Synthesis of Adamantancid Dienones: Decarboxylation

studies in 2,7-Dioxabicyclo[2.2.1]systems

A thesis presented by
James Edward Miller
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Department of Chemistry,
The University of Leicester. May, 1977.
To my Mother and Father with thanks
for all their help.
STATEMENT

The accompanying thesis submitted for the degree of Ph.D. entitled Synthesis of Adamantanoid Dienones: Decarboxylation studies in 2,7-Dioxabicyclo[2,2,1]heptanes is based on work conducted by the author in the Department of Chemistry of the University of Leicester mainly during the period between October 1973 and October 1976.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references. None of the work has been submitted for another degree in this or any other university.

Part of this research has been the subject of the following publications:


Signed

James Miller

May, 1977.
Acknowledgements

I wish to thank my supervisor, Dr. R.S. Atkinson, for his excellent supervision and inspiration throughout the whole of this research.

I would also like to thank Mrs Anne Crane for help with the diagrams, all the members of the Department who have assisted me during the last three years, and particularly Sue Jackson for her patience and typing.

Finally, I am much indebted to the S.R.C. for my grant.
### Abbreviations used in the Diagrams and Tables

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzyl</td>
</tr>
<tr>
<td>Ar</td>
<td>p-methoxyphenyl</td>
</tr>
<tr>
<td>Ar'</td>
<td>p-hydroxyphenyl</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyanobenzoquinone</td>
</tr>
</tbody>
</table>
# CONTENTS

## Introduction

<table>
<thead>
<tr>
<th>Part 1</th>
<th>Synthesis of the Adamantanoid Dienones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 1</td>
<td>Attempted Stereospecific Synthesis of the Bromide (5) <em>via</em> the Cyclopentenone (28).</td>
</tr>
<tr>
<td>Chapter 2</td>
<td>Synthesis of the Dienones <em>via</em> a nonstereospecific synthesis of the Bromide (5).</td>
</tr>
</tbody>
</table>

## Part 2

<table>
<thead>
<tr>
<th>Chapter 1</th>
<th>Synthesis and decarboxylation of 6-isobutyl-1,4-dimethyl-2,7-dioxabicyclo[2,2,1]heptane-6-carboxylic acids (67) (68).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 1</td>
<td>Identification of the endo- and exo-6-carboxylates (23) (24).</td>
</tr>
<tr>
<td>Chapter 2</td>
<td>Decarboxylation Review.</td>
</tr>
<tr>
<td>Chapter 3</td>
<td>Decarboxylation studies of the two bicyclic acetal acids (67) (68).</td>
</tr>
<tr>
<td>Chapter 4</td>
<td>Kinetic Results.</td>
</tr>
<tr>
<td>Chapter 5</td>
<td>Decarboxylation Results. Discussion and Mechanistic Interpretation.</td>
</tr>
</tbody>
</table>

## Experimental

Contents and general information. 92

| Part 1a | Synthesis of the cyclopentenones. 95 |
| Part 1b | Synthesis of the dienones. 105 |
| Part 2 | Bicyclic acetal work. 116 |

| Appendix 1 | 126 |
| Appendix 2 | 132 |
| References | 136 |
Introduction

The research described in this thesis stems from previous investigations into the synthesis of spiro- and bridged-ring dienones. The double intramolecular aryl participation (Ar^-6) that leads to formation of the spiro-dienone (2) from the dibromide (1) has been reported\(^1\), and an attempt at extending this reaction to give direct entry into bridged ring compounds (3 → 4) was made\(^2\).

\[
\text{HO}{\text{Br}}{\text{Br}}{\text{HO}} \quad \rightarrow \quad \text{O} = \text{C} = \text{C} \quad \text{HO}
\]

\[
\text{OH}
\]

During attempts at this latter double Ar^-6 participation using crude dibromide (3), a compound was isolated in low yield from the reaction mixture that gave similar spectral data to simple dienones, and which was formulated as the adamantancoid dieneone (7). As this dieneone was only isolated when crude dibromide was used, and never when the dibromide had been rigorously purified, the dieneone precursor was evidently an impurity present in the dibromide.
Under the conditions used to form the dibromide (HBr saturated at 0°, 130°), the most likely impurity present which could give rise to the adamantanoid dienone was considered to be the bromide (5), formed by an ionization of a bromide, hydride migration and electrophilic aromatic substitution on a p-hydroxyphenyl ring. In the subsequent base treatment the bromide could then undergo a participation involving desaromatisation to eventually give the adamantanoid dienone (7) (scheme 1, path A). Some evidence to support this came from isolation of the dibenzobicyclic compound (9) in low yield during initial attempts to synthesise the dibromide (scheme 1, path B). This could be formed by a second hydride shift in (5) and electrophilic attack on the meta position of the remaining p-hydroxyphenyl ring.

However conclusive identification and assignment of the adamantanoid dienone structure (7) was not achieved, and little support was forthcoming on the postulated precursor in the reaction scheme.

The work described in the first part of this thesis is the synthesis of the adamantanoid dienones shown below from the iodide corresponding to the bromide (5).
The work described in the second part of the thesis is the synthesis and decarboxylation of the exo- and endo-2,7-dioxabicyclo[2,2,1]heptane-6-carboxylic acids (67) (68). This bicyclic acetal system was encountered during a route to the above dienones, and proved interesting enough to merit further study.

\[ R = -\text{CH}_2\text{CH(CH}_3)_2 \]
Part 1

Synthesis of the Adamantanoid Dienones

Chapter 1

Attempted Stereospecific Synthesis of the Bromide (5) via the Cyclopentenone (28)

Our initial goal was a stereospecific synthesis of the phenolic bromide (5) since it is this stereoisomer that is required for the Ar₁₋₆ participation and which is presumed to be the precursor of the adamantanoid dienone. Although a stereospecific synthesis of the bromide is to be preferred it is noteworthy that the isomer (6) with the p-hydroxyphenyl and bromomethyl groups trans cannot undergo the intramolecular participation reaction due to the unfavourable geometry which would be involved. Synthesis of carbocyclic spiro-dienones via the Ar₁₋₆ participation reaction is well documented in the literature⁴, and it was thought that the transformation of the bromide into the dienone (7) would present few problems.
A synthetic scheme devised for (5) is that shown in scheme 2.

The key reactions of the scheme are the cyclization reaction of the cyclopentenone to give the benzobicyclo[3,2,1]-octane system (step 6), followed by an oxidative cleavage to give the tetrahydronaphthalene derivative in which the modifiable functional groups are in the required cis-position. There are several known precedents for this type of cyclization, and α,β-unsaturated ketones of the type below cyclize readily under acid conditions (10 → 11).

None of the above examples could be directly compared with the present cyclopentenone case in which electrophilic attack and ring closure at the deactivated meta-position of the p-methoxyphenyl ring demands a fairly rigid geometry, but model studies showed that the presumed perpendicular approach of the aromatic ring to the carbonium ion could be achieved.

The synthesis of the cyclopentenone via the 1,4-diketone contains no innovative reactions and there are numerous examples of both the synthesis and cyclization of 1,4-diketones. The only likely problem arises with the regioselectivity of the 1,4-diketone cyclization. Conditions for good yields of cyclopentenones appear to be critical, and in principle cyclization can occur to form both the tetrasubstituted enone
(12) and the trisubstituted enone (13). The latter was not considered a serious problem as work by McCurry and Singh\(^9\) has shown that the cyclization of 1,4-diketones of the type below will always yield the tetrasubstituted enone (12) in preference to the trisubstituted enone (13), as (12) is both the kinetically and thermodynamically favoured product.

\[
\begin{align*}
\text{12} & \quad \text{Me} \\
\text{13} & \quad \\
\end{align*}
\]

The final steps of the scheme, the oxidative cleavage, reduction and formation of the bromide were considered to contain no insurmountable steps.

**Results**

The benzyl ethyl malonate (14) was prepared and the anion formed from this using NaH-DMF gave the acyl malonate (16) when treated with p-methoxyphenylacetyl chloride. Hydrogenation to the ketoester (17) occurred readily, but alkylation of this with anisyl chloride gave the required ketoester (19) in only poor yield. Presumably the considerable scope in this reaction for cross condensations, alkylation at positions other than C-2, and dialkylation, led to the low yield as many products were formed which were hard to separate. This, coupled with the fact that none of the yields in the previous steps were good, and all the compounds were
hard to purify, encouraged us to synthesise a model cyclopentenone to test the key cyclization step (step 6, scheme 2).

It was decided that the simplest model cyclopentenone to synthesise was the 3-methyl-5-((p-methoxybenzyl)cyclopent-2-enone (28).

![Chemical Structure](image)

The synthesis of (28) was again based on cyclization of a 1,4-diketone derived from ethyl acetoacetate, but this time there were two modes of cyclization leading to both the required 3,5-disubstituted cyclopentenone (28) and to the 3,4-disubstituted cyclopentenone (29). It was hoped that cyclization conditions could be found which would give the 3,5-disubstituted cyclopentenone as the product, and that if both isomers were obtained they would be separable by chromatography or crystallisation. Failing this a reaction on the isomeric mixture would indicate if any cyclization was occurring, and any benzobicyclic product should be separable from the unchanged 3,4-disubstituted cyclopentenone.

The synthesis evolved as shown in scheme 3.

Ethyl acetoacetate was successfully alkylated at the 2-position using NaH-DMF and anisyl chloride, and this product (20) was reacted with chloroacetone under similar conditions. As this latter reaction proved to be unreliable and gave at best only a low yield of the required 1,4-diketone, perhaps because of carbene formation or Darzens type condensations between the reactive chloride and any neutral ester or ketone
Scheme 1

\[
\text{ArCH}^\text{Cl} + \text{CO}_2\text{Et} \xrightarrow{\text{NaH, DMSO}} \text{ArCH}_2\text{CO}_2\text{Et} \quad \xrightarrow{\text{CH}_3\text{COCH}_2\text{Cl, NaH, DMSO}} ?
\]

\[\begin{align*}
\text{NaH, DMSO} & \quad \xrightarrow{\text{CH}_3\text{C}:\text{CH}_2(\text{CH}_2\text{Cl})} \\
\text{O}_3 & \quad \xrightarrow{\text{NaOH}} \\
\end{align*}\]

\[\begin{align*}
\text{ArCO}_2\text{Et} \xrightarrow{\text{NaOH}} \text{ArCO}_2\text{Et} \quad \xrightarrow{\text{OsO}_4} \\
\text{NaOMe} & \quad \xrightarrow{\text{NaOH}} \\
\end{align*}\]

\[\begin{align*}
\text{ArCO}_2\text{Et} + \text{ArCO}_2\text{Et} \xrightarrow{\text{NaBH}_4} \\
\text{ArCO}_2\text{Et} + \text{ArCO}_2\text{Et} \xrightarrow{\text{NaBH}_4} \\
\end{align*}\]
present in the reaction mixture, the alkylation was repeated using methallyl chloride. This procedure gave the \( \gamma,\delta \)-unsaturated ketone (21) in good yield. Attempted decarboxethoxylation at this stage gave the lactone (22), and this step was therefore postponed till later. Oxidative cleavage of the \( \gamma,\delta \)-olefinic bond was first attempted using OsO\(_4\) peridate and gave a compound which had only one i.r. carbonyl band (ester) and no n.m.r. ketone methyl signals. This was later identified as a mixture of the epimeric bicyclic acetal systems (23,24). Although this was an unexpected result, a literature search revealed that formation of bicyclic acetal systems from hydroxylation of \( \gamma,\delta \)-unsaturated ketones is a well documented reaction. The mechanism of this reaction is discussed in the second part of this thesis.

It was hoped that basic decarboxethoxylation and then acid opening of the acetal ring could be used to continue the synthesis of the cyclopentenone. Attempted hydrolysis using NaOH-H\(_2\)O-EtOH indicated that one acetal epimer remained unchanged whilst the other formed a product characterized by a hydroxy-group (i.r. 3440cm\(^{-1}\), broad), no i.r. carbonyl or carboxy-bands, and an n.m.r. containing singlets at \( \delta \) 3.25 (2H) and \( \delta \) 1.70 (3H, broadened). These were assigned to the hydroxymethyl group and olefinic ring methyl, respectively, in the dihydrofuran structure (25).

Evidently one acetal epimer was unexpectedly stable to base, and this is discussed in greater detail in part two.

The 1,4-diketone (26) (i.r. 1735, 1715cm\(^{-1}\)) was eventually obtained from the \( \gamma,\delta \)-unsaturated ketone (21) by ozonolysis, and various attempts at the cyclization of the diketone to
the cyclopentenone (28), both before and after decarboxethoxylolation, showed that the best yield of the required 3,5-disubstituted cyclopentenone (28) was obtained by first refluxing the diketone (26) with dilute aqueous sodium hydroxide to form the decarboxethoxylated 1,4-diketone (27) (i.r. 1710 cm^{-1}) and then cyclizing this by refluxing in sodium methoxide solution. The product formed by this method was a mixture of the 3,5-disubstituted cyclopentenone (28) and the 3,4-disubstituted cyclopentenone (29) (ratio 3:2) from which the isomers were separated by chromatography. Not surprisingly identification of the isomers was not immediately obvious from the n.m.r. data. The 3,4-disubstituted isomer has one C-4 proton and two C-5 protons, whilst the situation is reversed in the 3,5-disubstituted isomer, and all the protons would be expected at similar chemical shifts.

The n.m.r. data (table 1) shows a difference in the coupling observed for the C-2 olefinic protons.
If it is assumed that the allylic coupling constants to the C-3 methyl and the C-4 proton(s) are equal or nearly equal, which is reasonable for this type of system, then the C-2 olefinic proton in the 3,4-disubstituted isomer (29) is allylically coupled to four protons with the same coupling constant (3 protons, C-3 methyl, and 1 proton, C-4 ring position), and the C-2 olefinic proton in the 3,5-disubstituted isomer (28) is allylically coupled to five protons with the same coupling constant (3 protons, C-3 methyl, and 2 protons, C-4 ring position). This would give rise to a 1:4:6:4:1 splitting pattern for (29) and a 1:5:10:10:5:1 splitting pattern for (28), which could appear in the n.m.r. as the observed broadened triplet and broadened quartet respectively (Fig. 1). If the coupling constants are not equal, then complex splitting patterns not resembling a triplet or quartet should be observed for both isomers. Thus a tentative structural assignment was made on this basis.
To try and secure the identification, an n.m.r. shift study was done on each isomer using the praseodymium (DPM)$_3$ shift reagent. Considerable peak broadening, and obscuring of the signals by both the methyl singlet and the signal due to the shift reagent meant that identification of all the peaks was impossible. However, the studies did show that the 3,5-disubstituted isomer (28) had a broad signal (1 proton, integration relative to the p-methoxy-group) shifting upfield faster than a second broad signal (2 protons), whereas this situation was reversed in the 3,4-disubstituted isomer (29). Also the aromatic signal in (28) collapsed to a singlet and then became a widely spaced quartet as the
concentration of shift reagent was increased, whereas in (29) a similar molar ratio of shift reagent to substrate only collapsed the aromatic signal to a singlet. This can be explained by assuming the ketone as the co-ordination site of the shift reagent. Then (29) has one C-5 proton and the aryl ring in close proximity to the shift reagent co-ordination site, whereas (28) has two C-5 protons close to the co-ordination site, and the aryl ring further away.

As this supported the tentative structural assignment made from the allylic coupling n.m.r. data above, cyclization attempts on (28) were attempted using phosphorus pentoxide-methane sulphonic acid (reagent a), aluminium trichloride (reagent b), and polyphosphoric acid (reagent c), under a wide variety of conditions (see table 5, p128). Under none of these conditions was there any sign of the required benzobicyclic system (31) in an n.m.r. analysis of the crude products: a benzobicyclic system should be clearly visible in the n.m.r. due to the new bridgehead methyl group (expected δ1.2, s), the lack of olefinic protons, and the change in splitting pattern and relative integration of the aromatic resonances.
The cyclization attempts either gave unchanged starting material, polymeric tars, or a mixture of both. An attempt to cyclize (29) using the same reagents, just in case our structural assignments were wrong, also gave no n.m.r. peaks characteristic of the required product and again only unchanged starting material, polymeric tars, or mixtures of both were obtained.

Failure to form the benzobicyclic system could be due to two reasons: the first is that in the highly acidic conditions used, protonation or complexation at the oxygen atoms of the methoxy-group is virtually complete, resulting in a deactivation of the aryl ring. Evidence for this comes from recent work by Katritzky on the reaction below

\[
\begin{align*}
\text{R}^1 \quad \text{N} \quad \text{R}^2 \\
\text{R}^3 \quad \text{R}^3 \\
\text{R}^1 \quad \text{N} \quad \text{R}^2 \\
\text{R}^3 
\end{align*}
\]

He found that cyclization involving a p-methoxyphenyl ring \((\text{R}^3=\text{O}Me)\) would only occur in poor yield under conditions (trifluoromethanesulphonic acid - heat) that completely cyclized unsubstituted and p-halogenated phenyl rings, and concluded that the p-methoxy-group was nearly completely protonated under his reaction conditions and was strongly deactivating.

The second reason could be that the initial delocalized carbonium ion (32) formed by protonation at the carbonyl
oxygen is more stable than the carbonium ion (33) formed after electrophilic attack on the ring, thus reducing any driving force for the reaction.

Attempts to remove the latter possibility by selective reduction of the cyclopentenone (28) to the unsaturated alcohol (34), using both aluminium hydride and later sodium borohydride, failed, as only the saturated alcohol (30) was formed.

