SYNTHETIC APPROACHES TO MEDIUM AND LARGE RINGS.

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FOR THE DEGREE OF Ph.D.

BY

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Lastly, I would like to thank my colleagues in crime, my fellow post-graduates, too numerous to mention by name, who made life bearable during my three years stay in the Chemistry Department research laboratories.

CONTENTS.

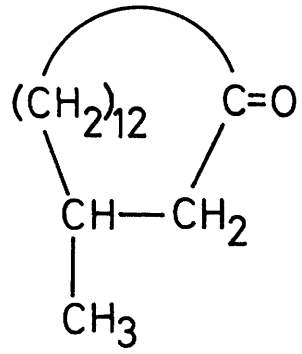
SUMMARY.

Synthetic routes to macrocyclic ketones and lactones via fused bicyclic, doubly bridged tricyclic and bridged tricyclic precursors have been investigated as follows :

(a) The condensation of diethylsuccinylsuccinate and acrolein gave two interesting compounds. The first compound was identified as a fused tricyclic system, an octahydroindacene-dione-dicarboxylic ester, whose structure was investigated and the ester groups found to be trans. The second was a complex bridged tetracyclic system, whose structure was elucidated by chemical and physical methods, including ^{13}-C nmr spectroscopy.

(b) The synthesis of cycloalkynones was investigated from $\Delta^{2,6}$-tricyclo-[6,3,1,$0^{2,6}$]-dodecan-5,12-diones by cleavage of the one-carbon bridge, followed by cleavage of the double bond by Eschenmoser's tosylhydrazone-epoxide ring opening reaction. The first half of this sequence was shown to be feasible, but lack of time precluded further investigation.

A direct approach to macrocyclic lactones from Δ^{9}-tetrahydrochroman-4-ones was not successful.



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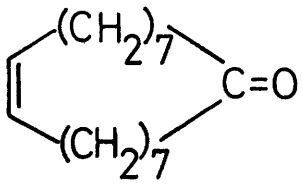

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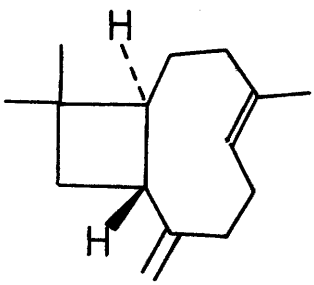

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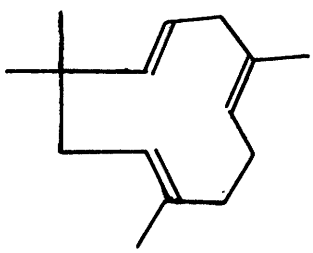

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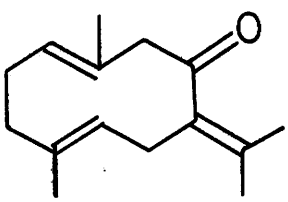

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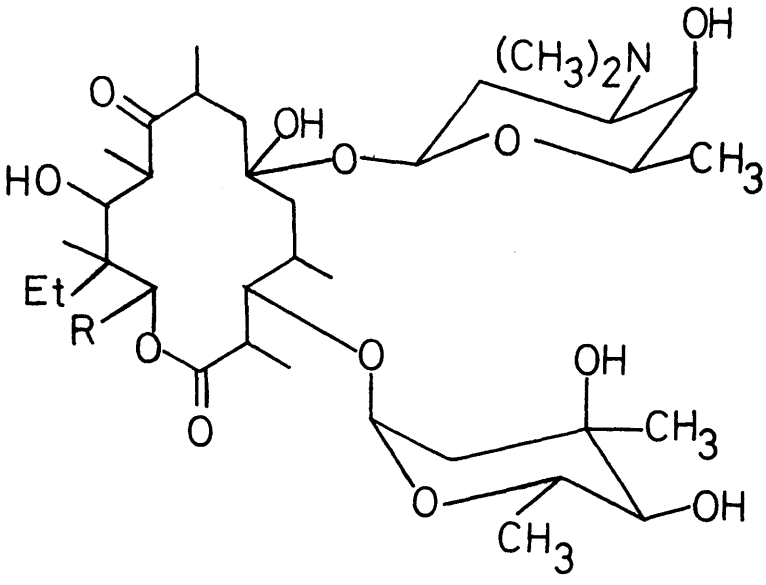
INTRODUCTION.

Although macrocyclic compounds have been known since 1926, when Ruzicka[1] and co-workers established the macrocyclic nature of muscone (1) and civetone (2) by synthesis from heavy metal salts of long chain carboxylic acids[2], practicable syntheses of these compounds only became feasible after 1947, when Prelog[3] and Stoll[4] independently introduced the " acyloin " condensation[5]. This route provided a practicable synthesis of medium-sized* carbocyclic rings, and served to stimulate research in this area. Further stimulus was applied by the discovery in 1949 of medium-sized rings in nature by Sorm[6], from his studies on the nature of caryophyllene (3), and, since then, many other sesquiterpenes isolated have been shown to contain similar ring systems, for example, humulene (4) and germacrone (5).

Another important group of macrocyclic compounds which have come to prominence since then are the macrolides, many of which are biologically active. In particular, those which possess, in common, a glycosidically substituted large ring lactone, Actinomycetes origins, as well as distinctive activity against bacteria (chiefly Gram-positive) and mycoplasma, have become important. Many such macrolides, for example,

*Note. In general, large rings are considered to be those containing 12, 13 or more atoms, while medium rings fall in the range of 8 to 12 atoms.



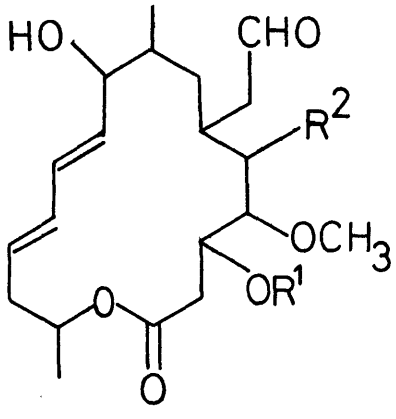
(Desosamine)

(Cladinose)

(6) R= OH, Erythromycin A.

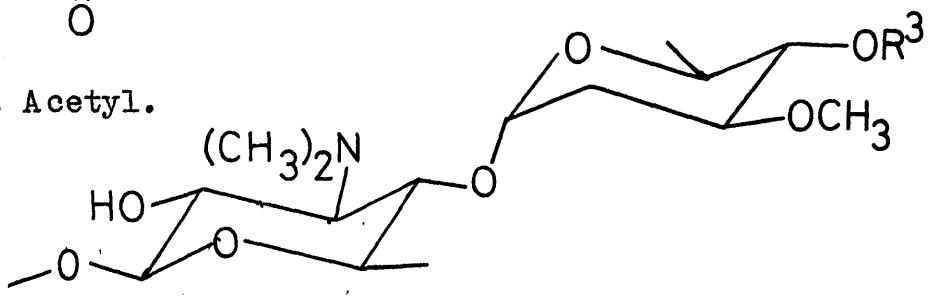
R= H , Erythromycin B.

(7) Leucomycins.

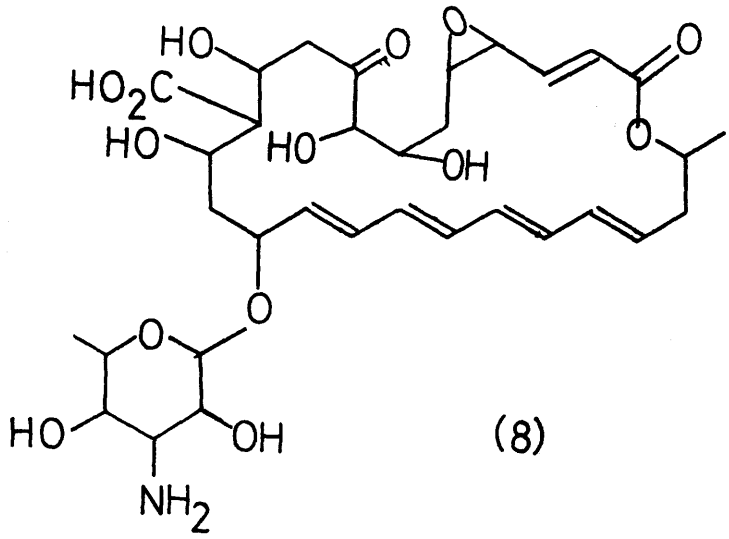


R^1 = H, Acetyl.

R^2 =



R^3 = iso-valeryl, iso-butyl, propionyl, acetyl.



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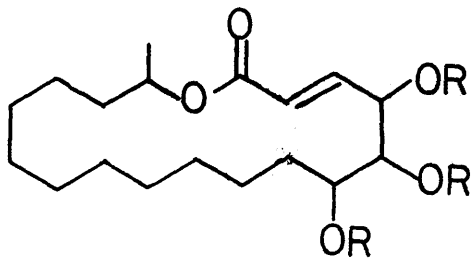

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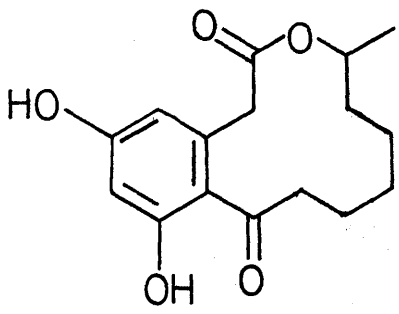

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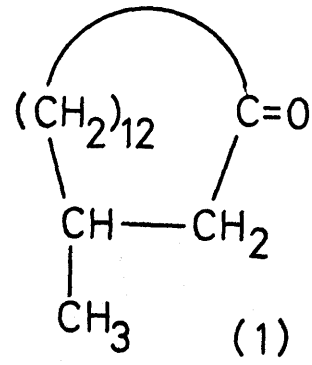
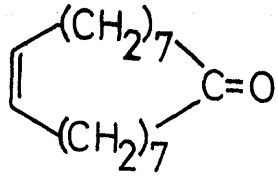


(1)

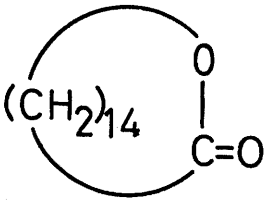


(2)

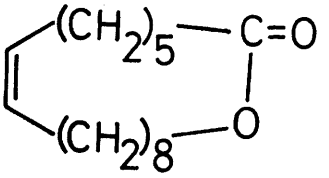
erythromycin (6) and the leucomycins (7), are produced as the free base, various salts, and/or as certain semi-synthetic ester derivatives, on a commercial scale. There is a continuous search for new macrolide products among fermentations, by chemical modifications, and through directed biosynthesis.

Many macrolides have been subjected to chemical studies, and some to X-ray studies, and are now structurally defined. Their overall constitutional structures reveal a wealth of stereochemical features involving numerous asymmetric centres and conformational possibilities about 12-, 14- or 16-membered lactone rings, containing a variety of substituents which include one, two or three glycoside units. As a result of these studies, total absolute configurations have been assigned to several macrolides, including erythromycin (6) and the leucomycins (7), while configurational data are available on several macrolide aglycones. These stereochemical studies, and configurational and conformational models have been the subject of a recent review and discussion by Celmer[7].

However, not all macrolides possess 12-, 14- or 16-membered rings, for example, pimaricin (8)[8] possesses a 26-membered ring, while aspicillin[9] (9) has a ring of 18 atoms, nor do they all possess antibiotic activity, curvularin (10) being one example, and there are also the macrocyclic ketones and lactones whose main feature is an odour much prized in perfumery, for example, muscone (1), civetone (2),


(CH2)14
O
C=O

(11)


(CH2)5
C=O
(CH2)8
O

(12)

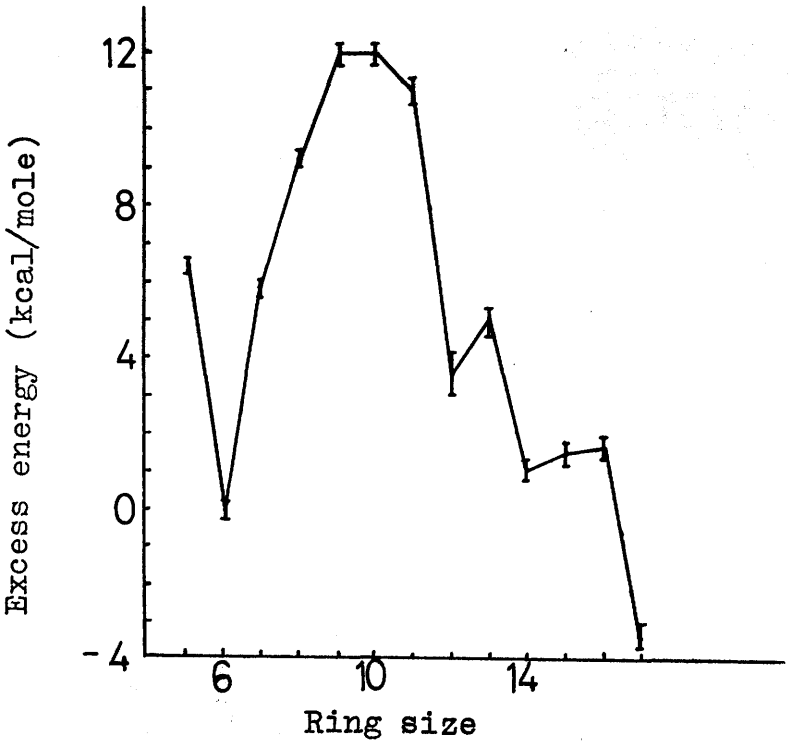

Excess energy (kcal/mole)
12
8
4
0
-4
6
10
14
Ring size

Fig. 1.

exaltolide (11) and ambrettolide (12).

The common structural feature in all these compounds is the presence of a medium or large ring. The medium rings have provided much interest to physical and organic chemists, as they show no regular interdependence of properties and ring size. A discontinuity in the physical and chemical properties of derivatives of 8- to 11-membered rings is seen, with the turning point at the 10-membered ring[10]. Cyclodecanone is particularly inert to cyanohydrin formation, while Dunitz and Prelog[11] have compared the excess enthalpy of the cycloalkanes over that of an infinite polymethylene chain (Fig. 1). The energy excess in medium-sized rings reaches a maximum at cyclononane and cyclodecane. The strain in these rings was initially attributed to Pitzer strain, Baeyer strain, and intramolecular overcrowding across the ring (transannular strain). Brown[12] termed this transannular strain, I-strain, and with it one can explain the reactivity and less expected chemical characteristics of medium ring compounds. A high rate of reaction indicates a relief of strain by a change in co-ordination number, i.e. I-strain is reduced by increasing the C-C-C angles in the ring by replacing an sp^3 carbon with an sp^2 carbon. There is therefore a driving force for tetrahedral centres to convert to trigonal centres readily, for example in acetolysis of cycloalkyl tosylates (C_5 - C_{14}), the medium-sized rings react more rapidly than cyclohexyl tosylate,

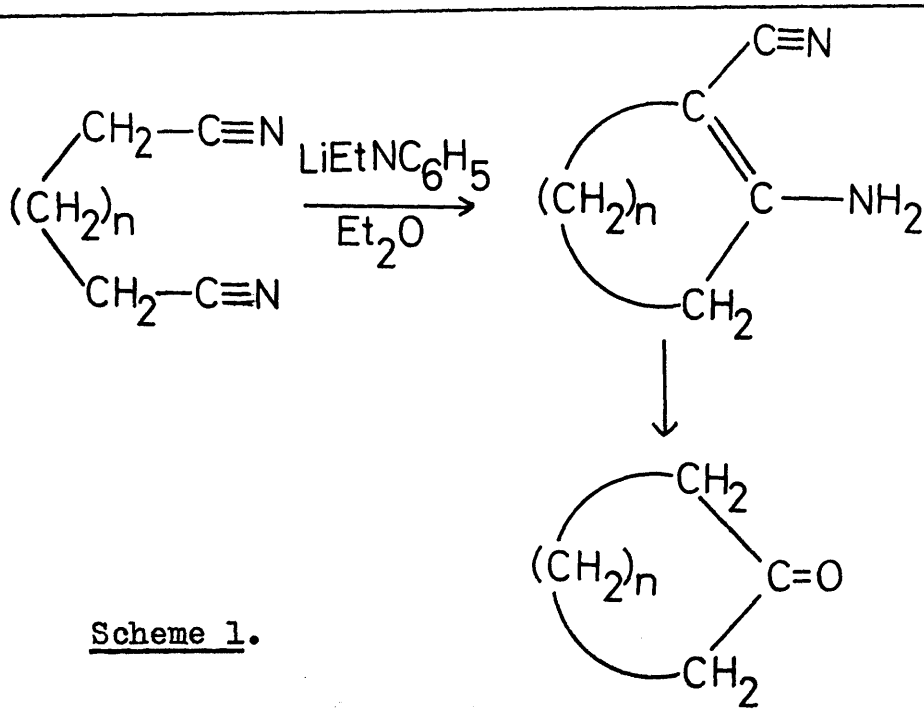
with a reaction rate maximum exhibited by cyclodecyl tosylate. The reverse, conversion of an sp^2 centre to an sp^3 centre is disfavoured, since the replacement of a trigonal carbon by a tetrahedral carbon leads to decreased bond angle, and hence increased strain, as exemplified by the non-reaction of cyclodecanone with hydrogen cyanide. Dunitz[13] and co-workers have investigated cyclononane and cyclodecane derivatives by X-ray methods in an attempt to elucidate their conformations. The conformations obtained by Dunitz indicate that there is high degree of steric compression and transannular strain. However, in the case of cyclodecane derivatives, there is practically no Pitzer strain, which is obtained by slight deformation of the C-C-C angles round the ring to 117°. The cyclononane derivatives have a much less regular shape, with similar transannular compression of hydrogen atoms and C-C-C angles of 117°. Unlike the 10-membered ring, the partial conformations around the 9-membered ring are not all favourably staggered, and Pitzer strain thus makes some contribution to the high energy content.

Much of the chemistry of the medium rings is governed by the conformation, which often brings opposite sides of the ring into close proximity. For instance, hydroxylation of cis-cyclodecene with performic acid gave only one 1,6-diol (thought to be cis[14]), while trans-cyclodecene gave the stereoisomeric 1,6-diol. Such transannular interactions do not occur in the

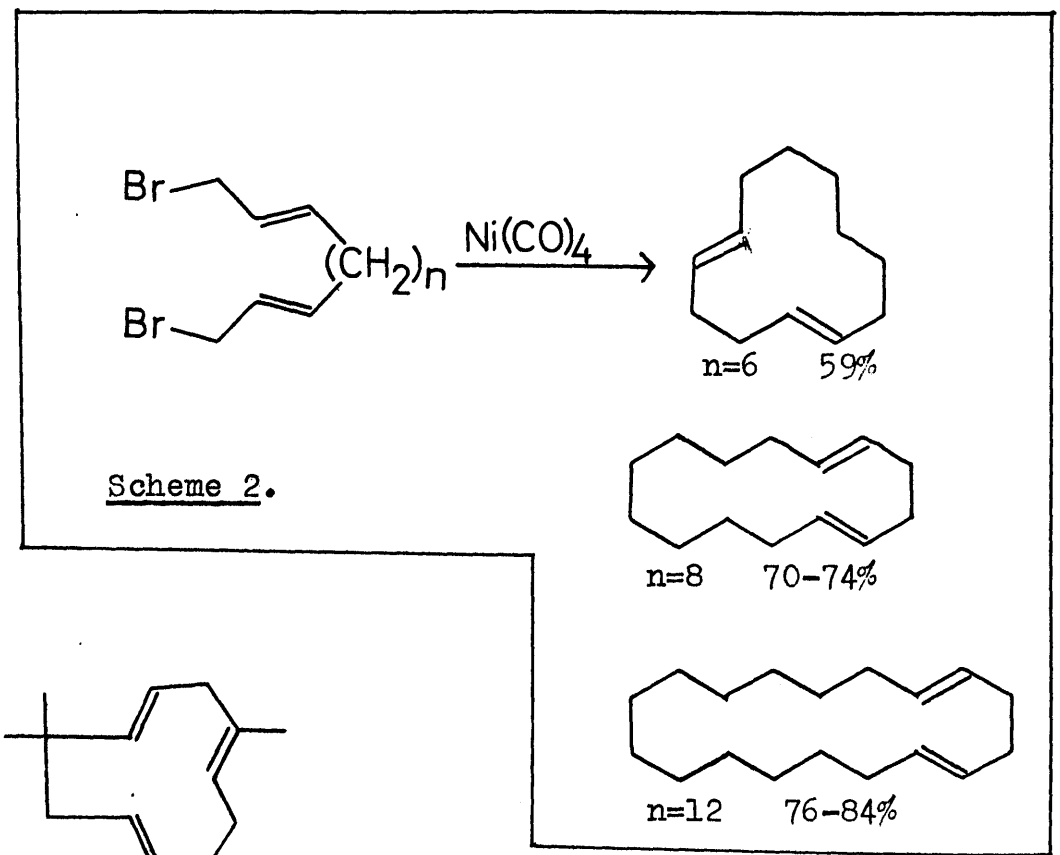
larger cycloalkane systems, as they are more spacious, for example, cyclododecene gives the expected 1,2-diols [15].

It can be seen that the medium rings present a challenge to both physical and organic chemists, while the synthesis of large rings has attracted the attention of organic chemists since their discovery.

There are two common methods of forming cyclic compounds. The first, and more obvious, is to synthesise a long chain compound with suitable functional groups at each end, and react these together in such a way as to produce a macrocyclic system. The difficulties encountered in this approach are due to the low statistical probability that the ends of a long chain will meet. The tendency to ring formation is a complex function of the distance between the functional groups and the loss of entropy associated with their fixation, Baeyer strain and Pitzer strain. For medium rings, the I-strain becomes an important factor. Two possible reactions can occur, and are in competition during cyclisation. These are intramolecular, when the desired ring formation occurs, and intermolecular, leading to the formation of polymeric material. In all cases other than the formation of a 5- or 6-membered ring, the intermolecular reaction is more favoured. This problem can be overcome by the use of high-dilution techniques, proposed by Ruggli[16] and applied by Ziegler[17], under which conditions opportunities for



Scheme 1.



Scheme 2.

(4)

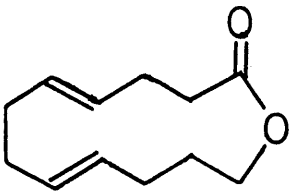
intermolecular reaction are limited and intramolecular reaction becomes more probable. This technique was brought to fruition in the Thorpe-Ziegler[17,18] synthesis of macrocyclic ketones from α,ω-dinitriles (Scheme 1) in quite high yields.

Apart from dilution, ease of cyclisation is dependant on several structural factors which influence the conformation of the chain, and hence the probability of a suitable conformation for cyclisation occurring. Replacement of a methylene by an oxygen atom, which diminishes conformational strain by replacement of a tetravalent atom by a divalent atom, or introduction of a rigid group, for example an acetylenic bond or aromatic ring, which decreases mobility, results in an increased yield of macrocyclic compound.
The influence of substituents on cyclisation of medium rings has been studied by Friedman[19] and Blomquist[20] and their co-workers, and is well defined.

Corey[21] has approached the problem of cyclisation of long chain molecules in a rather novel way. Allylic dibromides can be cyclised, in a high dilution reaction, to cyclic olefins with nickel carbonyl as catalyst (Scheme 2).

This method has been developed and applied to the total synthesis of humulene (4)[21], and the potential applicability to synthesis of other natural products has been mentioned[21].

Macrolides have also been synthesised by Corey by



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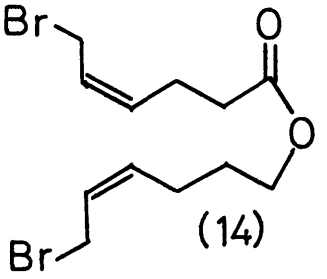

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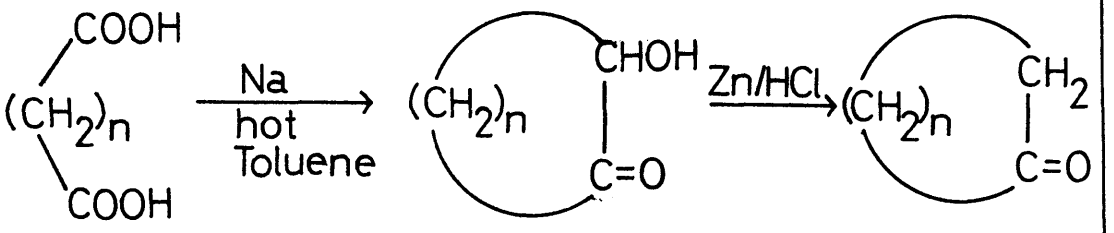
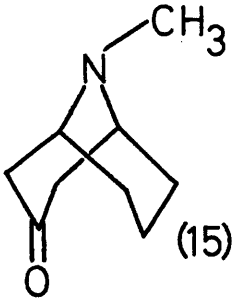


Scheme 3.



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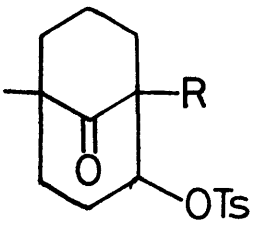

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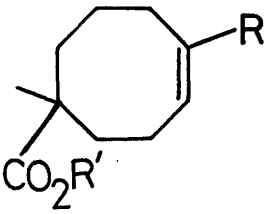

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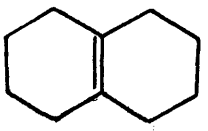

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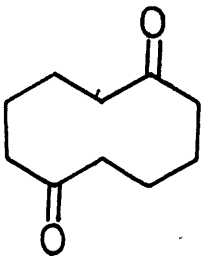


(19)

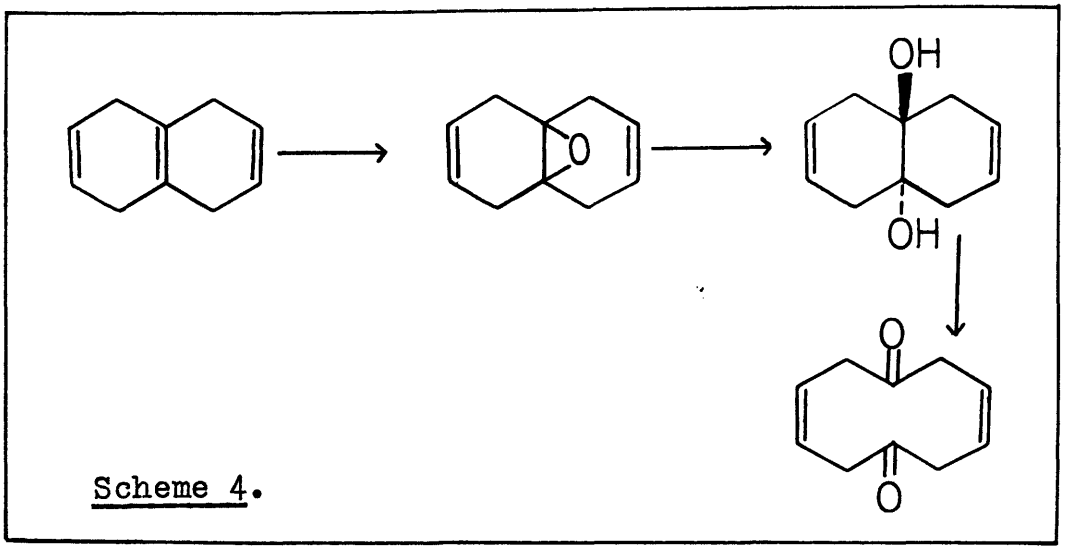
use of nickel carbonyl[22], and again there is potential for synthesis of other simple macrolides. An example of this use is the synthesis of the E,E-cyclododeca-5,8-dienolide (13) from the Z,Z-dibromoester (14).

However, high dilution techniques are not completely satisfactory, and the problem of high dilution was overcome by the " acyloin " condensation of Prelog[3] and Stoll[4], where chemisorption of an α,ω-diester on the surface of molten sodium favours cyclisation to form the acyloin, and hence the ketone, in high yield (Scheme 3). This reaction has, since its inception, undergone no noteworthy change in its procedure.

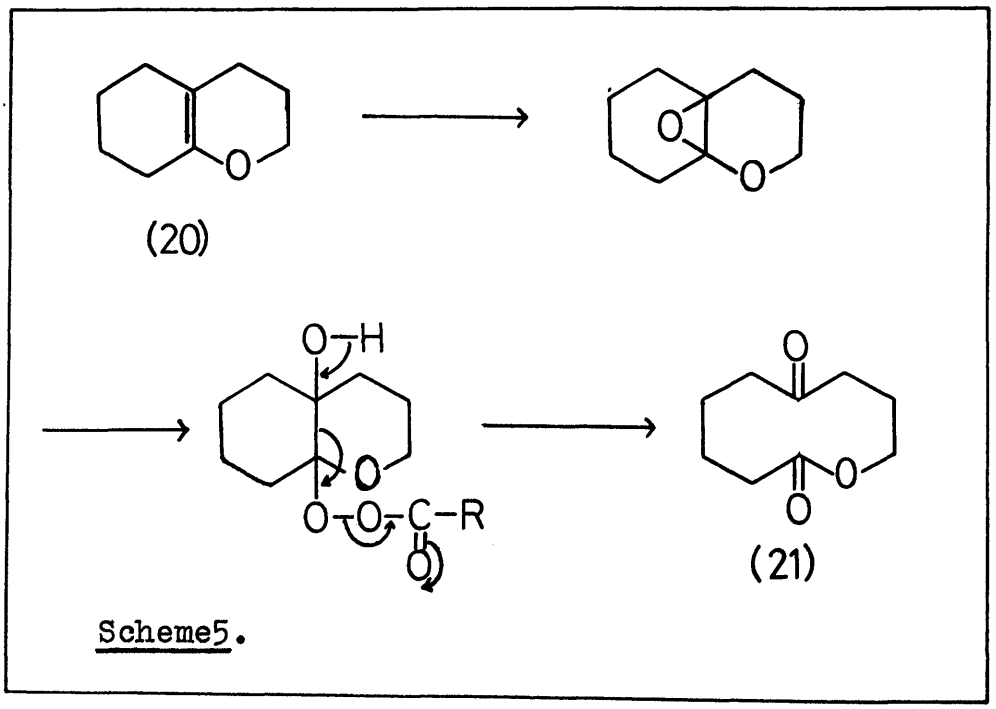
The second method of synthesis of medium and large ring compounds is by scission of one or more transannular bonds in bicyclic or polycyclic systems, of which a classical example is Willstätter's synthesis of cyclooctadiene[23] and cyclooctatetraene[24] from the alkaloid pseudopelletierine (15).

Bridge fission in the bicyclo-[3,3,1]-nonanes and related compounds has been the subject of a review by Buchanan[25], an example of which is the base promoted fragmentation of the tosylate (16) to the ring-opened product (17).

Macrocyclic compounds can be obtained from fused systems by several methods. Ozonolysis of Δ^9-octalin (18), followed by hydrolysis of the ozonide yields cyclodecan-1,6-dione (19), and Bailey and Golden[26]

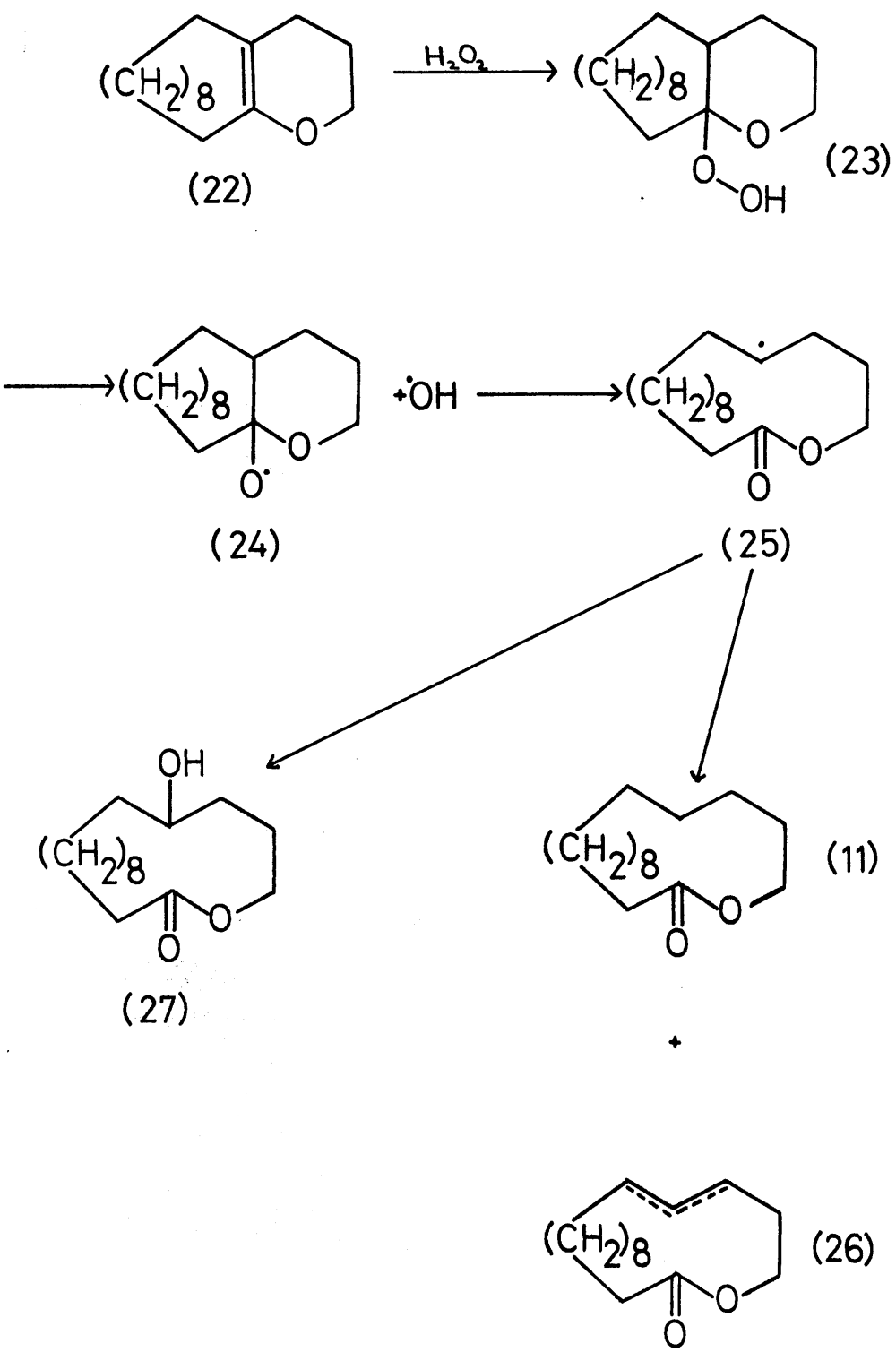


Scheme 4.



Scheme5.

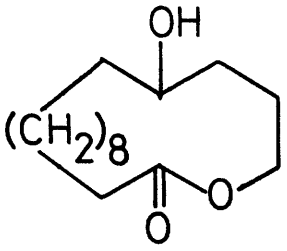
Scheme 6.



have investigated the ozonolysis products of several substituted Δ^9-octalins. This reaction can, of course, be used on any polycyclic system where there is a carbon-carbon double bond at the ring fusion.

Grob and Schiess[27] cleaved the transannular bond by use of perbenzoic acid, followed by hydrolysis and cleavage of the glycol (Scheme 4). Borowitz[28] and co-workers found that the reaction could be extended to the Δ^9-tetrahydrochromanone (20), and also that use of excess m-chloro-perbenzoic acid gave a 48% yield of the keto-lactone (21), by the process shown in Scheme 5. However, Borowitz found that it was extremely difficult to reduce the ketone function in the nonanolide (21). This difficulty of reduction is attributable to the conformation of the ring which, as discussed previously, "surrounds" the carbonyl carbon and hinders or prevents attack of the reducing agent on the carbonyl carbon.

Ohloff[29] and Becker have developed this process into an economically feasible synthesis of exaltolide (11) in greater than 65% yield (Scheme 6). Treatment of the tetrahydropyranyl ether (22) results in the formation of the hydroperoxide (23). This fragments with homolytic cleavage of the oxygen-oxygen bond and loss of hydroxyl radical to give the alkoxy radical (24), which fragments with fission of the C1-C15 bond to give the macrocyclic alkyl radical (25). This can either disproportionate to (26) and (11), or pick up



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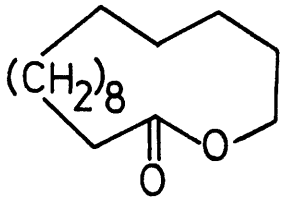

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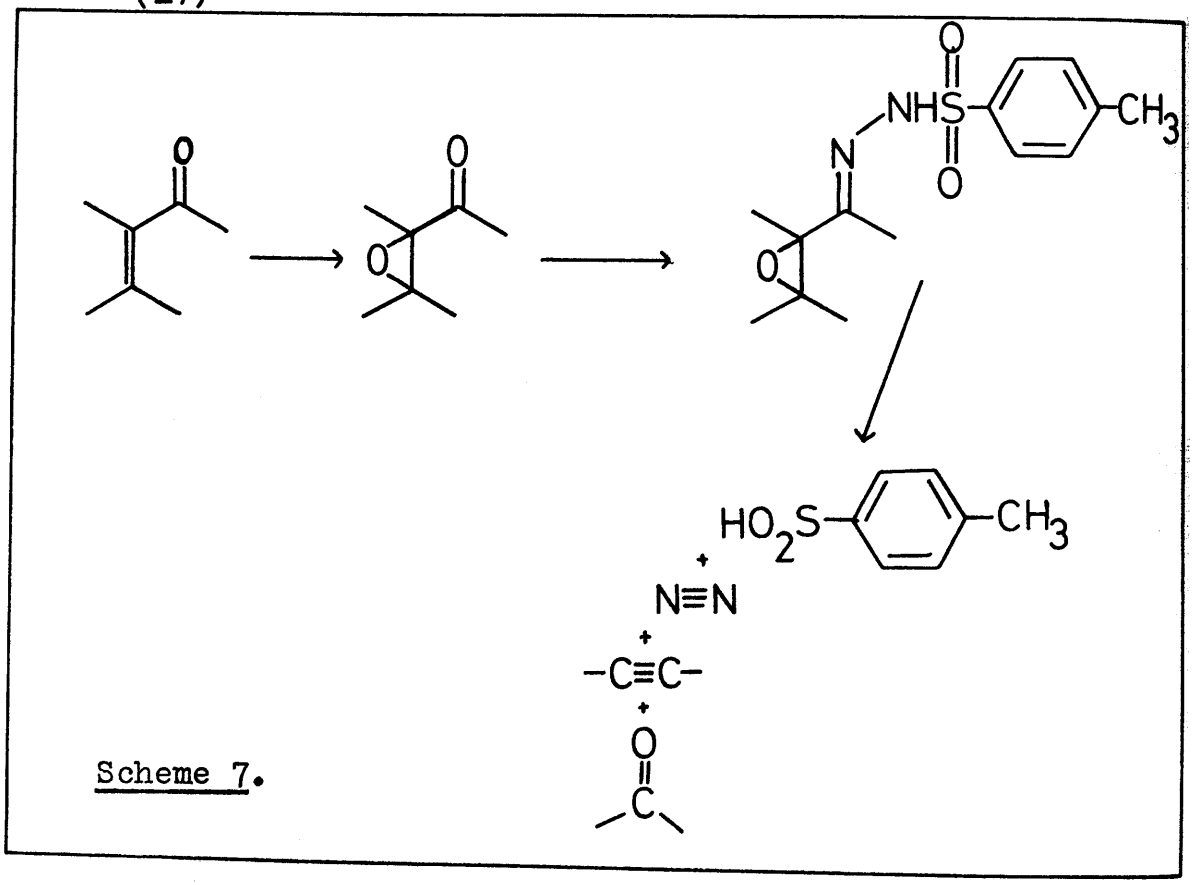
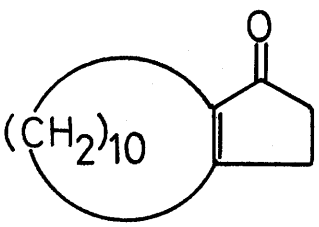


Scheme 7.



