SYNTHESIS AND REACTIONS OF

BRIDGED BICYCLIC COMPOUNDS

Thesis presented to the University of Glasgow

for the degree of Ph.D.

by

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SUMMARY

The research described in this thesis is devoted to synthetic and mechanistic studies in bridged bicyclic systems. The thesis is divided into three parts:-

Part I: The Total Synthesis of Racemic Guaiol.

The plant sesquiterpene guaiol has been synthesised in racemic form, from laevulinic acid and 2-methylcyclopentanone via an intermediate, 1-methyltricyclo-(6,2,1,$0^{2,6}$)-undec-2^{6}-en-5,11-dione. Bridge fission of this diketone yields a hydroazulene enone-ester which has been elaborated to guaiol.

Part II; The Acid Catalysed Cleavage of Bicyclo-(3,2,1)-oct-2-en-8-one.

Although bicyclo-(3,2,1)-oct-2-en-8-one derivatives cleave in acidic solution to cycloheptene carboxylic acid derivatives, the corresponding alcohols do not fragment under similar circumstances. The corresponding syn alcohol undergoes a facile transannular cyclisation when treated with bromine. A similar transannular cyclisation occurs when the ketone is treated with bromine in an alcoholic solvent.

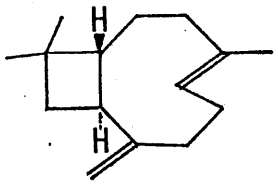
Part III: A Re-investigation of the Reduction and Hydrolysis of Unsaturated Medium Ring Gem-Diesters.

The previously reported base-catalysed transannular cyclisation of unsaturated medium ring gem-diesters has been re-investigated. In contrast to these earlier findings, the hydrolysis and reduction of these diesters proceed in the normal manner.

CONTENTS

PART I

THE TOTAL SYNTHESIS OF RACEMIC GUAIOL



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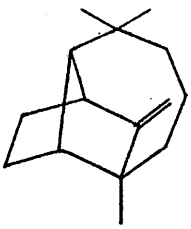

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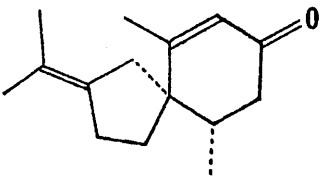

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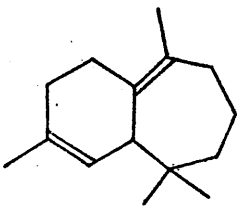

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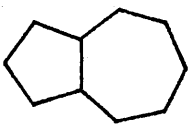

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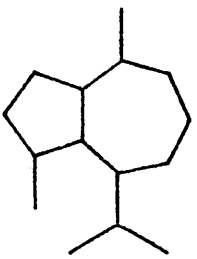

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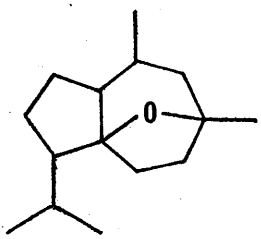

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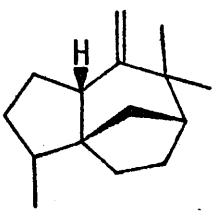

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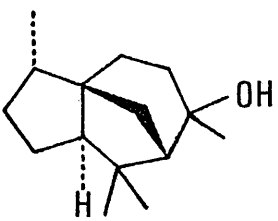

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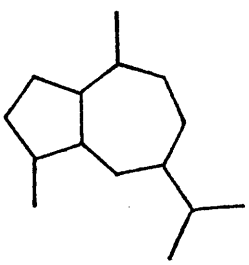

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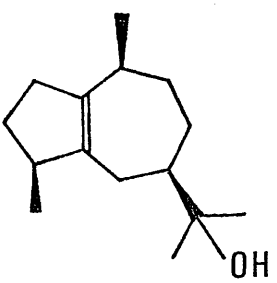


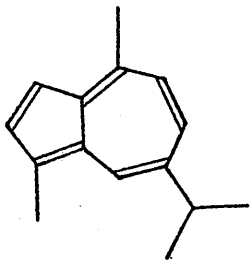
11

INTRODUCTION

The synthesis of natural products is an area of research which has attracted many chemists. In particular, the sesquiterpenes, though containing only fifteen carbon atoms, have presented a unique challenge because of their structural and stereochemical diversity. Indeed, many interesting observations and synthetic innovations have been the direct result of numerous elegant exercises in this field.[1] Some notable successes are the synthesis of caryophyllene(**1**),[2] longifolene(**2**),[3] β-vetivone(**3**)[4] and β-himachalene(**4**).[5]

A major group of sesquiterpenoids possess a basic bicyclo-(5,3,0)-decane or hydroazulene skeleton(**5**). Even within this group a wide variety of structural types exist, e.g. zierane(**6**), daucol(**7**), tricyclovetivene(**8**) and cedrol(**9**) however one of the simplest structural modifications of this class is the guaiane type sesquiterpenoids(**10**) exemplified by the alcohol guaiol(**11**).

Guaiol was first isolated by direct crystallisation from the wood oil of Bulnesia sarmentia L. in 1892.[6] Since then it has been reported as a constituent of a number of related botanical species.[7] Because of its ready availability



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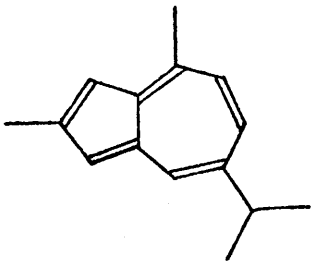

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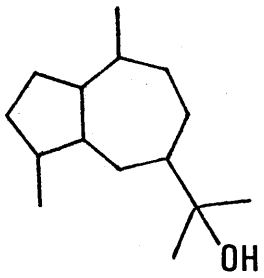

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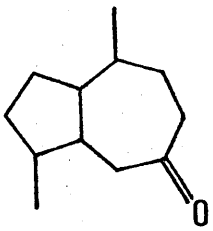

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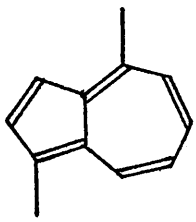
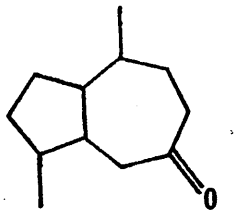


16

in pure form and its importance as a fixative in perfumes, guaiol became the target of a number of structural studies. Like so many of the earlier structure elucidations of natural products, dehydrogenation played an important role. Sulphur dehydrogenation[8] gave a blue azulene, S-guaiazulene(**12**), which was the predominant fact in establishing the now accepted bicyclo-(5,3,0)-decane skeleton. It is worth mentioning that dehydrogenation of guaiol with selenium gave a violet azulene, Se-guaiazulene(**13**), the structure of which was not established until 1951.[9]

The earlier work at the turn of the century[10] on the structure elucidation established the presence of a tertiary hydroxyl group but little else. It was not until the early 1940's that a group of Swiss chemists formulated the correct carbon skeleton and substitution pattern.[11] Catalytic hydrogenation (Raney nickel/H_2 at 100 atmospheres) afforded dihydroguaiol(**14**) proving the existence of two rings. This was dehydrated to an olefin mixture which on ozonolysis afforded acetone and a ketone $C_{12}H_{20}O$ (**15**). Reduction of this ketone furnished an alcohol which on dehydration and sulphur dehydrogenation produced 1,4-dimethylazulene(**16**), identified by comparison with an authentic sample. On treatment with methyl magnesium iodide, the ketone(**15**) was converted to the



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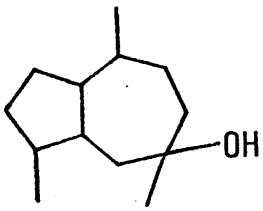

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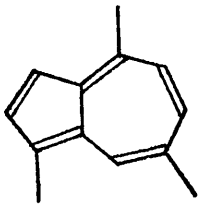

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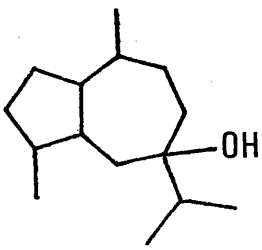

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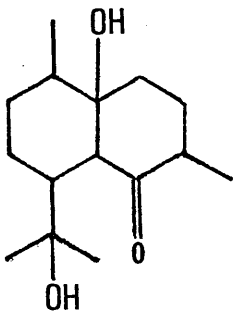

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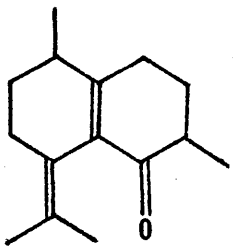

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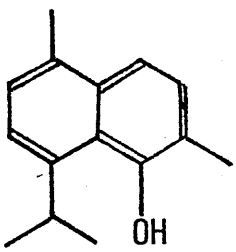

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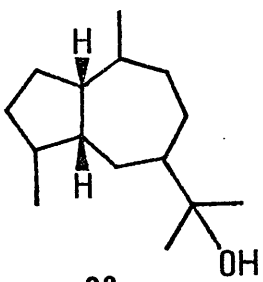

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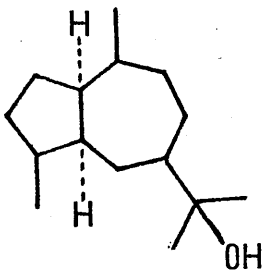

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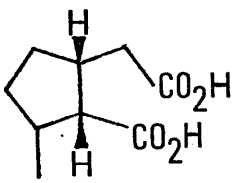

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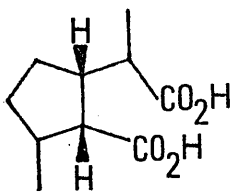
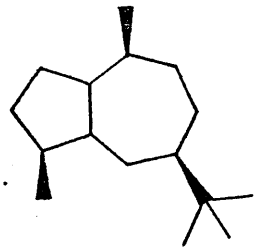


26

alcohol(**17**) which on similar treatment gave 1,4,7-trimethyl-azulene(**18**).

The position of the tertiary hydroxyl group was determined by reaction of ketone(**15**) with isopropyl magnesium iodide. Dihydroguaiol was not produced and hence structure(**19**) must be excluded. The reluctance of guaiol to catalytic hydrogenation was indicative of a fully substituted double bond. The location of this double bond was established by ozonolysis which gave a dihydroxyketone(**20**) that readily dehydrated to (**21**). The structure of this dienone was easily determined by dehydrogenation to 2,5-dimethyl-8-isopropyl-1-naphthol(**22**).

Although this solved the crude structure of guaiol, the problem of the relative stereochemistry of the three asymmetric centres remained unsolved until 1961. A partial solution was obtained in 1960 by Djerassi[12] who hydrogenated guaiol to a mixture of oily (+)dihydroguaiol(**23**) and crystalline (-)dihydro guaiol(**24**). The oily (+)dihydroguaiol was converted to the dicarboxylic acid(**25**) and this correlated with the same acid derived from nepetalinic acid(**26**) of known absolute configuration. Hence the stereochemistry at C-8 was determined. (For convenience guaiol has been numbered as a bicyclo-(5,3,0)-



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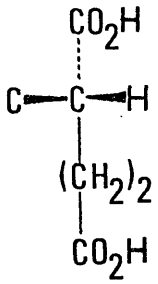

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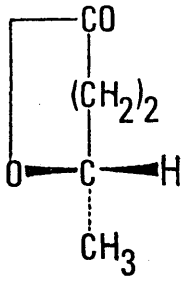

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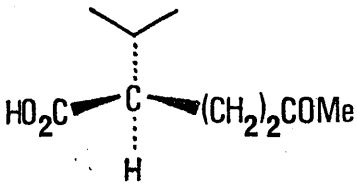

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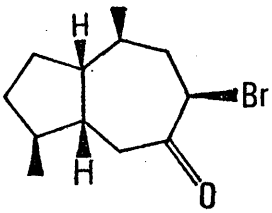

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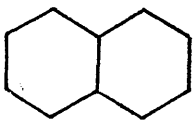

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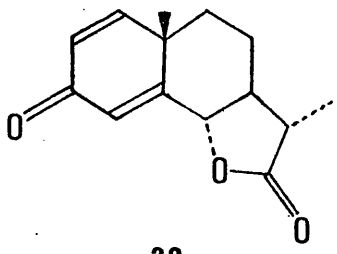
decane derivative.) Degradation of guaiol to (+)-α-methylglutaric acid(**27**) and (−)-γ-methylbutyrolactone(**28**) containing the original C-2 asymmetric centre, established the stereochemistry at this centre.[13] The final remaining problem, that of the stereochemistry at C-5 was resolved by degradation to (−)-γ-aceto-α-isopropylbutyric acid(**29**).[14] This compound was shown to have the S configuration,[15] and hence guaiol must be represented by the stereochemical formula(**11**). Final confirmation was derived from an X-ray study[16] of the bromoketone(**30**) prepared from guaiol.

When this project was initiated in 1968, very little research had been carried out on synthetic approaches to the guaiane class of sesquiterpenoids. This can be attributed, in some measure, to the dearth in methods of producing such bicyclo-(5,3,0)-decane systems in which substituents were introduced in a stereodefined manner. Consequently, all the synthetic approaches at that time had involved the construction of a hydronaphthalene skeleton(**31**) in which the conformational aspects were well defined and hence the stereochemistry could be controlled. Subsequent photolytic or solvolytic rearrangement of the hydronaphthalene provided the desired hydroazulene system.



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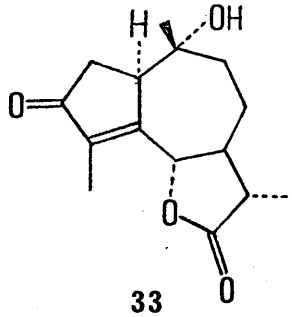

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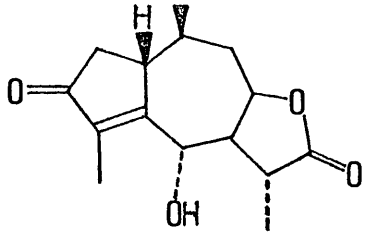

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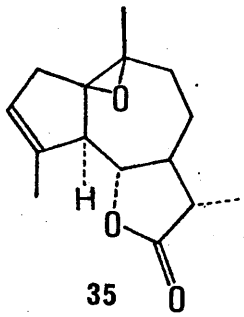

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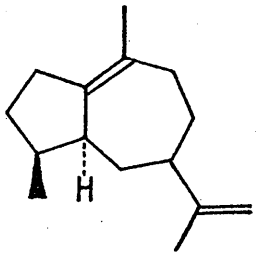

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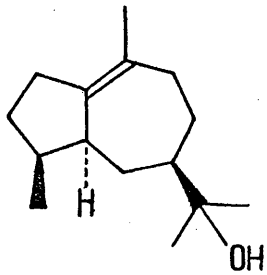

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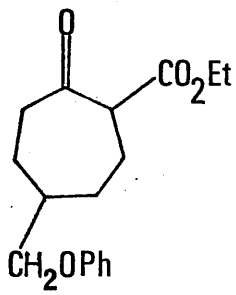

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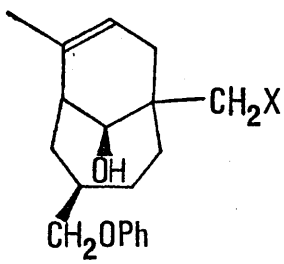

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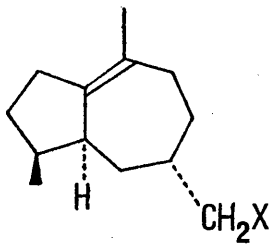

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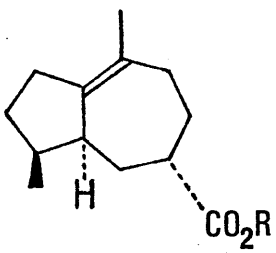

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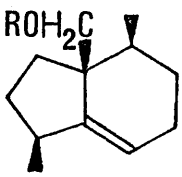

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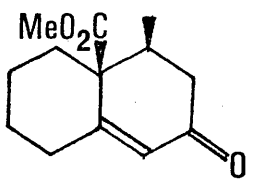

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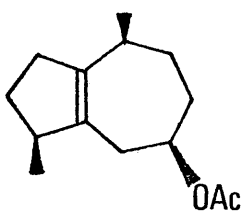

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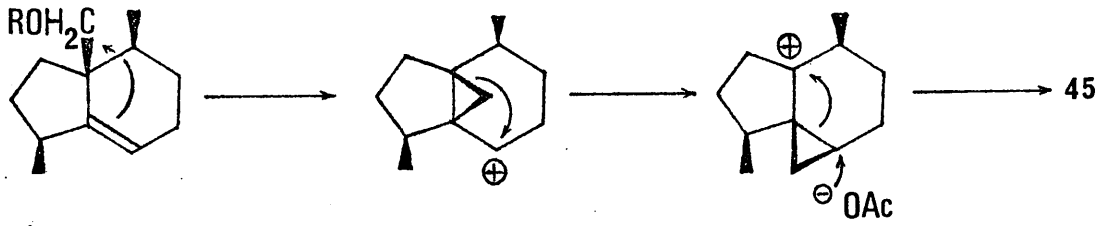
For example, the photoconversion[17] of santonin(**32**) to isophotosantonic lactone(**33**) represents a general reaction which has been utilised in the synthesis of geigerin(**34**),[18] arboresin(**35**)[19] and only recently α-bulnesene(**36**).[20] However within the last two years a number of solvolytic routes to hydroazulenes have been reported. J.A.Marshall and his associates at Northwestern University have been particularly prominent in this field and their synthesis of bulnesol(**37**)[21] and guaiol[22] are worthy of note. Bulnesol was prepared via a bicyclo-(4,3,1)-decane intermediate. Condensation of methyl vinyl ketone with the cycloheptanone(**38**) and subsequent cyclisation and selective reduction afforded (**39**). Solvolysis of the derived mesylate in acetate buffer gave the hydroazulene (**40**) in excellent yield. By suitable modification of the ester (**41**) it was possible to achieve a viable route to racemic bulnesol.

In the synthesis of guaiol, Marshall prepared the hydrindanyl mesylate(**42**) by a thirteen stage elaboration of the enone(**43**) derived from annelation of 2-methylcyclohexanone with methyl propenyl ketone. The stereochemistry at the projected C-8 centre was secured by kinetically controlled quenching of the extended enolate of (**44**). Solvolytic

Scheme A.



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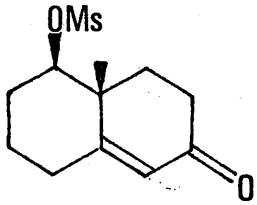

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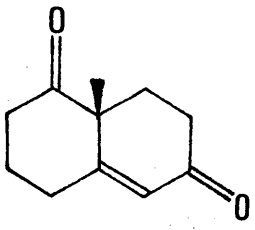

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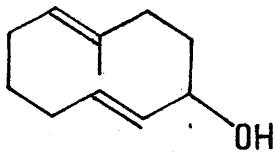

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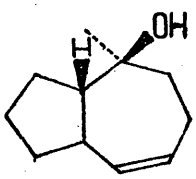

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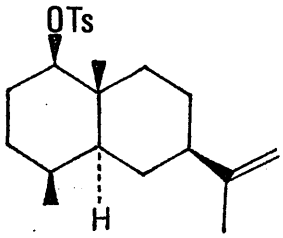

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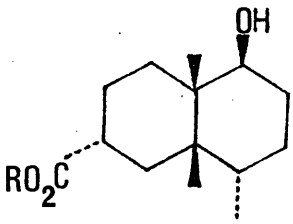

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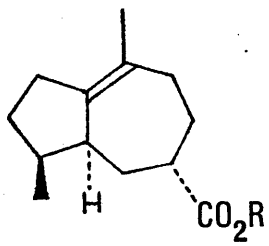

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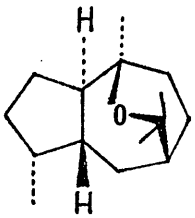

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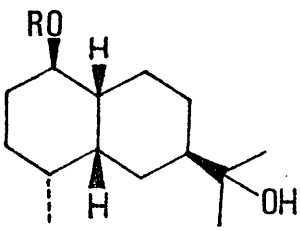

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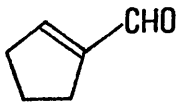
rearrangement of (**42**) in buffered acetate afforded an 80% yield of the acetate(**45**) which was presumed to be formed to be formed via the pathway shown (Scheme A) to account for the stereochemical control. Conversion of this acetate to racemic guaiol was achieved using standard reactions.

The same author has also devised a more general route to hydroazulenes.[23] Treatment of the mesylate(**46**) derived from the Wieland - Miescher ketone(**47**)[24] with diborane and sodium methoxide afforded the cyclodecadienol(**48**). Transannular cyclisation of its p-nitrobenzoate in dioxan/water gave the hydroazulene(**49**) in 70% yield.

Heathcock and Ratcliffe have also recognised the potential of the Wieland - Miescher ketone in a recent synthesis of bulnesol and α-bulnesene.[25] From this ketone they were able to prepare, in seventeen stages, the trans decalin tosylate(**50**) which on solvolysis produced a good yield of α-bulnesene.

As a variation of this method, Yoshikoshi[26] reported a synthesis of bulnesol by solvolytic rearrangement of the cis decalin(**51**) which gave the same ester(**41**) as Marshall had prepared. These Japanese authors have also reported the synthesis of kessane(**52**)[27] from the mesylate(**53**).



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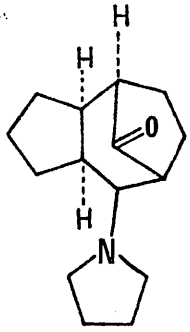

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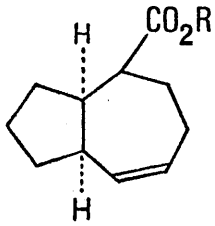

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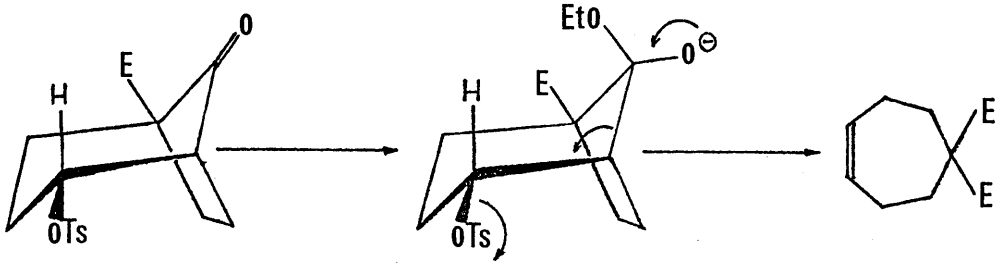
Scheme B.



57a

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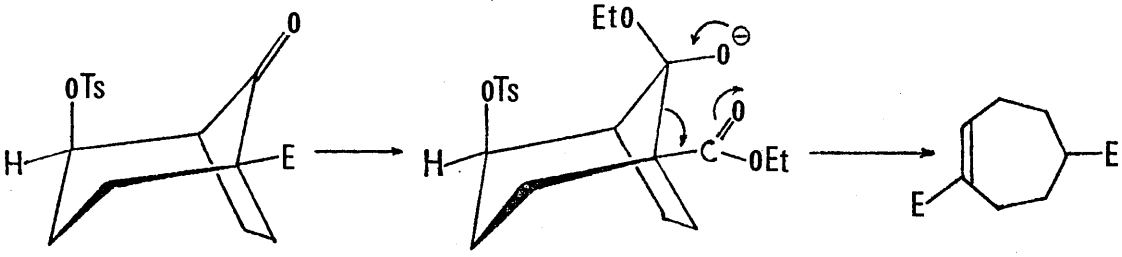
Scheme C.



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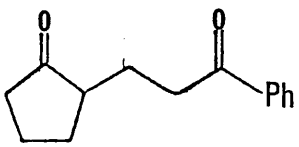

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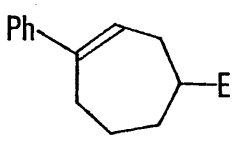

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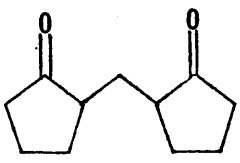

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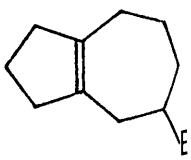

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An alternative route to hydroazulenes has been offered by Hendrickson[28] as an extension of the Stork enamine alkylation.[29] Condensation of 1-cyclopentenecarboxaldehyde(**54**) with the enamine of cyclopentanone gave stereoselectively the tricyclic amine(**55**). This was converted, in 25% yield overall, to the hydroazulene ester(**56**) by the normal procedure.

Recent work in this department has been focussed on the synthesis of medium size rings by bridge fission of suitable bicyclo-(m,n,1)-precursors.[30] For example, the tosylate epimers(**57**) under appropriate basic conditions were shown to produce seven membered carbocycles.[31] The equatorial tosylates(**57a**) afforded the gem-diester(**58**) by a concerted β-elimination (Scheme B), whereas the axial epimer(**57b**) gave the unsaturated diester(**59**) by a retro-Claisen reaction followed by elimination of tosic acid.(Scheme C)

An interesting variation on this theme, was the discovery that cyclopentanone 1,5-diketones(**60**), under acid catalysis, underwent a novel ring expansion to cycloheptene carboxylic acid derivatives(**61**).[32] By employing the readily available diketone(**62**) it was possible to extend this rearrangement to provide a simple yet efficient route to the bicyclo-(5,3,0)-decane skeleton. (i.e.(**62**)⟶(**63**).

The extension of this scheme to a synthesis of guaiane type sesquiterpenoids was, on paper, a feasible step. As well as providing an interesting synthetic challenge, it was hoped that such a project would illuminate some of the dark areas of hydroazulene conformational analysis.

Guaiol was considered as a suitable target for study.

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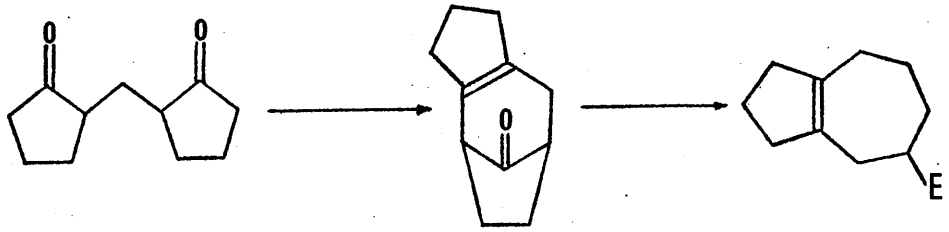
Scheme A.



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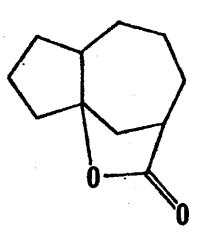

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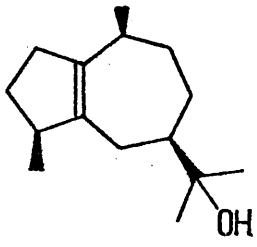

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DISCUSSION

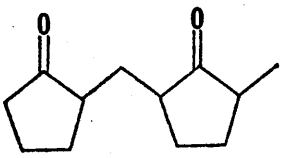
When this research was initiated in 1968, considerable investigation of the scope and flexibility of the acid catalysed cleavage of bicyclo-(3,2,1)-oct-2-en-8-ones had been completed.[1] Specifically this process transforms the readily available 1,5-diketone(**1**) into the bicyclic intermediate(**2**) which can open under appropriate conditions to form the bicyclo-(5,3,0)-decene ester(**3**)(Scheme A). However a suitable synthetic objective for this scheme, although discussed,[2] had not been attained. At that time, no total synthesis of the plant sesquiterpenoid guaiol(**4**) had been described,[3] and the extension of this cleavage to a synthesis of guaiol was a project which merited attention.

