"APPROACHES TO THE SYNTHESIS OF PHTHALIDEISQUINOLINES AND SYNTHESIS AND HYDROBORATION OF BENZOCYCLENE OXIDES"

A Thesis

Presented for the Degree of

Doctor of Philosophy

in

The University of Adelaide

by

Philip Andrew Marshall, B.Sc. (Hons)

Department of Organic Chemistry

1978

CONTENTS

CONTENTS

SUMMARY

Part I of this thesis is concerned with approaches to the synthesis of analogues of the biologically active alkaloid, bicuculline. The most promising route involved an acid-catalyzed condensation between a phthaldehydic acid electrophile and an indan-2-one to form the key intermediate 1-(3 phthalidyl)-indan-2-one. Considerable difficulty was encountered, however, in rearranging this ketone to the desired 1-(3 phthalidyl)-isoquinoline using either the Beckmann or Schmidt reaction, although the Schmidt was successful in the absence of substituents. The syntheses of a number of phthalideketones by this method are described.

Part II deals with the syntheses and reactions of benzocyclene oxides with diborane in tetrahydrofuran at 25°, in order to probe the stereochemical and electronic influences on the mode and direction of oxirane ring opening. It was shown that simple disubstituted epoxides cleaved preferentiall *via* the more stable incipient carbonium ion. If the oxirane ring bore a methyl group on the benzylic position, then elimination of hydrogen was the preferred reaction pathway and 1,3-diols were obtained after mild oxidation. The hydroboration of benzocyclenes is also examined and finally, a comparison between hydroboration and other cycloadditions to olefins is briefly discussed.

STATEMENT

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University and that, to the best of my knowledge and belief, the thesis contains no material previously published or written by another person except when due reference is made in the text.

P. A. Marshall

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to my supervisor, Dr R.H. Prager, for his guidance, enthusiasm and encouragement during his supervision of this work. In addition, I would like to extend my thanks to the following people: Dr A.D. Ward for his supervision while Dr Prager was on study leave, Dr G.E. Gream and Dr T.M. Spotswood for some rewarding discussions and to some other staff members and colleagues in the Department for advice and encouragement.

I also wish to express my appreciation of the understanding and tolerance shown by my family and friends.

Finally, this research was carried out during the tenure of a Commonwealth Postgraduate Research Award, which I gratefully acknowledge.

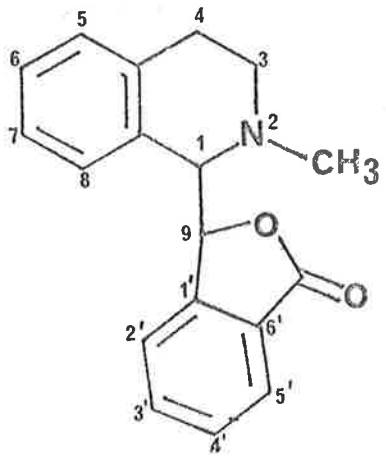
PART I

"APPROACHES TO THE SYNTHESIS OF PHTHALIDEISQUINOLINES"

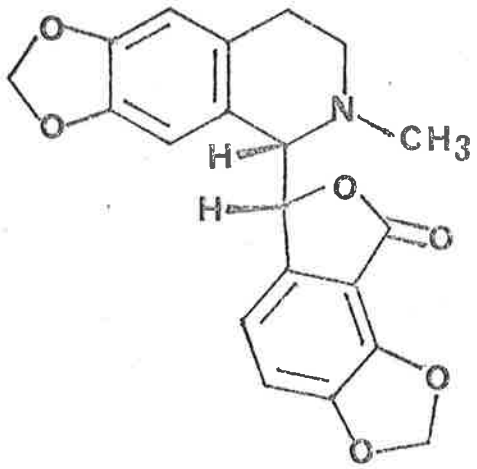
CHAPTER I

INTRODUCTION

The term "phthalideisoquinoline" is applied to a group of naturally occurring alkaloids[1-3] which are all derivatives of the parent compound (1), having as the name implies, a tetracyclic nucleus incorporating a γ-lactone (phthalide) and a tetrahydroisoquinoline system (fig. 1.1).



(1)



(2)

erythro
1S, 9R

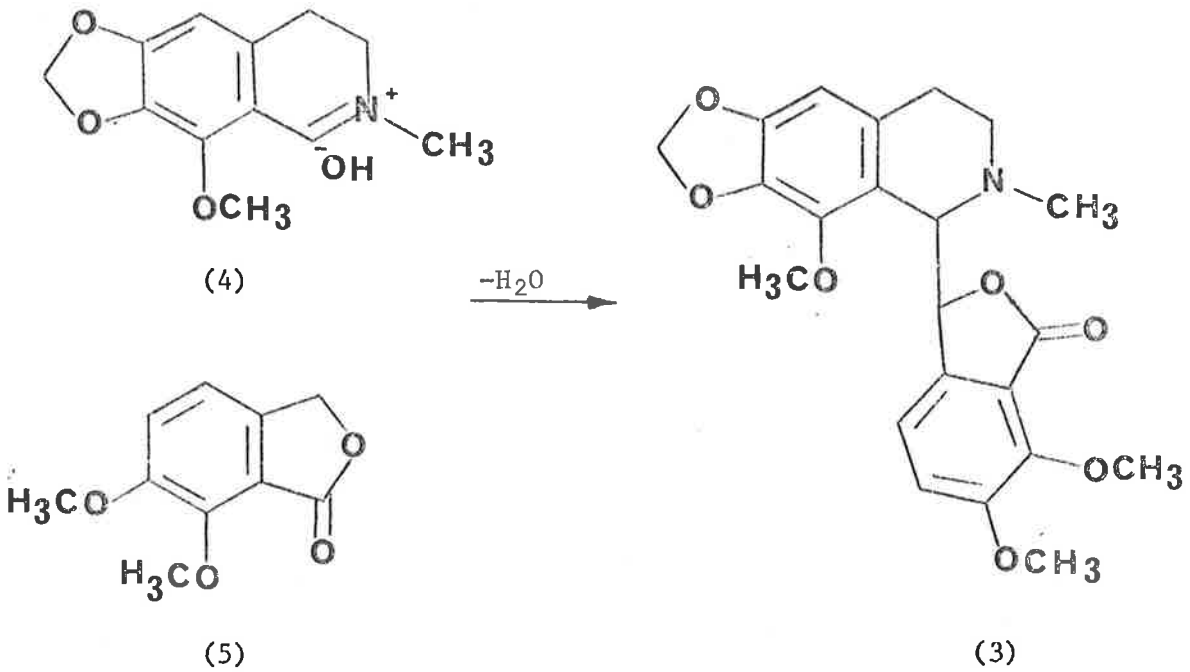
Fig. 1.1

(+) Bicuculline (2), a phthalideisoquinoline isolated from plants of the genera *Corydalis* and *Dicentra*[4-6] shows convulsant activity in vertabrates[7-9] apparently due to an antagonism of γ-aminobutyric acid (GABA) - a known synaptic inhibitory transmitter.[10-14]

The possible use of bicuculline and other phthalideisoquinolines as chemical therapeutics, and as precursors in the synthesis of other isoquinoline alkaloids[15] has regenerated interest to develop new and general synthetic methods for their preparation.

The first reported synthesis of a phthalideisoquinoline was accomplished when small quantities of (±) narcotine (gnoscopine) (3),

were obtained on boiling an alcoholic solution of cotarnine (4) and meconine (5) in the presence of potassium carbonate (Scheme 1.1).[16]



Scheme 1.1

It was consequently found that the condensation proceeded in better yields if base was omitted; indeed the use of strong alkaline conditions severely supressed the formation of alkaloid.[17] The introduction of a nitro group[18] or halide[17] in the aromatic ring of the phthalide increased the ease of condensation with cotarnine; in acid solution cotarnine exits mainly as the immonium ion, but in alkaline solution the pseudo-base form predominates (fig. 1.2).[19]

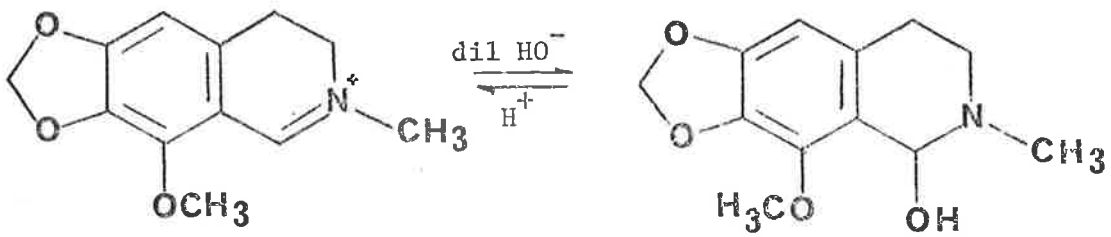
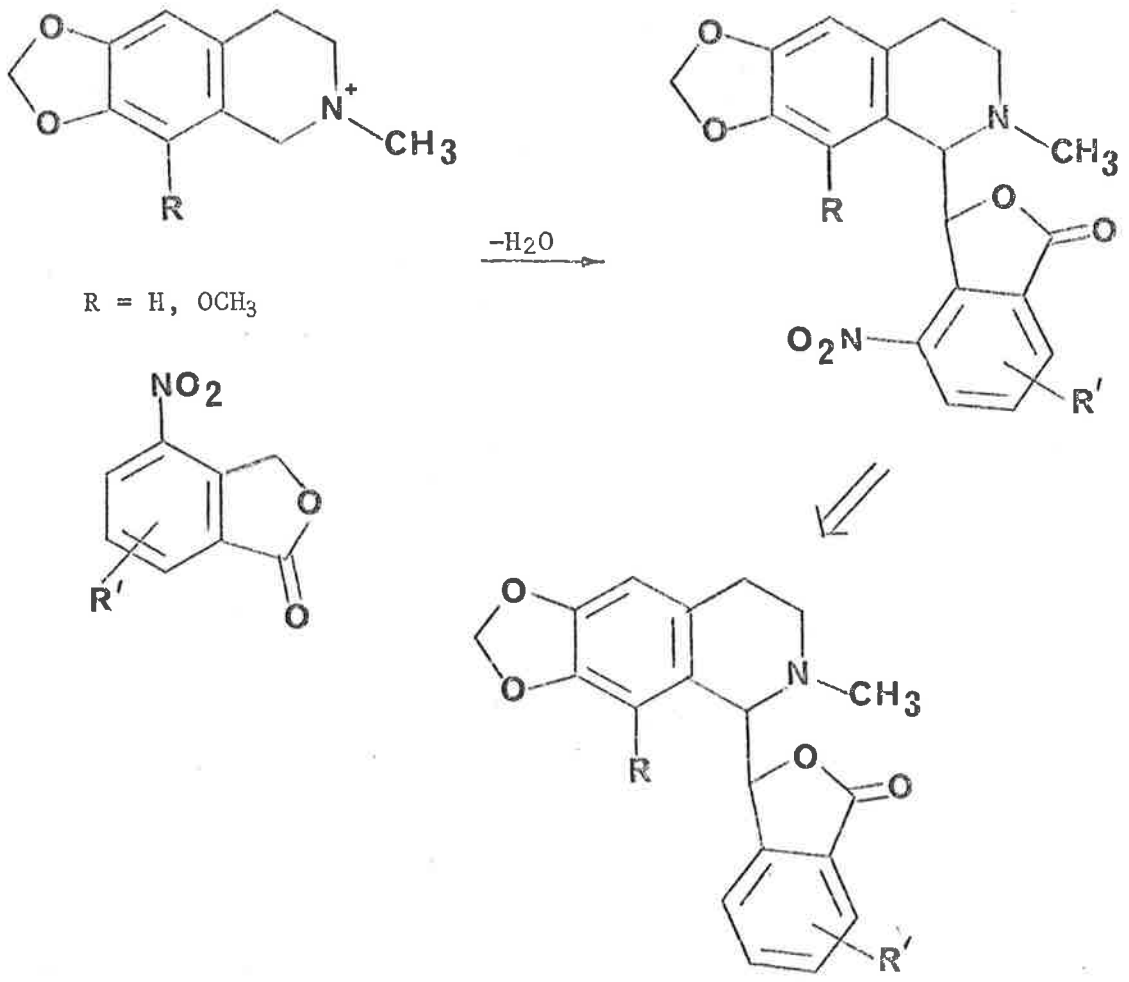


Fig. 1.2

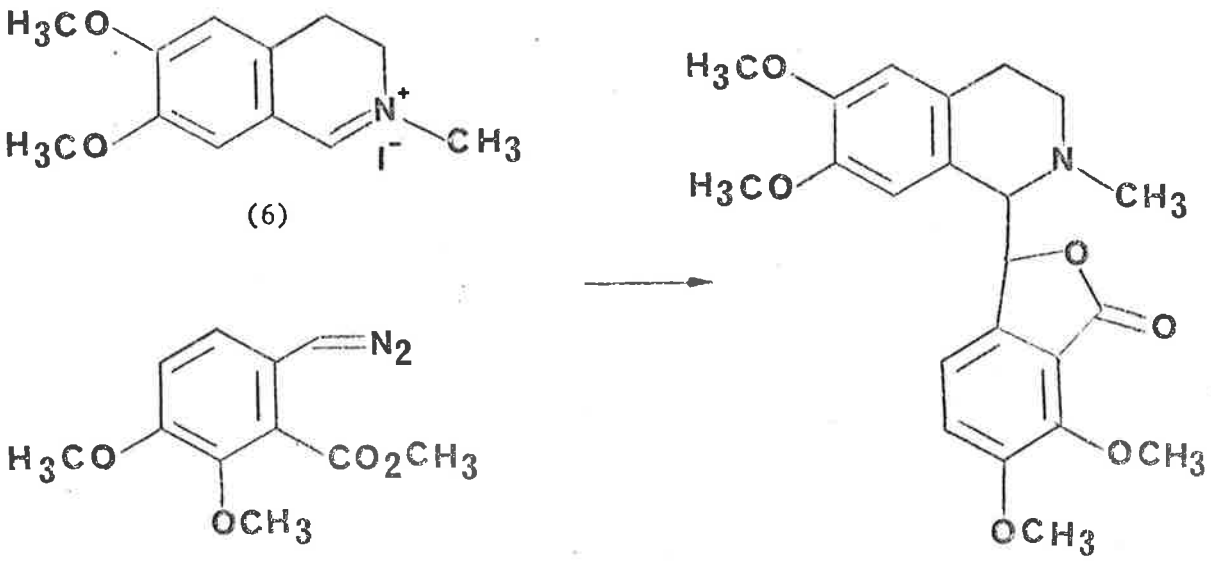
The above observation explains why little condensation product was obtained when strong base was used (Scheme 1.1); the equilibrium would be forced to the right thus reducing the availability of the immonium cation for reaction with phthalide anion. In addition, the introduction of the nitro group in the 4-position of phthalide would increase the acidity of the C-3 hydrogen thereby probably generating a higher concentration of the anion, thus making a bimolecular reaction more feasible. The nitro group of the condensation product was subsequently removed by reduction, diazotization and hydrolysis (Scheme 1.2); the syntheses of gnoscopine,[17,21] hydrastine,[22] bicuculline,[23] and adlumine[24] by this general method have been described.



Scheme 1.2

Removal of the nitro group, however, presented problems; low yields were often obtained and coupling of the aromatic rings during diazotization was often the preferred pathway. The stereospecifity of the initial condensation was not always reliable and workers had to depend on recrystallization techniques for purification of products. Current work has shown that crystallization of some phthalideisoquinolines is extremely difficult even after chromatographic purification and it is highly likely that both stereoisomers were formed in many cases but one isomer was lost during purification. In the light of modern ^{13}C nuclear magnetic resonance (n.m.r.)[26] and ^{1}H n.m.r.[27-29] spectroscopic methods for the stereochemical assignment of phthalideisoquinolines, much of the early work requires repetition so that accurate stereochemical assignments of the products can be made.

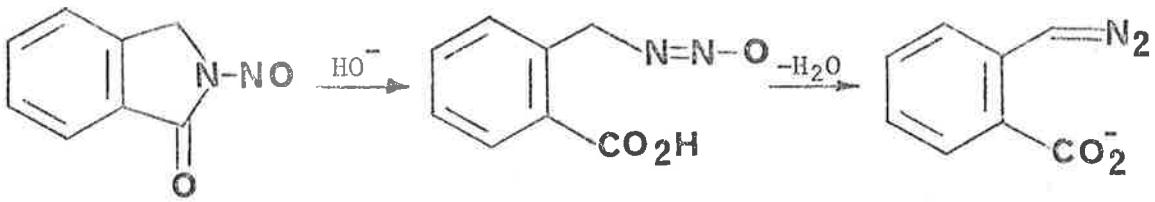
Cordrastine has been prepared by the coupling of 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium iodide (6) with methyl 6-diazomethyl-2,3-dimethoxybenzoate (7)[30] and gave a low overall yield of the desired phthalideisoquinoline (8); the preparation of the diazobenzoate (7) required, however, 10 steps (Scheme 1.3).



(6) (7) (8)

Scheme 1.3

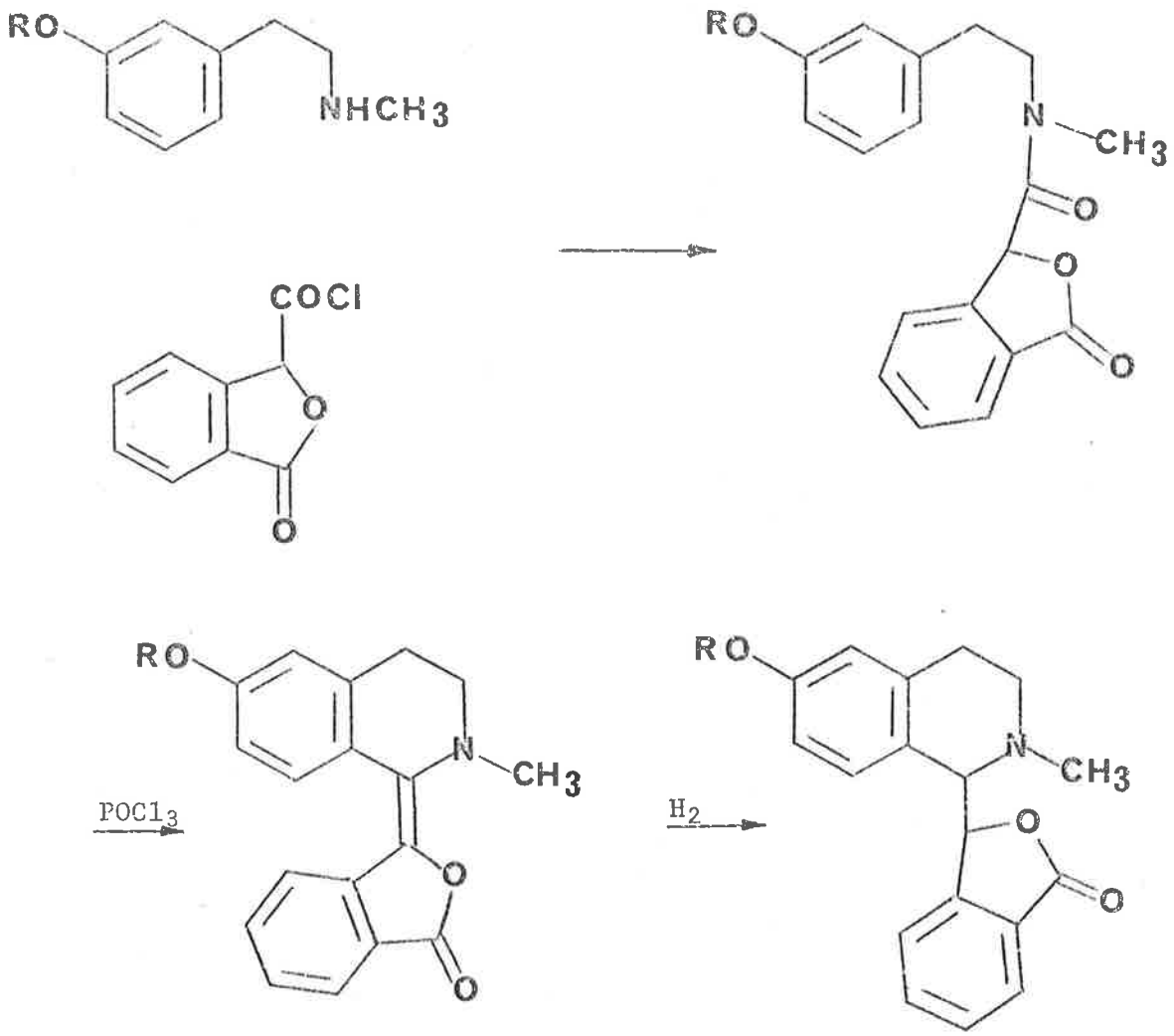
This method, which has recently been extended to the synthesis of hydrastine,[31] appears analogous to an earlier method of Hope and Robinson in their condensation of N-nitrosophthalimidine with cotarnine;[25] the reactive species was probably the diazocarboxylate (10) formed by reaction of the N-nitrosophthalimidine (9) with the hydroxyl ion from cotarnine (fig. 1.3).



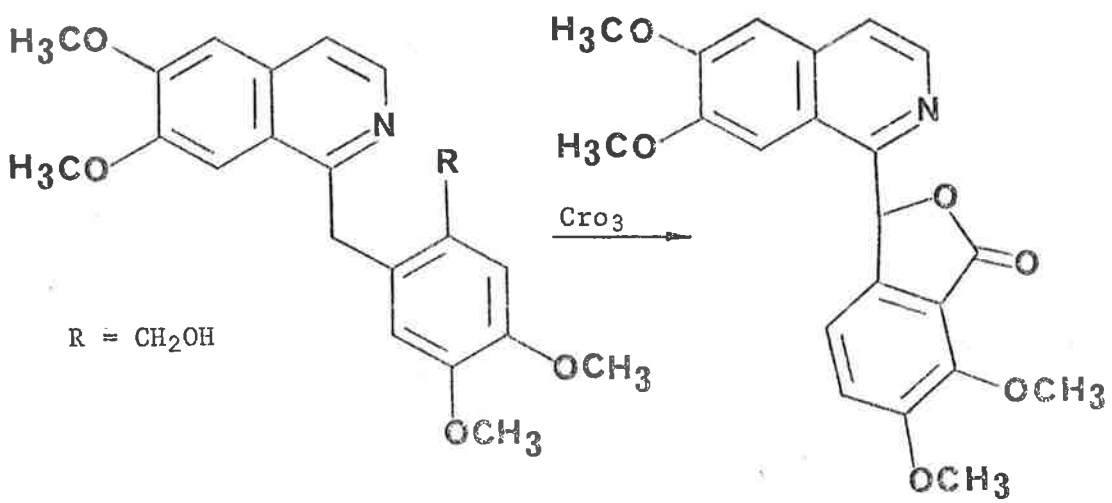
(9) (10)

Fig. 1.3

A different strategy utilized a Bischler-Napieralski cyclization of substituted phenylethylamides of phthalidecarboxylic acids followed by reduction of the intermediate dehydroisoquinoline (Scheme 1.4).[32,33] Since the success of this method depends heavily on the mesomeric directive effect of the oxygenated substituent in the 3-position of the phenylethylamide[34] it is unlikely that this method could be applied to the synthesis of phthalideisoquinolines substituted at the 7- or 8-positions.



A short but limited route which does not require the somewhat inaccessible meconine as a starting material, involved the oxidative cyclization of 2'-hydroxymethylpapaverine (Scheme 1.5), followed by reduction and N-methylation of the intermediate aromatic phthalideisoquinoline.



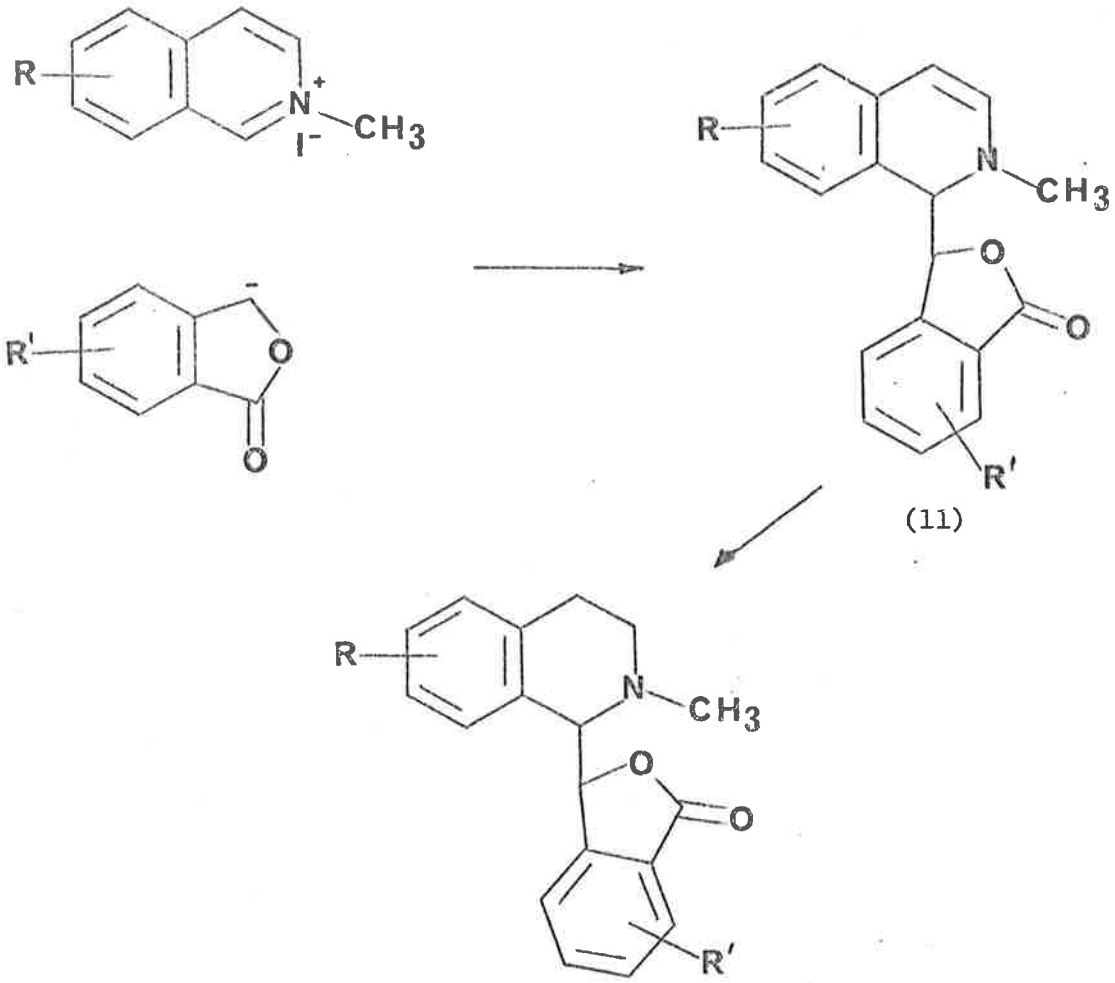
Scheme 1.5

An interesting synthesis, employing an acid-catalyzed rearrangement of a spirobenzylisoquinoline ring system to the phthalideisoquinoline system,[35] suffers, however, from the disadvantage that a 7 step sequence is involved, thus rendering this method inconvenient for the preparation of series of phthalideisoquinolines.

