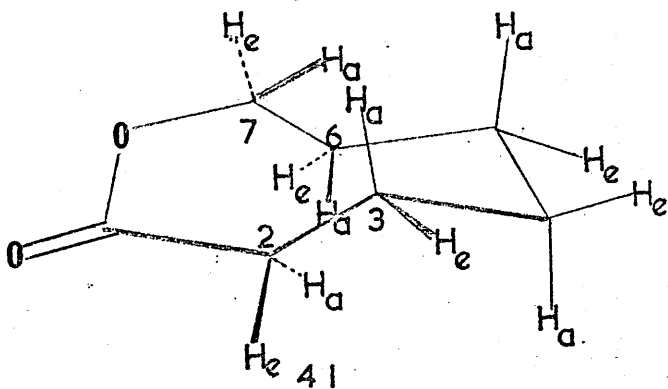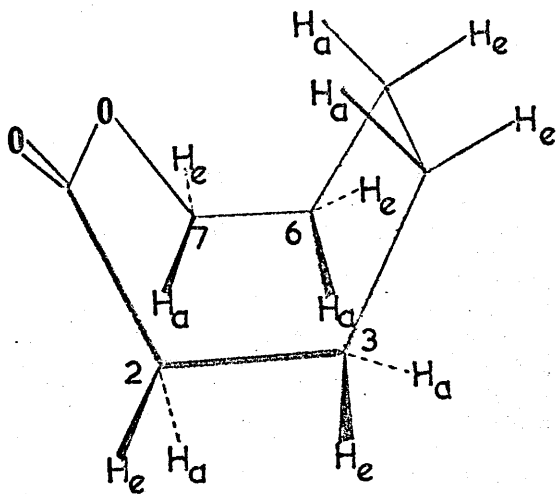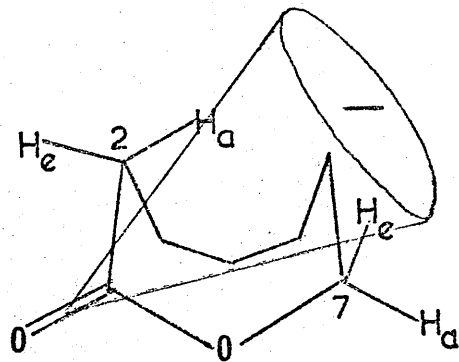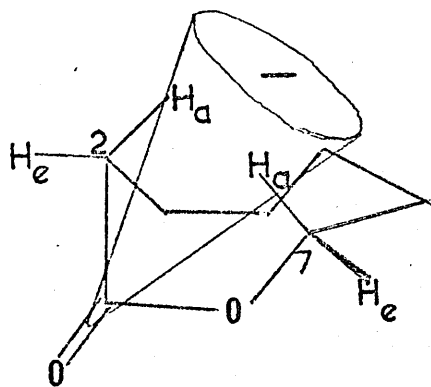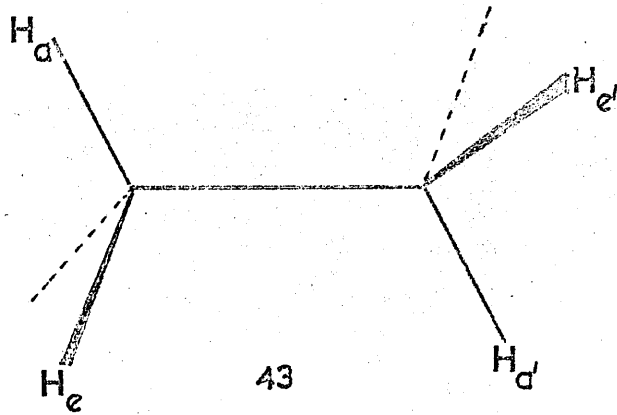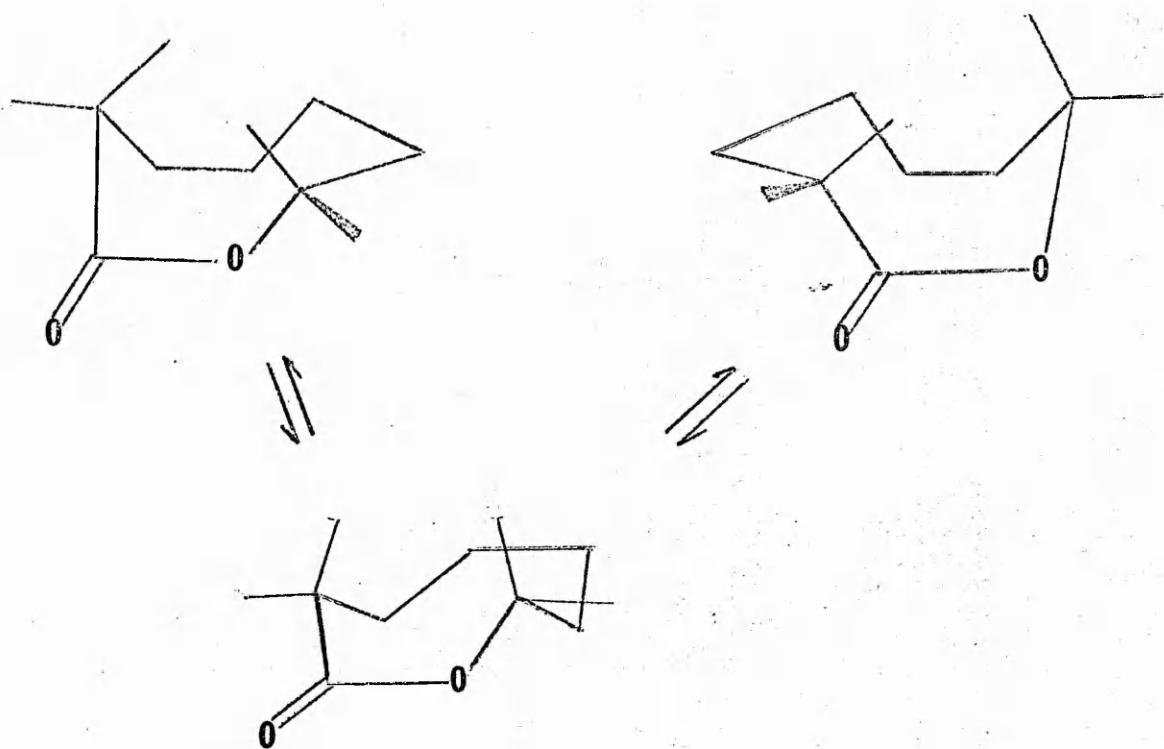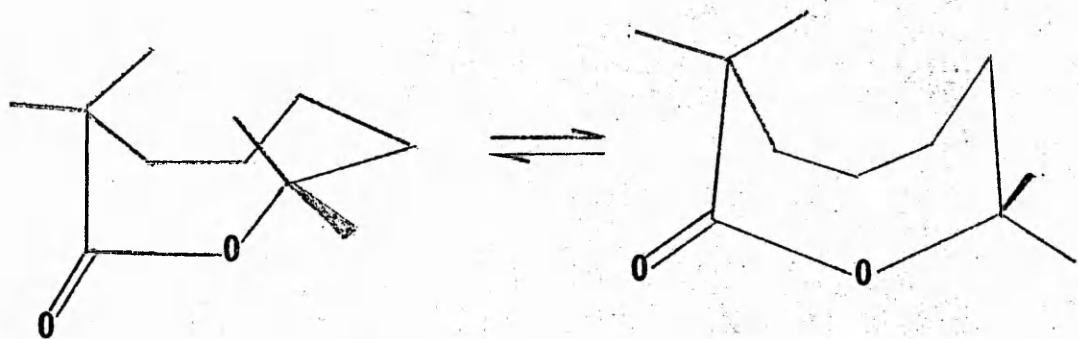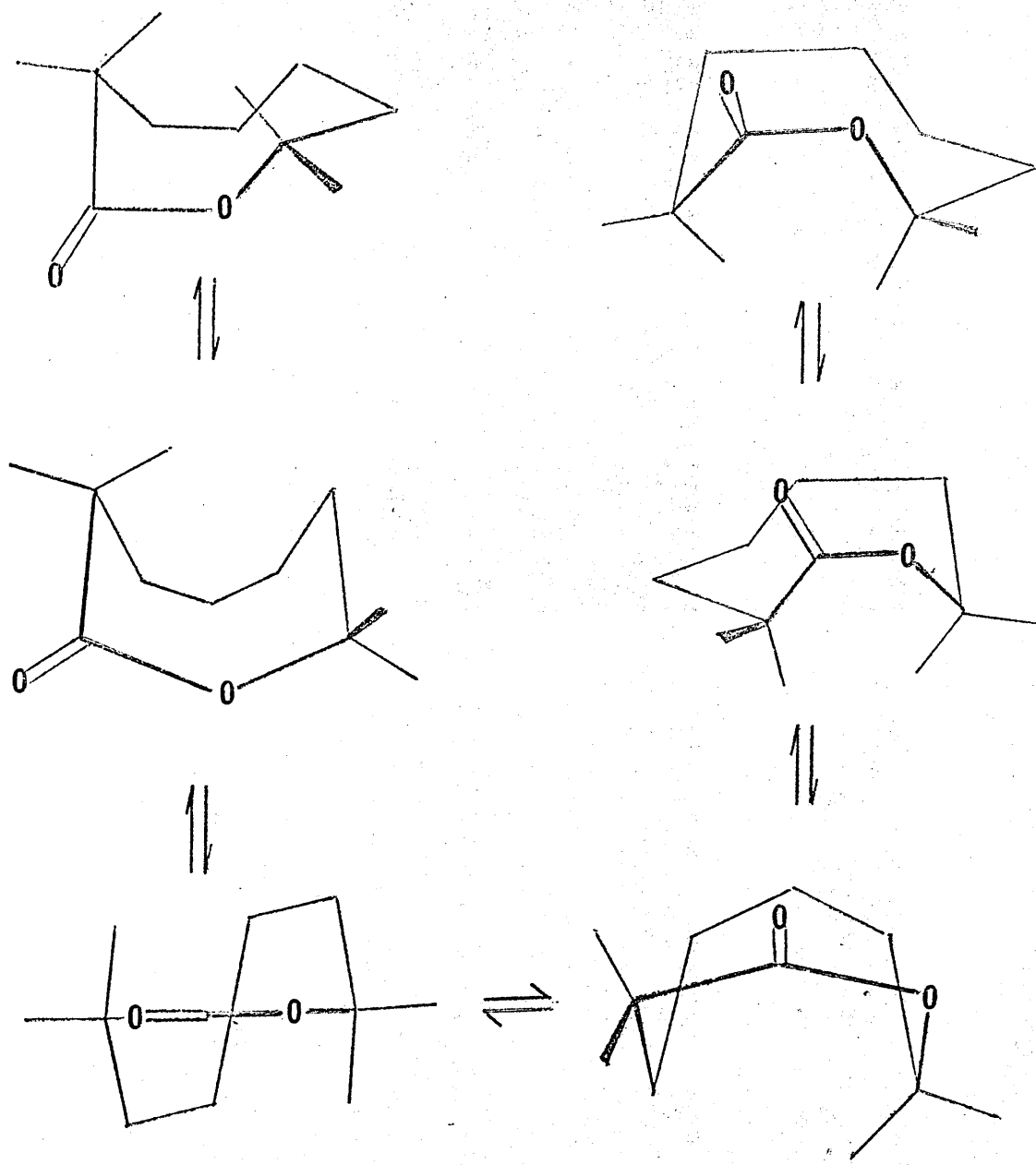
Scheme 1