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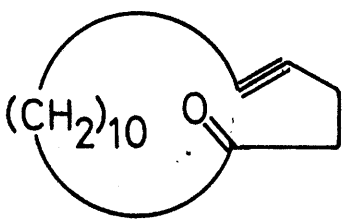

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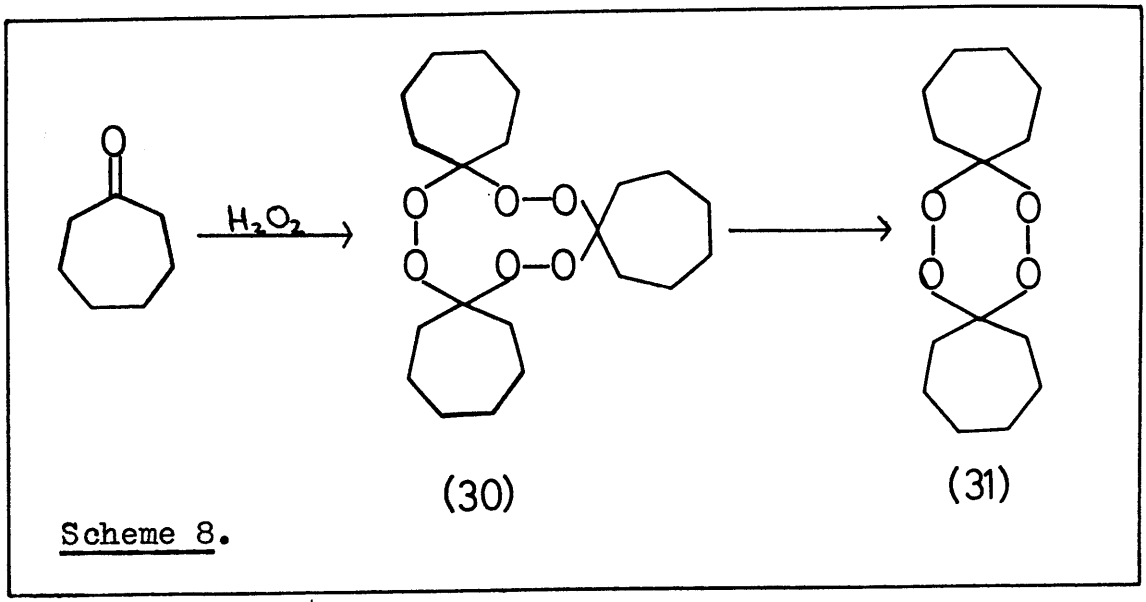

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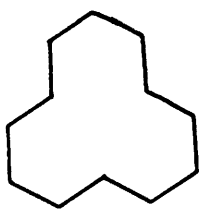
(31)

Scheme 8.



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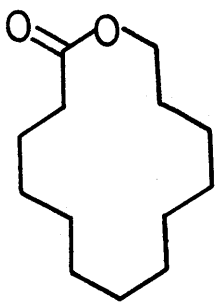

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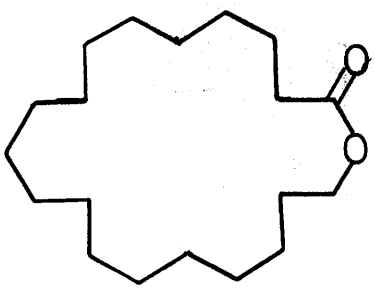

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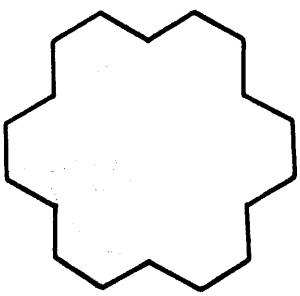


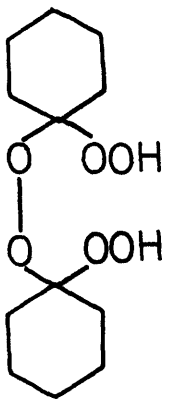
(35)

a hydroxyl radical to give (27). Dehydration of the mixture followed by catalytic hydrogenation yields the cyclopentadecanolide, exaltolide (11).

Eschenmoser[30] has approached the opening of a transannular bond differently. With co-workers, he had developed a heterolytic fragmentation of α,β-epoxy-toluene-p-sulphonylhydrazones, obtained from enones, which is shown in Scheme 7, and this was applied to the bicyclo-[10,3,0]-pentadec-14-en-1-one (28), to give the cyclopentadec-4-yn-1-one (29). Many bicyclic enones were treated in this manner, and the method found to be generally applicable[31].

Other workers have approached the problems of synthesis of macrocyclic compounds from other angles. Story[32] has developed a method of synthesis of a large number of macrocyclic lactones from C_8 to C_{33} by treatment of small ring ketones, e.g. cyclohexanone.

The Story synthesis is claimed to be applicable to the synthesis of virtually any macrocyclic compound. As yet, it has only been applied to macrocyclic lactones without any substituents, and the basic route is shown in Scheme 8. Cycloheptanone is heated with hydrogen peroxide under acid conditions to give initially the trimeric peroxide (30), then the dimer (31). It is impossible to isolate pure dimer or trimer. Decomposition of the peroxides, either photochemically or thermally in refluxing decane, yields the macrolide (32) and cycloalkane (33), and the macrolide (34) and cycloalkane (35) from the dimer and trimer



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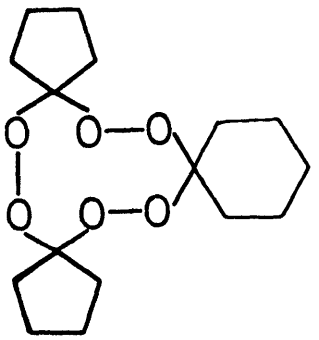

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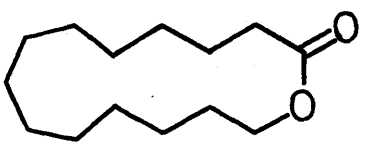

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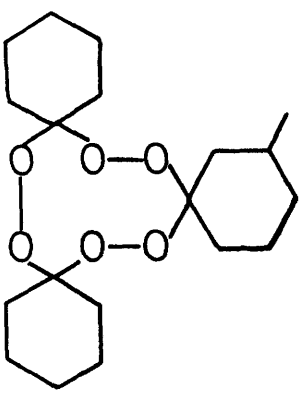

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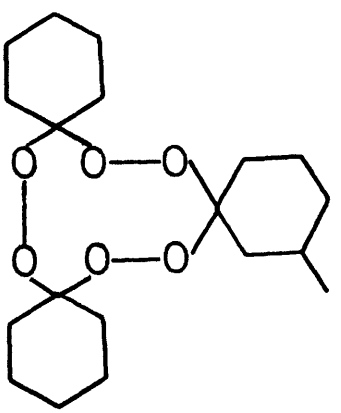
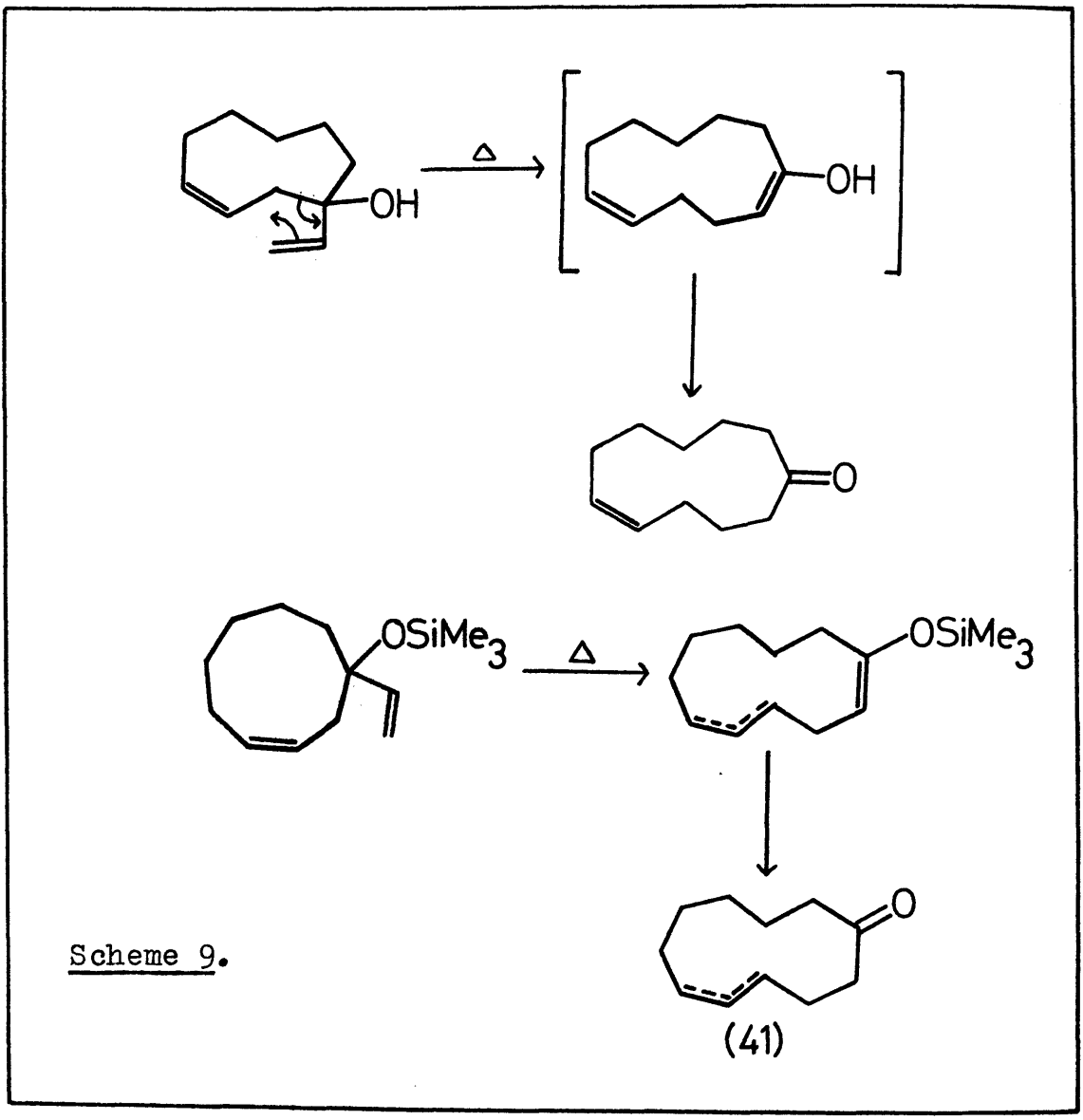


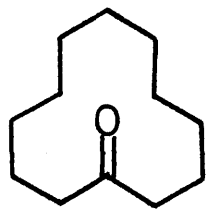
(40)

respectively. It is possible to synthesise mixed peroxides, by first synthesising the 1,1'-dihydroperoxy-dicycloalkyl peroxides, for example (36), followed by reaction at low temperatures with a cycloalkanone in propionic acid as solvent, and perchloric acid as catalyst. An example of a mixed peroxide synthesised by Story and Busch is (37) which, when thermolysed, yields 20% of C_{13} cycloalkane and 15% of the cyclotetradecanolide (38). It is difficult to see how substituents could be introduced onto specific carbon atoms in the ring by choice of suitably substituted cycloalkanones, since no evidence is available for specificity in orientation of addition of cycloalkanone to the dihydroperoxide (36). Addition of 3-methyl-cyclohexanone could result in two possible isomers, (39) and (40), and in fact, Story[32] quotes these as giving a C_{16} macrolide, but does not mention whether the product is one compound or a mixture of isomers. The review does not include experimental details or isomer distribution. A further problem could arise since the overall reaction from, for example, the isomeric peroxides (39) and (40) to give the C_{16} macrolide, is loss of $C_3H_2O_4$, and there appears to be no way at present of differentiating carbon and oxygen atoms lost or retained in the reaction. Of necessity, this will result in further " scrambling " of the methyl group around the ring. Hence, it would appear that the use of this method is limited unless a relationship



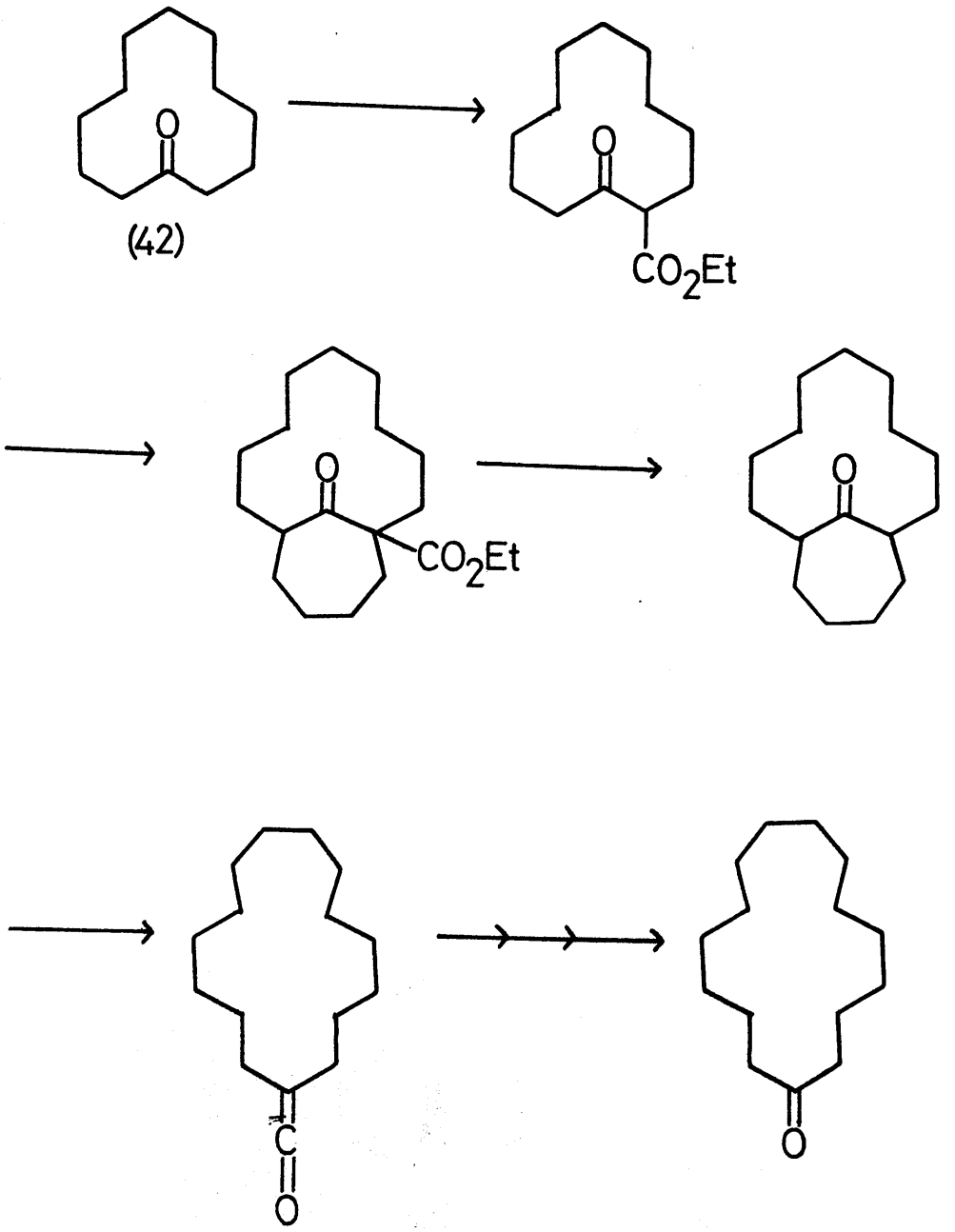
Scheme 9.

(41)



(42)

Scheme 10.

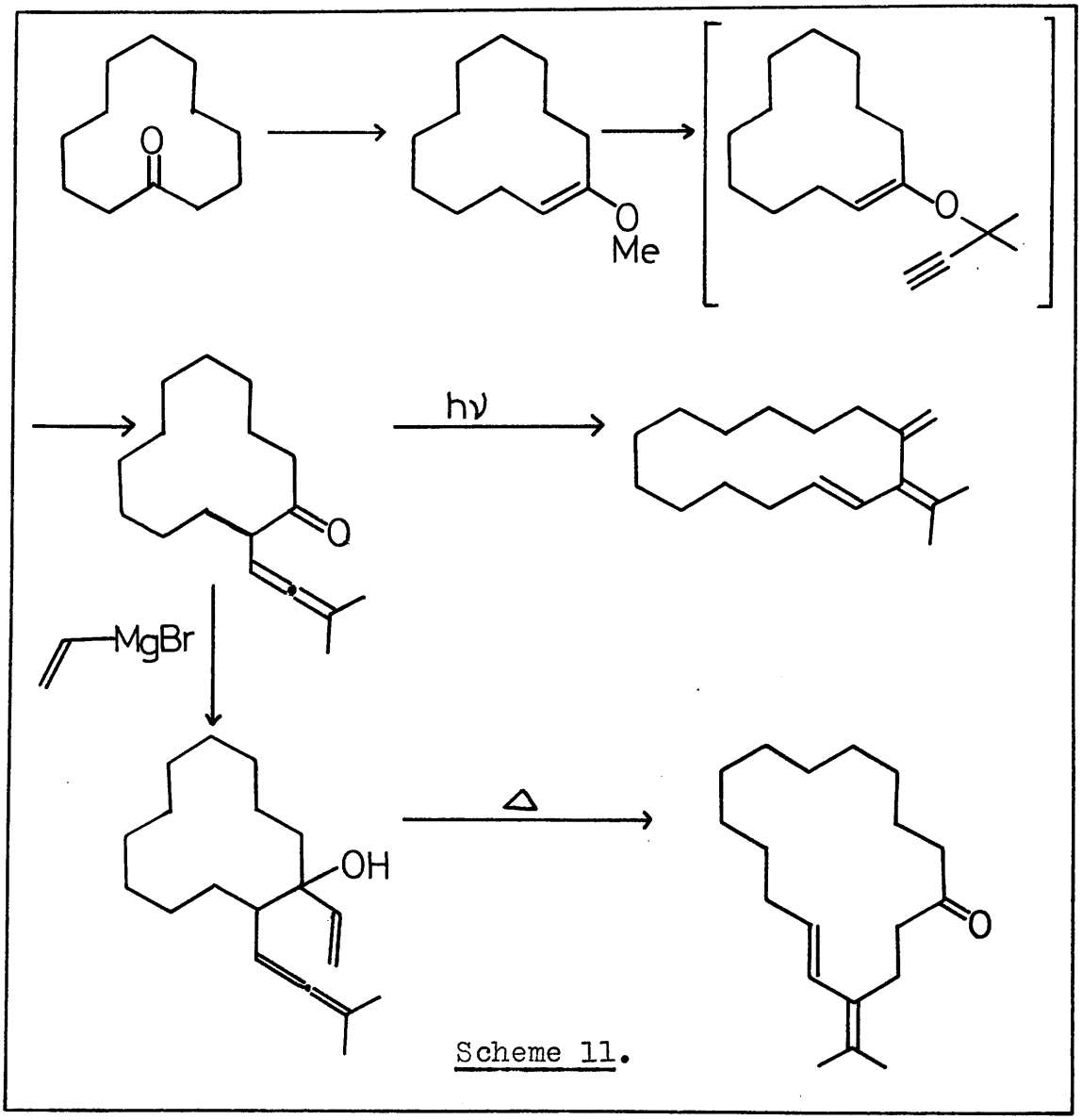


between substituents and loss of carbon and oxygen atoms is found.

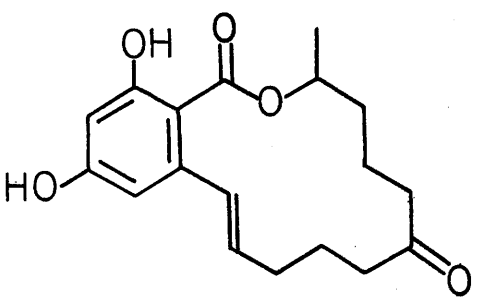
One further method of synthesis of macrocyclic compounds is by ring enlargement of smaller cyclic compounds, and there are many methods of ring enlargement known. The reaction of diazomethane on cyclic ketones gives a one-carbon ring expansion, and has been known for some time, whereas the two-carbon ring expansion of Thies[33] shown in Scheme 9 is more recent. The disadvantage of this reaction is that the oxy-Cope (i) gives a low yield, while the siloxy-Cope (ii), although going in fair yield, can give a mixture of difficultly seperable isomers (41), as well as there being the possibility of a [3,3] rearrangement in competition with the [1,3] rearrangement.

Nozaki[34] and co-workers have developed an interesting photochemical three-carbon ring expansion. Starting with cyclododecanone (42), which is now readily available commercially, cyclopentadecanone has been prepared by the ring expansion shown in Scheme 10. This method is not feasible when a complicated ketone containing photochemically sensitive groups, for example, several olefinic bonds, is required.

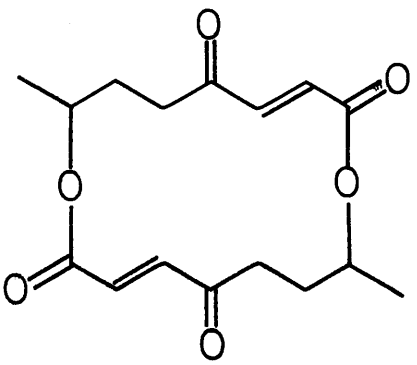
Another photochemical method which has been published is that of Cookson and Singh[34], which is specific for ketone synthesis, and gives a high yield, but again suffers from the limited application of a photochemical method. The two or four atom ring



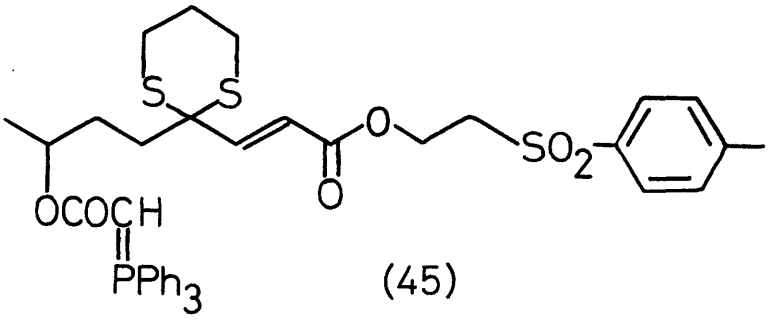
Scheme 11.



(43)



(44)



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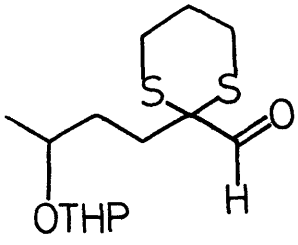
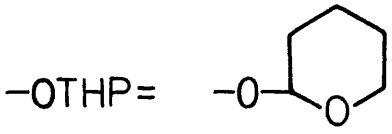
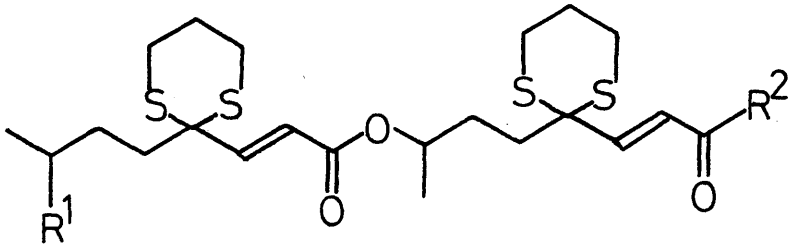
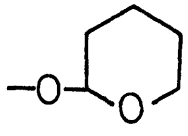
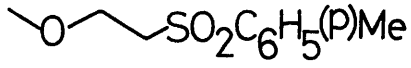
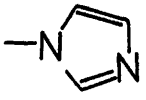


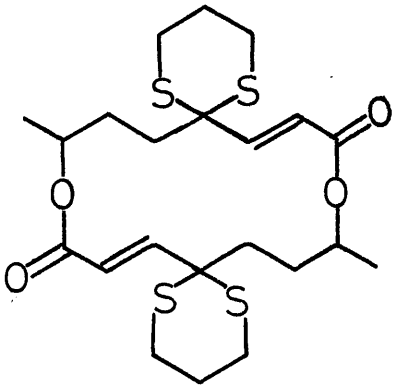
(46)





(47) a: R^1 =  , R^2 = 

b: R^1 = $-OH$, R^2 = 



(48)

expansion is shown in Scheme 11.

However, few, if any, of these methods have a general applicability to synthesis of complicated macrocyclic ketones and lactones, and in particular to synthesis of the macrolide antibiotics, with their multiplicity of substituents and asymmetric centres.

Until now, syntheses of macrolide compounds have been designed with one particular molecule in mind, and always by the method of long chain synthesis followed by cyclisation at a late stage in the synthesis. Examples of this type of synthesis are the synthesis of zearalenone (43) by Cross[35] and Taub[36] independently, and of pyrenophorin (44) by Colvin, Purcell and Raphael[37].

Both syntheses of zearalenone were by initial formation of two fragments of the ring, condensation to give a long chain, followed by cyclisation under high dilution and with an acid catalyst to yield a protected zearalenone, which was then treated to yield the free D,L-zearalenone (43).

Pyrenophorin, a dilactone, was synthesised by a different method. The protected dimer (47a) was formed by a Wittig reaction of (45) on (46), rather than esterification of two monomers of a hydroxy-acid, and the Wittig was followed by formation of an imidazole (47b), and cyclisation to the protected pyrenophorin (48). Removal of the protecting groups gave (±)-pyrenophorin (44) and the meso isomer.

It is clear, from the foregoing discussion, that better synthetic routes to large ring systems are still required, and this was the object of the work described in this thesis. In particular, it was envisaged that a more general approach to synthesis of highly substituted macrocyclic systems could be obtained by application of several methods of transannular bridge fission to a polycyclic molecule. The bridge fission reactions used would be Eschenmoser's opening of α,β-epoxy-toluene-p-sulphonyl hydrazones[30], and the base promoted opening of bicyclo-[n,3,1]-ketone systems. It was also felt that substituted macrocycles could be synthesised by careful choice of substituted starting compounds for the synthesis of polycyclic intermediates.

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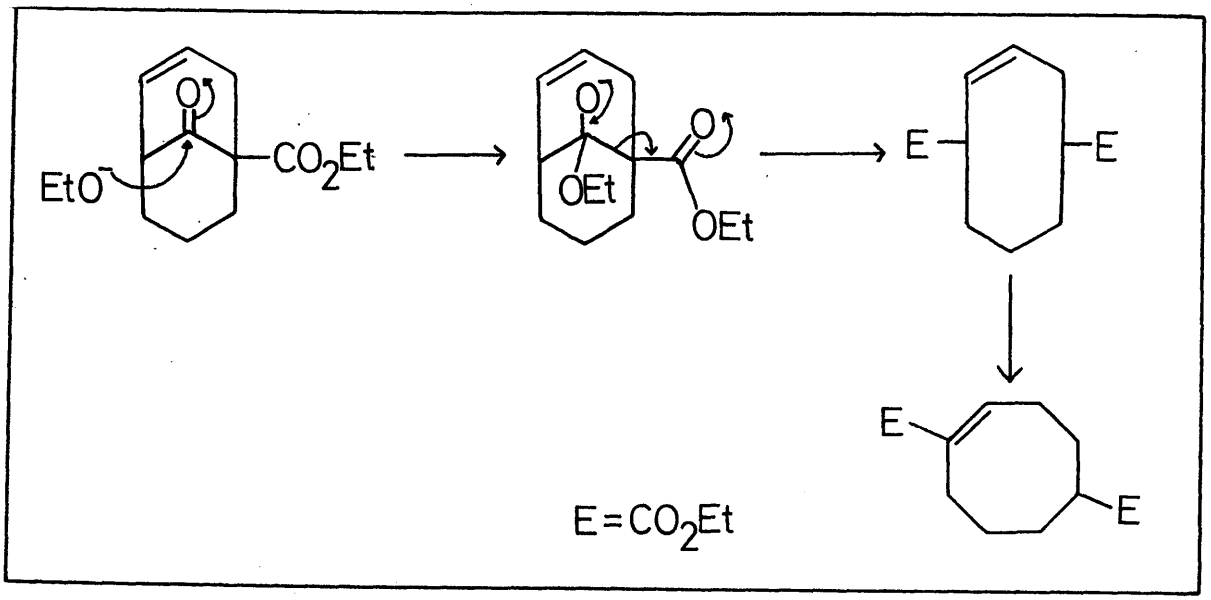
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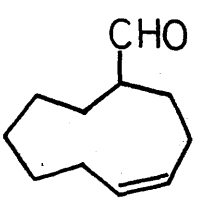
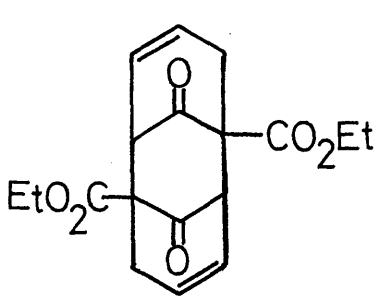
CO2Et
OEt
OEt
E
E
E
E
E=CO2Et


CHO

(1)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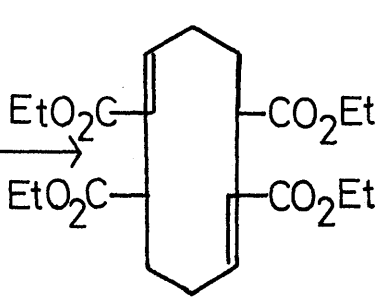
EtO2C

(2)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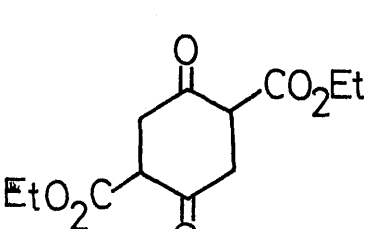
CO2Et
EtO2C
CO2Et

(3)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EtO2C

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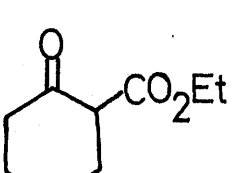

CO2Et

(5)

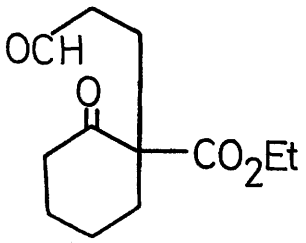
DISCUSSION.

PART 1.

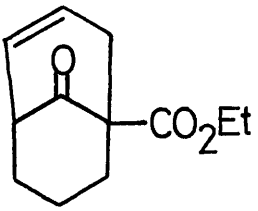
CARBOCYCLIC COMPOUNDS.

The synthesis of medium-ring compounds via bicyclic precursors has been investigated in some depth by many workers, both in this department[1], and elsewhere[2,3]. The method involves the fragmentative opening of a bicyclic tosylate (see Introduction, page 7) or a retro-acetoacetic ester reaction[2] on a bridged β-ketoester (Scheme 1). Synthesis of medium and large carbocyclic compounds should be possible by application of these methods to larger bicyclic systems, but the use of these methods is limited by the availability of the appropriate bicyclic precursors, although Marshall and Scanio[3] have successfully synthesised a C_{10} carbocycle, cis-cyclodec-1-en-5-carboxaldehyde (1), starting from cycloöctanone. A feasible alternative would be the application of these routes to a tricyclic system, for example, (2) to give (3).

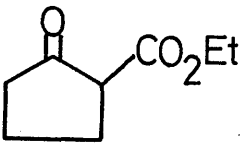
The synthesis of such a tricyclic compound was envisaged as the addition of acrolein to the bis-β-keto ester (4) under appropriate conditions. Cope and Synerholm[2] have investigated the reaction of acrolein with 2-carbethoxycyclohexanone (5) and found that a polymeric product was obtained. If, however, a small quantity of sodium ethoxide was used as the condensing



(6)



(7)



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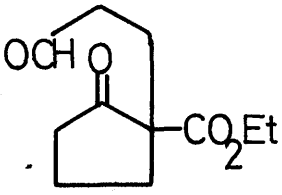

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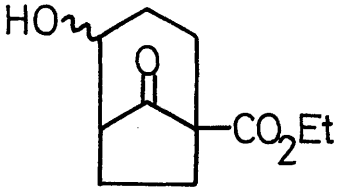

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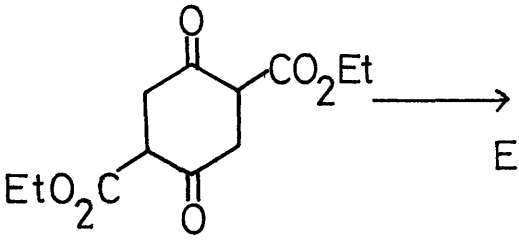

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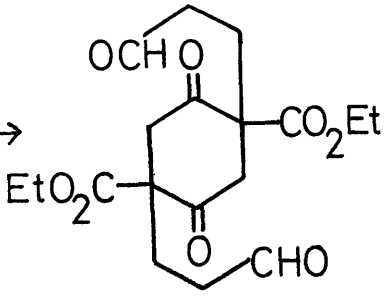

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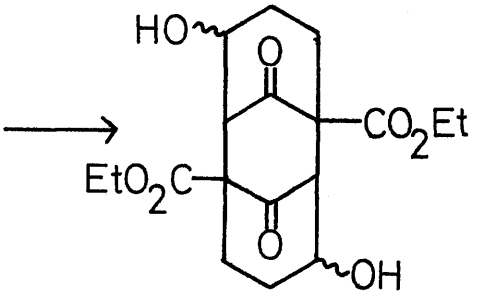

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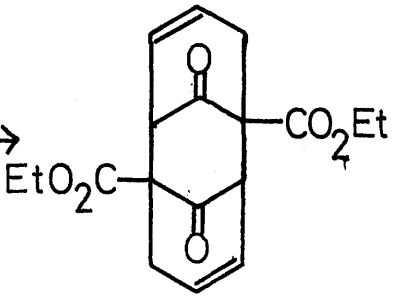


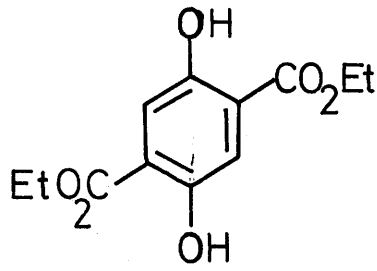
(13)

agent, a reasonable yield of the keto-aldehyde (6) could be obtained. Cyclisation of (6) with hydrochloric acid yielded the bicyclo-[3,3,1]-nonane structure (7).
It has been reported[4] that condensation of acrolein with 2-carbethoxycyclopentanone (8), with triethylamine as condensing agent, proceeds in high yield to the keto-aldehyde (9), which can be cyclised by acid to a mixture of bicyclic alcohols (10). However, prolonged treatment of (9) with triethylamine effected the ring closure to (10), and indeed the compound (10) could be obtained directly from acrolein and (8) by use of triethylamine on prolonged treatment.

Using diethylsuccinylsuccinate (4) as starting material, a C_{10} carbocycle could conceivably be produced from (12) via the tosylate fragmentation process, or from (13) by a bis-retro-acetoacetic ester reaction.
At the same time, it was realised that the cyclisation of (11) could occur by another route, but the possibility of the reaction proceeding in the desired way was felt to justify the experiment.

Diethylsuccinylsuccinate (4) was prepared by a modification of the literature preparation[5], and fully characterised by ultraviolet, infra-red and n.m.r. spectroscopy (see experimental).

Diethylsuccinylsuccinate (4) and acrolein were subjected to similar conditions to those of Buchanan and McLay[4] (stirring at room temperature for several days). The resulting oil was a complex mixture from which three pure substances were isolated. The first,I, was



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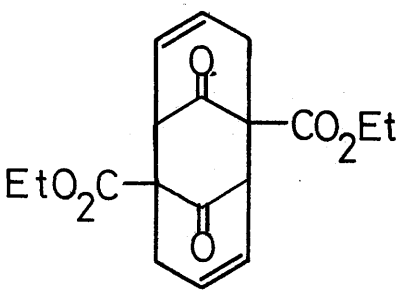
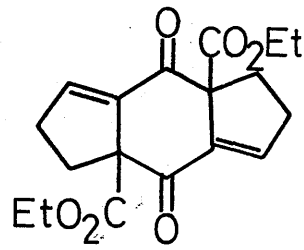
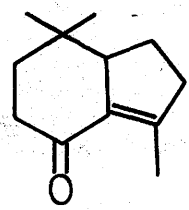


(13)



(15)

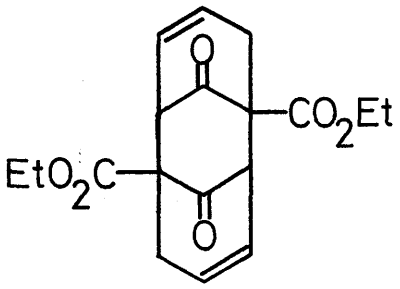


(16)

a yellow crystalline solid, which was identified as the diethyl ester of 2,5-dihydroxyterephthalic acid (14). The most effective method of minimising or completely inhibiting its formation was to carry out the reaction in an atmosphere of nitrogen (see experimental for physical characteristics).

The two colourless crystalline products, II and III, were isolated from the reaction mixture in varying yields, the relative amounts of each altering from one run to another in an inexplicable manner.

Product II melted at 184°C, had a molecular weight of 332 by mass spectroscopy and analysed for $C_{18}H_{20}O_6$. This molecular formula indicates that the compound was formed by loss of two moles of water from a compound produced by di-addition of acrolein to diethylsuccinyl-succinate. There are two possible products from this condensation, the hoped-for bridged tricyclic compound (13), and the fused tricyclic compound (15). Of these two, the infra-red, ultraviolet and n.m.r. spectra eliminated (13) and favoured (15); viz. $\nu_{CO}^{CCl_4}$ 1751 cm^{-1} (ester), 1720 cm^{-1} (shoulder), 1705 cm^{-1} (conjugated carbonyl) and 1623 cm^{-1} ($\nu_{C=C}$); λ_{max}^{EtOH} 264nm (ϵ =8,170), 235nm (4,960) and 205nm (5,040). Although this u.v. spectrum eliminates structure (13), it is also somewhat anomalous for (15). The expected value for (15), as calculated by Woodward's rules, is about 241 nm, and the closest model system (16)[6] shows λ_{max}^{EtOH} 265nm, which, after allowing 12nm for β-substitution, gives as λ_{max} for the enone a value of 253nm. Non-conformity to



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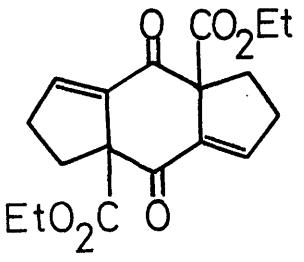
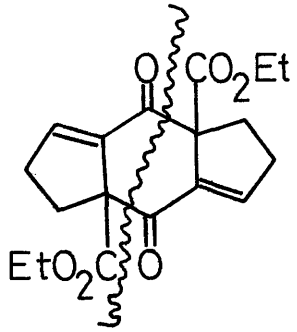


(15)

TABLE 1.

Base peaks m/e	Fragmentations
332	Parent ion
166	Symmetrical halving
138	166 - (CO)
93	166 - (CO_2Et)
63	93 - (CO) or
	138 - (CO_2Et)



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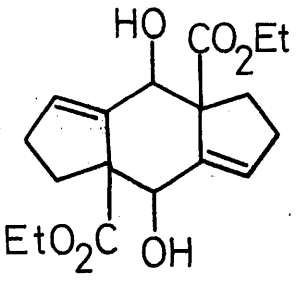


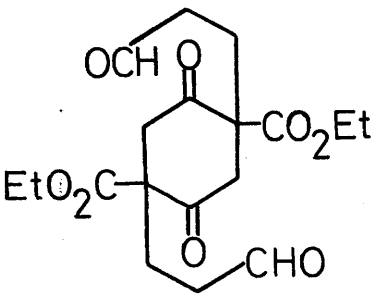
(18)

Woodward's rules in strained enone systems is not unknown, and an explanation for the anomaly in this compound may lie in this direction.

