ACID CATALYSED REACTIONS OF SOME CYCLOOCTYL AND ANISYL SYSTEMS.

A Thesis
presented for the degree of
Doctor of Philosophy
in the
Faculty of Science
of the
University of Leicester

by

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1974.

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This thesis is dedicated to

MY MOTHER and FATHER, and MY DEAR WIFE.

STATEMENT

The accompanying thesis submitted for the degree of Ph.D. entitled "Acid Catalysed Reactions of Some Cyclooctyl and Anisyl Systems" is based on work conducted by the author in the Department of Chemistry of the University of Leicester during the period between October, 1970 and August, 1973.

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

R. H. Green.

September, 1974.

ACKNOWLEDGEMENTS.

I wish to thank my supervisor, Dr. R.S. Atkinson, for his untiring help and encouragement throughout the course of the work described in this thesis.

I am very grateful to Mrs. N. Johnson for her patience in deciphering my writing and transforming it into this neatly typed copy.

For the provision of laboratory facilities I would like to thank Professor S. Trippett, and the University of Leicester.

I wish to acknowledge financial support from the Science Research Council and the University of Leicester Organic Sub-fund.

I could never hope to fully acknowledge the debt I owe to my parents for their financial and moral support during my university career. To my wife, Jenny, I owe a similar, inestimable, debt of gratitude.

CONTENTS.

Abbreviations Used in Diagrams.

Ac	Acetyl
Ar	p-Methoxyphenyl
Ar'	p-Hydroxyphenyl
Bros	p-Bromobenzenesulphonyl
Et	Ethyl
Me	Methyl
Mes	Methanesulphonyl
Ph	Phenyl
Tos	p-Toluenesulphonyl

NOTE

In all cases where a bicyclic structure is shown as a planar formula the bridging atom (or atoms) is considered to be on the β-face of the molecule.

1.1) Conformations of Medium Rings

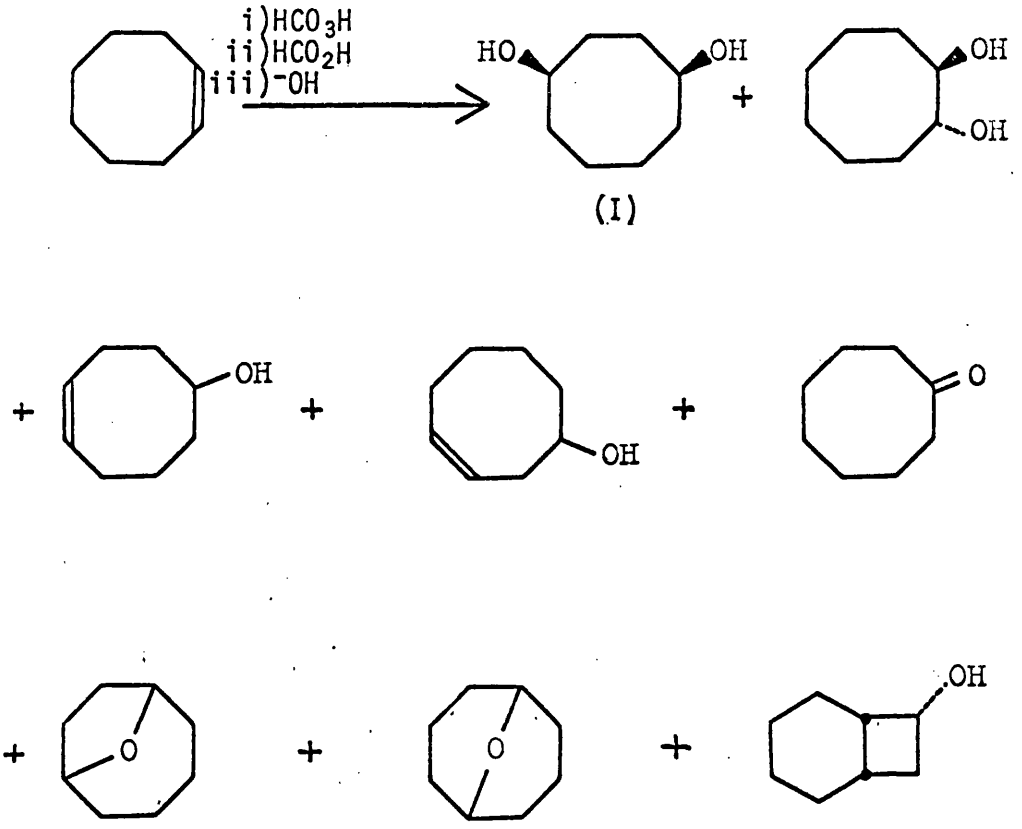
Acid-catalysed hydride shifts of an order greater than 1,2 in monocyclic systems were first noted in hydroxylation reactions of cyclooctene[1] and cyclodecene.[2] They are a consequence of the special geometry of these medium rings,[3] which causes opposite sides of the ring to come into close proximity.

Initially it was thought that this special geometry was due to a combination of destabilising forces, the most important of these being torsional strain and transannular interactions.[4] Early X-ray studies on these systems, however, indicated that they were virtually free of torsional strain.[5] The cyclooctane ring was shown to adopt a twist-boat-chair conformation in cyclooctane-cis-1,2-dicarboxylic acid,[6] cyclooctane-trans-1,2-dicarboxylic acid,[7] and dicyclooctanone peroxide.[8] Recent n.m.r. studies have shown that this is the predominant conformer in solution at low temperature for several cyclooctanes.[9] From the X-ray results the H-H 1,5 transannular contact distances were calculated,[10] and these implied a slight degree of overcrowding. These transannular interactions lead directly to the characteristic reactions of medium ring compounds.

1.2) Early Examples of Transannular Hydride Shifts

Transannular hydride shifts were discovered independently in

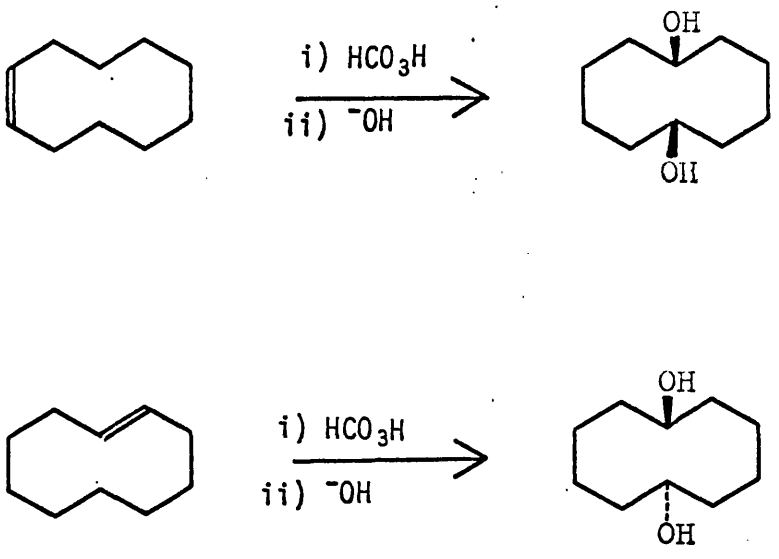
1952 by the groups of Cope[1] and Prelog.[2] Cope's group took cis-cyclooctene, hydroxylated it with performic acid, and after hydrolysis of the resulting formates, found that the major product was cyclooctane-1,4-diol (1). Further investigation of the reaction revealed the 1,4-diol produced to be the cis- isomer[11] and made a complete characterisation of the products possible (Scheme 1).[12]



Scheme 1

This showed that at least 40-45% of the products were derived by transannular hydride shifts.

Concurrently, Prelog found that when each separate isomer of cyclodecene was hydroxylated with performic acid and then saponified a stereospecific reaction ensued, giving only one stereoisomer of cyclodecane-1,6-diol (Scheme 2).[2]



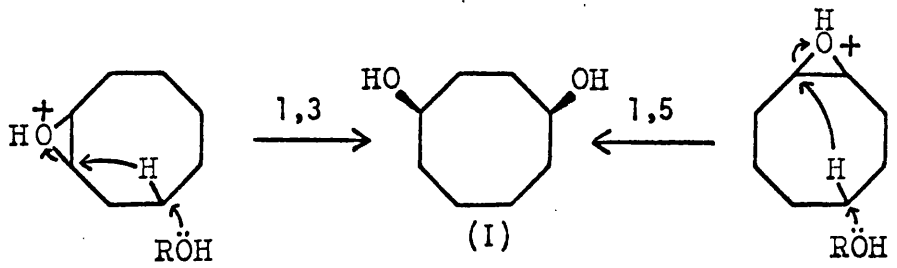
Scheme 2

The stereospecificity of the transannular reaction in these two cases has been explained by Prelog and Traynham:[13] normal reaction is prevented because the carbonium ion produced by opening of the epoxide ring is projecting into the centre of the ring system and is very close to the transannular hydrogens, nucleophilic attack directly on the cation is thus inhibited and the reaction is stereospecific in a transannular S_N2 type of reaction.

1. 3) Transannular Hydride Shifts in Isotopically Labelled, Mono-substituted Medium Rings.

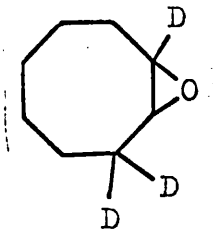
The hydroxylation of cyclooctene by transannular reaction could

be rationalised by either a 1,3, or a 1,5 hydride shift, or both (Scheme 3). Accordingly, 5d,6d-cyclooctene oxide was prepared and



Scheme 3

hydroxylated and the 1,4-diol and the cyclooct-3-en-1-ol produced were degraded to obtain an estimate of the relative amounts of 1,3 and 1,5 hydride shifts.[14] This showed that the diol was produced by 39% 1,3 and 61% 1,5 hydride transfer. The cyclooct-3--en-1-ol, however, was produced by 94% 1,5 hydride transfer, and only 6% 1,3 transfer. These differing amounts of 1,3 and 1,5 hydride transfer established that the alkene is not formed by dehydration of the diol. A study of the temperature dependence of the n.m.r. spectrum of the related deuterated cyclooctene oxide (2) appeared to



(2)

indicate that it existed in two major conformations, each conformation

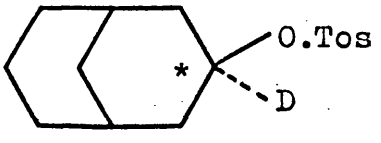
providing a transannular hydrogen in close proximity to a developing cation at C_1 or C_2.[15] The facility of the hydride shifts could thus be readily explicable.

The varying relative amounts of 1,3 and 1,5 hydride shift in the two cases cited is still obscure. It has been suggested that the 1,3 hydride shift is an unusual transannular reaction, and that its occurrence in the production of the cis-1,4-diol is entirely due to the distorted geometry of the cis-cyclooctene oxide.[27]

An extensive study has been made of the solvolysis of ^{14}C labelled cycloalkyl tosylates of ring sizes 7 and 9-12.[16] This showed that, while the C_{12} tosylate gave no transannular reaction and the C_7 tosylate only gave a very small amount, the C_9 - C_{11} tosylates solvolysed to a considerable extent by transannular reaction.

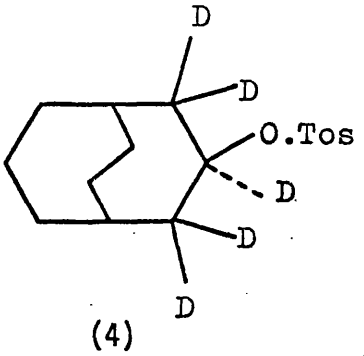
In the solvolysis of simple medium ring tosylates, products derived from transannular reaction are never the sole products. For example, in the solvolysis of 1,2,2,8,8-d_5 -cyclooctyl brosylate, hydride shifts occurred to the extent of 53% for acetolysis, 60% for formolysis, and 62% for trifluoroacetolysis.[17] This percentage drops markedly in the solvolysis of the doubly labelled exo-bicyclo[3.3.1]nonyl-3-tosylate (3)

* ≡ ^{14}C



(3)

a system which incorporates a cyclooctyl ring with the same degree of proximity of transannular hydrogens as a simple cyclooctyl ring. Acetolysis gave 3.56% 1,5 hydride shift, and solvolysis in aqueous acetone gave only 0.46% hydride shift.[18] In contrast to this, solvolysis of the less constrained system (4) gave a lower limit of 42%



(4)

1,5 hydride shift.[19] This apparent anomaly was later explained by postulating that the rate of elimination in the bicyclo[3.3.1]nonyl tosylate (3) may be greater than the rate of transannular reaction because of the relief of strain in the transition state for elimination.[20]

1. 4) Transannular Hydride Shifts in Di-Substituted Cyclooctanes

Transannular hydride shifts are considerably facilitated by electron donating substituents at the migration source. This is because a more stable tertiary ion is formed as the reaction proceeds. Cis- and trans- isomers of several 5-substituted cyclooctyl tosylates have been prepared and solvolysed and in all cases the cis- isomer

underwent much more 1,5 hydride shift than the trans- isomer; 1,3 hydride shift providing a very minor pathway. The collated results are shown in Table 1.

Table 1

Ref.		Products via 1,5 hydride shift (%)	Normal products[d] (%)	Solvolysis medium
21	a (R=cis-t-C_4H_9	99	-	ACOH/ACO$^-$
	(R=trans-t-C_4H_9	10-12	88-90	
22	b (R=cis-CH_3	89.8	9.7	ACOH/ACO$^-$
	(R=trans-CH_3	14.0	84.1	
23	c (R=cis-C_6H_5	81.2	13.8 (+ product derived from 1,2 shift = 2.5%)	HCO_2H/HCO_2^-
	(R=trans-C_6H_5	19	57.9 (+ product derived from 1,2 shift = 18.8%).	

NOTES (a) These figures are from the later paper by Allinger and Szkrybalo and refer to acetolysis of pure tosylates. The assignment of stereochemistry of the starting materials was based upon the relative amounts of hydride shift product for each isomer.

(b) Prepared stereospecifically from bicyclo[3.3.1]nonan-9-one

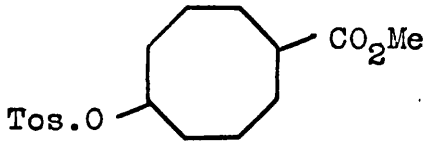
(c) Stereochemistry proved by stereospecific synthesis

(d) Total of elimination and displacement products.

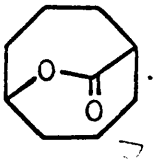
The most dramatic effect was seen in the solvolysis of cis-5-t-butyl-cyclooctyl tosylate, where 99% of the product was formed by a 1,5

hydride shift. In contrast, the trans- isomer gave only 10-12% transannular product. Measurements of the relative rates of these acetolyses showed that the cis- isomer solvolysed 53 times faster than the trans- isomer. This was interpreted as a neighbouring group effect in the acetolysis of the cis- isomer, with the migrating hydride ion participating in the ionisation of the C-tosyloxy bond. Later results, however, suggested that this rate difference was due only to relief of strain in the transition state of the solvolysis.

Transannular hydride shifts can also be inhibited by the presence of a suitable substituent at the migration source. Acid treatment of cyclooctanes (5)[24] and (6)[25] gave no products of 1,5 hydride shift, and

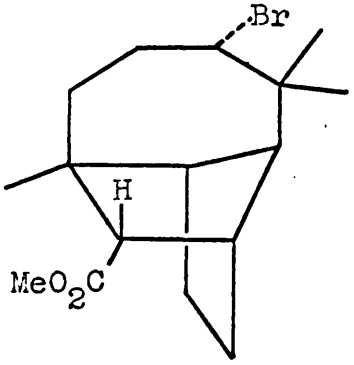


(5) cis and trans

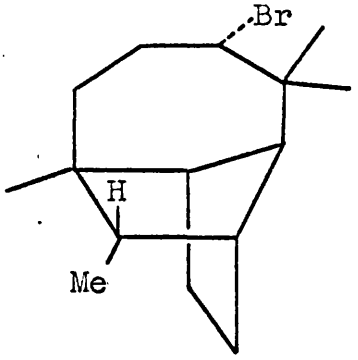


(6)

a similar effect was seen in the solvolysis of the longifolane (7).[26] The 7-methyl derivative (8) solvolyses with transannular hydride shift, and the 7-carbomethoxy derivative (7) undergoes preferential ring contraction.



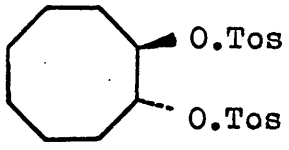
(7)



(8)

Substitution of the 3-position of a cyclooctyl tosylate by an electron donating t-butyl group, however, does not increase the amount of 1,3 hydride shift product; only about 1% of 1,3 hydride shift being seen.[27] This appears to confirm the postulate that such hydride shifts are an uncommon transannular reaction.

Substitution of a suitable group at the 5- position of a cyclooctyl ring increases the proportion of hydride shift product because it stabilises the incipient cation formed by such hydride shift. A similar enhancement of the proportion of transannular product can be achieved by destabilising the initially formed cation with electron withdrawing groups in the α-position. This was shown by solvolysing the 1,2-ditosylates (9 and 10).[28] The destabilising effect of the tosyloxy group adjacent to the initial cation caused the solvolysis to proceed in such a way that all the products could have been formed



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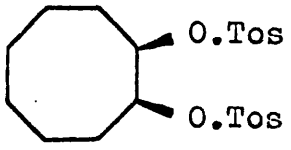


(10)

by 1,5 hydride shift. As a corollary to this result it was shown that solvolysis of the isomeric 1,4-ditosylate gave no transannular reaction.[28] From these results it was concluded that transannular hydride shifts will only occur if the "resulting cation is more stable than the first formed cation".[29]

Related work on the solvolysis of trans-2-hydroxycyclooctyl bromide and its related tosylate, and cyclooctyl bromide and cyclooctyl tosylate has been published.[30] The hydroxyl group was observed to have no effect upon the amount of transannular reaction occurring. This was rationalised by proposing that the destabilising effect of the hydroxyl group upon the neighbouring cation was balanced by the ability of the substrate to disperse charge by hydroxyl group participation. 1,2-Disubstituted cyclooctyl compounds have also been used to demonstrate the sensitivity of hydride shifts to the reaction conditions. By varying the reaction conditions from typical Sn2 to typical Sn1 the same compound can be made to undergo either normal, or transannular, reaction.[31] The amount of hydride shift occurring

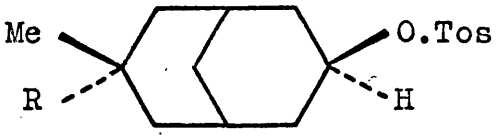
can also be dependent upon the particular acid used in acid catalysed reactions.[32] It has been suggested that for a given series of acids used to catalyse hydride shifts, the proportion of hydride shift product becomes greater as the nucleophilicity of the acid decreases. The ionising power of the medium was also thought to be important, low ionising power being associated with inhibition of hydride shift.

1. 5) Mechanism of Transannular Hydride Shifts.

Despite a considerable body of work the detailed mechanism of transannular hydride shifts is still uncertain. It is generally accepted that there is an optimum distance between the migration source and terminus for transannular hydride shift. Little consideration has been given, however, to the possible influence of stereoelectronic factors such as the orientation of the lobe of the carbonium ion to the C-H bond of the migrating hydride ion. The importance of such factors in the case of 1,2 hydride shifts has been convincingly demonstrated.[33]

The mechanistic detail which has aroused most controversy has been that of hydride assistance in the rate-determining step of the transannular migration. Studies of the solvolysis rates of the isomers of 5-phenylcyclooctyl tosylate and the corresponding 5-p-methoxyphenyl tosylates showed little difference between the rates of corresponding isomers and indicated no detectable assistance to solvolysis.[34] Most of the evidence for, and against, hydride assistance to solvolysis has been based upon studies of kinetic isotope effects.

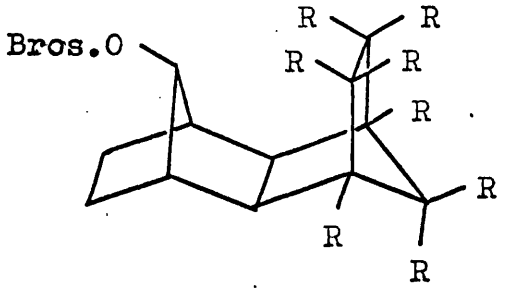
Cyclodecyl tosylate and its 5,5,6,6-d_4 analogue, upon solvolysis, showed no significant kinetic isotope effect ($\frac{k_H}{k_D}$ = 1.02)[35] and an identical low isotope effect was found in the acetolysis of 3,3,4,4,5,5,6,6,7,7-d_{10}-cyclooctanol.[36] These figures indicated little or no hydride assistance. Similar studies of the solvolysis rates of the bicyclo[3.3.1]nonane tosylates (11, R = H or D), showed



(11)

no detectable kinetic isotope effect.[37] All these studies, supported by the results on the effect of the reaction medium,[31,32] indicated the transient formation of a cation in a slow, rate-determining step, followed by rapid transannular migration of hydride.

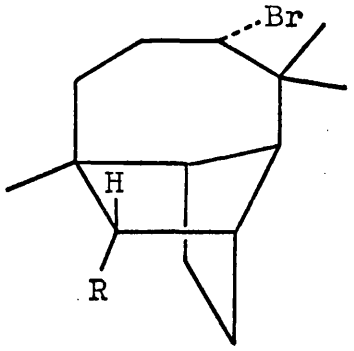
A rare case of a 1,5-shift where a significant kinetic isotope effect has been observed is the solvolysis of the brosylate (12).[38]



(12)

A kinetic isotope effect of $\frac{k_H}{k_D} = 1.24$ was found upon solvolysis of (12, R = H) and (12, R = D), and this, in conjunction with other factors, was taken as convincing evidence that hydride assistance to solvolysis had taken place.

A different approach to the study of hydride assistance in transannular hydride migration was adopted by Ourisson and his co-workers.[39] Theymeasured the rates of solvolysis of 3-bromo-longifolanes variously substituted at the migration source (13) and then plotted these results

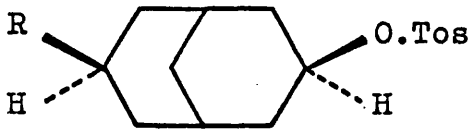


(13)

R = C≡N = CH_2OMe
= CO_2Me = CH_2OH
= C≡C.Cl = Me
= CH_2Br = Et
= CH_2I

against the Taft-Hammett parameters (σ^*)[40] for each of the substituents. If a straight line graph had resulted this would have implied that the only factor affecting the rate of reaction, whether it be ring contraction or hydride shift, was the inductive effect of the substituent. Any major deviation from a straight line would indicate that each type of reaction had separate rate-determining steps, and that ionisation of the C-Br bond was not a common rate-determining step. The results

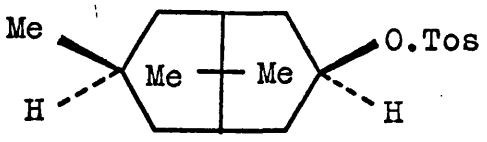
they obtained showed that the inductive effect of the substituent was not the only factor affecting the rate and implied a direct involvement of the migrating hydride ion in the rate-determining step. This approach was extended to a limited series of 7-substituted bicyclo[3.3.1]nonane-3-tosylates (14) and similar results were found,



R = C ≡ N
= CO_2Me
= CH_2OMe
= Me

(14)

although they were quantitatively less striking.[41] This was to be expected since the bicyclo[3.3.1]nonane skeleton is more flexible than that of longifolane, and the molecule flexes in such a way as to increase the distance between the migration termini at C_3 and C_7.[42] This will decrease the propensity for migration of the hydride ion. The importance of this effect was shown in the following paper on the solvolysis of the bicyclo[3.3.1]nonane (15).[43] The rate of solvolysis of this compound



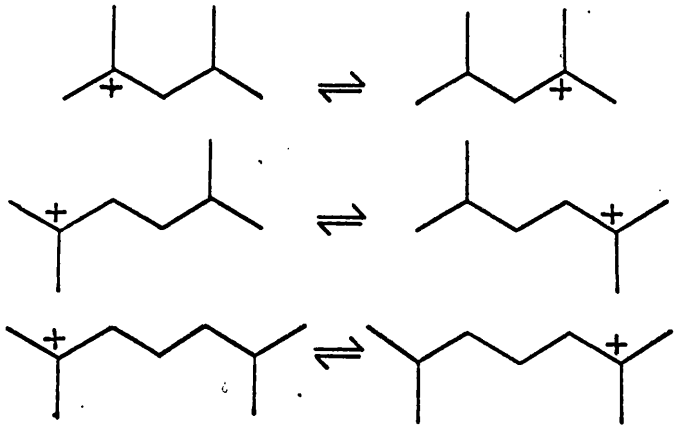
(15)

was four times higher than its non-geminally substituted analogue (14, R = CH_3). Furthermore it gave complete transannular hydride transfer, in contrast to the 55% transfer observed for (14, R = CH_3). This is the expected result, as the 9,9-dimethyl group on the bridge should "fix" the conformation and provide a conformationally unambiguous molecule, as in longifolane.

Ourisson's conclusions thus run contrary to many of the previous results obtained by studies of kinetic isotope effects. They explain this by reference to postulates by Hammond[44] and Westheimer[45] which show that, in any case where the intermediate ion in the hydride shift process is likely to be dissymetric, a low isotope effect would not necessarily preclude participation by the hydride ion. While this argument could be supported by most of the available results, it does not explain the very low isotope effects observed in the solvolyses of cyclodecyl[35] or cyclooctyl[36] tosylates where symmetrical, intermediate, ions would be expected. In view of this disparity it would be interesting to see Ourisson's method of studying hydride shifts applied to a series of differently 5-substituted cyclooctyl compounds. This may show whether hydride assistance to solvolysis is restricted to sterically congested systems, or whether the amount of hydride assistance varies with the system in hand.

Traynham and Foster made a study of the amounts of hydride shift in intimate ion pairs and in solvent-separated ion pairs.[46] By studying the chlorinolysis of cyclooctyl and cyclodecyl-2,4-dinitrobenzene sulphonates they concluded that transannular hydride shifts occur to about the same extent in either ion-pair species.

The activation energies of 1,3, 1,4, and 1,5 hydride shifts in simple acyclic systems have been determined by a variable temperature n.m.r. study.[47] The results are shown in Scheme 4.



E_A (kcal.mole^{-1})
8.5 ± 0.1
12-13
6 - 7

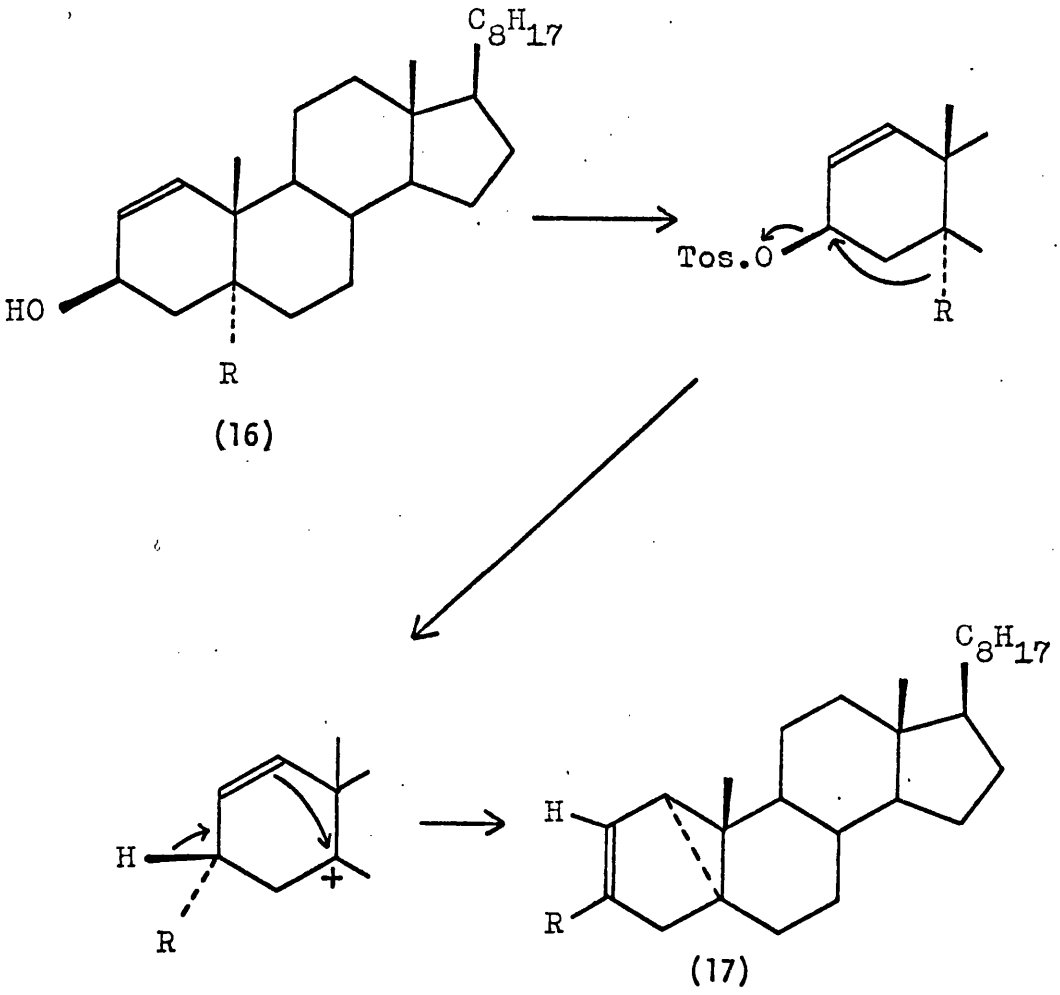
Scheme 4

1. 6) Examples of Hydride Shifts

The relative orders of magnitude of the energy barriers to 1,3 1,4 and 1,5 hydride shifts are reflected in the numbers of examples in the chemical literature. While there are many examples of 1,5 (and 1,6) hydride shift, only very few definitive examples of 1,4 hydride shift exist. Several excellent reviews have appeared on transannular hydride shifts.[48] Consequently, only a selection of the latest examples will be discussed.

1,3 Hydride Shifts

In 1968 Laing and Sykes reported a 1,3 hydride shift in the cholestenol (16, R = H) which was initiated by attempted tosylation of the alcohol.[49] (Scheme 5). Under the reaction conditions the



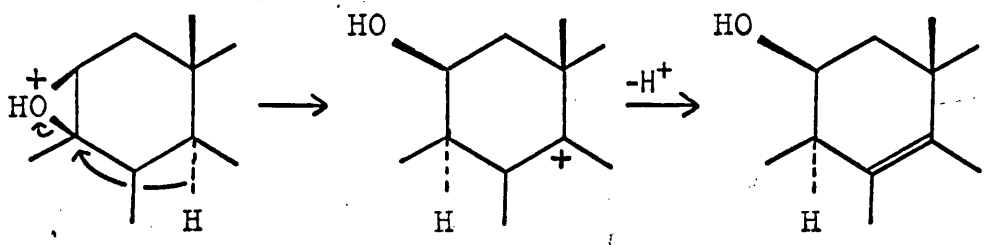
(16)

(17)

Scheme 5

tosylate was unstable and immediately rearranged to the cyclosteroid (17). Rearrangement of the deuteriated analogue (16, R = D) proved the reaction to have proceeded by 1,3 hydride shift only.

Acid catalysed fragmentation of the epoxide group in 9β,11β-oxido-Δ^4-pregnene-17α,21-diol-3,20-dione-21-acetate was reported to proceed by 1,3 hydride shift (Scheme 6).[50] Although this was not proved by deuterium labelling, the structure of the product was



Scheme 6

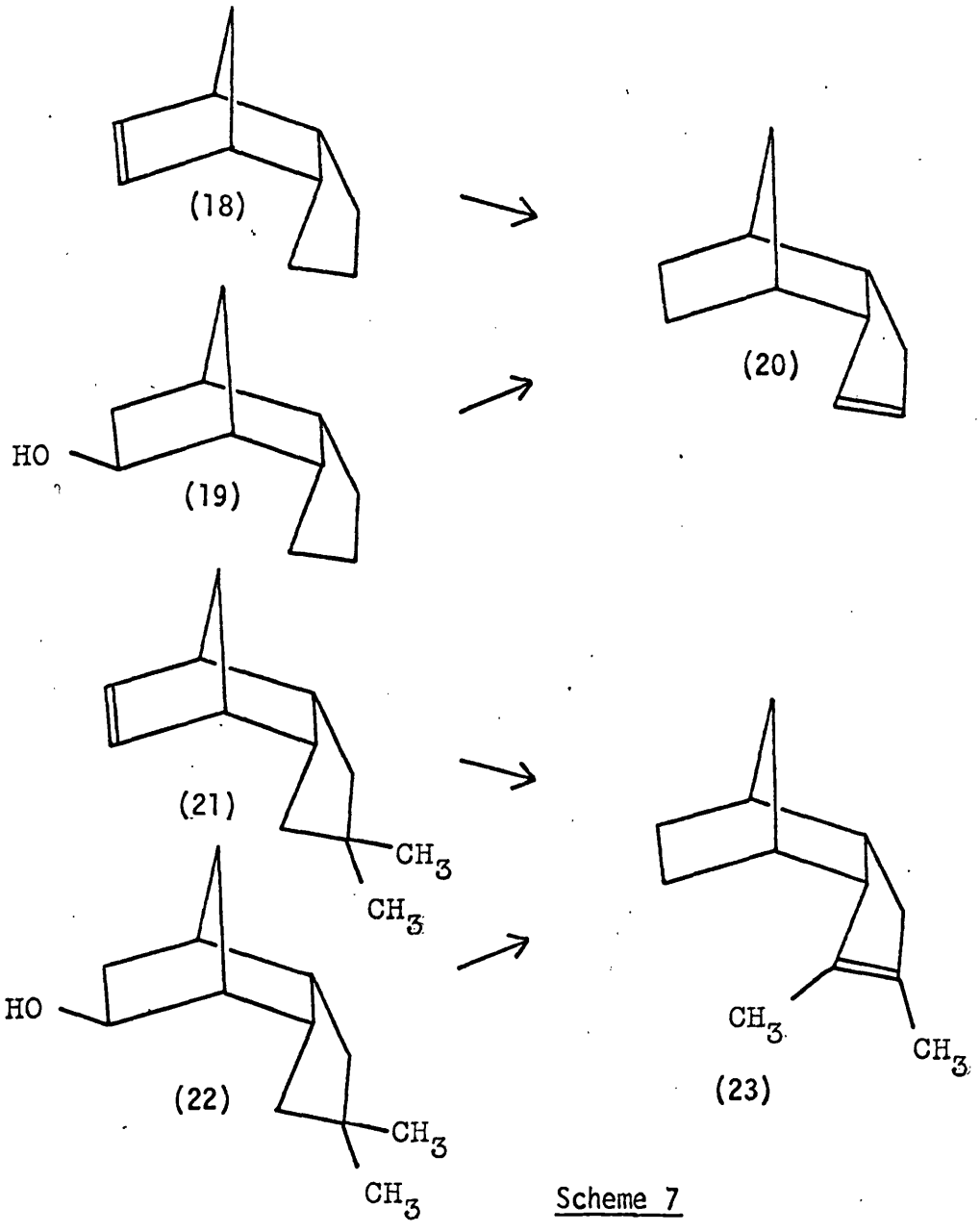
conclusively proved by degradation.

Other examples of 1,3 hydride shifts can be found in the acid catalysed isomerisation of kaurene[51] and in the solvolyses of the tosylate and brosylate of 1-hydroxymethylbicyclo[3.3.1]nonane.[52]

1,4 Hydride Shifts

1,4 Hydride shifts catalysed by acid or base are extremely rare reactions. From the available examples it is clear that the major requirement for such a shift is extreme proximity to the cationic centre.

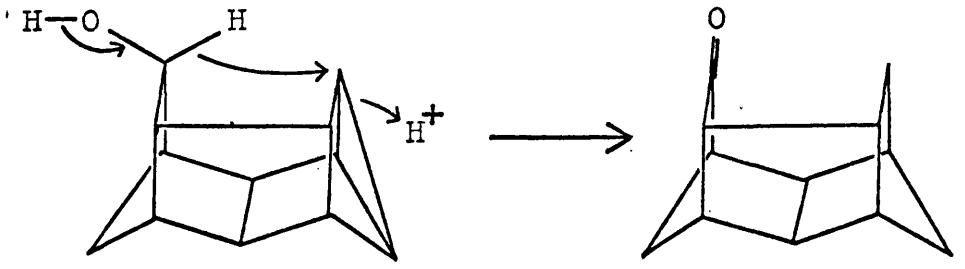
1,4 Hydride shifts were observed in the rearrangements of some dihydrodicyclopentadienes (Scheme 7).[53] The endo-fused isomers (18 and 19) (and their exo-fused isomers) were shown to give 25% of the 1,4 shift product (20), and 67% of the exo isomer, which



Scheme 7

can be produced by processes not involving 1,4 hydride shift. The gem-dimethyl analogues (21 and 22) gave 85% rearranged product (23). Studies of the reaction at high dilution (10^{-3} - 10^{-4}M) and analysis of the product ratios showed that these rearrangements proceeded by intramolecular paths, and the endo-fusion of the products implied an intramolecular 1,4 hydride shift.

Rearrangement completely by 1,4 hydride shift was observed when the cyclopropane half-cage alcohol (24) was treated with dilute



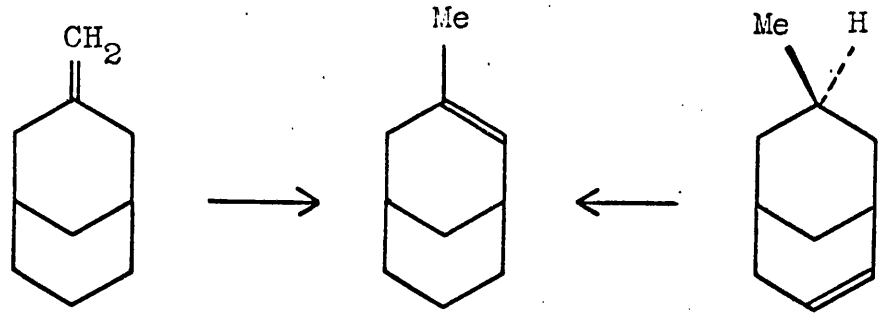
(24)

acid.[54] Although no proof was provided of the intramolecularity of this reaction, the extreme steric congestion of the molecule makes such intramolecularity extremely likely.

Examples of base catalysed 1,4 hydride shifts have also been reported.[55,56]

1,5 Hydride Shifts.[57]

A simple example of a 1,5 hydride shift was provided by the work of Appleton and Graham.[58] The bicyclo[3.3.1]nonanes (25 and 26) were separately equilibrated with boiling formic acid to an equilibrium mixture of 93% (27) and 7% (26) (Scheme 8). The trisubstituted alkene (27) is produced from (25) by a prototropic shift, and from (26) by protonation and 1,5 hydride shift.