The pertinent requirements of such a synthesis can be subdivided into three main objectives:-

1. The construction of the basic bicyclo-(5,3,0)-decane skeleton.

2. The introduction of the isopropyl alcohol group and the two methyl groups in the correct position on the nucleus.

3. The formulation of a sequence which would insure that these substituents would bear the correct stereochemical relationship to each other.



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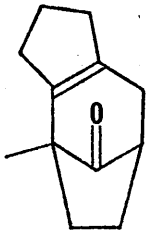

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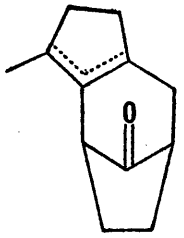

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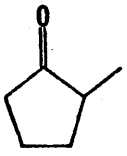

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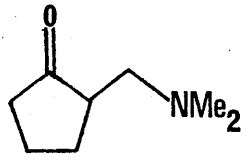

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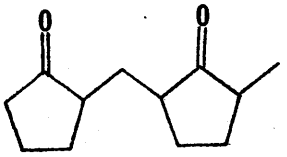
A route which constructed the bicyclo-(5,3,0)-decane system with a "handle" that could be elaborated to the tertiary alcohol function in guaiol was already established (Scheme A). The introduction of the methyl groups in the correct positions on the nucleus was thus the first goal.

It was apparent that the C-2 methyl group in guaiol might well be introduced from the start, if the cyclisation of the readily available diketone(**5**) were to occur in the correct sense. Specifically (**5**) could be expected to yield two isomeric bridged bicyclic ketones(**6**) and (**7**) under aldolising conditions but only (**6**) would produce a 2-methyl-hydroazulene on acid cleavage.

Dieckmann cyclisation of diethyl adipate followed by methylation and subsequent decarbethoxylation according to Nicole[4] afforded 2-methylcyclopentanone(**8**) in 40% yield overall. Condensation of (**8**) with the Mannich base of cyclo-pentanone(**9**) was effected by refluxing a mixture of the two components for three hours under typical Thermal Michael conditions.[5] These conditions, which involve an intermediate enamine, has been shown[6] to favour substitution at the less substituted centre adjacent to the ketone, whereas Michael[7] or Robinson-Michael[8] conditions favour substitution at the



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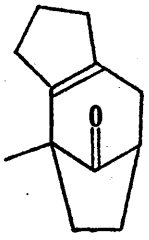

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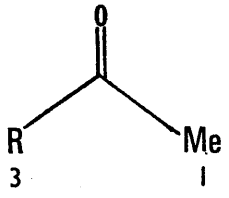


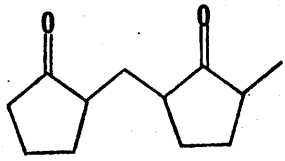
R ≠ Me

10

more highly substituted site.[9] After chromatographic purification the diketone(**5**) was obtained in 50% yield as a viscous oil. The presence of epimers was deduced from the overlapping methyl doublets at 8.9τ in the n.m.r. spectrum. This also confirmed that the condensation had occurred at the α-methylene centre of 2-methylcyclopentanone and not at the α-methine centre.

On aldolisation in p-toluenesulphonic acid / benzene the diketone(**5**) afforded only one bridged bicyclic ketone. Its identity was easily established as (**6**) by the n.m.r. spectrum which indicated a methyl singlet at 8.95τ. Had the aldolisation occurred in the other orientation, it would have been anticipated that the methyl group would resonate as a singlet (8.1—8.4τ) or as a doublet depending on the location of the double bond. The infra-red spectrum of (**6**) exhibited a high carbonyl stretching frequency (1760cm^{-1}), typical of the strained bicyclo-(3,2,1)-oct-2-en-8-one system.[10]

This mode of cyclisation was not unexpected.[11] Ketones of type(**10**) may condense with an electrophilic component at carbon-1 (1-condensation) or carbon-3 (3-condensation). In general, there are four principal factors which determine the structure of the product obtained at equilibrium.



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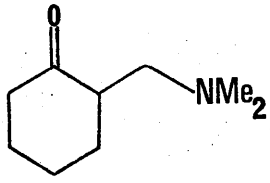

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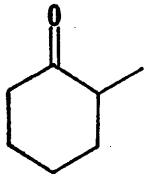

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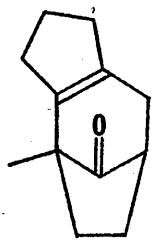
These are :-

1. The catalyst.
2. The nature of the substituents R' and R in the ketone.
3. The structure of the electrophilic component.
4. The solvent.

Although mixtures of 1 and 3-condensation products are possible, a single substance appears to predominate in most reactions. Normally acid catalysis favours 3-condensation, except where steric factors prevail, as enolisation to the most highly branched enol is generally reckoned to determine the course of condensation. By extrapolation to the diketone (**5**) it is not surprising that aldolisation occurs from the most highly substituted carbon atom. It is worth mentioning that the intermediate aldol product, under acid catalysis, normally dehydrates to the αβ unsaturated ketone. In this case, dehydration to an αβ enone would violate Bredt's rule[12] and so the double bond is required to adopt the fully substituted βγ position.

As a study in parallel, it was decided to examine the direction of aldolisation of the corresponding six-membered analogues. However difficulties were encountered at an early stage. It was envisaged that the Mannich base(**11**) and 2-methyl-cyclohexanone(**12**) under Thermal Michael conditions would



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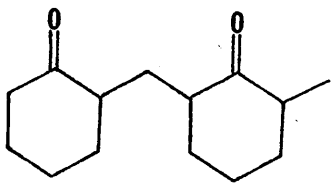

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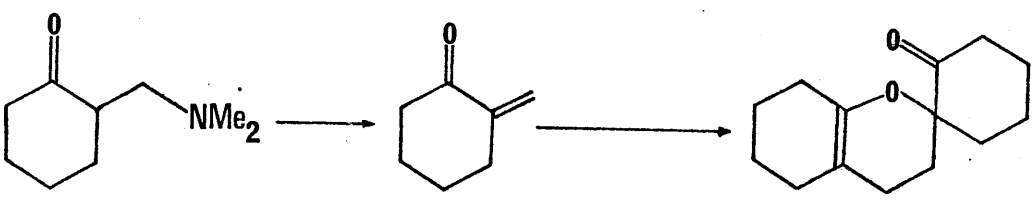
Scheme B.



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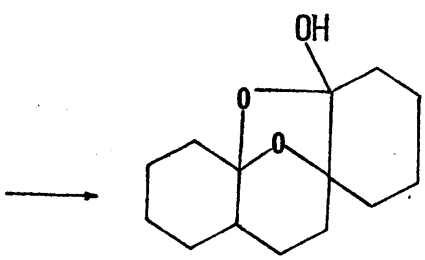

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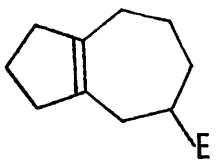
yield the adduct(**13**) which could then be utilised as a model for the aldol reaction. Thus these two reagents were refluxed for 4.5 hours and worked up in the usual manner. The yellow oil so obtained was chromatographed on a column of silica affording three components. The two least polar components were eventually recognised as (**14**) and (**15**) by comparison of their infra-red spectra with those published.[13] The third component, isolated in less than 10% yield, could have been the desired diketone(**13**) from the spectral data acquired, however a positive identification was not established.

Thus instead of undergoing the Thermal Michael reaction the Mannich base(**11**) favours thermal elimination to 2-methylenecyclohexanone which in turn undergoes a Diels-Alder reaction with another molecule to produce (**14**). Hydration of the highly polarised double bond in the predicted sense, followed by intramolecular hemiketalisation leads to the formation of the other product (**15**). This preference can be rationalised if it is assumed that the rate of enamine formation and subsequent reaction is slower than the rate of the Diels-Alder pathway (Scheme B). This is not an unreasonable premise.[14]

The bridge fission of the bicyclic ketone(**6**) was



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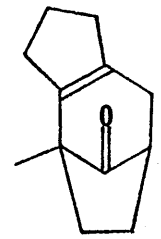

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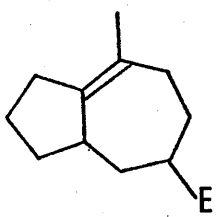

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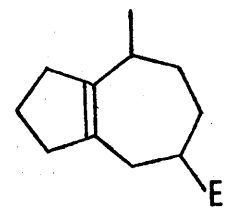

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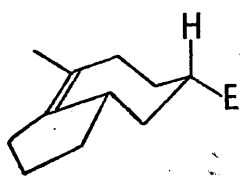

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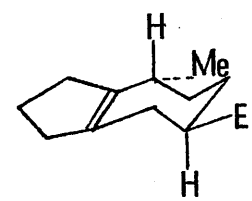

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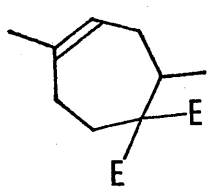

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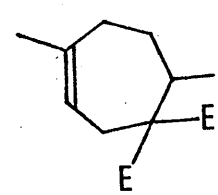

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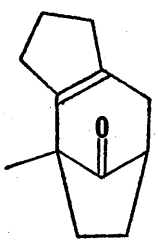
effected in the usual manner by refluxing overnight in acidic methanol. Analysis of the crude product by gas-liquid chromatography (g.l.c.) indicated a mixture of two components in roughly equal amounts. From the n.m.r. spectrum these were clearly the isomers (**16**) and (**17**). Specifically the signal at 8.36τ was consistent with the methyl group in (**16**) and the doublet at 9.0τ (J=7Hz.) was consistent with the methyl group in (**17**). Thus unlike the nor-methyl analogue(**3**), the initially formed methylhydroazulene(**16**) undergoes only partial isomerisation to (**17**). This merely reflects the small energy difference between these isomers, presumably in conformations (**18**) and (**19**), and from a naive viewpoint the destabilising interactions observed in molecular models are very similar in both compounds. A similar phenomenon has been reported[15] in the isomerisation of the cycloheptene diester(**20**) to (**21**) under acid catalysis.

Since these esters, (**16**) and (**17**), incorporated substituents in two of the three desired sites, attempts were made to effect substitution at C-5 of the tricyclic ketone(**6**). It was felt at this time, that the introduction of a ketone group at this position would be most advantageous. Hopefully, this would assist the bridge fission, conjugate the double



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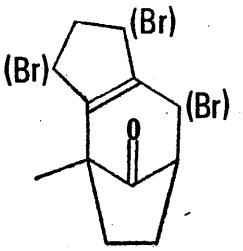
bond in the resultant hydroazulene ester, and provide a useful handle which could be modified in a stereodefined manner to furnish the methyl group in guaiol.

A number of reagents are reported in the literature to effect allylic oxidation.[16] However in the ketone(**6**) there are three allylic methylene centres at C-3, C-5 and C-7, which are susceptible to oxidation. Thus, if the route was to succeed a degree of selectivity had to be attained. The only reported reagents which exhibit any degree of selectivity are

1. Chromium trioxide/pyridine complex in methylene chloride
2. N-bromosuccinimide in aqueous dioxan.

In conformationally rigid molecules, as the ketone(**6**) is, chromium trioxide/pyridine complex is quoted as oxidising the allylic centres which are most accessible.[17] From molecular models, it appeared that the C-5 centre was least congested and that some selectivity might be possible. However under very mild conditions, no reaction was observed, whilst under the forcing conditions necessary to promote oxidation, a complex mixture was produced.

Treatment of the tricyclic ketone(**6**) with N-bromosuccinimide in wet dioxan[18] produced at least two components which could be separated by preparative thin layer



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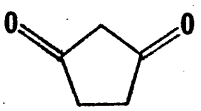
Scheme C.



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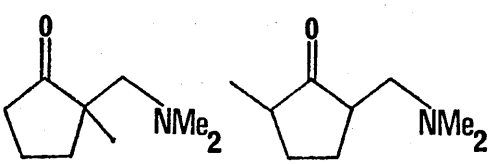

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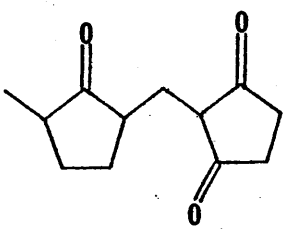

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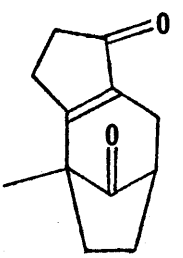

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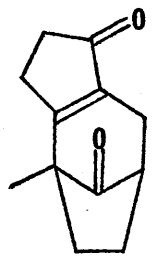
chromatography.(t.l.c.) The less polar fraction appeared to be a mixture of at least three compounds (three methyl singlets in the n.m.r. spectrum) and from the multiplet at 5.7τ could have been a mixture of allylic bromides(**22**). The more polar fraction exhibited an unusual ultra-violet spectrum, viz. λ_{max} 227nm. (ε=8100) and 247nm. (ε=9000), which at that time could not be explained. The infra-red spectrum was consistent with the desired ketone(**23**), having carbonyl stretching frequencies at 1760cm.$^{-1}$ and 1705cm.$^{-1}$ and indeed comparision with an authentic sample at a later date, established that this compound had the correct structure. A spectral analysis will be discussed later.

Chromyl chloride(CrO_2Cl_2) which also effects allylic oxidations[19] was also employed, but even at -78°, selectivity was not achieved.

At this time it was thought more profitable to pursue the synthesis via a pathway which would guarantee the required functionality at C-5. A logical extension of the existing route would involve the use of cyclopentan-1,3-dione(**24**) and is outlined in Scheme C. Hopefully condensation of this dione with the Mannich base of 2-methylcyclopentanone(**25**)[20] would afford the adduct(**26**) which would undergo aldolisation at



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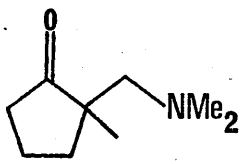

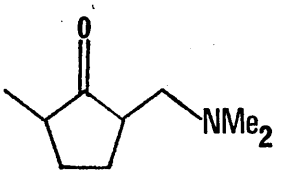

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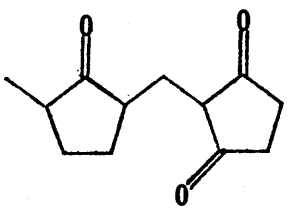

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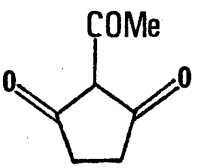

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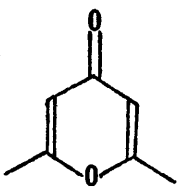

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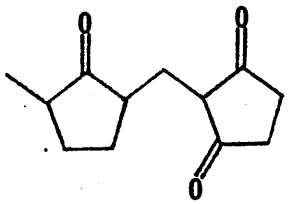
either carbonyl centre of the symmetrical dione nucleus giving (23).

Cyclopentan-1,3-dione was prepared in rather low yield by treatment of succinic anhydride with isopropyl acetate under Friedel-Crafts conditions.[21] Hydrolysis of the resultant 2-acetyl cyclopentan-1,3-dione(27) afforded the desired 1,3-dione. Under normal Thermal Michael conditions the base(25) and a threefold excess of this dione gave a dark brown oil. By sublimative purification it was possible to isolate 38% of a pure white crystalline compound. However spectral analysis soon dismissed the structure(26) as a possibility. From the n.m.r. spectrum - ONLY two singlets at 3.95τ and 7.7τ in the ratio 1 : 3 - it was obvious that the compound possessed a high degree of symmetry, while combustion analysis and mass spectroscopy established the molecular formula as $C_7H_8O_2$. By a process of elimination it was possible to deduce the structure as 2,6-dimethyl- -pyrone(28), which was confirmed by comparision with published spectra.[22] Although numerous attempts were made to devise a mechanism for this transformation, no scheme could be formulated to account for the production of this compound from the starting materials.

This route to (23) was abandoned at this point. The



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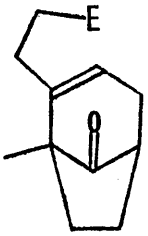

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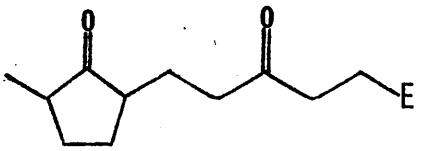

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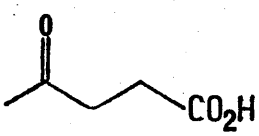

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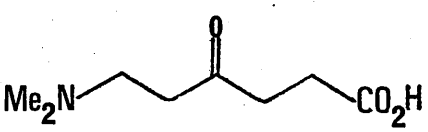

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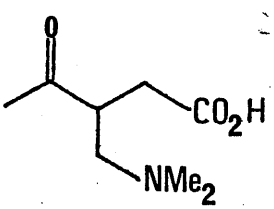

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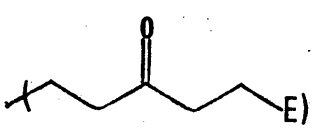

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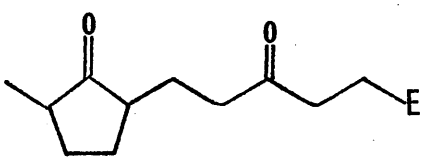
desired adduct(**26**) was not a major product, if even present, and the ability of the 1,3-dione system to enolise may have prevented facile aldolisation in the following step.

A new strategy was required.

An approach which appeared particularly attractive involved formation of a suitably substituted bicyclo-(3,2,1)-oct-2-en-8-one. If the substituent were a propionic acid derivative, as in (**29**), then it should be possible to effect an intramolecular Friedel-Crafts acylation which would provide the desired tricyclic intermediate. This bicyclic precursor, in turn, could be envisaged as the product of an internal aldol condensation of the dione-ester(**30**), assuming that aldolisation occurred in the correct sense. The synthesis of this compound was thus the primary objective.

Research in this department on the structure and reactions of Mannich bases[23] has established that laevulinic acid(**31**) forms a Mannich base exclusively on the methyl group; i.e. the dimethyl amine(**32**) is produced and not the isomer(**33**) which is also mechanistically feasible. Were this derivative used as a precursor for a Michael reaction it would provide a very useful synthon[24] for the introduction of a group of type(**34**). Indeed this is the very sidechain required in the



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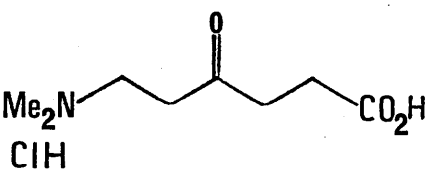

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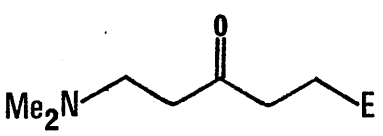

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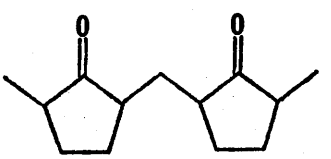

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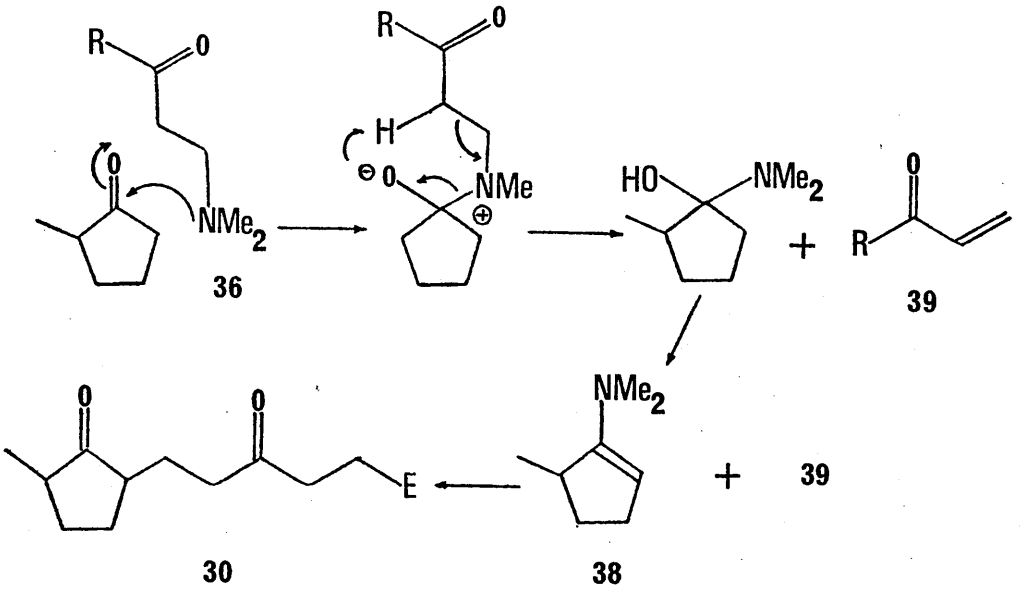
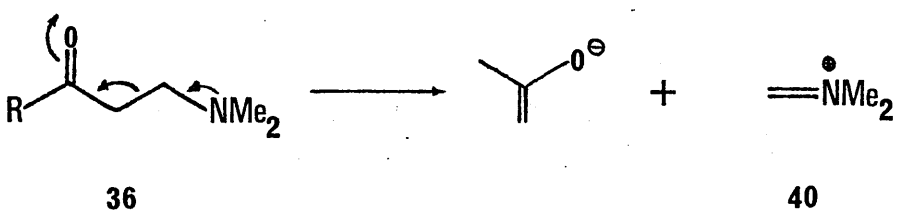
synthesis of the dione-ester(**30**).

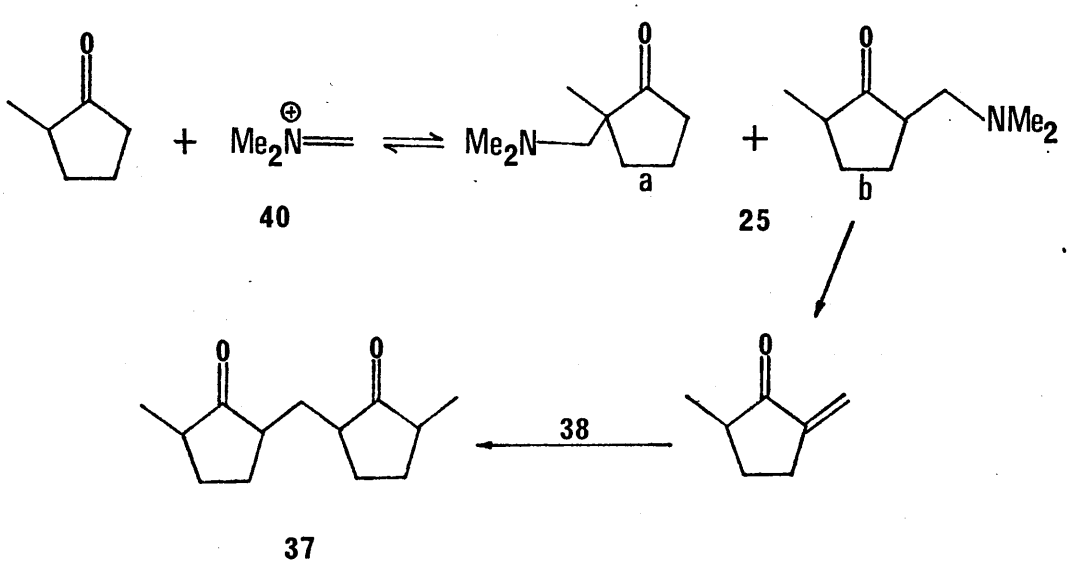
Experimentally the Mannich base is isolated as the amine hydrochloride(**35**). The free base, however, could not be liberated from this salt conveniently because of the dipolar nature of the amino acid and so, for practical reasons the hydrochloride was esterified. Refluxing the crude hydrochloride overnight in acidic ethanol afforded a 70% yield of the amine ester(**36**) which could be easily isolated by ether extraction from a basic solution. Without further purification the crude amine-ester was refluxed overnight with a threefold excess of 2-methylcyclopentanone. After normal work up and distillation of excess 2-methylcyclopentanone, the resultant oil was examined by g.l.c. and found to contain two components in the ratio of 17 ; 1. The minor component (4%) was isolated by column chromatography and shown to be the diketone(**37**) by spectral and combustion analysis. The presence of epimers was substantiated by the overlapping doublets (J=6Hz.) in the methyl region (8.9τ) of the n.m.r. spectrum. The infra-red spectrum exhibited a typical cyclopentanone carbonyl stretching frequency at 1739cm.$^{-1}$ The major product isolated in 68% yield, was obtained as a high boiling colourless oil. T.l.c. analysis of this oil indicated two compounds which

Scheme D.



Scheme E.

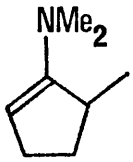




could be separated by careful preparative chromatography. These components exhibited very similar spectral characteristics, consistent with the required dione-ester(**30**), and because of this were treated as epimers at the C-2 centre. Microanalysis of the mixture indicated an empirical formula of $C_{14}H_{22}O_4$ which was established as the molecular formula by mass spectroscopy. In both compounds, the presence of methyl doublets (J=6Hz.) in the n.m.r. spectrum clearly established that both compounds were the 2,5-disubstituted isomers, as expected, and not the 2,2' isomers. The formation of these compounds can be easily rationalised as follows:-
The Mannich base(**36**) can react in two distinct ways:-[6]

Scheme D :- Direct condensation with 2-methylcyclopentanone leading to the formation of the desired dione-ester (**30**) via the enamine(**38**) and the enone(**39**).

Scheme E :- Thermal retrogression to form the highly electrophilic dimethylaminomethylene(**40**). This intermediate can then react with excess ketone to form the Mannich bases (**25a**) and (**25b**). From a study[20] of the n.m.r. spectrum of the mixture of bases produced from 2-methylcyclopentanone it has been confirmed that (**25a**) and (**25b**) are present in the ratio 9 : 1. However elimination of dimethylamine can only occur



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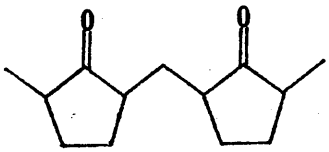

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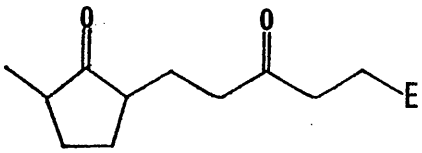

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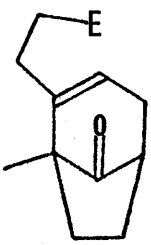
Scheme F.