This route to the dienones was abandoned at this stage as the results from the attempted cyclization to form the benzobicyclic system were very discouraging. It is noteworthy
that in Katritzky's reaction (which had not been published at this time) cyclization occurs in a rigid bicyclic system in which the aryl ring is held in close proximity to the site of the developing carbonium ion, to form a five membered ring. In the cyclopentenone (28) the aryl ring is free to rotate away from the vicinity of the cyclopentenone ring, although cyclization produces a six membered ring.
Chapter 2

Synthesis of the Dienones via a nonstereospecific synthesis of the Bromide (5)

Due to the failure of the stereospecific bromide synthesis a less ambitious synthesis of this bromide (5) was undertaken based on dimethyl malonate (scheme 4).

A disadvantage of this scheme was that it was not planned to be stereospecific and would be expected to lead to a mixture of both the bromides (5) and (6), with unavoidable reduction in the yield of the required stereoisomer (5). Separation of the bromides (5) and (6) was not envisaged as presenting any serious difficulty because even if fractional crystallisation or chromatography failed, the mixture could be used in the attempted participation reaction and any dienone products arising from (5) ought to be easily separable from the unchanged bromide (6).

The initial steps in the scheme as far as the dichloride (37) are all examples of well documented types of reaction, and no problems were foreseen for these steps, but both the alkylation of the malonate derivative with the dichloride (step 4) and the intramolecular cyclization (step 5) of the adduct are reactions in which problems could easily arise. However, the simplicity of the scheme, which uses a common alkylated malonate unit for the construction of both halves of the molecule (38) was appealing.

Experimentally the first part of the scheme evolved as shown in scheme (5). Alkylation of the dimethyl malonate with anisyl chloride (step 1) went in excellent yield after problems arising from disalkylation had been resolved. Reduction
Scheme 5

Scheme description:

1. Reaction of CO₂Me with clorinated aryl group (ArCl) in the presence of NaH in DMSO to form intermediate 35.
2. Reduction of 35 with LiAlH₄ to form 36.
3. Chlorination of 36 with POCl₃ and Pyridine to form 37.
4. Reaction of intermediate 38 with LiAlH₄ to form 39.
5. Treatment of 39 with NaCl in DMSO to form 40.
6. Hydrolysis of 40 with H⁺ to form 41.
7. Reduction of 41 with LiAlH₄ to form 42.
8. Hydrolysis of 42 with H⁺ to form 43.
9. Reaction of intermediate 44 with LiAlH₄ to form 45.
11. Reaction of intermediate 47 with POCl₃ and Pyridine to form 48.
12. Reduction of 48 with LiAlH₄ to form 49.
13. Hydrolysis of 49 with H⁺ to form 50.

Chemical structures and reagents:

- CO₂Me
- ArCl
- NaH
- DMSO
- LiAlH₄
- NaCl
- DMSO
- POCl₃
- Pyridine
- H⁺
of the diester (step 2) gave a good yield of the crystalline diol (36), and the dichloride (37) was obtained in moderate yield from the diol by heating with excess phosphorus oxychloride in pyridine. After considerable experimentation, conditions for the condensation between the alkyl malonate (35) and the dichloride (step 4) were found which gave the required crystalline allyl malonate (38) in moderate yield (35\%): the problems were avoiding reaction conditions both too mild, leading to recovery of the alkyl malonate (35), and too drastic, leading to the formation of polymeric type materials. Eventually the anion of the alkyl malonate (35) was generated using excess (2.5 equiv.) NaH-DMSO, and this was added to the dichloride in the hope of avoiding any complications arising from reaction of the product with the base; excess base was used to encourage formation of the allyl malonate by elimination of HCl. It is not known whether this elimination occurs before the condensation, resulting in reaction via an intermediate allyl chloride, or after the condensation, resulting in simple elimination from the condensation product. The allyl malonate (38) showed characteristic ester, olefinic and aromatic bands in the i.r. at 1735, 1645, 1615, and 1535 cm$^{-1}$ respectively and aromatic and olefinic signals in the n.m.r. at $\delta 6.75$ (3H) and $\delta 4.80$ (2H) respectively.

Cyclization of the allylmalonate (38) and the compounds derived from it (41, 44, 47, 49) requires the generation of the carbonium ion (39) and its attack on the meta-position of the aryl ring. However this carbonium ion (39) could easily undergo a 1,2-hydride shift to form the more stable p-methoxybenzylic carbonium ion and give rise to products derived from this carbonium ion. Another forseen problem
was that the carbonium ion (39) could undergo nucleophilic attack by the group (R) (R') to form the lactone (from R=−CO₂Me) or the furan (from R=−CH₂OH). It was thought that if this was the case, strong enough acid conditions (PPA or HI) would regenerate the carbonium ion and allow formation of the substituted tetrahydronaphthalene (48).

Also feasible is attack of the carbonium ion (39) on the para-position of the aryl ring to form the intermediate (51), but this mechanism would be indistinguishable from direct meta attack as the following 1,2- shift of the more substituted bond in (51) would form the same tetrahydronaphthalene (48).

Cyclization of the allyl malonate (38) under various acid conditions (table 6, p129) showed that none of the expected tetrahydronaphthalene (48) was formed, and the only product isolated was the lactone (40), presumably formed by nucleo-
philic attack of the ester oxygen on the carbonium ion. This lactone showed both lactone and ester bands in the i.r. (1760 and 1735 cm\(^{-1}\)), and two singlets in the n.m.r. (\(\delta\) 1.65, 2.2 protons and \(\delta\) 1.10, 0.8 protons) which were assigned to the methyl groups of the two stereoisomers. Attempts to open the lactone ring using PPA (150-200\(^{\circ}\)) and HI/P (130\(^{\circ}\)) led to increasing yields of polymeric type materials and decreasing yields of recovered lactone as the temperature was raised.

To test the hypothesis that the two ester groups were in some way preventing the desired reaction the crystalline diol (41) was prepared by LiAlH\(_4\) reduction of the diester, and its cyclization to the tetrahydronaphthalene was attempted using HBr, HBr/acetic acid, and HI/P (table 7, p130). The main products were the tetrahydrofuran (42) and the acetylated tetrahydrofuran (43) formed by nucleophilic attack of a hydroxy-oxygen on the carbonium ion: (42) had one characteristic hydroxy-proton (i.r. 3450 cm\(^{-1}\), broad; n.m.r. \(\delta\) 2.24, 1H, exch.D\(_2\)O), which was absent in the acetylated derivative (i.r. 1725 cm\(^{-1}\); n.m.r. \(\delta\) 2.10,(3H),s,acetyl methyl), and both had the spectra expected for this tetrahydrofuran system. Interestingly, the presence of only one sharp methyl singlet (n.m.r. \(\delta\) 1.2) for both these tetrahydrofurans indicated that only one of the two possible stereoisomers was produced, barring accidental chemical shift equivalence, although this is difficult to rationalise.

Attempts to cleave this ring system and form the tetrahydronaphthalene failed and the only products isolated were phenolic containing polymeric materials. The cyclization of analogues with R=H (44, 47) was then
studied since removal of a carbon is necessary for the final tetrahydronaphthalene (5). Decarbomethoxylation was carried out by heating with wet DMSO-\(\text{NaCl}\), and gave the monoester (44) (one ester carbonyl, i.r. 1735 \(\text{cm}^{-1}\); n.m.r. \(\delta\) 3.50,3H, s) in moderate yield. This decarbomethoxylation is thought to proceed by a nucleophilic catalysis mechanism\(^{12}\) in which the intermediate (46), formed by attack of chloride ion on one of the ester groups, undergoes carbon-carbon bond cleavage followed by protonation and hydrolysis of both the carbanion ion and chloroformate formed.

\[
\begin{align*}
R_1R_2C\leftarrow&\text{CO}_2\text{Me} + \text{Cl}^- \\
\xrightarrow{R_1R_2C\leftarrow&\text{CO}_2\text{Me} + \text{Cl}^-} & \xrightarrow{R_1R_2C\leftarrow&\text{CO}_2\text{Me} + \text{Cl}^-} \\
\end{align*}
\]

Attempted cyclization of the monoester (table 3, p131) gave the lactone (45) (i.r. 1770, 1735 \(\text{cm}^{-1}\)), polymeric materials, or mixtures of both.

The monoester was reduced (LiAlH\(_4\)) to the crystalline alcohol (47) in good yield (i.r. 3380, broad; no carbonyl bands; n.m.r. 1 proton exchangeable with \(D_2O\)), and the first cyclization attempt using refluxing HI/P gave a crude product containing i.r. and n.m.r. signals expected for the tetrahydronaphthalene (48). Chromatography gave a glassy foam which had: two phenolic hydroxy-protons appearing in the i.r. and n.m.r. as a broad band at 3340 \(\text{cm}^{-1}\) and a broad singlet at \(\delta 3.10\) (2H, exchangeable with \(D_2O\)) respectively; seven
aromatic protons at $\delta 6.86$; a resonance of the expected chemical shift and proton integration corresponding to exocyclic iodo-methyl groups in two stereoisomers at $\delta 3.28(2H,m)$; two sharp overlapping singlets at $\delta 1.24$ and $\delta 1.21$ corresponding to the C-1 methyl groups, indicating an isomer ratio of 3:1 and a mass peak at the expected value of 408 mass units.

This mixture was hard to purify due to its insolubility in many solvents and its instability in chlorinated solvents. Separation of the isomers by chromatography failed, as did an attempt to make the compound easier to handle by reconverting the phenolic hydroxy-groups into methoxy-groups using diazomethane when several inseparable compounds were formed. The alcohol (47) was also treated with POC1$_3$-pyridine to give a good yield of the chloride (49) (i.r. no hydroxy-group; n.m.r. $\delta 3.45, 2H,s$, broad; chloromethylene group), and PPA cyclization of this gave the chloride (50) in moderate yield. This gave similar i.r. and n.m.r. data to the iodide. Again chromatography failed to separate the two stereoisomers, but the above data and a correct analysis on the pure liquid chloride (50) is a good indication that the structural
assignments of both the chloride (50) and the iodide (48) were correct.

The success of the cyclizations from the chloride using PPA and the alcohol using HI/P, together with the lack of any identifiable products arising from hydride shifts in the postulated carbonium ion intermediate (39) and the formation of the furan (42) under mild conditions, suggest that no long-lived free carbonium ion was present during the cyclizations. Cyclization could proceed via an intermediate of the type (52) (X=Cl from (49) or X=OH or X=I from (47) depending whether the cyclization occurs before or after the hydroxy-group is displaced by iodide) in which initial attack on the carbonium ion is by halogen or oxygen. The intermediate cyclic ion thus formed preserves the initial carbonium ion from rearrangements, and attack by the aryl ring with displacement of halogen or oxygen leads to the tetrahydronaphthalene.

\[
\begin{align*}
\text{OMe} & \quad \text{Ar} \\
\text{X} & \quad \text{H}^+ \\
\end{align*}
\]

\[
\begin{align*}
\text{R} = \text{Me or H.} & \quad \text{Ar''} = \text{p-OMe or p-OH} \\
\text{X} = \text{Cl ; OH or I} & \\
\end{align*}
\]
In the cyclization attempts on the diester (38), the diol (41), and the monoester (44), either the lactone or tetrahydrofuran was formed under mild conditions, and polymeric materials were formed when more vigorous conditions were used. This implies that in these reactions the cyclic product was initially formed, and ring opening generated a species that polymerised faster than it formed the tetrahydro-naphthalene. Such a species could easily arise if the carbonium ion has a longer lifetime. Taking the tetrahydrofuran (42) as an example, strong acid conditions would protonate the ring oxygen and lead to ring opening to the carbonium ion (53). This could rearrange to the benzylic carbonium ion (54), and both carbonium ions could in principle lead to polymerisation.

The only difference in the compounds subjected to the cyclization attempts are the electronegativity and number of
group(s) capable of nucleophilic attack on the carbonium ion, and so the reason for cyclization instead of polymerisation must be some subtle steric or electronic effect associated with these substituent groups.

As separation of the iodide stereoisomers seemed to be extremely difficult, it was decided to use the mixture in attempts to form the dienone, and then separate the dienone from any unchanged iodide or breakdown product formed from the iodide during the reaction by crystallisation or chromatography. This should allow an estimation of the ratio of the two iodides present as only the isomer with the p-hydroxybenzyl group and the iodomethyl group in the cis-orientation can undergo the cyclization.

The iodides were heated in dry t-butanol with potassium t-butoxide in a sealed tube for 3 hours at 170° and workup gave a mixture of products containing both dienone and phenolic type compounds as judged from the spectral characteristics (scheme 6). These included: prominent i.r. bands at 3190 (broad), 1580 and 1500 cm⁻¹ and n.m.r. signals at δ 8.1 (broad) and 7.1-6.5(m), arising from phenolic rings; prominent i.r. bands at 1670, 1655 and 1625 cm⁻¹ and n.m.r. signals at δ 6.4-5.6 arising from dienone protons. Crystallisation of this crude product yielded a small amount of a dienone, and chromatography yielded several different fractions of which none were similar to the starting iodide or its expected primary breakdown products, the olefin (55) and the t-butyl ether (56); some of the later fractions contained more dienone. All the dienone fractions were combined and crystallised, and the total dienone obtained was recrystallised to give a low yield of the pure dienone. This yield (12%) is based on
the total iodide used in the sealed tube reaction. If the required cis-isomer was present as the minor constituent of the mixture, which is likely if the lesser steric interactions between the methyl versus p-methoxybenzyl group and the iodomethyl group determine the regioselectivity, then since the stereoisomer ratio is 3:1 the maximum possible dienone yield is 25%. The 12% obtained for the recrystallised pure dienone becomes respectable as purification was accompanied by loss of material.

The other column fractions were phenolic containing compounds which were not identified due to insuperable purification problems. A later attempt at basic hydrolysis of the iodides using 2 molar sodium hydroxide also gave a large number of inseparable compounds.

We subsequently found that different dienones were produced in the sealed tube reaction depending on the molar ratio of base to iodide. If excess base (2.5 equiv.) was used the crystalline phenolic dienone (57) was the only dienone isolated, but if 1.0 equivalents of base was used the crystalline adamantanoid dienone (7) was the only dienone product. These were easily identifiable from their spectra (Fig 2, p35) as the phenolic dienone has three aromatic protons and four dienone protons whereas the adamantanoid dienone only has five dienone protons.

The phenolic dienone was converted completely into the adamantanoid dienone using the sealed tube conditions (heat, t-butanol) with 0.5 equivalents of base and two drops of water, but only incompletely using 0.5 equivalents of base alone, and was recovered unchanged from heating in t-butanol for 3 hours when no base or water was present. The exact role
played by the base in determining which dienone is formed under these conditions remains obscure, but if there is an equilibrium between the two dienones, (scheme 7), then both the strength and nature of the base could affect the type of product formed. From the results using different equivalents of base it seems that in a basic solution (corresponding to 2.5 equivalents of base) the phenolic dienone is favoured over the adamantanoid dienone, probably because of the higher stability of the phenolate ion (58) relative to the enolate ion (59). Using 1.0 equivalents of base, the bulk of the base could be neutralized by reaction with the iodide, leaving only a catalytic amount present in the solution.

Scheme 7
The thermodynamic stability of the adamantanoid dienone (7) relative to the phenolic dienone (57) is then the determining factor and only the adamantanoid dienone is formed. It is worth pointing out that the amounts of base added in these sealed tube reactions are very small and although the tubes were washed with aqueous base, water, and dried before use they were not subjected to the basic conditions present in the sealed tube. The actual concentration of base in the sealed tubes is therefore problematical.

Only one of the two possible adamantanoid dienone C* epimers was formed, as shown in the n.m.r. spectrum by just one set of dienone protons and one sharp methyl resonance at δ1.09. From examination of models it would appear that thermodynamically (7a) is favoured over (7b) as a result of unfavourable steric interactions between the hydrogens shown, and that (7a) might also be kinetically favoured due to easier aryl-dienone p-orbital overlap in the assumed transition state.

The adamantanoid dienone (7) was converted to the crystalline adamantanoid bis-dienone (8) by heating in dry dioxane with excess DDQ. This reaction removes the ambiguity
that is present at C* in (7).

The n.m.r. spectra of the three dienones show very characteristic dienone bands (Fig. 2) and all the dienone protons can be assigned\(^\text{13}\). In the phenolic dienone two of the dienone protons are shifted upfield from the normal dienone resonance positions by \(\Delta \delta 0.7\) and the vicinal coupling constant of these two protons is increased by 2.5Hz relative to that between the other vicinal dienone protons. These effects must be due to shielding and steric interactions of the two dienone protons shown below and the phenolic ring with the cyclohexane ring in a chair conformation (57a).

![57a](image)

Presumably, if the cyclohexane ring adopted a boat conformation (57b) the n.m.r. would not show the observed effects.

To gain more information on the conformation adopted by the molecule, the u.v. spectrum was examined to determine if any aryl ring–dienone interactions present in (57a) would influence either the extinction coefficient or the wavelength of maximum absorption. However, the u.v. gave a dienone band \((\lambda_{\text{max}} 232, \epsilon_{\text{max}} 14,000)\) which is typical of simple dienones.

Evidence substantiating the assigned structures of the dienones (57), (7) and (8) comes from: (1) correct accurate-mass measurements on the molecular ion present; (2) the molecular ion peak in the mass spectrum of (8) is also the
Fig. 2
NMR spectra of dienones (57), (7) and (8).
Numbered resonances correspond to numbered
diene protons shown.
base peak, showing that (8) has no easy breakdown pathways; (2) n.m.r. and i.r. characteristics assignable to the postulated structures; (4) (7) and (8) have identical chemical and physical characteristics (spectra, m.p., chemical behaviour) with the two dienones previously synthesised (see introduction) and (5) a viable mechanism explaining formation of the dienones. Also the adamantanoid bis-dienone (8) was previously shown to remain unchanged after standing in trifluoroacetic acid for 1 week.

These are conditions which cause complete conversion of simple dienones to phenols via the dienone-phenol rearrangement, and the failure of (8) to undergo the rearrangement can be rationalised since this would involve the formation of a
homoadamantanoid skeleton, such as (60a) or (60b), with a 'bent' phenol ring and would be precluded in this case by the strain involved.