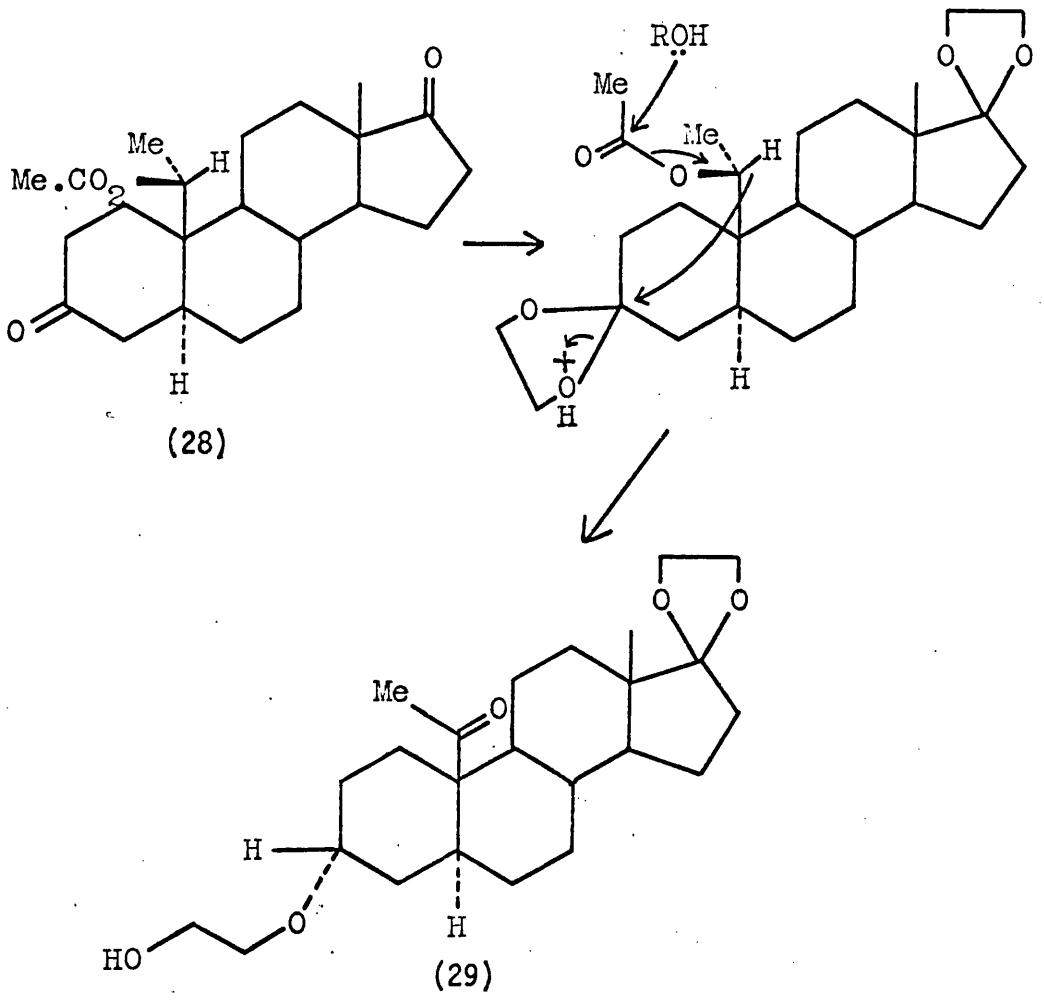


(25) (27) (26)

Scheme 8

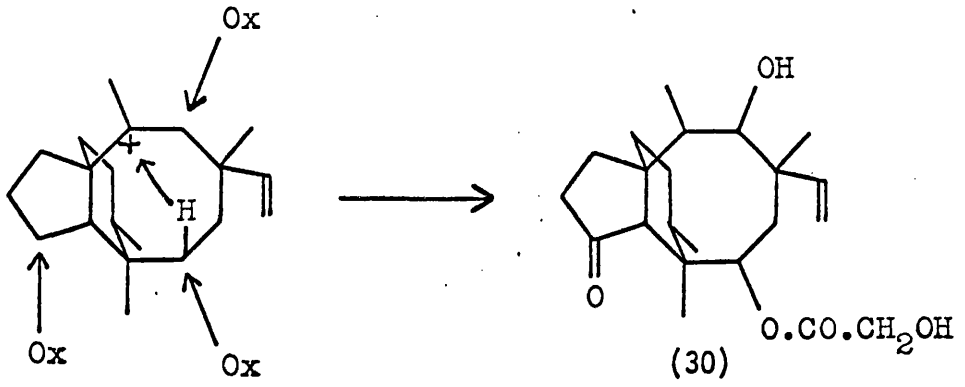
1,5 Hydride shifts in more complex systems have been reported, for example, those by Wicha and Caspi, and Arigoni and co-workers.

The earliest paper by Wicha and Caspi[59a] concerned a rearrangement observed when a bis-ketalisation of (28) was attempted. The major product was the expected bis-ketal, but an additional component was observed (13%) which proved to have the 10-acetyl structure (29). This was rationalised as formation of the bis-ketal, and then the breaking open of the 3-ketal by a 1,5 hydride shift (Scheme 9). A similar rearrangement was observed when the des-acetyl derivative was treated with alcoholic potassium hydroxide,[59b] and definitive proof of the 1,5 hydride shift was obtained by deuterium labelling.[59c]



Scheme 9

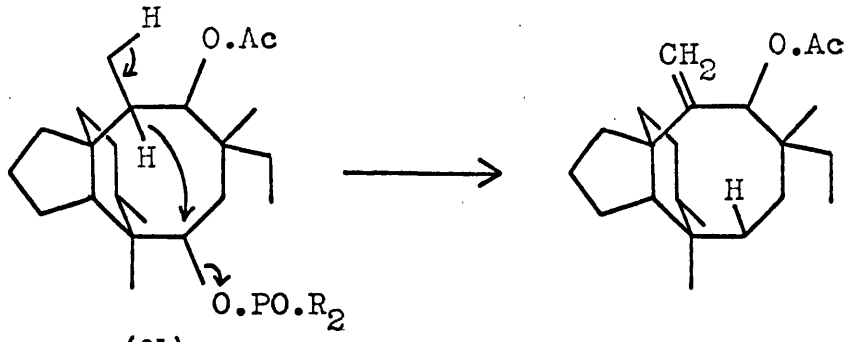
The concluding stages of the biosynthesis of the natural product pleuromutilin (30) were thought to involve a transannular hydride shift (Scheme 10).[60] By a considerable amount of meticulous work with stereospecifically labelled substrates this hypothesis was proved, and the stereochemistry of the process was also elucidated. In the course of this work a transannular



(30)

Scheme 10

dehydration of the alcohol (31) was noted upon treatment with phosphorus oxychloride in pyridine.

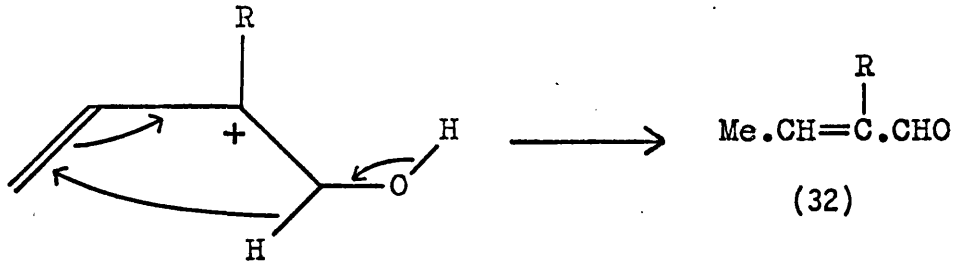


(31)

1,4 and 1,5 Hydride Shifts in Acyclic Systems

Few examples exist of 1,4 and 1,5 hydride shifts in acyclic systems. This is not surprising, since it is only in a few conformations that such hydride shifts can occur.

Karabatsos and his co-workers showed that in the deamination of deuterium labelled 1-amino-butane an upper limit of 2 - 3% 1,3 hydride shift occurred, and no 1,4 hydride shift was observed. A 1,4 hydride shift was suggested for the formation of (32) (Scheme 11) as an alternative to 1,2 hydride shift followed by prototropic

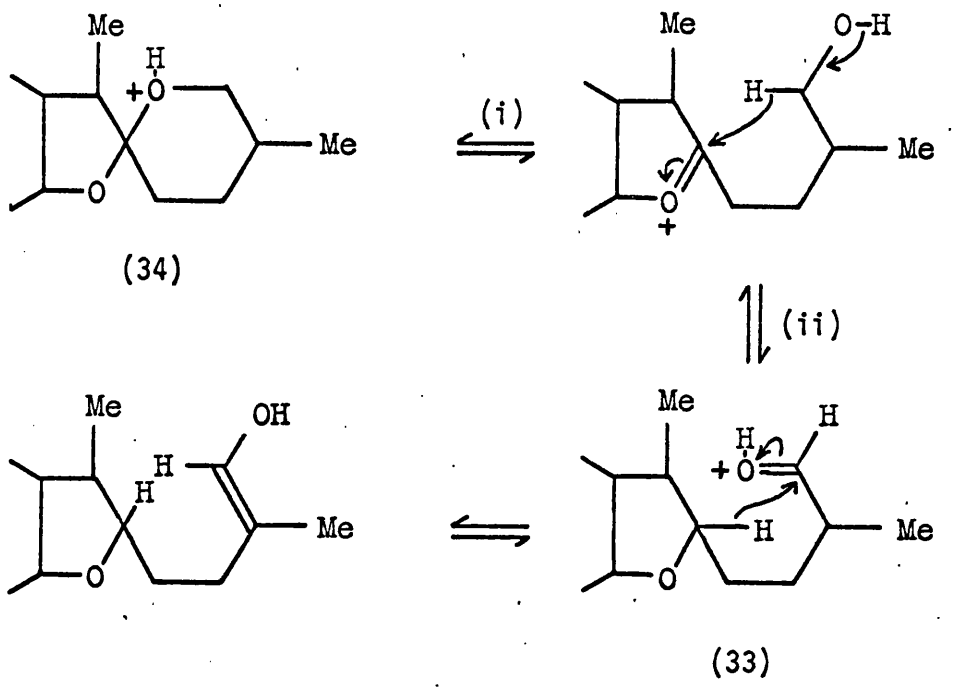


(32)

Scheme 11

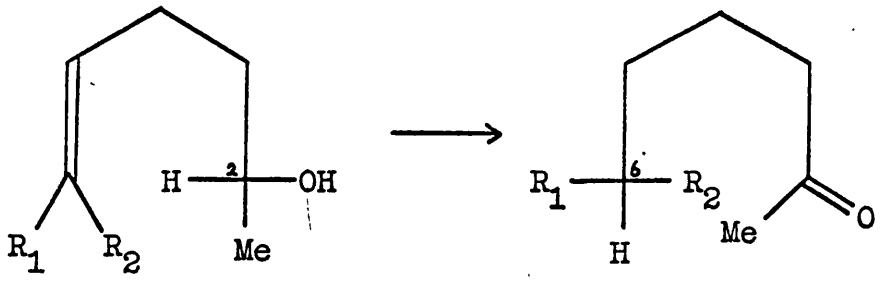
rearrangement.[62] However, in view of the rarity of 1,4 hydride shifts and the lack of definitive proof, this example must be regarded as very dubious.

The first example of a 1,5 hydride shift in a flexible acyclic system was reported in 1958 to explain the acid catalysed isomerisation of steroidal sapogenins (Scheme 12).[63] Indirect proof of this process was obtained by taking dihydrotigogenin aldehyde (33) and equilibrating it with acid. This gave tigogenin (34), as would be expected by a process involving steps (ii) and (i).



SCHEME 12

In 1963 Colonge and Brunie[64] reported two cases of isomerisation of 5-hydroxyolefins by acid (Scheme 13). They did not attempt to



(35) $R_1 = R_2 = Me$ (36) $R_1 = R_2 = Me$

(37) $R_1 = Ph$, $R_2 = Me$ (38) $R_1 = Ph$, $R_2 = Me$

SCHEME 13

elucidate the mechanism, however, merely listing 1,5 hydride shift as one possibility. That this reaction proceeded by a 1,5 hydride shift was proved by Hill and Carlson.[65] When (35), labelled in the 2-position with deuterium, was heated with polyphosphoric acid the ketone (36) was obtained which was specifically labelled with deuterium in the 6-position. Cross-over experiments with mixtures of alcohols 2-d-(35) and (37) led to the conclusion that the hydride shift was intramolecular, and could therefore be recognised as proceeding through a six-membered transition state. As this reaction proceeded through such a transition state, it was suspected that the reaction might be stereoselective. This was confirmed by carrying out the reaction with the S(+) enantiomer of (37) which produced (38) with an optical purity of 15%. This is consistent with a "chair" transition state, (Fig 1) with the substituent groups in the sterically most favourable positions.

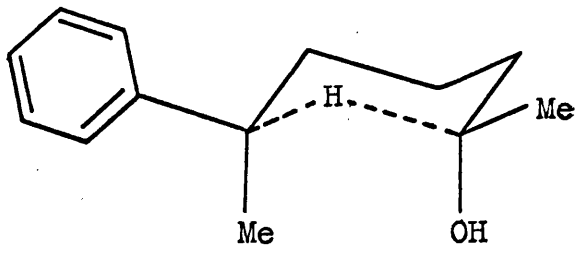
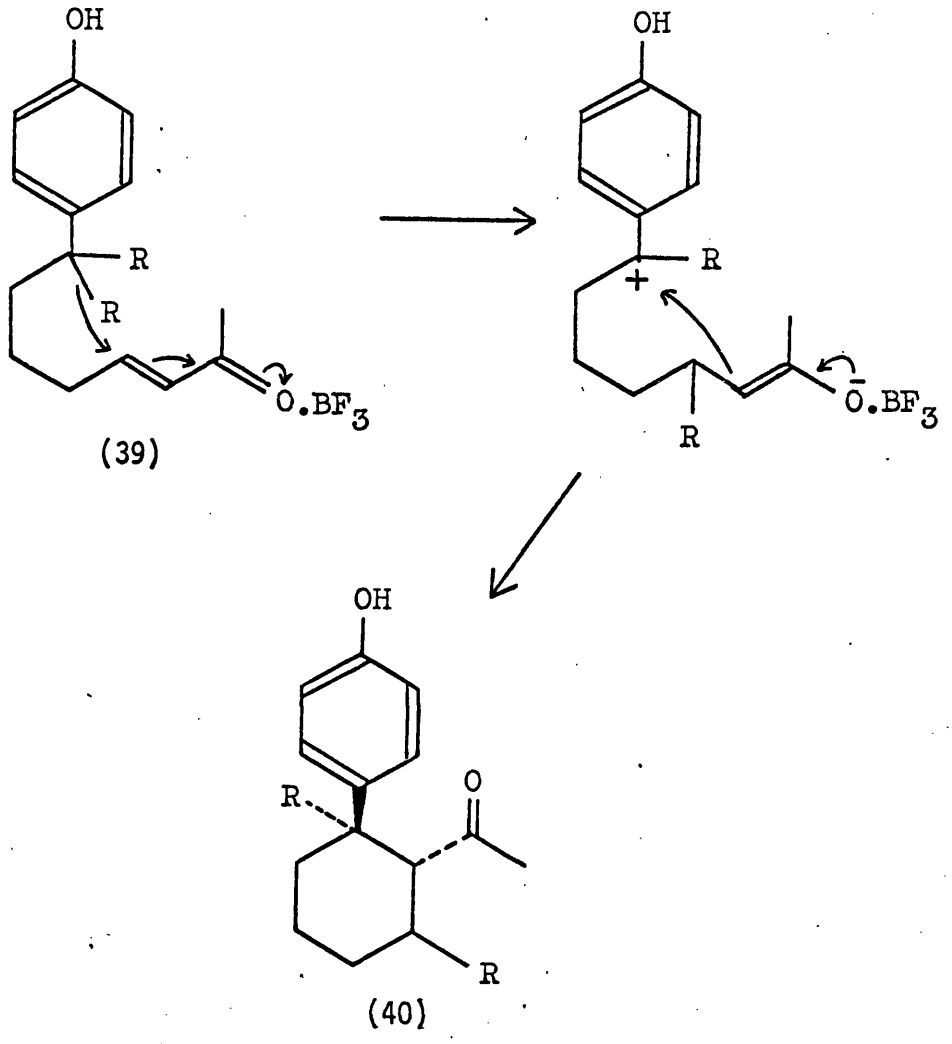


Fig. 1

The paper which initiated some of the work in the following chapter described the rearrangement of the α,β-unsaturated ketone

(39, R = H) to the cyclohexyl methyl ketone (40, R = H)[66] (Scheme 14), whose structure was proved by comparison with an authentic sample



(39)

(40)

Scheme 14

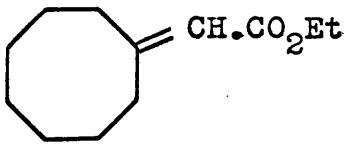
prepared by an alternative route. The suggested mechanism (involving a 1,5 hydride shift to produce a more stable cation, followed by dipolar ring closure) was proved by reacting (39, R = D) and determining the positions of the deuterium label in the product (40, R = D)

by mass spectral analysis. Cross-over experiments with a mixture of (39, R = H) and (39, R = D) showed the reaction to be intramolecular.

2.1) Hydride Shifts in Cyclooctylidene Systems

Formation of 9-aza- or 9-oxabicyclo[3.3.1]nonanes by intramolecular trapping of cyclooctyl radicals or cations is a well documented reaction.[67] It has been shown that the lead tetraacetate oxidation of cis- and trans-4- and 5-phenylcyclooctanols gives bicyclic ethers as major products.[68] Trans-5-phenylcyclooctanol, for example, gives 72% of 1-phenyl-9-oxabicyclo[3.3.1]nonane.[67a]

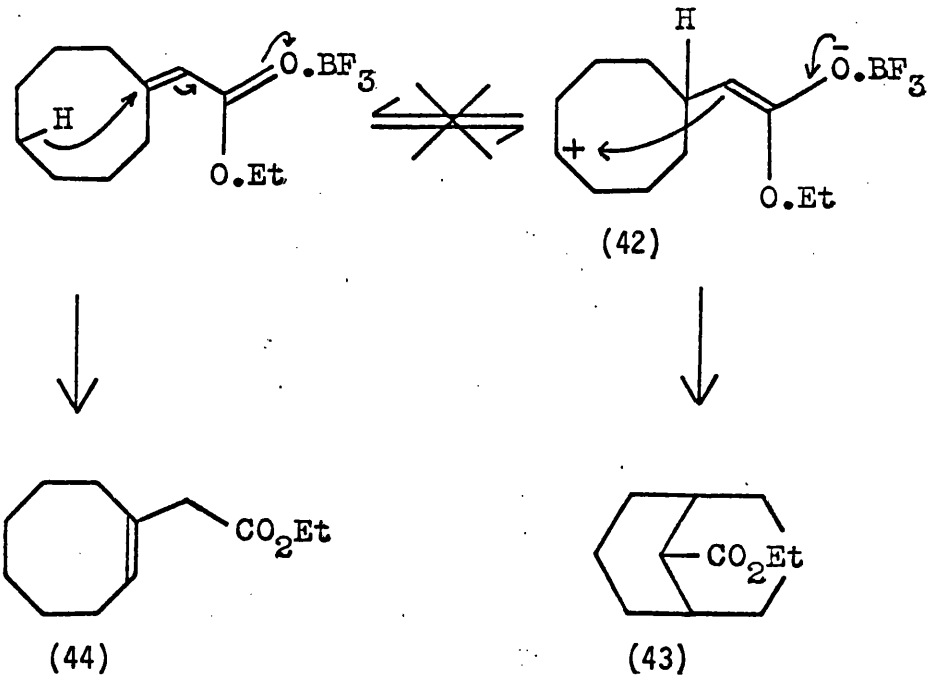
At the outset of this work the intramolecular trapping of a cyclooctyl cation by an enolate anion was considered. To test the plausibility of this reaction, ethyl cyclooctylidene acetate (41) was



(41)

prepared and reacted with boron trifluoride etherate, a mild Lewis acid. It was hoped that an initial 1,5 hydride shift would be followed by fast dipolar ring-closure, thus trapping out a small concentration of the cyclooctyl cation (42), to give 9-carboethoxybicyclo[3.3.1]nonane (43) (Scheme 15)

In the event this reaction only gave deconjugated starting material (44), even under forcing conditions. Treatment of the isomer of the ester (44) with toluene p-sulphonic acid in refluxing

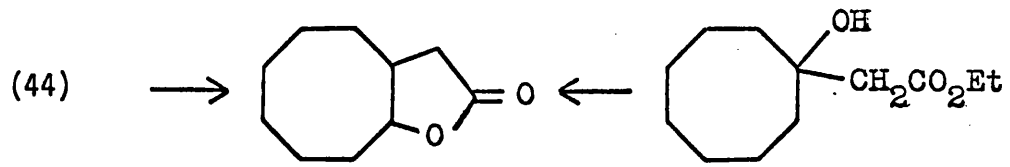


(42)

(44) (43)

Scheme 15

benzene for four days gave, as the only product isolated (31%), the lactone (45). The same lactone was prepared by brief treatment of ethyl 1-hydroxycyclooctaneacetate (46) with 70% sulphuric acid. This lactone structure was based on spectroscopic evidence, in particular the position of the C=O absorption band in the i.r. (1780 cm^{-1}). While the spectroscopic properties and analysis correspond to the structure



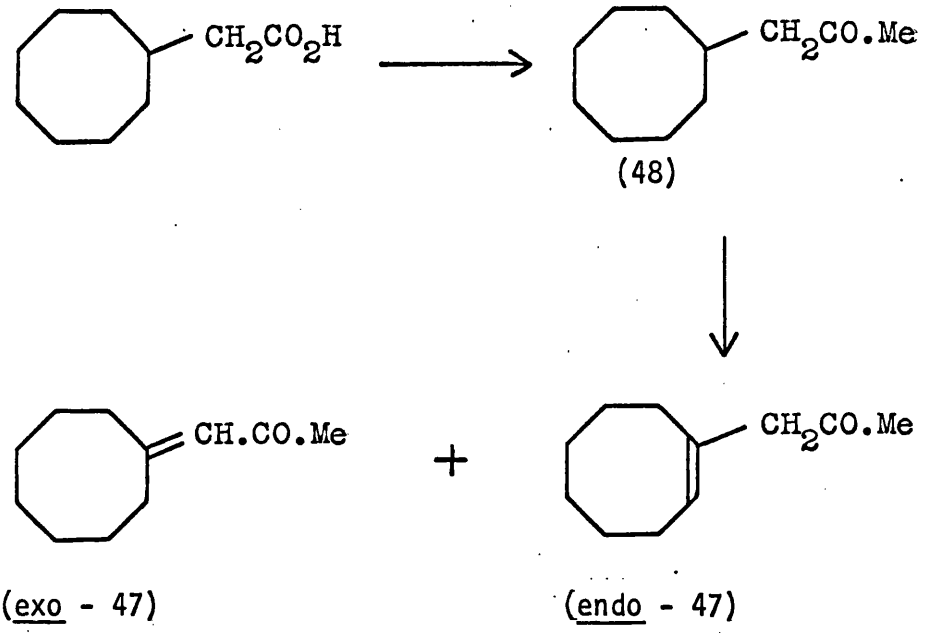
(45) (46)

(45), the boiling point (105-110°/1.5mm) is different to that reported previously by Saharia and Tyagi[69] (b.p. 135-136°/1 mm), who prepared the lactone by borohydride reduction of cyclooctanone--2-acetic acid.

It was thought possible that the desired reaction was being suppressed by very fast and irreversible isomerisation of the double bond. This could be favoured because, although the stabilisation by conjugation is lost, there is a relief of transannular interactions and torsional strain in the cyclooctyl ring when the double bond is endocyclic. Support for this argument is found by comparison with the behaviour of ethyl cyclooct-4-enylidene acetate under acidic conditions. In this case the double bond in the 4,5 position of the cyclooctyl ring removes many of the transannular interactions and the energy gained by conjugation of the exocyclic double bond becomes the major factor. Hence there is little isomerisation of the exocyclic double bond. Many other examples of this preference for an endocyclic double bond in cyclooctyl systems are known,[70] and the variation of this preference with the substituent has been examined.[71]

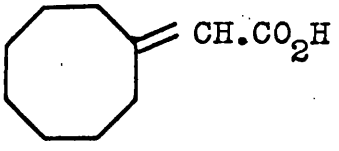
The energy gained by conjugation of a double bond with a methyl ketone would be expected to be greater than the energy of conjugation with an ester in a similar system. Hence, replacement of the ester function in (41) by a ketone may favour the α,β-unsaturated form necessary for the required reaction.

The required ketone (47) was prepared in 82% yield by bromination-dehydrobromination of cyclooctylacetone (48), itself prepared by reaction of methyl-lithium with cyclooctyl acetic acid (Scheme 16). The product was a 1:3 mixture (by n.m.r.) of



Scheme 16

α,β : β,γ isomers (exo- 47:endo-47). It was later found that the pure α,β-unsaturated ketone (exo- 47) was also obtained by treating cyclooctanylidene acetic acid (49) with methyllithium, although care



(49)

had to be taken to avoid liberating iodine in the work-up. However, distillation of this pure α,β-unsaturated ketone caused partial isomerisation to a mixture of α,β- and β,γ-isomers (2:1). Upon reaction of this partially isomerised mixture with boron trifluoride etherate in benzene the mixture merely isomerised to the equilibrium mixture of 1:3 α,β : β,γ-unsaturated ketones.

The failure of either the ester (41) or ketone (47) to react in the desired manner can be correlated with Cope's generalisation that hydride shifts will only occur when a more stable carbonium ion results. Inspection of the resonance forms of the boron trifluoride etherate complexes of the ester or ketone reveals a tertiary cation on the ring (Fig. 2). A 1,5 hydride shift to this

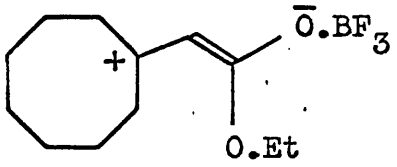


Fig. 2

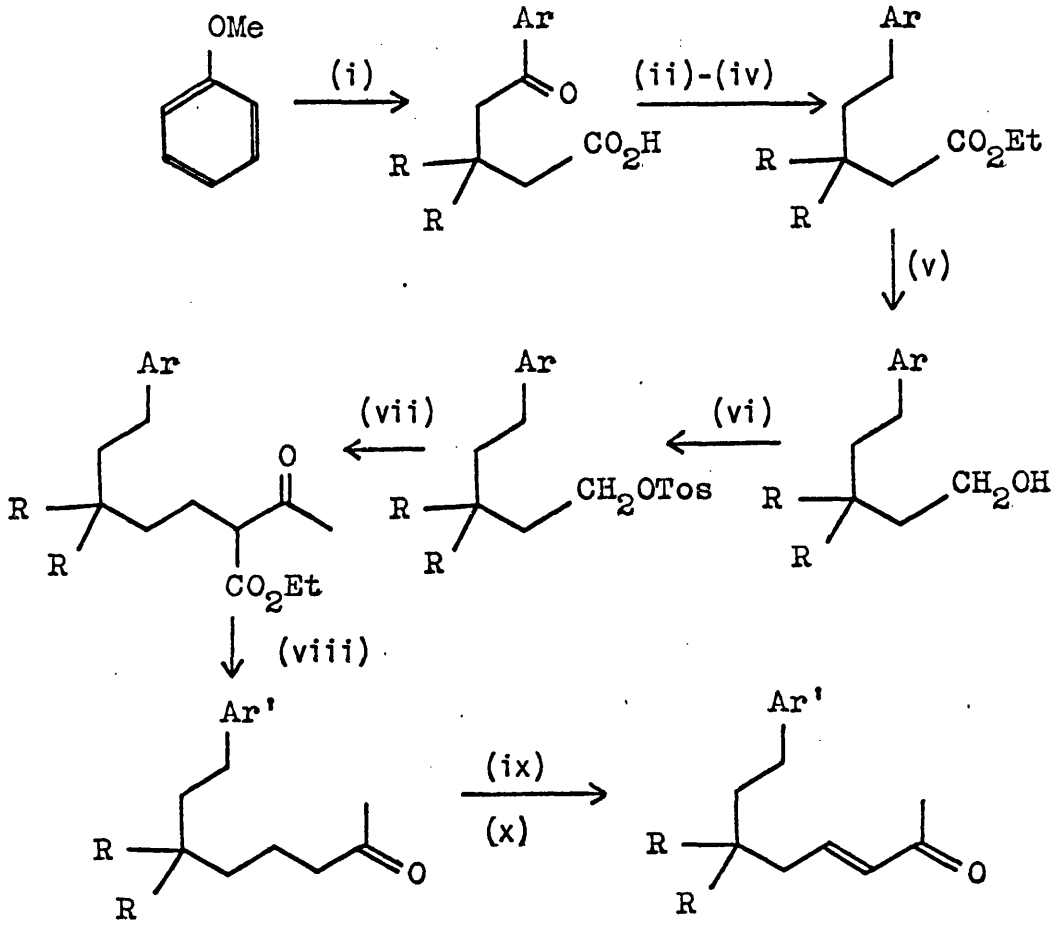
position would then result in a secondary cation with an associated increase of up to 11 kcal $mole^{-1}$ of energy.[72] For the postulated reaction to occur the 5-position of the cyclooctyl ring would have to be suitably substituted so as to form a tertiary cation at this position. Work on this aspect is continuing.

2. 2) Hydride Shifts in Anisylic Acyclic Systems

The work described in this section was initiated by the observation of a 1,5 hydride shift in 8-(p-hydroxyphenyl)-oct-3--en-2-one (39)[66] and its 6,6-dimethyl analogue.[73] Both of these α,β-unsaturated ketones were synthesised by the route shown below (Scheme 17). A weakness in this scheme was the alkylation step (Step vii) which gave O-alkylated material as the major product. The yield of hydride shift product with (39) was good (77%) and introduction of a geminal dimethyl group into the aliphatic chain would be expected to facilitate the reaction. This group should produce closer proximity of the migration source and terminus by the "gem-dimethyl effect"[74] and should result in an increased yield of hydride shift product. Little increase in yield was observed, however.

It was thought to be of interest to study the tolerance of the hydride shift process to variation in the substituent groups and the length of the aliphatic chain.

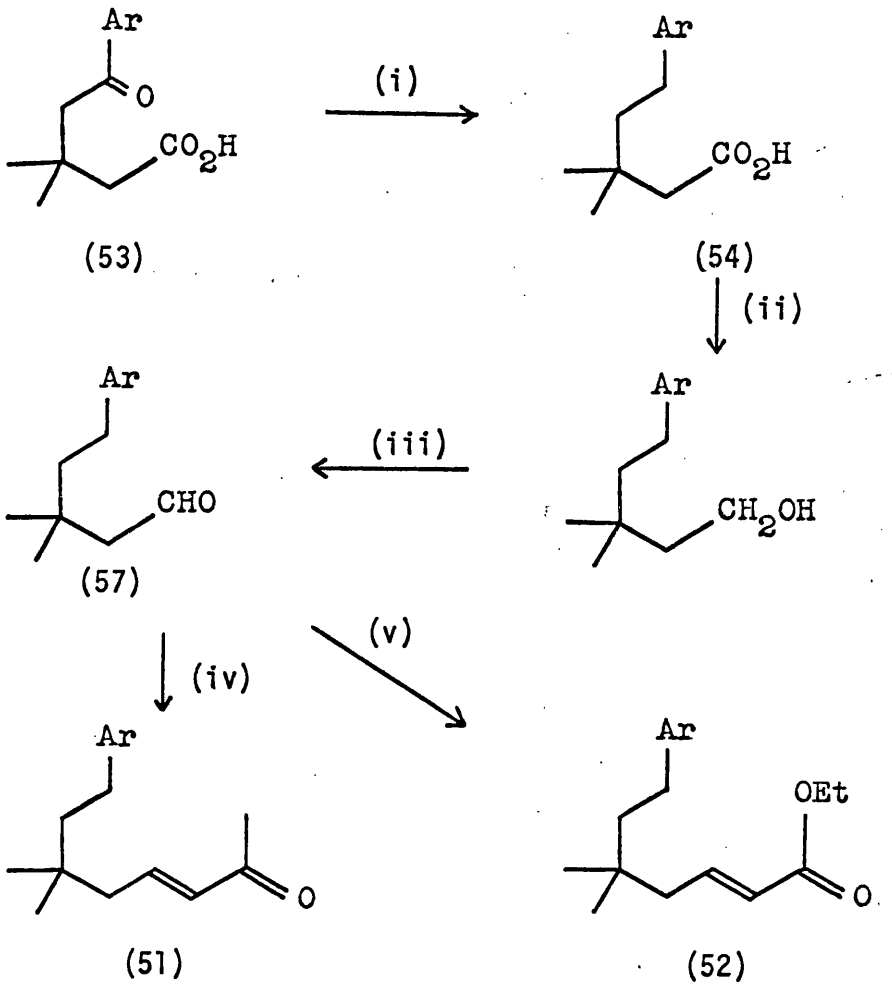
Homologation of aldehydes with acetonyl triphenylphosphonium chloride or triethyl phosphonoacetate is a well-documented reaction. By the use of this method a more flexible and efficient synthesis of the required compounds (51 and 52) was devised (Scheme 18). Wolff-Kishner reduction of the anisylic carbonyl resulted in partial demethylation of the aryl ether group, so the crude product



(39) R = H
(50) R = Me

(i) 3,3-Dimethylglutaric acid/ $AlCl_3$, (ii) Wolff-Kishner
(iii) Me_2SO_4, (iv) $EtOH/H^+$, (v) $LiAlH_4$, (vi) Tos.Cl
(vii) $MeCO.\bar{C}H.CO_2Et$, (viii) HBr/AcOH, (ix) $CuBr_2$
(x) $LiBr/Li_2CO_3/DMF$

Scheme 17

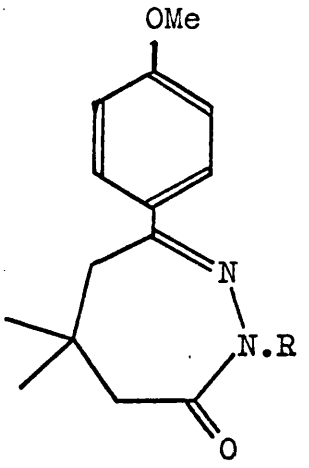


(i) Wolff-Kishner; Me_2SO_4, (ii) $LiAlH_4$, (iii) CrO_3/Py

(iv) $Ph_3\overset{+}{P}.\overset{-}{C}H.CO.Me$, (v) $(EtO)_2$ P $(O)\overset{-}{C}H.CO_2Et$

Scheme 18

from the first step was immediately remethylated with dimethyl sulphate. This gave the required acid (54) in 88% overall yield, in addition to a minor product (7%) which was assigned the 1,2-diazepinone structure (55) on the basis of its analysis and spectroscopic properties. The diazepinone was thought to arise



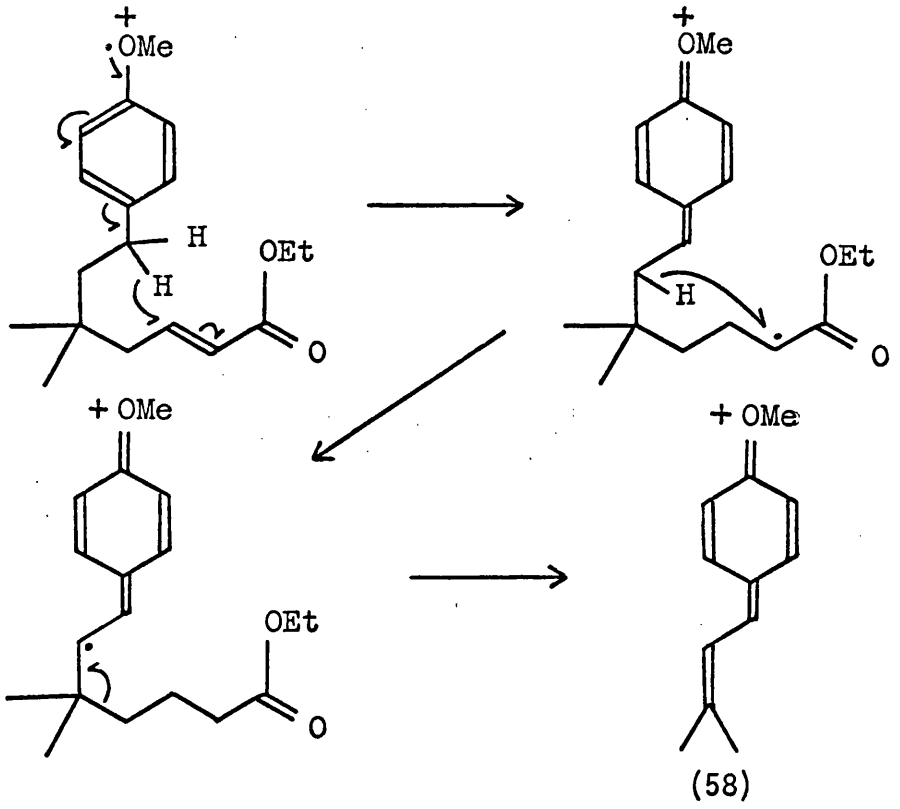
(55) R = Me (56) R = H

by intramolecular reaction of the intermediate Wolff-Kishner hydrazone with the acid group, or with the ester transiently formed in the dimethyl sulphate reaction. To test this possibility the acid (53) was treated with hydrazine hydrate, potassium carbonate, and dimethyl sulphate, conditions under which the hydrazone will be more stable and the acid will be esterified. This resulted in a 51% yield of the 1,2-diazepinone (56) which was N-methylated (dimethyl sulphate/sodium hydroxide) to provide a sample identical with (55). 1,2-Diazepinones have also been prepared by the reaction of a hydrazine with aroyl acid chlorides,[75] aroyl acids,[76] or with sulphonyl aroyl esters.[77]

The acid (54) obtained from the Wolff-Kishner reduction was reduced (lithium aluminium hydride) and oxidised to the aldehyde (57) with chromium trioxide/pyridine complex in dichloromethane. Reaction of this aldehyde with triethyl phosphonoacetate afforded the α,β-unsaturated ester (52) in 39% overall yield from the keto-acid (53), and

reaction with acetonyl triphenyl phosphonium chloride gave the ketone (51) in 38% overall yield.

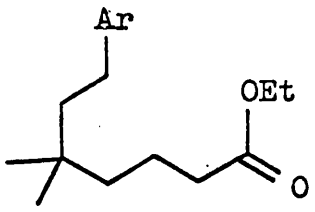
As the ketone (50) underwent a hydride shift, the ester (52) was tested for a similar reaction. The mass spectrum of this ester suggested the occurrence of some 1,5 hydrogen shift in the fragmentation of the molecule. The parent peak at m/e 175 could be from the ion (58), formed by the process shown (Scheme 19). Some support can be



(58)

Scheme 19

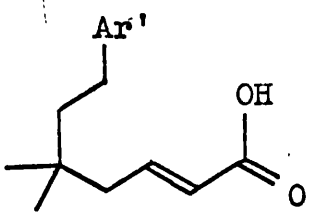
found for this fragmentation pattern by considering the mass spectrum of the saturated ester (59) which was prepared by hydrogenation of the ester (52). The m/e 175 peak, which is the parent peak in (52), drops to a relative intensity of 23% in (59). A study of the mass



(59)

spectra of phenyl substituted α,β-unsaturated ketones has been made by Djerassi and co-workers.[78] They show that, in 8-phenyloct-3-en--2-one, some intramolecular transfer of the benzylic hydrogen is occurring, although this is not a major process. A charge-stabilising component on the phenyl ring, however, such as p-methoxy, may favour this process more than any other.

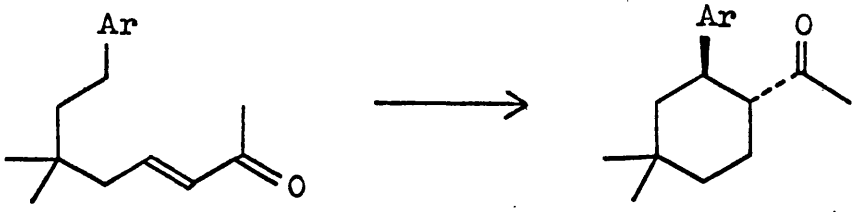
Encouraged by the fragmentation pathway for (52) an attempt was made to thermally rearrange this ester, but it merely distilled unchanged at 240-250°C. Polyphosphoric acid, perchloric, and trifluoroacetic acids similarly gave no rearrangement; and 1:1 hydrobromic acid/acetic acid only hydrolysed the ester and demethylated the aryl ether to give the acid (60) in 54% yield. This demonstrates the great effect that the substituent



(60)

group on the migration terminus can exert on the aliphatic hydride shift. Each of the above-mentioned acid treatments succeeded in causing a 1,5 hydride shift in the analogous ketones (39 and 50) but the ester proved completely inert. The p-(hydroxyphenyl)-acid (60) was similarly inert to boron trifluoride etherate treatment, and polyphosphoric acid only gave an intractable mixture of products.