Scheme 2

Scheme 3

46
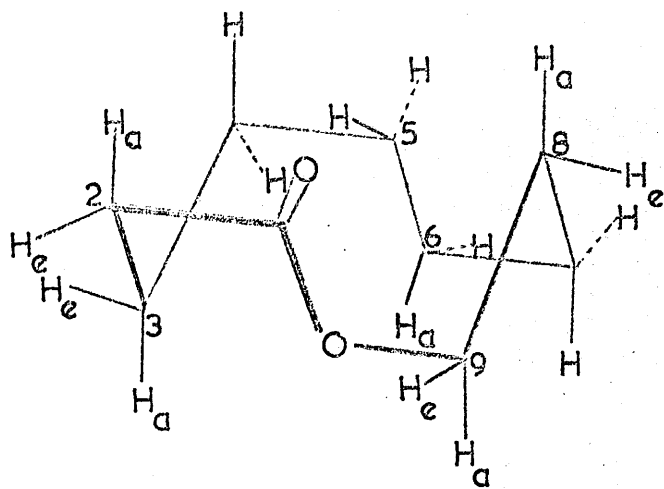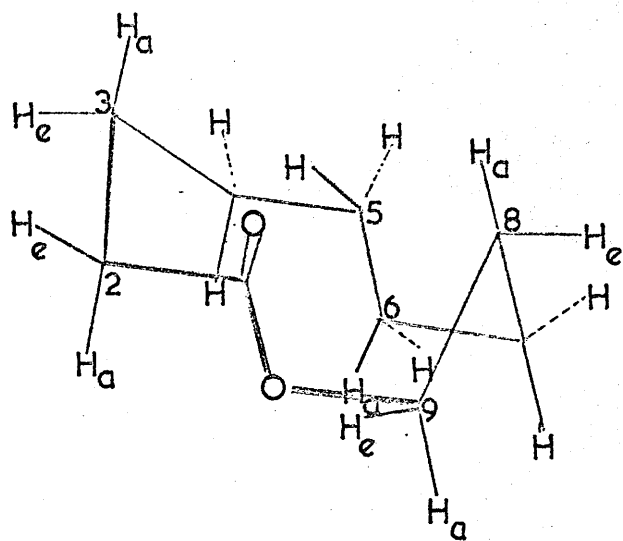
47
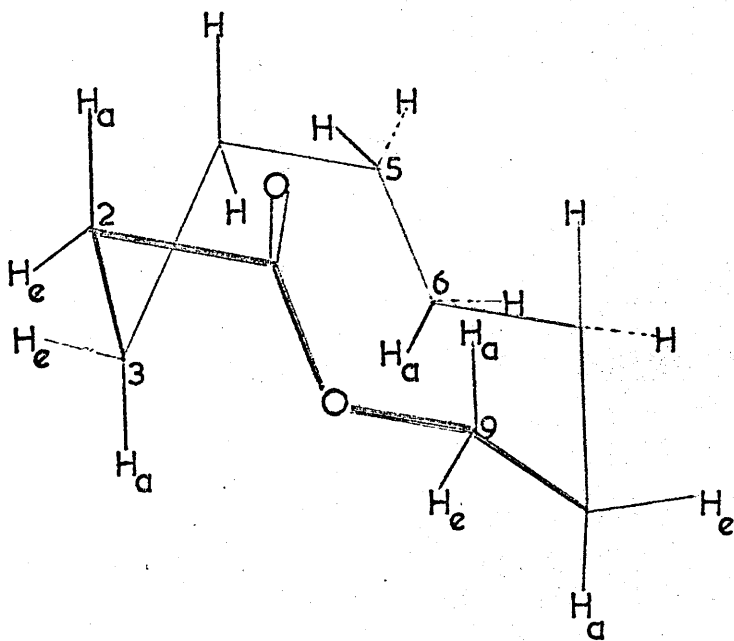
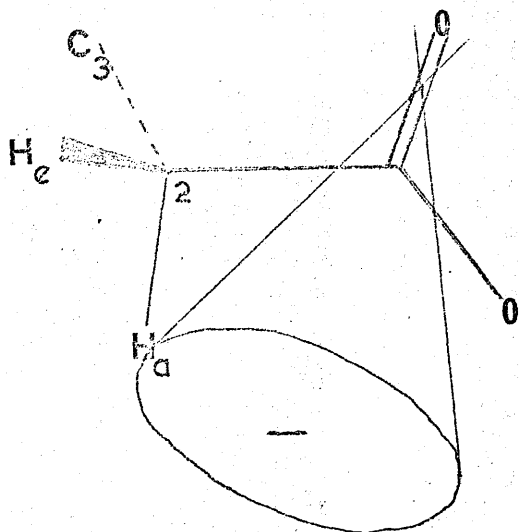

