INTRAMOLECULAR CARBON ALKYLATION

A THESIS

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by

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CONTENTS

SUMMARY

This thesis is presented in three parts and describes the examination of several successful procedures for the introduction of angular substituents into fused polycyclic molecules.

Part I of this thesis describes the preparation of 7,8-dihydro-4a,7-ethanonaphthalene-2,6(4aH,5H)-dione by two similar procedures firstly from 7-[(1'-bromo-2'-tetrahydropyranyloxy)ethyl]-5,6,7,8-tetrahydronaphth-2-ol and secondly from 7-diazoacetyl-5,6,7,8-tetrahydronaphth-2-ol.

The key transformation in each instance involves the introduction of the angular substituent by an intramolecular carbon alkylation. In the latter procedure, the accompanying modification of the aromatic nucleus appears to be the first reported example of aryl participation in an acid-induced reaction of a diazoketone.

Part II of this thesis describes an investigation of the scope and limitation of this novel alkylation procedure. The reaction of a series of ω-(p-hydroxyphenyl)alkyl diazomethyl ketones has been studied in an examination of the scope and limitation of the reaction.

It has been shown that aryl participation (Ar_1-n) is significant only for n=4,5, and 6. This observation of Ar_1-4 participation is unprecedented; the significance of this result is discussed. The observations are compared

with Winstein's earlier results on Ar_1-n participation and the trends discussed in terms of factors affecting the ease of ring closure.

The spirodienediones formed initially in this reaction were observed to undergo a dienone-phenol rearrangement; this process has been examined.

A possible mechanism for the alkylation of phenolic diazoketones is discussed.

Part III of this thesis describes the extension of this reaction to the intramolecular carbon alkylation of suitably placed olefinic bonds.

The preparation of 2-methoxygibb-1,3,4a,4b-tetraene-8-one by the trifluoroacetic acid-induced cyclisation of 2-diazoacetyl-1,2,3,4-tetrahydro-7-methoxyfluorene is described.

The formation of 1,2,3,9,10,10a-hexahydro-7-methoxy-1β,10aβ-ethanophenanthrene-12-one from 1-diazoacetyl-1,2,3,-4,9,10-hexahydro-7-methoxyphenanthrene occurs under similar conditions in quantitative yield.

This latter transformation constitutes the second reported example of participation by an olefinic bond three carbons removed from the reaction centre.

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.

David J. Beames.

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Dr. L. N. Mander for his advice, encouragement and enthusiasm during his supervision of this work.

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I am indebted to my wife for her assistance and understanding during the composition of this thesis, and also to my parents for their sacrifices and encouragement during the course of my studies.

To Maedi

PART I

INTRODUCTION

Probably the most difficult feature of the synthesis of polycyclic compounds such as steroids, diterpenes and triterpenes has been the problem of angular alkylation in terms of both stereoselectivity[1-3,4] and regio specifity.[1,5]

The intention of the present investigation has been the development of more versatile methods[6-28] for the stereospecific angular alkylation of preformed polycyclic substrates, in readiness for the projected synthesis of complex diterpenoid compounds e.g., the gibberellins[29] and the hetisine alkaloids.[30]

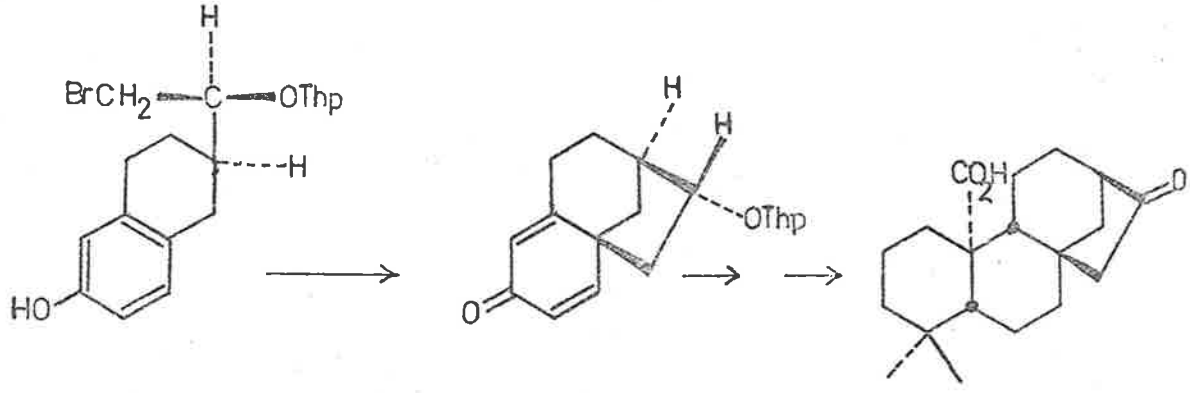
Corey[6,31] has stressed the important role of the benzenoid ring or "synthon" as a complex functional group, particularly in its application to the construction of complex molecules such as steroids,[32] alkaloids,[33] and terpenes.[34]

The conversion of the benzenoid synthon to a cyclic polyfunctional non-benzenoid system has been of immense value to synthetic chemistry, but there are a number of limitations involved with this conversion.[6,31] The conditions commonly employed[6] for the development of the latent functional groups in the synthon frequently preclude their use where reducible or base-sensitive groups are present in the molecule.

It should be immediately obvious that the synthetic potentiality of the benzenoid system is considerably augmented by the presence of an oxygen substituent, e.g. as in

anisole.[6] This utility can be severely restricted when it is desired that the synthon be transformed into a fused alicyclic ring bearing an angular substituent. This problem is particularly acute when the angular substituent, and the carbon atom carrying the oxygen function derived from the original methoxyl group bear a 1,4 relationship to one another. The transformation of oestrone into testosterone[28] succintly illustrates this problem. The relatively few solutions to this problem have been notable for their ingenuity rather than for their utility.[7,16,20,28,35]

One of the few exceptions to this generalisation is the intramolecular carbon alkylation employed by Masamune[36,37] in the preparation of the tetracyclic intermediate (3) (Scheme 1).

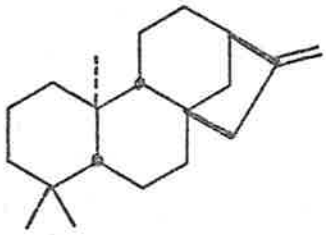


(1) (2) (3)

Scheme 1

The key intermediate (3) was the starting point for the total synthesis of a number of diterpenes and diterpene

alkaloids,[37] notably kaurene[34](4), garryine[30](5) and atisine[30](6).



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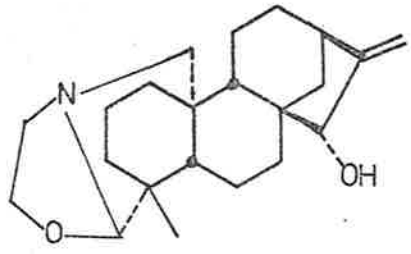

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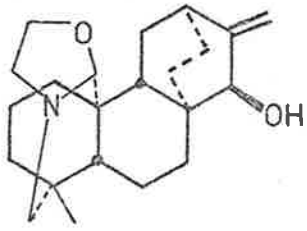

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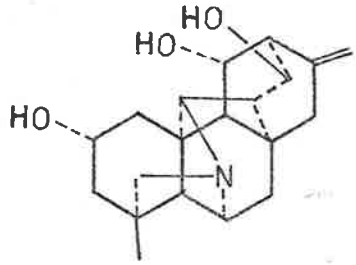


(7)

A synthesis based on this principle had appeal for a number of reasons;

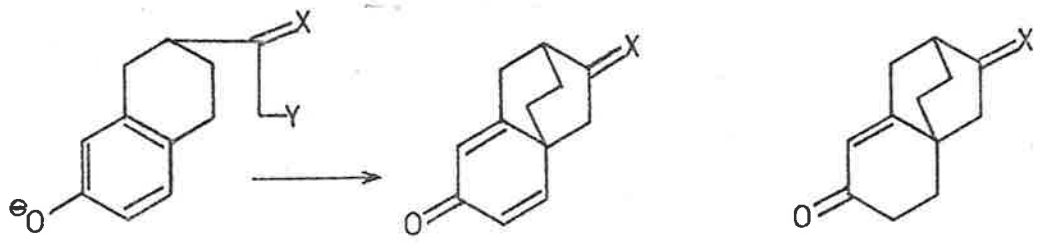
(a) it allowed the use of an aromatic synthon to conceal several functional groups[6] until required.

(b) it provided a solution to the problem of angular alkylation, which simultaneously accomplished the modification of the anisole synthon under essentially mild, non-reductive conditions.

(c) finally the bicyclo[3,2,1]octane moiety,[38] found in kaurene[34](4) and garryine[30](5), was formed in one

simple, elegant step.

In the synthesis of such complex alkaloids as those of the hetisine group (c.f. hetisine (7)) it was considered necessary that more direct methods be developed for the construction of the bicyclo [2,2,2] octane system.[39] Masamune's synthesis of atisine[37] (6) involved the conversion of a preformed bicyclo [3,2,1] octane moiety to a bicyclo [2,2,2] octane moiety. The synthesis of the tricyclic ketone (9),* based on a scheme which incorporates the concepts developed above, was therefore initiated (Scheme 2).



(8) (9) (10)

Scheme 2

Part I of this thesis will describe the synthesis of the tricyclic ketones (11), (12) and (13) via two different synthetic pathways; the key step in each synthesis involves the carbon alkylation of a fused phenolic substrate.

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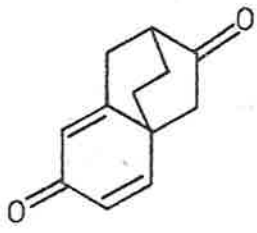
* In related work[40] the dihydro derivative 10 (X=O) has been prepared, but this required prior reduction of the aromatic ring.



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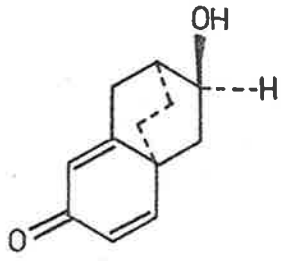

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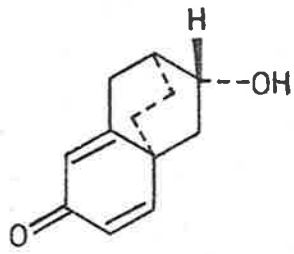

(13)

The tricyclic intermediates (11), (12) and (13), all appear suitable for a proposed synthesis of hetisine (7).

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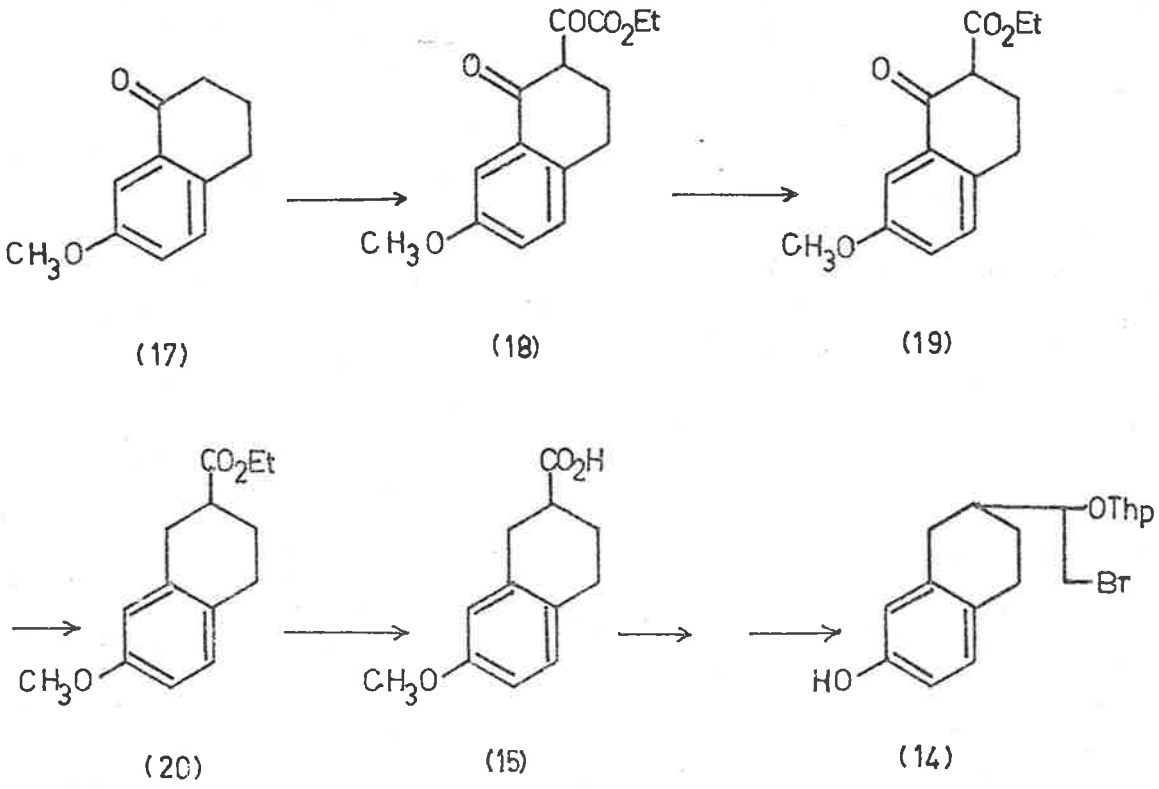
PART I

DISCUSSION

In order to test the feasibility of the intramolecular carbon alkylation previously outlined (Scheme 2) for the preparation of the tricyclic ketone (9), the synthesis of the phenolic bromide (14) was initiated. By analogy with previous work,[37] the methoxy acid (15) appeared to be a logical precursor; but although a method was available for the preparation of a dehydro derivative[41] of acid (15), it was found preferable to prepare the acid (15) by an alternative route.

The required acid (15) was originally synthesised by a modification of the procedure used by Jacques and Horeau[42] in a synthesis of an isomeric acid (Scheme 3).

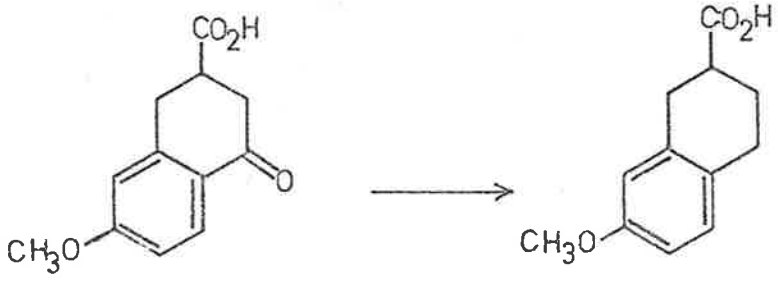


(17) (18) (19) (20) (15) (14)

Scheme 3

7-Methoxytetral-1-one (17) was prepared by a standard literature procedure[43] and subsequently converted to the glyoxylic ester (18) (ν_{max} 1720, 1620-1600cm^{-1}) by the method of Hunter and Korman.[44] Decarbonylation to the keto-ester (19) (ν_{max} 1730, 1680, 1640cm^{-1}) was accomplished by briefly heating the ester (18) in the presence of powdered glass.[44,45] Hydrogenolysis[46] of the benzylic carbonyl function in the presence of a palladium-charcoal catalyst afforded the ester (20) as a light pink liquid (ν_{max} 1720cm^{-1}), which on saponification yielded the desired methoxy-acid (15).

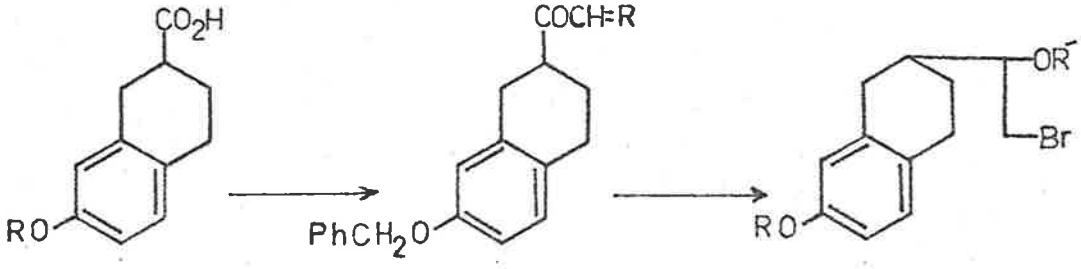
As a result of later related studies,[47] the keto-acid (21) became readily available. Clemmensen reduction of this keto-acid (21) by the Martin modification[48] afforded the methoxy-acid (15) in quantitative yield (Scheme 4). This acid was identical in all respects with that obtained from the first synthetic procedure.



(21) (15)

Scheme 4

The method used for elaboration of the phenolic bromide (14) is depicted in Scheme 5, and parallels that employed by Masamune[37] in the synthesis of the isomeric bromide (1).



R=CH_3 (15)	R= N_2 (24)	R'= H, R=CH_2Ph. (26)
R= H (22)	R=HBr.(25)	R'=Thp, R=CH_2Ph. (27)
R=CH_2Ph (23)	R= H_2 (25a)	R'=Thp, R= H. (14)

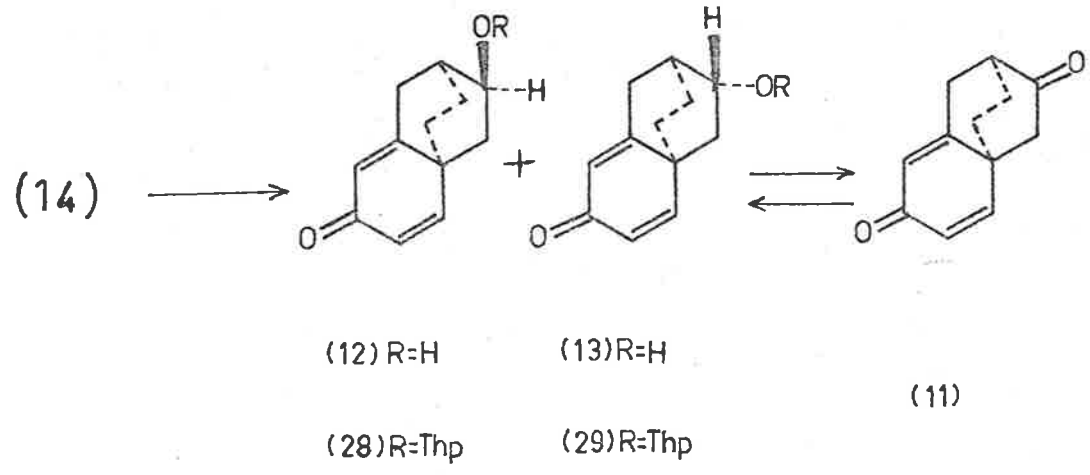
Scheme 5

Attempted demethylation of the methoxy-acid (15) by several standard procedures[49,52] gave either a poor yield or an impure product, but treatment with pyridine hydrochloride[50] afforded the phenolic acid (22) (ν_{max} 3300, 3150, 2700cm^{-1}) in 95% yield. Introduction of the benzyl residue was accomplished by treating a solution of the phenolic acid (22) in aqueous dioxan with excess potassium hydroxide and benzyl bromide. Sequential treatment[51] of the benzyloxy-acid (23) (ν_{max} 760, 740cm^{-1}) with oxalyl chloride and excess ethereal diazomethane produced a light yellow oil which was purified by alumina chromatography to give the crystalline diazomethyl-ketone (24)[ν_{max} 2140, 1620cm^{-1},

δ_{max} 5.25 (s, 1H, COCHN$_2$)] in 71% yield. When a cold ethereal solution of the diazoketone (24) was shaken briefly with concentrated hydrobromic acid,[53] the bromo-ketone (25)[ν_{max} 1710cm^{-1}, δ_{max} 3.95 (s, 2H, COCH$_2$Br)] was obtained in quantitative yield. The oily bromo-ketone, although homogeneous by thin layer chromatography (t.l.c.), could not be induced to crystallise, but treatment with zinc dust in acetic acid[54] afforded the corresponding methyl ketone (25a) which was characterized as its semicarbazone derivative. The oily bromo-ketone (25) was reduced by treatment with sodium borohydride while maintaining the pH of the solution in the range 7-9 by the addition of acetic acid; the resultant crystalline mixture of diastereoisomeric bromhydrins (26) (ν_{max} 3300cm^{-1}, no carbonyl absorption), when allowed to react with purified dihydropyran[55] in the presence of p-toluene sulphonic acid afforded the desired tetrahydro-pyranyl ether (27) (ν_{max} 1610, 1585cm^{-1}) in 90% yield. The non-crystallinity (homogeneous by t.l.c.) of this compound was ascribed to the presence of the tetrahydropyranyl moiety. Liberation of the masked phenolic hydroxyl was achieved by hydrogenolysis of the benzyl residue[56] in the presence of a palladium-charcoal catalyst, and afforded the phenolic bromide (14) in 90% yield as a clear glass (ν_{max} 3300, 1610, 1590cm^{-1}, no absorptions present in the 700-800cm^{-1} region ascribable to the mono-substituted aromatic ring).

A dilute solution of the diastereoisomeric phenols

(14) was treated with potassium t-butoxide[36,37] and heated under reflux for five hours. Purification of the crude product afforded a 3:1 epimeric mixture of the dienone ethers (28) and (29)[ν_{max} 1655, 1625, 1600cm^{-1} (dienone)] in 50% yield. (Scheme 6). Brief treatment of this mixture with dilute mineral acid afforded the epimeric mixture of alcohols (12) and (13)[ν_{max} 3320, 1650, 1615, 1580cm^{-1} (dienone)]. Recrystallisation of the crude mixture did not alter the

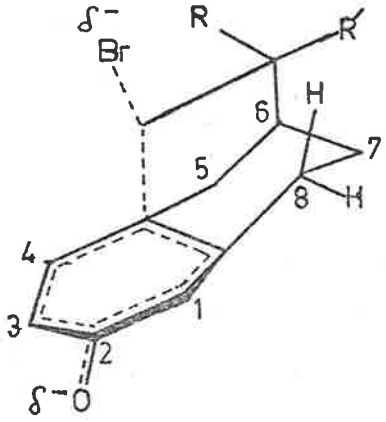


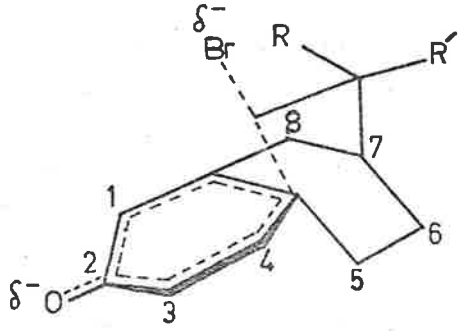
Scheme 6

composition of the epimeric mixture, however oxidation with the Jones[57] reagent at -15°C yielded only the homogeneous diketone (11) as a white crystalline solid[ν_{max} 1720 (saturated C=O), 1660, 1630, 1600cm^{-1} (dienone) λ_{max} 243nm. (ε 14,800)].

In contrast to the Ar_1-5 alkylation of the phenolic

bromide (1), the transition state for Ar_1-6 cyclisation* of the bromide mixture (14) requires that both diastereoisomers (Figure 1) have the side chain ether substituent eclipsed with a ring methylene group (C6-H and C8-H).





	R	R'	
(1)	OThp	H	⟶ (2)
(1')	H	OThp	⫽⟶ (2')

	R	R'	
(14)	OThp	H	⟶ (28)
	H	OThp	⟶ (29)

Ar_1-5 Figure 1 Ar_1-6

From an examination of Dreiding molecular models, this interaction would appear to be intermediate in severity between that for the bromide (1') (ether oxygen and C8-H) and

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* For use of the Ar_1-n convention, see ref. 58. The convention $Ar_1^{\ominus}$-n has been used for situations which involve participation by phenolic groups under basic conditions. As this latter $Ar_1^{\ominus}$-n convention has been employed only by Winstein, the more general Ar_1-n convention will be employed in this thesis.

its diastereoisomer (1) (hydrogen atom and C8-H). Moreover Masamune[37] has attributed the formation of a single stereoisomer (assigned structure (2)) as due to the failure of one of the diastereoisomers (1'?) to undergo cyclisation because of this severe interaction in the expected cyclic transition state.

Assuming the validity of this argument, the smaller yield of epimer (29) in the Ar_1-6 alkylation is probably due to the existence of the less important but extra 1,4 non-bonded interaction between the ether function and the syn* C5 hydrogen atom in the transition state leading to this product. The ratio of epimers (28) and (29) could conceivably be due to a biased diastereoisomeric mixture of the bromohydrins (26), but the immediate environment of the carbonyl group in the bromo-ketone (25) appears essentially symmetrical, and consequently reduction with sodium borohydride would be expected to yield approximately equal amounts of the bromohydrin diastereoisomers[59,60](26). The ratio of products (12) and (13) obtained from the reduction of the diketone (11) with sodium borohydride lends further weight to these conclusions. On selective reduction of the saturated carbonyl group a 2:3 mixture of the alcohols (12) and (13) was obtained. Hence the predominant product (13) from the reduction is that with the hydroxyl group in the

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* Naphthalene numbering system.

more crowded environment, corresponding to hydride delivery by the bulky borohydride reagent to the less hindered face of the carbonyl group.[61] This mixture of alcohols, as with that obtained directly from the mixture of (28) and (29), on oxidation afforded only the homogeneous diketone (11).

The structures of the various dienones (11)-(13), (28) and (29) follow from their modes of preparation and their various spectral characteristics.[62] The epimeric mixtures (12) and (13), and (28) and (29), could not be separated by fractional crystallization or chromatographic techniques, but in nuclear magnetic resonance (n.m.r.) spectra, the C4 olefinic proton[63] of the epimers (12) and (28) affords a doublet resonance (J10Hz) at slightly higher chemical shift (c.4Hz) than in epimers (13) and (29). Integration of these signals provides a simple method for the estimation of the epimer ratio.

It seems apparent that the presence of the ether function on the sp^3 hybridized carbon atom in the side chain results in appreciable non-bonding interaction in any transition state leading to the cyclic products. Ar_1-5 and Ar_1-6 alkylations, although employed occasionally[23,64-74] in the construction of bicyclic systems, have not been successfully employed as a method of angular alkylation in a preformed polycyclic molecule bearing an oxygenated bridging chain.*

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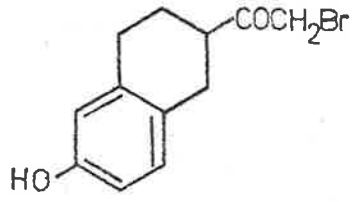
* For an exception, see ref. 37.

In more complex substrates the extra activation energy required for cyclisation (by virtue of a greater number of non-bonding interactions) could be expected to preclude cyclisation completely in the presence of more favourable alternatives, e.g. elimination, and intermolecular alkylation.

Clearly the replacement of the offending ether function with the sterically less demanding carbonyl group should overcome the problem of steric congestion in the transition state for cyclisation, while at the same time retain the oxygenated bridge, but Masamune[75] has reported that the bromoketone (30) corresponding to the bromide (1) failed to yield cyclic products.

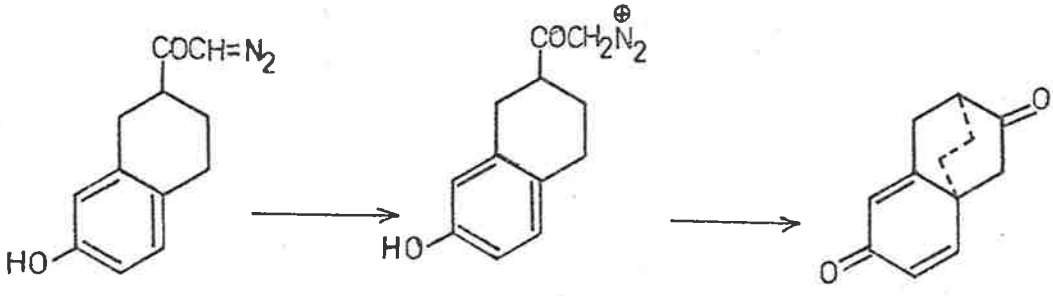


(30)

Accordingly it was decided to examine the feasibility of effecting cyclisation through the agency of the more reactive diazonium species (32) (Scheme 8).