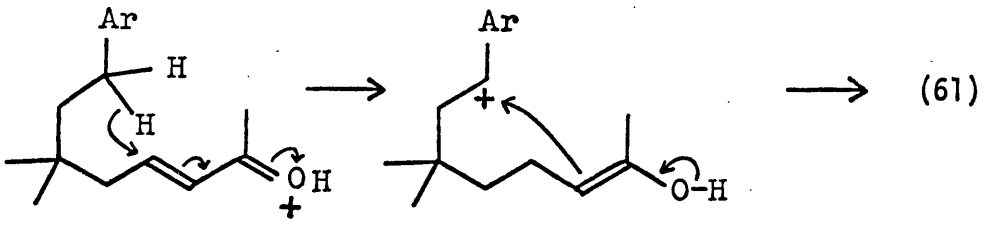
The p-(methoxyphenyl)-α,β-unsaturated ketone (51), however, rearranged readily in perchloric acid (Scheme 20) to give a cyclohexyl methyl ketone (61) (43%) analogous to that formed in the reaction of the phenol (50, R = CH_3) with acid.[73] The structure of



(51) (61)

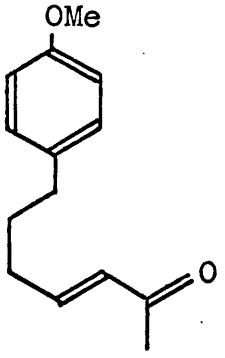
Scheme 20

(61) was proved by comparison with a sample prepared by methylation of 2-p-(hydroxyphenyl)-4,4-dimethyl cyclohexyl methyl ketone. Formation of this product is rationalised by a 1,5 hydride shift to form a more stable cation, followed by ring closure (Scheme 21).



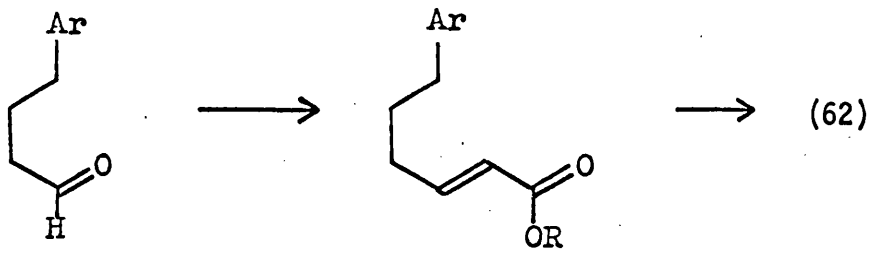
Scheme 21

An attempt has been made to duplicate the hydride shift occurring above using the α,β-unsaturated ketone (62) for which a 1,4 hydride shift is required.



(62)

The first synthesis attempted involved the production of the α,β-unsaturated ester (63), hydrolysis to the corresponding acid (64) and reaction with methyl-lithium (Scheme 22). This synthesis foundered at the last stage. Addition of methyl-lithium to a stirred solution of the acid (64) in various solvents only resulted in deposition of a thick, white precipitate which could be the

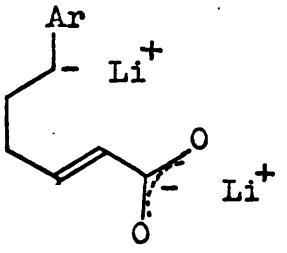


(63) R = Et

(64) R = H

Scheme 22

di-lithio intermediate (65). No further reaction ensued, and none of the required product was obtained. Evidence for the formation

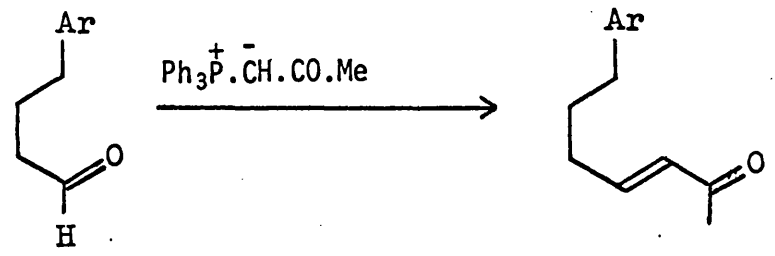


(65)

of the anisylic carbanion (65) is that 4-p-(methoxyphenyl)-4-methyl pentanoic acid, which has the anisylic position substituted by methyl groups, undergoes a normal reaction to give the desired ketone in excellent yield (see appendix).

Fortunately the alternative synthesis, patterned on that successful for (51), worked well to give a reasonable yield of the

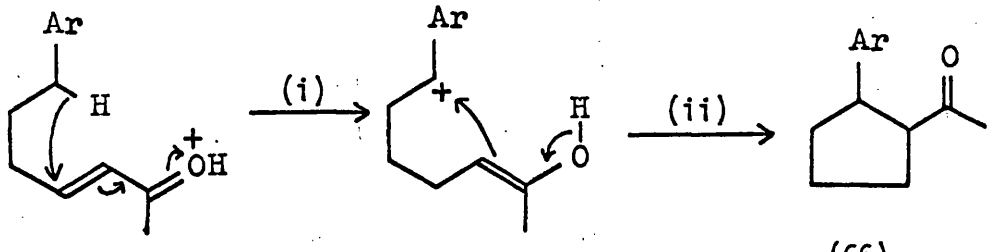
desired ketone (62) (Scheme 23).



(62)

Scheme 23

Attempted rearrangement of this ketone (62) with toluene-p-sulphonic acid in benzene, 4:1 acetic acid/hydrobromic acid, or with trifluoroacetic acid gave no reaction. Perchloric acid (70%), however, gave complete reaction after 2.5h. at room temperature to give a viscous brown oil whose i.r. spectrum had an absorption characteristic of a saturated ketone (1710 cm^{-1}). Distillation of this oil, after chromatography, gave only a small amount of material boiling below 250°/0.3mm, and this was shown to be starting material. The polymeric distillation residue proved to be intractable.

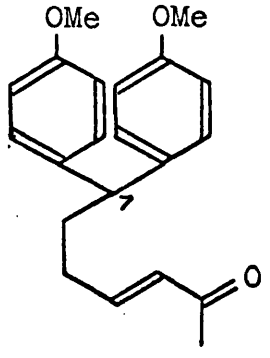


(66)

Scheme 24

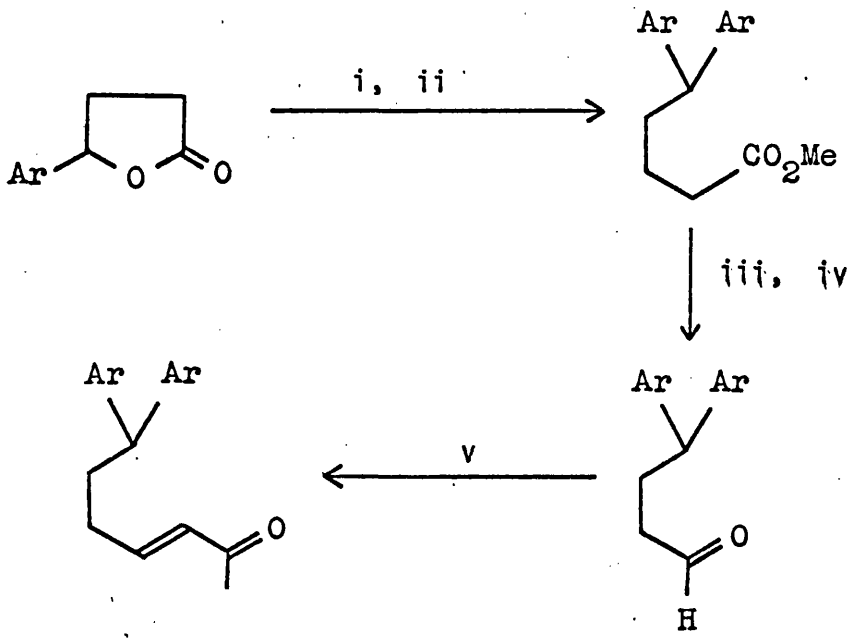
Formation of a five-membered ring (step ii in Scheme 24) would be expected to be kinetically favoured over formation of a six-membered ring. The failure of heptenone (62) to produce (66) in an analogous reaction to (51) seems, therefore, to lie in the step involving hydride shift.

It was then decided to prepare a system in which a 1,4 hydride shift would be more favoured. The ketone (67) fulfills this requirement. The extra p-(methoxyphenyl) group will stabilise the incipient cation at C_7 and result in a decrease in the energy of activation for



(67)

the hydride shift (relative to the heptenone (62)). Synthesis of (67) was achieved by the route shown in Scheme 25. The first two stages gave a poor overall yield (22%), but the succeeding stages all gave good yields.

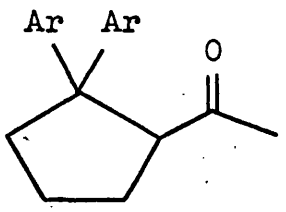


i) Anisole/$AlCl_3$, ii) Me_2SO_4/K_2CO_3, iii) $LiAlH_4$

iv) CrO_3, v) $Ph_3\overset{+}{P}.\overset{-}{C}H.CO.Me$

Scheme 25

Reaction of this ketone (67) with perchloric acid at room temperature for 2h, followed by chromatography, gave a heavy yellow oil. The mass spectrum of this oil indicated it to be monomeric, and the i.r. spectrum was consistent with that expected for the cyclopentyl methyl ketone (68). The n.m.r. spectrum, however,



(68)

showed no clear singlet for the methyl group of the methyl ketone. Distillation of this product at 250°/0.4mm gave a very small amount of partly crystalline clear oil. Crystallisation of this distillate gave a colourless solid (in 5% yield) but insufficient material precluded characterisation.

2. 3) Conclusions

The conclusions to be drawn from the research on this particular anisylic system are:-

i) 1,5 Hydride shifts in acyclic systems seem to be sensitive to the group attached to the migration terminus.

ii) 1,4 Hydride shifts in acyclic systems are less readily attainable.

3. ACID CATALYSED TRANSANNULAR π-CYCLISATIONS

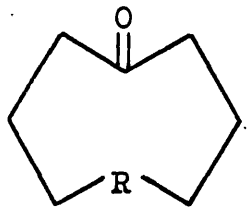
3.1 Introduction

As was shown in the first section, the conformations of cyclooctyl rings can lead to hydride shifts between non-vicinal centres. Suitably substituted cyclooctenyl compounds can also react transannularly and the chemical literature abounds with such examples. Similar reactions of bicyclo[3.3.1]nonene systems have become of great interest as a means of synthesising variously substituted adamantane derivatives.

The following discussion is divided into five sections. The first section largely concerns the work of N.J. Leonard and his co-workers on transannular interactions in heterocyclic cyclooctanones. This is followed by a discussion of some of the reactions of 1,5-cyclo-octadiene, a system which has been well studied and exemplifies many of the reactions of cyclooctenyl compounds. After discussions of solvolysis reactions of substituted cyclooctenyl compounds and the reactions of exo-methylenecyclooctanes this section will terminate with a description of some acid catalysed cyclisations of bicyclo[3.3.1] nonenes.

3.2 Transannular Effects

The study of the interactions of heteroatoms with transannularly disposed carbonyl groups has largely been the work of N.J.Leonard. In a long series of papers he has demonstrated these transannular interactions in many medium-ring heterocycles, but this section will only deal with heterocyclic cyclooctyl systems.



(69) R = N.Me[79]

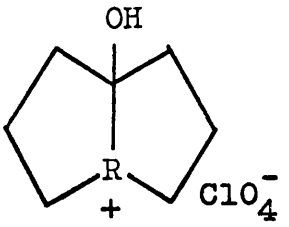
(70) R = N.C_6H_{11}[80]

(71) R = S[81]

(72) R = S=O[81,82]

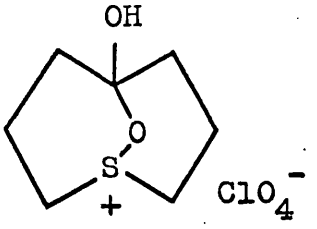
(73) R = O[81]

By studies of infra-red spectra,[79,80,81] dipole moments,[81,82] and 'apparent dissociation constants'[71] it was shown that compounds (69), (70) and (71) all exhibited some degree of interaction between the carbonyl group and the heteroatom in neutral solution. The N-cyclohexyl system (70) exhibited less interaction than the N-methyl (69) and this was attributed to the steric bulk of the cyclohexyl group preventing full proximity of the interacting groups. The degree of interaction was very dependent upon the polarity of the solvent. In a non-polar solvent the i.r. spectra recorded were as would be expected from these systems. As the solvent polarity was increased the degree of trans-annular interaction increased. The ether (73) exhibited no interaction in the i.r. spectrum, while the sulphoxide (72), although exhibiting no interaction in the i.r. spectrum, did show interaction in the u.v. spectrum. Upon treatment with perchloric acid compounds (69) and (71) formed full transannular bonds to give (74) and (75) respectively, whereas (72) reacted <u>via</u> the sulphoxide oxygen to give (76). The ether (73), however, upon treatment with dilute hydrochloric acid afforded (77), the postulated mechanism involving the transannular



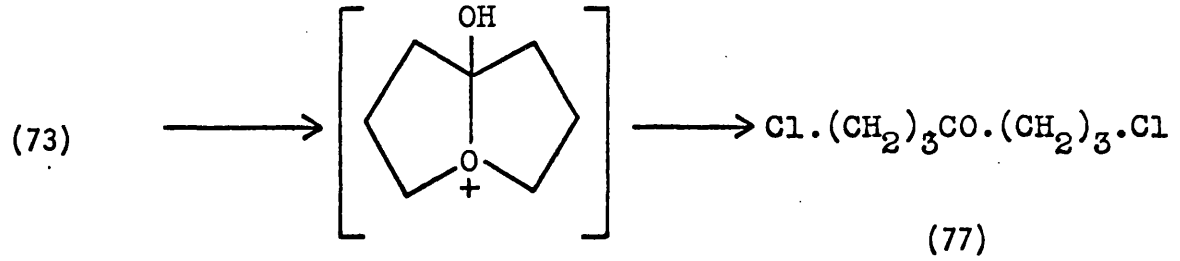
(74) R - N.Me

(75) R = S



(76)

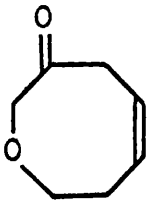
oxonium ion (78). (Scheme 26).



(78)

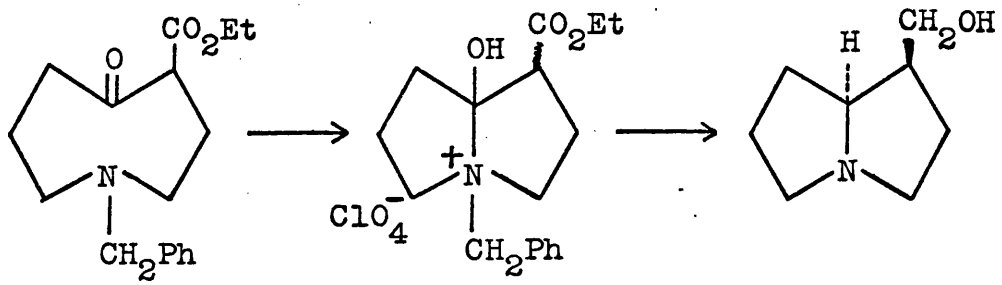
SCHEME 26

The postulated intermediacy of the ion (78) was supported later[83] by studies on 7,8-dihydro-2H-oxocin-3-(4H)-one (79). The reactions of this oxa-cyclooctyl system clearly demonstrated transient formation of an oxonium ion.



(79)

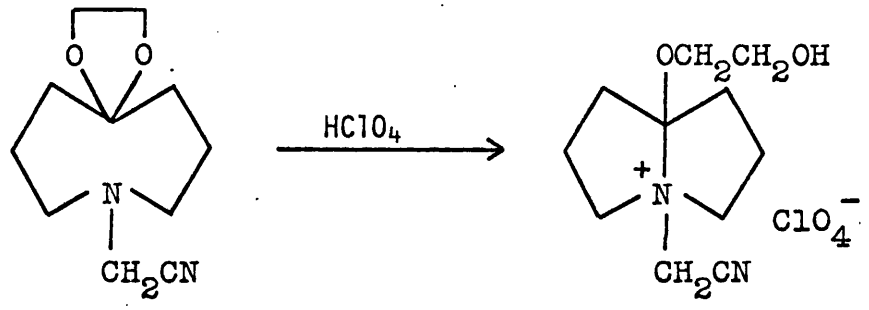
Transannular cyclisation in an azacyclooctan-4-one has been used in a synthesis of (±) isoretronecanol (80) from ethyl 1-benzyl-1--azacyclooctan-5-one-4-carboxylate (81).[84] (Scheme 27).



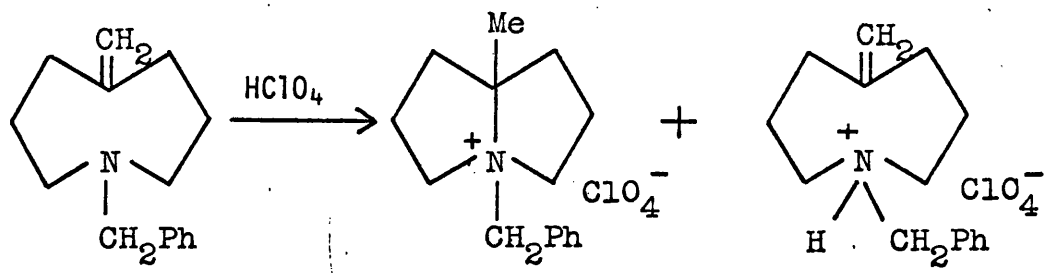
(81) (80)

Scheme 27

The same type of transannular cyclisation has been noted in the acid-catalysed reactions of the ketal (82) and the alkene (83).[85]



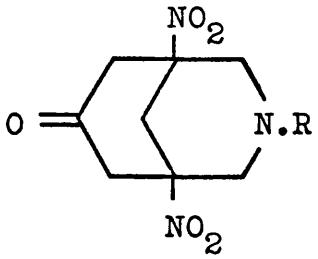
(82)



(83)

In 1970 Wall[86] prepared the 3-azabicyclo[3.3.1]nonan-7-ones (84 - 86) to test for possible transannular interaction. Interaction was not observed either by i.r. or n.m.r. spectroscopy. The amino-

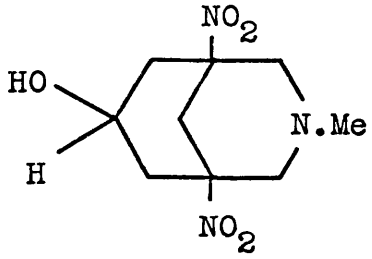
alcohol (87), however, did display very strong intramolecular H bonding in contrast to the epimer (88) which showed a free hydroxyl group.



(84) R = Me

(85) R = Et

(86) R = CH_2Ph

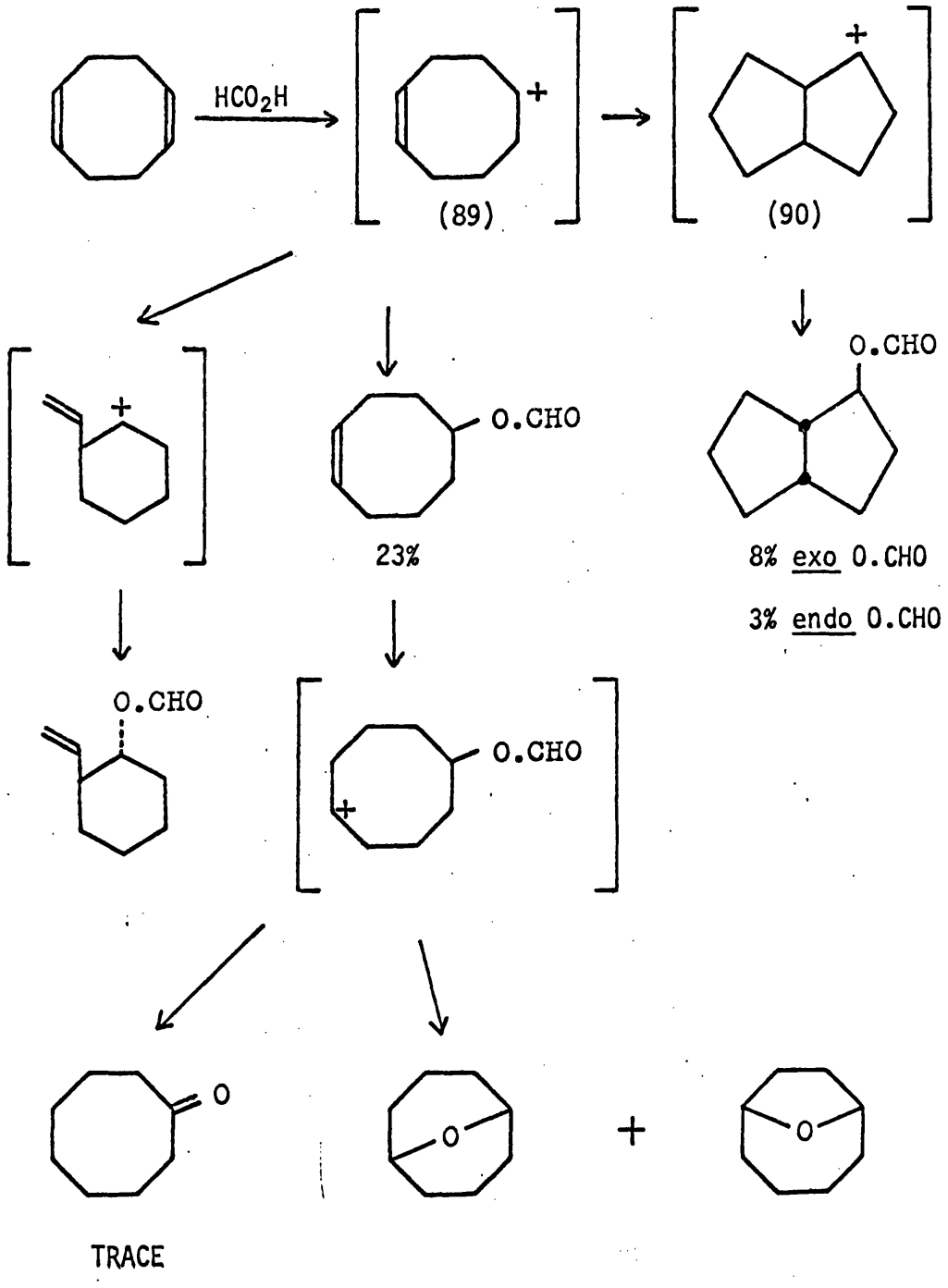


(87) endo - OH

(88) exo - OH

3.3 Electrophilic Addition Reactions of 1,5-Cyclooctadiene

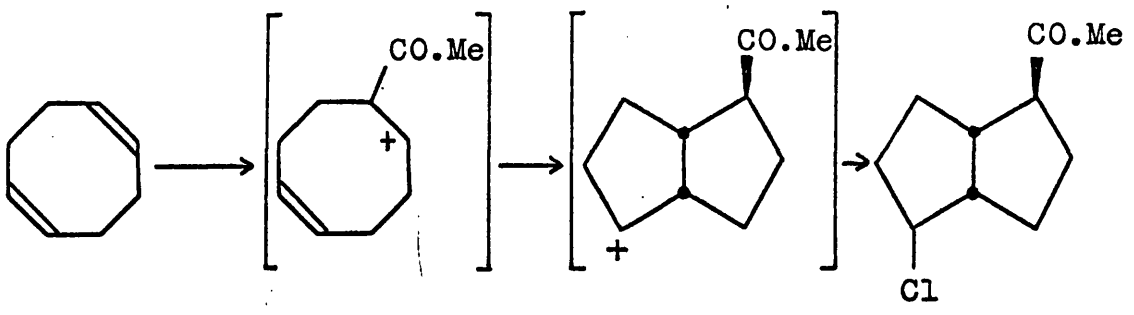
Some of the transannular reactions of 1,5-cyclooctadiene are of value in synthetic organic chemistry as routes to bicyclo[3.3.0]octanes and substituted cyclooct-4-enes. In 1959 Cope and Peterson[87] described a new synthesis of cyclooct-4-en-1-ol by formic acid addition to 1,5-cyclooctadiene. This formed several products, most of which were identified. All the products indicated the intermediacy of a cyclooct-4-enyl cation (89) (Scheme 28) which was partly trapped intramolecularly by the proximate double bond to give cation (90).



Scheme 28

In most examples of electrophilic additions to 1,5-cyclooctadiene the cyclooctadiene shows a marked reluctance to substitution of both double bonds. This is thought to be due to the great increase in transannular interactions when the ring is comprised solely of sp_3 carbons. An example of this is provided by the reaction of 1,5-cyclooctadiene with hydrogen bromide.[88] Only the mono-addition product is isolated, in good yield. This indicates that the rate of addition of the second mole of hydrogen bromide is extremely slow.

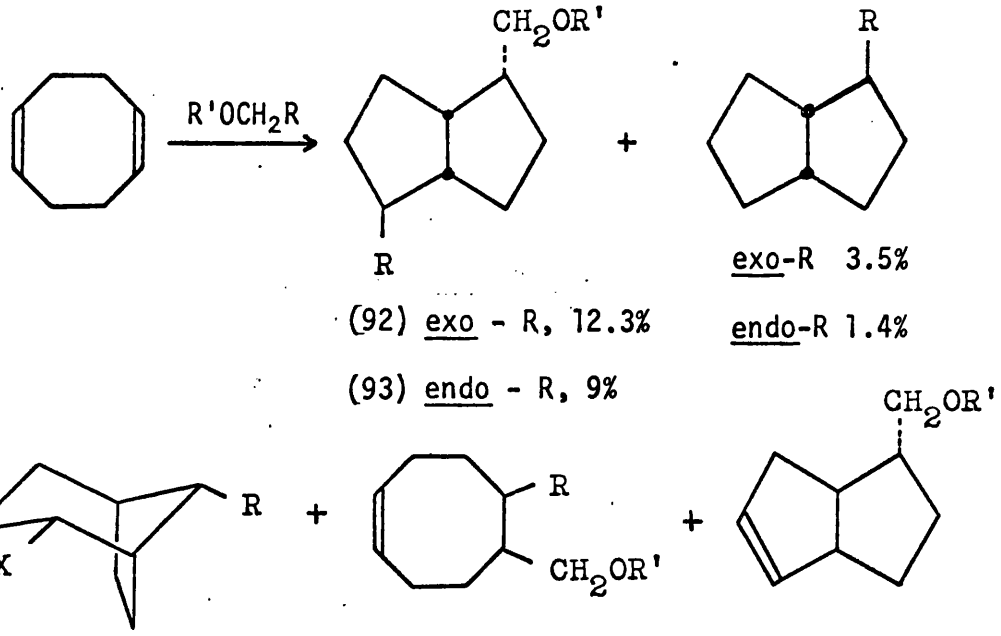
The Friedel-Crafts reactions of acetyl chloride with cyclooctene, 1,3-cyclooctadiene, and 1,5-cyclooctadiene have been studied by Cantrell and Strasser.[89] Reaction of 1,5-cyclooctadiene with acetyl chloride in dichloromethane, mediated by aluminium chloride, gave exo-2-acetyl--6-chlorobicyclo[3.3.0]octane (91) (48%) (Scheme 29). The ease of this reaction, and the ready availability of the starting materials make this reaction very useful for the preparation of 2,6 disubstituted bicyclo[3.3.0]octanes.



(91)

SCHEME 29

Further Friedel-Crafts reactions on 1,5-cyclooctadiene were reported by Tabushi, Fujita, and Oda,[90] who also obtained bicyclo-[3.3.0]octane systems, but with predominantly the opposite stereochemistry to that reported by Cantrell. By reacting 1,5-cyclooctadiene with a variety of electrophilic conditions they obtained similar products, but in different ratios. (Scheme 30).

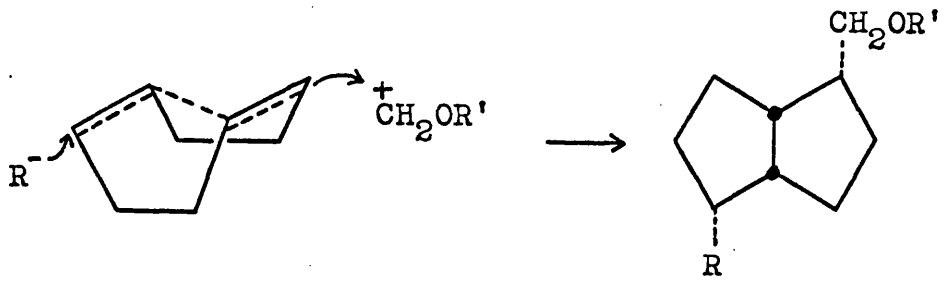


(a) Reaction of 1,5-cyclooctadiene with $Cl.CH_2.O.Me$ and $MeO.CH_2.OMe$ only gave products (92), (93), (94), and (95) with R' = Me and R = Cl or OMe. Yields given are for reaction with $MeO.CH_2.OAc$

(b) Reaction with $CH_2(OAc)_2$ gave no (95)

Scheme 30

By studying the dependence of product ratios upon nucleophilicity of the anion, they concluded that the tendency to cyclisation (via the transannular double bond) was increased as the nucleophilicity of the anion decreased. Hence there was competition between the anion and the transannular double bond for the cyclooctyl cation. The predominant formation of endo-C_2-bicyclo[3.3.0]octane systems rather than exo-isomers suggested a kinetically controlled reaction, as the exo- configuration is thermodynamically more stable. This conclusion led to the following concerted mechanism.[91] (Scheme 31).



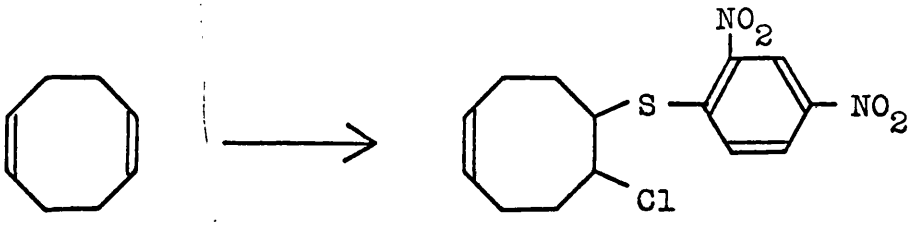
Scheme 31

Formation of bicyclo[3.2.1] products and some endo-C_2-exo-C_6-bicyclo-[3.3.0]octane, however, indicated that the attack of the anion may not be completely synchronous with the cyclisation process. Production of bicyclo[3.2.1]octanes is rationalised by a mechanism in which a bicyclo[3.3.0]oct-2-yl cation undergoes a 1,2-alkyl shift to produce a bicyclo[3.2.1]oct-8yl cation.[92] The varying ratios of exo- and endo-bicyclo[3.3.0]octanes in each reaction can be correlated by a relationship between the "concertedness" of the last step and the nucleophilicity of the attacking anion.

Tabushi, Fujita, and Oda present two reasons why the bicyclo-[3.3.0]octane formed in Cantrell's reaction is of opposite stereochemistry to theirs: (1) heterogeneity of the reaction, or (2) isomerisation from exo- to endo- isomer during the replacement of chlorine with hydrogen by sodium in t-butanol. While either of these reasons could be correct there is also the possibility that aluminium chloride could catalyse isomerisation of the C_2 centre in the product by enolisation. This should then produce the thermodynamically more stable exo-isomer.

In 1970 a German group reported several examples of addition to 1,5-cyclooctadiene.[93] Reaction with phosphoric acid gave bicyclo[3.3.0]octanes, and reaction with chlorine in dichloromethane, or perchloric acid in acetic acid gave bicyclo[3.3.0]octanes, 9-oxabicyclo[3.3.1]nonanes and 9-oxabicyclo[4.2.1]nonanes.

Reaction of 1,5-cyclooctadiene with electrophiles has been used to estimate the extent of charge development in the transition state.[94] Reaction of 2,4-dinitrobenzenesulphenyl chloride with 1,5-cyclooctadiene resulted in the formation of 1,2 addition product only (Scheme 32).



Scheme 32

The conclusion drawn from this finding was that in the episulphonium ion intermediate very little charge resided on the C_1 and C_2 cyclooctyl carbons. If either of these carbons had developed a charge, then bicyclic products would have been expected. This finding is in agreement with other work on this subject.[95] A similar conclusion may presumably be drawn from the reaction of hydrogen bromide with 1,5-cyclooctadiene, where no bicyclic products are observed.[88]

A paper has been published on the addition of methanesulphenyl chloride to 1,5-cyclooctadiene[96]. This gave 80 - 90% of monocyclic di-adducts and only 8 - 13% of the cyclooctenyl mono adduct (96). The formation of di-adducts was attributed to activation of the transannular π-bond by the sulphur atom (fig. 3).

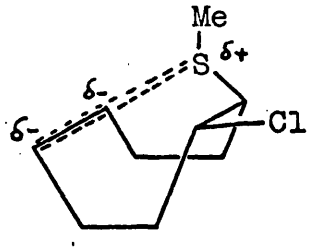
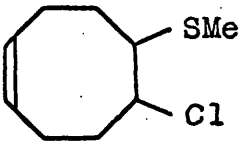


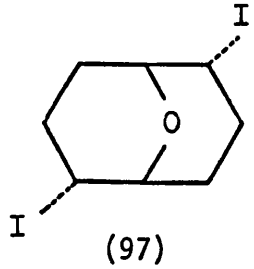
FIG. 3



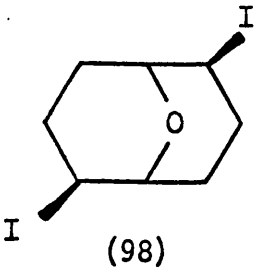
(96)

This intermediate was also suggested by the fact that 5-methylthiocyclo-oct-1-ene (96), upon reaction with benzenesulphenyl chloride or methanesulphenyl chloride, gave the same, or analogous, products as addition to 1,5-cyclooctadiene. The double bond in (96) also appeared to be activated to reaction with hydrogen iodide and hydrogen chloride.

The formation of only 1,2 adducts in the reactions of 1,5-cyclooctadiene with electrophiles has also been described by Labows and Swern.[97] Reaction of iodine isocyanate, iodine azide, or iodine nitrate gave only 1,2 adducts. This was rationalised by the same argument as Schmid used; postulating a "closed" iodonium ion where little charge resides on the ring carbons. However, reaction of 1,5-cyclooctadiene with iodine in methanol gave only one product, which was characterised as the 2,6-diiodo-9-oxabicyclo-[3.3.1]nonane (97) (an isomeric compound, prepared by the reaction

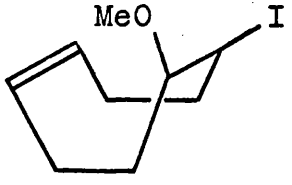


(97)

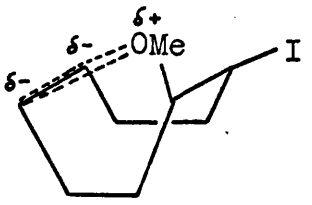


(98)

of cyclooctadiene with mercuric acetate, potassium iodide, and iodine[98] was shown to be the isomer (98)). The explanation for this is almost identical to that proposed for formation of the di-adducts from the methanesulphenyl chloride reaction. The initial formation of a methoxy-iodine adduct (99 , Scheme 33) is followed by activation of the transannular double bond by the ether oxygen (100), and then ring closure and iodination. A similar result was obtained when



(99)



(100)

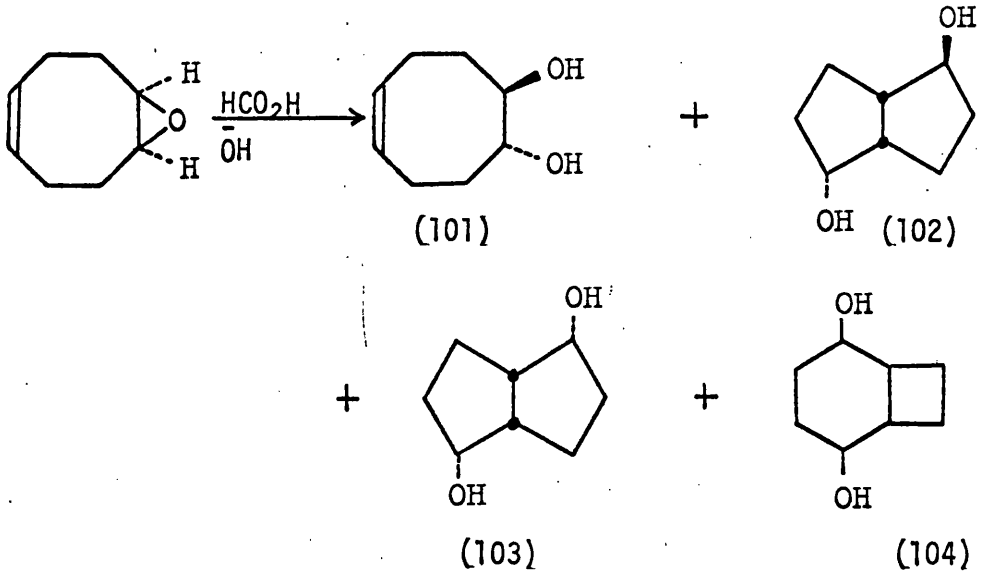
Scheme 33

5-methoxycyclooctene was treated with iodine in methanol, which tends to support the observed mechanism.

Numerous other examples exist of the production of heterocyclic systems by electrophilic substitutions of 1,5-cyclooctadiene. For example, 9-thiabicyclo[3.3.1]nonanes may be prepared by reacting 1,5-cyclooctadiene with sulphur dichloride,[99] and the reaction of diborane with 1,5-cyclooctadiene gives 9-borabicyclo[3.3.1]nonane, an extremely useful hydroborating agent.[100]

3.4 Solvolysis Reactions of Cyclooct-4-enyl Derivatives.

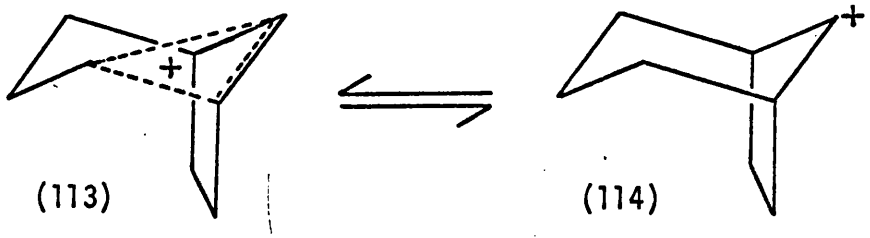
Formolysis of cis-1,5-cyclooctadiene mono-epoxide has been found to give the normal trans-1,2-diol (101) in 70% yield, and also three products derived by transannular reaction of the double bond (102-104) (Scheme 34) in a total of 25% yield.[101] As has been noted



Scheme 34

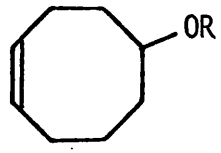
for the hydride shift reactions of cyclooctanes, the epoxide again presents an unusual result. In most solvolyses of cyclooct-4-enyl compounds bicyclo[3.3.0]octane products are predominant, yet in this example the normal product is by far in excess.

Solvolyses of cyclooct-4-enyl tosylate and brosylate have been reported and the product ratios are presented in Table [2]. There are notable differences between solvolyses of the brosylate and of the tosylate but the existence of transannular π-bonding is quite clear by the predominance of bicyclic products. Closson and Kwiatkowski point out that their results (on the acetolysis of the tosylate 105) are more in accord with the observed isomerisation of cyclooct-4-enyl tosylate to exo-bicyclo[3.3.0]oct-2-yl tosylate and thence to exo-bicyclo[3.2.1]oct-8-yl tosylate. They also conclude that the non-classical ion (113) and the classical ion (114) are approximately equally stable (Scheme [35]) in this system.