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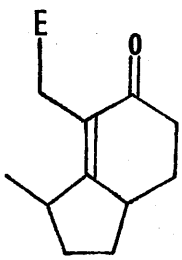

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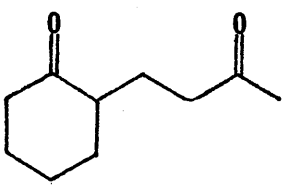

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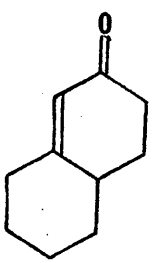

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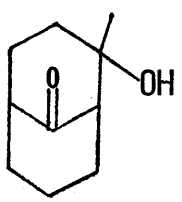

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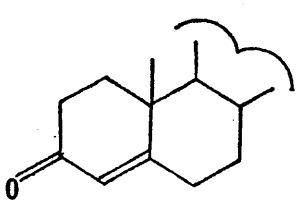

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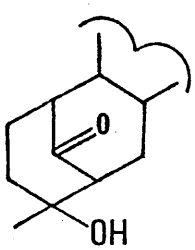

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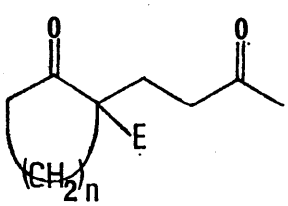

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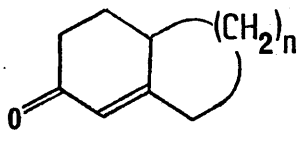
from the minor and this process provides the necessary Michael acceptor for the condensation with the enamine(**38**) to form the diketone(**37**).

The mixture of dione-ester epimers(**30**) was used in all subsequent experiments, as the next stage in the synthesis would involve enolisation to the C-2 centre. The formation of the bicyclo-(3,2,1)-oct-2-en-8-one represented the next task. From the outset it was recognised that the dione-ester(**30**) could undergo aldolisation in more than one way. The possibile pathways are outlined in Scheme F.

In a study of the related cyclohexanone system(**40**), Johnson[25] has shown that, under acid catalysis, this diketone produces the thermodynamically favoured enone(**41**) but proposed that the reaction proceeded via the kinetically favoured bicyclic ketol(**42**). In support of this concept, he obtained the conjugated enone(**43**) by base catalysed dehydration of the bridged ketol(**44**), thus demonstrating the interconversion of the aldol products.

The structure of the product in such cyclisation reactions often depends on the substituents and the ring size. For example, under acid catalysis compound(**45**) condenses at the ring methylene group if the ring is large enough



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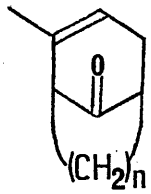

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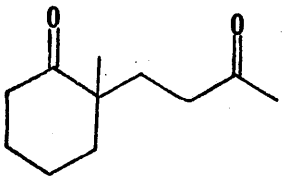

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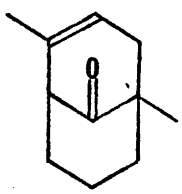

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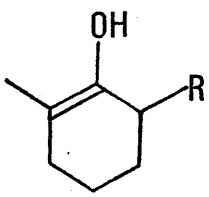

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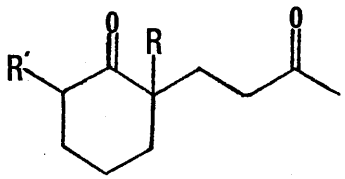

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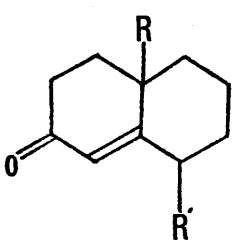
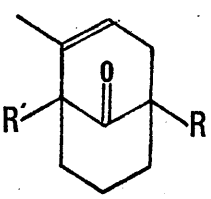
	R	R'
a	Me	H
b	H	Me
c	Me	Me

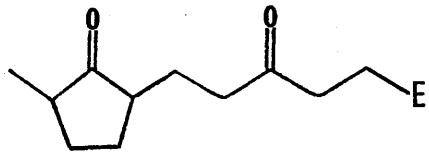


Scheme G ← **51** → Scheme H



(n 5-7,10 and 12).[26] If n is less than 5, then the fused bicyclic product(**46**) is produced. The "anti-Bredt" double bond so formed in (**47**) can be accommodated only if the adjacent ring contains at least eight atoms. It is worth pointing out that the carboalkoxy group is lost during the reaction, but if an alkyl group is present in either of the ring α-positions, as in (**48**), then acid catalysed condensation occurs at the ring methylene to produce the bicyclo-(3,3,1)-non-2-ene(**49**).[27]

Marshall has explained these observations from a number of standpoints.[27] In general, the ease of Scheme G will depend on the steric environment of the cyclohexanone carbonyl grouping and so methyl groups in the 2 or 6 position will retard this pathway. Also the energy difference between the conformer with an axial butanone sidechain (needed for Scheme H) and the equatorial sidechain conformer will be smaller when a methyl group is in the 2 position. Hyperconjugative stabilisation of the tetra-substituted enol(**50**) would occur in a 6-substituted cyclohexanone thus favouring the intermediate required for bridge formation. These factors were shown to be significant when the dimethyl derivative(**51c**) was found to cyclise much faster than either of the monomethyl



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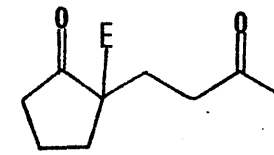


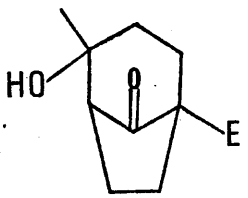
52

compounds (**51a**) and (**51b**).

These arguments go some way to explaining the apparent kinetic preference for the formation of bridged bicyclic intermediates in the aldol reaction. However it must not be forgotten that these reaction sequences are normally reversible and that often the product of thermodynamic control is isolated.[11]

One important difference between the bicyclo-(3,3,1)-non-2-en-9-one and the bicyclo-(3,2,1)-oct-2-en-8-one systems which must be mentioned in the light of any comparision, is the inherent strain in the latter. This is highlighted by the high carbonyl stretching frequency (1760cm.$^{-1}$) of this compound. If any strain energy was reflected in the transition state, then the apparent kinetic preference for bridge formation would be diminished and might well be lost. Bearing this in mind, would it then be possible to manipulate conditions to promote the formation of bridged bicyclic material from the cyclopentanone(**30**)?

The aldolisation of cyclopentanone derivatives has not been studied so extensively as cyclohexanones. However in 1960 Dauben and McFarland[28] examined the reaction of the diketone (**52**) in 95% sulphuric acid, and established that the solid



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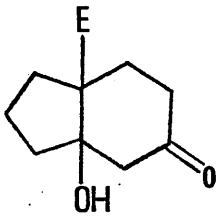

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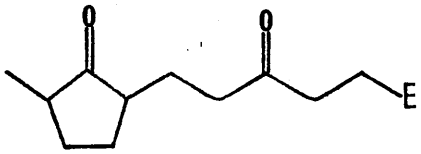

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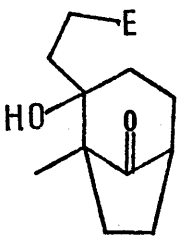

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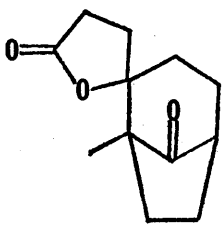

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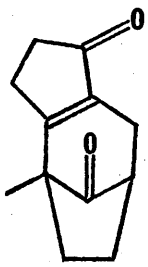

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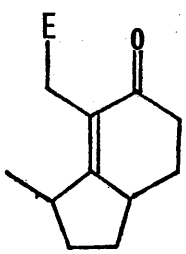

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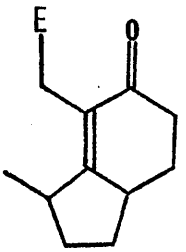
isomeric product, obtained in good yield, was in fact the bridged tertiary alcohol(**53**) and not the fused isomer(**54**). Appreciating that this was a 2,2'-disubstituted cyclopentanone but encouraged by these results it was hoped that cyclisation of the dione-ester(**30**) would afford the corresponding alcohol(**55**) which could be dehydrated in preparation for Friedel-Crafts acylation. It was also realised at this time that this alcohol might lactonise onto the ester function, thus displacing any equilibrium reaction to bridged bicyclic products. The spirolactone so formed, (**56**), could then be treated with polyphosphoric acid(PPA)[29] to yield the desired tricyclic ketone(**23**).

The cyclisation of (**30**) was attempted under a number of conditions. Anhydrous boron trifluoride/etherate afforded a mixture of two compounds with very similar chromatographic properties. These compounds were considered to be epimers of the undesired fused enone(**57**). This was deduced from the infra-red ($\nu_{max}^{C=O}$ 1732, 1664cm.$^{-1}$), ultra-violet (λ_{max} 243nm., ε=12000) and mass spectra (molecular ion at m/e 236). There was no evidence to suggest that any bridged bicyclic products had been produced.

p-Toluenesulphonic acid in benzene gave a more complex



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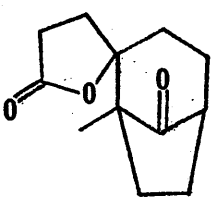

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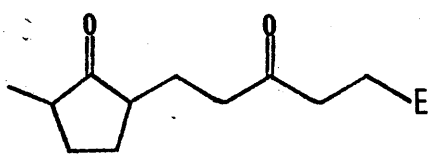

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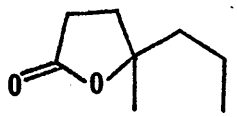
reaction mixture. The enone(**57**) was recognised as one of the products, but also formed in 28% yield was a single more polar compound which could be purified by preparative t.l.c. This compound exhibited spectral characteristics consistent with the lactone(**56**). The n.m.r. spectrum showed a singlet methyl resonance at 9.0τ as required, and the carbonyl stretching frequencies at 1780cm.$^{-1}$ (γ-lactone) and 1750cm.$^{-1}$ (bridge ketone) were in accord with this structure. It was now apparent that this compound would be a suitable target and that a more effecient synthesis should be pursued.

Reasoning that if the lactonisation step could be improved the synthesis of this intermediate would be promoted, it was decided that mineral acid might prove a better reagent. This would hydrolysis the ester function to the corresponding acid which would lactonise more readily. Indeed, on stirring the dione-ester(**30**) overnight in 10N hydrochloric acid it was converted in 80% yield to a mixture of the epimeric spiro-lactones(**56**). Although these epimers differed in their chromatographic properties, their spectral characteristics were very similar. While they could be easily separated by preparative t.l.c. and independantly characterised, this separation was considered extravagant as the asymmetric centre



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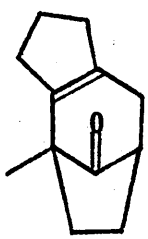

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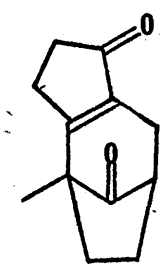


23

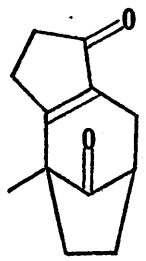
would become sp^2 hybridised in the following step.

These reactions illustrate very well the general principles that in acid catalysed aldol reactions of this kind;

1. Substitution on the cyclopentanone ring, though important in determining the structure of the product, is not paramount.

2. Reaction conditions can be varied to alter the nature of the products.

A literature survey soon established that polyphosphoric acid catalysed cyclodehydrations are very unpredictable and although some generalisations can be made,[30] the ease of the reaction can vary greatly with the substrate. Bearing this in mind, it was decided to mimic the conditions of Sukh Dev[31] who has achieved remarkable success with similar substrates e.g. (**58**). Thus stirring the epimeric mixture of spirolactones with a tenfold excess of PPA at 100° for three hours resulted in the consumption of both epimers and the production of a new compound, identical in all respects to the product of oxidation of the simple ketone(**6**) with NBS. This compound exhibited a molecular ion at m/e 190 and analysed for $C_{12}H_{14}O_2$, consistent with the desired tricyclic cyclopentenone(**23**). However the ultra-violet absorption (λ_{max} 247nm.ε=9000;



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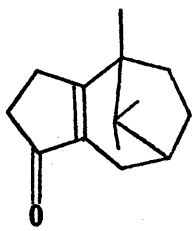

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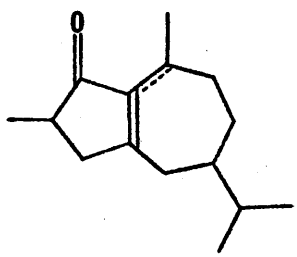

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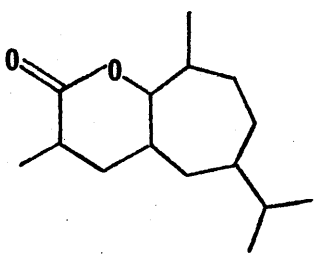

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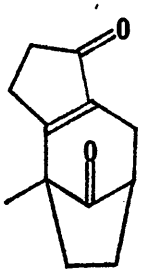
λ_{max} 227nm.ε=8100) is difficult to explain. The E.T. band should according to Woodward's rules,[32] occur at 238nm., however comparable bathochromic displacements have been observed in the spectra of other strained αβ-unsaturated ketones.[33] For example, the enone(**59**)[34] also exhibits a bathochromic maximum at 246nm. The occurrence of the absorption at 227nm. is similar (232nm.) to that observed in the cyclopentenone(**60**) obtained in the comparable cyclodehydration of the lactone(**61**).[35] The explanation proposed that the product was a mixture of double bond isomers and the high energy absorption was due to the presence of the cisoid enone. However any double bond migration in (**23**) would be easily detected in the olefinic region of the n.m.r. spectrum. No resonance in this region was observed and so the ultra-violet spectrum remains unexplained.

The work up procedure in this reaction, proved very troublesome, due to the apparent charring of organic material and although numerous attempts were made to diminish this charring, it was not possible to isolate more than 35% of the tricyclic ketone. During the course of these studies, it was found that at 60°, a single spirolactone epimer was converted by PPA into a mixture of both isomers.



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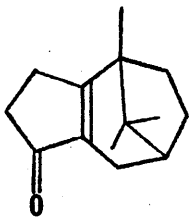

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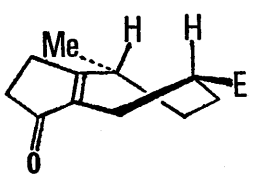
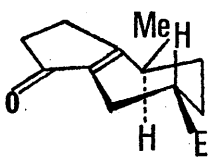


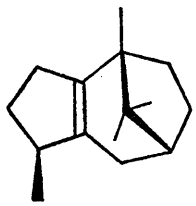
62a



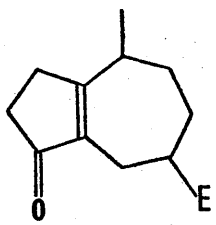
62b

The bridge cleavage of the tricyclic diketone(**23**) could be accomplished in two ways. Acid catalysed fragmentation resulted in a rather poor yield (50%) of the bicyclo-(5,3,0)-decane carboxylic ester(**62**). However realising that the ketone(**23**) was a non-enolisable vinylogous β-diketone it was anticipated that cleavage could be effected by a suitable nucleophile.[36] Indeed, refluxing the dione for two hours in dilute sodium methoxide solution resulted in an excellent yield (82%) of the desired enone-ester(**62**). This compound was purified by column chromatography whereupon some of the fractions were found to crystallise. Although these crystalline fractions appeared chromatography pure (5 g.l.c. columns and t.l.c.), the n.m.r. spectrum of each exhibited a doublet of doublets (of equal intensity) at 8.8τ. These signals were considered to be the methyl resonances of the cis and trans stereoisomers (**62a**) and (**62b**). Attempts to change this 50:50 ratio of isomers by chemical methods proved unsuccessful, but by a tedious process of fractional crystallisation (ether/petrol) it was possible to obtain a sample, enriched to the extent of 70:30 in one of the components. This assumption was based on integration of the n.m.r. spectrum.

Buchi[34] has shown that the ketone group in (**59**) can be



63



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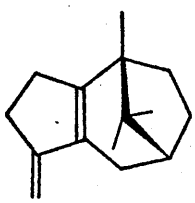
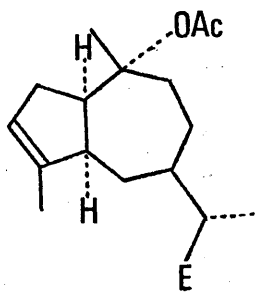


64

conveniently converted in a stereocontrolled manner to the methyl group in (**63**). Using this procedure, it was envisaged that a similar transformation could be effected on the enone-ester(**62**), affording the methyl group at C-8 in the desired β-orientation. Accordingly the 50:50 mixture of stereoisomers was stirred overnight with excess methyl lithium and then shaken with saturated ammonium chloride solution for five minutes. Without further purification the crude product was hydrogenated over 5% Pd/C. The uptake of hydrogen was very rapid, as reported for (**64**),[34] and after normal work up, a pale yellow oil was obtained which was examined by g.l.c. and found to contain four compounds. By combined gas chromatography -mass spectrometry (g.c.m.s.) these four compounds were found to possess a molecular weight of 222, and were therefore isomers of guaiol. All four compounds had identical t.l.c. properties to natural guaiol and because of this were considered to be the four possible stereoisomers of guaiol. By comparison of gas chromatographic and mass spectral data it was shown that the compound of shortest retention time (8.9 minutes on 1% OV 17 at 125°) was identical with natural guaiol. Unfortunately this compound comprised only 10% of the total mixture.

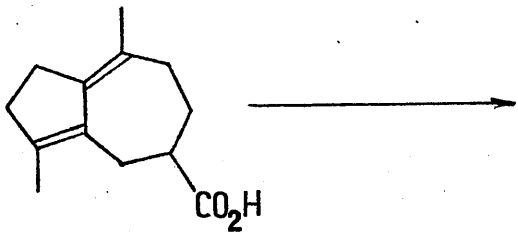


65

This yield is lower than anticipated, had the hydrogenation occurred in a stereocontrolled manner from the lower α-face. Therefore hydrogenation conditions which would result in increased stereoselectively were sought. Piers[37] in his recent synthesis of α-bulnesene has found that homogeneous catalysis with tris-(triphenylphosphine)-rhodium chloride was highly selective in the hydrogenation of the olefin(**65**). Consequently the above sequence was repeated using this homogeneous catalyst in benzene. After three hours the hydrogenation was terminated and the product inspected by g.c.m.s. In this case, three products were observed, but mass spectral measurements clearly indicated that, with each component of the mixture possessing a molecular weight of 220 reduction had not occurred; i.e. a series of dehydroguaiols had been produced. These were not investigated further.

Using the fraction enriched to the extent of 70:30, it was hoped that it might be possible to increase the proportion of synthetic material with the correct stereochemistry. However on repeating the sequence with this material afforded a product which on g.l.c. analysis was identical in composition to that obtained from the 50:50 mixture. Clearly the reaction conditions were sufficient to re-equilibrate the

Scheme J.



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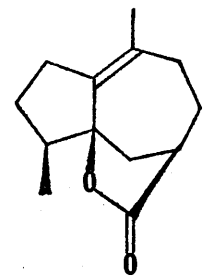

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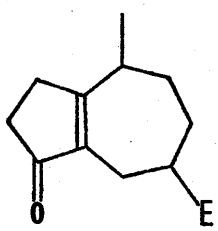

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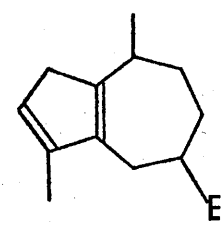


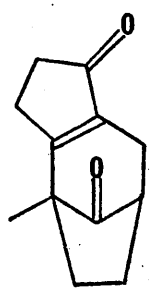
68

enriched mixture.

This result simply confirms the observation made from molecular models that the free energy difference between the chair and twist boat conformations is very small, and that the barrier to their interconversion is also minimal.

An alternative approach, which hopefully would improve the stereoselectively of the existing synthesis, would rely on the control provided by the lactonisation step shown in Scheme J, provided the diene(**66**) could be prepared. Related studies on the ester(**62**), however, indicate that this particular arrangement of double bonds is not favoured. Specifically when this ester was treated with one equivalent of methyl-lithium, followed by an acid work up, at least three compounds were formed. This could be deduced from the three -OMe signals and the complex methyl resonances in the n.m.r. spectrum. The ultra-violet spectrum of the crude mixture exhibited a maximum at 247nm. which is reasonable for a cyclopentadiene of type(**68**).

Attempts to introduce an exomethylene group at position 8 by a Wittig reaction on the enone-ester(**62**) were thwarted by competitive reaction at the ester function. Only products containing aromatic protons in the n.m.r. spectrum were found.



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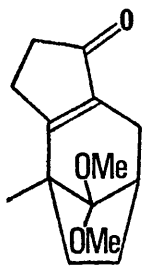

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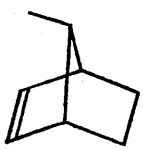

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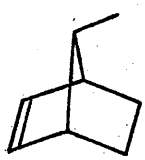
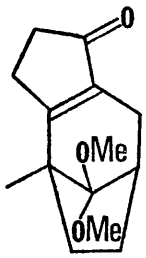


71

A series of experiments run in parallel were designed to test the feasibilty of the route shown in Scheme J. The dimethyl acetal(**69**) could be prepared conveniently by stirring the dione(**23**) in methanol containing a few drops of acetyl chloride. The ultra-violet spectrum (λ_{max} 245nm.) of (**69**) indicated that the enone carbonyl had not been acetalised. It is interesting to compare this spectrum with that of the dione(**23**). Whereas the dione exhibited two maxima at 227 and 247nm., the acetal exhibited only the single expected maximum at 245nm. It would seem reasonable that the high energy transition in the former can be attributed to some kind of interaction between the carbonyl at C-11 and the enone chromophore.

The n.m.r. spectrum of (**69**) was also interesting, in that two signals were observed for the -OMe protons at 6.70 and 6.76τ. Examination of a molecular model of the acetal, clearly shows that one set of methyl protons is located directly above the $^{\Delta}$2,6-double bond. This methyl group is thus in the diamagnetic shielding zone of the double bond and as a consequence resonates at a higher field. A similar phenomenon has been demonstrated with the isomers (**70**) and (**71**).[38] The syn-methyl in (**70**) was found to resonate at 9.3τ whereas in



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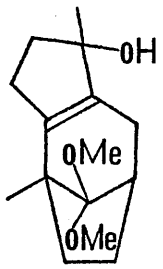

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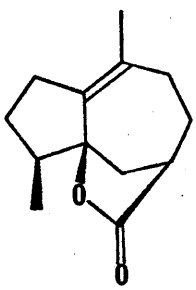

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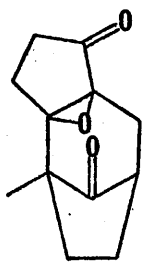

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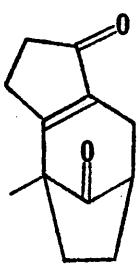

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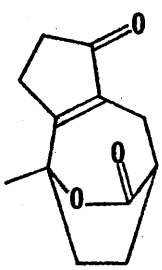


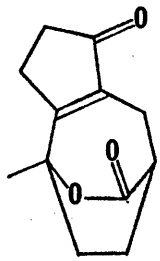
74

(**71**) the anti-methyl group resonated at 9.21τ.

Treatment of the acetal(**69**) with excess methyl lithium for two hours was sufficient to convert all starting material into a mixture of two more polar products, assumed to be epimers at C-5 in (**72**). By treating the lithium alkoxides so formed with methanesulphonyl chloride, it was hoped to effect mesylation as reported.[39] This procedure did not prove successful, as a complex mixture of products was obtained and in view of the known difficulty in hydrolysing the acetal function in systems like this[40] it was considered that this route was not worthwhile and hence terminated at this point.

It was considered possible that formation of the lactone(**67**) could be approached by acid catalysed ring opening of the epoxide(**73**). In order to test this idea, the enone(**23**) was treated with basic hydrogen peroxide under standard enone epoxidising conditions. However standard work up gave only acidic material, presumably arising from nucleophilic ring opening of the vinylogous β-diketone.

Another approach which was investigated was the action of peracid on the tricyclic ketone(**23**). It was hoped that Baeyer-Villiger oxidation of the ketone would be specific and insert an oxygen atom into the C-1 — C-11 bond forming (**74**).



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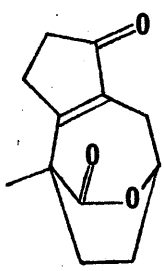


75

On stirring with one equivalent of m-chloroperbenzoic acid, the ketone was converted into a more polar compound, which could be easily purified by preparative t.l.c. Its ultra-violet spectrum (λ_{max} 240nm.) and carbonyl stretching frequency at 1705cm.$^{-1}$ confirmed the existence of the enone chromophore, while the absorption at 1752cm.$^{-1}$ clearly indicated the presence of a ε-lactone. However the n.m.r. spectrum exhibited two singlets at 8.4 and 8.6τ (in the ratio 3:2) indicative of the two methyl resonances in (**74**) and (**75**). This ratio of (**74**) to (**75**) was established as 3:2 (and not 2:3) by relative integration against the methyl signals of the broad multiplet at 5.1τ which was surely due to the resonance of the H-C-O proton in (**75**). Due to the separation problems this area of research was terminated at this point.

EXPERIMENTAL

General

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Routine infra-red spectra of liquid films and nujol mulls were recorded on a Unicam SP 200 instrument, while solution spectra were recorded on Perkin Elmer PE 225 and Unicam SP 100 instruments. Ultra-violet absorption spectra, measured on a Unicam SP 800 spectometer, refer to solutions in ethanol, unless otherwise stated. Nuclear magnetic resonance spectra were recorded on a Varian AT 60 spectrometer, or in the case of 100 MHz. spectra on a Varian HA 100 instrument, using approximately 0.3 molar solutions with tetramethyl silane as internal standard. Mass spectra were measured on an A.E.I. MS 12 mass spectrometer.

Thin layer chromatography (t.l.c.) was accomplished using silica (Kieselgel G (Merck) for analytical use, and Kieselgel HF_{254} (Merck) for preparative purposes.)

Gas-liquid chromatography (g.l.c.) was carried out on a Pye Argon chromatograph equipped with a β-ionisation detector. Combined gas chromatography - mass spectrometry (g.c.m.s.) measurements were recorded on an LKB 900 spectrometer.

Petrol refers to light petroleum fraction b.p. 60-80°. Organic solutions were dried over anhydrous magnesium sulphate.

2-(2'-Oxocyclopentylmethyl) cyclopentanone (**1**).[1]

This compound was prepared as a white solid (m.p. 71-72°) from the Mannich base of cyclopentanone and cyclopentanone.

I.R. (nujol mull) $cm.^{-1}$:- 1735 (s), 1160 (s).

Tricyclo-(6,2,1,$0^{2,6}$)-undec-2^{6}-en-11-one (**2**).

p-Toluenesulphonic acid (3g.) in toluene (100ml.) was refluxed on a water separator for two hours. The dione(**1**) (3g.) in dry toluene (20ml.) was added and the reflux continued for a further two hours. The dark brown solution so formed was cooled, anhydrous potassium carbonate (5g.) added and the suspension left overnight. Filtration of solid and evaporation of the solvent left a brown oil (2.16g.) which contained the desired tricyclic ketone(**2**) and a trace of the lactone(**3a**) later identified by its infra-red spectrum. Purification of the ketone was effected by column chromatography on silica. Elution with 5% ethyl acetate was sufficient to separate the less polar ketone from contaminants.

I.R. (liquid film) $cm.^{-1}$:- 1745 (s), 1180 (m), 1150 (m).

N.M.R. (CCl_4) :- Nothing below 7.0τ.

M.S. :- Significant peaks at m/e 162,134,119,106,105 and 91.

G.L.C. :- 1 peak R_t 7.5min. on 5% QF1 at 125°(flow rate 44ml.)

The infra-red spectrum of the lactone(**3a**) was characterised by the high carbonyl stretching frequency, viz.,

I.R. (liquid film) $cm.^{-1}$:- 1765 (s), 1130 (s) and 945 (s).