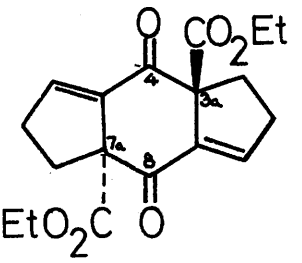
The n.m.r. of II showed the presence of two equivalent vinylic protons (3.4τ, J=2.5Hz), and, apart from the ethyl ester protons, 8 methylene protons in the 7.0-8.0τ region. As (13) requires a ratio of 2 methylene: 3 vinyl protons (neglecting esters), there was no doubt that this was not the structure of II. With the exception of the u.v. spectrum, the physical data were in agreement with the structure (15), the bis-enone. Further proof was obtained from the mass spectrum, in which the base peak, m/e 166, corresponded to a fragment of exactly half the molecular weight of the parent ion (M=332). This is most often indicative of the halving of a symmetrical molecule to give identical fragments, a feature which would explain the simple nature of the spectrum below m/e 166, [see table 1 and (17)].

Further evidence for the enone functionalities in the molecule was obtained by reduction with sodium borohydride in methanol to the diol (18). This showed no absorption in the u.v. above 220nm, and $\nu_{OH}^{CCl_4}$ 3600 (small), 3550 and 3480 cm^{-1} in the i.r. spectrum. An increase in molecular weight to 336 was observed (mass spectroscopy).

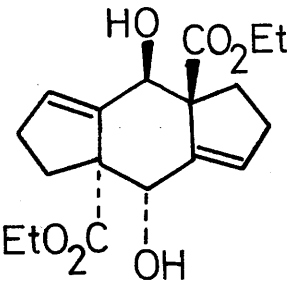
As there is a possibility of isomerism of the two carbethoxyl groups about the plane of the molecule, it was decided to investigate the stereochemistry. On steric grounds, it would be expected that cyclisation of the



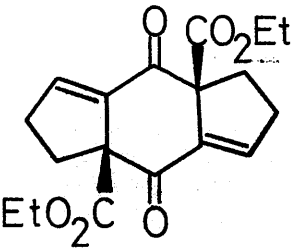
(11)



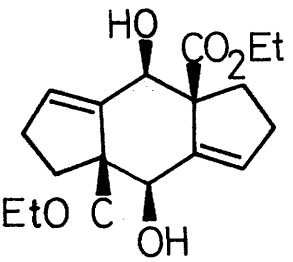
(19)



(20)



(21)



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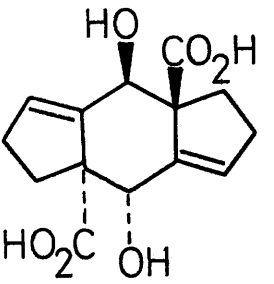
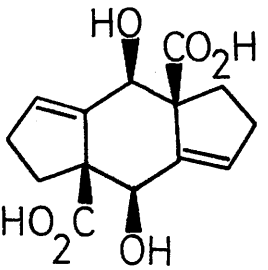
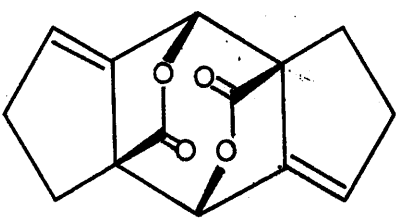


(23)



(24)



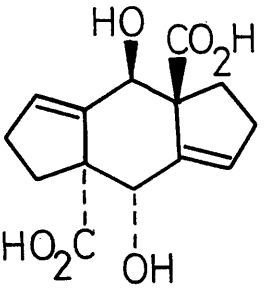
(25)

dialdehyde (11) would result in the least hindered molecule being formed i.e. where the two carbethoxyl groups are trans, as in (19). To investigate this, the dione diester was first reduced with sodium borohydride, then hydrolysed, and the product studied.

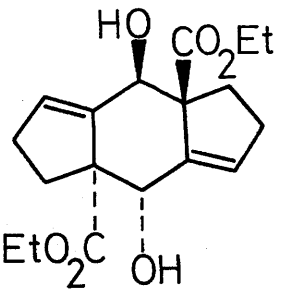
In the borohydride reduction, the bulk of the borohydride will preclude attack at the carbonyl on the same side of the tricyclic system as the carbethoxyl group, attack will occur on the opposite side, and the expected product will be the trans diol (20), where the 3a-carbethoxyl and 4-hydroxyl are cis, as are the 7a-carbethoxyl and 8-hydroxyl. In this configuration, there is the possibility of hydrogen bonding, and the i.r. spectrum of the diol shows $\nu_{OH}^{CCl_4}$ 3600, 3550, 3480 cm^{-1} and ν_{CO} 1740cm^{-1}, even on dilution. This compares with ν_{CO} 1750cm^{-1} in the dione (19), and proves the presence of intramolecular hydrogen bonding. The occurence of intramolecular hydrogen bonding establishes that each ester function is syn to the adjacent secondary alcohol.

The other isomer (21) would reduce to the cis diol (22), an all cis configuration, where hydrogen bonding can also occur.

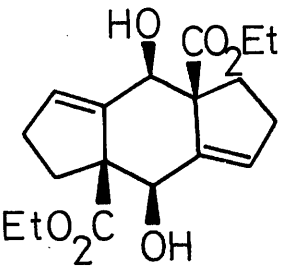
Under acid conditions, hydrolysis of the trans diol (20) would give the trans-cis diol diacid (23). Hydrolysis of the cis diol (22) would give the cis-cis diol diacid (24) where the 4-hydroxyl would be expected to lactonise with the 7a-carboxyl, and the 8-hydroxyl with the 3a-carboxyl to give the bis-lactone (25). Both lactones


HO
CO2H
HO2C
OH

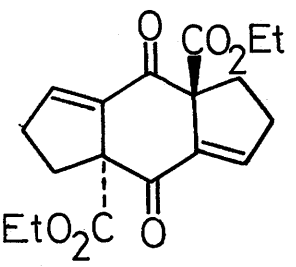
(23)


HO
CO2Et
EtO2C
OH

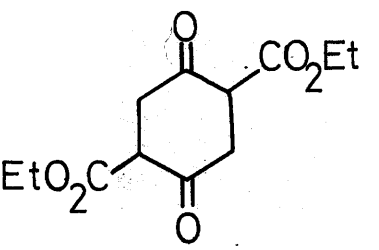
(20)


HO
CO2Et
EtO2C
OH

(22)


O
CO2Et
EtO2C
O

(19)


O
CO2Et
EtO2C
O

(4)

are γ-lactones, and will show a carbonyl absorption at approximately 1770cm^{-1} [7]. The 4-hydroxyl and 3a-carboxyl, or the 8-hydroxyl and the 7a-carboxyl, cannot lactonise, as this would result in the formation of strained β-lactones. Similarly, in the trans diacid (23), lactonisation cannot occur between adjacent hydroxyl and carboxyl groups. Lactonisation across the ring between the 4-hydroxyl and 7a-carboxyl cannot occur because of their stereochemistry about the tricyclic ring system.

Hydrolysis of the diol diester, (20) or (22), with hydrochloric acid in methanol gave a white crystalline solid, m.pt. 163-5°C, which analysed for $C_{14}H_{16}O_6$, and had a molecular ion at m/e 280. Infra-red spectroscopy showed $\nu_{OH}^{CHCl_3}$ 3490cm^{-1} (broad), ν_{CO} 1700cm^{-1} (broad), and a broad absorption in the range 3600-2400 cm^{-1}. There was no sign of a γ-lactone carbonyl absorption in the i.r. spectrum at 1770cm^{-1}.

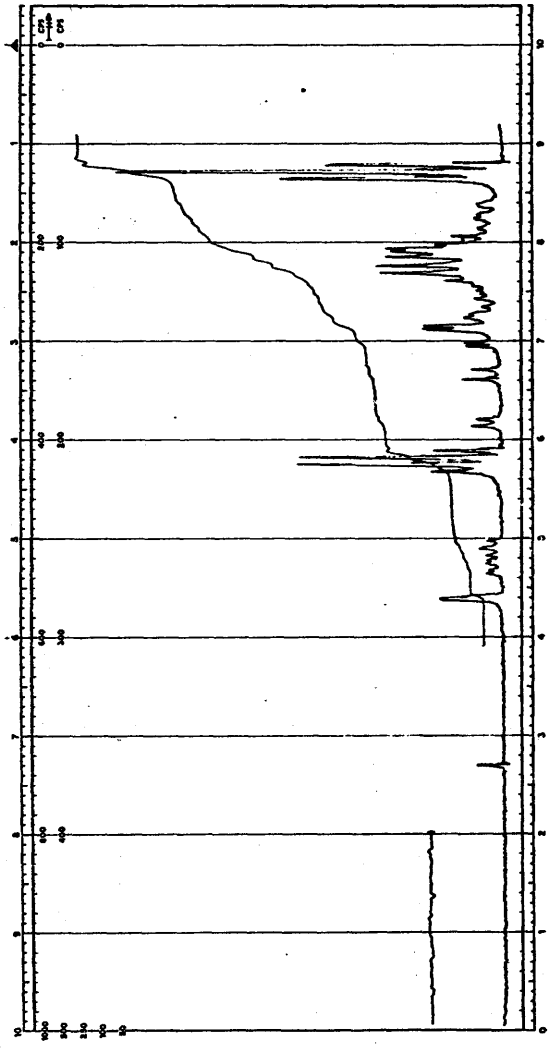
This information is consistent with hydrolysis of the ester groupings <u>without</u> subsequent lactonisation to a di-lactone. This is in agreement with the configuration of the trans-cis diol diacid (23).

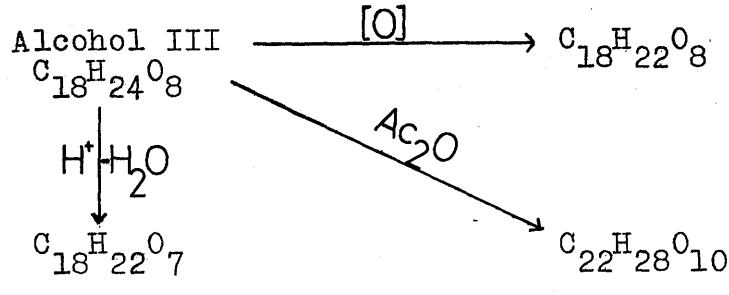
Thus the starting dione diester can be assigned the trans structure (19).

The third product to be obtained from the condensation of acrolein and diethylsuccinylsuccinate (4) was a colourless, crystalline solid, m.pt. 140°C, designated III.

Product III analysed for $C_{18}H_{24}O_8$ and had a parent

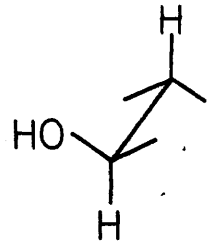
Fig.1



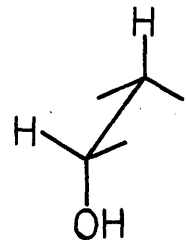

Alcohol III
$C_{18}H_{24}O_8$
[O]
$C_{18}H_{22}O_8$
$H^+ + H_2O$
Ac_2O
$C_{18}H_{22}O_7$
$C_{22}H_{28}O_{10}$

ion in the mass spectrum at m/e 368, with a ready loss of 2 molecules of water to an ion at m/e 332. The infra-red spectrum showed $\nu_{CO}^{CCl_4}$ 1741 and 1722cm^{-1}; ν_{OH} 3630 and 3580cm^{-1}. The carbonyl absorptions were assigned to ester and normal cyclohexanone types respectively. Measurement of extinction coefficients in the i.r. spectrum suggested the presence of two esters and one carbonyl in the molecule. The presence of two esters was proved by careful integration of the n.m.r. spectrum, the number of protons having been determined by microanalysis ($C_{18}H_{24}O_8$) and mass spectroscopy (M^+=368). The hydroxylic peaks were weak in carbon tetrachloride solution although they were strong in a nujol mull. The compound was very unstable to base and lost one mole of water on treatment with acid. It yielded a diacetate on treatment with acetic anhydride, and it could be oxidised by Jones reagent to a dehydro-derivative which showed a new carbonyl absorption in the i.r. spectrum. However, the oxidation product showed no OH absorption in the i.r. spectrum, and the diacetate showed a band at 1770cm^{-1}, which suggested an enol acetate. Thus it appears that the alcohol III is monohydric, and possesses two esters, one cyclohexanone type carbonyl and one hydroxyl.

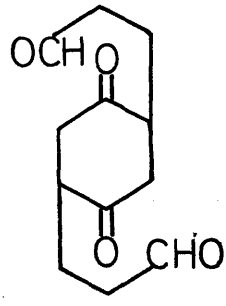
As well as the two ethyl ester proton absorptions [5.78τ,q,4H; 8.7τ,t,6H], the n.m.r. showed a peak at 4.4τ which integrated for one proton, and was a broad singlet (Fig. 1). There was a multiplet at 4.6-5.0τ, which could be resolved into two sets of double doublets,



(26a)

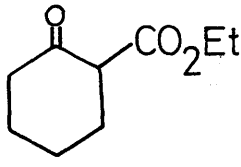
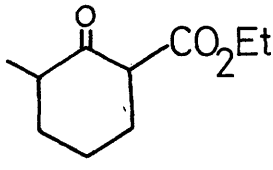
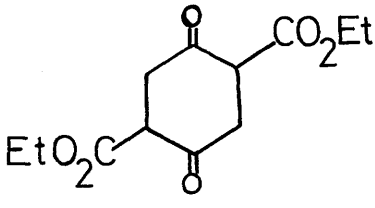
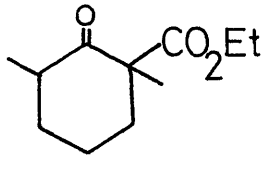


(26b)



(11)

Table 2.

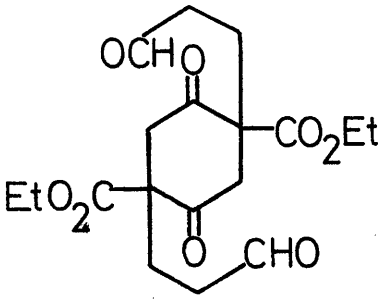
	λ_{max}(EtOH)	ϵ
	257	7,084
	258	12,129
	245	25,000
	266	160

one centred on 4.72τ (J=10,4 Hz) and the other centred on 4.90τ (J=7,9 Hz). The remaining assignable peaks were at 6.15τ, which was a doublet (J=7 Hz) and integrated for ½ proton, and at 6.65τ, also a doublet (J=10 Hz), which also integrated for ½ proton. Both doublets at 6.15τ and 6.65τ disappeared after addition of a little deuterium oxide. These signals were attributed to a mixture of two epimeric alcohols. In a decoupling experiment, irradiation at 6.65τ and 6.15τ resulted in the signals at 4.72τ and 4.90τ becoming doublets, J=4 and 9Hz respectively, which is consistent with axial-equatorial and axial-axial couplings respectively (26 a and b).

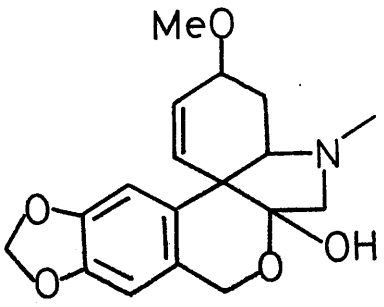
No aldehyde absorption could be detected in the n.m.r. spectrum, either under neutral or acidic conditions, and it was difficult to conceive of a structure which was derived from (11) without loss and which was consistent with (i) the conclusion derived above and (ii) the apparent presence of a single vinylic proton in the n.m.r. spectrum (4.4τ). In particular, the structure of the precursor (11) had not been proved.

As the alcohol III did not give a positive ferric chloride test, and did not absorb in the ultra-violet, it was assumed that the β-keto-ester functions in the alcohol III were no longer in a position to enolise.

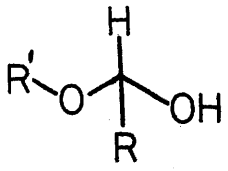
To check this assumption, the ultra-violet spectra of four β-keto-esters, three enolisable and one non-enolisable, were taken and the results are shown in table 2. This shows that enolisable β-keto-esters



(11)

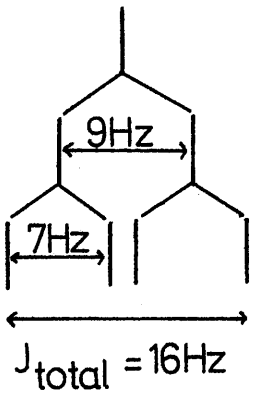


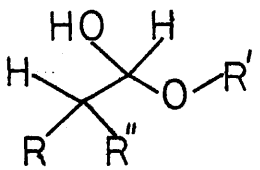
(27)



(28)

Fig.2



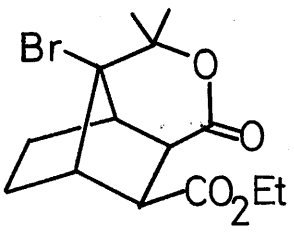


(29)

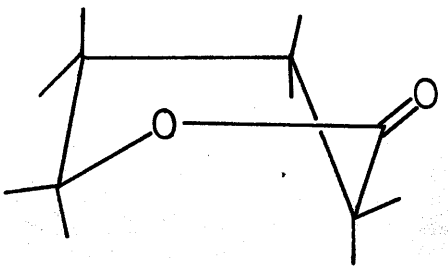
show strong u.v. absorption, whereas III does not. It is therefore assumed that in III the two acrolein molecules have added at the expected sites as shown in (11).

Additional information about the nature of the alcoholic group was obtained by running the n.m.r. spectrum in dimethylsulphoxide as solvent. A doublet at 3.38τ (J=7Hz) appeared in the spectrum, indicating that the hydroxyl was secondary, but available information[8] showed that only very few hydroxyl protons resonate at such low field. Hemiacetal and hemiketal protons appear as doublets and singlets respectively at lower fields (ca. 3.4τ) than normal, for example, tazettine (27) at 3.46τ, singlet.

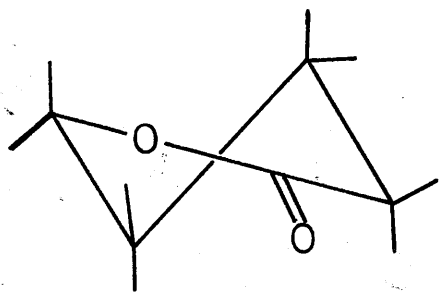
On this information, part of the structure of the alcohol III was considered to be (28). The possibility that a second resonance at 5.07τ (triplet, in dimethylsulphoxide) was due to a primary alcohol was dismissed on the chemical evidence and instead assigned to the α-hydrogen of the hemiacetal coupling with a β-hydrogen. In a carbon tetrachloride solution with deuterium oxide added, this appears as a doublet (J=9Hz) at much the same field position. The 5.07τ resonance in dimethylsulphoxide can be rationalised as two almost overlapping doublets, the overall J value of 16Hz embracing the 7Hz and 9Hz couplings involved (see Fig. 2). This led to the postulation of the partial structure (29). The chemical transformationsof the alcohol III, i.e. oxidation, dehydration, acetylation



(30)



(31)



(32)

and hydrogenation were investigated in order to obtain further structural information.

Oxidation of the alcohol III with standard Jones reagent gave a white crystalline product which analysed for $C_{18}H_{22}O_8$ and showed a decrease in molecular weight from 368 to 366 (by mass spectroscopy), consistent with oxidation of one hydroxyl. The infra-red spectrum showed $\nu_{CO}^{CCl_4}$ 1770, 1744, 1739 and 1723cm^{-1}. The 1723cm^{-1} absorption was unchanged from the alcohol III, the 1744cm^{-1} and 1739cm^{-1} peaks could be accounted for by the two ester groupings in non-equivalent environments, while the 1770cm^{-1} peak appeared to have arisen from the oxidation of the hydroxyl grouping. This absorption is encountered in γ-lactones[7], δ-enol-lactones[7] or with δ-lactones in a strained system. Wilder and Winston[9] reported that deviation from the normal δ-lactone carbonyl absorption occurred where the lactone was strained, an example given being (30), which shows $\nu_{CO}^{CCl_4}$ (lactone) 1772cm^{-1}, which is in agreement with the results of Overton et al.[10], who found that δ-lactones held in a boat conformation (31) had carbonyl absorptions in the range 1758-1765cm^{-1}, while the "normal" δ-lactone conformation, the half-chair (32), gave carbonyl absorptions in the range1730-1750cm^{-1}. The enol lactone structure can be eliminated as a possibility since Nakanishi[7] quotes a strong C=C absorption at 1685cm^{-1} for δ-enol-lactones, and this is not observed.

The proton n.m.r. spectrum showed changes when

Fig. 3

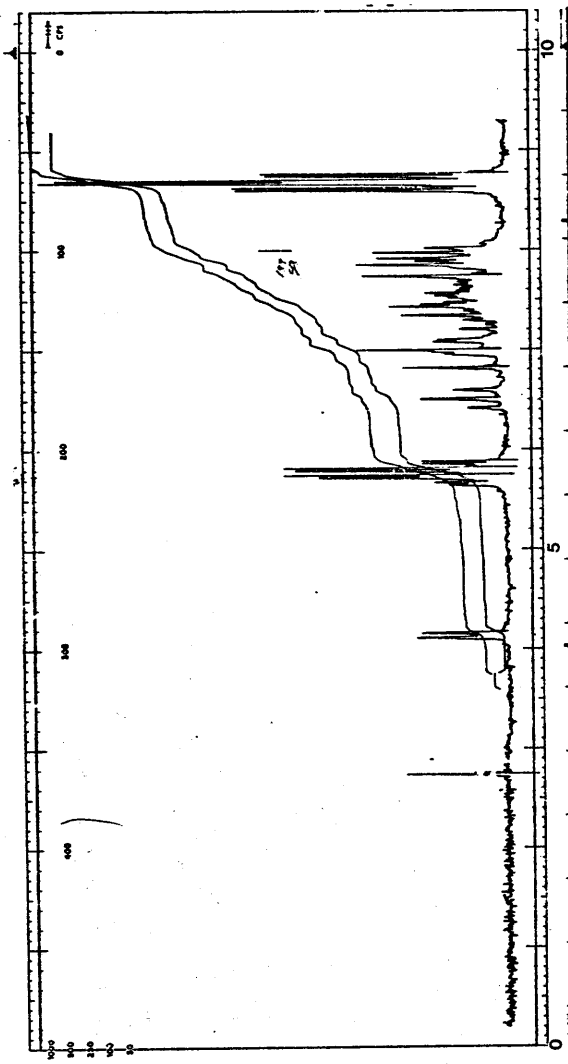
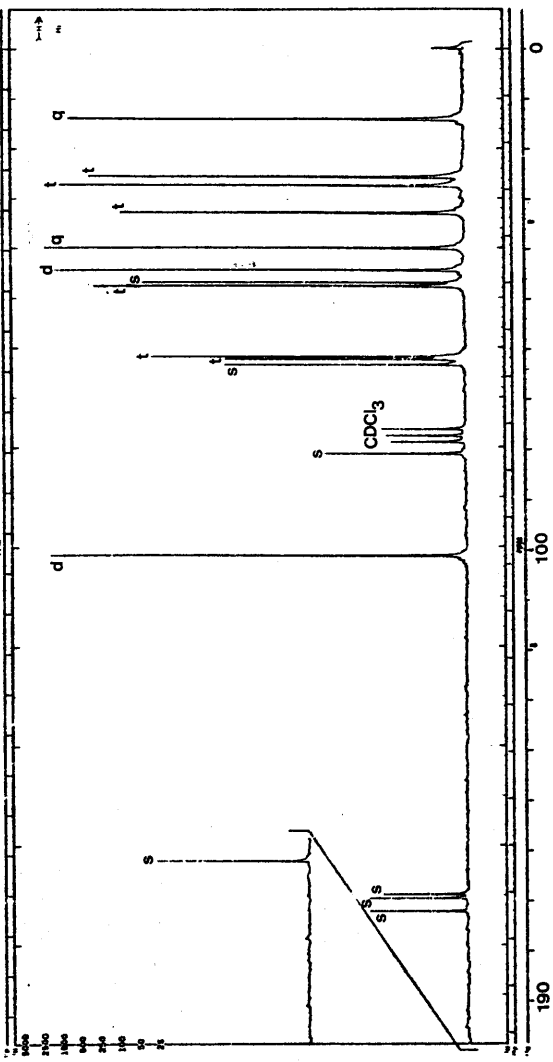
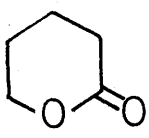


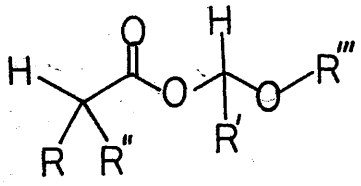
Fig. 4



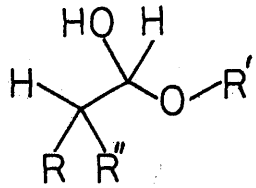


(33)

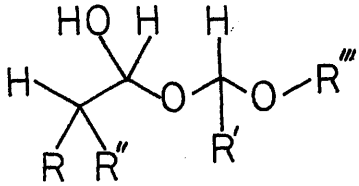
compared to that of the alcohol III (Fig. 3). The signals at 4.6-5.0τ, due to the hemiacetal proton, had disappeared, as had the alcohol signals at 6.15 and 6.65τ, as expected. The two esters had become non-equivalent, as evidenced by the appearance of two quartets, at 5.74 and 5.78τ, and two triplets at 8.68τ and 8.70τ. There remained the problem of assigning the signal at 4.4τ, which survived in the oxidation product, and which seemed to be vinylic in nature. No further information could be obtained from the proton n.m.r. spectrum, and it was decided to obtain a ^{13}C n.m.r. spectrum. This would provide the necessary information on the types of carbon atoms, the number of each type, and their substitution, i.e. primary, secondary, tertiary or quaternary. The noise-decoupled spectrum, together with the multiplicity of each signal as obtained from the off-resonance decoupled spectrum, is shown in Fig.4. From this, it can be seen that there are 17 different types of carbon atoms. The signal at 14 ppm is a quartet, and contains both methyls of the ethyl esters. The two methylenes of the ethyl esters appear at 61.5 and 62.0 ppm, and are triplets. The signal at 201.8ppm is characteristic of a carbonyl carbon in a cyclohexanone ring. The signals at 169.5 and 168.8ppm are due to the two ester carbonyl carbons in slightly different environments, while the signal at 172.1ppm is due to the carbonyl carbon in a δ-lactone, c.f. the carbonyl carbon absorption at 175.2ppm in (33)[11]. The signal at 101.0ppm is a doublet, and could conceivably be



(34)



(29)



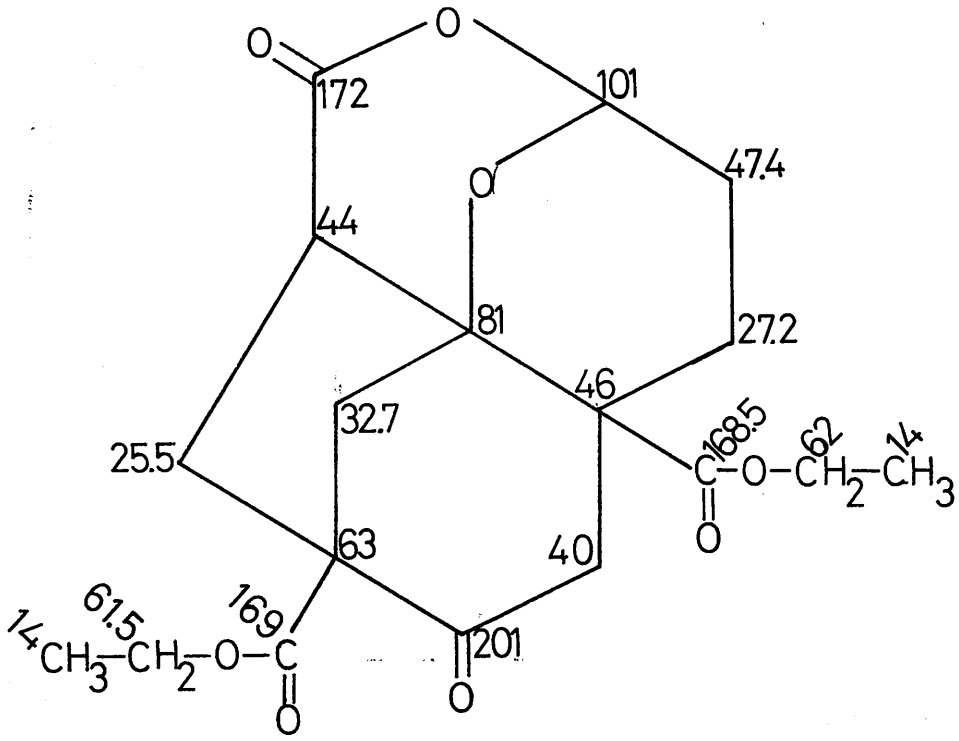
(29a)

attributed to an olefinic carbon. However, there is no other olefinic carbon signal present in the spectrum within the normal range (110-150ppm). Stothers[12] has tabulated the results of several investigations into the effect of substituents on the chemical shift of the α- and β-carbons in a variety of vinyl derivatives. The presence of electronegative substituents tends to deshield the α-carbon and shield the β-carbon, and it is observed that the downfield shift of the α-carbon is balanced by the upfield shift of the β-carbon, relative to ethylene (122.8ppm downfield from TMS). Hence, in methyl vinyl ether, the α-carbon resonates at 153.1ppm, 31ppm downfield from ethylene, while the β-carbon resonates at 85.5ppm, 37 ppm upfield from ethylene.

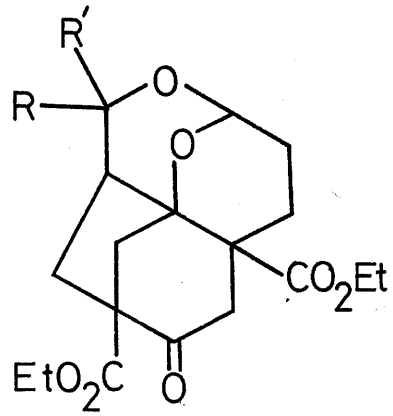
Thus, in the alcohol III, a signal at 101ppm would be expected to have an accompanying signal in the range 135-145ppm, and there is no such signal present. The conclusion to be drawn from this fact is that the molecule does NOT include a carbon-carbon double bond.

The other alternative for the signal at 101ppm is a carbon bearing one hydrogen, and bonded to two oxygen atoms[13]. As seven oxygen atoms, from the eight in the alcohol, have been accounted for, it is possible to draw a partial structure (34) for the oxidation product, using the partial structure (29) already drawn for the alcohol III. Consequently, (29) can be elaborated to (29a).

Of the remaining signals, there are two singlets,



(35)



(36)

a : R=H , R'=OH.

b : R=OH , R'= H.

indicating quaternary carbons, at 63.1ppm and at 46.7ppm. The chemical shift of the first indicates a carbon α to two carbonyls, while the second at 46.7ppm is a carbon α to one carbonyl and β to a second carbonyl. The signal at 44.3ppm is a doublet, and is accounted for by an aliphatic carbon bearing one hydrogen, and α to one carbonyl. The remaining signals, six in all, are five triplets and one quartet. All are aliphatic methylene carbons, but the latter must be held in a rigid conformation, in which the two hydrogens become non-equivalent.

On the basis of the ^{13}C n.m.r. data, and the partial structures obtained from the preceeding physical and chemical investigations, a structure for the oxidation product has been formulated, and the chemical shifts in the ^{13}C n.m.r. are shown on this (35). This structure explains the anomalous 1H signal at 4.15τ in the ^{1}H n.m.r. spectrum initially thought to be olefinic. This signal is due to the proton on the carbon bonded to two oxygen atoms (chemical shift in ^{13}C nmr:101ppm). This gives the structure of the alcohol III as (36a) and (36b), an epimeric mixture.

The dehydration product, obtained most conveniently by treatment of the alcohol III with toluene-p-sulphonic acid in refluxing benzene, was a colourless crystalline solid which analysed for $C_{18}H_{22}O_7$, and had a molecular weight of 350 (mass spectroscopy), indicating a loss of one molecule of water. The infra-red spectrum showed $\nu_{CO}^{CCl_4}$ 1750, 1742 and 1723cm^{-1}, and $\nu_{C=C}$ 1690cm^{-1}.

Fig. 5

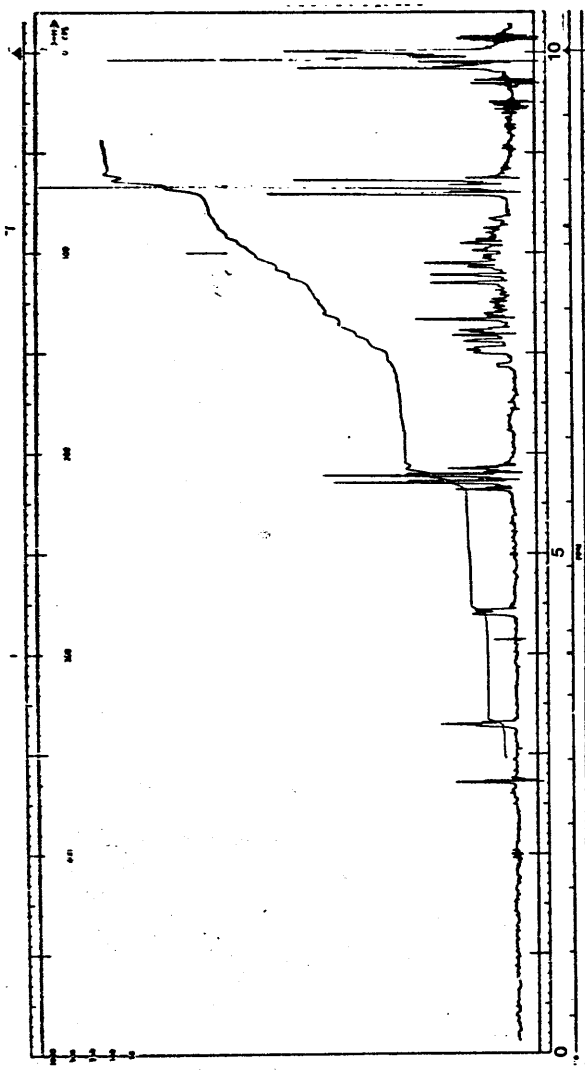
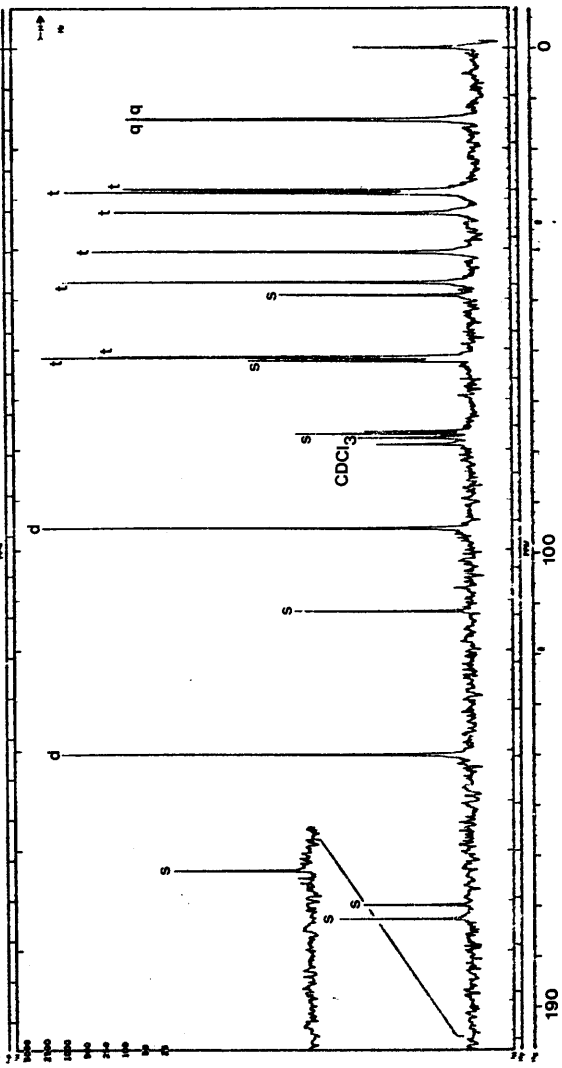
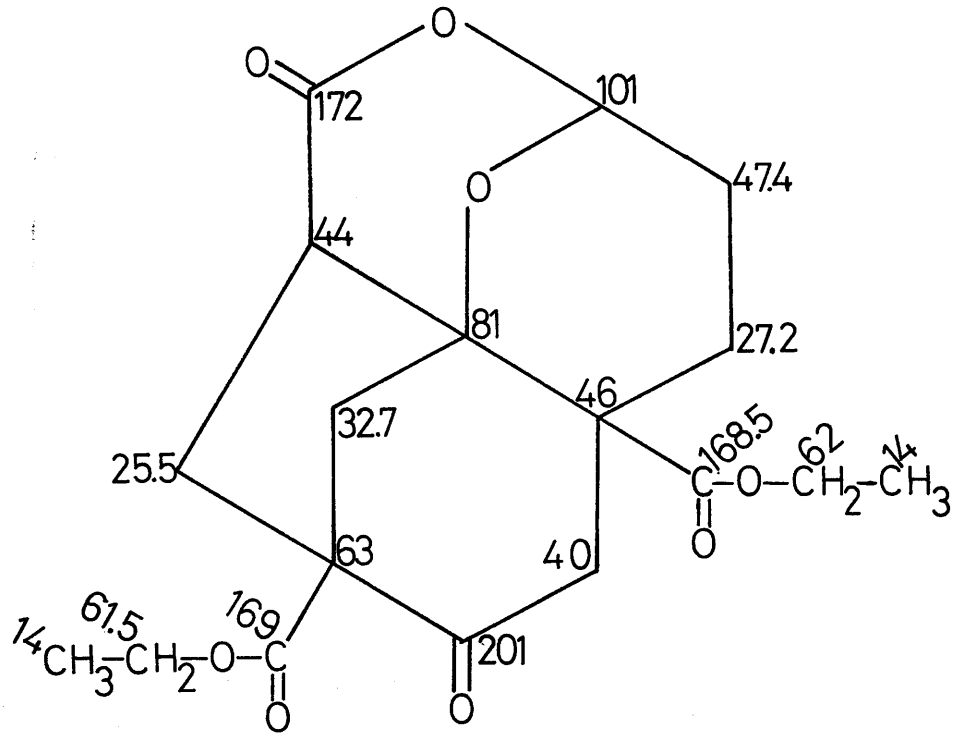
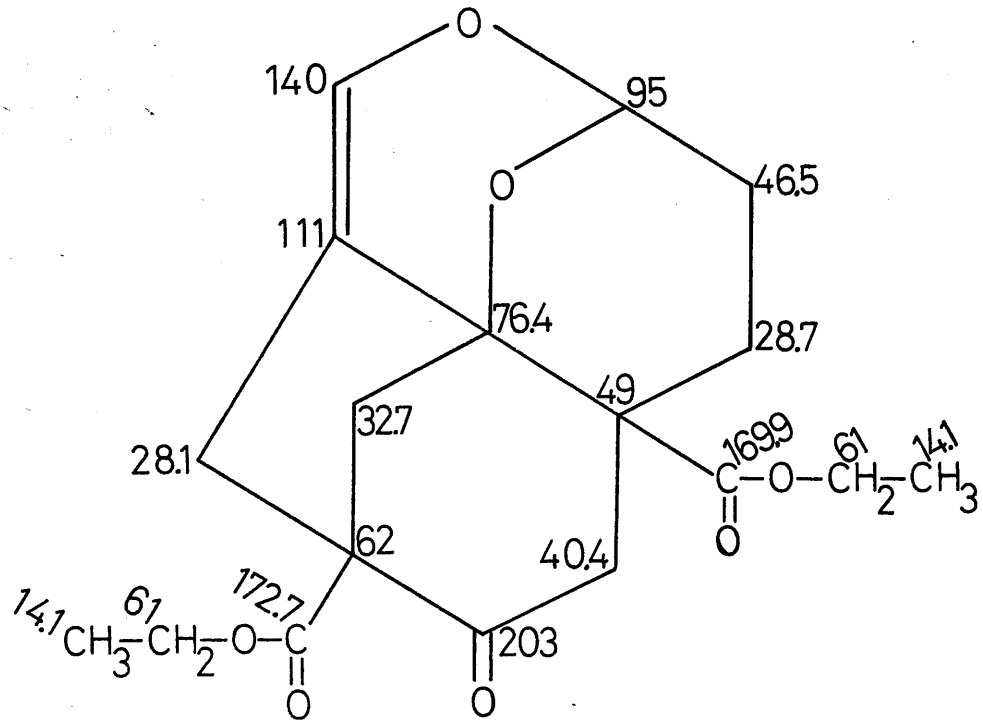


Fig. 6




O
O
172
101
O
47.4
44
81
27.2
46
32.7
168.5
62
14
25.5
C–O–CH2–CH3
O
63
40
61.5
169
14CH3–CH2–O–C
O
201
O

(35)


O
140
95
O
46.5
111
76.4
28.7
49
32.7
169.9
61
14.1
28.1
C–O–CH2–CH3
O
62
40.4
172.7
61
14.1
14CH3–CH2–O–C
O
203
O

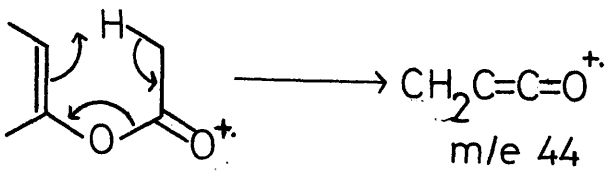
(37)

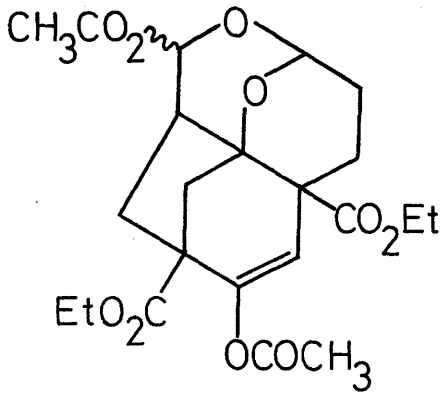
The ^{1}H n.m.r. (Fig. 5) showed the presence of one vinylic proton (3.3τ, finely split triplet), and the disappearance of the alcohol group and associated proton signals at 4.6-5.0τ, 6.15 and 6.65τ when compared to the ^{1}H n.m.r. spectrum of the alcohol III.

