6. 7. 72.

SYNTHESIS OF BICYCLO[3,2,1]OCTANE DERIVATIVES RELATED TO THE GIBBERELLINS

A THESIS
PRESENTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

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by

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CONTENTS

SUMMARY

This thesis investigates the preparation of tetracarbocyclic compounds whose C-D ring system is similar to the bicyclo[3.2.1]-octane C-D network found in the gibberellins. The results are presented in four Chapters.

In Chapter 1, the successful synthesis, by several routes, of the simple tetracyclic ketone 9 is described. A novel method for construction of polycyclic compounds, involving acid catalysed cyclization of an unsaturated diazoketone, is used as the key step in the most effective preparation of 9. A possible mechanism for this transformation is discussed.

In Chapters 2 and 3, the possibility of acid catalysed cyclization of some more complex unsaturated diazocompounds is examined. From the results presented in these Chapters, the scope and limitations of the cyclization reaction are partially defined.

Chapter 4 describes some preliminary investigations into further elaboration of the tetracyclic ketone 9.

STATEMENT

This thesis contains no material previously submitted for a degree in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

T.R. KLOSE

ACKNOWLEDGEMENTS

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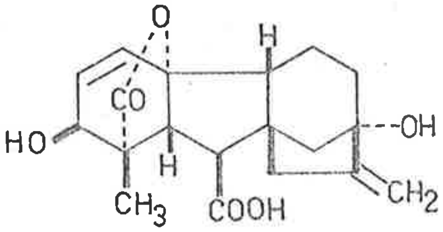
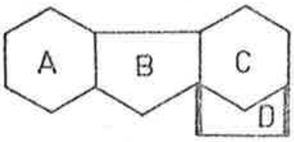
INTRODUCTION

The gibberellins, first isolated in 1938 from the culture filtrate of the fungus <u>Gibberella fujikuroi</u>,[1] are important plant growth stimulants.[2-4] Extensive chemical studies[2,3] indicated that the structure of gibberellic acid (gibberellin A_3), the best known and most easily obtained fungal gibberellin,[5,6] was <u>1</u>.[7-9] The stereochemistry of gibberellic acid, which had been the source of some controversy,[10-13] was finally resolved in favour of <u>1</u> by X-ray crystallographic[14-16] and circular dichroism[17] studies.



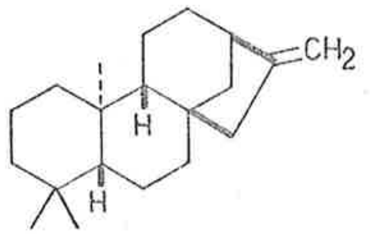
<u>1</u>

At least 27 gibberellins, all possessing the tetracarbocyclic gibbane skeleton <u>2</u>,[18] have now been isolated from various plant and fungal sources.[19-22] The pathway for biosynthesis of gibberellins has been studied.[23,24] They are modified diterpenes



<u>2</u>

biogenetically related to (-)-kaurene 3 and (-)-kaur-16-en-19-oic acid 4.



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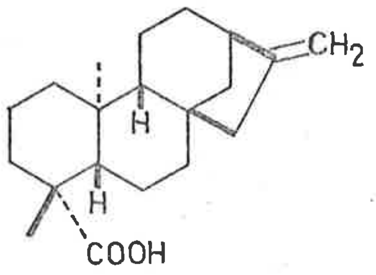

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Because of the obvious challenge to organic chemists, there has been enormous interest in the synthesis of gibberellins and similar tetracyclic diterpenes.[25] Recently, these endeavors have culminated in a striking total synthesis of gibberellin A_{15}[26] and formal total syntheses of gibberellins A_2, A_4, A_9, and A_{10}.[27,28]

Two main areas of difficulty become evident when the total synthesis of a compound as complex as gibberellic acid 1 is considered. First, the complexity and chemical sensitivity of the A ring poses many synthetic problems,[29-32] and requires that construction of this ring be left until a late stage. Secondly, the C and D rings constitute a bicyclo[3.2.1]octane network embodying an exocyclic methylene function adjacent to a bridgehead hydroxyl group. This thesis presents the results of an investigation directed towards the preparation of models of the C-D ring system of gibberellic acid.

It is relevant to examine critically the methods which have been reported in the literature for building a bicyclo[3.2.1] octane unit into a polycyclic framework as a part of diterpene synthesis. While syntheses of bicyclo[3.2.1]octanes can be based on rearrangements of isomeric bicyclo[2.2.2]octanes,[33] the synthesis of the latter bicyclic system is itself not simple. This route offers no particular advantage over one in which the five membered (D) ring is formed, by an intramolecular ring closure reaction, onto an already assembled six membered (C) ring. Indeed, the method of choice in most of the published research has been of this nature. Many types of cyclization reaction have been used. These can be classified broadly into groups depending on the type of reaction employed in the critical ring forming step.

In the following section (Parts 1-7), some of the useful cyclization methods are summarized.

1. Ring Closure by Dieckmann Condensation

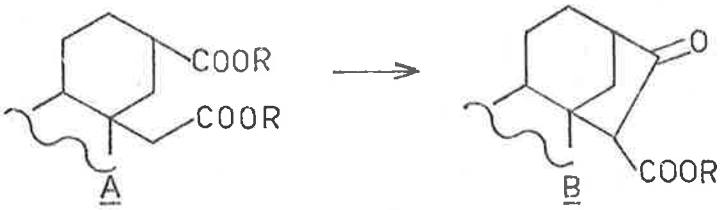


Figure 1≠

≠ To avoid confusion, partial structures, indicating only the gross features of the transformation being made, will be used in this section.

Successful[34] and unsuccessful[35] applications of this plan (Figure 1) have been reported. A closely related reaction, pyrolytic cyclization of a dicarboxylic acid (as its barium salt), has also been employed.[36-38] The dicarboxylic acid derivative A required as a precursor, however, is not easily accessible.[39,40]

2. Ring Closure using the Aldol Reaction.

Cyclization by the aldol reaction has provided a popular method for construction of bicyclo[3.2.1]octane derivatives. Several different aldol routes can be envisaged, and are discussed below.

(a)

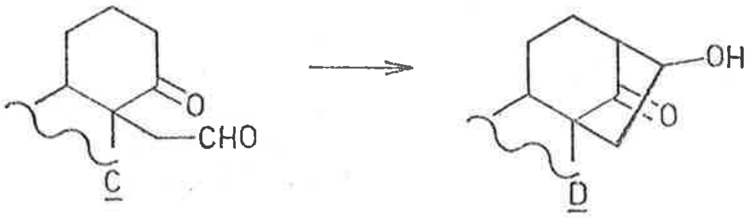


Figure 2

Numerous applications of this scheme (Figure 2) have been published.[41-46] A variant has also been employed[47,48] for synthesis of compounds which can be elaborated to models of the A ring of diterpene alkaloids.

A problem with this route is incorporation of the acetaldehyde residue at the ring junction in the precursor C. This problem has been circumscribed in two ways :

(i) alkylation of the methylene blocked ketone (corresponding to C) with a suitable alkylating agent.[43-46]

(ii) angular alkylation[41,42,49,50] using the Claisen rearrangement of a suitable vinyl ether.[51]

Both of these methods involve multi-step procedures.

(b)

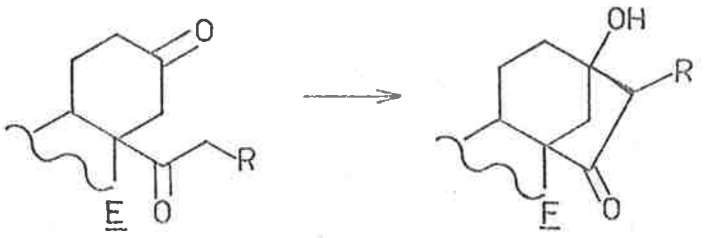


Figure 3

This mode of ring closure (Figure 3, R=H), originally reported in 1962,[52] has recently been used successfully by Nagata and his collaborators[53,54] in their total synthesis of atisine. House and Larson[55] reported difficulty with a very similar cyclization, but found that base catalysed aldol reaction of the derived β-ketosulphone (E, $R=SO_2CH_3$) proceeded more successfully. This has been substantiated in another communication.[56]

The product F of this scheme does have a bridgehead hydroxyl function. Although the carbonyl group in F is wrongly placed (for diterpene synthesis), F is nevertheless a versatile intermediate. It can be transformed by known pathways into either a bicyclo[2.2.2]octane derivative[53,54] or several useful bicyclo[3.2.1]octane derivatives.[55,57,58]

(c)

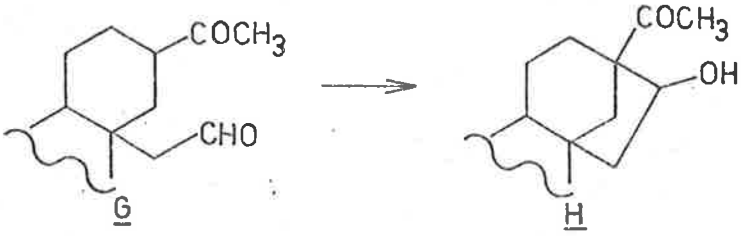


Figure 4

An example of this type of aldol cyclization (Figure 4) has been reported.[59,60] The bridgehead acetyl group in H can be degraded by a lengthy, though efficient, process to a bridgehead hydroxyl group.[59-61]

Several instances of formation of tetracyclic compounds involving ring closure by a similar aldol reaction have also been noted.[62,63]

(d)

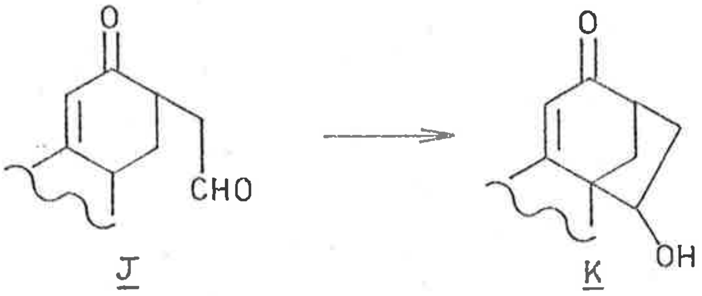


Figure 5

The usefulness of the vinylogous aldol reaction (Figure 5) to achieve cyclization has recently been demonstrated.[64] Both acid and base catalysis has been employed.[64]

3. Ring Closure by an Alkylation Reaction

Alkylation of an active methylene or methine group has not been greatly explored to effect cyclization to bicyclo[3.2.1] octanes. The pioneering work of Herz and his colleagues[63,65] demonstrated that the method was feasible. Two recent endeavors also use this type of cyclization.[26,66]

4. Ring Closure by Electrophilic Acylation.

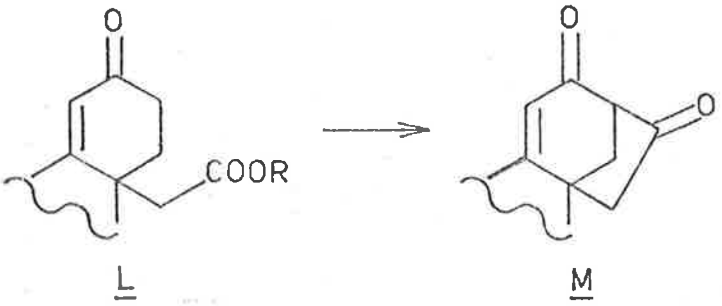


Figure 6

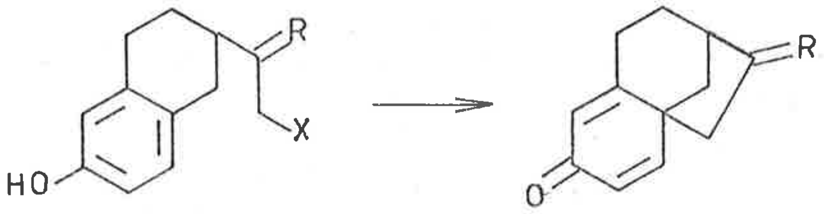
The acid catalysed intramolecular acylation of a keto-acid (Figure 6) has been extensively employed by Loewenthal[67-70] and Mori[71-78] and their co-workers for the synthesis of degradation products of gibberellic acid. Other similar applications have been explored.[46,79-81]

The sequence has proved popular because the precursor keto-acid (L, R=H) is easily accessible via a Robinson annelation reaction.

A general investigation of the usefulness of the reaction has been made.[82] It is not surprising that the corresponding base catalysed Claisen condensation of the keto-ester (L, R=CH_3)

fails.[67,71]

5. Cyclization by Ar$_1$-5 Participation.≠



N

P

Figure 7

This elegant ring closure (Figure 7) has been investigated by Masamune.[84,85] An important limitation of this approach occurs when the phenol N carries a bulky substituent next to the leaving group (e.g. R=H,OTHP). The diastereoisomer which would lead to *endo*-product P fails to cyclize, probably because of severe non-bonded interactions in the transition state leading to a cyclic product. Moreover, the bromo-ketone N (R=O, X=Br) containing the sterically less demanding carbonyl function, does not yield cyclic product P (R=O).[85]

An interesting variation of this route, involving participation by a C-C double bond, has been reported.[63,65,86,87]

≠ For the definition of the Ar$_1$-n nomenclature, see ref[83].

6. Ring Closure by Cycloaddition of a Carbenoid onto an Olefin.

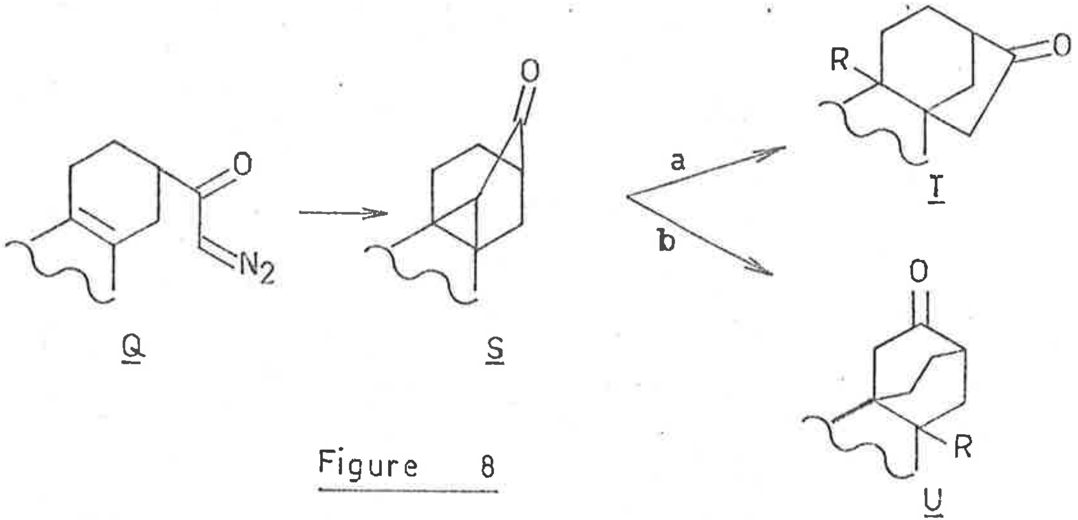


Figure 8

This approach, which requires two separate transformations, was explored initially and unsuccessfully by House and his collaborators.[88] The critical step is cleavage of one of the cyclopropyl bonds of the intermediate S (Figure 8). Thus, routes a or b, leading to different bicyclic derivatives could occur. House[88] found preferential formation of the bicyclo[2.2.2]octane U with an unactivated cyclopropyl ketone S. More recently, two independent communications[89,90] have shown that the approach can be extremely useful when production of the bicyclo[3.2.1]octane T is particularly facilitated.

Wenkert and co-workers[91] have reported that bicyclic systems can also be formed by C-H insertion of copper carbenoids.

7. Other Methods

Bicyclo[3.2.1]octanes can also be produced by intramolecular ring enlargement of a cyclic ketone by a diazoalkane.[92,93] Some approaches towards bicyclo[3.2.1]octanes incorporating a bridgehead hydroxyl group have been made.[53,59] The more noteworthy of these are :

(i) reductive cyclization of acetylenic ketones[94]

(ii) reductive cyclization of halo-ketones[95,96]

(iii) acyloin like condensation of keto-esters[97-99]

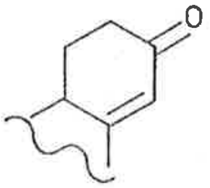
(iv) Clemmensen reduction of bicyclo[2.2.2]octanediones[100]

This last process has proved especially effective, and two further examples of its use have been reported.[78,101]

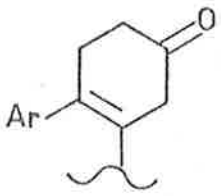
Very recently, a method quite unlike any of those mentioned above has been used with success in a model bicyclic compound.[102]

The research described in this thesis had as an objective the synthesis of tetracyclic compounds with C and D rings which reflect those found in the gibberellins. The tricyclic precursor chosen for these studies was a polyhydrophenanthrene with an aromatic A ring. From a view point of total synthesis of gibberellins, two considerations favoured this approach. Thus, after completion of the C-D ring structure, (i) the inert aryl ring could be modified (e.g. "Birch reduction") and elaborated to the hydroaromatic ring A of the gibberellins,[29] and (ii) ring B could be contracted to a five membered ring with extrusion of the potential ring B carboxylic acid function. Precedents for the latter transformation exist.[26,103-108]

One important consequence of this approach is worth noting. With an aromatic A ring, it is no longer possible to operate on a C ring conjugated carbonyl function (e.g. V, see refs[26,41,53]), for now the double bond preferentially moves to the tetra-substituted position, in conjugation with the aryl group (e.g. as in W). Therefore, variations of the methods discussed above were sought to enable the C-D system to be synthesised.



V



W

Three routes were studied for construction of the bicyclo [3.2.1]octane portion of the molecule. These were :

(1) A vinylogous extension of Masamune's Ar_1-5

alkylation.[84,85] This route, which was found to be unsatisfactory, is discussed more fully later (see Chapter 1).

(2) The carbenoid cycloaddition route.

(3) A new method based on intramolecular displacement of nitrogen from an α-ketodiazonium ion (protonated diazoketone) by a suitably placed olefinic bond. (see Figure 9)

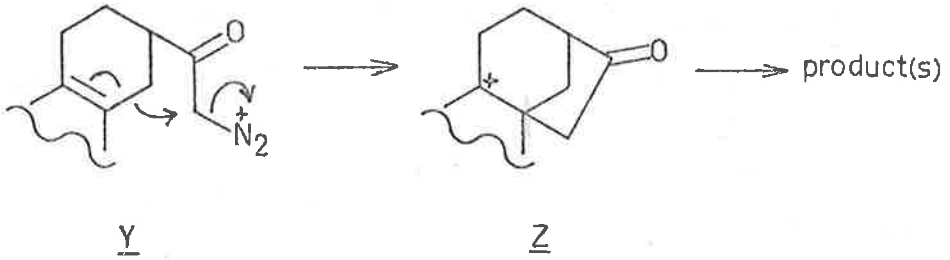
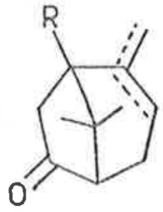


Figure 9

Of course, two different pathways could be followed, depending on which end of the double bond attacks. (For an analogous situation, see ref.[109]) If, however, the incipient carbonium ion Z leading to the desired product(s) is of sufficiently low energy (e.g. benzylic), then that pathway should take preference because of its lowered transition state energy. The aromatic A ring would then serve another purpose - that of directing the cyclization reaction.

Intramolecular nucleophilic displacement of nitrogen from protonated diazoketones by hydroxyl,[110,111] methoxyl,[112-114] acetoxyl,[112] nitro,[115] amino,[116,117] carbo-methoxyl[118] and aryl[119-122] groups has been observed. Although π-bond participation in solvolysis reactions is well known,[109,123] only one report of participation of a double bond in the acid catalysed decomposition of a diazoketone has appeared.[124] This paper, which was published after the completion of the results presented in this thesis, describes the conversion of the diazoketones 5 and 6 to the bicyclo[3.2.1]octanones 7 and 8 by treatment with boron trifluoride-etherate.[124]

5, R= COOEt
6, R= H



7 R=COOEt
8 R= H

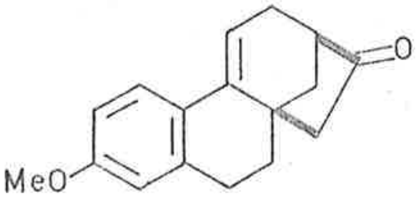
A major part of this thesis is devoted to the results of a study of the feasibility of the concept outlined in Figure 9. It has been shown that this approach does provide a short, highly efficient method for obtaining useful bicyclo[3.2.1]octane derivatives in certain cases, from readily accessible diazoketones.[≠]

The production of unsubstituted and bridgehead substituted

[≠] Some aspects of this work have been published in a preliminary communication.[125]

bicyclo[3.2.1]octanes has been examined, and the scope of the sequence has been partially delineated. This work is described in Chapters 1-3.

In Chapter 4, some reactions allowing further elaboration of the synthesised tetracyclic compounds are noted and discussed. For most of this research, the readily available tetracarbocyclic ketone 9, was used as the starting material.



9

RESULTS AND DISCUSSION

CHAPTER 1

SYNTHESIS OF THE SIMPLE TETRACYCLIC KETONE 9

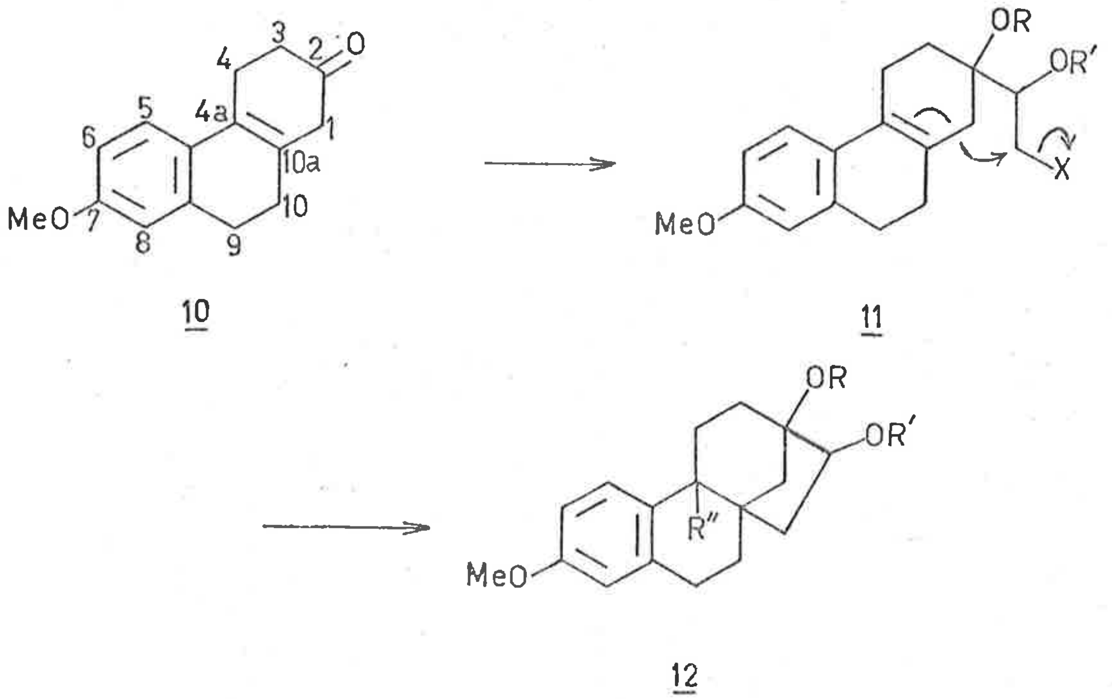
(a) Attempted solvolysis route to tetracyclic compounds

(b) Carbenoid type cyclization of diazoketone 28

(c) Acid catalysed cyclization of diazoketones 37 and 28

(a) Attempted Solvolysis Route to Tetracyclic Compounds

The plan which was originally devised as a possible construction of the C-D ring system is outlined in Scheme 1.



SCHEME 1

It was hoped that a two carbon atom unit, potentially functionalized at both carbon atoms, could be added across the carbonyl group of the known tricyclic ketone, 7-methoxy-3,4,9,10-tetrahydrophenanthren-2(1H)-one 10,[126] forming, after suitable elaboration, an intermediate 11. Solvolysis of 11 should then lead to a tetracyclic compound 12. It was felt that the influence of the aryl ring, by lowering the transition state activation energy for one pathway, would ensure that cyclization proceeded in the desired direction. (For an analogous case, see ref.[86])

This plan is essentially an extension of alkylation routes published by Masamune[84,85] and Herz.[63,65,86] Although the cyclization step would undoubtedly be subject to the steric controls reported by Masamune[85] (see Introduction), there seemed no reason to suppose that the additional substituent at C2 would affect this step.

It appeared that a vinyl group would serve admirably as the two carbon atom unit of this plan, since it could be easily introduced (with a vinyl Grignard reagent[127]) and then elaborated by standard procedures. Before ketone <u>10</u> was committed to this sequence, the reaction of vinyl magnesium bromide with a model bicyclic β,γ-unsaturated ketone <u>16</u> was studied.

Ketone <u>16</u> was synthesised as in Scheme 2. The ethylenedioxy acetal <u>14</u> of 6-methoxy-3,4-dihydronaphthalen-2(1H)-one <u>13</u>[≠] was reduced with lithium and ethanol in liquid ammonia. The

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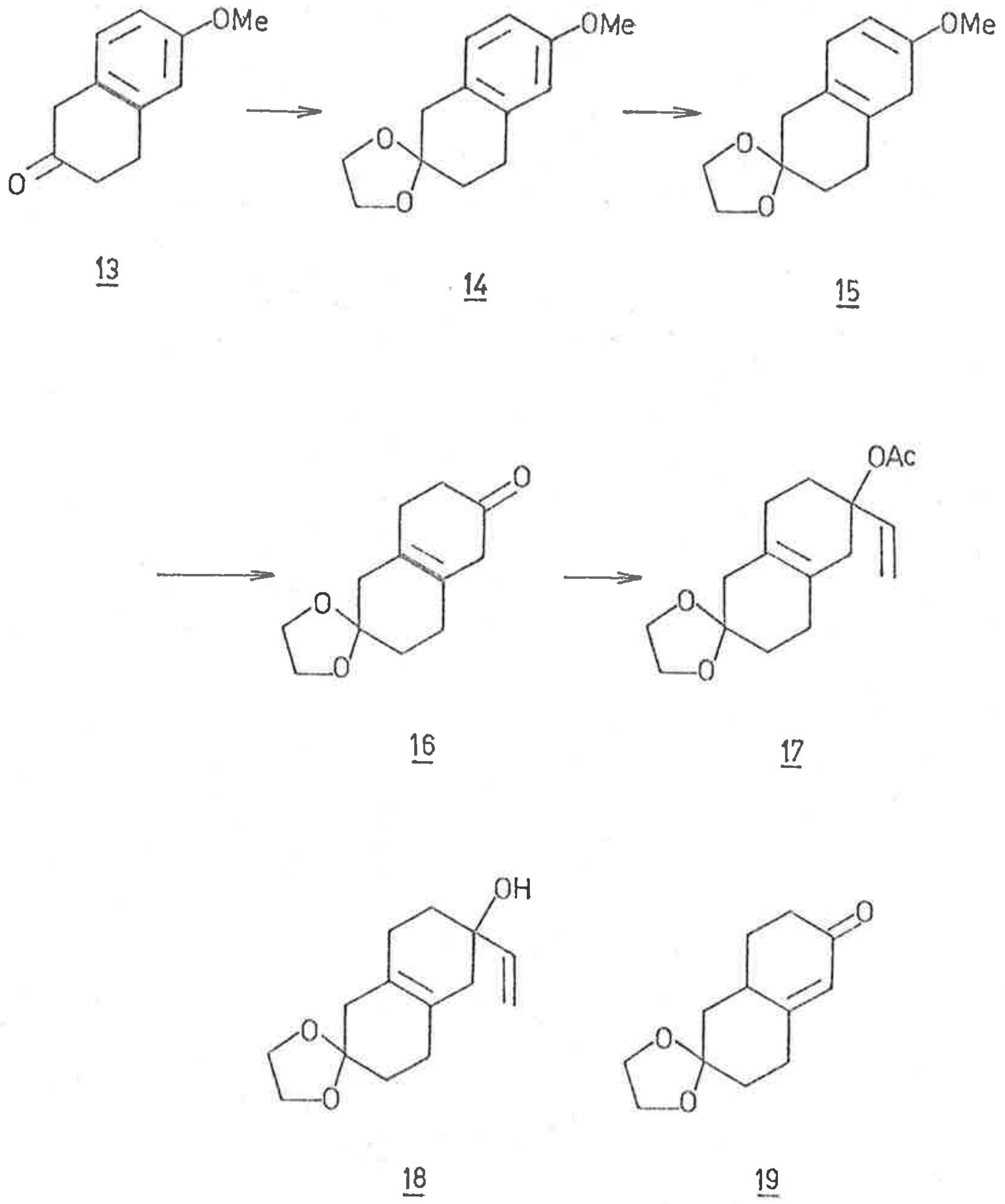
[≠] Compound <u>13</u> (6-methoxy-2-tetralone) was prepared from 6-methoxy-1-tetralone <u>24</u>[128] using the method of Nagata and Terasawa.[129] An alternative synthesis from p-methoxyphenylacetyl chloride and ethylene in the presence of aluminium chloride[130] was less satisfactory.

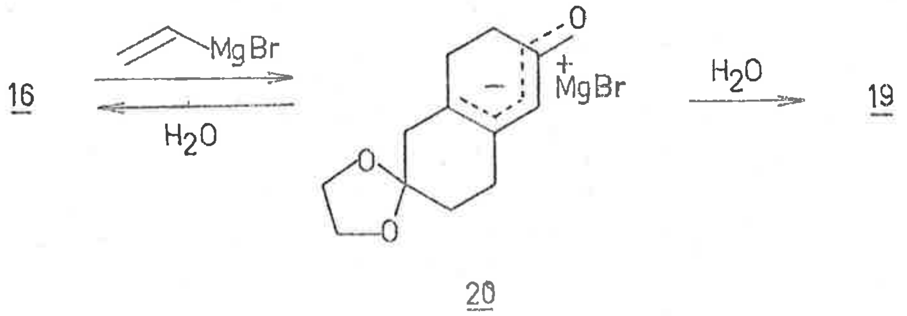


SCHEME 2

dihydroanisole 15 was obtained as an unstable but crystalline compound in 95% yield. The enol-ether group in 15 could be selectively hydrolysed, leaving the acetal function untouched, by treatment with oxalic acid in aqueous methanol at 0°. The β,γ -unsaturated ketone 16 which was produced in 50-60% yield was also an unstable crystalline compound.

Treatment of the ketone 16 with vinyl magnesium bromide at 0° afforded not the expected alcohol 18, but an oily mixture of compounds. The infrared spectrum of the crude product showed no absorption for a vinyl group. Instead, there were carbonyl absorptions at 1710 and 1660 cm^{-1}, indicating that the product was a mixture of starting ketone 16 and its conjugated isomer 19.

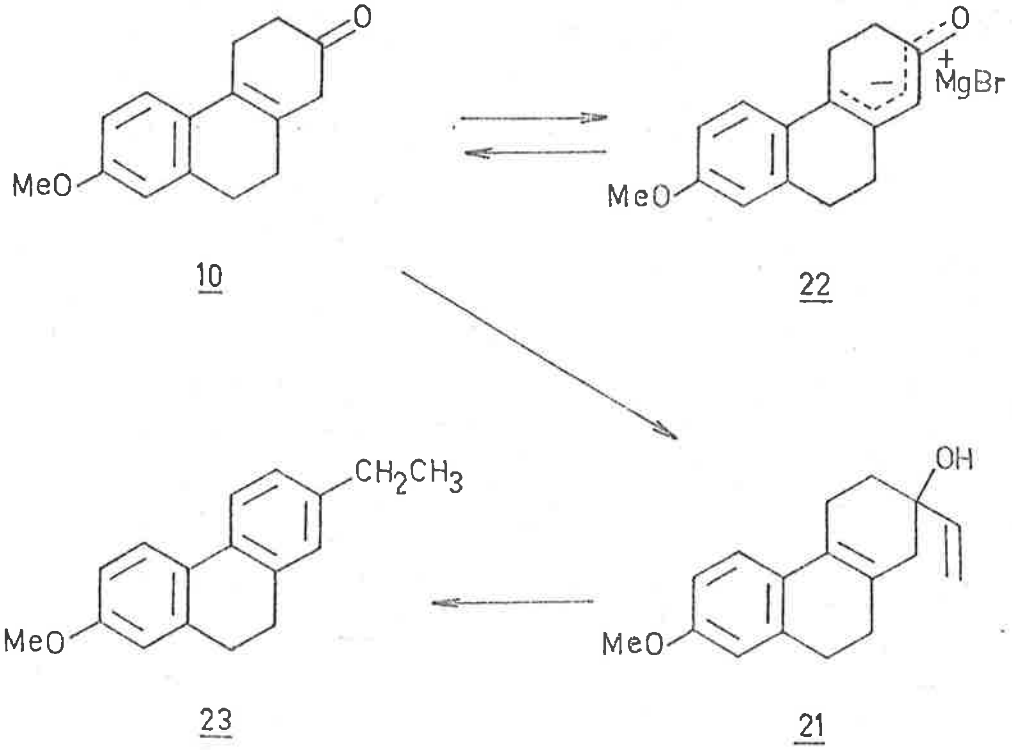
This result can be explained if it is assumed that the Grignard reagent, instead of adding across the carbonyl group, acts as a base and removes the acidic proton at C1 of unsaturated ketone 16.[131] The halo-magnesium enolate 20 (Scheme 3) would then be expected to give a mixture of ketones 16 and 19 on work up.