48
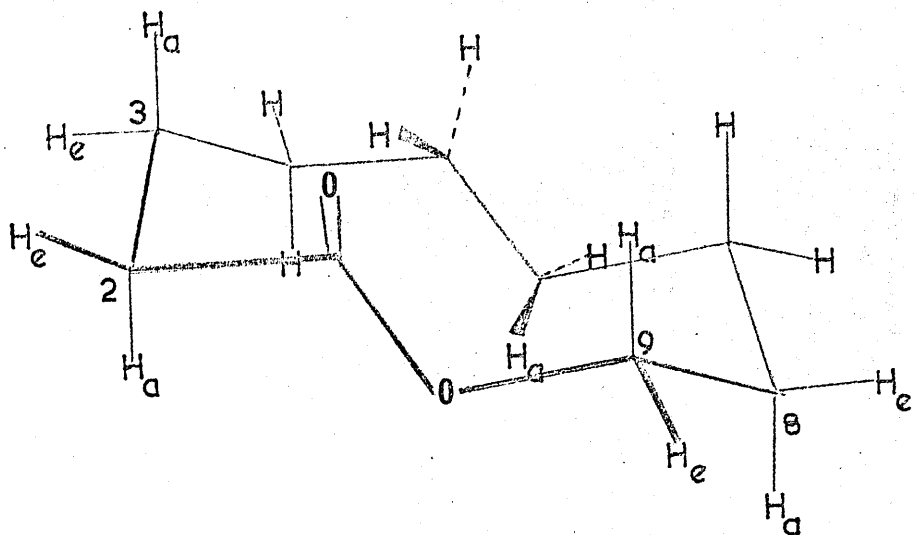
49
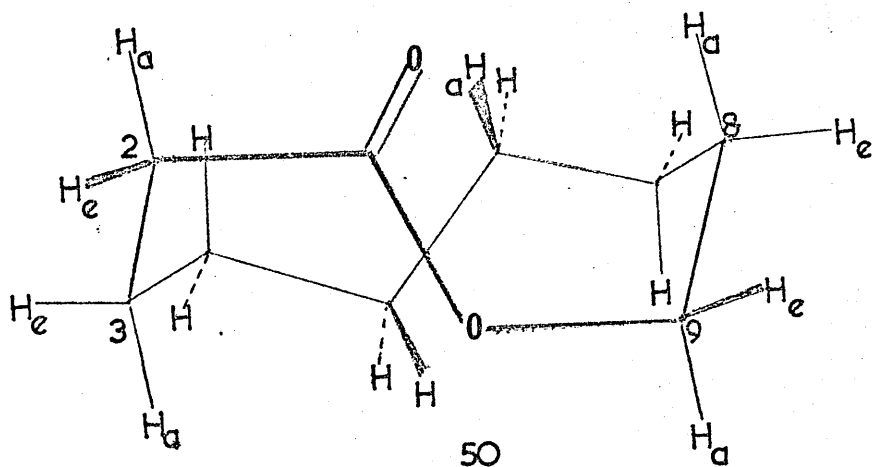
50
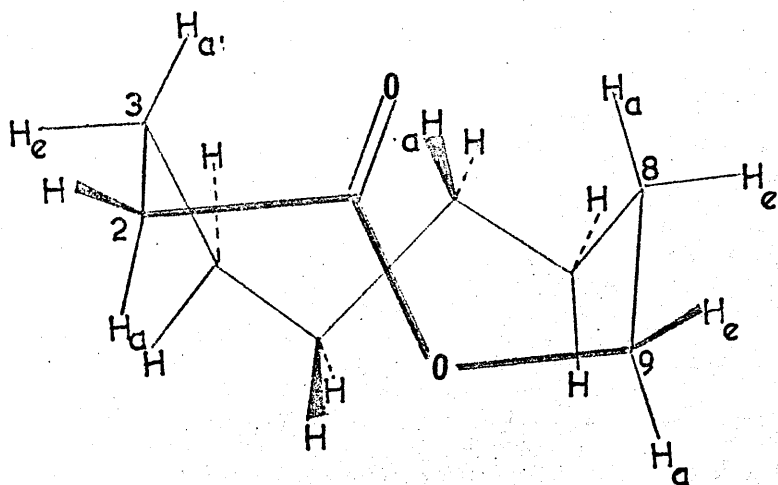
51
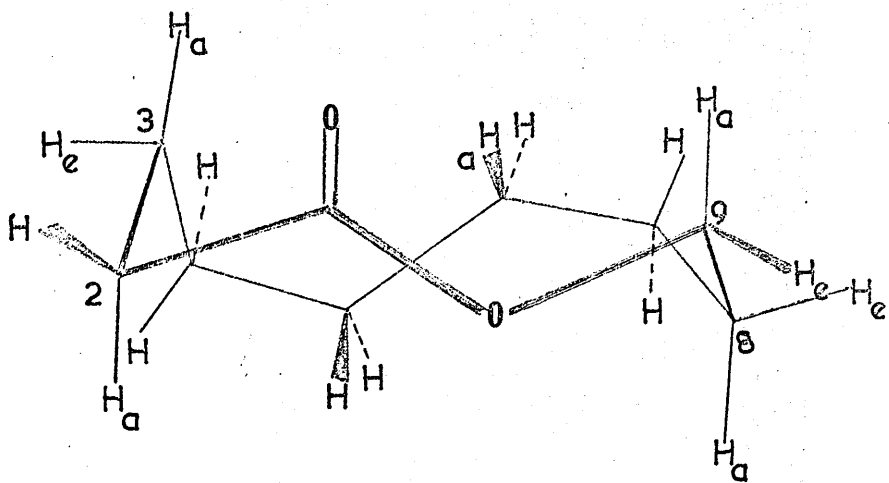
52
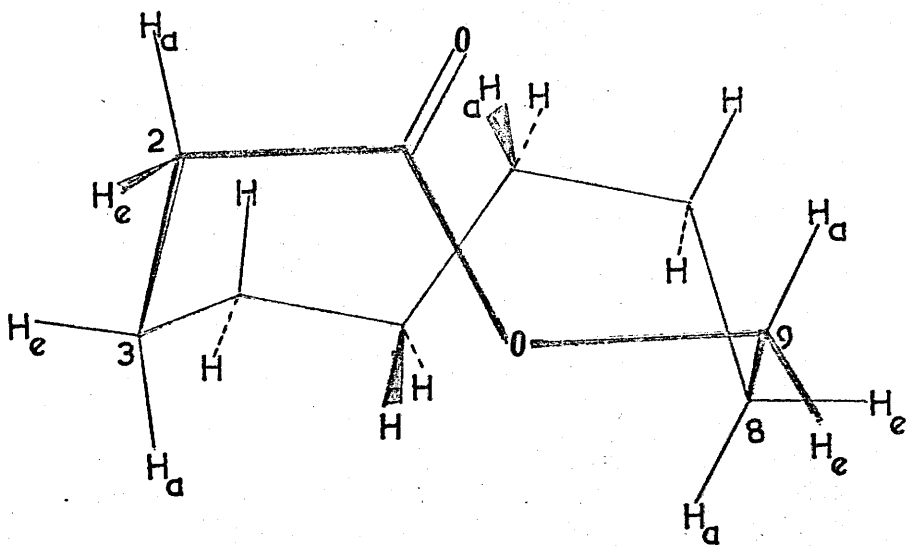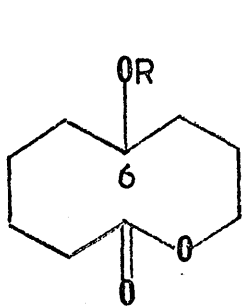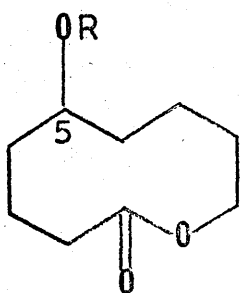

53
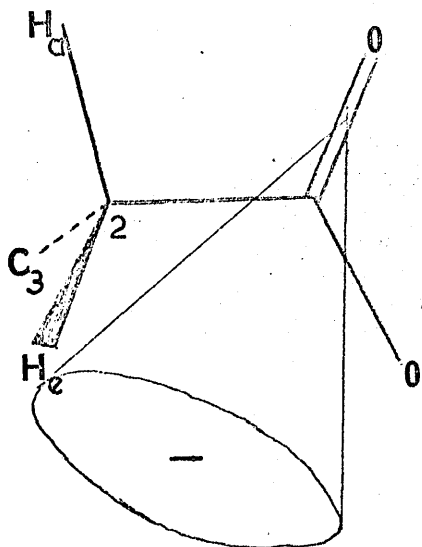
54

55
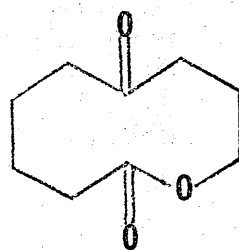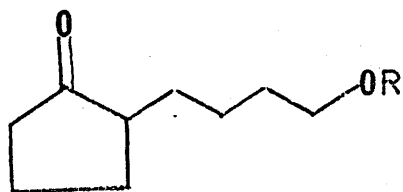
56 R=H
57 R=COCH₃

58 R=H
59 R=COCH₃

60
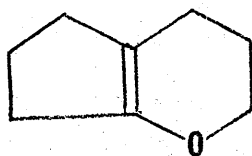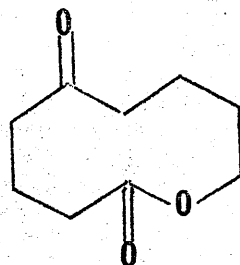
62 R=COCH₃
63 R=H
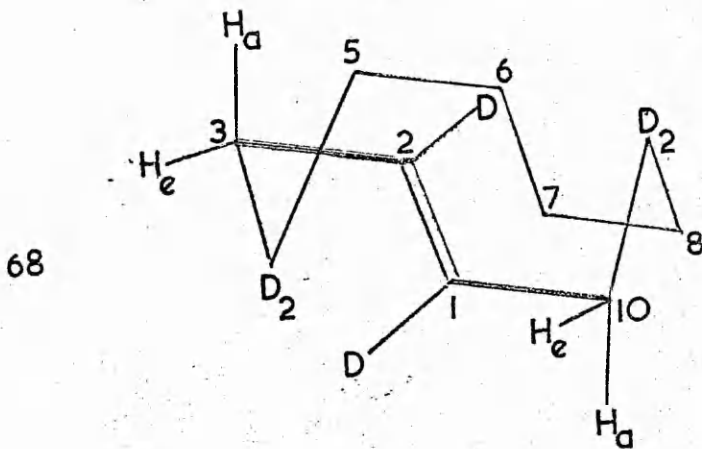
64