Further to this, a ^{13}C n.m.r. spectrum of the dehydration product was obtained. The noise-decoupled spectrum, with the individual signal multiplicities obtained fron the off-resonance decoupled spectrum, is shown in Fig.6. Apart from the absence of the lactone carbonyl signal (172ppm) and the tertiary carbon signal (44ppm), and the appearance of two olefinic carbon signals at 140ppm (doublet) and 111ppm (singlet), the rest of the spectrum is almost identical to that of the oxidation product, allowing for slight changes in chemical shift due to the different environment of a double bond in the molecule. For this reason, skeletal rearrangement can be excluded. The values of the olefinic carbon resonances, 140ppm and 111ppm, are what would be expected for a double bond with an electronegative substituent as in the dehydration product, an enol ether. The ^{13}C chemical shifts of the oxidation product (35) are shown for comparison with those of the dehydration product (37).

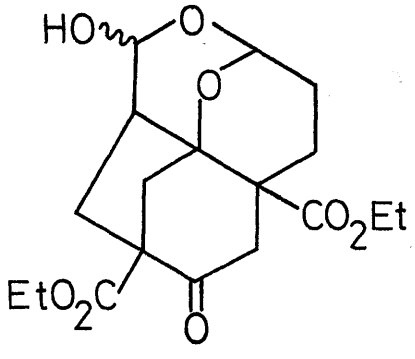
The product of acetylation of the alcohol III was a white crystalline solid which analysed for $C_{22}H_{28}O_{10}$ and which showed a molecular ion at m/e 452. The parent ion at m/e 452 showed two separate losses, one of m/e 60 and one of m/e 42, these being the loss of acetic acid and ketene respectively. This indicates

Scheme 2.





(38)



(36)

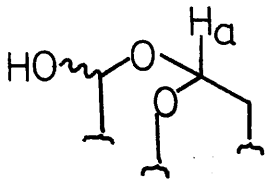
the formation of a diacetate, with one acetate attached to a saturated carbon (loses acetic acid in the mass spectrometer), and the other acetate is attached to a vinylic carbon (loses ketene, see Scheme 2).

Its infra-red spectrum shows $\nu_{CO}^{CCl_4}$ 1770, 1744 and 1725cm^{-1}, which is indicative of an enol acetate, saturated esters, and a cyclohexanone-type ketone[7].

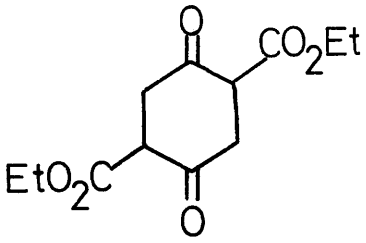
The ^{1}H n.m.r. shows the disappearance of the alcohol signals at 6.15 and 6.65τ, the broad singlet at 4.4τ becomes a broad doublet (J=8Hz, 1H), while the multiplet at 4.6-5.0τ shifts downfield to 4.05τ and is a double doublet (J= 9,4Hz; 1H). A vinylic signal appears at 4.7τ (1H, singlet), while the two acetate methyls appear as singlets at 7.85τ and 7.90τ.

This information, plus the structure obtained from the preceeding studies lead to (38) as the structure of the diacetate.

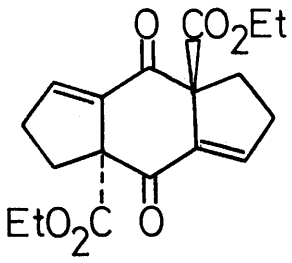
The remaining reaction which was carried out on the alcohol III,(36) was anomalous. It had been previously thought that a double bond was present in the molecule, and accordingly, a sample had been subjected to hydrogenation conditions. One molar equivalent of hydrogen was taken up, and a colourless oil, pure on analytical tlc, was obtained. This had a parent ion at m/e 354 in the mass spectrum, and accurate mass measurement gave a molecular mass of 354.1672, which corresponds to $C_{18}H_{26}O_7$, (m/e 354.1671), and can be accounted for by uptake of two hydrogens and loss of one oxygen.



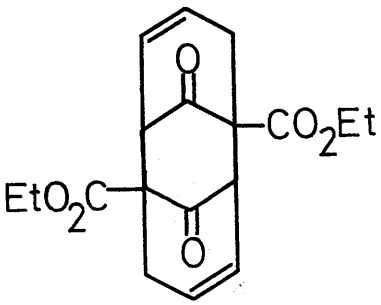
(39)



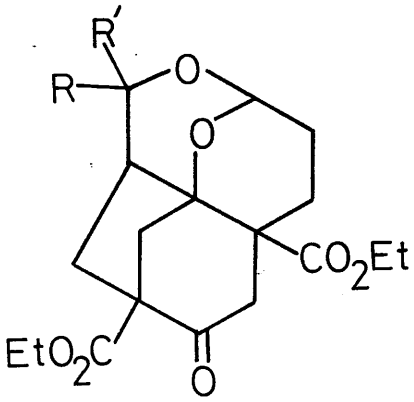
(4)



(19)



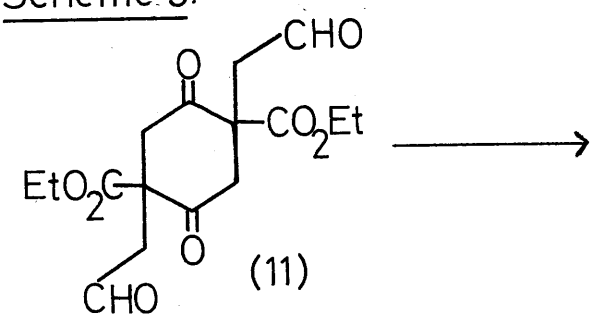
(13)



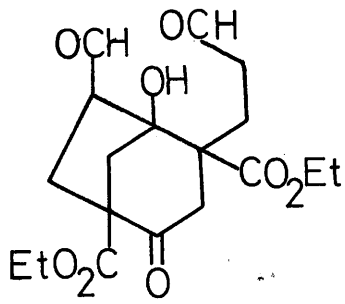
(36) a: R= H , R=OH.

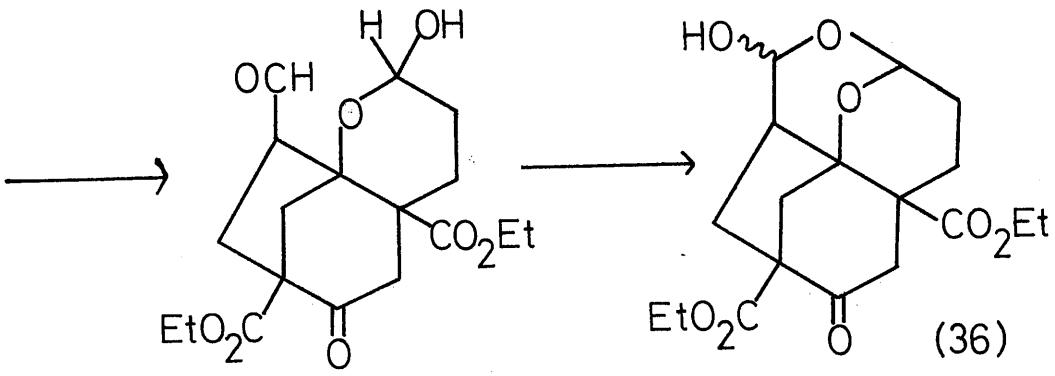
b: R=OH , R= H.

Scheme 3.



(11)





(36)

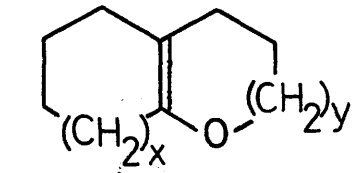
The infra-red spectrum shows $\nu_{OH}^{CCl_4}$ 3635, 3545 and 3460 cm^{-1}, and ν_{CO} 1745, 1723 and 1700 cm^{-1}, which indicates the presence of one more carbonyl than the starting alcohol. The ultra-violet spectrum shows only end-absorption.

The ^1H n.m.r. spectrum shows the disappearance of the signals at 4.4τ and 4.6-5.0τ, as well as the alcohol signals at 6.15τ and 6.65τ, while a two proton triplet (J= 7Hz) appears at 6.37τ, as well as a one proton broad doublet at 8.32τ, which disappears on shaking with deuterium oxide. The low field portion of the spectrum shows no aldehyde signal.

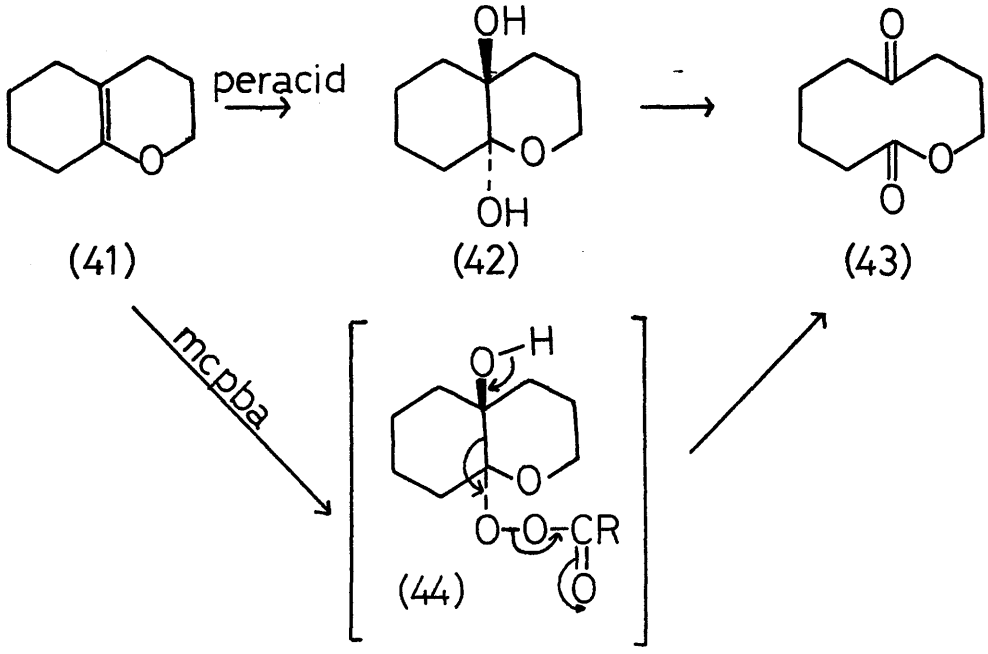
From the evidence, it would appear that hydrogenolysis rather than hydrogenation has occurred, and from the n.m.r. data, it is obvious that there has been a significant change in the hemiacetal-acetal group, since the proton signal [H_a in (39)] is no longer present.

No satisfactory explanation of the hydrogenolysis has been found, as it is difficult to visualise how cleavage of a carbon-oxygen bond can result in a product with the correct molecular weight, and which satisfies the observed physical data.

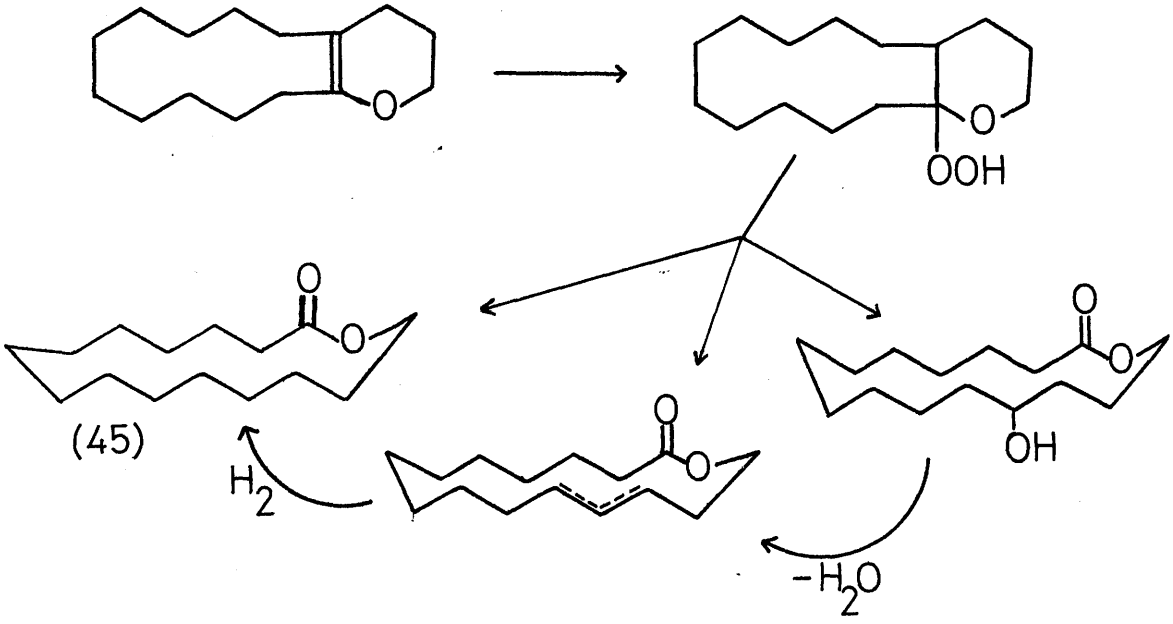
The products obtained from condensation of acrolein with diethylsuccinylsuccinate (4) were therefore the dione diester (19), as had been foreseen, and an epimeric mixture of alcohols, (36a) and (36b), which presumably arise by the route shown in Scheme 3, but not the desired tricyclic compound (13).



(40) x = 1,2
y = 1,2



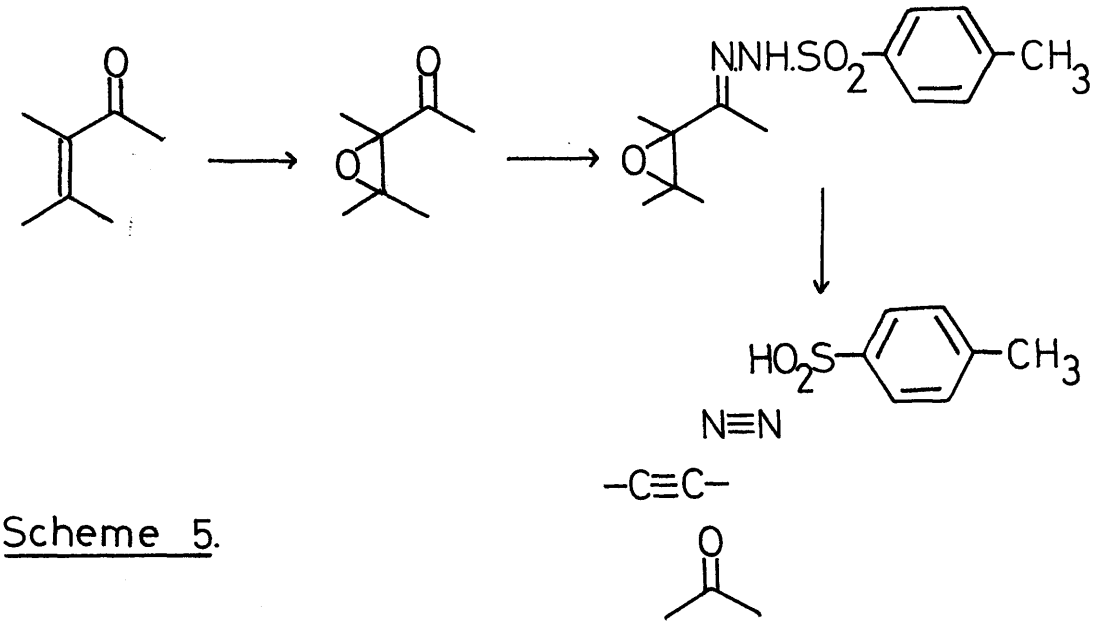
Scheme 4



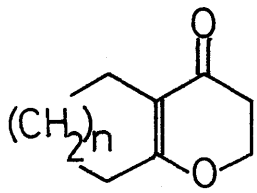
PART II

LACTONES.

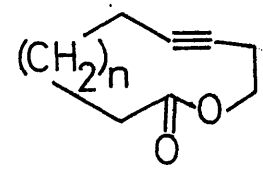
The synthesis of simple macrocyclic lactones from fused bicyclic precursors has been investigated by several workers. Borowitz[14] has investigated the synthesis of medium-ring keto-lactones which are structurally related to the macrolide antibiotics, while Ohloff and Becker[15] synthesised large-ring lactones and ketones for their perfumery properties. Borowitz[14] obtained keto-lactones by cleavage of the double bond in compounds of the type (40) by two routes : (a) treatment of the tetrahydrochroman (41) with perphthalic acid to give the glycol (42), followed by cleavage with lead tetraäcetate to the 6-keto-nonanolide (43); (b) one-step cleavage of the tetrahydrochroman (41) with m-chloro-perbenzoic acid to the 6-keto-nonanolide (43), probably via the hydroxy-perester (44). However, it was extremely difficult to reduce the ketone function, in accordance with the known slow rate of reaction of simpler 10-membered ketones.[16] Accordingly, if functionality is to be introduced into a medium-sized ring, the functional groups must be already present before double bond cleavage, or alternatively, the functional groups produced in the double bond cleavage must be capable of modification without the limitations imposed by ring strain, as discussed previously (Introduction page 3). This problem did not occur in the Ohloff synthesis (Scheme 4) since the non-functionalised lactone (45)



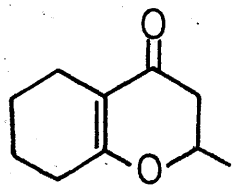
Scheme 5.



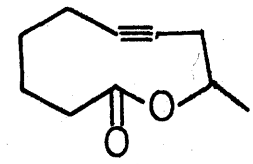
(46)



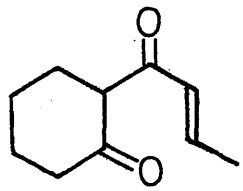
(47)



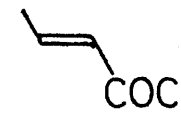
(48)



(49)



(50)



(51)

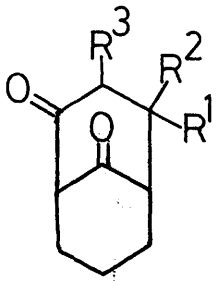
was required, and the reaction sequence was designed with this in mind.

It was felt that elaboration of an acetylenic bond in a ten-membered ring was possible, and that the fragmentation reaction of Eschenmoser[17] (Scheme 5), when applied to a suitable cyclic system, for example (46), would give an acetylenic lactone (47).

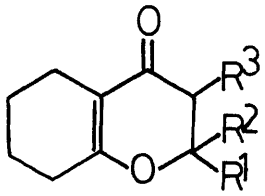
Another necessary feature of the starting material is a methyl group ∝ to the ring oxygen, as this is present in many macrolide antibiotics. A suitable compound for model studies on the fragmentative ring opening appeared to be the 2-methyl-5,6,7,8-tetrahydrochroman-4-one (48), since this appeared to be amenable to ready synthesis, and would give a rapid indication of the feasibility of the method for adaptation to macrolide synthesis. Fragmentative ring opening of (48) would give the acetylenic lactone (49), and it should be possible to alter the eventual lactone ring size by changing the size of the starting alkanone ring, or the size of the acid chloride used as starting material.

A feasible route to (48) was thought to be cyclisation of 2-crotonyl-cyclohexanone (50), prepared by acylation of cyclohexanone with crotonyl chloride (51), according to the method of Linn and Hauser[18]. However, reaction of cyclohexanone with sodamide, followed by addition of crotonyl chloride and subsequent work-up, gave 3g. of a pure compound which was not 2-crotonyl-cyclohexanone (50) (by i.r. and n.m.r. spectroscopy) and was not investigated.

An alternative synthesis of the tetrahydrochromanone (48)



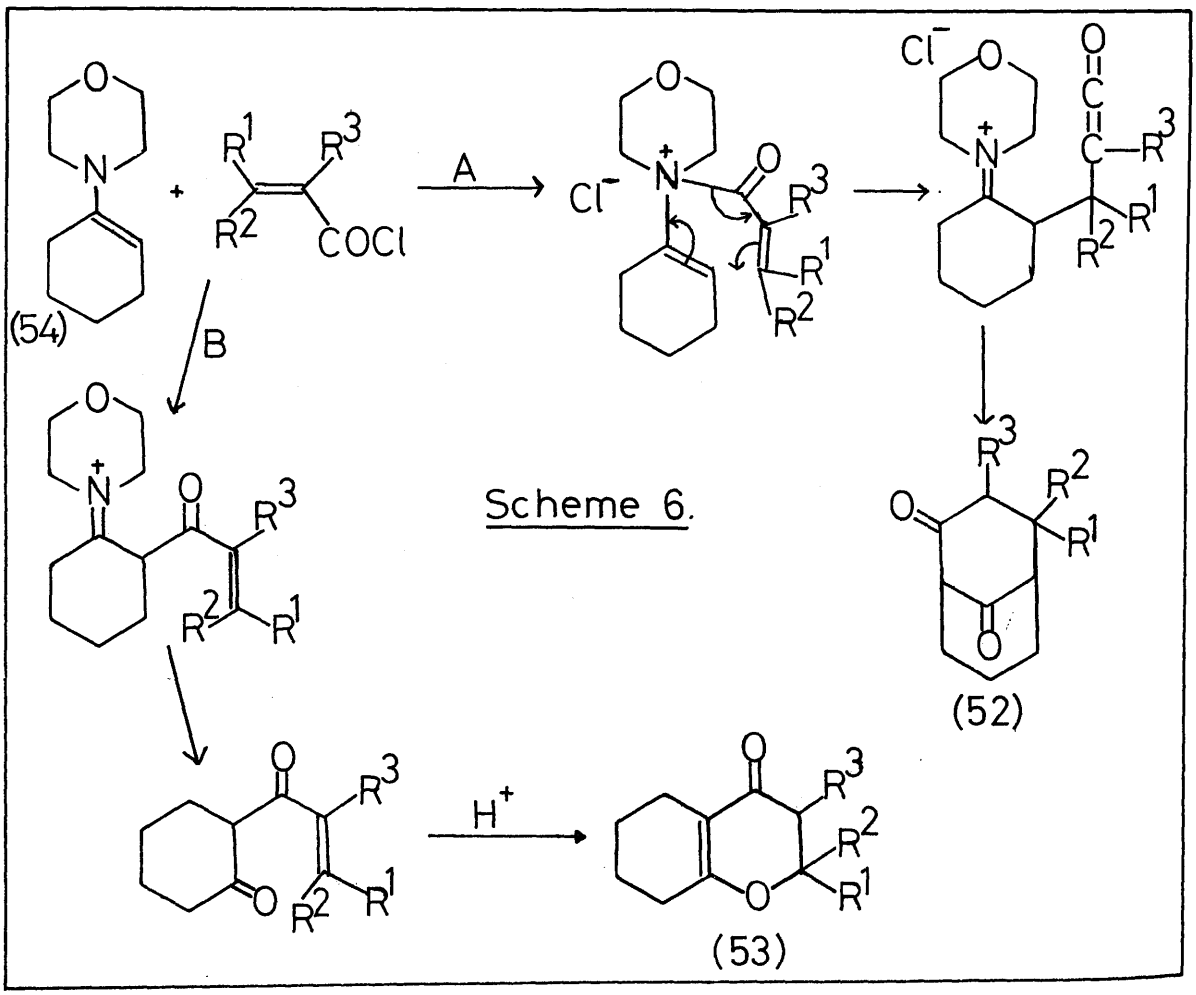
(52)



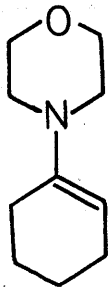
(53)

Table 3.

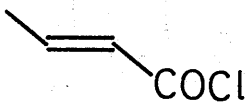
Acid chloride	Product(s)
CH_2=CHCOCl	52 + 53
CH_2=C(CH_3)COCl	52 + double acylation product
CH_3CH=CHCOCl	53
$(CH_3)_2$C=CHCOCl	53
CH_3CH=C(CH_3)COCl	53



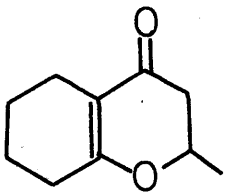
Scheme 6.



(54)



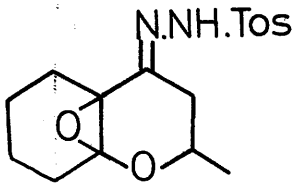
(51)



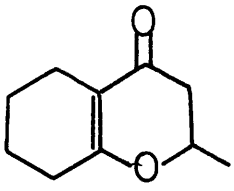
(48)

was sought. Gelin et al.[19] have reacted unsaturated acid chlorides with cyclic enamines according to the method of Hünig et al.[20], and have obtained either a bicyclo-[3,3,1]-nonanedione (52) or a tetrahydrochromanone (53), or a mixture of both, depending on the acid chloride used. The results of Gelin[19] are shown in table 3, and indicate that the presence of a β-methyl substituent results in formation of the tetrahydrochromanone (53) only. The formation of the bicyclo-[3,3,1]-nonanedione had already been interpreted by Hickmott et al.[21] as N-acylation followed by a sigmatropic rearrangement (route A in scheme 6). The formation of the tetrahydrochromanone is interpreted as C-alkylation, followed by hydrolysis and cyclisation in acid medium[22] (route B, scheme 6). This is therefore a ready source of the desired tetrahydrochromanone (48), [(53), $R^1=CH_3$, $R^2=R^3=H$].

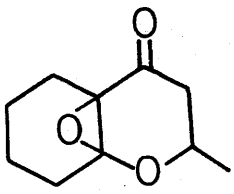
1-morpholino-cyclohex-2-ene (54) was prepared by the method of Hünig[20] and reacted with crotonyl chloride (51) as directed to yield pure 2-methyl-5,6,7,8-tetrahydrochroman-4-one (48) as a white crystalline solid, m.pt. 46-8°C [Lit. 46°C [19]]. The i.r. spectrum showed $\nu_{CO}^{CCl_4}$ 1670 cm^{-1} (conjugated carbonyl) and $\nu_{C=C}$ 1620cm^{-1}(strong), while there was an absorption at 271nm (ϵ=9,800) in the u.v. spectrum. The n.m.r. spectrum showed a one proton multiplet at 4.5τ(J_{CH_2-H}=8Hz, J_{CH_3-H}=7Hz), a doublet at 7.7τ(2H,J=7Hz) and a doublet at 8.6τ(3H,J=7Hz). This information is consistent with the tetrahydrochromanone (48) and is in agreement with literature values[19].



(55)



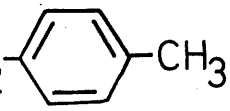
(48)

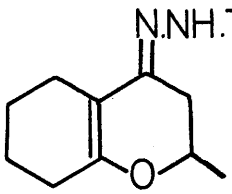


(56)

$Tos.N.NH_2$

(57)

Tos = 

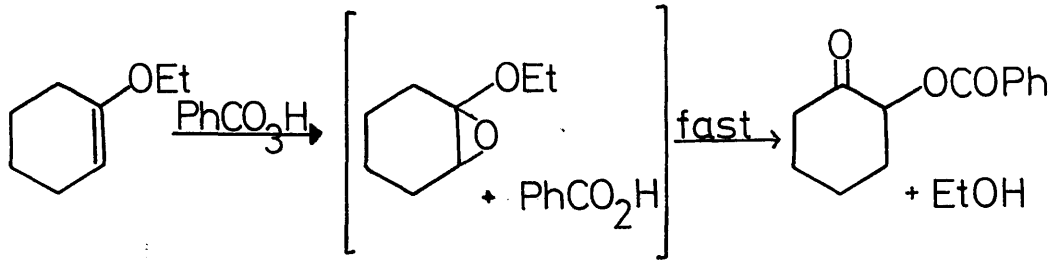


(58)

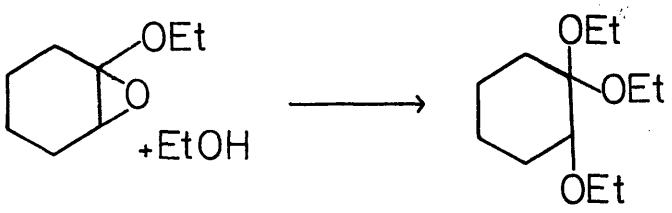
To obtain the necessary compound (55) for fragmentative ring opening by the Eschenmoser method, the double bond of the tetrahydrochromanone (48) has to be epoxidised to give (56), which is then treated with toluene-p-sulphonyl hydrazine (57) to give the epoxy-hydrazone (55), or alternatively, the hydrazone could be prepared first, followed by epoxidation to (55).

It was decided to attempt epoxidation followed by tosylhydrazone formation, and accordingly the tetrahydrochromanone (48) was treated with alkaline hydrogen peroxide[23]. After work-up, analytical tlc showed a large number of products present, and no separation was attempted.

The alternative route, tosylhydrazone formation then epoxidation was then tried. Treatment of the tetrahydrochromanone (48) with toluene p-sulphonyl hydrazine (57) gave a quantitative yield of the tosyl hydrazone (58), as pale yellow crystals, m.pt. 170-2°C (decomposes) and which gave satisfactory analysis figures. The mass spectrum showed a parent ion at m/e 334. The ir spectrum showed a weak N-H absorption at 3220cm^{-1}, and strong absorptions at 1640cm^{-1} (conjugated double bond) and 1600cm^{-1}(aromatic), as expected for structure (58). The nmr showed a multiplet at 2.3τ(4H, aromatic), typical of a para-disubstituted benzene ring (AB-like quartet, with additional weak lines), a one proton multiplet at 6.0τ(proton α to oxygen), a singlet at 7.7τ(3H, methyl) and a doublet at 8.85τ(3H, J=6.5Hz, methyl α to oxygen).

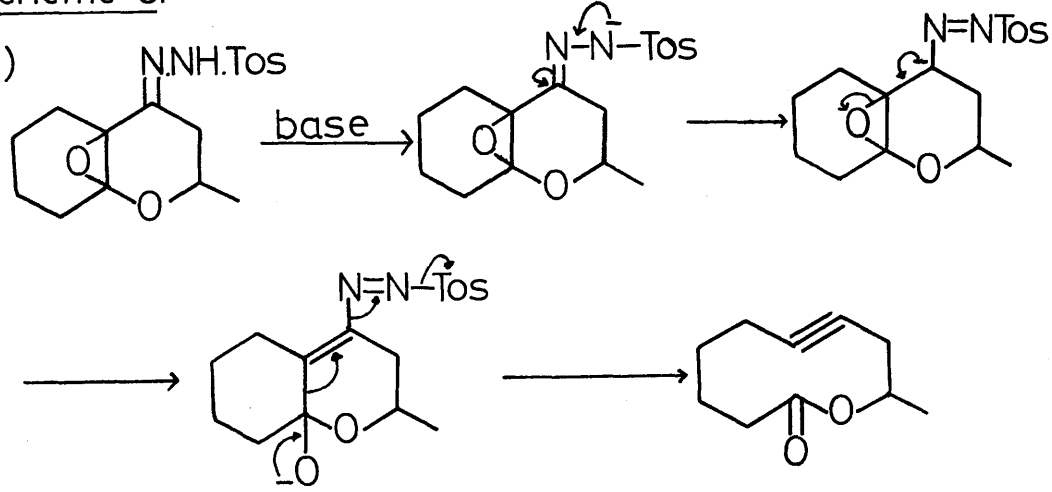


Scheme 7.

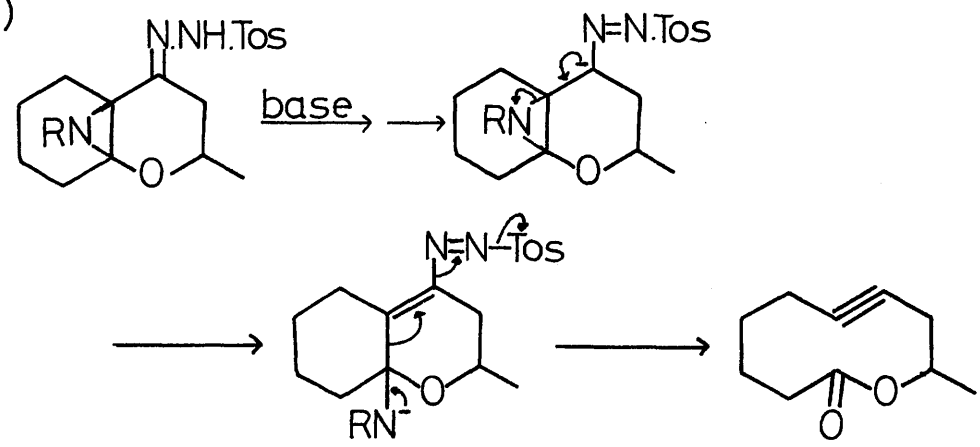


Scheme 8.

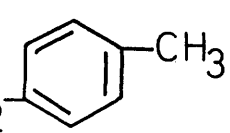
(i)

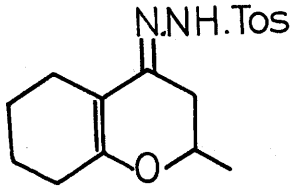


(ii)

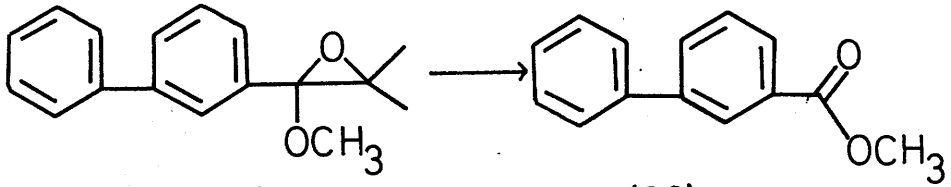


R = $-CO_2Et$

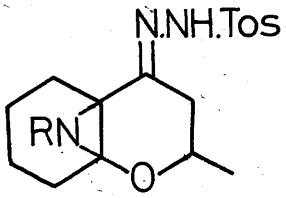
Tos = 



(58)



(59) (60)



R= $-CO_2Et$

(61)

$N_3.CO_2Et$

(62)

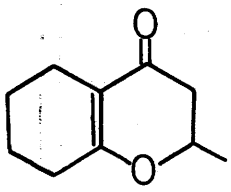
Attempted epoxidation of the tosylhydrazone (58) with hydrogen peroxide/sodium hydroxide[23] or hydrogen peroxide/benzonitrile[25] resulted in recovery of starting material. Treatment of (58) with m-chloro-perbenzoic acid[26] gave a complex mixture of products and some unreacted starting material. No single pure compound could be separated from this mixture.

The inability to form the epoxide of the tosyl hydrazone, or of the parent ketone, was attributed to the instability of the resulting epoxy-ether. Stevens and Tazuma[27] investigated the synthesis of epoxy-ethers and have reported them to be unstable at room temperature, unless stabilised by phenyl groups. They also reported that the epoxy-ether, once formed, could react with the reagents and products in the reaction vessel, and several products could be isolated (Scheme 7). Also, the epoxy-ether could be cleaved by excess peracid to give an ester as in (59) → (60).

As the route via the epoxide was therefore not available, it was decided to circumvent the problem of stability by synthesising an aziridine (61), which could fragment by a similar route to that of the epoxy-tosylhydrazone [Scheme 8(i) and (ii)].

Ethyl azidoformate (62) was prepared from ethyl chloroformate and sodium azide[28], and reacted with the tosylhydrazone (58) by the method of Huisgen[29], but no reaction was observed and unreacted starting material was recovered.

It was therefore apparent that the Eschenmoser



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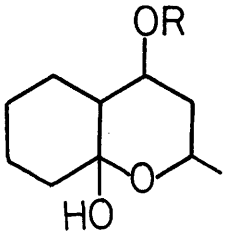
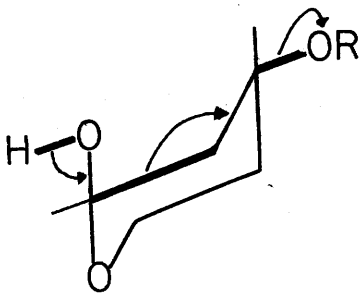
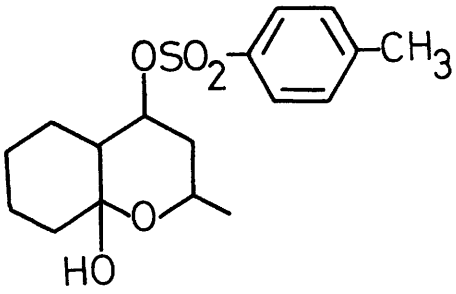


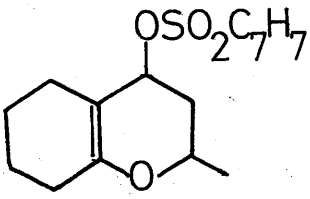
(63)



(64)



(65)



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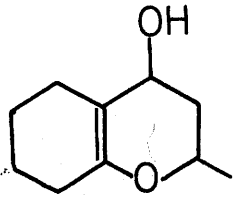


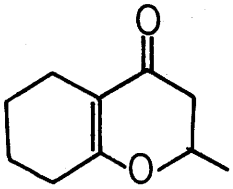
(67)

fragmentation sequence was not applicable to the tetrahydrochromanone (48), and another route to the opening of the fused bicyclic system was sought.

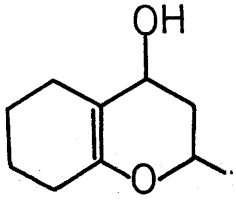
It should be possible to apply an elimination reaction to the system (63) obtained from the tetrahydrochromanone (48). A requirement for this elimination is that the eliminating groups or atoms are anti-periplanar, that is the molecule has the stereochemistry shown in (64).