Other syntheses of phthalideisoquinolines have been published[36-38] but these also suffer from the lack of broad applicability to a series of phthalideisoquinolines.

Of the syntheses so far discussed, the most promising methods have involved the coupling of phthalide moiety to the isoquinoline system, thus forming the C1-C9 bond in the key step. This approach allows the synthesis of a wide variety of compounds since many literature methods exist for the synthesis of alkoxy and methylenedioxy phthalides including: 4-methoxy,[39] 5-methoxy,[40] 6-methoxy,[41] 7-methoxy,[42] 4,5-dimethoxy,[43] 5,6-dimethoxy,[43] 6,7-dimethoxy,[43] 4,5-methylenedioxy,[44] 5,6-methylenedioxy[45,46] and 6,7-methylenedioxyphthalide.[47] Although the preparation of the majority of these phthalides require the often inefficient acylation of a substitued benzoic acid with formaldehyde,[39,41,43,47] slight modification of reaction conditions may, in some cases, afford improved yields.[48]

The concept of forming the C1-C9 bond in the key step was realized by Tippett[49] who successfully effected nucleophilic attack of a phthalide anion on the electrophilic isoquinolinium methiodide resulting in a diastereoisomeric mixture of the dihydroisoquinoline intermediate (11) which was then reduced by catalytic hydrogenation to the phthalideisoquinoline system. A number of phthalideisoquinolines were synthesized by this route (Scheme 1.6).[49]

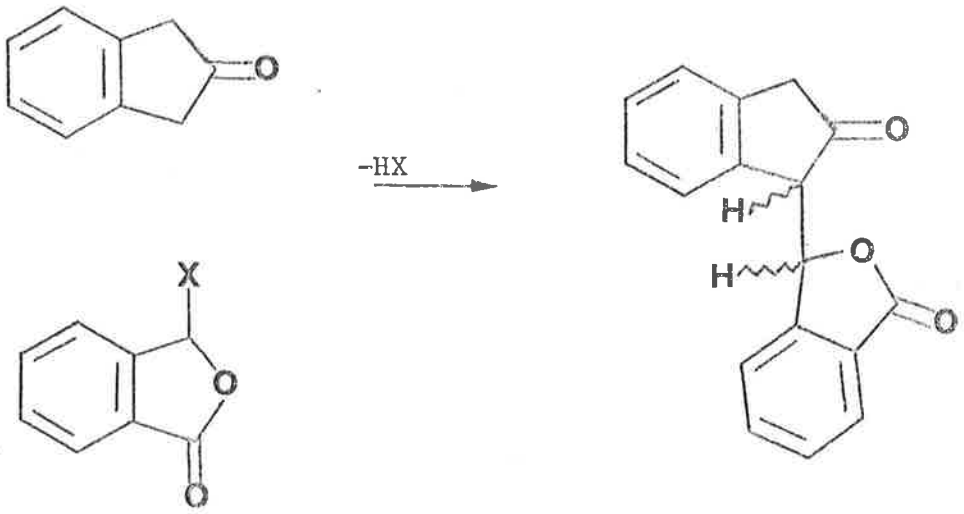


Scheme 1.6

Our approach was based on the successful production of an intermediate 1-(3' phthalidyl)-indan-2-one from the coupling of a phthalide substitued at the 3-position and indan-2-one (1,3-dihydro-2H-inden-2-one)*; the absence of substituents in the aromatic rings of both reactants was intended to give the model system (12) (Scheme 1.7).

---

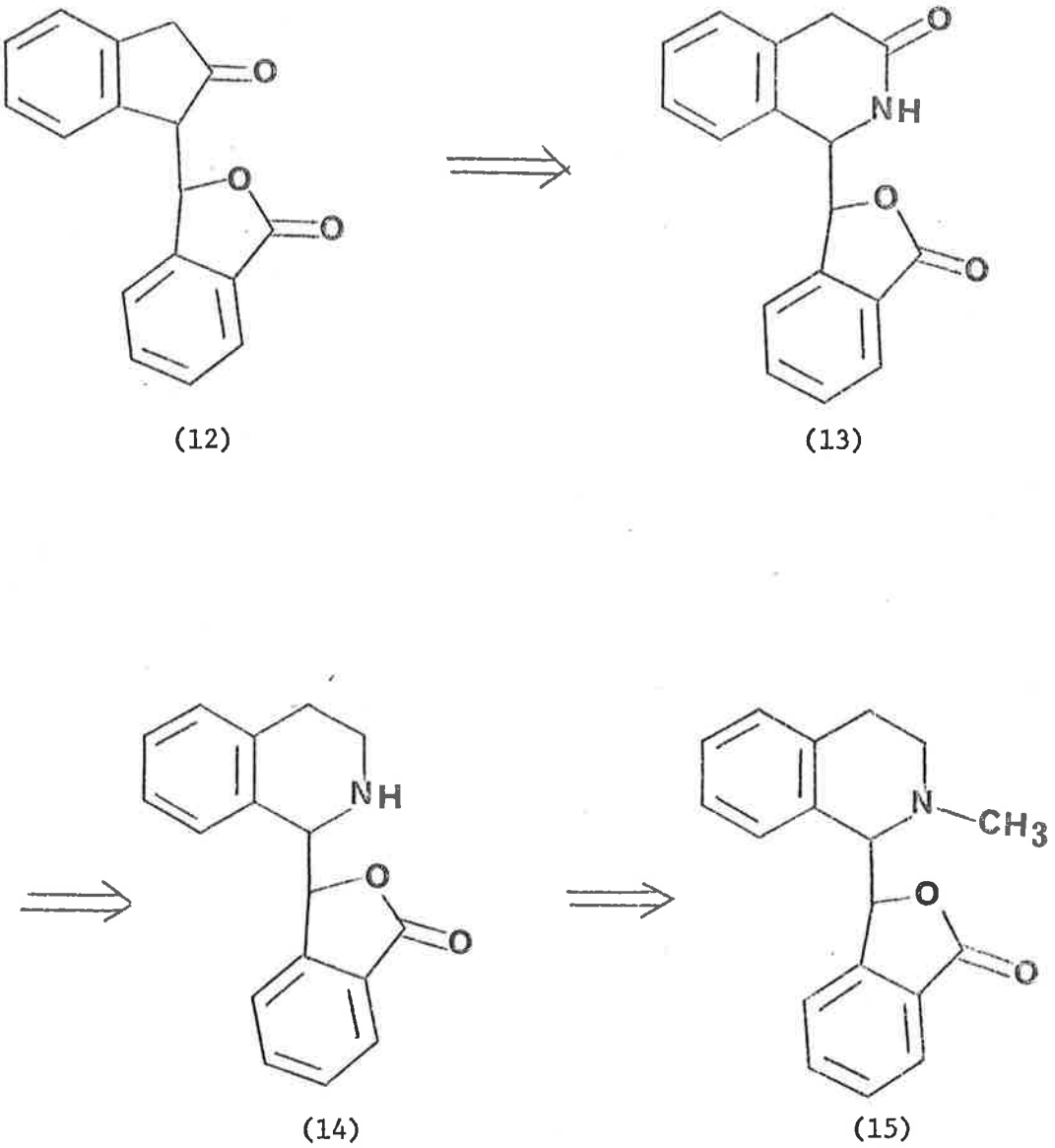
* For simplicity the term "indan" will often be substituted for "dihydro-inden" throughout this text.



(12)

Scheme 1.7

It was not anticipated that (12) would present major problems in its transformation to the isoquinoline system *via* the Schmidt reaction[50-53] or by a Beckmann rearrangement of the corresponding oxime.[54-56] In particular, it was expected that the more substituted bond would migrate[52, 57] in the Schmidt rearrangement of (12) to afford the amide (13). Having obtained (13) it was envisaged that conversion to the phthalideisoquinoline (14) would be achieved either by direct selective reduction of (13) (e.g. by sodium borohydride[59]) or by reduction of the imidochloride - formed by reaction with ethylchloroformate.[60, 61] The overall strategy having obtained (12) is outlined in Scheme 1.8.



(12) (13)

(14) (15)

Scheme 1.8

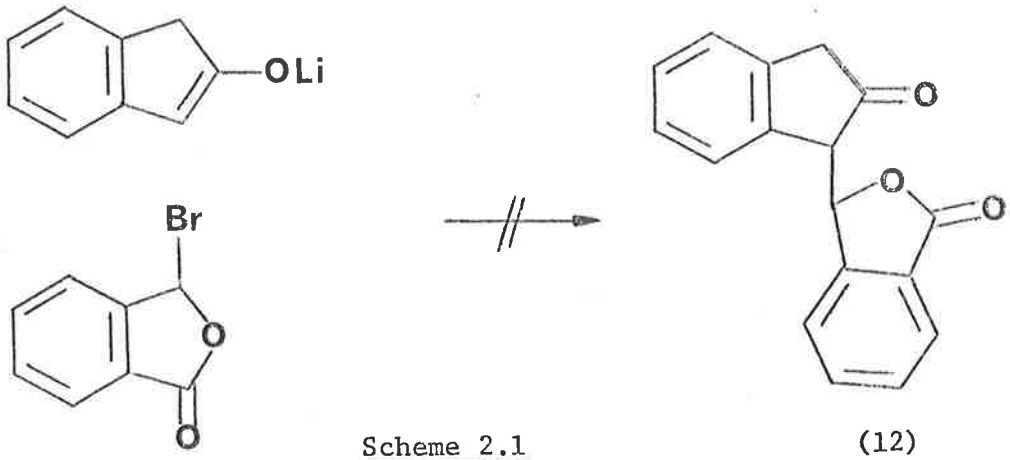
The N-methylation of (14) to afford the phthalideisoquinoline (15) was considered to be a straightforward step, as numerous methods exist for the N-methylation of amines.[28, 62]

CHAPTER 2.1

APPROACHES TO THE SYNTHESIS OF PHTHALIDEISQUINOLINES

For reasons previously outlined in the Introduction, the synthesis of the key intermediate 1-(3' phthalidyl)-indan-2-one (12) became the object of our initial investigation.

The initial approach was an attempt to acylate indan-2-one by means of nucleophilic attack of indan-2-one enolate anion on 3-bromophthalide. It was clearly desirable to use a non-nucleophilic base which could also generate the enolate anion irreversibly and quantitatively, thus minimizing unwanted side reactions such as Aldol condensation;[63] triphenylmethyllithium[64] seemed the reagent of choice (Scheme 2.1).



Scheme 2.1 (12)

When this reaction was attempted, however, in tetrahydrofuran at low temperature, a complex mixture of unidentified products was obtained, presumably due to polymerization of indan-2-one, since some 3-bromophthalide was recovered.

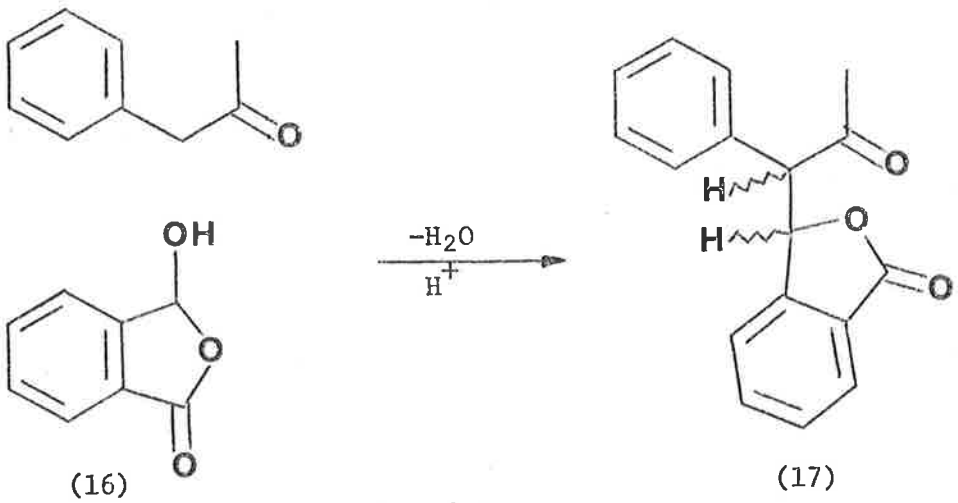
Acylation *via* the intermediate enamine[65] also proved fruitless* again base catalyzed polymerization appeared to be the favoured course of

---

* Enamine-alkylation of the related 3,4-dihydro-1H-naphthalen-2-ones has also been reported to be difficult.[66]

reaction as some 3-bromophthalide was again recovered* from the complex hydrolyzed reaction mixture. This lack of success was not surprizing since alkylations of indan-2-one enamines have been reported to give dismal yields of poor quality products.[68] Since this work concluded, however, an improved procedure for the enamine-alkylation of indan-2-one has appeared in the literature.[69] In any case this approach seemed shaky as there is no reported example in the literature of 3-bromophthalide being used successfully as an acylating agent, although recently it has been coupled to cinnolines[70] and work is currently in progress to explore the scope of this reaction.[70]

As indan-2-one was obviously sensitive to base, an alternative approach using phthalide as an electrophile was investigated; phthalaldehydic acid (16) readily undergoes uncatalyzed† nucleophilic substitution by a series of nucleophiles including alcohols, thiols, amines and amides to produce the corresponding 3-substituted phthalide.[71] Phthalaldehydic acid has also been condensed with 1-phenylpropan-2-one to yield the phthalideketone (17) as a *c.* 1:1 mixture of diastereoisomers (fig. 2.1).[49]



(16) (17)

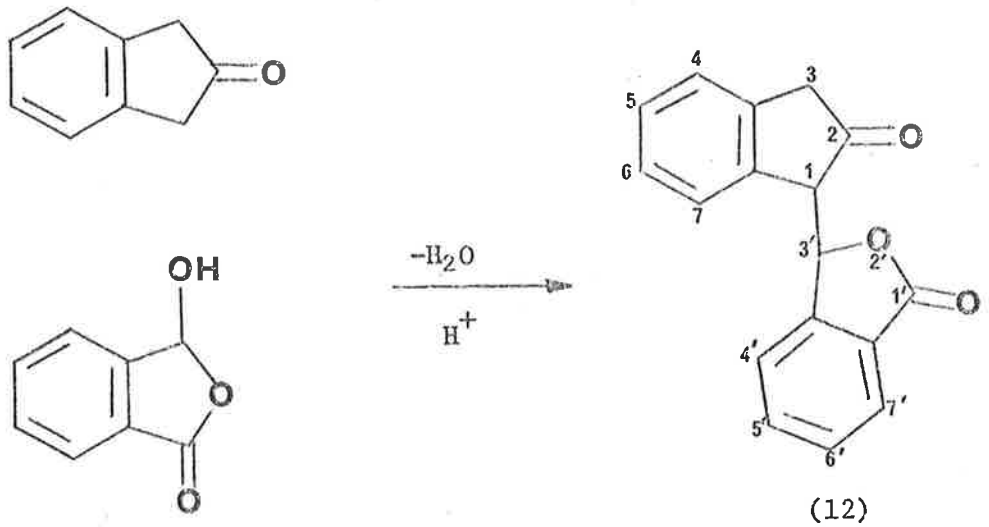
fig. 2.1

---

* This was mildly surprizing because 3-bromophthalide is readily converted to phthalaldehydic acid on warming with water.[67]

† Probably general acid catalysis using the proton of phthalaldehydic acid ($k = 3.6 \times 10^{-5}$, 25°[72]).

Indeed a similar coupling between indan-2-one and phthalaldehydic acid proceeded smoothly in refluxing benzene containing a catalytic amount of *p*-toluenesulphonic acid to give the desired 1-(3' phthalidyl)-indan-2-one (12) as a single diastereoisomer (Scheme 2.2).

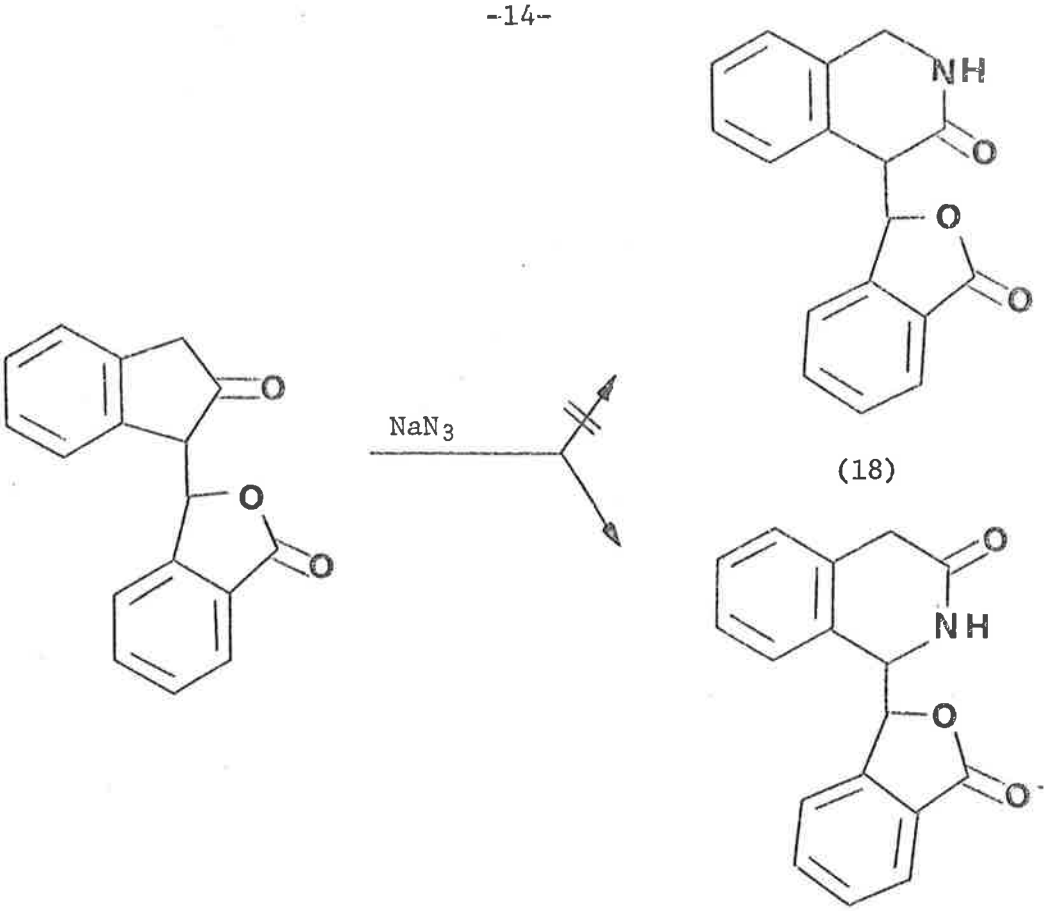


(12)

Scheme 2.2

The proton magnetic resonance spectrum ($CDCl_3$) of (12) indicated part of an AX quartet (J = 3Hz) at δ4.12 (C1-*H*) and δ6.2 (C3'-*H* overlapping with another doublet probably due to C4'-*H*) which simplified to a clear AX quartet (δ3.55 or δ5.58) when the spectrum was run in benzene-d_6/trifluoracetic acid-irradiation of either signal (δ3.55 or δ5.58) at that frequency caused the collapse of its partner.

The Schmidt reaction of (12) using sodium azide in polyphosphoric acid[73] proceeded on one occassion to yield the desired amide (13). Repeated attempts, however, under apparently identical conditions gave either polymeric tars, presumably from fragmentation products of (12), or returned the starting ketone (12); increasing the temperature accelerated polymerization (Scheme 2.3).



(18)

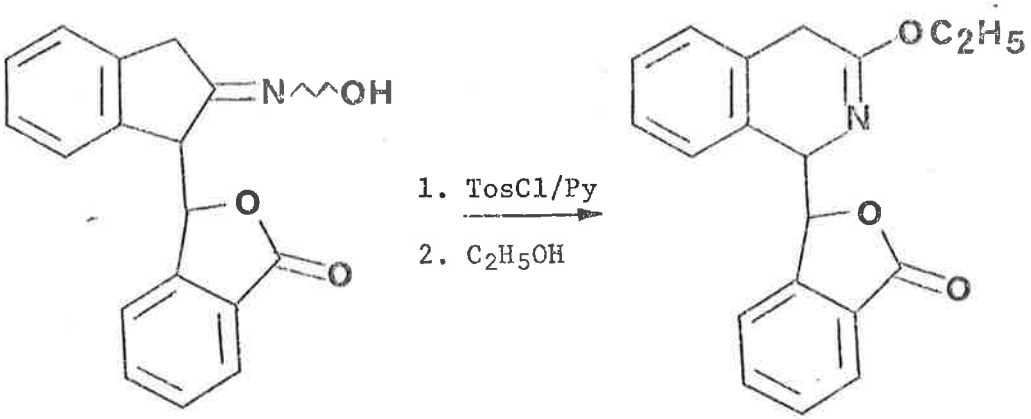
(13)

Scheme 2.3

Evidence for the formation of amide (13) (one diastereoisomer) and not the isomer (18) was based primarily on p.m.r. data; the C1-*H* signal appearing at δ5.21, shifted downfield (compared to the C1-*H* of (12)) due to the proximity of the electron-withdrawing nitrogen.[74] The formation of amide (13) would be expected to be favoured over (18) as it is well known that the more substituted bond generally migrates in the Schmidt reaction.[52, 57] Other conditions were tried for the Schmidt rearrangement of (12), but none was successful (giving polymeric tars) and in view of the non-reproducibility of the reaction in polyphosphoric acid, this route to the phthalideisoquinolines appeared non-viable. From a comparison of the chemical shifts of C1-*H*, C9-*H* and C2'-*H*, (δ5.21, δ5.71 and δ6.60 respectively) with the corresponding protons of some analogous norphthalideisoquinolines,[28] the relative configuration of (13) remains doubtful although the *erythro*

configuration appears favoured; all phthalideisoquinolines showing biological activity have the *erythro* configuration.

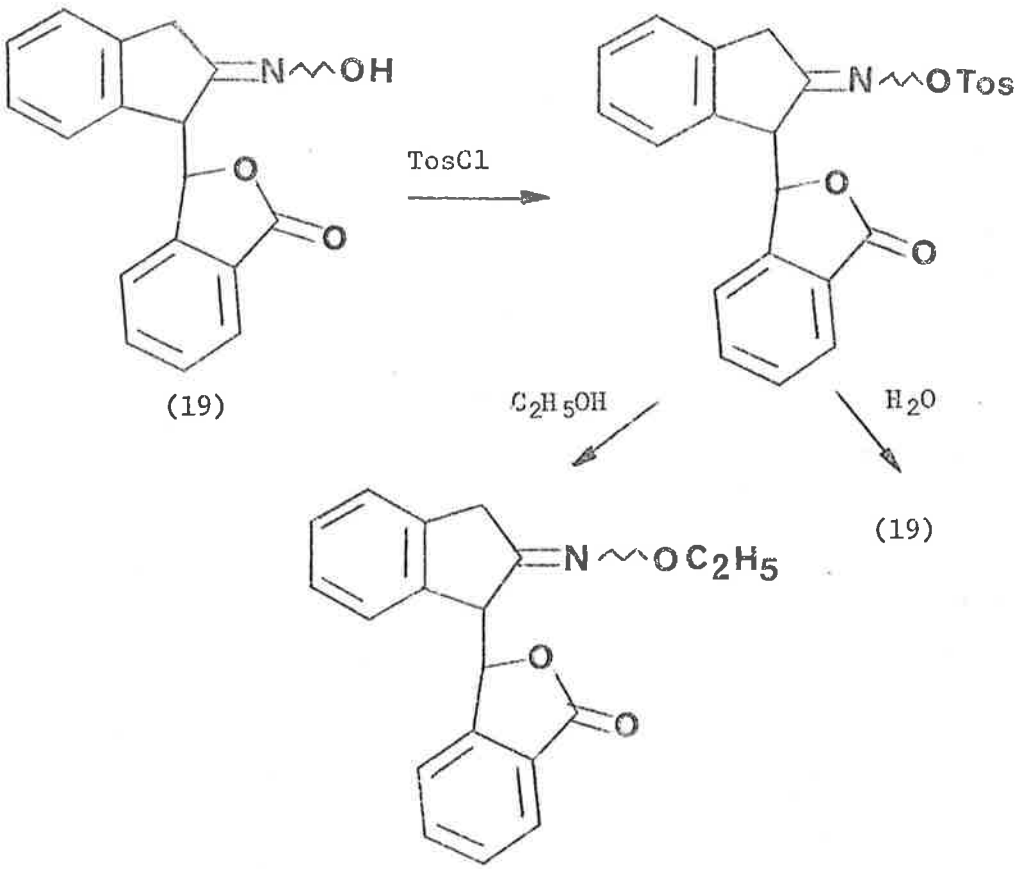
Attention was focussed on the Beckmann rearrangement of 1-(3' phthalidyl)--indan-2-one oxime (19), treatment of which with *p*-toluene-sulphonyl chloride in pyridine followed by ethanolysis[75] gave a low yield of a compound whose spectral data were consistent with the iminoether (20), together with polymeric products (Scheme 2.4).



(19) (20)

Scheme 2.4

This reaction also suffered from the lack of reproducibility as a similar reaction followed by an aqueous workup did not give the amide (13) but returned the starting oxime (19); this casts doubt over the structure obtained from the former Beckmann reaction using an ethanolic workup - the isomeric ether (21) may have in fact been obtained (Scheme 2.5).