61

65

66

67

68

(i)

(iv)

(ii)

(iii)

Scheme 4

CYCLOHEPTANOLIDE 173°K

5   6   7   8   9   TAU

Figure 2

CYCLONONANOLIDE 300 K

Figure 3

CYCLONONANOLIDE 230 K

Figure 4

CYCLONONANOLIDE 195 K

Figure 5

CYCLONONANOLIDE   193 K

Figure 6

CYCLONONANOLIDE   173 K

Tau
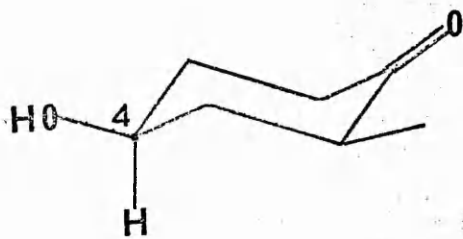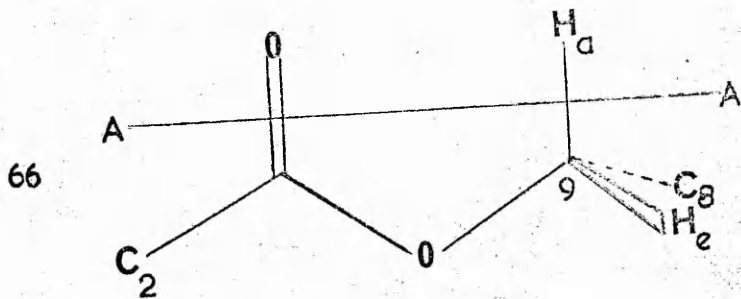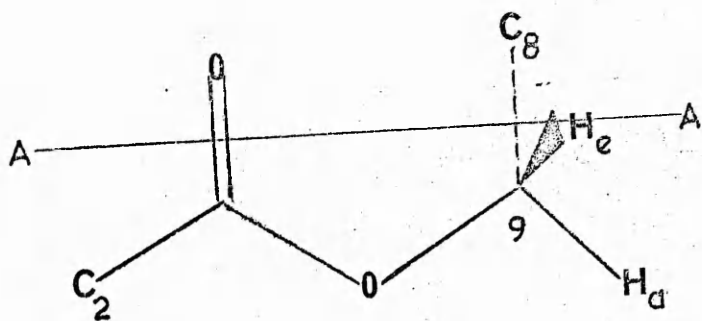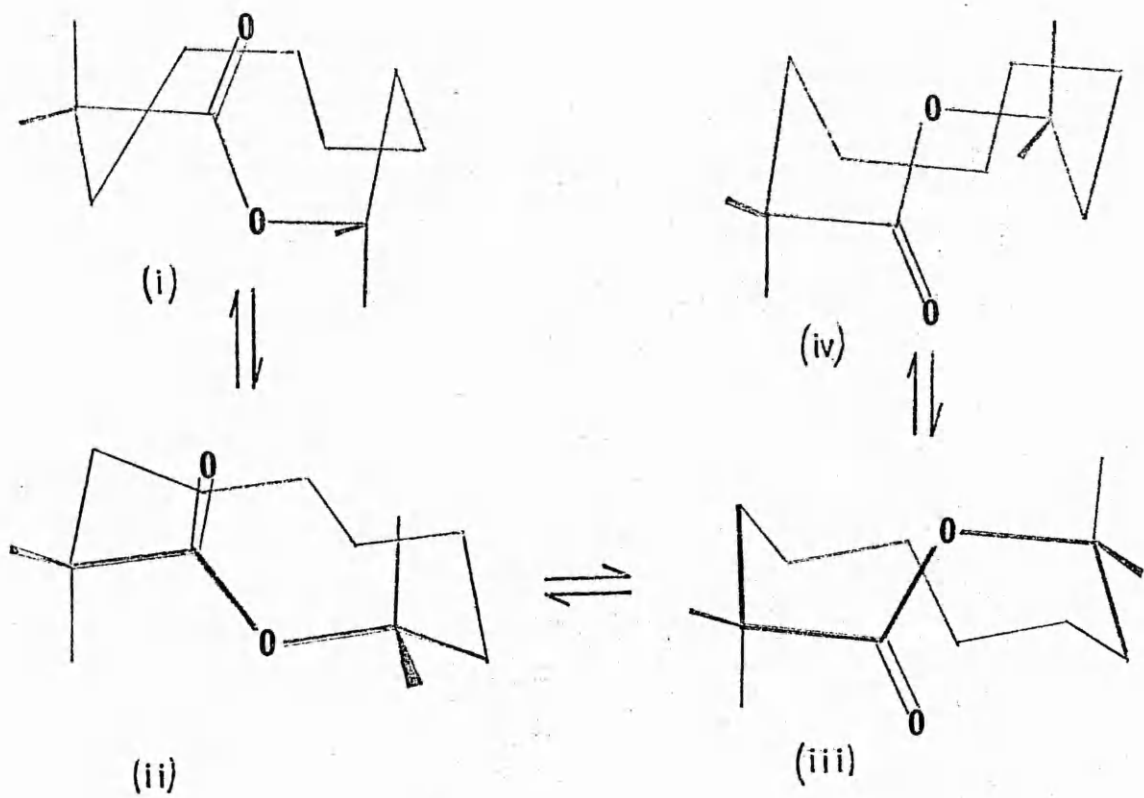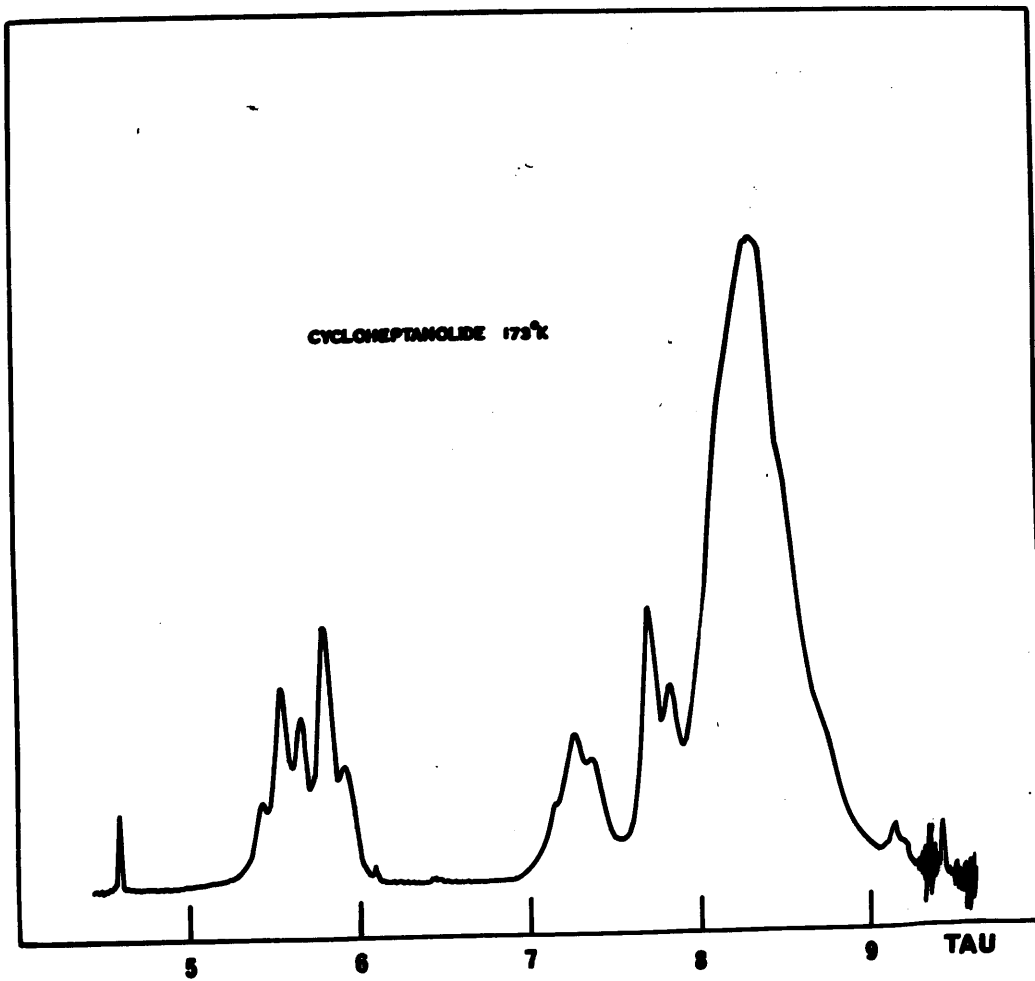