The compound of choice was the tosylate [(63, $R=SO_2C_6H_4(p)CH_3$], (65), and it was expected that this compound would be relatively unstable. It was hoped that the tosylate (65) could be obtained from (66), and could be opened in situ by the action of dilute sulphuric acid in dioxan. The tosylate (66) could be synthesised from the tetrahydrochromanone (48) by reduction of the ketone to the alcohol, followed by esterification with toluene p-sulphonyl chloride.

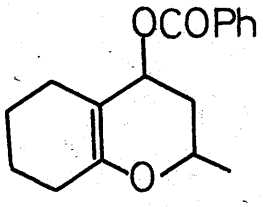
The tetrahydrochromanone (48) was reduced with sodium borohydride in methanol/water to give a mixture of two compounds as well as some starting material. A cleaner reduction was obtained by use of lithium aluminium hydride, which gave a quantitative yield of the alcohol, 2-methyl-5,6,7,8-tetrahydrochroman-4-ol (67) as white crystals, m.pt. 103-4°C, which analysed for $C_{10}H_{16}O_2$. The infra-red spectrum showed no carbonyl absorption, and appearance of a hydroxyl absorption at 3590cm^{-1}. The double bond showed as a strong absorption at 1680cm^{-1}, (enol ether), while the u.v. spectrum showed



(48)



(67)



(68)

no absorption above 210nm. The n.m.r. spectrum now showed two protons occurring as a multiplet at 6.0τ (protons on carbon bearing one oxygen), and a signal at 7.5τ which integrated for one proton, was a broad singlet, and disappeared on addition of a little deuterium oxide. The mass spectrum showed an increase in molecular weight from 166 to 168, and is consistent with reduction of the tetrahydrochromanone (48) to the tetrahydrochromanol (67).

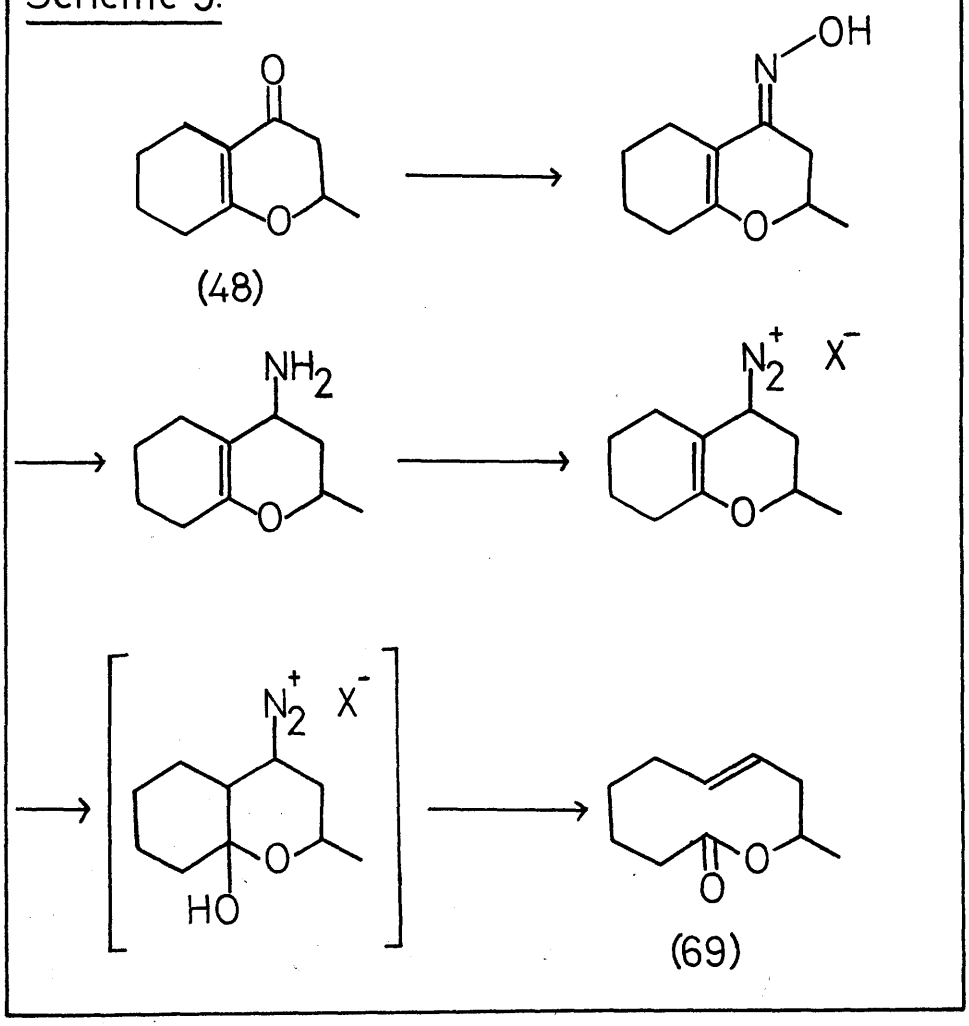
Attempts at making the tosylate of the alcohol (67) by treatment with toluene p-sulphonyl chloride in pyridine resulted only in an efficient recovery of toluene p-sulphonic acid.

Fortunately reaction of the alcohol (67) with benzoyl chloride followed by careful non-acidic work-up to avoid hydrolysis of the ester, gave a high yield of the benzoate (68) as white crystals, m.pt.52-4°C, which analysed for $C_{17}H_{20}O_3$ and had a molecular ion at m/e 272. The infra-red spectrum showed $\nu_{max}^{CCl_4}$ 1740(ester) and 1690cm^{-1}(enol C=C), while the nmr showed signals at 1.8τ(2H,aromatic); 2.5τ(3H,m,aromatic); 5.9τ(2H,m, protons on carbon bearing oxygen) and 8.7τ(d,J=5Hz,3H,methyl), which is consistent with the benzoate, (68).

Having now obtained a suitable substrate, the acid-catalysed hydration and subsequent ring-opening was attempted.

The benzoate (68) was dissolved in dioxan, dil. sulphuric acid was added and the mixture stirred for seven days. Work-up gave a mixture which, by analytical tlc,

Scheme 9.

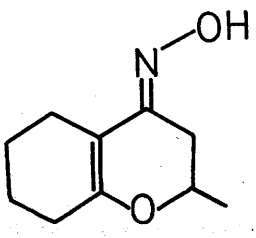


contained at least seven compounds. Preparative tlc separated out benzoic acid (57% of the mixture), identified by comparison (ir, m.pt) with authentic material. No starting material was recovered. Three other compounds were obtained in low yield, and investigated for vinylic protons in their nmr spectra, but no vinylic protons were observed, indicating that, whatever else, elimination to the ene-lactone (69) had not taken place.

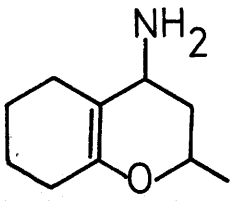
As the use of benzoate as leaving group in the elimination reaction had proved to be unsuccessful, another leaving group was chosen. The diazonium group, $-N_2^+$, should be a better leaving group than benzoate, as elimination of this group results in the formation of a neutral species, nitrogen gas, whereas elimination of benzoate results in the formation of a charged species, $PhCO_2^-$.

A feasible route to the diazonium salt was thought to be from the tetrahydrochromanone (48) and is shown in scheme 9. It was envisaged that the formation of the diazonium salt followed by hydration and ring-opening could be carried out in the same reaction vessel to obviate storage or handling of the diazonium salt, which would be unstable.

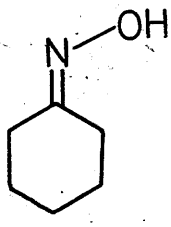
The tetrahydrochromanone(48) was treated with hydroxylamine hydrochloride and sodium hydroxide[31] to give a high yield of white crystals, m.pt. 169- 169.5°C (after recrystallisation from ethanol), which analysed for $C_{10}H_{15}NO_2$, and had a molecular weight of 181 (mass spectroscopy). The ir spectrum showed a hydroxylic



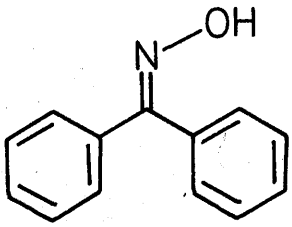
(70)



(71)



(72)

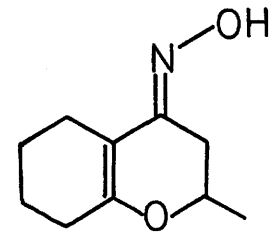


(73)

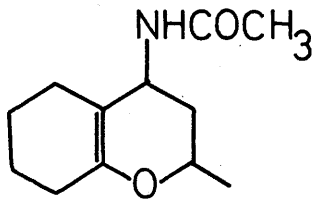
peak at 3600cm^{-1} and a double bond absorption of the enol ether at 1640cm^{-1}, and the nmr spectrum showed peaks at 6.0τ(1H,m, proton on carbon bearing oxygen), 6.85τ (2H,m, protons α to C=N) and 8.6τ(d,J=6Hz,3H, methyl). The 9 proton "envelope" between 7.5 and 8.7τ contained one hydroxyl, and was shown to be present by comparison of the integral of the normal spectrum with the integral of the spectrum where a little deuterium oxide had been added. These data agreed with the structure of the 2-methyl-5,6,7,8-tetrahydrochroman-4-one oxime (70).

The reduction of the oxime (70) to the amine (71) was then undertaken. Smith[32] and co-workers were able to repeat the work of several other workers, and reduce other oximes, using lithium aluminium hydride, to the corresponding amines. Varying ratios of lithium aluminium hydride were tried, and it was found that optimum yield was obtained at 2.2 mole lithium aluminium hydride to 1 mole oxime. It was also observed that, in the case of cyclohexanone oxime (72), the solvent affected the yield, being 61% of amine in ether, and 71% of amine in tetrahydrofuran.

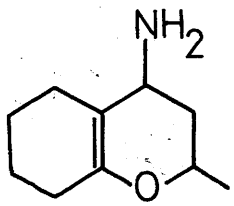
Accordingly, the oxime (70) was treated with a 2.2 molar excess of lithium aluminium hydride in refluxing ether. However, only starting material was recovered after work-up. Hochstein[33] had found that benzophenone oxime (73) was not reduced by lithium aluminium hydride in ether, and that the yield of amine using the higher boiling tetrahydrofuran was 60%. However, change to a higher boiling solvent had no effect



(70)



(74)



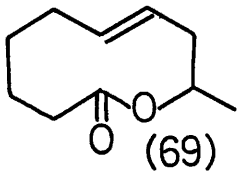
(71)

on the oxime (70), and starting material was again recovered.

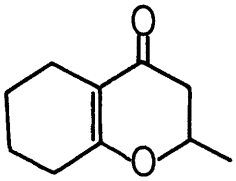
A more vigorous reducing agent was obviously required to reduce the oxime, and the reducing agent chosen was hydrogen, using Adams catalyst (platinum oxide) to effect hydrogenation.

The hydrogenation of the oxime (70) using Adams catalyst was carried out in acetic anhydride as solvent in order to trap the primary amine, which might be unstable, as the stable acetamide (74). After work-up and preparative tlc to remove some highly polar material, a yellow oily crystalline material, m.pt.26-8°C, was obtained. Its ir spectrum showed ν_{max} 1700cm^{-1}, and accurate mass measurement gave the molecular weight as 209.2814. The N-acetyl-4-amino-2-methyl-5,6,7,8-tetrahydrochroman (74), $C_{12}H_{19}NO_2$ requires m/e 209.2807.

The acetamide (74) was hydrolysed using 70% sulphuric acid by the method of Vogel[34]. After 90 minutes reflux, the acetamide was completely hydrolysed (shown by tlc). The amine (71) was not isolated, but diazotised immediately with sodium nitrite solution[35]. The diazonium salt was not isolated either, as the diazonium salt solution (in sulphuric acid) was heated on a steam-bath until evolution of gas had ceased, hopefully indicating that elimination of nitrogen was over. Work-up gave a mixture of many products (by analytical tlc). Preparative tlc separated four compounds which were investigated by infra-red and mass spectroscopy. No one of the compounds isolated had the



(69)

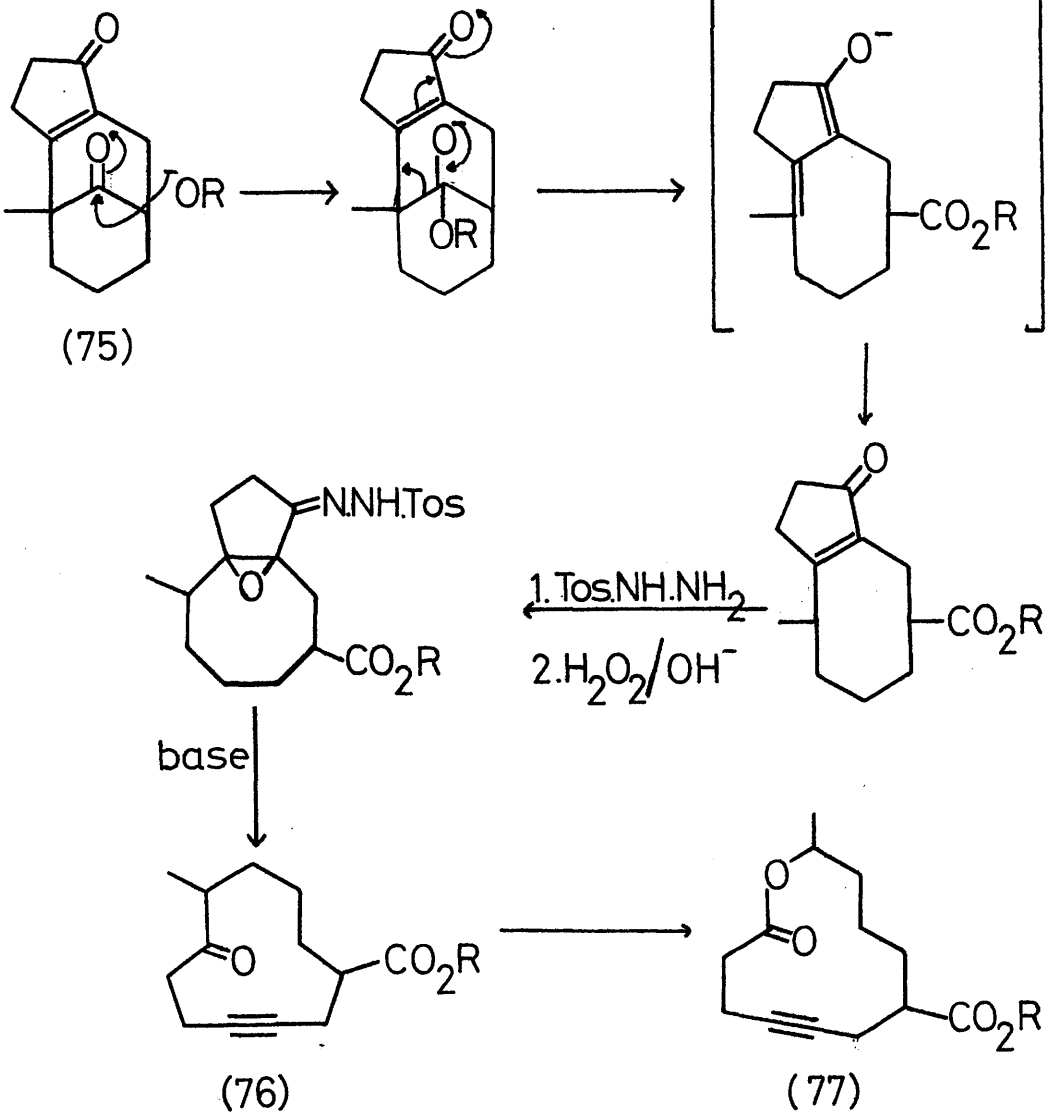


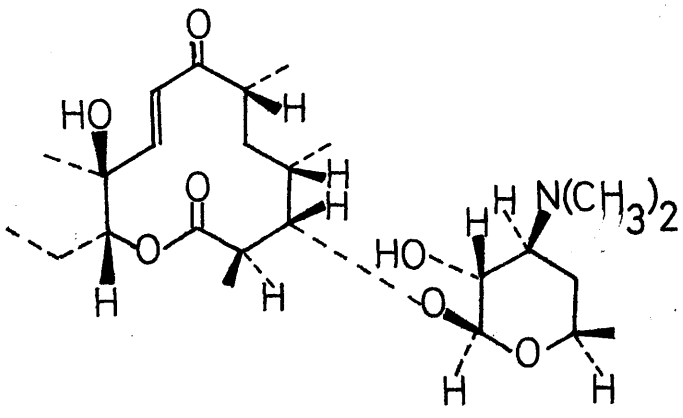
(48)

required ir or mass spectrum for the ring-opened product, the ene-lactone (69), and the products were not examined further.

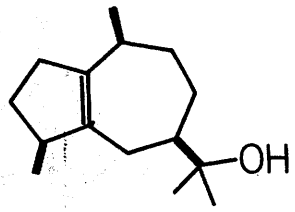
At this point, it was felt that all feasible openings of the tetrahydrochromanone system (48) had been explored, and this route to medium rings was abandoned.

Scheme 10.

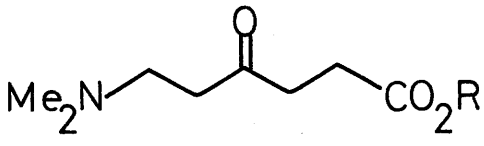




(78)

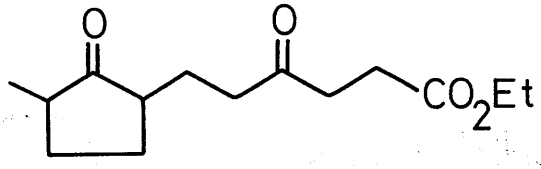


(79)

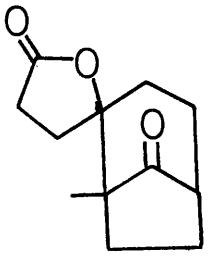


(80) R=H

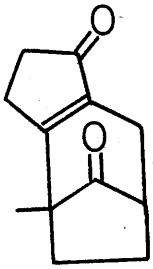
(81) R=Et



(82)



(83)



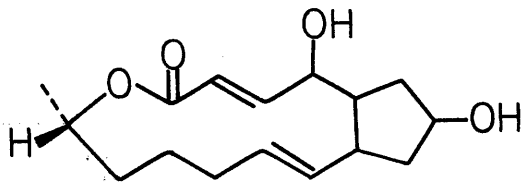
(84)

As the route to lactones from fused bicyclic ethers had proved to be fruitless, a route via carbocyclic precursors was sought.

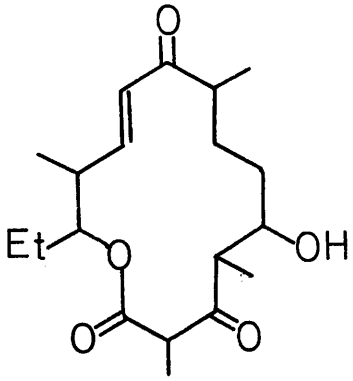
The compound chosen as a precursor for the ring-opening reactions was the tricyclic compound (75) which on opening would give a C_{11} macrocycle [Scheme 10]. The initial reaction is base promoted ring-opening of a vinylogous β-diketone which can only open in the manner shown, to give a cyclooctene, which is subjected to the Eschenmoser epoxide-tosylhydrazone opening to give an alkyl 8-methyl-7-oxo-undec-3-yne carboxylic ester (76). Baeyer-Villiger oxidation of (76) with peracid would yield a dodecanolide (77). Dodecanolides are common among the macrolide antibiotics, an example of a biologically active dodecanolide being methymycin (78)[36], and this route should, with modification of starting materials, provide a suitable route to these macrolides.

The route to the tricyclic precursor was an extension of part of the route of Buchanan and Young[37] to (±)-guaiol (79). In this synthesis, the Mannich base of laevulinic acid[38](80) was esterified and the ester (81) reacted with 2-methyl-cyclopentanone under Thermal-Michael conditions[39] to give the dione (82), which was cyclised with hydrochloric acid, and the aldol trapped as the spiro-lactone (83). This spiro-lactone was converted to an α,β-enone (84) using polyphosphoric acid.

It was envisaged that the synthesis of the desired α,β-enone (75) could be carried out by using 2-methyl-cyclohexanone in place of 2-methyl-cyclopentanone in



(85)



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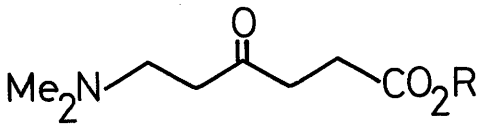
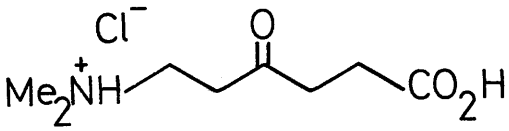
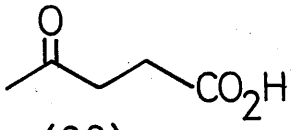


(80) R=H

(81) R=Et



(87)



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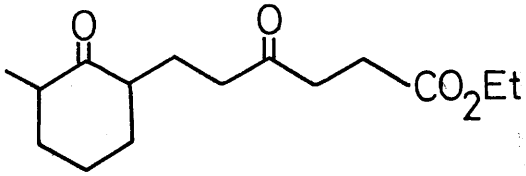


(89)

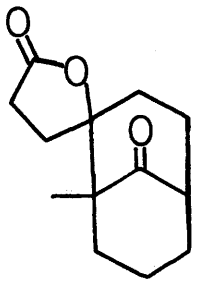
the guaiol synthesis.

This route should be suitable for modification to provide larger macrolides of the Brefeldin A[40] (85) or Narbonolide[41] (86) type, by use of larger cyclic ketones as starting materials.

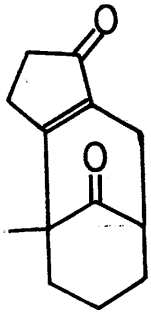
The Mannich base of laevulinic acid (80) was prepared[38] as the hydrochloride (87) by reacting laevulinic acid (88) with dimethylamine hydrochloride and paraformaldehyde. The Mannich base hydrochloride was not purified, and was esterified with ethanol and sulphuric acid[38]. Basic work-up yielded the free Mannich base of the ester (81) as a yellow oil, which was used without purification in a Thermal-Michael[39] reaction with 2-methyl-cyclohexanone. Work-up and removal of excess 2-methyl-cyclohexanone gave a mixture of products which, when distilled, gave three fractions in the range 94-200°C/0.08mm., and there were many products in each fraction on investigation by glc. Preparative column chromatography (grade III alumina; ethyl acetate:light petrol) gave 4-oxo-6-(2'-oxo-3'-methyl-cyclohexyl)-hexanoate (89), pure on analytical tlc, but was shown to contain three minor impurities on glc analysis.

The ester (89) showed ν_{max} 1740(ester), 1720(ketones), 1180 and 1160(C-O stretch)cm^{-1}, in the ir spectrum, and signals at 5.95τ(q, 2H, ester), 8.8τ(t, 3H, ester) and 9.05τ(d, J=6Hz, 3H, methyl) in the nmr spectrum. The mass spectrum showed a parent ion at m/e 268, in agreement with the structure of the ester (89).

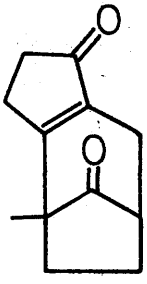
Cyclisation of the ester (89) by the method of



(90)



(75)



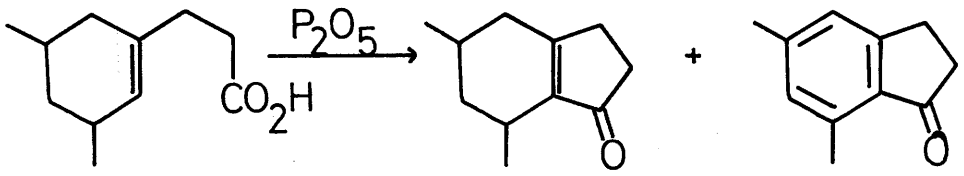
(84)

Buchanan and Young[37] with 10N hydrochloric acid gave the crude spiro-lactone (90) as a yellow oil which had a molecular ion at m/e 222 in the mass spectrum. The ir spectrum showed ν_{CO} 1780 and 1715cm^{-1}, as expected for a γ-lactone and bridgehead bicyclo-[3,3,1]-ketone[42] respectively. NMR showed the four γ-lactone protons as a multiplet between 7.2 and 7.8τ, and the methyl group as a singlet at 8.9τ.

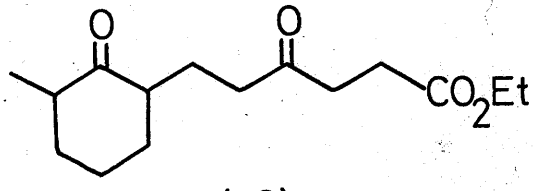
The spiro-lactone (90) was then to be converted to the α,β-enone (75) and the method of choice was that of Kulkarni and Dev[43], viz. stirring with hot polyphosphoric acid. Since attempting this reaction, an alternative method of promoting this cyclisation which has all the advantages of polyphosphoric acid and none of the disadvantages has been published. This is the use of phosphorus pentoxide in methanesulphonic acid[44] which can be stirred without difficulty at room temperature, unlike polyphosphoric acid which is viscous and difficult to stir even above 60°C. The work-up of the reaction is also easier.

The spiro-lactone (90) was stirred with technical polyphosphoric acid at 100°C for 5 minutes, and separated to give a mixture of products. Preparative tlc gave two compounds, neither of which had the correct ir spectrum for the enone (75), [by comparison with published values[37] for (84); see experimental].

This failure was thought to have been the result of using technical polyphosphoric acid, and the reaction was repeated using freshly prepared polyphosphoric acid,



(91) (92) (93)



(89)

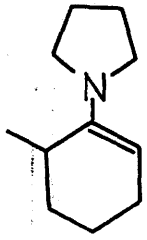
obtained from orthophosphoric acid and phosphorus pentoxide (see experimental). The crude product was subjected to column chromatography as it was a mixture of several compounds, (grade III alumina; ethyl acetate, light petrol as eluants). The fraction obtained at 75% ethyl acetate: light petrol crystallised out, and was further purified by sublimation to give a white crystalline product, m.pt. 84-85.5°C. Analysis gave the molecular formula as $C_{19}H_{22}O_3$, which has a molecular weight of 298, while the mass spectrum shows a parent ion at m/e 294. The ir spectrum showed ν_{max}1740,1695,1600,1590(m) and 1100cm^{-1}, while the nmr spectrum had signals at 2.75τ (1H,s) and 8.0τ(3H,s) plus methylene and methine proton signals.

The product may have arisen from a double Thermal-Michael reaction to give, after treatment with hydrochloric acid and polyphosphoric acid, an aromatic product. It is difficult to envisage how this could occur, although such aromatisation of alicyclic molecules is known, for example treatment of (91) with phosphorus pentoxide gives (92) and (93)[45].

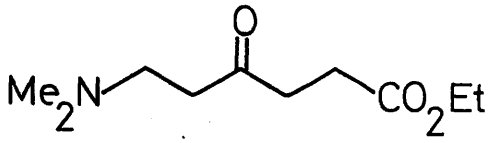
This product was not identified.

It appeared that the Thermal-Michael reaction gave rise to a large number of products which were only separable with much difficulty. A cleaner route to the Thermal-Michael product (89) was therefore sought.

Von Strandtman[46] and co-workers found that it was possible to alkylate the enamine of a ketone using a Mannich base, probably by initial loss of dialkylamine,



(94)



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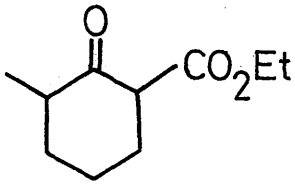
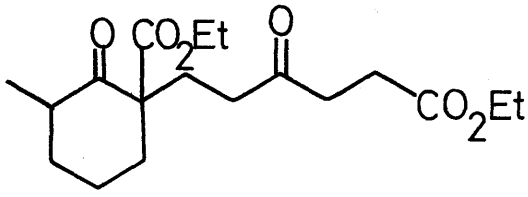


(95)



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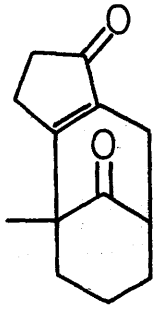


(75)

followed by Michael addition of the resulting unsaturated species to the enamine.

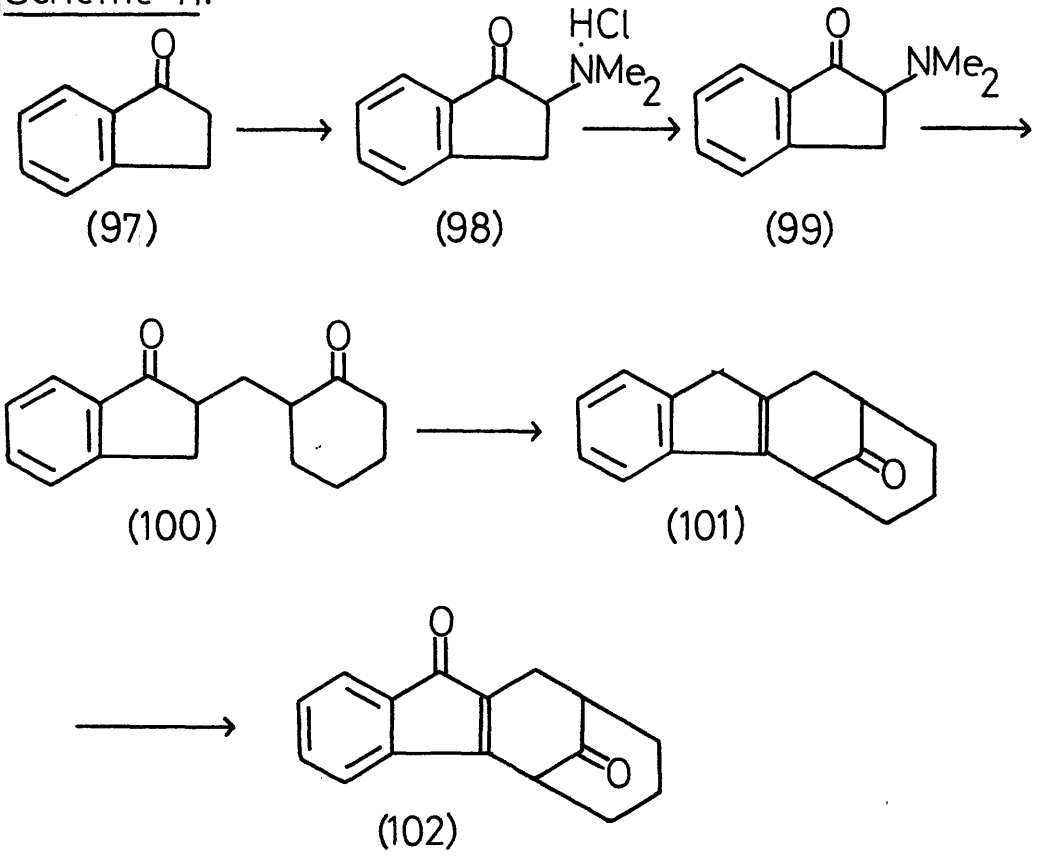
Therefore, the pyrrolidine enamine of 2-methyl-cyclohexanone (94), was reacted with ethyl 6-dimethylamino-4-oxo-hexanoate (81) under reflux in dioxan. Work-up gave 1.6g. crude product which, when distilled, gave ethanol as the only product.

This, then, was no improvement on the Thermal-Michael reaction.

The Thermal-Michael reaction was repeated using 2-carbethoxy-6-methyl-cyclohexanone (95), which was known to be pure (glc). Standard work-up and removal of excess ketone (95), followed by vacuum distillation of the residue gave a low (5%) yield of the Thermal-Michael product. This was purified by preparative tlc (25% ethyl acetate: light petrol) to give a clear oil which showed ν_{CO} 1740cm^{-1}(ester) and 1725cm^{-1}(broad, cyclohexanone and straight chain ketone) in the ir spectrum, and signals at 5.85τ(q, 2H, ester); 5.95τ(q, 2H, ester); 8.76τ(t, 3H, ester); 8.79τ,(t, 3H, ester) and 9.0τ,(d,J=6Hz, 3H) in the nmr spectrum. The parent ion in the mass spectrum was at m/e 340, in accordance with the structure expected for the Thermal-Michael product (96).

At this stage, it was felt that this route to the tricyclic compound (75) was not progressing satisfactorily. The Mannich base (81) could not be purified because of its thermal instability and high polarity, and this was thought to be a contributing factor to the multiplicity of products

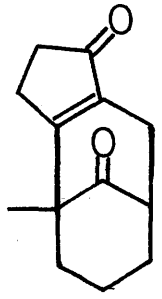
Scheme 11.



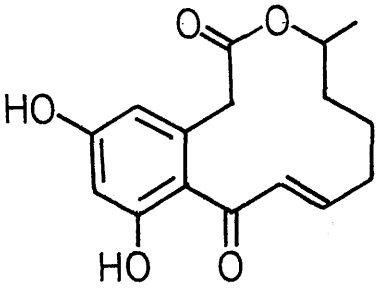
(97) (98) (99)

(100) (101)

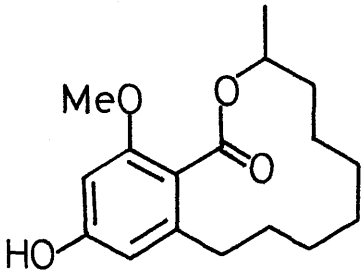
(102)



(75)



(103)



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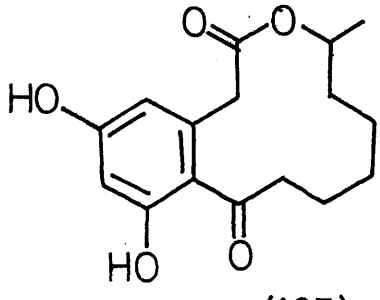


(105)

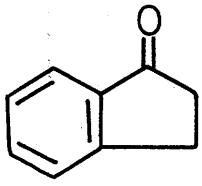
obtained in the Thermal-Michael reaction. A new route to the tricyclic compound, (75), or an analogue, was therefore necessary.

The analogue of the tricyclic compound (75) decided upon was the benzotricyclic compound (102) and the route to this compound is shown in Scheme 11. The reaction sequence was to be carried out using cyclohexanone rather than 2-methyl-cyclohexanone as a simpler product would beobtained from the Thermal-Michael reaction. The route could be repeated using the latter, once the synthetic problems of this route had been solved.

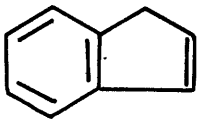
The benzotricyclic compound (102) was chosen because it embodies all the features necessary for ring-opening while possessing an aromatic ring. This aromatic ring should introduce reactivity into the molecule, and allow selective oxidation at the required site in the last step in scheme 11, while also increasing the molecular weight and giving, in all probability, solids, which are easier to handle.

Also, aromatic macrolides are known in nature, and, by suitable modification of starting materials, for example using cycloalkanones larger than C_5, and the synthetic route shown, it should be possible to synthesise macrolides such as α,β-dehydro-curvularin[47](103), lasiodiplodin[48](104) and curvularin[49](105).

Prior to the synthesis using cyclohexanone, a model study was carried out using cyclopentanone, as the Thermal-Michael reaction, and cyclisation, had already



(97)



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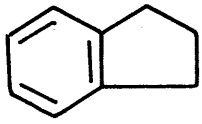
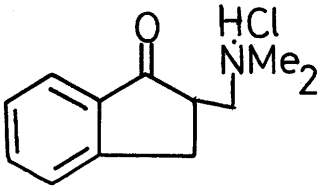
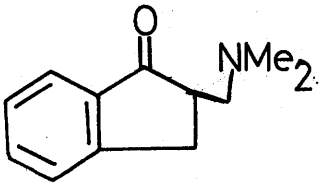


(107)



(98)



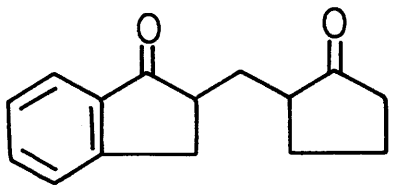
(99)

been investigated[50].

Indanone (97) was synthesised from indene (106) by the method of Pacaud and Allen[51]. As this method involved large scale steam distillation, an alternative synthesis was sought. Mazur[52] had investigated the photo-oxidation of olefins and benzene derivatives using ultra-violet light in the presence of mercuric bromide, and had found that indane (107) could be oxidised by this method to indanone (97) in high yield. Repeating this reaction, however, gave a much lower yield of indanone, and this synthesis of indanone was discarded. (see experimental for details).

Indanone Mannich base hydrochloride, [2-(N,N-dimethylaminomethyl)-indan-1-one hydrochloride (98)] was prepared by refluxing indanone with paraformaldehyde and dimethylamine hydrochloride in ethanol and hydrochloric acid[50].Addition of dry acetone to the cooled ethanol solution gave the crude indanone Mannich base hydrochloride (98) as an amorphous white solid which was recrystallised from absolute ethanol/dry acetone (1:4) to give a white crystalline solid, m.pt. 146-8°C. The ir spectrum showed absorptions at 2700-2600cm^{-1}($-NH_2^+$) and 1710cm^{-1}(conjugated C=O), while the nmr spectrum showed signals at 2.2-2.8τ(m, 4H, aromatic) and 7.0τ (s, 6H, N-methyls).

The indanone Mannich base (99) was liberated from its hydrochloride by treatment with 5% ammonium hydroxide solution on an equimolar basis. Salting out of the aqueous layer was found to improve the yield of free



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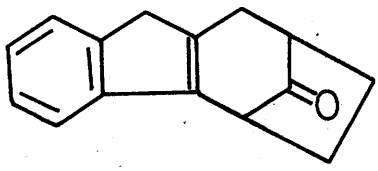


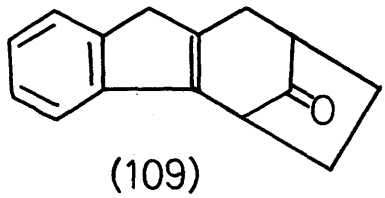
(109)

Mannich base. The infra-red spectrum of the crude Mannich base showed ν_{CO}1710cm^{-1}, and $\nu_{C=C}$ 1610, 1590cm^{-1} (conjugated aromatic ring).

The crude Mannich base was then subjected to Thermal-Michael conditions[39,50] with cyclopentanone to give the expected product, 2-(2'-oxo-cyclopentyl)-indan-1-one (108), as a yellow oil, b.pt. 154-6°C/0.05mm., whose ir spectrum showed ν_{CO}1735cm^{-1}(5-membered cyclic ketone), 1710cm^{-1} (conjugated ketone) and $\nu_{C=C}$1610, 1590 and 760cm^{-1}(aromatic). The nmr spectrum showed a ratio of 1:3 for aromatic to aliphatic protons, as expected for the diketone (108), but no fine structure was visible in the methylene "envelope". The mass spectrum showed a parent ion at m/e 228.

Two methods of cyclising the diketone (108) were then tried. The first method used was refluxing in benzene with a catalytic quantity of toluene p-sulphonic acid and a water-separator. Removal of acid and solvent gave a white crystalline solid, m.pt. 136-7°C [Lit.137°C[50]] and which showed a parent ion in the mass spectrum at m/e 210. The ir spectrum showed ν_{CO}1745cm^{-1}, while the nmr spectrum showed a complete absence of olefinic protons, and was different from the nmr of the starting material. The structure suggested for this product, the benzotricyclic ketone (109) is consistent with this information.