Information available on the mechanism[77-85] (i.e. the A-2 mechanism[76]) of the reaction of aliphatic diazoketones with nucleophiles in the presence of Bronsted acids provided ample justification for the suitability of the diazomethyl ketone (31) as a precursor for the diazonium

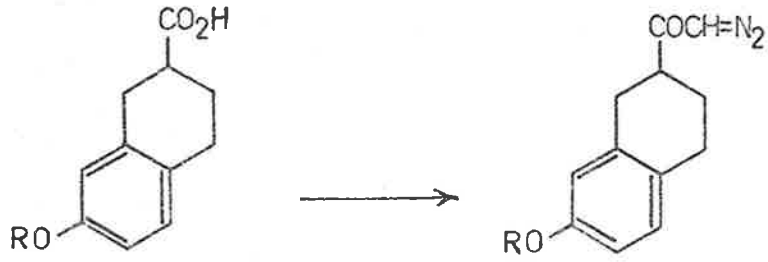
species (32).



(31) (32) (11)

Scheme 8

The synthesis of the phenolic diazomethyl ketone (31) from the readily available phenolic acid (22) is outlined in Scheme 9.



(22) R= H

(33) R= CH_3CO

(34) R= CH_3CO

(31) R= H

Scheme 9

The phenolic acid (22), upon treatment with sodium acetate and acetic anhydride afforded the acetoxy-acid (33)[ν_{max} 1750 ($ArOCOCH_3$), 1700cm^{-1} (CO_2H)] in quantitative yield. The acid (33), upon successive treatment[51] with oxalyl chloride and excess ethereal diazomethane, (by the general method described for diazoketone (24)) gave the diazoketone (34). Subsequent cleavage of the acetyl function was accomplished by brief treatment of the diazoketone (34) with sodium carbonate in aqueous methanol and afforded the phenolic diazoketone (31)[ν_{max} 3200 (OH), 2140 ($C\overset{+}{=}N\overset{-}{=}N$), 1620$cm^{-1}$ (C=O of $COCHN_2$)] in 83% overall yield from the phenolic acid (22).

When a dilute solution of the diazoketone (31) in anhydrous nitromethane was treated with boron trifluoride etherate, a single neutral product was obtained in c. 32% yield. This product was identical in all respects with the diketone (11) obtained via the base-induced Ar_1-6 alkylation.

Whilst acid-induced reactions of diazoketones involving alkyl* group participation (and/or migration) have been noted, particularly in strained bicyclic systems,[86] this appears to be the first example of aryl participation (excluding reactions proceeding via carbenoid intermediates[87]).

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* Both modes of participation have been observed with diazoalkanes,[88] however the mechanism operating here is probably $A\text{-}S_E2$.[89]

A variety of acids whose conjugate bases were expected to function poorly as nucleophiles, e.g. fluoroboric and perchloric acids, and 2-bromopyridinium perchlorate, were examined, but although useful results were obtained with most reagents, boron trifluoride was the superior reagent. A range of solvents was also examined, although most were either too nucleophilic or too poorly solvating, and the yield obtained with nitromethane could not be exceeded.

Despite the moderate yield obtained in the cyclisation of the phenolic diazomethyl ketone (31), due to the brevity and efficiency of the preceeding steps in the synthesis, this is quite obviously the preferred method for the preparation of (11).

The carbon alkylation of phenolic diazoketones appears to have excellent synthetic potential, not only in the context of angular alkylation of preformed polycyclics but also for the simultaneous modification of the anisole synthon. The scope and limitation of this method of alkylation will be discussed in Parts II and III.

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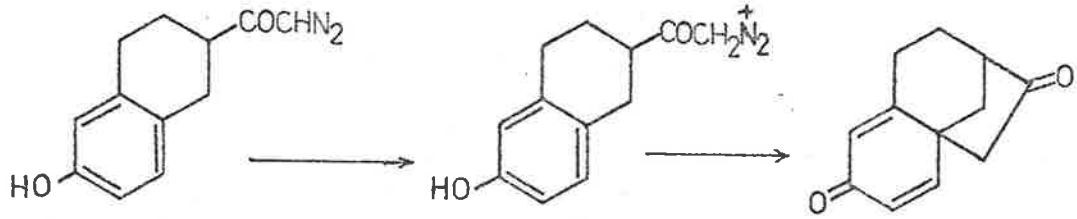
PART II

INTRODUCTION

While the work described in Part I of this thesis was in progress, closely related studies in these laboratories[90] showed that the phenolic diazomethyl ketone (35), on treatment with boron trifluoride etherate in nitromethane, produced the tricyclic diketone (37) in c. 70% yield (Scheme 10).



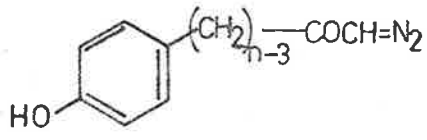
(35) (36) (37)

Scheme 10

This alkylation affords rapid and efficient access to the tricyclic system already prepared by Masamune,[37] and is significantly more efficient than the corresponding Ar_1-6 alkylation described in Part I. A comparison of Dreiding molecular models of the respective transition states for Ar_1-5 and Ar_1-6 alkylation revealed little difference in terms of non-bonding interactions.

It is apparent from the work of Winstein[71-74,91,92] and others[69,93] that the size of the ring being formed in reactions of this type could markedly affect the utility of

the alkylation. The ease of ring formation bears little relation to ring stability,[93,94] and for irreversible alkylations the products are those of kinetic control. If it is assumed that this reaction not only occurs by formal aryl participation[93] (i.e., A-2 mechanism[76]), but also that as in Ar_1-3 (ref. 94-100) and Ar_1-5 (ref. 91,101-103) solvolytic processes, the aryl assisted pathways are discrete, competitive processes, then the extent of cyclisation in a series of phenolic diazoketones (Fig. la), should be expected to exhibit a trend similar to that observed by Winstein.[72]



(38) n = 3
(39) n = 4
(40) n = 5
(41) n = 6
(42) n = 7

Figure la

Since this aspect of the alkylation warranted attention, a program directed towards the synthesis of the phenolic diazoketones (38)-(42) and a study of their reactions was initiated.

Part II of this thesis will describe the synthesis and intramolecular alkylation of these five diazoketones, compare the results with those of Winstein, and discuss the

trends observed in terms of factcrs affecting the ease of ring formation.

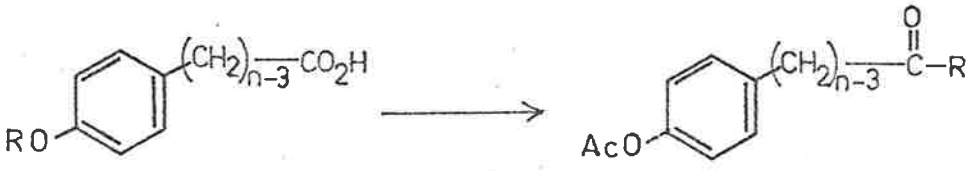
---oOo---

PART II

DISCUSSION

(a) Synthesis of the phenolic diazomethylketones (38)-(42).

A general synthetic plan for the preparation of diazoketones (38)-(42) is outlined in Scheme 11. This route was influenced by the successful synthesis of the bicyclic diazoketones (31) (Part I) and (35) (ref. 90).

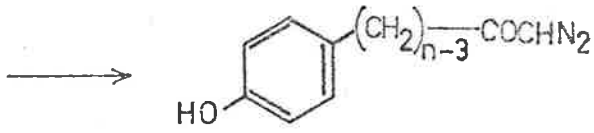


(43) R = CH_3

(44) R = H

(45) R = OH

(46) R = $CH{=}N_2$



(38) n = 3

(39) n = 4

(40) n = 5

(41) n = 6

(42) n = 7

Scheme 11

The methoxy-acids (43), n=3-7 were either commercially available, or prepared by standard literature procedures described in the experimental section. Except for the commercially available acid (44) n=3, the known phenolic acids (44) n=4-7 were best prepared by demethylation of the corresponding methoxy-acids (43) by the pyridine hydrochloride

method.[50] The use of other common reagents, e.g. hydrobromic-acetic acids,[52] or aluminum chloride,[49] resulted in inferior products, but the yields from the pyridine hydrochloride method were usually quantitative. The phenolic acids (44) were acetylated by treatment with acetic anhydride-sodium acetate; hydrolysis of the intermediate mixed anhydrides afforded the acetoxy-acids (45) (ν_{max} 1750, 1700cm^{-1}) normally in quantitative yield. The acetoxy-acid (45) (n=5) was also prepared by acetylation and then hydrogenation of p-coumaric acid. The acetoxy-acids (45), on sequential treatment[51] with oxalyl chloride and ethereal diazomethane afforded the corresponding acetoxy-diazoketones (46)[ν_{max} 2130, 1750, 1640cm^{-1}, δ_{max} 5.2 (s, 1H, COCHN$_2$)] in high yield. Hydrolysis of the acetyl function was achieved by brief treatment of the diazoketones (46) with sodium carbonate in aqueous methanol, this afforded the phenolic diazoketones (38)-(42) [ν_{max} 3300, 2130, 1620cm^{-1}, δ_{max} 5.2 (s, 1H, COCHN$_2$)] in excellent yield.

(b) Reaction of the phenolic diazomethylketones (38)-(42).

It is pertinent at this time to consider the nature and mode of formation of products expected from the intramolecular alkylation of the diazoketones (38)-(42) (Scheme 12). By analogy with the formation of the tricyclic diketones (11) (Part I) and (37) (Part II, Introduction), the dienedione (47) is the product expected from aryl participation. However,

this compound could undergo a dienone-phenol rearrangement[104,105] and form the benzocyclanones (48) and/or (49).* Products (50a) arising by the intervention of a nucleophilic solvent may also occur[53,80] if the diazonium ion (50) is the species undergoing reaction.

The reaction of aliphatic diazoketones (51) with nucleophiles in the presence of acid has been shown to occur via an A-2 mechanism[76-85] (Figure 2).

Therefore the use of nucleophilic protic and dipolar aprotic solvents was obviously not advisable, but the phenolic diazoketones were only sparingly soluble in non-polar solvents so that a compromise was necessary. No mention of nucleophilic reactions** involving nitro-alkanes could be found, in fact nitromethane is commonly employed as a solvent with reactive acylating agents.[107] Aromatic nitro groups behave as nucleophiles in some circumstances, but this normally occurs only when the nitro group is situated ortho to a reaction centre.[108,126] Nitromethane was therefore chosen as a dipolar aprotic solvent[109] with minimal nucleophilicity.

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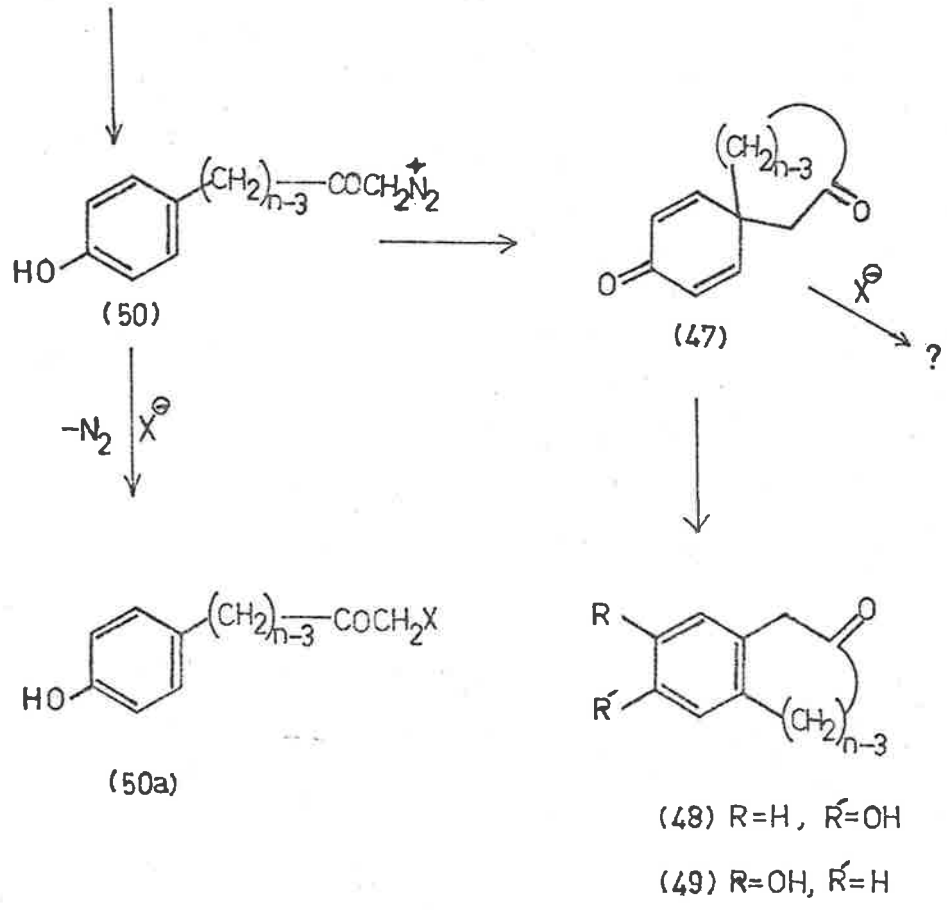
* This question will be considered later in this section.

** Attack by the oxygen atom only of the nitro group is considered here. The nucleophilic reactions of nitro alkanes under basic conditions normally procede via carbanion mechanisms.[106,110]

(38)-(42)



(48) R=H, R'=OH

(49) R=OH, R'=H

Scheme 12

$$RCOCHN_2 \underset{}{\overset{H^+ \text{ fast}}{\rightleftharpoons}} RCOCH_2\overset{+}{N}_2 \xrightarrow[\text{r.d.s.}]{X^-} RCOCH_2X$$

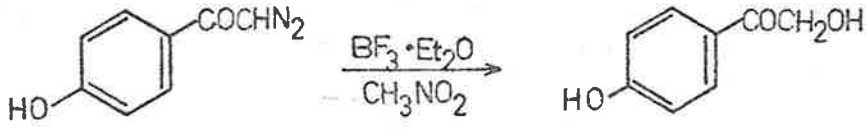
(51) (52) (53)

A-2 Mechanism X = H_2O, ROH, RNH_2, Cl, Br, I, etc.

Figure 2

(i) Reaction of the diazoketone (38) n=3.

When a dilute* solution of the phenolic diazomethyl ketone (38) n=3 in anhydrous nitro-methane was treated with boron trifluoride etherate, a vigorous evolution of nitrogen occurred, and on work-up a single product was obtained. This was identified as p-hydroxy phenacyl alcohol (54) from examination of its infra-red (ν_{max} 3430, 3250, 1670cm^{-1}) and n.m.r. [δ_{max} 4.75 (s, 2H, -COC$\underline{H}_2$OH)] spectra and comparison with previously reported data.[111]



(38) (54)

It was considered possible that the hydroxymethyl ketone (54) had arisen by reaction of an intermediate diazonium ion with traces of water in the "anhydrous" nitromethane. On examination, the nitromethane was shown to contain ⩽0.3% of water (c.f. experimental section) which was sufficient to account for the formation of the hydroxy-

---

* Approximately 0.05 molar solutions were employed to minimise intermolecular alkylation, as phenols will undergo oxygen alkylation with diazoketones in the presence of Lewis acids.[53]

methyl ketone (54). This possibility was discounted by the use of "ultra-dry" nitromethane (⩽0.01% water), hydroxymethyl ketone (54) was still the sole product. Since nitrogen was evolved before water was added (during the work-up procedure), it appeared that the weakly nucleophilic nitromethane had probably reacted with the intermediate diazonium ion (52) and that the product (56) had arisen by hydrolysis (during work-up) of an intermediate nitro-complex (55) (Figure 3).

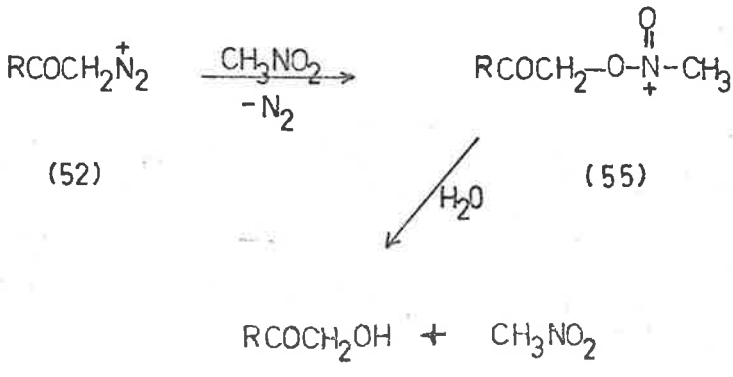
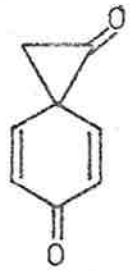


Figure 3

The reaction of a nitro group with a diazoketone moiety in an intra-molecular sense is not without precedent,[108,112] while the recent spectroscopic detection of α-keto-diazonium ions[113] and the fact that their reactions with various nucleophiles[53,80] are well documented, supports the postulation of (55) as a likely intermediate. Furthermore, when the reaction of diazoketone (38) with boron trifluoride etherate in nitromethane-d_3 was monitored by ob-

serving the n.m.r. spectrum, a singlet resonance was observed at δ 5.05 ($-CO-\underline{CH}_2-O-\overset{O}{\overset{\|}{\overset{+}{N}}}-CH_3$). On addition of D_2C this resonance disappeared, and another singlet resonance (δ 4.75) was observed. An n.m.r. spectrum of the alcohol (54) displays a singlet resonance at δ 4.75 ascribed to the $-CO-\underline{CH}_2-OH$ (ref. 116) grouping.*

In light of the current activity in the field of β-aryl (Ar_1-3) participation,[95-100,117-119] it is tempting to speculate on the possible intermediacy of the spirocyclopropanone (57) in the formation of the alcohol (54), particularly in view of the probable intermediacy of cyclopropanones during some Favorskii rearrangements.[120]



(57)

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* The diazoproton ($-COC\underline{H}N_2$) of ketone (38) was observed as a singlet resonance at δ 5.8 (ref. 115) before the addition of Lewis acid. Resonances at δ 4.1 and δ 4.25, ascribed to HOD and CHD_2NO_2 (ref. 114) respectively, were also observed. Aliphatic diazonium ions $R-COC\underline{H}RN_2$ display a one proton resonance at δ 9.3 (below $-50^{\circ}C$) (ref. 113).

Four pathways for the formation of stable products from the cyclopropanone (57) can readily be envisaged, (Figure 4) all are precedented, either in the chemistry of cyclopropanones[121] or strained spiro-cyclohexadienones.[74]

The infra-red spectrum of the crude product displayed no absorption in the region 1680-1800cm^{-1}, indicating the absence of the ketone (58) [or (59)]. As no trace of the acid (62) could be detected, pathways 1 and 2 both appear unimportant. It can be seen that pathways 3 and 4 both afford the alcohol (54), thus a product analysis cannot be used to infer the formation of cyclopropanone (57). When the reaction of the diazoketone (38) was monitored by observation of the n.m.r. spectrum in nitromethane-d_3 at room temperature, no resonance ascribable to the cyclopropanone (57) could be detected. In the absence of evidence to the contrary,* it would appear that alcohol (54) arises via direct attack of nitromethane on the intermediate diazonium ion.

(ii) Reaction of the diazoketone (39) n=4.

The diazoketone (39) n=4, on treatment with boron trifluoride etherate afforded a crude product containing

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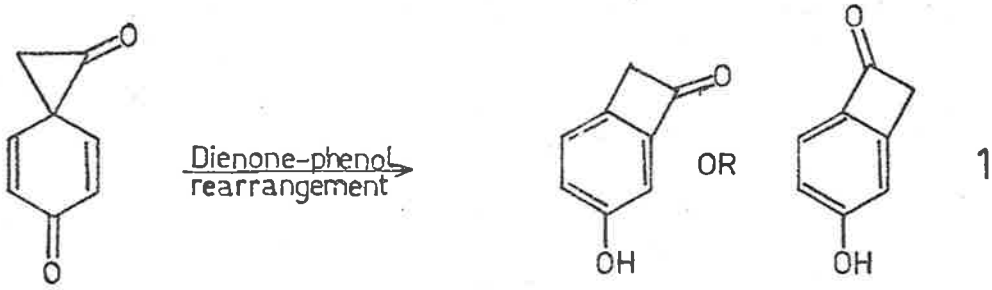
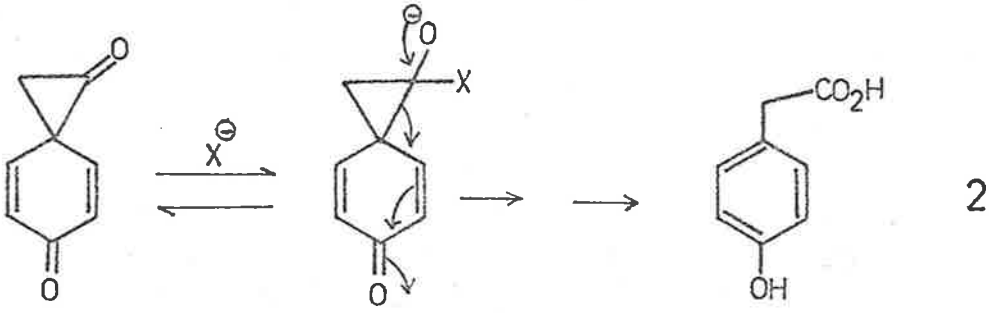
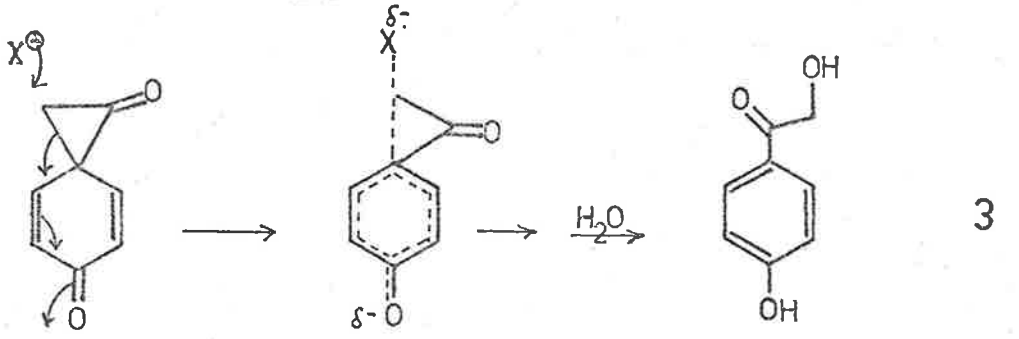
* If the cyclopropanone (57) were formed in the rate determining step, then a carbon isotope effect[122,224] might be observable; this appears to warrant investigation.



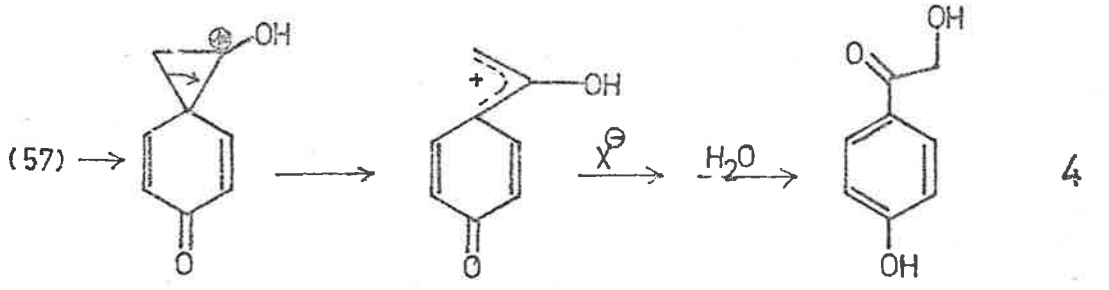
(57) (58) (59) 1



(57) (60) (62) 2



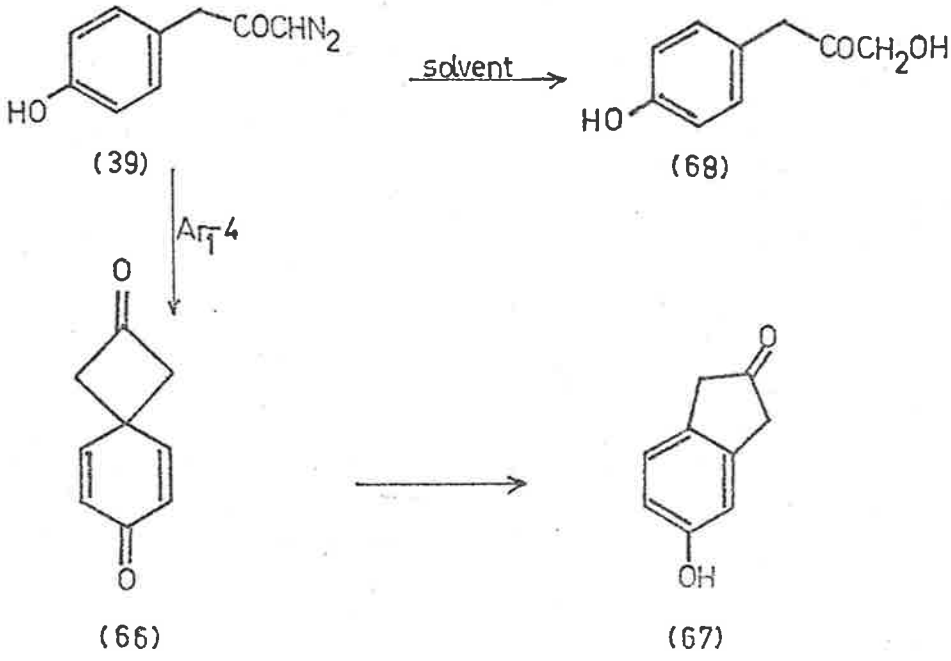
(57) (61) (54) 3



(63) (65) (54) 4

$X^{\ominus} = CH_3NO_2$

three compounds (t.l.c.). Column chromatography afforded the phenolic indanone (67)[ν_{max} 3300, 1735cm^{-1}, δ_{max} 6.7-7.3 (m, 3H, Ar-H)] and the hydroxymethyl ketone (68)[ν_{max} 33-3400, 1710cm^{-1}, δ_{max} 6.8 (q, J9Hz, 4H, Ar-H)].



On examination of the infra-red spectrum of the crude reaction mixture, absorptions were observed at 1785 and 1665cm^{-1}. This indicated that the dienedione (66), the expected product from Ar_1-4 participation, was probably present, but underwent decomposition or rearrangement during chromatography.

Under mildly acidic conditions, strained spiro-dienones undergo a rapid dienone-phenol rearrangement,[104] * thus

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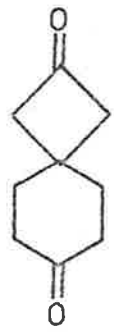
* For extremely strained systems, alternative modes of reaction are possible (c.f. Winstein[74]).

dienedione (66) would be expected to rearrange rapidly to the indanone (67). This was indeed the case, the proportion of dienedione (66) in the crude mixture (as judged by infra-red spectroscopy) was extremely sensitive to acid, but by careful selection of reaction conditions a mixture containing considerable quantities of dienedione (66) was obtained. Rapid preparative t.l.c. afforded the labile spiro-dienedione* (66) as an almost colourless liquid. The dienedione could not be characterised because of its lability, but this property, coupled with its mode of formation and characteristic spectral data,[62] (ν_{max} 1785, 1660, 1620cm^{-1}) appear firmly to establish its structure as (66). Hydrogenation of a crude reaction mixture, and subsequent purification afforded the corresponding tetra-hydro derivative (69) (ν_{max} 1770, 1700cm^{-1}) which further substantiated the structural assignment.



(69)

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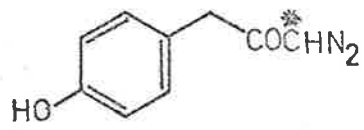
* The is the first reported example of Ar_1-4 participation. The significance of this result will be discussed later.