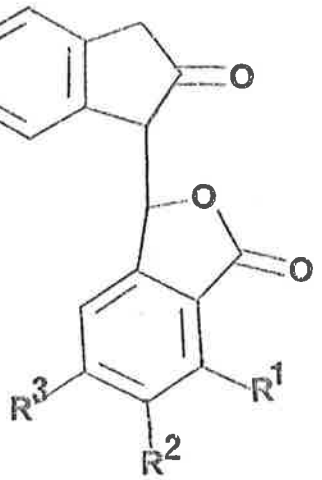


(19) (19) (21)

Other conditions for the Beckmann (e.g. polyphosphoric acid) led to polymeric tars which were not further characterized. In view of these discouraging incongruities from the Beckmann and Schmidt reactions, it was considered more worthwhile to investigate the scope of the initial condensation for the production of substituted 1-(3' phthalidyl)-indan-2-ones in the hope that the presence of electron-donating groups would make these ketones more likely to react favourably in either the Beckmann or Schmidt reactions.

Indan-2-one was treated with various phthalaldehydic acids under similar conditions described for the preparation of (12). In most cases a single diastereoisomer appeared to be formed although interpretation of the p.m.r. spectrum was hampered by overlapping peaks. The yields were only moderate as tituration was usually necessary to isolate the major product as a solid from the gummy residues; chromatographic

techniques were of little value in purification. The 1-(3' phthalidyl)-indan-2-ones obtained by this method are illustrated in fig. 2.2.



$R^1 = R^2 = R^3 = H$ (12)

$R^1 = R^2 = OCH_3$, $R^3 = H$ (22)

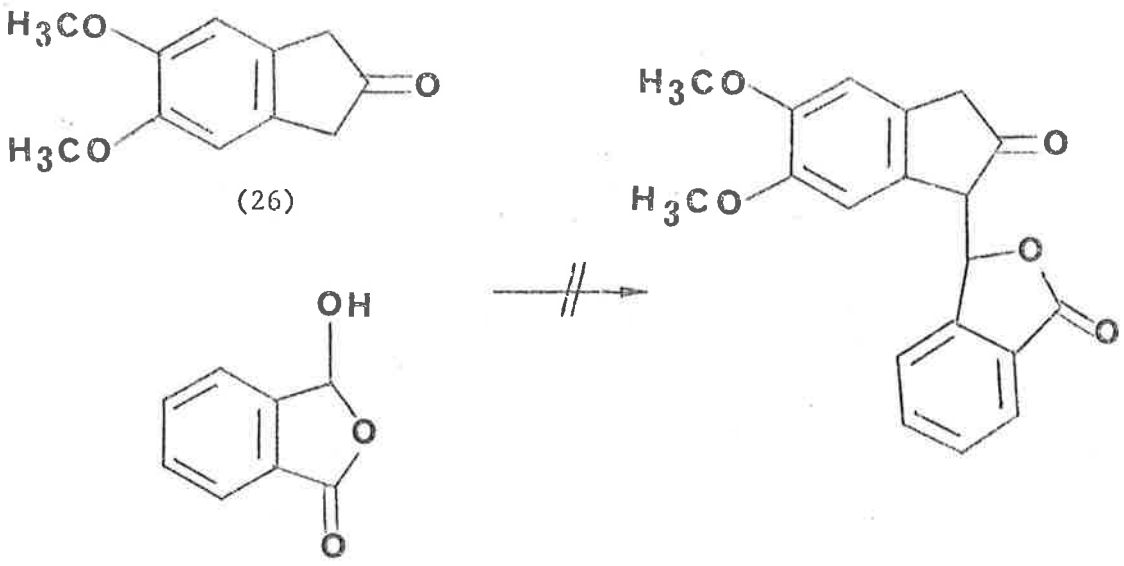
$R^1 + R^2 = O\text{-}CH_2\text{-}O$, $R^3 = H$ (23)

$R^1 = H$, $R^1 = R^2 = OCH_3$ (24)

$R^1 = R^3 = H$, $R^2 = OCH_3$ (25)

fig. 2.2

The naturally occurring phthalideisoquinolines all have oxygenated functions at the C6 and C7 positions and it was clearly desirable to achieve a successful condensation between a phthalaldehydic acid and (for example) 5,6-dimethoxyindan-2-one (26) (Scheme 2.6).



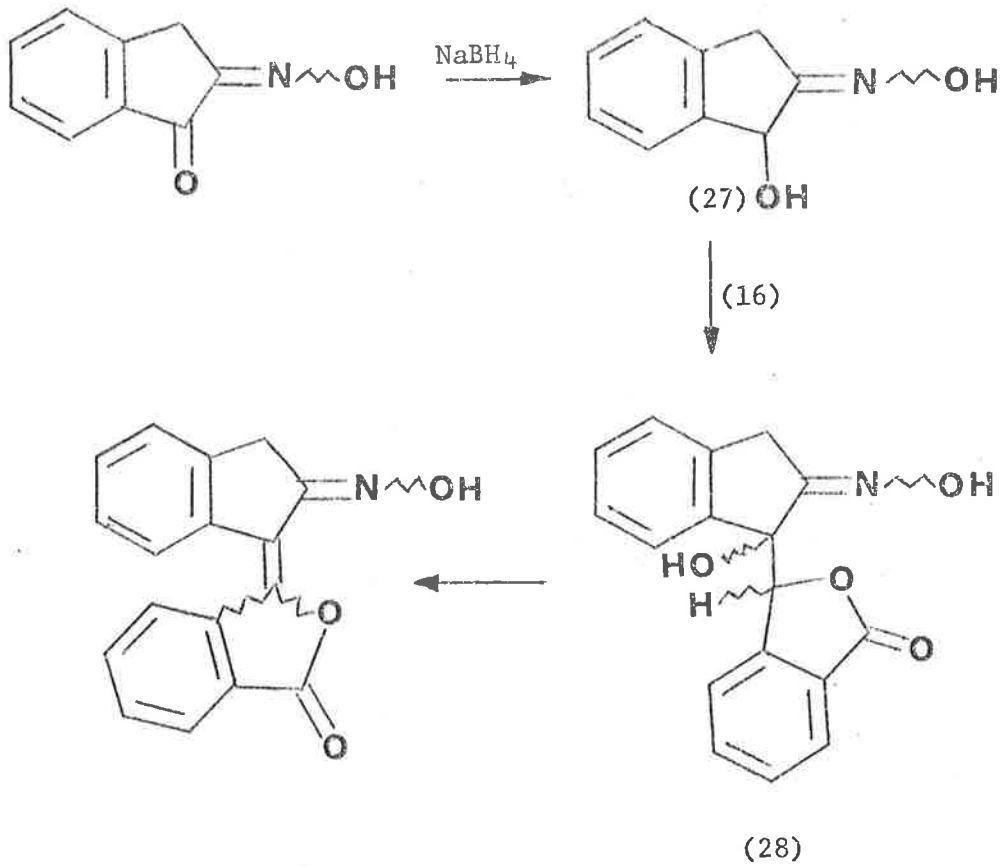
Scheme 2.6

The synthesis of 5,6-dimethoxyindan-2-one (26) proved extremely troublesome (see Chapter 2.3) and once accomplished, (26) failed to condense with either phthalaldehydic acid or more reactive opianic acid (5,6-dimethoxy-2-formylbenzoic acid) - in both cases polymerization of (26) was the preferred reaction pathway.

In view of this lack of reactivity and the observation that the ketone (21) also preferred to fragment rather than rearrange under the Beckmann conditions, this approach to the synthesis of phthalideisoquinolines was considered unworthy of further investigation and was abandoned. The problem of cleavage rather than rearrangement in the Schmidt[76] and Beckmann[77] reactions in which the incipient positive charge is stabilized by neighbouring groups has been noted by other workers.[76, 77]

Concurrently an alternative approach was an attempted coupling between 1-hydroxyindan-2-one oxime (27) with phthalaldehydic acid to

give the intermediate (28) which presumably would dehydrate under the reaction conditions to give the isomeric olefinic oximes (Scheme 2.7).



(28)

Scheme 2.7

Such an experiment resulted, however, in extensive tar formation probably due to electrophilic polymerization of *in situ* formed N-oxides (fig. 2.3).

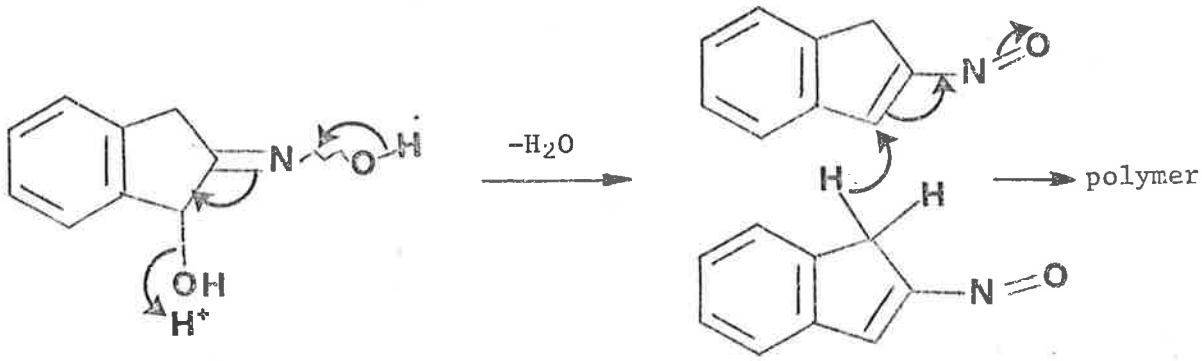
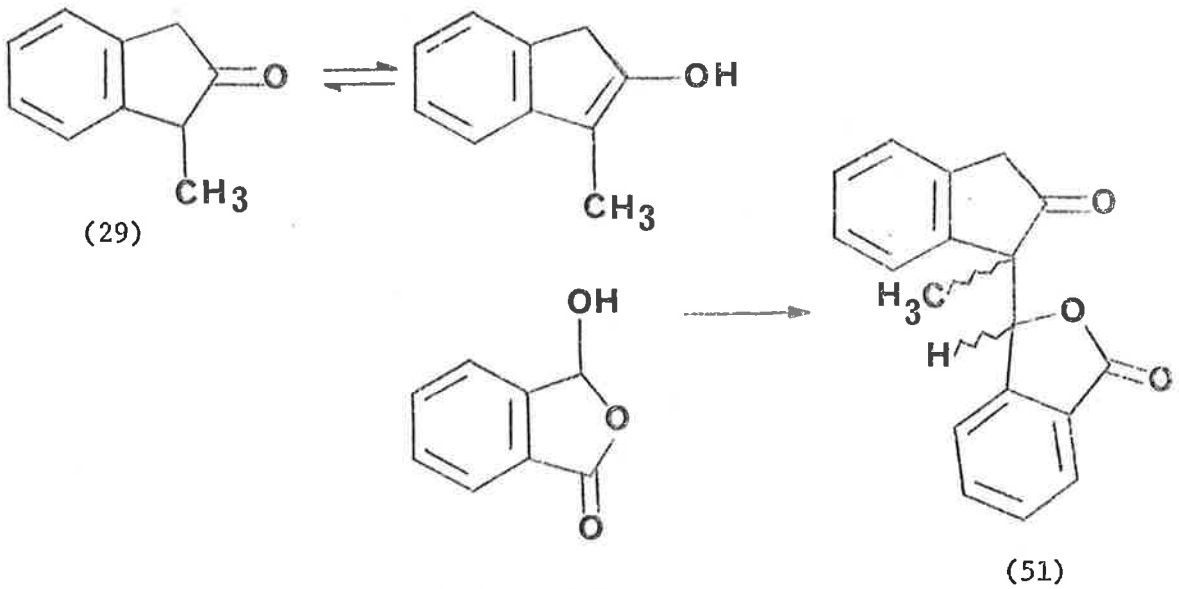


fig. 2.3

O-Methylation of the two hydroxyl groups of (27) may have retarded polymerization but (27) failed to react with ethereal diazomethane; base catalyzed methylations afforded tars and this pathway was also rejected.

Finally, a noteworthy condensation was the reaction of 1-methylindan-2-one (29) with phthalaldehydic acid (under the same conditions as for (12)), which yielded a *c.* 1:1 mixture of diastereoisomers (51); the reaction proceeded through the (presumably) more thermodynamically stable form of the ketone (29) (Scheme 2.8).



Scheme 2.8

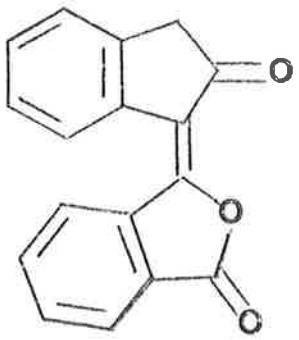
It was not immediately obvious to us why this reaction was non-stereospecific whereas the preparation of the analogous ketone (12) afforded only one diastereoisomer, although the explanation probably lies in the relative stabilities of the *threo* and *erythro* forms under the equilibrating conditions of condensation. While the assignment of the relative configuration of the ketone (12) remains speculative, further work in this area is required.

In any case, this approach seems of little value as the 1-(3' phthalidyl)-indan-2-ones are unstable under the tried conditions of the Schmidt and Beckmann reactions, thus rendering our approach to the general synthesis of phthalideisoquinolines untenable at this stage.

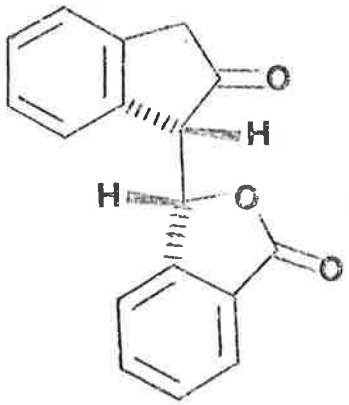
CHAPTER 2.2

UNSUCCESSFUL APPROACHES TO (30) AND (31)

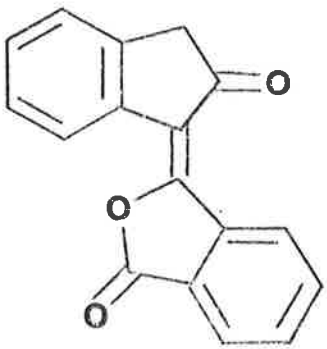
It was considered desirable to obtain both diastereoisomers of 1-(3' phthalidyl)-indan-2-one to determine firstly, if the stereochemistry of (12) was preserved in the Schmidt rearrangement and secondly, the relative stereochemistry of the adduct (12) obtained from the condensation between phthalaldehydic acid and indan-2-one discussed previously (Scheme 2.2). It was envisaged that hydrogenation of the isomeric ketones (30) and (31) would yield the *erthro* and *threo* isomers (12a) and (12b) respectively and thus (30) and (31) became synthetic targets (Scheme 2.9).



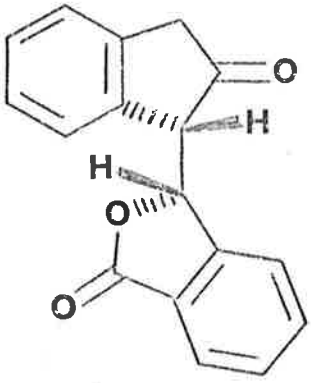
(30)



(12a) *erthro*



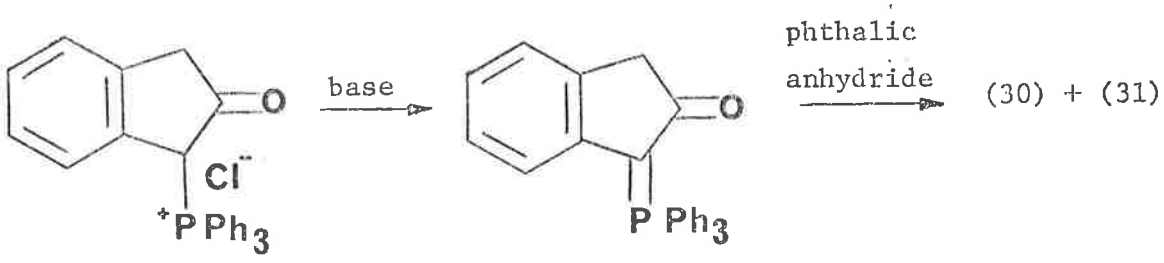
(31)



(12b), *threo*

Scheme 2.9

Wittig reactions between anhydrides and stabilized ylides have been reported in the literature[78] and it was hoped a Wittig reaction between phthalic anhydride and the phosphonium ylide (33) derived from the salt (32) (Scheme 2.10) would afford the desired (30) and (31).



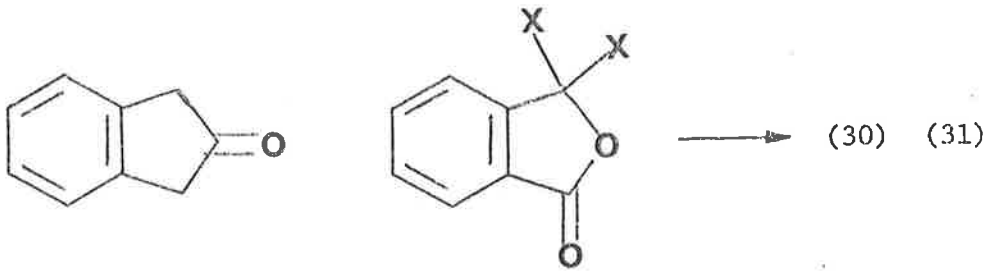
(32) (33)

Scheme 2.10

This reaction was unsuccessful due to the failure to prepare the phosphonium salt (32). The formation of α-ketophosphonium salts is generally favoured by the use of α-chloroketones, dipolar aprotic solvents with high reactant concentrations at elevated temperatures, and traces of base such as trimethylamine;[79] conditions which allegedly minimize undesirable side reactions such as dehydrohalogenation or enolphosphonium salt formation.[80a] Despite these findings, the reaction of 1-chloroindan-2-one with triphenylphosphine in refluxing benzene or dimethoxyethane afforded indan-2-one (from reductive dechlorination) and the use of a catalytic amount of trimethylamine enhanced polymerization.

It was obvious that any synthetic scheme involving indan-2-ones would require non-basic conditions to minimize self polymerization. Since indan-2-one reacted with phthalaldehydic acid, it was hoped that it might also condense with a suitable 3,3-disubstituted phthalide using acid catalysis. This approach was also fruitless, however, as either complex mixtures were obtained or no reaction occurred. The results are summarized in Table 2.1.

ATTEMPTED FORMATION OF (30) AND (31)



(30) (31)

X	SOLVENT	TEMPERATURE (°C)	TIME (h)	RESULT
Cl	benzene	80	0.5	no reaction [A]
Cl	none	120	0.5	polymer
OCH_3	benzene	80	0.5	no reaction
C=O [B]	none	120	0.5	polymer

A: no reaction as detected by p.m.r. spectroscopy.

B: phthalic anhydride.

Table 2.1

An attempted bromination-dehydrobromination approach applied to (12) was also unsuccessful as the ketone (12) failed to react cleanly with N-bromosuccinimide (NBS) in refluxing carbon tetrachloride, giving instead a complex mixture, the p.m.r. spectrum of which did not indicate any of the desired product.

In view of the experimental difficulties involved in the synthesis of (30) and (31) the pursuit of their preparation was postponed.

CHAPTER 2.3

SYNTHESIS OF 1,3-DIHYDRO-5,6-DIMETHOXY-2H-INDEN-2-ONE

The naturally occurring phthalideisoquinolines all have oxygenated functionality at the C6 and C7 positions, (either dimethoxy or methylenedioxy), and for reasons outlined in Chapter 2.1, it was considered essential to synthesize 1,3-dihydro-5,6-dimethoxy-2H-inden-2-one (5,6-dimethoxyindan-2-one) (26).*

Mander and coworkers[81] have demonstrated that phenolic diazoketones, when treated with trifluoroacetic acid, undergo cyclization *via* a *spiro* intermediate to afford indan-2-ones (fig. 2.4).

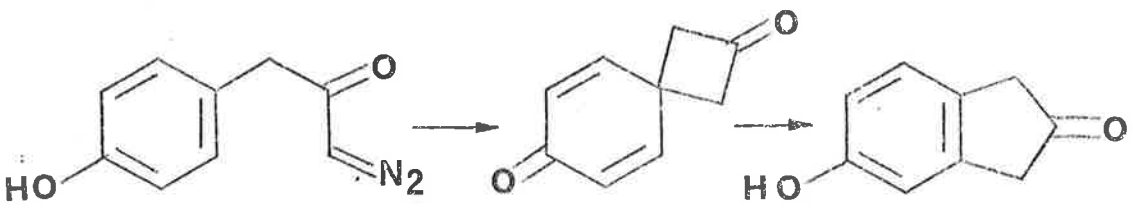


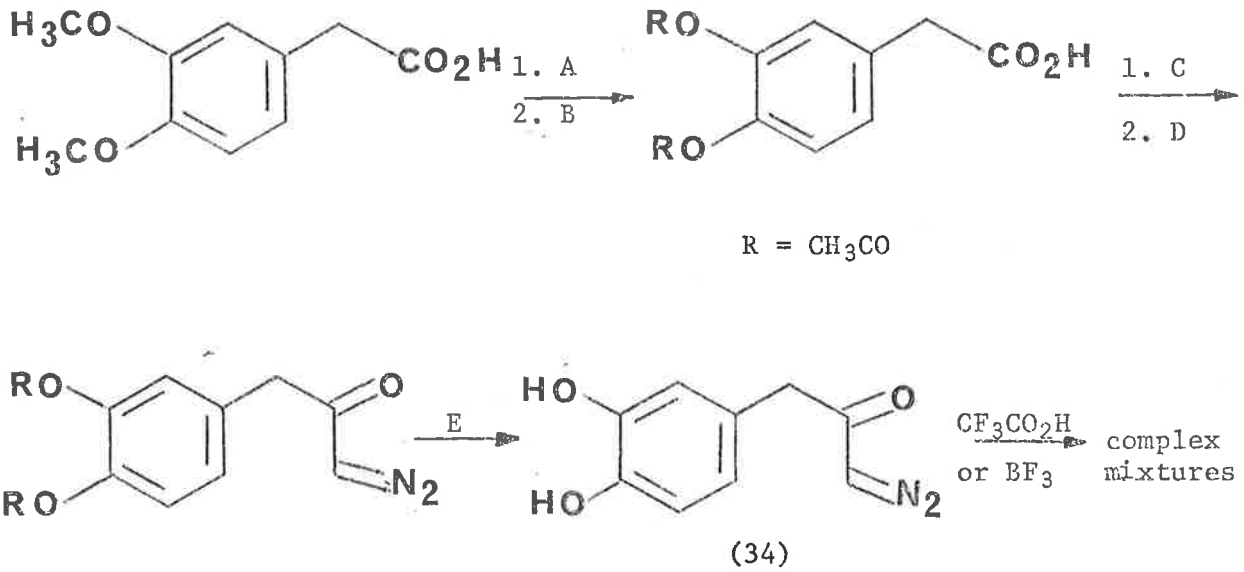
fig. 2.4

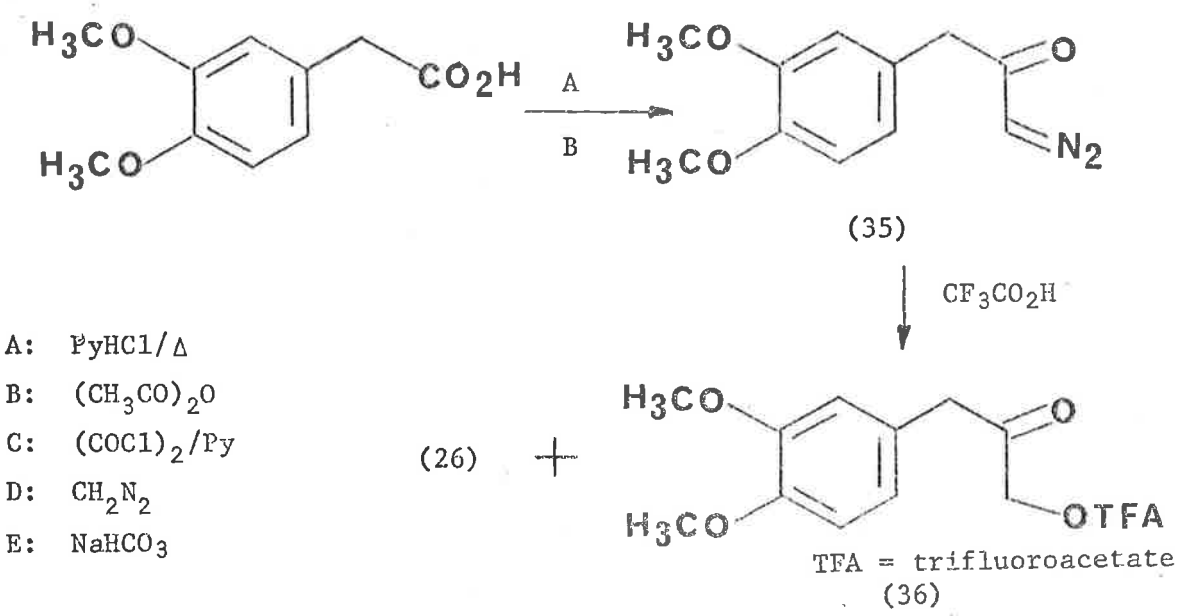
Attempts to cyclize either the analogous phenolic diazoketone (34) or the dimethoxydiazoketone (35) (both prepared in the normal manner[81]) met with stubborn resistance. In the latter case, however, small amounts of the desired ketone (26) could be detected (by p.m.r. spectroscopy) in the hydrolyzed reaction mixture after treatment with trifluoroacetic acid, albeit the major product appeared to be the

---

* Although the synthesis of this compound (25) has been reported, it is a lengthy preparation, beginning with the relatively inaccessible meconine.[82]

the acetoxyketone (36) which could not be induced to cyclize, a result independently obtained later by Mander.[83] Treatment of the diazoketone (34) with either boron trifluoride etherate[81a] or trifluoracetic acid[81b] afforded complex mixtures which were not further characterized. These results are summarized in Scheme 2.11.