**Conclusion**

The postulated mechanism for formation of the original dienone from the bromide (5) appears to have been vindicated by isolation of the iodide (48) and its conversion to both the phenolic dienone (57) and the adamantanoid dienone (7). The role played by the base in the sealed tube reactions is not obvious, but if the conversion of the phenolic dienone to the adamantanoïd dienone is a normal reversible Michael addition, then there could be an equilibrium between the two dienones in which the phenolic dienone is favoured in basic solution. This would also mean that complete conversion of the phenolic dienone to just the thermodynamically more stable adamantanoïd dienone is possible. The skeleton of the adamantanoïd products is supported by the spectral data but relies ultimately on the mechanism of formation.

This synthesis had as its goal a defined adamantane objective but it is fair to point out that the route could be used as a source of highly functionalised adamantanes. Synthesis of the dihalide (61) and its conversion to the dienone (62) would eliminate the problem of stereoisomers encountered with the iodide (48), raise the yield in the participation reaction, and produce a dienone capable of further elaboration.
The chloride (50) had a 2:1 stereoisomer ratio which is better than that of the corresponding iodide (48), assuming the minor isomer is that with the required stereochemistry, and a higher yield of the dienone might thus be obtained using this chloride as a basis for forming the dienones.
Part 2

Synthesis and decarboxylation of 6-isobutyl-1,4-dimethyl-2,7-dioxabicyclo[2.2.1]heptane-6-carboxylic acids (67) (68)
Chapter 1

Identification of the endo- and exo-6-carboxylates (23) (24)

Synthesis and identification of the bicyclic acids (67) (68)

During the synthesis of the cyclopentenones (scheme 3, p 10) two bicyclo[2,2,1]heptane stereoisomers (23) (24) were accidentally synthesised by reaction of a \( \gamma,\delta \)-unsaturated ketone with osmium tetroxide-periodate: hydrolysis of a mixture of these showed that one isomer remained unchanged whilst the other was hydrolysed completely to form what could have been a dihydrofuran. These results immediately gave rise to many questions, and these systems were studied further.

Our first task was to separate the two stereoisomers (23) and (24) which we presumed to be epimers at C-6. This proved to be difficult and was achieved only by fractional recrystallisation eventually giving both pure epimers as white crystalline solids.

\[
\begin{align*}
\text{Endo-ester} & \\
\text{H-5n deshielded} \\
\end{align*}
\]

\[
\begin{align*}
\text{Exo-ester} & \\
\text{H-5x deshielded} \\
\end{align*}
\]

Identification was achieved through their n.m.r. spectra, one had a double doublet at \( \delta 2.31(1H) \), whilst the other had a doublet at \( \delta 2.15(2H) \) which was later found to be two
coincidental doublets. Previous n.m.r. work on these bicyclic acetal systems\textsuperscript{15} shows the 5x proton to be deshielded in the \textit{exo}-ester, and its characteristic double doublet (caused by geminal coupling to the 5n proton and long range 'W' coupling to the 3x proton) to come at about $\delta 2.5$. The 5n proton is a doublet due to coupling with the 5x proton, and is not deshielded by the ester group and comes at about $\delta 1.3$.

In the \textit{endo}-ester the reverse situation obtains and the 5n proton is deshielded and comes about $\delta 2.7$ (doublet), whereas the 5x proton comes at $\delta 1.4$ (double doublet).

The n.m.r. spectra of the two esters (23) (24) are shown (Figs 3,4) along with the peak assignments; that of the \textit{exo}-ester is relatively straightforward to interpret as there are few overlapping signals, whereas that of the \textit{endo}-ester has been decoupled to help in the assignments (Fig 5): this showed that the doublet ($\delta 2.28$) collapsed into one doublet and a singlet when a decoupling frequency corresponding to either $\delta 3.34$ or $\delta 1.36$ was applied, and hence proved that the signal was a superimposition of two signals from two completely different protons. When a decoupling frequency corresponding to $\delta 2.28$ was applied, the multiplets at $\delta 3.4$-$3.1$ were resolved into a singlet ($\delta 3.34$), and a double doublet ($\delta 3.17$). We assign the two coupled protons at $\delta 3.34$ and $\delta 2.28$ to the diastereotopic benzylic protons, and the other 'half' of the doublet ($\delta 2.28$) to the deshielded 5n proton, coupled geminally to the 5x proton (which comes at $\delta 1.36$ and is hidden under the methyl peaks). INDOR confirms this to be the case.

Now that the two epimers had been separated and identified, hydrolysis using sodium hydroxide showed that after a 15 hour
Fig. 3 NMR spectrum. Exo-ester (24)
Fig. 4  NMR spectrum. Endo-ester (23)
Decoupling frequency corresponding to $\delta 1.36$

Decoupling frequency corresponding to $\delta 3.34$

Decoupling frequency corresponding to $\delta 2.28$

Fig. 5 From Endo-ester (23)

Decoupling of resonances at $\delta 2.28$ and $\delta 3.2$
reflux the endo-ester was virtually unchanged (83\% recovery) whereas the exo-ester was completely hydrolysed. The crude hydrolysis product consisted of several compounds as judged from t.l.c., but chromatography gave a fairly pure sample of the major product which could have been the dihydrofuran (25). Although it was never isolated pure enough for analysis, spectral characteristics included evidence for a hydroxy-group, an enol-ether olefinic band, no carbonyl group (i.r. cm\(^{-1}\): 3440, broad; 1680, weak), a possible hydroxy-methyl group and an olefinic ring methyl group (n.m.r. \(\delta\) 3.3, s, -CH\(_2\)OH; 1.7, s, broadened, -C=O-CH\(_3\)).

The reason for the difference in behaviour of the epimers towards base hydrolysis was not obvious, but as base induced hydrolysis is not reversible and the endo-ester was recovered, the difference lies either in the relative rates of formation of the tetrahedral intermediates by attack of the base on the esters or the relative ease of ethoxide loss from these tetrahedral intermediates, assuming a BaO\(_2\) hydrolysis mechanism.

\[
(24) \text{OH} \xleftrightarrow{} \text{OH} \\
\]

\[
(23) \text{OH} \xrightarrow{} \text{OH} \\
\noncoplanar bonds
\]

\[
(25) \text{OH} \xrightarrow{} \text{OH} \\
\coplanar bonds
\]
Normally the rate-determining step in this hydrolysis is formation of the tetrahedral intermediate and the endo-ester would be expected to be more hindered than the exo-ester. However, if decomposition of the tetrahedral intermediates were to become rate-determining, a fragmentation reaction (a), facilitated by a coplanar and anti-arrangement of the bonds undergoing cleavage could, conceivably, take place at a faster rate than the analogous fragmentation (b) because of the deviation from coplanarity of the corresponding bonds in the latter case. The product, if this mechanism were operative, would be the dihydrofuran directly and there would be no necessity to postulate an additional (rapid) decarboxylation step which must be present if a normal BAc2 mechanism is operative. There appeared to be no evidence in the literature on the thermal stability of exo- and endo-dioxabicyclo[2,2,1]heptane carboxylic acids which did not appear to have been previously prepared.

In order to study the problem further it was decided to synthesise the two benzyl esters (65) (66) (scheme 8), as hydrogenolysis would form the corresponding acids under very mild conditions and allow their isolation. A study of the thermal stability of the acids should indicate whether the exo-ester hydrolysis could proceed via the acid as an intermediate. This particular scheme was chosen as all the reactions were well proven, the only foreseen problem involving separation of the endo- and exo-epimers. It was anticipated that this separation could be achieved by chromatography or fractional crystallisation of either the esters or the acids. Also the di(methylallyl) substituted acetoacetate was chosen as the starting material for preparation of the bicyclic
acetals in preference to the p-methoxybenzylallylacetoacetate used previously as the former could be prepared in a 'one pot' reaction. Mono-epoxidation giving the unsaturated acetals (65) (66) was thought to be feasible if the amount of peracid was limited to avoid epoxidation of the unsaturated side chain in the product.

The scheme evolved as planned. Benzyl acetoacetate was prepared and the dialkylated acetoacetate (64) was obtained in excellent yield using NaH-DMSO-methallyl chloride in a two step reaction after initial problems with the second alkylation were resolved. Oxidation of the di(methylallyl)-acetoacetate to form the two bicyclic acetals (65) (66) went in moderate yield after the optimum quantity of peracid had been determined; the mechanism is believed to be that in scheme 9. After epoxidation of the olefinic bond, attack by the peracid on the epoxy-ketone (69) gives the tetrahydrofuran intermediate (71), presumably via the addition intermediate (70). Displacement of the peracid group by intramolecular attack by the side chain hydroxy-group yields the two bicyclic acetals (65) (66).

The two esters were separated at this stage by repeated chromatography and crystallisation to give the endo-ester as a colourless viscous oil and the exo-ester as a white crystalline solid. These were identified through their n.m.r. spectra as previously described: the endo-ester had both the $\delta$ 2.50 and 3.60 respectively, and the exo-ester had just the $\delta$x proton deshielded, coming at $\delta$ 2.60. Judging from the amounts of pure esters separated and the composition of the remaining mixture (from n.m.r.) the ratio of the esters
Scheme 8

$$\text{CO}_2\text{Bz} \quad 61 \xrightarrow{\text{Cl} \rightleftharpoons \text{NaH, DMSO}} \text{CO}_2\text{Bz} \quad 64$$

$$\downarrow \text{peracid}$$

Scheme 9

$$R^1 = -\text{CH}_2\text{CH(CH}_3\text{)}^2 \quad R = -\text{CH}_2\text{C}:\text{CH}_2$$

$$\text{R}^1 = \text{CO}_2\text{Ar} \quad 65 \quad \text{CO}_2\text{Bz} \quad 66$$
produced was $\sim 3:2$ endo:exo.

The acids (67) (63) were eventually prepared by the hydrogenolysis of the benzyl esters with concomitant saturation of the methylpropenyl side chain using a commercial palladium on charcoal catalyst in ethyl acetate solution. Initial attempts gave pungent smelling oils containing several compounds including one which could have been a dihydrofuran, and showed that both acids were susceptible to decomposition during the hydrogenolysis. This problem was overcome by rigorously purifying the ethyl acetate solvent immediately before hydrogenolysis, and hydrogenating for a specific length of time at a controlled temperature as both traces of water and changes in temperature seemed to markedly affect the nature of the reaction product. Traces of water and too high a temperature led to complete decomposition of the acids into a variety of unidentified compounds, whereas too low a temperature resulted either in no reaction occurring or the formation of the unsaturated acid (72) as the major product. The exo-acid was more sensitive to the reduction conditions than the endo-acid.

Acids (67) (63) were isolated as white crystalline solids, and were again easily identifiable from the chemical shifts of the 5x and 5n protons in the n.m.r.. In the endo-
acid the 5x proton was hidden, but the 5n proton was clearly visible at δ2.6 as was the 3n proton at δ3.6. In the exo-acid both the 5x and 5n protons were visible at δ2.5 and 1.4, respectively, as was the 3n proton at δ3.3.

At this point it is interesting to compare the n.m.r. spectra of all the bicyclic acetals synthesised and also show the deshielding effect of the carboxy-group on the ring protons in the exo- and endo-epimers. It can be seen that the carboxy-group not only deshields the adjacent syn-proton in the 5-position, but also the endo-carboxy-group deshilids the endo-proton in the 3-position (Fig 6).
Fig. 6

R = -CH₂CH(CH₃)₂

R' = -CH₂C=CH₂(CH₃)

R" = -CH₂Ar
Chapter 2
Decarboxylation Review

Heterolytic Decarboxylation

The decarboxylation of organic compounds has been extensively studied in both the gas and liquid phases, and these studies have shown that there are two possible modes of heterolytic decarboxylation. These are the uni- and bi-molecular electrophilic reactions shown below.\(^\text{18}\)

\[
\begin{align*}
\text{S}_{\text{E}1} & : \quad \text{RCO}_2^- \rightarrow \text{R}^- + \text{CO}_2 \\
\text{H}^+\text{RCO}_2^- & \rightarrow \text{RH} + \text{CO}_2
\end{align*}
\]

\[
\begin{align*}
\text{S}_{\text{E}2} & : \quad \text{RCO}_2\text{H} + \text{H}^+ \rightarrow \text{RH} + \text{CO}_2 + \text{H}^+ \\
\text{RCO}_2^- + \text{H}^+ & \rightarrow \text{RH} + \text{CO}_2
\end{align*}
\]

The most likely mechanism occurring in the heterolytic thermal unimolecular decarboxylations is fission of the carbon-carbon bond, but the nature of the decarboxylating species can vary depending on the molecular structure of the acid concerned. The three most likely species are:

(1) The undissociated acid molecule

\[
\text{R-} \begin{array}{c}\text{C} \\
\text{O} \\
\text{C-H}
\end{array} \rightarrow \text{R}^- + \text{CO}_2 + \text{H}^+
\]

\[
\text{Rate} = k \text{RCO}_2\text{H}
\]
(2) The acid anion

\[ \ce{R-O-C=O} \xrightarrow{\text{Rate} = k' \ \ce{RO_2^-}} \ce{R^- + CO_2} \]

(3) The zwitterion

\[ \ce{H^+R-O-C=O} \xrightarrow{\text{Rate} = k'' \ \ce{H^+RO_2^-}} \ce{RH + CO_2} \]

As the heterolysis of the carbon-carbon bond is favoured on general electronic grounds by increasing negative charge on the carboxy-group and by electron withdrawing groups \(\alpha\) or \(\beta\) to the carbon atom bearing the carboxy-group, the order for ease of decarboxylation is acid < anion < zwitterion due to a decreasing activation energy for fission of the carbon-carbon bond.

The results obtained from many kinetic measurements on rates of decarboxylation show that most acids undergo unimolecular decarboxylation from the anion, zwitterion, or both. \(\beta\)-keto acids are in a class of their own in which the collected data cannot distinguish between decarboxylation from the zwitterion and from hydrogen-bonded forms of the free acids via a concerted cyclic transition state (retro—ene reaction).

The acids which cannot form zwitterions and have electron withdrawing groups \(\alpha\) to the carbon atom bearing the carboxy-group seem to decarboxylate as the anions. The best known examples of these are the trihalogenacetic acids studied by Verhoek, and he showed that: (1) these acids are almost
completely ionized in water. (2) The activation energies for the decarboxylation of the acids and their sodium salts in water are identical. (3) The decarboxylation is approximately $10^7$ times slower in the non-ionizing solvent toluene than in water, and (4) in non-aqueous solvents in which the acids are only slightly ionized the rate is proportional to the concentration of anion produced by added bases. This evidence shows that these trihalogenacetic acids decarboxylate as the anions.

Further studies have shown that certain heterocyclic carboxylic and acetic acids decarboxylate exclusively from the zwitterions, as do certain β-hydroxy-acids. Examples of zwitterionic decarboxylation are given below, and evidence for the zwitterions comes from the fact that the free acids decarboxylate readily under conditions in which both the anion and cation are relatively unreactive.

\[
\begin{align*}
\text{H} & \quad \text{C} = \text{O} \\
\Theta & \quad \Theta
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{C} = \text{O} \\
\Theta & \quad \Theta
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{C} = \text{O} \\
\Theta & \quad \Theta
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{C} = \text{O} \\
\Theta & \quad \Theta
\end{align*}
\]
Scheme 10

2-pyridylacetic acid

\[
\begin{align*}
\text{2-pyridylacetic acid} & \quad \Leftrightarrow \quad [\text{pyridine} \cdot \text{carboxylate}]^+ \\
& \quad \downarrow \quad -\text{CO}_2 \\
& \quad \Leftrightarrow \quad \text{4-pyridylacetic acid}
\end{align*}
\]

4-pyridylacetic acid

\[
\begin{align*}
& \quad \text{CH}_2\text{CO}_2\text{H} \quad \Leftrightarrow \quad \text{CH}_2\text{CO}_2^\ominus \\
& \quad \text{H} \quad \text{H} \\
& \quad \Leftrightarrow \quad \text{CH}_3 \quad \text{CH}_2
\end{align*}
\]
The best evidence for zwitterions comes from studies by Taylor\textsuperscript{25} who used both 2- and 4-pyridylacetic acids. These are known to decarboxylate in water with comparable rates\textsuperscript{19,26}, and also to have very similar values for $\Delta H^+$ and $\Delta S^+$, implying that both acids decarboxylate by a similar mechanism. It is also known that the free acids decarboxylate relatively easily under conditions in which both the anion and cation are stable. These results mean that decarboxylation of both acids must be via the zwitterions even though the 2-isomer, due to the geometry of the molecule, can decarboxylate via a concerted pathway (scheme 10).

Studies on $\beta$-$\gamma$-unsaturated acids by Bigley and Thurman\textsuperscript{27} using both $^2$H and $^{14}$C labels have shown that these acids decarboxylate by the cyclic transition state (c). The three possible intermediates are:

\begin{center}
\begin{tabular}{ccc}
(a) & (b) & (c) \\
\end{tabular}
\end{center}

A kinetic isotope effect was observed when the carboxy-group was labelled with either $^2$H or $^{14}$C. This eliminates (a) as the intermediate as the carboxy-proton is transferred before the C$_1$-C$_2$ bond begins to break and it would not show a $^2$H isotope effect of the observed magnitude (an equilibrium between (a) and starting acid can be excluded). Neither can (a) be a transition state, since if it were no $^{14}$C isotope
effect would be observed, the $C_1-C_2$ bond breaking after the transition state.

The structure (b) formed by $C_1-C_2$ bond breaking before proton transfer can account for the observed isotope effects if it is a transition state with a partly broken carboxy-proton bond, but is unlikely as substituent effects are incompatible with the build up of negative charge at $C-2$.

Postulation of (c) as the transition state in which all bonds are partly formed or broken explains all the available data.