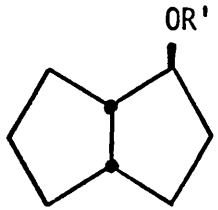


(113) (114)

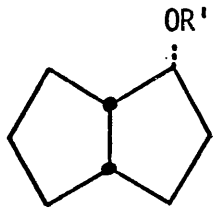
Scheme 35



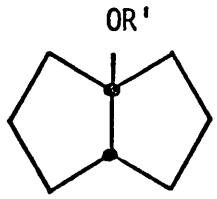
(105)



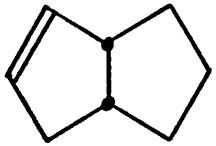
(106)



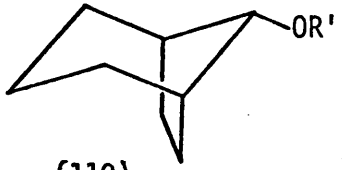
(107)



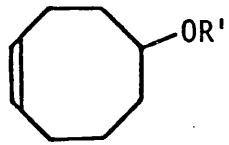
(108)



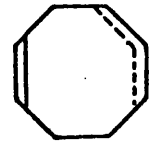
(109)



(110)



(111)



(112)

Ref.	Reaction Conditions	105	106	107	108	109	110	111	112
102	Acetolysis	R = Brosylate	19%	17%	-	12%	-	7%	6%
103	Trifluoro-acetolysis	R = Brosylate	22%	6%	7%	-	17%	3%	-
104	Acetolysis[b]	R = Tosylate	21%	33%	1%	21%	4%	≈10%	≈10%

(a) R' = H or Ac

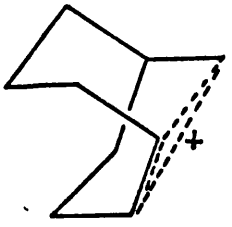
(b) Based upon 100% conversion to products

Table 2

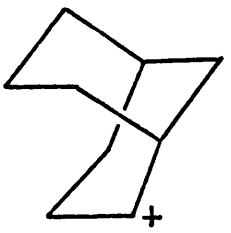
Solvolysis of 4-cyclooctenylmethyl tosylate (115) and brosylate (116) was a logical extension both of the above work and that of Le Ny on 4-cycloheptenylmethyl brosylate.[105] Hanack and Kaiser[106] reported that buffered acetolysis of the tosylate (115), followed by reduction with lithium aluminium hydride, gave some unidentified hydrocarbons and 60% of an alcohol fraction. This was shown to consist largely of bicyclo[3.3.1]nonan-2-ol of unspecified stereochemistry and 18% of a ketone which they tentatively assumed to be bicyclo[4.2.1]nonan-2-ol, and later proved by comparison with an authentic sample of the derived ketone.[107] By a comparison of the rate of this reaction (k_1) with the rate of solvolysis of the saturated tosylate (k_2) they were able to show the participation of the double bond in the rate-determining step ($k_1 = 50 \times k_2$).

A more thorough study of the reaction of the brosylate (116) was made by Cope, Nealy, Scheiner, and Wood,[108] and this was confirmed by the work of Baggaley and his co-workers[109] on the tosylate (115), and Parker and his co-workers on the brosylate (116).[110] Their combined results are presented in Scheme 36 .

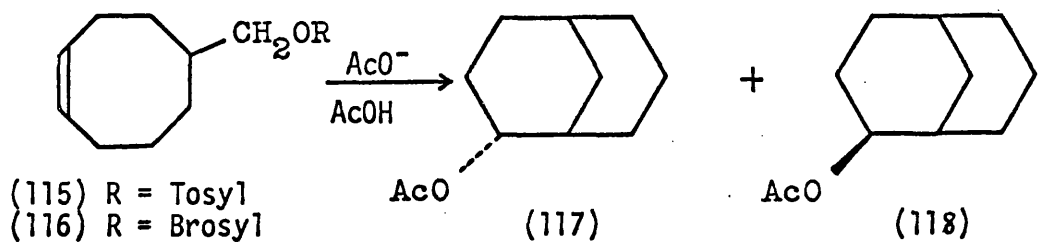
Cope originally proposed that the formation, and stereochemistry, of the major product was consistent with the intermediacy of the non-classical ion (122).



(122)

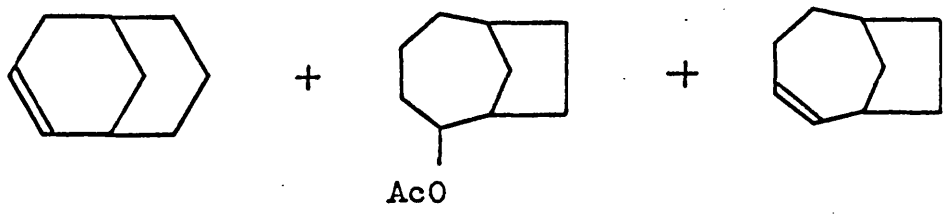


(123)



(115) R = Tosyl
(116) R = Brosyl

(117) (118)



(119) (120) (121)

Ref.	Starting Ester	117	118	119	120	121
108	116	75%	3%	14%	7%	-
109	115	67.6%	2.6%	10.9%	18.3%	0.6%
110	116[a]	77%	7%	-	0.8%	-

(a) Yields based on 85% monoacetate product

Scheme 36

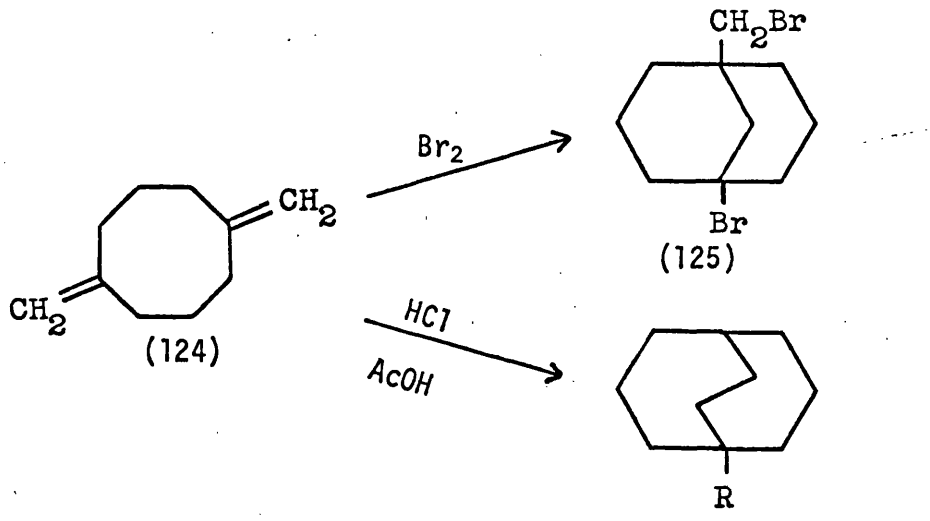
The weight of opinion appears to be against this suggestion, however. Parker's group[110a] postulated that, if the intermediate for the solvolysis of (115) or (116) is the ion (122), then solvolysis of endo-bicyclo[3.3.1]nonyl-2-brosylate should proceed through the same intermediate. The observation of different product ratios for each brosylate militated against a common non-classical intermediate. This explanation was also correlated with a discussion of conformational strain in the classical (123), and non-classical ions. The intermediacy of a classical cation (123) could explain the different stereochemistries of the products from each brosylate by postulating leaving-group hindrance to attack which Parker later modified to an explanation based on intimate ion-pairs.[110b] Hanack and his co-workers came to the same conclusion.[107] A non-classical ion was not, of course, completely ruled out; but the majority of the product would be formed via the classical ion (123).

Graham and Jonas later denied the intermediacy of any bicyclic ion, whether classical or non-classical.[114] By consideration of their results they concluded that the only consistent mechanism was that involving solvent attack and synchronous π-electron participation.

3.5 Transannular Reactions of Exocyclic Methylenecyclooctanes.

3,7-bis-Methylenebicyclo[3.3.1]nonane readily cyclises when treated with acid[111] or bromine[112] or upon mercuration,[112] to give adamantane derivatives. 7-Methylenebicyclo[3.3.1]nonan-3-one undergoes similar reactions when treated with acids.[111] Many examples of this type of reaction are known.

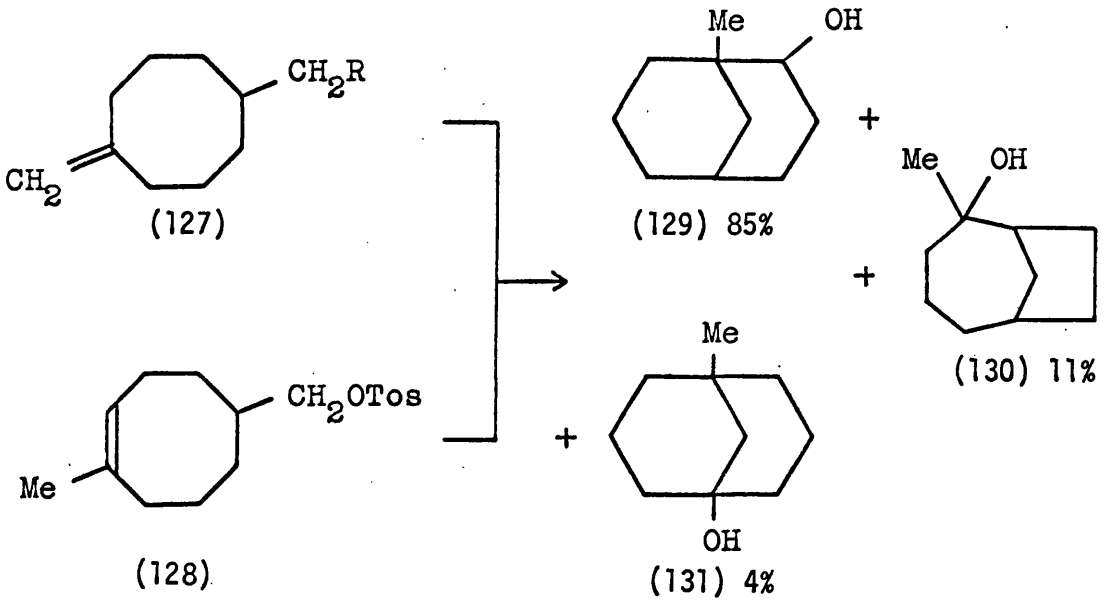
A rarer example of this type of reaction is provided by 1,5-bis-methylenecyclooctane (124).[113] Upon reaction with bromine two products were formed, of which only the major product was characterised. Analysis and spectroscopic data indicated this major product to be the dibromide (125). Surprisingly, however, the reaction of the bis-alkene (124) with a mixture of hydrochloric and acetic acids gave a mixture of products with the bicyclo[3.3.2]-decane skeleton (126). (Scheme 37).



(126) R = OH and
R = Cl

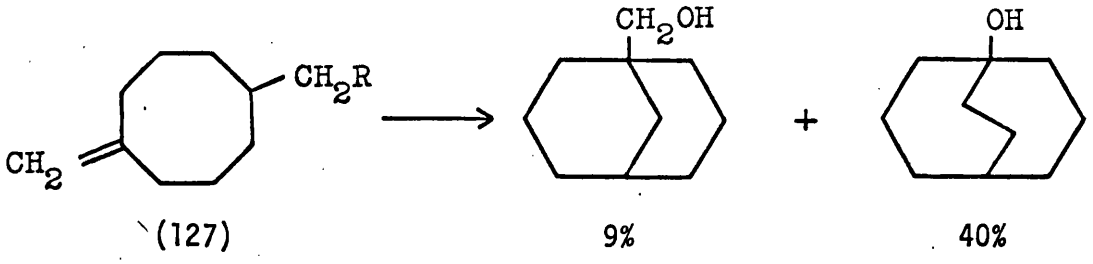
Scheme 37

The solvolysis reactions of the related 5-methylenecyclooctyl methyl compounds (127, R = tosylate, brosylate, or amino) have been studied.[114] Upon formolysis (127, R = tosylate or brosylate) gave only three products (Scheme 38). It was postulated that all these products arose by reaction after the double bond had isomerised. This was proved by formolysing (128), as the same product mixture was obtained.



Scheme 38

Diazotisation of the amine (127, R = NH_2) produced a completely different picture (Scheme 39). The nature of the products, and the



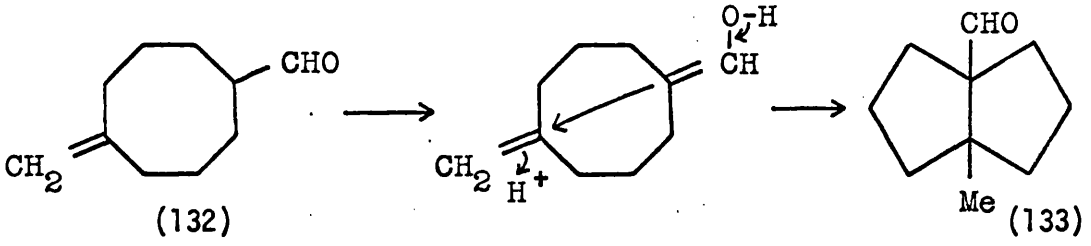
+ (129) 9% + 127, R = OH) 12%

+ (130) trace + (131) 30%

Scheme 39

very different ratio to that observed in solvolysis of the tosylate and brosylate, indicated that isomerisation of the double bond was a very minor process. The formation of 30% of (131) was rationalised by a 1,2 hydride shift before reaction of the exocyclic methylene with the resulting cation. The authors tentatively attributed this to a less ready interaction of cations with exocyclic double bonds than with endocyclic double bonds.

A further interesting example was provided by the reaction of the aldehyde (132).[115] Mild acid treatment at 100° produced the bicyclo[3.3.0]octane (133) by the transannular process shown (Scheme 40).

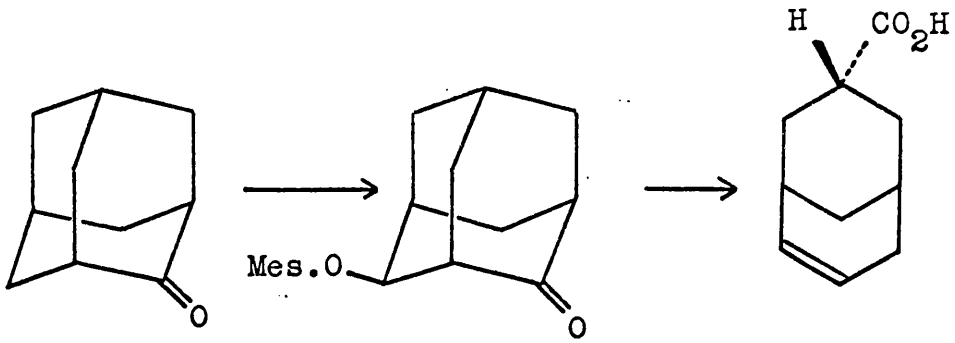


Scheme 40

3.6 The π-Route to Adamantane Derivatives.

π-Route cyclisation of bicyclo[3.3.1]nonane derivatives, or compounds which give bicyclo[3.3.1]nonane intermediates, has proved to be a convenient synthetic route to adamantane derivatives. Only selected examples, which produce non-bridgehead substituted adamantanes will be presented here.[116]

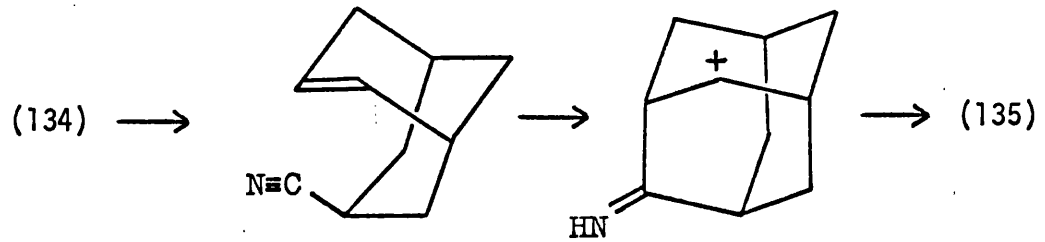
Sasaki, Eguchi, and Toru[117] showed that treatment of adamantanone (134) with sodium azide in methanesulphonic acid gave 4-methylsulphonoxyadamantanone (135), and not the expected amide. The stereochemistry of the product was later deduced from the facile transformation of (135) to (136) upon treatment with base.[118,119] This showed the mesyl group to be equatorial (Scheme 41);



(134) (135) (136)

Scheme 41

a conclusion which was proved by X-ray studies.[120] Isolation of some of the nitrile (137) when the methanesulphonic acid/sodium azide was performed at low temperatures proved that this rearrangement proceeded by a π-cyclisation as shown in Scheme 42 . The stereochemistry of

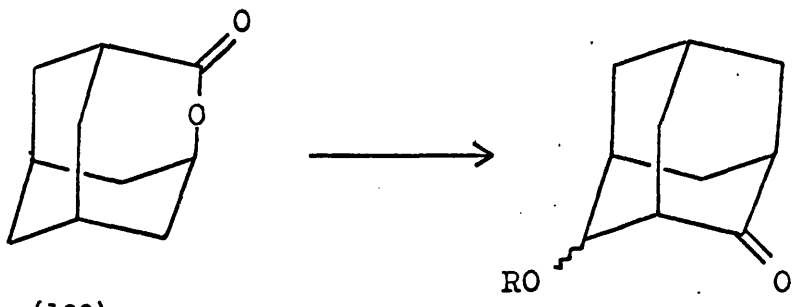


(137)

Scheme 42

the product was taken as evidence for a kinetically controlled reaction with little subsequent epimerisation of the product.

The same paper [118] also includes two other examples of the formation of adamantanes by a π-route. The lactone (138), when treated with hot sulphuric acid gave an equilibrium mixture of adamantanone (139) and starting material (6:1) and treatment with hot methanesulphonic acid gave the mesylate (140) (Scheme 43).



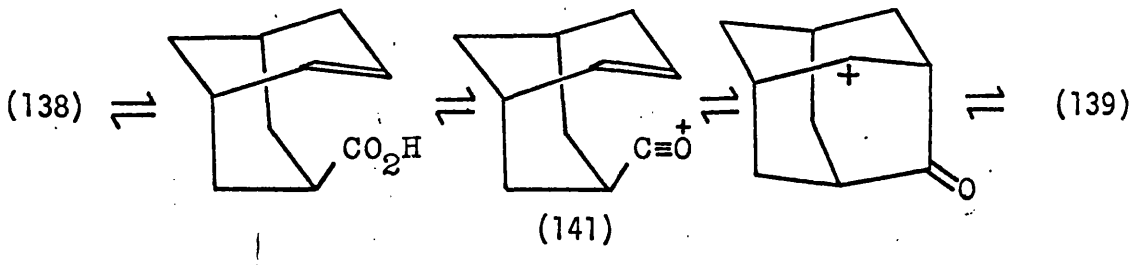
(138)

(139) R = H, 5:1 axial: equatorial

(140) R = Mesyl, 6:1 axial:equatorial

Scheme 43

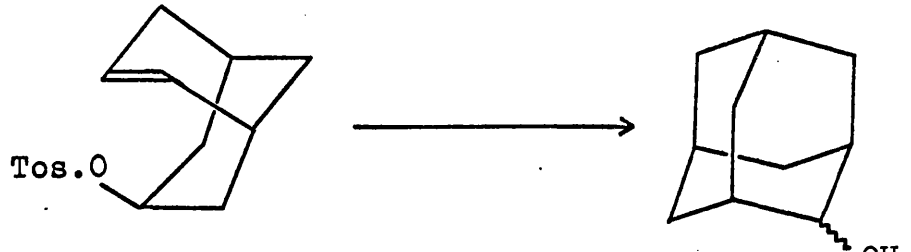
This was rationalised as a fragmentation of the lactone (138) to the bicyclo[3.3.1]nonane acyl cation (141) (Scheme 44) and subsequent closure to the adamantyl cation. This is a series of equilibria and gives the thermodynamically most favoured product (Scheme 44).



(141)

Scheme 44

A similar cyclisation was observed by Schleyer and his co-workers in the solvolysis of the bicyclo[3.3.1]nonene (142).[121] (Scheme 45). This reaction also occurs (in ca. 50% yield) when

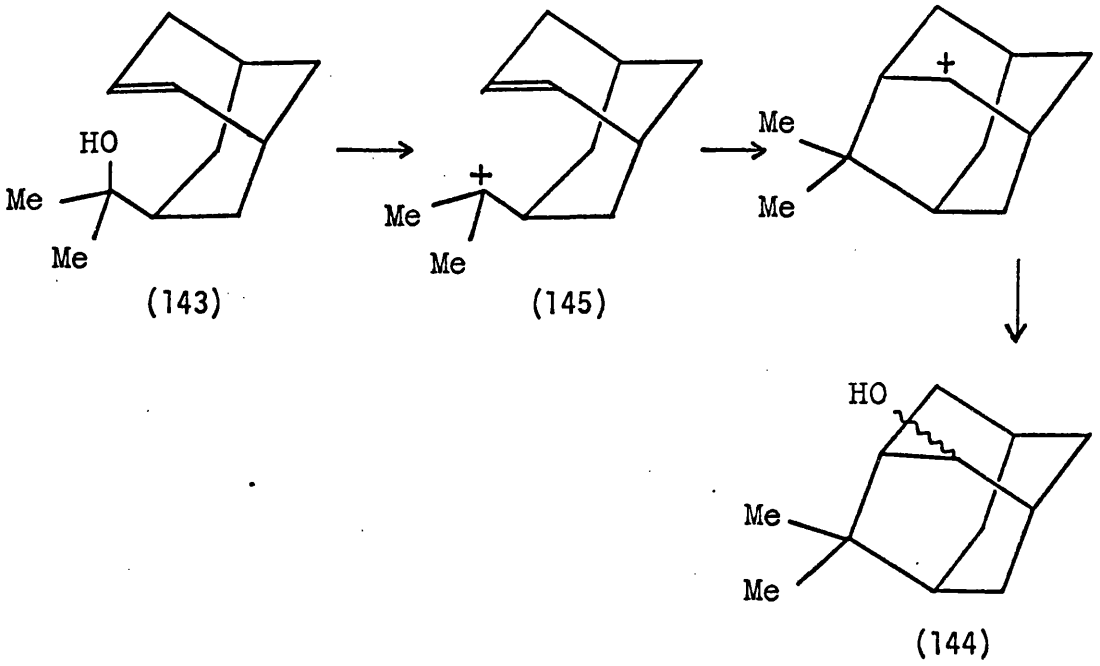


(142)

SCHEME 45

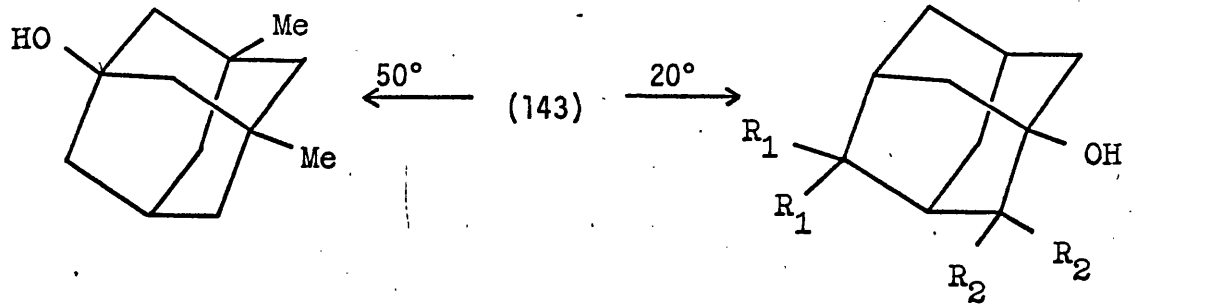
the tosylate (142) is set aside in deuterochloroform solution for 2 days at 6°. Comparison of the rate of solvolysis of (142) with the rate of its saturated analogue indicates that (142) solvolyses 2×10^4 faster at 25°. Thus there is a considerable rate enhancement implying participation by the double bond in the rate determining step.

An extension of this work by Blaney, Faulkner, McKervey, and Step provided a ready synthetic method of producing (2,4,4), (1,2,2), (1,4,4), (1,3,5), and (1,2) substituted adamantanes.[122] Treatment of the tertiary alcohol (143) with hot formic acid, followed by saponification, produced two epimeric alcohols (144) in a combined, isolated, yield of 82% (Scheme 46). The isomer ratio was shown to be 6:1 axial:equatorial alcohol and the mechanism proposed was as shown. Formation of the cation (145) was followed by cyclisation to an adamantyl cation and subsequent reaction with the formate anion.



Scheme 46

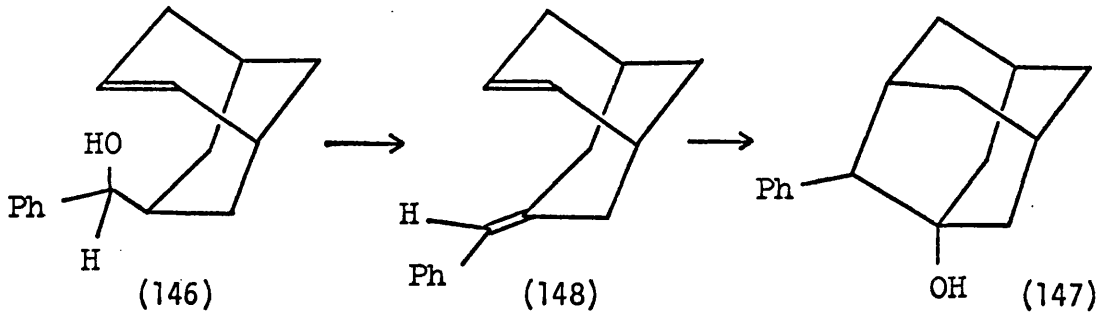
Upon treatment with concentrated sulphuric acid at different temperatures (143) was found to give different products (Scheme 47).



1 : 3 $R_1 = H, R_2 = Me$: $R_1 = Me, R_2 = H$

Scheme 47

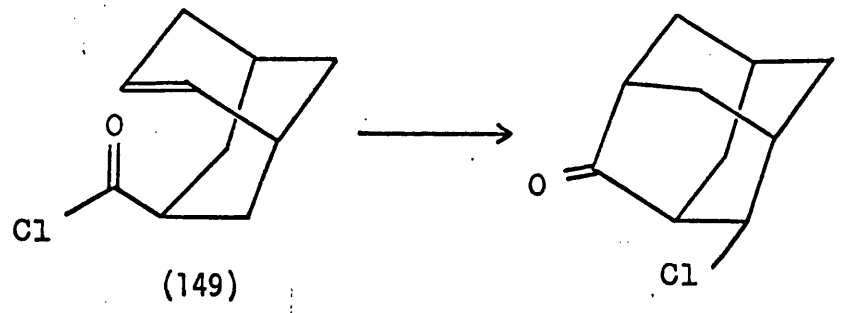
The related alcohol (146), after 2 days reflux in formic acid, was found to give 2-phenyladamantan-1-ol (147) as the major product. That this reaction proceeded by the diene (148) was



(146) (148) (147)

proved by preparing (148) and showing that it gave the same product under the same conditions.

A final example is provided by the rearrangement of the acid chloride (149) with boron trifluoride (Scheme 48).[123]



(149)

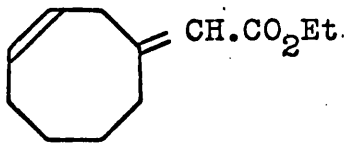
Scheme 48

4. INTRAMOLECULAR REACTION OF CYCLOOCT-4-ENYLIDENE DERIVATIVES

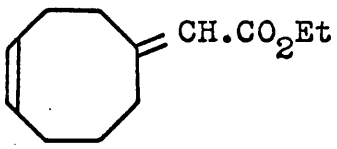
4.1 Assignment of Structure to Products.

It was thought to be of interest to study the reaction of substituted exo-methylene cyclooctenes with boron trifluoride etherate.

Ethyl (cyclooct-3-enylidene) acetate (150) was prepared by reaction of triethyl phosphonoacetate with cyclooct-3-enone. Upon reaction of this ester with boron trifluoride etherate in benzene a complex mixture of products was produced which proved to be inseparable by chromatography.



(150)

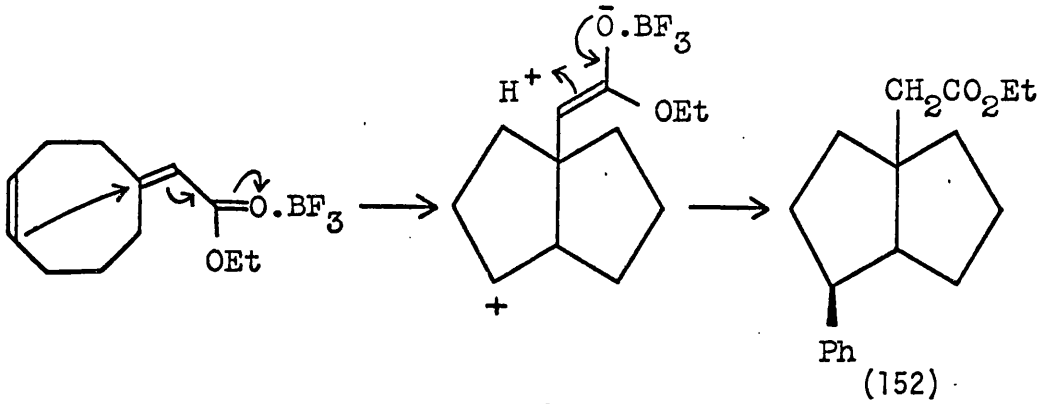


(151)

The isomeric cyclooct-4-enylidene ester (151), however, gave only one ester and its corresponding acid (in 40% and 15% yields respectively) upon treatment with boron trifluoride etherate in benzene. The i.r. spectrum of the ester produced showed disappearance of the α,β-unsaturation, and indicated the presence of a mono-substituted phenyl ring. Examination of the n.m.r. spectrum confirmed the presence of a phenyl group and showed no olefinic protons. A one proton singlet at τ 6.90 indicated there to be only one proton adjacent to either the ester or the phenyl group.

By analogy with the previously published work on cyclooct-4-enyl cations a transannular π-shift to produce a bicyclo[3.3.0]octane

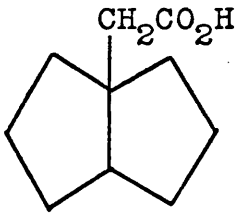
derivative (152) was considered (Scheme 49). For model compound



(152)

SCHEME 49

studies the unsubstituted bicyclo[3.3.0]octane acid (153) was prepared. Arndt-Eistert homologation of the known bicyclo[3.3.0]octane-1-carboxylic acid gave a 20% yield of the acid (153) whose n.m.r. spectrum exhibited



(153)

a clear singlet for the α-methylene protons, well downfield of the mass of aliphatic protons. This does not definitely exclude the postulated structure (152) (the α-methylene protons in (152) could give an AB system which would be shifted upfield into the mass of aliphatic protons by shielding from a cis-4-phenyl group) but it does render it unlikely.

Assignment of a structure to the boron trifluoride product clearly depended upon determining the nature of the one proton singlet at τ 6.90. If this was a benzylic proton then, in the absence of any unusual effects,

the ester function must necessarily be on a fully substituted carbon atom, and vice-versa.

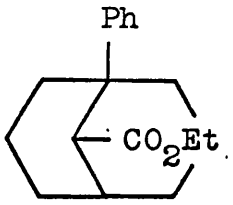
Reduction of the ester with lithium aluminium hydride gave a crystalline alcohol whose n.m.r. spectrum showed that the peak at τ 6.90 shifts upfield into the aliphatic protons and must therefore be due to the proton α to the ester grouping. Further information on the structure was obtained by consideration of the spin-spin coupling pattern of the signal from the hydroxymethylene group. An ABX pattern was observed which was consistent with the single proton β to the hydroxyl group splitting two non-equivalent hydroxymethylene protons. Hence the boron trifluoride product must have one proton adjacent to the ester function.

The alcohol was further reacted with phosphorus oxychloride in pyridine. This gave a mixture of the corresponding chloride and an alkene. The chloride was found to display a similar coupling pattern for the chloromethyl protons to that observed in the alcohol. Spin-decoupling experiments on this chloride proved the splitting pattern to be that postulated. Irradiation of the proton β to the chloride caused the ABX pattern to collapse to a simple AB pattern.

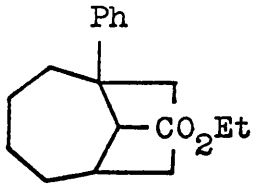
Conversion of the chloride to the alkene proved to be remarkably difficult. Reaction with potassium t-butoxide in refluxing t-butanol, with diazabicyclo[4.3.0]nonane in refluxing benzene, and with quinoline at 140 - 150° were uniformly unsuccessful. Dehydrochlorination was finally achieved by reacting the chloride with potassium hydroxide in ethylene glycol under reflux.

The alkene obtained showed only two olefinic protons in the n.m.r. which confirmed that the original ester had only one α-proton. A more significant point, however, could be drawn from the n.m.r. spectrum. The alkenic protons appeared as two doublets (J 2 Hz), the separate doublets being at τ 5.3 and τ 6.0.

The collated data on the ester product, and its derivatives, indicated (154) or (155) to be likely structures. This leads to (156)

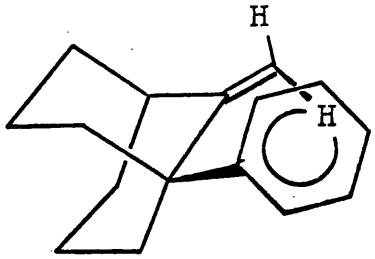


(154)

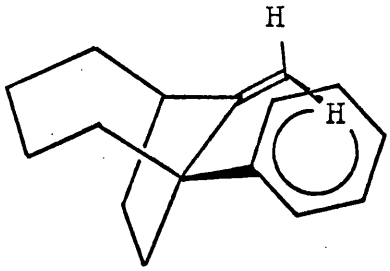


(155)

or (157) for the derived olefins, because, with either a [3.3.1] or a [4.2.1] skeleton, one of the olefinic protons will be held over the aromatic ring and resonate at a higher field (Fig. 4)



(156)



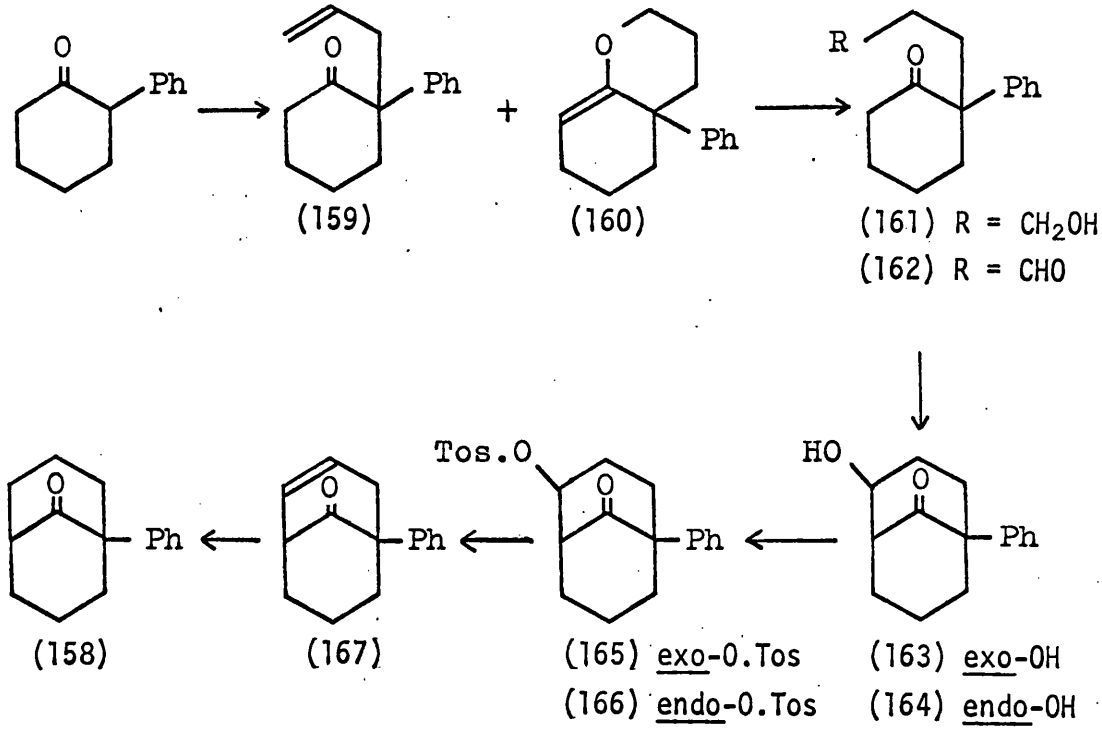
(157)

Fig. 4

Reaction of the alkene with osmium tetroxide/sodium periodate, or potassium permanganate in t-butanol/water, proved to be unsuccessful. However, ozonolysis followed by an oxidative work-up gave some of the required ketone which was isolated as colourless crystals. The spectroscopic data on this ketone did not allow a firm conclusion to be drawn between the two possible skeletons; however, it did make a suitable synthetic objective. Synthesis of the ketone (158) was chosen because this was deemed the most plausible structure.

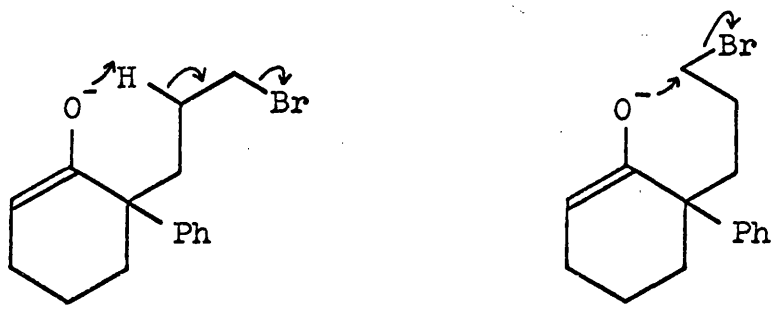
4.2 Synthesis of 1-Phenylbicyclo[3.3.1]nonan-9-one

This ketone was prepared by the route shown in Scheme 50.



Scheme 50

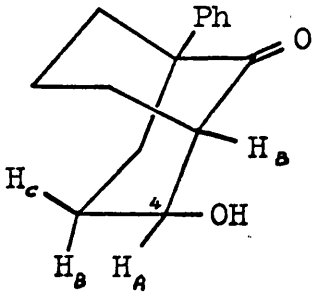
Alkylation of 2-phenylcyclohexanone with 1,3-dibromopropane gave the alkene (159) and the enol ether (160). Formation of these two products probably proceeds through the intermediacy of an ambident anion (Scheme 51). Formation of enol ethers in this way has been



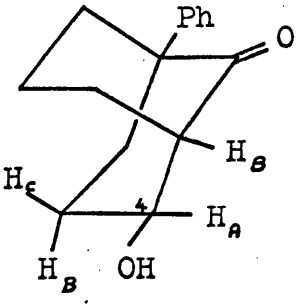
Scheme 51

observed in other systems.[124] Acid-catalysed opening of (160), followed by chromium trioxide/pyridine oxidation gave the aldehyde (162). This was cyclised by dilute acid[125] to produce the epimeric ketols (163) and (164) which could be easily separated by column chromatography and shown to be present in the ratio of 1:1.7.

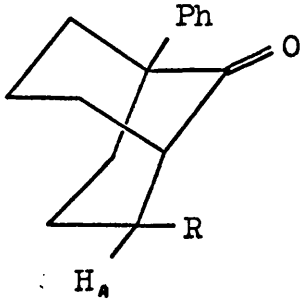
The stereochemistry of these ketols could be determined by n.m.r. spectroscopy.[126] In the majority of simple substituted bicyclononanes the preferred conformation is chair-chair, and hence the coupling constant between H_A and the protons H_B is the same whatever the substitution stereochemistry at C_4 (fig. 5). However, the dihedral angle between H_A and H_C clearly depends upon whether the substituent is axial or equatorial. As a result of this the width of the signal from H_A gives a clear indication of the stereochemistry at



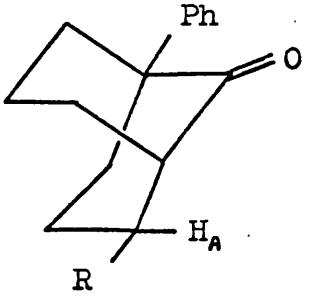
(163)



C_4. This can be seen from the results presented in the Table (3).