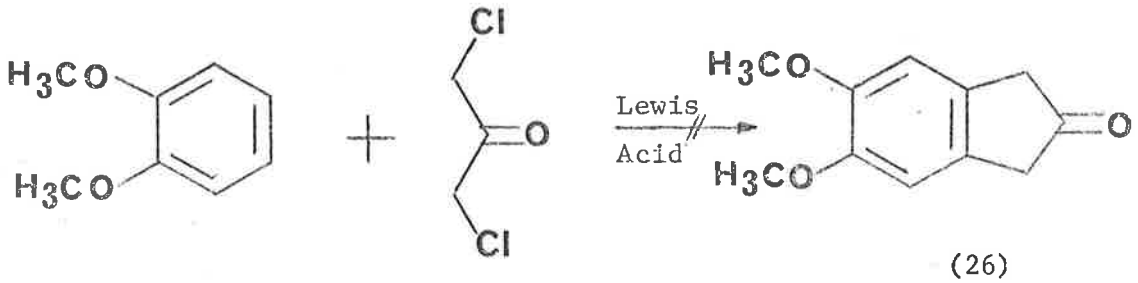




Scheme 2.11

An attempted "one-pot" Friedel-Crafts electrophilic substitution of 1,2-dimethoxybenzene by 1,3-dichloropropan-2-one also proved non productive as coupling could not be effected; higher reaction temperatures led to polymerization of 1,3-dichloropropan-2-one under a variety of conditions which are listed below in Table 2.2.

ATTEMPTED PREPARATION OF (26)



(26)

SOLVENT	LEWIS ACID	TEMPERATURE (°C)	RESULT
nitrobenzene	$ZnCl_2$	0,25	no reaction [A]
nitrobenzene	$AlCl_3$	0,25	no reaction
benzene	$AlCl_3$	25	no reaction
1,2-dichloroethane	$AlCl_3$	0,25	no reaction
1,2-dichloroethane	$AlCl_3$	60	polymer

A: No reaction as detected by thin layer chromatography (t.l.c.) and p.m.r. spectroscopy.

Table 2.2

The hydroboration-oxidation of indene affords predominantly indan-2-ol[84] and it was anticipated that attack by boron to the C2-position of 5,6-dimethoxyindene would be enhanced by the positive mesomeric effect of the C6 methoxy group (based on analogy to *p*-methoxystyrene[85]). Predominantly 5,6-dimethoxyindan-1-one (37) (by p.m.r. spectroscopy) was obtained, however when 5,6-dimethoxy-indene was treated with diborane followed by Brown's oxidation with sodium dichromate.[86] In this case, the combined negative inductive effects of the C5-methoxy and the aromatic ring outweigh the positive mesomeric effect of the C6-methoxy in governing the position of attack to the double bond. A transition state (38) is evidently favoured over an alternative transition state (39) having an incipient positive charge at the benzylic position (fig. 2.5).

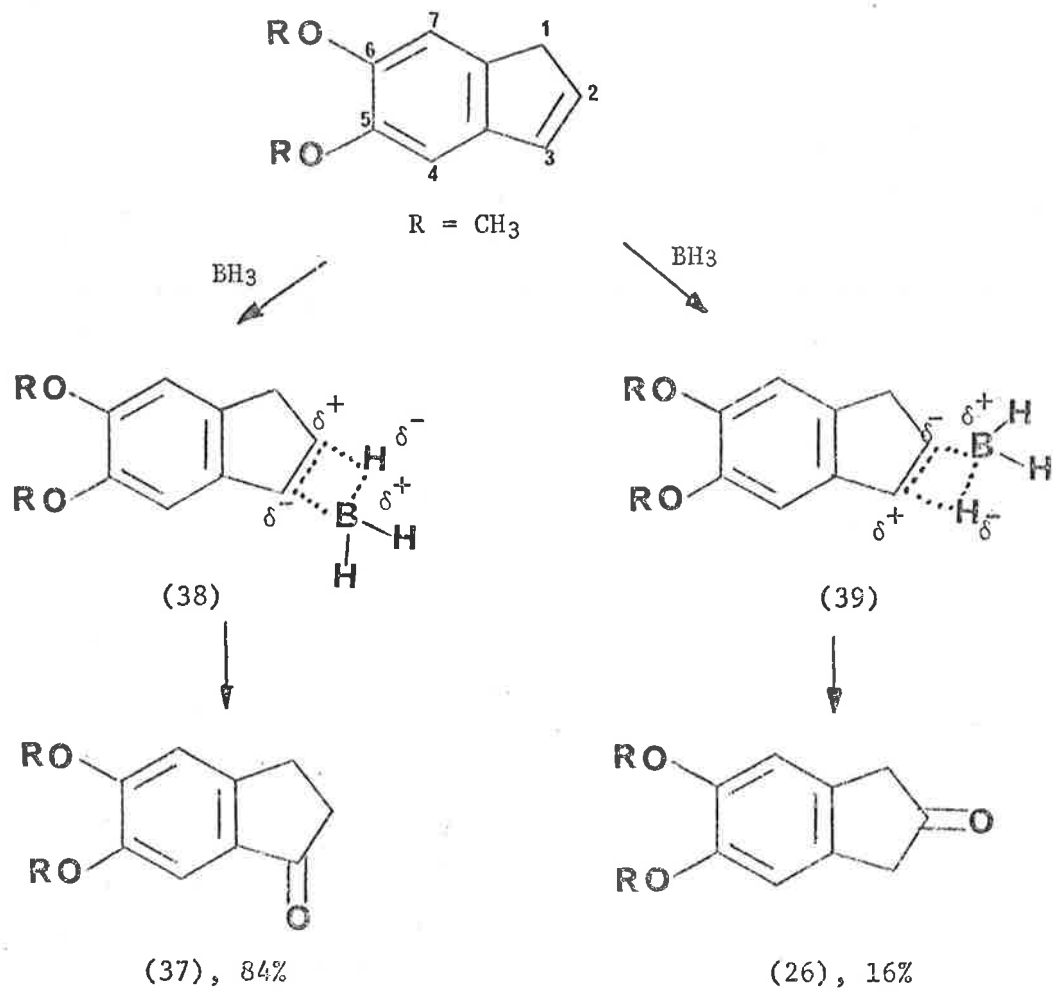
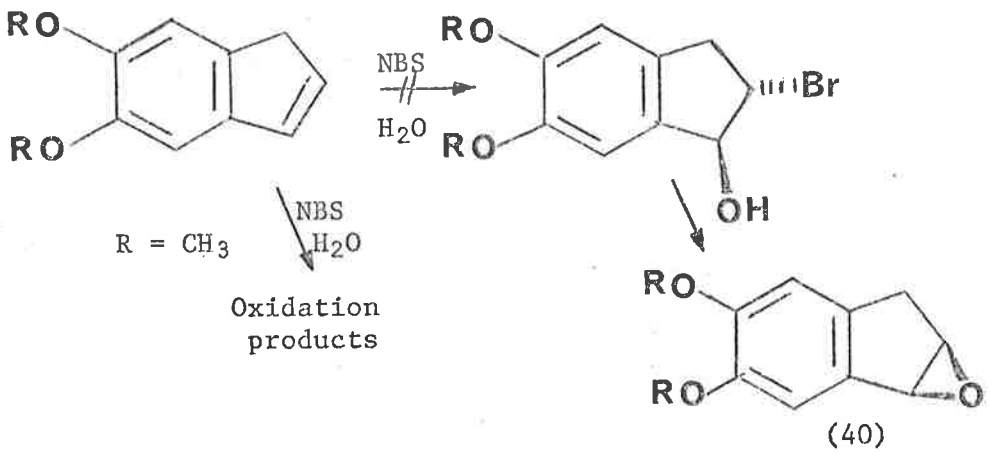


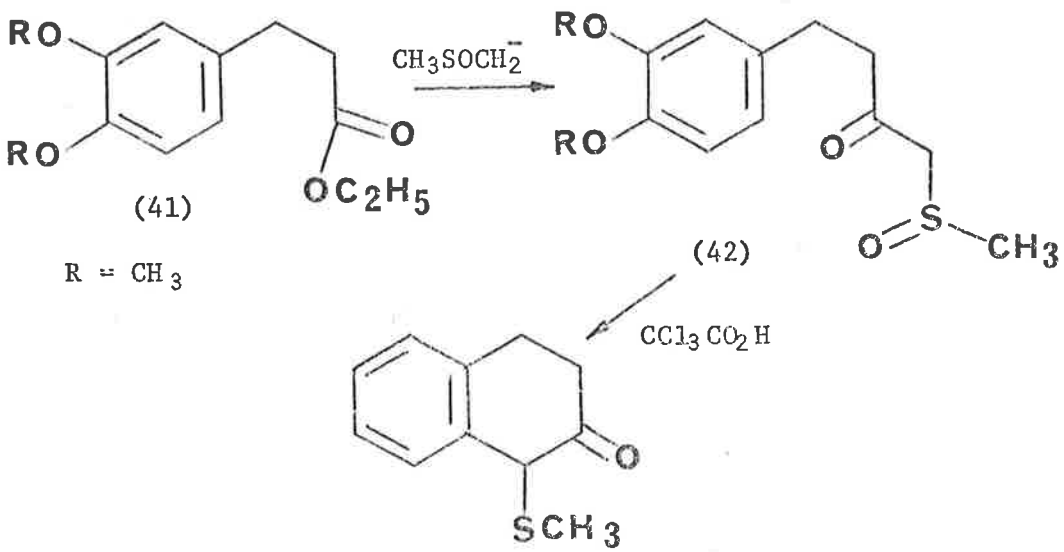
fig. 2.5

Although an acid catalyzed rearrangement of 5,6-dimethoxy-indene oxide (40) seemed promising the inability to synthesize the epoxide (40) by methods successful for indene[87] discouraged further investigation (Scheme 2.12).



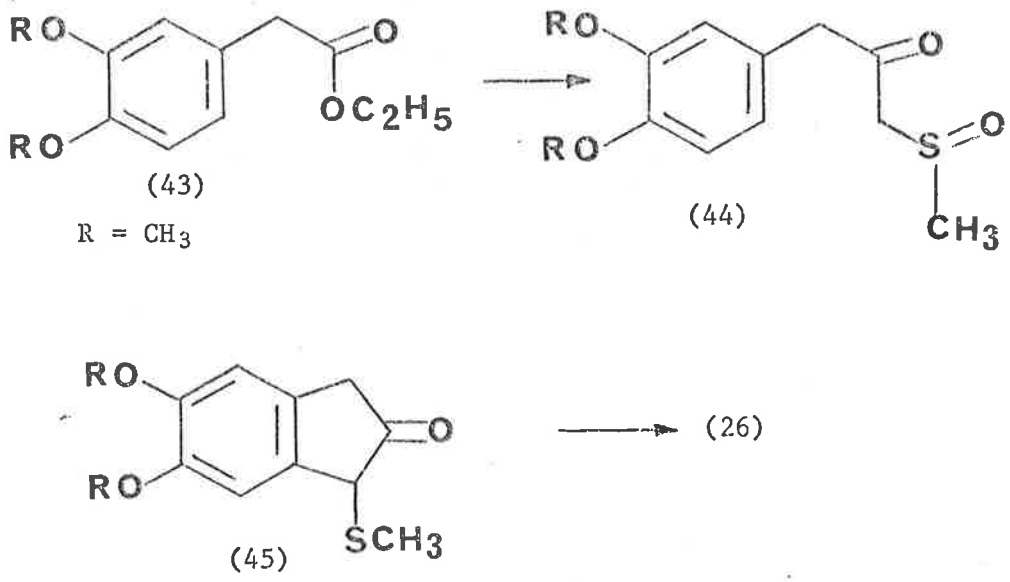
Scheme 2.12

As a consequence of the high acidity of the benzylic protons adjascent to the carbonyl function, 3,4-dihydronaphthalen-2-ones, are, like indan-2-ones, unstable compounds. They have recently been prepared by a Pummerer rearrangement of a β-ketosulphoxide (42) in which an intermediate cyclizes rather than is trapped by an external nucleophile.[88] The β-ketosulphoxides are normally prepared by nucleophilic attack of the corresponding ester by the anion of dimethylsulphoxide (dimsyl anion) (Scheme 2.13).[88b]



Scheme 2.13

It was thus envisaged that this reaction could be adapted to give the analogous 1,3-dihydro-5,6-dimethoxy-1-methylmercapto-2H-inden-2-one (45); the mercapto group should presumably be removable by subsequent treatment with Raney nickel,[89] (Scheme 2.14).



Scheme 2.14

Ethyl 3,4-dimethoxyphenylacetate (43) failed, however, to undergo nucleophilic attack by dimsyl anion to give the desired β-ketosulphoxide (44). Instead, the dimsyl anion preferred to act as a base and abstracted the benzylic proton, thereby rendering the resultant stabilized anion (46) inert to further nucleophilic attack (fig. 2.6).

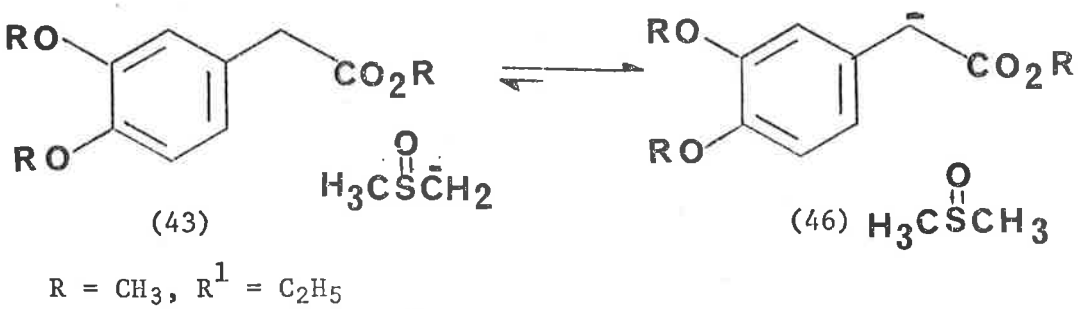
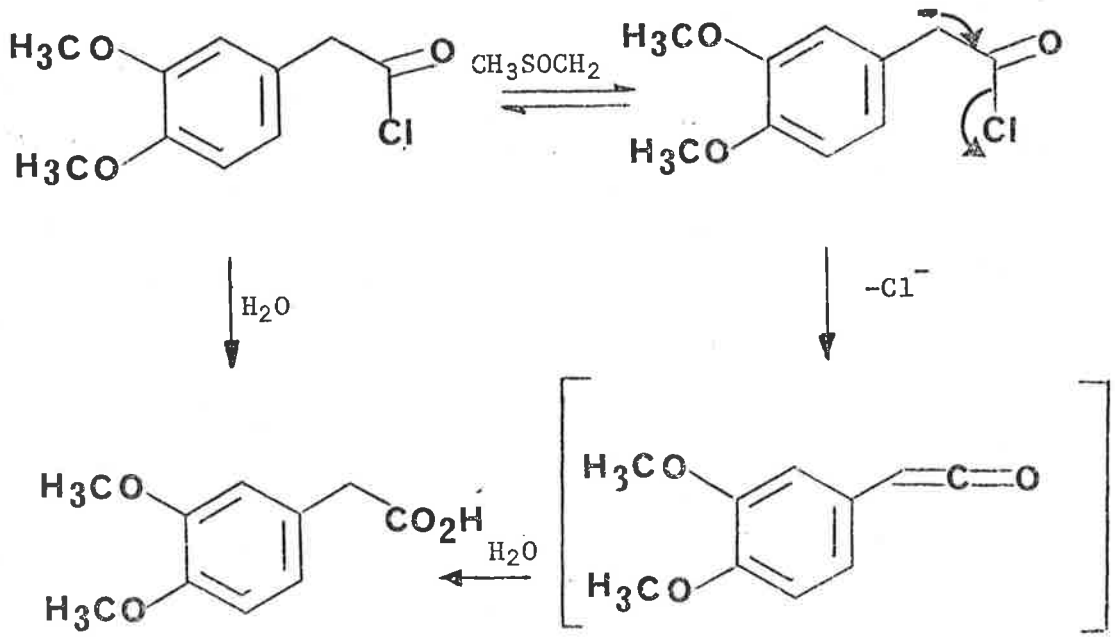


fig. 2.6

A probable explanation for this difference in reactivity of (43)

(compared to (41)) in its reaction with dimsyl anion lies in a comparison of the pkas of the relevant hydrogens: $CH_3-SO-CH_3$, pka 35; $PhCH_2CO_2C_2H_5$, pka *c.* 15-20; $PhCH_2CH_2CO_2C_2H_5$, pka *c.* 25.[80b] It would seem reasonable that in the equilibrium mixture of ethyl 3,4-dimethoxyphenylacetate (43) and dimsyl anion, the concentration of the anion (46) would be signigicantly higher than in the case of the ester (41) with dimsyl anion; therefore (46) would be relatively inert to nucleophilic attack. An excess molar amount of dimsyl anion did not overcome this resistance as starting ester (43) was recovered.

Treatment of 3,4-dimethoxyphenylacetyl chloride with dimsyl anion afforded, after an aqueous workup, 3,4-dimethoxyphenylacetic acid, possibly from hydrolysis of an intermediate ketene or more simply, hydrolysis of unreacted acid chloride (Scheme 2.15).



Scheme 2.15

The final, successful attempt was an exploitation of a Pinacol type rearrangement of indan-1,2-diol to indan-2-one. Suter[90] and Criegee[91] originally thought that the *cis*-diol rearranged faster than the *trans*-diol which isomerized to the *cis*-diol before dehydration. Subsequent, detailed studies by Rosen[92] have shown, however, that both *cis* and *trans*-diols are converted to indan-2-one at the same rate (fig. 2.7).

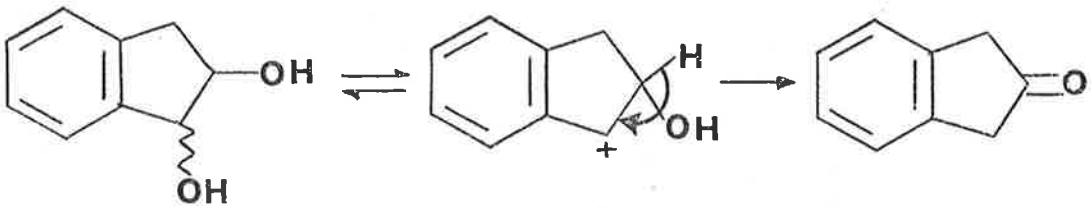
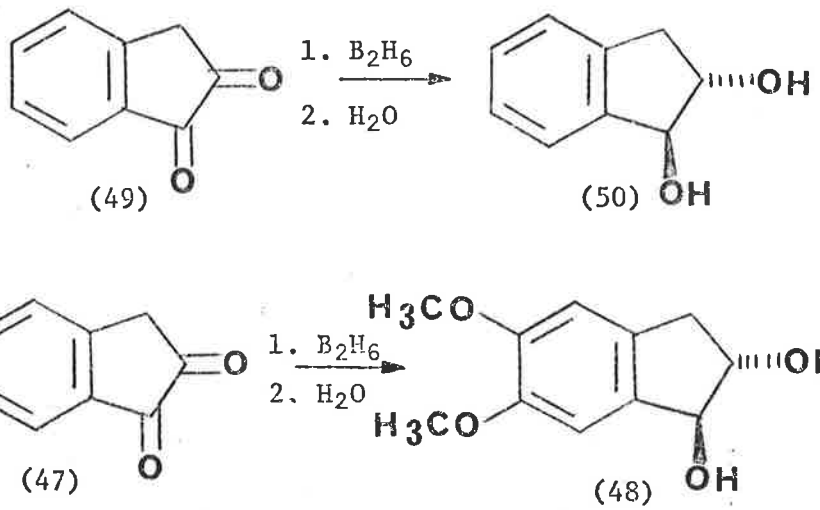


fig. 2.7

A similar reaction has been employed recently by Taub *et al*[93] in a synthesis towards prostaglandins.

Reduction of 5,6-dimethoxyindan-1,2-dione (47) with diborane afforded *trans*-5,6-dimethoxyindan-1,2-diol (48) in excellent yield. The assignment of (48) as having the *trans* configuration was based on the analogy that reduction of indan-1,2-dione (49) with diborane gave *trans*-indan-1,2-diol (50) (a known compound[92]) (Scheme 2.16).



Scheme 2.16

Considerable effort was extended to optimize conditions for the clean, facile rearrangement of the diol (48) to (26). As can be seen from Table 2.3, the most satisfactory method was warming the diol (48) in dilute oxalic acid which gave a reasonable yield of (26).

REARRANGEMENT OF DIOL (48) TO KETONE (26)

SOLVENT	ACID	TIME (h)	TEMPERATURE (°C)	YIELD %	RESULT
benzene	TosOH	48	25	95	isomerization [B]
benzene	TosOH	2	40	65	(26)
benzene	TosOH	1	80	65	(26)
water	H_2SO_4 [C]	1	60		polymeric tar
H_2O/EtOH	H_2SO_4 [C]	0.5	80		polymeric tar
DMSO [D]	none	3.5	160	<1	unknown
benzene	H_2SO_4	1	40	90	(26)
10% aq. oxalic acid		2	40	90	(48)
10% aq. oxalic acid		1	60	71	(26)

A: TosOH = *p*-toluenesulphonic acid (catalytic amount).

B: A *c.*1:1 mixture (by p.m.r. spectroscopy) of *cis*- and *trans*-5,6-dimethoxyindan-1,2-diol was obtained.

C: A catalytic amount was used.

D: DMSO = dimethylsulphoxide.

Table 2.3

Although it was disappointing to find after intense effort to prepare 5,6-dimethoxyindan-2-one (26), that it failed to react with phthalaldehydic acids, the eventual accomplishment of a novel synthesis of (26) was nevertheless rewarding and encouraging.

PART II

"THE SYNTHESIS AND HYDROBORATION OF BENZOCYCLENE OXIDES."

CHAPTER 1.

INTRODUCTION

Although methods for generating diborane have been available for many years,[1,2] it is chiefly since the development of more convenient[3,4] experimental procedures enabling this electrophilic[5] reducing agent to be prepared and stored in suitable quantities (normally as a solution in tetrahydrofuran[4] with which it complexes[6]) that it has enjoyed wider use in synthetic organic chemistry. Several programmes designed to investigate its reaction with a variety of functional groups including: olefins,* epoxides,[7] aldehydes and ketones,[8] carboxylic acids,[7] esters,[9] nitriles,[7] amides,[7,10] salts of nitroalkanes,[11] oximes,[12] and oxime ethers,[13] have been initiated. Brown, the leading contributor to this field has demonstrated the general order of relative reactivity of some representative groups toward diborane as:
carboxylic acids > olefins > ketones > nitriles > epoxides > esters > acid chlorides.[7] Thexylborane (1,1,2-trimethylpropylborane)[14] and disiamylborane (*bis*-(1,2-dimethylpropyl) borane)[15] show similar trends of reactivity.

Since the earlier studies,[16] the application of diborane and its derivatives to chemical synthesis has covered an enormous variety of reactions and a thorough survey of these is beyond the scope of this discussion - indeed the literature is already well served on this topic by a plethora of comprehensive reviews[17-26] and books.[27-33] Therefore in this text, discussion of boron hydrides shall be limited to their reactions with: firstly epoxides, and later,(Chapter 2.2) olefins.

---

* The hydroboration of olefins is examined later in Chapter 2.2.

Notwithstanding, an interesting example of the versatility of boranes comes from the study of alkynyl epoxides, which, on treatment with trialkylboranes in the presence of molecular oxygen, undergo a free radical transformation to allenic alcohols (fig. 1.1),[34] thus providing a novel and short route to these otherwise relatively inaccessible compounds.