3-Carbomethoxybicyclo-(5,3,0)-^{1,7}decene (**3**).[1]

The tricyclic ketone(**2**) (160mg.,1mmole) in dry methanol (10ml.) containing concentrated sulphuric acid (1ml.) was refluxed for 16 hours, cooled and the methanol removed under reduced pressure. The black residue was dissolved in ether and washed with dilute sodium bicarbonate solution (2x), then brine. The ethereal extract was dried and evaporated to yield the crude product (170mg.) Purification by preparative t.l.c. (2 x 10% ethyl acetate/petrol) afforded the pure ester as a colourless oil (102mg. 53%).

I.R. (liquid film) $cm.^{-1}$:- 1730 (s) and 1160 (s).

N.M.R. ($CDCl_3$) :- Singlet (3H) 6.36τ.

Multiplet (15H) 7.0 - 8.6τ.

Also isolated by t.l.c. was the starting diketone(**1**) (39mg.) identified by its infra-red spectrum.

2-Methylcyclopentanone (**8**).

This was prepared in 40% yield from diethyl adipate by

the method of Nicole[4] and obtained as a colourless oil b.p. 137-139°.

I.R. (liquid film) $cm.^{-1}$:- 1735 (s), 1180 (s) and 950 (m).

2-Methyl-5-(2'oxocyclopentylmethyl) cyclopentanone (**5**).

This compound was prepared via the Thermal Michael reaction of the Mannich base of cyclopentanone and 2-methyl-cyclopentanone,[2] and obtained in 50% yield as a colourless oil b.p. 118-120°(0.5mm.)

I.R. (liquid film) $cm.^{-1}$:- 1735 (s) and 1160 (s).

N.M.R. (CCl_4) :- Multiplet (15H) 7.4 - 8.8τ.

2 Overlapping doublets(J=6Hz.) (3H) 8.9τ.

G.L.C. :- 1 peak R_t 8.2min. on 5% QF1 at 125°(flow rate 28ml.)

1-Methyltricyclo-(6,2,1,$0^{2,6}$)-undec-2^{6}-en-11-one (**6**).

p-Toluenesulphonic acid (120mg.) was dissolved in benzene (20ml.) and refluxed for two hours on a water separator. The diketone(**5**) (260mg.,1.6mmole) in dry benzene (5ml.) was added and the reflux continued for four hours. On cooling, the solution was neutralised by standing over solid anhydrous potassium carbonate (200mg.) for twelve hours. The solid residue was filtered, then washed with hot benzene till colour-

less. Evaporation of the solvent afforded the crude product (248mg.) as a dark brown oil which was purified by preparative t.l.c. (20% ethyl acetate/petrol) yielding (**6**) (182mg.,65%) as a camphoraceous smelling, colourless oil.[2]

I.R. (liquid film) $cm.^{-1}$:- 1740 (s), 1240 (m), 1050 (m), 750.

N.M.R. ($CDCl_3$) :- Singlet (3H) 8.95τ.

Multiplet (13H) 7.0 - 8.7τ.

M.S. :- Significant peaks at m/e 176(M^+),148,133(base),120,91.

Attempted synthesis of 2-(3'methyl-2'-oxocyclohexylmethyl) cyclohexanone (**13**).

The Mannich base(**11**) (23g.) and 2-methylcyclohexanone(49g.) were refluxed for 4.5 hours, cooled and neutralised with acetic acid. The solution was extracted with ether and the organic phase washed with brine, dried and evaporated to leave a clear viscous oil. Removal of excess 2-methylcyclohexanone and distillation afforded the product (12.4g.) b.p. 119-121° (0.3mm.) However t.l.c. analysis indicated the presence of three major components which were separated by column chromatography on silica. The least polar fraction was isolated as a viscous oil (3.68g.) and characterised as (**14**) by spectral comparison.[13]

I.R. (CCl_4) $cm.^{-1}$:- 1725(s),1700(m),1300(w),1150(s) and 970(m).

N.M.R. (CCl_4) :- Nothing below 7.0τ.

M.S. :- Significant peaks at m/e 220(M^+),135,122,111(base), 110 and 67.

The second component was eluted as a white crystalline solid (6.42g.) m.p. 153°(ethyl acetate) and again characterised by spectral analysis as (**15**).[13]

I.R. (CCl_4) :- 3600 (sharp,w), 3500 - 3200 (m)

Very sharp fine structure in fingerprint area.

This spectrum was superimposable on the literature spectrum.[13]

N.M.R. (CCl_4) :- Singlet (1H) 5.98τ. (exchangeable)

Nothing else below 7.6τ.

M.S. :- Significant peaks at m/e 238(M^+),220,151,135,122, 111(base),110,98 and 67.

The third component, eluted with 20% ethyl acetate/petrol, was obtained as a colourless oil (1.02g.) and although not positively identified, could have been the desired diketone(**13**).

I.R. (liquid film) $cm.^{-1}$:- 1710(s),1310(m),1130(m) and 890(w).

N.M.R. ($CDCl_3$) :- Nothing below 7.2τ.

M.S. :- Molecular ion at m/e 222 (as required).

This product was not investigated further.

2-Methyl-5-carbomethoxybicyclo-(5,3,0)-decene (**17**).

The tricyclic ketone(**6**) (80mg.) in dry methanol (10ml.) containing concentrated sulphuric acid (1ml.) was refluxed for sixteen hours, cooled, and the methanol removed under reduced pressure. The residue was dissolved in ether and washed with dilute sodium bicarbonate solution (2x), then brine. The etheral extract was dried and the solvent removed to yield the crude product which was purified by preparative t.l.c. (20% ethyl acetate/petrol). The ester so obtained (42mg.,50%) was found, by g.l.c. and n.m.r. to contain a 50:50 mixture of isomers (**16**) and (**17**).

I.R. (liquid film) $cm.^{-1}$:- 1730 (s).

The fingerprint region was very similar to the ester(**3**).

N.M.R. (CCl_4) :- Singlet (3H) 6.4τ.

Singlet 8.36τ consistent with $C{\equiv}C-CH_3$.

Doublet (J=7Hz.) 9.0τ.

G.L.C. :- 2 peaks R_t 48min. and 67min. in the ratio 1:1 on 5% B34 / 5% DNP at 125°(flow rate 96ml./min.)

Also isolated during chromatography was the lactone(**17a**) (9mg.) which was identified by its infra-red spectrum.

I.R. (liquid film) $cm.^{-1}$:- 1760 (s).

The fingerprint region was very similar to the lactone(**3a**).

Attempted allylic oxidation of (**6**).

a) CrO_3 / $(pyridine)_2$.

To a stirred suspension of freshly prepared "Collin's reagent"[17] (2.2g.,6 equiv.) in dry methylene chloride (20ml.) was added the enone(**6**) (160mg.) under an atmosphere of nitrogen. Immediately a brown tar was deposited. Stirring was continued overnight, then the reaction heated at 70° for five hours. On cooling, dilute sodium bicarbonate solution was added and the organic phase washed several times with water, dried, and concentrated to yield the crude product (148mg.) Analytical t.l.c. indicated the presence of at least three products which were partially separated by multiple elution preparative chromatography. Spectral analysis of each fraction was not encouraging, and this together with the multiplicity of products, made the sequence a poor synthetic step.

b) N-bromosuccinimide in aqueous dioxan.

To a stirred solution of (**6**) (120mg.) in dioxan (10ml.) containing water (0.5ml.), was added calcium carbonate (250mg.) and N-bromosuccinimide (250mg.) On addition of the final reagent, the suspension was irradiated with visible light from a 100 watt light bulb for one hour. After this time, the

suspension was filtered, extracted twice with ether, and the ether extract washed with brine and dried. Purification of the resultant oil was effected using preparative t.l.c. (40% ethyl acetate/petrol) whereby two components were isolated in low yield. The less polar component (28mg.) exhibited spectra which demonstrated it was not the required dione(**23**).

I.R. (liquid film) $cm.^{-1}$:- 1750(s),920,910,900(all m), 790(m).

N.M.R. (CCl_4) :- Multiplet (1H) 5.7τ Maybe H-C-Br.

3 Methyl singlets 8.8 - 9.1τ.

U.V. :- End absorption only.

These results were consistent with allylic bromination at one or more sites.

The more polar component (19mg.) exhibited spectral characteristics which were consistent with the desired structure and comparision of spectra with the authentic dione later synthesised by an unambiguous route established that this compound was indeed the required enone(**23**) (See P **55**).

c) CrO_2Cl_2.

The ketone(**6**) (300mg.,1.6mmole.) was treated at -78° with a solution of CrO_2Cl_2 (0.4ml.,5mmole.) in methylene chloride (20ml.) The reaction mixture was stirred at -78° for

four hours, allowed to come to room temperature, and washed with water until the organic phase was colourless. The solution was dried and evaporated, affording the crude product (300mg.) T.l.c. analysis indicated at least three major products, labelled A,B and C in order of increasing polarity, which were separated by preparative t.l.c. (20% ethyl acetate/petrol).

Compound A.

I.R. (liquid film) $cm.^{-1}$:- 1740(s),1700(s),1200-1000(broad).

U.V. :- λ_{max} 229nm., shoulder at 260nm.

Compound B.

I.R.(liquid film) $cm.^{-1}$:- 1740(s),1700(s),1070(m) and a characteristic quintet between 980 - 880(w).

U.V. :- λ_{max} 228nm., shoulder at 250nm.

Compound C.

I.R. (liquid film) $cm.^{-1}$:- 1690(s) and 1090(s).

U.V. :- λ_{max} 248nm.

None of these three compounds were obtained in a state, pure enough for microanalysis. The overall yield from the reaction was low (40%) and none of the products was the required dione which was subsequently prepared by another method. Accordingly the reaction products were not investigated further.

2-Acetylcyclopentan-1,3-dione (**27**).[21]

Isopropenyl acetate (50g.) was added over 15 minutes to a stirred slurry of succinic anhydride (50g.), aluminium chloride (150g.) and ethylene dichloride (400ml.) The yellow solution so formed was refluxed for 15 minutes, cooled, and poured onto crushed ice (1Kg.) containing 6N HCl (250ml.) The aqueous phase was extracted continuously overnight with chloroform and the combined organic extracts washed, dried and concentrated. Distillation of the residue under reduced pressure afforded the desired trione as a yellow oil (b.p. 68° (0.3mm.) which solidified rapidly on standing. Extraction of this yellow solid with boiling petrol and evaporation of the solvent produced the trione as colourless plates m.p. 68-69° (lit. 69-71)[21] 8g.,12% yield. The i.r. and n.m.r. spectra were identical with those published.[21]

Cyclopentan-1,3-dione (**24**).

The trione(**27**) (8g.) was refluxed overnight in 6N HCl (600ml.) On removal of the water by reduced pressure distillation, the residue was sublimed at 130 and 0.1mm. to yield the dione (0.8g.) m.p. 149-151°(lit. 151-152°).[21] The infra-red spectrum (nujol) was identical with that reported.[21]

2,6-Dimethyl-γ-pyrone (**28**).

2-Methylcyclopentanone (7.8g.), paraformaldehyde (3.2g.) and dimethylamine hydrochloride (6.5g.) were refluxed overnight in ethanol (5ml.) On cooling, ice (50g.) and 6N HCl (5ml.) were added and the mixture extracted with ether. The aqueous phase was basified (4N NaOH) to pH 11 and then re-extracted with ether. This ether fraction was washed, dried and concentrated to yield the Mannich base(**25**) (10g.) as a yellow oil. This Mannich base (0.6g.) was added to cyclopentan-1,3-dione (1.2g.) whereupon the solution turned orange then dark red on refluxing for four hours. On cooling, the solution was neutralised with acetic acid and extracted with ether. The ether was washed, dried and evaporated to leave a dark brown oil. Sublimation at 60°/0.1mm. produced colourless rhomboids of 2,6-dimethyl-γ-pyrone(**28**) m.p. 131-132°(190mg.,38% based on Mannich base.)

Found:C,67.4;H,6.45. $C_7H_8O_2$ requires:C,67.7;H,6.50%.

I.R. (CCl_4) $cm.^{-1}$:- 1670(s),1630(s),1390(s),1150(m) and 930(m).

N.M.R. ($CDCl_3$) :- Singlet (2H) 3.95τ.

Singlet (6H) 7.70τ.

U.V. :- λ_{max} 247nm. (lit. 248nm.)[41]

M.S. :- Significant peaks at m/e 124,109,96,95,81,79 and 53.

6-Dimethylamino-4-oxo-caproic acid hydrochloride (**35**).

Laevulinic acid (120g.,1mole) and dimethylamine hydrochloride (80g.,1mole) were stirred together at 110° until a homogeneous solution was obtained. Paraformaldehyde (30g.) was added cautiously and the temperature maintained at 110° for one hour under a reduced pressure of 14mm. The cooled residue was filtered and ethanol (50ml.) and acetone (450ml.) added to precipitate the Mannich base hydrochloride as a colourless amorphous solid m.p. 108-112°(lit. 112-120°)[2] 120g.60%. The crude material, after drying, was pure enough for the next stage.

Ethyl 6-dimethylamino-4-oxo-caproate (**36**).

The crude hydrochloride(**35**) (20g.) was refluxed overnight in dry ethanol (50ml.) containing concentrated sulphuric acid (1ml.) The ethanol was then removed under reduced pressure and the residue dissolved in water, basified (4N NaOH), and extracted with ether. The ethereal phase was washed with brine dried and concentrated affording the free Mannich base(**36**) (13.2g.,70%) as a light yellow oil. This could be used without further purification.

I.R. (CCl_4) :- 2760 (w), 1720 (broad,s) and 1180 (s).

N.M.R. (CCl_4) :- Quartet (J=7Hz.) (2H) 5.9τ.

Multiplet (8H) 7.2 - 7.6τ.

Singlet (6H) 7.8τ.

Triplet (J=7Hz.) 8.7τ.

Condensation of (**36**) with 2-methylcyclopentanone.

The Mannich base ester(**36**) (13g.,0.067mole) and 2-methyl cyclopentanone (18g.,0.186mole) were refluxed for sixteen hours. On cooling, water (100ml.) and 6N HCl (10ml.) were added and the mixture extracted with ether (3x). The organic phase was washed with brine, dried and the ether evaporated to yield the crude product. Excess 2-methylcyclopentanone was distilled off under reduced pressure and the residue chromatographed on silica (480g.). Elution with 2% ethyl acetate/petrol afforded the diketone(**37**) (502mg.,4%) as a colourless oil which partially solidified to a waxy solid m.p. 44-52°.

Found:C,74.80;H,9.61. $C_{13}H_{22}O_2$ requires:C,74.96;H,9.68%.

I.R. (CCl_4) $cm.^{-1}$:- 1739 (s) and 1160 (m).

N.M.R. (CCl_4) :- 2 overlapping doublets (J=6Hz.) (3H) 8.9τ.

M.S. :- Significant peaks at m/e 208(M^+),111,110 and 98(base)

G.L.C. :- 1 peak R_t 4.0min. on 5% QF1 at 175°(flow rate 60ml.)

Elution with 10% ethyl acetate/petrol afforded a mixture of two components (total 11.2g.,68%) of very similar polarity but different staining properties. These compounds could not be separated on g.l.c. (5% QF 1) and were considered to be epimers of the dione-ester(**30**). An analytical sample was prepared by short path distillation (b.p. 131-132°/0.2mm.)

Found:C,66.40;H,8.55. $C_{14}H_{22}O_4$ requires:C,66.12;H,8.72%.

I.R. (CCl_4) $cm.^{-1}$:- 1737(v.s.),1728(shoulder),1190(m),1160(m)

N.M.R. (CCl_4) :- Quartet (J=7Hz.) (2H) 5.9τ.

Complex region (6H) 8.8τ.

M.S. :- Significant peaks at m/e 254(M^+),208,111, 101,55(base)

G.L.C.:- 1 peak R_t 14.5min on 5% QF1 at 175°(flow rate 60ml.)

Attempted cyclisation of the dione-ester(**30**).

a) BF_3.

Boron trifluoride[42] was prepared from ammonium fluoroborate (6g.), boric oxide (1g.) and concentrated sulphuric acid (6ml.) and bubbled into a solution of the dione-ester(**30**) (100mg.) in dry methylene chloride (15ml.) After ten minutes the solution turned cloudy and light yellow in colour and the gas flow was terminated. The solution was stirred overnight at room temperature, washed with dilute sodium bicarbonate

solution, brine then dried and the methylene chloride evaporated to yield the crude product (77mg.) G.l.c. analysis (5% QF1 at 175°, flow rate 60ml./min.) indicated three components

	Yield	R_t(min.)	
A	30%	4.5	--
B	50%	8.5	**(57)**
C	20%	9.0	**(57)**

Preparative t.l.c. (40% ethyl acetate/petrol) afforded B and C as an intimate mixture. These were considered to be epimers of the αβ-enone(**57**). An analytical sample was prepared by short path distillation (b.p.120°/0.5mm.)

Found:C,71.28;H,8.46. $C_{14}H_{20}O_3$ requires:C,71.16;H,8.53%.

I.R. (CCl_4) $cm.^{-1}$:- 1732(s), 1664(s), 1170(s) and 1030(m).

N.M.R. (CCl_4):- Quartet (J=6Hz.) (2H) 5.9τ.

Complex methyl region.

U.V. :- λ_{max} 243nm. (ε=12100).

M.S. :- Significant peaks at m/e 236(M^+),190,189,161(base),91.

Attempts to isolate A by chromatography were unsuccessful.

b) p-Toluenesulphonic acid.

P-Toluenesulphonic acid (350mg.) in benzene (20ml.) was refluxed on a water separator for two hours. The dione-ester(**30**)

(340mg.,1.34mmole.) in dry benzene (5ml.) was added and the reflux continued for a further two hours. On cooling, the solution was neutralised by standing over solid potassium carbonate (400mg.) for twelve hours. The solid residue was filtered, then washed till colourless with hot benzene. Evaporation of the benzene afforded the crude product (358mg.) which was chromatographed on thin-layer plates (40% ethyl acetate/petrol). This purification gave two major components. The less polar fraction was identified by chromatographic and spectral comparison to be the enone-ester(**57**) (81mg.,30%). The polar fraction (76mg.,28%) was isolated as a crystalline solid and identified by spectral analysis as (**56**). An analytical sample prepared by sublimation (80°/0.2mm.) had m.p. 106-107°.

Found:C,69.46;H,7.70. $C_{12}H_{16}O_3$ requires C,69.21;H,7.74%.

I.R. (CCl_4) $cm.^{-1}$:- 1780(s), 1750(s), 1165(s) and 1020(s).

N.M.R. (CCl_4) :- Multiplet (13H) 7.2 - 8.8τ.

Singlet (3H) 9.0τ.

M.S. :- Significant peaks at m/e 208(M^+),190,125,111,97(base).

G.L.C.:- 1 peak R_t 16.5min. on 5% QF1 at 175°(flow rate 56ml.)

Also observed on g.l.c. (of crude reaction mixture) was a compound (5%) R_t 32min., later identified as the epimeric spirolactone. (See P **55**).

c) Sodium ethoxide.

The dione-ester(**30**) (100mg.) was stirred at room temperature for two hours with sodium ethoxide (from Na(30mg) in ethanol (20ml.) Water (20ml.) was added and the solution washed with ether. No organic material was found in the organic extract, establishing that all products were base soluble. The basic aqueous layer was acidified (6N HCl) and extracted with ethyl acetate. The ethyl acetate was washed with brine, dried and evaporated to give the crude product as a yellow oil (68mg.) T.l.c. analysis indicated no starting material and the presence of an "acid tail". The identity of this material as the acid corresponding to (**57**) was established by basic hydrolysis (KOH/ethanol) of (**57**) and comparison of infra-red spectra.

I.R. (liquid film) $cm.^{-1}$:- 3500-2500(broad),1720(s),1705(s), 1660(s),1640(s) and 1180(m).

U.V. :- λ_{max} 241nm.

d) 10N HCl.

The dione-ester(**30**) (5.1g.,0.02mole) was stirred for twelve hours at room temperature with 10N HCl (60ml.) The red-green opalescent solution was flooded with water (150ml.) and extracted with ethyl acetate (3x). The organic extract was

washed with dilute sodium bicarbonate solution, brine, then dried and evaporated to yield the crude product (3.18g.,79%) as a brown oil which solidified on trituration with ether. Analysis of this oil, indicated the presence of the spirolactone previously prepared by method b), and another more polar component which was isolated by preparative t.l.c. (60% ethyl acetate/petrol). No enone-ester(**57**) was observed. The polar component had spectral characteristics very similar to the less polar component and consequently was considered to be the epimeric spirolactone(**56**). An analytical sample prepared by sublimation had m.p. 105-112°.

Found:C,68.95;H,7.65. $C_{12}H_{16}O_3$ requires C,69.21;H,7.74%.

I.R. ($CHCl_3$) $cm.^{-1}$:- 1772(s), 1758(s) and 946(m).

N.M.R. ($CDCl_3$) :- Multiplet (13H) 7.2 - 8.8τ.

Singlet (3H) 9.0τ.

M.S. :- Almost identical to the spirolactone of method b).

G.L.C. :- The ratio of (**56**) R_t 16.5min to (**56**) R_t 32min was established by g.l.c. on 5% QF1 at 175°(flow rate 56ml/min) to be approximately 1 : 5.

<u>1-Methyltricyclo-(6,2,1,$0^{2,6}$)-undec-2^6-en-5,11-dione (**23**)</u>.

The epimeric mixture of spirolactones(**56**) (3.6g.) were

stirred at 100° for three hours with polyphosphoric acid (40g.) A dark red solution was obtained which was poured onto ice (100g.) and the mixture stirred to ensure decomposition of the polyphosphoric acid. Ethyl acetate (100ml.) was added and the heterogeneous mixture filtered to remove charred material. The aqueous layer was further extracted with ethyl acetate (3x) the organic layers combined, washed with brine and dried. Evaporation of the ethyl acetate left a dark red gum (1.9g.) which was found to be greater than 90% one component. An aliquot was purified by preparative t.l.c. (60% ethyl acetate/ petrol) and an analytical sample (m.p. 100-102°) prepared by sublimation (110°/0.3mm.) The low yield (35% isolated) was attributed to charring. Attempts to reduce this by various methods were unsuccessful.

Found;-C,75.72;H,7.33. $C_{12}H_{14}O_2$ requires C,75.76;H,7.42%.

I.R. (CCl_4) $cm.^{-1}$:- 1760(s),1705(s),1635(m),1290(m) and 1065(w)

N.M.R. (CCl_4) :- Multiplet (11H) 7.2 - 8.6τ.

Singlet (3H) 8.9τ.

U.V. :- λ_{max} 227nm. (ε=8100), 247nm. (ε=9000) and 300nm. (ε=300)

M.S. :- Significant peaks at m/e 190(M^+),162,147,119,105(base)

G.L.C. :- 1 peak R_t 9.6min. on 5%QF1 at 175°(flow rate 58ml.)

2-Methyl-5-carbomethoxy-8-oxo-bicyclo-(5,3,0)-$\Delta^{1,7}$decene (62).

a) By acid treatment of the ene-dione(23).

The ene-dione(23) (110mg.) was refluxed for sixty hours in methanol (15ml.) containing concentrated sulphuric acid (1ml.) The methanol was removed under reduced pressure and the residue taken up in ether, washed with dilute sodium bicarbonate solution, brine and finally dried. Removal of the solvent left the product as a yellow oil which was purified by preparative t.l.c. (60% ethyl acetate/petrol), affording the ester as a colourless oil (58mg.,50%) b.p. 120°/0.3mm. Found;C,70.06;H,8.01. $C_{13}H_{18}O_3$ requires C,70.24;H,8.16%.

I.R. (CCl_4) $cm.^{-1}$:- 1735(s), 1704(s), 1642(s) and 1165(s).

N.M.R. ($CDCl_3$) :- Singlet (3H) 6.3τ.

Multiplet (12H) 7.2 - 8.6τ.

2 overlapping Doublets (J=7Hz.) of equal intensity (3H) 8.8τ.

U.V. :- λ_{max} 237nm. (ε=11900)

M.S. :- Significant peaks at m/e 222(M^+),190,162(base),105.

G.L.C. :- This compound, although believed to be a mixture of epimers was observed as a single peak R_t 12.5min. on 5% QF1 at 175°(flow rate 52ml./min.) A single peak was also observed on 1% OV 17 at 125°, 1% OV 1 at 125° and 10% PEGA at 150°.

b) By NaOMe induced cleavage of the ene-dione(**23**).

The ene-dione(**23**) (950mg.,5mmole) was refluxed for two hours in dilute sodium methoxide solution (from Na (230mg.) in methanol (40ml.). On cooling the methanol was evaporated and the residue treated with ether. The organic phase was then washed with dilute hydrochloric acid, brine and finally dried. The compound obtained on solvent evaporation was identical in every respect to (**62**) prepared by method a). Purification of the crude product (916mg.,82%) was effected by column chromatography on silica (30g.) Some of the fractions so obtained were found to crystallise on standing, however n.m.r. analysis indicated that no fractionation had occurred. Attempts to achieve fractional crystallisation were only partially successful. A 70:30 mixture (m.p. 48-74°) could be obtained using petrol/ether as solvent. This ratio was deduced from an integration of the methyl doublets in the n.m.r. spectrum.

Attempted synthesis of 2-methyl-5-carbomethoxy-8-methylene-bicyclo-(5,3,0)-$^{\Delta 1,7}$decene (**64**) by a Wittig reaction.

Sodium amylate solution (2ml. of a 1M solution in benzene) was added under nitrogen to a stirred suspension of triphenylmethylphosphonium bromide (720mg.,2mmoles) in dry

benzene (20ml.). After stirring for one hour at room temperature the enone-ester(**62**) (220mg.,1mmole) in dry benzene was added dropwise. Stirring was continued overnight, and the yellow suspension so formed washed thoroughly with water. The solution was dried and evaporated to leave the crude product as a viscous gum. Attempts to isolate the desired diene (**64**) proved unsuccessful as all fractions obtained by column chromatography were found to contain aromatic protons in the n.m.r. spectrum. Similar failures were observed in the attempted olefination using potassium t-butoxide in ether[43] or potassium t-butoxide in dimethyl formamide.[44]

Treatment of the enone-ester(**62**) with methyl-lithium.

a) One equivalent of methyl-lithium.

A solution of the enone-ester(**62**) (110mg.,0.5mmole) in dry ether (10ml.) was treated at 0° with methyl-lithium (0.2ml. of a 3M solution in ether, 0.6mmole). The reaction was stirred for fifteen minutes and terminated by the addition of water. The organic phase was separated and dried. T.l.c. analysis indicated two main components; one more polar and one less polar than the starting materials. On standing for thirty minutes the more polar component had almost completely

disappeared. The less polar component was then purified by preparative t.l.c. (40% ethyl acetate/petrol).

I.R. (liquid film) $cm.^{-1}$:- 1730 (s) and 1170 (s).

N.M.R. (CCl_4) :- Multiplet 4.36τ.

3 Singlets 6.4τ.

Multiplet 7.0 - 8.8τ.

Singlet 8.1τ.

Complex Methyl signal 8.9τ

U.V. :- λ_{max} 247nm.

These results were consistent with this fraction being a mixture of at least three compounds of which a cyclopentadiene of type (**68**) was a major constituent.

b) Excess methyl-lithium followed by hydrogenation.