SCHEME 3

McMurry,[132] when faced with a similar problem of enolisation competing with normal Grignard 1,2-addition, observed that the latter process could be increased at the expense of the former simply by operating at a lower temperature.[132] When the reaction of ketone 16 with vinyl magnesium bromide was repeated, this time at -70°, and the reaction terminated by adding acetic anhydride, the diene 17 (Scheme 2) was obtained in 25-50% yield. A significant amount (30-50%) of the non-crystalline unacetylated alcohol 18 was also obtained from this reaction. This result confirmed the usefulness of McMurry's simple procedure for the improvement of Grignard addition,[132] and was most encouraging for the projected reaction of tricyclic ketone 10 with the vinyl Grignard reagent.

Ketone 10 was prepared by annelation of 6-methoxy-2-tetralone 13 with methyl vinyl ketone, using essentially the method described by Nagata and his colleagues.[126] The reaction between 10 and an excess of vinyl magnesium bromide at -70° produced a mixture of the required alcohol 21 contaminated by a large amount (ca 50% by infrared analysis) of the starting ketone 10. (see Scheme 4). The most probable explanation for this result is that enolization is again interfering with Grignard 1,2-addition. Enolate 22 is formed, together with alcohol 21, in the reaction mixture. Protonation of 22 during work up then regenerates the starting ketone 10. That 10 was enolised partially at -70°,



SCHEME 4

whereas bicyclic ketone 16 appeared not to be, is probably a reflection of the greater acidity of the vinylogous 2-tetralone 10 compared with 16, a simple β,γ-unsaturated ketone.

The two compounds 10 and 21 were not readily separable by chromatography, and so the mixture was retreated twice with an excess of vinyl magnesium bromide at -70°. ≠ Unchanged ketone still

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≠ It was assumed that vinyl alcohol 21 already present in the mixture was not affected by these further treatments.[132]

present at this stage was then separated as the bisulphite adduct. The desired alcohol 21 was obtained as an oil with the expected infrared absorptions of the vinyl group at 1640, 1000 and 930 cm^{-1}[133] and the hydroxyl function at 3350 cm^{-1}. Unfortunately, vacuum distillation of the crude vinyl alcohol 21 gave a crystalline product which displayed neither -OH nor vinyl bands in the infrared spectrum. Apparently dehydration and bond migration with aromatization had occurred, producing the dihydrophenanthrene 23 (Scheme 4).[≠] The structure 23 was readily confirmed by the unique NMR spectrum of the product. In view of these difficulties, this route was not pursued.

[≠] Dehydration of the alcohol 21 could have been catalysed by traces of acidic materials on the surface of the glass apparatus used for the distillation.

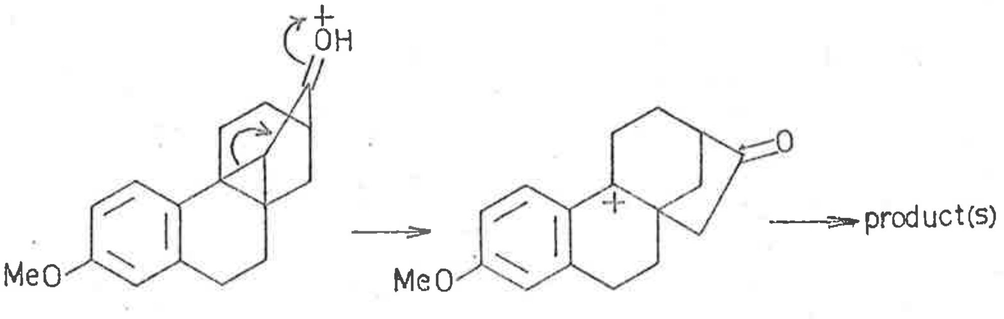
(b) Carbenoid Type Cyclization of Diazoketone 28

It was apparent that some two carbon atom unit, which would become the D-ring bridge, other than a vinyl group had to be considered. At this stage, it was decided to forgo, at least temporarily, the requirement of including a bridgehead hydroxyl group in the synthesis.

Attention was focussed upon the possibilities offered by the two carbon atoms of a diazomethyl ketone $-COCHN_2$ function. This is a potentially very reactive, but nevertheless simply introduced, functional group. It contains an excellent leaving group, molecular nitrogen. Loss of nitrogen can occur very readily under a variety of conditions - photolytic, thermal or catalytic-leaving formally a keto-carbene $-CO-\ddot{C}H$ or, in acidic media, an incipient keto-carbonium ion $-CO\overset{+}{C}H_2$, which can undergo diverse, and often synthetically useful, reactions.[134]

When thermally decomposed in the presence of copper catalysts, diazo-carbonyl compounds are believed to form copper carbenoid species[135-137] which do not normally suffer Wolff rearrangement.[136] With unsaturated diazoketones, the intramolecular addition of copper carbene complexes to a C-C double bond has become a standard operation for construction of polycyclic cyclopropyl ketones.[138-140] The cyclopropyl carbonyl unit can also be a useful synthetic intermediate.[141,142]

It was felt that the cyclopropyl ketone 29 could be transformed into a bicyclo[3.2.1]octane derivative, since, under

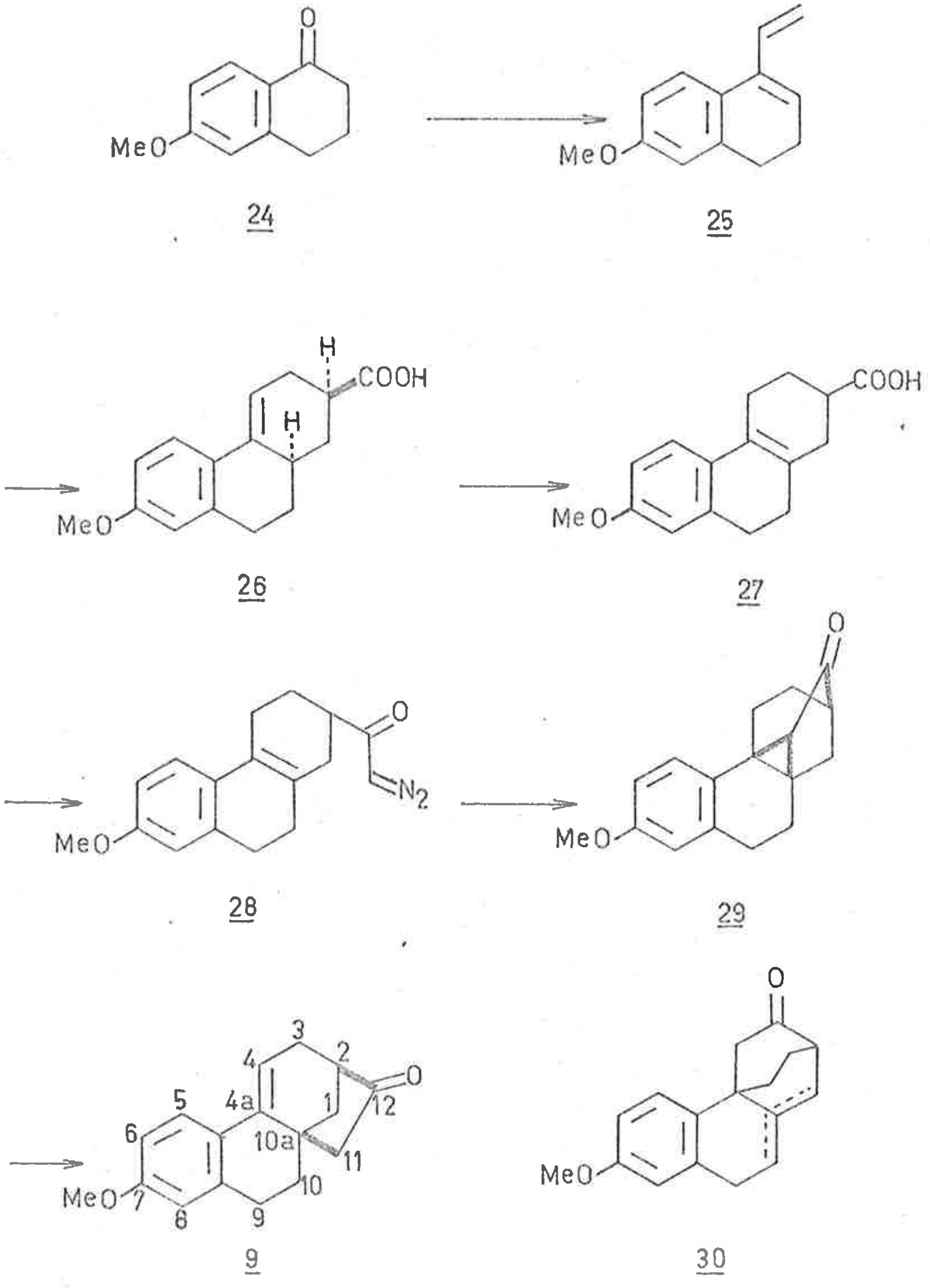


29

acidic conditions, the cyclopropyl bond conjugated to both the carbonyl group and the aromatic ring should cleave selectively. A similar cleavage of an aryl cyclopropyl ketone, labilised by incipient benzyl carbonium ion formation, has been observed.[143]

To test this hypothesis, it was necessary to prepare the cyclopropyl ketone 29. Therefore, the tricyclic acid 27 (see Scheme 5) was needed, since 29 should be available *via* intramolecular addition of the derived diazoketone 28. The carboxylic acid 27 is a known compound,[144] and is easily prepared by the literature method.[145,146] This route involves a four step sequence (Scheme 5) from the commercially available 6-methoxy-1-tetralone 24.[128]

The diene 25[145,147] and acrylic acid yield the Diels-Alder adduct 26,[145] as a single diastereoisomer after basic


O
MeO
24
MeO
25
H
COOH
H
MeO
26
COOH
MeO
27
O
N2
MeO
28
O
MeO
29
3
2
4
5
4a
1
12
O
6
10a
11
MeO
7
10
8
9
9
O
MeO
30

SCHEME 5

equilibration. Migration of the double bond of 26 into the tetrasubstituted position was smoothly achieved by hydrogen chloride in chloroform,[146] yielding the required carboxylic acid 27.

The acid 27 was converted to the diazoketone 28 in the usual way by sequential treatment with oxalyl chloride (8 molar equivalent) and diazomethane (5 molar equivalent).[148] Decomposition of 28 with copper powder in boiling cyclohexane led to the pentacyclic ketone 29 in 50-60% yield. Treatment of 29 with dry hydrogen chloride in chloroform resulted, as expected, in a specific breaking of the benzylic cyclopropyl bond. Tetracyclic ketone 9 was isolated in quantitative yield.

That the acid catalysed ring opening of 29 had indeed yielded the bicyclo[3.2.1]octane derivative 9 and not the possible alternative bicyclo[2.2.2]octane 30 (Scheme 5) was immediately obvious from the spectral characteristics of the product. The infrared spectrum showed typical cyclopentanone absorption at 1735 cm^{-1}, while confirmation of the structure 9 was obtained from the NMR spectrum. The C4 vinyl proton[≠] resonated as a triplet

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[≠] Numbering of all tetracyclic compounds is based upon the 2,10a-ethanopolyhydrophenanthrene system shown in Scheme 5. Although the ethano-bridge is depicted as β-oriented in this and subsequent compounds, all structures represent racemic mixtures.

(J3.5 Hz) at δ6.05 ppm, while the C5 aromatic proton appeared as a doublet (J 8 Hz) at δ7.57 ppm, a significant downfield shift when compared with the cyclopropyl ketone 29 (C5H at δ7.30). This downfield shift is undoubtedlycaused by the proximate double bond present in 9, and which would be absent in 30.

This result, together with those since published making use of very similar methods,[89,90] establishes the efficacy of the route for the synthesis of polycyclic compounds by introduction of a two carbon atom bridge. Other reports[141,142,149,150] also attest to the utility of the cyclopropyl carbonyl synthon in synthetic organic chemistry.

The efficiency for the conversion of tricyclic acid 27 to tetracarbocyclic ketone 9 was quite reasonable, approaching 50% overall yield. The major obstacle to more general utilization of the process is the moderate yield often obtained in the carbenoid addition step.[138-140]

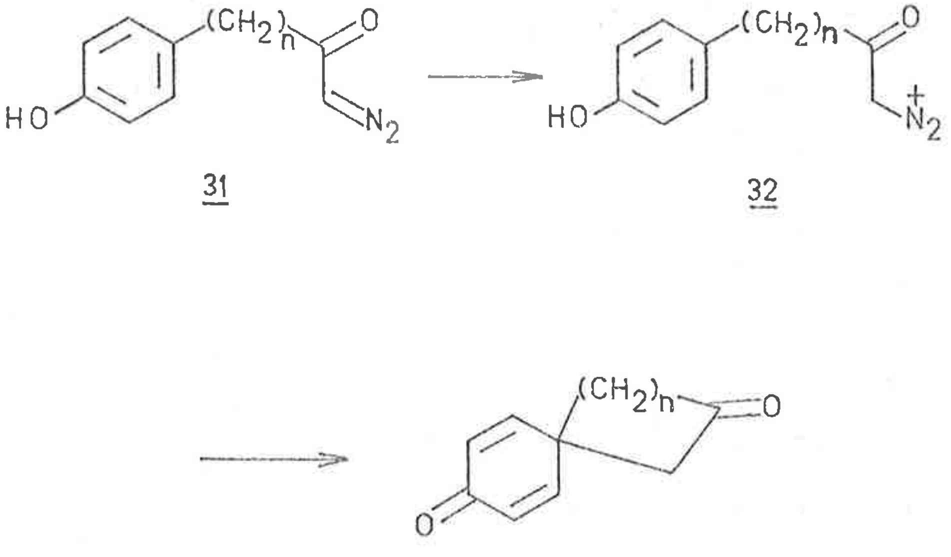
It became of interest, therefore, to determine whether diazoketone 28 could be cyclized to ketone 9 by a method not involving cyclopropyl ketone 29. This aspect of the work is discussed more fully in the next section.

(c) Acid Catalysed Cyclization of Diazoketones 37 and 28.

Reactions of diazoalkanes with acids have been extensively studied as a source of diazonium ions.[151,152] The acid catalysed decomposition of diazo-carbonyl compounds (diazoketones and ethyl diazoacetate) has been of great synthetic usefulness,[134] but the mechanisms leading to products from the intermediate keto-diazonium ions have not been unambiguously defined.

In aqueous acid, rapid and reversible protonation of the diazocarbonyl function occurs before loss of nitrogen.[153-156] In principle, rate determining loss of nitrogen could then occur by either an A-1 (unimolecular, carbonium ion intermediate) or A-2 (bimolecular displacement of nitrogen) mechanism. While some researchers have favoured an A-1 mechanism,[155] it is now recognized that their conclusions were based on criteria of dubious validity.[151,157] The A-2 mechanism is now widely accepted,[152,154,158] and has recently received definitive experimental support.[159] Although this discussion has referred chiefly to reactions in aqueous media, it may also be relevant in the non-aqueous systems which will be discussed below.

In this Department, it has been shown that phenolic diazoketones of structure 31 (Scheme 6), when treated with boron trifluoride-etherate (and other protonic acids with poorly nucleophilic conjugate bases), cyclise to give initially spiro-



31

32

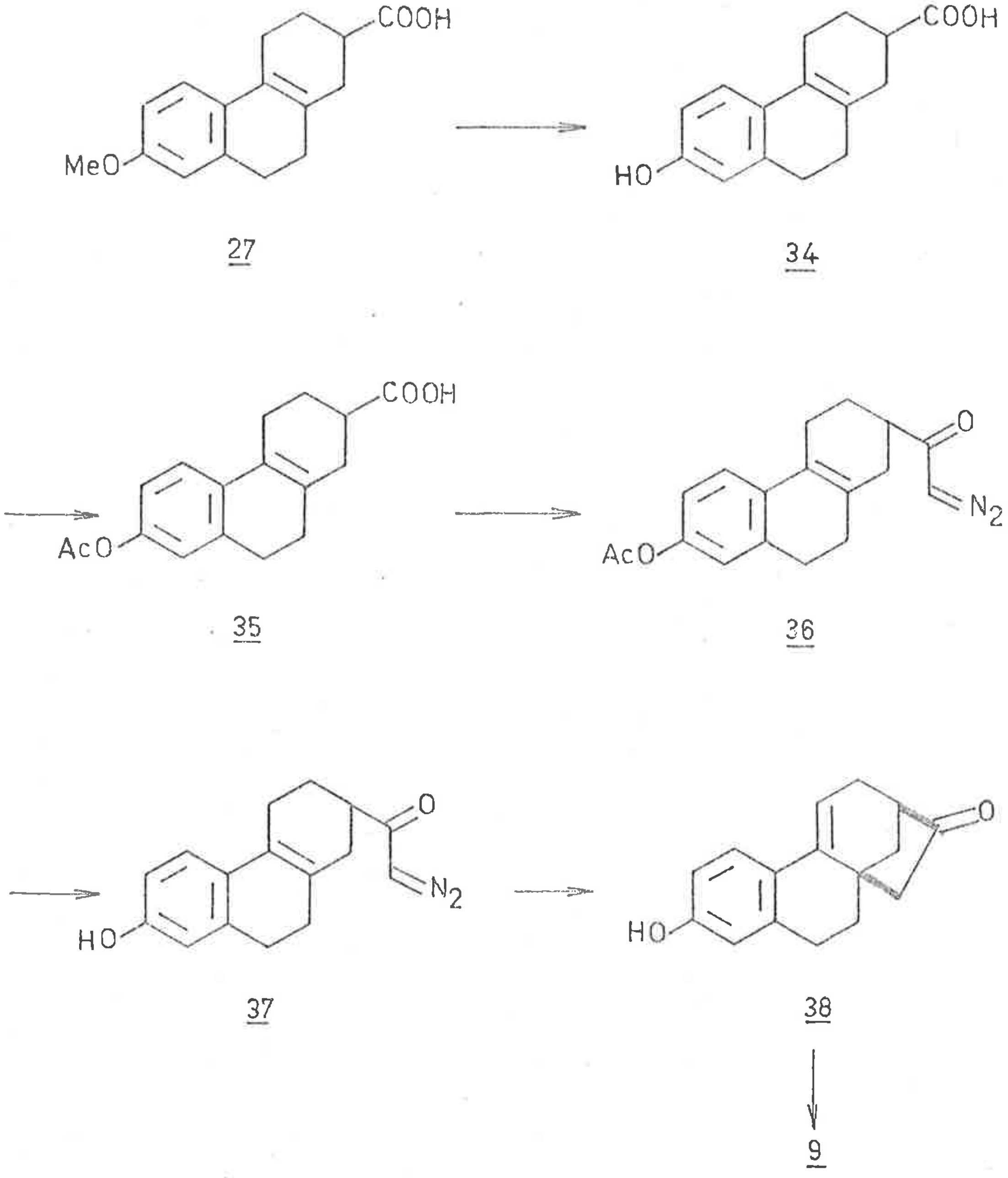
33

SCHEME 6 $n = 1-3$

dienediones 33.[160] It is believed that this conversion proceeds through the intermediate diazonium ion 32, with nitrogen displaced by the π-bond of the aromatic ring.[160,122]

It was of some considerable interest to determine whether this type of cyclization could be extended to a tricyclic precursor (e.g. the phenolic diazoketone 37), as this should lead in one step to a bicyclo[3.2.1]octane system. Diazoketone 37 was prepared by the multi-step procedure outlined in Scheme 7.

The carboxylic acid 27 (see page 24) was demethylated



SCHEME 7

by fusion with pyridine hydrochloride[161] at 200-220°. The phenolic acid 34 was obtained in excellent yield. The hydroxyl group of 34 was protected as the acetate 35, and the diazoketone 36 was then prepared in the usual way.[148] The protective acetyl group of 36 was smoothly removed by sodium carbonate in aqueous methanol, affording the required phenolic diazoketone 37 in good overall yield.

The reaction of 37 with a catalytic amount of boron trifluoride-etherate in nitromethane caused an immediate, vigorous evolution of nitrogen. The bicyclo[3.2.1]octane derivative 38 was isolated from the reaction mixture in 78% yield. Interrelation of 38 with the previously characterised tetracyclic ketone 9 was verified by methylation (dimethyl sulphate-sodium hydroxide), which gave only 9 and recovered starting material.

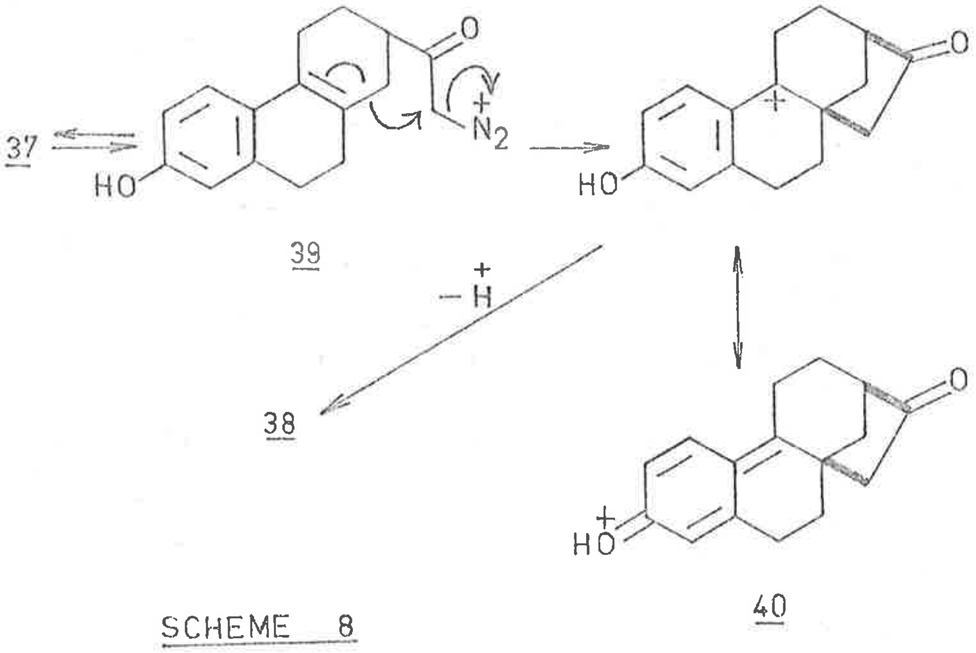
The mechanism of this Lewis acid catalysed reaction is no doubt closely related to that mentioned above for formation of the spiro-dienediones 33.[160] The diazoketone 37 is protonated ≠

≠ Protons necessary for the initial step may be released by interaction of boron trifluoride with the phenol,[162,163]

$$\mathrm{ArOH} + \mathrm{BF}_3 \rightleftharpoons \mathrm{ArO\bar{B}F}_3 + \mathrm{H}^+ .$$

An alternative mechanism, involving primary co-ordination of the diazoketone group with the vacant p-orbital of the Lewis acid, cannot be excluded.[114]

to the diazonium ion 39 (Scheme 8). This highly electrophilic species is attacked (probably in an S_N2 type reaction, comparable to the A-2 mechanism) by the strongly nucleophilic $\Delta^{4a,10a}$ - double bond, forming specifically the resonance stabilised benzylic carbonium ion 40. Collapse of the transient intermediate 40 leads directly to the observed product 38.



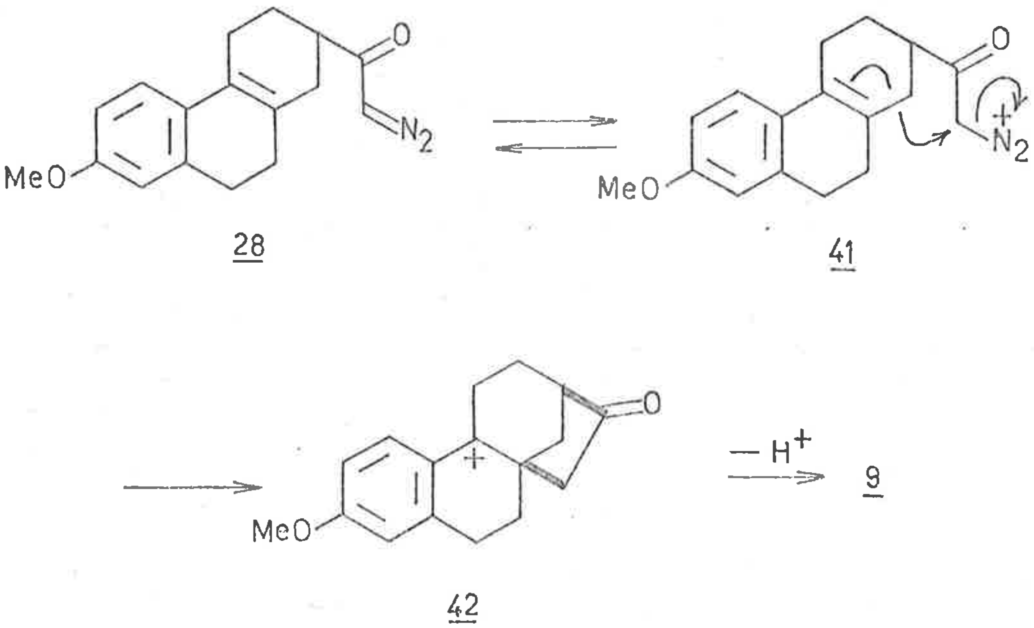
SCHEME 8

This result demonstrated that the concept which was briefly outlined in the Introduction, i.e. interaction of a C-C π-bond with an α-keto-diazonium ion, could be put into effect. The method does have practical significance for the production of the bicyclo[3.2.1]octane moiety since the critical cyclization step proceeded in high yield. Preparation of the precursor phenolic diazoketone 37 introduces a lengthy, but nevertheless efficient, synthetic sequency which clearly diminishes the effectiveness of the route.

If the rationale advanced for the cyclization step (Scheme 8) is substantially valid, there appears to be no reason why the methylated diazoketone 28 (page 24) should not also cyclize readily, on treatment with a suitable acid. The intermediate benzylic carbonium ion, if formed, should be stabilised to a comparable extent.

Indeed, when the diazoketone 28 was treated with a catalytic quantity of fluoroboric acid in nitromethane,[≠] the tetracyclic ketone 9 was isolated in excellent (>90%) yield (Scheme 9). The probably pathway of the reaction is also shown.

[≠] These conditions were selected because (i) the conjugate base of the acid was expected to be a poor nucleophile and (ii) the solvent has a low nucleophilicity and a high dielectric constant.



SCHEME 9

Three steps are involved :

(i) Initial protonation of diazoketone 28 leading to the transient α-keto-diazonium ion 41.

(ii) Disintegration of 41 by loss of nitrogen with nucleophilic participation by the C-C double bond.

(iii) Deprotonation of the benzylic carbonium ion 42 to give the observed product 9.

The conversion of diazoketone 28 to 9 could also be performed more simply, and in comparable yield, using trifluoroacetic acid[164] both as catalyst and solvent. Co-solvents (methylene chloride, chloroform) could be used without noticeable diminution in the yield of isolated product.

This last factor could be used in a particularly simple NMR technique for determining the course of attempted cyclization of diazoketones, without necessarily isolating any products. The diazoketone, as a solution (ca 10%) in deuterochloroform, was treated, in an NMR sample tube, with a drop of trifluoroacetic acid. When nitrogen evolution ceased, the spectrum of the mixture generally showed whether cyclization had occurred, and to what extent. Thus, the appearance of the C4 vinyl proton at ~6 ppm and the shift downfield, to ~7.5 ppm, of the C5 aromatic proton, was good evidence that the required cyclization had occurred.

The abridged route (via diazoketone 28) made possible a highly efficient synthesis of the bicyclo[3.2.1]octane derivative 9 involving only eight steps from 6-methoxy-1-tetralone 24. All the transformations were of consistently high yield ≠ (ca. 90% or

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≠ An exception is the Diels-Alder reaction, conversion of diene 25 to carboxylic acid 26, which gives a low yield of the required carboxylic acid.[145] A possible method which may circumvent this low yield step has recently been devised.[165]

greater).

The important difference between this method for construction of the bicyclo[3.2.1]octane framework, and most of those mentioned in the Introduction, is an obvious one. The problems involved with the introduction of a two carbon atom side chain at the (projected)B/C ring junction are not encountered in this new method. Here, the two carbon atom unit is introduced at an easily accessible position on the C ring and the cyclization step is then performed at the ring junction.

It may be anticipated that the ring closure reaction will find other applications in the synthesis of polycyclic compounds.[124] Several examples have already been reported.[125,160]

In this Chapter, three different routes to the tetracyclic ketone <u>9</u> have been discussed. Some further aspects of the chemistry of <u>9</u> are discussed in Chapter 4.

CHAPTER 2

CYCLIZATION OF SOME MORE COMPLEX DIAZOKETONES

(a) Diazoketone 47

(b) Diazoketone 66

(c) Diazoketone 71

In Chapter 1, the acid promoted cyclization of the diazoketone 28 was demonstrated to afford a high yield of the simple bicyclo[3.2.1]octane derivative 9. While this work was undoubtedly interesting, the reaction would be of little general utility if it could not be extended to the cyclization of more complex diazoketones. Logically, the most simple and useful extension would be to try diazoketones with a substituent on the same carbon atom as the diazomethyl ketone group. Then, if the cyclization was successful, this would lead to bicyclo[3.2.1]octanes substituted at the bridgehead, as shown :

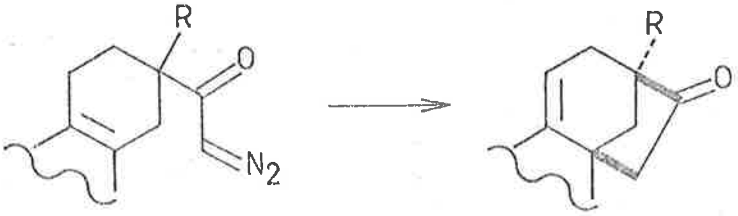

Figure 10

It was decided to attempt the preparation of bicyclo[3.2.1] octanes substituted at the bridgehead with (i) methyl, (ii) hydroxyl and (iii) bromo groups, using appropriately substituted diazoketones. These three cases are discussed separately in this Chapter.

(a) Cyclization of the Diazoketone 47

The synthesis of bicyclo[3.2.1]octanes incorporating a carbonyl function in the five membered ring adjacent to a bridgehead methyl group (Figure 10, R=CH_3) is an important task, for many of the degradation products of gibberellic acid 1 contain this array of functional groups as the C-D ring system.[2,3]

As the most simple extension of the cyclization reaction adumbrated in Chapter 1, it seemed that this ring system would now be accessible from the methyl substituted diazoketone 47. Accordingly, diazoketone 47 was prepared by the route outlined in Scheme 10.

Diels-Alder reaction between the diene 25[147] and 2-methylacrylic acid yielded a mixture, presumably of the diastereoisomers of acids 43 and 44.[≠] In order to reduce the number of possible isomers, the double bond was isomerized to the tetrasubstituted position by dry hydrogen chloride in chloroform.[146] The infra-red spectrum of the crude product indicated that

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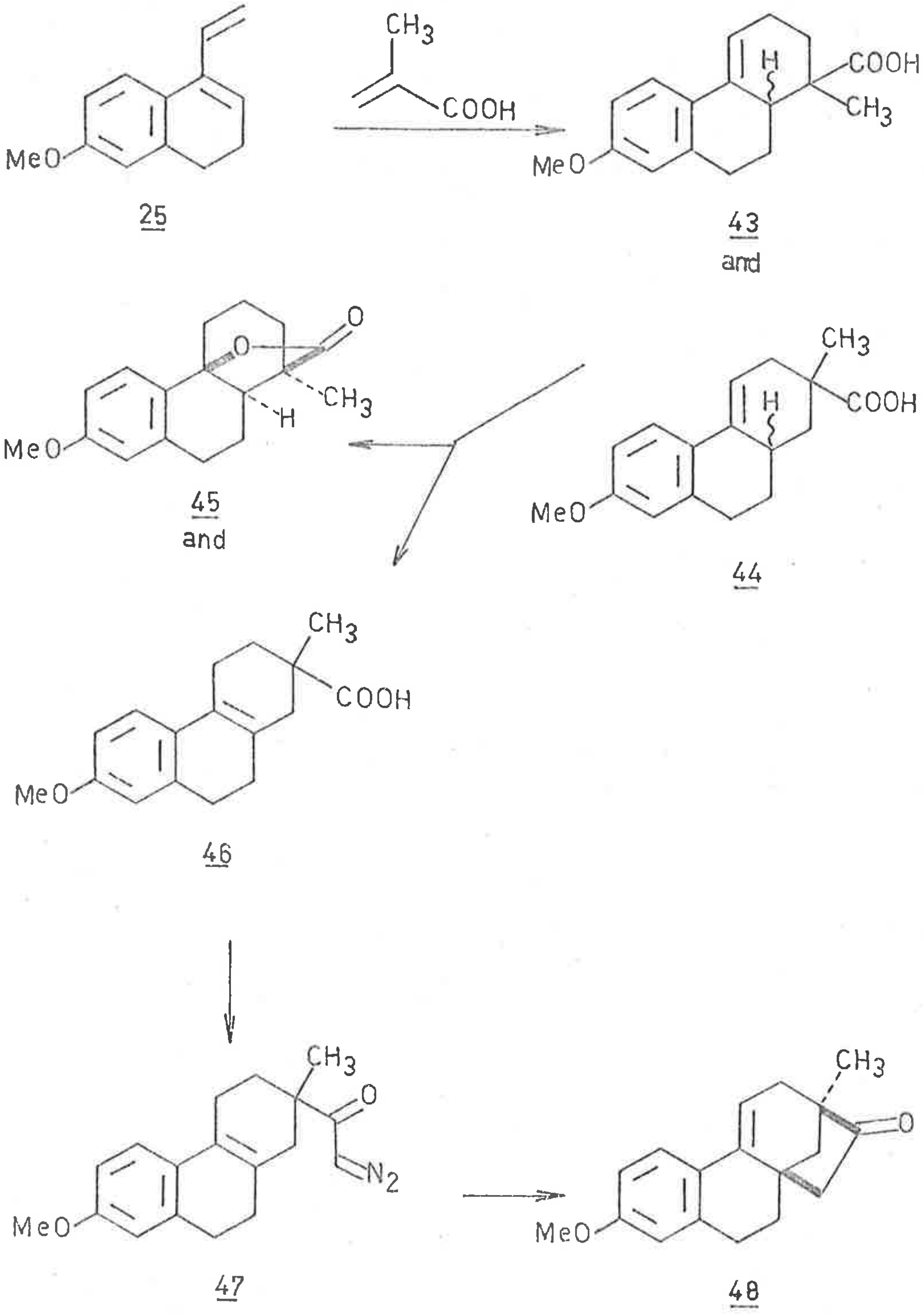
[≠] Although the presence of four possible acids in the mixture was not proved, it was supported by a cursory examination of the NMR spectrum of the crude product. This showed four distinct methyl resonances (singlets) in the region δ1.1-1.4 ppm.