(I)

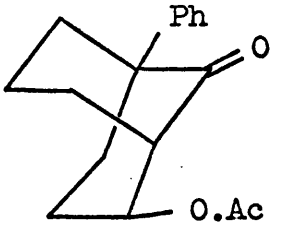


(II)

	$W^{\frac{1}{2}}$ (H_A).Hz	ν_{max}(OH)	ν_{max}(CO)
I (R = Cl)	7	-	1715
I (R=OAc)	8	-	1715
I (R=OH)(163)	8	3250(br)	1725(sh)
II (R=OH)(164)	15	3500(sh)	1705(br)
II (R=Cl)	20	-	1710

Table 3

The i.r. spectra of the separate ketols (163) and (164) as nujol mulls were markedly different (Table 3), implying that the axial ketol (163) is intramolecularly hydrogen bonded. A similar effect on ν_{max} (C = O) in 2-hydroxybicyclo[3.3.1]nonan-9-one was noted by Kraus, Rothenwöhrer, and Chassin.[126] Attempted dehydration of ketols (163) and (164) with phosphorus oxychloride/pyridine gave only the corresponding chlorides with complete inversion of configuration. The alkene (167) was, however, successfully prepared by solvolytic elimination of the tosylate. This was a method used by Parker and his co-workers in their synthesis of analogues of lycopodium alkaloids.[125] Tosylates were prepared of each epimer of the ketol and separately subjected to buffered acetolysis. The endo-tosylate (166) does not have the correct stereochemistry for concerted elimination and the major product (70%) is the acetate (168), produced



(168)

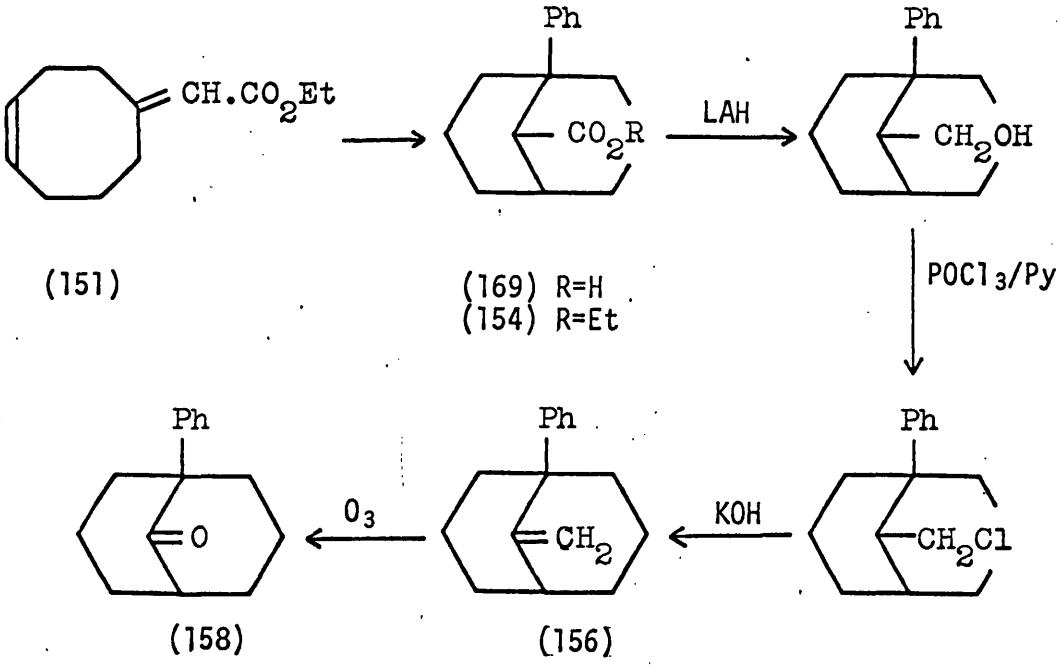
with complete inversion of configuration. Only 22% of the alkene (167) is obtained. The exo-tosylate, however, has the correct orientation for elimination and gives 75% of the alkene (167) and only 11% of acetate, of undetermined stereochemistry.

The alkene (167) was then hydrogenated to give 1-phenylbicyclo-

[3.3.1]nonan-9-one (158) which was shown to be identical to the ketone produced by degradation of the ester (154). Wittig methylenation of this ketone (158) gave a sample of the alkene (156) which was, again, identical with the sample prepared previously.

Subsequently it was found that 1-phenylbicyclo[3.3.1]nonan-9-one (158) had been prepared by an alternative route.[127] A sample kindly provided by Professor Nicoletti proved to be identical with the previously described samples.

The reaction of ethyl (cyclooct-4-enylidene)acetate with boron trifluoride etherate in benzene, therefore, must produce 1-phenylbicyclo[3.3.1]nonane-9-carboxylic acid and its corresponding ester. The degradative sequence is shown in Scheme 52.



Scheme 52

N.m.r. studies of the ester (154) utilising the paramagnetic shift reagent tris(dipivalomethanato)europium^{III} were also of some help in assigning the structure.[128] Table 4 shows that the methylene protons of the ethyl group, and the singlet assigned to H_9, are shifted to a considerable extent. The largest effect is seen, however, in the aromatic signal. From being a narrow, five proton multiplet the signal splits into a two proton and a three proton multiplet. These data are consistent with an ester having one α proton and a phenyl group whose ortho- protons are much closer to the ester grouping than the meta- or para- protons.

Table 4

Induced Paramagnetic Shifts

	(154)	(154)+Eu(DPM)$_3$[a]	Δτ
Ph-	2.80 (5H,m)	2.05 (2H,m)	0.75
		2.70 (3H, m)	0.10
-O.CH_2.CH_3	6.10 (2H,q)	4.60 (2H, q)	1.50
H_9	6.90 (1H,s)	5.30 (1H, s)	1.60

(a) 1:4 molar ratio of Eu (DPM)$_3$:Ester

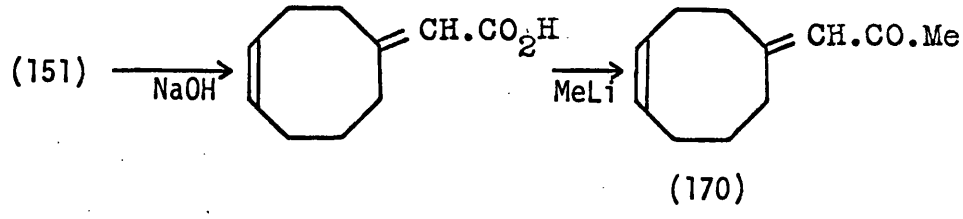
4.3 Other Examples

The reaction of ethyl (cyclooct-4-enylidene)acetate with nitrobenzene and boron trifluoride etherate at 80-90° for 17h gave no

homogeneous product. This indicates that a nucleophilic trapping by benzene may be important in trapping some intermediate.

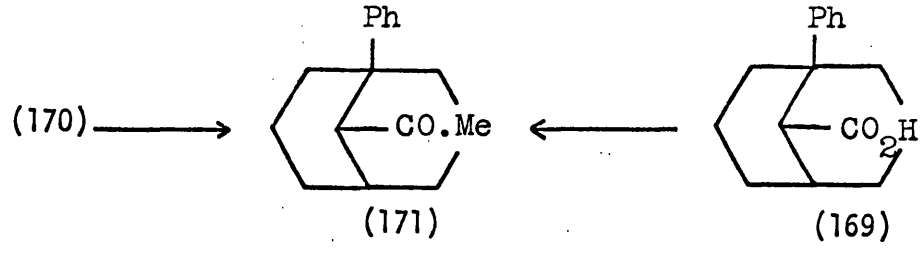
When toluene was substituted for nitrobenzene in the above reaction tolylbicyclo[3.3.1]nonane derivatives were produced in yields of 28% for the ester, and 21% for the acid. Crude estimates of the time needed for complete reaction, however, imply no great increase in rate over that of the reaction with benzene.

The methyl cyclooctenylidene ketone (170) was prepared by the method shown in Scheme 53 and subjected to the boron trifluoride etherate/benzene reaction conditions. This too gave a bicyclo[3.3.1]-nonane derivative (171) (25%), identical with the product obtained



Scheme 53

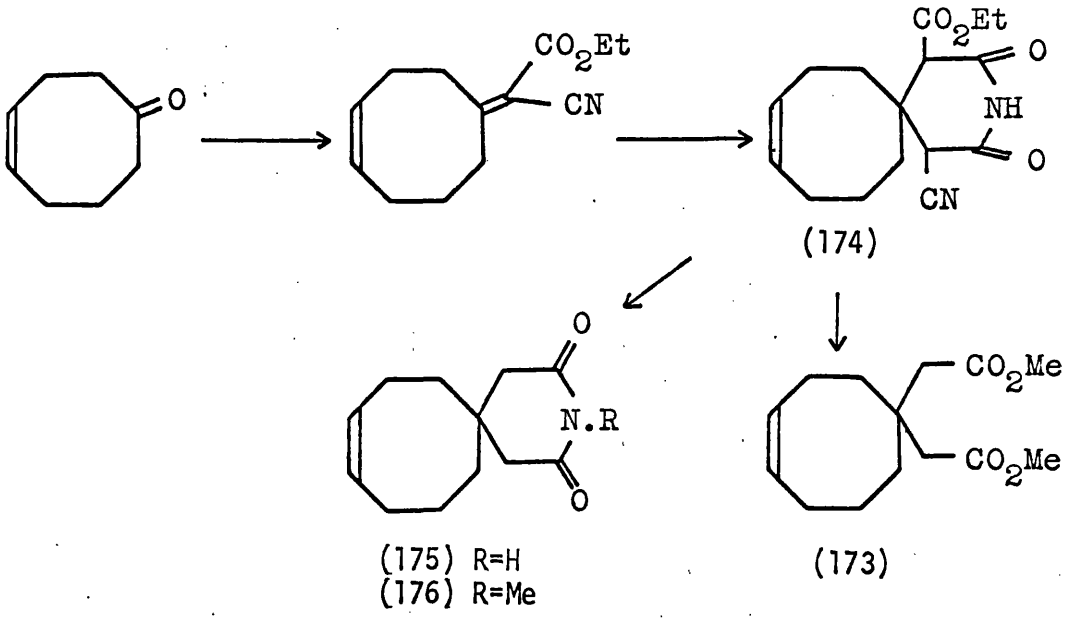
by treatment of (169) with methyl-lithium. (Scheme 54).



Scheme 54

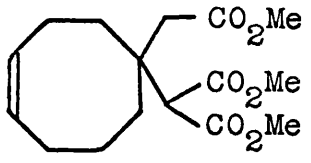
When ethyl (cyclooct-4-enylidene)acetate was refluxed with boron trifluoride etherate alone, and the ester product was hydrolysed with base, a 14% yield of a single acid was obtained. By comparison with an authentic sample[129] this was shown to be bicyclo[3.3.1]nonane--9-carboxylic acid (172). A slight improvement in the yield of this product was obtained by mixing dioxan with the reaction mixture and distilling off the displaced diethyl ether up to a temperature of 100°C. Heating under reflux for 16h then gave a 21% yield of the acid (172).

As an extension of this work it was decided to prepare a cyclooct-4-enyl acetate which was substituted at the 1-position. This had the additional advantage of providing a probe for certain aspects of the reaction mechanism. The required compound, dimethyl 3,3-(cyclooct-4'-enyl)glutarate (173) was prepared by a modified Guareschi reaction[130] from cyclooct-4-enone, as shown in Scheme 55.



Scheme 55

The dimethyl ester produced contained contaminants which were barely separable by chromatography. Preparative g.l.c., however, readily separated three components in the ratio of 43:53:3 (in order of elution from the column). An insufficient amount of the minor product was available for characterisation, but the first eluted compound was collected in an analytically pure state and shown to be the required ester (173). The second eluted fraction could not be collected pure, it was always contaminated with a little (173). Mass spectral analysis, and n.m.r. spectroscopy, indicated that this fraction could be the triester (177). All attempts to hydrolyse and



(177)

decarboxylate this postulated triester to the corresponding diester failed. In consequence this assignment must be considered provisional.

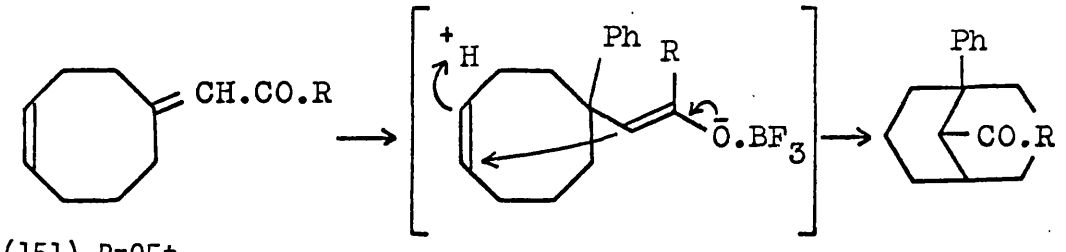
Reaction of the diester (173) with boron trifluoride etherate in refluxing benzene for 18h, or with toluene p-sulphonic acid in refluxing benzene, gave no reaction. The significance of this reaction will be discussed in the next section.

4.4 Mechanism

The possible mechanisms envisaged for this reaction fall into three main groups: (i) conjugate Friedel-Crafts addition of benzene

(or toluene) onto the exocyclic double bond, with subsequent ring closure; (ii) formation of a cation at the 5-position of the cyclooctyl ring, ring closure to a 1-bicyclo[3.3.1]nonyl cation and trapping of this cation by the aromatic system, (iii) involvement of a tricyclic intermediate.

The first type of mechanism is shown in Scheme 56 . The initial conjugate Friedel-Crafts addition is a well-documented



(151) R=OEt
(170) R=Me

(178)

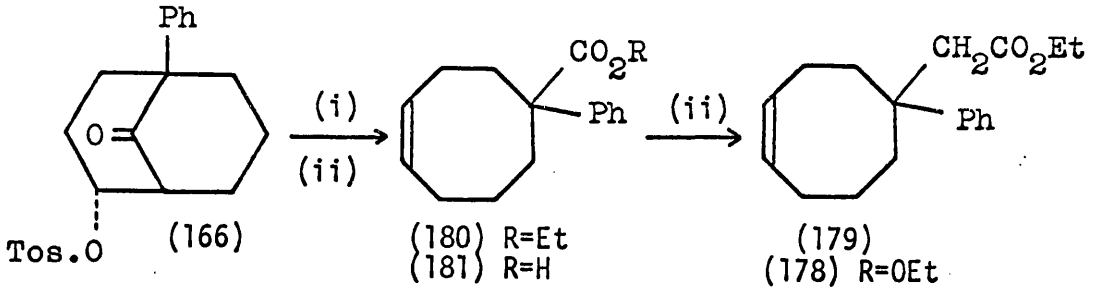
(182)

Scheme 56

reaction.[131] Interruption of the boron trifluoride etherate reaction before completion, however, gives only starting material and product, no (178) is detectable. This can only be accommodated by postulating that the second step is very fast, and therefore that the first step is rate-determining. The reaction of the ester (151) with boron trifluoride etherate in toluene would thus be expected to be faster than the reaction with benzene.

To test this mechanism it was necessary to synthesise the intermediate (178, R = CH_3 or OC_2H_5). Attempts to synthesise

(178 , R = CH_3) by copper-catalysed conjugate addition of phenyl magnesium bromide, or by conjugate addition of diphenyl copper lithium, to cyclooctenylidene methyl ketone (170) failed. The phenyl-substituted cyclooctenyl ester (178 , R = OC_2H_5), however, was accessible by synthesis from the previously prepared keto-tosylate (166) (Scheme 57). The endo- orientation of the tosylate group makes this group anti-



(i) NaOEt (ii) NaOH (iii) Arndt-Eistert, $EtOH/H^+$

Scheme 57

periplanar to the C_5 - C_9 bond; consequently, facile fission of this bond occurs (fig. 6). Many examples of this type of reaction exist.[132]

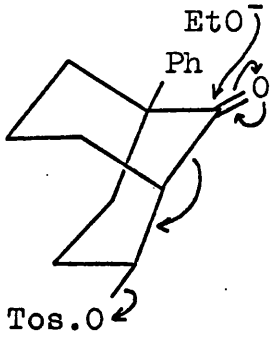


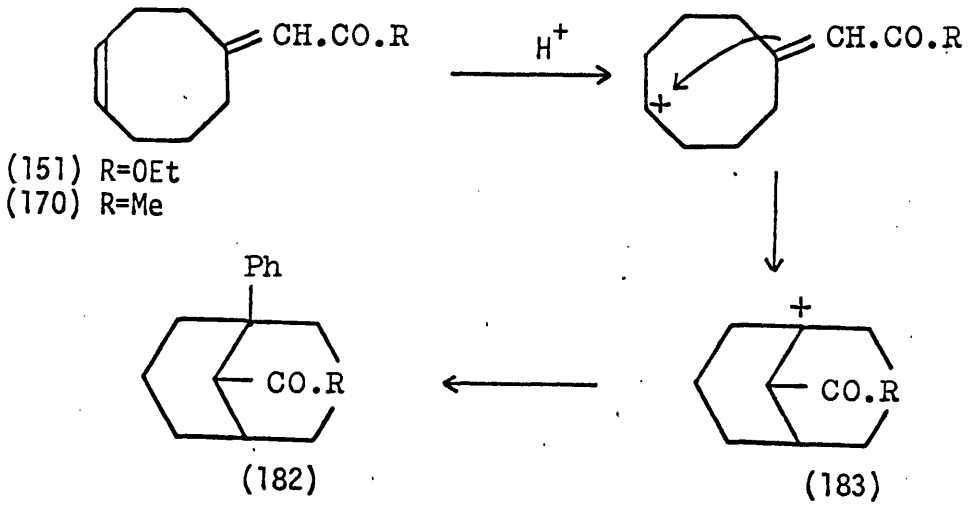
Fig. 6

Reaction of the keto-tosylate (166) with sodium ethoxide gave the ester (180) in good yield, and hydrolysis then gave the acid (181). Arndt-Eistert homologation of the corresponding acid chloride, followed by Fischer-Speier esterification, gave a mixture of starting ester (180) and homologated product (179). These were separated by selective hydrolysis ((179) has a primary ester group and is hydrolysed very much faster than (180)) followed by esterification and column chromatography.

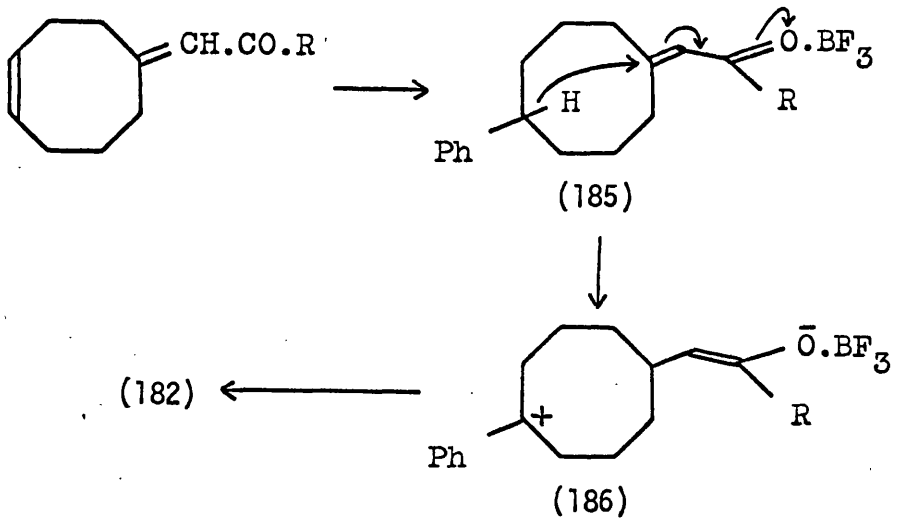
However, upon reaction of this ester (179) with boron trifluoride etherate in benzene none of the bicyclic ester (154) was produced. This clearly rules out this ester as an intermediate. The lack of reactivity displayed by the glutarate ester (173) in boron trifluoride etherate/benzene correlates well with the lack of reactivity of (179).

This postulated mechanism for the formation of bicyclononane derivatives (182) is hence shown to be untenable.

Mechanisms involving a 5-cyclooctyl cation could proceed by protonation of the endocyclic double bond (Scheme 58 a), or by Friedel-Crafts phenylation of the endocyclic double bond followed by a 1,5 hydride shift (Scheme 58 b). In the first mechanism the crucial step is the transannular ring closure to form the 1-bicyclo[3.3.1]-nonyl cation. Electrophilic cyclisation of this type is a well documented process.[133] The formation of the bridgehead cation (183) by such a cyclisation may be favoured by a relief of strain as it has been demonstrated that this cation is nearly strainless.[134]



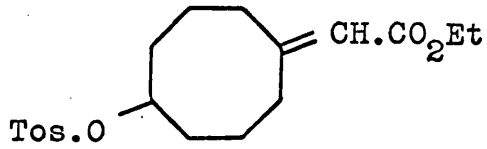
Scheme 58a.



Scheme 58b

Rearrangement to a 2-bicyclo[3.3.1]nonyl cation by 1,2 hydride shift would be inhibited by poor orbital overlap,[33] and loss of a proton is not favoured since the resulting alkene is strained.[135] Hence the only ready reaction path available for the 1-bicyclo[3.3.1]nonyl cation would be trapping by benzene (or toluene) to form (182). Some

support for this mechanism could be gained by solvolysing the tosylate (184) and seeking bicyclo[3.3.1]nonane products.

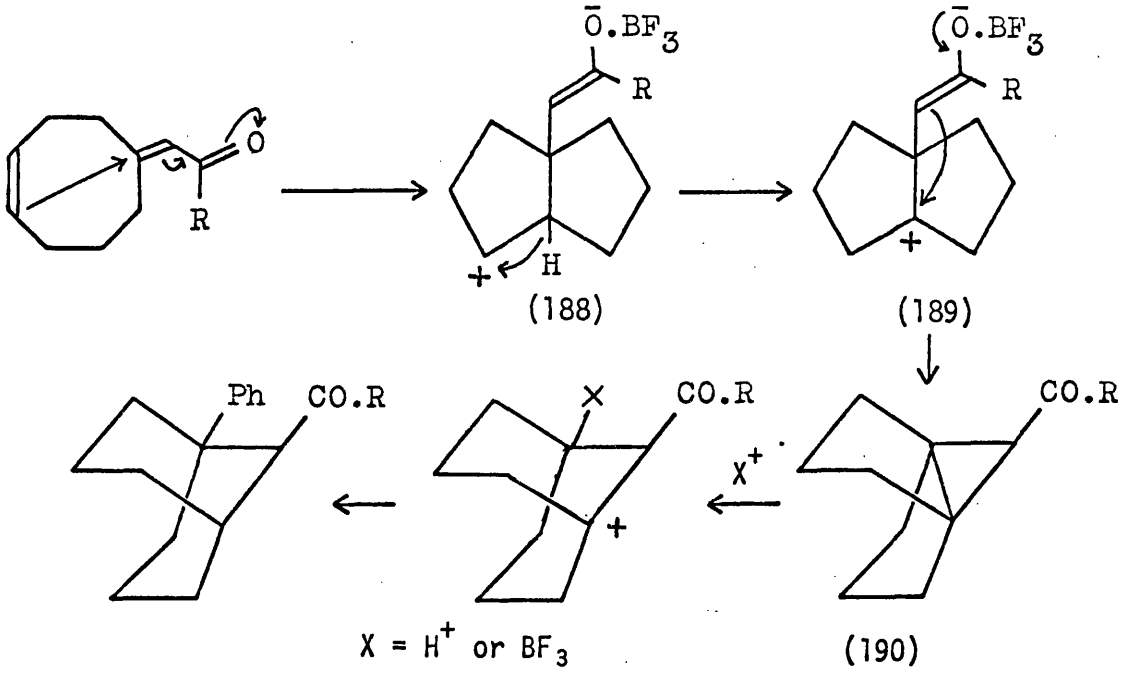


(184)

Scheme 58b illustrates a mechanism in which the first step is a Friedel-Crafts phenylation of the endocyclic double bond. This could be mediated by either the boron trifluoride etherate or by a trace of hydrogen fluoride in the Lewis acid. Hydrogen fluoride is a good Friedel-Crafts catalyst,[136] and boron trifluoride etherate has been reported to catalyse the alkylation of benzene with propene.[137] The 5-phenylcyclooctane (185) formed could then undergo a 1,5 hydride shift to produce the cation (186). By analogy with the previously discussed hydride transfer in various 5-substituted cyclooctyl tosylates this should be a favoured process. Transannular dipolar coupling of this cation would then produce the observed product. The postulated intermediate (185) is now being synthesised to test this postulate. (See Appendix 2).

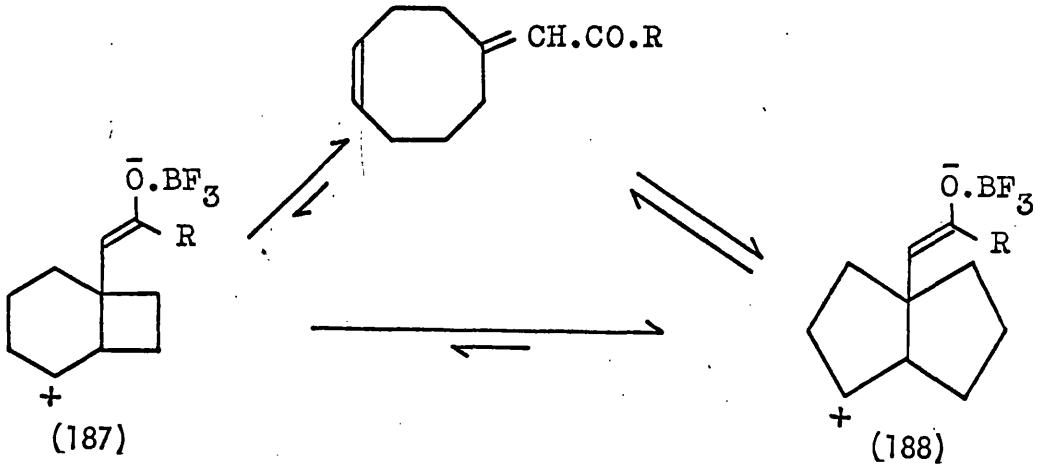
Both of these mechanisms suffer from the disadvantage that they require formation of a cation in the 5-position. Furthermore, only the first of these possible mechanisms can be used to explain the formation of 9-carboethoxybicyclo[3.3.1]nonane from boron trifluoride etherate treatment alone.

The remaining postulate involves the formation of a tricyclo[3.3.1.$0^{1,5}$]nonane intermediate (Scheme 59). If the first

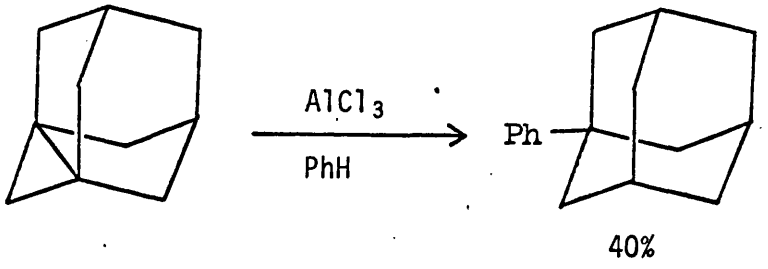


Scheme 59

step is written as an equilibrium between the dipolar species (187) and (188) (Scheme 60) with the bicyclo[3.3.0]octane skeleton as the most favoured form, then the final production of a bicyclo[3.3.1]nonane is readily accounted for. Rapid 1,2 hydride shift to form the cation (189)



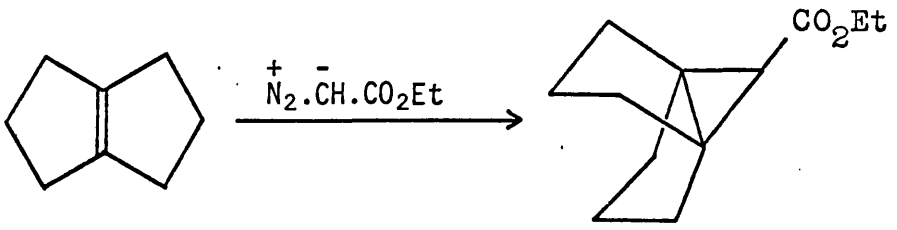
would then remove the cation (188) from the equilibration step (a similar process may be operative in the Koch-Haaf carboxylation of 1,5 cyclooctadiene[138]), and intramolecular dipolar trapping would then produce the tricyclic propellane (190). Tricyclo[3.3.1.0]nonanes have been prepared,[139] and their homologated analogue, 1,3-dehydroadamantane, is also known.[140] The central bond in this type of compound has increased p-character[140b] and is thus readily attacked by electrophiles. For example, 1,3-dehydroadamantane reacts readily with aluminium chloride in benzene (Scheme 61). This provides a good



Scheme 61

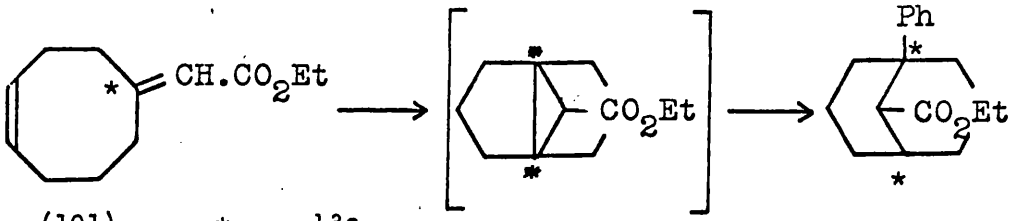
analogy for the postulated phenylation of the tricyclononane (190). The production of 9-carboethoxybicyclo[3.3.1]nonane from the reaction of the cyclooctenylidene acetate (151) with boron trifluoride etherate alone can also be explained by this type of mechanism. Formation of the tricyclic intermediate could be followed by complexation with boron trifluoride etherate and ring-opening by intermolecular hydride shift.

The propellane (190) may be preparable by carbene addition to $\Delta^{1,5}$-bicyclo[3.3.0]octene (Scheme 62). This olefin has been prepared



Scheme 62 (190)

previously[141] and tricyclic systems have been prepared by carbene addition to bicyclic systems.[142] If this propellane undergoes phenylation and reduction in the manner postulated then this would constitute support for the proposed mechanism. Definitive proof that this was the operative mechanism could, however, be difficult. A possible method would be to react ethyl(1-^{13}C-cyclooct-4-enylidene) acetate (191) with boron trifluoride etherate in benzene. As 9-carboethoxybicyclo[3.3.1]nonane is inert to these reaction conditions only a tricyclic mechanism would lead to scrambling of the ^{13}C label between the bridgehead positions of the product (Scheme 63). The



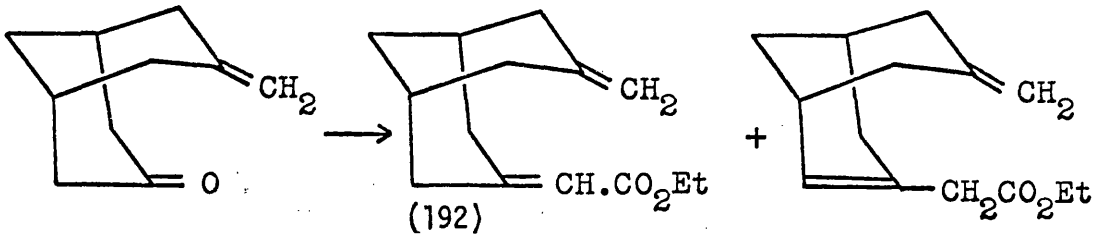
(191) * = ^{13}C

Scheme 63

^{13}C chemical shifts of the bridgehead carbons should be sufficiently different[143] to show whether scrambling had occurred.

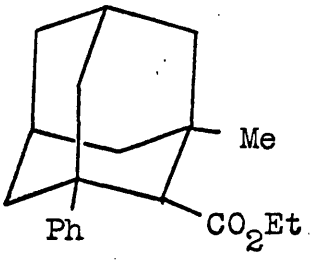
4.5 The Reaction of 7-exo-Methylenebicyclo[3.3.1]non-3-enylidene Acetate with Boron Trifluoride Etherate in Benzene.

The title ester (192), admixed with its β,γ unsaturated isomer, was prepared by the reaction of triethyl phosphonoacetate anion with 7-exo-methylenebicyclo[3.3.1]nonan-3-one (Scheme 64). This was



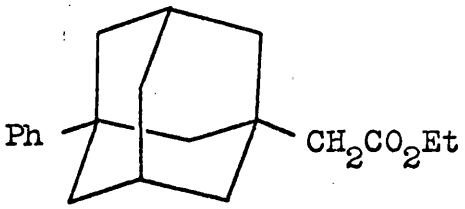
Scheme 64

subjected to the boron trifluoride etherate/benzene reaction conditions which had been successful for the cyclooctenylidene esters. By g.l.c. this was shown to produce a mixture of two esters in the ratio of 3:1. The major component could be separated by selective hydrolysis and crystallisation, as the rate of hydrolysis of the minor product was considerably faster. Spectroscopic data and elemental analysis were in accord with the structure (193) and this was confirmed by spin-decoupling experiments. Shortage of time precluded



(193)

characterisation of the second product. This component is known to be isomeric with (193) (mass spectrum) and its greater rate of hydrolysis is consistent with a primary ester. This suggests structure (194).



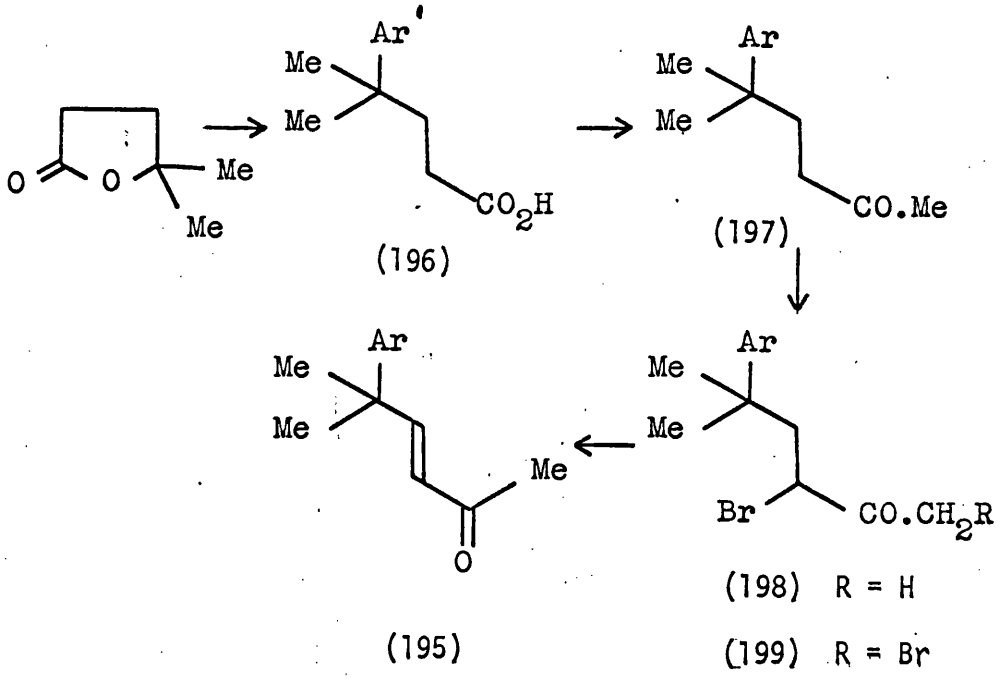
(194)

This reaction obviously cannot proceed by the tricyclic mechanism postulated for the cyclooctenyl case. Rearrangement following a Friedel-Crafts phenylation of the exo-methylene group is similarly untenable. The presence of mixed isomers in the starting, unsaturated, ester makes mechanistic conclusions difficult. Further work is obviously needed on this topic.

APPENDIX 1

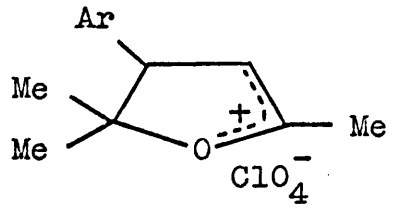
Preparation of 5-(p-methoxyphenyl)-5-methyl-hex-3-en-2-one and its Reaction with Perchloric Acid.

It was thought to be of interest to study the reaction of ketone (195) with acid. The mode of synthesis is shown in Scheme (65). Alkylation of anisole with dimethyl butyrolactone gave the phenol (196) which was methylated with dimethyl sulphate and converted to the ketone (197) with methyl-lithium. Bromination of this ketone with cupric bromide gave, in addition to the desired bromide (198), two further products. One of these by-products (formed in 7% yield) was shown to be a di-bromide (mass spectrometry) and further spectroscopic data unequivocally showed this product to be 1,3-dibromo-5--(p-methoxyphenyl)-5-methyl-hexan-2-one (199).



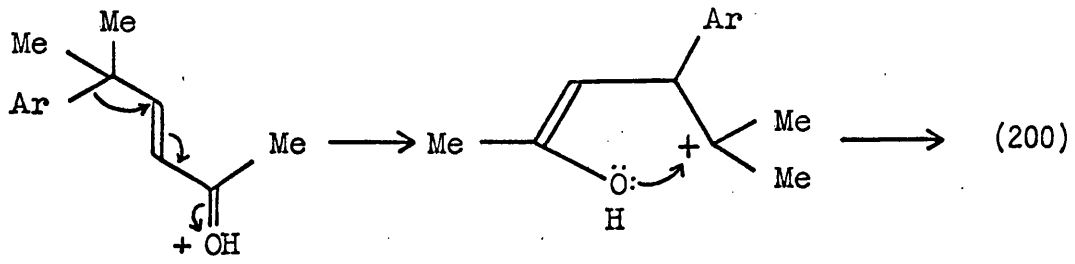
SCHEME 65

Upon dissolution in 70% aqueous perchloric acid the ketone (195) underwent complete reaction in 3h 40 min, the reaction being followed by n.m.r. spectroscopy. No intermediate was observed. The spectrum of the product thus observed was consistent with formation of the perchlorate salt (200). All attempts to isolate this product only resulted in an intractable mixture inseparable



(200)

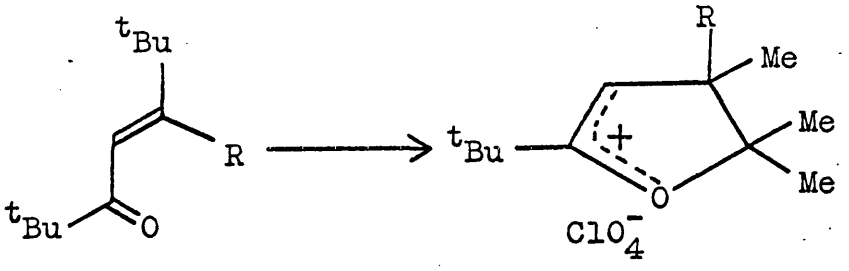
by chromatography. However, upon redissolving this mixture in perchloric acid, the furanylium spectrum was again observed. Formation of this product is rationalised by the mechanism shown in Scheme (66).



SCHEME 66

Formation of such furanylium salts has been observed previously. Treatment of the ketones (201) or (202) with perchloric acid gave salts

(203) and (204) respectively, by a similar mechanism to that postulated.[161] The ketone (202) was also cyclised with fluoroboric acid.[162] In all these cases the product was isolated as a crystalline salt. Rundel and Besserer conclusively proved the structure of the product by independent synthesis.



(201) R = Me

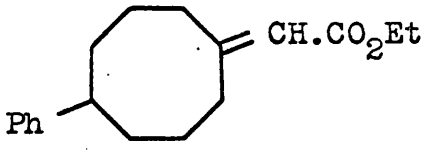
(202) R = H

(203) R = Me

(204) R = H

APPENDIX 2

One of the postulated mechanisms for the rearrangement of ethyl cyclooct-4-enylidene acetate to 1-phenylbicyclo[3.3.1]nonane-9-carboxylic acid (169) and its corresponding ester (154), involved the intermediacy of ethyl 5-phenylcyclooct-4-anylidene acetate (185) (p. 89). This ester



(185)

has now been synthesised [163] and shown not to be an intermediate in the rearrangement, no bicyclic ester (154) or acid (169) being observed upon treatment with boron trifluoride etherate in benzene.

(163) Personal communication from Dr. R.S. Atkinson.

EXPERIMENTAL

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

Infrared spectra were obtained on either a Perkin-Elmer 237 or 257 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian model T60 spectrometer, unless otherwise stated, with tetramethylsilane as an internal standard. 100 m Hz spectra were recorded on a Jeol JNM-PS-100 spectrometer. Mass spectra were obtained on an A.E.I. MS9 mass spectrometer, and ultraviolet spectra on a Unicam SP800.