The enone-ester(**62**) (120mg.,0.54mmole) in dry tetrahydrofuran (10ml.) was stirred overnight under nitrogen with methyl-lithium (2ml. of a 2M solution in ether). Saturated ammonium chloride solution was added and the two phase mixture shaken vigorously for five minutes. The organic layer was washed with brine, dried and the solvent removed under reduced pressure. The crude product was then hydrogenated at room temperature in a homogeneous solution of $(Ph_3P)_3RhCl$ (100mg.)

in dry benzene (20ml.). After three hours the solution was removed from the hydrogenator and the volume of benzene reduced to 10ml. This solution was chromatographed on a column of alumina (20g.,grade III,neutral). Elution with 6% ethyl acetate /petrol afforded a compound of similar R_f to natural guaiol, however not identical. This was analysed by g.l.c. and found to consist of three components.

Compound	% in mixture	R_t(a)	R_t(b)	M.W.(c)
A	30	6.3	35	220
B	60	6.85	38.6	220
C	10	9.5	57.2	220
Guaiol	--	3.8		222

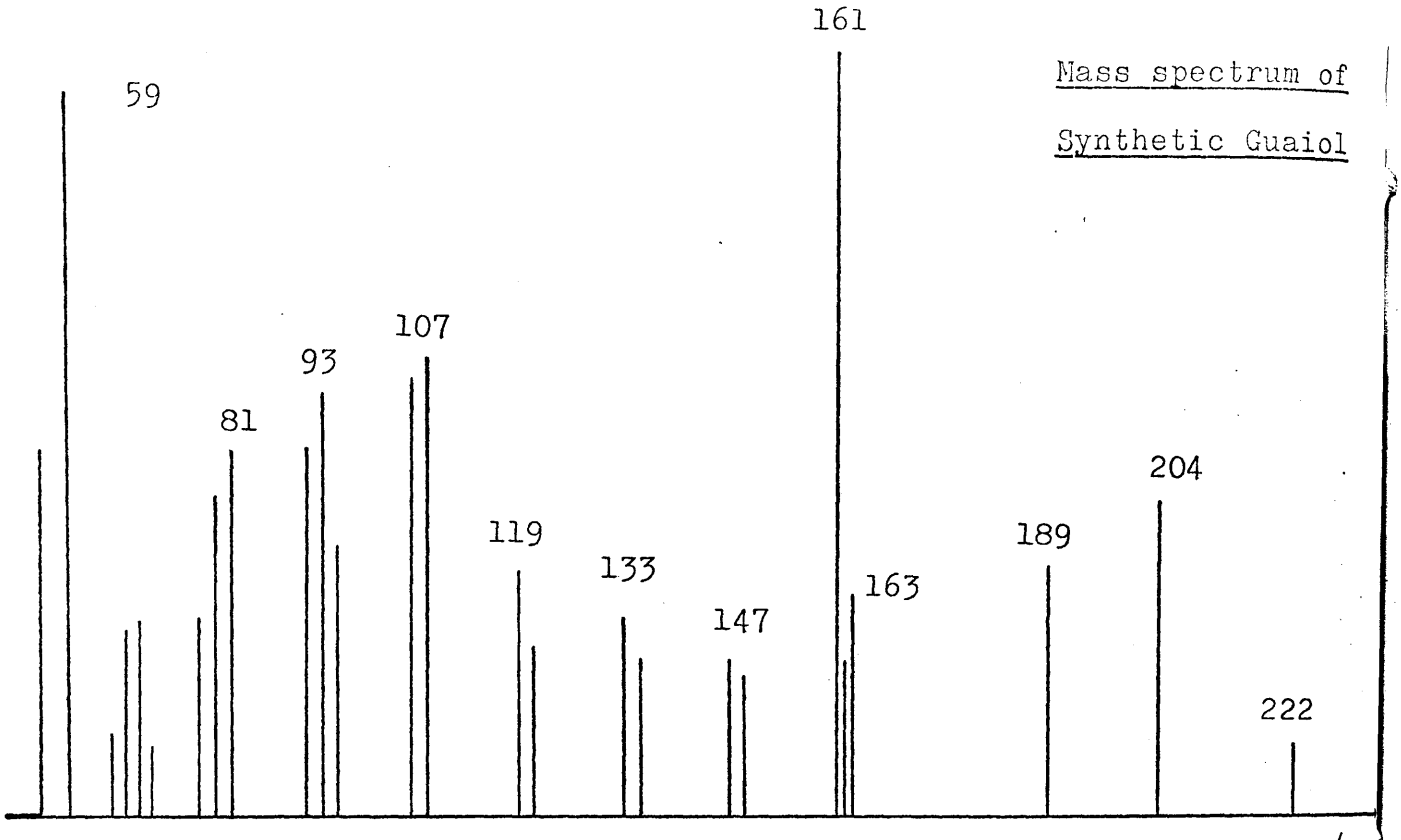
a) 1% OV 17 at 150

b) 1% OV 1 at 100

c) Combined g.c.m.s.

c) Excess MeLi / NH_4Cl / 5% Pd/C, H_2.

The enone-ester(**62**) (106mg.,0.48mmole) was treated with a solution of methyl-lithium (4mmole) and stirred overnight at room temperature. The reaction mixture was worked up as in method b) and subjected to hydrogenation in ethyl acetate over 5% Pd/C. Uptake of hydrogen was very rapid. The catalyst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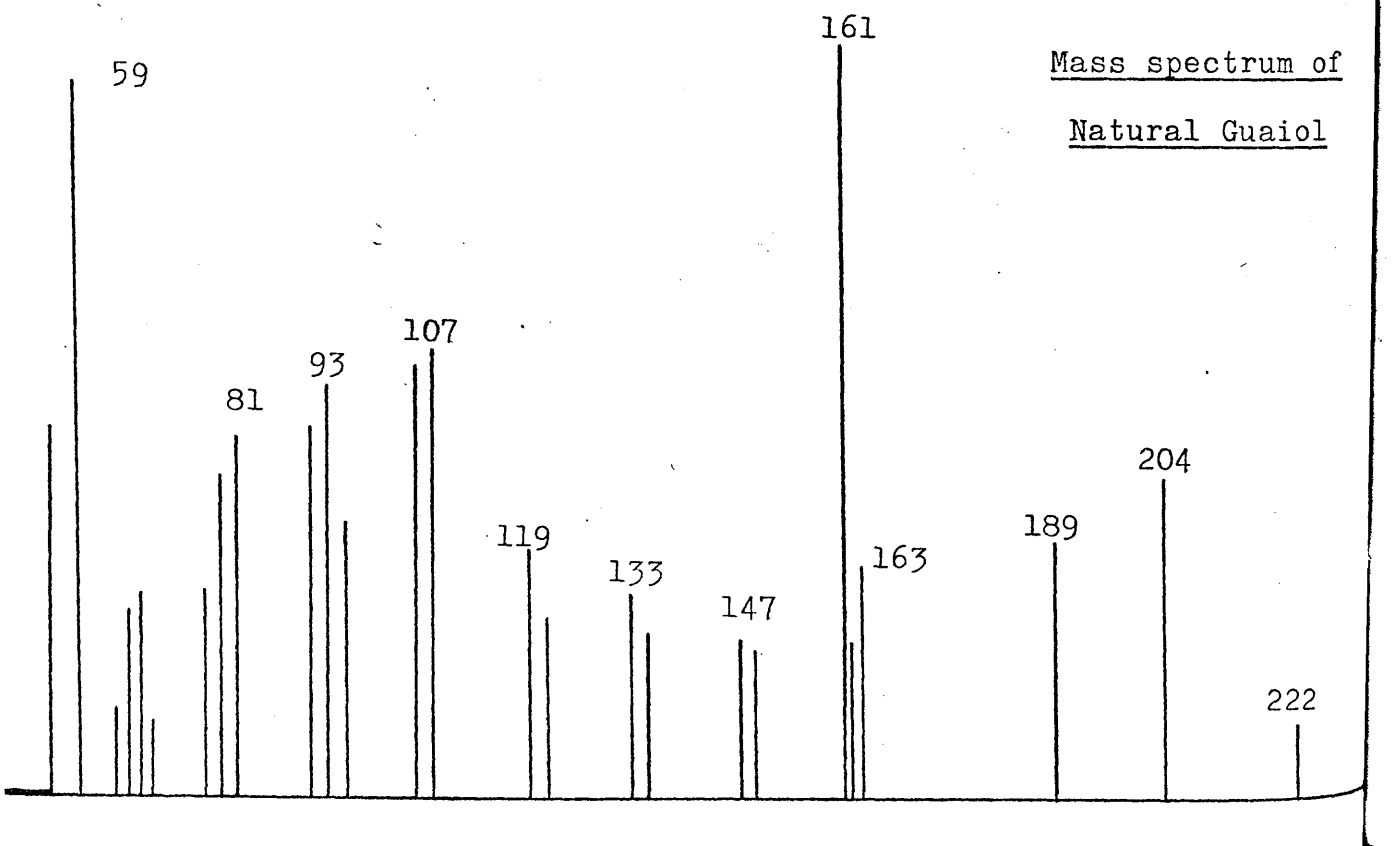
59
Mass spectrum of
Synthetic Guaiol
107
93
81
204
119
189
133
163
147
222
m/e


161
59
Mass spectrum of
Natural Guaiol
107
93
81
204
189
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163
133
147
222

was removed by filtration through celite and the solvent removed under reduced pressure. T.l.c. analysis (40% ethyl acetate/petrol) indicated that the product and natural guaiol had the same R_f value. However combined g.c.m.s. analysis showed the presence of four stereoisomers.

Compound	% in mixture	R_t(a)	R.I.	M.W.(b)
A	10	8.9	1715	222
B	25	9.7	1725	222
C	40	12.1	1775	222
D	25	12.9	1780	222
Guaiol		8.9	1715	222

a) 1% OV 17 at 125°

b) Combined g.c.m.s.

The chromatographic properties and mass spectra of A and natural guaiol were identical.

When the enone-ester(**62**) which had been enriched in one epimer, (to the extent of 70:30), was subjected to the above reaction sequence, an identical g.l.c. trace was obtained.

Dimethyl acetal of the enone(**23**).

The diketone(**23**) (150mg.) was stirred for sixteen hours at room temperature with methanol (10ml.) containing acetyl

chloride (1ml.). 1N KOH (10ml.) was added and the solution extracted with ethyl acetate (3x). Normal work up gave a brown oil which was purified by preparative t.l.c. (60% ethyl acetate /petrol) affording the acetal(**69**) (108mg.,60%) as colourless crystals. An analytical sample, m.p. 121-123°, was prepared by sublimation.(80°/0.2mm.)

Found:C,71.25;H,8.42. $C_{14}H_{20}O_3$ requires C,71.16;H,8.53%.

I.R. (CCl_4) $cm.^{-1}$:- 2830 (m), 1696 (s), 1642 (s) and 1110 (s).

N.M.R. (CCl_4) :- Singlet (3H) 6.70τ.
Singlet (3H) 6.76τ.
Multiplet (11H) 7.2 - 8.5τ.
Singlet (3H) 8.76τ.

U.V. :- λ_{max} 245nm.

M.S. :- Significant peaks at m/e 236(M^+),221,189,161,101(base).

G.L.C. :- 1 peak R_t 6.0min. on 5% QF1 at 175°(flow rate 54ml.)

Treatment of the acetal(**69**) with methyl-lithium.

The acetal(**69**) (40mg.) in ether (10ml.) was stirred at room temperature for two hours with methyl-lithium (two equivalents of a 2M solution in ether). T.l.c. analysis of an aliquot at this time indicated two polar compounds and the consumption of all starting material. Methanesulphonyl chloride

(20mg.) in ether (5ml.) was added to the suspension and the mixture stirred overnight. The reaction mixture was worked up in the normal manner and shown by t.l.c. to be a complex mixture. The route was abandoned at this point.

Attempted epoxidation of the ene-dione(**23**).

The ene-dione(**23**) (20mg.) was stirred overnight at room temperature with 30% hydrogen peroxide (10 drops), 4N NaOH (5 drops) in methanol (10ml.). Standard work up gave only acidic material.

Baeyer-Villiger oxidation of the ene-dione(**23**).

The ene-dione(**23**) (96mg.) in dry methylene chloride (5ml) was stirred at room temperature for two hours with m-chloro-perbenzoic acid (90mg.). The organic solution was washed with dilute sodium sulphite solution, dilute sodium bicarbonate solution and finally brine. On drying and solvent evaporation the crude product was obtained as a yellow oil. T.l.c. analysis (60% ethyl acetate/petrol) indicated a trace of starting material and a more polar component which was purified by preparative t.l.c.

I.R. (CCl_4) $cm.^{-1}$:- 1752(s), 1710(s), 1650(w), 1260(m), 1060(m)

N.M.R. ($CDCl_3$) :- Multiplet (less than 1H) 5.1τ.

Multiplet 6.8 - 8.4τ.

Singlet 8.4τ.

Singlet 8.6τ.

The signals at 8.4 and 8.6τ were in the ratio 3:2.

U.V. :- λ_{max} 240nm.

These results suggested that this material consisted of a mixture of the isomers (**74**) and (**75**) in the ratio 3:2.

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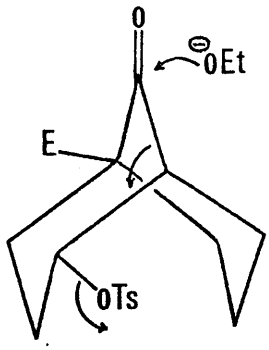
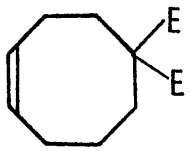
PART II

THE ACID CATALYSED CLEAVAGE OF

BICYCLO-(3,2,1)-OCT-2-EN-8-ONE

Scheme A





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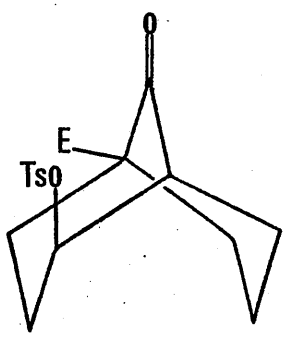
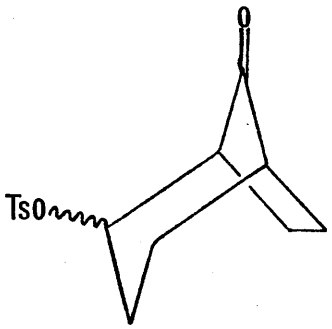


1b

INTRODUCTION

Research in the chemistry of medium and large sized rings was hindered for a long time by a lack of good synthetic routes to these compounds. The earlier methods of synthesis involved a ring closure reaction, the ease of which depended on the strain of the ring formed and the distance between the reacting sites. Although the Dieckmann[1] and Thorpe-Ziegler[2] reactions afforded rings with seven and greater than eleven carbon atoms in reasonable yield it was not until 1947, with the introduction of the acyloin[3] condensation that a good route to medium sized rings (8-11 membered) was made available.

An elegant pathway to seven, eight and nine membered rings involves the bridge fission of bridged bicyclic compounds. For example, the Beckmann[4] and Baeyer-Villiger[5] reactions convert a bridge ketone into a cyclic amino or hydroxy acid. However a reaction, studied in this department, which provides a practical route to substituted derivatives is the fragmentation of 2(endo)-substituted bicyclo-(3,n,1)-alkanes, as exhibited by the tosylate(**1a**),(Scheme A). Specifically the equatorial tosylate(**1a**) is very readily cleaved to the cyclooctene diester(**2**) whereas the axial epimer(**1b**) is unaffected by treatment with sodium ethoxide.



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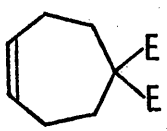

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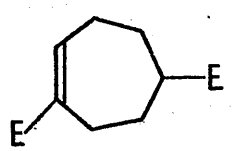

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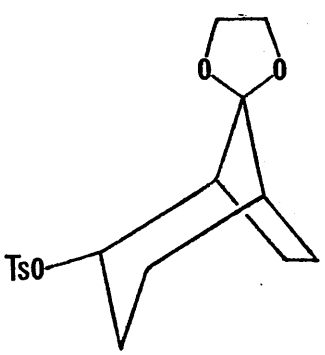

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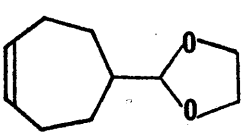

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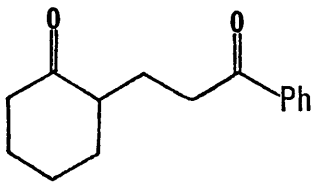
The preferential fragmentation of the 2(endo)-tosylate is due to the correct antiperiplanar relationship between the leaving group and the C-1 — C-9 bond. This geometry is required for a smooth fragmentation.[6] In the corresponding bicyclo-(3,2,1)-octane system the epimeric tosylates(**3**) can be separated by fractional crystallisation and treated independantly. It is found that the equatorial (endo) epimer undergoes a smooth fragmentation affording the diester(**4**), whereas the axial (exo) epimer yields the unsaturated diester(**5**) by a retro-Claisen reaction followed by a β-elimination of the tosyloxy group.

When a nucleophile is absent the fragmentation is suppressed,[7] i.e. when the tosylate(**3**) was subjected to acetolysis under anhydrous conditions the corresponding acetates were formed in good yield. Also, hydride induced cleavage of the acetal(**6**) to the cycloheptene(**7**) clearly shows that a carbonyl group on the bridge is not mandatory for cleavage.[8]

Although these tosylate elimination reactions can be carried out equally well on bicyclo-(3,3,1)-nonanes or bicyclo-(3,2,1)-octanes, a related cleavage which illustrates nicely the inherent ring strain in the bicyclo-(3,2,1)-oct-2-en-8-one



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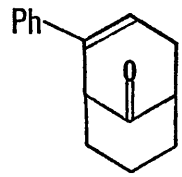

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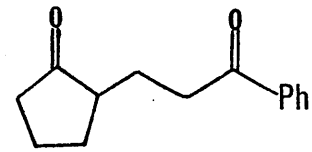

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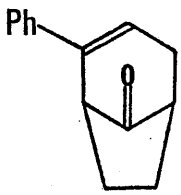

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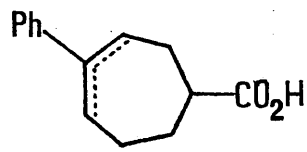

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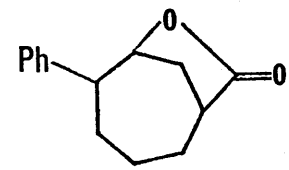

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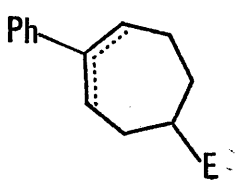

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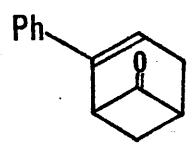

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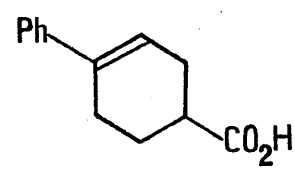

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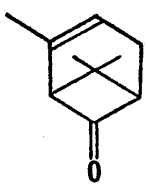

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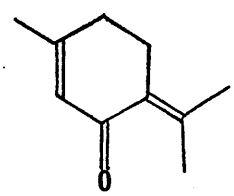

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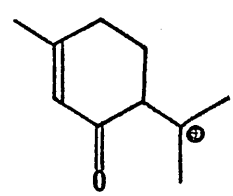

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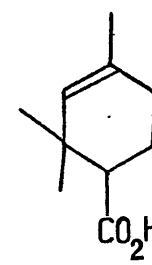

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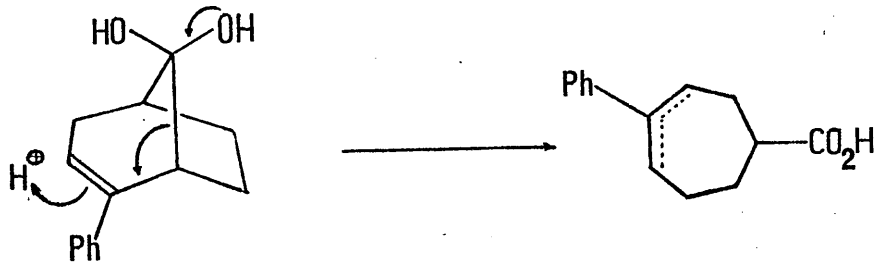
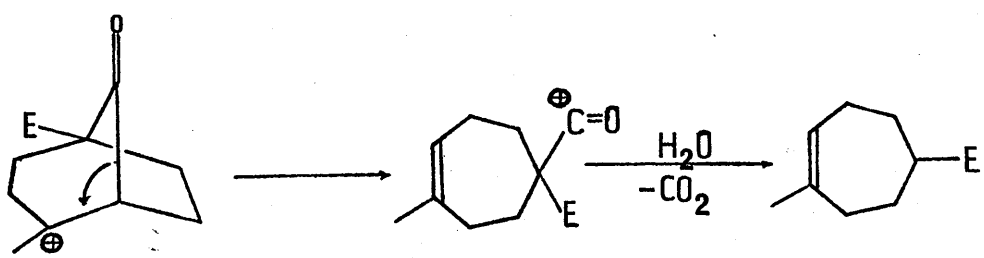
system has been described.[9] Under acid catalysis the 1,5-diketone(**8**) cyclised to the bicyclo-(3,3,1)-non-2-en-9-one(**9**), however application of the same reaction conditions to the corresponding cyclopentanone(**10**) afforded not the expected bicyclo-(3,2,1)-oct-2-en-8-one(**11**) but the cycloheptene acid(**12**) and the corresponding γ-lactone(**13**). Using acidic methanol as solvent it was possible to produce exclusively the ester(**14**). Later, it was found that under special conditions it was possible to isolate the bicyclic ketone(**11**) and establish that this compound was indeed an intermediate in the sequence.[10]

This factor of ring strain is apparent in smaller ring homologues. For example, attempts to prepare the bicyclo-(3,1,1)-hex-2-en-6-one(**15**) resulted in the unique formation of the fragmentation product, phenylcyclohexene-4-carboxylic acid(**16**).[11] The related natural product chrysanthenone(**17**) is converted under acid conditions to piperitenone(**18**) and not the expected cyclohexene carboxylic acid(**19**). This anomaly has been rationalised in terms of the stability of the tertiary carbonium ion (**20**). However on treatment with hydroxide[12] chrysanthenone undergoes a cleavage typical of βγ-unsaturated cyclobutanones forming the very same cyclohexene carboxylic acid(**19**) as expected on acid cleavage.

Scheme B



Scheme C



The mechanism for the cleavage of the bicyclo-(3,2,1)-oct-2-en-8-one has been visualised[11] as a fragmentation of the corresponding hydrate (Scheme B) followed by equilibration of the carbon - carbon double bond. Ring strain is proposed as the driving force for both hydration and subsequent cleavage. The important role of the protonation step has been highlighted by the introduction of electron donating substituents on the para position of the aromatic nucleus. In such cases the yield of cycloheptene increases whereas the introduction of a para nitro substituent reduces the yield of fragmentation products.

On the other hand, Dauben and McFarland[13] have isolated the cycloheptene ester(**21**) from the Wichterle reaction[14] of 2-carbethoxycyclopentanone, and postulated a simple acylium ion mechanism (Scheme C).

With the intention of employing this reaction in a projected synthesis of guaiol (see Part I of Thesis) and the apparent ambiguity in the reaction mechanism, it appeared worthwhile to examine the mechanistic aspects of this reaction in more detail. In particular, it was hoped that the true mechanism could be established.

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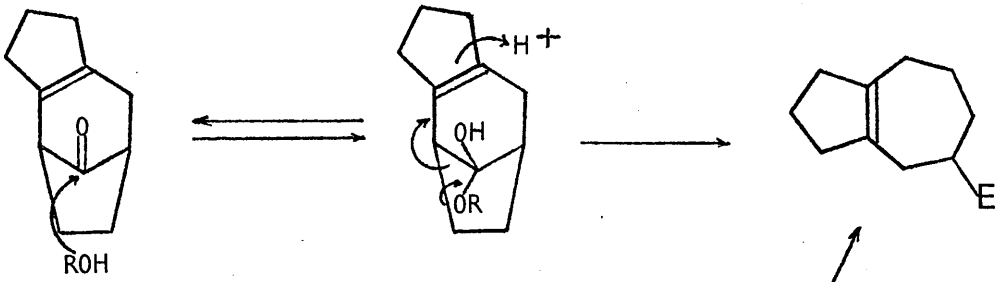
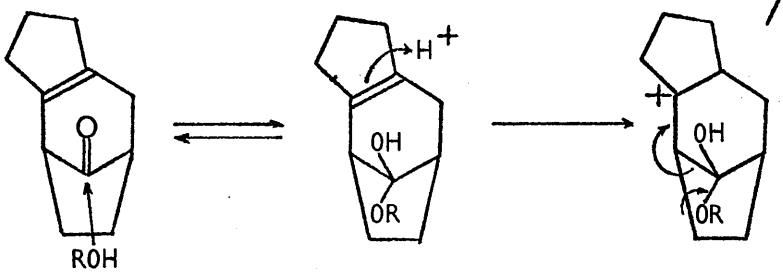
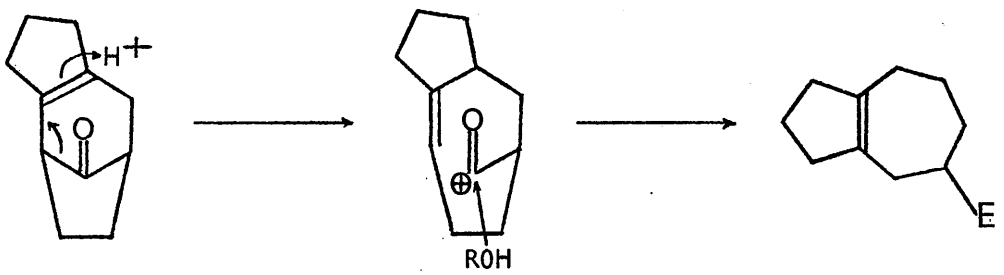
Scheme A.



Scheme B.



Scheme C.



Scheme D.

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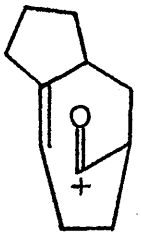
DISCUSSION

The acid catalysed bridge cleavage of a bicyclo-(3,2,1)-oct-2-en-8-one can be interpreted in terms of at least three mechanistic schemes (Schemes A, B and C). These schemes arise from the unusual strained nature of the system and in particular the tendency of the bridge ketone to become sp^3 hybridised by addition of a solvent nucleophile. This re-hybridisation has the effect of lowering the strain energy in the ring (cf. cyclopropanone ⟶ cyclopropanone hydrate.) This property is highlighted by the reluctance of the alcohol (**1**) to oxidise and of the acetal(**2**) to hydrolyse.[1] Thus in any mechanistic scheme either component of the equilibrium (Scheme D) could participate in the cleavage.

In two cases (A and B), the reaction can be described as a fragmentation in which the bridge ketone is required to become sp^3 hybridised whereas the other mechanism (C) involves a simple carbon - carbon bond cleavage to form an acylium ion, with subsequent capture of a solvent nucleophile. In an attempt to delve further into the mechanistic requirements of the cycloheptene formation, a number of questions seemed relevant.

1. If the process occurs via fragmentation of the hydrate, i.e. mechanisms A or B, will the corresponding C-8 alcohol also cleave?