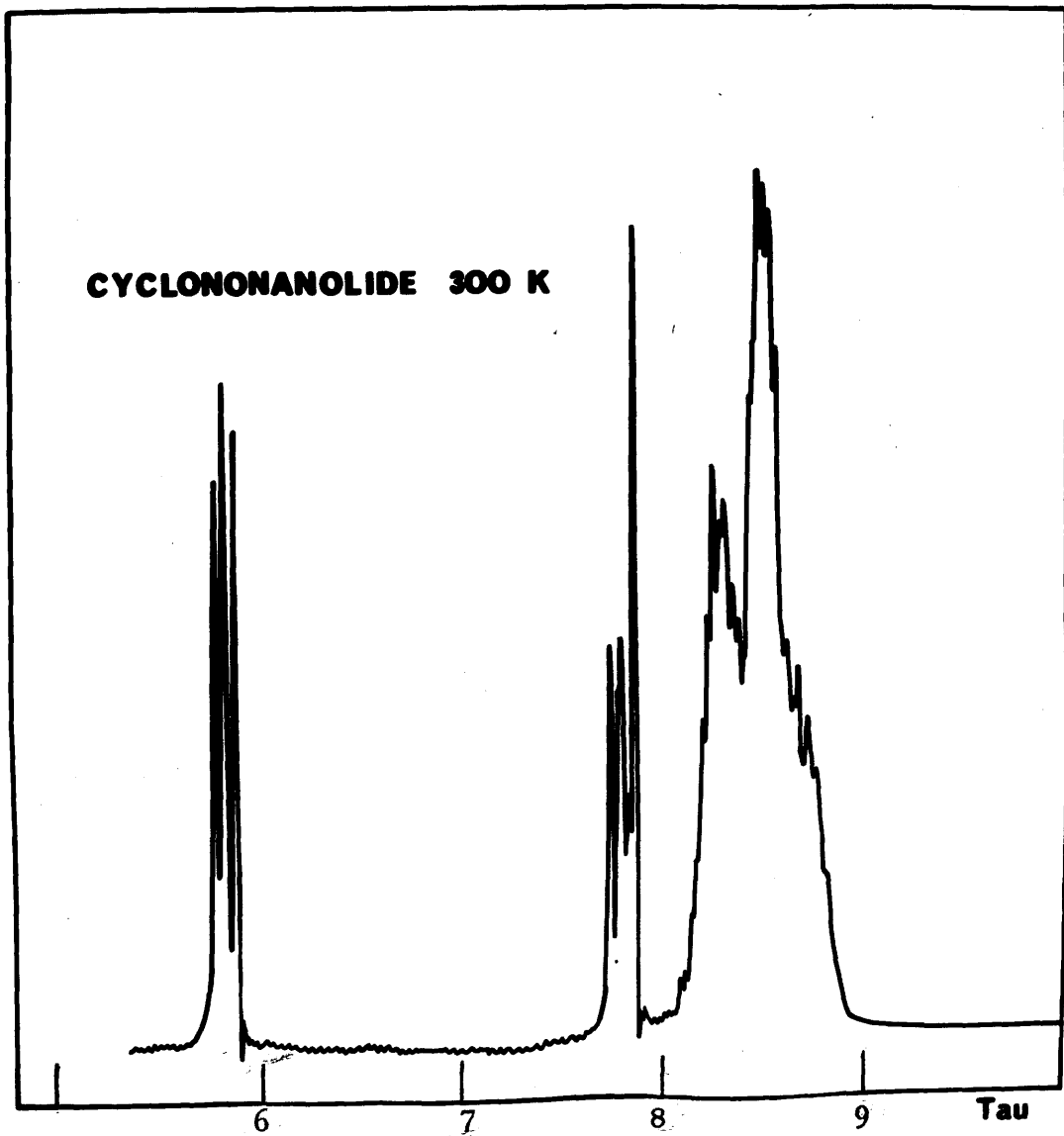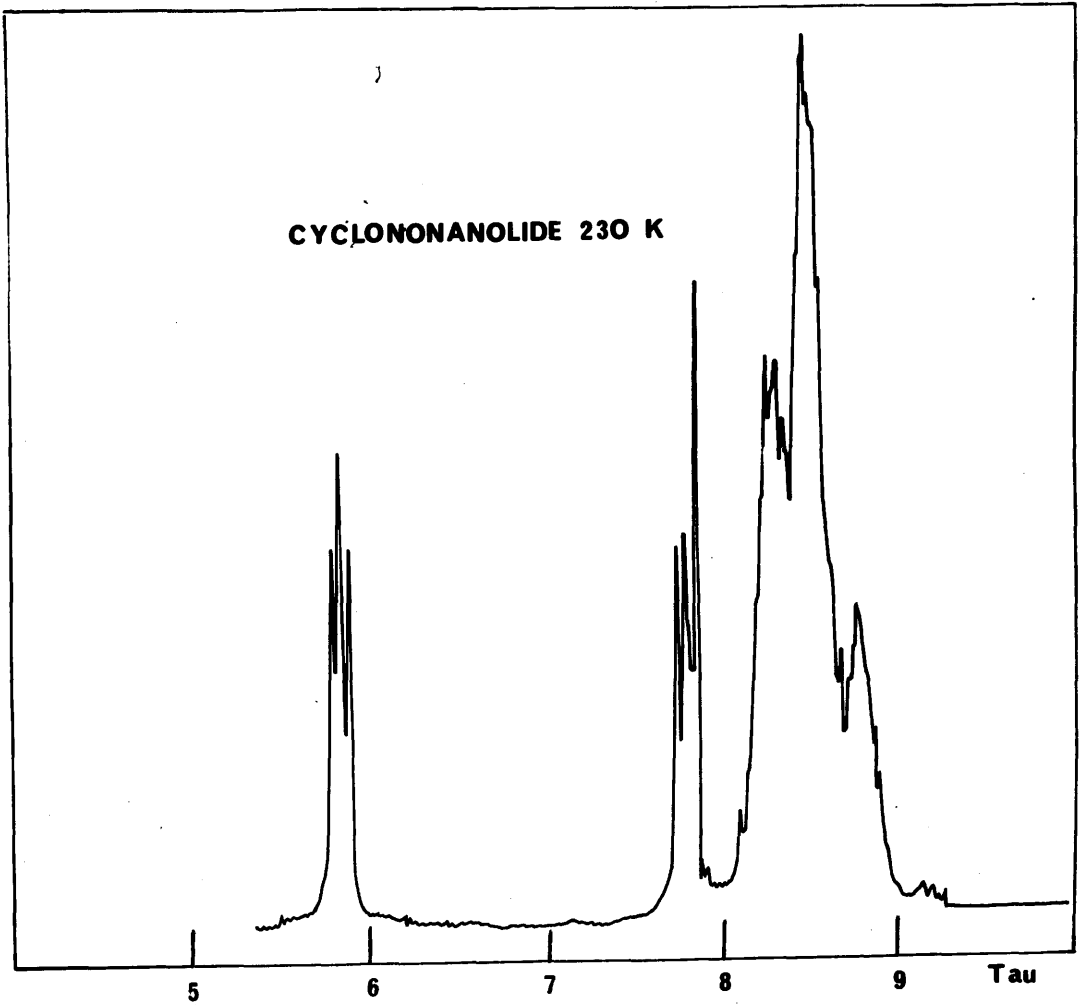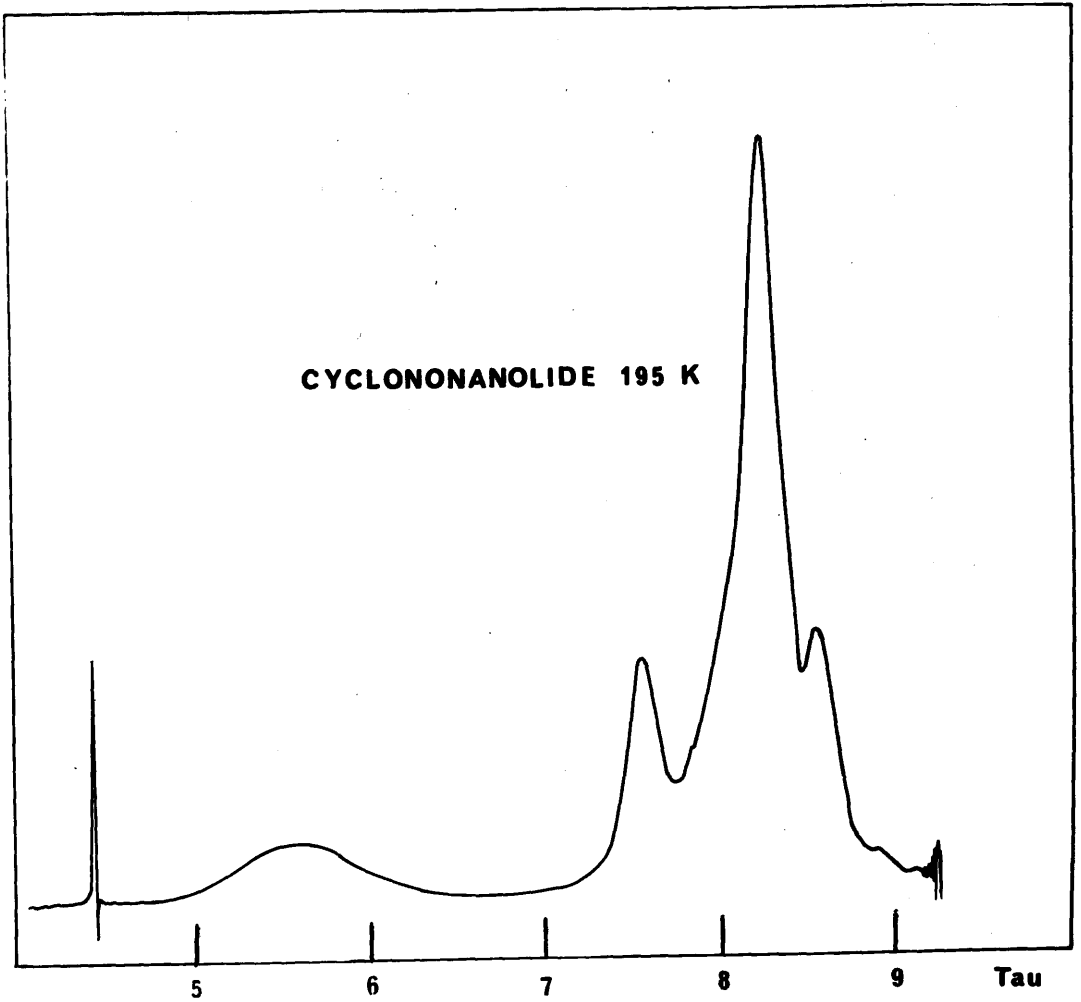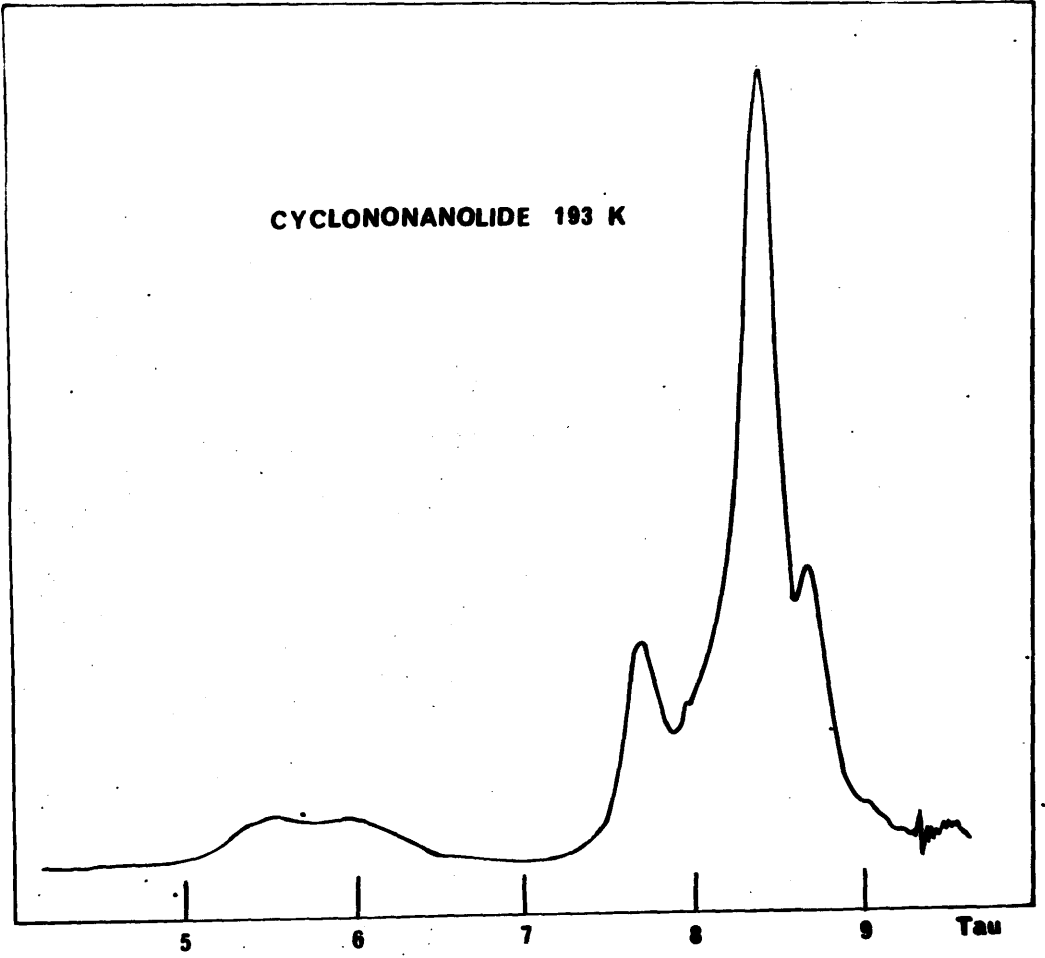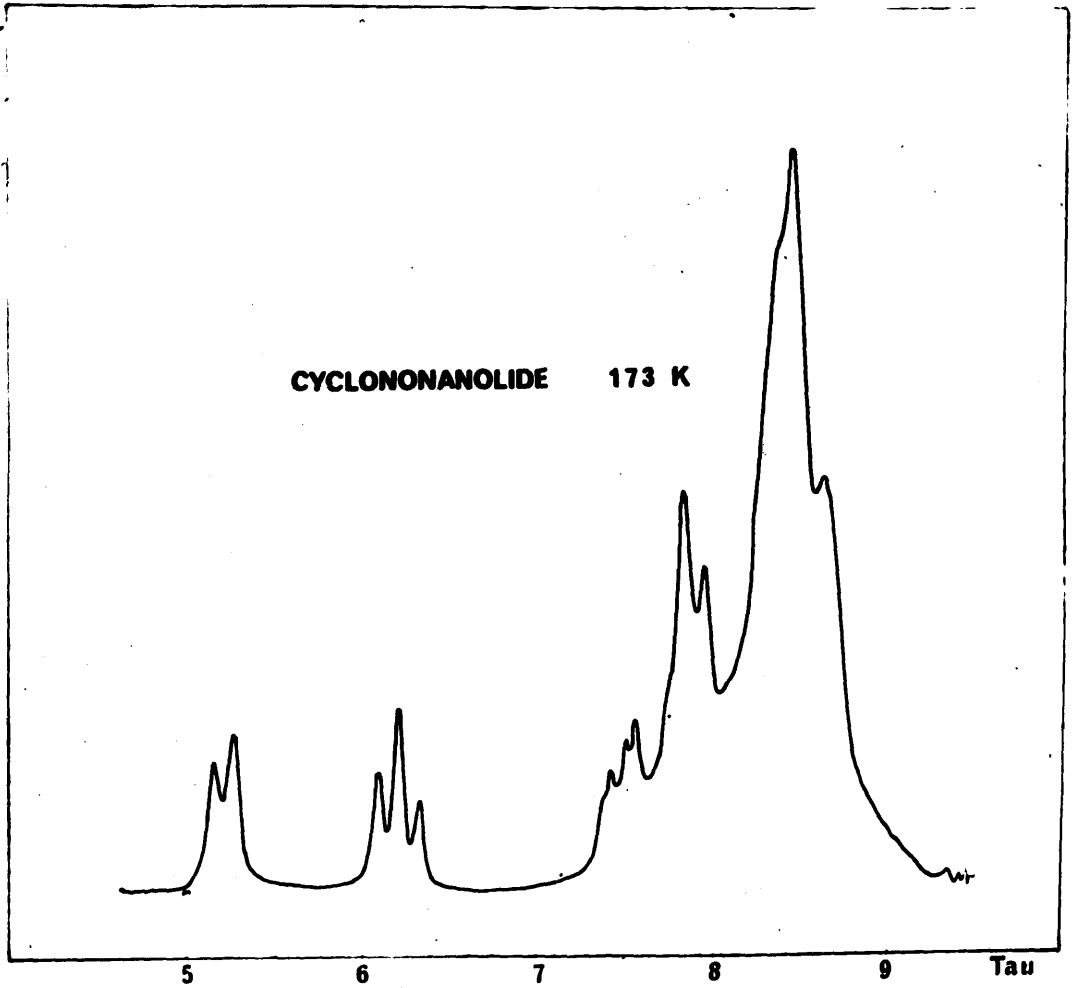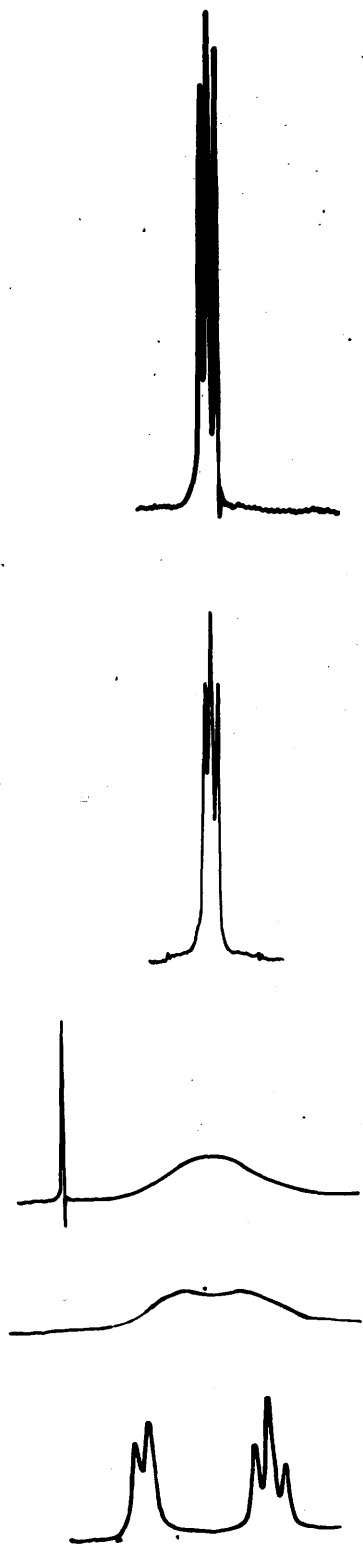
Figure   7