When the pure dienedione (66) was resubjected to the standard reaction conditions it underwent rapid and quantitative conversion to the indanone (67). Therefore the solvent-assisted and aryl-assisted pathways appear separate and competitive. The possibility that portion of the indanone (67) arises via a direct Ar_2-5 process[73] has been considered but not discounted. Winstein has shown that Ar_2-n modes of cyclisation are seldom significant unless n=6, and it also appears that Ar_2-5 and Ar_1-4 processes would have comparable rates only for equivalent degrees of activation,[123] i.e. when both modes lead to attack at a portion ortho or para to an electron donating substituent. A study of the isotopic distribution in the indanone (67) derived from the carbon labelled diazoketone (39a) should reveal the presence of any direct Ar_2-5 process.



(39a)

In view of the high proportion of dienedione (66) (relative to indanone (67)) present when the reaction is interrupted at approximately one half-life, it would appear that the rates of formation of (66) from (39), and (67) from

(66) are comparable, and the hitherto unprecedented Ar_1-4 process accounts for the formation of the indanone (67).

(iii) Reaction of the diazoketone (40) n=5.

When diazoketone (40) n=5 was allowed to react under the standard conditions two compounds were isolated, one of which was readily identified from its melting point and spectral characteristics[62] as the previously reported[69] dienedione (70), the product expected from the aryl-assisted pathway (Ar_1-5). The second product proved to be that derived from the solvent-assisted pathway, the hydroxymethyl ketone (71).

Although the rate of dienone-phenol[104] rearrangement of dienedione (70) was expected to be slower than that of the dienedione* (66), the absence of β-tetralone (72) was a little surprising,[69] but t.l.c. indicated the presence of a third product in the initial reaction mixture. Careful preparative t.l.c. afforded a compound which had spectral characteristics expected of ketone (72), but was extremely prone to oxidation, and could not be characterised.

In view of the failure to characterise adequately the ketone (72), the rearrangement of the dienedione (70) was of interest since a consideration of migratory aptitudes[124]

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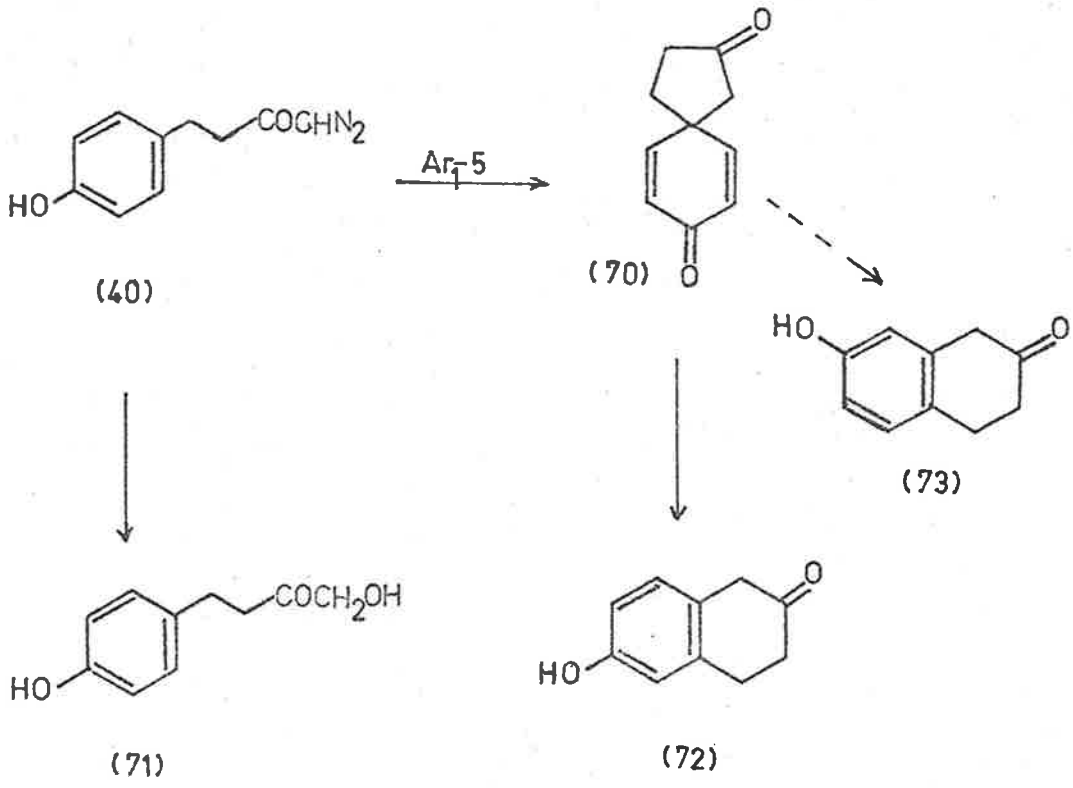
* This qualitative prediction is based solely on a consideration of relative ring strain energies in the ketones (66) and (70).



should lead to a selection of ketone (72) as the preferred product.

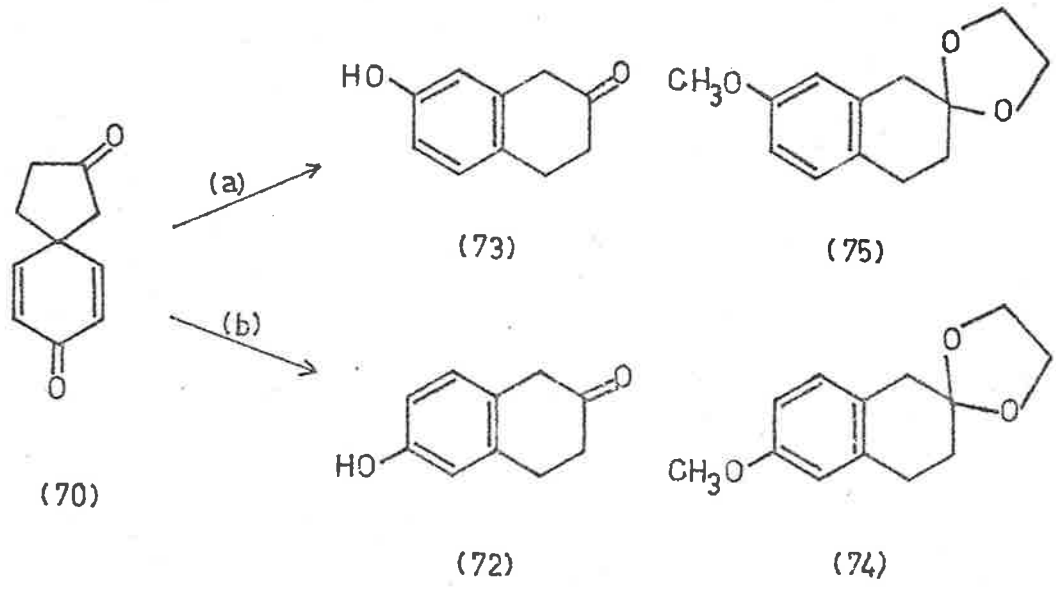
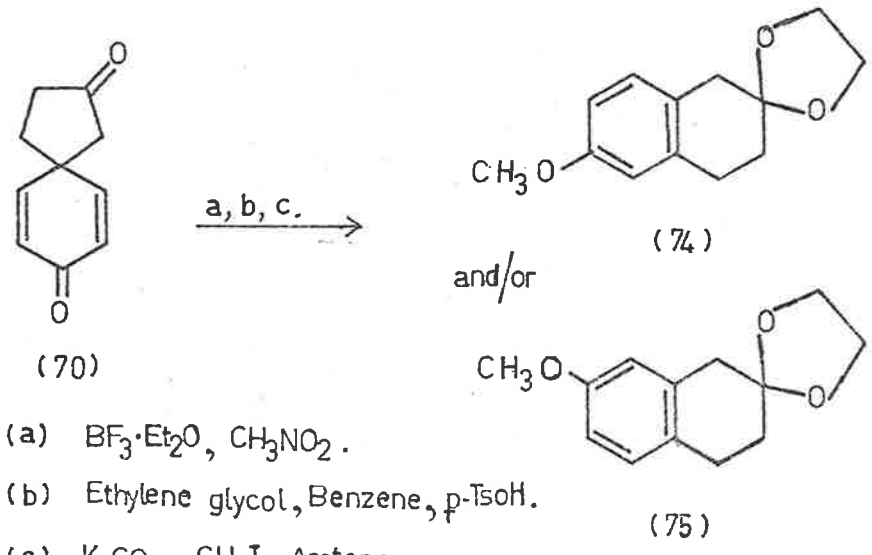


Figure 5

Previous workers[69] had not shown the absence of the alternative product (73), thus it was possible that "ketone (72)" might not be homogeneous.

Dienedione (70) underwent rapid rearrangement in the presence of boron trifluoride etherate, and afforded a product which was sequentially ketalised[125] and methylated[126] by standard procedures (Scheme 13). No trace of the hydroxymethyl ketone (71) could be detected.



Scheme 13

Authentic samples of the methoxy ketals (74) and (75) were prepared by standard procedures but had identical retention times on g.l.p.c. under a variety of conditions. Fortunately, it proved possible to detect the presence of ≥4% of ketal (75) in a mixture of ketals (74) and (75) by examination of n.m.r. spectra. The n.m.r. spectrum of the

product derived from the dienedione (70) was identical with that of ketal (74), i.e. dienedione (70) rearranges almost exclusively via pathway (b), (Figure 5), to yield ketone (72). Since Ar_1-5 and Ar_2-6 processes should have comparable rates only for equivalent degrees of activation,[123] direct formation of ketone (73) from diazoketone (40), although not discounted, appears unlikely.

(iv) Reaction of diazoketones (41) n=6 and (42) n=7.

Alkylation of diazoketone (41) n=6 under the standard conditions afforded predominantly the crystalline hydroxymethyl ketone (76) via the solvent assisted pathway (Figure 6),

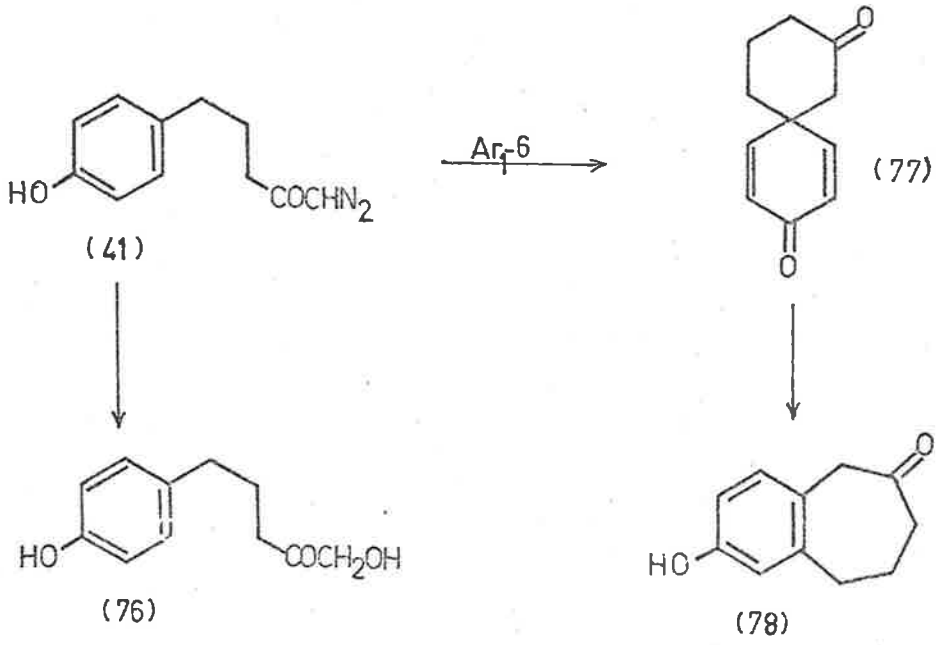


Figure 6

but spectroscopic examination of the initial fractions from

chromatography of the crude reaction mixture revealed that they contained mixtures of the dienedione (77), and the benzocycloheptanone* (78), totalling 11% in all.

Under identical conditions, the diazoketone (42) n=7 afforded almost entirely the hydroxymethyl ketone (79).

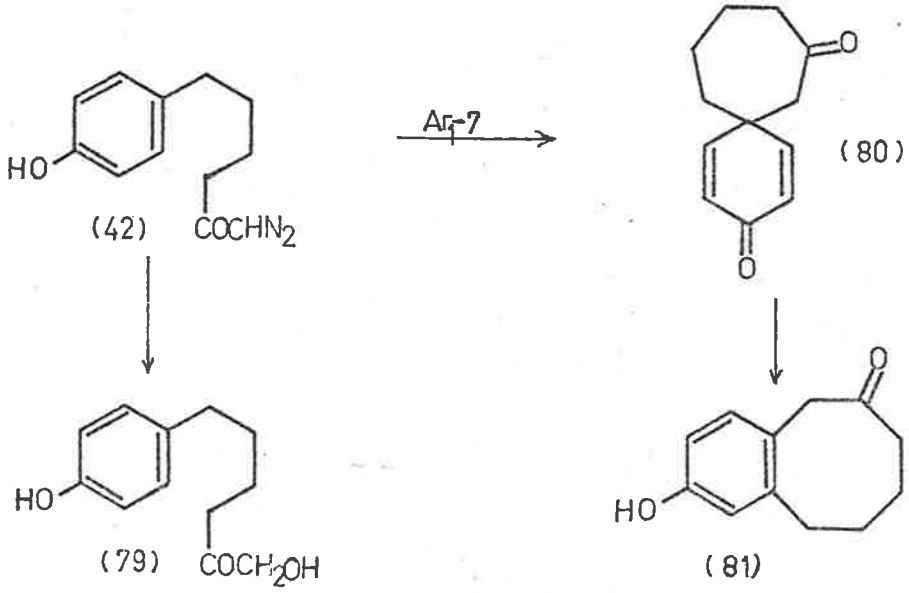


Figure 7

Spectroscopic examination of the remainder of the product revealed that dienedione (80) was absent, but a weak resonance in the n.m.r. spectrum at δ 3.65 (s, 2H, Ar-CH_2-CO-) suggested that the benzocyclo-octanone (81) was present in low yield (~3%).

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* The isomer was assigned by analogy with the formation of ketone (72) from the dienedione (70).

(c) A possible mechanism for the alkylation reaction.

By integration of appropriate resonances in the n.m.r. spectra of the total reaction mixtures, the proportions of products arising via aryl- and solvent-assisted pathways was measured. The results, expressed as percentage participation, are summarized in Table 1.

Table 1

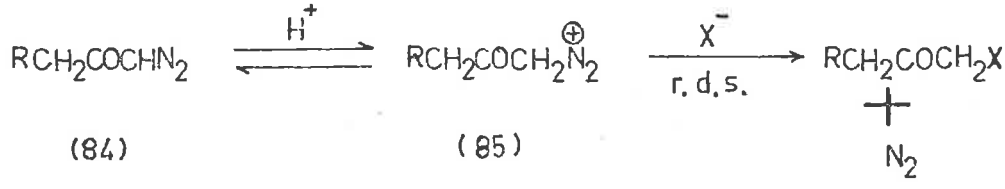
Percentage Aryl participation in the Diazoketones (38)-(42)

% participation ±5%	n (Ar_1-n)	Diazoketones
?	3	(38)
56%	4	(39)
67%	5	(40)
11%	6	(41)
3%	7	(42)

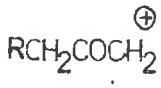
The high proportion of $aryl_1$-4 participation is of particular interest, since this is the first reported example of this mode of cyclisation, although a number of unsuccessful searches have been described.[69,72,127-130] An explanation of these trends will be presented following a brief discussion of mechanism. As the purpose of this investigation was a study of the scope of this alkylation in the context of synthesis, formal mechanistic studies have not been undertaken, but a reasonable picture of the probable

mechanism, based on observations during the study, and by analogy with earlier work can be obtained. Such a discussion is desirable for a comparison of the observed trends with Winstein's results.

The studies of the rearrangement of the dienediones (66) and (70) indicate that the aryl- and solvent-assisted pathways are discrete and competitive. Similar conclusions have been reached for solvolytic reactions in the Ar_1-3 (ref. 94-100) and Ar_1-5 (ref. 91, 101-103) systems, and also appear valid in the Ar_1-6 system.[102] The reaction of diazoketones (84) with nucleophiles under acidic conditions probably proceeds via an A-2 mechanism[76-85] (Figure 8), the diazonium ion (85) being the species actually reacting with the nucleophile. At various times, A-1 and A-S_E2 mechanisms[76]



(84) (85)

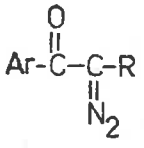


(85')

Figure 8

have been proposed as alternatives, the former mechanism (refs. 131-134,139) appears to have been adequately dis-

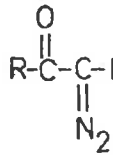
counted,[81,82,140] while the latter alternative* has been proposed by Jugelt and Berseck[135-138] to operate only for diazoketones of the type (86).



(86)

R=Aryl or Alkyl

$R \neq H$



(87)

R=R'=Alkyl

Although an α-keto-carbonium ion intermediate has been recently invoked,[141] studies in related bicyclic systems,[142] and steroids,[143] of general structure (87) have shown that the products can be rationalised adequately by an A-2 mechanism. Consequently the existence of a free carbonium ion (85') in the course of the alkylation appears unlikely. A number of the above examples are particularly relevant as they appear to involve neighbouring alkyl group participation in an A-2 process.[142,143] Thus it appears likely that the alkylation procedes via an A-2 mechanism, with the diazonium ion (85) (ref. 113) as a common intermediate. Although it is conceivable that an aprotic solvent could cause a change of mechanism (kinetic studies relating to diazoketones have been confined mainly to aqueous media), Roberts[79] and Lane[77]

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* It has also been pointed out that differentiation between A-S_E2 and A-S_E2' mechanisms from kinetic evidence is difficult.

have considered this possibility unlikely.

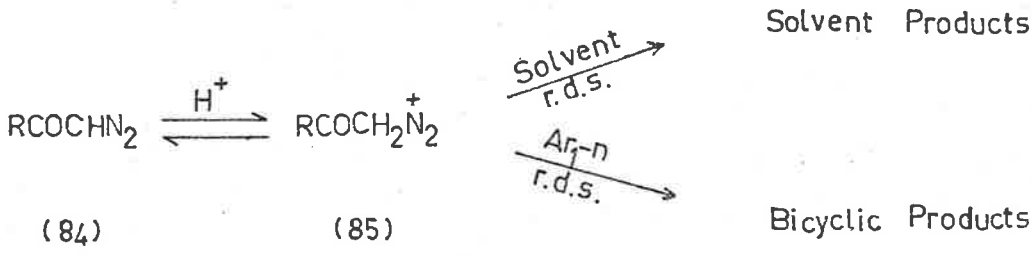
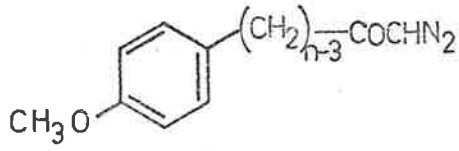


Figure 9

Preliminary studies of the alkylation showed that either a Lewis acid, or a Bronsted acid with a non-nucleophilic conjugate base, was necessary for reaction to occur, and both reagents afforded similar products. The corresponding methyl ethers (88), under normal conditions, failed to react in the presence of boron trifluoride etherate, but



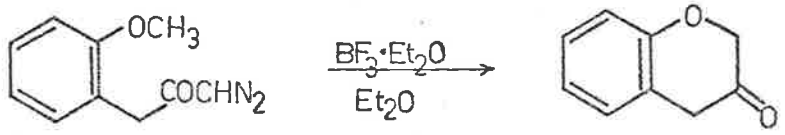
(88)

rapidly evolved nitrogen when treated with a Bronsted acid. In the presence of strongly co-ordinating solvents e.g. ether, tetrahydrofuran or acetonitrile,[144,145] reaction was either extremely slow, or did not proceed at all.

Lewis acids with both alcohols and phenols, form electron donor-acceptor complexes which behave as strong Brønsted acids.*[146] The alkylation of amines and alcohols by diazoalkanes[147] in the presence of Lewis acids is believed to be catalysed by such donor-acceptor complexes, while an analogous mechanism is probably operative in the transformations described by Newman[148] and Zorbach[149] (Figure 10). Identical products would be expected[77] if fluoroboric acid was used in place of boron trifluoride.

It is believed that the mechanism outlined in Figure 11 is consistent with these observations.

An alternative mechanism[152] has been postulated to account for the formation of ketone (97) (Figure 12).



(96) (97)

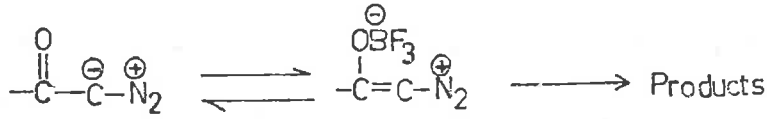


Figure 12

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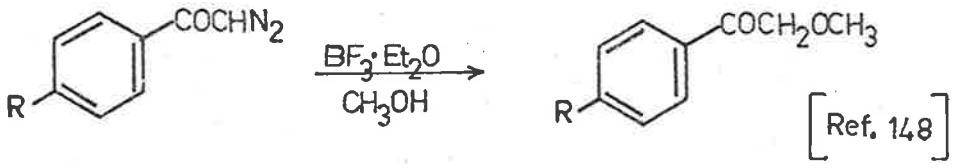
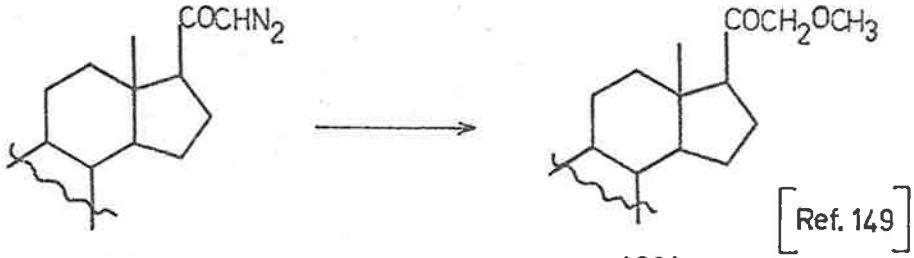
* Methyl ethers (88) react slowly with acetic acid ($pK_a \sim 4.8$) (ref. 150), but instantly with 2-bromopyridinium perchlorate ($pK_a \sim 0.9$) (ref. 151).



[Ref. 148]

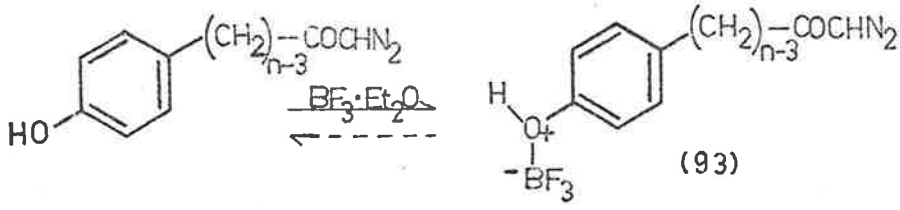
(89) R=H or CH_3O (90)



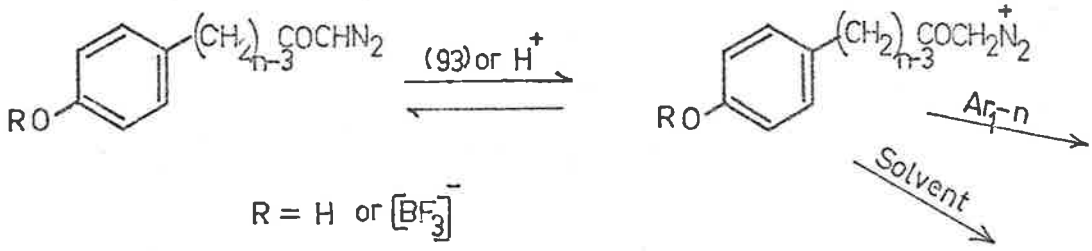
[Ref. 149]

(91) (92)

Figure 10



(93)



R = H or $[BF_3]^-$

Figure 11

Although interesting in view of the current interest in vinyl cations,[153] the success of this reaction is probably largely a consequence of the neighbouring methoxyl group,[154] since the methyl ethers (88) do not react with boron trifluoride etherate under the alkylation conditions. If this mechanism is in fact operative in the formation of ketone (97) it seems unlikely that it could compete* favourably with the mechanism depicted in Figure 11.

A carbenoid mechanism for the alkylation reaction, although considered, appears untenable in view of the nature of the products observed by Julia et al.[155-157]

(d) Factors influencing ring formation.

If the mechanism depicted in Figure 11 is acceptable, it is valid to compare the results of this study with the trends observed in the solvolysis of ω-aryl alkyl sulphonate esters,[72] (Table II).

Clearly Winstein's observations closely parallel the results of this study with the exception of the Ar_1-4 process. Not only is this observation unprecedented, but also quite unexpected on the basis of Winstein's kinetic

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* Boron trifluoride etherate was used in approximately equimolar quantities (ref. 152) in contrast to this work where catalytic amounts were employed.

data,* hence an explanation is in order.

Table II

Winstein's Work $\overset{'}{Ar}-(CH_2)_{n-1}-OSO_2\overset{''}{Ar}$		This Work $Ar-(CH_2)_{n-3}-COCHN_2$	
k_Δ/k_s		n (Ar_1-n)	% aryl participation ±5%
(a)	(b)		
92	1510	3	?
0.1	-	4	56%
0.4	3.6	5	67%
-	0.05	6	11%
-	-	7	3%

Winstein's results refer to the acetolysis at 75°C of p-bromobenzenesulphonate esters ($\overset{''}{Ar}$=p-Br-C_6H_4)

k_Δ = rate constant for anchimerically assisted solvolysis

k_s = rate constant for anchimerically unassisted solvolysis

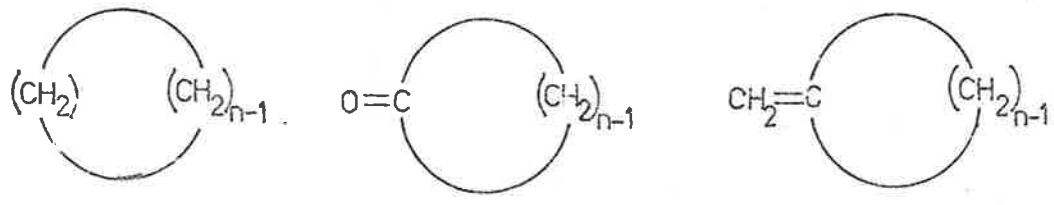
column (a), $\overset{'}{Ar}$=4-methoxyphenyl

column (b), $\overset{'}{Ar}$=2,4-dimethoxyphenyl

Since the products or intermediates in both cases are those of kinetic control, for an appreciation of the trends observed, the factors which determine the rate of

* c.f. however refs. 169-172.

ring closure should be considered. The relationship of the rate of formation of a ring system to its thermodynamic stability is complicated by other factors, namely entropy and inductive and electronic factors when the ring formation occurs by an intramolecular nucleophilic attack on a saturated carbon atom.[158-160] The trends observed in a series (Table II) can be explained adequately in terms of activation enthalpy and entropy. This approach has been successfully employed by Capon[158] to rationalize Winstein's results. It is apparent that the introduction of unsaturation into a side chain lowers the entropy loss on ring closure.[158] However, it is thought that the introduction of a single sp^2 hybridized carbon atom into a side chain will not automatically increase the ring strain and therefore the enthalpy of activation for ring closure. A comparison of the total ring strain energies[160,161] of the cycloalkanes (98) and the cycloalkanones (99) (Figure 13) should resolve this issue, but values of



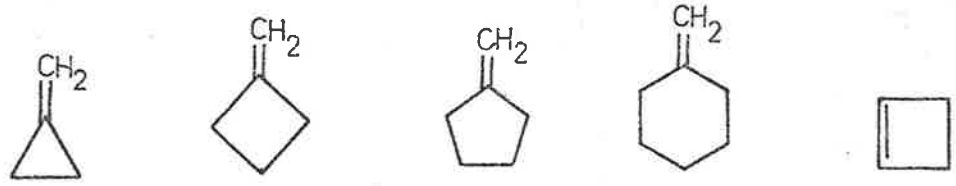
(98) (99) (100)

Figure 13

ring strain energy are not available for the cycloalkanones (99). Because of this deficiency, it has been assumed that the total ring strain energy for the methylene cycloalkanes (100) and the cycloalkanones (99) is approximately equal.