Gas-liquid chromatography was carried out on a Perkin-Elmer F11 or a Pye-Unicam series 104 chromatograph. Preparative gas-liquid chromatography was carried out on the Pye-Unicam series 104.

Elemental analyses were performed by Dr. F.B. Strauss Ltd., Oxford, or by Dr. F. Pascher, Bonn.

Solvents were dried and/or purified as follows:-

(a) Ether and benzene were dried by standing over sodium wire unless required very dry, in which case they were distilled from lithium aluminium hydride.

(b) Pyridine was freshly dried before use by distillation from barium oxide onto sodium hydroxide pellets.

(c) Dichloromethane was purified by distillation from chromium trioxide/pyridine immediately before use.

(d) Tetrahydrofuran was dried, and purified, by refluxing over potassium hydroxide pellets, and then distilling the decanted tetrahydrofuran from lithium aluminium hydride.

(e) Acetone was purified, and dried, by distillation from potassium permanganate, then from potassium carbonate.

(f) Nitrobenzene was dried by distillation at atmospheric pressure, the fore-run being discarded.

(g) Methanol was dried by distillation from magnesium methoxide.

(h) Dimethylformamide was dried by distillation, under reduced pressure, from calcium hydride.

(i) Boron trifluoride was freshly purified before use by the method of Zweifel and Brown.[144]

(j) Unless otherwise stated, the petroleum fraction used was that boiling at 60-80°C, referred to as "petrol".

"Kieselgel" refers to Merck Kieselgel 60 PF 254; "alumina" used was of the grade Spence type H.

In the presentation of the nuclear magnetic resonance spectra of para-substituted aromatic compounds the AA'BB' pattern is denoted by the positions of the four main peaks.

Mass spectra are denoted by the mass of the ion (in units of m/e) followed, in parentheses, by the relative intensity (expressed as a percentage).

Abbreviations used in the presentation of spectra are as follows:-

I.R. spectra - s strong, m medium, w weak, br broad.

N.M.R. spectra - s singlet, d doublet, t triplet, q quartet, dxd doublet of doublets, etc.

Infrared spectra of crystalline solids were taken as nujol mulls, those of liquid samples being taken as thin films.

Ethyl 1-Hydroxycyclooctane Acetate

Prepared by the method of Fieser et al.[145] b.p. 100-104°/0.4mm (lit. 98.5-100°/0.5mm).

Reaction of Ethyl 1-Hydroxycyclooctane Acetate with Sulphuric Acid

Ethyl 1-hydroxycyclooctane acetate (200mg) was added to a 70% solution of sulphuric acid in water (25ml) and set aside at room temperature for 10min. The reaction mixture was then saturated with water and extracted with ether. After washing the ethereal solution with water, drying ($MgSO_4$), and removing the solvent, the resulting oil was then run on a Kieselgel column (15g, 20:1 benzene:ethyl acetate as eluant) to give the lactone (45) (77mg, 50%) as a clear oil, b.p. 105-110°/1.5mm (lit.[69] 135-136°/1mm). ν_{max} 1780s cm^{-1}, τ (CCl_4) 5.30-6.10 (1 x H2, broad multiplet), 7.20-9.20 (15 x aliphatic H, m). (Found: C, 71.45; H, 9.65. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.6%). m/e 168 (100%, m^+), 139 (77%), 122 (75%), 108 (78%), 98 (77%), 96 (67%), 81 (65%).

Ethyl 1-Cyclooctenyl Acetate

Prepared by the method of Wolinsky and Erickson by using excess sodium hydride.[146] b.p. 106-107°/1.5mm (lit. 81-83°/0.58mm).

Reaction of Ethyl 1-Cyclooctenyl Acetate with Toluene p-Sulphonic Acid.

Ethyl 1-cyclooctenyl acetate (2g) and toluene p-sulphonic acid

(4g) were dissolved in benzene (400ml) and refluxed for 4 days. The benzene was then reduced in volume on a rotary evaporator, washed twice with water, dried ($MgSO_4$), and solvent removed to yield a pale yellow oil. This was purified by column chromatography (100g Kieselgel, benzene as eluant) to give the lactone (45) (530mg, 31%) contaminated by traces of starting material. A sample of this material was re--chromatographed to provide a sample, b.p. 110-115°/2.0mm, identical with the lactone prepared previously.

Reaction of Ethyl 1-Cyclooctenyl Acetate with Boron Trifluoride Etherate.

Ethyl 1-cyclooctenyl acetate (200mg) was mixed with benzene (10ml) and boron trifluoride diethyl etherate (10ml) and refluxed for 18h. The cooled reaction mixture was then worked up in the usual way to yield a dark brown oil. This was purified by column chromatography (15g, Kieselgel, chloroform as eluant) to give only starting material (135mg).

Ethyl Cyclooctylidene Acetate.

Prepared by the method of Wolinsky and Erickson,[146] b.p. 93-96°/0.70mm (lit. 81-83°/0.58mm).

Reaction of Ethyl Cyclooctylidene Acetate with Boron Trifluoride Diethyl Etherate.

Ethyl cyclooctylidene acetate (200mg) was dissolved in benzene (10ml) and boron trifluoride diethyl etherate (10ml) and refluxed for 24h. The cooled reaction mixture was then worked up in the usual way

and the resulting dark brown oil was chromatographed (10g Kieselgel, eluting with chloroform) to yield only ethyl 1-cyclooctenyl acetate (110mg).

Ethyl Cyclooctylidene Acetate and Ethyl 1-Cyclooctenyl Acetate.

Ethyl 1-hydroxycyclooctane acetate (24.7g) was dehydrated with phosphorus oxychloride/pyridine to give a pale yellow oil (18.2g, 81%) consisting of a mixture of the $\alpha\beta$ and $\beta\gamma$ isomers. This was used directly in the next step without any further purification.

Ethyl Cyclooctyl Acetate.

The mixture of ethyl 1-cyclooctenyl acetate and ethyl cyclooctenylidene acetate (18.2g) from the previous step was hydrogenated over palladium on charcoal (2g, 10%) at normal temperature and pressure until the uptake of hydrogen ceased. The resulting oil was then vacuum distilled to yield ethyl cyclooctyl acetate (13.4g, 73%), b.p. 103-103.5°/1.5mm, (lit.[147] 119-126°/14mm).

Cyclooctyl Acetic Acid.

Ethyl cyclooctyl acetate (13.4g) was hydrolysed with sodium hydroxide solution (280ml, 2N), and a little ethanol, by heating under reflux for 10h. Usual work-up gave a clear oil which was distilled to give cyclooctyl acetic acid (9g, 78%), b.p. 124-125°/0.6mm, (lit.[147] 130°/1mm).

Cyclooctylacetone

A solution of methyl-lithium was prepared from lithium (4g) and methyl iodide (40g) in very dry ether (200ml) and, after filtration, this was added dropwise over 3h to a stirred solution of cyclooctyl acetic acid (8.5g) in dry tetrahydrofuran (100ml). After stirring at room temperature for 3h the reaction mixture was poured cautiously into sodium thiosulphate solution (500ml, 10%), and the ethereal layer was separated. The aqueous layer was extracted twice more with ether, and the combined ethereal layers were washed twice with water, dried ($MgSO_4$), and the solvent removed to yield a pale yellow oil. This was distilled to yield cyclooctylacetone (7.6g, 83%), b.p. 80-82°/0.4mm, ν_{max} 1710 s, 1150 s, cm^{-1}, τ (CCl_4) 7.85 (2 x H3, broad singlet), 7.95 ($-COCH_3$, s), (15 x aliphatic H, m). The 2,4-dinitrophenylhydrazone had m.p. 96.5-97.5°C. (Found: C, 58.55; H, 6.60; N, 15.95. $C_{17}H_{24}N_4O_4$ requires C, 58.60; H, 6.95; N, 16.10%). m/e 348 (37%, m^+), 238 (82%), 207 (16%), 191 (14%), 178 (100%), 161 (27%), 152 (25%), 149 (24%), 44 (41%), 43 (46%).

Bromination-Dehydrobromination of Cyclooctylacetone.

Cyclooctylacetone (2.1g), cupric bromide (6g), and a mixture of ethyl acetate (16ml) and chloroform (16ml) were vigorously stirred under reflux for 3h. The precipitated cuprous bromide was filtered off from the cooled reaction mixture and then washed well with chloroform. The combined organic solutions were then washed three times with sodium bicarbonate solution, once with water, dried ($MgSO_4$), and solvent removed to give the bromo-ketone (2.8g, 91%) as a pale brown oil.

This was used directly in the next step, ν_{max} 1715 cm^{-1}.

The above product (2.8g) was mixed with lithium bromide (1.4g, anhydrous) and lithium carbonate (1.4g, anhydrous) in dry dimethylformamide (14ml) and refluxed, with vigorous stirring, for 3h. The cooled reaction mixture was poured into water, extracted four times with ether, and the combined ether extracts washed twice with water, dried ($MgSO_4$), and the solvent removed. Distillation of the resulting oil gave a 1:3 mixture (by n.m.r.) of the α,β and β,γ unsaturated ketones (1.7g, 89%), b.p. 80-85°/0.5mm, ν_{max} 1710s, 1680m, 1600m cm^{-1}, τ(CCl_4) 3.90 (=CHCOCH$_3$, s), 4.50 (=CH-, t, J 6Hz), 7.00 (2 x α β H_2, 2 x α β H_8, s), 7.25 (-CH$_2$COCH$_3$, d, J 6Hz), 7.50 - 8.10 (2 x β γ. H_3, 2 x β γ. H_8, m), 7.90 (-COCH$_3$, 2 x s), 8.50 (aliphatic H, m). The 2,4-dinitrophenylhydrazone had m.p. 100-101.5°. (Found: C, 58.55; H, 6.35; N, 16.0. $C_{17}H_{22}N_4O_4$ requires C, 58.95; H, 6.4; N, 16.2%). m/e 346 (50%, m^+), 236 (100%), 176 (30%), 123 (18%).

Cyclooctanylideneacetone

A solution of methyl-lithium was prepared from lithium (0.6g) and methyl iodide (6ml) in very dry ether (30ml) and this was added, over 10 min, to a well-stirred solution of cyclooctanylidene acetic acid (0.6g) in dry tetrahydrofuran (20ml). The reaction mixture was stirred for a further 1.5h, and then cautiously poured into sodium thiosulphate solution (100ml, 10%). After separating off the ether layer, the aqueous layer was extracted three times with ether and the combined ether layers were then washed with water and dried ($MgSO_4$). Removal

of the solvent gave a yellow oil whose IR indicated the presence of only the α,β unsaturated ketone (240mg, 27%), ν_{max} 1680s cm^{-1}. However, distillation of this product caused isomerisation to a ca. 2/1 mixture of α,β/β,γ isomers, b.p. 75-80°/0.5mm.

Reaction of Ketones (exo-47) and (endo-47) with Boron Trifluoride Etherate.

The mixture of α,β and β,γ unsaturated ketones (160mg, 2/1 mixture) was dissolved in a mixture of dry benzene (8ml) and boron trifluoride diethyl etherate (8ml) and refluxed for 3h. The usual work-up gave a crude product which was vacuum distilled to yield only starting material (140mg), b.p. 65-70°/0.4mm, as a 3:1 mixture of β,γ:α,β unsaturated ketones.

4-(p-Anisoyl)-3,3-dimethylbutyric Acid.

Prepared by the method of Atkinson.[148]

5-(p-Methoxyphenyl)-3,3-dimethylpentanoic acid and 2,4,5,6-Tetrahydro-7--(p-methoxyphenyl)-2,5,5-trimethyl-1,2-diazepin-3-one

4-(p-Anisoyl)-3,3-dimethylbutyric acid (10g), hydrazine hydrate (7.2g, 85%) and potassium hydroxide (7g) were dissolved in ethanediol (50ml) and heated under reflux for 0.5h. The apparatus was then converted to distillation and the reaction mixture was allowed to distil until the temperature of the distilling vapour reached 194°. The resulting yellow solution was then heated under reflux for a further 4h before cooling, and was then poured into water. The aqueous solution was

extracted with diethyl ether, acidified (concentrated hydrochloric acid), and then extracted with ethyl acetate. The ethyl acetate extracts were washed with water, dried ($MgSO_4$), and the solvent removed to yield a red oil (10g) whose i.r. spectrum indicated complete reaction, along with partial demethylation of the aromatic ether group. ν_{max} 3240s, 1705s, 1510s, 820m cm^{-1}. This was used in the next step without further purification.

The red oil was dissolved in ethanol (100ml, 95%), and dimethyl sulphate (10.1ml) and sodium hydroxide solution (56.5ml of a 10% solution) were simultaneously added to the vigorously stirred, refluxing solution. After heating under reflux for 4h the solvent was distilled off up to a temperature of 96° (vapour temp.) and the resulting solution was cooled. This was extracted with ether, and the ether extracts were dried ($MgSO_4$). The aqueous layer was then acidified (concentrated hydrochloric acid) and extracted a further three times with ether. These ether extracts were then combined, washed with water, dried ($MgSO_4$), and solvent removed to yield the required product as a crystalline mass (8.6g) which could be recrystallised from ethanol/water to yield 5-(p-methoxyphenyl)-3,3-dimethylpentanoic acid (8.3g, 88% overall yield from the keto-acid) as colourless needles, m.p. 80-81°, ν_{max} 2680 br, s, 1690s, 1510s, 845m, 835m cm^{-1}, τ ($CDCl_3$) 1.45 (-$CO_2\underline{H}$, s), 2.85, 2.00, 3.15, 3.30 (4 x aromatic H, AA'BB'), 6.20 (-$OC\underline{H}_3$, s), 7.20-7.65 (2 x Hs, m), 8.15-8.65 (2 x H4, m), 8.90 (2 x -$C\underline{H}_3$, s), (Found: C, 71.05; H, 8.6. $C_{14}H_{20}O_3$ requires C, 71.15; H, 8.55%). m/e 236 (17%, m^+), 218 (22%), 191 (19%), 121 (100%), 60 (80%), 59 (41%).

Solvent was removed from the ether extract of the basic solution to yield a colourless oil which crystallised on standing. This was purified by chromatography on silica (40g, eluting with ethyl acetate), and recrystallisation from ethyl acetate/petrol, to give colourless cubes of 2,4,5,6-Tetrahydro-7-(p-methoxyphenyl)-2,5,5-trimethyl-1,2--diazepin-3-one (0.8g, 7.7% overall yield from the keto-acid), m.p. 77-78°, ν_{max} 1645s, 1610m, 1560m, 1515m, 840m, 820m, 805m cm^{-1}, $\tau(CCl_4)$ 2.20, 2.35, 3.10, 3.25 (4 x aromatic H, AA'BB'), 6.20 ($-OCH_3$, s), 6.75 ($N-CH_3$, s), 7.40 (2 x H4, s), 7.90 (2 x H6, s), 8.90 (2 x CH_3, s). (Found: C, 69.05; H, 7.8; N, 10.55. $C_{15}H_{20}N_2O_2$ requires C, 69.2; H, 7.75; N, 10.75%). m/e 260 (100%, m^+), 217 (41%), 177 (27%), 175 (54%), 133 (68%), 83 (73%).

5-(p-Methoxyphenyl)-3,3-dimethylpentan-1-ol.

5-(p-Methoxyphenyl)-3,3-dimethylpentanoic acid (5.5g) was dissolved in dry ether (100ml) and this was added dropwise to a stirred suspension of lithium aluminium hydride (1.1g) in ether (50ml). This was heated under reflux for 2h, and the excess lithium aluminium hydride was destroyed by addition of ethyl acetate, and then water. The ethereal solution was decanted, and the precipitated lithium salts were well washed by further decantations. The combined ethereal solutions were washed with saturated sodium chloride solution, dried ($MgSO_4$), and solvent was removed to yield a colourless oil (4.3g). This was distilled to yield 5-(p-methoxyphenyl)-3,3-dimethylpentan-1-ol as a colourless oil (4.2g, 81%), b.p. 180-190°/0.6mm, ν_{max} 3340s, br, 1510s, 820m cm^{-1}, τ (CCl_4) 3.00, 3.15, 3.30, 3.45 (4 x aromatic H, AA'BB'), 6.35 ($-OCH_3$, s), 6.35 ($-CH_2OH$, t, J 8 Hz), 7.35-7.70 ($-OH$, 2 x H_5, m), 8.30-8.80 (2 x H_2,

2 x H_4, m), 9.10 (2 x $C\underline{H}_3$, s). This was identical with a sample previously prepared by Atkinson.[73]

Ethyl 7-(p-Methoxyphenyl)-5,5-dimethylhept-2-enoate.

Dry pyridine (21ml) was dissolved in purified dichloromethane (140ml), and chromium trioxide (12.7g) was added, in portions, to the well-stirred solution.[149] This was stirred for 20 min and then 5-(p--methoxyphenyl)-3,3-dimethylpentan-1-ol (1.5g), dissolved in pure dichloromethane (20ml), was quickly added. The reaction mixture was stirred for 1 min, and the dichloromethane solution was then decanted off the precipitated chromium salts. These salts were washed, by decantation, with more dichloromethane and the dichloromethane solutions were combined, washed with sodium hydroxide solution (2N), dilute hydrochloric acid (2N), sodium bicarbonate solution, and with sodium chloride solution. The dichloromethane layers were dried ($MgSO_4$) and the solvent removed, to give the aldehyde as a pale yellow oil (1.2g, 79%) which was used directly in the next step, ν_{max} 2740w, 1720s, 1510s, 815m cm^{-1}, τ (CCl_4) 0.5 (-C$\underline{H}$O, br, s), 2.95, 3.10, 3.25, 3.40 (4 x aromatic H, AA'BB'), 6.35 (-OC$\underline{H}_3$, s), 7.30-7.90 (2 x H_2, 2 x H_5, m), 8.20-8.80 (2 x H_4, m), 8.95 (2 x $C\underline{H}_3$, s).

Triethyl phosphonoacetate[150] (3.86g) in dry tetrahydrofuran (50ml) was added dropwise to a stirred suspension of sodium hydride (0.20g) in dry tetrahydrofuran (25ml) and this was stirred for 16h. The aldehyde (57) (2.2g) in dry tetrahydrofuran (50ml) was then added dropwise, and the reaction mixture was stirred for a further 0.75h before pouring into water and extracting with ether. The ether

extracts were washed with water, dried ($MgSO_4$), and solvent removed to yield a yellow oil (2.8g). This was purified by chromatography (110g, silica, eluting with benzene), and distillation, to give ethyl 7-(p-methoxyphenyl)-5,5-dimethylhept-2-enoate (2.0g, 69%) as a colourless oil, b.p. 170-180°/1.0mm. ν_{max} 1740s, 1650m, 1515s, 820m cm^{-1}, τ (CCl_4) 3.00, 3.15, 3.30, 3.45 (4 x aromatic H + -CH=CH.$COCH_3$, AA'BB' + t, J 16 Hz), 4.30 (-CH=CH.$COCH_3$, t, J 16 Hz), 5.90 (-OCH_2.CH_3, q, J 7 Hz), 6.25 (-OCH_3, s), 7.30-8.00 (2 x H_4, 2 x H_7, m), 8.75 (-OCH_2.CH_3, t, J 7 Hz), 8.20-8.90 (2 x H_6, m), 9.00 (2 x CH_3, s). (Found: C, 74.2; H, 8.7. $C_{18}H_{26}O_3$ requires C, 74.45; H, 9.0%). m/e 290 (m^+, 78%), 216 (63%), 202 (26%), 176 (30%), 175 (100%), 135 (38%), 134 (32%), 122 (65%), 121 (78%).

Attempted Thermal Rearrangement of Ethyl 7-(p-Methoxyphenyl)-5,5-dimethylhept-2-enoate.

Ethyl 7-(p-methoxyphenyl)-5,5-dimethylhept-2-enoate (80mg) was placed in a bulb tube and slowly distilled at atmospheric pressure under an atmosphere of nitrogen. The ester distilled unchanged at 240-250° leaving no residue.

Attempted Rearrangement of Ethyl 7-(p-Methoxyphenyl)-5,5-dimethylhept-2-enoate with Hydrobromic Acid/Acetic Acid.

Ethyl 7-(p-methoxyphenyl)-5,5-dimethylhept-2-enoate (202mg) was added to a mixture of hydrobromic acid (2ml, 48-50% w/w, distilled before use) and acetic acid (2ml) and heated under reflux for 1h. After cooling, the reaction mixture was cautiously poured into sodium

bicarbonate solution and extracted with dichloromethane. The dichloromethane extract was then dried ($MgSO_4$), and the solvent removed, to yield starting material (18.4mg). The basic, aqueous solution was then acidified (concentrated hydrochloric acid) and extracted with ether. These ether extracts were dried ($MgSO_4$), and removal of the solvent gave a clear oil which crystallised on standing. Crystallisation from ethyl acetate/petrol gave 94mg (54%) of material which was shown to be 7-(p-hydroxyphenyl)-5,5-dimethylhept-2-enoic acid by its spectroscopic characteristics, m.p. 130-132°, ν_{max} 3170m, br, 1685s, 1635m, 1520s, 820m cm^{-1}, τ (Trifluoroacetic acid) 2.35, 2.50. 2.60 (part of the signal from -CH=CH.$COCH_3$), 2.75, 2.90, 3.00, 3.15 (4 x aromatic H + part of the signal from -CH=CH.$COCH_3$), 3.95 (-CH=CH.$COCH_3$, d, J 18 Hz), 7.10-7.85 (2 x H_4, 2 x H_7, m), 8.15-8.70 (2 x H_6, m), 8.90 (2 x CH_3, s). (Found: C, 72.3; H, 7.95. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.1%). m/e 248 (100%, m^+), 238 (30%), 178 (17%), 161 (58%), 107 (62%).

Attempted Rearrangement of 7-(p-hydroxyphenyl)-5,5-dimethylhept-2-enoic acid with Boron Trifluoride Etherate.

7-(p-Phenoxy)-5,5-dimethylhept-2-enoic acid (82mg) was dissolved in dry benzene (4ml) and boron trifluoride etherate (4ml) and heated under reflux for 2h. The cooled reaction mixture was then cautiously poured into sodium bicarbonate solution and the aqueous mixture was acidified (concentrated hydrochloric acid) and extracted with ethyl acetate. The extract was then dried ($MgSO_4$), and the solvent removed to give only starting material (62.4mg after recrystallisation).

A further sample of the phenoxy acid was subjected to the same conditions for a total of 21.5h but, again, this gave only starting material.

Attempted Rearrangement of 7-(p-Hydroxyphenyl)5,5-dimethylhept-2-enoic Acid with Polyphosphoric Acid.

7-(p-Hydroxyphenyl)-5,5-dimethylhept-2-enoic acid (75mg) was added to polyphosphoric acid (5ml) and heated, with manual stirring, at 85° for 0.5h. This was then diluted well with water and extracted with ethyl acetate. Drying ($MgSO_4$) and removal of solvent gave a dark, viscous oil (42mg) from which no clean product could be extracted.

Attempted Rearrangement of Ethyl 7-(p-Methoxyphenyl)-5,5-dimethyl-hept-2-enoate with Polyphosphoric Acid.

Ethyl 7-(p-methoxyphenyl)-5,5-dimethylhept-2-enoate (95mg) was dissolved in polyphosphoric acid (1g) and heated at 80° for 1h. The product was recovered by dilution with water and extraction with ethyl acetate, and was shown to be starting material (84mg). This recovered starting material was then heated with polyphosphoric acid (5g) for a further 2h at 100°. The recovered product was purified by column chromatography and was shown to be starting material (61mg), no other product could be isolated.

Attempted Rearrangement of Ethyl 7-(p-Methoxyphenyl)-5,5-dimethyl-hept-2-enoate with Trifluoroacetic Acid.

Ethyl 7-(p-methoxyphenyl)-5,5-dimethylhept-2-enoate (107.5mg)

was dissolved in trifluoroacetic acid (1.5ml) and heated under reflux, the reaction being followed by taking NMR spectra at regular intervals. No change was observed in the NMR spectrum, however, after a total of 28h reflux.

Ethyl 7-(p-Methoxyphenyl)-5,5-dimethylheptanoate.

Ethyl 7-(p-methoxyphenyl)-5,5-dimethylhept-2-enoate (154mg) was dissolved in ethanol (2ml, 95%), palladium on carbon (13mg, 10%) was added, and the ester was hydrogenated until the uptake of hydrogen ceased. The catalyst was filtered off and the solvent removed to give a clear oil (153mg) which was purified by column chromatography (10g Kieselgel, benzene as eluant) and distillation giving ethyl 7-(p-methoxyphenyl)-5,5-dimethylheptanoate (146mg, 94%), b.p. 200-210°/0.8mm, ν_{max} 1730s, 1510s, 820m cm^{-1}, τ (CCl_4) 2.95, 3.10, 3.25, 3.40 (4 x aromatic H, AA'BB'), 5.90 ($-OC\underline{H_2}CH_3$, q, $\underline{J}$ 7 Hz), 6.30 ($-OC\underline{H_3}$, s), 7.30-8.00 (2 x H_2, 2 x H_7), 8.40-8.90 (2 x H_3, 2 x H_4, 2 x H_6, m), 8.80 ($-OCH_2C\underline{H_3}$, t, $\underline{J}$ 7 Hz), 9.10 (2 x $C\underline{H_3}$, s). (Found: C, 74.05; H, 9.65. $C_{18}H_{28}O_3$ requires C, 73.9; H, 9.65%). m/e 292 (77%, m^+), 247 (20%), 175 (23%), 135 (84%), 122 (73%), 121 (100%).

8-(p-Methoxyphenyl)-^{6},^{6}-dimethyloct-3-en-2-one.

Acetonyl triphenyl phosphonium chloride (2.4g) and sodium carbonate (0.8g,anhydrous) were dissolved in a mixture of water (7ml) and tetrahydrofuran (15ml) and stirred at room temperature for 0.5h, 5-(p-methoxyphenyl)-3,3-dimethylpentanal (1.2g) dissolved in tetrahydrofuran (8ml) was then quickly added and the reaction mixture

was stirred and heated under reflux overnight. The cooled reaction mixture was poured into water and extracted with ether, and the ether extract was washed with sodium chloride solution, dried ($MgSO_4$) and the solvent removed. The resulting brown oil was then triturated four times with petrol (b.p. 40-60°), the petrol extracts were combined, and the petrol was removed on a rotary evaporator to give a green oil (1.3g). This was purified by column chromatography (65g Kieselgel, eluting with 3/1 benzene/ethyl acetate) and distillation to give pure 8-(p-methoxyphenyl)-6,6-dimethyloct-3-en-2-one (0.95g, 67%), b.p. 173-175°/0.2mm, ν_{max} 1670s, 1625m, 1610m, 1510s, 820m cm^{-1}, τ (CCl_4) 2.85, 3.00, 3.15, 3.30 (4 x aromatic H + -CH=CH.$COCH_3$, AA'BB'), 5.95 (-CH=CH $COCH_3$, d, J 16 Hz), 6.25 (-OCH_3, s), 7.20-8.00 (2 x H_5, 2 x H_8, m), 7.80 (-$COCH_3$, s), 8.30-8.75 (2 x H_7, m), 9.05 (2 x CH_3, s). (Found: C, 78.2; H, 9.25. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.3%).

Rearrangement of 8-(p-Methoxyphenyl)-6,6-dimethyloct-3-en-2-one with Perchloric Acid.

8-(p-Methoxyphenyl)-6,6-dimethyloct-3-en-2-one (135mg) was stirred with perchloric acid (5ml of a 70% aqueous solution) for 2h at ambient temperature. The resulting red solution was cautiously poured into sodium carbonate solution and extracted with benzene. Solvent was removed to give a brown oil (65mg) which was purified by column chromatography (10g Kieselgel, benzene as eluant) and distillation, to give pure 2-(p-methoxyphenyl)-4,4-dimethylcyclohexyl methyl ketone (58.1mg, 43%), b.p. 200-210°/0.3mm. This was identical in all respects with an authentic sample prepared as described below.

2-(p-Methoxyphenyl)-4,4-dimethyl Cyclohexylmethyl Ketone.

2-(p-Hydroxyphenyl)-4,4-dimethylcyclohexyl methyl ketone (37mg) was mixed with dimethyl sulphate (36mg) and potassium carbonate (42.0mg, anhydrous) in dry acetone (3ml) and heated under reflux, with vigorous stirring, for 17h. The reaction mixture was then saturated with water and extracted with ether. Drying ($MgSO_4$) and evaporation of the ether extract gave a clear oil (33mg) which was purified by column chromatography (4g, Kieselgel, eluting with benzene) and distillation to give an authentic sample of 2-(p-methoxyphenyl)--4,4-dimethylcyclohexyl methyl ketone (28mg, 72%), b.p. 200-210°/0.3mm, ν_{max} 1710s, 1610m, 1515s, 825m, cm^{-1}, τ (CCl_4) 2.80, 2.95, 3.15, 3.30 (4 x aromatic H, AA'BB'), 6.20 ($-OCH_3$, s), 6.90-7.70 (H_1 + H_2, m), 8.15 ($-COCH_3$, s), 8.20-8.85 (2 x H_3, 2 x H_5, 2 x H_6, m), 8.95 (CH_3, s), 9.05 (CH_3, s). (Found: C, 78.5; H, 9.15. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.3%). m/e 260 (54%, m^+), 217 (22%), 175 (42%), 150 (100%), 107 (28%), 43 (48%).

2,4,5,6-Tetrahydro-7-(p-methoxyphenyl)-5,5-dimethyl-1,2-diazepin-3-one

4-(p-Anisoyl)-3,3-dimethylbutyric acid (1g) was dissolved in ethanol (100ml, 95%), hydrazine hydrate (1.3ml, 85%) was added, and the mixture was refluxed for 2h. Potassium carbonate (3g, anhydrous) was then added, followed by dimethyl sulphate (1.2g), and the reaction mixture was heated under reflux, with stirring, for a further 3h, and then stirred overnight. This was poured into water and extracted with ether, the ether extracts were dried ($MgSO_4$), and the solvent removed, giving a white solid. Crystallisation from ethanol gave 2,4,5,6-Tetrahydro-

-7-(p-methoxyphenyl)-5,5-dimethyl-1,2-diazepin-3-one as colourless needles (500mg, 51%), m.p. 180-181°, ν_{max} 1645s, 1600m, 1375s, 1360s, 810m cm^{-1}; τ ($CDCl_3$) 1.95, 2.10, 2.85, 3.00 (4 x aromatic H, AA'BB'), 2.55 (NH, concentration dependent, broad singlet), 6.05 ($-OCH_3$, s), 7.20 (2 x H_6, s), 7.70 (2 x H_4, s), 8.80 (2 x CH_3, s). (Found: C, 68.1; H, 7.45; N, 11.3. $C_{14}H_{18}N_2O_2$ requires C, 68.25; H, 7.35; N, 11.35%). m/e 246 (100%, m^+), 203 (28%), 175 (15%), 133 (20%), 97 (33%), 95 (31%), 83 (43%), 57 (37%).

A sample of this diazepinone was converted into its N-methyl derivative (in 39% yield) by treatment with sodium hydroxide/dimethyl sulphate. This sample corresponded exactly to the by-product found in the Wolff-Kischner reduction of 4-(p-anisoyl)-3,3-dimethylbutyric acid.

4-p-(Methoxyphenyl)butan-1-ol.

Prepared by the method of Baird and Winstein[151], b.p. 125-130°/1.55mm (lit. 160-160.9°/8mm).

4-(p-Methoxyphenyl)butanal.

Dry pyridine (12.7g) was mixed with pure dichloromethane (150ml) and chromium trioxide (8g) was quickly added at 0°. The reaction mixture was then stirred at room temperature for 20 min before adding 4-(p-methoxyphenyl)butan-1-ol (1.8g) dissolved in pure dichloromethane (50ml). After stirring for a further 20 min at room temperature the dichloromethane was decanted from the precipitated chromium salts, and these salts were well washed with dichloromethane. The combined

dichloromethane solutions were then washed with sodium hydroxide solution (2N), dilute hydrochloric acid (5%), saturated sodium bicarbonate solution, and finally with saturated sodium chloride solution. Drying ($MgSO_4$), and removal of the solvent, gave 4-(p-methoxyphenyl)butan-1-al (1.3g, 73%) which was used immediately in the next step. ν_{max} 2715m, 1725s, 1515s, 830m cm^{-1}; τ (CCl_4) 0.40 (C<u>H</u>O, br, s), 3.05, 3.20, 3.30, 3.45 (4 x aromatic H, AA'BB'), 6.30 ($-OCH_3$, s), 7.20-8.60 (2 x H_2, 2 x H_3, 2 x H_4, m).

<u>Ethyl 6-(p-Methoxyphenyl)hex-2-enoate.</u>

Triethyl phosphonoacetate[150] (1.85g) dissolved in dry tetrahydrofuran (10ml) was added to a stirred suspension of sodium hydride (0.174g) in dry tetrahydrofuran (5ml) and this was stirred for 18h. 4-(p-Methoxyphenyl)butanal (1.3g) dissolved in dry tetrahydrofuran (25ml) was then added dropwise and the reaction mixture was stirred for a further 3h. This was then poured into water and extracted with ether, the ether extract then being washed with water, dried ($MgSO_4$), and the solvent removed to give a yellow oil (1.9g). Column chromatography (80g silica, benzene as eluant) and distillation then gave pure ethyl <u>6-(p-methoxyphenyl) hex-2-enoate</u> (1.1g, 61%), b.p. 175-180°/1.5mm, ν_{max} 1720s, 1655m, 1515s, 830m cm^{-1}; τ (CCl_4) 2.85, 2.95, 3.10, 3.30 (4 x aromatic H superimposed on H_3), 4.20 (H_2, d, <u>J</u> 16 Hz), 5.80 ($CH_3.C\underline{H}_2-$, q, <u>J</u> 7 Hz), 6.20 ($-OCH_3$, s), 7.20-8.50 (2 x H_4, 2 x H_5, 2 x H_6, m), 8.70 ($C\underline{H}_3.CH_2-$, t, <u>J</u> 7 Hz). (Found: C, 72.9; H, 8.35. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.1%). m/e 248 (56%, $m^{\cdot+}$), 203 (32%), 134 (100%), 121 (38%).

6-(p-Methoxyphenyl)hex-2-enoic Acid.

Ethyl 6-(p-methoxyphenyl)hex-2-enoate (0.6g) was hydrolysed with sodium hydroxide solution (2N) containing ethanol for 1h. This gave 6-(p-methoxyphenyl)hex-2-enoic acid.(0.4g, 72%) as colourless crystals, m.p. 83-85° (ethyl acetate/petrol), ν_{max} 2660w, br, 1690s, 1645m, 1515s, 830m cm^{-1}; τ ($CDCl_3$) -1.3 (-CO_2H, s, br), 2.75, 2.90 3.05, 3.20 (4 x aromatic H, superimposed on H_3, AA'BB'), 4.10 (H_2, d, J 15 Hz), 6.25 (OCH_3, s), 7.20-8.85 (2 x H_4, 2 x H_5, 2 x H_6, m). (Found: C, 71.0; H, 7.15. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%).

Attempted Preparation of 7-(p-Methoxyphenyl)hept-3-en-2-one.

Reaction of 6-(p-methoxyphenyl)hex-2-enoic acid with four molar equivalents of methyl-lithium in mixtures of ether with tetrahydrofuran, monoglyme, or hexamethylphosphoramide gave no ketonic product.

7-(p-Methoxyphenyl)hept-3-en-2-one.

Acetonyl triphenyl phosphonium chloride (9.1g) and sodium carbonate (3.1g, anhydrous) were dissolved in a mixture of water (27ml) and tetrahydrofuran (70ml) and stirred at room temperature for 0.5h. 4-(p-Methoxyphenyl)butanal (3.5g) in tetrahydrofuran (20ml) was then added and the reaction mixture was heated under reflux, with stirring, for 17.5h, before cooling and pouring into water. This was extracted with ether and the ether extracts were washed with sodium chloride solution, dried ($MgSO_4$), and the solvent was removed to give a thick brown oil. This oil was triturated four times with petrol (b.p. 40-60°)

and the petrol solutions were combined, and the solvent removed to give a mobile, pale yellow oil (3.3g). This was purified by column chromatography (150g Kieselgel, chloroform as eluant) and distillation to give 7-(p-methoxyphenyl)hept-3-en-2-one (2.3g, 54%), b.p. 155-160°/ 0.4mm, ν_{max} 1680s, 1630m, 1515s, 820m cm^{-1}; τ ($CDCl_4$) 2.90-3.55 including peaks at 2.90, 3.05, 3.20, 3.35 (4 x aromatic H, superimposed on H_4), 4.05 (H_3, d, J 15 Hz), 6.25 (OCH_3, s), 7.90 (CH_3CO, s), 7.10-8.50 (2 x H_5, 2 x H_6, 2 x H_7, m). (Found: C, 77.55; H, 8.1. $C_{14}H_{18}O_2$ requires C, 77.05; H, 8.3%). m/e 218 (19%, m^+), 135 (37%), 134 (100%), 122 (37%), 121 (15%).

Attempted Rearrangement of 7-(p-Methoxyphenyl)hept-3-en-2-one with Toluene p-Sulphonic Acid.

7-(p-Methoxyphenyl)hept-3-en-2-one (220mg) was dissolved in benzene (10ml) and heated under reflux for 5h with toluene p-sulphonic acid (100mg). The cooled reaction mixture was then washed with sodium carbonate solution, dried ($MgSO_4$), and the benzene removed, to yield the starting material (210mg).

Attempted Rearrangement of 7-(p-Methoxyphenyl)hept-3-en-2-one with Trifluoroacetic Acid.

7-(p-Methoxyphenyl)hept-3-en-2-one (210mg) was dissolved in trifluoroacetic acid (5ml) and stood for 2h. This was then dissolved in benzene and washed three times with sodium carbonate solution. Drying ($MgSO_4$), and removal of solvent gave an oil which was purified by column chromatography (15g Kieselgel, chloroform as eluant) to

yield only starting material (180mg).

Attempted Rearrangement of 7-(p-Methoxyphenyl)hept-3-en-2-one with Perchloric Acid.

7-(p-Methoxyphenyl)hept-3-en-2-one (103mg) was dissolved in perchloric acid (5ml, 70% aqueous solution) and stirred for 2.5h. This was then cautiously poured into sodium carbonate solution and extracted with benzene. The benzene extract was dried ($MgSO_4$) and the solvent removed to give a viscous brown oil which was partially purified by column chromatography (15g Kieselgel, 1:1 benzene:ethyl acetate) and then distilled to remove polymeric material. This gave only 10mg of material boiling below 250°/0.3mm, which was shown to be starting material.

4-(p-Methoxyphenyl)butyrolactone.

Prepared by the method of Julia, Julia, and Bemont, m.p. 53-54°, lit.[152] 53-54°.

Methyl 4,4-Bis-(p-methoxyphenyl)butyrate.

Aluminium chloride (15.0g, ground to a fine powder) was dissolved in dry nitrobenzene (200ml) with stirring, at room temperature and the solution was cooled to 0°. Anisole (14.0g) was added, keeping the temperature of the reaction mixture below 5°, and, after a further 5min stirring, the lactone (9.1g) was added in small portions. The reaction flask was then securely stoppered and placed in a refrigerator

for 13 days. The resulting red solution was poured on to a 1:1 mixture of ice and concentrated hydrochloric acid and steam distilled to remove the nitrobenzene. After cooling, the residue was extracted with ethyl acetate and the ethyl acetate extract was extracted with sodium hydroxide solution (2N). These sodium hydroxide extracts were then acidified (concentrated hydrochloric acid) and re-extracted with ethyl acetate and these extracts were dried ($MgSO_4$). Removal of the solvent gave a dark brown oil (13.6g). The n.m.r. of this oil indicated it to be a mixture of the expected acid and its demethylated product(s).