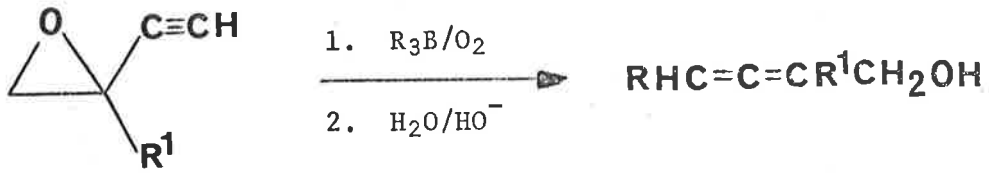


fig. 1.1

Uzarewicz has paid some attention to the hydroboration of α, β - unsaturated epoxides, particularly 3,4-epoxycyclohexenes.[35] Using a limited amount of diborane, allylic alcohols were obtained (after hydrolysis), whereas an excess of reducing agent yielded 1,3-diols (after mild oxidation) (fig. 1.2). It was suggested [35b] that borane added to the double bond of the α,β-unsaturated epoxide from a *cis* direction with regard to the epoxide ring, and preferentially to the carbon *alpha* to the oxygen function; a phenomonen sometimes noted in the hydroboration of other allylic systems.[36]

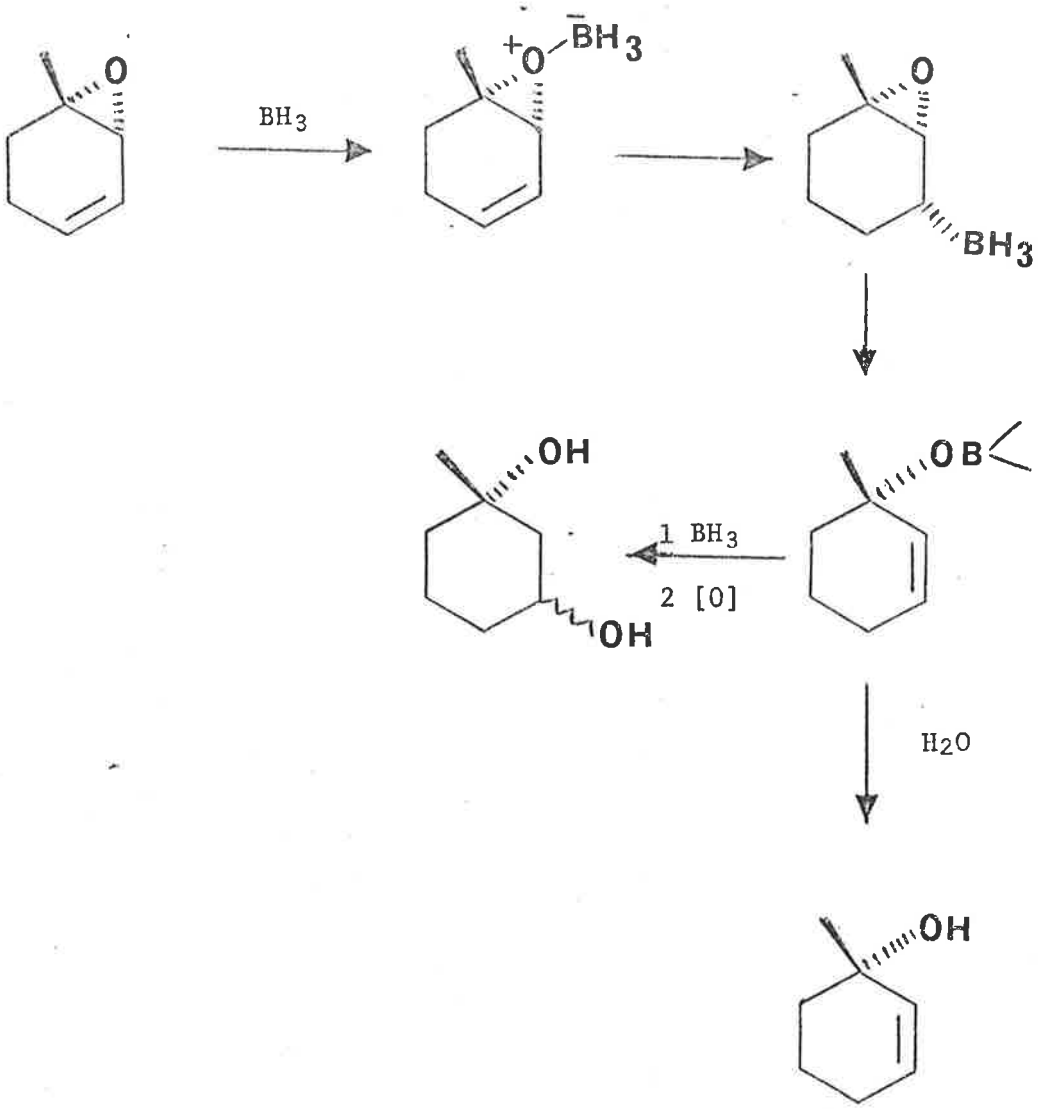


fig. 1.2

The reaction of epoxides with diborane in tetrahydrofuran* has been generally reported,[7,37] however, as slow, complex and as affording only

---

* In this discussion all reductions using diborane have been carried out using tetrahydrofuran as a solvent, unless specifically stated to the contrary.

moderate yields of products, often bespoiled by solvent participation.[37] For example, the reduction of 1,2-butylene oxide (1,2-epoxybutane, 2-ethyloxiran) with diborane at 25° proceeded relatively slowly and conceded only 48% of butanols (4% 1- and 96% 2- butanol) despite consumption of the stoichiometric amount of hydride required for quantitative reduction.[7] The reaction of 1-methylcyclohexene oxide(1) with diborane was accompanied by hydrogen evolution and yielded an organoborane (2) which was oxidized by alkaline hydrogen peroxide to the isomeric 2-hydroxymethylcyclohexanols (3) (fig. 1.3).[7]

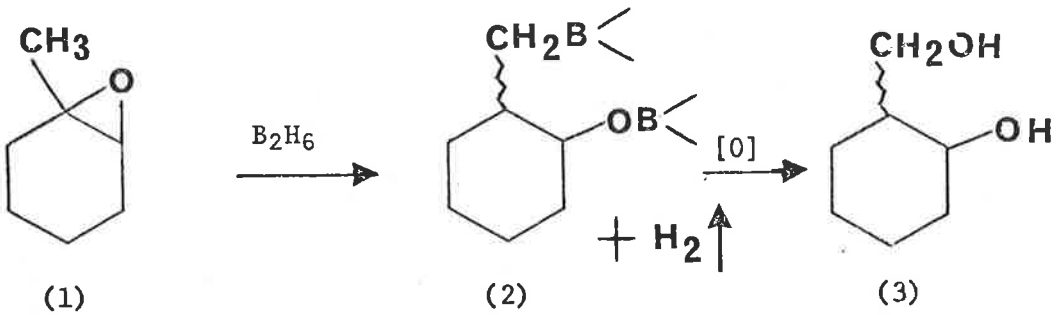
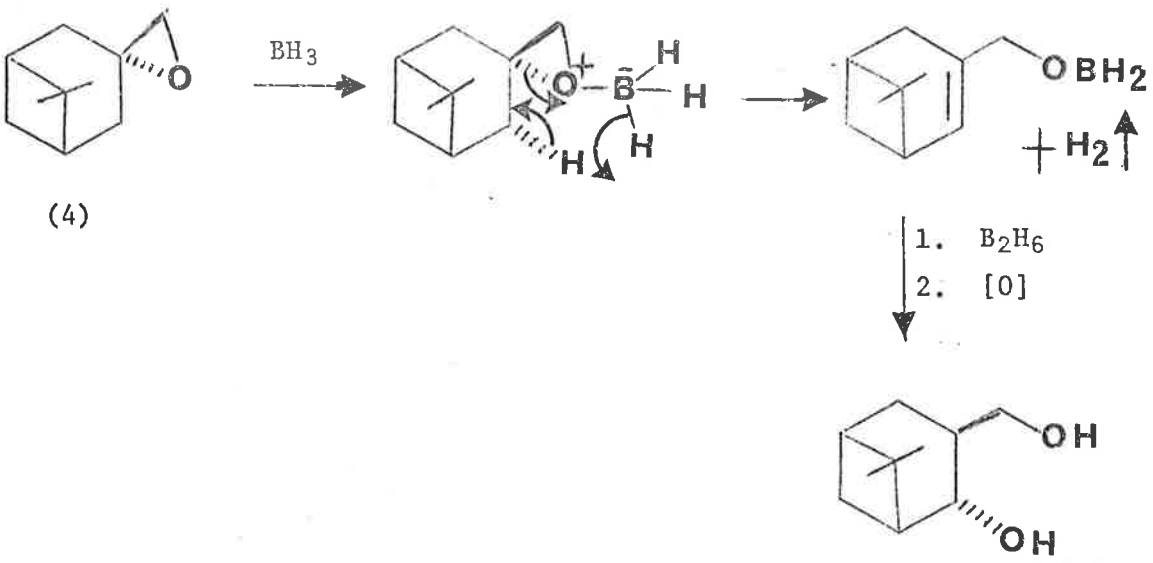
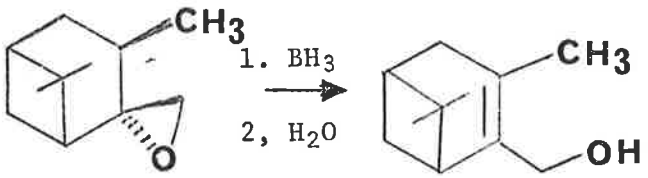


fig. 1.3

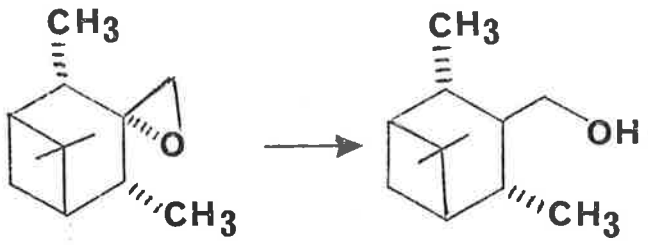
Reactions of this type, in which hydrogen is expelled, have been further studied by Bessiere-Chretien and coworkers[39] who established that a *cis* relationship between the carbon-oxygen and carbon-hydrogen bonds to be broken, was essential for hydrogen elimination. Thus (for example) the epoxides (4) and (5), which satisfy this steric requirement, undergo hydrogen evolution, whereas the third epoxide (6) in which the only available hydrogen atoms are *trans* to the oxirane ring, suffers simple cleavage (fig. 1.4). The scope and limitations of this reaction, however, await investigation.



(4)



(5)

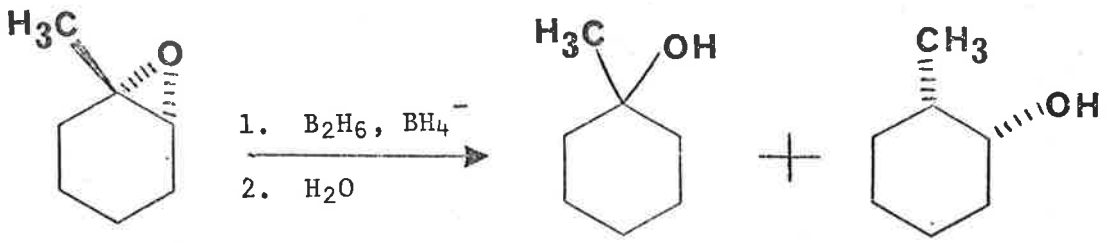


(6)

fig. 1.4

The presence of even minor amounts of either lithium or sodium borohydride has been found to drastically affect both the rate and direction of epoxide ring opening.[40] A case in point, 1-methylcyclohexene oxide (1) reacted quantitatively with diborane in the presence of sodium

borohydride to give 24% of 1-methylcyclohexanol (7) and 76% of *cis*-2-methylcyclohexanol (8) with no hydrogen evolution (fig. 1.5).[40a] This demonstrates a predominant anti-Markownikov opening of the epoxide ring.



(1) (7) (8)

fig. 1.5

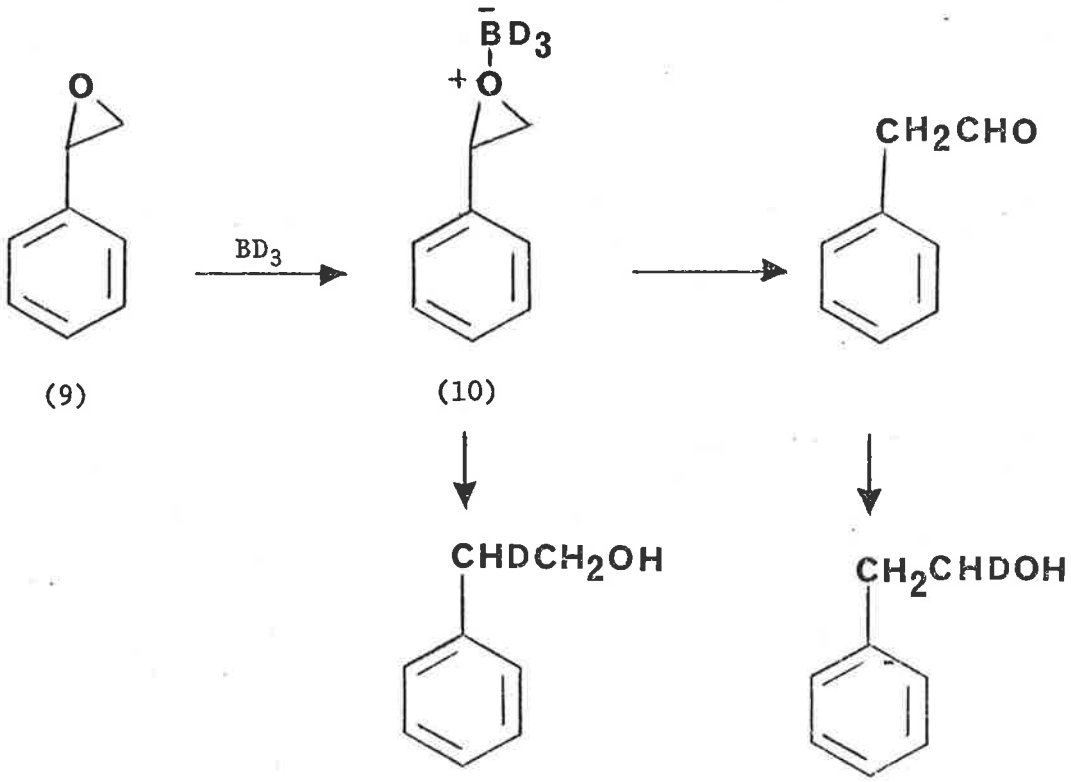
Traces of boron trifluoride also induce epoxides to undergo a fast anti-Markownikov reductive ring opening with diborane;[41] Brown suggests that this particular reaction proceeds by boron trifluoride catalyzed rearrangement of the epoxide to an aldehyde, or ketone, which is then reduced by diborane.*

Pasto observed that styrene oxide (9) after treatment with diborane-d_6 for 12 days at ambient temperature, followed by hydrolysis, yielded only 41% of 2-phenylethanol, 76% of which had been formed by a pathway involving hydride migration.[37] Analysis of the crude residue by gas chromatography revealed that extensive participation of solvent (tetrahydrofuran) had occurred. Other workers,[7,42,43] however, had

---

* In these cases of electrophilic reduction of epoxides using diborane[41] or aluminium hydride (alane)[38] involving assisted ring opening, both intermolecular and intramolecular hydride ion transfers may be implicated. Ring opening seems to occur at the carbon which is more able to stabilize a developing carbonium ion in the transition state.[46a]

found that styrene oxide reacted relatively rapidly with diborane at 25°, although Brown[7] also noted slow reduction of the aromatic ring when a fourfold excess of diborane was employed. Under the conditions of Marshall and Prager,[42,43] which involved adding the epoxide to a higher concentration of diborane-d_6 than that used by Pasto,[37] an 85% (isolated) yield of 2-phenylethanol, of which only 40% had arisen from hydride migration, was accomplished. A comparison of the two studies is outlined in Scheme 1.1.



A.	60%	40%
B.	24%	76%

A. high $[BD_3]/[epoxide]$ (ref. 43)

B. low $[BD_3]/[epoxide]$ (ref. 37)

Scheme 1.1

It was suggested[43] that the relative concentration of epoxide to borane would appear to be imprtant since the initial complex (10) reacts relatively slowly (within 6 hrs) with BH_3 and a high borane concentration would adequately compete with solvent (see reference 37).

It was, however, the reaction of epoxides with diborane during which hydrogen was evolved and which led, after oxidation, to 1,3-diols that we found intriguing and which prompted the initial investigation to probe the electronic and stereochemical demands of the reaction.[44] Arylethylene oxides, and particularly those having methyl groups on the 1- and 2- positions of the oxirane ring were considered as model systems, since examination of Dreiding stereo models had suggested that these epoxides possessed hydrogen atoms which could adopt a favourable orientation for abstraction on treatment with diborane. Relevant results of this study[42-44] shall now be discussed as a rationale for the extension of the investigation.

Simple phenylethylene oxides, on treatment with diborane at 25°, undergo selective cleavage of the benzylic carbon-oxygen bond and afford, after hydrolysis, the corresponding 2-phenylethanol (fig. 1.6).

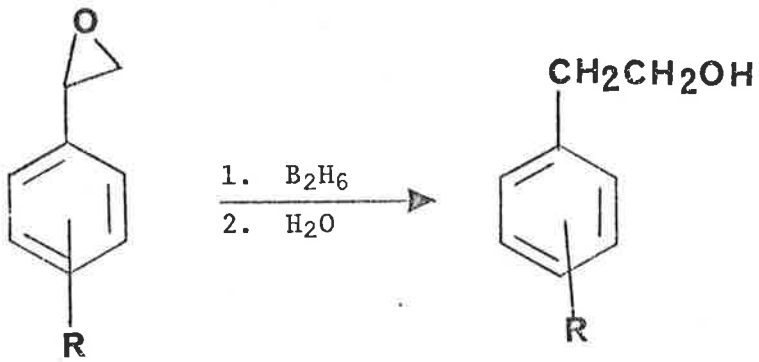
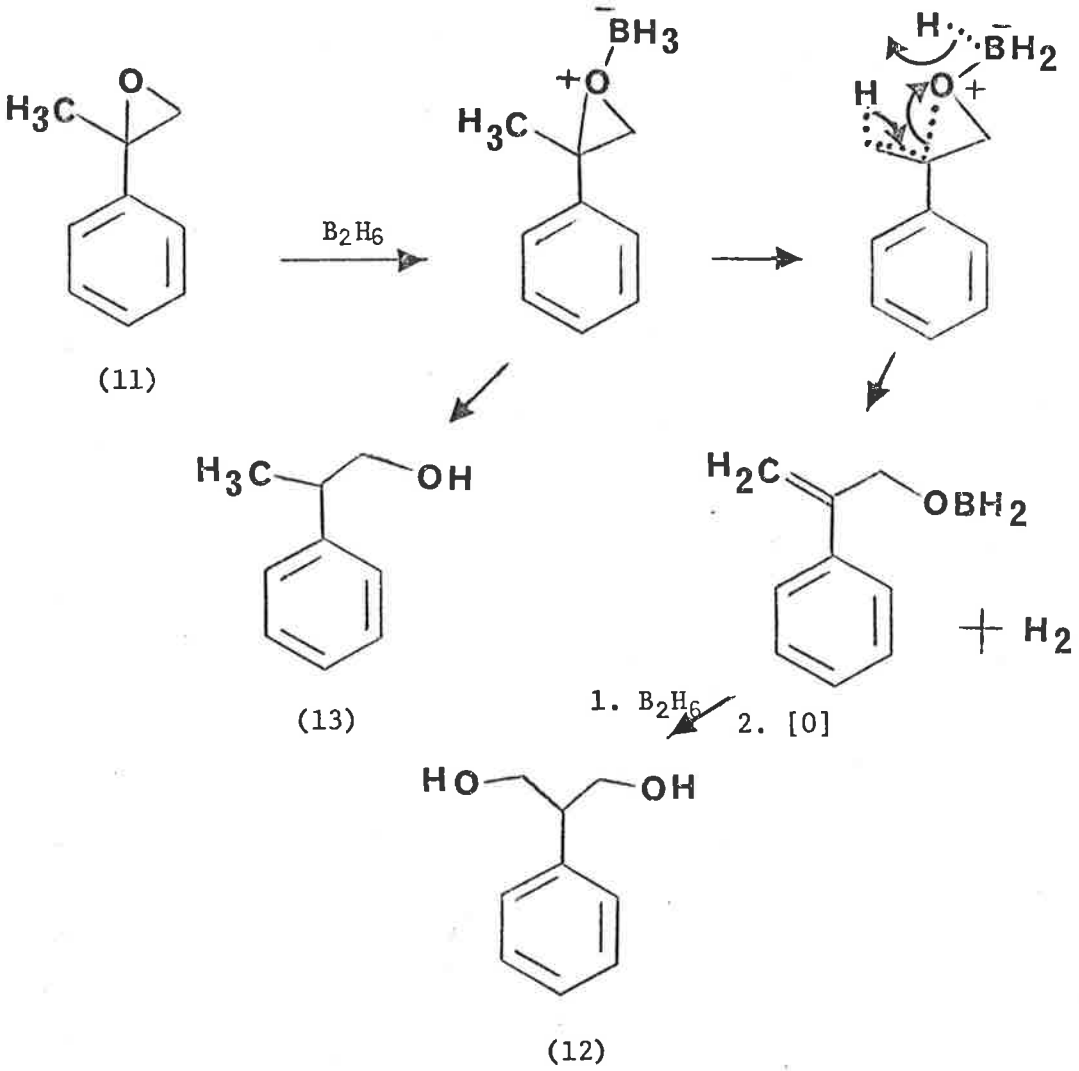


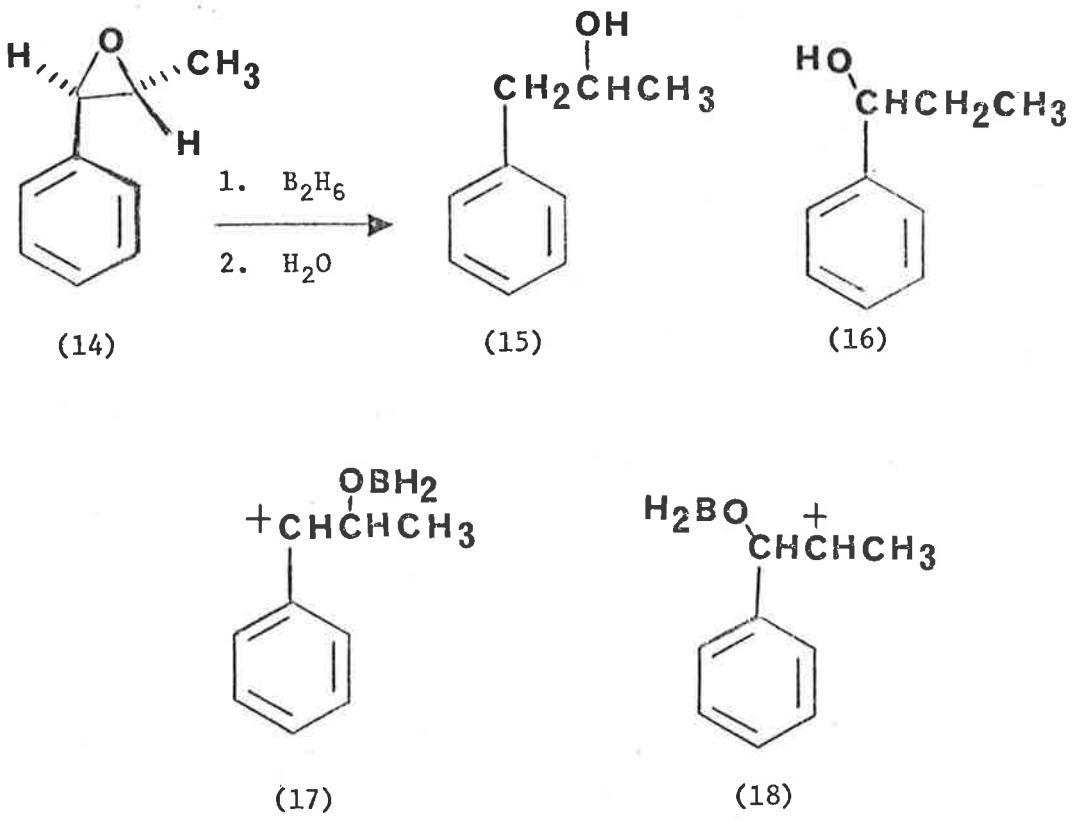
fig. 1.6

The reaction of diborane with 2-phenylpropene oxide (11), which has a hydrogen atom favourably positioned for elimination of hydrogen gas, proceeded with the evolution of 0.85 equivalents of hydrogen to give, after oxidation with alkaline hydrogen peroxide, 2-phenylpropane-1,3-diol (12) (85%) and 2-phenylpropanol (13) (15%), the latter alcohol being the sole product observed by Brown[41] when the same reaction was performed in the presence of boron trifluoride. It was proposed[42] that the products arose according to a mechanism outlined in Scheme 1.2, the relative amounts of (12) and (13) reflecting the preference for loss of hydrogen in what may be regarded as a $[\sigma_{2s} + \sigma_{2s} + \sigma_{2s}]$ pericyclic reaction over "normal" reductive cleavage of the oxirane ring, presumably a bimolecular process.



Comparison of the reaction of (E)- and (Z)-1-phenylpropene oxide, (14) and (19) respectively, with diborane strongly implied that steric crowding could prevent adequate stabilization of any developing postive charge at the benzylic carbon, thus making an alternative pathway involving the loss of hydrogen energetically attractive.

The (E)-epoxide (14) yielded only "normal" alcohols (15) (76%) and (16) (24%) from simple ring cleavage; the relative amounts of (15) and (16) (fig 1.7) probably reflect the relative energies of the carbonium ions (17) and (18) respectively, although no more than partial carbonium ion character has been inferred.