MeO
25
CH3
COOH
COOH
CH3
MeO
43
and
O
O
CH3
H
MeO
45
and
CH3
H
COOH
MeO
44
CH3
COOH
MeO
46
CH3
O
N2
MeO
47
CH3
O
MeO
48

SCHEME 10

partial lactonization had occurred [ν 1760 (γ-lactone) and 1695 cm^{-1}]. Thus it appeared that the C1 acid had lactonized forming the γ-lactone 45.[166,167] (The formation of a corresponding δ-lactone from acid 46, which was not observed, would be kinetically less favourable[166-168]). It was possible to isolate from the mixture the desired acid 46 and the γ-lactone 45,[≠] each in about 20% yield, based on diene 25.

The diazoketone 47 was readily prepared from acid 46 by the usual two step procedure.[148] Decomposition of 47 in trifluoroacetic acid afforded the bicyclo[3.2.1]octane 48 substituted at the bridgehead with a methyl group. The yield of 48 was quantitative.

Thus, the acid catalysed cyclization of unsaturated diazoketones can be usefully extended to examples in which the diazoketone has alkyl substitution on the carbon atom bearing the diazomethyl carbonyl function.

[≠] The stereochemistry of the lactone 45 is not known, but the B-C *trans* structure is suggested from the mode of formation.[63,167,168]

(b) Cyclization of the Diazoketone 66

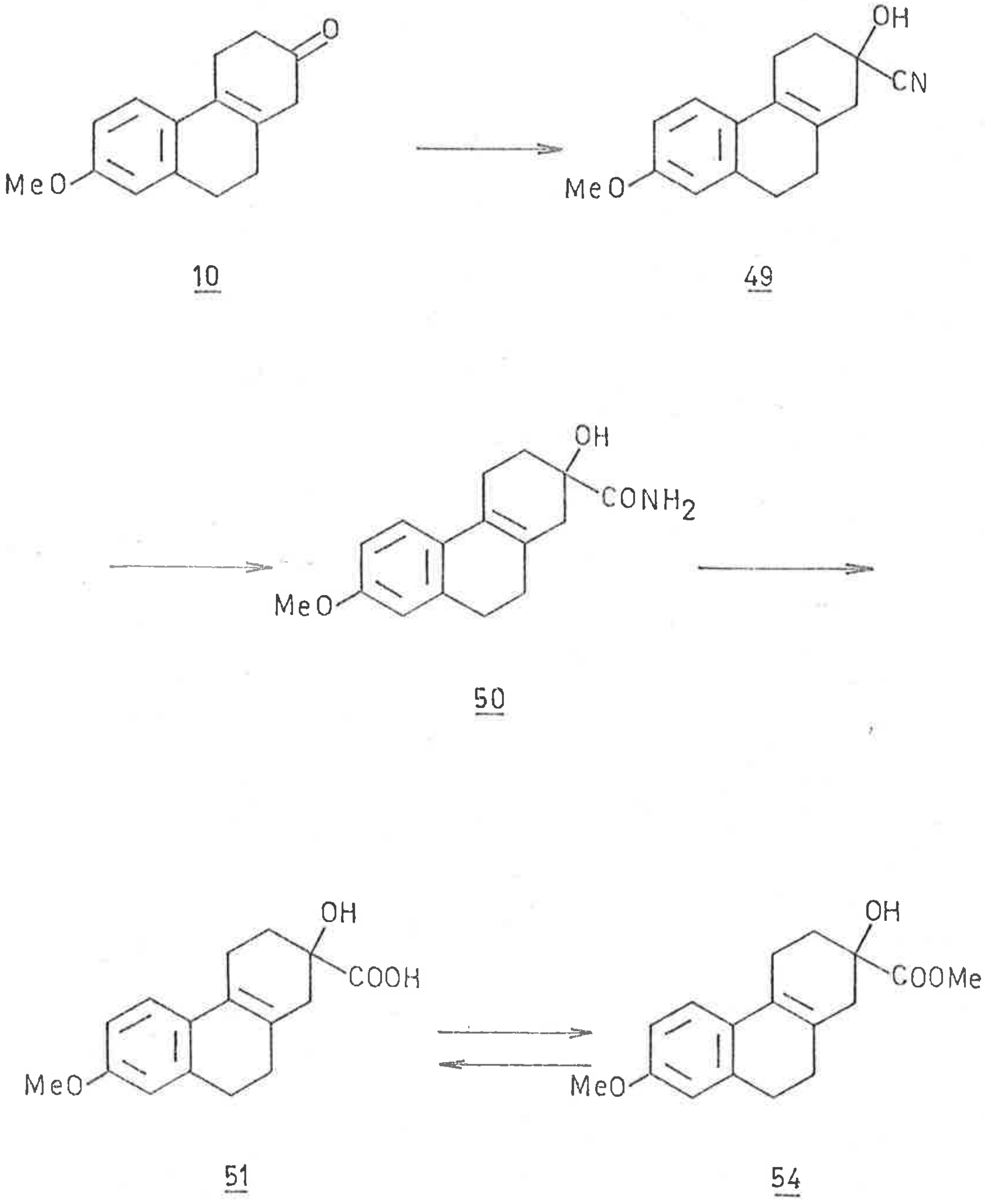
The next problem which was considered was whether acid promoted cyclization of simple diazoketones could be so modified as to allow a reasonably efficient synthesis of bicyclo[3.2.1] octanes functionalised at the bridgehead with an hydroxyl group. As mentioned previously, this was initially the basic objective of this research, and therefore these experiments were of crucial importance.

A suitable starting compound for this work appeared to be the α-hydroxy-acid 51, synthesised by the route shown in Scheme 11. Some aspects of this route deserve further comment.

The β,γ -unsaturated ketone 10 (see Chapter 1) was readily converted to the corresponding cyanohydrin 49, by treatment with sodium cyanide and hydrochloric acid in a two phase ether-water solvent system (c.f. ref[169]). The pure cyanohydrin 49 was obtained in 80% yield.

It was hoped that acid catalysed hydrolysis of the cyanohydrin 49 would lead simply, without complications, to the required hydroxy-acid 51.[173] Hydrolysis of 49, however, proved to be a very capricious reaction.≠

≠ This result was rather surprising. A model cyanohydrin 52, obtained from the 2-tetralone 13, was smoothly hydrolysed by


O
MeO
10
OH
CN
MeO
49
OH
CONH2
MeO
50
OH
COOH
MeO
51
OH
COOMe
MeO
54

SCHEME 11

Attempted hydrolysis of 49 with concentrated hydrochloric acid at 70° was unsuccessful and unchanged cyanohydrin was recovered. By raising the temperature to 110-120°, for 3 hr, hydrolysis could be effected, but extensive demethylation of the aromatic methoxyl group occurred concomitantly under these more vigorous conditions. No pure compound could be isolated from the mixture, even after acetylation and chromatography.

When the higher temperature hydrolysis was interrupted after a shorter time, a mixture containing acid, amide and other species was obtained. This was also unsatisfactory for preparative purposes. The use of acetic acid as a co-solvent had little ameliorating effect in any of the above modifications.

Finally, a method which has been used for hydrolysis of chemically sensitive nitriles[171,172] was found to be reasonably satisfactory for the cyanohydrin 49. Thus, solution of 49 in

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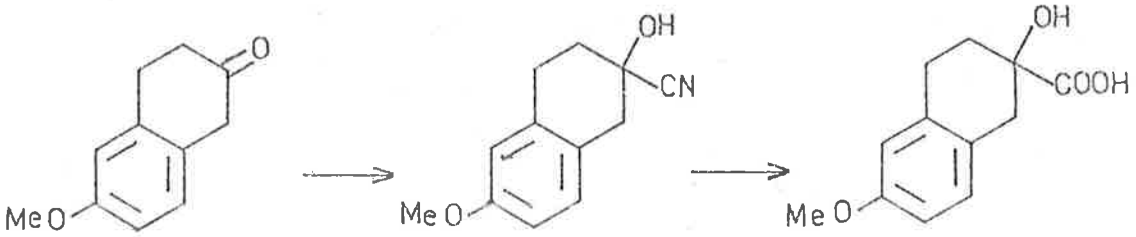
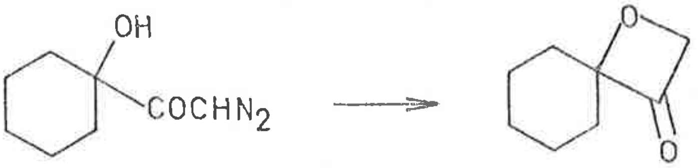
hot concentrated hydrochloric acid (70°, 4 hr). The hydroxy-acid 53 was obtained in 82% yield.[170]



13 52 53

concentrated sulphuric acid followed immediately by dilution with ice and water, gave the hydroxy-amide 50 in 60-65% yield. Hydrolysis of 50 with aqueous sodium hydroxide then gave the hydroxy-acid 51 which was purified and characterized as its methyl ester 54. Fortuitously, the ester 54 formed readily when an attempt was made to recrystallise the acid 51 from methanol. Pure ester 54 could be easily hydrolysed back to the desired hydroxy-acid 51. The overall yield of 51 from the ketone 10 was a disappointing 30%.[≠]

In 1952, Marshall and Walker[110] found that 1-diazoacetyl -1-hydroxycyclohexane 55 yielded the spiro-oxetanone 56 on treatment with acetic acid. Similar formation of a β-oxetanone



55 56

in the steroid field has also been noted.[111] It was therefore anticipated that the corresponding tricyclic α-hydroxy-diazoketone

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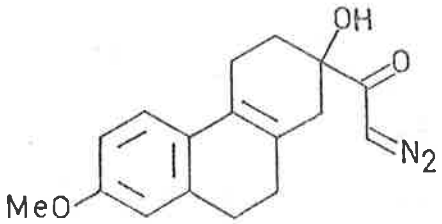
[≠] A more efficient synthesis of hydroxy-acid 51 has recently been devised.[165]

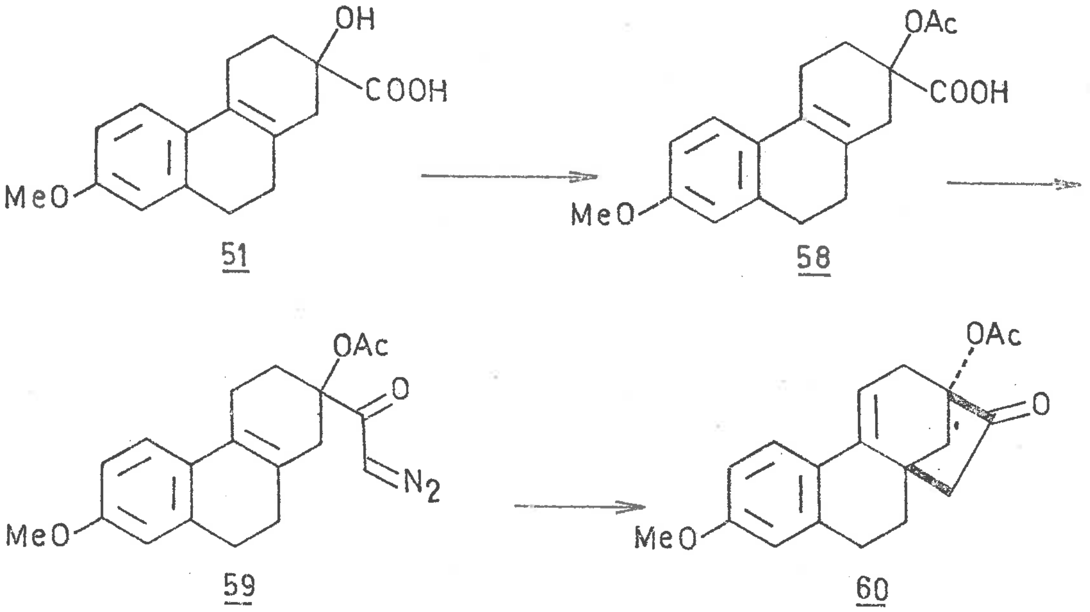
57 would cyclize preferentially by participation of the oxygen atom rather than by the double bond (i.e. the oxygen atom would probably be a more effective nucleophile than the π-bond for interception of the electrophilic diazonium ion). Moreover, diazoketone 57 would be difficult to prepare, since the hydroxyl group would need to be protected during introduction of the diazomethyl carbonyl function.



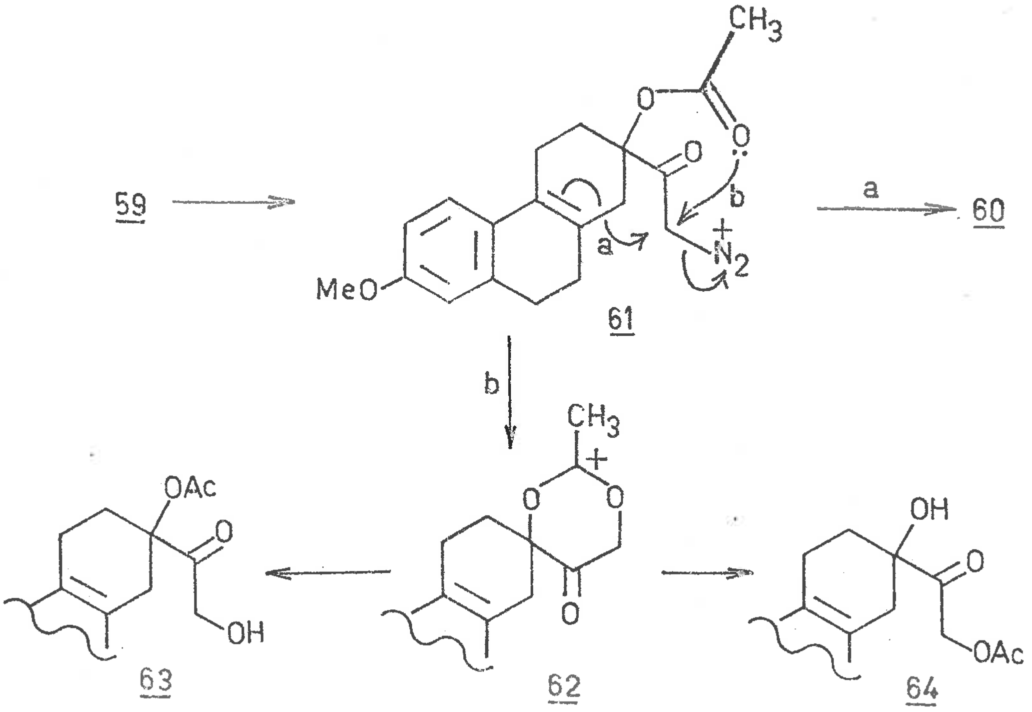
57

It was considered that a more fruitful approach would be to attempt the cyclization on a diazoketone in which the potential bridgehead hydroxyl group was masked with a protecting group. Use of the acetyl protecting group was investigated initially.

To this end, hydroxy-acid 51 was readily acetylated, yielding acetoxy-acid 58 (Scheme 12). Difficulty was experienced in converting this acid to the acid chloride. Only by using forcing conditions (2 hours' reflux with an excess of oxalyl



SCHEME 12



SCHEME 13

chloride in the presence of 1 molar equivalent of pyridine) could the acid chloride be prepared. Milder methods, either with or without pyridine failed.[≠] Once prepared, the acid chloride was easily converted to the diazoketone 59. The crude diazoketone 59, which was not very pure, was used for preliminary cyclization experiments.

A quick determination using the NMR technique described on page 34, provided evidence that the diazoketone 59 underwent partial cyclization on treatment with trifluoroacetic acid in deuterochloroform. Thus resonances at δ7.52 (d, C5H) and δ6.03 (t, C4H) ppm expected for the cyclized product 60, could be distinguished amongst other resonances. Integration of the triplet at δ6.03 ppm suggested that *ca.* 50% cyclization had occurred.

When the reaction was repeated on a larger scale, the product mixture was separated into two fractions by preparative thin layer chromatography. The higher R_F fraction (about 40%

[≠] Most of the other acids which were prepared in the course of this work, could be converted to their acid chlorides using very mild conditions (see Experimental). Another exception was the acid 65 which, like 58, contains an acyloxyl substituted tertiary carbon atom adjacent to the carboxyl group.

yield) appeared to be mainly the cyclized product 60 (δ7.53 and 6.03 ppm). The lower R_F material (about 30% yield) was still a mixture, but appeared to contain some of the uncyclized hydroxy-acetate 64 (δ5.13, s, $-COCH_2OAc$). No pure compounds could be isolated from either fraction.

One possible rationalization for the low yield of cyclized product 60 in this experiment is outlined in Scheme 13. It is proposed in this scheme that the intermediate diazonium salt 61 is attacked competitively by two different internal nucleophiles. Thus route a leads to cyclic product 60 *via* attack by the C-C double bond. In competition with this, route b, involving participation of the acetoxy group, gives the ion 62 which would be expected to lead to a mixture of hydroxy-acetates 63 and 64. However, only 64 was tentatively identified among the reaction products. Somewhat analogous nucleophilic participation of an acetate group is observed during the Woodward-Prevost reaction,[174,175] and in various solvolytic reactions.[176-178]

Three factors tend to make this particular method unsatisfactory for the synthesis of a bicyclo[3.2.1]octane system substituted at the bridgehead with an hydroxyl group. They are :

(i) Preparation of the diazoketone 59 is difficult.

(ii) Isolation of cyclized product is also difficult.

(iii) In any case, cyclization is not efficient.

For these reasons, another method was sought.

It was reasoned that a protective group which would render the whole oxy-substituent poorly nucleophilic would offer greater hope for a successful cyclization. Then interference by another intramolecular nucleophile (e.g. route b of Scheme 13) would be effectively suppressed in the critical step. A trifluoroacetyl group, because of the strongly electron with-drawing fluorine atoms, was therefore studied as an alternative protecting group.

Treatment of hydroxy-acid 51 with trifluoroacetic anhydride gave the trifluoroacetoxy-acid 65[≠] in quantitative yield. Although conversion of 65 to the diazoketone 66 (Scheme 14) proceeded without incident in a small scale trial experiment, when it was repeated on a larger scale, the crude diazoketone had partly lost the protecting group. In the infrared spectrum of the crude product, the normally strong carbonyl bond of the CF_3COO- group (1785 cm^{-1}) was abnormally weak. Moreover, the NMR spectrum showed at least two $-COC\underline{H}N_2$ resonances in the

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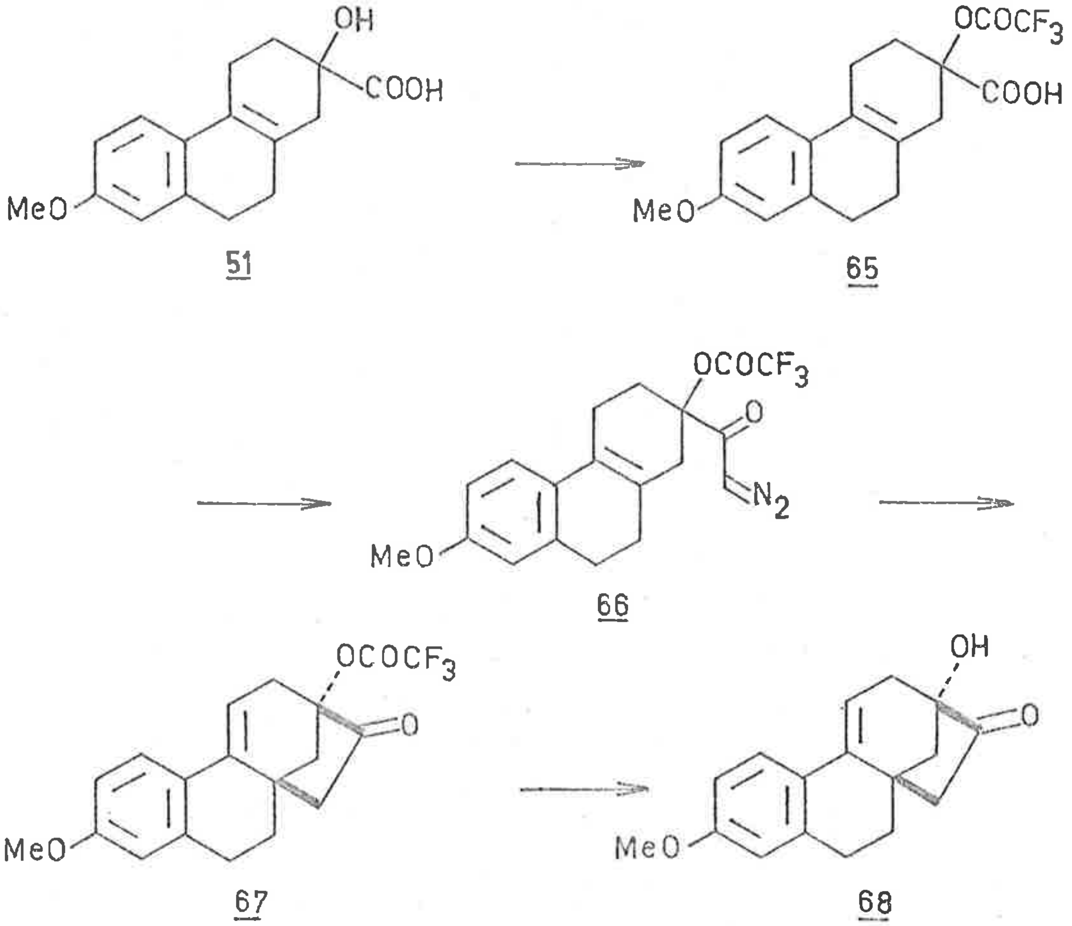
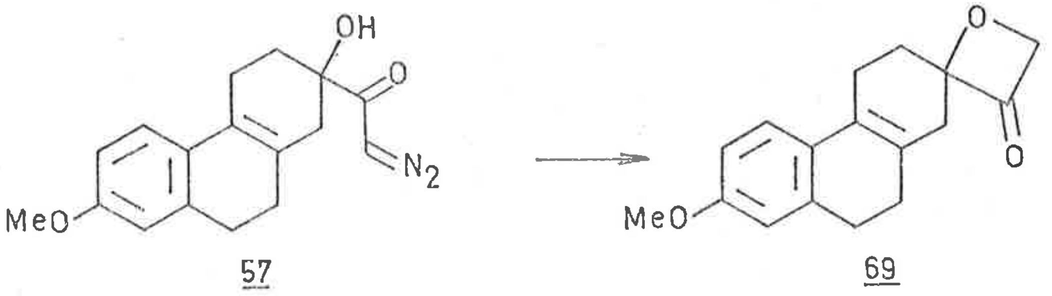
[≠] No attempt was made to purify any of the compounds containing a tertiary trifluoroacetoxy substituent. They were fully characterised spectrally.



SCHEME 14



SCHEME 15

δ5.5-5.9 region. This NMR sample was treated with trifluoroacetic acid, and from the new spectrum evidence was gained, in the usual way, which suggested that the desired cyclization had occurred to a limited extent. The product was isolated from this reaction and hydrolysed to remove the protecting group. The crude mixture now displayed infrared absorptions at 1815 (suggestive of a β-oxetanone) and 1750 cm^{-1} (cyclopentanone). All this evidence strongly suggests that the diazoketone originally obtained was a mixture of the required trifluoroacetoxy-diazoketone 66 and the hydroxy-diazoketone 57.

For useful results to be obtained in the cyclization, it was obvious by the above evidence that the contaminating hydroxy-diazoketone 57 had either to be removed or re-protected. The latter method was chosen. The mixture of diazoketones 57 and 66 was dissolved in trifluoroacetic anhydride containing pyridine (1 molar equivalent). After a short time (0.5 hr), a large excess of trifluoroacetic acid was added to effect cyclization. The crude ketol trifluoroacetate 67 was immediately hydrolysed to remove the labile protecting group. The desired ketol 68 was obtained, after chromatography, in ca 60% overall yield from the hydroxy-acid 51 without purification of the intermediates.

Thus the method is amenable to construction of bicyclo[3.2.1]octane systems containing a bridgehead hydroxyl group. It provides a relatively simple solution to the synthesis of the functional group array in the C-D ring system of gibberellic acid 1.[94,96,99,100]

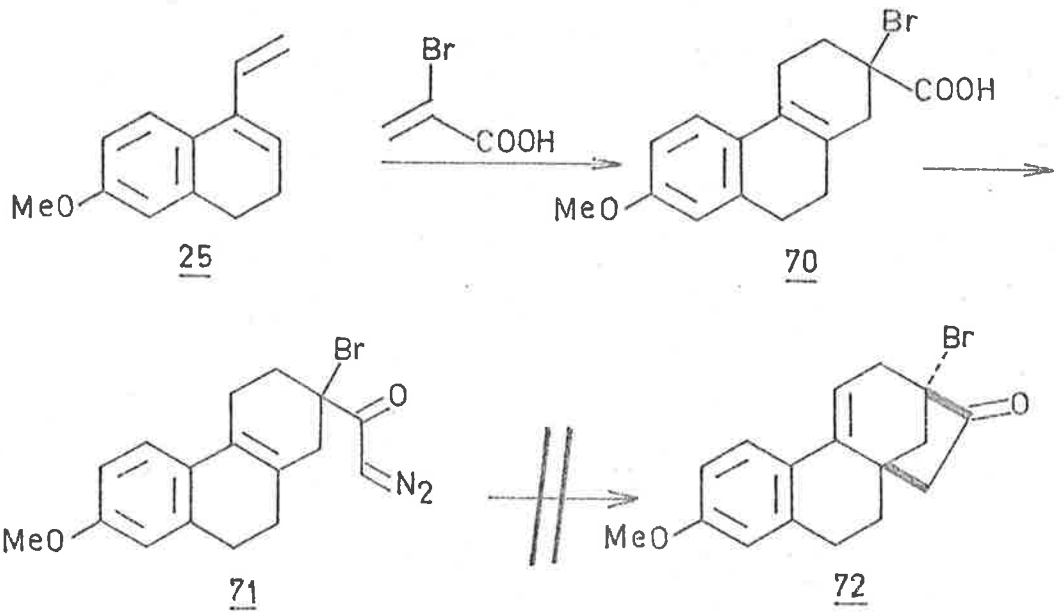
A small sample of the hydroxy-diazoketone 57 was secured by mild hydrolysis of a portion of the diazoketone mixture (66 and 57) referred to above. As expected, when 57 was decomposed with trifluoroacetic acid, only oxygen participation in displacement of nitrogen occurred.[110,111] The isolated product had the spectral characteristics expected of the spiro-β-oxetanone 69. (Scheme 15)

This result, and to a lesser extent those obtained with the acetoxy-diazoketone 59, points out very clearly one of the factors which must be considered in the cyclization of unsaturated diazoketones. Internal nucleophiles which can effectively compete with the π-bond must be rigorously excluded if the desired cyclization is to be achieved.

(c) Attempted Cyclization of the Diazoketone 71

Bicyclo[3.2.1]octane derivatives containing a halogen substituent at the bridgehead can be envisaged as useful intermediates for a number of purposes. In particular, if the halogen could be replaced by an hydroxyl group at some convenient stage, then a more efficient synthesis of a bridgehead hydroxyl substituted bicyclo[3.2.1]octane might result. Therefore, the preparation of a halogen substituted bicyclo[3.2.1]octane, by cyclization of the appropriately substituted diazoketone, was next investigated. The bromo-diazoketone 71 was chosen for detailed study and was synthesised by the route outlined in Scheme 16.

The Diels-Alder reaction between diene 25[147] and 2-bromoacrylic acid[179,180] afforded a single crystalline α-bromo-acid which precipitated from the reaction mixture, but in only 27% yield. The NMR spectrum of this product showed no vinyl proton resonance. It was therefore assumed that migration of the double bond into the tetrasubstituted $\Delta^{4a,10a}$ - position had occurred in situ. This migration of the double bond could have been catalysed by traces of hydrogen bromide released by partial decomposition of the unstable 2-bromoacrylic



SCHEME 16

acid.≠ It was assumed that the product was the C2 bromo-acid 70 and not the corresponding C1 isomer, from the well established

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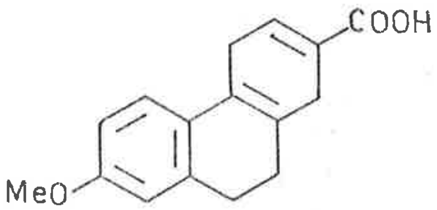
≠ It is significant that when the Diels-Alder reaction is performed in the presence of pyridine, an unrearranged Δ^4-bromoacid is obtained[165] (NMR δ6.07, m, C4 vinyl proton) presumably as a mixture of diastereoisomers. This product is converted quantitatively to acid 70 by hydrogen chloride in chloroform.

fact that, in similar Diels-Alder reactions, orientation of products is influenced by the polarity (and polarizability) of the diene and dienophile.[145,181] Particularly cogent supporting evidence is obtained from the reaction of ethyl 2-acetoxyacrylate with the diene 25. This dienophile, which would be expected to be polarized in the same direction as 2-bromoacrylic acid, affords only C2 substituted products.[165]

Strong corroborative evidence for structure 70 was obtained when the compound was treated with aqueous potassium carbonate. Although this experiment was performed with the idea of substituting an hydroxyl group for the bromo-group,[182,183] (which would have provided a shorter synthesis of hydroxy-acid 51) a dehydrobrominated product was instead produced. An unsaturated acid (ν 1675 cm^{-1}) was indicated by the infrared spectrum, but the ultraviolet absorption [λ_{max} 269 nm, ε16,000] did not suggest extensive conjugation. On the basis of NMR data, structure 73 was deduced for this dehydrobrominated product.



73

A triplet (J2.5Hz) at $\delta 5.73$ ppm was assigned to the C3 vinyl proton. In the $\delta 2.3$-3.4 region of the spectrum (i.e. allylic or doubly allylic protons), two distinct, but overlapping, AB quartets could be distinguished. Each quartet had J18Hz. These quartets could be seen even more clearly when the vinyl proton at $\delta 5.73$ was irradiated, to decouple secondary splittings. These separate AB quartets can be assigned to the C4 and C1 protons respectively with $J_{geminal}$ 18 Hz[≠] in both cases. This information is compatible only with structure 73 and no other.

If 73 is indeed the structure of the dehydrobrominated product (as all the spectral data consistently affirm), then the bromo-acid precursor must be the C2 isomer 70 (Scheme 16).

Acid 70 was converted to the diazoketone 71 by the standard stepwise procedure.[148] Diazoketone 71, however, underwent anomalous reactions in the presence of trifluoroacetic acid. Either without solvent, or in dilute methylene chloride solution, acid catalysed decomposition of 71 occurred *without*

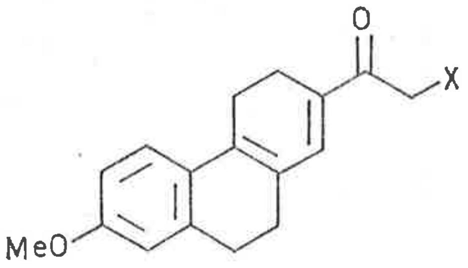
[≠] It is interesting to note that a geminal coupling constant of this absolute magnitude, implies that the methylene group is probably flanked by two π-bonded systems.[184]

apparent evolution of nitrogen,[≠] to form a brilliant red reaction mixture. Work up gave a very unstable oil, which decomposed rapidly, but which if triturated quickly with cold ether, yielded a small amount (ca 25%) of a bright yellow crystalline compound, which was reasonably stable in the solid state.

The infrared spectrum of the product showed strong bands at 1620 (conjugated C=O) and 1525 cm^{-1}. There was no absorption at ~1740 cm^{-1} for the expected bicyclo[3.2.1]octane derivative 72.