Using the Franklin group equivalent method[162] Wiberg[163] and Turner[164] have calculated from experimentally determined heats of hydrogenation, the total ring strain energies for methylene cyclopropane (101) and methylene cyclobutane (102). The same method* has been employed in this study** to calculate strain energies for the additional methylene alkanes (103) and (104).

These results are compared with the values for the



(101) (102) (103) (104) (105)

appropriate cycloalkanes (Table III).

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* This method has been recently criticized by Schleyer,[223] but in view of the qualitative nature of the discussion in this thesis, it is felt this procedure is adequate.

** An example calculation is included in the appendix.

Table III

Total ring strain energies** for the cycloalkanes (98) and the methylene cycloalkanes (100)

Ring Size	cycloalkanes (98)	methylene cycloalkanes (100)
3	27.6	41 (ref. 163)
4	26.1	24 (ref. 164)
5	6.5	4.5
6	0	0
7	6.3	-

** Values are for $+\Delta H$ k. cal. $mole^{-1}$.

Clearly the introduction of an sp^2 hybridized carbon atom into a ring does not increase its total strain energy except when n=3,* in fact even cyclobutene (105) with two sp^2 hybridized centres has a strain energy of only 28.5 k. cal. $mole^{-1}$.

The graph of ring strain versus ring size (Figure 14) for the two series (98) and (100) emphasizes the abnormally

* As evidence for Ar_1-3 participation could not be found by the methods employed in this study, it is not considered in subsequent discussion.

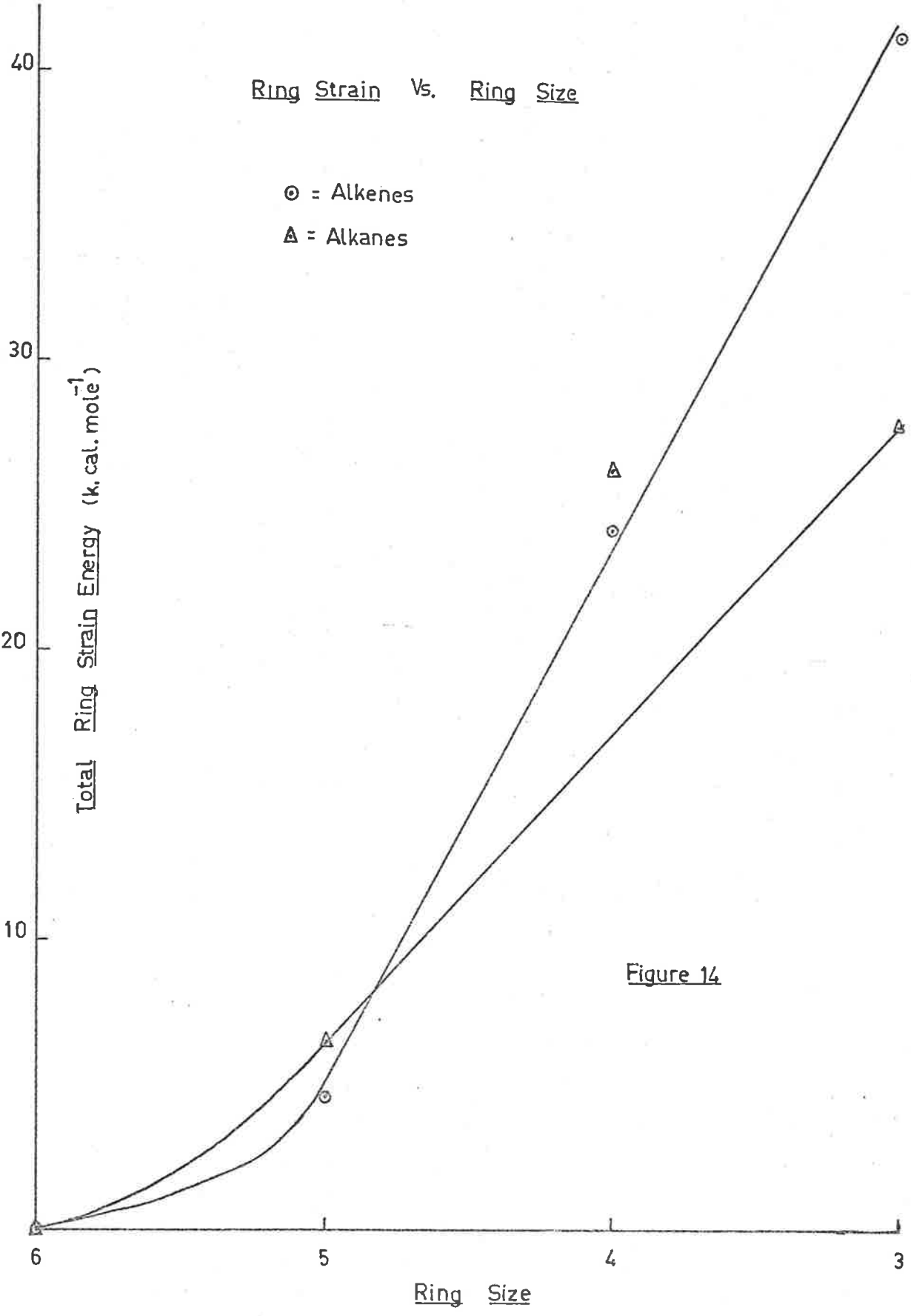
Ring Strain Vs. Ring Size
⊙ = Alkenes
Δ = Alkanes
Total Ring Strain Energy (k.cal.mole⁻¹)
40
30
20
10
6
5
4
3
Ring Size

Figure 14

high ring strain in cyclobutane relative to the other cycloalkanes (98).

This is supported by a variety of physical measurements.[165] Non-bonding interactions are so severe in cyclobutane that the molecule assumes a puckered conformation, thus increasing the already substantial[160] Baeyer strain present in the planar molecule. It would appear that the increase in angle strain caused by the introduction of an sp^2-hybridized carbon atom into a four membered ring is more than compensated for by the relief of non-bonding interactions.[164]

Thus the introduction of a carbonyl group into the side chain, i.e. in diazoketone (39) n=4, should result in ring formation being more favourable from a consideration of both entropy and enthalpy of activation.

In support of this hypothesis, the literature contains numerous examples of extremely efficient syntheses of β-lactones and β-lactams by methods involving ring closure by an intramolecular alkylation.[167-172] The saturated analogues, i.e. the oxetanes and azetidines, are formed in only very low yield by similar methods, presumably because of competitive intermolecular alkylation.[173,174]

It is believed that the trends in aryl participation observed in the reactions of the series of diazoketones (38) -(42) can now be adequately interpreted in terms of an increasing chain length (activation entropy for cyclisation de-

creasingly favourable) and decreasing ring strain* (activation enthalpy increasingly favourable) for the formation of rings of increasing size. Since nitrogen is an extremely good leaving group, and diazonium ions appear to react with quite low activation energies,[113] it is likely that for a strongly exothermic reaction, the transition state for cyclisation may resemble starting material[175] and so the ring strain may have less influence than expected in determining the contribution of enthalpy to the free energy of activation. This may further account for the high yield of Ar_1-4 products.

The failure to observe Ar_1-4 participation when a saturated carbon chain was employed[69,72,127-130] can probably now be rationalised in terms of the abnormally high total ring strain energy in cyclobutane. It is relevent that Schleyer[97-100] has recently concluded from studies in β-aryl ethyl systems that the extent of participation may be considerable, even in the absence of substantial rate increases. Although the absence of Ar_1-4 processes have been inferred from recent product studies[69,127,128] in saturated systems, Winstein's original work[72] discounted the Ar_1-4 process solely on the basis of kinetic evidence. Thus it appeared desirable to investigate the solvolysis of the p-nitrobenzene-

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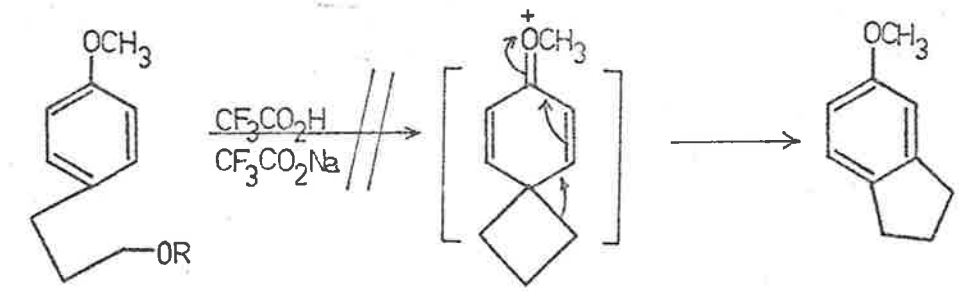
* This trend reverses for $n \geq 7$ (ref. 161).

sulphonate ester (106),* preferably in a solvent of high ionizing ability,[176] but low nucleophilicity.

High degrees of Ar_1-3 participation, and large rate increases have recently been detected[95,96,176,177] using trifluoroacetic acid which thus appeared to be the solvent of choice. The methoxyindane (108), by analogy with the Ar_1-5 process (c.f. Winstein[72]) was the product expected to result from Ar_1-4 participation (Figure 15).

Trifluoroacetolysis of the sulphonate ester (106) afforded a mixture of olefins and trifluoracetates, but g.l.p.c. analysis showed no trace of the indane (108) by comparison with an authentic sample.



(106) (107) (108)

R = p-NO_2-Ph-SO_2-

Figure 15

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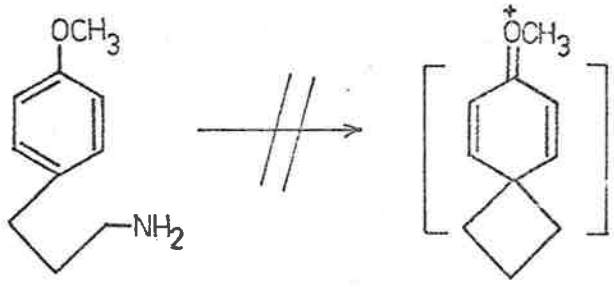
* The ester was prepared by a standard method from the corresponding known alcohol,[72] (see Experimental).

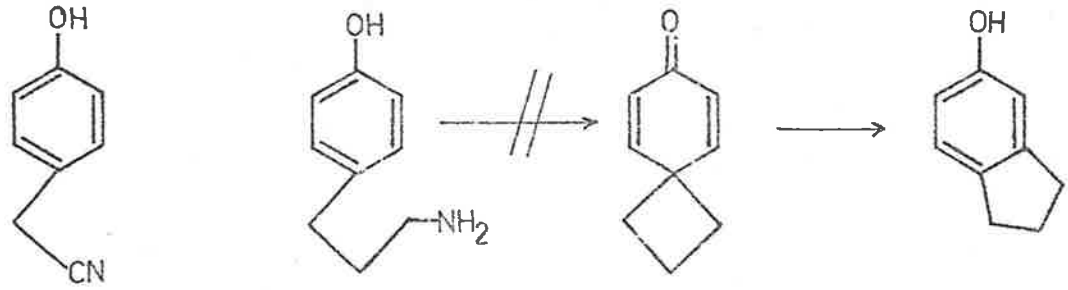
Roberts[130] detected no participation during the deamination of amine (109) (Figure 16), but as a final check



(109) (107)

Figure 16

the deamination of the phenolic amine (111) has been investigated. The amine was prepared by reduction of the known nitrile (110) (ref. 178) with sodium in alcohol.



(110) (111) (112) (113)

Figure 17

Deamination* of the amine (111) in acetonitrile solution afforded no trace of the phenolic indane (113). This evidence further suggests that when a saturated side chain is present, even under ideal conditions, the Ar_1-4 process is not significant in comparison with intermolecular processes.

Although the argument used in this discussion has been qualitative in nature, it is felt that the proposed model is adequate for predicting the course of the alkylation reaction. The following general conclusions can be made:

(i) the Ar_1-4 and Ar_1-5 processes show potential for the preparation of β-indanones and β-tetralones, while the latter process may be useful for the preparation of spirodienediones.

(ii) when the side chain bearing the diazomethyl ketone moiety constitutes part of a cyclic structure (Part 1), the activation entropy is favourably affected, resulting in an increased degree of participation so that the Ar_1-6 process also has synthetic value. The resistance of these initial products to further rearrangement greatly increases the utility of the reaction. These data are summarised in Table IV.

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* It was appreciated that if deamination occurred via an S_N1 process, any participation would not constitute anchimeric assistance.[179]

Table IV

% Aryl participation observed with the diazoketones (X)

	Monocyclic precursors	Bicyclic precursors (constrained side-chain)
Ar_1-4	56% (39)	-
Ar_1-5	67% (40)	70%* (35)
Ar_1-6	11% (41)	32%* (31)

* It should be appreciated that these figures represent absolute yields, % participation may be higher when allowance is made for intermolecular processes.

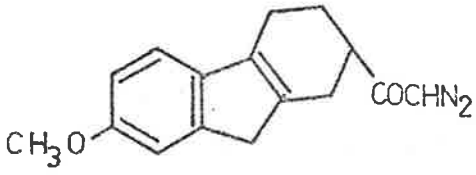
Clearly this alkylation affords a mild, general method for the modification of the anisole synthon, and shows excellent synthetic potential for the simultaneous angular alkylation of suitably substituted preformed polycyclic phenols.

PART III

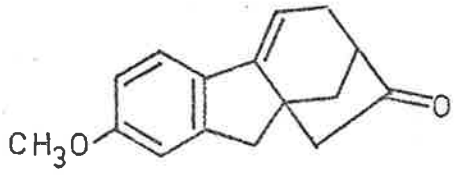
INTRODUCTION

In view of the synthetic potential offered by the intramolecular alkylation of diazoketones, an examination of the nature of the reaction with other carbon nucleophiles was undertaken, again in the context of preparing intermediates for diterpene synthesis.

Bartlett[180-183] and his co-workers have demonstrated that the nucleophilicity of an olefinic linkage is considerably greater than that of an aryl group provided that it is suitably disposed with respect to the reaction centre. In addition, Closs[184] has concluded that the double bond contained in a styrene system is more nucleophilic than an isolated vinyl group by a factor of ten. It therefore appeared interesting to examine the behaviour of the styrene double bond as a carbon nucleophile with the diazonium ion.



(114)



(115)

The tricyclic diazoketone[185] (114) was chosen for the initial investigation for a number of reasons:

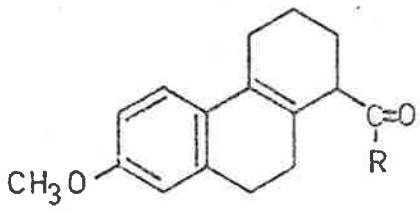
(i) not only is the olefinic bond suitably disposed[180,182] with respect to the diazoketone moiety, but it is also electron rich by virtue of alkyl substitution[181]

and an electron donating oxygen substituent.[186-188]

(ii) any cyclisation should be favourable because of the formation of a five membered ring.[72]

(iii) the product expected from this alkylation, the tetracyclic ketone (115), possessed a gibbane skeleton,[189] and appeared an ideal model for synthetic routes to C_{19} gibberellins.[189]

As the tricyclic acid (116) was available from related synthetic work, this provided an opportunity to test the utility of the alkylation for the preparation of four membered rings by an examination of the reaction of the tricyclic diazoketone (117).



(116) R=OH

(117) R=CHN_2

Part III of this thesis will describe the synthesis of the diazoketones (114) and (117), and a study of their intramolecular alkylation reactions.

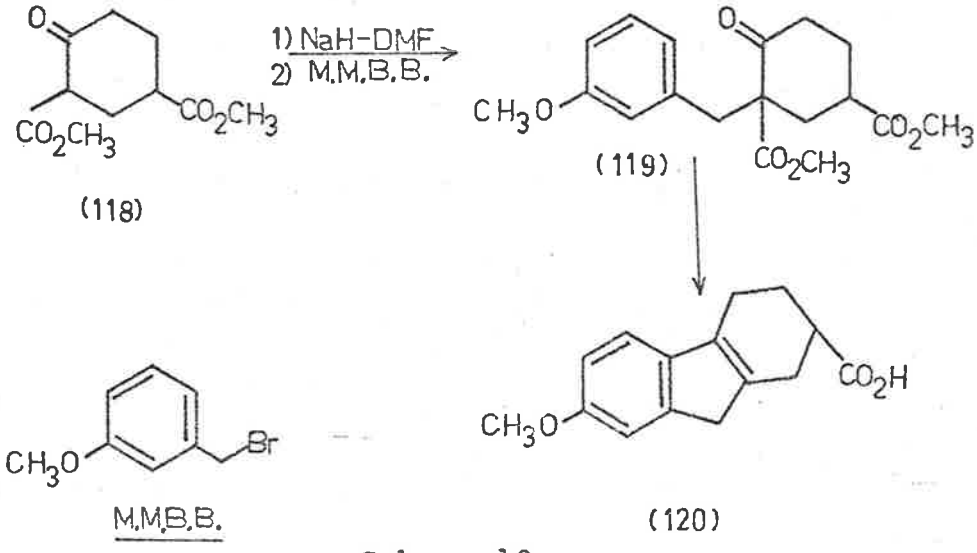
---oOo---

PART III

DISCUSSION

(a) Synthesis of the diazomethyl ketones (114) and (117).

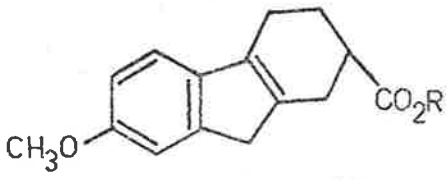
The synthetic approach outlined in Scheme 13 was employed in initial efforts to synthesize the tricyclic acid (120) and it is essentially the same as reported by Dasgupta et al.[185]



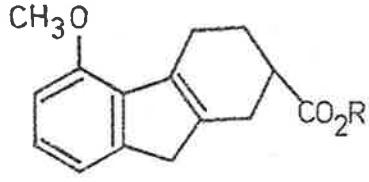
Scheme 13

Alkylation of the keto-diester (118) (ref. 190) with m-methoxy-benzyl bromide under normal conditions[191] afforded (in 72-76% yield) the diester (119), which on subsequent treatment with a mixture of hydrochloric and acetic acids,[185] gave a mixture of acids in c. 50% yield after extensive purification. The mixture of acids was converted to their t-butyl esters by treatment with oxalyl chloride, then with t-butyl alcohol in the presence of pyridine;[192] careful chromatography afforded two crystalline t-butyl esters (A) and (B). Cleavage of the respective t-butyl ester groupings under acidic conditions[192] gave two tricyclic acids (A) and

(B), the former, acid (A) appeared to be the compound already reported by Dasgupta *et al*[185] i.e. (120). Spectral and analytical data suggested that acid (B) was isomeric with acid (A), and accordingly it has been assigned structure (121) (Figure 18), which is consistent with its mode of formation. Dasgupta and co-workers failed to report the presence of acid, (121) but two isomeric products arising from a similar cyclisation have been observed by Loewenthal *et al*.[193]



(120) R=H (Acid A)



(121) R=H (Acid B)

(122) R=t-Butyl (Ester A)

(123) R=t-Butyl (Ester B)

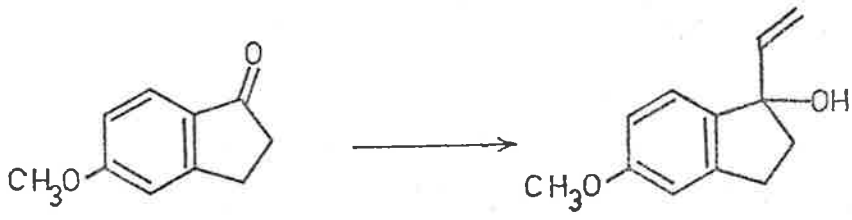
Figure 18

Although it was subsequently discovered that extensive fractional crystallisation afforded the pure acid (120), the poor yield (c.15%) precluded the use of this method for the synthesis of gibberellin analogues, and an alternative route was examined.

The key transformation in the second approach (Scheme 14) to the synthesis of the acid (120) is the Diels-Alder reaction of the diene (125) with acrylonitrile. An analogous

transformation has been successfully employed in the synthesis of perhydrophenanthrene derivatives[194-196] from the diene (129) (Scheme 15).

Treatment of the indanone[197] (130) with vinyl magnesium bromide by a modification of the literature procedure (ref. 198) afforded the carbinol (124) in quantitative yield, (Figure 19) but it was essential that an excess of Grignard

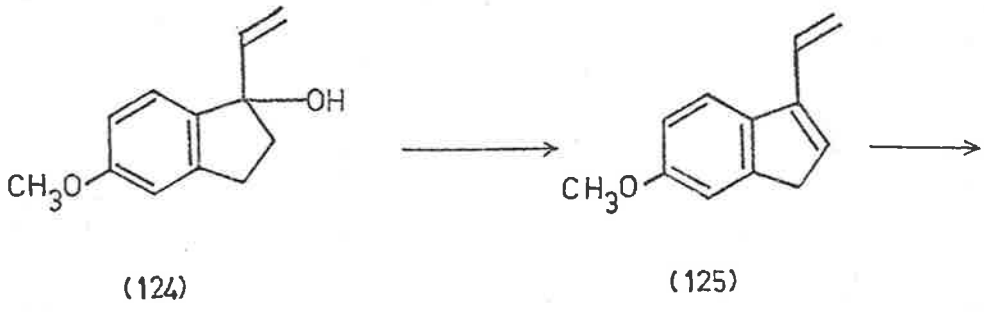


(130) (124)

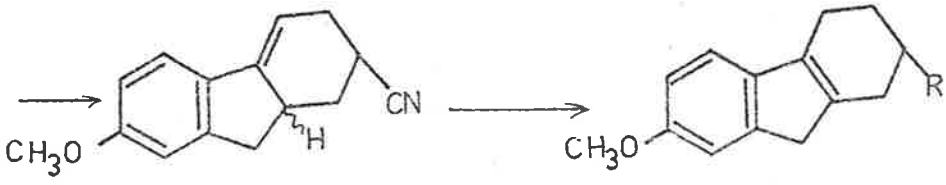
Figure 19

reagent be employed in conjunction with a low temperature ($<-15^{\circ}C$) or significant amounts of indanone (130) were observed in the product. In view of the weakly electrophilic ketone function present in the indanone (130), and the observation that the relative rates of nucleophilic addition and enolate anion formation are temperature dependant,[199] this result is not surprising. The labile carbinol (124) was employed in further reactions without purification, however, spectral examination indicated it was homogeneous.

Careful dehydration of the carbinol (124) with iodine[194-196] gave the very labile diene (125). This trans-



(124) (125)

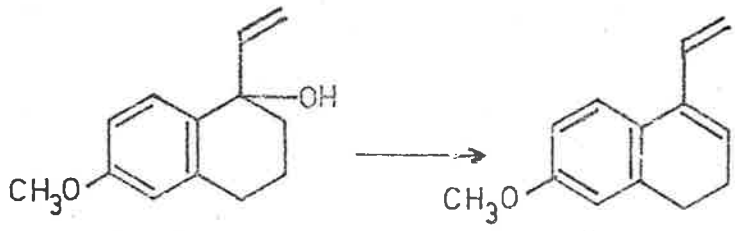


(126)

(127) R = CN

(120) R = CO_2H

Scheme 14

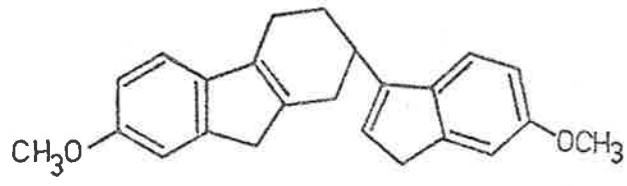


(128) (129)

Dienophile → Phenanthrene derivatives

Scheme 15

formation was a delicate operation as the iodine concentration proved a critical variable, in contrast to the analogous transformation in Scheme 15. It appeared that dimerisation of diene (125) was strongly catalysed by iodine,[200,221,222] as further heating of the diene (125) for a very short time



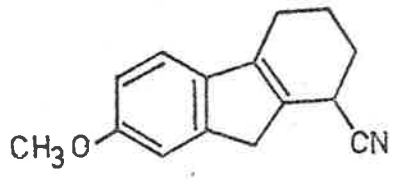
(131)

Figure 20

after dehydration afforded the crystalline dimer (131) (Figure 20), in excellent yield, (c.f. ref. 222) whereas removal of the iodine catalyst after dehydration, allowed isolation of the diene (125) in excellent yield.

Subsequent treatment of this diene (125) with acrylonitrile (4 hrs., 100°C) afforded the nitriles (126) accompanied by only minor quantities (~10%) of the dimer (131). Brief acid treatment of the crude mixture caused isomerisation of the double bond to the more stable position with concomitant removal of stereochemical ambiguity at C-8a, and afforded nitrile (127) in 54% overall yield from the indanone (130)

with no trace of the isomeric nitrile (132) (Figure 21).



(132)

Figure 21

Hydrolysis of the nitrile (127) gave in high yield a single acid which was identical in all respects with acid A i.e. (120), obtained via the previous synthetic approach; thus substantiating the assignment of structure (127) to the tricyclic nitrile, and providing an excellent synthetic route to the desired acid (120).

The absence of the nitrile (132) is interesting but not surprising in view of the profound influence of polar groups[200-202] on the course of Diels-Alder reactions. Goldberg and co-workers[194] observed that the diene (129) reacted smoothly with methyl vinyl ketone to yield predominantly the ketone (133)* (Figure 22), whereas the ketone (134) was obtained in only 1.5% yield. It appears that the selectivity of a dienophile (135) (Figure 23) undergoing a Diels-

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* Treatment with acid causes isomerisation of the olefinic bond.

Alder reaction with a diene (125 or 129) can be correlated qualitatively[200-202] with the group dipole moment[203] of the

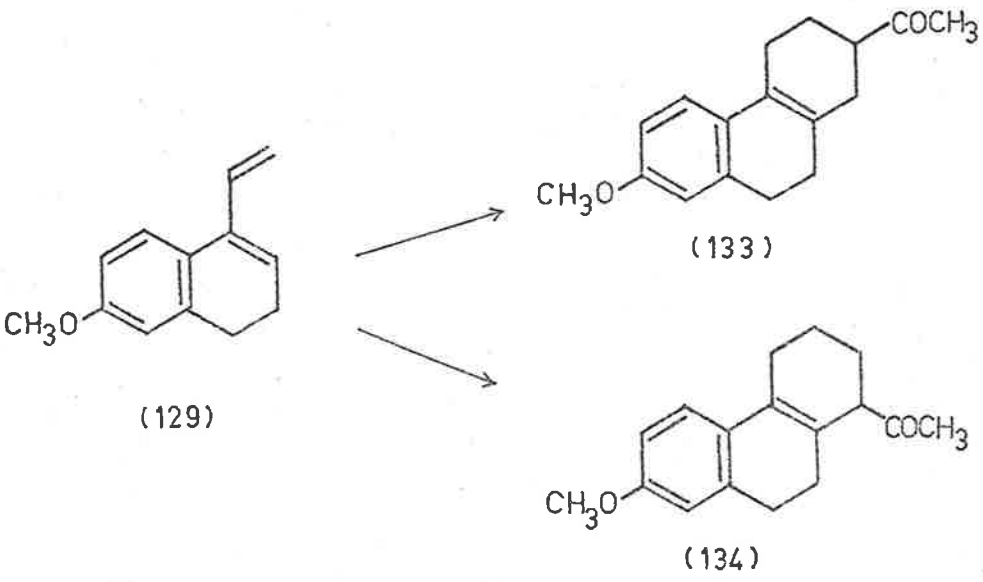
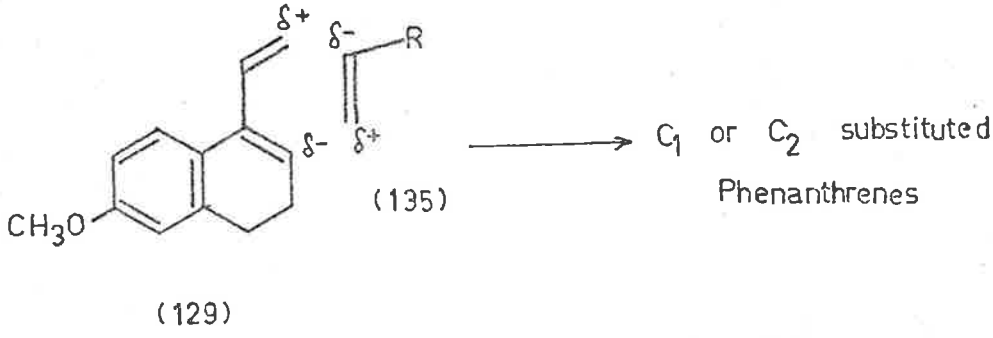


Figure 22



R= C≡N, $COCH_3$, CO_2R.