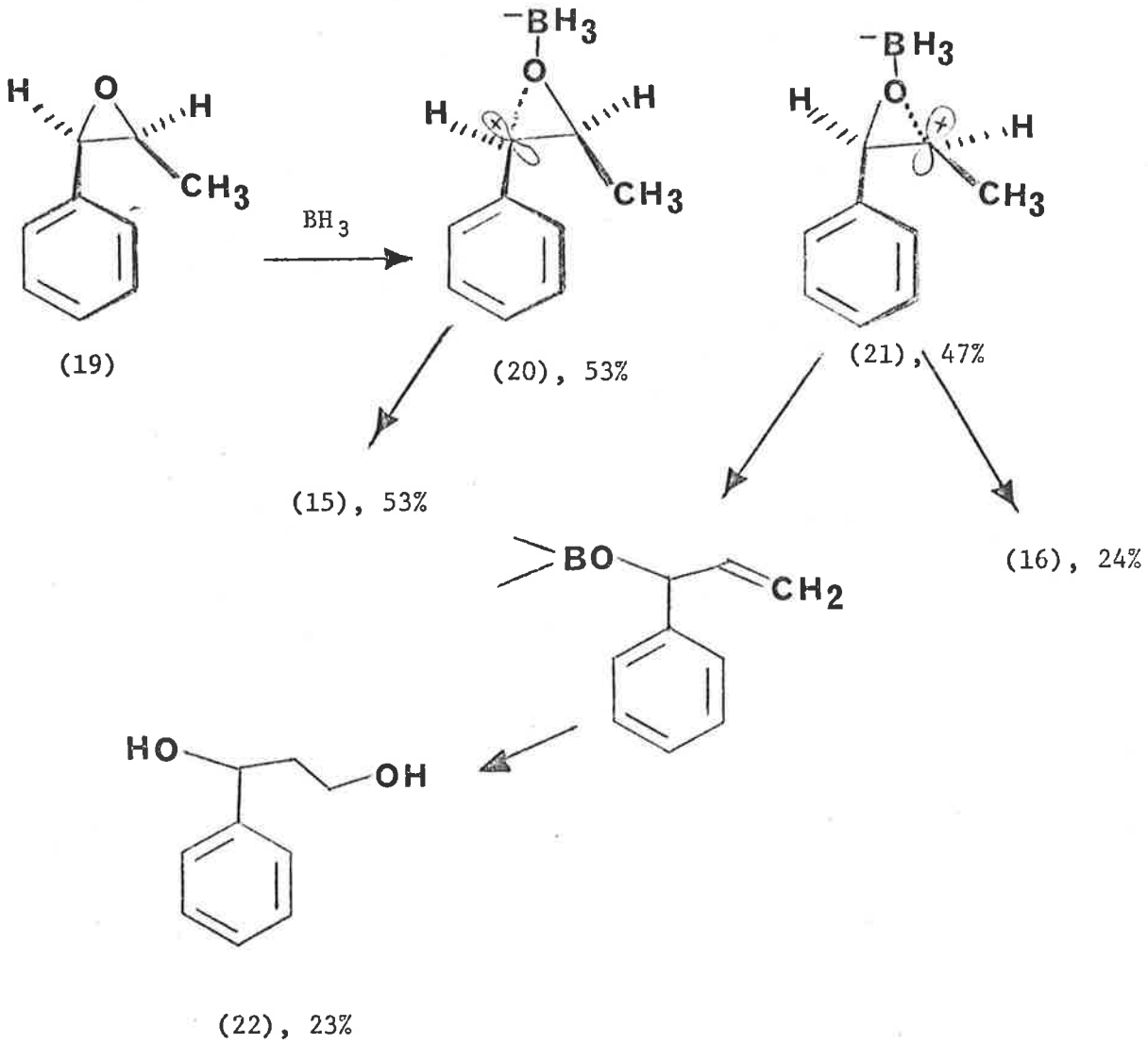


(14) (15) (16)

(17) (18)

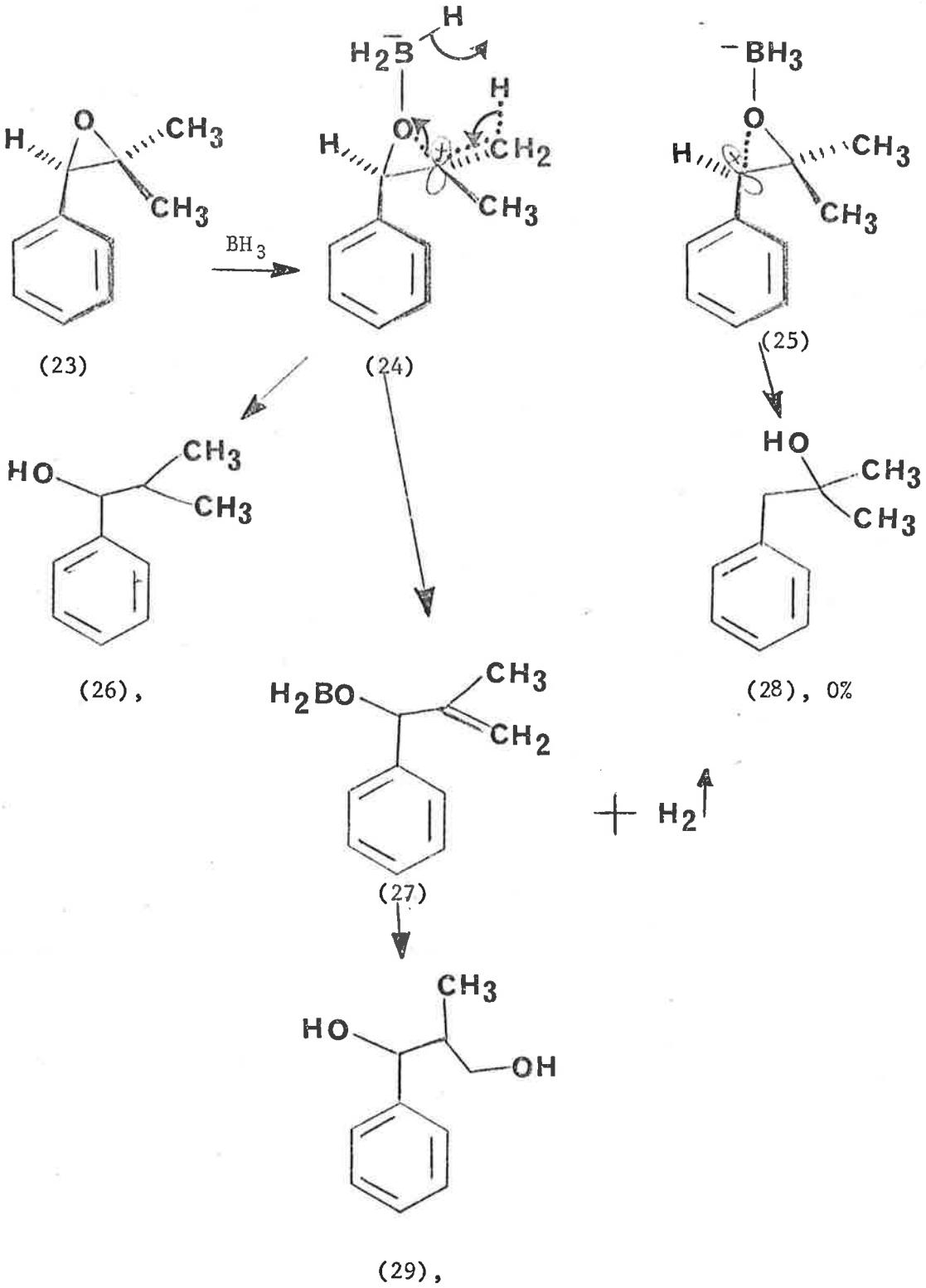
fig. 1.7

On the other hand, the (Z)-epoxide (19) reacted more slowly with diborane than the (E)-isomer (14) and gave, in addition to the alcohols (15) (53%) and (16) (24%), the 1,3-diol (22) (23%). It was suggested that in the case of (19), the phenyl ring is forced into a conformation in which overlap with a developing p orbital at the benzylic position is decreased, and the energy required to attain the transition state (20) becomes comparable to that of (21) (Scheme 1.3).



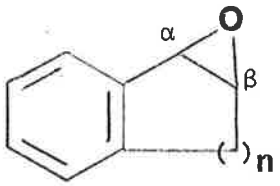
Scheme 1.3

This steric effect is obviously paramount in the reduction of 2-methyl-3-phenylpropene oxide (23); the large amount of diol (29) and the absence of alcohol (28) again most probably reflects the relative activation energies of the transition states (24) and (25). As in the example of (19), the transition state (25) required for simple ring cleavage (leading to alcohol (28)) would have a developing positive charge at the secondary benzylic position but would enjoy little or no stabilization by overlap with the aromatic π system - a consequence of the *cis* methyl group forcing the phenyl ring out of the plane of the developing carbonium ion lobe. An alternative transition state (24), in which the incipient carbonium ion at the 2 position is tertiary, would be of lower activation energy and would probably lead to the intermediate (27) which on further reaction, would afford the diol (29). (Scheme 1.4).


H
O
CH3
CH3
BH3
H2B
H
O
H
CH2
CH3
-BH3
O
H
CH3
CH3
(23)
(24)
(25)
HO
CH3
CH3
(26),
H2BO
CH3
CH2
(27)
+ H2
HO
CH3
OH
(28), 0%
(29),

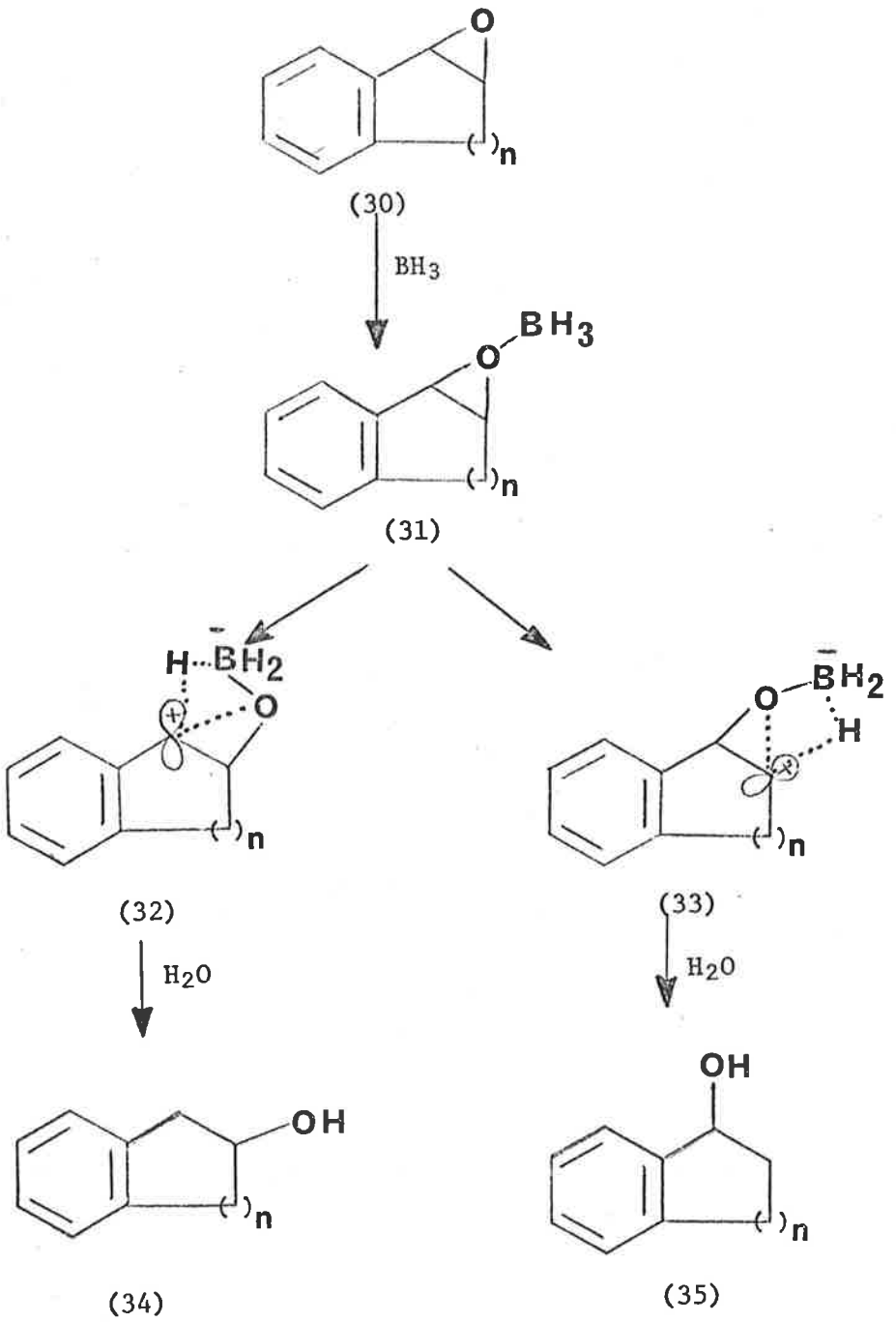
Scheme 1.4

Encouraged by these findings, it was decided to investigate the reaction of diborane with benzocyclene oxides (30), to further study the stereochemical and electronic requirements of this interesting and unusual reduction.



(30), n = 1,2...

Although these compounds are obstensibly related to the previously discussed phenyloxiranes, the increased rigidity imposed by the limited conformation(s) of the cycloalkene ring might be expected to cause these compounds to behave differently. Examination of accurate stereo models indicate that whenever n = 1 or 2, any developing carbonium ion character in the transition state (32) leading to the cleavage of the benzylic (or α) carbon-oxygen bond, could be stabilized by overlap with the p orbitals of the aromatic Π system. Alternatively, cleavage of the β carbon-oxygen bond would probably proceed *via* a transition state (33) having an incipient carbonium ion which, being secondary, would get no special stabilization. The former pathway to eventually give the alcohol (34) should therefore predominate (Scheme 1.5).



Scheme 1.5

In fact, the reduction of indene oxide (36) and 1,2-dihydronaphthalene oxide (37) by diborane, both proceeded rapidly and without significant hydrogen evolution to afford, after hydrolysis, indan-2-ol (38) and 1,2,3,4-tetrahydronaphthalen-2-ol (39) respectively. There

was no evidence (by p.m.r. spectroscopy) for the formation of indan-1-ol (40) or 1,2,3,4-tetrahydronaphthalen-1-ol (41) from the respective oxides (36) and (37).

Molecular models indicate that with increasing ring size, the lobe of the developing carbonium ion at the benzylic carbon would digress from ideal overlap with the aromatic Π system - a direct result of the limited cycloalkene ring conformations. As a consequence, the energy required to reach the transition state (32) may approach that needed for (33), ring cleavage would be of similar facility and an increase in the relative amount of (35) should be ovserved.

Moreover, whenever n = 3,4 etc., the cycloalkene ring could adopt a conformation* whereby a carbon -hydrogen bond comes into close proximity to a boron-hydrogen bond in the initially formed complex (31). Expulsion of hydrogen might then occur to give an intermediate allylic borate (42) which presumably would rapidly react further with a boron hydride to produce, after oxidation, 1,3-diols (43) (fig. 1.8).

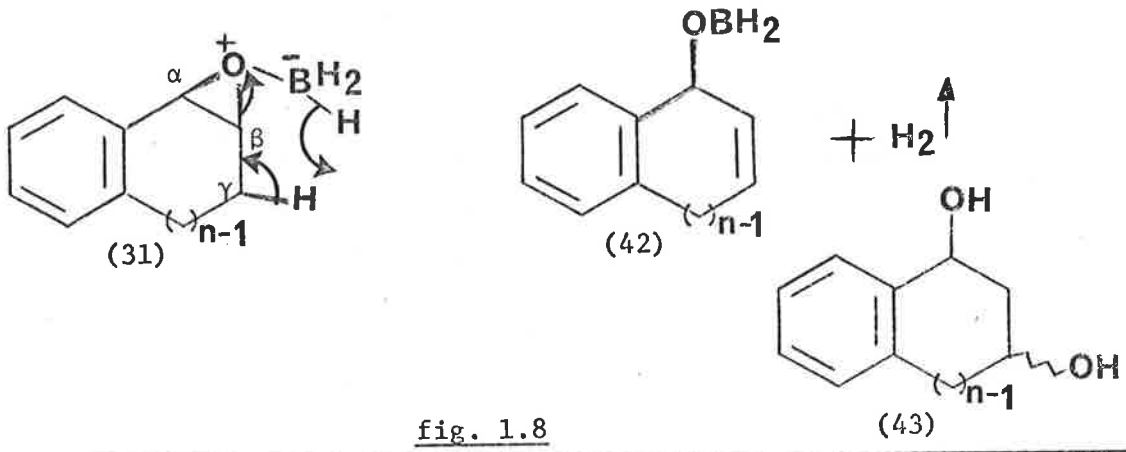


fig. 1.8

* In benzocycloheptene, for example, the activation energy required for the transformation from a chair to the less stable boat conformation is 10.9 kcal/mole.[45] From models, hydrogen is more likely to be eliminated when (31) (n = 3) is in a boat conformation.

In summary, the use of benzocyclene oxides (30) as model systems is to further resolve the electronic and stereochemical needs of the reaction of epoxides with diborane. It was anticipated that the mode and direction of reduction would be governed by the relative stabilities of the incipient carbonium ions in the first transition state (leading to oxirane ring cleavage), the establishment of which should be directly influenced by steric crowding from neighbouring groups.

CHAPTER 2

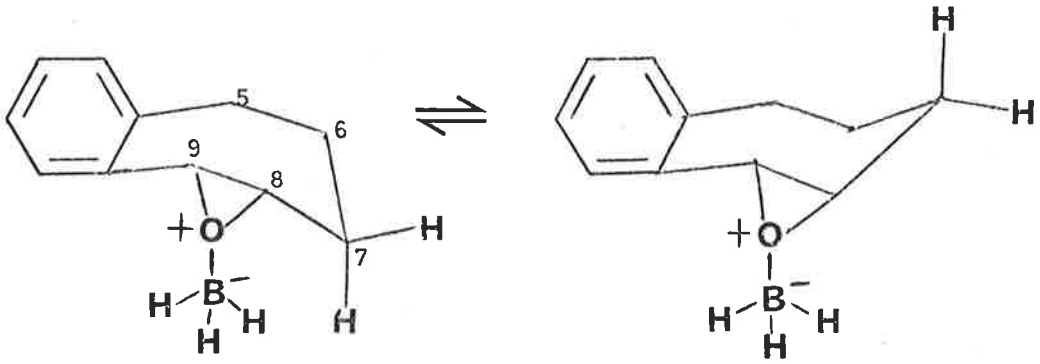
RESULTS AND DISCUSSION

CHAPTER 2.1

HYDROBORATION OF BENZOCYCLENE OXIDES

The reaction of indene oxide (36) and 1,2-dihydronaphthalene oxide (37) gave the expected alcohols, indan-2-ol (38) and 1,2,3,4-tetrahydronaphthalen-2-ol (39) respectively.[41] This is consistent with the observed mode of reaction of epoxides with another reducing agent which is also a Lewis acid, namely aluminium hydride (alane);[38, 46a] the reduction of epoxides using other reducing agents is well documented.[47-53]

The reaction of 6,7-dihydro-5H-benzocycloheptene oxide (44)* with diborane proceeded slowly and without significant hydrogen evolution to afford, after hydrolysis, 99% of the secondary alcohol (46) and only a trace of the alcohol (47) (93% conversion). Gas chromatographic analysis of the reaction mixture after mild oxidation (with alkaline hydrogen peroxide), did not indicate any appreciable change in the product composition. Although this result was somewhat disappointing, it did not come as a complete surprise since it was noted earlier that the most favourable conformation of the epoxide-borane complex (45) for hydrogen abstraction would probably need to be the boat (45a).



(45a) (45b)

---

* The numbering system of epoxides is that used by Chemical Abstracts.

Considerable effort has been made to establish the preferred conformations of cycloheptene and benzocycloheptene (48) and it is well known that both exist predominantly in the chair form.[45, 54-60] Indeed, the inversion scheme for (48) has already been described and inv involves a rate determining chair to boat step* and a less energetic psuedorotation between boat and twist-boat forms. The activation energy required for this inversion is 10.9 kcal/mol.[46]

Notwithstanding, it would appear that in a chair conformation of the complex (45b), the Cγ-H bond is too remote from the B-H bond for elimination of hydrogen gas. It is noteworthy that the alcohol (46), is also that obtained from reduction of (44) by lithium aluminium hydride;[62] the benzylic position is clearly favoured for attack by "hydride" in this epoxide.

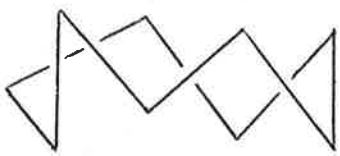
Steric and electronic factors also appear to direct attack to the benzylic position of the benzocyclooctene oxide (49) with diborane

---

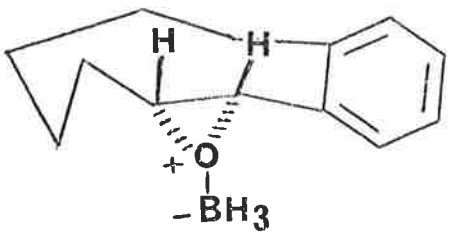
* The exact mechanism of this step is subject to mild debate,[56-58] and a recent nuclear magnetic resonance study[61] using deuterated benzocycloheptene and derivatives has failed to resolve the issue.

(Table 2.1). Analogous to the reduction of epoxide (44), the major product was the alcohol (50) arising from "hydride" attack at the more sterically-vulnerable* benzylic position. Only a minor amount of (51) was detected and no significant hydrogen evolution was noted, presumably for similar reasons outlined for the epoxide (44); the most stable conformation of (Z)-cyclooctene is estimated to be imtermediate between a chair and a boat.[59]

Early calculations of the strain energy of (Z)-cyclononene as a function of various geometric parameters suggest that this molecule is very mobile at room temperature and probably exists as a mixture of conformers.[59] A recent low temperature nuclear magnetic resonance study by Anet,[64] however, intimates a twist boat-chair (TBC) conformation for cyclononane and it is possible that the initial (Z)-benzocyclononene oxide-borane complex (55) would adopt an intermediate boat-chair conformation thus attaining minimum steric interaction (fig. 2.1).



TBC

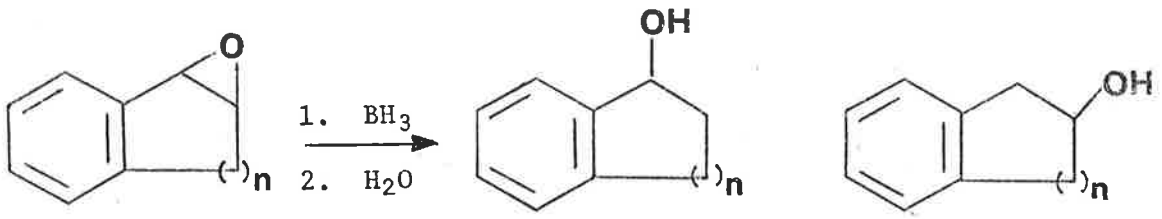


(55)

---

* The reduction of (49) with lithium aluminium hydride paralleled that of (44) as the nonbenzylic alcohol (50) was obtained.[63]

REDUCTION OF BENZOCYCLENE OXIDES WITH DIBORANE



(30) α-ol (35) β-ol (34)

		ALCOHOL PRODUCT			
n	Epoxide	β-ol	α-ol	Ratio [A]	% Yield
1	(36)	(38)	(40)	100:0 [B]	98
2	(37)	(39)	(41)	100:0 [B]	97
3	(44)	(46)	(47)	99:1	91
4	(49)	(50)	(51)	96:4	28
5	(52)	(53)	(54)	65:35	89

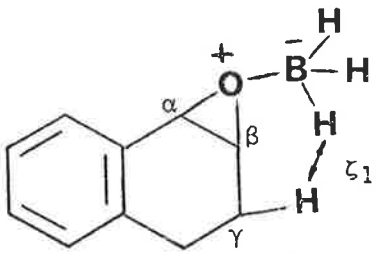
A Ratio refers to the relative yields of β-ol : α-ol as determined by gas chromatographic analysis.

B See reference 42.

Table 2.1

In addition, models suggest that in this conformation* any developing p orbital at the benzylic C-α position would not enjoy ideal stabliza-tion by overlap with the aromatic Π system, thus raising the energy required for cleavage of the Cα-O bond to that of the Cβ-O bond. Another conformational effect of the cyclononene ring is a decrease in the steric hindrance of the secondary Cβ position towards nucleophilic attack compared to the 7- and 8- membered homologues (44) and (49) respectively. Hence the increased relative yield of the alcohol (54) may be rationalized on both steric and electronic grounds.

The lack of hydrogen evolution leading eventually to 1,3-diols (43) is possibly due to the spatial geometry of the preferred conformation of the complex (31); the shortest interatomic distance (ζ) between C_γ-H and B-H is too great for elimination of hydrogen gas. This is supported by examination of accurate models where ζ is greater in the complex (31) than in a complex between borane and an epoxide bearing a methyl group on the oxirane ring as in the phenylpropene oxides (fig. 2.2) discussed earlier.



(31)

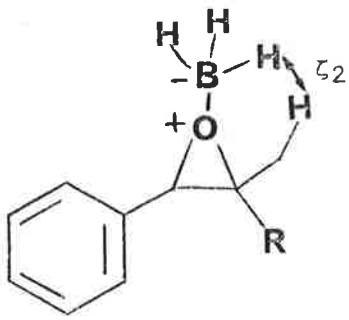


fig. 2.2

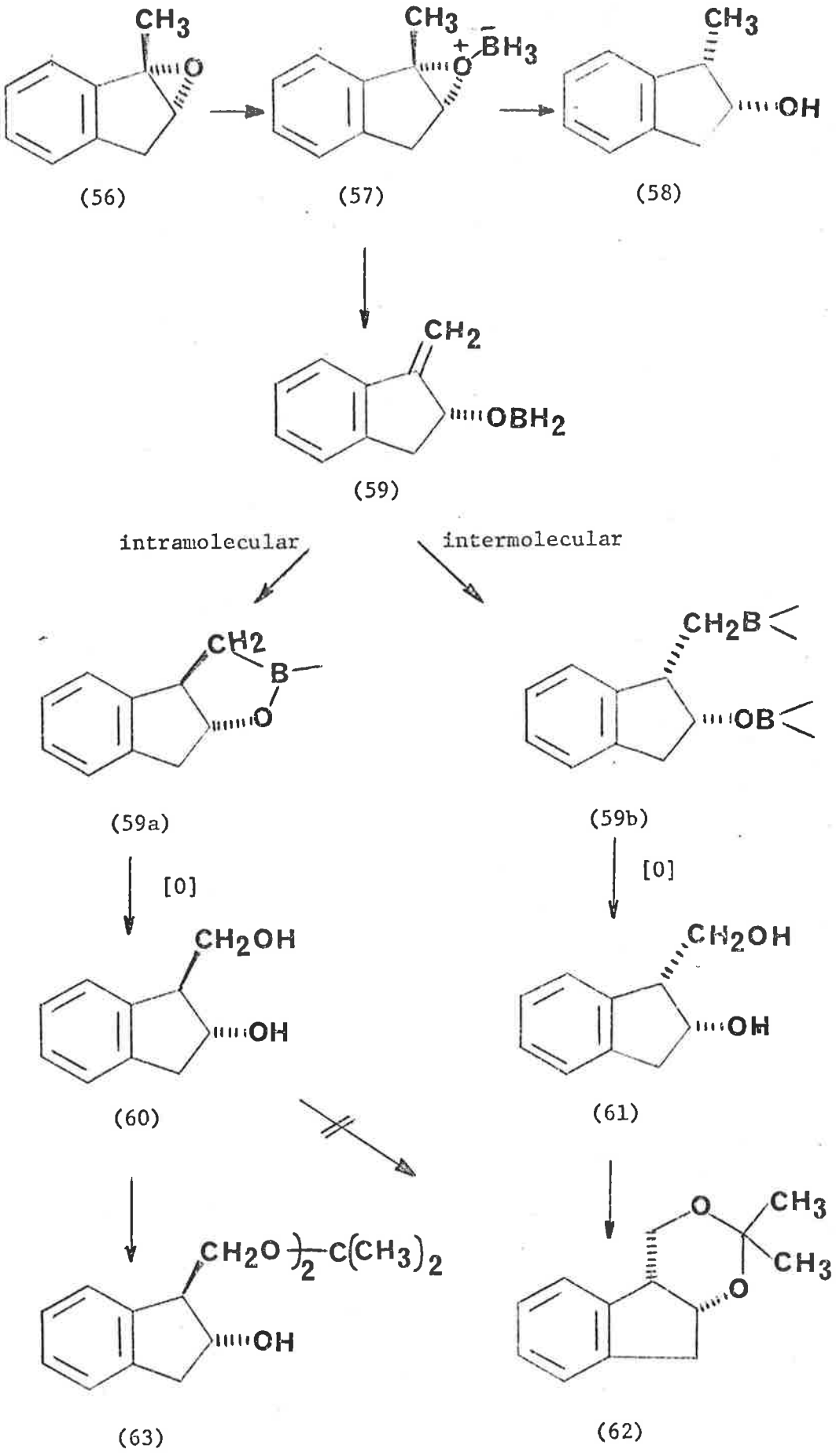
* Although it is realized that, by analogy to cyclononene,[59] the complex (55) could adopt many possible conformations, models suggest that those in which a partial positive charge at the benzylic position could be stabilized by overlap with the aromatic Π system, would seem to suffer from severe steric interactions elsewhere in the cyclononene ring.

Therefore our attention focussed on more direct analogues of these oxides viz., benzocyclene oxides having a methyl group on the oxirane ring, since these should, for reasons already outlined, afford 1,3-diols on hydroboration-oxidation.