Figure 8

EXPERIMENTAL

All solvents used in the I.R. and U.V. measurements were of "Analar" quality or had been specially purified for spectroscopic studies.

All infra-red measurements were performed on a Perkin-Elmer 225 spectrophotometer fitted with a synchronous motor of speed 14 cm^{-1} / min. Matched cells of 0.0525 mm., path length with sodium chloride windows were employed. The spectral slit width over the frequency range being examined was 0.64 cm^{-1}.

The integrated intensity measurements were made using the P.E. 225 spectrophotometer coupled to a linear log varicord Model 43, fitted with a Photovolt electronic integrator. The intensity values reported in table 2 are the mean of five different measurements on five individually prepared solutions. The uncertainty in the values listed is no greater than $\pm$0.06 intensity units. The assistance of Mrs. F. Lawrie in this part of the work was gratefully appreciated both in carrying out the measurements and in evaluating a number of the results.

The U.V. spectra were measured with a Cary recording spectrophotometer, Model 14, using matched 1.0 cm cells. The maxima quoted are probably accurate to within $\pm$ 1 nm., and the molar absorptivities (ϵ) to about $\pm$ 10%.

The low temperature n.m.r. spectra were recorded on a
Varian H.A. 100 equipped with a variable – temperature probe.
The temperatures were obtained by measuring the chemical
shift of the hydroxyl proton in methanol by means of a Hewlett-
Packard electronic frequency counter and reading off the temperature
on a calibration chart. The assistance of Mr. J. Gall in
recording these spectra was gratefully appreciated.

Baeyer Villiger Oxidation[21] of the Cyclic Ketones (1) n = 5 to 9.

Trifluoroacetic anhydride (10.2 ml., 0.072 mole) was added over 30 minutes from a chilled dropping funnel to a stirred suspension (cooled in an ice bath) of 90% hydrogen peroxide (1.64 ml., 0.05 mole) in dry methylene chloride (10 ml.). After stirring for 30 minutes at ice temperature, the resulting peroxytrifluoroacetic acid solution was transferred to a chilled dropping funnel and added over 1 hour to a stirred suspension of "Analar" anhydrous disodium hydrogen phosphate in dry methylene chloride (40 ml.) containing the cyclic ketone (0.04 mole). The solution was cooled to 0° C during addition and stirred for 3 hours at 0° C and for a further 3 hours at room temperature. (When oxidising cyclopentanone it was only necessary to stir for $1\frac{1}{2}$ hours at ice temperature.) Water (20 ml.) was added to dissolve the disodium hydrogen phosphate and the organic layer separated. The aqueous layer was extracted with methylene chloride (2 x 30 ml.). The methylene chloride solutions were combined, washed with sodium bicarbonate (2 x 20 ml.), brine (2 x 20 ml.) and finally dried.

Evaporation of the methylene chloride afforded the crude

lactones which were purified by distillation, using a short column, under reduced pressure. Final purification of cyclooctanolide and cyclononanolide was achieved by p.t.l.c. (ethyl acetate, pet ether 1 : 9) followed by distillation since it was difficult to separate the starting ketones from these lactones by distillation alone. The lactones were stored in a refrigerator since they were all observed to decompose rapidly on standing.

Purity in each case was established by t.l.c. and g.l.c. (5% QF – 1 and 10% carbowax). T.l.c. was a necessary check since in most cases the major impurities were polymers formed on decomposition which did not show up on g.l.c.

6 – Hydroxy-nonanolide (56) and 6 – Acetoxy-nonanolide (57).

6 – ketononanolide (60), prepared according to the method of Borowitz[17] (60) (717 mg., 3.8 m moles) was stirred with sodium borohydride (8.3 mg. 2.2 m moles) in methanol (20 ml.) for 10 minutes. The methanol was removed as quickly as possible under reduced pressure and brine (25 ml.) was added. The solution was extracted with chloroform (5 x 35 ml.) which was washed with brine and dried. Removal of the solvents under reduced pressure afforded an oily crystalline residue (600 mg.) which consisted of a mixture of starting material and a more polar product as shown

by t.l.c. The product was recovered by p.t.l.c. (ethyl acetate, petroleum ether 60:40) to yield (56) as a crystalline solid (220 mg.), m.p. 76 - 77°C (needles from pet-ether).

$V_{max}(CCl_4)$ 3624, 3605, 1751 cm^{-1}; n.m.r. showed a poorly resolved 1 H doublet (J = 12 Hz) at T 5.30; a 1 H broad singlet at T 6.0 overlapping a poorly resolved 1 H triplet (J = 12 Hz) at T 6.10; and a broad multiplet between T 7.2 and T 9.0.

(Found: C, 63.01; H = 9.33; $C_9H_{16}O_3$ requires C, 62.76; H, 9.36%.)

6 - hydroxy - nonanolide (56) (60 mg.) was allowed to stand overnight at room temperature in acetic anhydride (10 ml.) and dry pyridine (10 ml.). The solvents were removed under reduced pressure and the pale brown oil (62 mg.) purified by p.t.l.c. (ethyl acetate, pet-ether 20:80) to yield 6 -acetoxy - nonanolide (57) (35 mg.).

$V_{max}(CCl_4)$ 2960, 2925, 2860, 1735, 1250 cm^{-1}; n.m.r. showed 3 H singlet at T 8.0; 1 H diffuse triplet at T 6.10; 1 H diffuse doublet (J = 11 Hz) at T 5.30; 1 H broad singlet (W = 30 hz) at T 4.70.

2($4'$ - Acetoxy n - Butyl) - Cyclopentanone (62).

A mixture of 1 - pyrrollidinocyclopentene (46.5 g., 0.34 moles) and 4 - bromobutyl - acetate[34] (120 g., 0.7 moles) in toluene (470 ml.) was heated at reflux temperature under nitrogen for

15 hours. Water (95 ml.) was added and refluxing continued
for a further 50 minutes. The reaction mixture was cooled and
10% sulphuric acid added until the solution was acidic. The
mixture was extracted with ether (5 x 290 ml.) and the combined
ether extracts washed with brine. After drying, most of the
solvents were removed on a rotary evaporator under reduced
pressure.

The residue was distilled under reduced pressure (10 mm Hg.),
using a short fractionating column. The forerun was mainly
bromobutyl acetate (g.l.c. 5% QF - 1) and the required keto-
acetate (62) (15 g.) distilled between 143 - 145° C, and
showed one peak on g.l.c. (5% QF - 1).