Selectivity

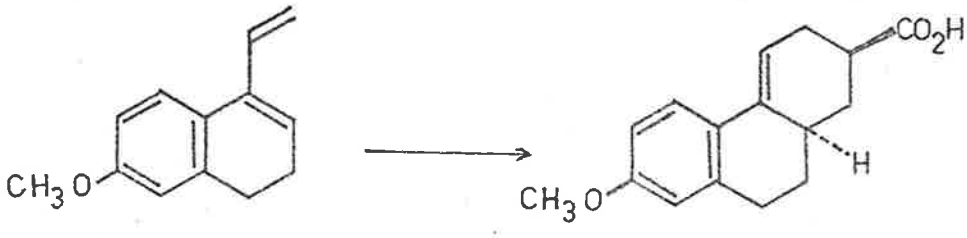
CN> $COCH_3$> CO_2R

Figure 23

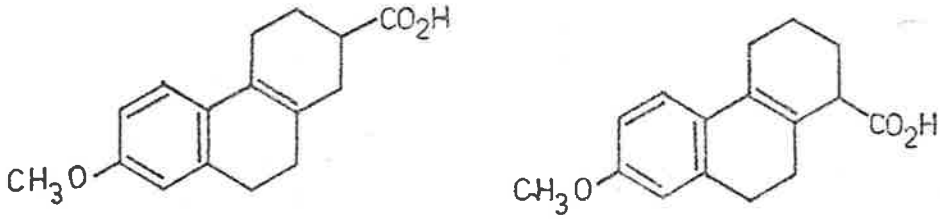
substituent R. i.e. CN> $COCH_3$> CO_2R, hence the specific form-

ation of the nitrile (127).*

The validity of this argument is further substantiated by the nature of the products[195] derived from the reaction of ethyl acrylate with the diene (129) (Figure 24). Goldberg[195] has reported the isolation of only the acid (136)



(129) (136)



(137) (116)

Figure 24

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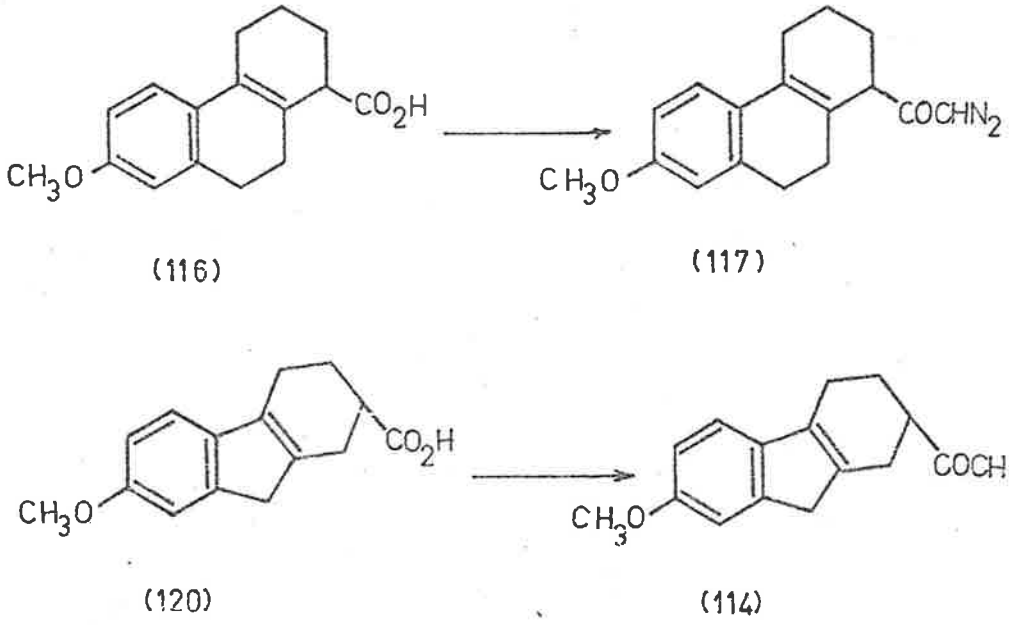
* Acrylonitrile has an advantage in that it is a reactive dienophile. With less reactive dienophiles e.g. ethyl acrylate, not only is dimer formation a competitive process, but the desired process may occur regio selectively[5] rather than regio specifically.[5]

in 33% yield, but a re-examination of this work showed that the acids (137) and (116) are in fact formed in a 2:1 ratio. This result is in accordance with the established behaviour of acrylate esters in Diels-Alder reactions,[201] and with predictions based on group dipole moments. The two acids (137) and (116) were easily separated by fractional crystallisation.

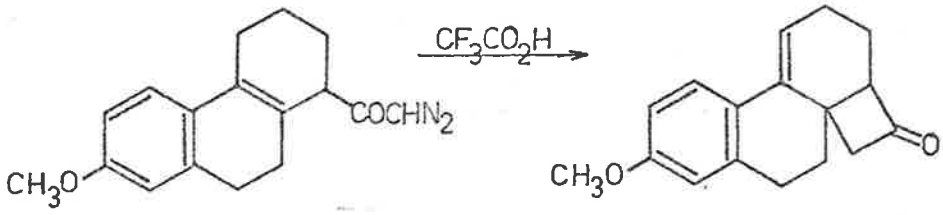
The two acids (116) and (120), on treatment with oxalyl chloride and then with excess ethereal diazomethane[51] in the normal way (c.f. Parts I and II), gave the crystalline diazoketones (117) and (114) (ref. 185) respectively in high yield (Scheme 16).



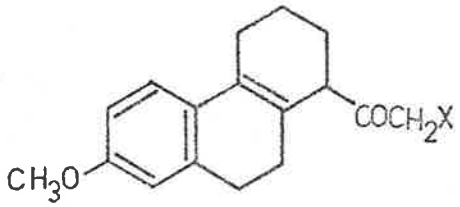
Scheme 16

(b) Intramolecular alkylation in the diazoketone (117).

When a solution of the diazoketone (117) in methylene chloride was treated with trifluoroacetic acid, an instant evolution of nitrogen was observed. Purification of the crude product (quant. yield) afforded a single crystalline product which has been assigned structure (138) on the basis of its spectral data, [ν_{max} 1762cm^{-1}, δ_{max} 7.5 (d, J8Hz, 1H, C5-H), 6.3 (t, J4Hz, 1H, C4H)] and probable mode of formation (Figure 25).



(117) (138)



(139) X= O-C(=O)-CF3

(141) X= OH

Figure 25

The n.m.r. spectrum of the total reaction product displayed a weak singlet resonance at δ 5.15 (s, 2H, $COCH_2OCOCF_3$)* which has been ascribed to the presence of the

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* Similar trifluoroacetoxy ketones prepared in this laboratory exhibit a resonance in the region 5.2-5.0 (c.f. ref. 116).

uncyclised trifluoroacetoxy ketone (139). Integration of the appropriate resonances in the n.m.r. spectrum indicated that the mixture contained 92% of the cyclobutanone (138), the remainder being the ketone (139). A similar result was obtained using nitromethane* as co-solvent in lieu of methylene chloride.

In view of trends previously observed in solvolytic studies the efficient formation of the cyclobutanone (138) is particularly interesting. Anchimeric assistance (or participation) from olefinic or acetylenic bonds four ($\Delta^{5,6}$) or two carbons ($\Delta^{3,4}$ i.e. homoallylic) removed from the reaction centre has been frequently observed,[180,182,184,186-188,204-215] but Berson et al. have only recently reported[216] the first example of anchimeric assistance by an olefinic bond three carbons (i.e. $\Delta^{4,5}$) removed from a reaction centre. It would appear that this exception to the general rule,[182,217-219] is assisted by the operation of abnormal steric effects, as closely related substrates solvolyse without observable anchimeric assistance.[220]

The solvolysis of systems in which the unsaturated bond is conjugated to a phenyl substituent, generally affords similar results,[184,204,206,207] but once again $\Delta^{4,5}$ double

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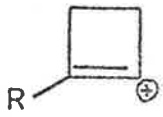
* The minor product in this case was the corresponding hydroxy methyl ketone (141).

and triple bonds fail to provide anchimeric assistance. The solvolysis of suitably constituted olefinic and acetylenic substrates frequently results in the formation of four membered rings via anchimerically assisted pathways, although such examples have been confined to homoallylic systems (refs. 207,208). Hanack has recently reported[153,211-215] results which are compatible with the formation of the vinyl cation (140) as an intermediate. This appears reasonable[209]



(140)

(105)

from a consideration of the ring strain in cyclobutene[163] (105) (Part II).

The formation of the cyclobutanone (138) in such high yield provides compelling evidence for participation by an olefinic bond three carbons ($\Delta^{4,5}$) removed from the reaction centre. The Ar_1-4 participation described in Part II can also be regarded as involving formal participation by a $\Delta^{4,5}$ double bond.

It is felt that the success of this alkylation may be attributed to factors similar to those responsible for the success of the Ar_1-4 alkylation discussed in Part II namely:

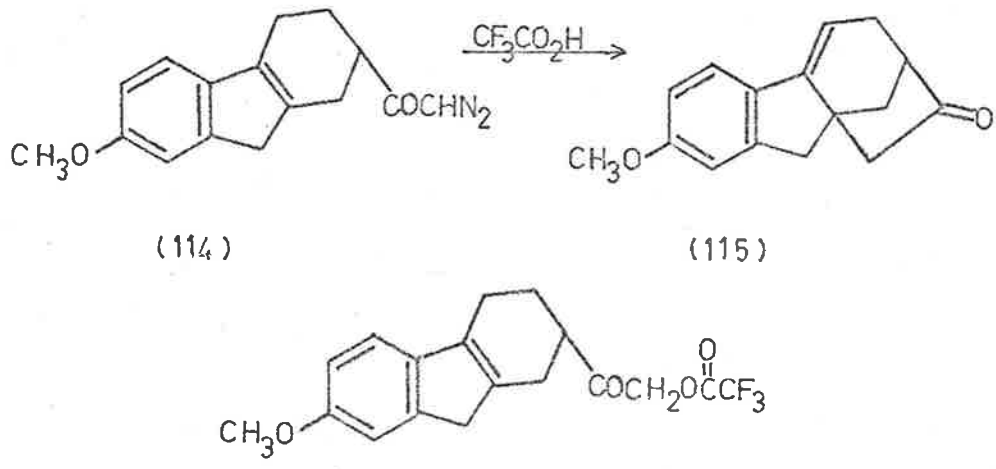
(i) the presence of the trigonal carbon atom in the side chain and its effect upon the enthalpy of activation.

(ii) a favourable entropy of activation due to (a), and the constraint of the methylene chain carrying the diazomethyl ketone in the polycyclic structure.

It is also probable that the greater nucleophilicity[184,204] of the styrene bond is an additional, important factor.

(c) Intramolecular alkylation in the diazoketone (114).

The diazoketone (114), in methylene chloride, when treated with trifluoroacetic acid, afforded the analogous alkylation product, the tetracyclic ketone (115) (Figure 26)



(114) (115)

(142)

Figure 26

in excellent yield. This product had properties in agreement with those already reported in the literature,[185] whilst its

n.m.r. spectrum was consistent with the assigned structure. Once again examination of the crude product by n.m.r. spectroscopy revealed a weak singlet resonance at δ 5.0 which was ascribed to the presence of the trifluoroacetoxy ketone (142). Weak absorption bands at 1790 and 1720cm^{-1} in the infra-red spectrum of the crude product supported this assignment. Integration of the appropriate resonances in the n.m.r. spectrum established that the mixture contained 95%$\pm$2% tetracyclic ketone (115), the remainder being the non-cyclised trifluoroacetate (142).

As a further manifestation of the anchimeric assistance provided by a $\Delta^{5,6}$ double bond, the formation of the tetracyclic ketone (115) is not unusual, but as an extension of the use of diazoketones for the angular alkylation of polycyclic molecules it appears of great value.

The results of this study and the few previous reports[204,206,207] of intramolecular alkylation through the agency of the styrene synthon, suggests that its utility in synthesis is considerable. In particular this styryl$_1$-5* alkylation, by virtue of its simplicity and efficiency, appears to have excellent synthetic potential for the construction of C_{19} gibberellin intermediates and polycyclic molecules containing a fused, bicyclo [3,2,1] octane system.

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* By analogy with the nomenclature of Winstein.

It is believed that the preceding work demonstrates some successful synthetic applications of the intramolecular reaction of the electrophilic α-ketodiazonium ion; and also gives an indication of the behaviour that could be expected from this alkylating agent in other intramolecular nucleophilic reactions.

---oOo---

Note added in proof.

A related transformation has been recently reported.[254]

EXPERIMENTAL

GENERAL

Melting points were measured on a Reichert hot-stage apparatus, and are uncorrected. Microanalyses were performed by the Australian Microanalytical Service, Melbourne. Infra-red spectra, unless otherwise indicated were measured as Nujol mulls on Perkin-Elmer 337 and Unicam SP200 spectro-photometers. Ultraviolet spectra were recorded in 95% ethanol on a Perkin-Elmer 137 instrument. Mass spectra were determ-ined with an Hitachi Perkin-Elmer RMU-6D double focussing mass spectrometer, operating at 70 eV. The nuclear magnetic resonance were recorded on Varian DA-60-IL and T60 spectro-meters operating at 60MHz. The spectra were measured in deuterochloroform solution relative to tetramethylsilane (δ0.00p.p.m.) unless stated otherwise; each signal is describ-ed in terms of chemical shift in p.p.m. from tetramethyl-silane, multiplicity, intensity, coupling constants in Hz and assignment in that order with the use of the following abbrev-iations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; e, envelope; and $W_{\frac{1}{2}}$, width of peak at half height.

Chromatographic adsorbents used were Spence type H alumina, Florisil and Sorbsil silica gel. Thin layer chrom-atography and preparative thin layer chromatography were carried out on layers of an equal mixture of Merck Kieselgel HF_{254} and Kieselgel G.

The expression "worked-up in the normal manner" implies

that the organic layer was washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure. Light petroleum refers to the fraction of b.p. 30-40°.

Dry nitromethane was prepared by azeotropic distillation;[225] the fraction b.p. 100.5-101° was collected and dried over B.D.H. molecular sieve type 4A. Ultra-dry nitromethane was prepared from dry nitromethane by treatment of the latter with trifluoroacetic anhydride (0.5% W:W); trifluoroacetic acid and excess trifluoroacetic anhydride were removed by distillation through a 50cm. glass column, and the nitromethane then redistilled; the fraction b.p. 100.5-101° was collected and stored over molecular sieve type 4A. Dry trifluoroacetic acid was prepared by the standard literature procedure[95] and distilled, the fraction b.p. 71.3-71.5° was collected. Boron trifluoride etherate was distilled under reduced pressure from calcium hydride and stored at 5° under an atmosphere of nitrogen.

The preparations described in the experimental section are listed in the order in which they occur within a synthetic sequence. Synthetic sequences are presented in the order in which they occurred in the discussion.

PART I

3,4-Dihydro-7-methoxy-1(2H)-naphthalenone (17).

This compound was prepared by the method of Haworth and Sheldrick.[43] It had b.p. 120-126°/0.3mm (lit.[43] b.p. 130-135°/0.5mm) and on cooling formed a light yellow solid.

2-Ethoxalyl-3,4-dihydro-7-methoxy-1(2H)-naphthalenone (18).

The method employed was basically that of Hunter and Korman[44] which has been used to prepare the corresponding methyl ester.

The ethyl glyoxalate was obtained as a viscous red oil (98%, crude yield), which solidified on standing. This product was in all cases sufficiently pure for conversion into the corresponding ethyl 1,2,3,4-tetrahydro-7-methoxy-1-oxo-2-naphthoate.

A portion of the crude ester was chromatographed on silica gel. Elution of the column with ether-light petroleum (1:20) gave the pure ester which crystallized from ether-hexane as bright yellow needles, m.p. 38.5-39.5° (Found: C, 65.5; H, 6.1. $C_{15}H_{16}O_5$ requires C, 65.2; H, 5.8%). ν_{max} 1720, 1620-1600cm^{-1} (β-oxo-glyoxylate). δ_{max} 1.38 (t, 3H, J 7 Hz, $COOCH_2\underline{C}H_3$), 3.8 (s, 3H, $ArOC\underline{H}_3$), 4.35 (q, 2H, J 7 Hz, $COOC\underline{H}_2CH_3$), 7.05, 7.45p.p.m. (m, 3H, Ar$\underline{H}$).

Ethyl 1,2,3,4-Tetrahydro-7-methoxy-1-oxo-2-naphthoate (19).

A mixture of crude glyoxylic ester (6.3g) and powdered chromatographic glass beads (3g) was heated at 180°, and stirred in an atmosphere of nitrogen until effervescence had ceased (30 min). The cooled mixture was dissolved in benzene and filtered; the solvent was removed in vacuum to yield a dark red oil which on distillation gave ethyl 1,2,3,4-tetrahydro-7-methoxy-1-oxo-2-naphthoate, b.p. 135-145°/0.05mm, (4.66g, 82%) as a light yellow viscous oil which crystallized from hexane as white needles, m.p. 46-47° (Found: C, 68.1; H, 6.7. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%). ν_{max} 1730 (ester C=O), 1680 (tetralone C=O), 1640cm^{-1} (bonded ester C=O).

1,2,3,4-Tetrahydro-7-methoxy-2-naphthoic Acid (15).

(A) To a solution of ethyl 1,2,3,4-tetrahydro-7-methoxy-1-oxo-2-naphthoate (10.5g) in glacial acetic acid (70ml) was added perchloric acid (3ml, 70% aqueous) and palladium on charcoal (1g, 5%) and the mixture stirred overnight under hydrogen at a pressure of 2 atm. The mixture was diluted with chloroform (150ml) and filtered through Celite. The colourless filtrate was washed with water until the washings were neutral and then dried (Na_2SO_4). Removal of the solvent in vacuum gave ethyl 1,2,3,4-tetrahydro-7-methoxy-2-naphthoate as a light pink liquid. ν_{max} (film) 1720cm^{-1} (ester C=O). The ethyl ester was dissolved in

methanol (50ml) and added to an aqueous methanolic solution of potassium hydroxide (20g) and heated under reflux on a steam-bath for 1 hr. The cooled mixture was acidified (hydrochloric acid, 10% aqueous), diluted with water (300ml), and extracted with ether. The ethereal extracts were washed with water, dried (Na_2SO_4), and evaporated in vacuum to yield 1,2,3,4-tetrahydro-7-methoxy-2-naphthoic acid (15) (7.3g, 85% crude yield) as a light yellow solid which crystallized from ether-hexane as colourless needles, m.p. 122.5-123.5° (Found: C, 69.7; H, 7.2. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%). ν_{max} 2600-3200, 1690, 960cm^{-1} (CO_2H).

(B) Amalgamated zinc wool (16g) was added to a mixture of 1,2,3,4-tetrahydro-7-methoxy-4-oxo-2-naphthoic acid (8.2g), concentrated hydrochloric acid (60ml), water (25ml), and toluene (60ml) and the mixture heated under reflux for eleven hours. The cooled mixture was diluted with ether (200ml), the organic layer separated, and the aqueous layer extracted with ether (2x50ml). The combined organic extracts were washed with water (3x30ml), dried (Na_2SO_4), and the solvent removed "in vacuo" to yield a white crystalline solid (7.7g, quant.). The infra-red spectrum of the product was identical with that of an authentic sample of 1,2,3,4-tetrahydro-7-methoxy-2-naphthoic acid (15). Crystallisation of a sample from hexane-ether gave white needles, m.p. and mixed m.p. 122-123°.

1,2,3,4-Tetrahydro-7-hydroxy-2-naphthoic Acid (22).

A mixture of 1,2,3,4-tetrahydro-7-methoxy-2-naphthoic acid (13.65g) and pyridine hydrochloride (50g) in an atmosphere of nitrogen was heated at 220-240° for 4½ hr. The cooled reaction mixture was dissolved in water and extracted with ether several times. The combined ethereal extracts were washed with water, hydrochloric acid (10% aqueous), and twice more with water, then dried (Na_2SO_4). The dried ethereal extracts were concentrated in vacuum to yield 1,2,3,4-tetrahydro-7-hydroxy-2-naphthoic acid (12g, 95% crude yield) as a pale yellow solid which crystallized from ether-hexane as white needles, m.p. 170-171° (Found: C, 68.35; H, 6.35. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%). ν_{max} 3300 (phenolic hydroxyl), 2700-3150, 1705cm^{-1} (CO_2H).

7-Benzyloxy-1,2,3,4-tetrahydro-2-naphthoic Acid (23).

A solution of benzyl bromide (50g, 0.293mol) in dioxan (200ml) was added in four portions to a well-stirred solution of 1,2,3,4-tetrahydro-7-hydroxy-2-naphthoic acid (13.3g, 0.046mol) and potassium hydroxide (15g, 0.268mol) in water (300ml) under an atmosphere of nitrogen and the mixture allowed to stir overnight at 70°. The cooled reaction mixture was filtered, concentrated in vacuum, and the residue partitioned between ether and water. The ethereal extracts were washed with water, then extracted four times with sodium hydroxide solution (5% aqueous). The combined basic

extracts were acidified, cooled, and extracted with ether. The ethereal extracts were washed and dried (Na_2SO_4); the solvent was removed in vacuum to yield a pale red oil (21g, 100%) which crystallized on trituration (ether). Recrystallization of the solid material gave the benzyloxy acid (11.6g, 60%) in two crops. Crystallization of a sample of this material from acetone-hexane yielded 7-benzyloxy-1,2,3,4-tetrahydro-2-naphthoic acid as white needles, m.p. 140-141.5° (Found: C, 76.3; H, 6.6. $C_{18}H_{18}O_3$ requires C, 76.6; H, 6.4%). ν_{max} 2600-3100, 1695 (CO_2H), 1610, 1580, 1510 (aromatic C=C stretching), 740, 760cm^{-1} (monosubstituted aromatic ring).

7-Diazoacetyl-5,6,7,8-tetrahydronaphth-2-yl Benzyl Ether (24).

A solution of 7-benzyloxy-1,2,3,4-tetrahydro-2-naphthoic acid (11.6g, 0.041mol) and pyridine (3.3g, 0.042mol) in dry benzene (100ml) was added dropwise during 1 hr to a solution of oxalyl chloride (8.7g, 0.068mol) in dry benzene (250ml) stirred at room temperature. The stirring was continued for a further hour after the addition was completed; then the cooled (10°) solution was filtered, and concentrated in a vacuum to yield a brown oil, ν_{max} (film) 1780cm^{-1}. The brown oil was dissolved in dry benzene (100ml) and added rapidly to an ethereal solution of diazomethane (in large excess), whilst maintaining the temperature below 10°. After 1 hr the solution was warmed to remove residual diazo-

methane, washed with water, dried (Na_2SO_4), and the solvent removed in vacuum. The oily residue (12g) was chromatographed on alumina (240g). Elution of the column with benzene-light petroleum (3:2) gave a pale lemon-yellow oil (9g, 71% yield) which solidified on standing. A sample recrystallized from ether-light petroleum as pale yellow platelets, m.p. 69-70° (Found: C, 74.5; H, 6.05; N, 9.05. $C_{19}H_{18}N_2O_2$ requires C, 74.5; H, 5.9; N, 9.15%). ν_{max} 3050 (C-H stretch of $COCHN_2$), 2140 ($C=N^+=N^-$), 1620 (C=O of $COCHN_2$ and aromatic C=C), 1580, 1510 (aromatic C=C), 700, 740cm^{-1} (monosubstituted benzene). ν_{max} (film) 1635 (C=O, $COCHN_2$), 1610, 1585, and 1510cm^{-1} (aromatic C=C). δ_{max} 7.35 (s, 5H, Ar$\underline{H}$), 6.5-6.9 (m, 3H, Ar$\underline{H}$), 5.25 (s, 1H, CO$\underline{CH}N_2$), 5.0p.p.m. (s, 2H, Ar$\underline{CH_2}$O).

7-Bromoacetyl-5,6,7,8-tetrahydronaphth-2-yl Benzyl Ether (25).

A solution of 7-diazoacetyl-5,6,7,8-tetrahydronaphth-2-yl benzyl ether (8.4g) in ether (250ml) was cooled to 0° and shaken with concentrated hydrobromic acid (15ml, 48% aqueous) until bubbles of nitrogen were no longer evolved (c. 1 min). The lower layer was run off and the ether layer washed with water (2x30ml), saturated sodium bicarbonate solution (1x30ml), and water (2x30ml). The dried (Na_2SO_4) ethereal layer was concentrated in vacuum to yield a light yellow oil (9.8g, 98% crude yield). Chromatography of a sample on silica yielded 7-bromoacetyl-5,6,7,8-tetrahydro-

naphth-2-yl benzyl ether as a colourless oil, ν_{max} (film) 1710 ($COCH_2Br$), 1610, 1590 (aromatic C=C), and 700, 740cm^{-1} (monosubstituted aromatic ring). δ_{max} 3.95 (s, 2H, $COC\underline{H}_2Br$), 5.0 (s, 2H, $ArC\underline{H}_2O$), 6.6-7.0 (m, 3H, Ar$\underline{H}$), 7.35p.p.m. (s, 5H, Ar$\underline{H}$). The oily bromo ketone, although homogeneous by t.l.c., would not crystallize. Brief treatment with zinc dust in acetic acid, however, yielded 7-acetyl-5,6,7,8-tetrahydronaphth-2-yl benzyl ether (25a) as a colourless liquid. The methyl ketone formed a white crystalline semicarbazone derivative, which was recrystallized from methanol, m.p. 167.5-169° (Found: C, 71.5; H, 7.1; N, 12.6. $C_{20}H_{23}N_3O_2$ requires C, 71.2; H, 6.9; N, 12.45%).

7-[(2'-Bromo-1'-hydroxy)ethyl]-5,6,7,8-tetrahydronaphth-2-yl Benzyl Ether (26).

A solution of 7-bromoacetyl-5,6,7,8-tetrahydronaphth-2-yl benzyl ether (9.5g) in absolute ethanol (500ml) was stirred at 30° and treated portionwise with sodium borohydride (5g) whilst maintaining the pH of the solution (determined by using a standardized pH-meter with glass-Calomel electrodes) within the range 7-9 by the dropwise addition of acetic acid. Stirring was continued for ½ hr after the addition of sodium borohydride, then the reaction mixture was poured into dilute hydrochloric acid (1%, aqueous, 100ml), and the ethanol removed under reduced pressure. The gummy residue was partitioned between ether and water, the ethereal layer washed with water and dried

(Na_2SO_4), and the solvent removed under reduced pressure to yield a light yellow oil (8.5g, 89% yield). The oil was dissolved in a small quantity of ether and cooled overnight below 0°. White crystalline bromohydrin (6.0g) was obtained in two crops. Repeated recrystallization (three times for ether-hexane) yielded 7-[(2'-bromo-1'-hydroxy)-ethyl]-5,6,7,8-tetrahydronaphth-2-yl benzyl ether as a colourless crystalline solid, m.p. 75-79° (mixture of diastereomers) (Found: C, 63.3; H, 6.05. $C_{19}H_{21}BrO_2$ requires C, 63.2; H, 5.9%). ν_{max} 3300 (O-H), 1610, 1580 (aromatic C=C), 740 and 700cm^{-1} (monosubstituted aromatic ring). δ_{max} 2.2 (s, 1H, O<u>H</u>), 3.55 (s, 3H, C<u>H</u>(OH)C<u>H</u>$_2$Br), 5.0 (s, 2H, ArC<u>H</u>$_2$O), 6.6-7.0 (m, 3H, Ar<u>H</u>), 7.35p.p.m. (s, 5H, Ar<u>H</u>).