The NMR spectrum was very informative. Aromatic proton resonances at δ7.20 (1H,m,C5H) and 6.68 (2H,m,C6 and C8H) ppm suggested that no cyclization with participation of the double bond had occurred. Further resonances were observed at δ6.93 (s,1H), 4.13 (s,2H), 3.80 (s,3H,-OMe) and 2.2-3.1 (m,8H) ppm. The singlet at δ6.93 was assigned to a C1 olefinic proton (i.e. a Δ^1-double bond had been introduced) and the two proton singlet at δ4.13 to a methylene group flanked by a carbonyl and another electron withdrawing function. This methylene had probably originated from the diazomethyl ketone group. The partial structure 74 was thus tentatively assigned to this anomalous compound.

[≠] In all other acid catalysed reactions of diazoketones, copious evolution of nitrogen was observed.



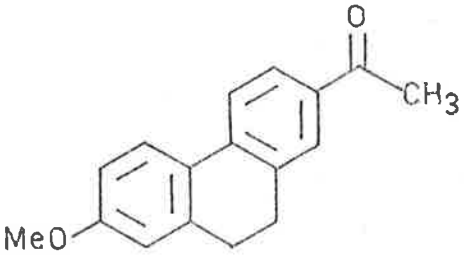
74

The highly conjugated nature of 74 was confirmed by the infrared data, and by the ultraviolet spectrum, which showed intense absorption at λ_{max} 404 nm (ε 23,000).

The compound gave a positive Bielstein test and microanalysis of the crude compound, although inaccurate, confirmed the presence of one bromine atom, and no nitrogen. The structure 74 (X=Br) was therefore assigned for this compound. A possible pathway accounting for the production of 74 (X=Br) will be discussed later, after attention has been drawn to some further aspects of the acid-catalysed decomposition of bromodiazoketone 71.

It was stated before that the yield of 74 (X=Br) obtained by acid decomposition of 71 was fairly low. The dark mother liquors remaining after crystallization of 74 (X=Br) were taken up in a large volume of ethanol and allowed to stand for several days. It was noticeable that this solution gradually lost most of its colour. From this solution, it was possible to isolate, by preparative TLC, a colourless crystalline compound in quite substantial amount.

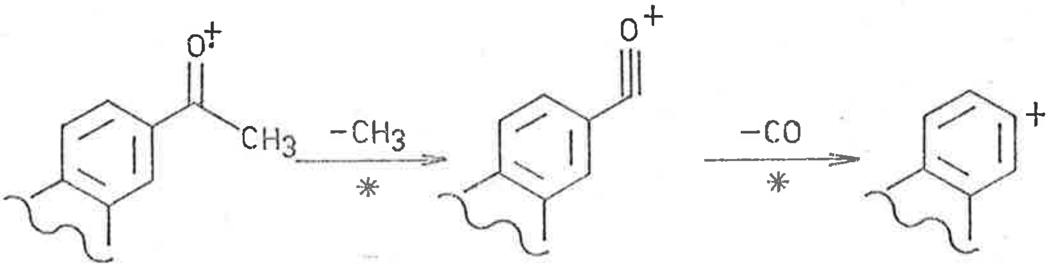
This new compound showed typical aromatic carbonyl absorption in the infrared (ν 1675 and 1595 cm^{-1}). The dihydrophenanthrene structure 75 could be readily derived for this compound from its NMR spectrum, which was unusally simple.



75

Thus, aromatic proton resonances centred at δ7.80 (m, 4H, C1, C3, C4 and C5 protons); and at δ6.85 (m, 2H, C6 and C8 protons) ppm could be readily assigned. Furthermore, singlet resonances at δ3.80 (3H), 2.88 (4H, slightly broadened) and 2.58 (3H) ppm were assigned to the -OMe, C9 and C10 protons, and -COCH$_3$ groups respectively. There were no other absorptions in the spectrum.

The mass spectrum provided corroborating evidence for structure 75. A strong molecular ion was apparent at m/e 252 ($C_{17}H_{16}O_2$=252) together with an almost equally strong daughter ion at m/e 237. This was no doubt due to loss of $CH_3^\bullet$ by α-cleavage from the molecular ion (substantiated by a metastable peak at 222.9) to give the stable aroyl ion 76. An ion at m/e 209 corresponded to loss of CO (also substantiated by a metastable peak at 184.3) from 76 to give the aryl cation 77 (Scheme 17).[185] Further decomposition of this ion was also in accord with the structure 75.



75 (m/e 252) 76 (m/e 237) 77 (m/e 209)

SCHEME 17

Thus, it has been shown that the trifluoroacetic acid catalysed decomposition of bromo-diazoketone 71 had yielded the bromo-ketone 74 (X=Br) in ca 25% yield as well as the dihydrophenanthrene 75 in *ca* 50% yield. It was of some importance to determine the relationship between these two products. Several simple experiments quickly demonstrated that 75 was formed by further decomposition of the bromo-ketone 74 (X=Br).

This evidence is summarized below.

(i) The yellow ethanolic solution of 74 (X=Br) used for determination of the UV spectrum decolourised within a few hours. The presence of 75 in the solution could now be detected by TLC. No other compounds were exposed by this analysis.

(ii) The course of the reaction was studied by the small scale NMR technique described earlier. At first, resonances of the bromo-ketone 74 (X=Br) could be clearly discerned. After 0.5 hr these had disappeared, and resonances due to the dihydrophenanthrene 75 could now be seen. The order of appearance of products was therefore ascertained, although other minor absorptions could also be seen in the spectra.

(iii) On one occasion during determination of the NMR spectrum of 74 (X=Br), the compound spontaneously decomposed in the sample tube. The resonances of 74 (X=Br) vanished, and were replaced *singly and completely* by those of 75. Moreover, copious evolution of gaseous hydrogen bromide was observed.

(iv) A sample of the bromo-ketone 74 (X=Br) when melted (m.p. 58-59°) was observed to resolidify. This solid

Melted again at the same temperature as the dihydrophenanthrene 75 (m.p. 132-133°).

(v) The mass spectrum observed for 74 (X=Br) was identical to that of 75. Thus, it appeared that thermal decomposition of 74 (X=Br) to 75 occurred before any sample reached the electron beam of the mass spectrometer.

The information which was obtained pertaining to the acid catalysed decomposition of bromo-diazoketone 71 can now be concisely stated :

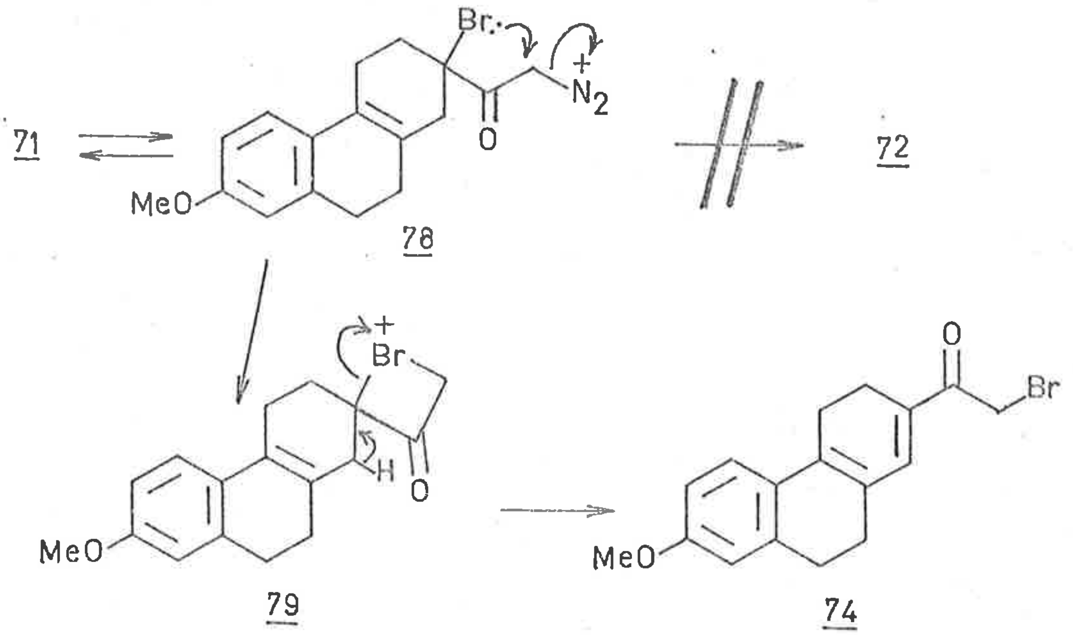
(a) The primary product of the decomposition is the bromo-ketone 74 (X=Br) in which the bromine atom has migrated to another position, and an extra double bond introduced.

(b) The secondary product, produced by further decomposition of the metastable intermediate 74 (X=Br), is the dihydrophenanthrene 75 which is formally a dehydrobrominated analogue of 74 (X=Br).

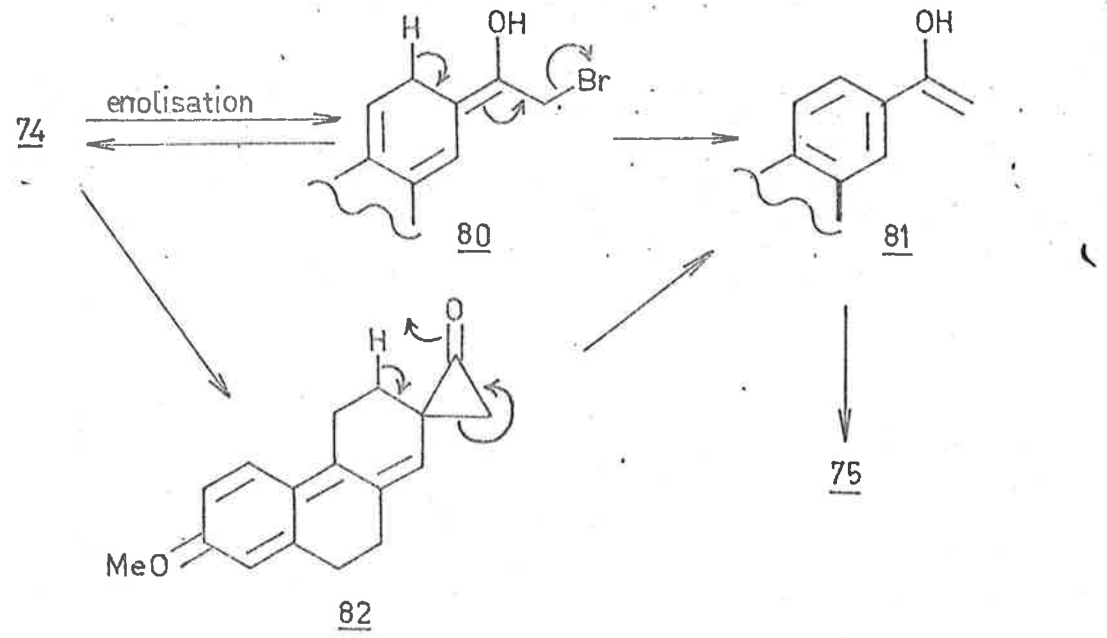
(c) Clearly, conversion of 74 (X=Br) to 75 is an extremely facile process (thermal and/or acid catalysed)

(d) None of the bromo-substituted bicyclo[3.2.1]octane derivative 72 is formed.

A mechanism which accounts for these transformations is outlined in Scheme 18. It is proposed (Scheme 18a) that the diazonium ion 78 from protonation of the diazoketone 71, loses nitrogen by attack of the bromine atom to form the bromonium salt 79. Collapse of ion 79 occurs with loss



SCHEME 18a



SCHEME 18b

of a C1 proton, giving the observed bromoketone 74.

Some aspects of this scheme deserve further comment. First, no double bond participation in the loss of nitrogen from diazonium salt 78 is observed. The bromine atom is apparently a much more effective internal nucleophile (for reasons which may be steric as well as electronic). Secondly, although the step 78 to 79 is indicated as formal displacement of nitrogen, no nitrogen was ever observed to be evolved, and the fate of the nitrogen atoms remains a mystery. Thirdly, some support for the intermediacy of bromonium ion 79 comes from some recently published work.[186,187] Smooth formation of three and five membered cyclic halonium ions, with consequent 1,2 or 1,4-halogen shifts, has been observed for some solvolytic reactions *in trifluoroacetic acid*. It was found, however, that four membered cyclic halonium ions could not be formed, because "..... favourable entropy effects cannot compensate for strain in the formation of four-membered-ring halonium ions....".[186]≠ With a carbonyl group in the four membered ring, however, some of the severe non-bonded interactions which normally make formation of four membered rings so

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≠ Notwithstanding this objection, a 1,3-bromine shift involving a presumed four membered cyclic bromonium ion has been detected.[188]

unfavourable, should be removed. This could have the effect of lowering the transition state energy sufficiently so that the balance of entropy and energy effects may now be opportune for formation of a four membered cyclic intermediate[≠] (e.g. bromonium ion 79).

Several routes can be imagined for dehydrobromination of bromoketone 74. Two of these are outlined in Scheme 18b. The simplest assumes that enolization of 74 occurs, followed by a 1,4-dehydrobromination[189,190] (i.e. 74 → 80 → 81) leading to the enol 81 of the observed product. A second possible route involves π-bond participation (expected to be very favorable) in displacement of bromide ion from 74 to form a cyclopropanone e.g. 82. Transfer of the C3 proton to oxygen (perhaps a 1,5-sigmatropic shift) should then lead to enol 81.[193] Other mechanisms involving 1,3-shift of bromine[191,192] followed by dehydrobromination, or zwitterionic intermediates (c.f. Favorskii rearrangement[193,194]) can also be envisaged.

The most pertinent factor of Scheme 18 concerns the reasoning advanced to explain why bromo-diazoketone 71 failed to cyclise. It is because diazoketone 71 incorporates within its

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[≠] In support of this idea, formation of four membered rings containing a carbonyl group is quite well known during acidic decomposition of diazoketones.[110,111,116,117,160] molecular structure a more effective internal nucleophile than the π-bond of the C-C double bond. This result recalls the failure of the hydroxy-diazoketone 57 (and to a lesser extent acetoxy-diazoketone 59) to undergo cyclization.

The unexpected result obtained with bromo-diazoketone 71 makes the concluding remarks of the last section [Chapter 2(b)] now appear much more cogent.

CHAPTER 3

SOME FURTHER EXAMPLES OF ACID CATALYSED DECOMPOSITION OF DIAZOCOMPOUNDS

(a) Diazoketone 87

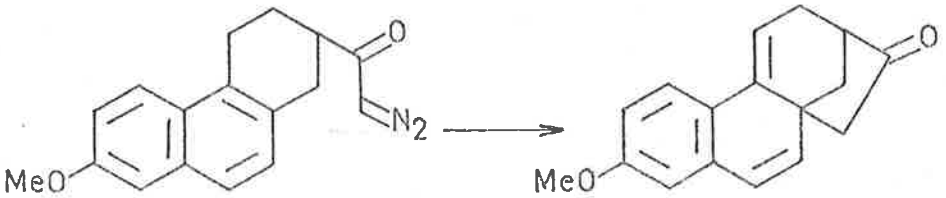
(b) Diazoacetic ester 98

It has been shown that acid catalysed cyclization of unsaturated diazoketones represents a promising method, in certain cases, for the preparation of synthetically useful polycyclic compounds. It is desirable to study further examples of this reaction in the hope that they (i) may lead to other useful polycyclic derivatives, and (ii) may reveal more clearly the course of the reaction. For these reasons, cyclization of two further diazocarbonyl compounds was attempted.

The compounds chosen were (a) the more highly unsaturated diazoketone 87 and (b) the diazoester 98. These two examples are discussed separately in this Chapter.

(a) Cyclization of the Diazoketone 87

In the Introduction, it was pointed out that one of the important factors in the present approach towards synthesis of gibberellins was the need to contract the B ring at some convenient stage. A double bond situated within ring B would be suitable to allow this contraction.[103-107] Therefore, a useful compound might be the bicyclo[3.2.1]octane derivative 88. A possible precursor of 88 is the diazoketone 87, as shown :



87 88

Clearly, the tetrahydrophenanthrene acid 86[≠] was required for this work. In principle, 86 can be made simply by selective dehydrogenation of the hexahydro-analogue 27 (see Chapter 1). In practice, this proved to be considerably more

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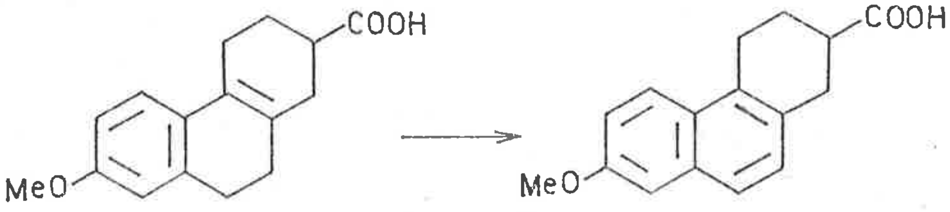
[≠] Acid 86 is a known compound and has been synthesised by two different methods.[145,196] Neither method was suitable for the present purposes, and a new route was sought.



27 86

difficult than it might at first appear.

One method which has been used on several occasions to effect specific dehydrogenation of alkyl aromatic compounds is a two-step bromination-dehydrobromination sequence.[197-199] N-Bromosuccinimide is usually the reagent of choice for the first step.

Treatment of acid 27 which N-bromosuccinimide (1 molar equivalent), using a variety of conditions, consistently afforded a bright yellow product. NMR analysis of this crude product showed it to be a mixture of at least three compounds (three distinct OMe signals). Moreover, it was apparent that dehydrobromination had occured concomitantly with bromination,[197,198] for there was no CHBr resonance. A more detailed analysis indicated that the desired acid 86 was present[≠] in the mixture and appeared to be

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[≠] Fortunately, an authentic sample of acid 86 was available (c.f. ref[234]) from some other research. Thus, direct NMR comparison was possible.

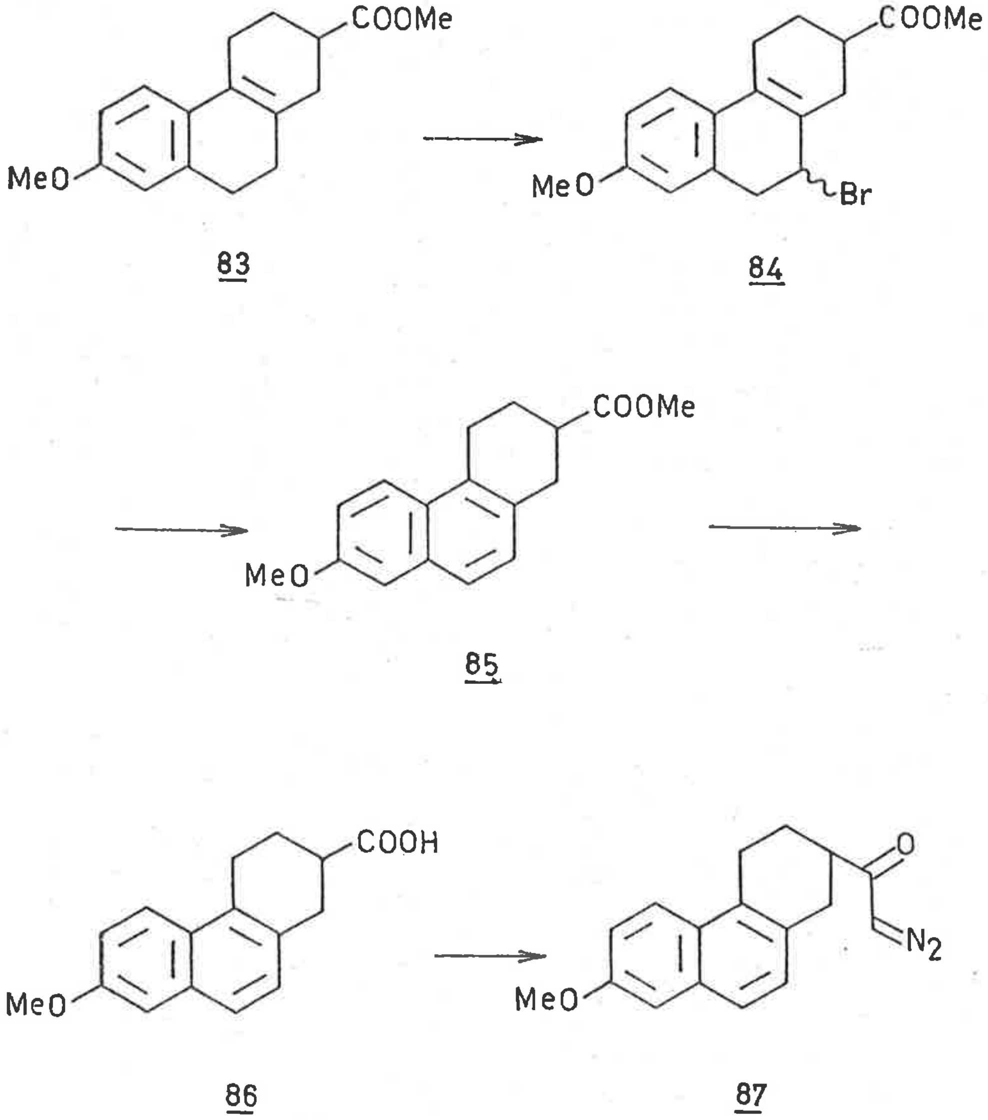
the major component (ca 50%). It was impossible, though, to separate any pure compound from the mixture.

The reason why this particular reaction proved so troublesome probably lies in the non-selectivity of the initial bromination step. Acid 27 has four sites (at C1, C4, C9, and C10) where bromination might occur. This could lead, of course, to several different dehydrogenated species. In fact, it is tempting to speculate that the bright yellow colour of the product mixture is due to the presence of the highly conjugated Δ^1-isomer (c.f. bromo-ketone 74). This would be an expected product if the 1-bromo-isomer was formed initially.

Attempted selective dehydrogenation of acid 27 with chloranil[200] was also fruitless. No dehydrogenation occurred with this reagent, and starting material was recovered.

A severe problem with the above reactions was the very poor solubility of acid 27 in the solvents used. It was thought that the more soluble methyl ester 83 of 27 would give less complicated reactions.

Accordingly, methyl ester 83 was prepared from acid 27 with diazomethane (Scheme 19). Very brief treatment of 83 with N-bromosuccinimide (1 molar equivalent) gave an almost colourless crystalline product. This product showed a one proton multiplet at δ5.23 ppm in its NMR spectrum, indicative of a CHBr



SCHEME 19

proton. The position of the bromine atom was not definitely determined. The compound was unstable and lost hydrogen bromide very readily. This process could be followed by NMR spectroscopy, and, except for traces ($<10\%$) of other compounds, the product was exclusively the desired tetrahydrophenanthrene ester 85. This suggests, though does not prove, that the intermediate bromo-compound may have been the C10 isomer 84.[≠] Apparently, ester 83 undergoes more selective bromination than the corresponding acid 27. The reason for this is not clear.

Large scale dehydrobromination of the bromo-ester 84 was effected with calcium carbonate in hot dimethylformamide.[201] The ester 85[196] was obtained in 50% overall yield from carboxylic acid 27. Hydrolysis of 85 then gave a quantitative yield of the required dehydrogenated acid 86.

Acid 86 was smoothly converted to the corresponding diazoketone 87, but trifluoroacetic acid decomposition of 87 gave a complex mixture of products containing none of the expected

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[≠] If the bromine atom had been at C9, rather than at C10, the benzylic CHBr proton would probably have been more highly deshielded and therefore further downfield. Thus, in a structurally related compound, a benzylic CHBr resonance occurred at $\delta 5.57$ ppm.[199]

bicyclo[3.2.1]octane derivative 88.

One of the components of the mixture which could be readily identified spectroscopically, but which was not isolated, was the uncyclized α-ketol trifluoroacetate 89. (Scheme 20) Thus, minor bands in the infrared spectrum at 1785 and 1720 cm^{-1}, and a singlet resonance at δ5.17 ppm in the NMR spectrum, were due to the product 89. Careful integration of the methylene singlet at δ5.17 suggested that 89 comprised about 15% of the mixture.≠

The major fraction (ca 80%) of the product was separated as a yellow oil by preparative TLC. This fraction, however, was

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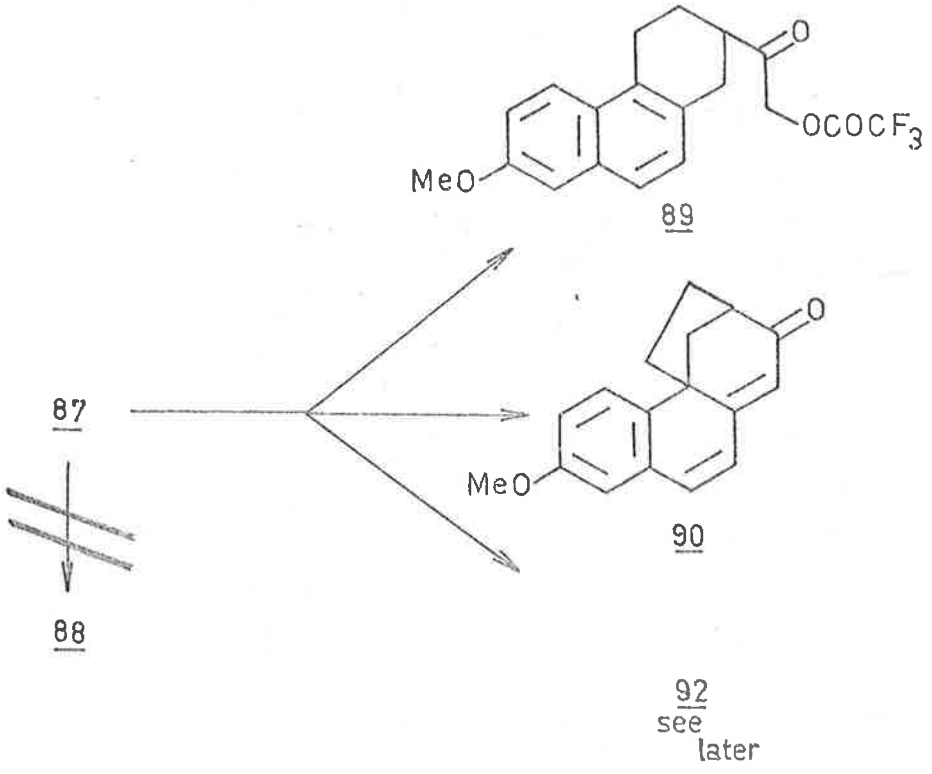
≠ The proportion of uncyclized 89 depended markedly on the way in which the reaction was performed. In trifluoroacetic acid without co-solvent, 89 was a very minor product, whereas if methylene chloride was used as solvent, then the proportion of 89 became considerably more abundant. This sort of behaviour has been noted in other cases,[160] and suggests that displacement of nitrogen from the diazonium ion by trifluoroacetate anion proceeds via an intimate ion-pair mechanism.[235] Other factors being equal, in the more strongly ionizing solvent, trifluoroacetic acid, the ion-pair is more readily disrupted, and so less of the product emanating from this pathway occurs.

still a mixture of two difficultly separable compounds in an approximate ratio of 3:1 (by NMR). The resonances due to the major component were easily distinguished, and suggested that the structure of this component was the conjugated dienone 90. (See Experimental for the spectral details). The structure 90 was supported by infrared (ν 1655 cm^{-1}) and ultraviolet [λ_{max} 368nm (ε 10,000)] absorptions.≠ Obviously, some skeletal rearrangement



SCHEME 20

≠ Wenkert and Stevens[202] have reported the preparation of a compound having a chromophore very similar to that in 90. They report IR: $\nu_{C=O}$ 1655 cm^{-1} and UV: λ_{max} 354 nm (ε 15,000).

had interceded in this reaction.

The identity of the minor component of the yellow oily mixture was not immediately apparent. Discussion of its structure will be deferred until the acid catalysed reaction of a related cyclopropyl ketone 91 is dealt with. Possible pathways accounting for the products will also be discussed then.

Since this cyclization reaction had not yielded any useful products, recourse was made to the carbenoid addition method [Chapter 1(b)] to achieve cyclization. It was hoped that this route would give a less complex result, and perhaps even yield the required bicyclo[3.2.1]octane derivative 88.

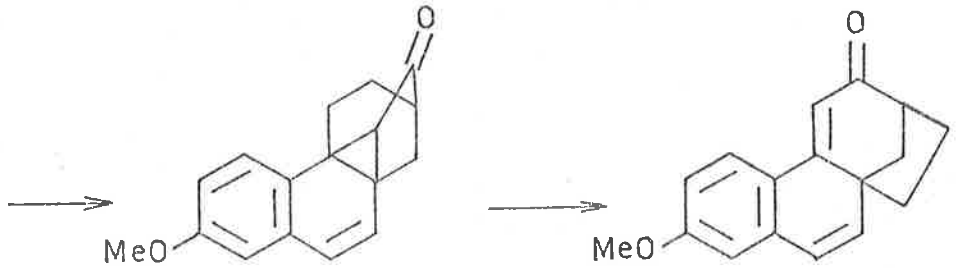
Cyclopropyl ketone 91 was formed, in 55-65% yield, when the diazoketone 87 was thermally decomposed in the presence of copper powder.

Comparison of cyclopropyl ketone 91 with its dihydro-analogue 29 uncovered an interesting feature. In 91 the cyclopropyl proton at C11 resonated as a doublet (J 1.3Hz, long range W coupling[203] with the C2 proton) at δ0.85 ppm, whereas the corresponding proton in 29 was at least 70 Hz further downfield (under the methylene envelope δ1.8-2.3). While the C11 proton in cyclopropyl ketone 91 may be shielded by the ring B double bond, it is difficult to imagine such a large effect from a single π-bond. It is tempting to speculate that the large shift is observed because the cyclopropyl proton, which is situated directly above the B ring (by models), is strongly shielded by the induced ring current in the formally homo-aromatic B ring.[204]

Cleavage of cyclopropyl ketone 91 was effected under very mildly acidic conditions (*p*-toluenesulphonic acid in acetone). This gave, in quantitative yield, a pale yellow oil which was pure by all the usual criteria. This product was different (IR, NMR) to the major product of acidic decomposition of diazoketone 87, but a close examination of the NMR spectra indicated that it was the same as the minor product from 87. It was not the bicyclo[3.2.1]-octane 88.

The spectral data for this compound also indicated its highly conjugated nature (IR: ν 1655 cm^{-1}; UV: λ_{max} 363nm(ε 16,000)]. The structure 92 (i.e. isomeric with compound 90) was in reasonable accord with this and the NMR data (see Experimental).

87



91

92

Thus, three facts seem clear.

(1) Acid catalysed cleavage of cyclopropyl ketone 91 gives quantitatively the rearranged bicyclo[3.2.1]octane derivative

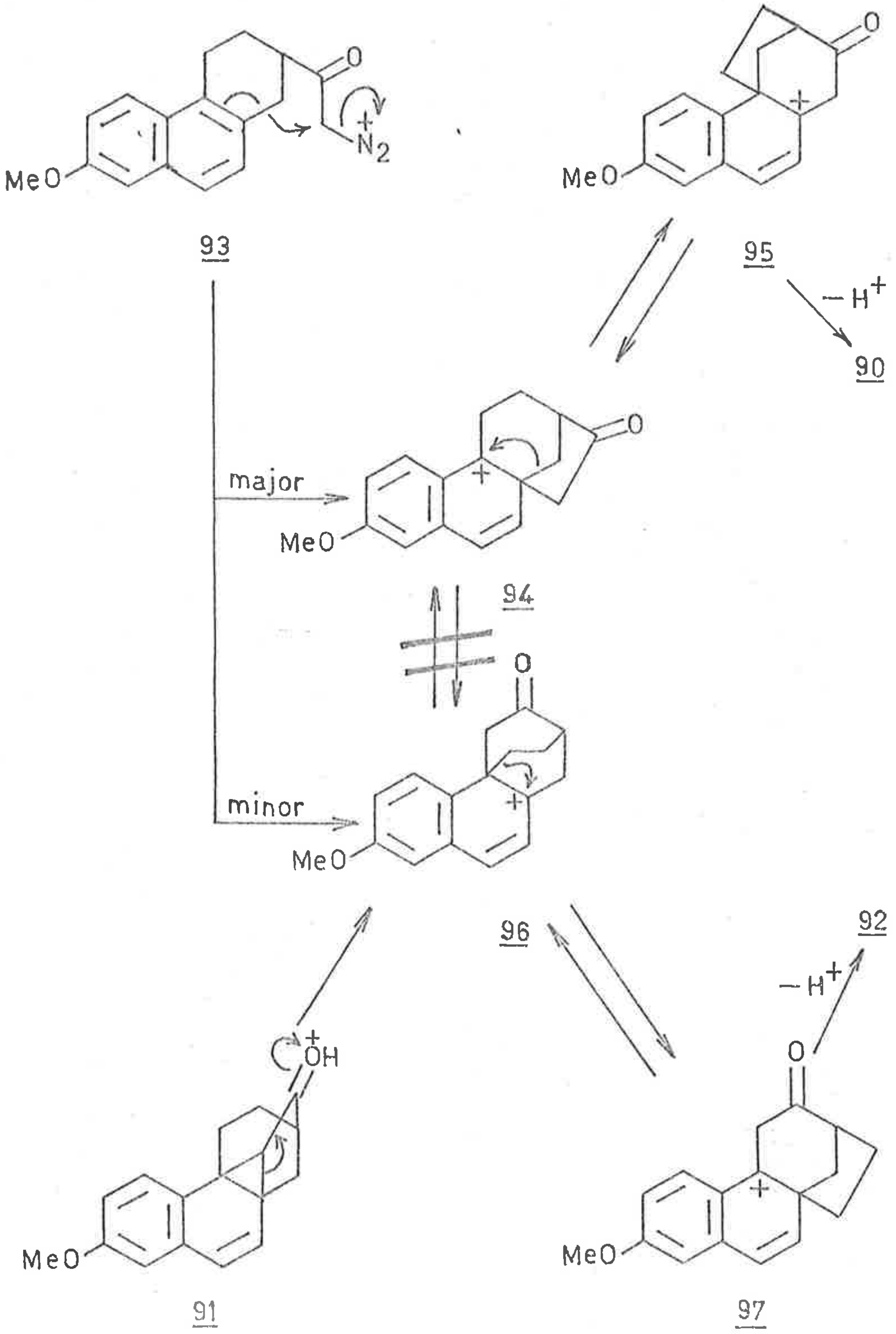
92.