Indeed, the reaction of 3-methylindene oxide (56) with diborane proceeded rapidly at room temperature, and with the vigorous evolution of hydrogen and gave, after mild oxidation: the *trans*-diol (60) and *cis*-1-methylindan-2-ol (58) (Scheme 2.1). Assignment of the *trans* configuration to (60) was based on the inability of the diol isolated from the reaction to form an acetonide on treatment with 2,2-dimethoxypropane and acetone under normal acid-catalyzed conditions;[42, 65] models strongly suggest that a *trans*-diol (60) would be sterically incapable of forming an acetonide whereas a *cis*-diol (61) should easily form the 1,3-dioxan (62). The product isolated from this reaction was an acetal, the spectroscopic data for which were consistent with the structure (63).* The formation of the *trans*-diol (60) presumably reflects a preference for intramolecular hydroboration of the intermediate allylic borate (59); perhaps steric interaction between the benzylic hydrogens force the molecule into a favourable conformation (59a) for facile intramolecular hydroboration.

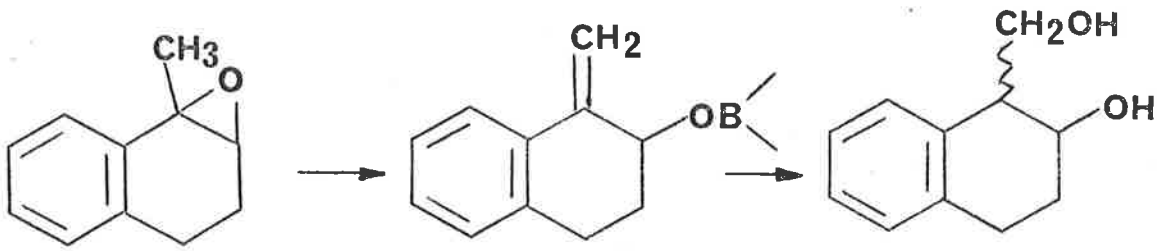
---

* It is irrelevant to the assignment of the stereochemistry to the diol whether the ether linkage in the acetal (63) is through the primary or secondary oxygen bridge; the formation of the acetonide (62) from a *cis*-diol would still be expected to be favoured over an acyclic acetal.[65] Since primary alcohols are usually stronger nucleophiles than secondary alcohols,[66] an acetal (63) through the primary C-O bond might be expected to be preferred.


CH3
O
BH3
OH
(56)
(57)
(58)
CH2
OBH2
(59)
intramolecular
intermolecular
CH2
B
O
CH2B
OB
(59a)
(59b)
[0]
[0]
CH2OH
OH
(60)
(61)
CH2O
C(CH3)2
2
O
CH3
(63)
(62)

Scheme 2.1

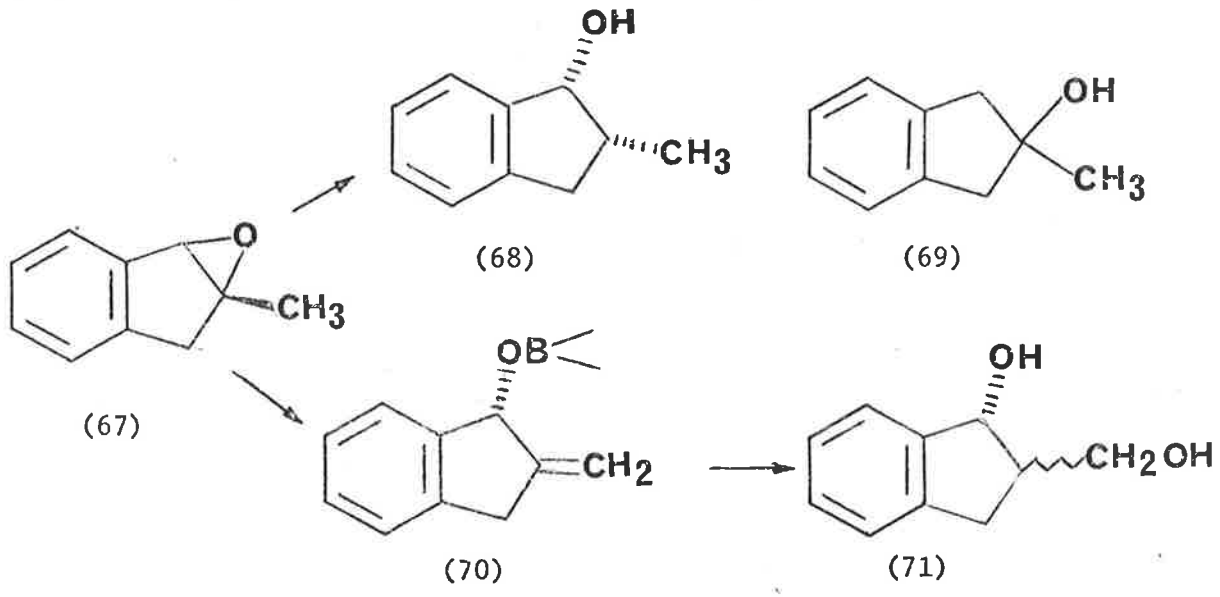
A rapid evolution of hdrogen also accompanied the addition of 3,4-dihydio-1-methylnaphthalene oxide (64) to diborane at ambient temperature (Scheme 2.2). Oxidative workup of the reaction mixture afforded the isomeric diols (65) in near quantitative yield. A model of (66) suggests that the intramolecular hydroboration of the intermediate (66) would be slowed down by steric interactions to allow intermolecular reaction to compete.



(64) (66) (65)

Scheme 2.2

The hydroboration of 2-methylindene oxide (67) proceeded more slowly than the isomer (56) and yielded an isomeric mixture of 1-hydroxy-2-indanmethanol (71), together with the alcohols (68) and (69) (Scheme 2.3).



(68) (69)

(67)

(70) (71)

Scheme 2.3

The lower amount of diol (71) from this reaction is probably a reflection of the slower rate of formation of (70) than (59) (from (57)) under comparable conditions; intramolecular and intermolecular hydroboration of (70) occur with comparable ease, unlike (59) where the intramolecular hydroboration seems sterically favoured. The relative amounts of (68) and (69) probably reflect the relative energies needed to achieve the transition states (72) and (73) respectively (fig. 2.3); relief in non-bonded hydrogen eclipsing being greater in (73) than in (72).

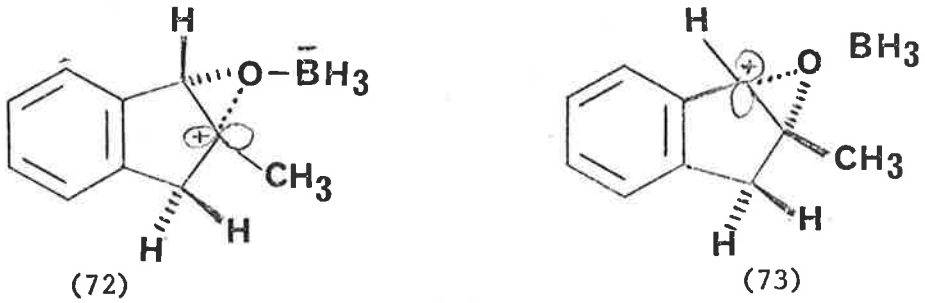
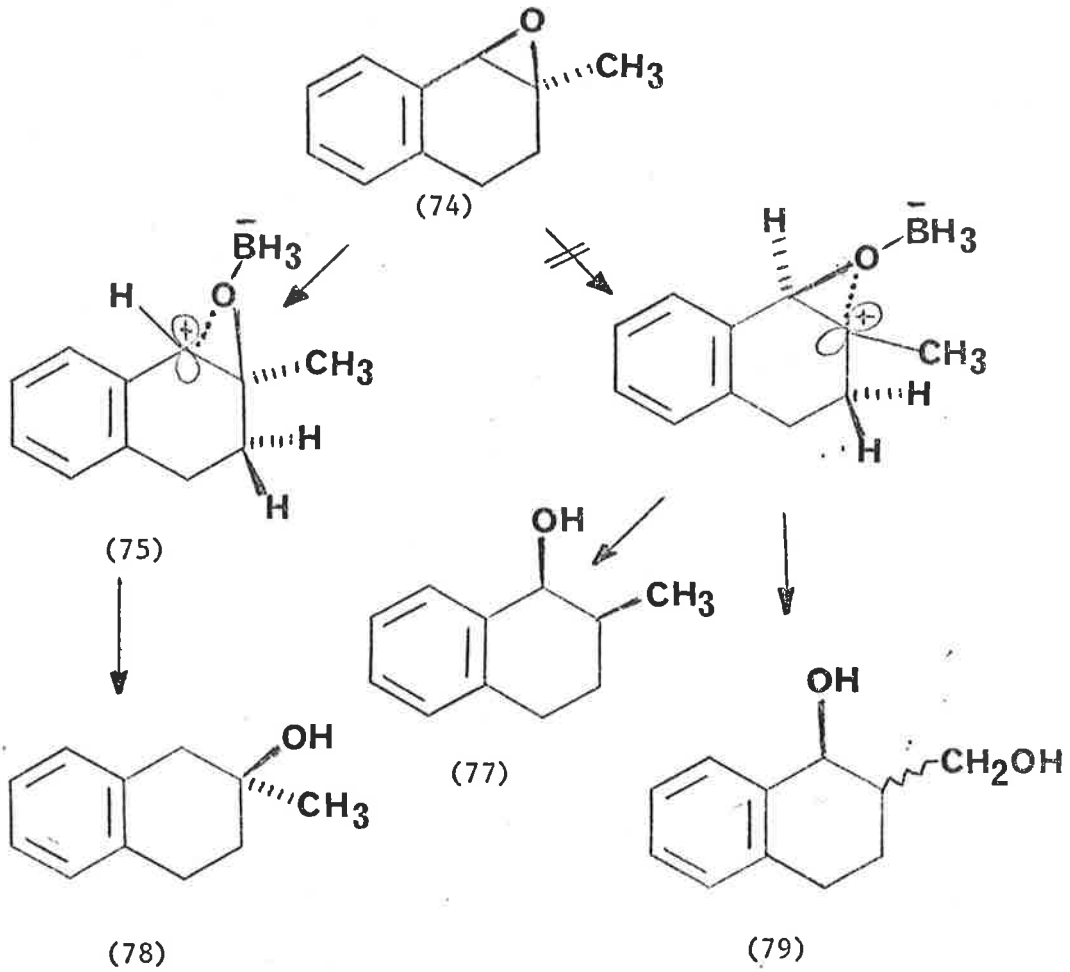


fig. 2.3

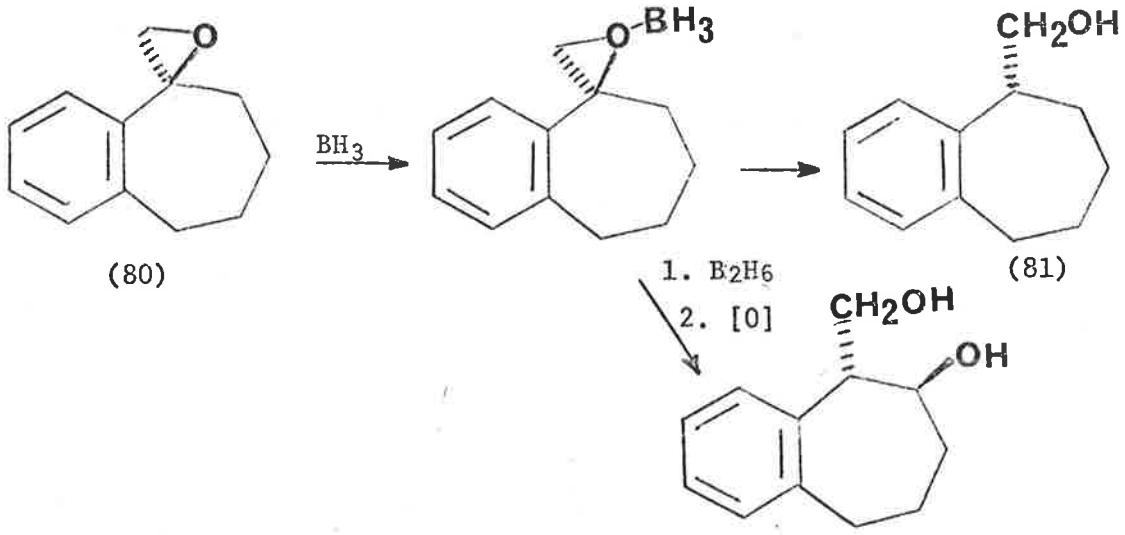
This unusual steric factor could drive the reaction *via* (72) to a greater extent than otherwise might have been expected in comparing a tertiary to a benzylic incipient carbonium ion.

In a six-membered ring, this eclipsing does not occur and indeed the reaction of the epoxide (74) with diborane proceeded through the transition state (75) to afford the tertiary alcohol (78) as the principal product. Very little hydrogen evolution with the consequent formation of (79) was observed; such a dramatic change in the direction of ring opening was not anticipated.



Scheme 2.4

Finally, in view of the observations of Bessiere-Chretien,[39] it was envisaged that the reductive cleavage of the exocyclic epoxide (80) with diborane should give, in addition to the primary alcohol (81), the diol (82), according to the mechanism outlined in Scheme 2.5.



Scheme 2.5

For reasons to be described in Chapter 2.3, the synthesis of (80) was not, however, accomplished.

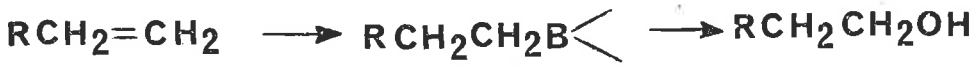
In conclusion, it has already been shown that exocyclic epoxides can undergo a reaction with diborane during which hydrogen is eliminated, provided certain steric requirements are fulfilled.[39] Epoxides which are inherently part of a ring system, e.g., the benzocyclene oxides (30) suffer simple ring cleavage and afford the alcohol predominantly from hydride attack at the carbon position best able to tolerate positive charge in the transition state, although this may be moderated by steric factors. Hydrogen evolution with the consequent formation of 1,3-diols, does not occur to any significant extent, possibly due to the inaccessibility of the Cγ-H for abstraction. On the other hand, if the oxirane ring has a methyl group on either the C-α (benzylic) or C-β position, 1,3-diols are often obtained after oxidation. In these cases, the pathway for simple cleavage is dominated by electronic factors and leads to the anti-Markownikov ring opened alcohol, that is *via* the more stable incipient carbonium ion.

CHAPTER 2.2

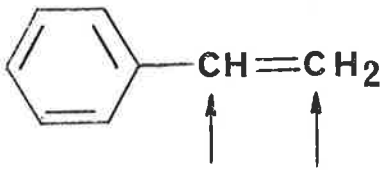
HYDROBORATION OF BENZOCYCLENES

Early observations of the reaction of diborane with olefins indicated that the addition was slow, and required elevated temperatures and extended reaction times.[67] Since the discovery that this reaction is catalyzed by ether solvents,[68] and that oxidation of the resulant organoborane with alkaline hydrogen peroxide yields the corresponding alcohol, chemists have been provided with a simple, efficient method for the anti-Markownikov hydration of olefins.[27, 30, 32]

Simple alkenes undergo hydroboration predominantly on the terminal position and this distribution is not altered markedly by branching on the alkyl group.[69, 70]



An aryl substituent, as in styrene, causes increased substitution to the non-terminal position.[70]



This distribution can be altered considerably by substituents in the aromatic ring.[70-72] For example, the presence of an *ortho* or *para* electron-donating substituent (e.g. *p*-methoxy) increases this

distribution to the terminal position whereas an electron-withdrawing group (e.g. *p*-chloro) decreases it (fig. 2.3);[70] the direction of hydroboration of these styrenes is related to the Hammett constant σ^+ of the substituent.[71]

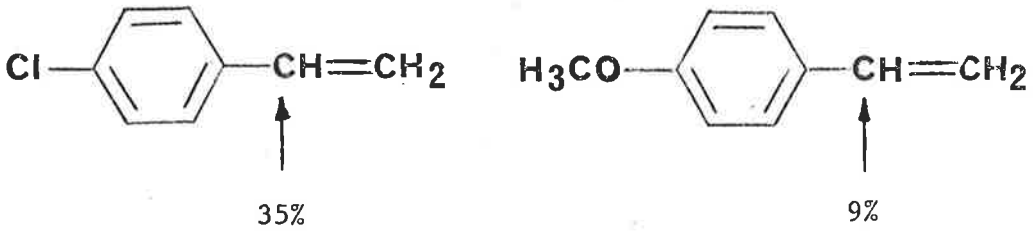


fig. 2.3

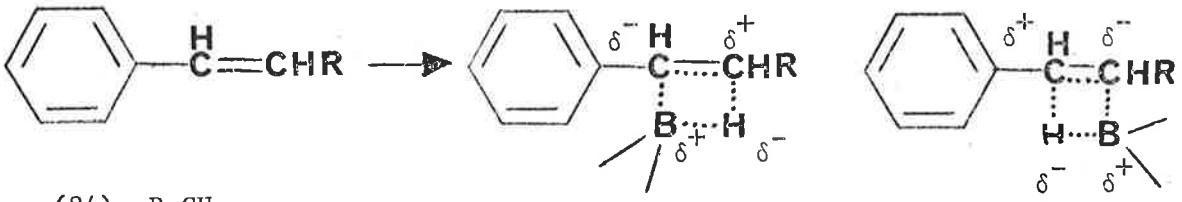
Electronegative substituents on alkenes can greatly influence the direction of addition of the boron-hydrogen bond.[31b, 36] For instance, the usual terminal mode of addition is reversed upon hydroboration of 1,1,1-trifluoroprop-2-ene.[73, 74] In this molecule, however, the effect of the electron withdrawing CF_3 group may be to shift the Π electrons of the double bond toward the central carbon atom, thus making this atom more susceptible for bonding to the vacant orbital of the attacking boron.

The hydroboration of cyclic olefins proceeds by an anti-Markownikov *cis* addition of the B-H bond to the Π bond of the olefin, entailing a cyclic, four-centre transition state,[70, 75-83] and it is thought that direction of addition is controlled by the preferred polarization of the B-H bond and the C-C double bond, and by steric factors.[70, 81, 82]

Indeed, this *cis* hydration has been exploited for the selective synthesis of diastereomeric alcohols.[84]

In order to account for the high stereospecificity upon hydroboration with diisopinocampheylborane (dimer), an alternate transition state involving a small perturbation from a triangular bridge is proposed[85] and this is supported by orbital symmetry considerations.[86] On the other hand, if the hydroboration is highly exothermic with low activation energy, then orbital symmetry control may not be important in an early transition state.

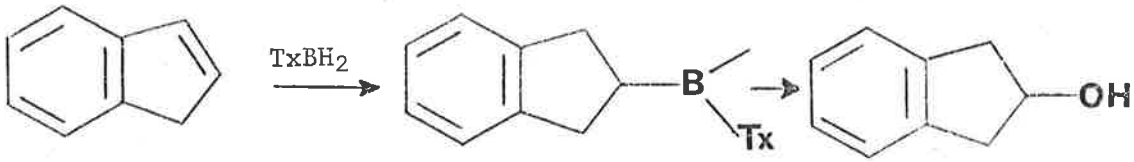
In an early study of the directive effects in the hydroboration of styrenes, Brown observed that, in (E)-1-phenylpropene (84), where the effects of the two groups were in direct competition, an 85% substitution to the carbon *alpha* to the phenyl group was obtained (fig. 2.4).[70]



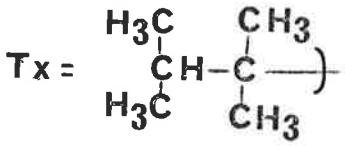
(84), R=CH_3

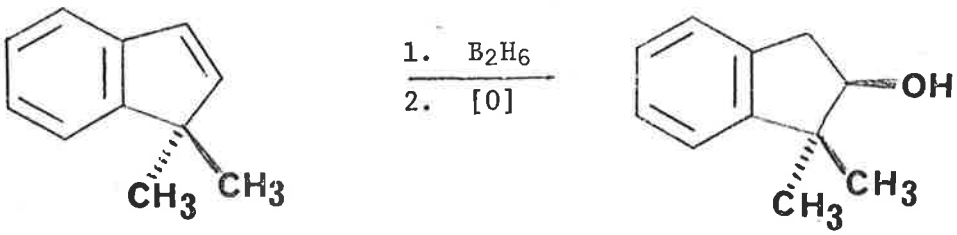
fig. 2.4

Recently it was found that the reaction of thexylborane with indene (85) proceeded to place the boron exclusively (by p.m.r. spectroscopy) on the carbon *beta* to the aromatic ring.[44] Remarkably the hydroboration-oxidation of 3,3-dimethylindene (86), in which the C_2-position is sterically crowded by the adjacent *gem*-dimethyl group, also afforded a good yield (70%) of the corresponding indan-2-ol (87) (fig. 2.5)[88]



(85)



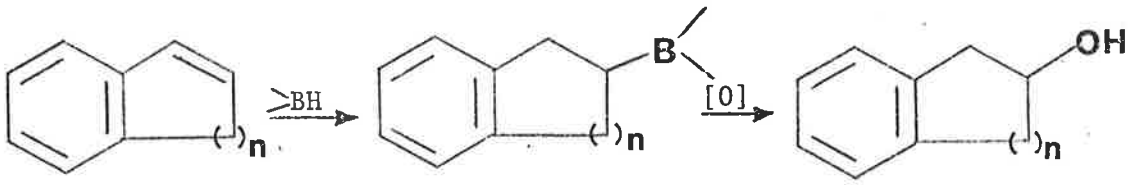


(86)

fig. 2.5

It was thus envisaged that the hydroboration of benzocyclenes (88) should provide a convenient and independent synthesis of the alcohol (34) obtained from the hydroboration of the benzocyclene oxides (30); this was in spite of Brown's observation on the hydroboration of (E)-1-phenylpropene.[70] Moreover, it was considered that employment of more

stereoselective thexylborane[89] would further promote attachment of boron to the carbon *beta*[*] to the phenyl ring (Scheme 2.6).



(88), n = 1-5 (34)

Scheme 2.6

The hydroboration-oxidation of the benzocycloheptene (89) (or (88), n = 3) with thexylborane afforded, however, the benzylic alcohol (47), with only a trace (by p.m.r. spectroscopy) of the alcohol (46) resulting from initial addition of boron to the β position. In the hope of explaining these apparently incongruous results, a detailed study of the reaction of benzocyclenes (88) with diborane and thexylborane was initiated.

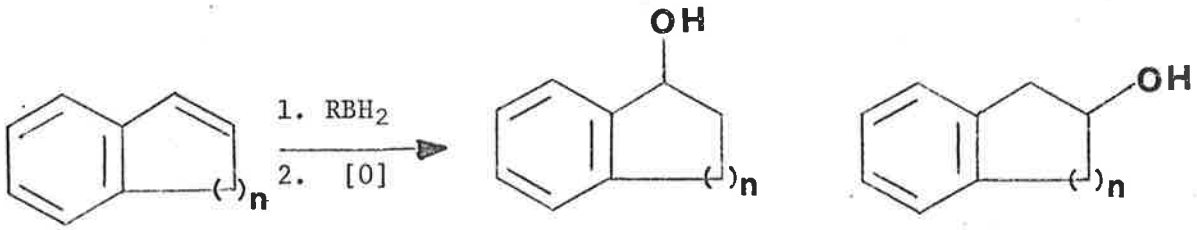
Each of the benzocyclenes was treated separately with diborane and freshly prepared thexylborane[89] at 0° for 0.5 hr and at *c*. 25° for 2.5 hr. The reaction was then cooled, oxidized with alkaline hydrogen peroxide and analalyzed by gas chromatography. These results[†] are summarized in Table 2.2.

---

* To avoid confusion, (due to the varied literature nomenclature of benzocyclenes), the olefinic carbon adjacent to the aromatic ring shall in this text, be referred to as the *alpha* (α) position, and its carbon partner the *beta* (β) position.

† A later search of the literature revealed that the hydroboration of 1,2-dihydronaphthalene yielded predominantly 1,2,3,4-tetrahydronaphthalen-1-ol.[90]

HYDROBORATION OF BENZOCYCLENES (88) WITH DIBORANE AND THEXYL BORANE.



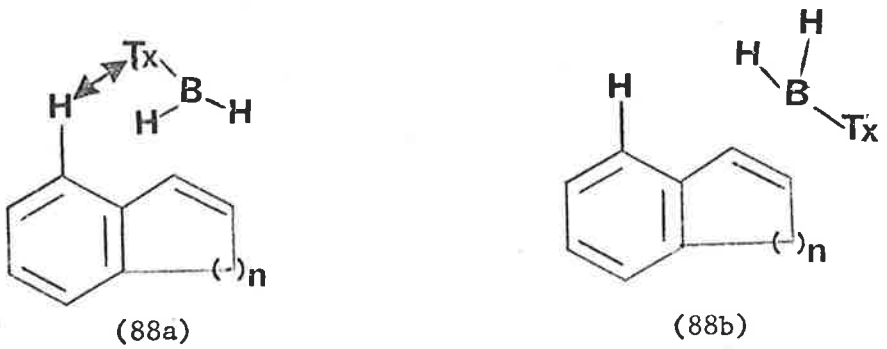
(88) α-ol β-ol

Benzocyclene n	% Yields [A] B_2H_6 α-ol : β-ol	% Yields [A] $TxBH_2$ (R = Tx) α-ol : β-ol
1, (85)	14 : 86	1 : 99
2, (90) [B]	92 : 8	—
2, (90)	90 : 10	90 : 10
3 (89)	94 : 6	88 : 12
4 (91)	86 : 14	75 : 25
5 (92)	89 : 11	62 : 38

A Yields are relative yields as determined by gas chromatography. The reaction went essentially to completion in each case.

B Reference 90.