<u>7-[(2'-Bromo-1'-tetrapyranyloxy)ethyl]-5,6,7,8-tetrahydronaphth-2-yl Benzyl Ether (27).</u>

A crystal of p-toluenesulphonic acid was added to a solution of 7-[(2'-bromo-1'-hydroxy)ethyl]-5,6,7,8-tetrahydronaphth-2-yl benzyl ether (4.15g) in purified dihydropyran (10.5g) and the mixture stirred for 1 hr. Solid potassium carbonate (1g) was added, and the mixture diluted with water (50ml). The mixture was extracted with ether, the ethereal extracts washed with water and dried (Na_2SO_4). Removal of solvent in vacuum yielded a pale yellow viscous oil (5.2g, quantitative yield) which showed no hydroxyl absorption in the infrared. Chromatography of the oil on

silica gel (150g) yielded, on elution of the column with benzene-light petroleum (4:1), the required tetrahydropyranyl ether (4.61g, 90%) as a colourless oil which was homogeneous on t.l.c. and showed ν_{max} (film) 1610, 1585, 1515 (aromatic C=C), 740 and 700cm^{-1} (monosubstituted aromatic ring). The non-crystallinity was ascribed to diastereoisomerism in the terahydropyranyl moiety, and the compound was not characterized further, but converted into the corresponding phenol (14).

7-[(2'-Bromo-1'-tetrahydropyranyloxy)ethyl]-5,6,7,8-tetrahydronaphth-2-ol (14).

A solution of 7-[(2'-bromo-1'-tetrahydropyranyloxy)-ethyl]-5,6,7,8-tetrahydronaphth-2-yl benzyl ether (3.91g) in ethyl acetate (100ml) was added to 5% palladium on charcoal (0.4g), and the mixture stirred at room temperature in an atmosphere of hydrogen. Uptake of hydrogen (300ml) ceased after 8 hr, and the reaction mixture was filtered through Celite and the solvent removed in vacuum to yield a colourless glass (3.2g, 100% crude yield). The mixture was chromatographed on Florisil (100g). Elution with benzene yielded the pure phenol (2.8g, 90%) as a clear glass. ν_{max} (film) 3300 (O-H); 1610, 1590cm^{-1} (aromatic (C=C), homogeneous by t.l.c.

Epimeric Mixture of 5,6,7,8-Tetrahydro-6-tetrahydropyranyloxy-4a,7-ethanonaphthalen-2(4aH)-ones (28) and (29).

A solution of pure 7-[(2'-bromo-1'-tetrahydropyranyloxy)ethyl]-5,6,7,8-tetrahydronaphth-2-ol (14) (1.36g, 0.0038mol) in carefully dried t-butyl alcohol (220ml) was degassed, and warmed with potassium t-butoxide (0.64g, 0.0057mol) at 80° for 5 hr in an atmosphere of nitrogen. The reaction mixture was evaporated to a small volume in vacuum and added to water (50ml). The mixture was extracted with ether (3x50ml) and the ethereal extracts washed and dried (Na_2SO_4). Removal of solvent under reduced pressure gave a light yellow oil (1.13g). ν_{max} (film) 3300, 1660, 1620, 1605cm^{-1}, which was separated into two homogeneous fractions by preparative thin-layer chromatography (silica gel, 20% ether in benzene). The higher R_F material (51%) was indistinguishable (t.l.c., i.r. spectra) from starting material, but on recycling in t-butyl alcohol-potassium t-butoxide afforded no cyclic material. The lower R_F material (47%), obtained as a colourless oil, proved to be a 3:1 epimeric dienone mixture of (28) and (29); ν_{max} ($CHCl_3$) 1655, 1625, 1600cm^{-1} (dienone). δ_{max} 6.67 (d, ¼H, J 10 Hz, epimer (29) COCH=CH), 6.62 (d, ¾H, J 10 Hz, epimer (28) COCH=CH), 6.14 (m, 2H, >C=CHCOCH=CH), 4.60 (e, 1H, -CH(O-)O-), 3.7p.p.m. (e, 3H, >CHO-).

Epimeric Mixture of 5,6,7,8-Tetrahydro-6-hydroxy-4a,7-ethanonaphthalen-2(4aH)-ones (12) and (13).

(A) A solution of the tetrahydropyranyl ether mixture (28) and (29) (0.135g) in acetone (5ml) was added to dilute hydrochloric acid (15ml, 10%). The mixture was kept at room temperature for 1.5 hr, diluted with water, and extracted with chloroform (3x30ml). The combined chloroform extracts were washed with water, dried (Na_2SO_4), and the solvent removed, leaving a white solid (85mg, 91%). Recrystallization from acetone-hexane gave material, m.p. 124-126°. ν_{max} (film) 3320 (OH), 1650, 1615, 1580cm^{-1} (dienone). λ_{max} 247nm (ε 12,200). δ_{max} 6.65 (d, ½H, J 10 Hz, epimer (13) COCH=C<u>H</u>), 6.62 (d, ¾H, J 10 Hz, epimer (12) COCH=C<u>H</u>), 6.15 (m, 2H, CH=C<u>H</u>COC<u>H</u>=C<), 4.05p.p.m. (e, 1H, >C<u>H</u>OH).

(B) The dienedione (11) (165mg, 0.0088mol) was dissolved in ethanol (10ml) and the solution cooled to 10°. Sodium borohydride (30mg, 0.0079mol) was added with swirling and the mixture left for 2 hr at room temperature. Acetone (2ml) was added to the mixture, then dilute hydrochloric acid (10ml, 5% aqueous) and the resultant mixture extracted with chloroform (6x20ml). The organic layers were washed with saturated brine (2x10ml), dried (Na_2SO_4), and the solvent removed in vacuum to yield a light pink gum (135mg, 82%) which crystallized on standing. A sample crystallized from acetone-hexane as white needles,

m.p. 122-132° (Found: C, 75.95; H, 7.4. $C_{12}H_{14}O_2$ requires C, 75.75; H, 7.4%). ν_{max} 3230 (O-H), 1650, 1615, 1590cm^{-1} (dienone). λ_{max} 247nm (ε13,400). δ_{max} 6.65 (d, 0.6H, J 10 Hz, epimer (13) COCH=C<u>H</u>), 6.62 (d, 0.4H, J 10 Hz, epimer (12) COCH=C<u>H</u>), 6.15 (m, 2H, CH=C<u>H</u>COC<u>H</u>=C<), 4.05p.p.m. (e, 1H, >C<u>H</u>OH).

<u>7,8-Dihydro-4a,7-ethanonaphthalene-2,6(4aH,5H)-dione (11).</u>

(A) The hydroxy dienone mixture (12)+(13) was dissolved in acetone (15ml) and cooled to -15° in an aqueous acetone-dry-ice bath. Jones reagent (0.1ml) was added to the stirred solution which was then left for 20 min. The reaction mixture was quenched (isopropyl alcohol, 1 drop), diluted with water, and extracted with ether (3x30ml). The ethereal extracts were washed, dried (Na_2SO_4), and the solvent removed in vacuum to yield a white crystalline solid (25mg, 42%). A sample recrystallized from acetone-hexane gave 7,8-dihydro-4a,7-ethanonaphthalene-2,6(4aH,5H)-dione as white needles, m.p. 113-114° (Found: C, 76.75; H, 6.6. $C_{12}H_{12}O_2$ requires C, 76.6; H, 6.45%). ν_{max} 1720 (C6 carbonyl), 1660, 1630, 1600cm^{-1} (dienone). λ_{max} 243nm (ε14,800). δ_{max} 6.7 (d, 1H, $J_{3,4}$ 10 Hz, C4-<u>H</u>), 6.17 (d of d, 1H, $J_{3,4}$ 10 Hz, $J_{1,3}$ 1.7 Hz, C3-<u>H</u>), 6.17p.p.m. (d of t, 1H, $J_{1,8}$ 1.8 Hz, $J_{1,3}$ 1.7 Hz, C1-<u>H</u>).

(B) To a solution of 7-diazoacetyl-5,6,7,8-tetrahydronaphth-2-ol (1.2g) in freshly distilled anhydrous

nitromethane (500ml) was added boron trifluoride etherate (c. 8 drops). This was stirred at room temperature (with exclusion of moisture) for 3 hr. To the reaction mixture was added saturated aqueous sodium bicarbonate solution (10ml) and the mixture stirred at room temperature for 10 min. The solution was reduced in vacuum to a small bulk, diluted with ethyl acetate, and shaken with water. The organic layer was extracted with dilute aqueous sodium hydroxide (5%, 3x25ml), washed with water, and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield a light yellow crystalline solid (0.33g, 32% yield). Sublimation (120°/0.005mm) yielded 7,8-dihydro-4a,7-ethanonaphthalene-2,6(4aH,5H)-dione as a colourless solid (0.31g, 30%).

7-Acetoxy-1,2,3,4-tetrahydronaphth-2-oic Acid (33).

A mixture of 1,2,3,4-tetrahydro-7-hydroxynaphth-2-oic acid (1g, 0.0052mol), sodium acetate (1g, anhydrous, 0.0122mol), and acetic anhydride (7ml) was heated on a steam-bath for 1 hr with exclusion of moisture. The mixture was cooled (35°) and water (10ml) added dropwise with swirling whilst keeping the temperature below 50° (by controlling the rate of addition). The mixture was diluted with chloroform (100ml), the chloroform layer washed with water (3x15ml), dried (Na_2SO_4), and solvent removed in vacuum to give a white solid (1.31g, 100%). Crystallization from ethyl

acetate gave 7-acetoxy-1,2,3,4-tetrahydronaphth-2-oic acid as white needles, m.p. 124-126° (Found: C,66.7; H, 6.0. $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.0%). ν_{max} 2650-3100 (CO_2H), 1750 ($ArOCOCH_3$), 1700cm^{-1} (CO_2H).

7-Diazoacetyl-5,6,7,8-tetrahydronaphth-2-yl Acetate (34).

To a stirred solution of oxalyl chloride (4g, 0.031 mol) in dry benzene (70ml) was added dropwise during 1 hr at room temperature, a solution of 7-acetoxy-1,2,3,4-tetrahydronaphth-2-oic acid (4.7g, 0.020mol) and pyridine (1.59g, 0.020mol) in dry benzene (100ml). The reaction mixture was stirred a further 1 hr at room temperature and filtered. The solvent and excess oxalyl chloride were removed in vacuum. The oily acid chloride was dissolved in dry benzene (40ml) and added dropwise during 15 min to a cold, well-stirred ethereal solution of diazomethane (from 20g of N-nitrosomethylurea). The mixture was stirred for 1 hr; it was then evaporated to a small bulk (hood) to remove excess diazomethane. The remaining solvent was removed in vacuum to yield a brown-yellow oil (5.9g, 100%). Chromatography on Florisil (120g) and elution with light petroleum and ether-light petroleum (1:20) yielded 7-chloroacetyl-5,6,7,8-tetrahydronaphth-2-yl acetate as a colourless, pungent oil (0.38g). Further elution with ether-light petroleum (1:10) yielded 7-diazoacetyl-5,6,7,8-tetrahydronaphth-2-yl acetate (c. 0.5g). Continued elution

with ether-light petroleum (1:5 and 2:5) yielded a mixture of the acetoxy-diazo-ketone and the phenolic diazo-ketone (31) (4.5g) produced by basic hydrolysis during chromatography. 7-Diazoacetyl-5,6,7,8-tetrahydronaphth-2-yl acetate crystallized from ether as yellow needles, m.p. 98.5-100° (Found: C, 65.1; H, 5.6; N, 10.8. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.45; N, 10.85%). ν_{max} 2140 ($C=N^+=N^-$), 1740 (C=O of acetate), 1640cm^{-1} (C=O of diazo ketone).

7-Diazoacetyl-5,6,7,8-tetrahydronaphth-2-ol (31).

The mixture of diazo ketones (4.5g) obtained in the previous experiment was dissolved in methanol (120ml). To this stirred solution at room temperature was added a suspension of aqueous sodium carbonate-bicarbonate (40ml water, 4.2g Na_2CO_3, 1g $NaHCO_3$, pH c. 10) and the mixture stirred at room temperature for 2hr. The mixture was diluted with water, cooled with ice chips, and ice-cold dilute oxalic acid solution (aqueous) added until pH 7. The mixture was extracted with ether, the ethereal extracts washed with water, and dried (Na_2SO_4). Removal of solvent yielded a yellow crystalline solid (3.6g, 83% yield from acetoxy acid). A sample crystallized from ethyl acetate gave 7-diazoacetyl-5,6,7,8-tetrahydronaphth-2-ol as pale yellow needles, m.p. 125-127° (dec.) (Found: C, 66.75; H, 5.55; N, 14.7. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 14.8%). ν_{max} (film) 3200 (OH), 2140 ($C=N^+=N^-$), 1620cm^{-1} (C=O of $COCHN_2$).

PART II

(a) Synthesis of the Diazoketones (38)-(42).

The five diazoketones (38)-(42) were prepared in a similar manner. The preparation of p-hydroxyphenyl diazomethyl ketone (38) n=3 is described in detail. The sequences of reactions leading to the remaining diazo ketones (39)-(42) are described in brief unless the method differs significantly from that normally employed. The nomenclature employed for the diazomethyl ketones in this section was chosen for reasons of clarity.

p-Acetoxybenzoic Acid (45) n=3.

A mixture of p-hydroxybenzoic acid (9g) and anhydrous sodium acetate (9g) in acetic anhydride (70ml) was warmed on the water bath with occasional swirling during one hour. Water was added dropwise to the cooled (room temperature) mixture at such a rate so as to maintain the temperature below 60°. When all the acetic anhydride had been consumed the solution was diluted further with water (200ml), the mixture extracted with chloroform (2x150ml) and the chloroform extracts washed with water (3x40ml) and dried (Na_2SO_4). The dried extracts were concentrated "in vacuo", to yield p-acetoxybenzoic acid (45) (11.0g, 94%) as a white crystalline solid m.p. 185-187° (lit.[226] m.p. 187°).

p-Acetoxyphenyl Diazomethyl Ketone (46) n=3.

A suspension of p-acetoxybenzoic acid (8g, 0.045mol) and dry pyridine (3.6g, 0.046mol) inanhydrous benzene (60ml) was added dropwise to a well stirred solution of oxalyl chloride (9.5g, 0.074mol) in dry benzene (50ml) at room temperature. The mixture was stirred for a further half an hour, filtered to remove pyridine hydrochloride, and the solvent and excess oxalyl chloride removed "in vacuo". The oily acid chloride was dissolved in benzene (40ml) and added dropwise with stirring to an ice-cold solution of ethereal diazomethane (large excess). After two hours the solvent was removed (hood), to yield the crude acetoxy-diazo ketone as a yellow solid, (12g, crude, containing solvent). Recrystallisation from ether-methylene chloride gave p-acetoxyphenyl diazomethyl ketone (46) n=3 (8g, 88%) as bright yellow needles, m.p. 108-109° (Found: C, 58.81; H, 3.91; N, 13.51. $C_{10}H_8O_3N_2$ requires C, 58.82; H, 3.95; N, 13.72%). ν_{max} 2130 ($C=N^+=N^-$), 1750 (C=O of acetate), 1610cm^{-1} (C=O of diazo ketone).

p-Hydroxyphenyl Diazomethyl Ketone (38) n=3.

p-Acetoxyphenyl diazomethyl ketone (46) n=3 (1.3g) was dissolved in methanol (25ml) and treated with a solution of sodium carbonate (1.3g) and sodium bicarbonate (1.5g) in water (15ml). The mixture was stirred for one hour at room temperature, then poured into ice water (200ml). The

cold solution was adjusted to pH 7-8 by the careful addition of cold dilute aqueous oxalic acid, the mixture was then extracted twice with ether (2x50ml). The ethereal extracts were washed with water (2x10ml) and dried (Na_2SO_4) and the solvent removed "in vacuo" to yield the phenolic diazo ketone as a yellow solid (0.95g, 92%). Recrystallisation from ethyl acetate gave p-hydroxyphenyl diazomethyl ketone (38) (0.73g, 71%) as yellow needles, m.p. 145-150°, (decomp.) (Found: C, 59.00; H, 3.69; N, 17.02. $C_8H_6O_2N_2$ requires C, 59.26; H, 3.73; N, 17.28%). ν_{max} 3200 (O-H), 2140 ($C=N^+=N^-$), 1610cm^{-1} (C=O of diazoketone). δ_{max} 7.3 [d, (A_2B_2), 2H, J 8 Hz, Ar-H, (ortho to diazoacetyl group)], 6.5 [d, (A_2B_2), 2H, J 8 Hz, Ar-H (meta to diazoacetyl group)], 5.8p.p.m. (s, 1H, Ar-COCHN$_2$).

p-Hydroxyphenylacetic Acid (44) n=4.

Commercial p-methoxyphenylacetic acid (20g) and anhydrous pyridine hydrochloride (53g) were heated at 210° in an atmosphere of nitrogen for three hours. The cooled reaction mixture was dissolved in water and extracted with ether. The ethereal extracts were washed with dilute hydrochloric acid (10% aqueous) and water and dried (Na_2SO_4). The solvent was removed "in vacuo" to yield p-hydroxyphenylacetic acid (43) n=3 (17.0g, 92% crude) as a white crystalline solid, m.p. 151-152° (lit.[227] m.p. 147-149°) ν_{max} 3200-2600, 1700cm^{-1}.

p-Acetoxyphenylacetic Acid (45) n=4.

This acid was prepared from the acid (44) n=4 by the general method already described for p-acetoxybenzoic acid (45) n=3, and was obtained in quantitative yield as a white crystalline solid, m.p. 106-107° (lit.[228] m.p. 108°) ν_{max} 3200-2600, 1740 (C=O of acetate), 1700cm^{-1}.

p-Acetoxybenzyl Diazomethyl Ketone (46) n=4.

This compound was prepared from the acid (45) n=4 by the general method described for p-acetoxyphenyl diazomethyl ketone (46) n=3, and was obtained as a brown viscous oil in quantitative yield. Purification by column chromatography (Florisil) afforded p-acetoxyphenyl diazomethyl ketone (46) n=4 as a light yellow viscous oil, ν_{max} (film) 2130 (C=N$^+$=N$^-$), 1750 (C=O of acetate), 1640cm^{-1} (C=O of -COCHN$_2$). δ_{max} 2.30 (s, 3H, OCOCH$_3$), 3.65 (s, 2H, Ar-CH$_2$-CO), 5.20 (s, 1H, COCHN$_2$), 7.0-7.4p.p.m. (m, 4H, Ar-H).

p-Hydroxybenzyl Diazomethyl Ketone (39) n=4.

This compound was prepared from the diazoketone (46) n=4 by the general method described for p-hydroxyphenyl diazomethyl ketone (38) n=3, and was obtained as a dark red oil (94%, crude), which crystallised on trituration (ether). This afforded a buff coloured solid (50%), while further quantities of diazoketone could be obtained by chromatography (Florisil) of the mother liquors. Recrystallisation or

chromatography afforded p-hydroxybenzyl diazomethyl ketone (39) n=4 as lemon coloured crystals, m.p. 98-99° (Found: C, 61.35; H, 4.74; N, 15.65. $C_9H_8O_2N_2$ requires C, 61.36; H, 4.58; N, 15.90%). ν_{max} 3300 (O-H), 2120 ($C=N^+=N^-$), 1625cm^{-1} (C=O of $COCHN_2$).

β-(p-Methoxyphenyl)-propionic Acid (43) n=5.

This compound was prepared by hydrogenation of p-methoxycinnamic acid; the crude product was obtained as a white crystalline solid, m.p. 100-103° (lit.[229] m.p. 104-105°) and was converted to the acid (44) n=5 without further purification.

β-(p-Hydroxyphenyl)-propionic Acid (44) n=5.

This compound was prepared from the acid (43) n=5 by the general method already described for acid (44) n=4; the crude product was obtained in quantitative yield as a white crystalline solid m.p. 125-127° (lit.[230] m.p. 129-130°).

β-(p-Acetoxyphenyl)-propionic Acid (45) n=5.

This compound was prepared from the acid (44) n=5 by the method described for the preparation of the acid (45) n=3, and was obtained in quantitative yield as a white crystalline solid. ν_{max} 1750 (C=O of acetate), 1710cm^{-1} (CO_2H). This product was used without purification.

2-(p-Acetoxyphenyl)ethyl Diazomethyl Ketone (46) n=5.

This compound was prepared from the acid (45) n=5 by the method described for the diazoketone (46) n=3, and was obtained in quantitative yield as a pale yellow crystalline solid. Recrystallisation from ether afforded 2-(p-acetoxyphenyl)ethyl diazomethyl ketone (46) n=5 (62%) as a yellow crystalline solid, m.p. 106-107° (Found: C, 61.96; H, 5.38. $C_{12}H_{12}O_3N_2$ requires C, 62.06; H, 5.21%). ν_{max} 2120 ($C=N^+=N^-$), 1740 (C=O of acetate), 1645cm^{-1} (C=O of $COCHN_2$). δ_{max} 2.2 (s, 3H, $OCOCH_3$), 2.75 (m, 4H, $Ar-CH_2-CH_2-COCHN_2$), 5.2 (s, 1H, $COCHN_2$), 7.05p.p.m. (q, A_2B_2, 4H, J_{AB} 9 Hz Ar-H).

2-(p-Hydroxyphenyl)ethyl Diazomethyl Ketone (40) n=5.

This compound was prepared from the diazoketone (46) n=5 by the method described for the diazoketone (38) n=3 and was obtained in quantitative yield as a viscous yellow oil. Chromatography on alumina afforded 2-(p-hydroxyphenyl)ethyl diazomethyl ketone (40) n=5 (homogeneous by t.l.c.) as a light yellow oil, ν_{max} (film) 3300 (O-H), 2130 ($C=N^+=N^-$), 1620cm^{-1} (C=O of $COCHN_2$). δ_{max} 2.75 (m, 4H, $Ar-CH_2-CH_2-COCHN_2$), 5.2 (s, 1H, $COCHN_2$), 5.7 (s, 1H, Ar-OH), 6.90p.p.m. (q, A_2B_2, 4H, J_{AB} 8 Hz, Ar-H).

β-(p-Methoxybenzoyl)-propionic Acid.

This compound was prepared by a modification of the

literature procedures;[231,232] it crystallised from water as white needles (87%), m.p. 146-148° (lit.[231] m.p. 147-148°).

γ-(p-Methoxyphenyl)-butyric Acid (43) n=6.

This compound was prepared from β-(p-methoxybenzoyl)-propionic acid by the Martin modification[48] of the Clemmensen reduction. The acid (43) n=6 crystallised from petroleum ether (b.p. 60-80°) as white needles, m.p. 57-59° (lit.[48] m.p. 60-61°) in 90% yield.

γ-(p-Hydroxyphenyl)-butyric Acid (44) n=6.

This compound was prepared from the corresponding acid (43) n=6 by the method described for the acid (44) n=4 and was obtained as white flakes (97% crude), m.p. 105-107° (lit.[233] m.p. 110-111°).

γ-(p-Acetoxyphenyl)-butyric Acid (45) n=6.

This compound was prepared from the corresponding acid (44) n=5 by the method described for the acid (45) n=3, and was obtained in 80% yield as a colourless liquid b.p. 170-172°/0.7mm (lit.[234] b.p. 163-164°/0.5mm) which crystallised to a white solid on standing.

3-(p-Acetoxyphenyl)propyl Diazomethyl Ketone (46) n=6.

This compound was prepared from the corresponding

acid (45) n=6 by the method described for the diazoketone (46) n=3, and was obtained in quantitative yield (crude) as a yellow oil. Column chromatography afforded 3-(p-acetoxyphenyl)propyl diazomethyl ketone (46) n=6 (homogeneous by t.l.c.) as a light yellow oil, ν_{max} (film) 2130 ($C=N^+=N^-$), 1750 (C=O of acetate), 1640cm^{-1} (C=O of $COCHN_2$). δ_{max} 2.3 (s, 3H, $OCOCH_3$), 5.2 (s, 1H, $COCHN_2$), 7.10p.p.m. (q, A_2B_2, 4H, J_{AB} 8 Hz, Ar-H).

3-(p-Hydroxyphenyl)propyl Diazomethyl Ketone (41) n=6.

This compound was prepared from the corresponding diazoketone (46) n=6 by the method described for diazoketone (38) n=3, and was obtained as a yellow oil in 80% overall yield from the acid (45) n=6. Column chromatography (alumina) afforded 3-(p-hydroxyphenyl)propyl diazomethyl ketone (41) n=6 as a light yellow viscous oil, (homogeneous on t.l.c.), ν_{max} (film) 3300 (O-H), 2130 ($C=N^+=N^-$), 1620cm^{-1} (C=O of $COCHN_2$). δ_{max} 5.25 (s, 1H, $COCHN_2$), 6.95p.p.m. (q, A_2B_2, 4H, J_{AB} 8 Hz, Ar-H).

γ-(p-Methoxybenzoyl)-butyric Acid.

This compound was prepared by a modification of the literature procedures,[235,236] and crystallised from ethanol as cream platelets, m.p. 138-139° (lit.[233] m.p. 138-139°) in 90% yield.

δ-(p-Methoxyphenyl)-valeric Acid (43) n=7.

This compound was prepared from the corresponding acid by the Martin modification[48] of the Clemmensen reduction, and crystallised from acetone-hexane as white platelets (85%) m.p. 111-113° (lit.[237,235] m.p. 114-114.5°, 113-114°).

δ-(p-Hydroxyphenyl)-valeric Acid (44) n=7.

This compound was prepared from the corresponding acid (43) n=7 by the method described for the acid (44) n=4, and was obtained in quantitative yield, m.p. 116-118° (lit.[238] m.p. 117-119°).

δ-(p-Acetoxyphenyl)-valeric Acid (45) n=7.

This compound was prepared from the corresponding acid (44) n=7 by the method described for acid (45) n=3, and was obtained as a white solid in quantitative yield. Crystallisation of a sample from ether afforded δ-(p-acetoxyphenyl)-valeric acid (45) n=7 as white needles, m.p. 92-93° (Found: C, 66.35; H, 6.69. $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.83%). ν_{max} 3200-2650 ($-CO_2H$), 1750 (C=O of acetate), 1700cm^{-1} (C=O of $-CO_2H$).

4-(p-Acetoxyphenyl)butyl Diazomethyl Ketone (46) n=7.

This compound was prepared from the corresponding acid (45) n=7 by the method described for the diazoketone

(46) n=3 and was obtained in quantitative yield as a yellow oil. Column chromatography (Florisil) afforded 4-(p-acetoxyphenyl)butyl diazomethyl ketone (46) n=7 as a homogeneous (t.l.c.) yellow oil. ν_{max} (film) 2130 ($C=N^+=N^-$), 1750 (C=O of acetate), 1640cm^{-1} (C=O of $-COCHN_2$). δ_{max} 2.25 (s, 3H, $OCOCH_3$), 5.2 (s, 1H, $COCHN_2$), 7.1p.p.m. (q, A_2B_2, 4H, J_{AB} 9 Hz, Ar-H).

4-(p-Hydroxyphenyl)butyl Diazomethyl Ketone (42) n=7.