The second method, treatment with concentrated hydrochloric acid in glacial acetic acid, gave two products on work-up. The first, a neutral product, was



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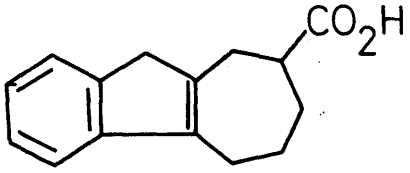

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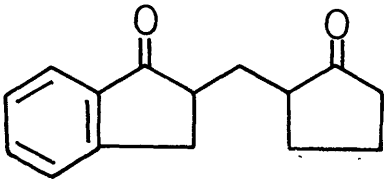

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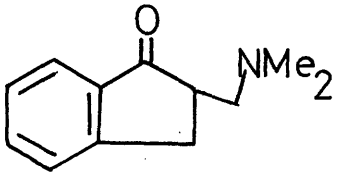

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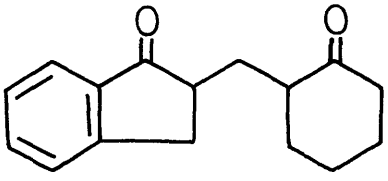
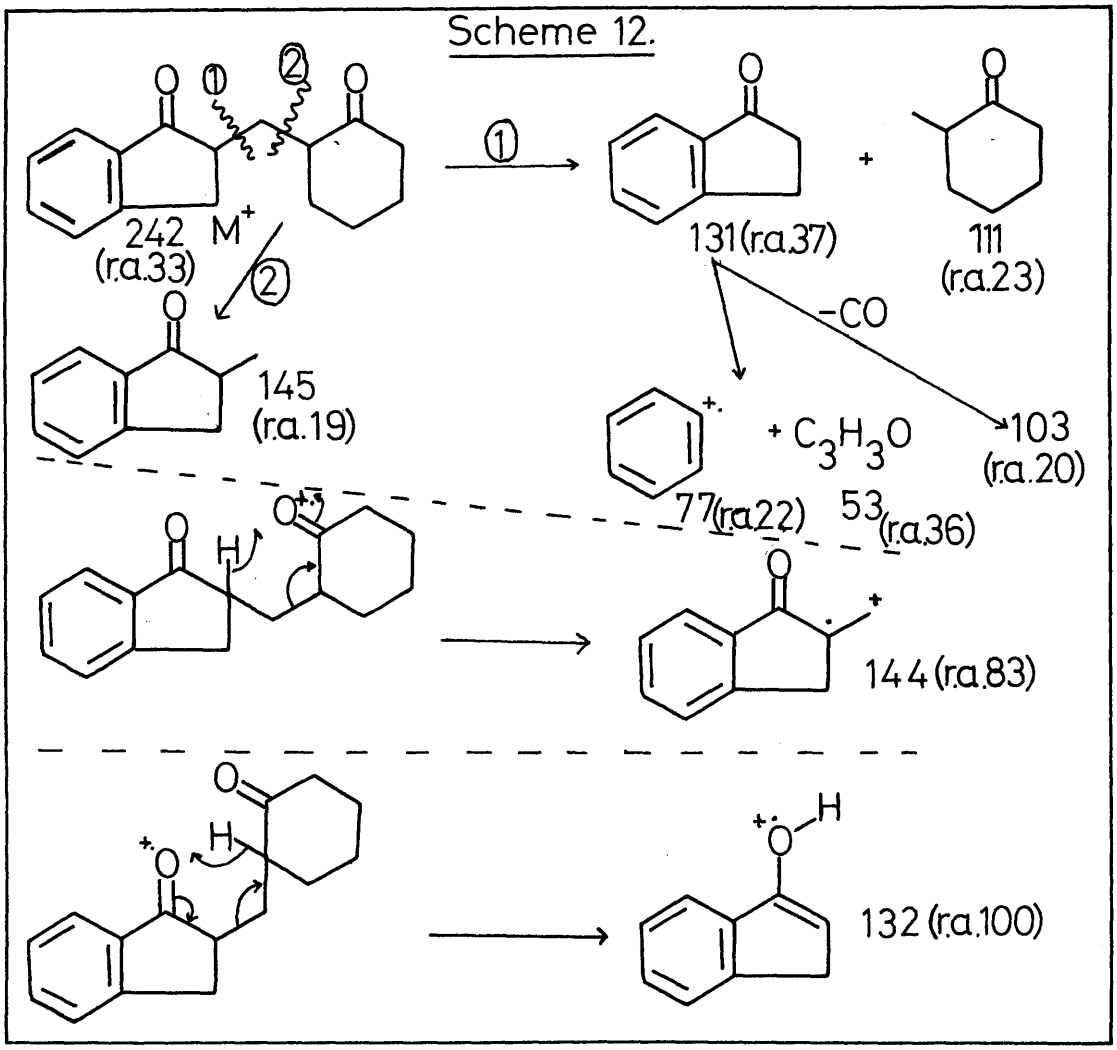


(100)

Scheme 12.

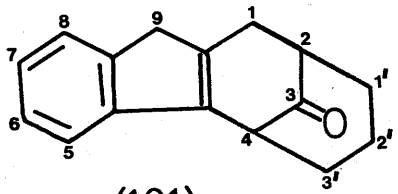


identified as the ketone (109) obtained from the first cyclisation, while the second was an acidic solid, m.pt. 157-9°C, and showed ν_{CO} 1705cm^{-1} in the ir spectrum. The nmr spectrum showed signals at 2.7τ(m, 4H, aromatic) and 6.6τ(s, 2H, indene methylene protons), while the mass spectrum showed a parent ion at m/e 228, indicating that the product was isomeric with the starting material. This product was the ring-opened cycloheptene acid (110)[50].

Having achieved the ring-closure of the diketone (108) without encountering any problems, the synthesis of the cyclohexanone analogue was commenced.

Indanone Mannich base (99) and cyclohexanone were reacted together under Thermal-Michael conditions[39,50] to give a 60% yield of pure 2-(2'-oxo-cyclohexyl)-indan-1-one (100) as a clear yellow oil which analysed for $C_{16}H_{18}O_2$ and which had a parent ion in the mass spectrum at m/e 242. Significant ions were observed at m/e 145, 144, 132(base), 131, 111 103, 77 and 53, and a fragmentation pattern is shown (scheme 12). The ir spectrum showed $\nu_{CO}^{CCl_4}$ 1718cm^{-1} and $\nu_{C=C}$ 1610, 1590cm^{-1} (conjugated aromatic ring). Nmr data was inconclusive, as the only information available from the spectrum was the ratio of aromatic to aliphatic protons, 2:7. The uv spectrum showed a conjugated carbonyl absorption at 244nm (ϵ=5,640). The theoretical value for λ_{max} for this ketone is 249nm[53]. The preceeding information is in agreement with the proposed structure of the ketone (100).

Cyclisation of the diketone (100) was then attempted



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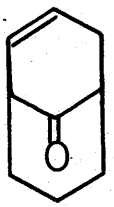


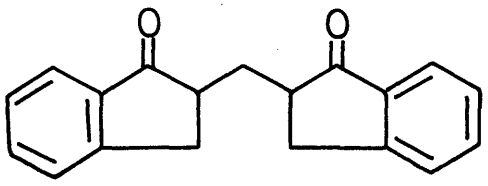
(111)

by refluxing with conc. hydrochloric acid in glacial acetic acid. However, this method, or treatment with toluene p-sulphonic acid in benzene, gave only a low yield of the desired cyclised product (101), identified by comparison with authentic ketone (101) obtained by another route.

Replacement of benzene by toluene as solvent in the toluene p-sulphonic acid catalysed cyclisation resulted in an increased yield (to about 20%) of 2,4-propano-1,2,3,4-tetrahydrofluoren-3-one (101), which was obtained as pale yellow crystals, m.pt. 101-2°C, GLC : essentially pure with a very small trace of non-polar impurity. The ketone (101) analysed for $C_{16}H_{16}O$ and had a molecular ion at m/e 224 in the mass spectrum. Ions corresponding to loss of CO (m/e 196) followed by loss of C_2H_5 (m/e 167) could be identified in the mass spectrum.

The infra-red spectrum showed $\nu_{CO}^{CCl_4}$ 1730, 1721cm^{-1}, c.f. ν_{CO} 1733 and 1725cm^{-1} in the bicyclononenone (111)[54], while the nmr showed signals at 2.6-3.0τ,(4H, m, aromatic); 6.6τ,(s,1H,proton on C-4) and 6.7τ,(s,2H,indene methylene protons). The uv spectrum showed a maximum at 259nm (ϵ=7,900).

After distillation of the ketone (101), crystals were observed in the tarry residue. Extraction with, and recrystallisation from, light petrol gave feathery white crystals, m.pt. 133-5°C, which analysed for $C_{19}H_{16}O_2$ and had a parent ion in the mass spectrum at m/e 276. The ir spectrum showed $\nu_{CO}^{CCl_4}$ 1710cm^{-1} (conjugated ketone),



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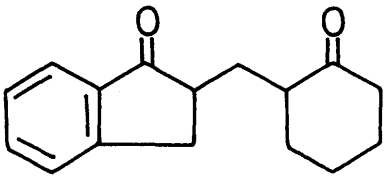

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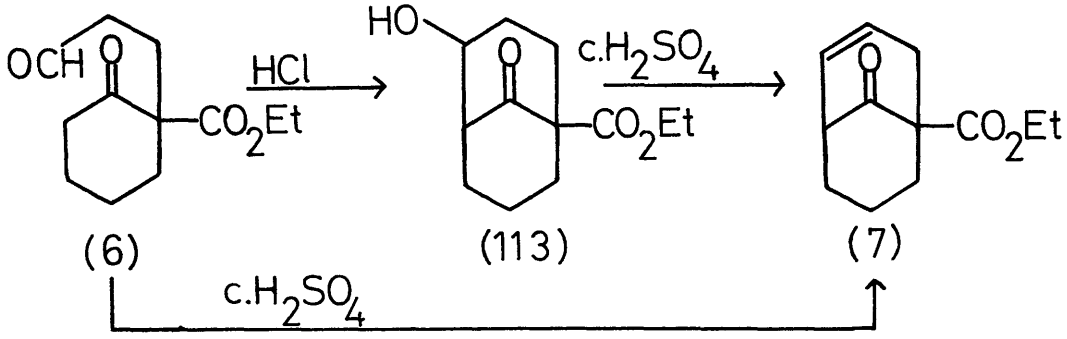
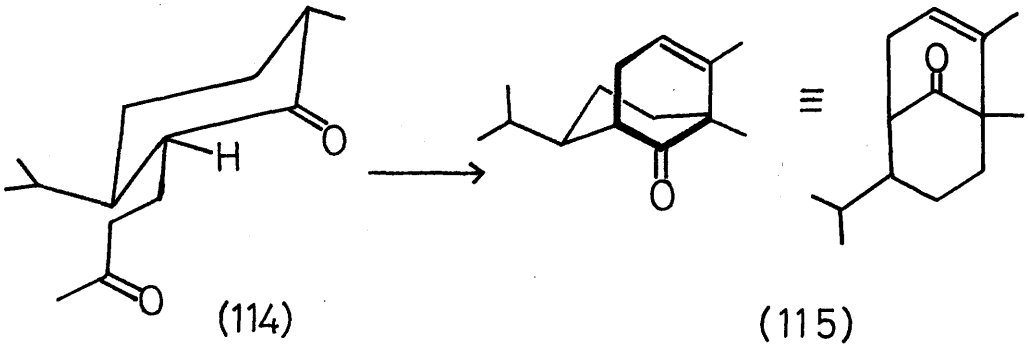
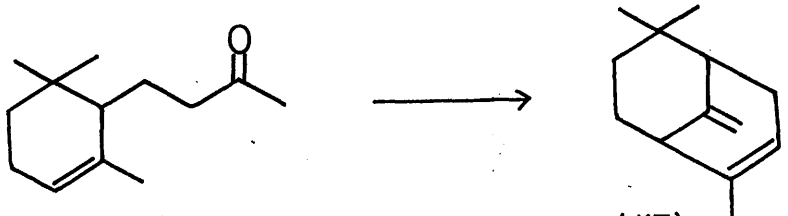


(6) (113) (7)



(114) (115)

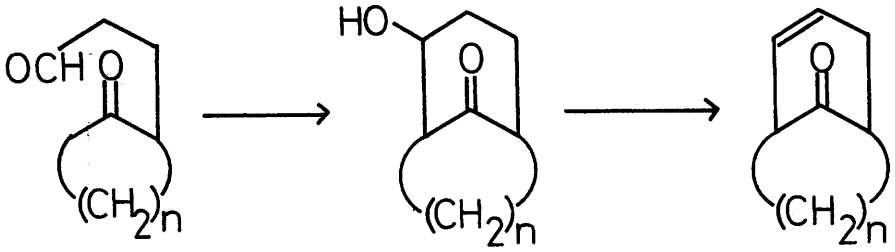


(116) (117)

while the nmr was fairly simple, showing four signals at 2.5τ(4H, m, aromatic), 6.55τ(1H,m),7.1τ(2H, finely split singlet) and 7.95τ(1H, t, J=8Hz). The uv spectrum showed three absorption maxima at 210nm (ϵ=23,200), 242nm(76,000) and 290nm(3,560). The structure assigned to this compound was the bis-indanonyl-methane (112), which was thought to have arisen from the Mannich base by trans-amino-methylation in the Thermal-Michael reaction.

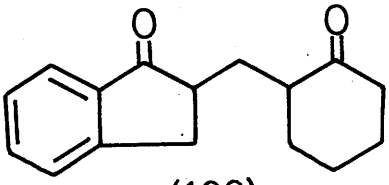
Although the cyclisation of the diketone (100) with toluene p-sulphonic acid in toluene was successful, it gave a low yield, and a higher yield cyclisation was sought.

Investigation of the literature revealed several potentially useful high yield methods of cyclisation using acid catalysts. Cope[2,55] used hydrochloric acid to effect cyclisation of the keto-aldehyde (6) to the hydroxybicyclononanone (113) which could be dehydrated with conc. sulphuric acid to the bicyclononenone (7), and indeed cyclisation of (6) to (7) directly could be effected using conc. sulphuric acid. Corey[56] used boron trifluoride to cyclise a 1,5-diketone (114) to an unsaturated bicyclic ketone (115) in 40% yield, while Buchi[57] used85% phosphoric acid to cyclise a keto-olefin (116) to a bicyclic diolefin (117), in low yield, as other products of cyclisation were obtained. Nevertheless, an improvement on the toluene p-sulphonic acid catalysed cyclisation was possible and all four methods were tried. All reagents, hydrochloric acid, conc. sulphuric acid,



(118) (119) (120)

n = 2,3,4



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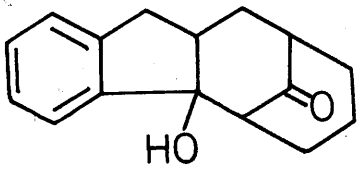
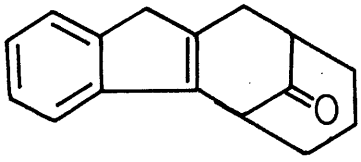


(121)



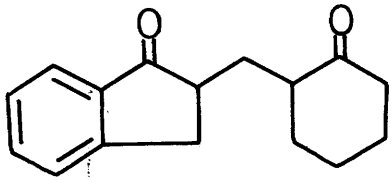
(101)

boron trifluoride etherate and 85% phosphoric acid were consistent, as they gave only starting material on work-up.

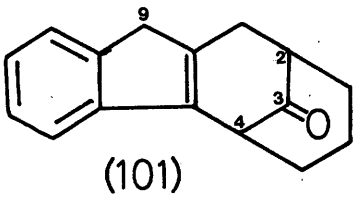
Another method of cyclisation which was considered was that of Allan and Wells[58,59] who had investigated the cyclisation of keto-aldehydes (118) to the bicyclic keto-alcohols (119) using initially 2N hydrochloric acid, which gave yields of 60-65%, and latterly Amberlite resins, which gave yields of 90-95%. The alcohols (119) were then dehydrated with conc. sulphuric acid to (120) in about 70% yield for $n>2$.

This cyclisation seemed promising, and the reaction was set up for the reflux of the diketone (100) with Amberlite-IR-120(H) resin in benzene, with a Dean and Stark water separator. It was hoped that by carrying out this reaction in this manner, the dehydration of the alcohol (121), the product of cyclisation, would occur to give the dehydrated product (101) in one pot. However, glc analysis of the material obtained after work-up showed that only about 5% of the starting material had been converted to the desired product (101), the remainder of the material being unreacted starting material.

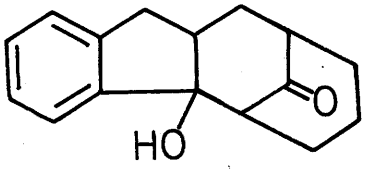
It was therefore decided to follow the proceedure of Allan and Wells[58,59] and perform the cyclisation with Amberlite IR-120(H) resin in water, to give the cyclised alcohol (121), then dehydrate with sulphuric acid to the desired product (101). When the reaction had been carried out, the product obtained, after



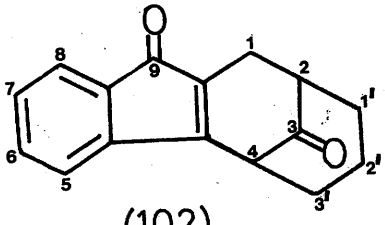
(100)



(101)



(121)



(102)

separation from unreacted diketone (100), was the (2,4-propano)-1,2,3,4-tetrahydrofluoren-3-one (101) in 75% yield overall [94% based on diketone (100) used]. The cyclisation product (121) apparently dehydrates in the presence of water, and this was attributed to the cyclisation occurring on the surface of the resin, where water is not necessarily present. Nevertheless, water appears to be necessary for this reaction, as cyclisation does not proceed in water-free benzene.

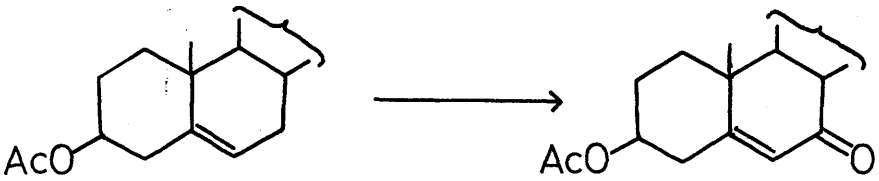
This reaction was an unexpected bonus, since the starting material and product were readily separable by distillation or chromatography.

The product from the Amberlite resin cyclisation was identical (ir, ms, nmr, m.pt.) with that obtained from the toluene p-sulphonic acid/toluene cyclisation.

The next step in the synthetic sequence to the ring-opening precursor (102) was the oxidation of (101). A brief literature search revealed that there were many methods of introducing an oxygen substituent, or a readily replaceable substituent, for example, a halide, onto an allylic or benzylic carbon atom. The 9-carbon of the ketone (101) is both benzylic and allylic, whereas the 1-carbon is allylic only, and it was thought that oxidation would occur preferentially at carbon-9.

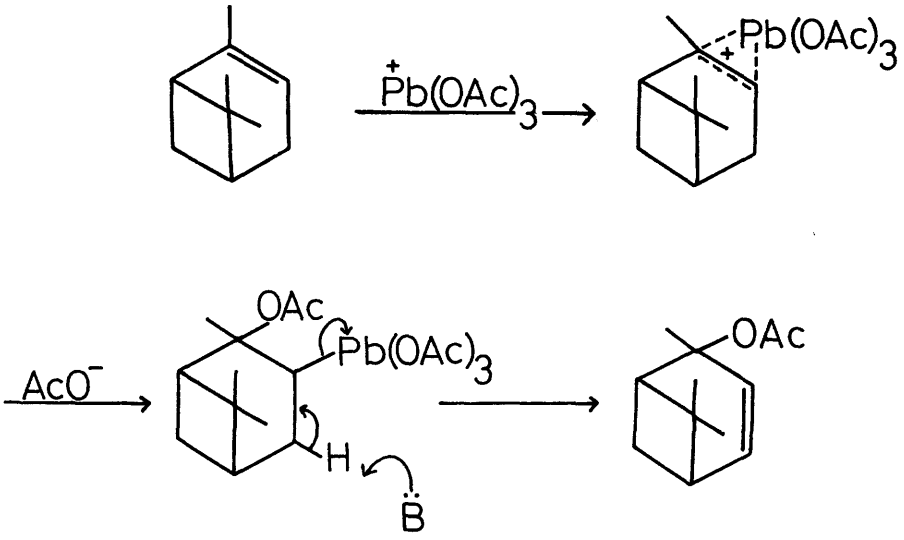
The most promising reagents appeared to be anhydrous sodium chromate, lead tetraacetate, mercuric acetate, N-bromo-succinimide, chromium trioxide in pyridine (Collins reagent), sodium dichromate and selenium dioxide.

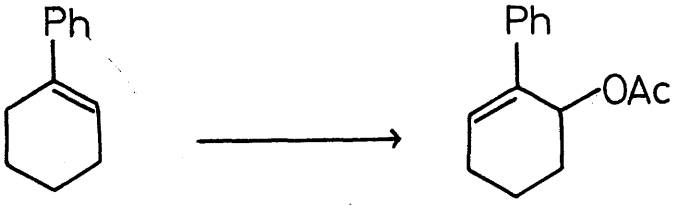
Sodium chromate (anhydrous) in acetic acid has been



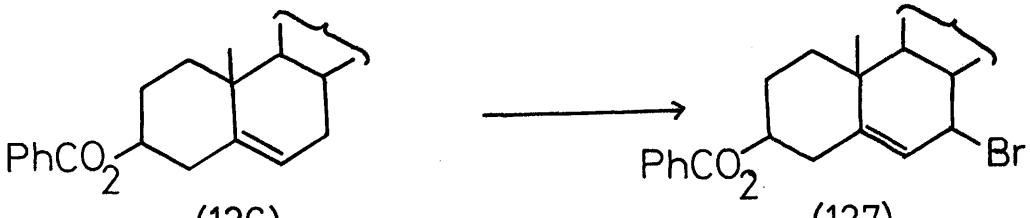
(122) (123)

Scheme 13.

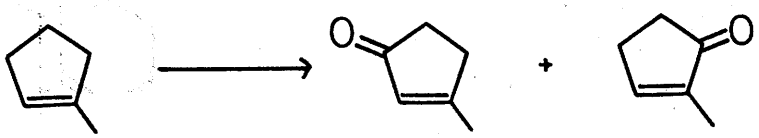




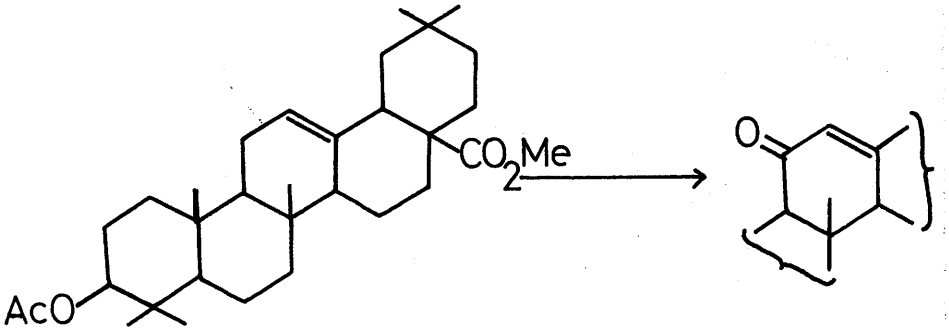
(124) (125)



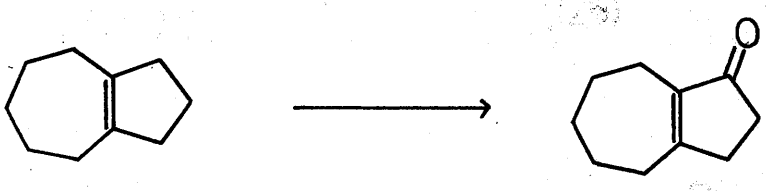
(126) (127)



(128) (129) (130)



(131) (132)



(133) (134)

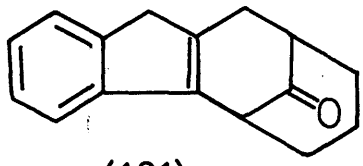
used by Marshall[60] in allylic oxidations of steroids [(122)→(123)], where a 75% yield was obtained. Wiberg and Nielsen[61] studied the allylic oxidation of several olefins using a variety of oxidising agents, and in particular, lead tetraacetate and mercuric acetate. They proposed that oxidation by both involved a symmetrical intermediate which was probably formed by decomposition of an allyl mercuric or an allyl lead intermediate [Scheme 13]. Triebs[62] used mercuric acetate in acetic acid on 1-phenyl-cyclohexene (124) to give a 71% yield of the allylic acetate (125) by the mechanism of scheme 13.

N-bromosuccinimide was used by Bernstein[63] in an investigation into reaction conditions of allylic bromination, and obtained the allylic bromide (127) from the olefin (126) in greater than 30% yield, although the allylic bromide was not isolated, but used directly.

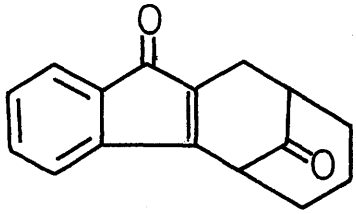
Dauben[64] has investigated the oxidation of many substituted cyclohexenes and one cyclopentene by chromium trioxide-pyridine. The yields from these oxidations varied from 21% to 95% for the cyclohexenes, while the cyclopentene (128) was oxidised to a mixture of cyclopentenones (129) and (130) in 54% yield overall.

Sodium dichromate dihydrate was used by Corey[65] in the allylic oxidation of (131) to (132), which was obtained in 80% yield. The remaining oxidising agent considered, selenium dioxide, has been the subject of several papers, reviews and articles[61,66,67].

An example of its use is the oxidation of (133) to (134) in 23% yield, which indicates that oxidation

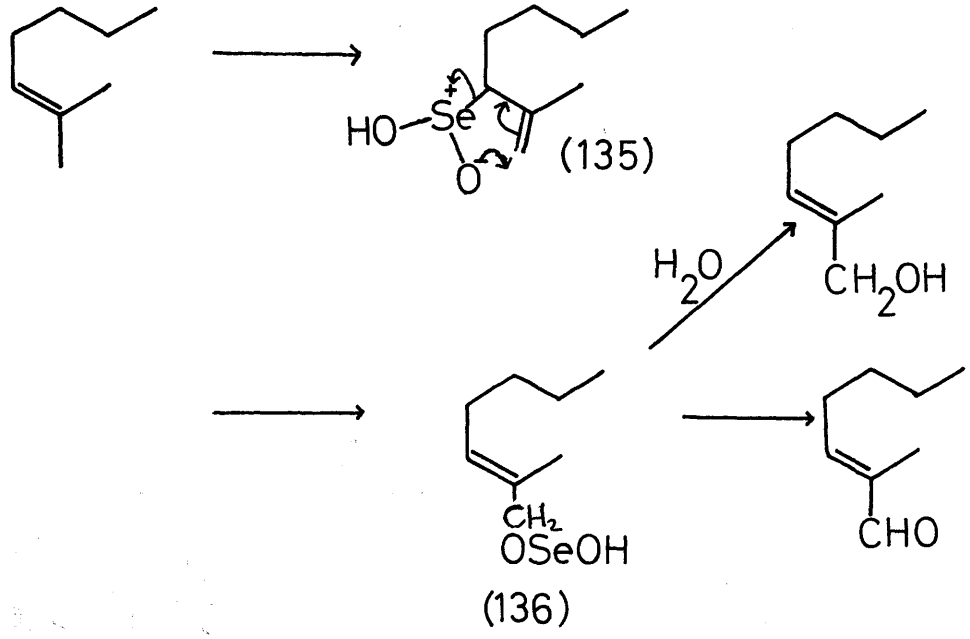


(101)

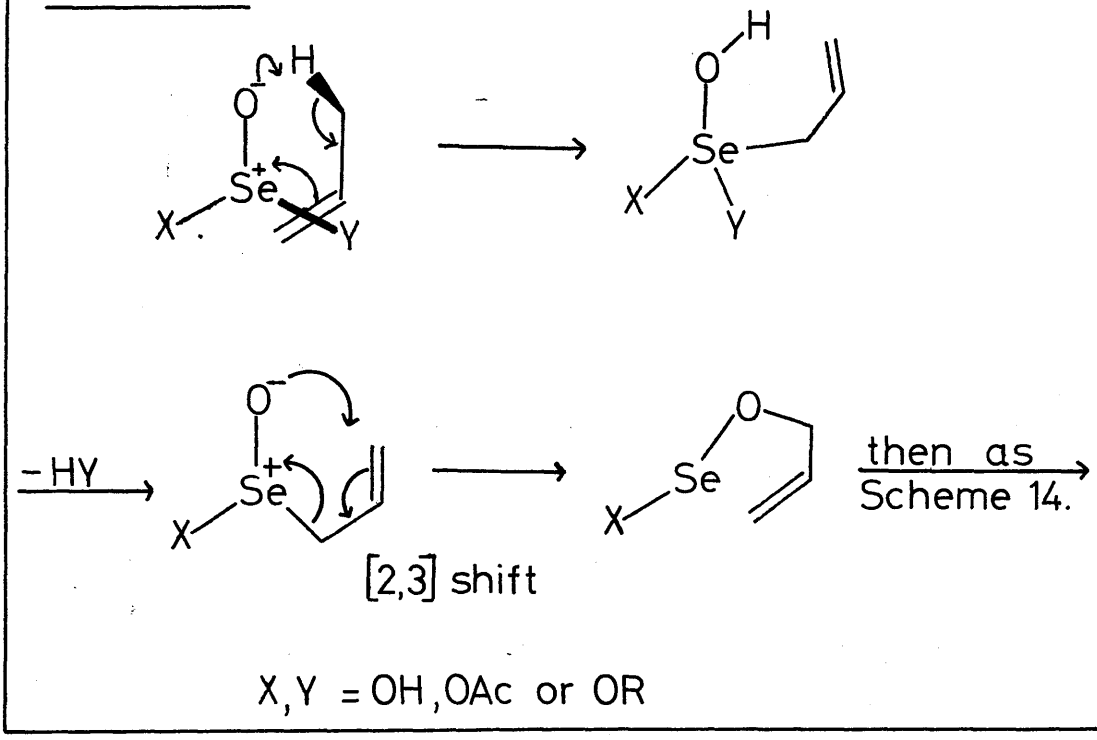


(102)

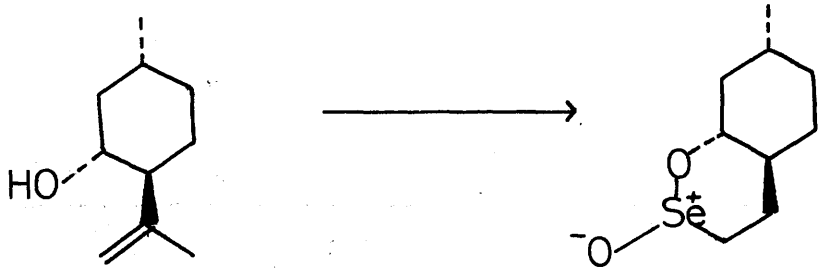
Scheme 14.



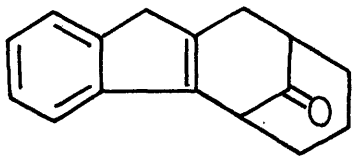
Scheme 15.



X, Y = OH, OAc or OR



(137) (138)



(101)

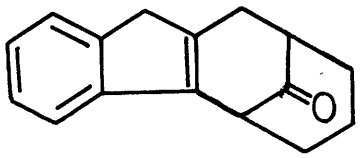
occurs preferentially in the cyclopentene rather than the larger cycloheptene, as required in the oxidation of (101) to (102).

Trachtenberg[68] has reviewed and discussed the various proposed mechanisms for selenium dioxide oxidations, but does not accept the mechanism of Wiberg and Nielsen[61] as it requires an allylselenic acid (135) and cites evidence against this intermediate. Sharpless and Lauer[69] have, however, proposed (Scheme 14) that the selenium dioxide allylic oxidation proceeds by initial formation of an allyl-selenic acid (135) as proposed by Wiberg and Nielsen[61], followed by a [2,3] sigmatropic rearrangement to (136), a rearrangement which is well known for allylic sulphinates and especially allylic sulphoxides.

Sharpless and Arigoni[70] have continued this investigation, have generalised selenium oxidations (Scheme 15), and have proved the intermediacy of allylselenic acids by use of l-isopulegol (137) to trap the allylselenic acid as the selenolactone (138), obtained in 39% yield.

Oxidation of the ketone (101) with sodium chromate or mercuric acetate gave only unreacted starting material, while lead tetraacetate gave 95% starting material with a trace of an oxidation product which was not investigated.

Treatment of (101) with N-bromosuccinimide gave several products which, on investigation by ir, nmr, uv and mass spectroscopy, were not the required product.



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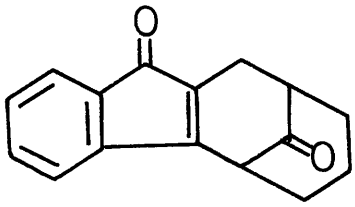
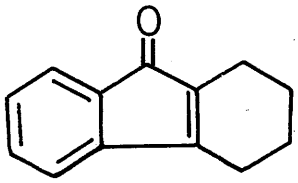
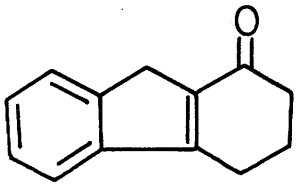


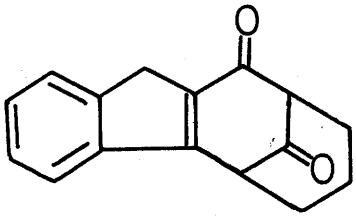
(102)



(139)



(140)

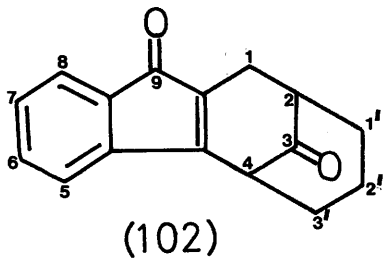


(141)

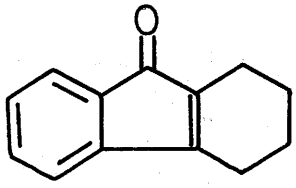
Collins oxidation of the ketone (101) was successful although the yield was low (<20%), and purification by preparative tlc gave a yellow oil, ν_{max} 1730, 1710 and 1670cm^{-1} in the ir spectrum, and with λ_{max}^{EtOH} at 242 and 301nm in the uv spectrum. This was not the required oxidation product (102) as indicated by comparison with the uv spectrum of (139), the desired indenone system, which has λ_{max}^{EtOH} 234nm(ϵ=39,700), 245nm(46,900) and 317nm(960)[72].

Sodium dichromate dihydrate oxidation gave a 25% yield of a yellow crystalline solid, m.pt. 154-8°C, which analysed for $C_{16}H_{14}O_2$ and which had a molecular weight of 238 (mass spectroscopy). Its ir spectrum showed ν_{max} 1730cm^{-1} (bicyclic 1-bridge ketone) and 1660cm^{-1} conjugated ketone), but the nmr spectrum was of little help, showing only aromatic and aliphatic protons as multiplets. The uv spectrum had absorption maxima at 233nm (ϵ=4,460), 240nm (4.310) and 308nm(9,520). This was not the required oxidation product (102), but an isomer of it. On the basis of the uv spectrum, and comparison with the ketone system produced by allylic rather than benzylic oxidation viz. 3,4-dihydro-fluoren-1(2H)-one (140) system, the sodium dichromate oxidation product was assigned the structure (141), 2,4-propano-1,2,3,4-tetrahydrofluoren-1,3-dione. The compound (140) has λ_{max}^{EtOH} 232nm(ϵ=6,300), 238nm (8,500) and 302nm(20,500)[73].

The oxidation of (101) with selenium dioxide was first carried out in ethanol under reflux to give a



(102)

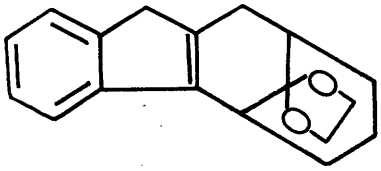


(139)

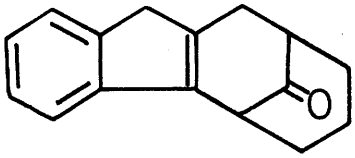
product which was different from starting material, but did not have the required uv spectrum [see Discussion page 59, line 8] and was different physically from authentic oxidation product obtained by a later route.

However, oxidation with selenium dioxide in acetic acid gave, after purification by column chromatography, a 25% yield of 2,4-propano-1,2,3,4-tetrahydrofluoren-3,9-dione (102) as a yellow crystalline solid, m.pt. 136-7°C (recrystallised from ethyl acetate).
The compound analysed for $C_{16}H_{14}O_2$ and had a molecular ion at m/e 238 in the mass spectrum. The ir spectrum of the dione showed ν_{max} 1738, 1732 and 1715cm^{-1}, which were attributed to the bicyclic bridge ketone, and the conjugated ketone in a 5-membered ring.
The nmr spectrum showed a four proton aromatic multiplet at 2.55τ; a one proton broad singlet at 6.2τ, which was assigned to the C-4 proton, which is α to both the double bond and the bridge ketone; a second broad singlet at 6.3τ(2H), attributed to the two protons on C-1; and a one proton multiplet at 6.75τ, assigned to the C-2 bridgehead proton. There was also a four proton multiplet at 7.7-8.0τ, due to the methylene protons of C-1' and C-3', and a two proton multiplet at 8.2-8.5τ, due to the remaining C-2' methylene protons. The uv spectrum showed the expected absorption maxima, λ_{max}^{EtOH} 239nm (ϵ=33,600) and 246nm (43,300), cf. (139)[72] λ_{max}^{EtOH} 234nm (ϵ=39,700), 245nm (46,900) and 317nm (960).

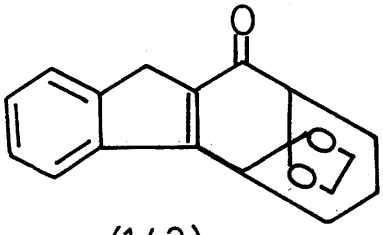
In an attempt to improve the yield, and perhaps change the site of oxidation in the case of sodium



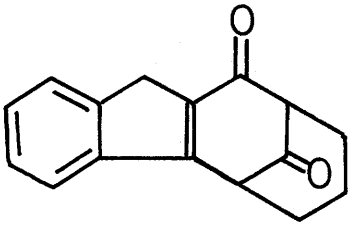
(142)



(101)



(143)



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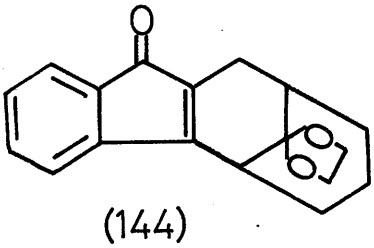


(144)

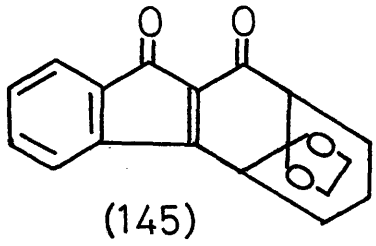
dichromate, the oxidation was repeated on the acetal (142) of the ketone (101).

Refluxing the ketone (101) with ethylene glycol and toluene p-sulphonic acid in benzene gave a 97% yield of 2,4-propano-1,2,3,4-tetrahydrofluoren-3-one acetal (142). Its ir spectrum showed the absence of ketone absorption, while the nmr spectrum showed a four proton multiplet due to the acetal at 6.0τ. The mass spectrum showed a parent ion at m/e 268 (base peak) and gave the correct mass for $C_{18}H_{20}O_2$.

The acetal (142) was then oxidised with sodium dichromate in acetic acid. Work-up and attempted purification by preparative tlc gave a 65% yield (estimated by glc) of an oxidation product which was tentatively identified as (143), (see experimental for physical data), and which corresponded to the 3-acetal of the product (141) obtained from the sodium dichromate oxidation of the ketone (101).

Oxidation of the acetal (142) with selenium dioxide gave, after work-up and preparative tlc, two products which could not be obtained pure (shown by glc). The first product was a viscous yellow oil, (approximately 30% of material) which on the basis of ir, nmr, uv and mass spectral evidence was the benzylic oxidation product, (144).