![Scheme 1](image)

Scheme 11
For decarboxylation of \( \beta \)-keto acids fission of the zwitterion (scheme 11, path II) and the concerted pathway (path I) are feasible; both the acid and zwitterion decarboxylate about five times as fast as the anion\(^{28} \), and the enol is formed in the rate determining step.

However studies on the kinetic isotope, solvent, substituent effects, and kinetic data do not distinguish between fission of the zwitterion\(^{18,28,29} \) and the concerted pathway\(^{32} \), presumably because of the very close similarity between the structures (Ia) and (IIa) above. (In (Ia) partial electrical charges are possible depending on the exact timing of bond fission and formation).

A bimolecular mechanism (S\(_{\text{E2}}\)) was first proposed by Schenkel\(^{31} \) and there are two possibilities. The proton can attack either the undissociated acid or the acid anion, but as formation of the anion will increase the electron density on the \( \alpha \)-carbon atom, the latter mechanism will require less activation energy.

\[
\begin{align*}
(a) \quad H^+ + RCO_2H & \longrightarrow HR + CO_2 + H^+ \quad \text{Rate} = k \ H^+ \ RCO_2H \\
(b) \quad H^+ + RCO_2^- & \longrightarrow HR + CO_2 \quad \text{Rate} = k' \ H^+ \ RCO_2^- 
\end{align*}
\]

Few acids seem to decarboxylate by bimolecular mechanisms but in some cases a qualitative increase in the rate of decarboxylation with increase in hydrogen ion concentration has been observed\(^{32} \). Johnson\(^{33} \) studied the rates of decarboxylation of a series of electronically similarly substituted cinnamic acids. Their order of rates can be correlated with the electronic effects of the substituent.
groups on the basis of the two step bimolecular mechanism shown below.

\[
\text{Ph-CR=CR'-CO}_2\text{H} + \text{HA} \rightleftharpoons \text{PhCR=CHR'-C}_2\text{O}_2\text{H} + \text{A}^- \\
\downarrow \\
\text{PhCR=CHR} + \text{CO}_2 + \text{H}^+
\]

Perhaps the best example of the bimolecular mechanism is the decarboxylation of 2,4,6-trimethylphenylacetic acid in which the exact proportionality between the pseudo first order rate constant and the hydrogen ion concentration was observed. The mechanism proposed was via an activated complex of the type below:

Homolytic Decarboxylation

Many examples of homolytic decarboxylation are known, and the most common are: (1) thermal decomposition of
peroxides\textsuperscript{35}, (2) photochemical decarboxylations\textsuperscript{36}, (3) Kolbe electrolysis\textsuperscript{37}, and (4) the Hunsdiecker reaction\textsuperscript{38}.

However, a homolytic mechanism for decarboxylation of the bicyclic acetal acids (67) and (68) is unlikely for reasons to be discussed and these routes are not considered in detail here.
Chapter 3

Decarboxylation studies of the two bicyclic acetal acids

(67) (68)

Now that the two target acids had been synthesised their decarboxylation could be studied. In order to try and distinguish between possible mechanisms it was decided to measure the kinetics of the decarboxylation of each acid under similar conditions to obtain the rate constant and order of the decarboxylation process. Also product studies were carried out to see if there was any evidence for the formation of the likely decarboxylation products, the dihydrofuran (73), dihydropyran (74), or decarboxylated bicyclic acetals (75).
It was appreciated that product studies might not be conclusive as the dihydropyran, dihydrofuran, and decarboxylated acetals might interconvert spontaneously. 16, 39.

Hydrolysis of a mixture of the benzyl esters (65) (66) under the same conditions used to hydrolyse the ethyl esters (23) (24) (2% NaOH, EtOH, 15h. reflux) showed that both benzyl esters were relatively unreactive (80% recovery) and that the endo:exo ratio had hardly changed.

Thermal decarboxylation of the pure acids (67) (68) alone was carried out in a bulb-tube apparatus heated in a thermostatically controlled oven, and the decarboxylation products were collected in a cooled bulb. In both cases decarboxylation gave rise to the same mixture of decarboxylated bicyclic acetals (75) with an epimer ratio of 1:1.3 as judged from the n.m.r. signals at $\delta 3.4$ (2xJ, H-3n, endo- and exo) and $\delta 1.3$ (2x$\gamma$, overlapping, ring methyl, endo- and exo). However, the endo- acid decarboxylated much more readily (virtually complete decarboxylation, 140° bath temperature, 15 minutes) than the exo-acid (virtually complete decarboxylation, 180° bath temperature, 30 minutes). This temperature range for decarboxylation is similar to those acids which are activated by electron-withdrawing groups on the $\alpha$-carbon atom (e.g. malonic acid, trichloroacetic acid, and acetoacetic acid all decompose readily at temperatures between 110-150°).

Studies in non-ionizing solvents ($\text{PhH}, \text{PhCl}$) confirmed this result, showing that the final decarboxylation products were the decarboxylated bicyclic acetals (75). These were chromatographed on kieselgel to remove a minor hydroxylic impurity, and yielded a pure sample as judged by i.r., n.m.r., and t.l.c. This pure neat sample was found to have sponta-
eously changed into the dihydrofuran (73) after refrigeration overnight and conversion was quantitative as judged from the spectroscopic data. In the i.r. the hydroxy-group and vinyl ether double bond were present at 3340 (broad), and 1695 cm⁻¹ (medium), respectively, and the n.m.r contained signals characteristic of the dihydrofuran, especially a two proton singlet at δ 3.4 assigned to the hydroxymethyl group, a three proton triplet with a small coupling constant (J 2 Hz.) assigned to homo-allylic splitting of the olefinic methyl by the ring methylene, and a three proton singlet at δ 1.2 assigned to the C-2 methyl. Curiously, during the running of the n.m.r. the characteristic signals of the bicyclic system were seen to grow and the characteristic signals of the dihydrofuran disappear. Complete conversion of the dihydrofuran into the acetals (75) was apparent after 20 minutes.

\[ \begin{align*} 
73 & \quad \xrightarrow{\text{catalysed by acid}} \quad 75 \\
1.2 & \quad \text{CH}_3 \\
3.4 & \quad \text{CH}_3 \\
\text{H}_3C & \quad \text{CH}_3 \\
\text{O} & \quad \text{CH}_3 \\
\text{HO} & \quad \text{H} \\
1.6 & \quad \text{H} \\
\end{align*} \]

Evidently there is a delicate equilibrium between the bicyclic acetals and the dihydrofuran. Further experiments showed the conversion of (73) to (75) was catalysed by acid.

Acetylation of the dihydrofuran with pyridine-acetic anhydride was complete in 3 hours at room temperature as judged from the n.m.r. integral of the acetoxy-group (δ 1.3, s) and the disappearance of the hydroxy-group. This is added proof for the structure of the dihydrofuran, which possesses
a primary hydroxy-group; the dihydropyran (74) possesses a tertiary hydroxy-group which would not be acetylated under these conditions, and the presence of the n.m.r. singlet at δ3.4 is also incompatible with the dihydropyran.

An investigation was then made into the thermal stability of the sodium salts of the two acids (76) (77). These were prepared by adding aqueous sodium hydroxide solution to a slight excess of the acid in ethanol, followed by evaporation of the solvent and trituration with petrol. Although never crystallised, n.m.r. and i.r. showed the salts to be free of contaminants with the bicyclic ring still intact, showing the characteristic deshielding of the O-5 proton adjacent to the carboxy-group, and there were two strong i.r. bands at ≈1580 and 1370 cm⁻¹ assignable to the salt. These salts proved to be much more thermally stable than the parent acids. The endo-salt decomposed into a tarry mixture of unidentified products at ≈210°, as did the exo-salt at ≈250° (bath temperatures). This would seem to indicate that protonation of some site, probably the 2- or 7- oxygen, in the acids is an integral part of the decarboxylation mechanism.

Initially attempts were made to follow the rate of decarboxylation by n.m.r. A sample of the acid was dissolved in chlorobenzene and the decarboxylation monitored by the disappearance of peaks characteristic of the acid while the sample was heated at a constant temperature. Although the methyl peaks in the region δ1.7-1.0 are characteristic they could not be used to monitor the concentration of acid remaining due to underlying and overlapping peaks which changed during the decarboxylation. However, the disappearance of the small double doublet at δ2.6 for the endo-acid and the small double
doublet at $\delta 2.5$ for the *exo*-acid were convenient for the purpose. Unfortunately a relatively high concentration of the acid (approx. 0.8M) had to be used in order to follow the decomposition over three half-lives, and even then data obtained for each kinetic run became subject to significant error as the peak size became smaller with time.

No reliable reproducible kinetic results were possible from this approach but it was apparent that the *endo*-acid decarboxylated faster at 70° than the *exo*-acid at 130°, and both proceeded at measurable rates under these conditions. What these n.m.r. studies also showed was that for the *endo*-acid at 70° the initial decomposition product was the dihydrofuran (73) and not the bicyclic acetics (75); (73) was readily identified by the presence of the hydroxy-methyl singlet at $\delta 3.4$, together with the broadened olefinic methyl group at $\delta 1.6$ and the C-2 methyl group at $\delta 1.2$, and these peaks were clearly visible despite the presence of the C-3 protons ($\delta 3.3, 3.2$) and methyl groups ($\delta 1.6, 1.3$) in the starting acid (Fig. 7). The dihydrofuran concentration was seen to rise steadily but additional peaks at $\delta 3.4, 3.3, 1.5$ and 1.3 appeared subsequently, characteristic of the decarboxylated bicyclic acetics (75). As the decarboxylation proceeded the concentrations of both the dihydrofuran and the bicyclic acetics grew, but after standing at 70° overnight the dihydrofuran signals were no longer visible and only the acetics remained.

In chlorobenzene solution, therefore, the *endo*-acid undergoes ring opening on decarboxylation to initially form the dihydrofuran, and the dihydrofuran then ring closes to reform the bicyclic acetics.
Decarboxylation of the endo-acid (67) at 70°C in chlorobenzene solution

This figure extends over three pages.
Page 66 shows the n.m.r. spectrum of the pure endo-acid over the region δ0.0 to δ4.0.
Page 67 shows the δ3.0-4.0 region, expanded, at the times shown. Note the immediate growth of the singlet at δ3.4 which is characteristic of the dihydrofuran (73), and the later appearance of the peaks characteristic of the decarboxylated bicyclic acetics (75).
Page 68 shows one expanded δ3.0-4.0 region, when the dihydrofuran concentration has just begun to decrease, superimposed on a spectrum of the final product; the decarboxylated bicyclic acetics (75).
NMR Spectrum. Enol-acid, pure. t=0 mins.
endo-acid
dihydrofuran
decarboxylated bicyclic acetals

t = 60m. 30s.

t = 32m. 0s.

t = 10m. 0s.

t = 2m. 30s.
NMR Spectrum.
Decarboxylated bicyclic acetals

(bottom) (75)

T = 110 m 0s.
The n.m.r. study of the exo-acid decarboxylation in bromobenzene solution at 145° was equally informative: the initial product contained a sharp singlet (δ 1.1), a broadened singlet (δ 1.7), and a broad doublet (δ 3.5, possible AB system). This was believed to be the dihydropyran (74) for which signals at the δ values indicated would be predicted; other signals from this compound were always obscured by those at δ 3.5 and 1.7 from the starting acid. Not only was the observed shift of the C-2 methyl group similar to that observed in the dihydrofuran but the multiplicity as a result of the allylic coupling was also similar.

In addition a broad singlet was also observed shifting upfield through the signals at δ 3.5 till it became obscured (δ 2.0) just before the dihydropyran concentration reached a maximum. This could have been the n.m.r. time-averaged position of the acid proton in the carboxylic acid and the hydroxy-proton in the dihydropyran moving upfield as the ratio of acid to dihydropyran decreased.

After the slow build up to a maximum the dihydropyran decayed rapidly giving rise to signals characteristic of both the bicyclic acetals (75) and the dihydrofuran (73). Eventually after 3 hours only the acetals (75) remained, with an epimer ratio similar to that from the endo-acid (Fig. 8).

A later attempt to isolate the unsaturated dihydropyran (73) from the unsaturated exo-acid (72) by heating as above, cooling when the unsaturated dihydropyran concentration reached its maximum, and chromatographing gave a nearly pure sample.
**Fig. 8**

Decarboxylation of the *Exo*-acid (68) at 145°C in bromobenzene solution

This figure extends over four pages. On each page is an n.m.r. spectrum, taken at the times shown during the decarboxylation.

Page 71 shows the pure *exo*-acid at t=0 min.
Page 72 shows the maximum concentration of the dihydropyran (74).
Page 73 shows the dihydropyran nearly completely decayed, and the growth of both the decarboxylated bicyclic acetals (75) and the dihydrofuran (73).
Page 74 shows the final product, which is a mixture of the decarboxylated bicyclic acetals. Note the similarity to that obtained from the *endo*-acid. (Fig. 7).
NMR Spectrum taken at 85 min. Maximum dihydroxyran (74)
concentration
NMR Spectrum taken at 165 min. Note the decay of the dihydropyran (74), and the growth of the decarboxylated bicyclic acetals (75) and the dihydrofuran (73).
The final product from \textit{exo}-acid decarboxylation.

(Decarboxylated acetals (75)).
of (78). This again showed similar n.m.r. signals to those predicted, especially the broad singlet at $\delta_{\text{CDCl}_3} 3.5(2H)$ and the two broad methyl singlets at $\delta 1.8$ and $1.7$.

The initial product from decarboxylation of the saturated exo-acid (68) in bromobenzene is therefore, the dihydropyran (74) which later ring closes to form the bicyclic acetics (75). (See p76.)
Schematic diagram showing the decarboxylation products from the endo- and exo- acids.
Chapter 4
Kinetic Results

The successful measurement of the decarboxylation kinetics was achieved by g.l.c. Experiments with the acids (67) (68) had shown that reaction with an ethereal solution of diazomethane at room temperature would generate the corresponding methyl esters directly in quantitative yield, and g.l.c. conditions were found that separated the methyl ester from the faster running decarboxylated products (3% APL column, 145°C, N₂=15p.s.i., Retention times: breakdown products and solvents 0-2 min., methyl ester 3.9 min., chloronaphthalene internal standard 3.2 min.).

Fig. 9

- Sampling syringe
- Dry nitrogen inlets
- Rubber seal
- Oil bath
- Lagging
- Heater
- Constant temperature probe
- Bicyclic acid and chloronaphthalene standard in chlorobenzene
The kinetic runs were carried out by simultaneously heating two samples of the acid (twice recrystallised from petrol immediately before use) in freshly distilled chlorobenzene (10.0 or 25.0 mg. in 5.0 ml.) containing a trace of chloronaphthalene in a thermostatted oil bath (±0.2°). Each sample was contained in a two necked flask equipped with stirrer bead and two condensers, one coupled to a dry nitrogen inlet and the other with a rubber seal through which samples could be withdrawn (Fig. 9).

During a kinetic run samples were withdrawn by syringe (0.02ml.) at timed intervals, immediately quenched in excess diazomethane solution, and the g.l.c. trace for the sample obtained as quickly as possible. The peak area of the methyl ester peak was measured relative to the area of the chloronaphthalene standard, and this value was used to construct the kinetic plots. To try and estimate the errors inherent in the method duplicate runs were carried out simultaneously in the same oil bath, samples were routinely repeated (i.e. three samples were withdrawn in quick succession), and the same sample was run through the g.l.c. several times. The external temperature (oil bath) was monitored throughout the run, and the internal temperature measured at the end of each run. Esterified samples were run through the g.l.c. as quickly as possible to prevent any possible reaction of the methyl ester or the internal standard, although blank experiments showed that the g.l.c. trace of a quenched sample remained unaltered overnight.

These results showed that the main source of error arose during the running of the quenched sample through the g.l.c., and when the ester peak became small and the error
was about $\pm 5\%$ sampling was discontinued.

In case the decarboxylation was being catalysed by the surface of the glass flask used to contain the solution, runs were carried out on both acids using flasks pre-washed in both basic ($2\text{M NaOH}$) and acidic ($2\text{M HCl}$) solution, and then washed and dried. This was found to make no appreciable rate difference for either acid.

Using this method no reliable kinetic measurements could be made until the system had reached thermal equilibrium after the flask containing the acid in solution had been lowered into the pre-stabilized oil bath to start the run (estimated 15-20 min.). This was not a serious problem as samples withdrawn after this time gave plots reliable enough to determine the order and rate of the reaction (the half lives of the endo- and exo-acids were approximately 30 and 150 minutes respectively). In retrospect this waiting period could have been avoided by adding the acid as a solid or concentrated solution to the prestabilized reaction flask containing the chlorobenzene - chloronaphthalene solution.

Using this system the rates of decarboxylation of the two acids in chlorobenzene solution were measured at two different concentrations, and the results are shown below (table 2), as are two typical kinetic plots (graphs 1 and 2).

The most accurate results show that the rates of decarboxylation for the acids are:

- **Endo-acid**  $3.7(\pm 0.2) \times 10^{-4} \text{ sec}^{-1}$ at $69.0^\circ$.
- **Exo-acid**  $7.3(\pm 0.4) \times 10^{-5} \text{ sec}^{-1}$ at $121.0^\circ$.

Hence both the decarboxylations are unimolecular with a large rate difference between the endo- and exo-acids.
Graph 1  Endo-acid.  T=69°.

First Order Plot: $\log_{10}(\text{peak weight})$ vs. time.
Graph 2 Exo-acid. T=121°.