V_{max}(film) 1735, 1240 cm^{-1}; n.m.r. showed multiplet
between T 7.5. and T 9.0 with a 3 H sharp singlet at T 8.0;
2 H triplet (J = 6 Hz) at T 5.93.

(Found: C, 66.48; H, 8.92; $C_{11}H_{18}O_3$ requires C, 66.64; H, 9.15%.)

2 - (4' Hydroxybutyl) Cyclopentanone (63) and 2 - Oxabicyclo -
(5. 3. 0.) Dec - 1 (7) - ene (64).

A solution of (62) (20.32 g., 0.1 mole) in methanolic potassium
hydroxide (KOH (9 g.) dissolved in water (7 ml.) and diluted with
methanol (120 ml.)) was kept at room temperature for 24 hours.
The methanol was removed under reduced pressure and the residue

thoroughly extracted with ether. After drying the ether was removed under reduced pressure and a colourless oil (63) (15 g.) remained which showed one spot on t.l.c. less mobile than starting material (ethyl acetate, pet-ether 30:70).

V_{max} (film) 3470, 1725 cm^{-1}.

(63) was used without further purification and taken up in dry benzene (80 ml.). p - toluene - sulphonic acid (30 mg.) was added and water, approximately (1 ml.) was azeotropically distilled out during three days. The benzene solution was washed with sodium carbonate solution, dried and distilled to give (64) (5 g.) as a colourless oil; b.p. 70 - 73° C (10 - 12 mm Hg.) g.l.c. one peak (5% QF - 1, 50° C).

V_{max}(CCl$_4$) 2920, 1679, 1316, 1297, 1240, 1042 cm^{-1}; n.m.r. showed 2 H triplet at T 6.5; 14 H broad multiplet at T 7.4 - 8.8.

Mass spectrum: Mol. weight 138; $C_9H_{14}O$ requires 138.

Because of volatility it was not possible to obtain a good combustion analysis.

5 - Keto-nonanolide (61)

(64) (1.2 g. 0.008 mole) in dry methylene chloride (4 ml.) was added over 30 minutes to m - chloroperbenzoic acid (85%, 5.40 g., 0.026 mole) in methylene chloride (28 ml.). The solution was stirred overnight at room temperature and the m - chlorobenzoic

acid filtered off. The solution was washed with saturated potassium iodide (2 x 10 ml.), sodium thiosulphate (2 x 10 ml.) and sodium carbonate solutions (2 x 10 ml.). After washing with brine and drying, removal of the solvents under reduced pressure afforded a pale brown oil (1.4 g.). The oil was purified by p.t.l.c. (ethyl acetate, petroleum ether 50:50) to give (61) (410 mg.).

$V_{max}(CCl_4)$ 1747, 1713 cm^{-1}; n.m.r. showed 2 H triplet at τ 6.04; broad overlapping multiplets centred at τ 7.4 and τ 8.2.

Mass spectrum: Mol. weight 170; $C_9H_{14}O_3$ requires 170.

(Found: C, 63.33; H, 8.23; $C_9H_{14}O_3$ requires C, 63.51; H, 8.29%.)

Action of Sodium Borohydride on 5 – Keto – nonanolide (61).

(61) (50 mg.) was dissolved in ethanol (1 ml.) and sodium borohydride (7 mg.) added. The solution was stirred at room temperature and the solution monitored by t.l.c. every 15 minutes. The reaction was very slow and after about 3 hours some very polar products had formed. Work up in the usual way afforded a colourless oil (30 mg.) which was mainly starting material, (IR and t.l.c. comparison).

Action of Lithium Aluminium t – Butoxide on the 5 – Keto – nonanolide (61).

(61) (50 mg., 0.3 m mole) in dry T.H.F. was added to a stirred suspension of lithium aluminium t – butoxide (127 mg., 0.45 m mole)

in dry T.H.F. (1 ml.) under nitrogen. After stirring overnight, water (10 ml.) was added and the solution extracted with ether. After drying and removal of solvents, a colourless oil (40 mg.) was recovered which was mainly unchanged starting material, (I.R. and t.l.c. comparison).

Catalytic Hydrogenation of 5 – Keto – nonanolide (61).

(61) (120 mg.) was dissolved in "Analar" acetic acid (5 ml.), platinum oxide (70 mg.) was added and the mixture stirred under an atmosphere of hydrogen for 5 days.

The catalyst was removed by filtration and the acetic acid distilled of by azeotroping with benzene under reduced pressure. A pale brown oil (89 mg.) was recovered which showed starting material together with a product of similar polarity to the 6 – hydroxy – nonanolide (56) as judged by t.l.c. The product was isolated by p.t.l.c. (ethyl acetate, pet-ether 60:40) to yield a colourless oil (20 mg.).

$V_{max}(CCl_4)$ 3630, 3520, 3460, 1050, 1090 cm^{-1}; n.m.r. showed singlet at T 8.0 (disappears on addition of D_2O); high field multiplet T 5.8 – T 9.0 and low field multiplet T 5.8 – T 7.0.

REFERENCES

1. R. Huisgen and H. Ott,

    Tetrahedron, 1959, 6, 253.

2. T. Burer and H. Gunthard,

    Helv. Chim. Acta., 1956, 39, 356.

3. H. E. Hallam and Christine M. Jones,

    J. Mol. Structure, 1, (1967-68), 413.

4. J. B. Hendricksen,

    J. Amer. Chem. Soc., 1967, 89, 7036.

5. J. D. Dunitz, "Perspectives in Structural Chemistry"

   Vol. 2, J. Wiley and Sons (in press).

6. K. K. Cheung, K. H. Overton, and G. A. Sim,

    Chem. Comms., 1965, 634.

7. R. W. Kilb, C. C. Lin, and E. B. Wilson Jr.,

    J. Chem. Phys., 1957, 26, 1695.

8. R. F. Curl Jr.,

    J. Chem. Phys., 1959, 30, 1529.

9. J. B. Hendricksen,

    J. Amer. Chem. Soc., 1961, 83; 4537.

10. J. D. Roberts,

    Angew. Chem., (Int. Ed.) 1967, 556.

11. C. G. Overberger and H. Kaye,

        J. Amer. Chem. Soc., 1967, 89, 5646.

12. G. Snatzke, H. Ripperger, Chr. Horstmann, and K. Schreiber,

        Tetrahedron, 1966, 22, 3103.

13. F. A. L. Anet, M. St. Jacques,

        J. Amer. Chem. Soc., 1966, 88, 2585.

14. A.C. Cope, C. R. Ganellin and H. W. Johnson Jr.,

        J. Amer. Chem. Soc., 1962, 84, 3191.

15. A.C. Cope and B. A. Pawson,

        J. Amer. Chem. Soc., 1965, 87, 3649.

16. A.C. Cope et al.,

        J. Amer. Chem. Soc., 1965, 87, 3644.

17. I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp and G. J. Williams,

        J. Org. Chem., 1966, 31, 3032.

18. P. Ganis and J. D. Dunitz,

        Helv. Chim. Acta., 1967, 50, 2379.

19. N.l. Owen and N. Sheppard,

        Proc. Chem. Soc., 1963, 264.

20. G. Binsch and J. D. Roberts,

        J. Amer. Chem. Soc., 1965, 87, 5157.

21. E. E. Smissman, J. F. Muren and N. A. Dahle,

        J. Org. Chem., 1964, 29, 3517.

22. T. L. Brown,

    Spectrochim. Acta., 1962, 18, 1615.

23. K. Noack,

    Spectrochim, Acta., 1962, 18, 1625.

24. W. D. Closson and P. Haug,

    J. Amer. Chem. Soc., 1964, 86, 2384.

25. H. S. Gutowsky and C. H. Holm,

    J. Chem. Phys., 1956, 25, 1228.

26. J. W. Emsley, J. Feeney and L. H. Sutcliffe,

    "High Resolution Nuclear Magnetic Resonance Spectroscopy"

    Volume 1, Pergamon Press, 1965, Chapter 9.

27. I. C. Calder and P. J. Garret,

    J. Chem. Soc., (B), 1967, 660.

28. S. Glasstone, K. J. Laidler and H. Eyring,

    "The Theory of Rate Processes," McGraw – Hill

    Book Co., Inc., London, 1941, Chapter 1.

29. K. B. Wiberg,

    J. Amer. Chem. Soc., 1965. 87, 1070.

30. G. J. Karabatsos, G. C. Sonnichsen, N. Hsi and D. J. Fenoglio,

    J. Amer. Chem. Soc., 1967, 89, 5067.

31. F. A. L. Anet and J. S. Hartman,

    J. Amer. Chem. Soc., 1963, 85, 1204.