The second product was more polar than the first oxidation product (144), and was an orange oil. Nmr gave only the ratio of aromatic to aliphatic protons, as 1:3, while the ir spectrum showed $\nu_{CO}^{CCl_4}$ 1740 and 1715cm^{-1}. Uv showed the presence of an indenone system



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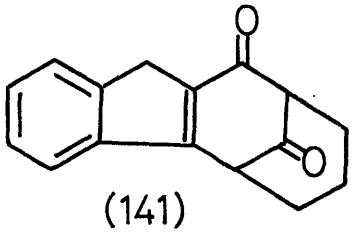
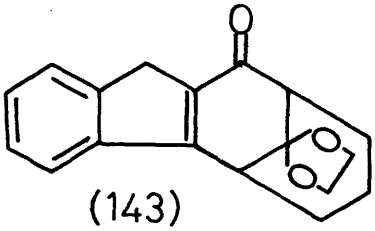


(141)



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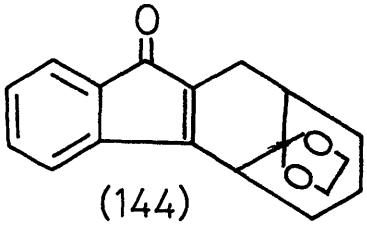
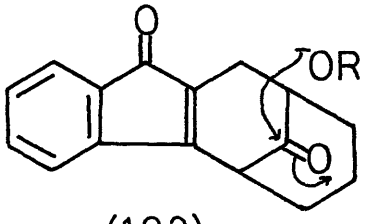


(144)

Scheme 16.



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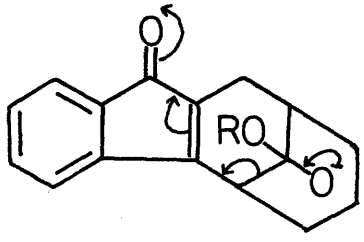
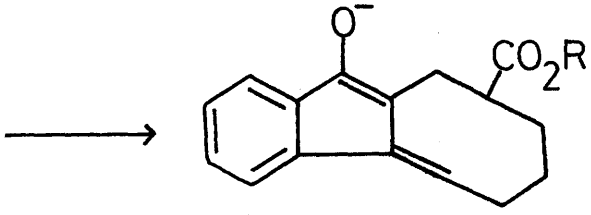
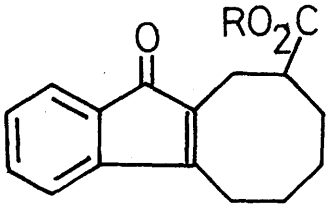
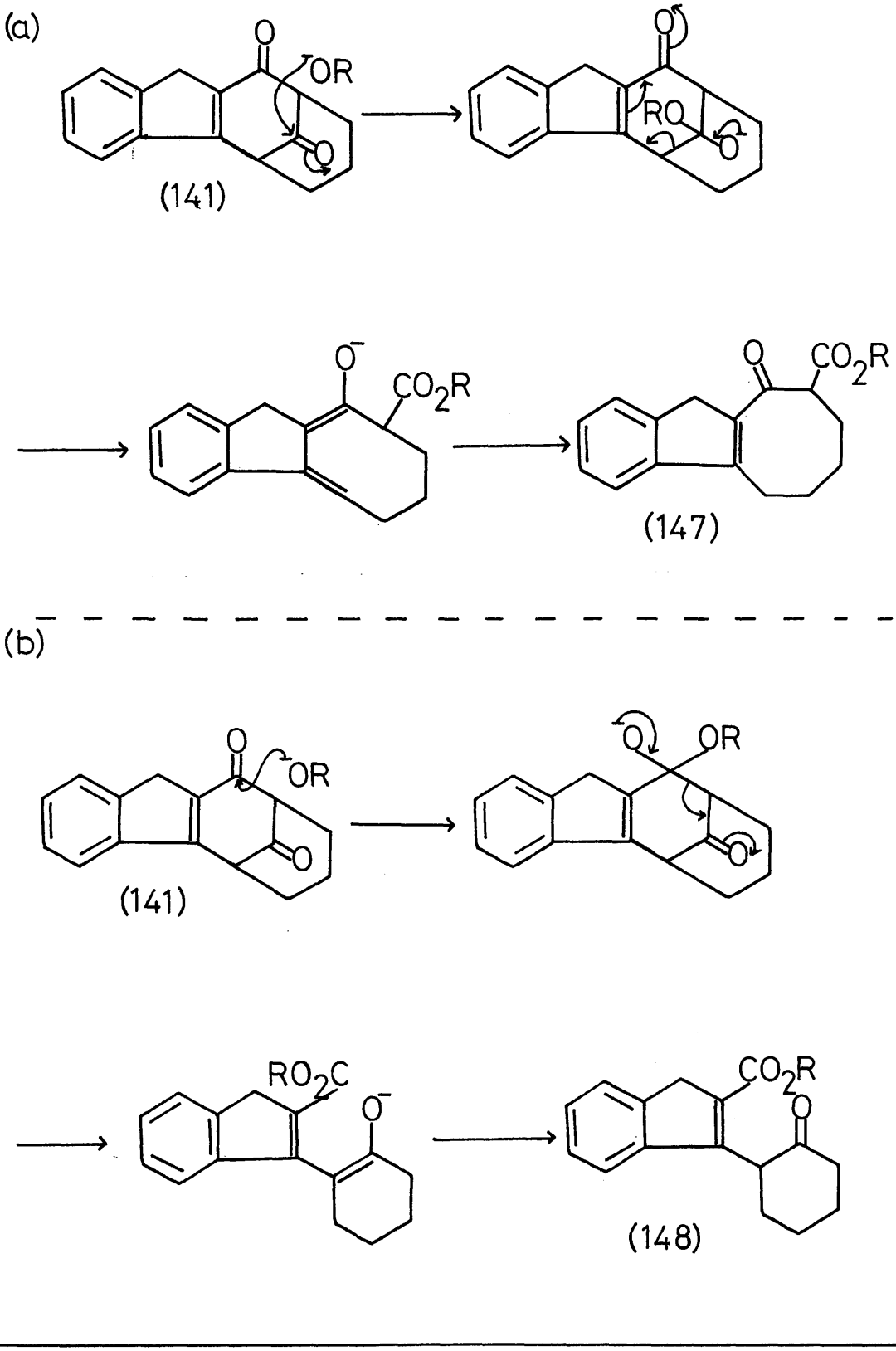


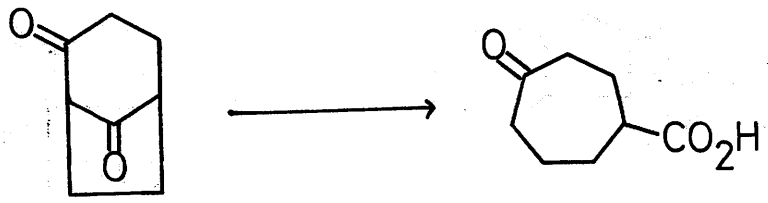




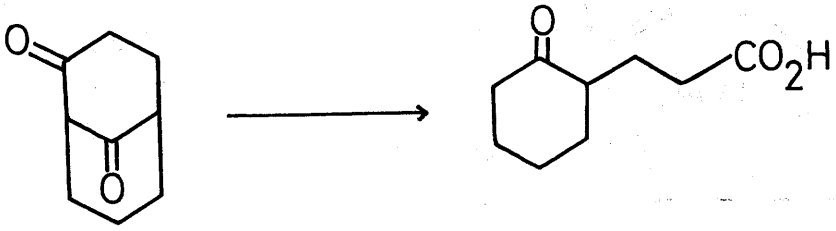
(146)

Scheme 17

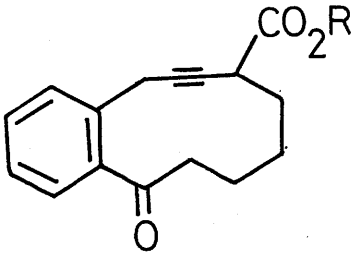




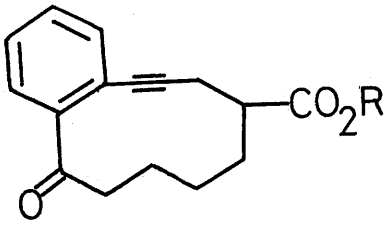
(149) (150)



(151) (152)



(153)



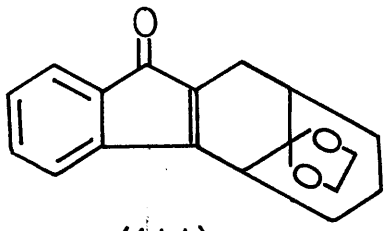
(154)

with λ_{max}^{EtOH} 237.5nm (ϵ=20,000) and 243.5nm (21,100) [cf. (139), page 60, line 26], and the mass spectrum showed an ion at m/e 296 (M^+). This product was tentatively assigned the structure (145), a double oxidation product.

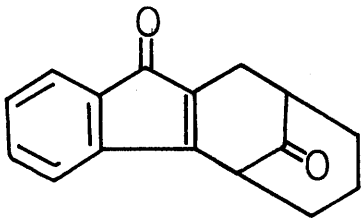
The product from sodium dichromate oxidation is therefore that produced by allylic oxidation, (141, 143), while the selenium dioxide oxidation gives the benzylic oxidation product (102, 144).

The selenium dioxide oxidation product (102), the 3,9-dione, can be opened in only one way, attack of base on the bridge 3-ketone (Scheme 16) which gives a cyclooctene (146), while attack of base on the sodium dichromate oxidation product (141) can occur at either the 1- or 3-ketone. Attack at the 3-ketone occurs as in scheme 16 to give a cyclooctenone (147) (Scheme 17a), while attack at the 1-ketone results in the substituted indene (148) being formed (Scheme 17b). This second route is in contrast to the bicyclo-[3,2,1]-octan-diones (149), which under acid conditions open readily to the cycloheptan-4-one carboxylic acids (150) because of ring strain[74], while the unstrained dione (151) opens readily to (152).

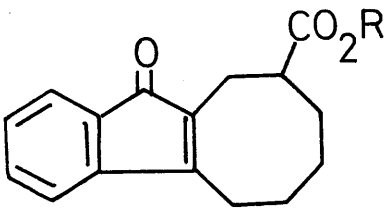
If the 1,3-dione (141) opened to give the cyclooctene (147), it should be possible to carry out the Eschenmoser tosyl hydrazone-epoxide ring opening to give the acetylenic ketone (153), which is isomeric with the acetylenic ketone (154) obtained by successive ring openings on the 3,9-dione (102).



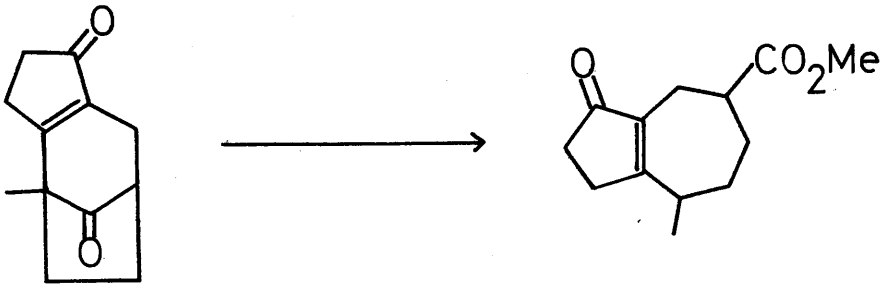
(144)



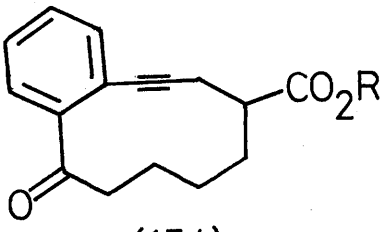
(102)



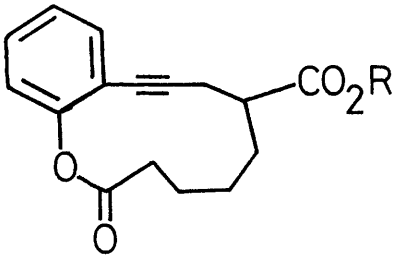
(146)



(155) (156)



(154)



(157)

An attempt was made to epoxidise the keto-acetal (144), prior to an Eschenmoser type ring opening, using basic hydrogen peroxide, but only starting material was recovered, and routes involving the acetal were abandoned.

As discussed previously, treatment of the dione (102), which is a vinylogous β-diketone, should give the substituted cyclooctene (146), cf. the opening of (155) to (156)[37].

Treatment of the dione (102) with sodium methoxide in methanol[37], sodium hydroxide in ethanol, or sodium ethoxide in ethanol gave only one product in low yield. This product was yellow, crystalline and had a parent ion at m/e 256 in the mass spectrum. Infra-red spectroscopy showed $\nu_{max}^{CCl_4}$ 3500(broad), 1725, 1715 and 1610cm^{-1}, indicative of a carboxylic acid containing a carbonyl conjugated to an aromatic ring. This was tentatively identified as the ring-opened acid (146, R=H). Repetition of this reaction using sodium methoxide and a careful work-up should yield the methyl ester (146, R=Me) in reasonable yield.

Research into this synthetic route stopped at this point, but the route shows potential for opening to the required macrocyclic ketone (154), and thence the macrolide (157).

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EXPERIMENTAL.

GENERAL.

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Routine infra-red spectra of liquid films and nujol mulls were recorded on a Unicam SP1000 instrument, while solution spectra were recorded on a Perkin-Elmer PE225 and a Unicam SP100 instruments. Ultraviolet absorption spectra, measured on a Unicam SP800A spectrometer, refer to solutions in ethanol, unless otherwise stated. Nuclear magnetic resonance spectra were recorded on Varian T-60 and HA-100 spectrometers, using approximately 0.3 molar solutions with tetramethylsilane as internal standard. Routine mass spectra were recorded on an A.E.I.-G.E.C. MS12 spectrometer, while high resolution mass spectra were recorded using an A.E.I.-G.E.C. MS902 mass spectrometer.

Thin layer chromatography (tlc) was accomplished using silica, Kieselgel HF_{254} (Merck) for both analytical and preparative purposes.

Gas-liquid chromatography (glc) was carried out on a Pye-Argon chromatograph equipped with a β-ionisation detector, and on a Perkin-Elmer F.11 chromatograph equipped with a flame ionisation detector.

Drying of organic phases, except where specifically mentioned, was with anhydrous magnesium sulphate. Light petrol refers to that fraction of petroleum ether which boils in the range 60°-80°C.

Preparation of Diethylsuccinylsuccinate (4).

This method is a modification of the literature preparation in Organic Reactions, 1,283.

54g. sodium wire was covered with a minimum amount of toluene, to which was added 406g. diethyl succinate and 30ml. dry ethanol. The mixture was refluxed for 24 hours, then excess sodium was destroyed with ethanol, and acidified with dil. sulphuric acid. The mixture was left overnight, filtered and the crystalline diethylsuccinylsuccinate washed with water. The toluene layer was separated from the filtrate, and the toluene evaporated to leave further crystalline material, which was recrystallised with the first crop from a 95% ethanol solution after treatment with animal charcoal. This gave 210g. (72%) of diethylsuccinylsuccinate (4), as pale yellow needles, m.pt. 126-7°C [Lit. 126-7°C].

IR(CCl_4): $\nu_{max.}$ 1668, 1624 cm^{-1} (no ν_{OH})

NMR : -2.25τ(s); 5.72τ(q); 6.82τ(s); 8.67τ(t).

UV : $\lambda_{max.}$ 243nm.

Condensation of diethylsuccinylsuccinate with acrolein[4].

4.15g.(74m.moles) acrolein was added carefully to an ice-cold, stirred solution of 9.5g.(37m.moles) diethylsuccinylsuccinate and 1ml. dry triethylamine in 400ml. dry tetrahydrofuran. The solution was stirred for 24 hours under an atmosphere of nitrogen. The solution was neutralised with glacial acetic acid, and the tetrahydrofuran removed under reduced pressure. The residue was taken up in ether and washed with brine,

water, saturated sodium bicarbonate solution, and water. The ether solution was dried and evaporated to yield a pale yellow oil.

Three products were separated from this oil by crystallisation from ether.

I. Recrystallisation from ethanol gave yellow needles, m.pt.134-135.5°C. This was the diethyl ester of 2,5-dihydroxy-terephthalic acid (14), [Lit. m.pt. 134-135.5°C]. Found C,57.14; H,5.37; $C_{12}H_{14}O_6$ requires C,56.69; H,6.07%. Molecular weight 254 (by mass spectrometry).

IR : ν_{max}^{nujol} 3480cm^{-1}(bonded hydroxyl) and 1690cm^{-1} (conjugated ester carbonyl).

NMR : 0.12τ(2H,s, hydroxyls); 2.66τ(2H, s, aromatics); 5.59τ(4H,q, ester methylenes); 8.56τ(6H,t, ester methyls).

II. was a white crystalline material with a melting point of 184°C. Found C,64.86; H,5.96; $C_{18}H_{20}O_6$ requires C,65.05; H,6.07%.

IR(CCl_4) : ν_{max} 1751, 1720(shoulder), 1705 and 1623cm^{-1}.

UV : λ_{max}^{EtOH} 264nm(ϵ=8,170); 235nm(4,960); 205nm(5,040).

Mass spectrum showed a parent ion at m/e 332 [base m/e 166].

NMR : 3.4τ(fine triplet,J=2.5Hz, 2H); 5.91τ(q,4H); 8.87τ(t,6H); 7.0-8.0τ (unresolved multiplet, 8H).

It was concluded that compound II was 3a,7a-dicarbethoxy-4,8-diketo-2,3,3a,4,6,7,7a,8-octahydroindacene (19).

III. was a colourless, crystalline solid, m.pt.140°C. Found C,58.37; H,6.14; $C_{18}H_{24}O_8$ requires C,58.69; H,6.57%.

Mass spectroscopy showed a parent ion at m/e 368, which exhibited a ready loss of two molecules of water to give an ion at m/e 332.

UV : $\lambda_{max.}^{EtOH}$ 210nm.

IR : $\nu_{max.}^{CCl_4}$ 3630, 3580, 1741,1722 cm^{-1}.

NMR : 4.4τ(1H, broad singlet); 4.6-5.0τ(1H, multiplet - two sets of double doublets); 5.78τ(4H,q); 6.15τ($\frac{1}{2}$H,d, J=7Hz, disappears in D_2O, alcohol); 6.65τ($\frac{1}{2}$H,d, J=10Hz, disappears in D_2O, alcohol); 8.7τ(6H,t), and an eleven proton methylene envelope between 6.9τ and 8.0τ.

NMR (D_2O exchange): signals at 6.15τand 6.65τ disappear. Signals at 4.6-5.0τ simplify to two doublets - one at 4.72τ(J=4Hz), and the other at 4.9τ(J=9Hz). Signal at 4.4τ simplifies slightly.

From this data, plus data from ^{13}C studies on the dehydration product and oxidation product, this was given the structures (36a) and (36b), a mixture of epimeric alcohols.

Reduction of 3a,7a-dicarbethoxy-4,8-diketo-2,3,3a,4,6,-7,7a,8-octahydroindacene (19).

67mg. of the dione (19) was stirred in a mixture of sodium borohydride (34mg.), methanol (27ml.) and water (2.7ml.) for 24 hours at room temperature. The solution became homogeneous as the reaction proceeded. The reaction mixture was flooded with 75ml. water, and extracted with ether. The ether extract was washed with water, dried and evaporated to yield 53mg.(80%) of a

white crystalline solid, m.pt.150-1°C, which was the 4,8-dihydroxy-3a,7a-dicarbethoxy-2,3,3a,4,6,7,7a,8-octahydroindacene (20).

IR : $\nu_{max}^{CCl_4}$ 3600, 3550, 3480, 1740 cm^{-1}.

UV spectrum showed complete disappearance of the 264nm absorption of the dione (19).

NMR : 4.05τ(m,2H); 5.84τ(q,4H); 5.61τ(m,4H); 7.55τ(m,8H); 8.75τ(t,6H).

Found C,64.21; H,7.27; $C_{18}H_{24}O_6$ requires C,64.27; H,7.19%.

The mass spectrum showed a parent ion at m/e 336.

Hydrolysis of 4,8-dihydroxy-3a,7a-dicarbethoxy-2,3,3a,4, 6,7,7a,8-octahydroindacene (20).

To a stirred solution of 52mg. of the diol (20) in 20ml. AnalaR methanol was added 10 drops of conc. hydrochloric acid and the mixture stirred overnight. The mixture was diluted with 20ml. water and solid sodium chloride added. This was extracted with ether (3x), the ether extracts combined, washed with brine, dried and evaporated to yield 25mg. of a white crystalline solid, m.pt. 163-65°C.

IR ($CHCl_3$) : ν_{max} 3490(broad), 1700(broad), 1100, 1010, 925 cm^{-1}, and broad carboxylic acid absorption 3600-2400cm^{-1}.

Found C,59.89; H,5.79; $C_{14}H_{16}O_6$ requires C,60.00;H,5.75%.

Mass spectroscopy showed a parent ion at m/e 280.

This is consistent with the diol diacid (23).

Oxidation of the alcohol (36).

250mg. (0.67m.mole) of the alcohol (36) in 20ml. acetone were cooled in an ice-bath, and 8N Jones reagent added until an orange colour persisted. The mixture was extracted with 50ml. ether, washed with water, dried and evaporated to yield 233mg. of a white crystalline product, m.pt. 157-9°C. (94%).

Found C,59.06; H,6.13; $C_{18}H_{22}O_8$ requires C,59.01; H,6.05%.

Mass spectrum showed a parent ion at m/e 366.

IR : $\nu_{max}^{CCl_4}$ 1770, 1744, 1739, 1723 cm^{-1}.

NMR (^1H) : 4.15τ(1H,d, J=5Hz); 5.74τ(2H,q); 5.78τ(2H,q); 6.5τ(1H,t, J=9Hz); 8.68τ(3H,t); 8.70τ(3H,t); and a 10 proton "envelope" at 6.8-8.1τ.

^{13}C NMR (ppm from Tetramethylsilane) :

201.869 (s)	63.094 (s)	39.820 (q)
179.097 (s)	61.984 (t)	32.729 (t)
169.562 (s)	61.486 (t)	27.281 (t)
168.790 (s)	47.440 (q)	25.562 (t)
101.004 (d)	46.739 (s)	14.050 (q)
80.722 (s)	44.284 (d)	

This information is consistent with the structure (35).

Dehydration of the alcohol (36).

60mg. of the alcohol (36) was refluxed overnight in a Dean and Stark water separator with 5mg. toluene-p-sulphonic acid and 20ml. benzene. Solid potassium bicarbonate was added and the mixture left for 24 hours before filtering. The filtrate was washed with brine,

dried and evaporated under reduced pressure to yield an oily crystalline mixture. Recrystallisation from ethanol gave a colourless crystalline solid, m.pt.132-4°C, (50mg., 88%).

Found C,62.09; H,6.02; $C_{18}H_{22}O_7$ requires C,61.71; H,6.33%.

IR (CCl_4): ν_{max} 1750, 1742, 1723, 1690 cm^{-1}.

UV showed only end absorption at 216nm. Mass spectrum showed a parent ion at m/e 350.

^1H NMR : 3.3τ(finely split singlet, 1H); 4.42τ(broad doublet, J=3Hz, 1H); 5.74τ(q,2H); 5.76τ(q,2H); 8.65τ(t,6H), plus a 10 proton "envelope" at 6.8-8.4τ.

^{13}C NMR : (ppm from tetramethyl silane)

202.860 (s)	76.385 (s)	40.448 (q)
172.670 (s)	62.020 (s)	32.681 (q)
169.876 (s)	61.407 (t)	28.702 (t)
139.901 (d)	61.260 (t)	28.073 (t)
111.390 (d)	49.019 (s)	14.126 (q)
95.003 (d)	46.485 (q)	14.026 (q)

This information is consistent with the structure suggested (37).

Acetylation of the alcohol (36).

151mg. of the alcohol (36) was refluxed in 1.5ml. acetic anhydride and 3ml. anhydrous pyridine for 90 minutes. After cooling, the reaction mixture was poured onto ice and the white crystalline solid filtered off. The crystalline product of acetylation melted at 123-5°C,

and its mass spectrum showed a parent ion at m/e 452, with two separate losses, one of m/e 60 and the other of m/e 42. These were assigned as loss of acetic acid and ketene respectively, indicating that one of the acetates was attached to a saturated carbon, while the other acetate was vinylic.

Found C,58.64; H,6.70; $C_{22}H_{28}O_{10}$ requires C,58.40; H,6.24%.

IR (CCl_4): ν_{CO} 1770, 1744, and 1725 cm^{-1}.

UV : Only end absorption.

NMR : 4.05τ(dd,1H, J=9,4Hz); 4.4τ(broad doublet,1H,J=8Hz); 4.7τ(s,1H, vinylic); 5.7τ(double quartet,4H); 7.85τ(s,3H); 7.9τ(s,3H); 8.7τ(t,6H).

This was in agreement with the assigned structure (38).

Hydrogenation of the alcohol (36).

124mg. of the alcohol (36) was stirred with 124mg. 10% palladised charcoal in 20ml. ethanol in an atmosphere of hydrogen at room temperature and pressure, until hydrogen uptake ceased. Removal of the catalyst by filtration through Celite, and evaporation of solvent under reduced pressure gave 120mg. of the reduced product, as a colourless oil. Mass spectroscopy showed a parent ion at m/e 354, and accurate mass measurement gave the mass as 354.1672. $C_{18}H_{26}O_7$ requires a mass of 354.1671.

IR(CCl_4) : ν_{max} 3635, 3545, 3460, 1745, 1723 and 1700cm^{-1}.

UV showed only end absorption.

NMR : 5.7τ(2H,q); 5.8τ(2H,q); 6.37τ(t,J=7Hz, 2H); 8.32τ(1H, broad doublet, disappears in D_2O exchange); 8.68τ(t,3H); 8.72τ(t,3H).

Jones oxidation of the hydrogenated alcohol.

133mg. of the hydrogenated alcohol was dissolved in 20ml. AnalaR acetone and cooled to 0°C. Jones reagent (8N) was added until an orange colour persisted. The reaction mixture was diluted with ether (50ml.), washed with water until the washings were colourless, dried and evaporated to yield 100mg. product, which on analytical tlc contained 2 components. These were separated by preparative tlc (50% ethyl acetate:light petrol). The less polar material (40mg., R_f=0.5) was a white crystalline material, m.pt. 147-151°C.
IR (CCl_4) : ν_{max} 3490(broad), 1770, 1740(broad), 1720cm^{-1}.
Mass spectrum showed a parent ion at m/e 326.

Hydrogenation of the oxidised alcohol (35).

124mg.(0.34m.mole) of the oxidised alcohol (35), and 124mg. 10% palladised charcoal were stirred in 99.9% ethanol under an atmosphere of hydrogen. After hydrogen uptake had ceased (6ml.), the solution was filtered through Celite, dried and evaporated to give 120mg. material. Preparative tlc to remove polar material and traces of palladised charcoal gave 115mg. of a white crystalline material which was identical (m.pt., mixed m.pt., IR, NMR, MS) with starting material.

Attempted Preparation of 2-crotonyl-cyclohexanone (50)[18].

30g.(0.3mole) cyclohexanone in 75ml. dry ether was added over 15 minuted to a stirred suspension of 11.7g. (0.3mole) freshly prepared[75] sodium amide in 300ml. ether at -45°C. Dry nitrogen was bubbled through the mixture for 20 minutes, and to the resulting suspension was added, over 5 minutes, 13.0g. (0.13mole) crotonyl chloride(51)[76] in 50ml. dry ether. The cooling bath was removed and the reaction stirred for 15 minutes. The reaction mixture was then cautiously poured into 27ml. conc. hydrochloric acid in ice, shaken, and the ether layer separated. The aqueous layer was extracted with ether, and the ether extracts combined with the first layer. The ethereal phase was washed with saturated sodium bicarbonate solution, dried and evaporated and the residue distilled. The first fraction obtained was cyclohexanone. The second fraction (4.3g., 120-4°C/0.15mm) contained 3 compounds by analytical tlc (30% ethyl acetate: light petrol). The second fraction was purified by column chromatography on 160g. alumina (grade III) with light petrol and ethyl acetate as eluants. 3g. of pure material was obtained, but did not have the correct IR and NMR spectra for 2-crotonyl-cyclohexanone (50), and was not investigated further.

1-morpholino-cyclohex-1-ene (54)[19].

9.72g. (0.1mole) redistilled morpholine, 9.81g. (0.1mole) cyclohexanone and 0.5g. toluene p-sulphonic acid were dissolved in 100ml. toluene and refluxed with

a Dean and Stark water separator for 5 hours. The toluene was removed and the residue distilled to yield 1-morpholino-cyclohex-1-ene (54), 8.5g., 50%, 70-2°C/0.4mm. [Lit: 117-120°C/10mm.][19].

2-methyl-5,6,7,8-tetrahydrochroman-4-one (48)[19,20].

8.51g. (0.5mole) 1-morpholino-cyclohex-1-ene (54) and 6.0g. sodium-dried triethylamine were dissolved in 75ml. chloroform and heated to 35°C. 5.75g. crotonyl chloride[76] in 25ml. chloroform was added dropwise with stirring over 30 minutes. The reaction mixture was stirred overnight at room temperature. 25ml. dilute hydrochloric acid was added and the mixture refluxed for 5 hours with vigorous stirring, The reaction mixture was cooled and washed with water until the aqueous washings had a pH of 5-6 . The aqueous phase and washings were combined and extracted with chloroform (6x). The chloroform layer and extracts were combined, dried and the chloroform removed under reduced pressure. The residue was distilled twice. Initially, cyclohexanone distilled over, followed by almost pure 2-methyl-5,6,7,8-tetrahydrochroman-4-one (48), distilling at 130-6°C/19mm. to give 2.6g. (48) (31%) as a white crystalline solid m.pt. 46-8°C [Lit. 46°C[19]].

1.8g. pure (48) was obtained by purification of the distillate by chromatography on 130g. alumina (grade III) (15% ethyl acetate:light petrol).

IR: (CCl_4) ν_{max} 1670cm^{-1}, 1620cm^{-1}.

NMR : (CCl_4) 4.5τ multiplet, 1H, J_{CH_3-H}=7Hz, J_{CH_2-H}=8Hz.
7.7τ doublet, 2H, J=8Hz,
7.6-8.5τ m, 8H, 8.6τ doublet, 3H, J=7Hz.

UV : λ_{max}^{EtOH} 271nm, ϵ=9,800

Attempted epoxidation of 2-methyl-5,6,7,8-tetrahydrochroman-4-one (48) with hydrogen peroxide/base.[23]

To 250mg.(15.mmole) of (48) dissolved in 2.5ml. ethanol was added 0.5ml. 10% sodium hydroxide solution and 0.5ml. 15% hydrogen peroxide solution, and the mixture heated under reflux for 2 hours. The reaction mixture was diluted with 5ml. water and extracted with ether. The ether was washed with water, dried and evaporated to yield 200mg. material which was shown by analytical tlc (15% ethyl acetate:light petrol) to contain a multiplicity of products and was not investigated.

2-methyl-5,6,7,8-tetrahydrochroman-4-toluene-p-sulphonyl-hydrazone (58).

573mg.(3mmole) toluene p-sulphonyl hydrazine (57) in 10ml. methanol was added to a solution of 510mg.(3mmole) of (48) in 10ml. methanol and the mixture refluxed for 2 hours. The reaction mixture was cooled to give 1.8g. (98%) of (58) as pale yellow crystals, m.pt. 170-2°C (decomp.) which were filtered off.

IR : (nujol mull) ν^{N-H} 3220cm^{-1}, ν_{max} 1640, 1600cm^{-1}.

NMR : 2.3τ, 4H, aromatic, peaks typical of a para-disubstituted benzene ring; 6.0τ, multiplet, 1H; 7.7τ, singlet, 3H; 8.85τ, doublet, J=6.5Hz, 3H; 7.0-8.8τ, 10H "envelope".

MS:M^+ m/e 334.

Analysis : C,61.11; H,6.61;N,8.40; S,9.50. $C_{17}H_{22}N_2O_3S$ requires C,61.03; H,6.63; N,8.38; S,9.59%

Attempted epoxidation of 2-methyl-5,6,7,8-tetrahydro-chroman-4-toluene-p-sulphonyl-hydrazone (58).

(a) with hydrogen peroxide/sodium hydroxide[23].

A solution of 150mg.(0.45mmole) of (58) in 5ml. ethanol was warmed on a steam bath with 0.5ml. 10% sodium hydroxide solution and 0.5ml. 15% hydrogen peroxide. The solution turned red ,and after 5 minutes was flooded with water and extracted with ether. The ether was washed with brine to neutrality, dried and evaporated to yield 140mg. of material which was found to be identical with starting material.

(b) with hydrogen peroxide/benzonitrile[25].

A solution of 503mg.(1.5mmole) of (58) in 1.1ml. ethanol was stirred at room temperature with 192mg. benzonitrile and 126mg. 50% hydrogen peroxide solution for 40 hours. The reaction mixture was diluted with water (5ml.), and extracted with chloroform (3x5ml.). The combined chloroform extracts were dried and evaporated to yield 490mg. crystalline material which was identical with starting material.

(c) with 3-chloroperoxybenzoic acid[26].

100mg. (0.3mmole) of (58) in 10ml. methylene chloride was added dropwise to a stirred solution of 66mg. (0.38mmole) 3-chloroperoxybenzoic acid in 10ml. methylene chloride and the temperature maintained at 20-2°C for 30 minutes. Excess peracid was destroyed by adding 10% sodium sulphite until no reaction occurred

with starch-iodide paper, then washed with 5% sodium bicarbonate solution, water and brine, and the methylene chloride phase dried and evaporated to yield 80mg. crude product. Analytical tlc showed the presence of many products, with some starting material. No separation was attempted.

Ethyl azidoformate (62)[28].

An aqueous solution of 3.6g.(55mmole) sodium azide was added to 2.5g.(23mmole) ethyl chloroformate and the mixture shaken for 5 minutes. The smell of ethyl chloroformate disappeared, and a heavy oil separated out. The oil was separated, dried and distilled under reduced pressure, (ethyl azidoformate is explosive when heated strongly) to yield 1.03g. ethyl azidoformate (62)
b.pt. 35-40°C/8mm.
IR (liquid film) : ν_{N_3} 2190(s), 2140(s) cm^{-1}

Attempted preparation of N-carbethoxy-11-aza-3-methyl-2-oxa-tricyclo[4,4,1,$0^{1,6}$]-undecan-5-toluene-p-sulphonyl-hydrazone (61)[29].

To a solution of 338mg.(1mmole) of (58) in 32ml. pentane was added 117mg.(1.1mmole) ethyl azidoformate and the mixture stirred in a sealed flask for 7 days. No reaction was observed and starting material was recovered.

2-methyl-5,6,7,8-tetrahydrochroman-4-ol (67).

(a) from sodium borohydride on the ketone (48).

100mg.(0.6mmole) of (48) was dissolved in 25ml.

ethanol and water added until the solution turned turbid. 5.7mg.(0.15mmole) sodium borohydride was added and the mixture stirred at room temperature for 2 hours, by which time the mixture had become homogeneous. 10ml. water was added, and the aqueous mixture extracted with ether (3x10ml.). The ether extracts were combined, dried and the ether removed to yield 90mg. crude product, which was shown by analytical tlc to contain starting material and 2 products, and was not separated.

(b) from lithium aluminium hydride on the ketone (48).

To a stirred solution of 1g.(6mmole) of (48) in 25ml. ether under nitrogen was added 300mg.(7.9mmole) lithium aluminium hydride, and the mixture stirred for 30 minutes. Water was added cautiously to destroy excess lithium aluminium hydride, and the residue was extracted with ether. The ether was dried and evaporated to yield 2-methyl-5,6,7,8-tetrahydrochroman-4-ol (67), 0.98g. (98%) as white crystals, m.pt. 103-4°C (after purification). Analysis : C,71.12; H,9.46; $C_{10}H_{16}O_2$ requires C,71.39; H,9.59%.

IR (CCl_4) : ν_{OH} 3590cm^{-1}, $\nu_{C=C}$ 1680cm^{-1} (enol ether).

NMR : 6.0τ, m, 2H; 7.5τ, broad singlet, 1H (-OH, disappears in D_2O exchange); 8.75τ, d, J=6Hz, 3H; 7.6-8.8τ, 9H "envelope".

MS : M^+ 168.

Attempted preparation of 2-methyl-5,6,7,8-tetrahydrochroman-4-(toluene p-sulphonate) (66)[30].

100mg.(0.6mmole) 2-methyl-tetrahydrochroman-4-ol (67) and 230mg.(1.2mmole) toluene p-sulphonyl chloride were dissolved in 10ml. AnalaR pyridine and left for 4 days, when the solution had turned red. The pyridine solution was poured onto ice and dil. hydrochloric acid added until the mixture was acid. The aqueous mixture was extracted with ether (3x10ml.), the ether extracts combinedand washed with water to neutrality. The ether was dried and evaporated to give 78mg. material which proved to be mainly toluene p-sulphonic acid. No tosylate (66) was observed.

2-methyl-5,6,7,8-tetrahydrochroman-4-benzoate (68).

To a solution of 168mg.(1mmole) of (67) in 1ml. AnalaR pyridine was added 170mg.(1.2mmole) benzoyl chloride, and the mixture refluxed for 30 minutes. The reaction mixture was cooled, diluted with 10ml. ether, washed with water (2x10ml.) and dil. copper sulphate solution until no copper sulphate-pyridine complex was formed. The ether was dried and evaporated to yield 215mg. (79%) 2-methyl-5,6,7,8-tetrahydrochroman-4-benzoate (68) as white crystals, m.pt. 52-4°C. Analysis : C,74.89; H,7.48; $C_{17}H_{20}O_3$ requires C,74.97; H,7.40%.
Mass spectrum shows M^+ at m/e 272.
IR (CCl_4) : ν_{max} 1740, 1690 (enol ether) cm^{-1}.
NMR ($CDCl_3$) : 1.8τ, m, 2H, aromatic; 2.5τ, m, 3H, aromatic; 5.9τ, m, 2H; 8.7τ, d, J=5Hz, 3H; 7.0-9.0τ, 10H, m.

Attempted hydration and ring opening of the benzoate (68).

200mg.(0.73mmole) of (68) was dissolved in 5ml. dioxan, 5ml. dil. sulphuric acid was added, and the reaction mixture stirred at room temperature for 7 days. The brown solution was extracted with ether (3x15ml.), the ether extracts combined, washed with brine to neutrality, dried and evaporated to yield 97.8mg. material which was shown on analytical tlc to contain at least 7 compounds. An attempt was made to obtain pure compounds by preparative tlc (25% ethyl acetate:light petrol), and 4 bands were extracted. The band at R_f=0.3 (56.4mg.) was found to be benzoic acid by comparison (ir, m.pt.) with authentic material. The remaining 3 bands were investigated for vinylic protons using nmr, but no vinylic protons were observed.

2-methyl-5,6,7,8-tetrahydrochroman-4-one oxime (70)[31].

To a solution of 310mg.(1.8mmole) of 2-methyl-5,6,7,8-tetrahydrochroman-4-one (48) and 255mg.(3.7mmole) hydroxylamine hydrochloride in 2ml. ethanol and 0.4ml. water, was added 470mg. powdered sodium hydroxide, with stirring and external cooling. The mixture was refluxed for 5 minutes, cooled and diluted with water. Solid sodium chloride was added and the mixture was extracted with ether. The combined ether extracts were washed with brine to neutrality, dried and evaporated to yield 300mg.(1.65mmole,86%) of the oxime (70), as white crystals, m.pt. 169-169.5°C. Analysis : C,66.65; H,8.17; N,7.85; $C_{10}H_{15}NO_2$ requires C,66.27; H,8.34; N,7.73%.

IR (CCl_4) : ν_{max} 3600, 1640cm^{-1}.

NMR : 6.0τ, m, 1H; 6.85τ, m, 2H; 8.6τ, d, 3H; 7.5-8.7τ, 9H "envelope" which contains the -OH proton, based on change in integral on D_2O exchange.

Attempted reduction of 2-methyl-5,6,7,8-tetrahydrochroman-4-one oxime (70).

(a) with lithium aluminium hydride in ether[32].