This compound was prepared from the corresponding diazoketone (46) n=7 by the method described for the diazoketone (38) n=3, and was obtained in 75% overall yield from δ-(p-acetoxyphenyl)-valeric acid as a light yellow oil. Chromatography on alumina afforded 4-(p-hydroxyphenyl)butyl diazomethyl ketone (42) n=7 as a homogeneous (t.l.c.) light yellow oil. ν_{max} (film) 3300 (O-H), 2130 ($C=N^+=N^-$), 1620cm^{-1} (C=O of $COCHN_2$). δ_{max} 1.6 (m, 4H, $-CH_2-CH_2-CH_2-CH_2-$), 2.45 (m, 4H, $Ar-CH_2-$, $-CH_2-CO$), 5.25 (s, 1H, $COCHN_2$), 6.9p.p.m. (q, A_2B_2, 4H, J_{AB} 8 Hz, Ar-H).

(b) Alkylation Reactions of the Diazoketones (38)-(42).

As all alkylation reactions were conducted under essentially identical conditions, a detailed account of the experimental procedure for the reaction of the diazoketone (38) n=3 is presented, however, the purification and identification of the various products is described in detail as the methods varied according to the nature of the compounds.

(i) Reaction of p-Hydroxyphenyl Diazomethyl Ketone (38) n=3.

To a vigorously stirred solution of the diazoketone (38) (1.65g) in anhydrous nitromethane (150ml) under an atmosphere of dry nitrogen was added boron trifluoride etherate (c. 5 drops). Stirring was continued for a further fifteen minutes (during which a vigorous evolution of nitrogen was observed), then diluted with water (25ml) and stirred for an additional five minutes. The reaction mixture was then diluted with brine solution (200ml) and extracted with ethyl acetate (3x100ml). The combined organic extracts were washed with brine (2x50ml) and water (2x30ml) and dried (Na_2SO_4). Removal of solvent gave a light orange solid (1.35g, 81%) which was homogeneous by t.l.c. A sample recrystallised from ethyl acetate afforded p-hydroxyphenacyl alcohol (54) as light pink prisms, m.p. 170-171° (lit.[111] m.p. 170-172°). ν_{max} 3430 (O-H), 3250 (O-H), 1670 (C=O of $ArCOCH_2OH$), 1610, 1590cm^{-1} (aromatic C=C). δ_{max} (DMSO-d_6), 4.25 (e, $W_{\frac{1}{2}}$ 16 Hz, 1H, CH_2-O<u>H</u>), 4.7 (s, 2H,

$COCH_2OH$), 6.9 (d, A_2B_2, 2H, J_{AB} 9 Hz, 3,5-Ar-H), 7.85 (d, A_2B_2, 2H, J_{AB} 9 Hz, 2,6-Ar-H), 10.15p.p.m. (s, 1H, Ar-OH). Sublimation afforded a colourless crystalline sample, but did not alter the melting point. The infra-red spectrum of the crude mixture and that of the purified product were essentially identical.

(ii) Reaction of p-Hydroxybenzyl Diazomethyl Ketone (39) n=4.

A solution of the diazoketone (39) (1.0g) in dry nitromethane was treated with boron trifluoride etherate in the manner described for diazoketone (38) n=3. The reaction mixture was worked-up in the normal manner and afforded a dark brown oil (900mg), ν_{max} (film) 33-3400, 1785, 1700-1735, 1655, 1620 and 1600cm^{-1}, which was chromatographed on Sorbsil. Chloroform-ethyl acetate mixtures (1:50) eluted 5-hydroxyindan-2-one (67) (200mg) as a white crystalline solid. Recrystallisation of a sample from ether afforded white prisms, m.p. 182-184° dec. (Found: C, 72.56; H, 5.48. $C_9H_8O_2$ requires C, 72.96; H, 5.44%). ν_{max} 3300 (O-H), 1735 (C=O), 1620, 1580cm^{-1} (aromatic C=C). δ_{max} 3.4-3.9 (m, 4H, $-CH_2-CO-CH_2-$), 5.8 (e, 1H, Ar-OH), 6.6-7.2p.p.m. (m, 3H, Ar-H).

Further elution with ethyl acetate-chloroform (1:9) afforded p-hydroxybenzyl hydroxymethyl ketone (68) (410mg) as a white crystalline solid. A sample crystallised from

ethyl acetate as white needles, m.p. 70-72°. (Found: C, 64.94; H, 6.11. $C_9H_{10}O_3$ requires C, 65.05; H, 6.07%). ν_{max} 33-3400 (O-H), 1710 (C=O), 1610, 1600cm^{-1} (aromatic C=C). δ_{max} ($CDCl_3$, DMSO-d_6), 3.6 (s, 2H, Ar-C<u>H</u>$_2$-CO-), 4.1 (broad s, $W_{\frac{1}{2}}$ 6 Hz, 2H, COC<u>H</u>$_2$OH), 5.0 (t, poorly resolved, 1H, CH$_2$O<u>H</u>), 6.8 (q, A_2B_2, 4H, J_{AB} 9 Hz, Ar-<u>H</u>), 9.05p.p.m. (s, 1H, Ar-O<u>H</u>). When the sample was shaken with D_2O the resonances formerly observed at δ5.0 and δ9.05 were no longer visible.

<u>Isolation of Spiro[3,5]nona-5,8-diene-2,7-dione (66).</u>

A stirred solution of diazoketone (39) (200mg) in dry nitromethane (15ml) was treated with boron trifluoride etherate (2 drops), and worked up after thirty minutes. The infra-red spectrum of the product displayed strong absorption bands at 1785 and 1660cm^{-1}. Preparative thick layer chromatography, using ethyl acetate-methylene chloride (1:2) as the developing solvent, afforded spiro-3,5 nona-5,8-diene-2,7-dione (66) (30mg) as a colourless liquid. ν_{max} ($CHCl_3$ solution) 1785 (cyclobutanone C=O), 1660, 1625cm^{-1} (dienone). δ_{max} 3.40 (s, 4H-C<u>H</u>$_2$-CO-C<u>H</u>$_2$-), 6.4 (d, 2H, J 10.4 Hz, C6-<u>H</u>, & C8-<u>H</u>), 7.15p.p.m. (d, 2H, J 10.4 Hz, C5-<u>H</u> & C9-<u>H</u>). The dienone (66) was extremely labile, and even in the presence of traces of acid rearranged rapidly to the corresponding indanone (67).

Rearrangement of Spirodienedione (66).

The spirodienedione (66) (c. 30mg) was dissolved in nitromethane (5ml), treated with one drop of boron trifluoride etherate and stirred for half an hour. Work-up in the normal way afforded a yellow oil which solidified on standing. T.l.c. and comparison of infra-red spectra indicated that only indanone (67) was present.

Isolation of Spiro[3,5]nona-2,7-dione (69).

A sample of diazoketone (39) (5.8g, crude) was treated with boron trifluoride in the usual manner. The reaction mixture after work-up in the normal way gave a dark red oil (5.9g) ν_{max} (film) 1785, 1660cm^{-1} (*inter alia*). The oil was dissolved in ethyl acetate (100ml) and shaken in an atmosphere of hydrogen (2 atm.) with palladium on carbon catalyst (5%, 0.5g) for several hours. The solution was filtered (celite), and the solvent removed "*in vacuo*" to yield a dark red gum (5.9g). The red gum (5.0g), dissolved in ethyl acetate-chloroform, was filtered quickly through a short column of Florisil; removal of solvent afforded a light yellow viscous oil (1.7g). Chromatography of the yellow oil (1.0g) on alumina, and elution with benzene afforded a colourless oil (90mg) ν_{max} (film) 1780, 1710cm^{-1}, which crystallised on standing. Sublimation (80°/0.1mm) of this material afforded a white solid, m.p. 54-56° which on recrystallisation from ether-light petrol afforded pure

spiro[3,5]nona-2,7-dione (69) as white needles, m.p. 57-58° (Found: C, 70.79; H, 7.95. $C_9H_{12}O_2$ requires C, 71.02; H, 7.95%). ν_{max} 1770 (cyclobutanone C=O), 1700cm^{-1} (cyclohexanone C=O). δ_{max} 2.0-2.5 (2xt, partly resolved, 8H, C-H of cyclohexanone), 3.0p.p.m. (s, 4H, -CH$_2$-CO-CH$_2$-, cyclobutane). Mass spectrum: m/e 152 (M^+) ($C_9H_{12}O_2$, M.W. =152).

Measurement of Percentage Aryl Participation.

As the indanone (67) and the spirodienedione (66) proved sensitive to oxidation and rearrangement respectively, a procedure involving direct isolation would be expected to give a biased result, consequently the diazoketone (39) was allowed to react with boron trifluoride etherate, until indanone (67) and ketone (68) were the sole products; the ratio of these two products in the mixture was then determined by integration of the appropriate resonances in the n.m.r. spectrum of the total product mixture. This method was applicable to all four diazoketones (39)-(42). With the product mixtures from diazoketones (41) and (42), removal of polymeric material by preliminary column chromatography was possible due to the stability of the products. Preparative t.l.c. was used to purify the reaction mixture from the diazoketone (39), consequently the experimental value for aryl participation may be slightly less than the actual degree of aryl participation in this case. The product

mixture derived from the diazoketone (40) contained a β-tetralone (72) and was extremely sensitive to oxidation, hence measurements in this system were conducted directly on the crude reaction mixture. A description of the method is given for the diazoketone (39).

Measurement of Ar_1-4 Participation.

The diazoketone (39) (130mg) was dissolved in dry nitromethane (3ml) and treated at room temperature with boron trifluoride etherate (1 drop). The mixture was stirred at room temperature for one hour, then worked-up in the usual manner to yield a product mixture (110mg) which contained no residual diazoketone (39) or dienedione (66) (by t.l.c. and infra-red). Preparative t.l.c. (solvent system, ethyl acetate-methylene chloride, 1:1) afforded 60mg of material which was dissolved in a mixture of dimethyl sulphoxide-d_6 and deuterochloroform. Integration of the appropriate resonances in the n.m.r. spectrum afforded a value of $56\pm5\%$ Ar_1-4 participation.

$$\% \text{ Aryl participation} = \frac{\text{Total yield of bicyclic product} \times 100}{\text{Total yield of monomeric products}}$$

As the method for the determination of the % aryl participation was essentially the same in the other cases, it will not be duplicated in the experimental section.

(iii) Reaction of 2-(p-Hydroxyphenyl)ethyl Diazomethyl Ketone (40) n=5.

A solution of the diazoketone (40) n=5 (1.0g) in nitromethane was treated with boron trifluoride (5 drops) in the usual way; work-up in the normal manner afforded a red oil (900mg) which was chromatographed on Sorbsil (20g). Chloroform eluted spiro[4,5]deca-6,9-diene-2,8-dione (70) as a white crystalline solid (320mg). A sample crystallised from ether-light petroleum (b.p. 30-40°) as white fluffy needles, m.p. 72-74° (lit.[69] m.p. 74°) ν_{max} 1735 (saturated C=O), 1665, 1625cm^{-1} (dienone) δ_{max} 2.2-2.6 (m, 6H, -C$\underline{H}_2$-CO-C$\underline{H}_2$-C$\underline{H}_2$-), 6.3 (d, 2H, J 10.4 Hz, C7-$\underline{H}$, C9-$\underline{H}$), 6.95p.p.m. (d, 2H, J 10.4 Hz, C6-$\underline{H}$, C10-$\underline{H}$).

Ethyl acetate-chloroform mixtures eluted 2-(p-hydroxyphenyl)ethyl hydroxymethyl ketone (71) as a white crystalline solid (185mg) which crystallised from ether as white needles, m.p. 113-114°. (Found: C, 66.42; H, 6.77. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71%) ν_{max} 33-3400 (O-H), 1710cm^{-1} (C=O). δ_{max} 2.7-3.2 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-), 4.2 (d, poorly resolved, J ~ 4 Hz, 2H, -CO-C$\underline{H}_2$-OH), 6.9 (q, A_2B_2, 4H, J_{AB} 8 Hz, Ar-$\underline{H}$).

Isolation of 6-Hydroxytetral-2-one (72).

Diazoketone (40) (0.55g) was treated with boron trifluoride etherate in the normal manner but left to stir overnight. The reaction mixture when worked-up in the normal manner afforded a red brown gum (0.53g). Preparative

t.l.c. afforded 2-(p-hydroxyphenyl)ethyl hydroxymethyl ketone (c. 150mg) as a white solid, and 6-hydroxytetral-2-one (72) (90mg) as a light brown solid. Crystallisation from deoxygenated solvents eventually afforded a white waxy solid, m.p. 140-146, (decomp). ν_{max} 3300 (O-H), 1705cm^{-1} (C=O) δ_{max} 2.4-2.7 (m, 2H), 2.8-3.1 (m, 2H), 3.6 (s, 2H, Ar-C$\underline{H}_2$-CO-), 6.6-7.2p.p.m. (m, 3H, Ar-$\underline{H}$). This ketone was rapidly oxidised in air; correct analytical figures could not be obtained.

Rearrangement of Dienedione (70).

A solution of the crystalline dienedione (70) (90mg) in nitromethane (10ml) was treated with boron trifluoride etherate (3 drops) and stirred at room temperature for five hours. T.l.c. indicated that no dienedione (70) was present. Work-up in the normal manner afforded a brown solid (90mg) which was dissolved in benzene (25ml). Ethylene glycol (300mg) and a catalytic quantity of p-toluenesulphonic acid were added to the solution, which was deoxygenated, then heated under reflux in an atmosphere of nitrogen. When an aliquot afforded a negative tetralone blue test (two hours), the solution was cooled, diluted with water, and extracted with ether (2x30ml). The combined organic extracts were washed with dilute sodium bicarbonate solution (½% aqueous, 1x5ml), with water, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a light red oil (95mg)

whose infra-red spectrum displayed no absorption bands in the region 1650-1750cm^{-1}. The red oil (95mg) was dissolved in anhydrous acetone (4ml) and treated with anhydrous potassium carbonate (150mg), and methyl iodide (300mg) and the solution carefully deoxygenated by the passage of a slow stream of dry nitrogen. The mixture was refluxed overnight, then cooled and poured into water and extracted with ether (2x20ml). The ether extracts were washed with water and dried (Na_2SO_4) and concentrated "in vacuo" to yield a light yellow liquid (95mg). T.l.c. indicated that no starting material was present. The mixture was dissolved in benzene and filtered through a short column of alumina (1.8g). Removal of the solvent afforded a colourless oil (66mg), whose n.m.r. and infra-red spectra were identical with those of a sample of the authentic methoxy-ketal (74). The two samples possessed identical retention times by g.l.p.c. under a variety of conditions. The n.m.r. spectra of the methoxy-ketals (74) and (75) were sufficiently dissimilar in the region δ 6.4-7.0p.p.m. to enable the detection of $\geq$ 4% of ketal (75) in the presence of ketal (74). No trace of the ketal (75) could be detected in the sample above.

2,2-Ethylenedioxy-1,2,3,4-tetrahydro-6-methoxynaphthalene (74).

A solution of 6-methoxytetral-2-one (1.0g), ethylene glycol (1.6g), and p-toluenesulphonic acid (5mg) in benzene

(70ml) was deoxygenated and then heated under reflux until an aliquot afforded a negative tetralone blue test (one hour). The solution was cooled, treated with solid potassium carbonate (20mg), and diluted with water. The mixture was extracted with benzene (2x30ml) and the combined organic extracts washed with water (2x20ml) and dried (Na_2SO_4). The solvent was removed "in vacuo", and the residual light yellow oil was dissolved in light petroleum and filtered through a column of alumina (12g). Removal of the solvent afforded 2,2-ethylenedioxy-1,2,3,4-tetrahydro-6-methoxynaphthalene (74) (1.03g, 82%) as a colourless liquid, b.p. 125-130°/0.2mm. (Found: C, 70.65; H, 7.37. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%) ν_{max} (film) 1610, 1580 (aromatic C=C), 815cm^{-1}. δ 1.8 (t, 2H, J 7 Hz, Ar-CH_2-CH_2-), 2.85 (t+s, 4H, Ar-CH_2-C(O)O-, Ar-CH_2-CH_2-), 3.70 (s, 3H, -OCH_3), 3.90p.p.m. (s, 4H, -O-CH_2-CH_2-O-). The resonances ascribed to the aromatic protons are described in Hz for ease of comparison with those of the ketal (75). Aromatic resonances: m, 3H, 388, 390, 394, 396, 403, 406, and 412 Hz downfield from tetramethylsilane.

2,2-Ethylenedioxy-1,2,3,4-tetrahydro-7-methoxynaphthalene (75).

Commercially available 2,7-dihydroxynaphthalene was methylated by the procedure of Horrom and Zaugg.[239] 2,7-Dimethoxynaphthalene crystallised from methanol as

cream platelets, m.p. 136-138° (lit.[240] m.p. 139°). This compound was reduced by the method of Cornforth et al[241] using sodium in alcohol, and afforded a light yellow liquid enol ether, ν_{max} (film) 1675, 1640cm^{-1}. A solution of the enol ether (3.28g) and ethylene glycol (5g) in anhydrous benzene (150ml) was treated with a catalytic quantity of p-toluenesulphonic acid and heated under reflux for two hours. The cooled reaction mixture was treated with solid potassium carbonate (10mg), diluted with water, and extracted with benzene (2x50ml). The combined organic extracts were washed with water (2x20ml), dried (Na_2SO_4) and the solvent removed "in vacuo" to yield a light red liquid which was dissolved in petroleum ether and filtered through alumina (100g). Removal of the solvent from the combined eluates afforded 2,2-ethylenedioxy-1,2,3,4-tetrahydro-7-methoxynaphthalene (75) as a colourless liquid, b.p. 125-130°/0.2mm. (Found: C, 70.62; H, 7.49. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%). ν_{max} (film) 1610, 1580 (aromatic C=C), 840cm^{-1}. δ_{max} 1.8 (t, 2H, J 7 Hz, Ar-CH_2-$\underline{CH}_2$-), 2.85 (t&s, 4H, Ar-$\underline{CH}_2$-C(O)O-, Ar-$\underline{CH}_2$-CH_2), 3.70 (s, 3H, O$\underline{CH}_3$), 3.90p.p.m. (s, 4H, -O-$\underline{CH}_2$-$\underline{CH}_2$-O-). Aromatic resonances: m, 3H, 387, 395, 397, 410, 415 and 417 Hz downfield from tetramethylsilane. G.l.p.c. analysis under a variety of conditions showed a single peak of retention time identical to that of the isomeric ketal (74).

Aryl$_1$-5 Participation Measurement.

The measurements were conducted in the manner described for the diazoketone (39) n=4.

(iv) Reaction of 3-(p-Hydroxyphenyl)propyl Diazomethyl Ketone (41) n=6.

A solution of the diazoketone (41) n=6 (1.2g) in nitromethane was treated with boron trifluoride etherate in the normal way; work up in the usual manner afforded a brown yellow oil (1.03g) which was chromatographed on Sorbsil (29g). Elution with ethyl acetate-chloroform (1:50) afforded a light yellow oil (94mg). Further elution with ethyl acetate-chloroform (1:10) afforded 3-(p-hydroxyphenyl)-propyl hydroxymethyl ketone (76) (758mg) which crystallised from ether as white needles, m.p. 86-87°. (Found: C, 67.89; H, 7.12. $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.27%). ν_{max} 3300 (O-H), 1705 (C=O), 1610, 1595cm^{-1} (aromatic C=C). δ_{max} 4.2 (s, broad, $W_{\frac{1}{2}}$ 6 Hz, 2H, $COC\underline{H}_2OH$), 6.9p.p.m. (q, A_2B_2, 4H, J_{AB} 9 Hz, Ar-$\underline{H}$).

The oil (94mg) from the initial fractions from the column appeared to contain a mixture of the spirodienedione (77) and the benzocycloheptanone (78). ν_{max} (film) 1705-1710 (cyclohexanone and cycloheptanone C=O), 1660, 1620 (dienone), 1600 (aromatic C=C) δ_{max} 3.65 (s, Ar-$C\underline{H}_2$-CO), 6.5 (d, J 12 Hz, 2X-CO-C$\underline{H}$=CH-). Partial separation of the two compounds was achieved by preparative t.l.c. The com-

pounds were not characterised further. On the assumption that no other products were present, calculation afforded a value of 11% for Ar_1-6 participation.

(v) Reaction of 4-(p-Hydroxyphenyl)butyl Diazomethyl Ketone (42) n=7.

A solution of diazoketone (42) n=7 (1.8g) in nitromethane was treated with boron trifluoride etherate in the normal way; work up in the usual manner gave a light yellow oil (1.6g) which was chromatographed on Sorbsil (40g). Elution of the column with ethyl acetate-chloroform (1:50) afforded a light yellow oil (92mg). Further elution with ethyl acetate-chloroform (1:20, 1:10) afforded 4-(p-hydroxyphenyl)butyl hydroxymethyl ketone (79) as a white solid (1.03g). A sample recrystallised from ether had m.p. 95.5-97°. (Found: C, 69.27; H, 7.82. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74%) ν_{max} 33-3400 (O-H), 1715 (C=O), 1610, 1595cm^{-1} (aromatic C=C). δ_{max} 4.2 (s, 2H, $COCH_2OH$), 6.85 (q, A_2B_2, 4H, J_{AB} 8 Hz, Ar-H).

Examination of the yellow oil (92mg) by spectroscopic methods revealed the presence of two compounds, one of which was probably the chloromethyl ketone δ_{max} 4.35 (s, $COCH_2$-Cl) corresponding to the hydroxymethyl ketone (79). A resonance at δ 3.65 (s, Ar-CH_2-CO-) suggested that the other component was the benzocycloöctanone (81), [ν_{max} (film) 1720cm^{-1}]. These compounds could not be separated by pre-

parative t.l.c. and were not characterised further. Calculation on the basis of these assumptions affords a value of 3% Ar_1-7 participation.

3-(p-Methoxyphenyl)propan-1-ol.

Reduction of β-(p-methoxyphenyl)-propionic acid (43) n=5 with lithium aluminium hydride by the conventional procedure afforded 3-(p-methoxyphenyl)propan-1-ol as a colourless liquid, b.p. 168-169°/20mm (lit.[242] b.p. 133-134°/4mm) in 90% yield. The alcohol had a melting point near room temperature, and g.l.p.c. analysis showed a single peak.

p-Nitrobenzenesulphonate Ester of 3-(p-methoxyphenyl)propan-1-ol (106).

A solution of the corresponding alcohol (700mg) in dry pryidine (2ml) was cooled in ice and treated dropwise with a precooled solution of p-nitrobenzenesulphonyl chloride (1g, m.p. 76-77°) in pyridine (4ml). The mixture was stirred and cooled during the addition (five minutes). The mixture was allowed to stand at 0° for forty minutes, then water (0.2ml) was added and the mixture allowed to stand for an additional fifteen minutes. The mixture was then poured onto ice with stirring, and the light yellow precipitate collected and dried. Crystallisation of a sample (1g) from ether at -78° afforded the sulphonate ester (106) (700mg) as pale yellow platelets, m.p. 89.5-90°. (Found: C, 54.55; H, 4.84;

N, 3.76; S, 9.1. $C_{16}H_{17}NO_6S$ requires C, 54.69; H, 4.86; N, 3.99; S, 9.13%) δ_{max} (trifluoroacetic acid as solvent and T.M.S. capillary) 2.0 (m, 2H, Ar-CH_2-CH_2-CH_2-O-), 2.65 (t, 2H, J 6 Hz, Ar-CH_2-), 3.95 (s, 3H, OCH_3), 4.25 (t, 2H, 6 Hz, -CH_2-O-), 7.0 (q, A_2B_2, 4H, J_{AB} 9 Hz, MeO-Ar-H), 8.3p.p.m. (q, A_2B_2, 4H, J_{AB} 9 Hz, NO_2-Ar-H).

5-Methoxyindane (108).

This compound[243] was prepared from 5-methoxyindan-1-one (130) (see experimental, Part III) by the Martin modification[48] of the Clemmensen reduction, in 95% yield as a sweet smelling liquid. ν_{max} (film) 1610, 1585cm^{-1} (aromatic C=C), no absorption band in the region 1615-1800cm^{-1}. δ_{max} 2.05 (m, 2H, -CH_2-CH_2-CH_2-), 2.85 (2xt, 4H, 2xAr-CH_2-), 3.7 (s, 3H, -OCH_3), 6.65 (m, 2H, C_4-H, C_6-H), 7.0p.p.m. (d, 1H, J 8 Hz, C_7-H). The crude product was homogeneous by g.l.p.c.

Trifluoroacetolysis of the Sulphonate Ester (106).

Dry trifluoroacetic acid was prepared by the conventional procedure,[95] and treated with one percent by weight of redistilled trifluoroacetic anhydride. Anhydrous sodium trifluoroacetate was added until the solution was 0.056 molar in sodium trifluoroacetate; this stock solution was employed for solvolyses.

The sulphonate ester (106) (69mg, 0.196 mmol) was dissolved in stock solution (5ml, 0.270mmol of sodium tri-

fluoroacetate), and heated overnight at 90° in a sealed ampoule. The cooled ampoule was broken open and the reaction poured into water and extracted with ether (2x20ml). The ethereal extracts were washed with sodium bicarbonate solution (1% aqueous, 2x10ml), and water, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residual oil analysed by g.l.p.c. Comparison with authentic 5-methoxyindane (108) showed that this compound was not present in the mixture. A sample after filtration through a short silica column showed ν_{max} (film) 33-3400 (O-H), 1630 (C=C), 1610, 1580cm^{-1} (aromatic C=C) δ_{max} 3.8 (s, $OC\underline{H}_3$), 7.0p.p.m. (q, A_2B_2, J_{AB} 9 Hz, Ar-$\underline{H}$). These data are compatible with the presence of a mixture of olefins and trifluoroacetates, but as none of the indane (108) was present, the analysis was not pursued further.

β-(p-Hydroxyphenyl)propionitrile (110).

This compound was prepared by the method of Johnston and Gross[178] in 65% yield, and was obtained as a light yellow oil, b.p. 162-167°/1.5mm (lit.[178] b.p. 157-163°/1.0mm) which crystallised on standing. Crystallisation of a sample from ether-light petroleum afforded a colourless crystalline solid, m.p. 54-56° (lit.[178] m.p. 58-59°). ν_{max} 3350-3400 (O-H), 2250 (C≡N), 1615, 1595cm^{-1} (aromatic C=C). δ_{max} 2.65 (m, A_2B_2, 4H, $-C\underline{H}_2-C\underline{H}_2-$), 6.2 (e, $W_{\frac{1}{2}}$ 9 Hz, 1H, Ar-O$\underline{H}$), 6.90p.p.m. (q, A_2B_2, 4H, J_{AB} 8 Hz, Ar-$\underline{H}$).

3-(p-Hydroxyphenyl)propylamine (111).

This amine proved to be only sparingly soluble in organic solvents, and was most conveniently prepared from the corresponding nitrile (110) by the reduction procedure employed by Barger[244] for the preparation of tyramine. The amine hydrochloride was obtained as a white crystalline solid in 88% yield and crystallised from ethanol-ether as white silky needles, m.p. 156-157°. The amine hydrochloride, on treatment with sodium carbonate (1 equivalent) afforded the phenolic amine as a colourless solid, in quantitative yield. Sublimation (130°/0.02mm) afforded the pure amine as snow white crystals, m.p. 101-102°. (Found: C, 71.64; H, 8.71; N, 9.57. $C_9H_{13}NO$ requires C, 71·49; H, 8.67; N, 9.26%) δ_{max} (DMSO-d_6), 1.6 (m, 2H, $-CH_2-\underline{CH}_2-CH_2-$), 6.8p.p.m. (q, A_2B_2, 4H, J_{AB} 9 Hz Ar-$\underline{H}$). Mass spectrum: m/e 151 ($M^{\ddagger}$) ($C_9H_{13}NO$, mw=151).

5-Hydroxyindane (113).

This compound was prepared by demethylating 5-methoxyindane (108) with hydrobromic and acetic acid by the standard procedure.[52] The crude product was chromatographed on Sorbsil; petroleum ether-benzene (1:1) eluted the indanol (113) as a colourless liquid which solidified on standing. Two recrystallisations from light-petroleum (b.p. 30-40°) afforded colourless platelets m.p. 52-53° (lit.[245] m.p. 55°) ν_{max} 33-3400 (O-H), 1610, 1595cm^{-1} (aromatic C=C).