(2) Acid catalysed cyclization of the diazoketone 87 is also accompanied by rearrangement and affords mainly a *different* isomeric bicyclo[3.2.1]octane derivative 90. Smaller amounts of 92 and uncyclized product 89 are also formed and complicate product analysis.

(3) Compounds 90 and 92 are the result of divergent pathways, and there seems to be only minor "crossover" between these pathways. Possible mechanisms for these reactions are outlined in Scheme 21.

In the decomposition of diazoketone 87, it seems clear that aryl participation in displacement of nitrogen from the derived diazonium salt 93 occurs to give predominantly the benzylic ion 94. Ion 94 probably rapidly equilibrates with the allylic carbonium ion 95 by a reversible 1,2-alkyl shift (i.e. Wagner-Meerwein rearrangement). Proton loss from 95 then gives the observed conjugated dienone 90; the driving force is simply the extra conjugation attainable in 90.

Acid catalysed ring opening of cyclopropyl ketone 91 is more difficult to explain. Clearly, the 4a,11-cyclopropyl bond cannot be cleaved during the reaction (in contrast to cyclopropyl ketone 29) for this would lead to ion 94 and thence inexorably to dienone 90. No trace of 90 was observed in the product from cyclopropyl ketone 91. The 10a,11-cyclopropyl bond must break


MeO
O
$\overset{+}{N}_2$
93
MeO
O
95
− H+
90
major
MeO
O
94
minor
O
MeO
96
92
− H+
$\overset{+}{O}H$
MeO
91
O
MeO
97

SCHEME 21

specifically, proceeding to the bicyclo[2.2.2]octyl cation 96. This specificity probably means that, of the two carbonium ions 94 and 96, the allylic ion 96 is the more stable.[143] ≠ Rapid equilibration of 96 with its Wagner-Meerwein rearrangement ion 97 then leads, *via* proton loss from 97, to the observed dienone 92. The driving force for rearrangement is once again seen as the stability gained by conjugation.

One question remains unanswered by this mechanistic rationale : why does not the diazonium ion 93 cyclize preferentially to give the ion 96, which is apparently more stable than 94? Obviously, cyclization of 93 to 96 does occur to a limited extent (*ca* 25%) for some of the product 92 is observed in the complex mixture derived from diazoketone 87. Two possible explanations

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≠ Some support for this idea may come from the relative ease of fragmentation of cyclopropyl ketones 91 and 29. The dihydrocyclopropyl ketone 29 was the more difficult to open and required the more strongly acidic conditions for cleavage. Thus, ring opening of 29 proceeding through an intermediate analogous to benzylic carbonium ion 94 appears to be *less favourable* than ring opening of 91 going to allylic carbonium ion 96.

are advanced to account for this apparent anomaly.

The first is that kinetically controlled cyclization of 93 occurs preferentially at C10a, to give a five membered cyclic intermediate 94, rather than at C4a, which affords a six membered cyclic intermediate 96. Diazonium ions are believed to react with low activation energies,[237] and therefore it is probable that the transition state for cyclization resembles starting material.[238] Thus, any effects of extra non-bonded interactions should be of only minor importance at the transition states for either mode of cyclization. However, it is apparent from a consideration of the ratio of products observed that energy effects in this step may indeed by very subtle.

The second is that cyclization of 93 does in fact give initially the more stable ion 96, but the more strongly acidic conditions (i.e. trifluoroacetic acid *versus* *p*-toluenesulphonic acid) then allow equilibrium to be set up between ions 94 and 96. Thus, the dienone mixture obtained from diazoketone 87 may merely reflect the relative thermodynamic stabilities of dienones 90 and 92.[≠]

If this second explanation is valid, then treatment of cyclopropyl ketone 91 with trifluoroacetic acid should give a

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[≠] The dienone 90 would perhaps possess slightly greater thermodynamic stability.

similar mixture of products. When this experiment was performed, using conditions identical to the treatment of the diazoketone 87, only the dienone 92 was again formed, and no trace of the other dienone 90 could be detected. The second of the above explanations is thus experimentally shown to be untenable.

Apparently, there is no equilibration between ions 94 and 96. Such an equilibration would involve a presumably less favorable Wagner-Meerwein rearrangement. The production of both the dienones 90 and 92 from diazonium ion 93 probably results from competitive cyclization at C10a and C4a respectively, in a ratio of 3:1.

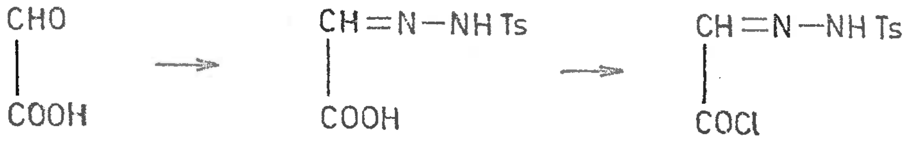
The rearrangements observed here fall in the general field of bicyclo-octane rearrangements,[205] which have been thoroughly studied. It is interesting that qualitatively similar rearrangements to those above have been observed in gibberellic acid chemistry[206] and in another tetracyclic compound.[77]

In this section, attempted cyclizations have been encountered where, although the actual cyclization is successfully accomplished, the products obtained are complicated by post-cyclization rearrangements. The extra double bond in the B ring lowers the transition state energy of routes other than those expected, and allows the products to achieve maximal conjugative stabilization by rearrangement. Obviously, factors of this nature must be considered when cyclization of an unsaturated diazoketone is proposed.

(b) Attempted Cyclization of Diazoester 98

The utility of the diazoketone cyclization reaction would be greatly improved if it could be shown that other unsaturated diazocarbonyl compounds (e.g. diazo-acetates) also underwent acid-catalysed cyclization.[≠] Cyclization of the diazoester 98 was attempted to investigate this possibility. If successful, cyclization of 98 would give the δ-lactone 99 which, in turn, should be a precursor of the synthetically useful keto-ester 100[99] and other similar compounds (Figure 11). Thus, this might provide a particularly simple method of achieving angular alkylation. (c.f. ref[236])

House and Blankley have reported that diazo-acetates ($ROCOCHN_2$) can be prepared very simply from the corresponding alcohol (ROH) by using the reagent 103.[209] Compound 103 is very readily available from glyoxylic acid 101 via the tosyl hydrazone 102.[209] This is the method of choice for synthesis of



101 102 103

[≠] Interestingly, the cyclization, by displacement of nitrogen from some olefinic alkyl diazonium ions has been observed.[207,208] The diazonium ions were generated by diazotization of the cognate alkyl amine.

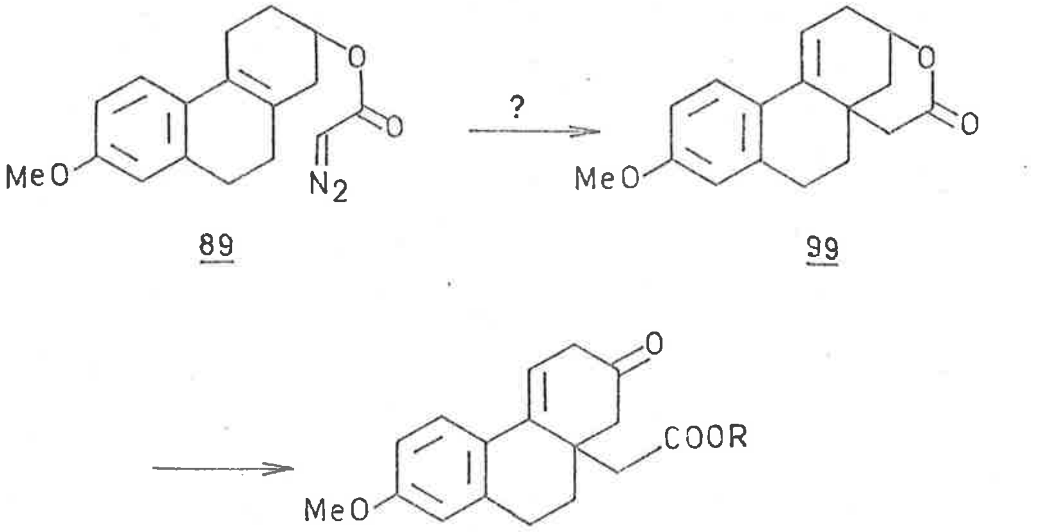
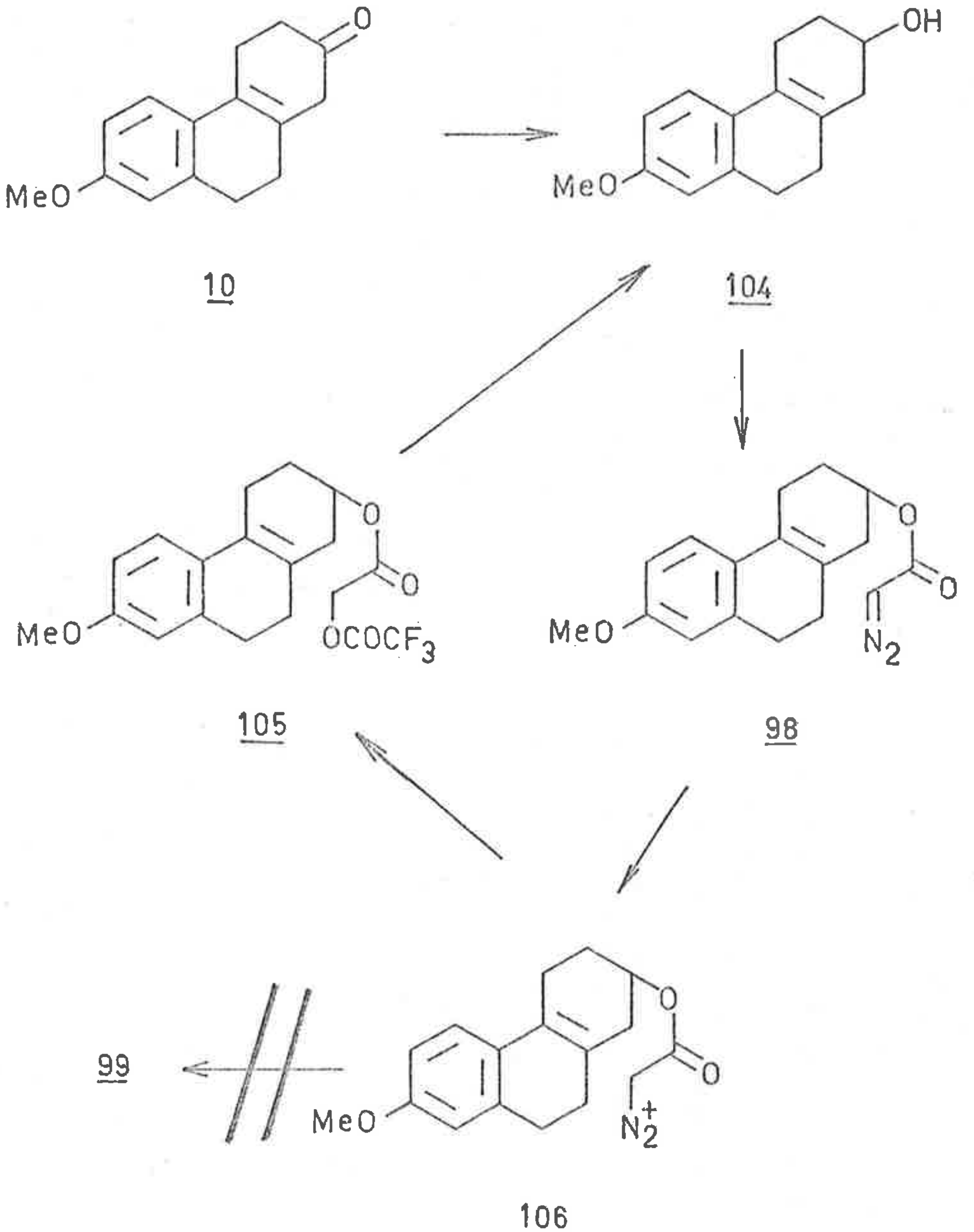


Figure 11

diazoesters since the sensitive diazocarbonyl function is introduced as the final step.

Reduction of ketone 10 (see Chapter 1) with lithium aluminium hydride yielded the necessary alcohol 104. (Scheme 25) Treatment of 104 with the House reagent 103 in the presence of triethylamine (>2 mole) gave the diazoester 98 as a stable, crystalline compound. Diazoester 98 appeared to hydrolyse readily during chromatorgraphic purification, for large amounts of the alcohol 104 were recovered from the column. The yield of 98 (based on recovered alcohol) was 75%.

Unfortunately, diazoester 98 did not cyclise at all on



SCHEME 25

treatment with trifluoroacetic acid. Using a variety of conditions, both with and without added co-solvent, the only product which could be detected by spectroscopic methods (NMR, IR) was the uncyclized diester 105. This is the product expected when the intermediate diazonium ion is intercepted by the weakly nucleophilic trifluoroacetate ion (assuming an ion-pair mechanism is operative). The diester 105 was very unstable and could not be fully characterised. However, evidence was secured that 105 was indeed uncyclized. Thus, hydrolysis of 105 gave, in almost quantitative yield, the starting alcohol 104.

The reasons for the complete failure of diazoester 98, or diazonium ion 106, to cyclize are not well understood. A combination of several distinct effects possibly contribute to the observed result, although no single effect appears to be sufficiently marked as to prevent cyclization altogether. It was thought that the highly nucleophilic double bond of 98 would overcome any small factors tending to make cyclization more difficult. The double bond proved to be a totally ineffective nucleophile in this case.

Some of the factors which may contribute to the failure of diazoester 98 to cyclize are summarised below.

(i) Effect of the six membered cyclic transition state.

All of the other successful cyclizations described in this thesis involve five membered cyclic transition states. It has been shown in some other work that diazoketone cyclization leading to a five membered ring gives a higher yield of cyclic product than a similar cyclization leading to a six membered cyclic product.[122,125,160] That result may have little bearing on the present case, for the compounds were significantly different, and the effect was not so great as to prevent cyclization altogether.

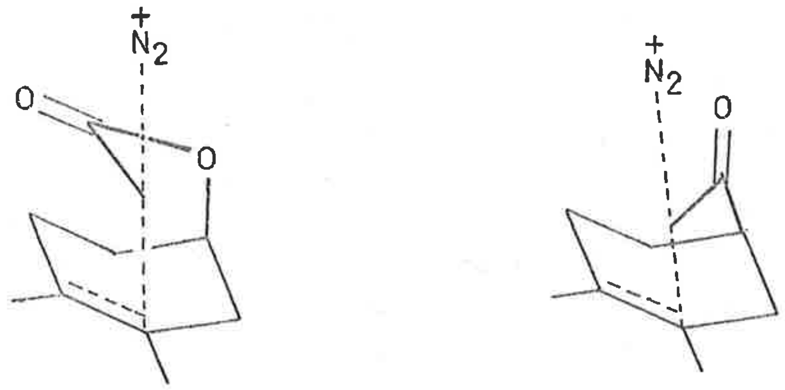
(ii) Unfavourable entropy effect. Obviously, a three membered side chain ("propyl") has more degrees of freedom than a two membered one ("ethyl"). More possible ground state conformations which are unsuitable for cyclization are available, and therefore cyclization may be less efficient. An analogous case has been noted in solvolysis reactions.[210] This effect also manifests itself very clearly in the reduced efficiency of cyclization of diazoketones 31 leading to spirodienones 33 (see p. 28).

(iii) Collinearity at the transition state. It is reasonable to assume that the π-electron nucleophile, primary carbon and potential leaving group must approach collinearity[211] in the transition state for reaction to take place effectively. Models indicate that this is difficult in the diazonium ion 106 and, moreover, introduces some unfavourable non-bonded interactions. This adverse energy effect of a "propyl" compared with an "ethyl" side chain has also been noted previously.[210]

(iv) Electron withdrawal by the oxygen atom. The electron withdrawing effect of the extra oxygen atom in the diazoester 98 may make the derived diazonium ion 106 more reactive, and therefore more susceptible to attack in a less favourable fashion, i.e. by the poorly nucleophilic trifluoroacetate ion.

(v) Participation by oxygen. The extra oxygen atom may participate in displacement of nitrogen from the diazonium ion. This seems unlikely, though, for the species formed would still be highly electrophilic and susceptible to nucleophilic attack by the π-bond.

(vi) Orientation of the carbonyl group in the transition state. In Figure 12, the transition states for cyclization of



(a) 106

(b) 41

Figure 12

diazonium ions 106 and 41 are schematically represented. In can be seen that with diazonium ion 41 [Figure 12(b)] which cyclizises successfully, the leaving group nitrogen must depart in a direction parallel to the C=O bond, or orthogonally to the C=O π-system. However, with diazonium ion 106 [Figure 12(a)], which does not cyclize, the nitrogen would leave in a direction parallel to the C=O π-system and orthogonal to the C=O bond. This orientation as in Figure 12(a) may be especially unfavourable (or alternatively that in Figure 12(b) may be extraordinarily favourable) for cyclization. Hence, the preferred orientation of the carbonyl group at the transition state may be a crucial factor in the success of a particular cyclization.

It is not possible, without further experimentation, to say which of the above effects are of more or less importance in determining the fate of diazonium ion 106. Several judiciously chosen experiments should allow one to distinguish between the importance of electronic effects (i.e. of the extra oxygen atom) and steric effects. This work, however, has not been pursued.

CHAPTER 4

SOME REACTIONS INVESTIGATING THE FURTHER ELABORATION OF SYNTHESISED COMPOUNDS

It has been seen that successful cyclization of suitable unsaturated diazoketones (e.g. 28, 47 and 66) produces tetracyclic compounds containing a Δ^4-double bond. (e.g. 9, 48 and 68). This double bond is a relatively inert functional group ("synthon"), and compounds possessing it are potentially capable of being further elaborated to either B-C trans- or B-C cis-compounds providing that the appropriate stereoselective operations are available.

Obviously, in a synthetic approach towards gibberellins, it would be desirable to be able to prepare compounds with a B-C cis-ring fusion, as in the natural products. Most of the work discussed in this Chapter was performed with this objective.

At the outset, it must be pointed out that compounds in the B-C trans- series will probably be more readily accessible. The D-ring bridge should hinder approach to one side of the Δ^4-double bond. Thus, reagents which attack the double bond from the less hindered side (i.e. opposite to the D-ring bridge) will inevitably lead to trans- compounds.[82,90] Nevertheless, compounds containing a B-C cis-ring junction have been sought.

Most of the research described in this Chapter used as a starting material the simple bicyclo[3.2.1]octane derivative 9, which was readily available in substantial quantities. Some other compounds, which were considered as likely precursors to B-C cis- compounds were also used. No problems would be anticipated in applying any of the reactions attempted in the more complex bridgehead substituted cases.

(a) Hydrogenation Approach.

The first reaction studied in this series was hydrogenation of the cyclopropyl ketone 29 [see Chapter 1(b)]. Hydrogenolysis of cyclopropanes has been investigated in some detail.[212,213] It has been found that palladium catalysed hydrogenation of conjugated cyclopropanes invariably results in selective (and often specific) hydrogenolysis of the conjugated cyclopropyl bond.[213-215] Therefore, in cyclopropyl ketone 29, the 4a,11 bond should be most rapidly hydrogenolysed. Moreover, one might naively expect a cis-addition of the two hydrogen atoms, and therefore a cis-fused product 107 to be formed (Figure 13).

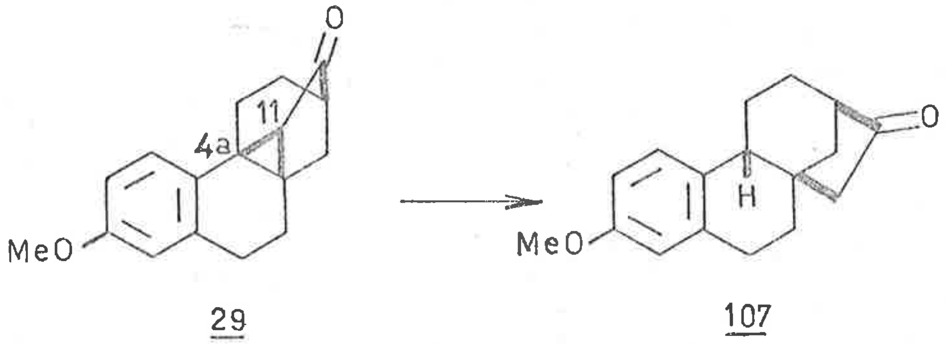


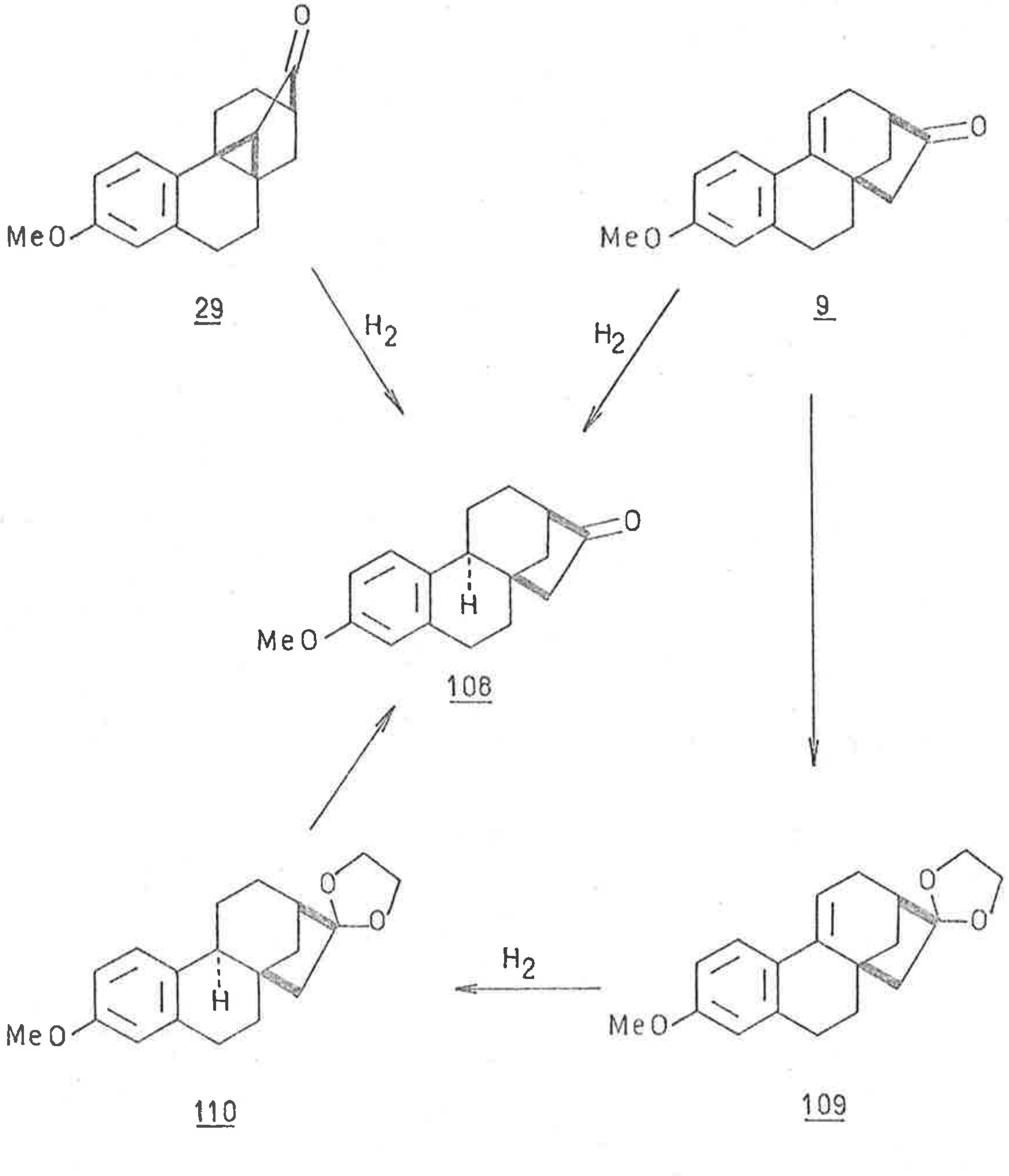
Figure 13

Hydrogenation of 29 (5% palladium on carbon, atmospheric pressure) did indeed yield a single, crystalline, saturated bicyclo[3.2.1]octane derivative (ν 1735 cm^{-1}). This was tentatively assigned the cis- structure 107.

To check this prediction, unsaturated tetracyclic ketone 9 was hydrogenated. Because addition of hydrogen should occur from the less hindered side of 9, this was expected to give a product with *trans*-fused stereochemistry.[82,90] A single ketone was indeed obtained, but this was identical in all respects to that formed by hydrogenolysis of the cyclopropyl ketone 29. Therefore, *trans*-fused B-C ring junction stereochemistry can be assigned to the ketone 108 (Scheme 22) obtained from both sources.

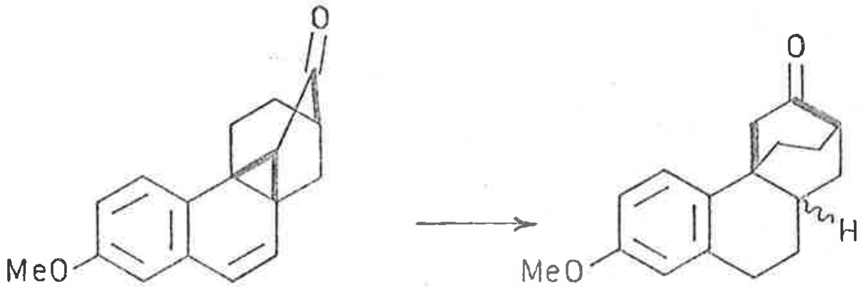
To make absolutely certain that this assignment was correct (since the two results were apparently in conflict), the ethylenedioxy acetal 109 of ketone 9 was also hydrogenated. The bulky acetal group in 109 greatly increases hindrance of approach to the β-side of the molecule, so that addition of hydrogen from the less hindered α-side is assured.[77] The product of this hydrogenation was thus the *trans*-fused acetal 110. Removal of the protective acetal function of 110 gave, once again, the *trans*-ketone 108 identical with that previously obtained. It may be said, then, that hydrogenation of ketone 9, and other similar derivatives, leads only to compounds with a B-C *trans*-ring fusion. This information is summarized in Scheme 22.[≠]

[≠] The methyl-substituted tetracyclic ketone 48 on hydrogenation also gave a *trans*-fused product, as expected. This product is a known compound.[77]



SCHEME 22

It is interesting to contrast the hydrogenolytic behaviour of cyclopropyl ketone 29 discussed above, with that of its dehydro-analogue, cyclopropyl ketone 91. Hydrogenation of 91 over palladium on carbon at atmospheric pressure afforded a product which showed typical six membered ring carbonyl absorption (ν 1715 cm^{-1}) in the infrared spectrum, suggesting that the product was a bicyclo[2.2.2]octane derivative. This was confirmed by the NMR spectrum, which indicated also that it was a mixture of diastereoisomers represented by structure 111.



91

111

This result means that the cyclopropyl ring must hydrogenolyse either prior to, or in concert with, saturation of the double bond. If the double bond were hydrogenated first, then cyclopropyl ketone 29 would be an intermediate and ketone 108 should then have been obtained. However, in general it seems that for vinyl substituted cyclopropanes, the cyclopropyl ring is hydrogenolysed more rapidly than reduction of the double bond,[216] so this is not surprising. Moreover, partial migration of the B-ring double bond after hydrogenolysis of the cyclopropyl ring,[216] adequately explains the non-stereospecificity of the reaction.

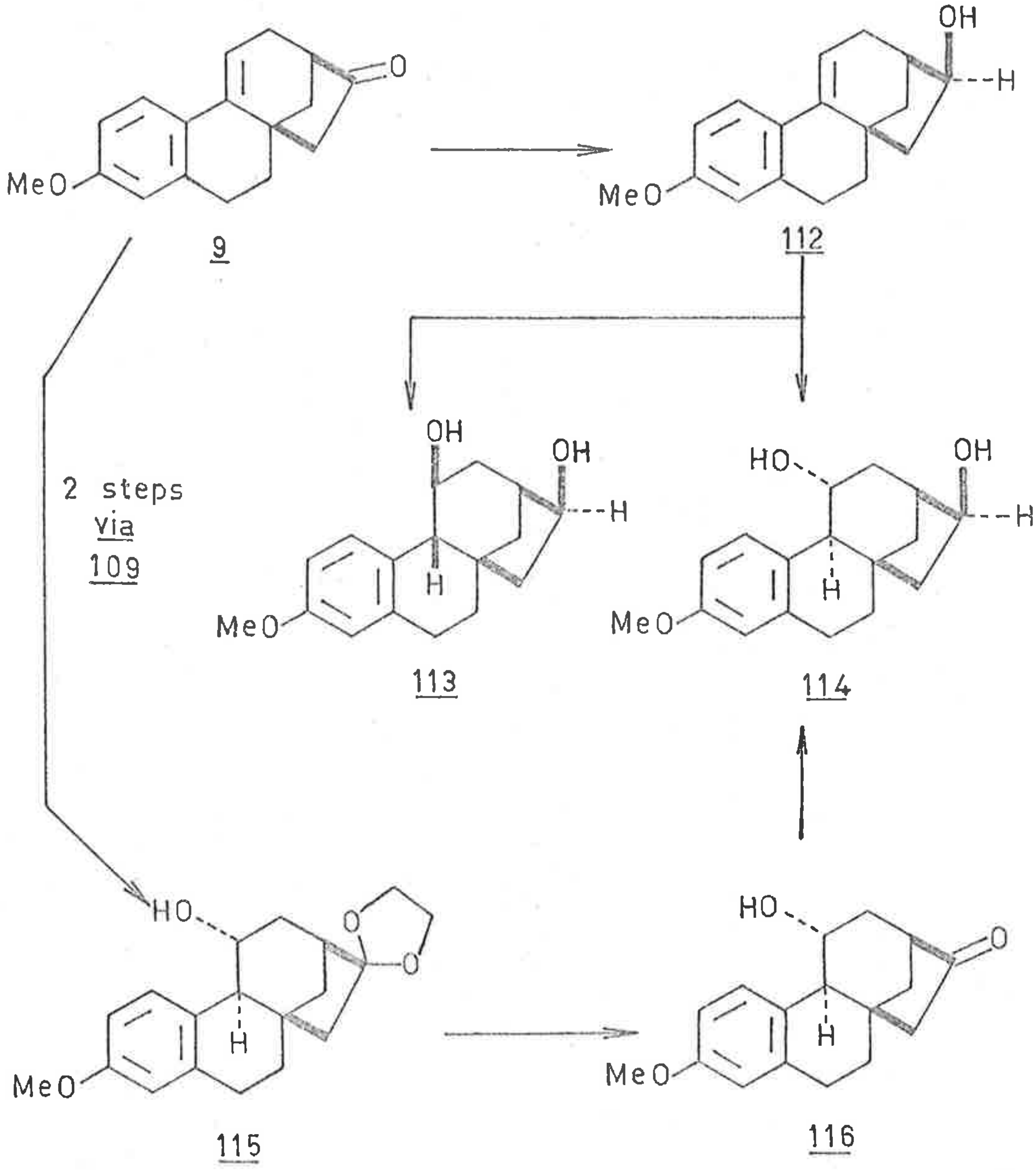
(b) Hydroboration Approach.

Another approach towards saturation of the olefinic bond in tetracyclic ketone 9 is by hydroboration. However, it is well established that diborane adds to double bonds in a *cis*- manner from the less hindered side of a molecule.[217] Ketone 9 or its derivatives should therefore yield *trans*- compounds on hydroboration (see later for an example).

In spite of the known steric course of hydroboration, it has been reported[218] that hydroboration of a Δ^{14}-steroid containing a 17β-tetrahydropyranyloxy group affords the product of addition of borane from the more hindered β-face of the molecule. The explanation proposed was that the reagent complexed with the oxygen atom of the pyran ring of the 17β-THP group, and therefore addition to the double bond could only occur from the β-side.[218] This represents intramolecularly *directed* hydroboration from the more hindered side of the molecule.

It seemed an attractive idea that a similar directed hydroboration might also be useful in obtaining compounds having a B-C *cis*-ring fusion. In particular, if the *endo*-alcohol 112 could be prepared from ketone 9, then the alcohol group might direct addition of diborane to the double bond from the more hindered face of 112 (see Scheme 23). This would lead, after appropriate oxidation, to the *cis*-fused diol 113.