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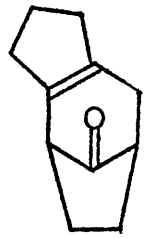

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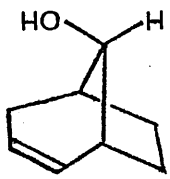

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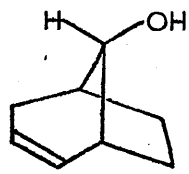

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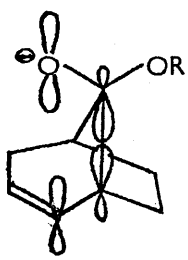

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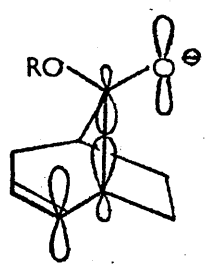

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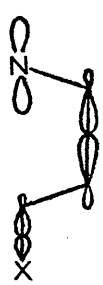

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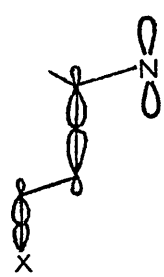


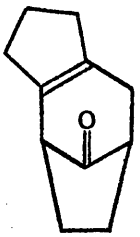
2. Is the fragmentation promoted by other electrophilic reagents - i.e. other than protons?

3. Will the ease of formation of a carbonium ion at C-2 promote the formation of cycloheptene acid derivatives?

4. Can the proposed intermediate acylium ion(**3**) be trapped?

For practical reasons, the readily available tricyclo-(6,2,1,$0^{2,6}$)-undec-2^{6}-en-11-one(**4**), which incorporates the desired functional elements, was chosen as a suitable model for study.

If the bridge ketone undergoes "carbonyl addition"[2] producing a sp^3 hybridised carbon atom, as a hydrate or hemi-ketal depending on the solvent, and the subsequent cleavage is effected by an electrofugal[3] shift of electron density, then the geometrical and first order electronic requirements should be satisfied by either the syn(**5**) or anti(**6**) alcohols. Indeed, it is only necessary to invoke participation of the oxygen lone pair and not the electrons of the oxygen - hydrogen bond. Although it is conceivable that a solvent nucleophile e.g. water or methanol could approach the bridge ketone from either face, either intermediate (**7**) or (**8**) would have the correct antiperiplanar geometry required for a smooth fragmentation. (see opposite).



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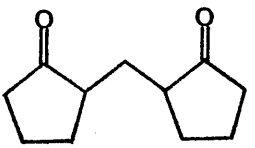

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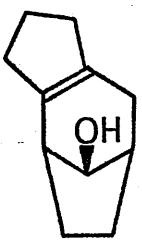

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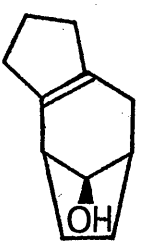

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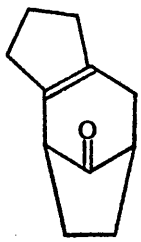
Accordingly, the enone(**4**) was prepared by acid catalysed aldol condensation of the 1,5-diketone(**10**) and purified by column chromatography. On treatment with sodium borohydride in aqueous ethanol for one hour, the enone was reduced to a single solid compound, identified as the syn alcohol(**11**). The configuration of this alcohol function was readily determined by the multiplicity of the carbinol (C<u>H</u>-OH) proton in the n.m.r. spectrum. From a molecular model of the syn isomer it is apparent that the carbinol proton would couple to both bridgehead protons producing a triplet, whereas in the anti alcohol(**12**) these protons are aligned at right angles and so no such splitting should be observed. The product from boro-hydride reduction exhibited a triplet ($J = 4Hz.$) at 6.1τ for the carbinol proton, thus confirming the syn configuration. The infra-red spectrum in dilute solution also exhibited a strong O-H $\longrightarrow \pi$ hydrogen bond at 3580 $cm.^{-1}$ which can only arise from the syn isomer. In accord with the above theory the anti alcohol(**12**) exhibited a singlet for the resonance of the carbinol proton.

The production of the syn epimer exclusively has been observed in related systems[4] and although the anti epimer(**12**) is more stable, this result merely reflects the kinetic



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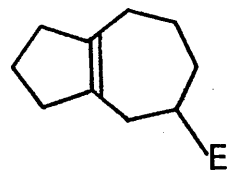

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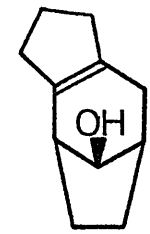

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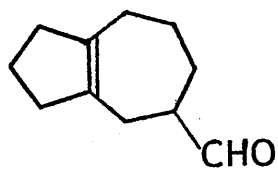

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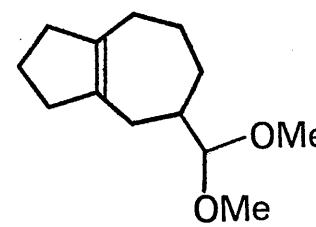

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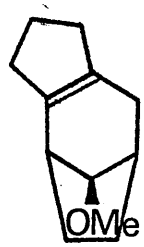

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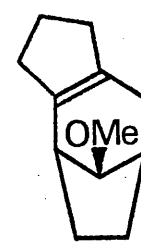
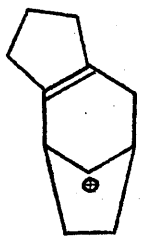


17

preference for approach from above the five-membered ring.

The ketone(**4**) has been shown to cleave to the cycloheptene ester(**13**) in refluxing acidic methanol, so the same conditions were employed on the syn alcohol(**11**). It was anticipated that the corresponding aldehyde(**14**) would be formed, which under the reaction conditions would acetalise to (**15**). On refluxing the alcohol(**11**) with methanolic sulphuric acid overnight, two compounds were formed, which could be separated by preparative t.l.c. and identified by spectral analysis. The less polar component analysed for $C_{12}H_{18}O$ and exhibited a singlet (1H) at 6.58τ and another singlet (3H) at 6.8τ. The infra-red spectrum was transparent in both hydroxyl and carbonyl regions and the only significant feature was the absorption at 2840 $cm.^{-1}$ These characteristics indicated the gross structure of the methyl ether(**16**) which, because of the singlet carbinol proton, was established as the anti isomer(**16**).

The polar component, again isolated as a colourless oil exhibited very similar spectral properties and also analysed for $C_{12}H_{18}O$. The obvious distinguishing feature was the triplet (J = 4Hz.) at 6.48τ in the n.m.r. spectrum. This signal was compatible with the carbinol proton of the syn methyl ether(**17**).



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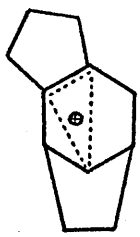

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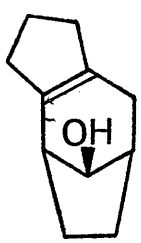


11

20

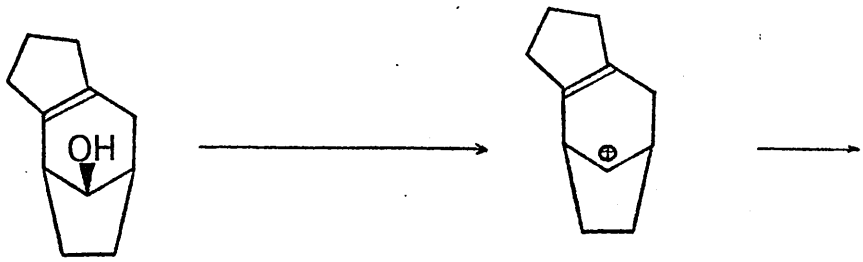
a syn
b anti

It was not possible to determine accurately the relative abundance of these epimers due to the fact that they were inseparable on g.l.c. However a rough estimate based on recovery of material suggested that these compounds were formed in the ratio anti : syn 2 : 1. No trace of carbonyl containing material was observed.

The formation of these compounds can be explained in terms of protonation of the hydroxyl function, followed by loss of water and subsequent solvent capture of the so formed carbonium ion(**18**). It was realised that this classical ion could also exist in a non-classical form(**19**) which would only solvate from the anti face. However the above results suggest that such an ion does not contribute greatly to the product distribution. Indeed, Lebel and Spurlock[4] have examined the solvolysis of the simple bicyclic tosylates(**20**) and indicated that the syn epimer(**20a**) produces products which can be derived purely from the classical ion.

When the alcohol(**11**) was refluxed in an aprotic solvent (dioxan / HCl) as before, five compounds were identified by g.l.c. analysis. Of these, three were non-polar and could be readily separated by preparative t.l.c. from the other two more polar components. The minor polar component (6%) was

Scheme E.



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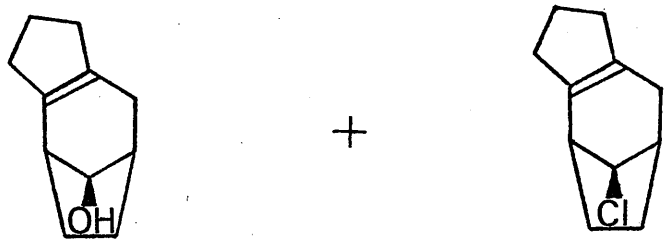

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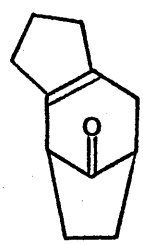

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identified as starting material while the major polar component (68%) was considered to be the anti alcohol(**12**). This assumption was based on combustion and spectral analysis. The compound analysed for $C_{11}H_{16}O$, possessed a molecular weight of 164, and exhibited a singlet (1H) at 5.96τ in the n.m.r. spectrum and a hydroxyl stretching frequency of 3627 cm^{-1} (non-bonded) in the infra-red spectrum. All these features were in accord with the structure for the anti alcohol(**12**). This anti alcohol could be oxidised with Jones reagent to the enone(**4**), thus establishing the integrity of the bicyclic skeleton.

The major non-polar material was initially difficult to identify. However the isotopic molecular weights of 184 and 182, with fragments corresponding to the loss of mass units of 35 and 37, clearly indicated the incorporation of a chlorine atom. The only other significant spectral feature was the sharp singlet (1H) at 5.8τ in the n.m.r. spectrum. Accordingly this compound was assigned the anti chloride structure (**21**). The minor non-polar components were not identified but from their infra-red spectra, appeared to be ethereal.

It would appear that this reaction can be best represented by Scheme E , involving the formation of the

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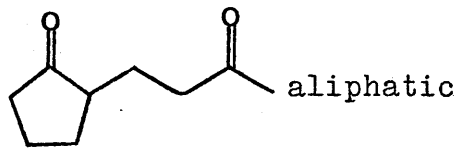

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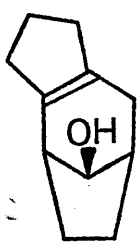

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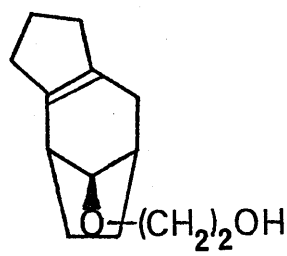

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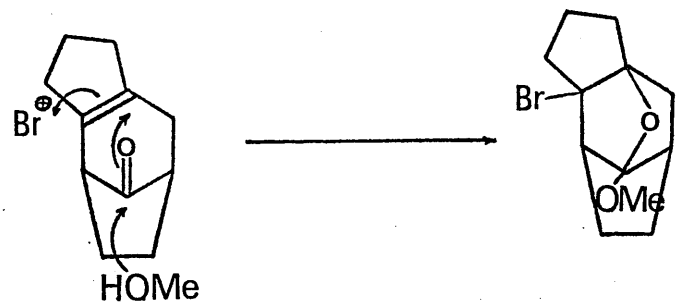
carbonium ion (**18**) which in the absence of a solvent nucleophile prefers to undergo ion-pair return rather than skeletal rearrangement which has been observed on solvolysis of the tosylates (**20**).[4] The high degree of selectivity in the ion-pair return merely reflects the greater thermodynamic stability of the anti alcohol.

In summary, the failure of both epimeric alcohols to undergo bridge fission in acid solution can be attributed to protonation of the hydroxyl function in preference to the double bond. This is in accord with the principles of hard[5] and soft acids and bases. Any reaction then appears to proceed via the corresponding carbonium ion, which is unlikely to cleave as desired.

In a study of the acid catalysed behaviour of purely aliphatic 1,5-diketones of type (**22**), it was found that only under forcing conditions (refluxing ethylene glycol) was it possible to effect bridge fission. Possibly the cleavage occurred via a high energy pathway which was being masked.

Consequently the syn alcohol(**11**) was refluxed for two hours in ethylene glycol containing a few crystals of para-toluene sulphonic acid. However, in parallel with the other results the only product identified was the glycol monoether(**23**).

Scheme F.



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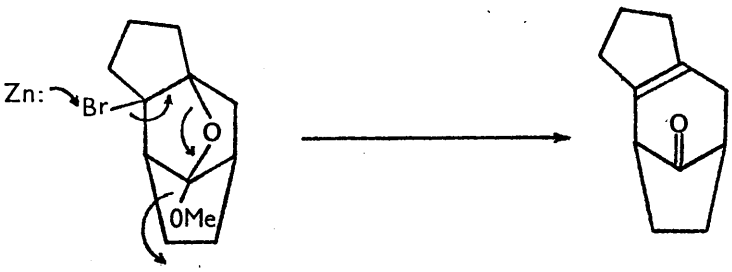
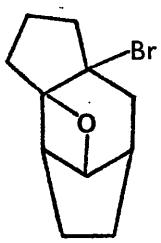
The singlet (1H) at 6.36τ in the n.m.r. spectrum again suggested the anti configuration.

In order to test the effect of a more electrophilic reagent (i.e. an agent which would readily promote the formation of a carbonium ion at C-2), the enone(**4**) was treated with bromine. When the enone was stirred in CCl_4 at room temperature for five minutes with one equivalent of bromine, a complex mixture of tars was obtained. However if methanol was employed as solvent, then even at -50°, a rapid decolourisation was observed. After normal work-up, a mobile liquid was obtained which gave a positive Beilstein test, and analysed for $C_{12}H_{17}O_2Br$. The presence of a singlet (3H) at 6.58τ in the n.m.r. spectrum clearly indicated a $-OCH_3$ group. The infra-red spectrum exhibited no obvious functionality but the sharp fingerprint region with strong C-O absorption, suggested a rigid ethereal structure.

On the basis of this spectral evidence and mechanistic intuition, the most likely structure would appear to be the bromo-acetal(**24**) which can arise according to Scheme F. Although this acetal was resistant to acid catalysed hydrolysis it was possible to re-generate the ketone(**4**) by treatment with zinc in acetic acid; a reaction used extensively in the

Scheme G.





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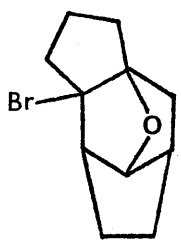

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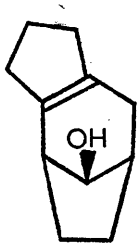

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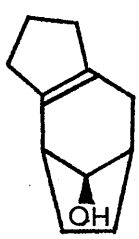

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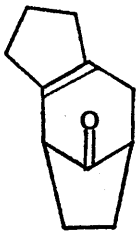
steroid field.[6] The mechanism can be formulated as shown in Scheme G.

Molecular models clearly show the close proximity of the syn oxy-anion function to the transannular double bond, thus explaining this unusual example of a transannular cyclisation in a six-membered ring as a direct consequence of the rigid geometry of the bicyclic system. The site of addition to the double bond was so chosen, as addition to C-2 would result in the formation of the highly strained 2,11-epoxy-tricyclo-(6,2,1,$0^{2,6}$)-undecane(**25**).

When the corresponding syn alcohol(**11**) was treated with bromine in a similar manner, a colourless mobile oil was again obtained. This oil exhibited a positive Beilstein test and analysed for $C_{11}H_{15}OBr$. The infra-red spectrum showed no obvious functionality and the only distinguishing feature in the n.m.r. spectrum was the triplet (1H, J = 4.5Hz.) at 5.4τ. These characteristics were in accord with the cyclic ether(**26**).

The anti alcohol(**12**) under similar circumstances produced only tarry material which was not investigated further.

This type of transannular reaction occurred every time a compound containing a syn hydroxyl function was treated with



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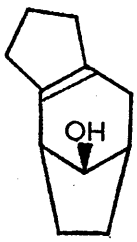

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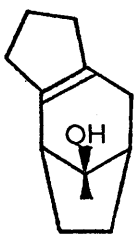

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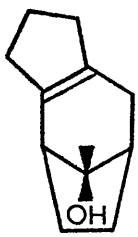

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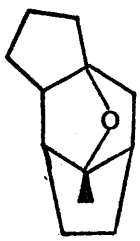

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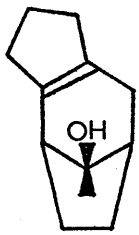
bromine. Indeed, when the enone(**4**) was treated with methyl magnesium chloride at room temperature for one hour, a single compound was obtained. By analogy with previous experiments this was assumed to be the syn alcohol(**27**) resulting from attack of the "methyl carbanion" from above the five-membered ring. Because of the absence of a carbinol proton it was not possible to discern the configuration of the alcohol from the n.m.r. spectrum. However confirmation of the syn configuration was obtained from the infra-red spectrum which exhibited a strong O-H $\longrightarrow \pi$ hydrogen bond at 3570 $cm.^{-1}$ No trace of the anti alcohol(**28**) was observed.

On low temperature treatment with bromine this compound produced a colourless mobile oil whose spectral properties were in accord with the structure(**29**). Evidently any cleavage pathway is thwarted by the preference to undergo a low energy cyclisation. In all the cases of bromine induced cyclisation the bromo-ethers so formed did not exhibit a parent ion in the mass spectrum, but always showed a strong $(M-Br)^+$ peak. This is consistent with the findings of McLafferty[7] on the mass spectral fragmentation of tertiary bromides.

The tertiary alcohol(**27**) behaved in a different manner to the secondary alcohol(**11**) when treated with acid. On



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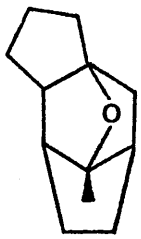

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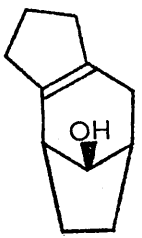
refluxing the alcohol(**27**) for three hours in methanolic acid as before, two less polar compounds of very similar chromatographic properties were obtained. By sacrificial preparative t.l.c. it was possible to isolate the major component in pure form. Unlike the previously reported example this was not the corresponding methyl ether. In fact, micro-analysis and mass spectra established that this compound was an isomer of the starting material(**27**). The infra-red spectrum exhibited no obvious functionality, although a complex finger-print region was apparent, and assuming no skeletal rearrangement had occurred the most likely structure would appear to be the cyclic ether(**30**). The minor component could not be isolated in pure form however the infra-red spectrum was transparent in both hydroxyl and carbonyl regions. The n.m.r. spectrum showed unresolved resonances between 6 and 7τ, but from this meagre evidence it was not possible to determine the structure of this compound. In any event, it was apparent from the infra-red spectrum that cleavage had not occurred. However the cleavage was not thwarted in this case by protonation and subsequent loss of the hydroxyl group, but by transannular cyclisation.

These results pose several interesting questions.



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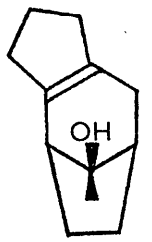
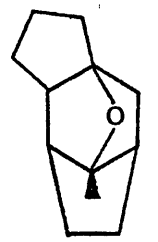


27



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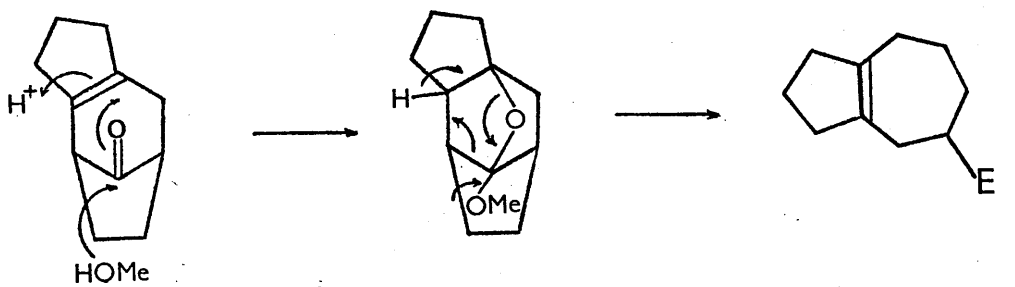
Scheme H.



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31

1. Why do the secondary alcohol(**11**) and the tertiary alcohol(**27**) behave differently in acidic methanol?

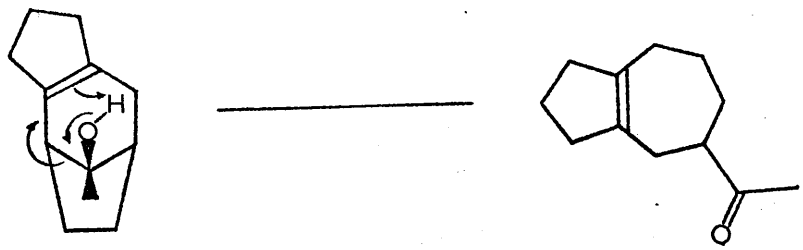
2. For the formation of the bridged ether(**30**) the double bond must presumably undergo protonation. If this is so, then why does the alcohol(**27**) not cleave to form a seven membered ring?

3. By analogy with this tertiary alcohol, is it possible that the ketone(**4**) undergoes cleavage via a corresponding bridged acetal(**31**) which undergoes electronic shifts as shown in Scheme H? This scheme, though unusual on paper is plausible on stereoelectronic grounds. The fragmentation of the ether(**30**) would not be possible due to the inability of the methyl group to donate electrons.

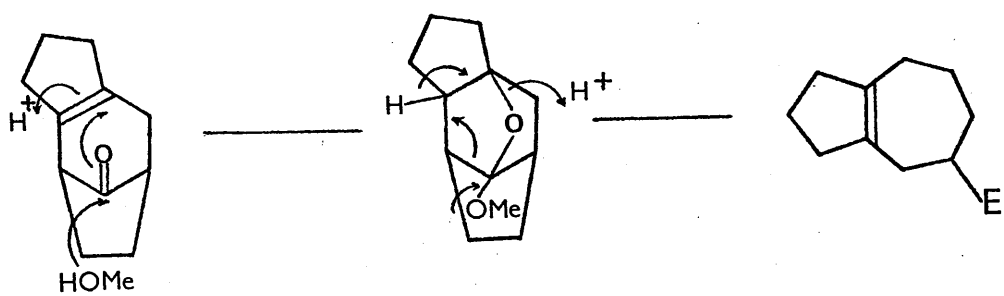
The answer to the first question is not immediately apparent. Steric factors appear to be very similar in both alcohols and in both cases protonation of the double bond appears more difficult. In any event, an equilibrium would surely be set up in which both hydroxyl and olefinic sites are protonated. Evidently any subsequent reaction occurs from different sites of protonation.

Presumably the answer to the second question lies in the

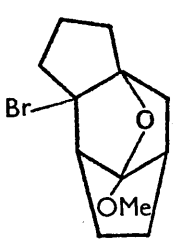
Scheme J.



Scheme H.



4 31



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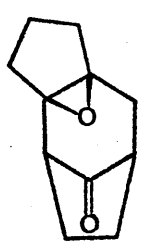


32

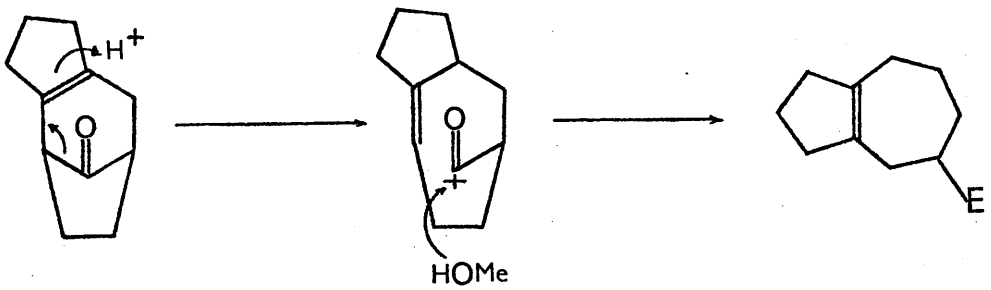
fact that the mechanism (Scheme J), which is little different from that published to explain the ketone cleavage, is incorrect. This naturally casts doubt on this published route.

The mechanism (Scheme H) has some obvious disadvantages. The bromo-acetal(**24**) has been prepared very readily by solvent assisted bromine addition to the enone(**4**). This is the bromo analogue of the proposed intermediate(**31**) and on paper this compound could break down to form a cycloheptene derivative by the same procedure, only involving a 1,2 Bromide shift.

The effect of aromatic ring substitution (in the 2 position) on the ease of fragmentation, can be explained if it is assumed that the slow rate-determining step is the break-down of the cyclic mixed acetal(**31**). Electron donating substituents on the aromatic ring would be expected to aid the hydride transfer step and hence account for the observed results. On this premise, an obvious test to distinguish this mechanism from that published is a kinetic study using CD_3OD.

Attempts to generate a carbonium ion at C-2 by boron trifluoride treatment of the epoxide(**32**) did not prove to be rewarding. Treatment of the enone(**4**) with one equivalent of m-chloroperbenzoic acid in methylene chloride proceeded very

Scheme C.



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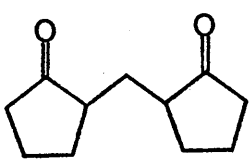

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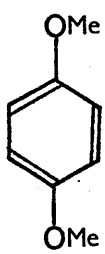
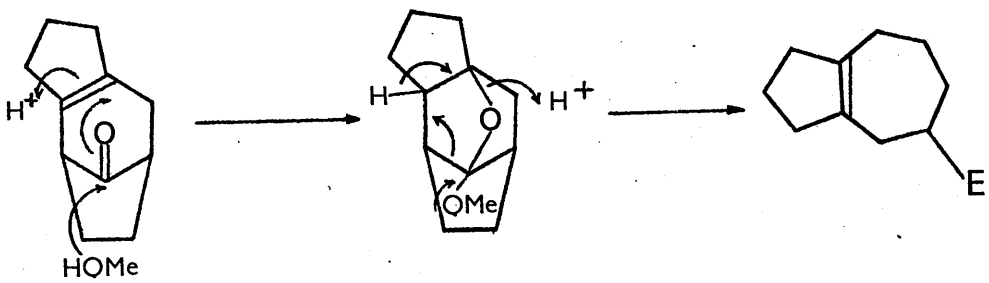


33

smoothly providing a single epoxide as a colourless solid. The carbonyl stretching frequency of this compound was very high (1765 $cm.^{-1}$) suggesting some kind of interaction with the epoxide ring, and because of this and by analogy with similar compounds[8] the epoxide was considered to have the configuration as shown. The absence of a low field proton in the n.m.r. spectrum ensured that Baeyer-Villiger oxidation had not occurred. On stirring the epoxide with BF_3/etherate, however, a complex mixture of products was obtained. The infra-red spectrum of this mixture was transparent in the carbonyl region, and consequently was not investigated further.