Deamination of 3-(p-Hydroxyphenyl)propylamine (111).

A solution of the amine (111) (151mg, 1mmol) in anhydrous acetonitrile (6ml) was treated with a solution of trifluoroacetic acid (114mg, 1mmol) in acetonitrile (2ml), then with a solution of freshly distilled n-amyl nitrite (150mg) in acetonitrile (2ml) and allowed to stir at room temperature for two hours. The solvent was removed "in vacuo" and the total reaction product examined by n.m.r. spectroscopy. The n.m.r. spectrum was complicated, but no indanol (113) could be detected. The principal products appeared to be a mixture of olefins δ_{max} 2.0 (d, J~4 Hz, C=CH-C$\underline{H}_3$?) ν_{max} 1635cm^{-1} (C=C) and trifluoroacetates. ν_{max} (film) 1785cm^{-1} (C=O of -OCOCF_3) δ_{max} 4.35 (m, -C$\underline{H}_2$-OCOCF_3). The spectrum was complicated by the presence of nitrosation products of the phenol nucleus, but removal of these products substantiated that indanol (113) was not present; the aromatic protons now appeared as a clean quartet. δ_{max} 7.0 (q, A_2B_2, 4H, J_{AB} 8 Hz, Ar-$\underline{H}$).

PART III

Dimethyl Cyclohexanone-2,4-dicarboxylate (118).

This compound was prepared from trimethyl pentan-1,3,5 tricarboxylate by the sodium hydride method of Koehler and co-workers,[190] and was obtained, after fractionation through a 30cm column, as a colourless liquid (6.5%), b.p. 116-118°/0.8mm (lit.[190] b.p. 135-138°/5.0mm) which on standing formed a white crystalline solid, m.p. 39-41° (lit.[190] m.p. 42-43°). The compounds necessary for the preparation of the keto-diester (118) were obtained by the procedure of Koehler *et al*[190] with the exception of 4,4-dicarbomethoxy-pimelonitrile, which was prepared by the method of Bruson and Reiner[246] and was obtained as a white crystalline solid, m.p. 60-62° (lit.[246] m.p. 62°). All compounds exhibited spectral characteristics in accordance with the assigned structures.

Dimethyl 2-(m-Methoxybenzyl)-cyclohexanone-2,4-dicarboxylate (119).

This compound was prepared by alkylation of dimethyl cyclohexanone-2,4-dicarboxylate (118) with m-methoxybenzyl bromide by the standard alkylation procedure of Zaugg *et al*[191] using sodium hydride in dimethylformamide. Distillation of the crude product afforded a colourless viscous liquid, (72%) b.p. 184-190/0.3mm which appeared to be the desired

keto-ester (119), contaminated with traces (<5%) of the oxygen alkylated product. A sample purified by column chromatography (silica gel) afforded the pure keto-diester (119) as a colourless viscous liquid, b.p. 184-190°/0.3mm. (Found: C, 64.55; H, 6.66. $C_{18}H_{22}O_6$ requires C, 64.65; H, 6.63%) ν_{max} (film) 1725-1705 (cyclohexanone and ester C=O), 1600, 1580cm^{-1} (aromatic C=C), δ_{max} 3.6, 3.63 (2xs, 2x3H, 2x-$CO_2C\underline{H}_3$), 3.7 (s, 3H, -$OC\underline{H}_3$), 6.65, 7.05p.p.m. (m, 4H, Ar-$\underline{H}$). The initial distillate was sufficiently pure for the preparation of the acid (120).

Cyclisation of the keto-diester (119).

A solution of the keto-diester (119) (30g) in glacial acetic acid (250ml) was treated with concentrated hydrochloric acid (250ml) and the mixture heated under reflux for five hours.[185] The reaction mixture was cooled, poured into water, and the precipitate collected by filtration and washed free of acid. Crystallisation of the solid from methanol afforded a light yellow crystalline solid (6.0g, sample I). The residue (16g) obtained from the mother liquors was chromatographed on silica gel (340g). Elution with ethyl acetate-chloroform mixtures (1:25-1:10) afforded a further quantity of cream crystalline solid (5.8g, sample II).

Sample I, recrystallised twice from methanol afforded 1,2,3,4-tetrahydro-7-methoxyfluorene-2-carboxylate (120) (3.4g, 15%) as light yellow needles, m.p. 205-209° (lit.[185]

m.p. 213°). (Found: C, 73.83; H, 6.74. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60%) ν_{max} 32-2600 (CO_2H), 1690 (C=O of $-CO_2H$), 1610, 1580cm^{-1} (aromatic C=C) δ_{max} (DMSO-d_6/$CDCl_3$) 3.75 (s, 3H, $-OCH_3$), 6.7-7.2p.p.m. (m, 3H, Ar-H).

A suspension of sample II (5.8g) and dry pyridine (2.0g) in anhydrous benzene (100ml) was added dropwise to a stirred solution of oxalyl chloride (6.0g) in dry benzene (50ml) at room temperature. The mixture was stirred for an additional one hour, and then filtered. The filtrate, and washings (benzene) were concentrated under reduced pressure, to give the corresponding acid chloride(s). ν_{max} (film) 1790cm^{-1}. A solution of the acid chlorides in benzene (50ml) was added to a cooled (10°) solution of pyridine (1.95g) and dry t-butyl alcohol (1.85g) in ether (50ml) and stirred for two hours. The mixture was then refluxed for a further two hours, cooled and diluted with water and then extracted with ether. The combined organic extracts were washed with water and dried (Na_2SO_4), and the solvent removed "in vacuo" to give a light brown oil (6.65g) which was chromatographed on Florisil (140g). Elution of the column with ether-petroleum ether mixtures (1:50) afforded a white crystalline solid (0.97g, ester A), which crystallised from ether as white needles, m.p. 122-122.5°. (Found: C, 75.69; H, 8.21. $C_{19}H_{24}O_3$ requires C, 75.97; H, 8.05%) ν_{max} 1720cm^{-1} (ester C=O), δ_{max} 1.45 (s, 9H, $-C(CH_3)_3$), 3.25 (s, broad, $W_{\frac{1}{2}}$ 6 Hz, 2H, 2xC9-H), 3.85 (s, 3H, $-OCH_3$), 6.7-7.2p.p.m. (m, 3H, Ar-H).

This compound (ester A) was subsequently shown to be t-butyl 1,2,3,4-tetrahydro-7-methoxyfluorene-2-carboxylate (122).

Further elution of the column afforded a semi-crystalline solid (2.0g, mixture of esters A and B) followed by a light yellow crystalline solid (0.78g, ester B) which crystallised from ether-light petroleum as light yellow platelets , m.p. 105-106°. (Found: C, 76.09; H, 7.77. $C_{19}H_{24}O_3$ requires C, 75.97; H, 8.05%) ν_{max} 1720cm^{-1} (ester C=O). δ_{max} 1.45 (s, 9H, -C($\underline{CH}_3$)$_3$), 3.25 (s, broad, $W_{\frac{1}{2}}$ 6 Hz, 2H, 2xC9-$\underline{H}$), 3.85 (s, 3H, -O$\underline{CH}_3$), 6.7-7.2p.p.m. (m, 3H, Ar-$\underline{H}$). The structure of this compound (ester B) has been tentatively assigned as t-butyl 1,2,3,4-tetrahydro-5-methoxy-fluorene-2-carboxylate (123).

1,2,3,4-Tetrahydro-7-methoxyfluorene-2-carboxylate (120).

A solution of ester A (0.28g, m.p. 120-121°), and a crystal of p-toluenesulphonic acid in dry benzene (40ml) was heated under reflux until all the ester was consumed (t.l.c., 3½ hours). The cooled reaction mixture was diluted with ethyl acetate (40ml), washed with water (2x10ml) and dried (Na_2SO_4), and the solvent removed under reduced pressure to yield a light yellow solid (0.22g, 96%). Crystallisation from ethyl acetate afforded light yellow needles, m.p. 205-209° (lit.[185] m.p. 213°) of acid (120), which was identical (m.p.; mixed m.p.; infra-red and n.m.r. spectra) with

that obtained from crystallisation of sample I.

1,2,3,4-Tetrahydro-5-methoxyfluorene-2-carboxylate (121).

A solution of ester B (0.25g, m.p. 104-106°) and a crystal of p-toluenesulphonic acid in dry benzene (40ml) was heated under reflux for three hours, then cooled and diluted with ethyl acetate (40ml). The organic layer was washed with water (2x10ml), dried (Na_2SO_4), and the solvent removed under reduced pressure to yield a yellow solid (0.17g, 84%). Crystallisation of a sample from ethyl acetate afforded golden flakes, m.p. 194-197°. (Found: C, 74.04; H, 6.66. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60%) ν_{max} 3200-2600 ($-CO_2H$), 1690cm^{-1} (C=O of $-CH_2H$). Mixed (with acid (120)) m.p. 180-198°.

Methyl β-(m-Methoxyphenyl)-propionate

This compound was prepared via a standard sequence of reactions from m-methoxybenzaldehyde. m-Methoxycinnamic acid was prepared by the method of Dale and Hennis,[247] and converted to β-(m-methoxyphenyl)-propionic acid by hydrogenation in the presence of a palladium catalyst. This crude acid was a white crystalline solid m.p. 44-46° (lit.[248] m.p. 45°). The acid was converted to the methyl ester by the conventional procedure. Fractional distillation afforded the methyl ester (80% overall yield from m-methoxybenzaldehyde) as a colourless liquid, b.p. 158-160°/20mm (lit.[249]

b.p. 154-156°/16mm) which solidified (lit.[249] m.p. 28-29°) on standing. It had infra-red and n.m.r. spectra in accordance with its structure.

5-Methoxyindan-1-one (130).

This compound was prepared from methyl β-(m-methoxyphenyl)-propionate by polyphosphoric acid-induced cyclisation. The method employed was essentially that of Levshina et al,[250] and afforded the indanone (130) as an amber solid. Crystallisation from ethyl acetate afforded the pure indanone (61%) as white needles, m.p. 107-109° (lit.[248] m.p. 109°). ν_{max} 1695cm^{-1} (indanone C=O).

5-Methoxy-1-vinylindan-1-ol (124).

Vinyl magnesium bromide was prepared from vinyl bromide (37g) and clean magnesium turnings (6g) in dry tetrahydrofuran (40ml) by the normal procedure.[251,252] The preparation was conducted in an atmosphere of dry nitrogen. At the completion of the preparation a further quantity of dry tetrahydrofuran (70ml) was added and the mixture cooled to -35°. To this stirred solution was added dropwise during one hour, a solution of 5-methoxyindan-1-one (12g) in dry tetrahydrofuran (60ml) while maintaining the temperature below -30°. The mixture was vigorously stirred at -20° for a further two hours, allowed to warm to room temperature during three hours, and finally heated at 50° with

stirring for a further twenty minutes. The cooled reaction mixture was poured onto a mixture of ice and ammonium chloride, and extracted with ether. The ethereal extracts were washed several times with water and dried over sodium sulphate. Removal of the solvent under reduced pressure afforded 5-methoxy-1-vinylindan-1-ol (124) (14.2g, quant.) as~light yellow liquid.[198] ν_{max} (film) 3350-3400 (O-H), 1610, 1580cm^{-1} (aromatic C=C), no absorption band at 1695cm^{-1}. δ_{max} 2.25 (m, 2H, 2xC2-H), 2.95 (m, 2H, 2xC3-H), 3.8 (s, 3H, -OCH$_3$), 5.04 and 5.12 (d of d, 1H), 5.10 and 5.22 (d of d, 1H) ($J_{geminal}$ 2 Hz, J_{cis} 10 Hz, J_{trans} 18 Hz, 2xC2'-H, vinyl protons), 5.92, 6.08, 6.20, 6.38 (d of d, 1H, J_{cis} 10 Hz, J_{trans} 18 Hz, C1'-H), 6.8 (m, 2H, C4-H, C6-H), 7.18p.p.m. (d, 1H, J 9 Hz, C7-H). Attempted purification of the alcohol by distillation led to dehydration and polymerisation, however the crude alcohol was satisfactory for the preparation of the diene (125).

6-Methoxy-3-vinylindene (125).

A solution of the carbinol (124) (9.9g) in benzene (500ml) was treated with quinoline (c. 0.5ml) and a solution of iodine in benzene (30ml, ½% w:v), and the mixture heated under reflux for thirty minutes with the removal of water. The cooled reaction mixture was washed with water, then with sodium thiosulphate solution (2x20ml, 5% aqueous) and again with water, and dried (Na_2SO_4). Removal of the solvent

"in vacuo" gave the diene (125) contaminated with a small amount of quinoline. The diene was obtained as a light yellow liquid ν_{max} (film) 1615, 1580 (aromatic C=C), 920cm^{-1} (=CH_2), no absorption band in the region 31-3600cm^{-1}. δ_{max} 3.25 (d, partly resolved, 2H, 2xCl-H), 3.7 (s, 3H, -OCH_3), 5.15, 5.35 (d of d, 1H), 5.55, 5.85 (d of d, 1H) ($J_{geminal}$ 2 Hz, J_{trans} 18 Hz, J_{cis} 10 Hz, 2xC2'-H, i.e. -CH=CH_2), 7.4p.p.m. (d, 1H, J 8 Hz, C4-H). The remainder of the aromatic and vinylic protons gave a complex set of resonances in the region 6.2-7.0p.p.m. which could not be satisfactorily assigned, but integrated satisfactorily for four protons.

Preparation of the tricyclic nitrile (127).

The crude diene (125) from the preceding preparation was dissolved in acrylonitrile (50ml), the mixture was freed of oxygen and then heated with stirring (100°), for four hours. The cooled reaction mixture was concentrated "in vacuo" to yield a pink solid (12.2g, containing a trace of acrylonitrile) which was dissolved in methylene chloride (500ml) and treated briefly with dry hydrogen chloride gas. The reaction mixture was extracted with dilute hydrochloric acid (3x20ml, 10% aqueous) and the organic layer washed with sodium bicarbonate solution (2x10ml, 1% aqueous), and water (2x20ml). The dried (Na_2SO_4) extracts were concentrated "in vacuo" to afford a crystalline solid (9.8g). Crystallisation of the solid from ethyl acetate afforded 2-cyano-

1,2,3,4-tetrahydro-7-methoxyfluorene (127) (6.0g, 54% overall yield from the indanone (130)) as white needles, m.p. 145-146° (Found: C, 80.16; H, 6.78; N, 6.26. $C_{15}H_{15}ON$ requires C, 79.97; H, 6.71; N, 6.22%) ν_{max} 2240 (C≡N), 1620, 1580 (aromatic C=C), 1040cm^{-1} (O-CH_3). δ_{max} 3.24 (s, $W_{\frac{1}{2}}$ 7 Hz, 2H, 2xC9-H), 3.82 (s, 3H, -OCH_3), 6.7-7.3p.p.m. (m, 3H, Ar-H).

The residue (3.46g) obtained from the mother liquors, afforded after filtration through alumina (55g), light pink crystalline material (2.8g) which appeared to contain dimer (131) and further quantities of the nitrile (127).

When the iodine catalyst was not removed prior to the addition of acrylonitrile, silica gel chromatography of the resultant reaction mixture normally afforded, besides the nitrile (127), variable quantities of a yellow crystalline material. Crystallisation of a sample of this material from ethyl acetate afforded the dimer (131) as light yellow platelets, m.p. 155-156° (Found: C, 84.02; H, 7.09. $C_{24}H_{24}O_2$ requires C, 83.69; H, 7.02%) ν_{max} 1610, 1580 (aromatic C=C), 1040cm^{-1} (O-CH_3) δ_{max} 3.3 (s, $W_{\frac{1}{2}}$ 6 Hz, 4H, benzylic protons), 3.8 (s, 6H, 2x-OCH_3), 6.1 (t, poorly resolved, 1H, -CH_2-CH=), 6.7-7.2p.p.m. (m, 6H, Ar-H).

Hydrolysis of the nitrile (127).

A solution of the nitrile (127) (7.8g) in acetic acid (100ml) was treated with concentrated hydrochloric

acid (55ml) and heated under reflux for two hours. The warm solution was treated with water (50ml), cooled in ice, and the crystals collected by filtration and dried. The crude acid (6.02g, 72%), had m.p. 199-203°. Crystallisation of a sample from ethyl acetate afforded pale yellow needles, m.p. 206-210° (lit.[185] m.p. 213°). This material was identical (m.p.; mixed m.p.; infra-red and n.m.r. spectra) with acid (120) obtained from the cyclisation of the keto-diester (119).

1,2,3,4,9,10-Hexahydro-7-methoxyphenanthrene-1-carboxylic acid (116).

A solution of the diene (129) in benzene was allowed to react with ethyl acrylate according to the method of Hajos, Parrish and Goldberg.[195] The mixture of esters obtained was hydrolysed by the literature procedure[195] and the solid acids (c. 45%) isolated and dried. The mixture of acids was dissolved in methylene chloride and treated with dry hydrogen chloride, and worked up in the normal manner. This procedure afforded a mixture of $\Delta^{4a,10a}$ (an n.m.r. spectrum of the mixture showed no resonance for a C4 olefinic proton) acids (51g) which was fractionally crystallised from acetone, and gave firstly 1,2,3,4,9,10-hexahydro-7-methoxyphenanthrene-2-carboxylic acid (137), (32.3g) as faintly yellow crystals, m.p. 185-187° (lit.[253] m.p. 184-188°). Concentration of the mother liquors afforded

1,2,3,4,9,10-hexahydro-7-methoxyphenanthrene-1-carboxylic acid (116) (15.6g) as white needles, m.p. 145-150°. A sample recrystallised from acetone afforded the pure acid (116) as white needles, m.p. 147-151°. (Found: C, 74.50; H, 7.23. $C_{16}H_{18}O_3$ requires C, 74.39; H, 7.02%) ν_{max} 3300-2600 (CO_2H), 1690 (C=O of CO_2H), 1610, 1585 (aromatic C=C), 1045 (O-CH_3), 885 and 820cm^{-1}. δ_{max} 3.73 (s, 3H, -OC$\underline{H}_3$), 6.6 (m, 2H, C6-$\underline{H}$, C8-$\underline{H}$), 7.05p.p.m. (d, 1H, J 9 Hz, C5-$\underline{H}$). Mass spectrum: m/e 258 ($M^{\ddagger}$) ($C_{16}H_{18}O_3$, m.w.=258).

2-Diazoacetyl-1,2,3,4-tetrahydro-7-methoxyfluorene (114).

A solution of the acid (120) (3g) in methylene chloride (40ml) was added dropwise with stirring to a solution of oxalyl chloride (2.7g) in methylene chloride (40ml). The mixture was stirred at room temperature for several hours, then the solvent and excess oxalyl chloride were removed under reduced pressure. The crude acid chloride, ν_{max} (film) 1790cm^{-1}, was dissolved in anhydrous methylene chloride (20ml), and added dropwise with stirring to a large excess of ethereal diazomethane. The mixture was stirred at 0° for thirty minutes, then allowed to warm to room temperature. Removal of the solvent (hood) afforded a yellow oil which was chromatographed on alumina (60g); elution with benzene afforded the diazoketone (114) (3.2g, 97%) as a pale yellow solid. Crystallisation of a sample from ether afforded pale yellow crystals, m.p. 96-98°

(lit.[185] m.p. 103°) ν_{max} 2120 ($C=N^+=N^-$), 1635 (C=O of $-COCHN_2$), 1620 (shoulder) and 1580cm^{-1} (aromatic C=C) δ_{max} 3.2 (s, $W_{\frac{1}{2}}$ 7 Hz, 2H, 2xC9-H), 3.8 (s, 3H, $-OCH_3$), 5.3 (s, 1H, $COCHN_2$), 6.7-7.2p.p.m. (m, 3H, Ar-H).

1-Diazoacetyl-1,2,3,4,9,10-hexahydro-7-methoxyphenanthrene (117).

A solution of the acid (116) (3.0g) in dry methylene chloride (60ml) was added dropwise and with stirring to a solution of oxalyl chloride (3.0g) in methylene chloride (30ml). The mixture was heated under reflux for one hour, and the solvent and excess oxalyl chloride were removed "in vacuo". The crude acid chloride, ν_{max} 1790cm^{-1}, was dissolved in methylene chloride (20ml) and added dropwise and with stirring to an ice-cold solution of ethereal diazomethane (in large excess). The mixture was stirred for two hours, and then concentrated to small bulk and filtered through celite. Removal of the solvent gave a yellow oil (3.7g) which was chromatographed on Florisil (100g). Elution with benzene-petroleum ether (1:3) mixtures yielded the solid diazoketone (2.38g, 73%). Crystallisation of a sample from ether afforded analytically pure 1-diazoacetyl-1,2,3,4,9,10-hexahydro-7-methoxyphenanthrene (117) as yellow prisms, m.p. 95.5-96.5° (Found: C, 72.29; H, 6.51; N, 9.80. $C_{17}H_{18}N_2O_2$ requires C, 72.32; H, 6.43; N, 9.92%). ν_{max} 2140 ($C=N^+=N^-$), 1630 (C=O of $COCHN_2$), 1610, 1580cm^{-1} (aromatic

C=C). δ_{max} 3.72 (s, 3H, $-OC\underline{H}_3$), 5.35 (s, 1H, $COC\underline{H}N_2$), 6.58 (m, 2H, C6-$\underline{H}$, C8-$\underline{H}$), 7.05 (d, 1H, J 9 Hz, C5-$\underline{H}$).

Cyclisation of the Diazoketone (117).

A solution of the crystalline diazoketone (117) (197mg) in anhydrous methylene chloride (2ml) was added quickly to a vigorously stirred solution of ice-cold trifluoroacetic acid (6ml), and stirred under an atmosphere of dry nitrogen for three minutes. The mixture was diluted with methylene chloride (50ml) and poured into water (30ml). The organic layer was washed with water (2x10ml) and dried (Na_2SO_4) and the solvent removed "in vacuo" to yield a light yellow crystalline solid (175mg, 99%). Column chromatography (Florisil) or crystallisation (ether) afforded 1,2,3,9,10,10a-hexahydro-7-methoxy-1β,10aβ-ethano-phenanthrene-12-one (138) as a snow white crystalline solid, m.p. 124-126° (Found: C, 80.11; H, 7.43. $C_{17}H_{18}O_2$ requires C, 80.28; H, 7.13%). ν_{max} 1765 (C=O of cyclobutanone), 1635 (C=C), 1600, 1585 (aromatic C=C), 1040 (O-CH_3), 885, 830cm^{-1}. δ_{max} 3.8 (s, 3H, $-OC\underline{H}_3$), 6.27 (t, 1H, J 5 Hz, C4-$\underline{H}$), 6.6-6.9 (m, 2H, C6-$\underline{H}$, C8-$\underline{H}$), 7.5p.p.m. (d, 1H, J 8 Hz, C5-$\underline{H}$). Mass spectrum: m/e 254 ($M^{\cdot+}$) ($C_{17}H_{18}O_2$, m.w.=254).

Under these reaction conditions, ketone (138) was the only product which could be detected. When the diazoketone (117) was dissolved in methylene chloride and to this solution was added trifluoroacetic acid, the crude product

obtained after work-up in the normal manner contained a second product. The infra-red spectrum of the crude product now exhibited extra, but weak absorption bands at 1790 and 1720cm^{-1}. The n.m.r. spectrum of the crude product exhibited a weak singlet resonance at δ 5.15p.p.m., (s, $COC\underline{H}_2OCOCF_3$) which has been attributed to the presence of the ketone (139). Integration of the appropriate resonances in the n.m.r. spectrum of this sample indicated the presence of 8%$\pm$2% of the ketone (139).

Cyclisation of the Diazoketone (114).

A solution of the crystalline diazoketone (114) (204mg) in anhydrous methylene chloride (2ml) was added quickly to a vigorously stirred solution of ice-cold trifluoroacetic acid (6ml), and the mixture stirred under an atmosphere of dry nitrogen for three minutes. The reaction mixture was diluted with methylene chloride (60ml) and worked-up in the manner described for the previous example. This afforded a light yellow crystalline solid (182mg, quant.) which on crystallisation from ether yielded 2-methoxygibb-1,3,4a,4b-tetraene-8-one (115) as pale yellow crystals, m.p. 124-125° (lit.[185] m.p. 128°) ν_{max} 1735 (C=O of cyclopentanone), 1605, 1580 (aromatic C=C), 1050cm^{-1} (O-CH_3). δ_{max} 3.8 (s, 3H, $OC\underline{H}_3$), 5.65 (t, poorly resolved, 1H, C5-$\underline{H}$), 6.75 (m, 2H, C1-$\underline{H}$, C3-$\underline{H}$), 7.25p.p.m. (d, 1H, J 9 Hz, C4-$\underline{H}$).

When diazoketone (114) was treated with trifluoro-

acetic acid by the inverse addition method described for diazoketone (117), a second product was also formed. The infra-red spectrum (ν_{max} 1790, 1720cm^{-1}) and the n.m.r. spectrum[δ_{max} 5.0p.p.m. (s, $COCH_2OCOCF_3$)] of the crude product both suggested the presence of the ketone (142) in the mixture. Integration of the appropriate resonances in the n.m.r. spectrum of this sample indicated the presence of 5%$\pm$2% of the ketone (142).

APPENDIX

Application of the Franklin group equivalent method to the calculation of total strain energy.

Total strain energy is defined as

ΔH_f° (exp) - ΔH_f° (s.f.)

where ΔH_f° (exp) = heat of formation of the real molecule

ΔH_f° (s.f.) = heat of formation of the hypothetical strain free molecule

(1) $5C + 4H_2 \longrightarrow$ methylenecyclopentane. $\Delta H = \Delta H_f^{\circ}$ (1)

(2) $5C + 5H_2 \longrightarrow$ methylcyclopentane. $\Delta H = \Delta H_f^{\circ}$ (2)

(3) methylenecyclopentane + $H_2 \longrightarrow$ methylcyclopentane. $\Delta H = \Delta H_h$

(a) Heat of formation of methylenecyclopentane

now

ΔH_f° (1) = heat of formation of methylenecyclopentane

ΔH_f° (2) = heat of formation of methylcyclopentane

ΔH_h = heat of hydrogenation of methylenecyclopentane

It is clear that

$$\Delta H_f^{\circ} (2) - \Delta H_h = \Delta H_f^{\circ} (1)$$

Now both ΔH_h and ΔH_f° (2) have been determined experimentally,[163,164] or in the case of the latter can be calculated with a reasonable degree of accuracy.[162,164]

$\therefore$ ΔH_f° (l) can be calculated from experimental values

ΔH_f° (2) = -25.5 k. cal. mole^{-1} (ref. 163)

ΔH_h = -26.9 k. cal. mole^{-1} (ref. 164)

$\therefore$ ΔH_f° (l) (experimental) = +1.4 k. cal. mole^{-1}

(b) Heat of formation of "strain free" methylenecyclopentane

The heats of formation of the strain free assemblies of atomic groupings in methylenecyclopentane can be calculated by the Franklin group equivalent method.[162,164]

ΔH_f° (l) (strain free) = calculated heat of formation for the hypothetical, strain free methylenecyclopentane.

4 x $-CH_2-$	=	4 x -4.926	= -19.704
1 x $>C=CH_2$	=	1 x 16.890	= +16.890

ΔH_f° (l) (s.f.) = -2.8 k. cal. mole^{-1}

$\therefore$ ΔH_f° (l) (exp) - ΔH_f° (l) (s.f.) = +4.2 k. cal. mole^{-1}

(c) Calculation by the group equivalent method, affords a value of -24.9 k. cal. mole^{-1} for ΔH_f° (2). This figure

leads to a value of +4.8 k. cal. mole^{-1} for the strain energy.

$\therefore$ Total ring strain energy of methylenecyclopentane

$= 4.5 \pm 0.3$ k. cal. mole^{-1}

N.B. Reference 164 contains several errors.

Methylenecyclobutane in lines 28 and 39 should read Methylcyclobutane.

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