Reduction of ketone 9 with sodium borohydride gave


OH
O
H
MeO
9
112
OH
OH
H
HO
OH
H
2 steps
via
109
H
H
MeO
113
114
HO
O
O
HO
O
H
H
MeO
115
116

SCHEME 23

a product which, although non-crystalline, appeared to be only a single diastereoisomer. The compound was pure by TLC, and NMR evidence indicated the presence of only one diastereoisomer. Moreover, on the basis of the C$\underline{H}$-OH resonance position (δ4.55, m, $W_{\frac{1}{2}}$ 18Hz) which is a normal position for this type of proton, the alcohol was assumed to be the *desired* endo-isomer **112**. The presence of the *exo*-isomer would have been indicated by a resonance at higher field, due to shielding of this proton by the double bond.[≠]

A similar case of stereospecific reduction of a related bicyclo[3.2.1]octanone **117** has been noted,[219] where the sole

117 **118**

[≠] Kotera and co-workers[219] have reported some NMR data on structurally similar benzo-bicyclo[3.2.1]octanol derivatives (e.g. **118**). Their reported chemical shifts of the C$\underline{H}$-OH resonance for *endo*-alcohols are in excellent agreement with that found for **112**, whereas the chemical shifts for *exo*-alcohols are 0.3-0.4 ppm upfield.

product was the *endo*-alcohol 118. The stereospecificity observed during reduction of 9 may be due to hindrance of *endo*-attack on the carbonyl group by the C3β (quasi-equatorial) proton.

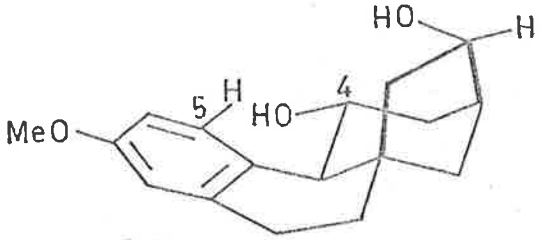
Hydroboration-oxidation of *endo*-alcohol 112 yielded two products which were separated by preparative TLC. These products were isomeric diols.

The minor, higher R_F (intramolecular hydrogen bonded?) product was obtained in 20% yield. This was assigned the desired *cis*-fused structure 113 (Scheme 23) on the basis of its NMR spectrum, in which the two C$\underline{H}$-OH resonances were cleanly separated. One was at δ4.40 (m, $W_{\frac{1}{2}}$ 21 Hz, C12 *exo*-proton) and the other at δ4.72 (m, $W_{\frac{1}{2}}$ 10 Hz) ppm was assigned to the C4 proton. Clearly, this second narrow signal must be due to an equatorial proton (axial protons give rise to broad signals).[220] Taking into account that,

(i) the six membered ring of a bicyclo[3.2.1]octane is locked in a chair conformation, and

(ii) *cis*-addition of diborane to the double bond is essential,[217] then the NMR information is compatible only with structure 113, in which the C4α-proton is equatorial.

The major, lower R_F diol was obtained in 65% yield. This had the *trans*-fused structure 114. In the NMR spectrum, the C$\underline{H}$-OH resonances overlapped, forming a very broad multiplet centred at δ4.30 ($W_{\frac{1}{2}}$ 26 Hz) ppm. This is consistent with the axial-*exo* arrangement of these protons required by structure 114. The C5 aromatic proton in this compound occurs at δ8.12 (d, J8.5 Hz), which is a very large downfield shift from the normal position. In contrast, the C5 proton in 113 resonates at δ7.20 (d, J8 Hz) ppm. This shift is due to the very close proximity[221] of the C4α-hydroxyl group and C5 proton in the trans-structure 114 (c.f. Figure 14).



114

Figure 14

This large deshielding effect can obviously only be observed in the trans- compounds (c.f. refs[239,240]) and is therefore strong corroborative evidence of structure 114 for the lower R_F diol.

Further corroboration of structure 114 came from an indepent synthesis of this compound by the route also shown in Scheme 23. Thus, hydroboration-oxidation of the ethylenedioxy acetal 109 of ketone 9 gave a single alcohol 115. The diborane attacked from the less hindered α-side of 109, giving the trans-fused alcohol 115, as shown by the large downfield shift (c.f.

above) of the C5 aromatic proton to δ8.12 (d, J8.5 Hz) ppm. It was considered less likely that the ethylenedioxy group would "direct" hydroboration in this case, for there could be only association between borane and this group, whereas, with the OH group in 112, a chemical reaction probably occurs to form an alkoxy borane, which then partly hydroborates the double bond from the β-side.

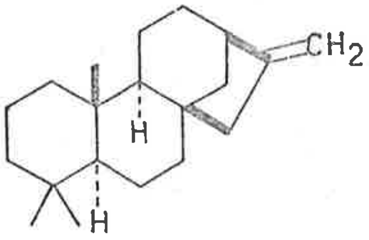
Removal of the protective acetal group of 115 afforded ketol 116. Reduction of 116 with lithium aluminium hydride, which is well known to involve exo-attack in similar cases,[222] gave the trans-diol 114, identical with the major product of hydroboration of endo-alcohol 112. This synthesis also secures the structure of the cis-diol 113 obtained as the minor product of that hydroboration.

Although the yield of cis-diol 113 in this experiment was low, at least it gave some indication that compounds in the cis-series would be accessible. The conditions used in this single experiment may not have been optimal for "directed" hydroboration, and it seems likely that conditions giving a greater amount of addition from the more hindered side of endo-alcohol 112 can be found. When these conditions have been optimized, then protonlysis[223] of the intermediate cyclic borane should make possible the synthesis of compounds having the C-D ring system of gibberellins.

From the results presented so far in this Chapter, it is obvious, however, that compounds in the trans- series are much simpler to prepare. A more efficient approach to gibberellins might therefore be to introduce a B-C trans-ring junction by e.g. hydrogenation. This is not a great drawback for the D-ring bridge can be inverted at a later stage, thus leading to a B-C cis-ring junction as in the natural products. Many examples of this type of "inversion", by Wagner-Meerwein rearrangement, are known.[57,59, 224-226]

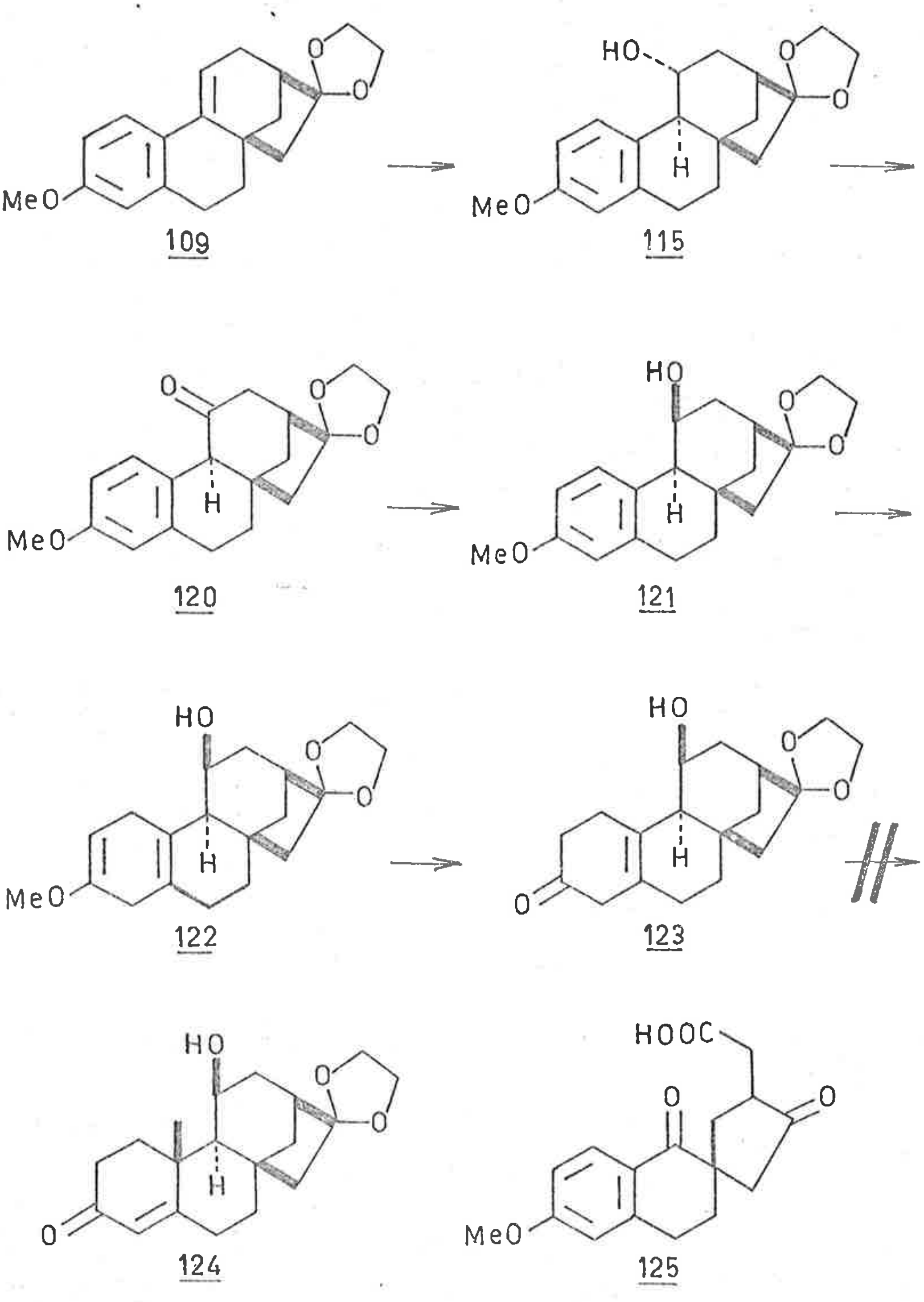
(c) Attempted introduction of a 4bβ-methyl group.

As compounds in the B-C trans- series could be readily obtained, it seemed that a useful exercise would be to attempt a synthesis of phyllocladene 119.[241] To achieve this aim, some method for stereospecific introduction of an angular 4bβ-methyl group must be found (c.f. refs[227-229]). Fried and co-workers[230] found that Simmons-Smith methylenation of 17β -acetoxy-11β-hydroxyestr-5(10)-en-3-one resulted in formation of a 10β-methyl compound, probably because of a particular juxtaposition of functional groups in the starting compound.[230] This seemed to offer a particularly attractive method for inserting the 4bβ-methyl group, if a model starting material containing a sterically similar array of functional groups was available. One such compound appeared to be the 4β-hydroxy-trans-fused compound 123. A route for construction of 123, using standard reactions, is outlined in Scheme 24.



119

The trans-4α-alcohol 115 (see p 96) was oxidised with


MeO
109
HO
H
MeO
115
O
H
MeO
120
HO
H
MeO
121
HO
H
MeO
122
HO
H
O
123
HO
H
O
124
HOOC
O
O
MeO
125

SCHEME 24

Jones' reagent[231] yielding the ketone 120. This simple reaction proved to be exceedingly delicate, and gave variable quantities of the over-oxidised diketo-acid 125 (the acetal group was lost during work up) as well as the required ketone 120 in up to 60% yield. Pfitzner-Moffatt oxidation[232,233] of 115 gave more consistent yields (>80%) of ketone 120. Reduction of 120 with lithium aluminium hydride then gave the 4β-alcohol 121, the product expected by attack of the hydride from the less hindered side of 120. Spectral data fully supported structures 115, 120, 121, and 125.

Birch reduction of 121 with lithium and ethanol in liquid ammonia gave the dihydroanisole 122 which was hydrolysed (oxalic acid) to the oily β,γ-unsaturated ketone 123.[≠] Treatment of 123 with methylene iodide in the presence of zinc-copper couple, however, did not yield the 4bβ-methylated compound 124. The ketone 123 appeared to be not affected by this treatment, for it was recovered unchanged.

A possible explanation for this result may be that the 4β-hydroxyl and $\Delta^{4b(8a)}$-olefinic bond in 123 are excessively shielded by the D-ring ethano-bridge, substituted as it is with a bulky ethylenedioxy acetal group. Perhaps Fried's procedure

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[≠] Compounds 122 and 123 were not purified, but were characterised spectrally.

for angular methylation[230] will be suitable only for compounds with severe structural limitations.

It seems that a different method for the required alkylation will be needed. No further studies pursuing this subject were carried out.

EXPERIMENTAL

General Topics

(i) Melting points were determined with the aid of a Kofler hot-stage apparatus. All melting points are uncorrected.

(ii) Infrared spectra were recorded on either a Perkin-Elmer 337 or a Unicam SP200 spectrophotometer. All data refer to mulls in Nujol unless otherwise stated.

(iii) NMR spectra were obtained with either a Varian DA-60 or a Varian T-60 spectrometer. NMR data are given in the following manner : chemical shifts (δ) are in ppm from internal TMS. Multiplicity : s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; exch. implies that the signal exchanges on shaking with D_2O. Relative intensities are given in numbers of protons. Observed splittings of resonances are measured in Hz, but do not necessarily imply coupling constants, as only first order analysis was attempted.

(iv) Ultraviolet spectra were recorded, in ethanol solution, on a Unicam SP800 spectrophotometer.

(v) Mass spectra were measured on a Hitachi-Perkin-Elmer RMU-6D instrument operating at 70eV.

(vi) Chromatographic adsorbents used were Spence type H alumina, Sorbsil silica gel, and Florisil. Analytical and preparative thin layer chromatography were carried out on layers containing an equal mixture of Merck Kieselgel G and HF_{254}.

(vii) Solvents were purified by standard procedures.[242] Light petroleum refers to the fraction bp 50-60°.

(viii) Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

General method for the preparation of diazomethylketones from carboxylic acids.

Unless otherwise specified, diazoketones were prepared by the following two-step sequence from the corresponding carboxylic acids.[148] This general method afforded the diazoketone in high yield and high purity. Usually no further purification of the diazoketone so prepared was necessary.

(a) Preparation of the acid chloride.

The solid acid (1 mole) was added in portions, at room temperature, to a stirred solution of oxalyl chloride (ca 8 mole) in benzene. The mixture was stirred at room temperature for 2-3 hr (the acid generally dissolved fairly slowly) and the reaction was completed by warming to 50° for 15 min. The solvents were removed under reduced pressure. The residual oxalyl chloride was removed by adding two further portions of benzene, and separately re-evaporating *in vacuo*. The crude acid chloride so obtained was used immediately in the next step.

(b) Reaction of the acid chloride with diazomethane.

The crude acid chloride (1 mole) in benzene was added slowly (over 15-20 min) to a stirred, ice-cold solution of ethereal diazomethane (ca 5 mole). The solution was stirred at -10-0° and allowed to warm slowly to room temperature. Finally, after ca 5 hr at room temperature, the solution was warmed on a water bath to drive off the excess of diazomethane. Evaporation of the solvents under reduced pressure yielded the (usually) crystalline diazoketone.

Ethereal diazomethane was prepared from N-nitroso-N-methylurea[243] or from p-tolylsulphonylmethylnitrosamide[244] by standard procedures. The solution was dried briefly over potassium hydroxide pellets before use.

CHAPTER 1

6-Methoxy-3,4-dihydronaphthalen-2(1H)-one 13

6-Methoxy-2-tetralone 13 was prepared in three steps from 6-methoxy-1-tetralone 24[128] by the method of Nagata and Terasawa.[129] The preparation is summarised below :

(i) Tosyl hydrazone of 6-methoxy-1-tetralone

This compound, mp 202-203° (lit.[129] 207-210°), was obtained in 90% yield from 6-methoxy-1-tetralone 24 and p-toluenesulphonylhydrazine.

(ii) 6-Methoxy-3,4-dihydronaphthalene

Treatment of the above tosylhydrazone with sodium in ethylene glycol at 200° afforded 6-methoxy-3,4-dihydronaphthalene (72%) as a colourless oil b.p. 124-128° (13mm) [lit.[129] 112-118° (5-6mm)].

(iii) 6-Methoxy-2-tetralone 13

The above dihydronaphthalene was oxidised with peracetic acid, and the intermediate heated under reflux with copper powder and hydrochloric acid in ethanol. 6-Methoxy-2-tetralone 13 was obtained in 55% yield as a colourless oil b.p. 110-112° (0.3mm) which crystallised on cooling; mp 32-35° (lit.[129] 34-35°).

An alternative preparation from p-methoxyphenylacetyl chloride and ethylene in the presence of aluminium chloride[130] gave 13, identical to that from the above route, in 21% yield, after chromatography on silica gel and distillation.

2,2-ethylenedioxy-6-methoxy-1,2,3,4-tetrahydronaphthalene 14

6-Methoxy-2-tetralone 13 (4.5g, 0.026 mole), ethylene glycol (9.0g, 0.15 mole), and p-toluenesulphonic acid (50mg) were heated together under nitrogen, in refluxing benzene (100 ml). Water was removed using a Dean-Stark apparatus. After 3.5 hr, the reaction mixture was poured into 5% sodium bicarbonate solution (100 ml) and extracted with ether (2x100 ml). The combined extract was washed with water, dried ($MgSO_4$), and evaporated. A yellow oil (5.4g) was obtained which was purified by filtration through a small column of alumina. The acetal 14 was obtained as a pale yellow oil (5.2g, 92%) which solidified on cooling, but melted again on warming. A small sample was distilled b.p. 80-85° 0.05mm [lit.[160] 125-130 (0.2mm)] ν_{max} (film) 1610, 1580, 1510 (aromatic C=C). δ (CCl_4) 6.4-6.9 (3H, m, ArH); 3.87 (4H, s, OCH_2CH_2O); 3.67 (3H, s, OMe); 2.8 (4H, m, C1 and C4 protons); 1.78 (2H, t, J7Hz, C3 protons).

2,2-ethylenedioxy-6-methoxy-1,2,3,4,5,8-hexahydronaphthalene 15

Lithium (8g, 1.1g. atom) was added in pieces to liquid ammonia (800 ml) which had been distilled from sodium. The acetal 14 (16.5g, 0.075 mole) in dry ether (250 ml) was added dropwise under nitrogen with vigorous stirring. After 10 mins, absolute ethanol (85 ml) was added over a 2 hr period. When the solution decolourised (1 hr), ammonium chloride (60g) was added, and the remaining ammonia was allowed to evaporate. The residue was taken up in water (500 ml) and extracted with ether (3X200 ml). The combined extract was washed with water until the washings were neutral, dried ($MgSO_4$), and evaporated, yielding a pale brown oil (16.0g, 96% crude yield) which crystallised readily, mp 51-53°. The dihydroanisole 15 was not purified further, but was immediately hydrolysed with oxalic acid (see below).

ν_{max} 1700, 1665 (enol ether). δ (CCl_4) 4.45 (1H, br. s, C7 vinyl proton); 3.83 (4H, s, OCH_2CH_2O); 3.43 (3H, s, OMe); 2.52 (4H, br. s, C5 and C8 protons); 2.0 (4H, m, C1 and C4 protons); 1.63 (2H, t, J6Hz, C3 protons).

6,6-ethylenedioxy-3,4,5,6,7,8-hexahydronaphthalen-2(1H)-one 16

The above dihydroanisole (3.6g, 0.018 mole) in methanol (200 ml) was cooled in an ice-bath and treated with oxalic acid (4.5g, 0.036 mole) in water (40 ml). The reaction mixture was stirred at 0° for 1 hr. Sodium bicarbonate (6.8g) was added, and the resulting mixture was diluted with water (500 ml) and extracted with ether (2 X 200 ml). The combined extract was washed with water, dried ($MgSO_4$), and evaporated. The crude oily product (2.9g) was chromatographed on silica gel (140g). Elution with ether-light petroleum (3:1) and ether gave the ketone <u>16</u>;colourless crystals (2.3g, 61%), mp 56-60°. This compound was unstable, and so was not purified further.

ν_{max} 1705 (C=O).

δ (CCl_4) 3.90 (4H, s, OCH_2CH_2O); 2.70 (2H, br. s, C1 protons); 1.6-2.5 (10H, m, other protons).

Reaction of ketone 16 with vinyl magnesium bromide

Vinyl magnesium bromide was prepared from magnesium (2g, 0.08 g-atom) and vinyl bromide in dry tetrahydrofuran (100 ml) in the usual way.[127] The Grignard reagent was cooled to -70° (precipitation occurred), and ketone <u>16</u> (5.0g, 0.024 mole) in ether (100 ml) was added dropwise with stirring. The mixture was kept at -70° under nitrogen for 4 hr. Acetic anhydride (8 ml) was added very slowly. The mixture was allowed slowly to warm to -20°, when 5% sodium bicarbonate solution (200 ml) was added all at once. The organic layer was separated, and the aqueous layer was extracted with ether (100 ml). The combined extract was washed with water, dried ($MgSO_4$), and evaporated yielding a pale yellow, semi-crystalline oil (6.6g). The crude product was chromatographed on Florisil (280g). Elution with ether-light petroleum (1:5) gave 2-acetoxy-2-vinyl-6,6-ethylenedioxy-1,2,3,4,5,6,7,8-octahydronaphthalene <u>17</u> as colourless crystals (1.7g, 26%), mp 98-100°. An analytical sample, mp 99.5-100°, was obtained by recrystallization from ether-light petroleum.

(Found : C, 68.9; H, 8.2. $C_{16}H_{22}O_4$ requires C, 69.0; H, 8.0%).

ν_{max} 1725, 1260 (acetate), 985, 935 (vinyl).

δ ($CDCl_3$) 6.08 (1H, m, C<u>H</u>=CH_2); 5.12 (2H, m, CH=C<u>H_2</u>); 3.93 (4H, s, OCH_2CH_2O); 1.96 (3H, s, $OCOCH_3$); 1.6-2.5 (10H, m, other protons).

Further elution of the column with ether gave a colourless oil (3.0g, 54%) believed to be 2-hydroxy-2-vinyl-6,6-ethylenedioxy-1,2,3,4,5,6,7,8-octahydronaphthalene <u>18</u>.

ν_{max} (film) 3440 (OH), 1640, 990, 915 (vinyl)

<u>7-Methoxy-3,4,9,10-tetrahydrophenanthren-2(1H)-one 10</u>

Ketone <u>10</u> was prepared by the method of Nagata and co-workers[126] from 6-methoxy-2-tetralone <u>13</u> and methyl vinyl ketone. Distillation of the crude product under reduced pressure gave two fractions;

(i) The first, bp 96-110° (0.05mm), was unchanged starting material <u>13</u> (15% recovery).

(ii) The second fraction, bp 160-170° (0.05mm), was a yellow oil, which was crystallised from ether-light petroleum to give ketone <u>10</u> as colourless crystals, mp 75-76.5° (lit.[126] 78-78.5°) in 63% yield.

<u>Reaction of ketone 10 with vinyl magnesium bromide</u>

Vinyl magnesium bromide, prepared from magnesium (0.8g, 0.03g-atom) and vinyl bromide in THF (25ml), was cooled to -70° (dry ice-acetone). The tricyclic ketone 10 (4.2g, 0.019 mole) in ether - THF (1:1, 50 ml) was added under nitrogen over a 6 hr period, adn the mixture was kept at -70° for 9 hr. Saturated aqueous ammonium chloride (100 ml) was added, and the organic layer was separated. The aqueous layer was extracted with ether (100 ml), and the combined extract was washed with water, dried ($MgSO_4$), and evaporated. The oily product (4.8g) showed ν_{max} (film) 1710 indicating the presence of starting ketone 10.

The mixture was retreated twice with vinyl magnesium bromide (0.03 mole) at -70°, using the procedure described above. A small amount of ketone 10 (ν 1710) still remained in the oily product (4.9g). The crude material was taken up in ethanol (50 ml), treated with a solution of sodium metabisulphite (2g) in water (20 ml), and stirred at room temperature for 2 hr. The bisulphite adduct of ketone 10 (0.7g) was removed by filtration. The filtrate was diluted with water and worked up in the normal way, to give 2-hydroxy-2-vinyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene 21 as a red oil (3.5g, crude yield 70%).

ν_{Max} (film) 3350 (OH), 1640, 1000, 930 (vinyl), 1605, 1575, 1510 (aromatic C=C).

The crude product was distilled under reduced pressure [160° (bath temperature,) 0.2mm] in a bulb to bulb apparatus. The pale yellow product (1.7g) crystallised on cooling, and was recrystallised twice from methanol; white plates mp 69.5-70°. This product was not alcohol 21, but 2-ethyl-7-methoxy-9,10-dihydrophenanthrene 23. (Found: C, 85.8; H, 7.6. $C_{17}H_{18}O$ requires C, 85.7; H, 7.6%).

ν_{max} 1605, 1580, 1485 (aromatic C=C).

$\delta(CCl_4)$ 7.50 (2H, m, C4 and C5 protons); 6.83 (4H, m, C1, C3, C6 and C8 protons); 3.77 (3H, s, OMe); 2.78 (4H, s, C9 and C10 protons); 2.60 (2H, q, J7Hz, Ar $C\underline{H}_2CH_3$); 1.22 (3H, t, J7Hz, Ar $CH_2C\underline{H}_3$).

7-Methoxy-1,2,3,9,10,10aβ-hexahydrophenanthrene-2α-carboxylic acid 26

The Δ^4-carboxylic acid 26 was prepared in three steps from 6-methoxy-1-tetralone 24 according to literature procedures.[145,147] The crude product was recrystallised from acetone; pale yellow crystals mp 181-183° (lit.[145] 184-186°).

7-Methoxy-1,2,3,4,9,10-hexahydro-phenanthrene-2-carboxylic acid 27

Dry hydrogen chloride was bubbled through a chilled, stirred solution of the crude Δ^4- acid 26 (23.0g, 0.09 mole) in chloroform (2.4l) for 20 min, according to the method of Goldberg *et al.*[146] The solution was stirred at 0° for a further 20 min, and diluted with chloroform (0.6l). The reaction mixture was washed with water (2 X 1l), dried ($MgSO_4$), and evaporated. The residue was recrystallised from acetone, giving the desired $\Delta^{4a(10a)}$-acid 27 (20.4g, 88%) as pale yellow crystals, mp 185-188° (lit.[144] 184-188°).

ν_{max} 3100-2500, 1695 (COOH), 1645 (C=C), 1600, 1575, 1505 (aromatic C=C).

δ (d_6DMSO-$CDCl_3$) 7.07 (1H, m, C5 ArH); 6.67 (2H, m, C6 and C8 ArH); 3.73 (3H, s, OMe); 1.8-2.8 (11H, m, other protons).

$M^{+\cdot}$ 258 ($C_{16}H_{18}O_3$=258).

2-Diazoacetyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene 28

The $\Delta^{4a(10a)}$-acid 27 (2.0g, 7.8 mmole) was converted to the acid chloride in the usual way with oxalyl chloride (7.5g, 59 mmole) in benzene (100 ml). The acid chloride was obtained as a yellow-orange crystalline solid mp 60-65°.

ν_{max} 1800 (COCl), 1645 (C=C), 1600, 1570, 1500 (aromatic C=C).

δ ($CDCl_3$) 7.08 (1H, m, C5 ArH); 6.72 (2H, m, C6 and C8 ArH); 3.77 (3H, s, OMe); 1.8-3.0 (11H, m, other protons).

The crude acid chloride in benzene (40 ml) was converted to the diazoketone in the usual way be treatment with diazomethane (ca 40 mmole) in ether (120 ml) at 0°. The diazoketone 28 was thus obtained as a yellow crystalline solid (2.2g, 100%), mp 120-126° dec. An analytical sample, recrystallised from ether, melted at

125-129° dec. (Found: C, 72.6; H, 6.6; N, 9.8. $C_{17}H_{18}N_2O_2$ requires C, 72.3; H, 6.4; N 9.9%).
ν_{max} 3085, 2100, 1640 ($COCHN_2$) 1605, 1570, 1495 (arómatic C=C).
δ ($CDCl_3$) 7.10 (1H, m, C5 ArH); 6.72 (2H, m, C6 and C8 ArH); 5.30 (1H, s, $CO\underline{CH}N_2$); 3.77 (3H, s, OMe); 1.7-2.9 (11H, m, other protons).

Cyclopropyl ketone 29

The diazoketone 28 (380 mg, 1.5 mmole) was dissolved in boiling acetone (5 ml). Hot cyclohexane (40 ml) was added all at once. The solvent mixture was distilled unitl the temperature of the vapours reached 80°, and a further quantity of hot cyclohexane (30 ml) was added. Copper powder (1.5g) was introduced, and the mixture was heated under reflux, with vigorous stirring, for 2 hr. The hot mixture was filtered through Celite. Evaporation of the filtrate yielded a dark yellow oil (370 mg).

The crude product was preadsorbed on kieselguhr and chromatographed on alumina (20g). Elution with methylene chloride-light petroleum (2:3) gave the cyclopropyl ketone 29 (185 mg, 55%) as a colourless oil which was crystallised from ether-light petroleum to form colourless rods, mp 108-110°. (Found : C, 80.0; H, 7.2. $C_{17}H_{18}O_2$ requires C, 80.3; H, 7.1%).
ν_{max} 1715 (C=O), 1610, 1575, 1505 (aromatic C=C).

δ ($CDCl_3$) 7.30 (1H, d, J8Hz, C5 ArH); 6.70 (2H, m, C6 and C8 ArH); 3.77 (3H, s, OMe); 1.8-2.8 (12H, m, other protons inc. cyclopropyl proton).

7-Methoxy-2,10a-ethano-1,2,3,9,10,10a-hexahydrophenanthren-12-one 9

Dry hydrogen chloride was bubbled through a chilled solution of cyclopropyl ketone 29 (30mg, 0.12 mmole) in chloroform (10 ml) for 5 min. The solution was stirred for 15 min, washed twice with water, dried (Na_2SO_4), and evaporated. The crude tetracyclic ketone 9 (30 mg, quant.) crystallized on addition of ether. An analytical sample melted at 115-117° after recrystallization from methylene chloride-light petroleum.

(Found: C, 80.0; H, 7.35. $C_{17}H_{18}O_2$ requires C, 80.3; H, 7.1%).

ν_{max} ($CHCl_3$) 1730 (C=O), 1620 (shoulder, C=C), 1605, 1570, 1500 (aromatic C=C).

δ ($CDCl_3$) 7.57 (1H, d, J8Hz, C5 ArH); 6.72 (2H, m, C6 and C8 ArH); 6.05 (1H, t, J3.5Hz, C4 vinyl proton); 3.78 (3H, s, OMe); 1.7-2.9 (11H, m, other protons).

7-Hydroxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid 34

The 7-methoxy carboxylic acid 27 (5.0g, 0.019 mole) and pyridine hydrochloride[245] (11g, 0.095 mole) were melted together, under nitrogen, at 200-220° for 2 hr. The cooled mixture solidified, and was ground with water (20 ml). The resulting mixture was poured into water (150 ml) with vigorous stirring. The precipitate of phenolic acid 34 (4.6g, 97%) was collected, washed thoroughly with water, and dried; mp 196-200°.

A sample was sublimed at 160-170° (0.01 mm) to give pure 34 as a white microcrystalline solid, mp 209-212°. (Found : C, 73.8; H, 6.9. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.6%).
ν_{max} 3250 (OH), 3000-2400, 1700 (COOH), 1645 (C=C), 1600, 1500 (aromatic C=C).

7-Acetoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid 35

A solution of phenolic acid 34 (4.5g, 0.018 mole) in acetic anhydride (50 ml) and pyridine (5 ml) was allowed to stand at room temperature overnight. Water was added very slowly until all the acetic anhydride had hydrolysed, and the resulting mixture was poured into water (400 ml). The acetate 35 was collected and recrystallised from acetone, to yield colourless crystals (4.5g, 86%), mp 200-203°.

An analytical sample, obtained by two further recrystallizations from acetone, melted at 205-208°. (Found : C, 71.3; H, 6.3. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%).
ν_{max} 3200-2500, 1695 (COOH), 1750, 1220 ($OCOCH_3$), 1645 (C=C), 1600, 1580, 1500 (aromatic C=C).
δ ($CDCl_3$) 8.20 (1H, br. s, COO<u>H</u>, exch.); 7.20 (1H, m, C5 ArH);

6.92 (2H, m, C6 and C8 ArH); 2.28 (3H, s, OCOC$\underline{H}_3$); 1.8-3.0 (11H, m, other protons).

7-Acetoxy-2-diazoacetyl-1,2,3,4,9,10-hexahydrophenanthrene 36

The above carboxylic acid 35 (4.4g, 0.015 mole) was converted to its acid chloride in the usual way with oxalyl chloride (12g, 0.095 mole) in benzene (50 ml). The acid chloride was thus obtained as an off-white crystalline solid.

ν_{max} 1780 (COCl), 1755, 1210 (OCOCH$_3$), 1650 (C=C), 1600, 1580, 1500 (aromatic C=C).

δ(CDCl$_3$) 7.17 (1H, m, C5 ArH); 6.92 (2H, m, C6 and C8 ArH); 2.27 (3H, s, OCOC$\underline{H}_3$); 1.5-3.2 (11H, m, other protons).

The acid chloride in benzene (50 ml) was converted into the diazoketone by the usual method using diazomethane (0.045 mole) in ether (140 ml). The crude product was recrystallised from acetone-light petroleum affording the diazoketone 36 (3.6g, 80%) as pale yellow prisms,123-125° dec. An analytical sample, mp 124-126.5° dec., was procured as yellow prisms by one further recrystallization from ethyl acetate-light petroleum bp 60-80°. (Found : C, 69.45; H, 5.9; N9.1. $C_{18}H_{18}O_3N_2$ requires C, 69.7; H, 5.85; N9.0%).