The enone(**4**) was prepared by aldol cyclisation of the 1,5-diketone(**9**) in p-toluenesulphonic acid / benzene. If the cleavage of the enone occurred via an acylium ion (Scheme C), it would not be unreasonable to expect that under these conditions this acylium ion could be formed and be trapped by Friedel-Crafts acylation of the benzene ring. The fact that no acylated benzene was isolated in the aldol reaction, may merely reflect the difficulty in acylating a non-activated aromatic nucleus. Accordingly the enone(**4**) was refluxed overnight in hydroquinone dimethyl ether(**33**) containing a few

Scheme H.



crystals of p-toluenesulphonic acid from which the water of crystallisation had been removed. T.l.c. analysis of the mixture the following morning, however, indicated the presence of only starting materials.

Although a completely satisfactory mechanistic conclusion has not been attained, Scheme H represents at present the best explanation for the results obtained.

Tricyclo-(6,2,1,$0^{2,6}$)-undec-2^{6}-en-11-one (**4**).

For the synthesis of this compound, see Part I, p.38.

2-(2'-Oxocyclopentylmethyl) cyclopentanone (**10**).

For the synthesis of this compound, see Part I, p.38.

Syn-tricyclo-(6,2,1,$0^{2,6}$)-undec-2^{6}-en-11-ol (**11**).

The enone(**4**) (160mg., 0.98mmole) in ethanol(10ml.) containing water(1ml.) was stirred with excess sodium borohydride at room temperature for one hour. After this time, the reaction was neutralised (dilute HCl) and thoroughly extracted with ether. The organic extract was dried and the ether evaporated affording only the syn alcohol(**11**), 140mg., 86%, as a colourless solid. An analytical sample (m.p. 51-52.5°) was prepared by sublimation. (70°/0.5mm.)

Found:-C,80.26;H,9.55. $C_{11}H_{16}O$ requires C,80.44;H,9.82%.

I.R. (CCl_4) $cm.^{-1}$:- 3634(w), 3580(m), 1170(m) and 1082(s).

N.M.R. (CCl_4) :- Triplet (J = 4Hz.) (1H) 6.1τ.

Multiplet (15H) 7.4 - 8.8τ.

M.S. :- Significant peaks at m/e 164(M^+),146,133,118(base),91.

G.L.C. :- 1 peak R_t 5.6min. on 10% PEGA at 140°(flow rate 36ml./min.

Syn alcohol(**11**) in methanol / HCl.

The alcohol(**11**) (786mg., 4.8mmole) was refluxed overnight in methanol(30ml.) containing concentrated hydrochloric acid (1ml.) The methanol was removed under reduced pressure and the dark solution taken up in ether, washed with dilute sodium bicarbonate solution, then brine. The solution was dried and the ether evaporated, yielding a dark brown oil, (732mg.) This oil (182mg.) was chromatographed on thin layer plates (10% ethyl acetate/petrol) affording the two major components as colourless oils.

Less polar anti methoxide (**16**) :- b.p. 60°/0.9mm.

Found:-C,80.63;H,9.92. $C_{12}H_{18}O$ requires C,80.85;H,10.18%.

I.R. (CCl_4) $cm.^{-1}$:- 2840(m), 1370(m), 1202(m) and 1104(s).

N.M.R. (CCl_4) :- Singlet (1H) 6.58τ.

Singlet (3H) 6.80τ.

Multiplet (14H) 7.4 - 8.6τ.

M.S. :- Significant peaks at m/e 178(M^+),146,131,118(base),91.

G.L.C. :- Analysis of the two epimers indicated one symmetrical peak R_t 8.0 min. on 10% PEGA at 125° (flow rate 42ml./min.)

More polar syn methoxide (**17**) :- b.p. 60°/0.9mm.

Found:-C,80.58;H,10.08. $C_{12}H_{18}O$ requires C,80.85;H,10.18%.

I.R. (CCl_4) :- 2840(m), 1368(m), 1224(s) and 1100(m).

N.M.R. (CCl_4) :- Triplet (J = 4Hz.) (1H) 6.48τ.

Singlet (3H) 6.75τ.

Multiplet (14H) 7.4 - 8.6τ.

M.S. :- Significant peaks at m/e 178(M^+),146,131,118,71(base).

Syn alcohol(**11**) in ethylene glycol/p-toluenesulphonic acid.

The alcohol(**11**) (104mg., 0.63mmole) was refluxed for one hour in ethylene glycol(10ml.) containing a few crystals of p-toluenesulphonic acid. The solution was poured into 2N sodium hydroxide solution and extracted with ether. The organic phase was washed thoroughly with water, dried and evaporated to a dark brown oil (98mg.) T.l.c. analysis (30% ethyl acetate/petrol) indicated a complex mixture containing one major component which could be purified by preparative methods. An analytical sample (b.p. 140°/1mm.) was prepared by short-path distillation.

Found:-C,74.92;H,9.59. $C_{13}H_{20}O$ requires C,74.96;H,9.68%.

I.R. (liquid film) :- 3600-3000(broad),1100(s),1060(s),886(m).

N.M.R. (CCl_4) :- Singlet (1H) 6.36τ.

Multiplet (4H) 6.4 - 6.6τ.

Multiplet (15H) 7.4 - 8.6τ containing a singlet at 8.0τ (exchangeable).

M.S. :- Significant peaks at m/e 208(M^+),146,131,118(base),91. From this data, this compound was considered to be the glycol monoether(**23**) with the anti configuration.

Syn alcohol(**11**) in dioxan / HCl.

The syn alcohol(**11**) (134mg., 0.8mmole) was refluxed overnight in dioxan(20ml.) containing concentrated HCl(1ml.) The green solution so formed was neutralised (NaOH) and extracted with ether. Normal work-up gave a yellow oil(130mg.) which was analysed by g.l.c. (10% PEGA at 125°, flow rate 40ml./min.) and found to contain five components.

Compound	R_t (min.)	% abundance	identification
A	3.25	1	-
B	4.25	20	(**21**)
C	7	4	-
D	9.5	6	(**11**)
E	15	68	(**12**)

The polar components (D and E) could be separated from the

non-polar components (A,B and C) by preparative t.l.c. (30% ethyl acetate/petrol). Further separation of the non-polar components (44mg.) was achieved in pentane as solvent. Compound B was isolated as a colourless mobile oil (b.p. 100°/16mm.) and identified as the anti chloride(**21**). A positive Beilstein test was established.

Found:-C,72.49;H,7.98. $C_{11}H_{15}Cl$ requires C,72.31;H,8.28%.

I.R. (liquid film) $cm.^{-1}$:- 1235(m), 1220(w), 910(m), 815(m) and 747(s).

N.M.R. (CCl_4) :- Singlet (1H) 5.8τ.
Multiplet (14H) 7.2 - 8.8τ.

M.S. :- Significant peaks at m/e 184(M^+),182(M^+),147,145,119 117,105, and 91(base peak).

Compound C was not identified due to shortage of material but appeared to be ethereal.

I.R. (liquid film) $cm.^{-1}$:- 1100(s).

Compound E could be isolated by multiple elution preparative chromatography (10% ethyl acetate/petrol) and characterised as the anti alcohol(**12**). An analytical sample (m.p. 87°- 88.5°) was prepared by sublimation. (60°/0.5mm.)

Found:-C,80.54;H,9.67. $C_{11}H_{16}O$ requires C,80.44;H,9.82%.

I.R. (CCl_4) :- 3627(m), 3560-3400(w), 1084(m), 1066(m) 1023(s).

N.M.R. ($CDCl_3$) :- Singlet (1H) 5.96τ.

Multiplet (15H) 7.4 - 8.8τ.

M.S. :- Significant peaks at m/e 164(M^+),146,133,118(base),91.

Oxidation of anti alcohol(**12**).

The anti alcohol(**12**) (58mg., 0.36mmole) in acetone(5ml.) was treated with Jones reagent (8N), until the red colour persisted. Water was added and the solution extracted thoroughly with ethyl acetate. The organic extract was washed free of chromium salts, dried and evaporated affording the enone(**4**) (31mg., 54%) as a colourless oil. The identity of (**4**) was established by chromatographic and spectral comparison.

Reaction of tricyclo-(6,2,1,$O^{2,6}$)-undec-2^6-en-11-one(**4**) with bromine.

a). In CCl_4 at room temperature.

The ketone(**4**) (100mg., 0.62mmole) in CCl_4(5ml.) was stirred for five minutes with a solution of bromine in CCl_4 (1ml. of a 1M solution). The solution was washed with dilute sodium thiosulphate solution, brine and finally dried. Removal of the solvent gave a yellow gum, which on t.l.c. analysis

(20% ethyl acetate/petrol) indicated a complex mixture. This was not investigated further.

b). In methanol at -50°.

A solution of the ketone(**4**) (480mg., 3mmole) in dry methanol(15ml.) was cooled to -50° in an acetone/solid CO_2 bath. To this stirred solution, was added over two minutes, a solution of bromine in methanol (10ml. of a 0.2M solution) and the mixture allowed to come to room temperature. The solvent was evaporated and the residue taken up in ether and washed with dilute sodium thiosulphate solution and brine. Removal of the ether afforded the crude product (810mg.) which was chromatographed (20% ethyl acetate/petrol) yielding (**24**) as a colourless oil b.p. 90°/0.4mm.(320mg., 40%). A positive Beilstein test was established.

Found:-C,53.36;H,6.33. $C_{12}H_{17}O_2Br$ requires C,52.84;H,6.27%.

I.R. ($CHCl_3$) $cm.^{-1}$:- Sharp fingerprint absorptions and C-O stretch. 2840(w), 1340(s), 1115(s) and 870(s).

N.M.R. ($CDCl_3$) :- Singlet (3H) 6.58τ.
Multiplet (14H) 7.4 - 8.4τ.

M.S. :- No parent ion but significant peaks at m/e 193,161, 133(base peak),105 and 91.

G.L.C. :- 1 peak R_t 6.75min. on 5% QF1 at 125°(flow rate 44ml)

Attempted acid hydrolysis of 2-bromo-11-methoxy-6,11-epoxy-tricyclo-(6,2,1,$0^{2,6}$)-undecane (**24**).

The mixed acetal(**24**) (12mg., 0.046mmole) was refluxed overnight in acetone(5ml.) containing a few crystals of p-toluenesulphonic acid. T.l.c. analysis the following morning indicated that the major component in the mixture was starting material.

Treatment of (**24**) with zinc / acetic acid.

The mixed acetal(**24**) (108mg., 0.42mmole) was refluxed overnight in acetic acid(5ml.) containing powdered zinc(100mg). The zinc was removed by filtration through celite and the solvent evaporated under reduced pressure. The residue was chromatographed on thin layer plates (20% ethyl acetate/petrol) affording starting material(15mg.) and a more polar component (48mg.), identified as the enone(**4**) by comparison of spectral and chromatographic data.

2-Bromo-6,11-epoxytricyclo-(6,2,1,$0^{2,6}$)-undecane (**26**).

The syn alcohol(**11**) (72mg., 0.44mmole) in methanol(5ml.) was stirred for five minutes with a solution of bromine in methanol (4ml. of a 1.25M solution, 0.5mmole). The solvent

evaporated under reduced pressure and the residue purified by preparative t.l.c. (20% ethyl acetate / petrol) affording (**26**) (85mg., 80%) as a colourless mobile oil. An analytical sample (b.p. 100°/0.8mm.) was prepared by short-path distillation. A positive Beilstein test was established.

Found:-C,54.25;H,6.09. $C_{11}H_{15}OBr$ requires C,54.32;H,6.22%.

I.R. (CCl_4) $cm.^{-1}$:- 1104(m), 1041(s) and 862(m).

N.M.R. (CCl_4) :- Triplet (J = 4.5Hz.) (1H) 5.4τ.

Multiplet (14H) 7.5 - 8.5τ.

M.S. :- No parent ion at m/e 243, but significant peaks at m/e 163$(M-Br)^+$,145,135,91 and 67.

Anti-11-methyltricyclo-(6,2,1,0)-undec-2^6-en-11-ol (**27**).

The enone(**4**) (296mg., 1,9mmole) in dry ether(10ml.) was stirred at room temperature for one hour with methylmagnesium chloride (0.7ml. of a 3M solution in tetrahydrofuran, 2.1mmole) The solution was acidified (1N HCl) and extracted with ethyl acetate. After drying and solvent evaporation the product, a colourless mobile oil, was examined by g.l.c. and found to be a single compound. (248mg., 74%). An analytical sample was prepared by short-path distillation. (b.p. 60°/0.2mm.)

Found:-C,80.69;H,9.95. $C_{12}H_{18}O$ requires C,80.85;H,10.18%.

I.R. (CCl_4) $cm.^{-1}$:- 3570(m),1380(s),1132(s),1020(s) and 932(s).

N.M.R. (CCl_4) :- Multiplet (15H) 7.3 - 8.6τ.

Singlet (3H) 8.8τ.

M.S. :- Significant peaks at m/e 178(M^+),135(base),117,108,91.

G.L.C. :- 1 peak R_t 10.6min. on 10% PEGA at 125°(flow rate 34ml./min.)

On the basis of these data this compound was assigned the syn structure(**27**).

Syn alcohol(**27**) in methanol / HCl.

The alcohol(**27**) in methanol(20ml.) containing hydrochloric acid(1ml.) was refluxed for three hours and worked up in the normal manner. T.l.c. analysis(20% ethyl acetate/petrol) indicated a trace of starting material and two less polar compounds. By sacrificial preparative t.l.c. it was possible to purify the major component to analytical purity.

Found:-C,80.68;H,10.12. $C_{12}H_{18}O$ requires C,80.85;H,10.18%.

I.R.(CCl_4) $cm.^{-1}$:- 1380(m), 1165(s), 1135(s) and 920(s).

N.M.R. (CCl_4) :- Singlet (3H) 8.7τ.

M.S. :- Identical to the alcohol(**27**).

G.L.C. analysis of the crude mixture showed the major product(**30**) R_t 4min.(65%) and the minor product R_t 4.8min.(35%) on 10%PEGA at 125°(flow rate 34ml./min.)

2-Bromo-11-methyl-6,11-epoxytricyclo-(6,2,1,$0^{2,6}$)-undecane (**29**).

The alcohol(**27**) (37mg., 0.21mmole) in methanol(5ml.) was stirred for ten minutes with a solution of bromine in methanol (2ml. of a 1.25M solution, 0.25mmole). The solvent was removed under reduced pressure and the residue purified by preparative t.l.c. (20% ethyl acetate/petrol) affording the bromo-ether(**29**) (41mg., 76%) as a colourless mobile oil. (b.p. 60°/0.3mm.) A positive Beilstein test was again shown. Found:-C,55.83;H,6.66. $C_{12}H_{17}OBr$ requires C,56.05;H,6.66%.

I.R. (liquid film) $cm.^{-1}$:- 1380(m),1023(s),910(m) and 860(s).

N.M.R. (CCl_4) :- Multiplet (14H) 7.6 - 8.5τ.
Singlet (3H) 8.6τ.

M.S. :- No parent ion at m/e 257 but significant peaks at m/e 177(M-Br,base),159,133,105,91,79.

Epoxidation of tricyclo-(6,2,1,$0^{2,6}$)-undec-2^{6}-en-11-one (**4**).

The ketone(**4**) (150mg., 0.92mmole) in dry chloroform(15ml) was stirred at room temperature with m-chloroperbenzoic acid (150mg., 1.1mmole) for thirty minutes, when an aliquot, analysed by t.l.c., indicated the completion of the reaction. The chloroform solution was washed with dilute sodium bisulphite solution, sodium bicarbonate solution (2x), and finally brine.

Evaporation of the organic solvent left the crude epoxide(**32**) as a colourless viscous oil. Purification by preparative t.l.c. (40% ethyl acetate/petrol) and sublimation afforded an analytical sample (90mg., 55%), m.p. 58-59°.

Found:-C,74.41;H,8.11. $C_{11}H_{14}O_2$ requires C,74.13;H,7.92%.

I.R. (CCl_4) $cm.^{-1}$:- 1765(s), 1090(m) and 920(m).

N.M.R. (CCl_4) :- Nothing below 7.2τ.

M.S. :- Significant peaks at m/e 178(M^+),136,119,105,91(base).

G.L.C. :- 1 peak R_t 11.25min. on 5% QF1 at 175°(flow rate 20ml)

Treatment of 2,6-epoxytricyclo-(6,2,1,$0^{2,6}$)-undecan-11-one(**32**) with boron trifluoride/etherate.

The epoxyketone(**32**) (48mg., 0.28mmole) in dry benzene (10ml.) was stirred at room temperature for two hours with boron trifluoride/etherate (5 drops). The solution turned dark green after this period. Chromatographic analysis (t.l.c. - 40% ethyl acetate/petrol and g.l.c. - 5% QF1 at 175°, flow rate 20ml./min.) indicated a complex mixture of at least three major components. An infra-red spectrum of the crude mixture showed the carbonyl region to be transparent; consequently the mixture was not investigated further.

Attempted trapping of the acylium ion of Scheme C.

p-Toluenesulphonic acid(250mg.) was refluxed for two hours on a water separator with benzene(10ml.) After this time the solvent was removed under reduced pressure and the anhydrous acid added to a solution of the enone(**4**) (1.02g.) in hydroquinone dimethyl ether(**33**) (8.82g.). This mixture was refluxed overnight, diluted with ether, and worked up in the normal manner. T.l.c. analysis (20% ethyl acetate/petrol) however, indicated the presence of only starting materials.

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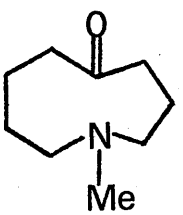
PART III

A RE-INVESTIGATION OF THE REDUCTION AND HYDROLYSIS OF UNSATURATED MEDIUM RING GEM-DIESTERS



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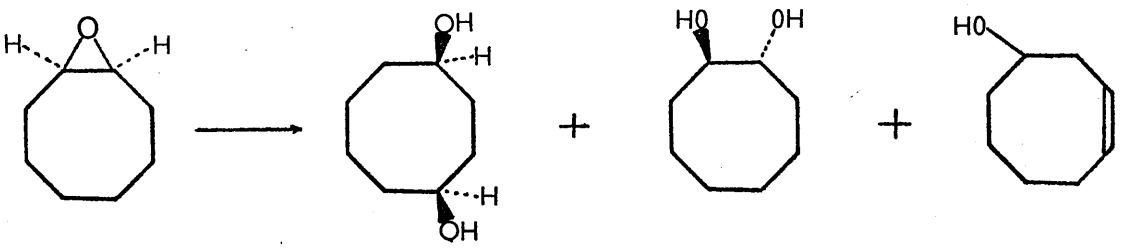
INTRODUCTION

The chemistry of medium size rings (eight to eleven membered) is unique in that these compounds exhibit special properties as a direct consequence of their molecular geometry. One of the most important features of this is the possibility that in certain conformations, opposite sides of the ring can come into close proximity to each other. This property has been used to explain a number of anomalous spectroscopic observations. For example, the infra-red spectrum of 1-methyl -1-azacyclooctan-5-one(**1**) clearly indicates that ground state interactions between the lone pair electrons on nitrogen and the carbon atom of the carbonyl group are important.[1] In acid solution, the electron drift is completed and a full single bond between these two sites is formed. This type of trans-annular reaction has been found to be very common in medium size rings, and as expected ring closure reactions abound. Indeed the biosynthesis of several natural products have been shown to occur via similar transannular cyclisations.[2]

Such transannular reactions, in general, can be conveniently classified according to the electronic nature of the transition state through which they proceed. Accordingly, by far the greatest number of transannular reactions occur under conditions which are generally accepted

Scheme A.



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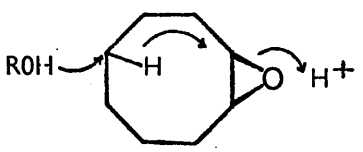
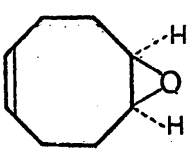
Scheme B.





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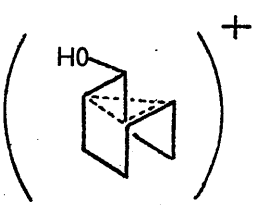

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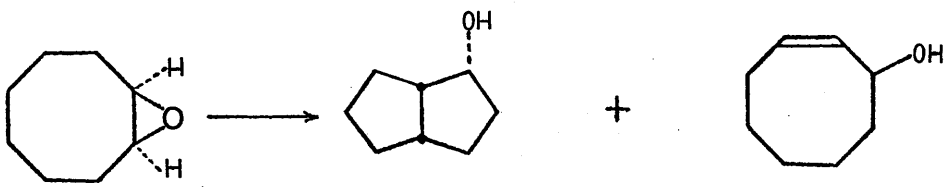
to proceed via carbonium ion intermediates. Perhaps the best example to illustrate this, is the systematic study carried out in the early 1950's by Cope and his co-workers, on the formolysis of the cycloalkene oxides. Cis-cyclooctene-1,2-oxide(**2**), on treatment with formic acid, and subsequent hydrolysis, gives rise to at least eight products. (Scheme A). The explanation for this involves a number of simple trans-annular hydride migrations. (Scheme B).[3]

Another type of transannular reaction (not involving hydride shifts) is possible; namely the shift of a pair of electrons from a double bond resulting in the formation of a single bond across the ring. Specifically when cis-cis-cyclo-octa-1,5-diene monoepoxide(**3**) is solvolysed under conditions which lead to a transannular hydride shift in the epoxide(**2**), then all the bicyclic products can be explained by simple double bond migration, and no hydride shift need be invoked.[4] The non-classical ion(**4**) has been proposed as a possible intermediate.

On the other hand, reactions which proceed via carbanions or carbenes are comparatively rare. Using the example of cis-cyclooctene-1,2-oxide(**2**) again, under the action of strong base, lithium diethylamide, it undergoes predominantly an

Scheme C.



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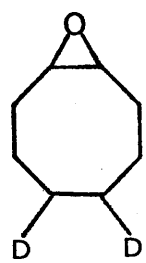

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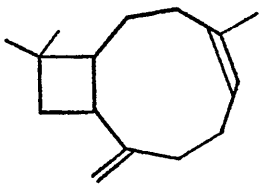
intramolecular alkylation with the formation of endo-cis-bicyclo-(3,3,0)-octan-2-ol(**5**).(Scheme C). Two different pathways for this reaction appear possible.[5]

1. The base removes a proton from the carbon atom located across the ring from the epoxide with concerted opening of the epoxide by the carbanion so formed. If the opening proceeds with Walden inversion then the cis-oxide would give rise to the endo-alcohol, as found.

2. The base removes the proton from the carbon atom of the epoxide and this is followed by fission of the C-O bond. This results in the formation of a carbenoid species. A valence bond can then be formed to the carbon atom across the ring with transfer of a hydrogen atom to the carbenoid centre. The sequence must presumably proceed in a concerted manner to explain the single stereoisomer produced. Support for this concerted carbenoid intermediate was obtained from the deuterated epoxide(**6**), which on treatment with lithium diethylamide afforded the bicyclic alcohol(**5**) containing 1.97 atoms of deuterium per molecule, indicating that no deuterium atoms had been removed from C-5 or C-6 during the reaction.

A much more unusual transannular reaction has been claimed by previous workers in this department.[6] In the course



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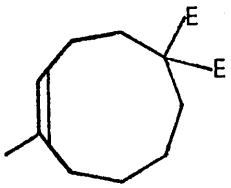

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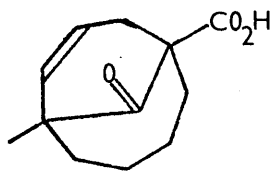

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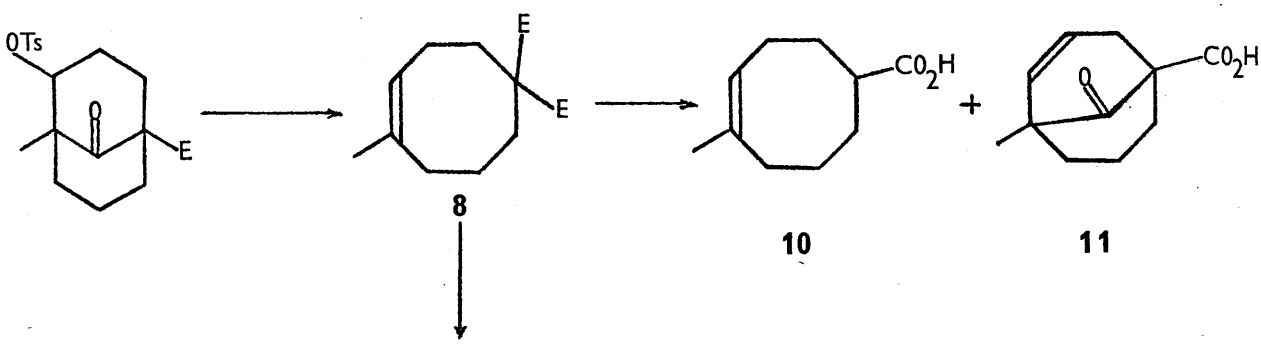
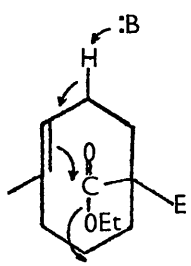


Scheme E.



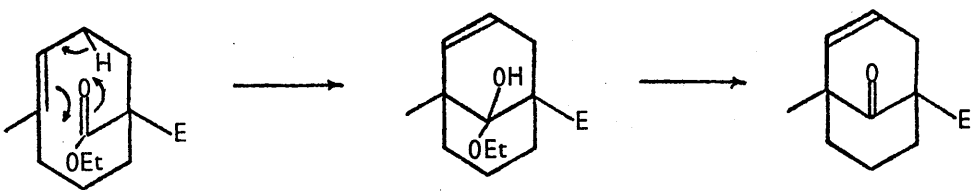
of a projected synthesis of isocaryophyllene(**7**) (Scheme D)- they examined the hydrolysis and reduction of the cyclooctene and cyclononene gem-diesters(**8**) and (**9**). The cyclooctene diester(**8**) was reported to undergo hydrolysis and decarboxylation to the acid(**10**) but also afforded about 5% of the acid(**11**). More surprisingly reduction with lithium aluminium hydride was reported to yield ONLY the bicyclic diol(**12**). The intermediate presumed in both reactions was the bicyclo-(3,3,1)-non-2-en-9-one ester(**13**), formed by a transannular acylation.

Alkaline hydrolysis of the cyclononene gem-diester(**9**) appeared to give a much greater yield of cyclised product(**14**), and this was apparently consistent with the fact that transannular reactions are more likely in cyclononenes than in cyclooctenes.

Two mechanisms can be considered for these processes:-

1. Base catalysed:- If base removes the weakly activated allylic proton and the carbanion so formed behaves as shown in Scheme E, then this will account for the formation of the bicyclic material. An examination of molecular models clearly shows that the flexibility of the cyclooctene ring allows an ester group to approach very close to the double bond, thus permitting such a pathway.

Scheme F.



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2. Thermal:- It is conceivable that the base is incidental and that heat induces an ene-reaction[7] as shown in Scheme F. This process leads via (**15**) to the bridged keto-ester(**13**) which thereafter undergoes hydrolysis or reduction, according to the reaction conditions employed.

With the dearth of established base-catalysed trans-annular reactions these transformations seemed sufficiently unusual to justify re-investigation.

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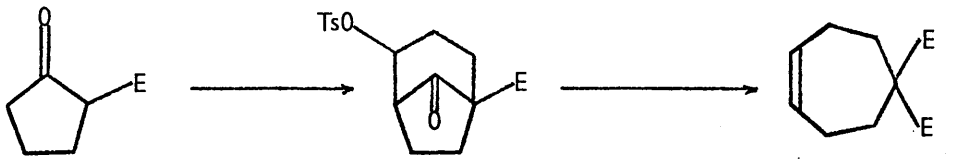
Scheme A.