First Order Plot: \( \log_{10}(\text{peak weight}) \) vs. time.
### Table 2. Kinetic Results

<table>
<thead>
<tr>
<th>Run</th>
<th>Acid</th>
<th>Conc. (mg. in 5.0ml PhCl)</th>
<th>Temperature °C internal</th>
<th>Order</th>
<th>Rate Constant sec⁻¹</th>
<th>Difference %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Endo</td>
<td>10</td>
<td>69.0</td>
<td>1st</td>
<td>3.65 x 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Endo</td>
<td>10</td>
<td>69.0</td>
<td>1st</td>
<td>3.74 x 10⁻⁴</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>Endo</td>
<td>25</td>
<td>69.3</td>
<td>1st</td>
<td>3.77 x 10⁻⁴</td>
<td>5.5</td>
</tr>
<tr>
<td>2</td>
<td>Endo</td>
<td>25</td>
<td>69.3</td>
<td>1st</td>
<td>3.98 x 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Endo</td>
<td>10</td>
<td>68.2</td>
<td>1st</td>
<td>3.31 x 10⁻⁴</td>
<td>6.0</td>
</tr>
<tr>
<td>3</td>
<td>Endo</td>
<td>25</td>
<td>68.2</td>
<td>1st</td>
<td>3.52 x 10⁻⁴</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Exo</td>
<td>10</td>
<td>121.6</td>
<td>1st</td>
<td>8.35 x 10⁻⁵</td>
<td>5.5</td>
</tr>
<tr>
<td>4</td>
<td>Exo</td>
<td>10</td>
<td>121.6</td>
<td>1st</td>
<td>7.90 x 10⁻⁵</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Exo</td>
<td>10</td>
<td>121.0</td>
<td>1st</td>
<td>7.82 x 10⁻⁵</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>Exo</td>
<td>25</td>
<td>121.0</td>
<td>1st</td>
<td>7.71 x 10⁻⁵</td>
<td></td>
</tr>
</tbody>
</table>

In order to obtain some rate comparisons with the bicyclic acids (67) (68) the model acid (80) was synthesised in good yield (scheme 12).

![Scheme 12](image-url)
Acid (80) proved to be stable enough to distil (b.p. 100°/0.2 mm) and the hydrogenolysis of the benzyl ester (79) to form the acid presented none of the problems that accompanied this step in the bicyclic acid synthesis.

Thermal decarboxylation of (80) either neat or in solution showed that the product formed was the dimethyl dioxolane (81); there was no n.m.r. evidence for any intermediate ring-opened product.

The kinetics of the decarboxylation in this case were studied by n.m.r. since g.l.c. determination of the unchanged acid as its methyl ester gave inconsistent results. Both the acid and the product have very simple n.m.r. spectra allowing the decarboxylation to be easily monitored by the decay of the two proton singlet in the acid (δ 2.70, -CH$_2$-CO$_2$H) relative to a bromotoluene internal standard and the unchanging four proton singlet at δ 4.00 (-OH$_2$-CH$_2$O-) which comes at exactly the same δ value in the acid (80) and product (81).

Rate studies showed that the decarboxylation was first order with a rate considerably slower than either of the bicyclic acids (67) (68). (Table 3 and graph 3 below).

Table 3. Kinetic Results for (80)

<table>
<thead>
<tr>
<th>Rate (sec$^{-1}$)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.86 x 10$^{-5}$</td>
<td>137.7</td>
</tr>
<tr>
<td>3.91 x 10$^{-5}$</td>
<td>138.0</td>
</tr>
<tr>
<td>4.15 x 10$^{-5}$</td>
<td>138.5</td>
</tr>
</tbody>
</table>

Since decarboxylation of both bicyclic acids is faster than that of the model acid, it seems reasonable to assume that relief of ring strain is an important factor in the rate determining step, especially for the endo-acid.
Graph 3 Model acid. T=138°.

First Order Plot: log_{10}(peak weight) vs. time.

Time, Sec.

log_{10}(peak weight)
Decarboxylation of the organic acids reviewed in chapter 2 shows that there are many different mechanisms by which the bicyclic acids (67) (68) can decarboxylate. The main possibilities are homolytic bond fission, and heterolytic bond fission from the zwitterion, anion, or free acid; the latter can proceed via a cyclic transition state.

The preceding studies on (67) and (68) show that (1) decarboxylation is unimolecular with the endo-acid proceeding at a considerably greater rate than the exo-acid and both (67) and (68) decarboxylating faster than the model acid (80), (2) the acid sodium salts (76) (77) are very stable relative to the parent acids, (3) the bicyclic ring is opened during decarboxylation; C₁-O₂ bond fission occurs in the endo-acid to form the dihydrofuran, whereas C₁-O₇ bond fission occurs in the exo-acid to form the dihydropyran, (4) both the dihydrofuran and dihydropyran isomerise to the bicyclic acetalts (75) in chlorobenzene solution.

Decarboxylation mechanisms for (67) and (68) which do not involve acetal ring opening are ruled out by the product studies, and those which do not feature protonation at some site on the acid prior to or during decarboxylation are ruled out by the stability of the sodium salts. Decarboxylation from the acid anions is likely to be in the latter class. Also the large rate difference between (67) and (68) cannot be explained by a homolytic mechanism in which the rate determining step is either formation of the carboxy-radical or homolytic fission of the C-6-carboxy-group bond.
The most probable mechanisms are (1) formation of an intermediate zwitterionic species (82) (83) by intramolecular protonation of the ring oxygen adjacent to the carboxy-acid followed by decarboxylation and ring opening, and (2) decarboxylation from the acids via the cyclic transition states (84) and (85) (schemes 13 and 14).

The Zwitterionic Mechanism

This mechanism can explain both the product and rate difference between the two bicyclic acids (67) and (68) since (a) the geometry of the bicyclic system is such that intramolecular proton transfer from the carboxy-acid to the 2-oxygen in the endo-acid is probably easier than the corresponding proton transfer to the 7-oxygen in the exo-acid; if zwitterion formation is rate determining, the endo-acid would decarboxylate faster, (b) The 7-oxygen is likely to have a lower basicity than the 2-oxygen because the smaller bond angle at the bridging 7-position relative to the 2-position increases the p-character in the bonding orbitals and the s-character in the lone pair orbitals of the 7-oxygen. Thus the lone pair electrons are less easily protonated than those of the 2-oxygen and this would tend to raise the concentration of the zwitterion formed from the endo-acid (32) relative to that from the exo-acid (35). If decomposition of the zwitterions were rate-determining this would raise the relative rate of the endo-acid decarboxylation accordingly.

Loss of carbon dioxide from zwitterions (82) (83) could proceed directly or stepwise and if the stepwise mechanism were operating, the stabilization of an incipient carbonium ion at C-1, formed by C₁-O₂ bond cleavage before loss of
Scheme 13. Decarboxylation via the Zwitterion.
Scheme 14. Decarboxylation via the cyclic transition state.
carbon dioxide would be greater by the 7-oxygen in (86) than the 2-oxygen in (87) (scheme 15). This can be seen from models where the geometry of the bicyclic system allows better overlap between a 7-oxygen lone pair and the incipient 0-1 carbonium ion (86) formed from the endo acid than between a 2-oxygen lone pair and the carbonium ion (87) formed from the exo-acid.

If C₁-O₂ or C₁-O₇ bond cleavage in (82) (83) was the rate determining step (subsequent loss of carbon dioxide from the respective carbonium ions being rapid) then this could also account for the disparity in decarboxylation rates between the two acids.

Direct loss of carbon dioxide from the zwitterions (82) and (83) (by-passing formation of carbonium ions at C₁ in the stepwise mechanism above) is also a possibility though
this would require a syn-elimination of \( \text{CO}_2^- \) and \(-\text{OH}^+\). 

Assuming the model acid (80) decarboxylates by the same mechanism as that for (67) and (68), the slower rate of the model acid may be due to either relief of ring strain in (67) and (68) during decarboxylation, or to the rigid geometry of the bicyclic system which allows easier intramolecular protonation by the carboxy-group. The lack of any ring opened product (89) from the model acid could be due to a fast isomerization of (89) to the observed dimethyl dioxolane (81), a process likely considering the smaller ring strain in the monocyclic dioxolane (81) relative to the bicyclic acetals (75).

**The Concerted Mechanism**

This mechanism in which elimination of carbon dioxide from (67) and (68) to give the observed dihydrofuran and dihydropyran primary products, and from (80) to give (89) (scheme 14), proceeds via a cyclic transition state, cannot be ruled out by the decarboxylation studies.
If the two transition states (84) and (85) are close in geometry to the products of decarboxylation, which, from examination of models appears necessary for good overlap of the orbitals involved, then it is not apparent why such a large disparity in the decarboxylation rates of (67) and (68) should be found.

**Conclusion**

Although no firm conclusions as to the detailed pathway for decarboxylation of the bicyclic acids (67) (68) can be reached at this point, an attractive working hypothesis is that zwitterions are involved.

Solvent effects might give additional information on the mechanism operating, but these can be ambiguous as any change in the reaction medium that increases the proportion of zwitterion present is likely at the same time to increase its stability\(^4\). Studies on the acids (90-93) which lack one of the bicyclic oxygens would show the importance of carbonium ion character at O-1 in the decarboxylation transition state; if this were important then the rate of decarboxylation of (90) would be significantly slower than (67). The acids (91) and (92) would show the importance of easy intramolecular protonation by the carboxy-group.
EXPERIMENTAL
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>General experimental details and instrumentation.</td>
<td>93</td>
</tr>
<tr>
<td>Part 1a. Synthesis of the cyclopentenones.</td>
<td>95</td>
</tr>
<tr>
<td>Part 1b. Synthesis of the dienones.</td>
<td>105</td>
</tr>
<tr>
<td>Part 2. Bicyclic acetal work.</td>
<td>116</td>
</tr>
</tbody>
</table>
• General Experimental Details

Instrumentation

Melting points were determined on a Kofler block, and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer 237 spectrometer.

Nuclear magnetic resonance spectra were recorded on a Varian T 60 or a Jeol JNM PS 100 spectrometer.

Mass spectra were recorded on an A.E.I. MS 9 or a V.G. Micromass 16 B spectrometer. Accurate mass spectra were obtained through the Physico-Chemical Measurements Unit, Harwell.

Ultraviolet spectra were recorded on a Pye-Unicam SP 800 spectrophotometer.

Gas-liquid chromatography was carried out on a Pye-Unicam series 104 chromatograph.

Basic Experimental

Diethyl ether (ether), petroleum spirit (b.p.60-80° is referred to as petrol), and benzene were dried over sodium wire.

Dimethylformamide (DMF) and dimethylsulphoxide (DMSO) were dried by distillation, under reduced pressure, from calcium hydride.

Pyridine was dried by distillation from barium oxide onto sodium hydroxide pellets.

Dioxane was dried by distillation from lithium aluminium hydride.
t-Butanol was dried by reaction with potassium metal and distillation.

Sodium hydride (50% dispersion in oil) was washed with dry petrol prior to use. (Weights given in Experimental refer to oil dispersion.)

Kieselgel refers to Merck Kieselgel 60 PF 254.

Alumina refers to Spence type H.

The sodium bicarbonate and sodium chloride solutions used in the workup of the reactions were saturated solutions.

All organic solutions were dried over anhydrous magnesium sulphate.

All air sensitive reactions were carried out under a dry nitrogen atmosphere.

Distillations carried out using a Kugelrohr oven (bulb-tube apparatus) are recorded as b.p. (oven).

**Physical Data**

Infrared spectra are reported by denoting the position of significant peaks in cm⁻¹, and were obtained as thin films, or nujol mulls where stated.

Mass spectra are reported by giving the mass peak first (in units of m/e) followed by peaks of significant intensity.

Nuclear magnetic resonance spectra were run at 60MHz. in carbon tetrachloride, unless otherwise stated, and the δ value given is the estimated centre of the resonance relative to TMS as internal standard. This is followed in parenthesis by the proton count of the integral, the signal multiplicity, and the coupling constants (J). Abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; AA'BB', p-disubstituted benzene multiplet; m, multiplet(s).
Part 1a

Synthesis of the cyclopentenones
p-Methoxyphenylacetyl chloride (15)

This was prepared by the method of Elderfield and Meyer^42. Distillation gave the chloride (85%). b.p. 108-110°/1.1 mm. (Lit.43 143°/10 mm.).

i.r. 1780, 1590, 1565, 1490, 1225, 1005, 760.
n.m.r. 6.95 (4H,AA'BB'), 3.95 (2H, s), 3.65 (3H, s).

Benzyl ethyl propanedioate (14)

This was prepared by the method of Bowman and Fordham^44. Fractional distillation gave the propanedioate (70%), b.p. 140-142°/4.0 mm. (Lit.44 124°/1.5 mm.).

i.r. 1755, 1735, 1500, 1335, 1150, 1035.
n.m.r. 7.25 (5H, s), 5.10 (2H, s), 4.15 (2H, q, J 7 Hz), 3.25 (2H, s), 1.20 (3H, t, J 7 Hz).

Benzyl ethyl p-methoxyphenylacetyl propanedioate (16)

This was prepared by the general method of Bowman and Fordham^44. Distillation gave the acylpropanedioate (55%), b.p. 195-205° (oven)/0.5 mm.

i.r. 1745, 1730, 1620, 1585, 1530, 1260, 1150, 1035, 750.
n.m.r. 7.20 (4H, AA'BB'), 6.35 (5H, s), 5.05 (2H, s),
4.10 (2H, q, J 7 Hz), 3.70 (3H, s), 3.45 (1H, s),
3.30 (2H, s), 1.15 (3H, t, J 7 Hz).

Ethyl 4-(p-methoxyphenyl)-3-oxobutanoate (17)

This was prepared by the method of Bowman^45. Distillation (130-200° (oven)/0.1 mm), followed by kieselgel chromatography (50:1; 1:1 ethyl acetate: cyclohexane eluent) gave the butanoate
This was prepared by the method of Quelet and Allard. Distillation gave the chloride (90%), b.p. 103-106°/1.0mm. (Lit. 113°/10mm).

Ethyl 2-(p-methoxybenzyl)-4-(p-methoxyphenyl)-3-oxobutanoate (19)

A solution of ethyl 4-(p-methoxyphenyl)-3-oxobutanoate (5.0g.) in DMF (15ml.) was added dropwise to a stirred suspension of washed sodium hydride (1.0g.; 1.1 equiv.) in DMF (100ml.) at 0°. The solution was warmed to 50°, stirred (0.5h.), cooled to 0°, and p-methoxybenzyl chloride (4.9g.; 1.5 equiv.) added dropwise. The solution was warmed to 50°, stirred (2h.), cooled, and poured into iced water (250ml.). This was extracted with benzene (3x50ml.), and the combined benzene extracts washed with water (4x30ml.), dried, and evaporated to yield the crude product as a brown tar (4.0g.). Alumina Chromatography (50:1;9:1 cyclohexane:ethyl acetate eluent) gave the title keto ester as a pale yellow viscous oil (1.0g.; 14%).

i.r. 1735, 1710, 1615, 1585, 1510, 1305, 1250, 1180,
Ethyl 2-((p-methoxybenzyl)-3-oxobutanoate (20)

Ethyl acetoacetate (20.0g.) was added dropwise to a stirred suspension of sodium hydride (8.6g.; 1.2 equiv.) in DMF (250ml.) at 0°. The solution was stirred (20°) till no more hydrogen was evolved, cooled to 0°, and p-methoxybenzyl chloride (28.0g.; 1.2 equiv.) was added dropwise. The solution was stirred (20°; 3h.), poured into iced water (500ml.), and this was extracted with benzene (3x100ml.). The combined benzene extracts were washed with water (4x100ml.), dried, and evaporated to give the crude product as a viscous yellow oil. Distillation gave the title keto ester as a pale yellow viscous oil (14.8g.; 40%), b.p. 143-145°/0.5mm.

\[ \text{i.r.} \quad 1740, 1710, 1610, 1580, 1510, 1245, 1175, 1030, 815. \]
\[ \text{n.m.r.} \quad 6.85 (4H,AA'BB'), 4.05 (2H,q,J \ 7Hz), 3.55 (4H, m; includes s 3.55 ), 2.95 (2H,d,J 8Hz), 2.10 (3H,s), 1.20 (3H,t,J 7Hz). \]
\[ \text{m.s.} \quad 250, 205, 193, 192, 147, 122, 121, 91, 78, 77, 43. \]

Attempted reaction of ethyl 2-((p-methoxybenzyl)-3-oxobutanoate (20) with chloroacetone

This was attempted using the sodium hydride-DMF method above. Various conditions were tried, but the reaction proved to be unrepeatable and gave a variety of products (tabulated). The crude products were distilled to aid identification of the major product. See table 4, p127.
Ethyl 2-((p-methoxybenzyl)-2-(2'-methylpropenyl)-3-oxobutanoate (21)

The keto ester (20) (12.0g.) was added to sodium hydride (2.7g.; 1.2 equiv.) in DMF (200ml.), and freshly distilled methallyl chloride (5.2g.; 1.2 equiv.) was added dropwise.

Workup, followed by kieselgel chromatography (40:1; 4:1 cyclohexane:ethyl acetate eluent) gave the title product as a colourless oil (9.0g.; 65%).

i.r. 1730, 1710, 1645, 1610, 1580, 1510, 1245, 1175, 1045, 775.

r.m.r. 6.75 (4H, AA'BB'), 4.70 (2H, m), 4.10 (2H, q, J 7Hz), 3.75 (3H, s), 3.10 (2H, s), 2.55 (2H, s), 1.95 (3H, s), 1.85 (3H, s), 1.25 (3H, t, J 7Hz).