ν_{max} 3050, 2120, 1625 (COCHN$_2$), 1750, 1220 (OCOCH$_3$), 1650 (shoulder, C=C), 1580, 1500 (aromatic C=C).

δ(CDCl$_3$) 7.15 (1H, m, C5 ArH); 6.90 (2H, m, C6 and C8 ArH); 5.33

(1H, s, $COC\underline{H}N_2$); 2.27 (3H, s, $OCOC\underline{H}_3$); 1.6-3.0 (11H, m, other protons).

2-Diazoacetyl-7-hydroxy-1,2,3,4,9,10-hexahydrophenanthrene 37

The diazoketone 36 (1.12g, 3.6 mmole) in methanol (150 ml) was treated with a solution of sodium carbonate (6g) in water (50 ml). The resulting mixture was stirred at room temperature for 3.5 hr, diluted with methylene chloride (100 ml) and the pH adjusted to ~7 by the addition of solid carbon dioxide. The organic layer was removed, and the aqueous layer was extracted with methylene chloride (2 X 50 ml). The combined extract was washed twice with water, dried (Na_2SO_4) and evaporated, leaving an amorphous residue of diazoketone 37 (0.96g, quant.) A sample, crystallised from acetone-light petroleum bp 60-80°, gave pale yellow plates, mp 150-151° dec. (Found : C, 71.4; H, 5.9; N, 10.7. $C_{16}H_{16}O_2N_2$ requires C, 71.6; H, 6.0; N,10.4%). ν_{max} 3230 (OH), 3050, 2120, 1610 ($COCHN_2$), 1645 (C=C), 1570, 1500 (aromatic C=C).

7-Hydroxy-2,10a-ethano-1,2,3,9,10,10a-hexahydrophenanthren-12-one 38

Phenolic diazoketone 37 (0.83g, 3.1mmole) suspended in nitromethane (40 ml) was treated with boron trifluoride-etherate (1 drop). The diazoketone dissolved, with evolution of nitrogen, to form a deep red solution. Water (100 ml) was added, and the mixture was extracted with methylene chloride (1 X 100 ml, 2 X 50 ml). The combined extract was washed twice with water, dried (Na_2SO_4), and evaporated, leaving a yellow oil (0.77g) which slowly crystallised. The crude product was preadsorbed on kieselguhr and chromatographed on silica gel (30g). Elution with methylene chloride-acetone (100:1) gave the phenolic tetracyclic ketone 38 (0.57g, 78%) as colourless crystals mp 175-176.5°. The analytical sample, recrystallized from acetone-hexane, was obtained as colourless plates mp 176.5-177.5°. (Found : C, 79.8; H, 7.0. $C_{16}H_{16}O_2$ requires C, 80.0; H, 6.7%).

ν_{max} (CH_2Cl_2) 3500 (OH), 1730 (C=O), 1625 (C=C), 1610, 1575, 1500 (aromatic C=C).

δ ($CDCl_3$) 7.52 (1H, d, J8Hz, C5 ArH); 6.67 (2H, m, C6 and C8 ArH); 6.03 (1H, t, J3.5Hz, C4 vinyl proton); 5.45 (1H, br. s, ArOH, exch.); 1.6-2.9 (11H, m, other protons).

Methylation of tetracyclic phenol 38

Phenol 38 (170 mg, 0.7 mmole) in methanol (5 ml) containing sodium hydroxide (120mg, 3 mmole) and water (2 ml), was treated dropwise with methyl sulphate (200 mg, 1.6 mmole). The solution was stirred at 50-60° for 0.5 hr, diluted with water (20 ml) and extracted with ether (2 X 20 ml). The combined extract was washed with 5% sodium hydroxide solution (10 ml) and water, dried ($MgSO_4$), and evaporated. The crystalline residue, mp 112-115° (50 mg, 28%), was identical to the ketone 9 obtained by acid cleavage of the cyclopropyl ketone 29.

The basic washings from the above extraction were acidified, and worked up in the usual way to give the starting phenol (113 mg, 67% recovery).

Acid catalysed cyclization of diazoketone 28

(a) Fluoroboric acid catalysis

Methoxy diazoketone 28 (8.1g, 0.029 mole) was suspended in nitromethane (200 ml) and treated with a solution (ca. 5%) of anhydrous fluoroboric acid in nitromethane (2 ml). Nitrogen evolution was slow, and further portions of the acid solution were added until all the diazoketone dissolved. The solution was allowed to stand at room temperature overnight. The volume of the reaction mixture was reduced to ca. 50 ml by distillation under reduced pressure. Water (150 ml) was added, and the mixture was extracted with methylene chloride (2 X 100 ml, 1 X 50 ml). The combined extract was washed with water and saturated brine, dried ($MgSO_4$), and evaporated leaving a crystalline residue (8g). The crude product was preadsorbed on kieselguhr and chromatographed on silica gel (250g). Elution with methylene chloride and methylene chloride-acetone (19:1) gave tetracyclic ketone 9 (6.5g, 90%) as pale yellow crystals mp 113-116°. This compound was identical to previous samples obtained by the other methods.

(b) In trifluoroacetic acid

Diazoketone 28 (4.7g, 0.017 mole) was added portionwise to ice-cold trifluoroacetic acid (20 ml) with vigorous stirring. The red solution was diluted with water (200 ml) and extracted with methylene chloride (1 X 100 ml, 2 X 50 ml). The combined extract was washed three times with water, dried (Na_2SO_4) and evaporated. A yellow crystalline residue mp 110-115° (4.2g, quant.) of tetracyclic ketone 9 was obtained. Ketone 9 was more easily purified as its ethylenedioxy acetal 109 (see Chapter 4).

CHAPTER 2

7-Methoxy-2-methyl-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid 46

(a) Diels-Alder reaction between diene 25 and 2-methylacrylic acid

Diene 25 (5.6g, 0.03 mole) in benzene (50 ml) was treated dropwise with 2-methylacrylic acid (7.0g, 0.08 mole) under a slow stream of nitrogen. The resultant solution was kept at room temperature under nitrogen for 72 hr, and heated under reflux for 2 hr. Evaporation of the solvent left a semi-solid mass (9.0g) containing a mixture of the Δ^4-acids 43 and 44.

ν_{max} 3300-2400, 1695 (COOH), 1635 (C=C), 1605 1575, 1505 (aromatic C=C).

δ ($CDCl_3$) 6.1 (1H, m, C4 vinyl proton).

(b) Migration of the double bond

The above mixture of acids (9.0g) in chloroform (500 ml) at 0°, was treated with a stream of dry hydrogen chloride gas for 20 min. The solution was stirred at 0° for a further 30 min, washed with water (3 X 200 ml), dried and concentrated. A semi-solid residue (9.0g), ν_{max} 1760, 1696, was obtained. The crude product was chromatographed on silica gel (500g) and eluted with chloroform. Fractions of 200 ml were collected. Three distinct compounds were obtained;

(i) Fractions 4-6 yielded a colourless oil (1.2g) which showed no carbonyl absorption in the infrared spectrum. This was believed to be a mixture of dimers of the diene 25 (22% yield based on diene 25).

(ii) Fractions 9-12 afforded, after fractional recrystallization from ether-methylene chloride, 1β-carboxy-4aβ-hydroxy-7-methoxy-1α-methyl-1,2,3,4,4a,9,10,10aα-octahydrophenanthrene-1→4a-lactone 45 (1.1g, 18%). A sample was recrystallized from ether-methylene chloride; white cubes mp 171.5-173.5°. (Found : C, 74.7; H, 7.5. $C_{17}H_{20}O_3$ requires C, 75.0; H, 7.4%).

ν_{max} 1755 (C=O), 1605, 1580, 1500 (aromatic C=C).

δ ($CDCl_3$) 7.45 (1H, d, J8Hz, C5 ArH); 6.75 (2H, m, C6 and C8 ArH); 3.78 (3H, s, OMe); 1.18 (3H, s, CMe); 1.3-2.9 (11H, m, other protons).

(iii) Fractions 13-15, together with the mother liquors from fractions 11 and 12, afforded after fractional recrystallization from ether, and then acetone, the desired acid 46 (1.2g, 20%). An analytical sample, mp 154-156°, was obtained after one further recrystallization from acetone. (Found : C, 75.0; H, 7.5. $C_{17}H_{20}O_3$ requires C, 75.0; H, 7.4%).

ν_{max} 3200-2500, 1695 (COOH), 1645 (C=C), 1605, 1575, 1510 (aromatic C=C).

δ ($CDCl_3$) 9.90 (1H, br. s, COO$\underline{H}$, exch.); 7.10 (1H, m, C5 ArH);

6.70 (2H, m, C6 and C8 ArH); 3.78 (3H, s, OMe); 1.27 (3H, s, CMe); 1.6-2.9 (10H, m, other protons).

2-Diazoacetyl-7-methoxy-2-methyl-1,2,3,4,9,10-hexahydrophenanthrene 47

Diazoketone 47 was prepared in the usual way from the corresponding acid 46 (0.54g, 2 mmole) via the acid chloride [yellow oil, ν_{max} (film) 1775]. Diazoketone 47 (0.52g, 88%) was thus obtained as an almost colourless semi-solid which resisted attempts at further purification.

ν_{max} 3100, 2115, 1625 ($COCHN_2$), 1645 (C=C), 1600, 1570, 1500 (aromatic C=C).

δ ($CDCl_3$) 7.15 (1H, m, C5 ArH); 6.77 (2H, m, C6 and C8 ArH); 5.45 (1H, s, $CO\underline{CH}N_2$); 3.82 (3H, s, OMe); 1.18 (3H, s, CMe); 1.5-2.9 (10H, m, other protons).

7-Methoxy-2-methyl-2,10a-ethano-1,2,3,9,10,10a-hexahydrophenanthren-12-one 48

Diazoketone 47 (370 mg, 1.25 mmole) was added to vigorously stirred, ice-cold trifluoroacetic acid (5 ml). The orange reaction mixture was diluted with water (50 ml) and methylene chloride (50 ml). The organic extract was separated, washed twice with water, dried (Na_2SO_4), and evaporated. A pale yellow crystalline residue (330 mg, quant.) of tetracyclic ketone 48 was obtained. A

sample, recrystallised from acetone-hexane and then hexane, was obtained as colourless crystals mp 138-139°. (Found : C, 80.7; H, 7.4. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%).
ν_{max} 1730 (C=O), 1630 (C=C), 1605, 1570, 1495 (aromatic C=C).
δ ($CDCl_3$) 7.55 (1H, d, J8.5Hz, C5 ArH); 6.73 (2H, m, C6 and C8 ArH); 6.05 (1H, t, J3.5Hz, C4 vinyl proton); 3.80 (3H, s, OMe); 1.18 (3H, s, CMe); 1.7-3.0 (10H, m, other protons).

<u>Hydrogenation of Δ^4- ketone 48</u> (see Chapter 4)

The above tetracyclic ketone 48 (160 mg, 0.6 mmole) in ethanol (40 ml) was hydrogenated at atmospheric pressure over 10% palladium on charcoal (20 mg) for 5.5 hr. The catalyst was removed by filtration, and the filtrate was concentrated, affording a colourless crystalline residue [ν_{max} 1725 (C=O)] of 7-methoxy-2α-methyl-2,10aβ-ethano-1,2,3,4,4aα,9,10,10a-octahydrophenanthren-12-one (145 mg, crude yield 90%). Recrystallization from aqueous methanol gave colourless crystals mp 130-133° (lit.[77] 135.5-136.5°).

<u>2-Cyano-2-hydroxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene 49</u>

A solution of the tricyclic ketone 10 (6.8g, 0.03 mole) in ether (300 ml) and water (150 ml) was deoxygenated and treated with sodium cyanide (5g, 0.1 mole). Concentrated hydrochloric acid (10 ml, 0.1 mole) was added over a period of 1 hr, with very vigorous stirring (c.f. ref[169]). The ethereal layer was separated, and the aqueous solution was extracted with a further quantity of ether (200 ml). The combined extract was washed with water (3 X 200 ml) and saturated brine, dried ($MgSO_4$), and evaporated, giving a pale orange crystalline residue (7.35g). Recrystallization from acetone-light petroleum afforded the cyanohydrin 49 as pale orange crystals, mp 126.5-129° (6.0g, 80%). One further recrystallization from the same solvent pair gave colourless rods mp 128-128.5°. (Found : C, 75.0; H, 6.8; N, 5.5. $C_{16}H_{17}O_2N$ requires C, 75.3; H, 6.7; N, 5.5%).

ν_{max} 3340 (OH), 2220 (C≡N), 1640 (C=C), 1615, 1580, 1510 (aromatic C=C).

δ ($CDCl_3$) 7.08 (1H, m, C5 ArH); 6.70 (2H, m, C6 and C8 ArH); 3.77 (3H, s, OMe); 3.03 (1H, s, OH, exch.); 1.9-2.8 (10H, m, other protons).

2-Hydroxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxamide 50

Cyanohydrin 49 (1.0g, 3.9 mmole) was added in portions, with shaking, to 96% sulphuric acid (15 ml). The red solution was kept at room temperature for 5 min, and added dropwise to a stirred mixture ice and water (250 ml). The mixture was neutralized with aqueous ammonia, and the precipitate was collected and washed with water. This material was combined with another batch from cyanohydrin (4.0g, 15.6 mmole) and sulphuric acid (50 ml), and recrystallized from acetone. The amide 50 was obtained as colourless crystals, mp 192-193° (3.3g, 62%), in two crops of 2.7 and 0.6g. One further recrystallization from acetone yielded white crystals mp 193-194°. (Found : C, 70.65; H, 6.95; N, 5.3. $C_{16}H_{19}O_3N$ requires C, 70.3; H, 7.0; N 5.1%).

ν_{max} 3340, 3210 (NH_2), 1675, 1645 ($CONH_2$), 1605, 1580, 1505 (aromatic C=C).

δ (d_6DMSO-$CDCl_3$) 7.10 (1H, m, C5 ArH); 6.70 (2H, m, C6 and C8 ArH); 3.77 (3H, s, OMe); 7.0 and 3.0 (ca. 3H, OH and NH_2, exch.); 1.7-2.8 (10H, m, other protons).

2-Hydroxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid 51

Hydroxy-amide 50 (3.8g, 0.014 mmole), suspended in methanol (60 ml), was treated, under nitrogen, with a solution of sodium hydroxide (4.0g, 0.1 mole) in water (70 ml). The mixture was heated under reflux for 3 hr, during which time the amide 50 dissolved. Most of the methanol was removed by distillation *in vacuo*, and the aqueous residue was acidified with 50% sulphuric acid. The pale pink precipitate of hydroxy-acid 51 (ν_{max} 3350, 1700) was collected.

An attempt to recrystallise this crude product from methanol was unsuccessful. A pale brown, neutral, crystalline residue (3.9g) was obtained by evaporation of the solvent. This was easily purified by chromatography on Florisil (250g). Elution with methylene chloride afforded methyl 2-hydroxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylate 54 (3.4g, 85%) as almost colourless crystals mp 92-94°. An analytic sample was obtained by low temperature recrystallization from ether-hexane; white crystals mp 94-95°. (Found : C, 71.2; H, 7.0. $C_{17}H_{20}O_4$ requires C, 70.8; H, 7.0%).

ν_{max} 3440 (OH), 1715 (COOMe), 1650 (C=C), 1605, 1575, 1510 (aromatic C=C).

δ ($CDCl_3$) 7.15 (1H, m, C5 ArH); 6.72 (2H, m, C6 and C8 ArH); 3.80 (6H, s, OMe and COOMe); 3.05 (1H, s, OH, exch.); 1.8-2.8 (10H, m, other protons).

The hydroxy-ester 54 (3.2.g, 0.011 mole) was stirred, at 110-120° (bath temperature), with sodium hydroxide (5g, 0.12 mole) in methanol (50 ml) and water (100 ml) for 1.5 hr. The cooled mixture was poured into water (1.5l) containing concentrated hydrochloric acid (15 ml). The precipitate was collected, and recrystallised from ether. The desired hydroxy-acid 51 was obtained as pale tan crystals mp 157.5-159.5° (2.4g, 80%), in two crops of 1.9 and 0.5g.

ν_{max} 3440, 3300 (OH), 3200-2500, 1705 (COOH), 1605, 1565, 1500 (aromatic C=C).

2-Acetoxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid 58

Hydroxy-acid 51 (0.48g, 1.8 mmole) was suspended in acetic anhydride (10 ml) and pyridine (0.3 ml). The mixture was kept at room temperature for 24 hr. Acetic anhydride (10 ml) and pyridine (0.5 ml) were added, and the resulting mixture was heated at 70-80° for 1 hr to complete the reaction. Water was added very slowly to hydrolyse the excess of acetic anhydride. The precipitate was collected and recrystallised from acetone, thus giving the acetoxy-acid 58 as colourless crystals (0.47g, 86%). A pure smaple, mp 224°, was obtained after one more recrystallization from acetone. (Found : C, 68.4; H 6.4. $C_{18}H_{20}O_5$ requires C, 68.3; H, 6.4%).

ν_{max} 3100-2500, 1705 (COOH), 1735 ($OCOCH_3$), 1645 (C=C), 1600, 1565, 1500 (aromatic C=C).

δ (d_6DMSO-$CDCl_3$) 6.4 (1H, br. s, COOH, exch.); 7.12 (1H, m, C5 ArH); 6.70 (2H, m, C6 and C8 ArH); 3.78 (3H, s, OMe); 2.03 (3H, s, $OCOC\underline{H}_3$); 1.8-2.9 (10H, m, other protons).

2-Acetoxy-2-diazoacetyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene 59

Acetoxy-acid 58 (250 mg, 0.8 mmole) was added in small portions to a stirred solution of oxalyl chloride (2.25g, 18 mmole) in benzene (15 ml). Pyridine (80 mg, 1 mmole) was added, and the resulting mixture was heated at 60-70° for 2 hr. Pyridinium salts were removed by filtration. The filtrate was evaporated, giving the corresponding acid chloride as a yellow oil [ν_{max} (film) 1790, 1740]. The acid chloride was converted to the diazoketone 59 in the usual way with diazomethane (5 mmole) in ether (15 ml). Diazoketone 59 was obtained as a dark yellow oil (260 mg) whose purification was not attempted.

ν_{max} (Film) 2110, 1630 ($COCHN_2$), 1740 ($OCOCH_3$), 1600, 1570, 1500 (aromatic C=C).

δ (CCl_4) 6.92 (1H, m, C5 ArH); 6.57 (2H, m, C6 and C8 ArH); 5.30 (1H, s, $CO\underline{CH}N_2$); 3.73 (3H, s, -OMe); 2.00 (3H, s, $OCOC\underline{H}_3$). Resonances due to impurities were also evident.

Attempted cyclization of diazoketone 59

The crude diazoketone from the above reaction (220mg, 0.6 mmole) in methylene chloride (10ml) at 0° was treated, all at once, with trifluoroacetic acid (5 ml). The reaction mixture was diluted with water (20 ml) and methylene chloride (20 ml). The organic layer was separated, washed twice with water, dried (Na_2SO_4), and concentrated. A yellow oil (200 mg) was obtained which was separated into two main fractions by preparative TLC using methylene-chloride-acetone (9:1).

(i) The higher R_F fraction (80 mg) was semi-crystalline. Spectral data [ν_{max} 1750, 1725; δ ($CDCl_3$) 7.53 (1H, d, J8Hz, C5 ArH); 6.03 (1H, t, J4Hz, C4 vinyl proton).] indicated that this fraction was mainly the cyclized α-ketol acetate 60.

(ii) The lower R_F fraction (60 mg) was an oil, and showed spectral data [ν_{max} (film) 3450, 1740; δ($CDCl_3$) 5.13 (s, $COC\underline{H}_2$ OAc)] in accordance with the presence, *inter alia*, of the uncyclised hydroxy-acetate 64.

Further purification of either fraction could not be effected.

7-Methoxy-2-trifluoroacetoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid 65

Hydroxy-acid 51 (1.5g, 5.5 mmole) was added to trifluoroacetic anhydride (10 ml) at room temperature. The acid dissolved in *ca.* 5 min to form a red solution. The reaction mixture was allowed to stand at room temperature for 8 hr. The excess of trifluoroacetic anhydride was removed *in vacuo*, and the residue was taken up in ethylacetate (200 ml). This solution was washed with water (4 X 150 ml) and saturated brine (3 X 150 ml), dried, and concentrated. The residue crystallised readily, giving the trifluoroacetoxy-acid 65 (2.0g, quant.) as bright yellow crystals mp 156-160°.

ν_{max} 3200-2500, 1720 (COOH), 1790, 1220, 1170 ($OCOCF_3$) 1605, 1500 (aromatic C=C).

δ ($CDCl_3$) 8.1 (1H, br. s, COOH, exch.); 7.13 (1H, m, C5 ArH); 6.75 (2H, m, C6 and C8 ArH); 3.80 (3H, s, OMe); 2.0-3.0 (10H, m, other protons).

Attempted preparation of diazoketone 66

Trifluoroacetoxy-acid 65 (1.8g, 4.9 mmole) was added in small portions to a stirred solution of oxalyl chloride (15g, 0.12 mole) in benzene (100 ml). Pyridine (400mg, 5 mmole) was added, and the mixture was heated at 50-70° for 2 hr. The precipitated salts were removed by filtration. Evaporation of the filtrate yielded the acid chloride (1.9g) as a deep yellow oil [ν_{max} (film)1780].

The crude acid chloride was immediately converted to the diazoketone in the standard way. The semi-crystalline product (1.8g) was shown to be a mixture of the required diazoketone 66 and the hydroxy-diazoketone 57 (see page 50 for full details).

Reprotection and *in situ* cyclization of the mixture of diazoketones 57 and 66

The crude diazoketone mixture (1.65g) from the previous experiment was dissolved in methylene chloride (50 ml). Pyridine (0.5 ml) and trifluoroacetic anhydride (5 ml) were added, in that order, and the resulting solution was stirred at room temperature for 0.5 hr, when trifluoroacetic acid (10 ml) was added all at once. The solution was diluted with methylene chloride (200 ml) and water (100 ml). The organic extract was washed with water

(3 X 100 ml), dried (Na_2SO_4), and evaporated. The α-ketol trifluoroacetate 67 was obtained as a red oil (1.9g), which was not purified further, but was immediately hydrolysed (*vide infra*) ν_{max} (film) 1780, 1230, 1170 ($OCOCF_3$), 1755 (C=O), 1605, 1570, 1505 (aromatic C=C).

2-Hydroxy-7-methoxy-2,10a-ethano-1,2,3,9,10,10a-hexahydrophenanthren-12-one 68

The crude oily α-ketol trifluoroacetate 67 (1.9g) in methanol (60 ml) was treated with a solution of potassium carbonate (5g) in water (10 ml). The mixture was stirred at room temperature for 1.5 hr. Water (500 ml) and ether (200 ml) were added. The ether extract was removed, and the aqueous layer was extracted with methylene chloride (2 X 50 ml). The combined organic extract was dried (K_2CO_3) and evaporated, leaving a brown oil (1.3g) which crystallised slowly. The crude product was preadsorbed on kieselquhr and chromatographed on silica gel (150g). Elution with methylene chloride-acetone (19:1) gave the tetracyclic α-ketol 68 (0.68g, *ca*. 60% yield from 51) as a yellow crystalline solid mp 144-148°. An analytical sample, mp 145-147°, was obtained after further purification by filtration through a small column of Florisil followed by recrystallization from ethyl acetate-light petroleum, bp 60-80°. (Found : C, 75.3;

H, 6.65. $C_{17}H_{18}O_3$ requires C, 75.5; H, 6.7%).

ν_{max} 3420 (OH), 1735 (C=O), 1600, 1495 (aromatic C=C).

δ ($CDCl_3$) 7.55 (1H, d, J8Hz, C5 ArH); 6.73 (2H, m, C6 and C8 ArH); 6.08 (1H, t, J4Hz, C4 vinyl proton); 3.82 (3H, s, OMe); 3.12 1H, br. s, OH, exch.); 1.7-2.9 (10H, m, other protons).

2-Diazoacetyl-2-hydroxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene 57

The mixture of diazoketones 57 and 66 (100 mg) in methanol (20 ml) was treated for 1 hr with a solution of potassium carbonate (1g) in water (10 ml). The reaction mixture was diluted with water (50 ml) and extracted with methylene chloride (3 X 10 ml). The combined extract was washed with water, dried (Na_2SO_4), and evaporated. The semicrystalline residue was crystallised from ether, giving the hydroxy-diazoketone 57 (43 mg) as yellow crystals. This compound was used immediately in the next reaction.

ν_{max} 3435 (OH), 3135, 2100, 1630 ($COCHN_2$), 1610, 1575, 1500 (aromatic C=C).

δ ($CDCl_3$) 7.13 (1H, m, C5 ArH); 6.70 (2H, m, C6 and C8 ArH); 5.78 (1H, s, $COC\underline{H}N_2$); 3.80 (3H, s, OMe); 1.6-3.2 (11H, m, other protons inc. OH).

Reaction of hydroxy-diazoketone 57 with trifluoroacetic acid

The hydroxy-diazoketone 57 (43 mg) in deuterochloroform (0.4 ml) was treated with trifluoroacetic acid (1 drop). Work up in the usual way afforded a yellow oil (35 mg), which was purified by preparative TLC, using methylene chloride as solvent. The semi-crystalline spiro-β-oxetanone 69 (26 mg) was obtained from the major band. This compound resisted further purification by crystallization, but the spectral data left no doubt as to its structure.

ν_{max} 1800 (C=O), 1610, 1570, 1505 (aromatic C=C).
δ ($CDCl_3$-CF_3COOH) 7.17 (1H, m, C5 ArH); 6.78 (2H, m, C6 and C8 ArH); 5.47 (2H, s, $COC\underline{H}_2O$); 3.87 (3H, s, OMe); 1.9-3.0 (10H, m, other protons).

2-Bromoacrylic acid

2-Bromoacrylic acid was prepared from 2,3-dibromopropionic acid[179] by the method of Owen and Babatunde Somade.[180]

2-Bromo-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid 70

A solution of 2-bromoacrylic acid (3.5g, 0.023 mole) in benzene (15 ml) was added dropwise, under nitrogen, to a solution of diene 25 (2.5g, 0.013 mole) in benzene (10 ml). The resulting solution was kept at room temperature, under nitrogen, overnight.

The pale yellow crystalline precipitate of the α-bromoacid 70 mp 176-179° (1.2g, 26%) was collected. The dark brown mother liquors were discarded. This compound lost HBr very readily, and gave a low bromine analysis and correspondingly high carbon analysis. Compounds derived from 70, however, gave acceptable microanalytical figures (vide infra). Spectral data for the crude product were :

ν_{max} 3100-2400, 1700 (COOH), 1600, 1570, 1505 (aromatic C=C).
δ (d_6DMSO-$CDCl_3$) 7.08 (1H, m, C5 ArH); 6.68 (2H, m, C6 and C8 ArH); 6.0 (1H, br. s, COOH, exch); 3.75 (3H, s, OMe); 1.9-3.1 (10H, m, other protons).

Dehydrobromination of bromo-acid 70

A solution of bromo-acid 70 (250 mg, 0.7 mmole) and potassium carbonate (750 mg) in water (20 ml) was heated under reflux for 4 hr. The cooled solution was acidified with concentrated hydrochloric acid, and poured into water. The yellow amorphous precipitate was collected, dried, and recrystallized from acetone, giving 7-methoxy-1,4,9,10-tetrahydrophenanthrene-2-carboxylic acid 73 (135mg, 77%) as a pale yellow solid. The analytical sample, obtained as white crystals after one further recrystallization from acetone, melted at 190-191°. (Found : C, 75.2; H, 6.5. $C_{16}H_{16}O_3$

requires C, 75.0; H, 6.3%).

ν_{max} 3200-2400, 1675 (conjugated COOH), 1605, 1575, 1500 (aromatic C=C).

δ (d_6DMSO-$CDCl_3$) 7.52 (1H, m, C5 ArH); 4.05 (2H, m, C6 and C8 ArH); 5.73 (1H, t, J2.5Hz, C3 vinyl proton); 3.80 (3H, s, OMe); 1.5-3.4 (8H, m, other protons) - see p. 55 for further details.

λ_{max} 269, 276, 300, 311 nm ε 16000, 15000, 3700, 2600.

2-Bromo-2-diazoacetyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene 71

Bromo-acid 70 (0.67g, 2 mmole) was converted to the corresponding bromo-diazoketone 71 in the standard way, *via* the acid chloride [brown, semi-crystalline oil; ν_{max} (film) 1770]. The crude crystalline diazoketone 71 was recrystallized from ether-light petroleum to give orangelumps (0.57g, 80%). An analytical sample, orange-yellow crystals mp 132-134 dec., was obtained by one more recrystallization from ether. (Found: C, 56.8; H, 4.8; N, 7.3. $C_{17}H_{17}O_2N_2Br$ requires C, 56.5; H, 4.7; N, 7.8%).

ν_{max} 3100, 2120, 1620 ($COCHN_2$), 1655 (C=C), 1605, 1570, 1500 (aromatic C=C).

δ ($CDCl_3$) 7.13 (1H, m, C5 ArH); 6.73 (2H, m, C6 and C8 ArH); 5.90 (1H, s, $CO\underline{H}N_2$); 3.80 (3H, s, OMe); 1.9-3.1 (10H, m, other protons).

Trifluoroacetic acid catalysed decomposition of bromo-diazoketone 71

Recrystallized bromo-diazoketone (200 mg, 0.55 mmole) in methylene chloride (50 ml) was cooled to 0°, and treated dropwise with trifluoroacetic acid (0.5 ml). Nitrogen did not appear to be evolved, but a bright red reaction mixture was formed. After 2 min, water (50 ml) was added, and the organic layer was separated and dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded a yellow-brown oil (197 mg), which was immediately triturated with ether, giving a deep yellow crystalline substance (45 mg) mp 58-59°. Microanalysis was performed without further purification. (Found : Br, 19.2; N, $<$0.5. $C_{17}H_{17}O_2Br$ requires Br, 24.0; N, 0.0%). This compound was 2-bromoacetyl-7-methoxy-3,4,9,10-tetrahydrophenanthrene 74. (see p. 56-57 for spectral details). The yield was 25%.

The mother liquors from the crystallization of bromo-ketone 74 were dissolved in ethanol (200 ml) and allowed to stand at room temperature for 2 days. Evaporation of the ethanol gave a crystalline solid which was purified by preparative TLC, using the solvent methylene chloride. The major, highly fluorescent band was eluted and the product crystallised from ether-light petroleum to give 2-acetyl-7-methoxy-9,10-dihydrophenanthrene 75 as pale yellow crystals (80 mg, 58%). A sample was recrystallized from hexane; colourless crystals mp 132.5-133°. (Found : C, 81.0; H 6.6.

$C_{17}H_{16}O_2$ requires C, 80.9; H 6.4%).

The assigment of structure 75 for this compound was based on spectral data discussed in detail on p. 58-59.

CHAPTER 3

Methyl 7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylate 83

A suspension of the $\Delta^{4a(10a)}$-acid 27 (7.2g, 0.028 mole) in methylene chloride (100 ml) was treated, with stirring at room temperature, with a solution of diazomethane (0.07 mole) in ether (120 ml). The acid dissolved rapidly with evolution of nitrogen. The solution was stirred at room temperature for 0.5 hr, and warmed on a water bath to remove the excess of diazomethane. The solution was evaporated giving a pale yellow oil which crystallised readily. The crude product in ether (100 ml) was slurried with Florisil (35g) and filtered. Evaporation of the filtrate yielded the methyl ester 83 (7.6g, 100%) as a colourless crystalline solid, mp 48.5-50.5°, suitable for use without further purification. An analytical sample was obtained by recrystallization from hexane at -70°; white plates mp 50-51°. (Found : C, 74.85; H 7.5; $C_{17}H_{20}O_3$ requires C, 75.0; H 7.4%).

ν_{max} 1720 (C=0), 1645 (C=C), 1610, 1570, 1505 (aromatic C=C).

δ (CCl_4) 7.00 (1H, m, C5 ArH); 6.60 (2H, m, C6 and C8 ArH); 3.75 and 3.67 (3H ea., s, OMe and COOMe); 1.5-2.9 (11H, m, other protons).

Bromination of the methyl ester 83 with N-bromosuccinimide

N-Bromosuccinimide (4.85g, 0.027 mole) and benzoyl peroxide (30 mg) were suspended in carbon tetrachloride (10 ml). The methyl ester 83 (7.4g, 0.027 mole) in carbon tetrachloride (90 ml) was added, and the mixture was heated to reflux with vigorous stirring. A vigorous reaction ensued, with so much frothing that the reaction was moderated by cooling. After ca. 1 min, frothing stopped, and the reaction mixture gave only a weakly positive test with starch-iodide paper. The yellow mixture was cooled and filtered, and the precipitate of succinimide was washed with carbon tetrachloride (2 X 20 ml). Evaporation of the filtrate yielded a yellow solid, which was purified by washing with ice-cold ether (100 ml). Methyl 10-bromo-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylate 84 (or some other isomer) was thus obtained as a pale yellow crystalline solid (7.0g, 74%) which melted at 93-95° immediately after purification. The compound was extremely unstable and a satisfactory analysis could not be obtained. The spectral data, however supported the structure 84 for this product.