This crude product was dissolved in dry acetone (200ml), potassium carbonate (7.3g, anhydrous), and dimethyl sulphate (6.6g) were added and the reaction mixture was stirred and heated under reflux for 9h. Most of the acetone was removed under vacuum, water added, and the solution extracted with ether. The ether extract was washed with sodium hydroxide solution (2N), sodium chloride solution, dried ($MgSO_4$) and evaporated. A dark brown oil (4.6g) was obtained which was purified by chromatography (180g silica, 2:1 benzene:ethyl acetate as eluant) and then distillation to give methyl 4,4-bis-(p--methoxyphenyl)butyrate (3.2g, 22%) as a glass, b.p. 190-200°/0.06mm, ν_{max} 1735s cm^{-1}; τ ($CDCl_3$) 2.75, 2.90, 3.10, 3.25 (8 x aromatic H, AA'BB'), 6.20 (2 x $-OCH_3$, s, superimposed on H_4), 6.35 ($-CO_2CH_3$, s), 7.65 and 7.70 (2 x H_2, 2 x H_3, 2 very narrow m). (Found: C, 72.95; H, 6.9. $C_{19}H_{22}O_4$ requires C, 72,6; H, 7.05%). m/e 314 (20%), 281 (25%), 228 (22%), 227 (100%), 121 (16%).

7,7-Bis-(p-methoxyphenyl)hept-3-en-2-one.

4,4-Bis-(p-methoxyphenyl)butan-1-ol was obtained by reduction of the above ester with excess lithium aluminium hydride in ether. The product was purified by chromatography (silica, 2:1 ethyl acetate: benzene as eluant) to give the alcohol (79%), ν_{max} 3380m, br cm^{-1}; τ ($CDCl_3$) 2.80, 2.95, 3.15, 3.30 (8 x aromatic H, AA'BB'), 6.30 (2 x -O$\underline{CH_3}$, superimposed on H_4), 6.45 (2 x H_1, t, $\underline{J}$ 6 Hz), 7.7-8.7 (2 x H_2, 2 x H_3 and -O$\underline{H}$, m).

The foregoing alcohol (0.5g) was oxidised with chromium trioxide (1.43g) in dichloromethane (40ml) and pyridine (2.3ml) as described earlier except that the solution was stirred for 15 min at room temperature before the reaction mixture was worked up. This gave 4,4-bis-(p-methoxyphenyl)butan-1-al (0.3g, 62%), ν_{max} 2710w, 1725s, 1515s, 825s cm^{-1}, τ (CCl_4) 0.55 ($\underline{CH}O$, br, s), 2.75, 2.90, 3.10, 3.25 (8 x aromatic H, AA'BB'), 6.25 (2 x O$\underline{CH_3}$ superimposed on H_4, singlet, obscuring the H_4 triplet), 7.50-7.90 (2 x H_2, 2 x H_3, m).

The foregoing aldehyde (0.3g) was converted to the title ketone with acetonyl triphenyl phosphonium chloride (0.5g) and sodium carbonate (0.17g) in water (1.5ml) and tetrahydrofuran (5ml) as described earlier. Chromatography (Kieselgel, eluting with 3:1 benzene :ethyl acetate) and distillation gave 7,7-bis-(p-methoxyphenyl)hept--3-en-2-one (240mg, 70%) as a colourless oil, b.p. 240-250°/0.5mm, ν_{max} 1670s, 1625m, 1510s, 820m cm^{-1}; τ ($CDCl_3$) 2.85, 3.00, 3.20 3.35 (8 x aromatic H superimposed on H_4, AA'BB'), 4.05 (H_3, d, $\underline{J}$ 16 Hz), 6.30 (2 x O$\underline{CH_3}$ superimposed on H_7, s), 7.90 ($\underline{CH_3}CO$, 2 x H_5,

2 x H_6, singlet superimposed on a narrow multiplet). (Found: C, 77.75; H, 7.35. $C_{21}H_{24}O_3$ requires C, 77.75; H, 7.4%). m/e 324 (10%, m^+), 227 (100%), 190 (18%), 134 (64%), 121 (94%).

Attempted Rearrangement of 7,7-Bis-(p-methoxyphenyl)hept-3-en-2-one with Perchloric Acid.

7,7-Bis-(p-methoxyphenyl)hept-3-en-2-one (96.5mg) was dissolved in perchloric acid (10ml, 70% aqueous solution) and set aside for 2h. Work-up gave a pale yellow oil (83.4mg) which was partially purified by chromatography (7g Kieselgel, 1:1 benzene:ethyl acetate) and distillation (250°/0.4mm) to give a semi-crystalline oil. Crystallisation from ethanol/petrol gave a colourless solid (4mg)' m.p. 91-96°, ν_{max} 1705s, 1512s, 1245s, 825s cm^{-1}; m/e 324 (10%, m^+), 190 (73%), 189 (46%), 175 (64%), 161 (79%), 159 (39%), 134 (67%), 121 (100%), 91 (75%).

Cyclooct-4-enone.

Prepared by the method of Heap and Witham[153], b.p. 50-51°/1mm (lit. 86-88°/20mm).

Ethyl (Cyclooct-4-enylidene) acetate.

Triethyl phosphonoacetate (22.3g) was added dropwise to a stirred suspension of sodium hydride (2.23g) in dry tetrahydrofuran (100ml) under an atmosphere of dry nitrogen. The reaction mixture was then stirred for 40h at room temperature before dropwise addition

of cyclooct-4-enone (12.0g, dissolved in 150ml dry tetrahydrofuran). This mixture was stirred for a further 120h before pouring into water (500ml) and extracting with ether. The ethereal extracts were combined, washed twice with water, once with saturated sodium chloride solution, and then dried ($MgSO_4$). Evaporation of the ether yielded a pale yellow oil (18g), which was distilled under vacuum giving ethyl (cyclooct-4-enylidene)acetate as a colourless oil (12.5g, 65%), b.p. 104-106°/1mm, ν_{max} 1710s, 1640s, 722m, cm^{-1}; τ (CCl_4) 4.25 (3 x olefinic H, m), 5.85 ($CH_3\underline{CH_2}$, q, J 8 Hz), 6.85-8.90 (10 x aliphatic H, m), 8.70 ($\underline{CH_3}$ CH_2, t, J 8 Hz); λ_{max}^{EtOH} 225nm, log ε 4.21. (Found: C, 74.3; H, 9.3. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.35%). m/e 194 (62%, $m^{\cdot+}$), 149 (48%), 123 (90%), 121 (100%), 112 (56%), 107 (92%), 95 (59%), 93 (68%), 91 (54%), 81 (79%), 79 (87%), 67 (57%).

Reaction of Ethyl (Cyclooct-4-enylidene)Acetate with Toluene p-Sulphonic Acid.

Ethyl (cyclooct-4-enylidene)acetate was heated under reflux in benzene with toluene p-sulphonic acid for 3h. Only starting material was recovered.

Ethyl 1-Phenylbicyclo[3.3.1]nonane-9-carboxylate and 1-Phenylbicyclo-[3.3.1]nonane-9-carboxylic Acid.

Ethyl (cyclooct-4-enylidene)acetate (1.12g), dissolved in dry benzene (50ml), was mixed with boron trifluoride etherate (50ml) and the solution was heated under reflux for 17h. The cooled reaction mixture was then cautiously poured into sodium carbonate solution

(500ml, 10%) and shaken until evolution of carbon dioxide had ceased. After separation of the benzene layer the aqueous layer was extracted twice more with benzene, and the combined organic extracts were then washed once with sodium carbonate solution (50ml, 10%), twice with water, and dried ($MgSO_4$). Evaporation of the solvent gave a dark brown oil (0.74g). Chromatography (40g silica, benzene as eluant) gave the bicyclic ester (154) as a colourless oil (0.47g, 30%), b.p. 145-150°/0.3mm, ν_{max} 1740s, 755s, 695s cm^{-1}; τ (CCl_4) 2.80 (5 x aromatic H, m), 6.1 ($CH_3\underline{CH_2}$, q, J 7 Hz), 6.90 (H_9, br. s), 7.00-9.30 (13 x aliphatic H, m), 8.90 ($\underline{CH_3}CH_2$, t, J 7 Hz). (Found: C, 79.4; H, 8.95. $C_{18}H_{24}O_2$ requires C, 79.35; H, 8.9%). m/e 272 (35%, m^+), 229 (22%), 226 (68%), 199 (87%), 198 (65%), 183 (57%), 155 (73%), 117 (40%), 115 (55%), 91 (100%), 77 (30%).

The combined basic washings from the extraction were acidified with concentrated hydrochloric acid and extracted with chloroform. The combined chloroform extracts were then washed with water, dried ($MgSO_4$), and the solvent evaporated. This gave the bicyclic acid(169) as a white solid (0.27g) which was crystallised from chloroform/petrol as colourless flakes (0.22g, 19%), m.p. 165.5-166.5°, ν_{max} 2700s, br, 1705s, 755s, 695s cm^{-1}, τ ($CDCl_3$) -2.03 ($CO_2\underline{H}$, s), 2.70 (5 x aromatic H, m), 6.85 (H_9, br. s), 7.10-8.35 (13 x aliphatic H, m). (Found: C, 78.7; H, 8.15. $C_{16}H_{20}O_2$ requires C, 78.7; H, 8.2%). m/e 244 (9.5%, m^+), 243 (48%), 201 (24%), 199 (25%), 91 (28%), 58 (100%), 44 (90%).

9-Hydroxymethyl-1-phenylbicyclo[3.3.1]nonane.

Ethyl 1-phenylbicyclo[3.3.1]nonane-9-carboxylate (800mg) dissolved in dry tetrahydrofuran (10ml) was added dropwise to a stirred suspension of lithium aluminium hydride (250mg) in dry tetrahydrofuran (20ml). This mixture was refluxed for 2h. Excess lithium aluminium hydride was destroyed by addition of ethyl acetate and then water; precipitated lithium salts were filtered off, and the tetrahydrofuran was saturated with water. The product was extracted with ether, the ethereal extract dried ($MgSO_4$), and solvent removed to yield a white solid which was crystallised from petrol. This gave 9-hydroxymethyl-1-phenylbicyclo[3.3.1]nonane (658mg, 97%), m.p. 78-79°, ν_{max} 3305s, br, 745s, 695 cm^{-1}; τ ($CDCl_3$) 2.70 (5 x aromatic H, m), 6.50 and 6.65 ($-C\underline{H}_2OH$, t, J 11 Hz, overlaid by d x d, J 6 Hz and 11 Hz), 7.40-9.00 (15 x aliphatic H, m). (Found: C, 83.4; H, 9.6. $C_{16}H_{22}O$ requires C, 83.45; H, 9.65%). m/e 230 (64%, m^+), 228 (15%), 212 (13%), 200 (20%), 199 (100%), 187 (26%), 91 (69%).

Dehydration of Alcohol

The foregoing alcohol (443mg), phosphorus oxychloride (0.7ml) and dry pyridine (2.0ml) were heated under reflux for 2h. The cooled reaction mixture was then poured into ice-water and extracted three times with ether. The combined ether layers were then washed twice with hydrochloric acid (2N), twice with sodium bicarbonate solution, twice with saturated sodium chloride solution, dried ($MgSO_4$), and solvent removed to give a clear oil. Column chromatography (30g Kieselgel, benzene as eluant) gave a clear oil (350mg) whose g.l.c. (3% OV 17,

oven temperature 250°C, N_2 flow rate 50 ml min^{-1}) showed two components in the ratio of 45:55 (retention times were, respectively, 1.3min and 2.9min). The major product was subsequently shown to be 9-chloromethyl-1-phenylbicyclo[3.3.1]nonane.

9-Methylene-1-phenylbicyclo[3.3.1]nonane was obtained by refluxing the mixture from the phosphorus oxychloride reaction (153mg) with ethylene glycol (4ml) and potassium hydroxide (400mg), under nitrogen, for 3h. The cooled reaction mixture was then poured into water, extracted with ether, and the ethereal extracts dried ($MgSO_4$). This gave a clear oil (154mg) whose n.m.r. indicated total conversion to the alkene. Minor contaminants were removed by Kieselgel chromatography and distillation, to yield pure p-methylene-1-phenylbicyclo-[3.3.1]nonane (135mg), b.p. 85°/0.1mm, ν_{max} 1640m, 890s, 745s, 700s cm^{-1}; τ (CCl_4) 2.75 (5 x aromatic H, 3H, m at 2.70, 2H s at 2.80), 5.25 (olefinic H, d, J 2.2 Hz), 5.95 (olefinic H, d, J 2.2 Hz), 7.30 (H_5, br, s), 7.60-8.55 (12 x aliphatic H, m). (Found: C, 90.2; H, 9.65. $C_{16}H_{20}$ requires C, 90.5; H, 9.5%). m/e 212 (92%, m^+), 183 (29%), 169 (50%), 159 (92%), 86 (100%).

1-Phenylbicyclo[3.3.1]nonan-9-one and 9-Chloromethyl-1-phenylbicyclo-[3.3.1]nonane

The mixture of 9-chloromethyl-1-phenylbicyclo[3.3.1]nonane and 9-methylene-1-phenylbicyclo[3.3.1]nonane from the phosphorus oxychloride reaction was used for this reaction.

The alkene/chloride mixture (180mg) was dissolved in chloroform

(5ml), cooled to -76°, and ozone was passed through until the I.R. band at 890 cm^{-1} had disappeared. The reaction mixture was then slowly warmed up to ambient temperature and chloroform was removed on a rotary evaporator. This gave a viscous oil which was shaken for 10 min with water (10ml) and then extracted into ether. The ethereal extract was dried ($MgSO_4$), and solvent removed, to yield a clear oil (176mg). Column chromatography of this clear oil (12g Kieselgel, benzene as eluant) gave 9-chloromethyl-1-phenylbicyclo-[3.3.1]nonane (80mg) which was recrystallised from ethanol as colourless cubes, m.p. 74.5-75.5°, ν_{max} 1595m, 1025s, 775s, 755s, 735s cm^{-1}; τ ($CDCl_3$) 2.75 (5 x aromatic H, m), 6.45 and 6.75 (-CH_2-Cl, t, J 11 Hz, overlaid by d x d, J 3 Hz and 11Hz. Upon double irradiation at τ 7.55, chloroform as lock, this system simplified to a doublet of doublets), 7.30-8.65 (13 x aliphatic H). (Found: C, 76.9; H, 8.25. $C_{16}H_{21}Cl$ requires C, 77.25; H, 8.5%). m/e 250 (15%, m^+, ^{37}Cl), 248 (45%, m^+, ^{35}Cl), 212 (60%), 205 (50%), 199 (55%), 169 (54%), 131 (45%), 130 (50%), 129 (45%), 128 (35%), 115 (45%), 95 (40%), 91 (100%), 81 (46%), 77 (33%).

The next eluted fraction was 1-phenylbicyclo[3.3.1]nonan-9-one (20mg) which was recrystallised from ethanol as colourless needles, m.p. 81.5-83.0°. The i.r., mass spectrum, and mixed melting point were identical with the material synthesised by the method described below.

2-Phenylcyclohexanone.

Prepared by the method of Newman and Farbman, m.p.56-57°, lit 56-57°.

Alkylation of 2-Phenylcyclohexanone with 1,3-Dibromopropane.

2-Phenylcyclohexanone (12g) was dissolved in dry dimethylformamide (50 ml) and sodium hydride (1.9g) was added with vigorous stirring. The reaction mixture was then warmed up to 43° and stirred for 25 min. 1,3-Dibromopropane (14g) was then added dropwise over 5 min, followed by more sodium hydride (1.9g). After stirring at 43° for 2h, and at ambient temperature for a further 1h, the reaction mixture was cautiously poured into water (750ml) and extracted four times with benzene. The combined benzene extracts were then washed three times with water, once with sodium chloride solution, and dried ($MgSO_4$). Removal of the solvent gave a yellow oil (18.5g) which was used directly in the next step.

0.5g of this yellow oil was chromatographed on Kieselgel (1:2 benzene: petrol as eluant). This gave the enol ether (160) (140mg, 35%) as a clear oil which could not be distilled without decomposition, ν_{max} 1670s, 1145s, 760s, 700s cm^{-1}; τ (CCl_4) 2.70 (5 x aromatic H), 4.65 (olefinic H, t, J 3Hz), 5.75 - 6.65 ($-OCH_2-$, m), 7.35 - 9.20 (10 x aliphatic H, m).

Further elution gave 3-(1'-phenylcyclohexan-2'-one-1'-yl)propene (139mg, 35%) as a clear oil, b.p. 126-129°/0.25 mm, ν_{max} 1635m, 915s, 760s, 705s cm^{-1}; τ (CCl_4) 2.80 (5 x aromatic H, m), 4.10 - 5.40 (3 x olefinic H), 7.10 - 8.80 (10 x aliphatic H, m). Found: C, 84.1; H, 8.55. $C_{15}H_{18}O$ requires C, 84.0; H, 8.4%). m/e 2.4 (25%, m^+), 173 (37%), 145 (43%), 129 (42%), 91 (100%), 77 (25%).

3-(1'-Phenylcyclohexan-2'-one-1'-yl)propanol, (161)

The crude product from the previous reaction (18.5g) was dissolved in acetone (200ml) and water (10ml), and concentrated sulphuric acid (10ml) was cautiously added. The reaction mixture was then stirred at room temperature for 18h, before reducing the volume of acetone on a rotary evaporator, saturating with water, and extracting with ethyl acetate. The aqueous layer was then neutralised with solid sodium bicarbonate and extracted twice more with ethyl acetate. The combined extracts were then washed twice with sodium bicarbonate solution, dried ($MgSO_4$), and solvent removed, to yield a brown oil (17.0g). This was filtered through silica (350g, benzene in eluant) giving a yellow oil, further elution with ethyl acetate then gave the crude alcohol (9.6g).

The alcohol was purified by chromatography on Kieselgel with 3:2 benzene:ethyl acetate as eluant. This gave the pure alcohol as a clear oil (4.36g), b.p. 175-180°/0.3mm, ν_{max} 3385 s, br, 1700 s, 1060 s, 760 s cm^{-1}; τ (CCl_4) 2.80 (5 x aromatic H, m), 6.65 ($-CH_2OH$, t, J 6 Hz), 6.90 (-OH, s, disappears on shaking with D_2O), 7.05 - 9.30 (12 x aliphatic H, m). (Found: C, 77.55; H, 8.5. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.7%). m/e 232 (14%, m^+), 214 (48%), 1455 (57%), 129 (57%), 128 (42%), 117 (45%), 115 (60%), 103 (47%), 91 (100%), 77 (49%).

Oxidation of Keto-Alcohol (161)

Chromium trioxide (9.9g) was added to a stirred mixture of

purified dichloromethane (130ml) and dry pyridine (16ml), and the resulting deep red solution was stirred at room temperature for 15 min. The foregoing alcohol (161) (0.99g) was rapidly added and the reaction mixture was stirred at room temperature for a further 5 min. The dichloromethane was then decanted, and the residual chromium salts were washed three times with dichloromethane. Hydroquinone (10mg) was added to the combined dichloromethane layers, and these were then washed three times with sodium hydroxide solution (2N), twice with dilute hydrochloric acid (10%), twice with sodium bicarbonate solution, once with water, and dried ($MgSO_4$). Removal of the solvent gave a light brown oil (700mg, 71%) whose i.r. indicated complete reaction. This product was used directly in the next step without further purification. ν_{max} 2710 w, 1720 s, 1705 s, 740 s, 710 s cm^{-1}; τ (CCl_4) 0.5 (-CHO, broad s), 2.75 (5 x aromatic H, m), 7.00 - 9.10 (12 x aliphatic H, m).

4-Hydroxy-1-Phenylbicyclo[3.3.1]nonan-9-one

The previous aldehyde (870 mg) was dissolved in dioxan (5ml), and a solution of hydrochloric acid (6N, 3ml) in dioxan (5ml) was added dropwise, with stirring, at 0°, under nitrogen. This was then stirred for 24h, at ambient temperature, in the dark, before saturating with water and extracting with ether. The ethereal solution was washed with sodium bicarbonate solution and sodium chloride solution, dried ($MgSO_4$), and solvent removed, to yield a yellow oil (700mg). Column chromatography (65g Kieselgel, 3:2 benzene:ethyl acetate as eluant) gave endo-4-hydroxy-1-phenylbicyclo[3.3.1]nonan-9-one which crystallised as colourless needles from ethyl acetate/petrol (210mg)

m.p. 98 - 99°, with a second crop (23mg) melting at 96.5 - 98.0°, ν_{max} 3500 s, sh, 1705 s, 1060 s, 760 s, 700 s cm^{-1}; τ (CCl_4) 2.75 (5 x aromatic H, m), 5.75 - 6.25 (-C<u>H</u>OH, m, $W^{\frac{1}{2}}$ 15 Hz), 6.80 (-O<u>H</u>, s, disappears on shaking with D_2O), 7.05 - 8.20 (11 x aliphatic H, m). (Found: C, 78.0; H, 7.65. $C_{15}H_{18}O_2$ requires C, 78.25; H, 7.9%). m/e 230 (100%, m^+), 212 (16%), 202 (32%), 184 (19%), 145 (52%), 144 (50%), 130 (65%), 91 (75%), 77 (20%).

Further elution gave a mixture of epimers (49.4mg) followed by pure <u>exo</u>-4-hydroxy-1-phenylbicyclo[3.3.1]nonan-9-one. This crystallised as long, colourless needles from chloroform/petrol (124mg) m.p. 130-131°, ν_{max} 3300 and 3240 m, br, 1725 s, sh, 935 s, 750 s, 705 s cm^{-1}; τ (CCl_4) 2.70 (5 x aromatic H, m), 5.50 - 5.80 (-C<u>H</u>OH, m, $W^{\frac{1}{2}}$ 8 Hz), 7.00 (-O<u>H</u>, s, disappears on shaking with D_2O), 7.10 - 8.50 (11 x aliphatic H, m), (Found: C, 77.95; H, 7.7. $C_{15}H_{18}O_2$ requires C, 78.25; H, 7.9%). m/e, 230 (25%, m^+), 212 (10%), 184 (12%), 129 (42%), 128 (50%), 115 (64%), 91 (76%), 44 (100%).

The total yield of 4-hydroxy-1-phenylbicyclo[3.3.1] nonan-9-one was 47% (including the small, mixed, column fraction).

<u>Attempted Dehydration of exo-4-Hydroxy-1-phenylbicyclo[3.3.1] nonan-9-one with Phosphorus Oxychloride/Pyridine.</u>

<u>exo</u>-4-Hydroxy-1-phenylbicyclo[3.3.1] nonan-9-one (37.0mg) was mixed with phosphorus oxychloride (0.1ml, redistilled) and dry pyridine (3ml) and heated at 100° for 2h. The cooled reaction mixture was then poured into ice-water and extracted twice with ether. The combined

organic layers were then washed twice with dilute hydrochloric acid (10%), once with saturated sodium chloride solution, dried ($MgSO_4$), and solvent removed to yield a white solid. Crystallisation from petrol gave endo-4-chloro-1-phenylbicyclo[3.3.1] nonan-9-one as long colourless rods (33.9mg, 85%), m.p. 115 - 116°, ν_{max} 1710 s, 745 s, 695 s cm^{-1}; τ ($CDCl_3$) 2.70 (5 x aromatic H, m), 5.25 - 5.85 (-CHCl, m, $W^{\frac{1}{2}}$ 20 Hz), 6.70 - 8.60 (12 x aliphatic H, m). (Found: C, 72.4; H, 6.9. $C_{15}H_{17}ClO$ requires C, 72.5; H, 6.85%). m/e 250 (34%, $m^{\cdot +}$, ^{37}Cl), 248 (100%, $m^{\cdot +}$, ^{35}Cl), 213 (17%), 212 (60%), 185 (66%), 143 (91%), 91 (74%), 77 (34%).

Attempted Dehydration of endo-4-Hydroxy-1-phenylbicyclo[3.3.1] nonan-9-one with Phosphorus Oxychloride/Pyridine.

Treatment of the endo- isomer (36.8mg) under the conditions described above gave an oily white solid. T.l.c. (benzene/silica) showed only one product. Crystallisation from chloroform/petrol gave colourless cubes, of exo-4-chloro-1-phenylbicyclo[3.3.1] nonan-9-one (34mg, 82%), m.p. 99 - 99.5°, ν_{max} 1715 s, 750 s, 700 s cm^{-1}; τ ($CDCl_3$) 2.70 (5 x aromatic H, m), 5.10 - 5.40 (CHCl, m, $W^{\frac{1}{2}}$ 7 Hz), 6.75 - 9.30 (12 x aliphatic H, m), (Found: C, 72.6; H, 7.1. $C_{15}H_{17}ClO$ requires C, 72.5; H, 6.85%). m/e 250 (34%, $m^{\cdot +}$, ^{37}Cl), 248 (100%, $m^{\cdot +}$, ^{35}Cl), 213 (22%), 212 (40%), 185 (68%), 143 (100%), 115 (56%), 91 (76%), 77 (40%).

1-Phenylbicyclo[3.3.1]non-3-en-9-one

The endo- alcohol (0.104g) was added to a solution of toluene

p-sulphonyl chloride (0.110g) in dry pyridine (0.55ml) at 0°C, and then set aside at room temperature for 30h. The reaction mixture was then poured into water and extracted three times with ether and the combined organic layers were washed twice with dilute hydrochloric acid (10%), twice with water, dried ($MgSO_4$), and solvent removed to give a clear oil (0.1006g, 59%). IR showed the disappearance of the OH stretching bond. The crude tosylate was used directly without further purification. ν_{max} 1725 s, 1190 s, 1175 s, 750 s, 700 s cm^{-1}.

The endo- tosylate (0.182g) was added to a suspension of sodium acetate (39.6mg, fused) in glacial acetic acid (5.7ml) and the mixture refluxed under nitrogen for 28h. The cooled reaction mixture was then poured into water and extracted three times with ether. The combined ether layers were then washed twice with sodium carbonate solution, twice with saturated sodium chloride solution, dried ($MgSO_4$), and solvent removed to give a light brown oil (0.132g). Column chromatography (10g Kieselgel, 4:1 benzene:ethyl acetate as eluant) gave 1-phenylbicyclo[3.3.1]non-3-en-9-one (22.4mg, 22%), b.p. 155 - 160°/1mm, ν_{max} 1720 s, 1660 s, 750 s, 700 s cm^{-1}; τ (CCl_4) 2.70 (5 x aromatic H, m), 3.80 - 5.40 (2 x olefinic H, structured m), 6.80 - 7.25 (2 x H_2 and H_5, m), 7.55 - 8.45 (6 x aliphatic H, m), m/e 212 (100%, m^+), 184 (27%), 169 (29%), 141 (38%), 129 (24%), 128 (24%), 115 (30%), 91 (38%), 77 (23%).

Further elution gave exo-4-acetoxy-1-phenylbicyclo-[3.3.1] nonan--9-one (91.2mg, 70%) as a clear oil which rapidly crystallised on standing. This was recrystallised from ethyl acetate/petrol as long

needles, m.p. 105 - 105.5°, ν_{max} 1730 s, 1715 s, 1250 s, 1240 s, 1230 s, 760 s, 700 s cm^{-1}; τ ($CDCl_3$) 2.65 (5 x aromatic H, m), 4.40 - 4.70 (-C<u>H</u>-OAc, m, $W^{\frac{1}{2}}$ 8 Hz), 6.90 - 8.40 (14 x aliphatic H, m, including $C\underline{H}_3CO_2$-, s, at τ 8.00). (Found: C, 74.75; H, 7.3. $C_{17}H_{20}O_3$ requires C, 74.95; H, 7.5%). m/e 272 (68%, $m^{\cdot+}$), 230 (10%), 229 (12%), 212 (68%), 156 (62%), 155 (62%), 91 (100%), 77 (32%), 43 (100%).

The <u>exo</u>-tosylate was prepared in the same way as the <u>endo</u>-tosylate in a yield of 59%. IR indicated complete reaction and this product was used directly in the next step, ν_{max} 1725 s, 1190 s, 1175 s, 750 s, 700 s cm^{-1}.

Buffered acetolysis of the <u>exo</u>-tosylate (100.6mg) gave a brown oil (58.2mg) which was purified by column chromatography (6g Kieselgel, 8:1 benzene:ethyl acetate as eluant) to give 1-phenylbicyclo [3.3.1]non--3-en-9-one (41.6mg, 75%) identical with that prepared previously. Further elution gave an oily product (8.0mg, 11%) which had an i.r. spectrum very similar to the above acetate.

The alkene obtained in these reactions was used directly for the next step with no further purification.

<u>1-Phenylbicyclo [3.3.1] nonan-9-one</u>

1-Phenylbicyclo[3.3.1]non-3-en-9-one (52.7mg) was mixed with 5% palladium on charcoal (6mg) and glacial acetic acid (5ml) and hydrogenated at normal temperature and pressure until the uptake of hydrogen ceased. The palladium/charcoal was filtered off and the

residue saturated with water and extracted with ether. The ether extracts were washed twice with sodium carbonate solution, once with water, and dried ($MgSO_4$). Removal of the solvent gave a clear oil which was chromatographed (6g Kieselgel, benzene as eluant) to give a colourless solid. Crystallisation from ethanol gave 1-phenyl-bicyclo [3.3.1] nonan-9-one (36.4mg, 69%) as colourless needles, m.p. 81.5 - 83.0°, ν_{max} 1715 s, 750 s, 700 s cm^{-1}; τ ($CDCl_3$) 2.70 (5 x aromatic H, m), 6.75 - 8.90 (13 x aliphatic H, m). (Found: C, 84.15; H, 8.3. $C_{15}H_{18}O$ requires C, 84.05; H, 8.45%). m/e 214 (86%, $m^{\cdot+}$), 186 (45%), 157 (66%), 155 (55%), 144 (66%), 143 (90%), 142 (34%), 141 (45%), 130 (40%), 129 (100%), 128 (66%), 115 (90%), 91 (86%), 77 (62%), 44 (90%).

This compound was identical in all respects with the product isolated by ozonolysis of 9-methylene-1-phenylbicyclo [3.3.1] nonane, and it was also identical with a sample of this ketone kindly supplied by Professor Nicoletti.

Wittig Methylenation of Ketone (158)

Methyl triphenylphosphonium bromide (368mg) was suspended in very dry ether (3ml) with stirring, and n-butyllithium (1.45ml of a 0.705m solution in pentane) was added over 5 min by a syringe. This was stirred for 10 min at ambient temperature before the addition of 1-phenylbicyclo [3.3.1] nonan-9-one (200mg dissolved in 5ml ether). The reaction mixture was refluxed for 3h, stirred overnight at ambient temperature, and worked up by pouring the reaction mixture into water and extracting with ether. The combined ethereal layers were washed

with water, dried ($MgSO_4$), solvent removed, and the product distilled. This gave 9-methylene-1-phenylbicyclo [3.3.1] nonane (0.180g, 91%), identical in all respects with the product derived by dehydration of 9-hydroxymethyl-1-phenylbicyclo [3.3.1] nonane.

Reaction of Ethyl (Cyclooct-4-enylidene)acetate with Boron Trifluoride Diethyl Etherate in Nitrobenzene.

Ethyl (cyclooct-4-enylidene)acetate (500mg) was dissolved in a mixture of dry nitrobenzene (25ml) and boron trifluoride diethyl etherate (15ml) and heated for 17 h at 80 - 90° (bath temp.). No recognisable product could be isolated from this reaction.

Ethyl 1-p-tolylbicyclo[3.3.1]nonane-9-carboxylate and 1-p-tolylbicyclo-[3.3.1] nonane-9-carboxylic acid.

Ethyl (cyclooct-4-enylidene)acetate (387mg) was dissolved in dry toluene (20ml, dried by standing over sodium wire) and boron trifluoride diethyl etherate (20ml) and heated at 90°C (bath temperature) for 17h. The cooled reaction mixture was then cautiously poured into sodium carbonate solution and, after vigorous shaking, the toluene layer was separated off. The aqueous layer was then extracted twice more with benzene, and the combined organic layers were then washed once with water and dried ($MgSO_4$). Removal of solvent yielded a pale yellow oil (500mg) which was purified by column chromatography (25g Kieselgel, benzene as eluant) to give a colourless oil which was distilled (176mg) b.p. 165 - 170°/0.2mm. This oil crystallised on standing and was recrystallised twice from petrol to give 9-carboethoxy-1-p-tolylbicyclo-

[3.3.1]nonane (148 mg, 28%) as colourless flakes, m.p. 53 - 55°, ν_{max} 1735 s, 800 s, cm^{-1}; τ (CCl_4) 2.80, 2.95, 3.00, 3.15 (4 x aromatic H, AA'BB'), 6.15 (-O.CH_2.CH_3, q, J 7 Hz), 7.00 (H_9, br.s), 7.20 - 8.65 (16 x aliphatic H, m; with -CH_3, s, at τ 7.75), 9.00 (-OCH_2CH_3, t, J 7 Hz). (Found: C, 79.9; H, 9.15. $C_{19}H_{26}O_2$ requires C, 79.7; H, 9.15%). m/e 286 (70%, $m^{\cdot+}$), 243 (38%), 213 (100%), 197 (45%), 169 (50%), 105 (85%), 91 (38%).

The aqueous, basic, layer from the extraction of the reaction mixture was acidified (concentrated hydrochloric acid) and extracted three times with chloroform. The combined extracts were then washed with water and dried ($MgSO_4$). Removal of the chloroform gave a white solid (130mg) which crystallised from chloroform/petrol to yield 1-p-tolylbicyclo[3.3.1]nonane-9-carboxylic acid (110mg, 21%), m.p. 196 - 198°, ν_{max} 2720 w, br, 1710 s, 805 s cm^{-1}; τ ($CDCl_3$) -2.70 (-CO_2H, br. s, disappears on addition of D_2O), 2.60, 2.75, 2.80, 2.95 (4 x aromatic H, AA'BB'), 6.85 (H_9, br. s), 7.35 - 8.55 (16 x aliphatic H, m, including CH_3, s, at τ 7.70). (Found: C, 78.6; H, 8.45. $C_{17}H_{22}O_2$ requires C, 79.03%, H, 8.58%). m/e 258 (10%, $m^{\cdot+}$), 240 (6%), 215 (9%), 169 (13%), 115 (29%), 105 (40%), 91 (29%), 43 (100%).

(Cyclooct-4-enylidene)Acetic Acid.

Ethyl(cyclooct-4-enylidene)acetate (1.0g) was added to sodium hydroxide solution (20ml, 2N) and brought to reflux. Sufficient ethanol was then added to just bring the ester into solution, which was then refluxed for 6h. The cooled reaction mixture was poured into water (100ml) and extracted twice with ether. Acidification of the basic,

aqueous solution with concentrated hydrochloric acid, followed by extraction with chloroform, drying ($MgSO_4$) of the chloroform layers, and removal of solvent gave an oil which crystallised on standing. This was recrystallised from ethanol/water to give (cyclooct-4-enylidene) acetic acid (0.63g, 74%) as a colourless microcrystalline powder, m.p. 80 - 81°, ν_{max} 2660 m, br, 1685 s, 1630 s cm^{-1}; τ ($CDCl_3$) -2.30 (-$CO_2\underline{H}$, s, disappears on addition of D_2O), 4.20 - 4.45 (olefinic H_4, H_5, structured m), 4.70 (=$C\underline{H}.CO_2H$, s), 6.90 - 8.55 (10 x aliphatic H, m). (Found: C, 72.05; H, 8.65. $C_{10}H_{14}O_2$ requires C, 72.25; H, 8.5%). m/e 166 (49%, $m^{\cdot+}$), 151 (16%), 148 (9%), 138 (26%), 137 (53%), 121 (100%), 111 (38%), 93 (44%), 81 (33%), 79 (50%), 67 (74%).

(Cyclooct-4'-enylidene)propan-2-one

The above acid (1.8g) was dissolved in very dry ether (50ml) and to this stirred solution was added methyl-lithium (prepared from 1.4g lithium and 14 ml methyl iodide in 100ml dry ether) over 20 min at room temperature. After stirring for 1/2h the solution was cautiously poured into sodium thiosulphate solution and the ether layer was separated. The aqueous layer was extracted twice with ether, and the combined ether layers were then washed once with water and dried ($MgSO_4$). Removal of the solvent gave a yellow oil which was purified by column chromatography (60g Kieselgel, benzene as eluant) and distillation to give the required ketone(170) (1.0g, 51%) as a clear oil, b.p. 85 - 90°/ 1.5mm, ν_{max} 1680 s, 1610 s, 715 m cm^{-1}; τ (CCl_4) 3.90, 4.05 (=$C\underline{H}COCH_3$, 2 x s), 4.10 - 4.80 (olefinic H_4' and H_5', m), 7.00 - 8.80 (13 x aliphatic H, m), including -$COC\underline{H}_3$, s, at τ 7.90). (Found: C, 80.3; H, 9.8. $C_{11}H_{16}O$ requires C, 80.45; H, 9.85%). m/e 164 (100%, $m^{\cdot+}$), 149 (30%), 136 (28%), 135 (27%), 123 (38%), 121 (60%), 109 (39%), 106 (31%), 95 (59%), 79 (44%), 43 (91%).

9-Acetyl-1-phenylbicyclo[3.3.1] nonane.

The ketone (170) (250 mg) was dissolved in a mixture of boron trifluoride diethyl etherate (5ml) and dry benzene (5ml) and refluxed for 17h. The solution was then cautiously poured into sodium carbonate solution and the benzene layer separated. The aqueous layer was extracted twice with benzene and the combined benzene extracts were washed with water and dried ($MgSO_4$). Removal of solvent gave a pale yellow oil which was chromatographed (40g alumina, 1:1 benzene:petrol as eluant) to give, as the first fraction, a colourless, paraffinic oil (148mg), and then 9-acetyl-1-phenylbicyclo [3.3.1] nonane (92mg, 25%) as a colourless oil, b.p. 160 - 170°/0.3mm, ν_{max} 1705 s, 750 s, 690 s cm^{-1}, τ (CCl_4) 2.85 (5 x aromatic H, m), 6.75 (H_9, br. s), 7.45 - 8.50 (16 x aliphatic H, m, including $-COCH_3$, s, at τ 8.05). (Found: C, 84.0; H, 9.05. $C_{17}H_{22}O$ requires C, 84.25; H, 9.15%). m/e 242 (100%, $m^{\cdot+}$), 224 (41%), 199 (55%), 157 (23%), 117 (42%), 95 (28%), 91 (51%), 77 (9%).

9-Acetyl-1-phenylbicyclo[3.3.1]nonane

A solution of methyl-lithium was prepared by adding methyl iodide (230mg dissolved in 4ml very dry diethyl ether) to lithium wire (23mg, suspended in 1ml dry ether) and stirring at room temperature for 30 min. A solution of 1-phenylbicyclo [3.3.1]nonane-9-carboxylic acid (100mg) dissolved in very dry ether (2ml) was then rapidly added and the mixture was stirred for a further 30 min before pouring into sodium thiosulphate solution. Extraction with ether, washing of the ether extract with water, drying ($MgSO_4$), and removal of solvent gave a yellow oil which

was chromatographed (10g Kieselgel, 1:1 benzene:petrol as eluant). This gave the title ketone (89mg, 90%) as a colourless oil, identical in all respects to the sample from the above boron trifluoride diethyl etherate reaction.

Reaction of Ethyl (Cyclooct-4-enylidene)acetate with Boron Trifluoride Diethyl Etherate.

Ethyl (cyclooct-4-enylidene)acetate (1.0g) was dissolved in boron trifluoride diethyl etherate (25ml) and refluxed for 17h. The cooled reaction mixture was poured into sodium carbonate solution and, after vigorous shaking, this was extracted with ether. The ether extracts were washed with water, dried ($MgSO_4$), and the solvent removed to give a dark brown oil (0.919g). The basic, aqueous layer from the extraction was acidified (concentrated hydrochloric acid), extracted with chloroform and the chloroform extracts dried ($MgSO_4$). Removal of the solvent then gave a partly crystalline, dark brown, oil (60mg).

The ether extracts from the basic solution were hydrolysed by refluxing them for 16h. with sodium hydroxide solution (2N, 50ml) and sufficient ethanol to just bring the ester into solution. The ethanol was then removed from the solution on a rotary evaporator and the resulting aqueous solution was extracted with ether. The aqueous solution was then acidified (concentrated hydrochloric acid), extracted with chloroform, and the chloroform extracts were washed with water and dried ($MgSO_4$). Removal of the solvent gave a brown oil (0.175g) which was combined with the previous 60mg and distilled (b.p. 125 - 135°/

0.6mm) to give a clear oil which slowly crystallised. Crystallisation from chloroform/petrol gave colourless rhomboids (123mg, 14%) of bicyclo[3.3.1]nonane-9-carboxylic acid, m.p. 129 - 131°, amide, m.p. 111 - 113°, m/e 168 (m^+).