Attempted decarboxylation of ethyl 2-((p-methoxybenzyl)-2-(2'-methylpropenyl)-3-oxobutanoate (21)

The title keto ester (1.0g.) was refluxed (3h.) in a mixture of glacial acetic acid (15ml.), conc. hydrochloric acid (1ml.), and water (1ml.). The bulk of the acid was removed by evaporation, and the residue neutralized with sodium bicarbonate solution, extracted into chloroform, washed, dried, and evaporated. Distillation gave the lactone (22), as a colourless viscous oil (0.6g.; 65%), b.p. 175-180°(oven)/1.0mm.

i.r. 1755, 1710, 1610, 1580, 1510, 1270, 1250, 1130, 1030.

r.m.r. 6.70 (4H, AA'BB'), 3.60 (3H, s), 2.70 (2H, AB; -CH2Ar), 2.25 (3H, s), 1.85 (2H, m; ring methylene), 1.15 (3H, s), 0.95 (3H, s).

m.s. 276, 233, 217, 173, 173, 121, 98, 43.
Attempted cleavage of ethyl 2-((p-methoxybenzyl)-2-(2'-methylpropenyl)-3-oxobutanoate (21) using osmium tetroxide-periodate

This was carried out by the osmium tetroxide-aqueous dioxane method of Pappo. The keto ester (21) (3.0g.) was added to a mixture of dioxane (55ml.), water (20ml.) and osmium tetroxide (56mg.), and stirred. Sodium metaperiodate (4.7g.) was added in portions over a period of 2.5h. and the solution stirred for a further 3h. Workup gave a black oil (3.9g.), and kieselgel chromatography (50:1; 4:1 cyclohexane: ethyl acetate eluent) gave three major fractions. Fraction 1; unchanged starting material (0.4g.; 13%). Fraction 2; Ethyl 6-(p-methoxybenzyl)-1,4-dimethyl-2,7-dioxabicyclo[2,2,1]heptane-6-carboxylates (23) (24) (0.5g.; 16%). Fraction 3; Ethyl 2-(p-methoxybenzyl)-3-oxobutanoate (0.3g.; 12%).

Data for the bicyclic acetal epimer mixture (fraction 2).

i.r. 1720, 1610, 1580, 1380, 1240, 1175, 1040, 995, 845, 740.

n.m.r. (100MHz) 6.9-6.5 (4H,m), 4.2-3.8 (2H,m; -O-CH2OH2), 3.66 (3H,s), 3.6-2.0 (6H,m), 1.7-1.1 (9H,m).

m.s. 320, 260, 245, 206, 187, 161, 121, 108, 78, 77, 43.

Hydrolysis of the ethyl 6-(p-methoxybenzyl)-1,4-dimethyl-2,7-dioxabicyclo[2,2,1]heptane-6-carboxylate epimer mixture (23) (24)

A mixture of the acetals (300mg.) was refluxed overnight in sodium hydroxide (2M; 3ml.) and ethanol (3ml.). After cooling, the basic solution was extracted with chloroform (2x3ml.), acidified and re-extracted (chloroform; 2x3ml.). The extracts were washed with sodium chloride solution (3x2ml.), dried, and evaporated to give a neutral fraction (extract
from basic solution; 200mg.), and an acidic fraction (30mg.).
The neutral fraction was chromatographed on kieselgel (100:1; 5:1 cyclohexane:ethylacetate eluent) to give two major fractions (50mg. and 35mg.). The first was identified as unchanged endo-ester (23) and the second was probably an impure sample of 2-hydroxymethyl-2,5-dimethyl-4-(p-methoxybenzyl)-2,3-dihydrofuran (25). The acid extract contained a mixture of products which were not identified.

**Fraction 1. Endo ester** See text p.39 for complete n.m.r. identification.

* i.r. 1725, 1610, 1580, 1505, 1380, 1295, 1240, 1185, 1000.
* n.m.r. 6.65 (4H,AA'BB'), 4.10 (2H,q,J 7Hz), 3.70 (3H,s), 3.50 (1H,d,6Hz), 3.4-3.1 (2H,m), 2.30 (2H:d, J 12Hz, and AB, coincidental), 1.60 (3H,s), 1.30 (7H: t,J 7Hz, with s (1.40) superimposed).
* m.s. 320, 260, 245, 206, 187, 161, 122, 121, 108, 43.

**Fraction 2. Dihydrofuran (25)**

*i.r. 3440, 1690(weak), 1610, 1585, 1510, 1240, 1030, 785.
*n.m.r. 6.8 (4H,m), 3.7 (3H,s), 3.3-2.0 (7H,m; includes s 3.2 ,-CH_2OH), 1.7 (3H,s,broad), 1.3 (3H,s).

*The i.r. and n.m.r. signals were all broadened, indicating that the sample contained impurities. Only the main features are recorded above.

Ozonolysis of ethyl 2-(p-methoxybenzyl)-2-(2'-methylcrotonyl)-5-oxobutanoate (21)

This was carried out by the general method of Smith, Greenwood, and Hudrlik. The keto ester (21) (10.0g.) was
dissolved in dichloromethane (60ml.), and ozone passed through
the cooled solution (−78\degree) till no more ozone was absorbed
(3h.). The solution was warmed and poured into a mixture of
acetic acid (50%;60ml.) and zinc powder (6g.). This was
refluxed (0.8h.), and the dichloromethane layer separated
and washed with potassium iodide solution (3x10ml.), sodium
bicarbonate solution (3x15ml.), and sodium chloride solution
(2x10ml.). The organic layer was dried and evaporated to
give ethyl 2-acetyl-2-(p-methoxybenzyl)-4-oxopentanoate (26)
as a viscous yellow oil (8.0g.). This was chromatographed
in portions (4x2.0g.) on kieselgel (50:1; 5:1 petrol:ethyl acetate eluent) to give the pure 1,4-diketone as a colourless oil (6.1g; 60%).

\[\text{i.r. 1735, 1715, 1615, 1585, 1510, 1250, 1175, 1040.}\]
\[\text{n.m.r. 6.75 (4H, s), 4.15 (2H, q, J 7Hz), 3.70 (3H, s),}\]
\[3.20 (2H, AB; -CH\_2Ar). 2.85 (2H, s), 2.35 (3H, s),\]
\[2.00 (3H, s), 1.20 (3H, t, J 7Hz).\]

3-(p-Methoxybenzyl)-2,5-hexanedione (27)

Ethyl-2-acetyl-2-(p-methoxybenzyl)-4-oxopentanoate (26) (12.0g)
was refluxed (0.5h.) in a mixture of aqueous sodium hydroxide
(2M.;200ml.) and ethanol (10ml.). The cold solution was
extracted with dichloromethane (3x30ml.), the combined extracts
washed with sodium chloride solution (3x20ml.), dried, and
evaporated to give the hexanedione as a brown viscous oil
(8.1g.). Kieselgel chromatography (30:1; 5:1 petrol:ethyl acetate eluent) gave the hexanedione as a colourless viscous oil (5.8g.; 65%).

\[\text{i.r. 1710, 1610, 1580, 1510, 1245, 1175, 1040.}\]
\[\text{n.m.r. 6.70 (4H, AA'BB'), 3.65 (3H, s), 3.3-2.2 (5H, m),}\]
4-and 5-p-Methoxybenzyl-3-methylcyclopent-2-enones (28) (29)

3-(p-methoxybenzyl)-2,5-hexanedione (3.0g.) was refluxed (2h.) in sodium methoxide solution (5%; 50ml.), and after the methanol was removed by evaporation, water (25ml.) was added. This was extracted with dichloromethane (3x15ml.) and the combined extracts washed with sodium chloride solution (3x15ml.), dried, and evaporated to give a mixture of the isomeric 4-and 5-substituted methylcyclopent-2-enones as a yellow viscous oil (2.8g.). This was chromatographed on kieselgel (50:1; 3:1 petrol:ethyl acetate eluent) to separate the isomers, and gave three main fractions, all colourless viscous oils. Fraction 1; pure '5' isomer (0.6g.; 21%). Fraction 2; mixture isomers (1.2g.; 43%). Fraction 3; pure '4' isomer (0.2g.; 7%).

i.r. (mixture isomers) 1710, 1630, 1620, 1590, 1520,
1250, 1185, 1040.
m.s. (mixture isomers) 216, 201, 122, 121, 78, 77.
n.m.r. (100MHz)

'5' isomer (28)
6.92 (4H, AA'BB'), 5.78 (1H, s, broadened), 3.72
(3H, s), 3.04 (1H, m), 2.7-2.2 (4H, m) 2.00
(3H, s, broadened).

'4' isomer (29)
6.92 (4H, AA'BB'), 5.84 (1H, s, broadened), 3.78
(3H, s), 3.02 (2H, m), 2.3-1.8 (6H, m; includes s 2.09).

See p12.

Derivatives
The '5' isomer was characterized through its 2,4-dinitrophenylhydrazone derivative, m.p. 172.5-175.5° (from methanol:chloroform).

**Analysis**
Found C 60.59, H 5.10, N 14.25; \( \text{C}_{20}\text{H}_{20}\text{N}_{4}\text{O}_{5} \)
requires C 60.61, H 5.11, N 14.14.

The '4' isomer was characterized through its semicarbazone derivative, m.p. 185-186° (from methanol).

**Analysis**
Found C 66.09, H 6.93, N 15.10; \( \text{C}_{15}\text{H}_{19}\text{N}_{3}\text{O}_{2} \)
requires C 65.93, H 6.96, N 15.38.

**Attempted cyclization of 4- and 5-n-methoxybenzyl-3-methylcyclopent-2-enones (28) (29)**

The cyclization was attempted (a) in phosphorous pentoxide-methanesulphonic acid using the method of Eaton, Carlson and Lee,49 (b) in aluminium trichloride-nitrobenzene,50 and (c) in polyphosphoric acid.

**General Method**

The cyclopentenone (150mg.) was heated with the reagent of choice (3.0g. phosphorus pentoxide-methanesulphonic acid, 10%; 3.0g. polyphosphoric acid; 0.67g. aluminium trichloride in 2.6g. nitrobenzene) at constant temperature for the required time. Saturated sodium bicarbonate solution was added carefully in portions to the cooled solution, and this was extracted with ether or chloroform (3x20ml.). The combined organic extracts were washed with sodium bicarbonate solution (2x10ml.), sodium chloride solution (3x20ml.), dried, and evaporated. Any crude product was analysed by i.r. and n.m.r. See table 5, p128, for the results.
Reduction of 5-(p-methoxybenzyl)-3-methylcyclopent-2-enone (28)

This was carried out by the method of Jorgenson\textsuperscript{52} using an aluminium hydride reagent, and also using sodium borohydride in ethanol. In both cases workup gave the saturated 2-(p-methoxybenzyl)-4-methylcyclopentan-1-ols (30) (80%).

\textit{i.r.} 3370, 1610, 1580, 1510, 1245, 1175, 1035.

\textit{n.m.r.} 6.80 (4H,m), 3.65 (3H,s), 2.5-1.3 (10H,m; includes s 1H, 1.70, broad exchangeable with $\text{D}_2\text{O}$), 1.2-0.8 (3H,m).
Part 1b

Synthesis of the dienones
Dimethyl p-methoxybenzyl propanedioate (35)

Dimethylmalonate (110g.; 2.8 equiv.) was added dropwise (1h.) to a stirred suspension of washed sodium hydride (16g.; 1.0 equiv.) in DMSO (600ml.) stabilized at 25°. The mixture was stirred till no hydrogen was evolved (0.5h.), p-methoxybenzyl chloride (52g.; 1.1 equiv.) was added (0.5h.), and the reaction mixture heated to 80° and stirred till the pH stopped changing (3h.). The cooled solution was poured into cold water (1.4l.), and extracted with ether (4x150ml.). The combined ether extracts were washed with water (4x100ml.), dried and evaporated to yield a brown oil (120g.). Distillation gave the title anisylmalonate as a colourless mobile liquid (73g.; 95%), b.p. 140-150°/1.0mm., after a forerun containing mostly dimethyl malonate (50-60°/1.0mm.). The large excess of dimethyl malonate was needed to prevent dialkylation, which occurred readily if excess chloride was present.

i.r. 1745, 1750, 1610, 1585, 1510, 1250, 1180, 1040.
n.m.r. 6.70 (4H, AA'BB'), 3.6-3.5 (10H, m; includes 2xs 3.60 , overlapping), 3.00 (2H, m).

2-(p-Methoxybenzyl)-1,3-propanediol (36)

The diester (31) (22g.) was added dropwise to a stirred suspension of lithium aluminium hydride (6.8g.; 2 equiv.) in dry ether (350ml.), and the mixture refluxed for 2.5h. Workup and crystallisation (ether) gave the diol as a white crystalline solid (18.5g.; 90%), m.p. 66-67°.

i.r. (nujol) 3260, 1610, 1530, 1510, 1250, 1040.
n.m.r. (CDCl₃) 6.70 (4H, AA'BB'), 3.60 (7H, m; includes 3.65 ), 2.50 (4H, unresolved m; 2H exchangeable
with D$_2$O, 2x-OH; and -CH$_2$Ar), 1.90 (1H, m).

**Analysis** Found C 67.40, H 8.19; C$_{11}$H$_{16}$O$_3$ requires C 67.35, H 8.16.

2- (p-Methoxybenzyl)-1,3-dichloropropane (37)

Phosphorus oxychloride (34g.; 2.0 equiv.) was added dropwise to a cooled solution of the 1,3-propanediol (22g.) in pyridine (250ml.) and then heated at 100° (1h.). The solution was cooled, poured into ice cold hydrochloric acid (2.0M.; 750ml.), and this was extracted with ether (3x150ml.). The combined ether extracts were washed with hydrochloric acid (2.0M.; 4x100ml.), sodium bicarbonate solution (2x50ml.), and sodium chloride solution (1x150ml.), dried and evaporated to give a viscous brown oil (21g.). Distillation gave the 1,3-dichloropropane as a colourless mobile oil (14.1g.; 55%), b.p. 110–115°/0.3mm.

**i.r.** 1610, 1580, 1510, 1245, 1050, 800.

**n.m.r.** 7.20 (4H, AA'BB'), 3.90 (3H, s), 3.70 (4H, m; -CH$_2$Cl) 2.80 (2H, m; -CH$_2$Ar), 2.40 (1H, m).

**m.s.** 256, 254, 252, 122, 121, 91, 78, 77, 65, 51, 49, 39.

Dimethyl n-methoxybenzyl-2-(n-methoxybenzyl)allyl -
propanedioate (33)

Dimethyl 2-p-methoxybenzyl propanedioate (7.6g.; 1.0 equiv.) was added dropwise to a stirred suspension of washed sodium hydride (3.6g.; 2.5 equiv.) in DMSO (120ml.) at 25°. The reaction mixture was heated to 60° till no hydrogen was evolved (1h.), cooled, and added (0.2h.) to 2-(p-methoxybenzyl)
-1,3-dichloropropane (6.9g.; 1.0 equiv.) in DMSO (90ml.) at 25°. The mixture was stirred (30°; 2.5h.), cooled, poured into cold water (500ml.), and extracted with benzene (4x75ml.). The combined benzene extracts were washed with sodium chloride solution (4x50ml.), dried, and evaporated to give a viscous brown oil (8.3g.). This was chromatographed on alumina (50:1; 5:1 petrol:ethyl acetate eluent) to give a white solid (5.5g.), and crystallisation (ether) gave the title allyl malonate as a white crystalline solid (4.5g.; 35%), m.p. 50.5-51.5°.

**i.r.** (nujol) 1735, 1645, 1585, 1510, 1245, 1175, 1085, 900, 840, 805.

**n.m.r.** (CDCl₃) 6.75 (8H, m), 4.80 (2H, s, broad), 3.65 (6H, 2xs, overlapping; 2x-Ar-OCH₃), 3.55 (6H, s; 2x-CO₂CH₃), 3.20 (4H, s, broad), 2.55 (2H, s, broad).

**m.s.** 412, 259, 227, 161, 160, 144, 122, 121, 77, 44, 40.

**Analysis** Found C 69.71, H 6.79; C₂₄H₂₈O₆ requires C 69.90, H 6.80.

4-Hydroxymethyl-2,4-di(p-methoxybenzyl)pent-1-ene-5-ol (41)

This was prepared by lithium aluminium hydride reduction of the diester, and crystallised from petrol-ether to give the diol (90%), m.p. 84-85°.

**i.r.** (nujol) 3380, 1640, 1615, 1585, 1510, 1250, 1180, 1030, 1015, 910, 900, 800.

**n.m.r.** 5.30 (8H, m), 4.90 (2H, s, broad), 3.75 (6H, s; 2x-Ar-OCH₃), 3.50 (4H, s, broad; 2x-CH₂OH), 3.30 (2H, s, broad), 2.60 (2H, s, broad), 2.00 (4H, s, broad; 2H exchangeable with D₂O).

**m.s.** 356, 235, 162, 161, 159, 147, 122, 121, 91, 77, 43.

**Analysis** Found C 74.31, H 3.00; C₂₂H₂₈O₄ requires C 74.16,
Methyl p-methoxybenzyl- 2-(p-methoxybenzyl)allyl acetate (44)

This was prepared by the general method of Krapcho and Lovey\textsuperscript{12} for monodecarboxylation of geminal diesters. The diester (5.0g.) was heated in wet DMSO (60ml.) with sodium chloride (1.0g.) and water (2.0g.) at 195° (3h.). Workup gave the crude monoester as a brown oil (5.1g.), and alumina chromatography (50:1; 5:1 petrol:ethyl acetate eluent) gave the pure monoester as a colourless oil (2.6g.;60%).

\textit{i.r.} 1735, 1645, 1615, 1585, 1510, 1250, 1180, 1035, 900, 830.

\textit{n.m.r.} 6.80 (8H,m), 4.75 (2H,s,broad), 3.65 (6H,s; 2x-Ar-0CH\textsubscript{3}), 3.50 (3H,s;-CO\textsubscript{2}CH\textsubscript{3}), 3.20 (2H,s, broad), 2.8-1.9 (5H,m).

\textit{m.s.} 354, 192, 161, 121, 91, 77, 44, 43.

\textit{Analysis} Found C 74.36, H 7.39; C\textsubscript{22}H\textsubscript{26}O\textsubscript{4} requires C 74.58, H 7.34.

2,4-Di(p-methoxybenzyl)pent-1-ene-5-ol (47)

The monoester was reduced using lithium aluminium hydride (2 equiv.) to give the title alcohol as a yellow solid. Crystallisation (ether) gave the product as a white crystalline solid, m.p. 59-60°, (75%).