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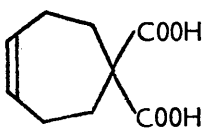

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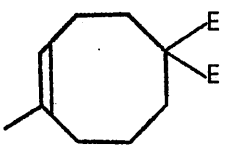

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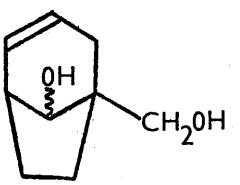

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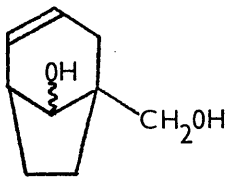
DISCUSSION

Although the previous workers had not examined the analogous cycloheptene gem-diester, it was decided to extend the scope of the investigations to include this case.

The gem-diester(**1**) could be prepared by acrolein annelation of 2-carbethoxycyclopentanone, ring closure, and ethoxide induced cleavage of the derived equatorial tosylate. (Scheme A). In this case, the equatorial tosylate could be easily purified by fractional crystallisation.

The alkaline hydrolysis of the diester(**1**) had been fully investigated in this department[1] and found to yield only the corresponding gem-diacid(**2**); nevertheless, further investigation was considered unnecessary. However the unusual cyclisation of the cyclooctene gem-diester(**3**) on reduction with lithium aluminium hydride, prompted the question:- Will a similar cyclisation occur in the seven membered analogue? Accordingly, the ester(**1**) was refluxed for forty-eight hours in an ethereal suspension of the complex hydride and the product shown by g.l.c. to be a single substance. If a transannular reaction had occurred then the diol(**4**) would be the expected product. However, although an authentic sample was not available, spectral analysis soon established that reduction had proceeded in the normal fashion to produce the



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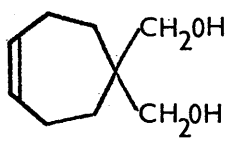

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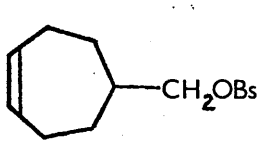

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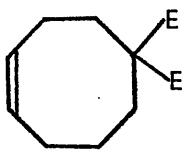
monocyclic diol(**5**). The simplicity and symmetry of the n.m.r. spectrum was an obvious pointer. Also, the integration of the $C\underline{H}_2OH$ protons clearly indicated the presence of four isochronous protons, inconsistent with structure(**4**). An obvious distinguishing feature between the two possible diols is the molecular weight difference of two mass units. However although no peak at m/e 156 was observed in the mass spectrum of the reduction product, the peaks at 138 $(M-18)^+$ and 120 $(M-36)^+$ were in accord with the structure for the proposed monocyclic diol(**5**).

From molecular models it is apparent that for cyclisation to occur the seven membered ring has to adopt a boat conformation in which one of the ester groups is located in close proximity to the transannular double bond. This conformation is obviously of higher energy than the corresponding chair and the energy of ring flipping and subsequent cyclisation may be much higher than reaction via an alternate pathway (e.g. reduction). However the fact that the brosylate (**6**) undergoes transannular solvolysis almost exclusively,[2] clearly indicates that such transannular conformational arguements are of secondary importance.

From the above results it would appear that in the



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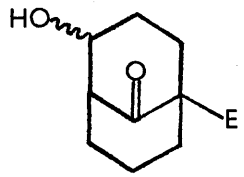

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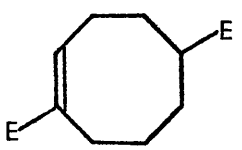

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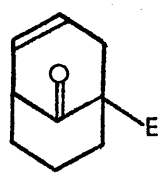

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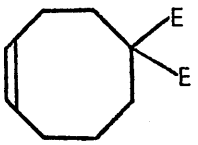
cycloheptene case, transannular reactions of the type previously reported for eight and nine membered rings do not occur.

Accordingly the corresponding cyclooctene diester(**7**) was prepared by a route exactly analogous. Sodium ethoxide catalysed condensation of acrolein with 2-carbethoxycyclopentanone and subsequent ring closure with strong acid afforded the bicyclic alcohol(**8**) as a mixture of epimers. Treatment of the corresponding tosylate epimers (as a mixture) with sodium ethoxide gave the gem-diester(**7**), which could be purified by preparative t.l.c. The analytical purity of this compound was confirmed by g.l.c.

Also isolated during chromatographic purification was the conjugated ester(**9**) which was easily identified by spectral analysis. This compound can arise by thermal elimination of p-toluenesulphonic acid to form the bicyclic olefin(**10**) which has been shown to undergo a reverse acetoacetic ester condensation affording the monocyclic ester(**9**)[3]. Alternatively the order may be reversed.

The gem-diester(**7**) was subjected to alkaline hydrolysis in the normal manner, and found to produce a product whose melting point was 20° above the melting point of the bicyclic



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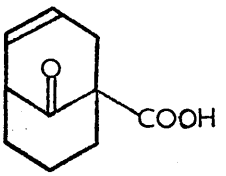

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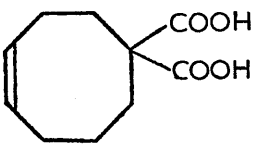

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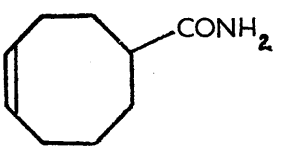

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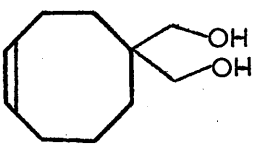

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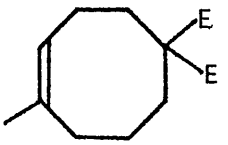
monoacid(**11**)[4] which would be the product of a transannular reaction. The identity of this compound was established by a comparison of the integration of the n.m.r. signals due to the olefinic and acid protons. The ratio of these signals was unity, confirming the structure(**12**). This diacid could be decarboxylated by refluxing in pyridine containing a trace of copper powder. The monoacid so formed was converted via the acid chloride to the amide(**13**) which had a melting point in agreement with that published.[5] The infra-red spectrum exhibited features in accord with the structure(**13**), viz. (N-H stretch) at 3342 and 3166 $cm.^{-1}$ (C=C-H stretch) at 3020$cm.^{-1}$ Amide I band at 1658 $cm.^{-1}$ Amide II band at 1629 $cm.^{-1}$

On complex hydride reduction as before, the ester(**7**) afforded a single compound (symmetrical peak on g.l.c.). The identity of this compound was again established by spectral analysis. Specifically the mass spectrum again exhibited no molecular ion at m/e 170 but the peaks at m/e 169 $(M-1)^+$, 152 $(M-18)^+$ and 134 $(M-36)^+$ strongly suggested the monocyclic diol(**14**). The n.m.r. spectrum was amenable to first order analysis, and the ratio of carbinol protons (CH_2OH) to olefinic protons was 2 : 1, in accord with structure(**14**). The infra-red spectrum, though not informative was compatible



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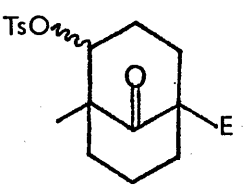

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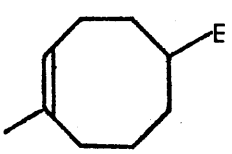

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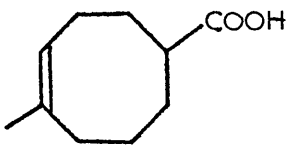
with this structure. It appeared that these reactions followed the expected course and did not produce any transannular products, as in neither case was any bridged bicyclic product observed. Could it be that the cyclisation depended on the presence of a methyl group on the double bond?

Accordingly the methyl cyclooctene diester(**15**), which according to McKillop[6] underwent transannular transformation, was prepared by the established method from 6-methyl-2-carbethoxycyclohexanone. The intermediate tosylate epimers(**16**) were found to exist in the ratio of equatorial : axial 3 : 2. This could be discerned by the relative integration of the C-4 proton attached to the carbon atom bearing the tosyloxy grouping. The axial proton could be distinguished by its larger coupling constants. The diester(**15**) was then prepared by sodium ethoxide treatment of this tosylate mixture and purified by preparative t.l.c. Also isolated during chromatographic purification was the monoester(**17**) which presumably arises from decarbethoxylation of (**15**). The structure of (**17**) was inferred from the ratio of the olefinic proton (1H) to the methylene protons (2H) of the ester group.

The diester(**15**) was subjected to the same conditions of alkaline hydrolysis as that reported by McKillop.[6] The



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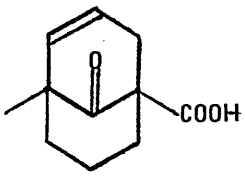

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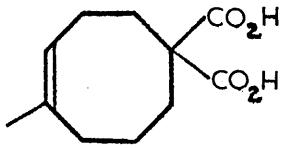

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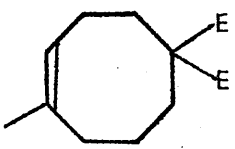

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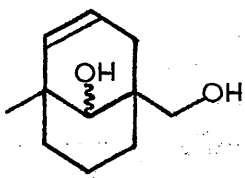

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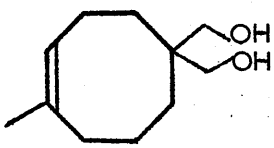

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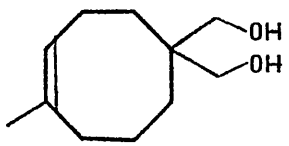
product was identified as the cyclooctene monoacid(**18**) already reported. In this case, unlike the nor-methyl analogue the malonic acid initially formed must decarboxylate under the reaction conditions. The identity of this compound was substantiated by the relative integration of the acid proton (1H at 0.1τ) against the olefinic proton (1H at 4.6τ). Any other structure e.g. (**19**) or (**20**) would exhibit a different integration ratio. There was no evidence to suggest that any bicyclic material had been produced.

Reduction of (**15**) with lithium aluminium hydride afforded a single compound (from g.l.c. analysis) which was totally different chromatographically and spectroscopically from the bicyclic diol(**21**)[7]. However the spectral properties of this compound were consistent with the monocyclic diol(**22**). The n.m.r. spectrum was relatively simple and amenable to first order analysis. The olefinic proton appeared as a sub-split triplet (J = 5Hz, 1Hz.) and the carbinol protons as a singlet (4H). The bicyclic alcohol(**21**) on the other hand, exhibited two anisochronous olefinic protons, as complex multiplets, and two broad singlets at 6.4τ (1H) and 6.5τ (2H) for the carbinol protons. The infra-red spectra of the two alcohols were also quite different, while the mass spectrum of the reduction



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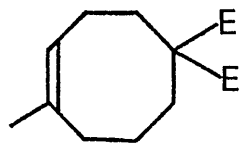

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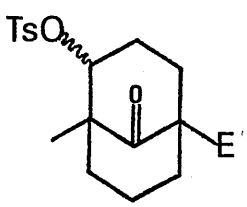

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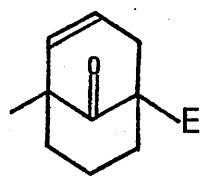

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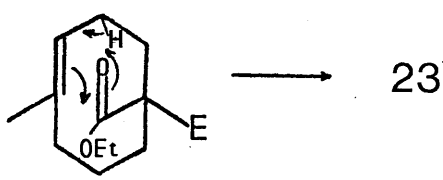
Scheme B.

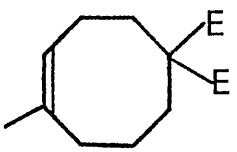


product showed a small molecular ion at m/e 184, consistent with only the monocyclic diol(**22**).

These results were in direct conflict with those of McKillop.

On re-examination of the published method it was noted that in the purification of the gem-diester(**15**) the product had been distilled from the crude reaction mixture. Since the fragmentation (**16**) ⟶ (**15**) is known to proceed very readily on the equatorial tosylate but not at all on the axial epimer, it may be assumed that the crude reaction product contained unreacted axial tosylate. It was therefore conceivable that during this distillation process the temperature was high enough to induce thermal elimination of p-toluenesulphonic acid from the axial tosylate, producing directly the bicyclic keto-ester(**23**). The p-toluenesulphonic acid so formed could then act as an acid catalyst for the transannular cyclisation.

Alternatively the mere action of heat could have produced a purely thermal "ene-reaction" (Scheme B). Consequently the action of heat and acid were independently studied on the pure diester(**15**). Heating the ester neat at 150 (the approximate distillation temperature) for three hours produced no change. (any reaction was monitored by g.l.c.).



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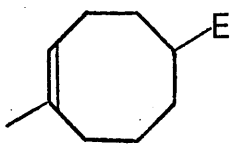

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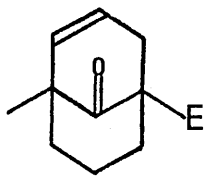

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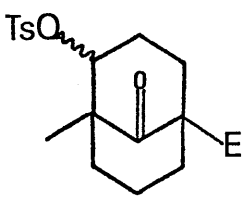

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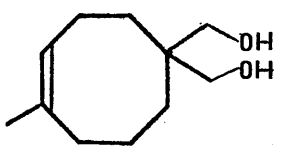

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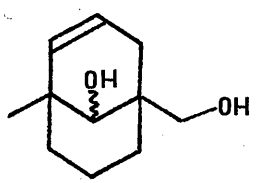

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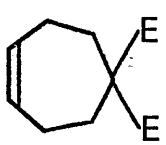

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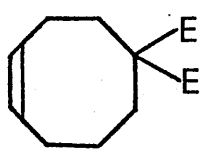

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However on addition of a crystal of p-toluenesulphonic acid at this temperature the mixture turned dark brown. After one hour, an aliquot analysed by g.l.c. indicated that the ratio of monocyclic diester(**15**) : bicyclic keto-ester(**23**) was 3 : 1. These results suggest that a thermal "ene reaction" could be discounted, but an acid catalysed cyclisation was feasible.

When a large scale (7.4g.) tosylate elimination was carried out and the product isolated by distillation, the initial fractions were rich in (**15**) although they contained small amounts of (**17**) and (**23**). The latter fractions, however, contained (**23**) as the major component with (**15**) as a contaminant. If the fractions were combined the total distillate would have contained 28% (**23**), 68% (**15**) and 4% (**17**). It appears likely that this is the source of bicyclic material.

Summary :- The transannular cyclisation of the gem-diester(**15**) to (**23**) is not effected thermally. It has been shown to be catalysed by acid and not by base. This bicyclic keto-ester(**23**) is also formed by elimination of pTSA from the axial tosylate (**16**). The ester(**15**) undergoes reduction in the normal manner to the diol(**22**) and not to (**21**) as previously reported. The esters (**1**) and (**7**) also behave normally on hydrolysis and reduction.

Diethyl cyclohept-4-ene 1,1 dicarboxylate (1).

This compound was prepared by sodium ethoxide induced fragmentation of the equatorial tosylate derived from acrolein annelation of 2-carbethoxycyclopentanone. In this case it was possible to separate the epimeric tosylates by fractional crystallisation (ethanol) and use only the equatorial epimer m.p. 94-95°, thus facilitating easier purification of the gem-diester on t.l.c. (20% ethyl acetate/petrol).

I.R. (liquid film) $cm.^{-1}$:- 1730 (s), 1240 (s).

G.L.C. :- 1 peak R_t 12.4min. on 5% QF1 at 125° (flow rate 44ml.)

5,5 Dihydroxymethylcycloheptene (5).

The ester(1) (120mg.,0.5mmole) in anhydrous ether(30ml.) containing lithium aluminium hydride(40mg.,1.1mmole) was refluxed for forty eight hours. Normal work up afforded a single compound (62mg., 80%) as a white solid.(m.p. 78-79° benzene). An analytical sample was prepared by sublimation.

Found:C,69.31;H,10.11. $C_9H_{16}O_2$ requires C,69.19;H,10.32%.

I.R. ($CHCl_3$) $cm.^{-1}$:- 3615(m), 3580-3100(broad), 1652(w),1065(s).

N.M.R. ($CDCl_3$) :- Triplet (J = 4Hz.) (2H) 4.4τ.

Singlet (4H) 6.4τ. Multiplet (4H) 7.8-8.1τ.

Singlet (2H) 7.7τ. Multiplet (4H) 8.4-8.6τ.

The mass spectrum exhibited no detectable molecular ion at m/e 156, however significant peaks were observed at 138,120, 92,91,79(base peak) and 67.

G.l.c. analysis of the crude reaction mixture indicated 1 symmetrical peak R_t 8.3min. on 1% OV1 at 125°(flow rate 37ml.)

Diethyl cyclooct-4-ene-1,1-dicarboxylate (7).

This compound was prepared by sodium ethoxide induced fragmentation of the corresponding bicyclic tosylates derived from acrolein annelation of 2-carbethoxycyclohexanone. Purification was effected by preparative t.l.c. (20% ethyl acetate/petrol).

I.R. (liquid film) $cm.^{-1}$:- 1725(s), 1245(s) and 1180(s).

N.M.R. (CCl_4) :- Subsplit doublet (J = 6Hz.) (2H) 4.5τ.
Quartet (J = 6Hz.) (4H) 5.9τ.
Multiplet (10H) 7.6-8.8τ.
Triplet (J = 6Hz.) (6H) 8.8τ.

G.L.C. :- 1 symmetrical peak R_t 6.2min. on 5% QF1 at 150° (flow rate 80ml./min.)

Also isolated during chromatography was the conjugated ester(9) identified by spectral analysis.

I.R. (liquid film) $cm.^{-1}$:- 1730(s),1710(s),1645(m),1200(s).

N.M.R. (CCl_4) :- Triplet (J=9Hz.) (1H) 3.0τ.

2 non-equivalent quartets (J=6Hz.) (4H) 5.9τ.

Multiplet (11H) 7.4-8.8τ.

2 non-equivalent triplets (J=6Hz.) (6H) 8.8τ.

U.V. :- λ_{max} 222nm. ε=10160. (lit. value[8] λ_{max} 221nm. ε=9820).

Cyclooct-4-ene-1,1-dicarboxylic acid (**12**).

The diester(7) (40mg.,0.16mmole) was refluxed overnight in 15% aqueous potassium hydroxide(10ml.) containing ethanol (2ml.). The cooled solution was extracted with ether, acidified (2N HCl) and then re-extracted with ether. On drying and evaporation of the ether, large chunky crystals of the product were obtained. A sample recrystallised from ethanol/water had m.p. 156-158°, 20° above the melting point of the bicyclic monoacid(11).[4]

I.R. ($CHCl_3$) $cm.^{-1}$:- 3500-2500(broad), 1710(s) and 1240(s).

N.M.R. ($CDCl_3$) :- Broad signal (2H) 0.7τ.

Multiplet (2H) 4.4τ.

Multiplet (10H) 7.5-8.9τ.

The gem-diacid(**12**) (26mg.) could be decarboxylated by refluxing for one hour in pyridine(10ml.) containing a small amount of copper powder. The copper was removed by filtration through cotton wool and the resultant solution neutralised with 6N HCl and extracted with ether. The organic phase was dried and concentrated affording the residue which was stirred with oxalyl chloride (5 drops) in benzene (10ml.) for one hour. The benzene was evaporated and the residue taken up in ether. Ammonia gas was then bubbled into this solution through a pipette and immediately a precipitate was observed. Water was added after fifteen minutes and then methylene chloride. The organic extract was washed with water, dilute sodium hydroxide solution, brine and finally dried and evaporated yielding the crude amide(**13**). m.p. 198-199°, (lit. m.p. 201-202°)[5].

I.R. (KBr) $cm.^{-1}$:- 3342(m),3166(m),3020(w),1658(s) and 1629(s).

5,5-Dihydroxymethylcyclooctene (**14**).

A solution of the diester(**7**) (30mg.,0.12mmole) in anhydrous ether(10ml.) was treated in the normal manner with lithium aluminium hydride(20mg.). The suspension was refluxed for forty-eight hours and worked up in the normal manner. This gave a single product (18mg., 82%) as a colourless solid.

An analytical sample, prepared by sublimation had m.p. 57-59°.
Found:C,70.27;H,10.44. $C_{10}H_{18}O_2$ requires C,70.55;H,10.66%.

I.R. (CCl_4) $cm.^{-1}$:- 3640(m), 3560(w), 1062(s) and 1028(s).

N.M.R. (CCl_4) :- Subsplit doublet (J = 5Hz.) (2H) 4.5τ.
Broad singlet (2H) 6.1τ.
Singlet (4H) 6.6τ.
Multiplet (4H) 7.8-8.0τ.
Multiplet (6H) 8.2-8.8τ.

M.S. :- No parent ion at m/e 170, but significant peaks at m/e 169,152,134,121,119 and 93.

G.l.c. analysis of the crude reaction mixture showed only one symmetrical peak R_t 4.2min. on 1% OV1 at 160°(flow rate 47ml./min.).

1-Carbethoxy-4-hydroxy-5-methylbicyclo-(3,3,1)-nonan-9-one (16).

This was prepared as a colourless oil b.p. 120-124°(0.6mm) by the method of McKillop[6] and tosylated in the normal manner. N.M.R. integration of the H-C-OTs proton[9] in the epimeric mixture of tosylates indicated a composition of equatorial : axial 3 : 2. This epimeric mixture was used in all subsequent experiments.

Diethyl-5-methylcyclooct-4-ene-1,1-dicarboxylate(15).

The tosylate epimers(16) (320mg.,0.8mmole) in anhydrous ethanol(10ml.) were added to a solution of sodium ethoxide (from ethanol(10ml.) and sodium(25mg.,1.1mmole) and the solution refluxed for two hours. On cooling, the mixture was poured onto ice(50g.), acidified(6N HCl), and extracted with ether. The ethereal solution was washed, dried and evaporated to give the crude diester(15) contaminated with unreacted tosylate and small amounts of the monocyclic monoester(17) arising from decarbethoxylation of the diester. Purification was effected by preparative t.l.c. (20% ethyl acetate/petrol) affording (15) as a colourless oil (90mg.,42%) and (17) also as a colourless oil (18mg.,9%). The gem-diester was shown to be chromatographically pure by t.l.c. and g.l.c.

I.R. (liquid film) $cm.^{-1}$:- 1725(s) and 1260(s).

G.L.C. :- 1 symmetrical peak R_t 10.5min. on 5% QF1 at 150 (flow rate 42ml./min.)

The structure of (17) was inferred from the n.m.r. spectrum viz. :- N.M.R. (CCl_4) :- Multiplet (1H) 4.6τ.

Quartet (2H) 5.9τ.

Multiplet (17H) 7.6-9.0τ.

5-Methylcyclooct-4-ene carboxylic acid (18).

Hydrolysis of (15) was effected as before[6] to give the known acid(18) as a colourless oil, which resisted all attempts at crystallisation. The n.m.r. spectrum was in accord with this structure. viz.,

N.M.R. (CCl_4) :- Broad singlet (1H) -0.1τ.
Multiplet (1H) 4.6τ.
Multiplet (14H) 7.4-8.9τ.

There was no evidence to suggest that any bicyclic material had been produced.

5,5-Dihydroxy-1-methylcyclooct-1-ene (22).

A solution of the diester(15) (120mg.,0.5mmole) in anhydrous ether(5ml.) was added dropwise to a stirred slurry of lithium aluminium hydride(40mg.,1.1mmole) in ether(20ml.). Stirring was continued under gentle reflux for twenty-four hours, when excess hydride was decomposed by the addition of ethyl acetate. The organic layer was then washed with dilute hydrochloric acid, brine and finally dried and concentrated to give the monocyclic diol as a colourless solid m.p. 70-71°. (benzene/petrol).

An analytical sample was prepared by sublimation. (62mg.,79%)
Found:C,71.66;H,10.97. $C_{11}H_{20}O_2$ requires C,71.70;H,10.94%.

I.R. (KBr) $cm.^{-1}$:- 3300(m),3040(w),1050(s),1035(s) and 820(m).

N.M.R. ($CDCl_3$) :- Triplet (J=5Hz.) (1H) 4.6τ.
Singlet (2H) 6.2τ. Multiplet (4H) 7.6-8τ.
Singlet (4H) 6.5τ. Singlet (3H) 8.3τ.
Multiplet (6H) 8.3-8.8τ.

M.S. :- Significant peaks at m/e 184(M^+),166,148,135,125,93.

G.L.C. :- Analysis of the reaction product indicated only one symmetrical peak R_t 15min. on 1% OV1 at 140°(flow rate 45ml./min.). Under the same conditions the bicyclic diol(**21**) had retention time 8 minutes.

The spectral properties of the bicyclic diol were also quite different.

Effect of heat and acid on the diester(**15**).

The diester(**15**) (38mg.) was heated in a small Craig tube at 150° and the course of any reaction monitored by g.l.c. on 5% QF1 at 150°. After five hours at 150° the diester was unchanged. A small crystal of p-toluenesulphonic acid was added and the mixture immediately turned dark brown. G.l.c. analysis one hour later indicated a 1 : 3 mixture of bicyclic

monoester(23) R_t 8min. : monocyclic gem-diester(15) R_t 10.5min. and also a number of unidentified products of longer retention time.

Large scale preparation of the diester(15).

The epimeric mixture of tosylates(16) (7.4g.,0.02mole) was added to a solution of sodium ethoxide (from sodium(240mg.) in absolute ethanol(50ml.) and the solution refluxed for two hours. On cooling, the mixture (containing precipitated sodium tosylate) was poured onto ice(70g.) and 6N HCl(10ml.), then extracted with ether. The ethereal solution was washed, dried and concentrated to give a viscous oil which was distilled under vacuum. Three fractions were obtained, and these examined by g.l.c. (5% QF1 at 150°.)

b.p.(0.3mm.)	Mass.	% (17)	% (23)	% (15)
102-106	0.525g.	16	8	76
106-112	1.089g.	1	7	92
112-118	0.900g.	1	59	40

This is the likely source of the bicyclic ester(23).

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7. Sample kindly supplied by Prof. W.Parker.

SUMMARY

The research described in this thesis is devoted to synthetic and mechanistic studies in bridged bicyclic systems. The thesis is divided into three parts:-

Part I: The Total Synthesis of Racemic Guaiol.

The plant sesquiterpene guaiol has been synthesised in racemic form, from laevulinic acid and 2-methylcyclopentanone via an intermediate, 1-methyltricyclo-(6,2,1,$0^{2,6}$)-undec-2^{6}-en-5,11-dione. Bridge fission of this diketone yields a hydroazulene enone-ester which has been elaborated to guaiol.

Part II; The Acid Catalysed Cleavage of Bicyclo-(3,2,1)-oct-2-en-8-one.

Although bicyclo-(3,2,1)-oct-2-en-8-one derivatives cleave in acidic solution to cycloheptene carboxylic acid derivatives, the corresponding alcohols do not fragment under similar circumstances. The corresponding syn alcohol undergoes a facile transannular cyclisation when treated with bromine. A similar transannular cyclisation occurs when the ketone is treated with bromine in an alcoholic solvent.

Part III: A Re-investigation of the Reduction and Hydrolysis of Unsaturated Medium Ring Gem-Diesters.

The previously reported base-catalysed transannular cyclisation of unsaturated medium ring gem-diesters has been re-investigated. In contrast to these earlier findings, the hydrolysis and reduction of these diesters proceed in the normal manner.