To a stirred solution of 26mg.(0.14mmole) of the oxime (70) in 5ml. sodium-dried ether under nitrogen was added an excess (20mg.,0.5mmole) of lithium aluminium hydride in 15ml. sodium-dried ether, and the mixture refluxed for 30 minutes. The reaction mixture was cooled, and excess lithium aluminium hydride destroyed by cautious addition of water. The residue was filtered and washed with ether, and the ether filtrate dried and evaporated to yield 25mg. of material which was found to be unreacted starting material.

(b) with lithium aluminium hydride in tetrahydrofuran[32].

To a stirred solution of 20mg.(0.5mmole) lithium aluminium hydride in 5ml. dry tetrahydrofuran at 0°C under nitrogen was added 27mg.(0.14mmole) of the oxime (70) in 5ml. dry tetrahydrofuran. The mixture was refluxed for 4 hours, cooled and excess lithium aluminium hydride destroyed by cautious addition of water. The complex was destroyed by addition of 10ml. of 20% Rochelle salt solution, followed by stirring at room temperature for 30 minutes. The slurry was extracted with ether for

18 hours (continuous extraction), the ether was dried and evaporated to yield 30mg. crude material, which was recrystallised from ethanol to give 25mg. pure crystalline material which was found to be starting material.

(c) by hydrogenation with Adams catalyst in acetic anhydride.

300mg. Adams catalyst (PtO_2) was suspended in 25ml. acetic anhydride and reduced in an atmosphere of hydrogen until no further hydrogen was absorbed. 762mg. of crude oxime (70) in 25ml. acetic anhydride was added and stirred in an atmosphere of hydrogen at atmospheric pressure until uptake of hydrogen ceased (160ml.). The reaction mixture was filtered through Celite, and the solvent removed under reduced pressure to give a red oil, which was stirred overnight with 2 drops water in an attempt to induce crystallisation, without success. The oil was dried and purified by preparative tlc (30% ethyl acetate:light petrol) to give 500mg. of N-acetyl-4-amino-2-methyl-5,6,7,8-tetrahydrochroman (74), as yellow oily crystalline material, m.pt. 26-8°C. High resolution mass spectroscopy gave the molecular weight as 209.2814; $C_{12}H_{19}NO_2$ requires an accurate mass of 209.2907.

IR : ν_{max} 1700cm^{-1}.

Hydrolysis[34], diazotisation[35] and attempted opening of N-acetyl-4-amino-2-methyl-5,6,7,8-tetrahydrochroman (74).

480mg.(1.66mmole) of the acetamide (74) was dissolved in 10ml. of 70% sulphuric acid and refluxed for 90 minutes

by which time the acetamide had been completely hydrolysed. The silution was cooled on an ice-bath and 150mg.(2.2mmole) AnalaR sodium nitrite in 2ml. water added slowly. Some gas was seen to evolve. The mixture was warmed to room temperature, then heated on a steam bath for 10 minutes, until gas evolution had ceased. 10ml. water was added and the solution extracted with ether. The ether extracts were combined, washed with brine, dried and evaporated to yield 200mg. material which, on analytical tlc, contained many products. Preparative tlc (30% ethyl acetate:light petrol) gave 4 compounds, which were investigated by ir and mass spectroscopy. No compound gave the required ir or mass spectrum and the products were not investigated further.

6-dimethylamino-4-oxo-caproic acid hydrochloride (87)[38].

Laevulinic acid (88)(120g.,1mole) and dimethylamine hydrochloride (80g.,1mole) were stirred together at 110°C until a homogeneous solution was obtained. Paraformaldehyde (30g.) was added cautiously and the temperature maintained at 110°C for 1 hour under a reduced pressure of 15mm. The cooled residue was filtered and dry ethanol(50ml.) and dry acetone(500ml.) added to precipitate the Mannich base hydrochloride (87) as a colourless amorphous solid, m.pt. 109-112°C [Lit. 112-120°C][38], 120g.(60%) after drying. The dry crude material was sufficiently pure for the next stage.

Ethyl 6-dimethylamino-4-oxo-caproate (81)[38].

The crude hydrochloride (87),(20g.) was refluxed overnight in dry ethanol (50ml.) containing 1ml. AnalaR conc. sulphuric acid. The ethanol was then removed under reduced pressure, and the residue dissolved in water, basified with 4N sodium hydroxide solution, and extracted with ether. The ethereal phase was washed with brine, dried and concentrated to yield the free Mannich base (81), (13g.,68%) as a light yellow oil. This could be used without further purification.

IR (liquid film) : ν_{max} 2860, 1730(broad), 1180cm^{-1}.

NMR (CCl_4) : 5.9τ, q, J=7Hz, 2H; 7.2-7.8τ, m, 8H; 7.8τ, s, 6H; 8.8τ, t, J=7Hz, 3H.

Condensation of (81) with 2-methyl-cyclohexanone.

2-methyl-cyclohexanone and (81) were reacted

together under the Thermal Michael conditions of Buchanan et al.[39].

In a typical condensation, the Mannich base ester (81), (22g., 0.11mole) and 2-methyl-cyclohexanone (37g.,0.33mole) were refluxed together for 18 hours, by which time evolution of dimethylamine had ceased. The reaction mixture was cooled, diluted with 300ml. water, neutralised with glacial acetic acid and extracted with ether (3x). The ethereal phase was washed with brine, dried and the ether evaporated to yield a mixture of the condensation product and 2-methyl-cyclohexanone excess. The excess 2-methyl-cyclohexanone was distilled off, and the residue distilled under vacuum to yield 4 fractions : 1. Remainder of 2-methyl-cyclohexanone.

2. 4.5g. material, 94-110°C/0.08mm.

3. 9.0g. material, 120-160°C/0.08mm.

4. 10.2g. material, 160-200°C/0.08mm.

On analytical tlc, fraction 2 contained at least 5 compounds, while fractions 3 and 4 were identical and contained at least 3 compounds. Glc showed the presence of at least 8 compounds in fraction 3, and at least 6 in fraction 4. Fractions 3 and 4 combined were columned on 400g. grade III alumina. Several compounds were obtained impure, and were not identified. At 20-30% ethyl acetate: light petrol 6g. of ethyl 4-oxo-6-(2'-oxo-3'-methyl-cyclohexyl)-hexanoate (89) was obtained, and was pure on analytical tlc, but on glc was shown to contain 3 minor impurities (Main peak: R_t=3.2mins. 5%QF-1, 100°C, N_2- 22psi).

IR (liquid film) ν_{max} 1740, 1720, 1180, 1160cm^{-1}

NMR (CCl_4) : 5.95τ, q, ($-CH_2-$ of ester), 2H; 8.8τ, t, 3H,(methyl of ester); 9.05τ, d, J=6Hz, 3H, (methyl of methylcyclohexanone); and an "envelope" of 16 protons.

MS : M^+ m/e 268.

Cyclisation of Ethyl 4-oxo-6-(2'-oxo-3'-methyl cyclohexyl)-hexanoate (89)

(a) with 10N hydrochloric acid[37].

4.5g.(16.8mmole) of (89) were stirred with 7.5ml. 10N hydrochloric acid for 17 hours at room temperature. A yellow oily solid separated out and the solution turned yellow. 15ml. water was added and the reaction mixture extracted with ethyl acetate (3x). The ethyl acetate extracts were combined, washed with saturated sodium bicarbonate solution, brine, dried and evaporated to yield 1.81g. crude (90), as a yellow oil.

IR (liquid film) ν_{max} 1780, 1715cm^{-1}.

NMR (CCl_4) : 7.2-7.8τ, m, 4H of -lactone; 8.9τ, s, 3H, methyl; 7.8-9.0τ, 11 proton "envelope".

MS : M^+ m/e 222.

(b) with phosphorus pentoxide/orthophosphoric acid.

12g. phosphorus pentoxide and 8ml. syrupy orthophosphoric acid were heated together at 100°C for 5 minutes with stirring. To this mixture was added dropwise 96mg. of (89), and the mixture stirred at 100°C for 3 hours. The reaction mixture was poured onto 100g. ice and stirred for 30 minutes to ensure complete

destruction of the polyphosphoric acid. The aqueous mixture was extracted with 100ml. ethyl acetate, then 3x20ml. ethyl acetate. The combined extracts were washed with brine, dried and evaporated to give 74mg. of a crude product which was not the required cyclopentenone (75) (by ir spectroscopy).

IR : ν_{max} 1800, 1740(broad), 1710(broad)cm^{-1}.

Treatment of the lactone (90) with polyphosphoric acid.

(a) with technical polyphosphoric acid[43].

99mg. of the lactone (90) was stirred with 1.1g. technical polyphosphoric acid at 100°C for 3 hours. The reaction mixture was cooled and 3g. ice and 4ml. ethyl acetate added, then extracted with ethyl acetate (3x). The combined ethyl acetate extracts were washed with brine to neutrality, dried and evaporated to give 70mg. crude product, which was purified by preparative tlc (25% ethyl acetate:light petrol). Two bands were observed and extracted.

1. R_f=0.6; 5mg., IR (liquid film) ν_{max}1800,1750,1680cm^{-1}
2. R_f=0.5;10mg., IR (liquid film) ν_{max}1770,1745,1680cm^{-1}.

Neither appeared to be the desired enone product (75).

(b) with freshly prepared polyphosphoric acid.

20g. polyphosphoric acid was prepared by stirring 12g. phosphorus pentoxide with 8ml. syrupy phosphoric acid at 100°C for 5 minutes. To this mixture was added 1.81g. of the lactone (90), and the mixture stirred at 100°C for 3½ hours. The reaction was worked up as in (a)

above, to yield 1.38g. crude product. This was columned on 90g. alumina (grade III) using light petrol and ethyl acetate as eluants. The fraction at 75% ethyl acetate: light petrol crystallised out to give 71mg. crystalline material. This was sublimed to give a white crystalline product, m.pt. 84-85.5°C.

NMR (CCl_4) : 2.75τ, s, 1H; 7.8τ, s, 3H; 6.9-8.0τ, 7 proton "envelope".

IR (liquid film) : ν_{max} 1740, 1695, 1600, 1590(medium) and 1100cm^{-1}.

MS : M^+ m/e 294.

Analysis: C,77.27; H,7.61; $C_{19}H_{22}O_4$ requires C,77.55; H,7.48%.

This crystalline product was not identified.

<u>6-methyl-1-pyrrolidino-cyclohex-1-ene (94)[77]</u>.

71.2g.(0.86mole) redistilled pyrrolidine, 86g. (0.77mole) 2-methyl cyclohexanone and 0.77g. toluene p-sulphonic acid were refluxed together in 250ml. toluene with a Dean and Stark water separator for 22 hours. The reaction mixture was cooled, and the toluene and excess pyrrolidine removed under reduced pressure. 86g.(68%) 6-methyl-1-pyrrolidino-cyclohex-1-ene (94) distilled at 108-110°C/13mm.

IR (Liquid film) : ν_{max} 1640, 790cm^{-1}.

NMR (CCl_4) : 5.92τ, t, J=8Hz, 1H.

Attempted condensation of 6-methyl-1-pyrrolidino-cyclohex-1-ene (94) with ethyl 6-dimethylamino-4-oxo-hexanoate (81)[46].

2g.(20mmole) of (94) and 3.3g.(20mmole) of (81) were dissolved in dioxan (10ml.) and refluxed for 22 hours. 30ml. water was then added and the reaction mixture stirred for a further 1 hour. The dioxan and water were removed under reduced pressure to give 4.3g. crude product, which was dissolved in chloroform, washed with dil. hydrochloric acid, water and dried with anhydrous sodium sulphate. The chloroform was removed under reduced pressure to give 1.6g. crude product which, when distilled, yielded ethanol as the only product.

Condensation of 2-carbethoxy-6-methyl-cyclohexanone (95) with ethyl 6-dimethylamino-4-oxo-hexanoate (81).

2g.(10mmole) of (95) and 4.52g.(30mmole) of (81) were refluxed together for 18 hours at 145-150°C. The cooled reaction mixture was diluted with 50ml. water and neutralised with glacial acetic acid. The mixture was extracted with ether (3x), the ether extracts were combined, washed with brine, dried and evaporated to yield 5.6g. crude product. The crude product was distilled and 3 fractions obtained:

1. 54-122°C/20mm., which by analytical tlc, ir and nmr was identical with 2-carbethoxy-6-methyl-cyclohexanone (95).
2. 90-100°C/0.1mm., 200mg.
3. 100-120°C/0.1mm., 200mg.

Fractions 2 and 3 were identical by analytical tlc, and

contained 2 compounds. A sample was purified by preparative tlc (25% ethyl acetate:light petrol).

IR : $\nu_{max}^{CCl_4}$ 1740, 1725 (broad) cm^{-1}.

NMR (CCl_4) : 5.85τ, q, 2H, J=7Hz; 5.95τ, q, J=7Hz, 2H;
8.76τ, t, J=7Hz, 3H; 8.79τ, t, J=7Hz, 3H;
9.0τ, d, J=6Hz, 3H; and a 13 proton "envelope"
at 7.3-9.1τ.

MS : M^+ m/e 340 .

100mg. of crude fraction 2 gave 42mg. of (96).

Indan-1-one (97).

(a) from indene (106).

Indan-1-one was prepared from indene by the method of Pacaud and Allen[51]. The yield of indan-1-one was 85.5g. (56%) b.pt. 122-4°C/20mm. [Lit.[51] 125-6°C/17mm.], m.pt. 39-41°C.

IR (nujol mull) ν_{max} 1720, 780, 760cm^{-1}.

(b) from indane (107).

Indan-1-one was prepared by the method of Mazur[52]. 1.75g.(15mmole) indane and 5.6g.(15mmole) mercuric bromide were dissolved in 200ml. cyclohexane and the solution stirred magnetically during irradiation with a Hanovia medium pressure lamp for 18 hours. The solution was filtered and the cyclohexane removed under reduced pressure to give 2.6g. crude product which was exhaustively steam-distilled. The distillate was extracted with ether (3x), the ether extracts combined , dried and evaporated to yield 1g. material which contained only indane and indan-1-one (by analytical tlc). These were separated by distillation, but the overall yield of indan-1-one was low and the reaction was not repeated.

2-(N,N-dimethyl-aminomethyl)-indan-1-one hydrochloride (98).[50]

85.5g.(0.65mole) indan-1-one (97), 41g. paraformaldehyde, and and 57.5g.(0.7mole) dimethylamine hydrochloride were dissolved in 355ml. absolute ethanol and 11ml. conc. hydrochloric acid was added. The mixture was refluxed for 2 hours, cooled and poured into 1 litre AnalaR acotone. The solution was cooled overnight, filtered

and the amorphous white solid collected. The mother liquor was collected, concentrated and poured into acetone to yield further white solid. The total yield of crude product was 220g. (wet with acetone), and this was recrystallised from absolute ethanol/acetone (1:4) to yield 90g. 2-(N,N-dimethyl-aminomethyl)-indan-1-one hydrochloride (98) m.pt. 146-8°C.

IR (Nujol mull) : 2700-2600 ($-NH_2^+$); ν_{CO} 1710cm^{-1}.

NMR : 2.2-2.8τ, m, 4H; 7.0τ, s, 6H.

2-(N,N-dimethyl-aminomethyl)-indan-1-one (99).

In a typical experiment, 5g.(22mmole) of the Mannich base hydrochloride (98) was dissolved in 50ml. water. 3ml. 5% ammonium hydroxide (25mmole) was added. A white precipitate formed which was extracted with ether. The aqueous layer was saturated with sodium chloride and extracted with ether. The ether extracts were combined, washed with brine, dried and the ether remover to yield 3.5g. crude 2-(N,N-dimethyl-aminomethyl)-indan-1-one (99), 85%.

IR (thin film) : 2840, 2800 cm^{-1} [$\nu_{CH_3-N,-CH_2-N}$]

ν_{max} 1710, 1610, 1590, 990, 755cm^{-1}.

The crude Mannich base (99) was used without purification.

2-(2'-oxo-cyclopentyl)-indan-1-one (108)[50].

2.05g.(11mmole) of the Indanone Mannich base (99) and 2.9g.(34mmole) cyclopentanone were refluxed together for 2 hours until evolution of dimethylamine had ceased. The reaction mixture was diluted with 10ml. ether,

100ml. water was added and the mixture neutralised with glacial acetic acid, The ether layer was separated and the aqueous layer extracted with ether. The ethereal layer and ether extracts were combined, washed with brine, dried and evaporated to give 5g. of material. Excess cyclopentanone was distilled off under reduced pressure, and the residue distilled under vacuum to yield 1.54g. (63%) 2-(2'-oxo-cyclopentyl)-indan-1-one (108), b.pt. 154-6°C/0.05mm., as a yellow oil.

IR (liquid film) ν_{max} 3020(m), 1735, 1710, 1610, 760cm^{-1}.

NMR : Ratio of aromatic to aliphatic protons is 1:3 but no fine structure is visible in the aliphatic proton "envelope".

MS : M^+ m/e 228.

Cyclisation of 2-(2'-oxo-cyclopentyl)-indan-1-one (108).

(a) with toluene p-sulphonic acid in benzene[50].

115mg. (0.5mmole) of the diketone (108) and 10mg. toluene p-sulphonic acid in 25 ml. benzene were refluxed with a Dean and Stark water separator for 16 hours. The solution was cooled, solid potassium carbonate was added and left for 3 hours. The benzene solution was filtered and the benzene evaporated to give 80mg.(75%) of an orange oily solid. Trituration of this solid with ether gave a white crystalline solid, m.pt. 136-7°C [Lit. 137°C[50]] which was the bicyclic ketone (109).

Mass spectrum showed the parent ion at m/e 210.

IR (nujol mull) ν_{CO} 1745cm^{-1}.

NMR : ($CDCl_3$) showed complete absence of olefinic protons,

and was different from the nmr spectrum of the starting material.

(

(b) with hydrochloric/glacial acetic acid[50].

100mg.(0.44mmole) of the diketone (108) was dissolved in 2ml. glacial acetic acid, 0.5ml. conc. hydrochloric acid was added, and the mixture refluxed for 8 hours. The acetic acid was removed under reduced pressure and the residue flooded with 50ml. water. The aqueous mixture was extracted with ether (3x), the ether extracts were combined and washed with 6N. sodium hydroxide, brine, dried and evaporated to give 10mg. of material which proved to be starting material and the cyclisation product already obtained in (a), (109).

The basic washings were combined, acidified with 4N hydrochloric acid and extracted with ether (3x). The combined ether extracts were washed with brine, dried and evaporated to give 65mg.(65%) of a white solid which was recrystallised from light petrol. This was the acid (110), m.pt. 157-9°C. Mass spectrum showed a parent ion at m/e 228.

IR : ν_{CO} 1705cm^{-1}.

NMR (CCl_4) : 2.7τ, m, 4H; 6.6τ,s, 2H, indene methylene protons.

2-(2'-oxo-cyclohexyl)indan-1-one (100).

15.7g.(83mmole) of the indanone Mannich base (99) and 24.5g.(250mmole) cyclohexanone were refluxed together for 2 hours until evolution of dimethylamine ceased.

Water (100ml.) was added, and the mixture neutralised by addition of glacial acetic acid. The aqueous mixture was extracted with ether (3x), the ether extracts were combined, washed with brine, dried and evaporated. Excess cyclohexanone was distilled off under reduced pressure and the residue distilled under vacuum. After a trace of cyclohexanone distilled over, 11.8g. (60%) of 2-(2'-oxo-cyclohexyl)-indan-1-one (100) distilled at 186-190°C/0.01mm, as a clear yellow oil. Found : C,79.43; H,7.37. $C_{16}H_{18}O_2$ requires C,79.31; H,7.49%. NMR showed 4 aromatic protons and a 14 proton aliphatic "envelope".

IR (liquid film) : ν_{max} 1728 (broad), 1610, 770, 730cm^{-1}.

(CCl_4) ν_{max} 1718 (broad), 1610 cm^{-1}.

UV (EtOH) λ_{max} 244nm (ϵ=5,640)

Mass spectrum showed a parent ion at m/e 242, and significant ions at m/e 145, 144, 132(base), 131, 111, 103, 98, 77 and 53.

Cyclisation of 2-(2'-oxo-cyclohexyl)-indan-1-one (100).

(a) with conc. hydrochloric acid/glacial acetic acid.[50]

The diketone (100), (155mg.,0.65mmole) was refluxed for 3 hours in 0.3ml. conc. hydrochloric acid and 2ml. glacial acetic acid. The acetic acid was removed under reduced pressure and the residue flooded with 25ml. water. The aqueous mixture was extracted with ether (3x), the ether extracts combined, washed with 2N sodium hydroxide solution, brine and dried. The ether was evaporated to yield 140mg. crude product which by

analytical tlc was shown to be 2 compounds, one of which was starting material. The less polar compound was the required cyclised product (101), by comparison (ir, nmr, ms) with material synthesised by another route.

(b) toluene p-sulphonic acid in benzene[50].

126mg. of the diketone (100) and 5mg. toluene p-sulphonic acid in 25ml. benzene were refluxed with a Dean and Stark water separator for 16 hours. The solution turned a fluorescent green as the reaction proceeded. After cooling, solid sodium bicarbonate was added and left for 4 hours. The solution was filtered, washed with brine, dried and evaporated to give 115mg. of a brown oil, which contained at least 6 compounds on an analytical tlc plate. Preparative tlc (25% ethyl acetate:light petrol) separated 3 bands staining with 2,4-dinitrophenylhydrazine spray. The band at R_f= 0.5 (20mg.) was later shown to the required bicyclic ketone (101). Mass spectrum showed m/e 224 (M^+).
IR (thin film) ν_{max} 1720, 770, 750cm^{-1}.
UV (EtOH) λ_{max} 260nm (ϵ=10,000)

(c) toluene p-sulphonic acid in toluene.

1g. of the diketone (100) and 1g. toluene p-sulphonic acid in 50ml. toluene were refluxed with a Dean and Stark water separator for 17 hours. After cooling, the acid was neutralised with solid sodium bicarbonate, the solution filtered, washed with brine, dried and evaporated to yield 1.2g. material, which was

distilled under vacuum. Fraction 1 (b.pt. 160-180°C /0.04mm.) fraction 2 (180-190°C/0.04mm.) were identical by analytical tlc, but glc showed the presence of several compounds in both fractions. Trituration with light petrol afforded yellow crystals in low yield. Glc showed this to be essentially pure, with a very small trace of non-polar material (R_t=9.4 mins., 5%QF-1,150°C, N_2 22psi). The compound was the desired cyclised product (101), m.pt. 100-1°C.

IR (CCl_4) ν_{max} 1730, 1721cm^{-1}.

NMR (CCl_4) 2.6-3.0τ, m, 4H, aromatic; 6.6τ, s, 1H; 6.7τ, s, 2H;

UV (EtOH) λ_{max} 259nm (ϵ=7,900).

Mass spectrum showed significant ions at m/e 224 (M^+) 196, 167, 165, 156, 153, 152, 128, 115.

Found : C,86.14; H,7.49. $C_{16}H_{16}O$ requires C,85.68; H,7.19%.

After distillation, a by-product was found crystallised out in the tarry residue in the distillation flask. This was recrystallised from light petrol to give feathery white crystals, m.pt. 133-5°C.

Found : C,82.85; H,5.89; $C_{19}H_{16}O_2$ requires C,82.58; H,5.84%.

IR (CCl_4) ν_{max} 1710cm^{-1}.

UV (EtOH) λ_{max} 210nm(ϵ=23,200), 242nm(76,000); 290nm(ϵ=3,560).

NMR : 2.5τ, m, 4H; 6.55τ, m, 1H; 7.1τ, 2H, finely split singlet; 7.95τ, t, J=8Hz, 1H.

This was assigned the structure (112).

(d) conc. sulphuric acid[2].

To 111mg. of the diketone (100) stirred at 0°C, was added dropwise 2ml. conc, sulphuric acid. The mixture was allowed to warm up to room temperature over 4 hours, then poured into ice and extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate solution and brine to neutrality. The ether was dried and evaporated to give 106mg. crude product which was shown by analytical tlc to contain only starting material, and this was confirmed by ir spectroscopy.

(e) boron trifluoride etherate.[56]

To 106mg. of the diketone (100) in 10ml. methylene chloride stirred at 0°C was added 0.5ml. boron trifluoride etherate (48% w/w) and the mixture allowed to warm up to room temperature, then stirred for 18 hours. The reaction mixture was poured into 15ml. brine and extracted with ether (3x). The combined ether extracts were washed once with brine, dried and evaporated to yield 95mg. material, which was shown by analytical tlc to be starting material.

(f) 7N hydrochloric acid[55].

212mg. of the diketone (100) was added to 2ml. 7N hydrochloric acid at 0°C, stirred under nitrogen for 2½ hours, allowed to warm up to room temperature and stirred for a further 24 hours. After work-up, 206mg. starting material was recovered.

(g) 85% phosphoric acid[57].

To 100mg. of the diketone (100) stirred under nitrogen at 0°C was added 5ml. 85% phosphoric acid over a period of 5 minutes. The reaction mixture was warmed to room temperature and stirred for 2 hours. 10g. ice was added cautiously. The aqueous mixture was extracted with ether (4x), the combined ether extracts were washed with satd. sodium bicarbonate solution and brine, then dried and evaporated to give 96mg. material which was shown to be starting material.

(h) Amberlite IR-120(H) resin in benzene.

105mg. of the diketone (100) and 8ml. Amberlite IR-120(H) resin were refluxed in 40ml. benzene, with a Dean and Stark water separator, for 48 hours. The resin was filtered off and washed with light petrol. The benzene and petrol extracts were combined and dried, then evaporated to give 97mg. material, which on glc investigation was shown to be predominantly starting material, with about 5% of the desired cyclised product (101) present.

(i) Amberlite IR-120(H) resin in water[58].

In a typical experiment, 8.6g.(35mmole) of the diketone (100) and 290ml. Amberlite IR-120(H) resin in 500ml. water were refluxed with rapid stirring to prevent bumping, for 90 hours. The resin was filtered off while hot, washed with 250ml. hot water, cooled and

washed with 4x50ml. portions of ether. The aqueous phase was extracted with ether (3x100ml.), the ether extracts combined, washed with brine, dried and evaporated to yield 9.0g. crude product. The crude product was chromatographed on 500g. silica with light petrol and ethyl acetate as eluants, to yield 6.0g. of 2,4-propano-1,2,3,4-tetrahydrofluoren-3-one (101), and 1.6g. of starting material. The yield of bicyclic ketone (101) is 94% based on the diketone (100) used, and 75% overall. The product melted at 94-5°C and was identical to that obtained from the ptsa/toluene reaction.

IR (CCl_4) : ν_{max} 1730, 1722, 1605cm^{-1}

NMR (CCl_4) : 2.6-3.0τ, m, 4H, aromatic; 6.5τ, m, 1H;

6.7τ, s, 2H, indene methylene protons.

Mass spectrum showed a parent ion at m/e 224.

2,4-propano-1,2,3,4-tetrahydrofluoren-3-one acetal (142).

270mg. of the ketone (101), 1g. ethylene glycol and 20mg. toluene p-sulphonic acid were dissolved in 250ml. benzene and refluxed with a Dean and Stark water separator for 21 hours. The reaction mixture was cooled, diluted with 100ml. ether, washed with water (3x), dried and evaporated to yield 330mg. crude product which was purified by column chromatography on 10g. silica. 314mg. (97%) pure 2,4-propano-1,2,3,4-tetrahydrofluoren-3-one acetal (142) was obtained (10% ethyl acetate:light petrol as eluant).

IR (CCl_4) : 3020 (w), 1630(w), 1605(w), 1130(m), 1105(s)cm^{-1}.

NMR : 2.5-2.9τ, m, 4H, aromatic; 6.0τ, m, 4H, acetal;

6.7τ, s, 2H.

MS : showed a parent ion at m/e 268 (base peak). Accurate mass measurement gave the mass as 268.1575; $C_{18}H_{20}O_2$ requires an accurate mass of 268.1582.

Oxidation of 2,4-propano-1,2,3,4-tetrahydrofluoren-3-one (101).

(a) with anhydrous sodium chromate[60].

25mg.(0.11mmole) of the ketone (101) were dissolved with stirring in 1.35ml. glacial acetic acid and 0.75ml. acetic anhydride and heated to 35-40°C in an oil-bath. 36.2mg.(0.22mmole) of freshly prepared anhydrous sodium chromate was added and the reaction stirred for 30 hours. 20ml. water was added and the reaction stirred for a further 5 minutes. The aqueous mixture was extracted with ether (3x) and the ether extracts combined, washed with satd. sodium bicarbonate solution and brine, then dried and evaporated to yield 27mg. material which was identical to starting material on glc (1%ES-30, 180°C, N_2 22psi, R_t=2.2mins), although tlc showed the presence of several more polar compounds in small quantities.

(b) with lead tetraacetate[61].

25mg. of the ketone (101) was added to 40mg. lead tetraacetate (wet with acetic acid) in 2ml. glacial acetic acid and stirred at 105°C for 5 hours. The reaction was stopped by addition of 10ml. cold water. The reaction mixture was extracted with ether (3x), the ether extracts combined, washed with satd. sodium bicarbonate solution and brine to neutrality, then dried and evaporated to

yield 24mg. material. Glc (1%SE-30, 180°C) showed approximately 95% starting material with 5% of a more polar compound (R_t=3.4mins; R_t of starting material=2.2mins), but no attempt was made to separate this material.

(c) with mercuric acetate.[62]

25mg.(0,11mmole) of the ketone (101) was added to 71mg.(0.22mmole) mercuric acetate in 5ml. glacial acetic acid and stirred at 100°C for 50 hours. The reaction mixture was cooled, poured into 10ml. water, and extracted with ether. The ether extracts were combined, washed with satd. sodium bicarbonate solution and brine, then dried and evaporated to give 22mg. material which was, by glc, identical with starting material.

(d) with N-bromosuccinimide[63].

25mg.(0.11mmole) of the ketone (101) in 0.5ml. carbon tetrachloride was added to 23mg.(0.13mmole) of N-bromosuccinimide in 1.0ml. carbon tetrachloride and refluxed for 6 hours. The reaction mixture was cooled, diluted with 10ml. ether, washed with water (2x), dried and evaporated to yield 38mg. material. This was chromatographed on silica and 2 bands extracted. All data on these compounds (ir, nmr, ms and uv) indicated that these were not the desired bromination product, and were not investigated further.

(e) with chromium trioxide-pyridine (Collins reagent)[64,71].

The chromium trioxide (AnalaR, 1g., 10mmole) was added in small portions to a magnetically stirred solution of anhydrous pyridine (1.6g., 17mmole) in 16ml. dry methylene chloride at 0°C. After 1 hour, a solution of 90mg.(4mmole) of the ketone (101) in 5ml. dry methylene chloride was added and the mixture stirred for 24 hours at room temperature. The supernatant liquid was decanted and the tarry residue extracted with boiling ethyl acetate. The combined washings were evaporated to small volume and the pyridine removed by co-distillation with benzene under vacuum. The residue in ethyl acetate was washed with 4N hydrochloric acid, water to neutrality and dried. Removal of solvent gave a yellow oil which was purified by preparative tlc to give 25mg. material (40% ethyl acetate:light petrol); R_f=0.5.

IR (thin film) 1730(s), 1710(s), 1670(m), 765(m,broad)cm^{-1}.

UV : (EtOH) λ_{max} 242nm, 301nm.

This was not the required oxidation product and was not investigated further.

(f) with sodium dichromate dihydrate[65].

The ketone (101), (24mg.,0.1mmole) in 5ml. glacial acetic acid was added to a stirred solution of sodium dichromate (57mg.,0.2mmole) in 2ml. glacial acetic acid and heated at 60°C for 3 hours. The reaction was stopped by addition of 10ml. water and extracted with ether (2x). The combined extracts were washed with satd, sodium

bicarbonate solution, brine to neutrality, dried and evaporated to dryness to yield 19.7mg. crude product. This was purified by prep. tlc. One band which stained with 2,4-dinitrophenylhydrazine spray was extracted to give 5mg. of a yellow crystalline solid, m.pt. 154-8°C, and was pure on glc analysis (R_t=3.6min., 1%SE-30, 180°C, N_2 22 psi).

UV (EtOH) λ_{max} 233nm(ϵ=4,460), 240nm(4,310), 308nm(9,520).

IR (thin film) ν_{max} 1730(broad), 1660cm^{-1}.

Found : C,80.49; H,6.03; $C_{16}H_{14}O_2$ requires C,80.65; H,5.92%.

Mass spectrum showed a parent ion at m/e 238.

This was the oxidation product (141), 2,4-propano-1,2,3,4-tetrahydrofluoren-1,3-dione.

(g) with selenium dioxide in ethanol[66].

The ketone (101), (25mg.,0.11mmole) was added to 25mg.(0.22mmole) selenium dioxide in 10ml. 95% ethanol, and refluxed for 24 hours. The selenium was filtered off, the filtrate dried and the solvent removed. Glc showed the presence of 3 compounds, at R_t= 1.0, 2.2, and 3.4 minutes.(1%SE-30,180°C, 22psi N_2). The peak at 2.2 minutes was starting material. The material at 3.4 minutes did not have the required uv spectrum[72], and by later comparison with known oxidation product (by glc), was not the required product.

(h) with selenium dioxide in acetic acid[61].

In a typical reaction, 1.0g.(4.5mmole) of the

ketone (101) was dissolved in 25ml. glacial acetic acid and added to a refluxing solution of 1.0g. (9.0mmole) of freshly sublimed selenium dioxide in 25ml. glacial acetic acid and refluxed for 30 minutes. The reaction mixture was flooded with 150ml. water and extracted with ether (5x50ml.). The combined ether extracts were washed cautiously with satd. sodium bicarbonate solution until evolution of gas ceased, then with brine to neutral pH. The ether solution was dried and evaporated to yield 1.4g. material, which was purified by column chromatography on silica, then preparative tlc to give 250mg. (25%) of 2,4-propano-1,2,3,4-tetrahydrofluoren-3,9-dione (102), (glc; 1%OV-1, glass column, 200°C, 22psi N_2, R_t=1.6min.), recrystallised from ethyl acetate, m.pt. 136-7°C.

IR (CCl_4) : ν_{max} 1738(s), 1732(s,shoulder), 1715(s), 1225(s) cm^{-1}.

NMR : 2.55τ, m, 4H; 6.2τ, broad singlet, 1H; 6.3τ, broad singlet, 2H; 6.75τ, m, 1H; 7.7-8.0τ, m, 4H; 8.2-8.5τ, m, 2H.

UV (EtOH) λ_{max} 239nm(ϵ=33,600), 246nm(43,300).

Ms showed a parent ion at m/e 238.

Found : C,80.69; H,5.98; $C_{16}H_{14}O_2$ requires C,80.65; H,5.92%.

Oxidation of 2,4-propano-1,2,3,4-tetrahydrofluoren-3-one acetal (142).

(a) with sodium dichromate dihydrate[65].

To 354mg.(2.4mmole) sodium dichromate dihydrate in

10ml. glacial acetic acid was added 317mg.(1.2mmole) of the acetal (142), in 10ml. glacial acetic acid, and the mixture refluxed for 2 hours. To the cooled reaction mixture was added 25ml. water, and the aqueous mixture extracted with ether (3x). The combined ether extracts were washed with water (1x), satd. sodium bicarbonate solution and brine, then dried and evaporated to yield 280mg. crude product, which was purified by preparative tlc (30% ethyl acetate:light petrol) to give 220mg. (143) as an orange oil.

IR (CCl_4) ν_{max} 1667, 1655(shoulder)cm^{-1}.

NMR : 2.6τ, m, 4H, aromatic; 6.05τ, m, 4H, acetal;
6.4τ, s, 2H; 6.85τ, m, 1H; 7.5τ, m, 1H.

MS showed a parent ion at m/e 282 and gave its accurate mass as 282.1248. $C_{18}H_{18}O_3$ requires a mass of 282.1256.

UV (EtOH) λ_{max} 309nm (ϵ=15,900), 241nm(12,700), 234nm (12,000).

(b) with selenium dioxide.

To 81mg.(0.7mmole) selenium dioxide (freshly sublimed) in 5ml. glacial acetic acid was added 94mg. (0.35mmole) of the acetal (142) in 5ml. glacial acetic acid and the mixture refluxed for 4 hours. The cooled reaction mixture was poured into 25ml. water and extracted with ether (3x). The ether extracts were combined, washed with water (1x), satd. sodium bicarbonate solution until evolution of gas had ceased, and brine to neutrality. The ether solution was dried and evaporated to give 90mg. crude product which was separated by

preparative tlc (30% ethyl acetate:light petrol).

Two compounds were obtained.

The first band at R_f=0.4 gave 28mg. of a yellow oil.

IR : $\nu_{max}^{CCl_4}$ 1735, 1715, 1240 and 1220cm^{-1}.

NMR : 2.7τ, broad m, 4H, aromatic; 6.0τ, broad singlet, 4H, acetal; 6.5τ, m, 1H; 7.2τ, m, 1H; 7.85τ, d, J=2Hz, 2H.

UV λ_{max}^{EtOH} 237.5nm(ϵ=26,100), 244nm(28,500).

Mass spectrum showed a parent ion at m/e 282.

This was thought to be the benzylic oxidation product (144).

The second band at R_f=0.25 gave 43mg. of an oily yellow solid.

NMR : ratio of aromatic to aliphatic protons is 4:12 but no signals were separable from the methylene and methine "envelope".

IR : $\nu_{max}^{CCl_4}$ 1740, 1715, 1665, 1215(broad)cm^{-1}.

UV : λ_{max}^{EtOH} 237.5nm(ϵ=20,000), 243.5nm(21,200).

The mass spectrum showed a parent ion at m/e 296.

This compound was thought to be the double oxidation product (145).

It was not possible to obtain pure samples of either oxidation product even after repeated preparative tlc.

<u>Attempted epoxidation of 2,4-propano-1,2,3,4-tetrahydro-fluoren-9-one-3-acetal (144)[23].</u>

To 46mg.(0.16mmole) of the acetal(144) dissolved in 1.4ml. methanol was added 0.22ml. 30% hydrogen peroxide and 0.1ml. 10% sodium hydroxide solution and the mixture

stirred at room temperature for 6 hours. The mixture was diluted with water and extracted with ether. The combined ether extracts were washed with 10% sodium metabisulphite solution (2x) and brine to neutrality. Drying and evaporation of solvent gave 40mg. of material which was identical with starting material (ir, nmr, ms).

Ring opening of 2,4-propano-1,2,3,4-tetrahydrofluoren-3,9-dione (102).

(a) with sodium ethoxide[37].

To 30mg.(0.12mmole) of the ketone (102) in 2ml. ethanol was added 17mg.(0.25mmole) sodium ethoxide in 6.5ml. ethanol and the mixture refluxed for 2 hours. The solution turned a deep red. After cooling, the ethanol was removed under reduced pressure and the residue dissolved in ether. The ether solution was washed with dilute hydrochloric acid, brine to neutrality, dried and evaporated to yield 28mg. material. Preparative tlc (40% ethyl acetate: light petrol) gave 7mg. of a yellow crystalline product which had a molecular weight of 256 (mass spectroscopy), plus some highly polar material.

IR : $\nu_{max}^{CCl_4}$ 3500(broad), 1725, 1715, 1610cm^{-1}

This was tentatively identified as the ring-opened acid (146), and was identical with the product obtained by treatment of the ketone (102) with sodium hydroxide in (b).

(b) with sodium hydroxide.

To 37mg.(0.15mmole) of the ketone (102) in 2ml. ethanol was added 12.2mg(0.3mmole) sodium hydroxide in 2ml. ethanol and the mixture refluxed for 2 hours. The solution turned red initially and darkened on refluxing. Work-up of the reaction was as in (a). 5mg. of starting material was recovered on preparative tlc (40% ethyl acetate:light petrol). A band at R_f=0.5 was collected which gave 10mg. of a white crystalline product and was identical (m.pt., ir, ms) with the product from (a) - the ring-opened acid (146).

(c) with sodium methoxide[37].

48mg. of the ketone (102) was dissolved in 10ml. methanol and 12mg. sodium methoxide in 3.5ml. methanol added. The mixture was refluxed for 2 hours, cooled and worked-up as in (a) to yield 15mg. of a product which was identical with that from (a) and (b).