\textit{i.r.} (nujol) 3380, 1640, 1610, 1580, 1510, 1240, 1180, 1030, 835, 805.

\textit{n.m.r.} (CDCl\textsubscript{3}) 7.15 (8H,m), 5.00 (2H,s,broad), 3.90 (6H,s; 2x-Ar-0CH\textsubscript{3}), 3.65 (2H,s,broad;-CH\textsubscript{2}OH), 3.35 (2H,s,broad), 2.60 (2H,s,broad), 2.10 (3H,m),
1.40 (1H, s, broad; exchangeable with D₂O).

m.s. 326, 308, 187, 184, 164, 161, 147, 121, 91, 77.

Analysis. Found C 77.34, H 8.04; C₂₁H₂₆O₂ requires C 77.30, H 7.98.

5-Chloro-2,4-di(p-methoxybenzyl)pent-1-ene (49)

The above alcohol (1.0g.) was heated with phosphorus oxychloride (0.9g.; 2.0 equiv.) in pyridine (50ml.) at 90° (1h.). Workup and distillation gave the title chloride as a colourless oil (90%), b.p. 150-160°(oven)/0.1mm.

i.r. 1645, 1615, 1590, 1515, 1250, 1180, 1040, 900, 840, 805.

n.m.r. (CDCl₃) 6.95 (8H, m), 4.95 (2H, s, broad), 3.90 (6H, s; 2x-Ar-OC₆H₅), 3.45 (2H, s, broad; -CH₂Cl), 3.20 (2H, s, broad), 2.60 (2H, s, broad), 2.10 (3H, s, broad).

Attempted cyclizations of the diester (38), diol (41), monooester (44), alcohol (47), and chloride (49)

General method

The cyclizations were attempted using a variety of reagents and reaction conditions. (See tables 6-8, p.129-131)

The general methods used for every attempt are outlined below.

The compound (200mg.) was added to the reagent of choice (10ml.) and heated with vigorous stirring at the required temperature for the required time. The cooled reaction mixture was poured into water, extracted with ethyl acetate, and the combined extracts washed with sodium chloride solution, dried, and evaporated to yield the crude product. This was chromato-
graphed on kieselgel (50:1; petrol:ethyl acetate eluent).

In the hydriodic acid – red phosphorus reactions, the ethyl acetate extracts were filtered to remove any phosphorus, washed with sodium thiosulphate solution to remove any free iodine, and then washed with sodium chloride solution.

The hydriodic acid – red phosphorus reagent was made from 55% hydriodic acid distilled from red phosphorus (10ml.), and added red phosphorus (250mg.). The other acids used were: $\text{H}_2\text{SO}_4$ conc.; $\text{HBr}$ 48%; $\text{CH}_3\text{CO}_2\text{H}$ glacial.

(a) Using the diester (38)

Cyclization attempts produced a mixture of the epimeric lactones (40) as a colourless gum. The epimer ratio (2.7:1), as judged from the two methyl singlets in the n.m.r., was similar in every case.

\[
\begin{align*}
\text{i.r.} & : 1760, 1735, 1615, 1590, 1515, 1250, 1180, 1120, 1040, 835, 810. \\
\text{n.m.r.} & : 6.95 (8\text{H,m}), 3.95 (9\text{H,s,broadened}), 3.6-2.0 (6\text{H,m}), 1.65 (2.2\text{H,s;}-\text{O-CH}_3 \text{ one epimer}), 1.10 (0.8\text{H,s;}-\text{O-CH}_3 \text{ other epimer}).
\end{align*}
\]

(b) Using the diol (41)

The major isolable products were the tetrahydrofuran (42) and the acetylated tetrahydrofuran (43). Judging from the n.m.r. methyl singlet at $\delta 1.2$, only one epimer was formed.

Tetrahydrofuran (42)

\[
\begin{align*}
\text{i.r.} & : 3450, 1615, 1585, 1240, 1170, 1025, 830, 815. \\
\text{n.m.r.} (\text{CDCl}_3; 100\text{MHz}) & : 6.94 (8\text{H,m}), 3.75 (6\text{H,s}), 3.7-3.1 (4\text{H,m}), 2.64 (4\text{H,m}), 2.24 (1\text{H,s; exchangeable with D}_2\text{O}), 1.9-1.3 (2\text{H,m}), 1.13 (3\text{H,s}). \\
\end{align*}
\]
Acetylated tetrahydrofuran (43)

**i.r.** 1725, 1610, 1580, 1510, 1245, 1175, 1030.

**n.m.r.** 6.70 (8H,m), 3.8-3.4 (10H,m; includes s 3.70 ), 2.65 (4H,m), 2.10 (3H,s), 1.9-1.6 (2H,m), 1.25 (3H,s).

(a) Using the monoester (44)

The lactone (45) was the only identifiable product, and judging from the sharp n.m.r. methyl singlet at δ1.25 only one epimer was formed.

**i.r.** 1770, 1735, 1615, 1585, 1515, 1250, 1180, 1035,

**n.m.r.** 6.75 (8H,m), 3.85 (6H,s), 3.5-2.1 (7H,m), 1.25 (3H,s).

(d) Using the chloride (49)

Polyphosphoric cyclization gave the required 3-chloro-methyl-7-methoxy-1-methyl-1-(p-methoxybenzyl)-1,2,3,4-tetrahydronaphthalene epimers (50) as a clear oil after kieselgel chromatography (50:1; 5:1 petrol:ethyl acetate eluent). The maximum yield (50%) was obtained by heating at 115° (0.5h.), and the epimer ratio was 2:1 judging from the n.m.r. methyl singlets at δ1.25.

**i.r.** 1615, 1585, 1255, 1185, 1045, 860.

**n.m.r.** (CDCl₃) 6.85 (7H,m), 3.75 (6H,4xs overlapping), 3.45 (2H,m), 3.1-1.2 (10H,m; includes 2xs 1.25 , overlapping, ratio 2:1).

**m.s.** 346, 344, 226, 225, 224, 223, 222, 187, 159, 147, 121.

**Analysis** Found C 72.62, H 7.25, Cl 11.18; C₂₁H₂₅ClO₂ requires C 73.15, H 7.26, Cl 10.30.
(a) Using the alcohol (47)

The alcohol (500mg.) was heated in hydriodic acid (20ml.) with red phosphorus (500mg.) at 130° for 0.5h. with vigorous stirring. Workup gave a white glassy foam (520mg.), and kieselgel chromatography (40:1; 1:1 petrol:ethyl acetate eluent) gave the 7-hydroxy-3-iodomethyl-1-methyl-1-(p-hydroxybenzyl)-1,2,3,4-tetrahydronaphthalene epimers (48) (the first fractions) as a white glassy foam (275mg.; 45%). Later fractions contained a number of compounds which were not identified. The iodides (48) were unstable to chlorinated solvents.

\[ \text{i.r. (nujol) } 3340, 1615, 1515, 1225, 810, 755. \]

\[ \text{n.m.r. (CD}_2\text{COCD}_2; 100\text{MHz)} 3.10 (2H, s, broad, exchangeable with D}_2\text{O}; 2\text{Ar-CH}_2\text{OH}, 6.36 (7H, m), 3.28 (2H, m; -CH}_2\text{I), 2.8-0.9 (10H, m; includes 2xs 1.24 and 1.21, overlapping, ratio 3:1; -CH}_3, 2 \text{ epimers).} \]

\[ \text{m.s. 408, 301, 175, 174, 173, 172, 159, 158, 157, 146, 145, 128, 127, 107.} \]

Sealed tube reactions: Formation of the dienones (7) (57)

Both dienones were obtained by the procedure outlined below. The phenolic diene (57) was formed if excess base (2.5 equiv.) was present, and the adamantanoïd diene (7) using 1.0 equivalents.

General Method

The iodide (48) (180mg.) was dissolved in dry t-butanol (60ml.) and the required amount of a solution of potassium t-butoxide in t-butanol was added. The reaction mixture was poured into the sealed tube, dry nitrogen gas bubbled through (0.5h.), and the mixture frozen. The tube
was evacuated, sealed, and heated at 170° for 3 hours. When cool, the tube was opened, acetic acid (0.5M.; 2ml.) was added to neutralise any remaining base and to assist in evaporation of the t-butanol. The residue left after evaporation was dissolved in ethyl acetate (30ml.), the ethyl acetate layer washed with sodium thiosulphate solution (2x10ml.), sodium chloride solution (4x10ml.), dried, and evaporated to give a pale brown foam (120mg.). This was crystallised from petrol-ethyl acetate to give a white crystalline solid (typically 10mg.). Chromatography of the residue on kieselgel (50:1; 1:1 petrol:ethyl acetate eluent) gave eight different fractions. None of these were similar to the starting iodide, and some of the later fractions contained the required dienone. Crystallisation of these from petrol-ethyl acetate yielded the dienone as an off-white crystalline solid (typically 20mg.). Combination of the crystalline dienone fractions and recrystallisation gave the pure dienone as a white crystalline solid (typically 15mg.; 12% overall).

See text p34 for n.m.r. details.

**Phenolic dienone** (57)

m.p. 216-219°.

i.r. (nujol) 3190, 1655, 1610, 1580, 1500, 1240, 865, 850, 820.

n.m.r. (CD$_3$COCD$_3$; 100MHz) 8.10 (1H, s, broad, exchangeable with D$_2$O), 7.1-6.6 (4H, m), 6.28 (1H, dd, J 12.5 and 2.5Hz), 6.00 (1H, dd, J 10 and 2.5Hz), 5.60 (1H, dd, J 12.5 and 2.5Hz), 3.4-1.4 (9H, m), 1.30 (3H, s).

m.s. 280, 173, 172, 171, 160, 159, 158, 145, 144, 131, 122, 107, 91, 77.
UV. (EtOH) \( \lambda_{\text{max}} \) 230 (\( \epsilon \) 14,000), 278 (\( \epsilon \) 2,100).

Accurate Mass Found 280.1460; \( C_{19}H_{20}O_2 \) requires 280.1463.

Adamantanoid dienone (7)

M.P. 237-239°.

i.r. (nujol) 1665, 1655, 1625, 1600, 1290, 1170, 890.

n.m.r. (CDCl₃; 100MHz) 6.72 (2H,d, J 10Hz), 6.38 (2H:dd, J 10 and 2 Hz, with superimposed s, 6.32), 5.94 (1H,d, J 10Hz), 2.5-1.4 (12H,m), 1.09 (3H,s).


Accurate Mass Found 280.1463; \( C_{19}H_{20}O_2 \) requires 280.1463.

Conversion of the phenolic dienone (57) to the adamantanoid dienone (7)

The phenolic dienone (30mg.) was dissolved in t-butanol (30ml.), and potassium t-butoxide solution (0.5 equiv.) and water (0.2ml.) were added. The sealed tube conditions (170°; 3h.) and workup gave a white solid (30mg.) containing the adamantanoid dienone and only small amounts of contaminants. Crystallisation (ethanol) yielded the pure adamantanoid dienone (12mg.; 40%).

Conversion of the adamantanoid dienone to the bis-dienone (8)

The adamantanoid dienone (13mg.) was sealed in a bulb with freshly distilled dioxane (5ml.) and D.D.q.* (110mg.), and heated at 102° for 4.5 days. The resulting solution was evaporated to half bulk, cooled, and filtered to remove the crystallised quinol. The residual solution was evaporated to dryness and chromatographed on alumina (50:1; 3:2 benzene:
ethyl acetate eluent) to yield a white solid (14 mg.). Crystallisation (ethanol) gave the bis-dienone as a white crystalline solid (6 mg.; 35%).

**M.p.** 195-202°

**i.r.** (nujol) 1655, 1625, 1295, 1285, 1130, 945, 905, 880, 855, 800, 755.

**n.m.r.** (CDCl₃; 100 MHz) 7.09 (1H, d, J 10 Hz), 6.79 (1H, d, J 10 Hz), 6.51 (1H, dd, J 10 and 1.5 Hz), 6.29 (1H, dd, J 10 and 1.5 Hz), 6.18 (1H, d, J 1.5 Hz), 6.12 (1H, d, J 1.5 Hz), 2.6-1.4 (9H, m), 1.24 (3H, s).

**m.s.** 278, 263, 195, 194, 167, 166, 165, 152, 130, 121, 115. **Accurate mass** Found 278.1306; C₁₉H₁₈O₂ requires 278.1307.

*2,3-Dichloro-5,6-dicyanobenzoquinone. (Crystallised from benzene).*
Part 2

Bicyclic acetal work
Separation of the \textit{endo}-and \textit{exo}-ethyl 6-(p-methoxybenzyl)-1,4-
dimethyl-2,7-dioxabicyclo[2,2,1]heptane-6-carboxylates (23) (24)

These were separated by fractional recrystallisation from petrol (40-60°), and identified through their n.m.r. spectral characteristics.

See text P 39.

\textbf{Exo-ester} (24)

\textbf{m.p.} 69-70°

\textbf{i.r.} (nujol) 1730, 1610, 1580, 1510, 1380, 1290, 1250, 1190, 985.

\textbf{n.m.r.} (100MHz) 6.67 (4H, AA'BB'), 3.96 (2H, q, J 7Hz), 3.62 (3H, s), 3.44 (1H, d, J 6Hz; H-3endo), 3.3-3.0 (2H: dd, H-3exo, one AB, -CH$_2$Ar), 2.67 (1H, AB; -CH$_2$Ar) 2.31 (1H, dd, J 12 and 2.5Hz; H-5exo), 1.48 (7H: d, H-5endo, with overlapping s, 1.41 ), 1.18 (3H, t, J 7Hz).

\textbf{Analysis} Found C 67.44, H 7.54; C$_{18}$H$_{24}$O$_5$ requires C 67.50, H 7.50.

\textbf{Endo-ester} (23)

\textbf{m.p.} 88.5-90.5°

\textbf{i.r.} (nujol) 1725, 1610, 1580, 1505, 1380, 1295, 1240, 1185, 1000.

\textbf{n.m.r.} (100MHz) 6.68 (4H, AA'BB'), 4.12 (2H, q, J 7Hz), 3.70 (3H, s), 3.51 (1H, d, J 6Hz; H-3endo), 3.4-3.1 (2H: dd, 3.17 ,H-3exo, one AB 3.34 , -CH$_2$Ar), 2.28 (2H,d, J 12Hz; H-5endo, coincidental with AB, -CH$_2$Ar) 1.58 (3H, s), 1.40 (3.5H, s), 1.28 (3.5H, t, J 7Hz).

\textbf{Analysis} Found C 67.40, H 7.52; C$_{18}$H$_{24}$O$_5$ requires
C 67.50, H 7.50.

m.s. (mixture epimers) 320, 260, 245, 206, 187, 161, 122, 121, 108, 43.

Hydrolysis of the exo and endo ethyl esters (23) (24)

Each epimer (100mg.) was hydrolysed by refluxing (15h.) in a mixture of aqueous sodium hydroxide (2M.; 2ml.) and ethanol (2ml.). Workup gave a neutral and an acidic fraction, typically 80mg. and 15mg. respectively. The acid fraction contained a number of compounds which were not identified. The neutral fraction from the exo-ester was chromatographed on kieselgel (40:1; 5:1 petrol:ethyl acetate eluant) to give a yellow oil (25mg.) which was probably the dihydrofuran (25). The neutral fraction obtained from the endo-ester was the unchanged crystalline ester (70mg.).

Dihydrofuran (25)

i.r. 3400, 1680 (weak), 1610, 1585, 1510, 1385, 1250, 1160, 1040, 1005, 850.

n.m.r. 6.7 (4H, m), 3.8 (3H, s), 3.4-2.0 (7H, m; includes s, 3.2; -CHOH), 1.7 (3H, s, broad), 1.3 (3H, s).

Benzyl 3-oxobutanoate (63)

This was prepared by the method of Bowman and Fordham44. Distillation gave the keto ester (80%), b.p. 126-128°/2.0mm. (Lit.53 155-157°/15mm.).

i.r. 1735, 1715, 1310, 1260, 1150, 1025, 740, 690.

n.m.r. 7.05 (5H, s), 4.90 (2H, s), 3.25 (2H, s), 2.05 (3H, s).
Benzyl 2,2-di-(2'-methylpropenyl)-3-oxobutanoate (64)

This was prepared by a 'one pot' two step dialkylation of the keto ester (63) in DMSO using sodium hydride and methallyl chloride. The reaction conditions are critical, and should be followed exactly for a good yield.

1st alkylation The keto ester (30.0g.) was added dropwise to a stirred suspension of washed sodium hydride (7.9g.; 1.05 equiv.) in dry DMSO (400ml.), at 25°. The reaction mixture was then stirred till no hydrogen was evolved (0.8h.), and methallyl chloride (15.7g.; 1.1 equiv.) was added dropwise (10 min.). The reaction was heated to 70°, stirred till the pH changed from 11 to 8 (3h.), and cooled to 25°.

2nd alkylation Excess base must not be present in this alkylation, otherwise a very poor yield of dialkylated keto ester is obtained.

Washed sodium hydride (7.1g.; 0.95 equiv.) in dry DMSO (50ml.) was added to the reaction mixture in 1g. portions (0.5h.), and this was stirred at 25° till no hydrogen was evolved (1.2h.). Methallyl chloride (30.0g.; 2.1 equiv.) was added (15 min.), the temperature raised to 80°, and the reaction mixture stirred till the pH stopped changing (2.5h.).