ν_{max} 1725 (C=O), 1630 (shoulder, C=C), 1610, 1575, 1510 (aromatic C=C).

δ ($CDCl_3$) 7.37 (1H, d, J8Hz, C5 ArH); 6.70 (2H, m, C6 and C8 ArH); 5.23 (1H, m, CHBr at C10); 3.78 and 3.75 (total 6H, two s, OMe and COOMe); 2.0-3.6 (9H, m, other protons).

Methyl 7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-carboxylate 85

The crude bromo-ester 84 (6.7 g, 0.019 mole) and anhydrous calcium carbonate (20 g, 0.2 mole) were heated at 120-130° in dry dimethylformamide (130 ml) for 4 hr. The cooled reaction mixture was filtered, and the residue was washed with dimethylformamide (2 X 40 ml). The filtrate was poured slowly into water (1.2l); the yellow precipitate which formed was collected and dried briefly *in vacuo*. Recrystallization from hexane yielded the required ester 85 (2.4g) as yellow leaflets.

The residue from recrystallization was chromatographed on silica gel (120g). Elution with methylene chloride-light petroleum (3:2), and recrystallization of the product from ether afforded a further amount of the ester 85 (0.8g). Total yield was 3.2g (67%).

A final recrystallisation from hexane gave the methyl ester 85 as pale yellow rods, mp 106-108° (lit.[196] 105-106°).

ν_{max} 1730 (C=O), 1625, 1605, 1575, 1500 (aromatic C=C).

δ (CCl_4) 6.93-7.77 (5H, m, ArH); 3.83 (3H, s, OMe); 3.67 (3H, s, COOMe); 1.6-3.2 (7H, m, other protons.

λ_{max} 227, 264, 273, 320 335 nm ε 80000, 7800, 7600, 2900 3500.

7-Methoxy-1,2,3,4-tetrahydrophenanthrene-2-carboxylic acid 86

A suspension of the methyl ester 85 (2.8g, 0.010 mole) in methanol (30 ml) was treated with a solution of sodium hydroxide (5g, 0.12 mole) in water (70 ml). The mixture was heated, with stirring, at 100-110° (oil bath temperature) for 1.5 hr. The cooled reaction mixture was poured into water (1 l) containing concentrated hydrochloric acid (15 ml). The precipitate was collected and recrystallised from chloroform. The carboxylic acid 86 (2.6g, 98%) was obtained, in two crops of 2.0 and 0.6g, as pale yellow needles mp 201-203° (lit.[196] 201-203°).

ν_{max} 3100-2400, 1695 (COOH), 1620, 1600, 1500 (aromatic C=C).
δ (d_6DMSO-$CDCl_3$) 7.1-7.9 (5H, m, ArH); 3.87 (3H, s, OMe); 1.7-3.3 (7H, m, other protons).

2-Diazoacetyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene 87

Diazoketone 87 was synthesised from the acid 86 (2.0g, 7.8 mmole) *via* the corresponding acid chloride [pale yellow crystals, mp 88-90°; ν_{max} 1785]. Diazoketone 87 (2.15g, 98%) was thus obtained as yellow crystals. The analytical sample was recrystallized from acetone-hexane; yellow prisms, mp 132-135° dec. (Found : C, 72.85; H, 5.8; N 9.9. $C_{17}H_{16}O_2N_2$ requires C, 72.8; H, 5.75; N 10.0%).

ν_{max} 3090, 2100, 1625 ($COCHN_2$), 1600, 1505 (aromatic C=C).
δ ($CDCl_3$) 7.1-7.9 (5H, m, ArH); 5.32 (1H, s, $CO\underline{CH}N_2$); 3.90 (3H, s, OMe); 1.5-3.3 (7H, m, other protons).

Trifluoroacetic acid catalysed decomposition of diazoketone 87

Diazoketone 87 (280 mg, 1.0 mmole) was added in portions to ice-cold trifluoroacetic acid (5 ml). Water (50 ml) and methylene chloride (50 ml) were added to the orange reaction mixture. The organic layer was separated, washed twice with water, dried (Na_2SO_4), and concentrated. A yellow oil (274 mg) was obtained. The infrared spectrum of this product showed minor bands at 1790, and 1750, due to the presence of the uncyclized ketol trifluoroacetate 89 (see p. 72).

Preparative TLC using methylene chloride-acetone (19:1) gave, from the major band, a yellow oil (200 mg). This oil was still a 3:1 mixture of two compounds (NMR), but absorptions of the major component, which are set out in detail below, dominated the spectra and allowed its structure to be deduced as 7-methoxy-3,4a-ethano-4,4a-dihydrophenanthren-2(3H)-one 90.

ν_{max} (film) 1655 (conjugated C=C), 1605, 1570, 1500 (conjugated C=C and aromatic C=C).

δ (CCl_4) 7.27 (1H, d, J8Hz, C5 ArH); 6.73 (3H, m, C6 and C8 ArH, and C9 vinyl proton); 6.30 (1H, d, J9Hz, C10 vinyl proton); 5.70 (1H, poorly resolved d, Jca. 1Hz, C1 vinyl proton, coupled to C3 proton); 3.77 (3H, s, OMe); 3.02 (1H, m, C3 proton); 1.4-2.6 (6H, m, other protons).

λ_{max} 216, 243, 265, 323, 332, 368 nm. ε 22000, 16000, 13000, 12000 11000, 10000.

The minor component of this mixture was later identified (by comparison of NMR spectra) as the isomeric dienone 92 (see below).

Cyclopropyl ketone 91

Hot cyclohexane (300 ml) was added all at once to a solution of the diazoketone 87 (1.0g, 3.57 mmole) in boiling acetone (10 ml). The solution was distilled until the temperature of the vapours reached 80°. Copper powder (5 g) was added, and the mixture was heated under reflux, with vigorous stirring, for 2.5 hr. The warm mixture was filtered through a small pad of Celite, and the residue was washed three times with ether. The filtrate was evaporated, leaving a pale yellow oil which crystallised on addition of a small quantity of ether. The crude product was purified by chromatography on alumina (50g). Elution with methylene chloride-light petroleum (1:4), gave the cyclopropyl ketone 91 (0.57g, 64%) as colourless prisms mp 92-93° after recrystallization from ether-light petroleum. (Found : C, 80.9; H, 6.5. $C_{17}H_{16}O_2$ requires C, 80.9; H, 6.4%). ν_{max} 1715 (C=O), 1640 (C=C), 1610, 1575, 1510 (aromatic C=C). δ ($CDCl_3$) 7.50 (1H, d, J8.5Hz, C5 ArH); 6.82 (2H, m, C6 and C8 ArH); 6.41 and 6.28 (2H, ABq, J_{AB} 9.5 Hz, C9 and C10 vinyl protons);

3.80 (3H, s, OMe); 0.85 (1H, d, J1.3Hz, C11 cyclopropyl proton); 1.8-3.0 (7H, m, other protons).

Acid catalysed fragmentation of cyclopropyl ketone 91

(a) With p-toluenesulphoric acid

p-Toluenesulphonic acid (several crystals) was added to a solution of cyclopropyl ketone 91 (250 mg, 1 mmole) in acetone (10 ml). The resultant yellow solution was stirred at room temperature for 1 hr, and dilated with aqueous 5% sodium bicarbonate solution (20 ml). The mixture was extracted with ether (3 X 20 ml), and the combined extract was washed with water and saturated brine, dried ($MgSO_4$), and evaporated. A very pale yellow oil (250 mg, quant.), which contained a single component by the usual criteria, was obtained. This compound was shown, by the spectral data set out below, to be 7-methoxy-2,10a-ethano-1,10a-dihydrophenanthren-3(2H)-one 92. A small sample was purified by evaporative distillation; bp 140° (block temperature), 0.01 mm. (Found C, 80.6; H 6.3; $C_{17}H_{16}O_2$ requires C, 80.9; H 6.4%).

ν_{max} (film) 1655 (conjugated C=O), 1605, 1575, 1500 (conjugated C=C and aromatic C=C),

δ (CCl_4) 7.57 (1H, d, J8.5 Hz, C5 ArH); 6.72 (1H, dd, J8.5 and 2.5 Hz, C6 ArH); 6.58 (1H, d, J2.5 Hz, C8 ArH); 6.42 (1H, d, J9.5 Hz, C9 vinyl proton); 6.20 (1H, poorly resolved dd, J ca. 1Hz, C4 vinyl proton coupled to C2 and C9 protons); 5.85 (1H, dd, J9.5 and ca.

1 Hz, C9 vinyl proton); 3.80 (3H, s, OMe); 2.98 (1H, m, C2 proton); 1.4-2.5 (6H, m, other protons).

λ_{max} 270, 278, 326, 341, 363 nm ε27500, 27000, 12000, 14000, 16000.

The DNP of 92 crystallized from acetic acid as dark red needles, mp 261-263°. (Found : C, 63.0; H, 4.9; N 12.7. $C_{23}H_{20}O_5N_4$ requires C, 63.9; H, 4.7; N 13.0%).

(b) With trifluoroacetic acid

Cyclopropyl ketone 91 (45 mg) in deuterochloroform (0.5 ml) was treated with trifluoroacetic acid (1 drop). Work up of the yellow solution in the usual way gave a pale yellow oil (45 mg, quant.), identical in all respects to the dienone 92 obtained in the previous experiment. No trace of the isomeric dienone 90 could be detected by examination of the NMR spectrum.

Tosyl hydrazone of glyoxylyl chloride 103

The reagent 103 was prepared in two steps from glyoxylic acid according to the procedure of House and Blankley.[209]

2-Hydroxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene 104

Ketone 10 (1.1g, 4.8 mmole) in ether (75 ml) was treated portionwise with lithium aluminium hydride (0.6g, 0.016 mole). The suspension was stirred at room temperature for 2 hr, and heated under reflux for 10 min. Water was added very carefully until a granular white precipitate was just formed. The mixture was dried ($MgSO_4$) and filtered. Evaporation of the filtrate gave the alcohol 104 (1.08g, 97%) as colourless crystals, mp 70-73°. This crude product was pure enough for use without further purification. ν_{max} 3200 (OH), 1640 (C=C), 1600, 1570, 1500 (aromatic C=C). δ ($CDCl_3$) 7.10 (1H, m, C5 ArH); 6.67 (2H, m, C6 and C8 ArH); 3.98 (1H, m, C<u>H</u>OH); 3.78 (3H, s, OMe); 1.95 (1H, s, OH, exch.); 1.5-3.0 (10H, m, other protons).

2-Diazoacetoxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene 98

The tosyl hydrazone of glyoxyl chloride 103 (1.30g, 5.2 mmole) in methylene chloride (15 ml) at 0°, was treated with a solution of the alcohol 104 (1.15g, 5 mmole) and triethylamine (0.52g, 5.2 mmole) in methylene chloride (10 ml). The resulting solution was allowed to warm to room temperature over 2 hr, when an additional quantity of triethylamine (0.70, 7 mmole) was added. After 2 hr at room temperature, the solution was evaporated under reduced pressure. The residue, in benzene, was filtered through a column of Florisil (20g), yielding the diazoester 98 as a yellow oil (1.3g) which could not be successfully crystallized. Further purification was effected by careful chromatography on Florisil (80g). Elution with benzene-light petroleum (7:3) afforded pure (by TLC) diazoester 98 (0.45g), which crystallised as yellow needles, mp 78-80°, from light petroleum containing a small quantity of methylene chloride. An analytical sample, mp 80-81 °, was obtained by one further crystallization from the same solvent pair. (Found : C, 68.2; H, 6.1; N, 9.3. $C_{17}H_{18}O_3N_2$ requires C 68.4; H, 6.1; N9.4%).

ν_{max} 3050, 2140, 1675 ($OCOCHN_2$), 1610, 1575, 1505 (aromatic C=C). δ (CCl_4) 6.97 (1H, m, C5 ArH); 6.57 (2H, m, C6 and C8 ArH); 5.07 (1H, m, $C\underline{H}OCOCHN_2$); 4.63 (1H, s, $OCOC\underline{H}N_2$); 3.73 (3H, s, OMe); 1.8-2.9 (10H, m, other protons).

Further elution of the above column with chloroform gave crystalline starting alcohol 104 (0.62g). The yield of diazoester 98 based on this recovery was 75%.

Attempted cyclization of diazoester 98

Diazoester 98 (33 mg, 0.11 mmole) was added in portions to ice-cold trifluoroacetic acid (1 ml). The green solution was diluted with water (10 ml) and methylene chloride (10 ml). The organic extract was washed with water, dried (Na_2SO_4), and evaporated, giving a colourless, unstable oil (41 mg). This was shown to be the non-cyclized diester 105 (crude yield 96%) by the spectral data :

ν_{max} (film) 1790, 1220, 1150 ($OCOCF_3$), 1745 ($OCOCH_2O$), 1640 (C=C), 1605, 1565, 1500 (aromatic C=C).

δ (CCl_4-CF_3CO_2H) 7.03 (1H, m, C5 ArH); 6.67 (2H, m, C6 and C8 ArH); 5.23 (1H, m, C$\underline{H}$OCO); 4.83 (2H, s, COC$\underline{H}_2$O); 3.83 (3H, s, OMe); 1.8-2.9 (10H, m, other protons).

The crude diester 105 was immediately hydrolysed (see next experiment).

Hydrolysis of diester 105

The crude diester 105 (41 mg, 0.105 mmole) in methanol (2 ml) was treated with a solution of sodium hydroxide (200 mg, 5 mmole) in water (1 ml). The mixture was stirred at room temperature for 2 hr. Most of the methanol was removed in a stream of nitrogen. The residue was diluted with water (10 ml) and extracted with ether (2 X 10 ml). The combined extract was washed with water, dried ($MgSO_4$) and evaporated. The crystalline residue mp 70-73°, was identical (TLC, mixed mp, spectra) to the alcohol 104, the starting material for the sequence. The yield was 21 mg (86%).

CHAPTER 4

Hydrogenation of cyclopropyl ketone 29

Cyclopropyl ketone 29 (100 mg, 0.4 mmole) in ethanol (20 ml) was hydrogenated at atmospheric pressure over palladium on carbon (15 mg) for 40 hr. The catalyst was removed by filtration, and the filtrate was evaporated to give a colourless oil which crystallised from ether. Colourless crystals, mp 133-136° (70 mg, 70%), were obtained. This compound proved to be the *trans*-fused saturated bicyclo[3.2.1]octane derivative 7-methoxy-2,10aβ-ethano-1,2,3,4,4aα,9,10,10a-octahydrophenanthren-12-one 108 (*vide infra*). An analytical sample, mp 136-136.5°, was obtained as white needles from hexane. (Found : C, 79.6; H, 8.0. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.9%).

ν_{max} 1735 (C=O), 1615, 1575, 1510 (aromatic C=C).

δ($CDCl_3$) 7.15 (1H, d, J8Hz, C5 ArH); 6.72 (2H, m, C6 and C8 ArH); 3.78 (3H, s, OMe); 1.0-3.0 (14H, m, other protons).

Hydrogenation of tetracyclic ketone 9

Ketone 9 (145 mg, 0.57 mmole) and palladium on carbon (20 mg) in ethanol (25 ml) were stirred under hydrogen at atmospheric pressure overnight. The reaction mixture was filtered and the filtrate evaporated, leaving an oil (140 mg) which crystallised on adding ether.

The crude product was purified by preparative TLC using ether-methylene chloride (1:19). The major band was removed and eluted, yielding a colourless oil (105 mg, 72%) which crystallised from ether; white crystals mp 133-136°. This product, expected to be the trans-fused ketone 108, was identical (TLC, mixed mp, spectra) to the product of the previous experiment.

12,12-Ethylenedioxy-7-methoxy-2,10a-ethano-1,2,3,9,10,10a-hexahydrophenanthrene 109

A mixture of ketone 9 (1.93g, 7.6 mmole), ethylene glycol (5 ml) and p-toluenesulphonic acid (100 mg) in benzene (200 ml) was heated under reflux, using a Dean-Stark water separator, for 5.5 hr. The cooled mixture was poured into 5% aqueous sodium bicarbonate (250 ml) and diluted with ether (200 ml). The organic extract was washed with water and saturated brine, dried ($MgSO_4$), and evaporated. The crude oily product was purified by filtration, in methylene chloride-light petroleum (3:2), through a small column of Florisil. The acetal 109 (1.90g, 84%) was thus obtained as colourless crystals, mp 91-92°. A small sample was recrystallized from hexane; white cubes mp 93-94°. (Found : C, 76.6; H, 7.6; $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%).

ν_{max} 1630 (C=C), 1610, 1575, 1505 (aromatic C=C).

δ ($CDCl_3$) 7.62 (1H, d, J8.5 Hz, C5 ArH); 6.72 (2H, m, C6 and C8

ArH); 6.07 1H, t, J3.5 Hz, C4 vinyl proton); 3.90 (4H, s, OCH_2CH_2O); 3.80 (3H, s, OMe); 1.5-2.8 (10H, m, other protons).

12,12-Ethylenedioxy-7-methoxy-2,10aβ-ethano-1,2,3,4,4aα,9,10,10a-octahydrophenanthrene 110

The above acetal 109 (170 mg, 0.57 mmole) in ethanol (25 ml) was hydrogenated at atmospheric pressure over palladium on charcoal (25 mg) for 6 hr. Work up in the usual way gave a colourless crystalline residue (155 mg, 90%) of the trans-fused acetal 110, mp 110-115°. This compound tended to lose the acetal group on recrystallization, and so was used without purification in the following reaction.

ν_{max} 1605, 1580, 1510 (aromatic C=C).
δ ($CDCl_3$) 7.17 (1H, d, J8Hz, C5 ArH); 6.68 (2H, m, C6 and C8 ArH); 3.87 (4H, s, OCH_2CH_2O); 3.77 (3H, s, OMe); 1.2-3.9 (14H, m, other protons).

Hydrolysis of acetal 110

Crude acetal 110 (115 mg, 0.38 mmole) in warm acetone (10 ml) was treated with 3N hydrochloric acid (2 ml), and the solution heated under reflux for 0.5 hr. Water (20 ml) was added, and the aqueous mixture was extracted with ether (3 X 10 ml). The combined extract was washed with water and saturated brine, dried ($MgSO_4$), and evaporated. Colourless crystals, mp 134-136° (95mg, 98%) were obtained. The product, *trans*-fused ketone 108, was identical by all the usual criteria, to the product previously obtained by two different routes (*vide supra*).

Hydrogenation of cyclopropyl ketone 91

Cyclopropyl ketone 91 (90 mg, 0.36 mmole) was hydrogenated in ethanol (10 ml) over palladium on carbon (20 mg) for 1.5 hr. Two molar equivalents of hydrogen were absorbed during this time. Work up in the usual way gave a crystalline residue (90 mg) with a melting range of *ca.* 30°. Spectral data indicated that this product was a mixture of the bicyclo[2.2.2]octane diastereoisomers 7-methoxy-2,4a-ethano-1,2,3,4,4a,9,10,10a ξ-octahydrophenanthren-3-one 111.

ν_{max} (CCl_4) 1715 (C=O), 1605, 1575, 1505 (aromatic C=C).

δ ($CDCl_3$) 7.03 and 6.98 (total 1H, two d, C5 ArH of each diastereoisomer); 6.57 (2H, m, C6 and C8 ArH); 3.70 (3H, s, OMe); 1.0-2.9 (14H, m, other protons).

12β-Hydroxy-7-methoxy-2,10aβ-ethano-1,2,3,9,10,10a-hexahydrophenanthrene 112

Sodium borohydride (0.7g, 18 mmole) was added in portions to a solution of tetracyclic ketone 9 (0.44g, 1.7 mmole) in ethanol (40 ml). The resulting solution was kept at room temperature overnight. Most of the ethanol was evaporated under reduced pressure, and the residue was treated with 1% hydrochloric acid (70 ml). The aqueous mixture was extracted with ether (1 X 60 ml, 3 X 30 ml), and the combined extract was washed with water and saturated brine, dried ($MgSO_4$), and evaporated. A colourless oil (0.45g, quant.) was obtained. This product could not be crystallised, but the spectral data agreed with the endo-alcohol structure 112.

ν_{max} (film) 3340 (OH), 1630 (C=C), 1605, 1575, 1500 (aromatic C=C). δ ($CDCl_3$) 7.57 (1H, d, J8.5Hz, C5 ArH); 6.72 (2H, m, C6 and C8 ArH); 6.10 (1H, m, C4 vinyl proton); 4.55 (1H, m, exo CHOH at C12); 3.80 (3H, s, OMe); 3.08 (1H, s, OH exch.) 1.4-2.9 (11H, m, other protons).

Hydrobroation of endo-alcohol 112

A solution of borane (~14 mmole) in anhydrous tetrahydrofuran was prepared under nitrogen, by dropwise addition of boron trifluoride-etherate (2.3g, 16 mmole) to an ice-cold suspension of sodium borohydride (0.4g, 10.5 mmole) in tetrahydrofuran (20 ml). The endo-alcohol 112 (0.43g, 1.7 mmole) in tetrahydrofuran (10 ml) was added, the mixture allowed to warm to room temperature, and stirred, under nitrogen, at room temperature overnight. Water (10 ml) was added, followed by aqueous 10% sodium hydroxide (10 ml), and 30% hydrogen peroxide (10 ml). The aqueous mixture was extracted with ether (1 X 50 ml, 3 X 30 ml), and the combined extract was washed with water and saturated brine, dried (Na_2SO_4), and evaporated. A pale pink oil (0.46g) was obtained. TLC indicated the presence of two compounds in the crude product. They were separated by preparative TLC using ether-methylene chloride (2:3). These compounds were:

(a) Higher R_F - colourless crystals (90 mg, 20%) with mp 190-194° after recrystallization from acetone. This compound was the cis-fused diol 4β,12β-dihydroxy-7-methoxy-2,10aβ-ethano-1,2,3,4,4aβ,9,10,10a-octahydrophenanthrene 113. (Found : C, 74.4; H, 8.3. $C_{17}H_{22}O_3$ requires C, 74.4; H, 8.1%).

ν_{max} 3240 (OH), 1615, 1575, 1510 (aromatic C=C).

δ ($CDCl_3$) 7.20 (1H, d, J8Hz, C5 ArH); 6.78 (2H, m, C6 and C8 ArH); 4.72 (1H, m, $W_{\frac{1}{2}}$ 10 Hz, equatorial C<u>H</u>OH at C4); 4.40 (1H, m, $W_{\frac{1}{2}}$ 21 Hz, exo C<u>H</u>OH at C12); 3.80 (3H, s, OMe); 3.35 (2H, s, O<u>H</u>, exch.); 1.2-3.0 (12H, m, other protons).

(b) Lower R_F - colourless crystals (300 mg, 65%) with mp 140-141.5° after recrystallization from acetone-light petroleum. This compound was the trans-fused diol 4α,12β-dihydroxy-7-methoxy-2,10aβ-ethano-1,2,3,4,4aα,9,10,10a-octahydrophenanthrene 114. (Found : C, 74.5; H, 8.3. $C_{17}H_{22}O_3$ requires C, 74.4; H, 8.1%).

ν_{max} 3300 (OH), 1610, 1580, 1505 (aromatic C=C).

δ ($CDCl_3$) 8.12 (1H, d, J8.5 Hz, C5 ArH); 6.68 (2H, m, C6 and C8 ArH); 4.30 (2H, m, $W_{\frac{1}{2}}$ 26 Hz, C<u>H</u>OH at C4 and C12); 3.77 (3H, s, OMe); 1.97 (2H, s, OH, exch.); 1.2-2.9 (12H, m, other protons).

The structure of the latter diol 114 was corroborated by the indepent synthesis described below.

12,12-Ethylenedioxy-4α-hydroxy-7-methoxy-2,10aβ-ethano-1,2,3,4,4aα, 9,10,10a-octahydrophenanthrene **115**

Diborane (~14 mmole) generated in the usual way[217] in diglyme (20 ml) was carried by a slow stream of nitrogen into a chilled, stirred solution of acetal **109** (1.85g, 6.2 mmole) in dry tetrahydrofuran (40 ml). The solution was stirred under nitrogen at room temperature overnight. Water (20 ml) was added, followed by 10% sodium hydroxide (15 ml) and 30% hydrogen peroxide (10 ml). The aqueous mixture was extracted with ether (3 X 50 ml), and the extract was washed with water, dried, and evaporated, affording the *trans*-fused alcohol **115** (1.85g, 94%) as a colourless crystalline residue, mp 118-121°. Recrystallization from acetone-hexane gave white needles mp 122-123.5°. (Found : C, 72.3; H, 8.0. $C_{19}H_{24}O_4$ requires C, 72.1; H, 7.65%).

ν_{max} 3400 (OH), 1610, 1570, 1500 (aromatic C=C).

δ ($CDCl_3$) 8.12 (1H, d, J8.5 Hz, C5 ArH); 6.72 (2H, m, C6 and C8 ArH); 4.15 (1H, m, $W_{\frac{1}{2}}$ 16 Hz, axial CHOH at C4); 3.85 (4H, s, OCH_2CH_2O); 3.77 (3H, s, OMe); 1.83 (1H, s, OH, exch.); 1.2-2.9 (12H, m, other protons).

4α-Hydroxy-7-methoxy-2,10aβ-ethano-1,2,3,4,4aα,9,10,10a-octahydrophenanthren-12-one 116

The above hydroxy-acetal 115 (180mg, 0.56 mmole) in acetone (20 ml) was treated dropwise with 3N hydrochloric acid (4 ml) and the solution heated under reflux for 0.5 hr. The solution was diluted with water (40 ml) and extracted with ether (3 X 15 ml). The combined ethereal extract was washed with water and saturated brine, dried ($MgSO_4$), and evaporated yielding the ketol 116 (150mg, 97%) as colourless crystals, mp 133.5-136°. The analytical sample, recrystallized from acetone-hexane, formed almost transparent rectangular prisms, mp 135.5-137° (Found : C, 75.0; H, 7.7. $C_{17}H_{20}O_3$ requires C, 75.0; H, 7.4%). ν_{max} 3430 (OH), 1735 (C=O), 1610, 1575, 1510 (aromatic C=C).

Reduction of ketol 116

Lithium aluminium hydride (250 mg, 6.6 mmole) was added, in portions, to a stirred solution of ketol 116 (100 mg, 0.37 mmole) in ether (25 ml). The resulting suspension was stirred at room temperature for 1 hr, and heated under reflux for 1 hr. Water was added very carefully until a white granular precipitate had formed. The mixture was dried ($MgSO_4$), filtered, and evaporated. The crude crystalline product (70 mg, 70%) was recrystallized from acetone-light petroleum; colourless crystals, mp 139-140.5°, of the trans

-diol 114 were obtained. This product was identical (TLC, mixed mp, spectra) to the lower R_F component separated after hydroboration of *endo*-alcohol 112.

12,12-Ethylenedioxy-7-methoxy-2,10aβ-ethano-1,2,3,4,4aα,9,10,10a-octahydrophenanthren-4-one 120

(a) By Jones' oxidation of the alcohol 115

Alcohol 115 (1.0g, 3.2 mmole) in acetone (500 ml) was cooled to -12° (ice-salt bath) and treated with 8N chromic acid (2.0 ml, 8.0 mmole). The mixture was stirred and maintained at -12° for 10 min, when 2-propanol (0.5 ml) was added to destroy unused reagent. After dilution with benzene (150 ml), the mixture was washed with water (2X150 ml), 1% sodium hydroxide solution (40 ml), and water (150 ml). The organic layer was dried ($MgSO_4$), and evaporated leaving an orange oil (0.80g) which crystallised on trituration with ether. The crude product was recrystallised from ethanol, giving the ketone 120 (0.52g, 54%) as tiny white needles mp 159-161°. One more recrystallization from ethanol raised the melting point to 163-164.5°. (Found : C, 72.65; H, 7.1. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.05%).

ν_{max} 1705 (C=O), 1610, 1580, 1510 (aromatic C=C).

δ ($CDCl_3$) 7.42 (1H, d, J8Hz, C5 ArH); 6.68 (2H, m, C6 and C8 ArH); 3.85 (4H, s, OCH_2CH_2O); 3.78 (3H, s, OMe); 3.67 (1H, s, C4a proton);

1.7-3.0 (11H, m, other protons).

The basic washings from this experiment were acidified with 2N hydrochloric acid and extracted with benzene-methylene chloride (9:1, 100 ml); Work up in the usual way gave the ring C *seco*-diketo-acid 125 (0.15g, 16%) as colourless prisms, mp 165-168°, after two recrystallizations from acetone. (Found : C, 67.6; H 6.2. $C_{17}H_{18}O_5$ requires C, 67.5; H, 6.0%).

ν_{max} 3200-2400, 1705 (COOH), 1730 (cyclopentanone), 1655 (aryl C=O), 1600, 1500 (aromatic C=C).

δ ($CDCl_3$) 8.03 (1H, d, J8.5 Hz, C5 ArH); 6.79 (2H, m, C6 and C8 ArH); 4.85 (1H, br. s, COOH, exch.); 3.88 (3H, s, OMe); 1.9-3.2 (11H, m, other protons).

(b) By Pfitzner-Moffatt oxidation of alcohol 115

Pyridine (85 mg, 1.1 mmole) and dichloroacetic acid (85mg, 0.7 mmole) were introduced into a solution of the alcohol 115 (320 mg, 1.0 mmole) in dimethylsulphoxide (10 ml). Dicyclohexylcarbodiimide (640 mg, 6.0 mmole) was added, and the resultant solution was kept at room temperature overnight. Dilution with ethyl acetate (20 ml) was followed by addition of a solution of oxalic acid (380 mg) in methanol (10 ml). The precipitated dicyclohexylurea was removed by filtration. The filtrate was washed with 5% sodium bicarbonate solution, water, and saturated brine, dried (Na_2SO_4), and evaporated. Purification of the crude crystalline product was achieved by filtration, in methylene chloride, through a small column of Florisil (20 g) and recrystallization of the eluted material from ethanol. This gave the ketone 120 (0.26g, 82%), mp 159-162°, identical with the major product obtained from oxidation of 115 with Jones' reagent.

12,12-Ethylenedioxy-4β-hydroxy-7-methoxy-2,10aβ-ethano-1,2,3,4,4aα,9,10,10a-octahydrophenanthrene 121

Ketone 120 (0.75 g, 2.4 mmole) in tetrahydrofuran (50 ml) and ether (50 ml) was treated with lithium aluminium hydride (1.0g, 0.026 mole). The resulting suspension was stirred at room temperature for 2 hr, and heated under reflux for 0.5 hr. Work up in the usual manner afforded the 4β-alcohol 121 (0.71 g, 94%) as colourless crystals. A sample recrystallized from acetone melted at 170.5-172.5°. (Found : C, 72.0; H, 7.6. $C_{19}H_{24}O_4$ requires C 72.1; H, 7.65%).

ν_{max} 3400 (OH), 1610, 1570, 1505 (aromatic C=C).

δ ($CDCl_3$) 7.28 (1H, d, J8Hz, C5 ArH); 6.70 (2H, m, C6 and C8 ArH); 4.62 (1H, m, $W_{\frac{1}{2}}$ 9Hz, equatorial C<u>H</u>OH at C4); 3.92 (4H, s, OCH_2CH_2O); 3.77 (3H, s, OMe); 1.3-3.0 (13H, m, other protons inc. OH).

12,12-Ethylenedioxy-4β-hydroxy-2,10aβ-ethano-1,2,3,4,4aα,5,8,9,10,10a-decahydrophenanthrene 122

Lithium (280 mg, 40 g-atom) was added in small pieces to freshly distilled liquid ammonia (150 ml). The 4β-alcohol 121 (0.65g, 2.1 mmole) in tetrahydrofuran (40 ml) was added, under nitrogen, to the metal ammonia solution. After 15 min, ethanol (5 ml) was added very slowly over a period of 2 hr. When the blue colour of the reaction mixture had faded, ammonium chloride (10g) was added, and the excess of ammonia allowed to evaporate. The residue was partitioned between ether (50 ml) and water (50 ml). The ethereal layer was washed three times with water, dried, and concentrated. A crystalline residue of the enol ether 122 (0.61g, 90%) was obtained. This was used without further purification in the next reaction.

ν_{max} 3400 (OH), 1690, 1660 (enol ether).

Hydrolysis of enol ether 122

Crude enol ether 122 (0.57 g, 1.8 mmole) in acetone (25 ml) was cooled to 0^{o} and treated with a solution of oxalic acid (500 mg, 4 mmole) in water (10 ml). The reaction mixture was stirred at 0^{o} for 1.5 hr, and solid sodium bicarbonate (1 g) was added. The resulting mixture was taken up in water (50 ml) and ether (50 ml). The ethereal layer was washed with water and saturated brine, dried, and evaporated. The β,γ-unsaturated ketone 123 was obtained as an oil (0.55g, quant.) which was used immediately.

ν_{max} 3400 (OH), 1710 (C=O).

Attempted introduction of 4bβ-methyl group

Freshly prepared zinc-copper couple[246] (1.0 gm) was added to a solution of crude β,γ-unsaturated ketone 123 (0.55 g) in ether (10 ml). The mixture was heated under reflux and treated dropwise with methylene iodide (1.2 g) over a period of 1 hr. Reflux was continued for 4 hr. The excess of couple was removed by filtration, and the filtrate worked up in the usual way (washing, drying, etc) gave a gummy residue (0.52g) whose infrared spectrum was almost identical with that of the starting ketone 123. Work on this reaction was not pursued.

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