This sample was identical in all respects with an authentic sample kindly provided by Professor H.O. House.[129]

The above experiment was repeated using 1g of ester, but in boron trifluoride diethyl etherate/dioxan mixture (10ml, 1:1) at 100°C. This was refluxed for 16h. The same work-up procedure gave 0.882g of crude esters and 33mg of acidic product (after crystallisation). The crude ester product was purified by chromatography (45g alumina, benzene as eluant) to give 9-carboethoxybicyclo[3.3.1]nonane, ν_{max} 1730 s, 1180 s cm^{-1}, (254mg). This ester, however, could not be freed of a minor contaminant so it was hydrolysed (as before) and the resulting acid crystallised to give bicyclo[3.3.1]nonane-9-carboxylic acid (145mg). The total yield of the acid being 178mg (21%).

Bicyclo[3.3.0]octane-1-acetic acid.

Bicyclo[3.3.0]octane-1-carboxylic acid[155] (3.8g) was refluxed with thionyl chloride (4ml) for 1/2h, and the thionyl chloride was then removed under vacuum. Traces of thionyl chloride remaining were removed by azeotroping with dry benzene and the acid chloride obtained was then dissolved in dry ether (10ml). An ethereal, alcohol free solution of diazomethane (prepared from 21g N-methyl-N-nitrosotoluene-4-sulphonamide[156]) was then cooled to 0° and the acid chloride solution

was added dropwise. The reaction mixture was allowed to warm up to room temperature, and set aside for 2h. The ether and excess diazomethane were then removed under reduced pressure and the resulting orange oil was dissolved in chloroform, washed twice with sodium carbonate solution, and dried ($MgSO_4$). Removal of the solvent gave the intermediate diazoketone (1.0g),(ν_{max} 2100s cm^{-1}) which was decomposed[157] by adding it dropwise to a refluxing mixture of benzyl alcohol (9ml, purified and re-distilled) and s-collidine (9ml, redistilled). After heating until all the nitrogen had been evolved (7min) the solution was cooled and poured into dilute hydrochloric acid (2N). Extraction with ether, followed by a further washing of the ether extracts with dilute hydrochloric acid and drying ($MgSO_4$), gave, after removal of the solvent, the benzyl ester dissolved in benzyl alcohol.

The crude benzyl ester was immediately hydrolysed by refluxing for 10h with sodium hydroxide solution (75ml, 2N) with sufficient ethanol added to ensure a homogeneous solution. The cooled solution was extracted with ether, and the basic, aqueous layer acidified (concentrated hydrochloric acid) and extracted with chloroform. After washing once with water and drying ($MgSO_4$) the solvent was removed to give crude bicyclo[3.3.0]octyl-1-acetic acid which was distilled to give pure bicyclo[3.3.0]octyl-1-acetic acid (0.85g, 20%) as a colourless oil, b.p. 125 - 130°/0.4mm, ν_{max} 2660 m, br, 1700 s cm^{-1}; τ ($CDCl_3$) -3.25 (-CO_2H, s, disappears upon addition of D_2O), 7.30 - 8.85 (15 x aliphatic H, m, including -CH_2.CO_2H, s, at τ 7.55).

A small sample of this acid was converted to the amide to furnish an analysis sample, m.p. 91 - 94° (from ethyl acetate/petrol).

(Found: C, 71.8; H, 10.3; N, 8.65. $C_{10}H_{17}NO$ requires C, 71.8; H, 10.25; N, 8.4%). m/e 167 (19%, $m^{\cdot+}$), 153 (45%), 136 (24%), 109 (37%), 108 (87%), 72 (65%), 67 (45%), 60 (61%), 59 (100%).

Synthesis of Dimethyl 3,3-(Cyclooct-4'-enyl)gluterate

(i) (Cyclooct-4-enylidene)cyanoacetamide

Cyclooct-4-enone (2g) was mixed with cyanoacetamide (1.8g), ammonium acetate (1g), acetic acid (2.1g) and benzene (60ml) and refluxed for 16h with continuous removal of water. The reaction mixture was then cooled and the solvents removed under reduced pressure, and the resulting brown oil was dissolved in chloroform. Water was added, and then sodium carbonate until the pH of the aqueous layer reached 6. The chloroform layer was separated and the aqueous solution extracted twice more with chloroform. The combined chloroform layers were dried ($MgSO_4$) and the solvent removed to give a light brown oil (3.3g) which was crystallised from ethanol to yield pure (cyclooct--4-enylidene) cyanoacetamide (1.8g, 59%) as colourless needles, m.p. 115.5 - 116°, ν_{max} 3330 w, 3260 m, 3130 m, 1690 s, 1580 s cm^{-1}; τ ($CDCl_3$) 2.20 - 3.90 (-$CONH_2$, br. s), 3.90 - 4.45 (olefinic H_4 and H_5, m), 6.70 - 8.50 (10 x aliphatic H, m). (Found: C, 69.6; H, 7.5; N, 15.0. $C_{11}H_{14}NO$ requires C, 69.45; H, 7.4; N, 14.75%). m/e 190 (100%), 176 (42%), 174 (33%), 163 (79%), 162 (46%), 146 (37%), 137 (63%), 136 (46%), 68 (33%).

(ii) 5-Carbomethoxy-1-cyano-3-azaspiro[5,7]tridec-9-en-2,4-dione (174)

(Cyclooct-4-enylidene)cyanoacetamide (1.7g) dissolved in dry

methanol (8ml) was added to a solution of sodium methoxide in dry methanol (prepared by adding 0.41g sodium to 13ml dry methanol) and dimethyl malonate (2.35g) was then added. After standing at room temperature for 63h, a large amount of white solid separated which dissolved on neutralisation with concentrated hydrochloric acid. The solution was evaporated, the residue distributed between chloroform and water and the chloroform layer separated. The remaining aqueous layer was extracted twice more with chloroform, and the total chloroform extracts combined. These extracts were then themselves extracted twice with sodium hydroxide solution (2N) and the combined basic extracts were re-extracted with chloroform after neutralisation with hydrochloric acid. The chloroform extracts of the final acidic solution were then dried ($MgSO_4$), and the solvent was removed to give a thick brown oil (1.8g). This was crystallised from ethanol/water to yield pure 5-carbomethoxy--1-cyano-3-azaspiro[5,7]tridec-9-en-2,4-dione (1.4g, 54%) as a colourless solid, m.p. 135 - 137° (decomp.), ν_{max} 3190 m, 3090 m, 1750 w, 1725 s, 1700 s cm^{-1}. (Found: C, 62.75; H, 6.45; N, 10.25. $C_{15}H_{18}N_2O_4$ requires C, 62.05; H, 6.25; N, 9.65%. This compound would not analyse satisfactorily, the reported figures represent the most accurate analysis obtained). m/e 290 (1%, $m^{\cdot +}$), 258 (15%), 203 (18%), 189 (15%), 164 (63%), 150 (25%), 138 (17%), 125 (40%), 91 (30%), 79 (41%), 67 (61%), 44 (100%).

(iii) Dimethyl 3,3-(Cyclooct-4'-enyl)glutarate

The substituted glutarimide (174) (3.6g) was mixed with water (9ml), concentrated hydrochloric acid (9ml), and glacial acetic acid (30ml) and refluxed for 17h. All the solvent was then removed on a

rotary evaporator and the resulting light brown oil was mixed with sodium hydroxide solution (35ml, 10N) and refluxed for 50h. A solution of concentrated sulphuric acid (14g) in water (40ml) was then added and the reaction mixture was refluxed for a further 1/2h before cooling. The reaction mixture was then extracted with ether, the ether extracts washed with saturated sodium chloride solution, dried ($MgSO_4$), and the solvent removed to yield a clear oil (3.2g). This product was then immediately esterified with diazomethane [158] and the ester thus obtained was distilled to yield a clear oil (2.38g), b.p. 185 - 200°/2.0mm. Gas-liquid chromatography on this oil (3% OV17 column, oven temperature = 250°, nitrogen flow rate = 50 ml min^{-1}) showed three components in the ratio of 16:20:1 (retention times = 2 min, 4 min, and 3 min respectively). A pure sample of the first eluted component was collected by preparative gas-liquid chromatography (10% SE 30 column, oven temperature = 235°, nitrogen flow rate = 40ml min^{-1}) and was shown to be the required title diester, b.p. 190 - 200°/2mm, ν_{max} 1735 s cm^{-1}; τ (CCl_4) 4.10 - 4.65 (olefinic H_4 and H_5, m), 6.45 (2 x $-CO_2\underline{CH}_3$, s), 7.60 (2 x $-\underline{CH}_2.CO_2CH_3$, s), 7.70 - 8.05 (2 x H_3, 2 x H_6, m), 8.30 - 8.65 (2 x H_2, 2 x H_7, 2 x H_8, m). (Found: C, 65.95; H, 8.9. $C_{14}H_{22}O_4$ requires C, 66.1; H, 8.7%). m/e 254 (23%,$m^{\cdot+}$), 223 (93%), 222 (84%), 194 (30%), 190 (24%), 181 (92%), 180 (94%), 149 (78%), 148 (45%), 121 (71%), 120 (66%), 107 (100%), 106 68%), 93 (48%), 91 (35%), 79 (65%), 74 (40%), 67 (41%). The other major product eluted was not positively identified.

Attempted Rearrangement of Dimethyl 3,3-(cyclooct-4'-enyl)glutarate with Boron Trifluoride Diethyl Etherate

Dimethyl 3,3-(cyclooct-4'-enyl)glutarate (20mg) was dissolved

in a mixture of dry benzene (1.0ml) and boron trifluoride diethyl etherate (1.0ml) and refluxed for 17h. The cooled reaction mixture was then cautiously poured into sodium carbonate solution and, after vigorous shaking, the benzene layer was separated off. The aqueous layer was re-extracted with benzene and the combined benzene solutions were then washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield a clear oil which was distilled, b.p. 180 - 190°/1.7mm, and shown to be homogeneous starting material by spectroscopic data and gas-liquid chromatography. Similar lack of reactivity was observed when this diester was heated with toluene-p--sulphonic acid in benzene.

3-Azaspiro[5,7]tridec-9-en-2,4-dione (175)

The glutarimide (1g) was mixed with potassium hydroxide (1.5g) and ethylene glycol (30ml) and refluxed for 1.1/4h under nitrogen. The cooled solution was then poured into water, acidified to pH6 (concentrated hydrochloric acid) and extracted with ether. The combined ethereal extracts were then washed with saturated sodium chloride solution, dried ($MgSO_4$), and solvent removed. Recrystallisation of the pink solid residue from ethanol gave colourless flakes of 3-azaspiro[5,7]tridec-9-en-2,4-dione (500mg, 71%), m.p. 152 - 155°, ν_{max} 3210 w, 3085 w, 1730 m, 1675 s cm^{-1}; τ ($CDCl_3$) 4.20 - 4.50 (olefinic H_9, H_{10}, m), 7.45 (2 x H_3, 2 x H_5, s), 7.40 - 8.10 (NH and 2 x H_8, 2 x H_{11}, m), 8.15 - 8.65 (2 x H_7, 2 x H_{12}, 2 x H_{13}, m). (Found: C, 69.3; H, 8.2; N, 6.65. $C_{12}H_{17}NO_2$ requires C, 69.55; H, 8.25; N, 6.65%). m/e 207 (48%, $m^{\cdot+}$), 178 (17%), 164 (40%), 139 (19%), 138 (54%), 125 (100%), 67 (48%).

3-Methyl-3-azaspiro[5,7]tridec-9-en-2,4-dione (176)

The foregoing glutarimide (175) (500mg) was dissolved in dry dimethylformamide (10ml) and sodium hydride (82mg) was added, in portions. This was stirred at room temperature for 1/2h, then methyl iodide (500mg) was added, and the reaction mixture was stirred overnight. Excess methyl iodide was removed under reduced pressure and the residue was saturated with water and extracted with ether. The combined ethereal extracts were washed with water, dried ($MgSO_4$) and the solvent removed to yield a brown oil. This was crystallised from ethanol to give the N-methylimide as fine needles (410mg, 77%), m.p. 72 - 74°, ν_{max} 1720 m, 1670 s cm^{-1}; τ ($CDCl_3$) 4.10 - 4.75 (olefinic H_9, H_{10}, m), 6.90 (N-CH_3, s), 7.40 (2 x H_3, 2 x H_5, s), 7.40 - 8.60 (10 x aliphatic H). (Found: C, 70.3; H, 8.55; N, 6.35. $C_{13}H_{19}NO_2$ requires C, 70.55; H, 8.65; N, 6.35%). m/e 221 (49%, $m^{\cdot+}$), 192 (15%), 179 (14%), 178 (36%), 153 (18%), 152 (44%), 140 (15%), 139 (100%), 95 (17%), 67 (18%), 41 (27%).

Synthesis of Ethyl (1'-phenylcyclooct-4'-enyl)acetate

(i) 1-Phenylcyclooct-4-ene-1-carboxylic Acid.

4-(Toluene-p-sulphonyloxy)-1-phenylbicyclo[3.3.1]nonan-9-one (4g of an epimeric mixture) was added to a solution of sodium ethoxide in ethanol (prepared by dissolving 3.7g sodium in 450ml ethanol) and refluxed for 25min. Glacial acetic acid (4ml) was then added and the ethanol was reduced in volume on a rotary evaporator, and then saturated with water. Ether extraction, washing of the ether extracts with sodium carbonate solution, drying ($MgSO_4$), and removal of solvent

gave a yellow oil which was purified by column chromatography (150g Kieselgel, chloroform as eluant) to give 1-carboethoxy-1-phenylcyclooct--4-ene (1.7g, 63%) as a clear oil, b.p. 160 - 165°/0.2mm, ν_{max} 1720 s, 1090 m, 750 m, 695 s cm^{-1}; τ (CCl_4) 2.70 (5 x aromatic H, m), 4.25 - 4.80 (olefinic H_4, H_5, m), 5.90 ($-OC\underline{H_2}CH_3$, q, J 7Hz), 7.10 - 8.60 (10 x aliphatic H, m), 8.85 ($-OCH_2C\underline{H_3}$, t, J 7 Hz). m/e 258 (100%, $m^{\cdot+}$), 212 (12%), 185 (68%), 184 (24%), 177 (26%), 143 (29%), 117 (34%), 115 (17%), 91 (69%), 81 (77%), 77 (13%).

The above ester (1.7g) was added to sodium hydroxide solution (150ml, 2N) and brought to reflux. Sufficient ethanol was then added to just take the ester into solution, and the reaction mixture was then refluxed for 46h. Ethanol was then removed on a rotary evaporator and the resulting aqueous solution was extracted three times with ether. The aqueous layer was acidified (concentrated hydrochloric acid), extracted with chloroform, and the combined chloroform layers were washed with water and dried ($MgSO_4$). Removal of the solvent gave a white solid which was recrystallised (ethanol/water) to yield 1-phenylcyclooct-4-ene-1-carboxylic acid (608mg, 40%), m.p. 121 - 122°, ν_{max} 2670 w, br, 1690 s, 720 m, 695 m cm^{-1}; τ ($CDCl_3$) -1.55 ($-C\underline{O_2H}$, s, disappears on addition of D_2O), 2.70 (5 x aromatic H, m), 4.05 - 4.80 (olefinic H_4, H_5, m), 6.90 - 9.10 (10 x aliphatic H, m). (Found: C, 78.3; H, 7.8. $C_{15}H_{18}O_2$ requires C, 78.25; H, 7.9%). m/e 230 (54%, $m^{\cdot+}$), 212 (12%), 185 (38%), 184 (24%), 91 (100%), 82 (45%), 81 (80%), 67 (46%).

Ethyl (1'-phenylcyclooct-4'-enyl)acetate (179)

1-Phenylcyclooct-4-ene-1-carboxylic acid (700mg) was dissolved

in thionyl chloride (5ml) and vigorously stirred for 4h at room temperature with a stream of nitrogen over the reaction mixture. The excess thionyl chloride was then removed under reduced pressure and the acid chloride was dissolved in very dry ether (10ml) and added dropwise to a solution of diazomethane in ether (prepared from 5.4g N-methyl-N-nitrosotoluene-4-sulphonamide, total volume of solution = 80ml, dried over powdered potassium hydroxide). After 3h standing at room temperature the ether and excess diazomethane were removed under reduced pressure and the residue was dissolved in ether and washed with sodium carbonate. Drying ($MgSO_4$) of the ethereal solution, and removal of the solvent gave a yellow oil consisting of a mixture of the starting ester and the required diazoketone, ν_{max} 2100 s cm^{-1}. This mixture was decomposed immediately by adding it, dropwise, to a refluxing mixture of benzyl alcohol (10ml, purified) and s-collidine (10ml, re-distilled) and refluxing, under nitrogen, for 8 min. The cooled solution was then poured into dilute hydrochloric acid (30ml, 50%) and extracted with ether. The ether extracts were washed twice more with dilute hydrochloric acid, dried ($MgSO_4$), and the solvent removed, to give a red oil. This was hydrolysed by refluxing it with sodium hydroxide solution (50ml) containing ethanol for 35 min. The ethanol was then removed on a rotary evaporator and the resulting aqueous solution was extracted with ether, acidified, and extracted with chloroform. The chloroform extract was washed with water, dried ($MgSO_4$), and the solvent removed, to yield a clear yellow oil (263mg). This was esterified with ethanol and a trace of hydrogen chloride in the usual way to give a mixture of 1-carboethoxy-1-phenylcyclooct-4-ene and the required ester (202mg). This mixture was further enriched in the homologated ester by re-hydrolysing for 15 min, and then re-esterifying

with ethanol. The resulting mixture was distilled, b.p. 160 - 170°/0.2mm, to give a clear oil which was a 1:1 mixture of the two esters (by N.M.R.) (79mg).

Part of this mixture of esters (70mg) was separated by chromatography (7g, Kieselgel, benzene as eluant) to give the required ester as a clear oil (20mg), b.p. 165 - 175°/0.2mm, ν_{max} 1730 s, 1155 s, 760 m, 700 s cm^{-1}; τ (CCl_4, 100 m Hz), 2.60 - 3.05 (5 x aromatic H, m), 4.20 - 4.90 (olefinic H_4, H_5, m), 6.20 ($-OC\underline{H}_2CH_3$, q, J 7Hz), 7.40 - 8.95 (12 x aliphatic H, m, including $-C\underline{H}_2.CO_2C_2H_5$, s, at τ7.50), 9.05 ($-OCH_2C\underline{H}_3$, t, J 7Hz). (Found: M^+ 272.1770. $C_{18}H_{24}O_2$ requires M^+ 272.1776). m/e 272 (12%, $m^{\cdot +}$), 185 (22%), 184 (26%), 169 (14%), 155 (16%), 143 (23%), 141 (20%), 129 (50%), 118 (37%), 117 (53%), 115 (51%), 105 (43%), 104 (35%), 91 (100%), 81 (47%), 77 (40%).

Rearrangement of Ethyl (1'-phenylcyclooct-4'-enyl)acetate with Boron Trifluoride Diethyl Etherate.

The ester (179) (16.4mg) was dissolved in a mixture of boron trifluoride diethyl etherate (1ml) and dry benzene (1ml) and refluxed for 17h. The reaction mixture was then cautiously poured into sodium carbonate solution, shaken vigorously, and the benzene layer separated off. The aqueous layer was extracted twice more with benzene, and the combined benzene layers were then washed with water and dried ($MgSO_4$). Removal of the solvent gave a yellow oil (15.7mg) which was purified by column chromatography (1g silica, benzene as eluant) to give a pale yellow oil (12mg). An N.M.R. spectrum (100 m Hz) of this oil showed the complete absence of any 9-carboethoxy-1-phenyl-

bicyclo[3.3.1]nonane, no peaks due to the H_9 singlet or the ester group being observed.

7-exo-Methylenebicyclo[3.3.1]nonan-3-one

This was prepared by the method described by Geigy, A.G.[159]

Ethyl (7-exo-Methylenebicyclo[3.3.1]non-3-enylidene)acetate

Triethyl phosphonoacetate (3.5g) dissolved in dry tetrahydrofuran (20ml) was added dropwise to a stirred suspension of sodium hydride (0.32g) in dry tetrahydrofuran (20ml), under nitrogen, and then stirred at room temperature for 40h. 7-exo-Methylene-bicyclo[3.3.1]-nonan-3-one (1.3g) dissolved in dry tetrahydrofuran (20ml) was added, and the reaction mixture was warmed to 45 - 50° for 8h, and then refluxed for 40h. After cooling, the reaction mixture was poured into water (300ml) and extracted with ether. The ethereal extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), and the solvent removed, to give a pale yellow oil which was chromatographed (60g, Kieselgel, 3:1 benzene:ethyl acetate as eluant). This gave the required ester, heavily contaminated with a paraffinic oil (1.1g) as one fraction, followed by the starting ketone (450mg). The ester fraction was then purified by bulb-to-bulb distillation to give pure ethyl (7-exo-methylenebicyclo[3.3.1]non-3-enylidene)acetate as a clear, mobile, oil (836mg, 44%), b.p. 140 - 145°/0.7mm. G.l.c. analysis of this product (3% OV 17, oven temperature = 220°, nitrogen flow rate = 40 ml min^{-1}) indicated the presence of three components

in the approximate ratio of 6:1:3 (retention times 1.70min, 1.85 min, and 2.15min respectively). This was interpreted as a mixture of three isomers with the α,β and β,γ unsaturated esters predominating, and this interpretation was borne out by the spectroscopic data. ν_{max} 1735 s, 1710 s, 1645 m, 1150 s cm^{-1}; τ (CCl_4) 4.30 - 4.70 and 5.20 - 5.90 (3 olefinic protons, m), 5.90 ($-OC\underline{H}_2.CH_3$, q, J 7Hz), 7.15 ($-C\underline{H}_2$, $CO_2C_2H_5$, s), 7.30 - 8.50 (remaining aliphatic protons, m), 8.75 ($-OCH_2C\underline{H}_3$, t, J 7Hz). (Found: C, 76.65; H, 8.9. $C_{14}H_{20}O_2$ requires C, 76.3; H, 9.15%). m/e 220 (80%, $m^{\cdot+}$), 190 (32%), 188 (35%), 179 (35%), 165 (48%), 164 (34%), 119 (48%), 105 (49%), 91 (100%), 79 (42%).

Reaction of Ethyl (7-exo-Methylenebicyclo[3.3.1]non-3-enylidene)acetate with Boron Trifluoride Diethyl Etherate.

The title ester (210mg) was dissolved in a mixture of boron trifluoride diethyl etherate and dry benzene (20ml, 1:1 mixture) and heated under reflux for 18h and then worked up in the usual way. No acidic product was obtained. The ester products were chromatographed (18g Kieselgel, 1:1 ether:petrol as eluant) and distilled to give a clear oil (173mg), b.p. 160 - 180°/0.3mm. Gas-liquid chromatography of this oil showed only two products in the ratio of 3:1 (retention times were 8.2 and 14.7 min, respectively). Hydrolysis with sodium hydroxide solution (20ml,2N) and ethanol (2ml) under reflux for 10h gave an acid fraction (86mg), and a residual ester fraction (104mg) which partly crystallised upon standing. Crystallisation from petrol gave 2-carboethoxy-1-methyl-3-phenyladamantane (19mg) as colourless cubes, m.p. 77 - 79°, ν_{max} 1735 s, 1150 s, 765 s, 715 s cm^{-1}; τ (CCl_4, 100 m Hz) 2.60 - 3.10 (5 x aromatic H, m), 6.40 ($-OC\underline{H}_2CH_3$,

ABX, J_{AB} 10 Hz, J_{AX} 7 Hz), 6.90-8.95 (13 x aliphatic H, m), 9.20 ($-CH_3$, s), 9.30 ($-OCH_2CH_3$, t, J 7 Hz). (Found: C, 80.75; H, 8.65. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.80). m/e 298 (m^+, 100%), 252 (27%) 225 (73%), 224 (100%), 169 (31%), 168 (27%), 91 (36%), 77 (11%).

Cyclooct-3-enone.

Prepared by the method of Heap and Witham, b.p. 55-60°/2mm lit. 80°/12mm.[153]

Ethyl (Cyclooct-3-enylidene) Acetate.

This was prepared by the method described for the synthesis of ethyl (cyclooct-4-enylidene) acetate. Chromatography and distillation gave the title ester (1.21g, 61%) as a clear oil, b.p. 100-110°/1.5mm, ν_{max} 1710s, 1630s cm^{-1}; τ (CCl_4) 4.05-4.55 (H_3, H_4, = $CHCO_2Et$, m), 5.90 ($-OCH_2CH_3$, q, J 7 Hz), 6.85-7.30 (2 x H_2, m), 7.30 - 8.55 (8 x aliphatic H, m), 8.75 ($-OCH_2CH_3$, t, J 7 Hz). (Found: C, 74.25; H, 9.5. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9,35). m/e 194 (m^+, 100%), 149 (57%), 121 (58%), 91 (48%).

Reaction of Ethyl (Cyclooct-3-enylidene) Acetate with Boron Trifluoride' Diethyl Etherate.

The fore-going ester (200mg) was dissolved in a mixture of boron trifluoride diethyl etherate and benzene (20ml of a 1:1 mixture) and heated under reflux for 17h. Normal work up gave a non-crystalline mixture of acids (32mg), and an ester fraction (141mg). The

mixture of esters formed proved to be inseparable.

4-(p-Hydroxyphenyl)-4-methyl-pentanoic Acid.

Aluminium chloride (195g, anhydrous) was dissolved in dry nitrobenzene (600ml) at room temperature, and then cooled to 0°. Anisole (77g) was added dropwise, keeping the temperature below 5°, and to this mixture was added γ,γ-dimethylbutyrolactone[160] (56g) dissolved in dry nitrobenzene (100ml). The reaction mixture was stirred at room temperature for 5 min, and then securely stoppered and placed in a refrigerator at 0° for two weeks. It was then carefully poured onto a 1:1 mixture of ice and hydrochloric acid (600g), well stirred, and then filtered. The organic layer was separated, mixed with sodium hydroxide solution (6N, 50ml), and steam distilled to remove nitrobenzene. The aqueous residue from the steam distillation was extracted with ether, and then acidified (concentrated hydrochloric acid) and re-extracted with ether. The ethereal extract of the acidic solution was washed with water, dried ($MgSO_4$), and the solvent removed to give a dark brown crystalline mass. Crystallisation from chloroform/petrol gave 4-(p-hydroxyphenyl)-4--methyl-pentanoic acid (39g, 38%) as a white solid, m.p. 110 - 112°, ν_{max} 3140 s, br, 2700 m, br, 1680 s, 825 m cm^{-1}; τ (D_6 acetone) 2.70, 2.85, 3.10, 3.25 (4 x aromatic H, AA'BB'), 8.00 (2 x H_2, 2 x H_3, s), 8.70 (2 x CH_3, s). (Found: C, 68.8; H, 7.6. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.75%). m/e 208 (10%, $m^{\cdot +}$), 149 (26%), 136 (10%), 135 (100%), 107 (100%), 91 (16%).

4-(p-Methoxyphenyl)-4-methyl-pentanoic Acid.

4-(p-Hydroxyphenyl)-4-methyl-pentanoic acid (21g) was dissolved in ethanol (200ml), and sodium hydroxide solution (125ml, 10% w/w) and dimethyl sulphate (22.5ml) were simultaneously added dropwise to the stirred solution. The reaction mixture was refluxed for 6h and the solvent was then distilled off until the temperature of the distilling vapour reached 93°. After cooling, the reaction mixture was extracted with ether and the ethereal extract was dried ($MgSO_4$). Removal of the solvent gave crude methyl 4-(p-methoxyphenyl)-4-methyl pentanoate, which was immediately hydrolysed with sodium hydroxide solution (200ml, 2N) and ethanol (sufficient to take the ester into solution) by heating under reflux for 14h. After the usual work-up this gave 4-(p-methoxyphenyl)-4-methyl-pentanoic acid (7.8g).

The basic, aqueous, solution from the dimethyl sulphate reaction was acidified (concentrated hydrochloric acid) and extracted with ether. This ether extract was washed with water, dried ($MgSO_4$), and the solvent removed to give 4-(p-methoxyphenyl)-4-methyl pentanoic acid (12g) directly.

The combined acidic product was then recrystallised from petrol to give 4-(p-methoxyphenyl)-4-methyl-pentanoic acid (15.5g, 69%), as a white solid, m.p. 64 - 65°, ν_{max} 2650 w, br, 1715 s, 1515 s, 830 s cm^{-1}; τ ($CDCl_3$) -1.5 (-$CO_2\underline{H}$, s), 2.75, 2.90, 3.20, 3.35 (4 x aromatic H, AA'BB'), 6.25 (-$OC\underline{H}_3$, s), 8.00 (2 x H_2, 2 x H_3, s), 8.70 (2 x -$C\underline{H}_3$, s). (Found: C, 70.5; H, 8.1. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.15%). m/e 222 (28%, m^+), 207 (9%), 161 (16%), 150 (42%), 149 (100%), 121

(59%), 109 (32%), 91 (40%), 77 (28%), 58 (57%), 43 (80%).

5-(p-Methoxyphenyl)-5-methyl-hexan-2-one.

4-(p-Methoxyphenyl)-4-methyl-pentanoic acid (12.0g) was dissolved in very dry ether (400ml) and the reaction flask was swept out with nitrogen. Filtered methyl-lithium (prepared from 21.2g lithium and 220g methyl iodide in 1l of very dry ether) was added dropwise to the stirred solution of acid over 1/2h, and the reaction mixture was stirred for a further 1/2h at room temperature. This was then cautiously poured into sodium thiosulphate solution (500ml, 20% w/w) and the ether layer separated. The aqueous layer was extracted twice with ether and the combined ethereal extracts were washed with water and dried ($MgSO_4$). Removal of the solvent gave a yellow oil which was distilled to yield 5-(p-methoxyphenyl)-5-methyl--hexan-2-one (11.0g, 93%), b.p. 159 - 160°/4mm, ν_{max} 1715 s, 1515 s, 825 s cm^{-1}; τ (CCl_4) 2.80, 2.95, 3.25, 3.40 (4 x aromatic H, AA'BB'), 6.25 (-$OC\underline{H}_3$, s), 7.65 - 8.35 (2 x H_3, 2 x H_4, m, including $COC\underline{H}_3$, s, at τ8.05), 8.70 (2 x -$C\underline{H}_3$, s). The 2,4-dinitrophenylhydrazone had m.p. 140.5 - 141° (from methanol, then ethanol). (Found: C, 59.6; H, 5.85; N, 13.8. $C_{20}H_{24}N_4O_5$ requires C, 60.0; H, 6.05; N, 14.0%). m/e 400 (20%, $m^{\cdot +}$), 203 (15%), 150 (25%), 149)73%), 121 (30%), 109 (13%), 91 (12%), 58 (30%), 43 (100%).

3-Bromo-5-(p-methoxyphenyl)-5-methyl-hexan-2-one

5-(p-Methoxyphenyl)-5-methyl-hexan-2-one (1.0g) was dissolved in a mixture of ethyl acetate (6ml) and chloroform (6ml), cupric

bromide (2.12g, anhydrous) was added, and the reaction mixture was refluxed, with vigorous magnetic stirring, for 1h, and then stirred for 2h at room temperature. The cooled reaction mixture was filtered, insoluble salts were well washed with chloroform, and the combined organic solutions were washed with saturated sodium bicarbonate solution, water, and dried ($MgSO_4$). Removal of the solvent gave a pale brown oil which was chromatographed (60g, Kieselgel, 4:1 benzene:chloroform). The first fraction eluted was a clear oil (185mg) with no C=O stretch in the I.R., mass spectrometry indicated this to be a dibromide, but on attempted further purification by distillation the compound rapidly decomposed. The second fraction was a clear oil which slowly crystallised on standing. This was crystallised from petrol as colourless flakes of 1,3-dibromo-5-(p-methoxyphenyl)-5-methyl-hexan-2-one (120mg, 7%), m.p. 44 - 45°, ν_{max} 1740 s, 1510 s, 840 s cm^{-1}; τ ($CDCl_3$) 2.70, 2.85, 3.10, 3.25 (4 x aromatic H, AA'BB'), 5.65 (H_3, d x d, $J_{3,4}$ 4Hz and $J'_{3,4}$ 8Hz), 6.20 (-OCH_3, and 2 x H_2, s), 7.15 (H_4, d x d, $J'_{4,3}$ 8Hz and $J_{4,4}$ 15Hz), 7.80 (H_4, d x d, $J_{4,3}$ 4Hz and $J_{4,4}$ 15Hz), 8.70 (2 x -CH_3, 2 x s). m/e 380 (4.6%, m^+, ^{81}Br), 378 (8.5%, m^+, $^{79}_{81}Br$), 376 (4.9%, $m^{\cdot+}$, ^{79}Br), 150 (25%), 149 (100%), 148 (27%), 133 (22%), 121 (24%), 91 (15%). An analysis was precluded by the instability of this compound.

Further elution gave pure 3-bromo-5-(p-methoxyphenyl)-5-methyl--hexan-2-one (710mg, 52%) as a colourless oil, ν_{max} 1720 s, 1510 s, 830 s cm^{-1}; τ (CCl_4) 2.70, 2.85, 3.10, 3.25 (4 x aromatic H, AA'BB'), 5.95 (H_4, d x d, $J_{3,4}$ 4 Hz, $J_{3,4}$ 8 Hz), 6.25 (-OCH_3, s), 7.25 (H_4, d x d, $J_{4,3}$ 8 Hz and $J_{4,4}$ 15 Hz), 7.80 (H_4, d x d, $J_{4,3}$ 4 Hz and $J_{4,4}$ 15 Hz), 8.00 (-$COCH_3$, s), 8.70 (2 x -CH_3, 2 x s). m/e 300 (9.5%, m^+, ^{81}Br),

298 (10.5%, m^+, ^{79}Br), 149 (100%), 91 (9%). An analysis was, again, precluded by the instability of this compound.

5-(p-Methoxyphenyl)-5-methyl-hex-3-en-2-one

3-Bromo-(5-p-methoxyphenyl)-5-methyl-hexan-2-one (700mg) was mixed with dry dimethylformamide (7ml), lithium bromide (0.7g, ground, anhydrous) and lithium carbonate (0.7g, anhydrous) and refluxed, under nitrogen, with vigorous stirring, for 2h. The cooled reaction mixture was then poured into water and extracted three times with benzene. The combined benzene layers were then well washed with water, dried ($MgSO_4$), and solvent removed. The resulting brown oil was then purified by column chromatography (30g, Kieselgel, chloroform:benzene 3:1) to yield 5-(p-methoxyphenyl)-5-methyl-hex-3-en-2-one (425mg, 83%) as a colourless oil, b.p. 160 - 165°/0.3mm, ν_{max} 1675 s, 1620 s, 1515 s, 830 s cm^{-1}, τ (CCl_4) 2.70, 2.85, 3.10, 3.25 (4 x aromatic H, AA'BB'), 3.15 (H_4, d, J 17 Hz), 4.10 (H_3, d, J 17 Hz), 6.20 ($-OCH_3$, s), 7.80 ($-COCH_3$, s), 8.55 (2 x $-CH_3$, s). (Found: C, 77.1; H, 8.35. $C_{14}H_{18}O_2$ requires C, 77.0; H, 8.3%). m/e 218 (64%, $m^{\cdot+}$), 203 (20%), 175 (64%), 161 (39%), 160 (40%), 149 (30%), 145 (43%), 121 (23%), 91 (22%), 43 (100%).

Rearrangement of 5-(p-Methoxyphenyl)-5-methyl-hex-3-en-2-one with Perchloric Acid.

5-(p-Methoxyphenyl)-5-methyl-hex-3-en-2-one (125mg) was dissolved in perchloric acid (0.5ml, 70% aqueous solution) in an n.m.r. tube, and the ensuing reaction was followed by taking spectra at

regular intervals. A very clean reaction occurred, with no observable intermediates, which was complete after 3h 40min (probe temperature = 35°). The spectrum obtained after this time was consistent with a 4-(p-methoxyphenyl)-2,5,5-trimethyl dihydrofuranylium perchlorate salt, τ ($HClO_4$, TMS as external standard), 2.65, 2.80, 2.90, 3.05 (4 x aromatic H, AA'BB'), 5.85 (2 x H_3, H_4, m), 6.10 ($-OC\underline{H}_3$, s), 6.85 ($C_2-C\underline{H}_3$, s), 8.05 ($C_5-C\underline{H}_3$, s), 8.75 ($C_5-C\underline{H}_3$, s).

This reaction mixture was then poured into sodium carbonate solution, extracted with benzene, and the benzene extracts were washed with water, and dried ($MgSO_4$). Removal of the solvent gave a brown oil (92mg) whose t.l.c. indicated at least five components. Column chromatography gave no pure, recognisable products, and N.M.R. spectroscopy of the crude product (in $CDCl_3$) showed no peaks of structural significance except the AA'BB' pattern of the aromatic protons and the methoxyl singlet. Redissolving the crude product in perchloric acid, however, regenerated the spectrum of the perchlorate salt.

When the reaction mixture was worked up by adding it dropwise to a well stirred solution of sodium methoxide in methanol, usual work-up gave a crude product showing an additional singlet at τ 6.70 ($CDCl_3$). However, no identifiable product could be isolated.

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ABSTRACT.

A discussion of hydride shifts of an order greater than 1,2 is followed by some illustrative examples.

Ethyl cyclooctylidene acetate and cyclooctylidene methyl ketone were reacted with boron trifluoride etherate, but the only reaction observed was isomerisation to cyclooct-1-ene derivatives. Sulphuric, or toluene p-sulphonic, acids treatment of either double bond isomer of the ester gave 1-oxabicyclo[6.3.0]undecan-2-one.

8-(p-Methoxyphenyl)-6,6-dimethyloct-3-en-2-one underwent a 1,5 hydride shift upon treatment with perchloric acid to give 2-(p-methoxyphenyl)-4,4-dimethylcyclohexyl methyl ketone. Treatment of ethyl 7-(p-methoxyphenyl)-5,5-dimethylhept-2-enoate with hydrobromic acid/acetic acid gave only 7-(p-hydroxyphenyl)-5,5-dimethylhept-2-enoic acid. Attempts to induce a 1,4 hydride shift by acid treatment of 7-(p-methoxyphenyl)hept-3-en-2-one or 7,7-bis-(p-methoxyphenyl)hept-3-en-2-one were unsuccessful.

Wolff-Kishner reduction of 4-(p-anisoyl)-3,3-dimethylbutyric acid, followed by methylation with dimethyl sulphate, gave 2,4,5,6-tetrahydro-7--(p-methoxyphenyl)-2,5,5-trimethyl-1,2-diazepin-3-one.

Transannular π-reactions and interactions in alicyclic systems are reviewed.

Ethyl (cyclooct-3-enylidene) acetate reacted with boron trifluoride etherate in benzene to give an inseparable mixture of products, whereas ethyl (cyclooct-4-enylidene) acetate and cyclooct-4-enylidene methyl ketone, under the same conditions, gave 1-phenylbicyclo[3.3.1]nonane-9-carboxylic

acid and its ethyl ester, and 9-acetyl-1-phenylbicyclo[3.3.1]nonane, respectively. The structure of the ester product was proved by degradation to 1-phenylbicyclo[3.3.1]nonan-9-one, whose identity was proved by rational synthesis. An authentic sample of 9-acetyl-1--phenylbicyclo[3.3.1]nonane was prepared from 1-phenylbicyclo[3.3.1]-nonane-9-carboxylic acid. Treatment of ethyl (cyclooct-4-enylidene) acetate with boron trifluoride etherate alone, followed by esterification, gave 9-carboethoxybicyclo[3.3.1]nonane; with toluene as co-solvent 1-(p-tolyl)bicyclo[3.3.1]nonane-9-carboxylic acid and its ethyl ester were produced. Nitrobenzene as a co-solvent in this reaction gave no discernible products. Under the usual reaction conditions dimethyl 3,3-(cyclooct-4'-enyl)glutarate and ethyl 2-(cyclooct-4'-enyl)-2-phenyl acetate did not react. Possible mechanisms for this reaction are discussed. A similar reaction was observed when 7-exo-methylene-bicyclo[3.3.1]non-3-enylidene acetate was treated with boron trifluoride etherate in benzene, but the products were not fully characterised.