The cooled reaction mixture was poured into cold water (2l.), and this was extracted with benzene (4x200ml.). The combined benzene extracts were washed with sodium chloride solution (5x150ml.), dried, evaporated, and distilled to give the dialkylated keto ester as a colourless mobile oil (43g., 90%), b.p. 130-140°/0.5mm.

i.r. 1735, 1710, 1645, 1135, 1150, 895, 695.

n.m.r. 7.05 (5H,s), 4.95 (2H,s), 4.60 (2H,s,broad), 4.50 (2H,s,broad), 2.55 (4H,s), 1.90 (3H,s), 1.50 (6H,s).
Benzyl 6-(2'-methylpropenyl)-1,4-dimethyl-2,7-dioxabicyclo-
\[2.2.1\]hentane-6-carboxylates (65) (66)

These were prepared by oxidation of the 2,2-di-(2'-methyl-
propenyl)-3-oxobutanoate with m-chloroperbenzoic acid in
chloroform following the general method of Gaoni. The
highest yields were obtained using an excess (25%) of commercial
peracid (80%) and stirring at room temperature for 15 hours.
A greater excess of peracid leads to decreasing yields as the
methylpropenyl side chain in the bicyclic acetal product is
also epoxidised. Workup gave a yellow viscous oil containing
mainly starting material and the title epimeric acetals, and
this was initially chromatographed on alumina (40:1; 5:1
petrol:ethyl acetate eluent) to give the starting material
(15% recovery), the bicyclic acetals (colourless viscous
oil; 40%), and slower running fractions probably containing
the epoxidised bicyclic acetals (colourless viscous oil; 5%).
The fractions containing the title acetals were chromatographed
on kieselgel (50:1; 8:1 petrol:ethyl acetate eluent) in 1g.
portions to separate the epimers, as this scale gave the
greatest recovery of the acetals from the column. A typical
column gave the pure endo-ester as a colourless viscous oil
(200mg.; 31% of recovered acetals), a mixture of the two epimers
(300mg.; 46% of recovered acetals), and pure exo-ester as a
white solid (150mg.; 23% of recovered acetals). The total
recovery from the column was 65%. Overall yields for the
oxidation after crystallisation of some exo-epimer from the
mixed fractions were: endo, 12%; mixture (containing 2:1
endo:exo ratio) 13%; exo, 10%. 
Endo-ester (65)

\[ \text{b.p. 170-175^\circ (oven) / 0.2 mm.} \]

\[ \text{i.r. 1725, 1640, 1380, 1190, 1140, 1125, 995, 890.} \]

\[ \text{740, 690.} \]

\[ \text{n.m.r. 7.20 (5H, s), 5.00 (2H, s; -CH_2-Ph), 4.65 (1H, s, broad),} \]

\[ 4.55 (1H, s, broad), 3.60 (1H, d, J 6 Hz; H-3\text{endo}),} \]

\[ 3.20 (1H, dd, J 6 \text{ and } 3 Hz; H-3\text{exo}), 2.50 (2H, d, J} \]

\[ 12 Hz, H-5\text{endo}, \text{ one AB, } -\text{CH}_2-\text{C(CH}_3\text{):CH}_2-, 1.90} \]

\[ (1H, AB; -\text{CH}_2-\text{C(CH}_3\text{):CH}_2-, 1.55 (6.5H, s), 1.40} \]

\[ (3.5H, s, shows shoulder).} \]

\[ \text{m.s. 316, 256, 165, 145, 144, 92, 91, 43.} \]

\[ \text{Analysis Found C 72.16, H 7.69; C_{19}H_{24}O requires C} \]

\[ 72.15, H 7.60.} \]

Exo-ester (66)

\[ \text{m.p. 65-66^\circ (from 40-60^\circ petrol)} \]

\[ \text{i.r. (nujol) 1710, 1650, 1385, 1315, 1210, 1200, 1145,} \]

\[ 1050, 875, 755, 750.} \]

\[ \text{n.m.r. 7.10 (5H, s), 4.95 (2H, s), 4.45 (1H, s, broad),} \]

\[ 4.35 (1H, s, broad), 3.35 (1H, d, J 5 Hz; H-3\text{endo}),} \]

\[ 3.15 (1H, dd, J 5 \text{ and } 2.5 Hz; H-3\text{exo}), 2.8-2.0} \]

\[ (3H, m), 1.55 (3.5H, s, broadened), 1.45 (3.5H, s,} \]

\[ \text{shows shoulder), 1.30 (3H, s).} \]

\[ \text{m.s. 316, 256, 248, 225, 200, 165, 145, 92, 91, 43.} \]

\[ \text{Analysis Found C 72.13, H 7.63; C_{19}H_{24}O requires C} \]

\[ 72.15, H 7.60.} \]
Exo and endo-6-isobutyl-1,4-dimethyl-2,7-dioxabicyclo[2,2,1]heptane-6-carboxylic acids (67) (68)

These were prepared by hydrogenation of the exo- and endo-benzyl esters with concomitant saturation of the 2-methylpropenyl side chain, and the exact conditions below must be followed for good yields as the hydrogenation is very sensitive to both changes in temperature and traces of water.

The pure epimer (500mg.) and the palladium on charcoal catalyst (25mg.; 10%) were stirred vigorously in ethyl acetate (8ml., freshly washed with sodium bicarbonate solution, dried over 'super dry' magnesium sulphate, and distilled) at 20° for 1 hour under a hydrogen atmosphere. Filtration and evaporation yielded the acid as a white solid, crystallisable from dry petrol (40-60°). Typical yields after two recrystallisations were: exo-acid, 210mg. (60%); endo-acid, 280mg. (80%). See text p. 48.

Exo-acid (68)

m.p. 82-87° (decomp.)

i.r. (nujol) 3500-2500, 1690, 1390, 1160, 1135, 1125, 1010, 890, 875, 860.

* n.m.r. (PhCl; 100MHz) 9.4 (1H, s, broad), 3.3 (1H, d, J 6Hz; H-3endo), 3.2 (1H, dd, J 6 and 3Hz; H-3exo), 2.5 (1H, dd, J 12 and 3Hz; H-5exo), 2.1-1.8 (1H, m), 1.6 (5H, m, includes s, 1.6 ), 1.4 (1H, d, J 12Hz; H5-endo), 1.3 (3H, s), 0.8 (6H, d, J 5Hz).

m.s. (no mass peak) 185, 184, 141, 125, 45, 44.

Endo-acid (67)

m.p. 84-89° (decomp.)
i.r. (nujol) 3300-2400, 1685, 1385, 1150, 1000, 990, 895, 875, 850.

*n.m.r. (PhCl; 100MHz) 11.1 (1H, s, broad), 3.6 (1H, d, j 6Hz; H-3endo), 3.2 (1H, dd, j 6 and 3Hz; H-3exo), 2.6 (1H, d, j 12Hz; H-5endo), 2.1-1.8 (1H, m), 1.7 (3H, s), 1.7-1.1 (6H, m; includes s, 1.2), 0.8 (6H, d, j 6Hz).

m.s. (no mass peak) 184, 141, 122, 44, 43.

*n.m.r. fault. Values only accurate to ±0.1.

Sodium salts of the acids (76) (77)

These were prepared by adding aqueous sodium hydroxide solution (0.07M; 6ml.) to a solution of the acid (100mg.; 1.1 equiv.) in ethanol (1ml.). The ethanol and water were pumped off under vacuum to give the salt as a white solid (110mg.; 100%). The salt was triturated with cold water and then with petrol, filtered, and dried.

Exo-sodium salt (77)

m.p. 175-185°(decomp.)

i.r. (nujol) 1575, 1375, 1130, 1010, 850.

n.m.r. (D₂O) 3.65 (1H, d, j 6Hz), 3.35 (1H, dd, j 6 and 3Hz), 2.65 (1H, dd, j 12Hz), 2.0-1.2 (10H, m; includes s, 1.55, broad), 0.90 (6H, d, j 6Hz).

Endo-sodium salt (76)

m.p. 155-170°(decomp.)

i.r. (nujol) 1585, 1370, 1260, 1160, 1005, 870.

n.m.r. (D₂O) 3.75 (1H, d, j 6Hz), 3.30 (1H, dd, j 6 and 3Hz), 2.60 (1H, d, j 12Hz), 2.2-1.2 (10H, m; includes 1.70
and 1.50, 2xs), 0.95 (6H,2xd,J 6Hz,overlapping).

6-Isobutyl-1,4-dimethyl-2,7-dioxabicyclo[2,2,1]heptanes (75)

These were prepared by thermal decarboxylation of the bicyclic acids in the solid state and in solution. Typically heating the acid (exo; 180°, 30min.: endo; 140°, 15min.) gave a mixture of the decarboxylated title acetals as a pungent yellow oil (100% crude). Kieselgel chromatography (50:1; 3:1 petrol:ethyl acetate eluent) gave the pure mixture as a colourless oil (55%).

i.r. 1460, 1380, 1160, 1060, 1010.
*n.m.r. (PhCl; 100MHz) 3.4 (1H,2xd,J 6Hz; H-3endo),
3.3 (1H,dd,J 6 and 3Hz; H-3exo), 2.2-1.0 (12H, m; includes s,1.5 and 2xs,1.3 ), 0.9-0.7 (6H,m).

m.s. 184, 141, 109, 81, 68, 43.

2-Hydroxymethyl-4-isobutyl-2,5-dimethyl-2,3-dihydrofuran (73)

A mixture of the 6-isobutyl-1,4-dimethyl-2,7-dioxabicyclo[2,2,1]heptanes was refrigerated neat overnight to yield the dihydrofuran (100%).

i.r. 3440, 1695(medium), 1465, 1220, 1050.
*n.m.r. (PhCl; 100MHz) 3.4 (2H,s; -CH2-CH), 2.6-1.3 (9H, m; includes t,J 2Hz, 1.6 , CH2-CH=0), 1.2 (3H,s), 0.8 (6H,d,J 6Hz).

m.s. 184, 169, 166, 141, 109, 67, 43.

*n.m.r. fault. Values only accurate to ±0.1.
Acetylation of 2-hydroxymethyl-4-isobutyl-2,5-dimethyl-2,3-dihydrofuran (73)

The dihydrofuran was acetylated using the method of Gaoni.\textsuperscript{15} Acetylation using excess acetic anhydride in pyridine at room temperature gave the mono-acetylated dihydrofuran (70) after 3 hours. (80%).

\textit{i.r.} 1740, 1700, 1380, 1225, 1040.
\textit{n.m.r.} 3.5 (2H, s), 2.7-1.3 (11H, m; includes 1.9, s, and 1.6, t, J 2Hz), 1.3 (3H, s), 0.9 (6H, d, J 6Hz).

Benzyl 2-methyl-1,3-dioxolane-2-carboxylate (79)

This was prepared by the method of Salmi\textsuperscript{54} to give the benzyl ester as a colourless liquid (80%), b.p. 140-150\textdegree/0.5mm. (Lit.\textsuperscript{54} 134-140\textdegree/0.2mm.).

\textit{i.r.} 1740, 1380, 1180, 1040, 740, 690.
\textit{n.m.r.} (CDCl\textsubscript{3}) 7.30 (5H, s), 5.15 (2H, s), 3.90 (4H, s), 2.70 (2H, s), 1.45 (3H, s).

2-Methyl-1,3-dioxolane-2-carboxylic acid (80)

This was prepared by hydrogenation of the benzyl ester, and was recrystallised from petrol:ether to give the acid as a white crystalline low melting point solid (85%), m.p. 15\textdegree (approx.). (Lit.\textsuperscript{55} b.p. 100\textdegree/0.2mm.).

\textit{i.r.} 3600-2400, 1715, 1380, 1180, 1045, 950.
\textit{n.m.r.} (CDCl\textsubscript{3}) 10.35 (1H, s, broad), 4.00 (4H, s), 2.70 (2H, s), 1.50 (3H, s).
\textit{m.s.} 146, 131, 89, 37, 59, 58, 45, 44, 43, 42, 41, 39.
2,2-Dimethyl-1,3-dioxolane (81)

This was obtained by thermal decarboxylation of the dioxolane acid in solution or in the solid state (200°; 3h.; 95%). The dimethyl dioxolane was distilled for purification (85%), b.p. 90°(oven)/760mm.

i.r. 1380, 1370, 1215, 1150, 1065, 840.
n.m.r. (CDCl₃) 4.00 (4H,s), 1.40 (6H,s).
This appendix contains tables giving the exact reaction conditions and product formed during:

1. the attempted reaction of the keto ester (20) with chloroacetone

2. the attempted cyclization of the cyclopentenones (28) and (29)

and 3. the cyclization attempts to form the tetrahydro-naphthalene.
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<th></th>
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Table 4 (See p97)
Table 5. Cyclization of cyclopentenones (See p 103 and p 15).

Cyclization attempts on '5' substituted isomer (28)

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<th>Product</th>
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<td>°C</td>
<td>h.</td>
<td>% tar</td>
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<td>-</td>
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<tr>
<td>a</td>
<td>85</td>
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<td>-</td>
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<tr>
<td>a</td>
<td>85</td>
<td>3</td>
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<tr>
<td>a</td>
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<tr>
<td>a</td>
<td>150</td>
<td>½</td>
<td>20</td>
</tr>
<tr>
<td>b</td>
<td>120</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>b</td>
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<td>1</td>
<td>5</td>
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<td>200</td>
<td>½</td>
<td>10</td>
</tr>
<tr>
<td>c</td>
<td>40</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>c</td>
<td>110</td>
<td>1</td>
<td>-</td>
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<td>c</td>
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Cyclization attempts on '4' substituted isomer (29)

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<td>°C</td>
<td>h.</td>
<td>% tar</td>
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<td>b</td>
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<tr>
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<tr>
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Attempted Cyclization to the tetrahydronaphthalene (See p109 and p23)

Table 6. Cyclization using dimethyl p-methoxybenzyl-2-(p-methoxybenzyl)allylpropanedioate (38)

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<th>Time(h.)</th>
<th>Product</th>
<th>Yield %</th>
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<tr>
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<td>reflux</td>
<td>1</td>
<td>lactone (40)</td>
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<td>PPA</td>
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<td>lactone (40)</td>
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<td>1</td>
<td>lactone (40)</td>
<td>15</td>
</tr>
<tr>
<td>PPA</td>
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<td>½</td>
<td>tar</td>
<td>-</td>
</tr>
<tr>
<td>HI/P</td>
<td>80</td>
<td>1</td>
<td>lactone (40)</td>
<td>25</td>
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<tr>
<td>HI/P</td>
<td>130</td>
<td>½</td>
<td>tar</td>
<td>-</td>
</tr>
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<td>Reagent</td>
<td>Temp.</td>
<td>Time</td>
<td>Product</td>
<td>Yield</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------</td>
<td>------</td>
<td>----------------------------------------------</td>
<td>-------</td>
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<tr>
<td>HBr/HAc (1:1)</td>
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<td>10</td>
<td>tetrahydrofuran (42) and acetylated tetrahydrofuran (43)</td>
<td>30% 10%</td>
</tr>
<tr>
<td>HBr/HAc (1:1)</td>
<td>reflux</td>
<td>½</td>
<td>tar</td>
<td>-</td>
</tr>
<tr>
<td>HBr/DMF (1:1)</td>
<td>20</td>
<td>6</td>
<td>tetrahydrofuran (42)</td>
<td>55%</td>
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<tr>
<td>HBr/DMF (1:1)</td>
<td>reflux</td>
<td>½</td>
<td>tetrahydrofuran (42) and acetylated tetrahydrofuran (43)</td>
<td>15% 10%</td>
</tr>
<tr>
<td>H₂SO₄/HBr (1:4)</td>
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<td>5 min.</td>
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<td>-</td>
</tr>
<tr>
<td>HI/P</td>
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<td>½</td>
<td>tar</td>
<td>-</td>
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Table 8. Cyclization using methyl p-methoxybenzyl-2-(p-methoxybenzyl)allyl acetate (44). (See p25 and p109)

<table>
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<th>Reagent</th>
<th>temp.</th>
<th>time (h.)</th>
<th>Product</th>
<th>Yield %</th>
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<td>tar</td>
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Appendix 2

Raw data for the kinetic runs

The first order graphs were constructed by plotting $\log_{10}$ peak weight vs time (seconds).
Table 9. Enzo-acid  \( T=69^\circ \) (internal)

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<th>peak weight</th>
<th>peak weight</th>
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40. We are grateful to Mr. W. Cookson for this valuable work.


The synthesis of two adamantanoid dienones (3) and (4) has been achieved from the phenolic iodide (1) via an Ar, interaction involving desaromatization. The phenolic iodide was synthesised as a mixture of stereoisomers and on heating in a sealed tube with potassium t-butoxide in t-butanol two different dienones were formed depending on the concentration of base used: using 2.5 equivalents, the phenolic dienone (2) was isolated, but using 1.0 equivalents the adamantanoid dienone (3) was obtained. The adamantanoid bis-dienone (4) was formed by dehydrogenation of (3).

Ultimately the adamantanoid skeleton for (3) was assigned by a consideration of the mechanism involved (scheme 1), but considerable evidence supports this assignment.
Part 2

Endo- and exo-6-isobutyl-1,4-dimethyl-2,7-dioxabicyclo[2,2,1]heptane-6-carboxylic acids (1) (2) have been synthesised and identified from the chemical shifts of the 5-endo and coupled 5-exo-protons.

Decarboxylation of the endo-acid (1) was found to be considerably faster than the exo-acid (2), and both decarboxylated faster than a model monocyclic acid (3). Product studies showed that (1) decarboxylated to initially form the dihydrofuran (6), whereas the exo-acid initially formed a product formulated as the dihydropyran (7). Both (6) and (7) isomerise to yield a similar mixture of the bicyclic acetals (8).

An explanation for the faster rate of decarboxylation of (1) over (2) is that decarboxylation takes place from the zwitterions (4) and (5) (scheme 1). The less favourable geometry for proton transfer and expected lower basicity of the 7-oxygen would result in a lower concentration of (5) relative to (4). Also any incipient carbonium ion character at position 1 would be stabilized better by the 7-oxygen in (4) than by the 2-oxygen in (5), but the exact timing of bond breaking and making in these decarboxylative eliminations is unknown.

Scheme 1.