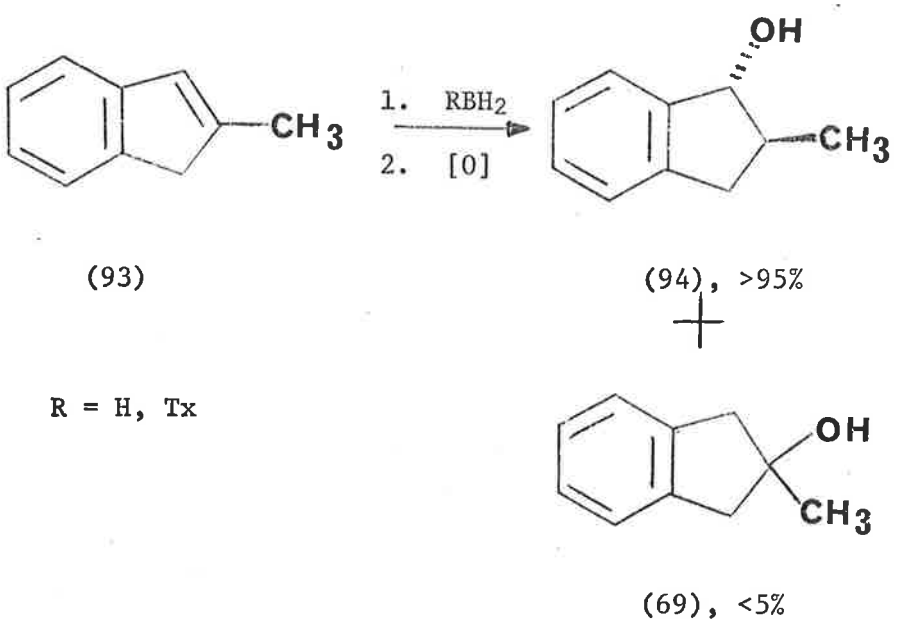
From Table 2.2 it can be seen that indene was peculiar in that hydroboration proceeded to place the boron on the β carbon, whereas all the other cases (n = 1) had the boron attacking the α carbon. It is noteworthy that the use of thexylborane led to a decrease in regio-specificity of addition. This strongly intimates that the β carbon was favoured sterically, but the α carbon was preferred electronically as the position to which boron was attached in (88) (n ≠ 1). The increase in amount of β-ol (34) from the use of thexylborane was presumably due to steric interaction between the *peri* hydrogen on the aromatic ring and the bulky thexyl group, thus discouraging the boron from attacking the α position (88a) rather than the β position (88b) (fig. 2.6).



(88a) (88b)

fig. 2.6

The "normal" direction of addition was reversed in the hydroboration of 2-methylindene (93), the boron preferring the less substituted α carbon and this selectivity was enhanced by the use of thexylborane. Similarly the β-ol was the almost exclusive product from the hydroboration-oxidation of 1-methyl-3,4-dihydronaphthalene (95) (Scheme 2.7).



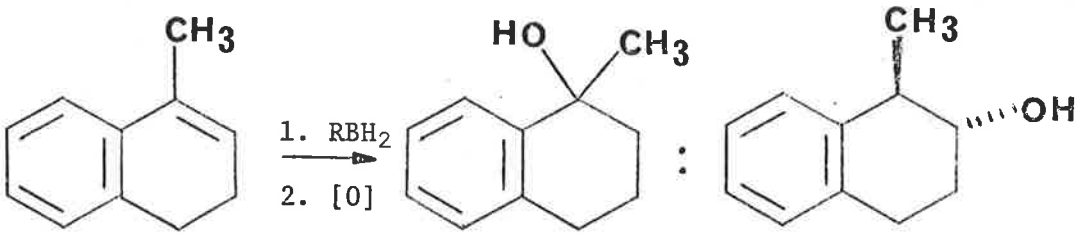
(93)

(94), >95%

+

R = H, Tx

(69), <5%



(95) (96) (97)

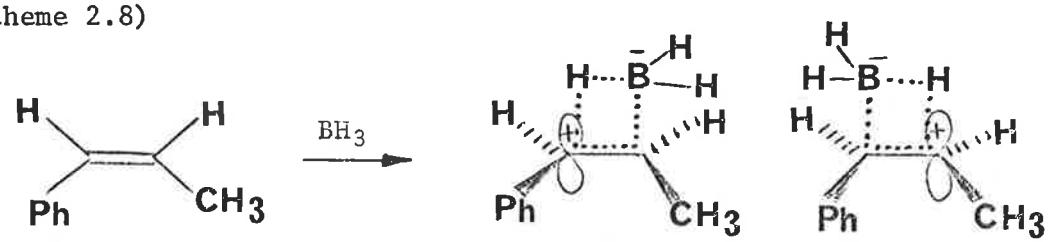
R = H	9	:	91
R = Tx	0	:	100

Scheme 2.7

This is, of course, consistent with the usual observed mode of addition to trisubstituted double bonds in the hydroboration reaction.[69,70]

If steric interaction between the allylic hydrogens of benzocylene (88) ($n \neq 1$) and the attacking boron hydride was an important factor in directing attack to the α carbon, then an increase in the relative yield of α-ol should have been observed when thexylborane was used, but in fact the opposite occurred in all cases of (88). Steric

interaction between the *peri* hydrogen and the attacking boron hydride also appears an unlikely reason for the high specificity using diborane, (which has a low steric demand), since models indicate that this repulsion would be more severe in the higher benzocyclenes (88) (n > 1) where attack is favoured on the α carbon. By analogy, an increase might be expected in the relative yield of 1-phenylpropan-1-ol (16) from the hydroboration of (Z)-1-phenylpropene (98) compared to its (E)-isomer (84), if the transition state (99) was of less significance due to the methyl group forcing the phenyl ring out of planarity with the double bond, thus preventing effective stabilization of a developing p orbital with the aromatic ring. Experimentally, the difference in the distribution of the alcohols (15) and (16) from the hydroboration of (98) is only marginal suggesting that the inductive effect of the phenyl group is more important than stabilization of the incipient positive charge (Scheme 2.8)



(98) (99) (100)

(15), 86 : (16), 14

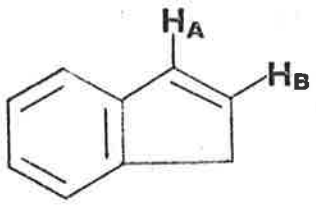
(84) ⟶ 85 : 16

Scheme 2.8

Reasons for the strong preference of boron to bind to the β carbon of indene are clouded. Since the use of thexylborane increased the proportion of attachment at the β position in all cases of (88),

obviously it is this position which is sterically favoured. A comparison of the chemical shifts of the α- and β- olefinic protons (H_A and H_B respectively) of (88) show, that with increasing ring size, there is an upfield shift of H_A and H_B (compared to indene) indicating that these hydrogens are less deshielded[91] (Table 2.3). This, in turn, implies that the double bond is no longer in complete conjugation with the aromatic ring, unlike planar indene; a direct consequence of the increasing distortion of the cycloalkene ring from planarity.

CHEMICAL SHIFTS OF H_A AND H_B OF BENZOCYCLENES



n	H_A (p.p.m.) [A]	H_B (p.p.m.)
1	6.84, 6.82 [B]	6.47, 6.50 [B]
2	6.41, 6.32 [C]	5.87, 5.82 [C]
3	6.37	5.77
4	6.40	5.84
5	6.57	5.77

A Recorded as solutions in CCl_4 on a Varian T-60 Spectrometer operating at 60 MHz

B Reference 92.

C Reference 93.

Perhaps because of this slight decrease in overlap of the olefinic Π orbitals with the aromatic Π orbitals, the negative inductive effect of the aromatic ring possibly outweighs the positive mesomeric effect, with the net result the α carbon would be the principal donor of the olefinic Π electrons to the vacant orbital of the attacking boron. Indeed, calculations show that in 1,2-dihydronaphthalene, the electron density of the α carbon is greater than the β position[94] and this is presumably also the case for the other benzocyclenes (88) (n = 3-5).

If the β carbon of indene was favoured electronically for attack then this position might be expected to have a higher electron density than the α carbon. This is not supported by Hückel, extended Hückel[95] or Pariser, Parr and Pople[96] methods of electron configuration calculations for indene; these all predict that the α carbon has a higher electron density than the β carbon and that anionic, cationic, and free radical reactions should all proceed through the α carbon (analogous to styrene).[96] Presuming that the positive mesomeric effect of the aromatic ring was more important than the negative inductive effect in the reaction of indene with electrophiles, the β carbon should then be able to donate the Π electrons to the vacant boron orbital with equal or facility than the α carbon, as is the case with styrene.[70]

An alternative explanation is that the β position of indene is thermodynamically favoured and the α position kinetically preferred for attack. This implies that the reaction is reversible at 25° and that analysis of the oxidized reaction mixture after hydroboration at low temperature (-80°) would show an increase in the relative amount of indan-1-ol (40) than that ovserved at 0 or 25°.

In fact, such an experiment did not reveal any significant difference in the ratio of indanols from that observed if the reaction had been performed

at higher temperature (0° to 25°), even for extremely short reaction times. Although the reversibility of the hydroboration reaction (dehydroboration) has been known for some time,[97] it is generally recognized that high temeratures are required for any organoborane isomerization;[98] the boron goes to the least sterically crowded carbon in the alkyl chain.[99] This temperature factor would thus seem to render a reversibility argument completely untenable.

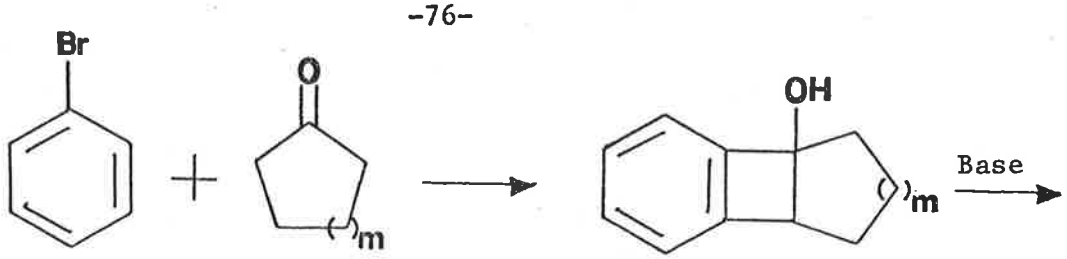
To summarize, the hydroboration of benzocyclenes (88) ($n \neq 1$) is governed by electronic factors and progresses to place the boron atom predominantly on the α carbon although the β carbon is sterically favoured. This mode of addition is reversed, however, if the otherwise preferred carbon is substituted e.g. with a methyl group. The hydroboration of indene appears anomolous, however, since the boron almost exclusively attacks the β position unless prohibited to do so by steric factors. This direction of addition is probably controlled by electronic factors which are not fully understood and require further research, from kinetic studies (for example) of the reactions of suitably substituted indenes with other electrophiles.

As will be discussed shortly, (Chapter 3), the hydroboration reaction appears the only known cycloaddition where the additions of the attacking species to indene and 1,2-dihydronaphthalene are in an opposite direction.

CHAPTER 2.3

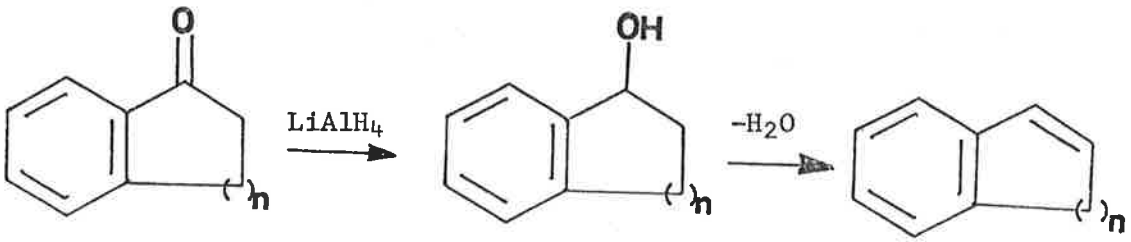
SYNTHESIS OF PRODUCTS AND REACTANTS

The benzocyclenes (89), (91), (92) and their respective epoxides (44), (49) and (52) were prepared according to the general route outlined in Scheme 2.9. The formation of ketones (104), (105) and (106) was achieved by an initial condensation between benzyne and an appropriate cycloalkanone enolate anion - a reaction first developed by Caubere[100] since used in the synthesis of other benzocycloalkenones.[101] Superior yields of ketones (105) and (106) were obtained if the intermediate alcohols ((102) and (103) respectively) were isolated and purified rather than a "one-pot" reaction which was applicable for (104).[100] Elaboration to the olefins (89), (91), (92) and the epoxides (44), (49) and (52) was effected by standard literature procedures and generally presented little difficulty.

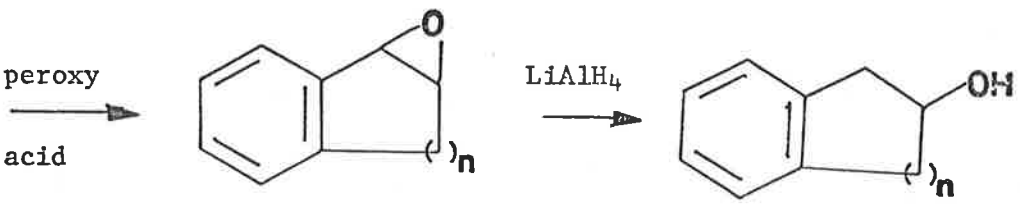


m = 1,2,3 (m = n+2)

m = 1 (101)
2 (102)
3 (103)



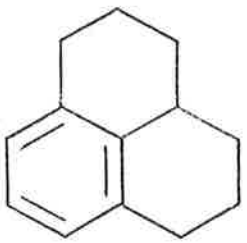
n = 3...	(104)	(47)	(89)
4...	(105)	(51)	(91)
5...	(106)	(54)	(92)



n = 3...	(44)	(46)
4...	(49)	(50)
5...	(52)	(53)

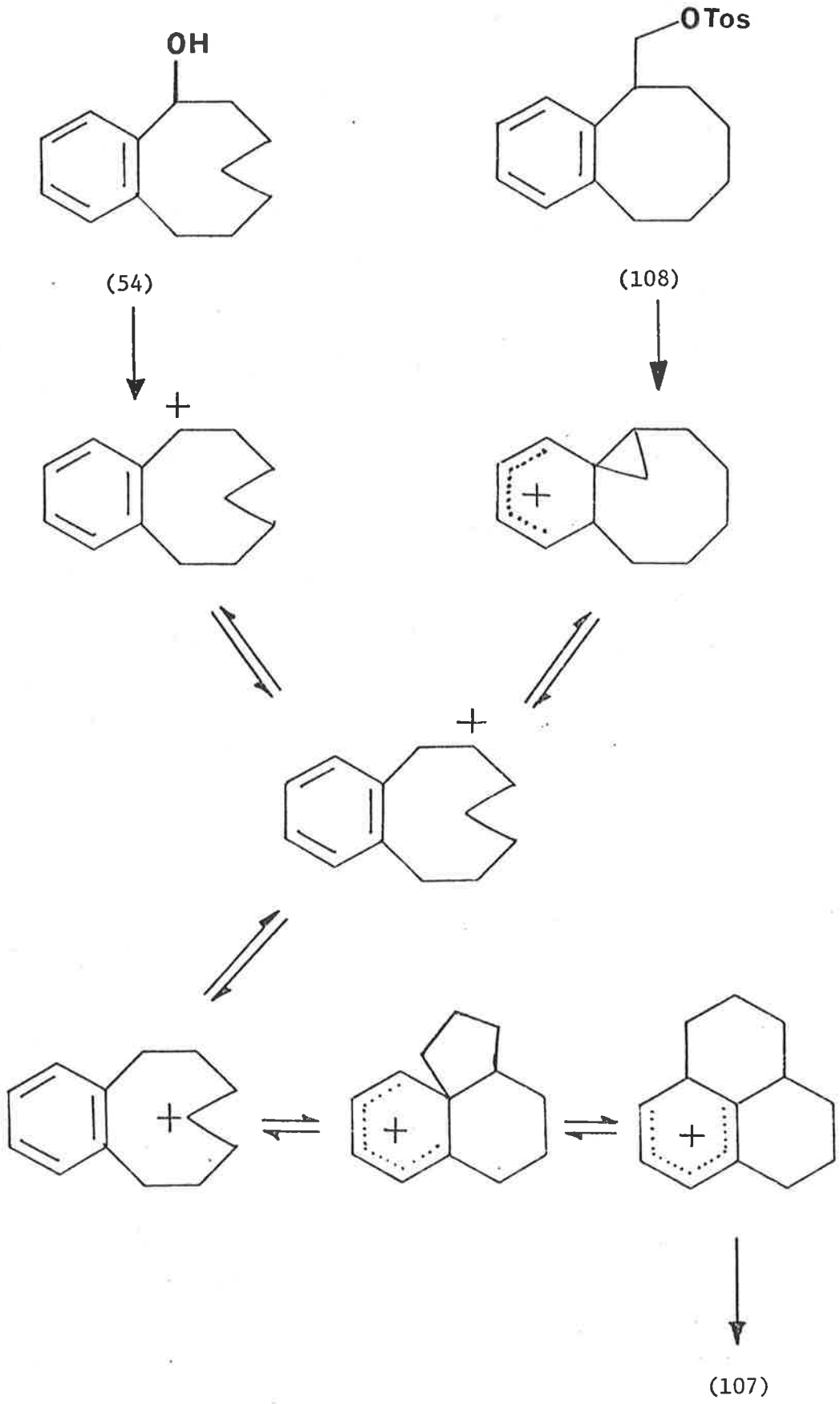
Scheme 2.9

The dehydration of the alcohol (54) to afford the olefin (92) proved, however, unexpectedly troublesome. Polyphosphoric acid had been used successfully for the clean, efficient synthesis of the analogous olefin (91) from (51)[63] and it was not anticipated that this reagent should present any obvious problems for the preparation of (92). A colourless liquid (of *c.* 95% purity by g.l.c. analysis) was isolated after the brief treatment of (54) with warm polyphosphoric acid, showed only hydrocarbon absorbances in the infrared spectrum and had a molecular weight of 172 (by mass spectrometry); both spectral data were consistent with a molecular formula $C_{13}H_{16}$. Analysis of the p.m.r. spectrum, however, did not indicate any significant olefinic resonaces between δ5 and δ6.5, but indicated a ratio of aromatic to benzylic protons as 3 : 5 - consistent with the proposed structure (107).



(107)

The solvolysis of the benzocyclooctenylmethyl tosylate (108) also gave the hydrocarbon (107) and Huisgen proposed the mechanism outlined in Scheme 2.10 for its formation.[102] It was considered highly probable that (107) was derived from (54) by a similar mechanism; precedence of aryl participation is well established.[103-105]



Scheme 2.10

Heating the alcohol (53) with boric acid yielded the olefin (92) without any reported rearrangement.[102] Treatment of the isomeric alcohol (54) with this acid, however, gave a mixture of at least four isomeric hydrocarbons, which were separated by preparative gas chromatography. The hydrocarbons each have spectral data consistent with their proposed structure, and are illustrated in fig. 2.7 together with the relative yields (by g.l.c. analysis) of formation, and are presumably formed by a similar mechanism to that of (107) in Scheme 2.7.

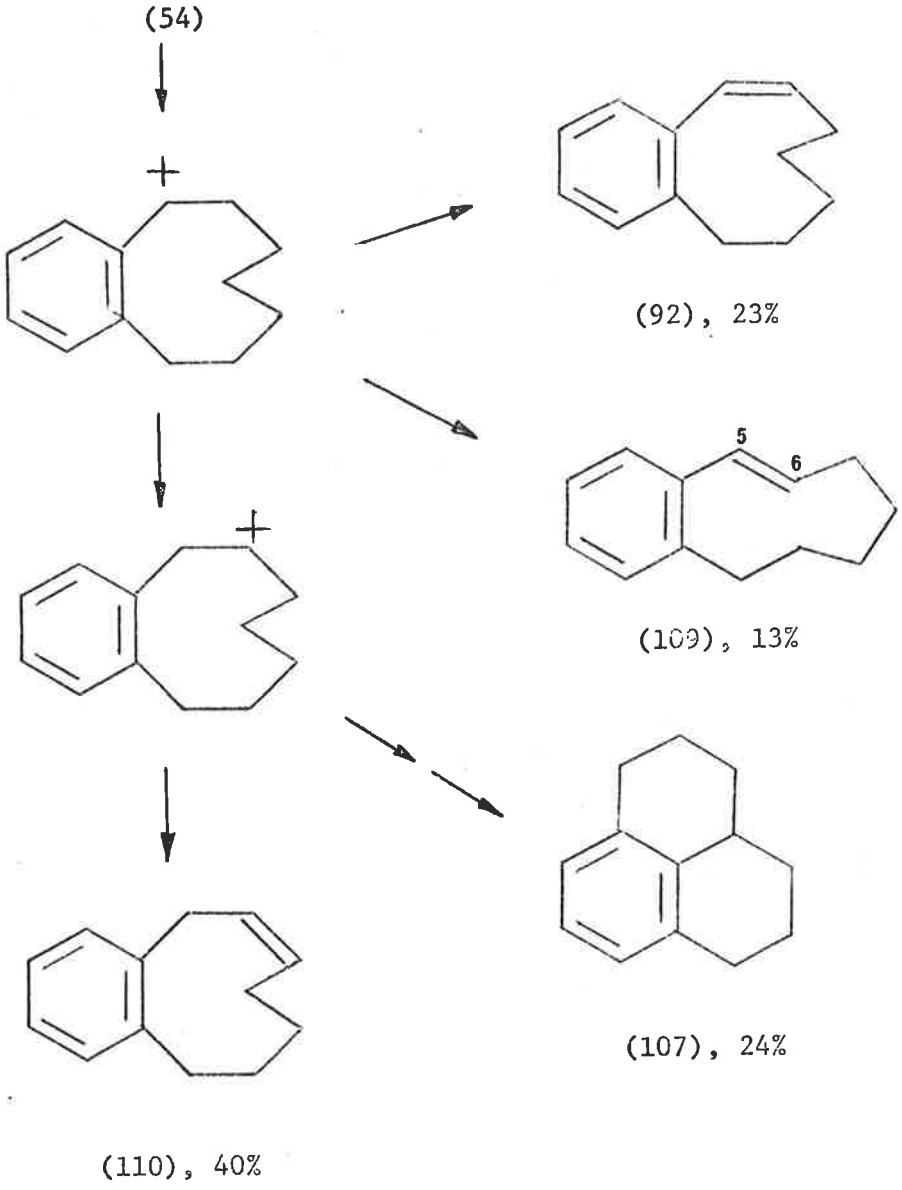


fig. 2. 7

The assignment of (109) as the (Z)-isomer of (92) was based on its p.m.r. spectrum, which showed a complex signal between δ5.1 and δ6.0, accounting for 2 protons by integration. An examination of a stereo model of (109) having a conformation with minimum steric interactions, showed that the C_5-C_6 double bond would be at nearly right angles to the aromatic ring thereby shifting the benzylic olefinic (α) hydrogen substantially upfield. Signals at δ2.5 (4 hydrogens) and δ2.4-1.6 (6 hydrogens) accounted for the other protons of the cyclononene ring.

Similarly, the p.m.r. spectrum was consistent with the (Z)-hydrocarbon (110) shown in fig. 2.7; a doublet (J = 7Hz) at δ3.3 attributable to the two magnetically equivalent* benzylic and allylic methylene protons, together with olefinic resonances from δ6-5, were the important features of the spectrum. Examination of a model of the alternative (E)-isomer indicated severe steric interactions across the cyclononene ring and was thus rejected as a viable structure. Since the hydrocarbon (107) had been prepared by independent synthesis, its presence in the reaction mixture could be easily verified by gas chromatography and by comparing the spectra of the authentic and isolated samples. The desired Z-olefin (92) which would be expected to be more thermodynamically stable than the (E)-isomer (109)[59] was independently made in high yield by heating the alcohol (54) in dimethylsulphoxide - a neutral dehydrating agent renowned for the conversion of benzylic alcohols to olefins.[106]

Epoxides (56) and (64) were both prepared according to a general pathway outlined in Scheme 2.11. Treatment of the appropriate ketone with methylmagnesium iodide gave the corresponding alcohol which was

---

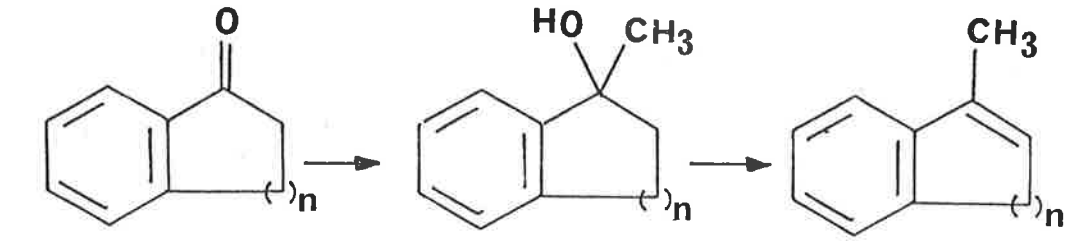
* The ring system appeared to be highly mobile (from study of a model) which would render the two benzylic and allylic protons essentially equivalent over a period of time.

dehydrated to the desired olefin. Direct epoxidation of the olefin (95) with *m*-chloroperoxybenzoic acid was not successful as the ketone (119), presumably formed by the acid-catalyzed rearrangement of the initially formed epoxide (64), was isolated - a problem noted earlier in the use of peroxybenzoic acid.[107] The problem of acid promoted isomerization was not solved by buffering the system under conditions successful with other acid sensitive epoxides.[108] Treatment of the olefins (114) and (95) with aqueous N-bromoacetamide (a superior reagent to N-bromosuccinimide for the preparation of bromohydrins[109]) yielded (115) and (116) respectively which were then converted to their corresponding epoxides (56) and (64) by cautious addition to base. Traces of water in the reaction mixture of the bromohydrin (115) and sodium methoxide proved extremely deleterious as the epoxide (56) readily underwent nucleophilic ring opening to the 1,2-diol (117).* In addition, attempted separation of a mixture containing (117) and (56) by chromatography on either silica or alumina resulted in isomerization of the epoxide to 1-methylindan-2-one (118). The problem of decomposition of epoxides on alumina or silica is not new and has been used as a synthetic tool by "doping" the adsorbent with a suitable nucleophile.

These problems could be avoided, however, if sufficient care was taken to exclude moisture from the reaction.

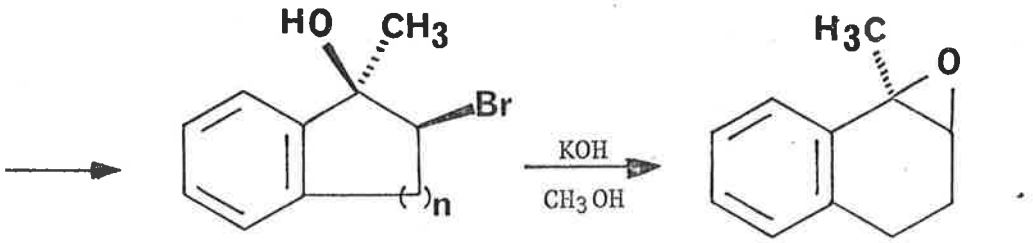
---

* The alcohol (117) was assumed to have to *trans* configuration, based on the general observation that nucleophilic attack of epoxides usually leads to *trans* products.[110, 111]



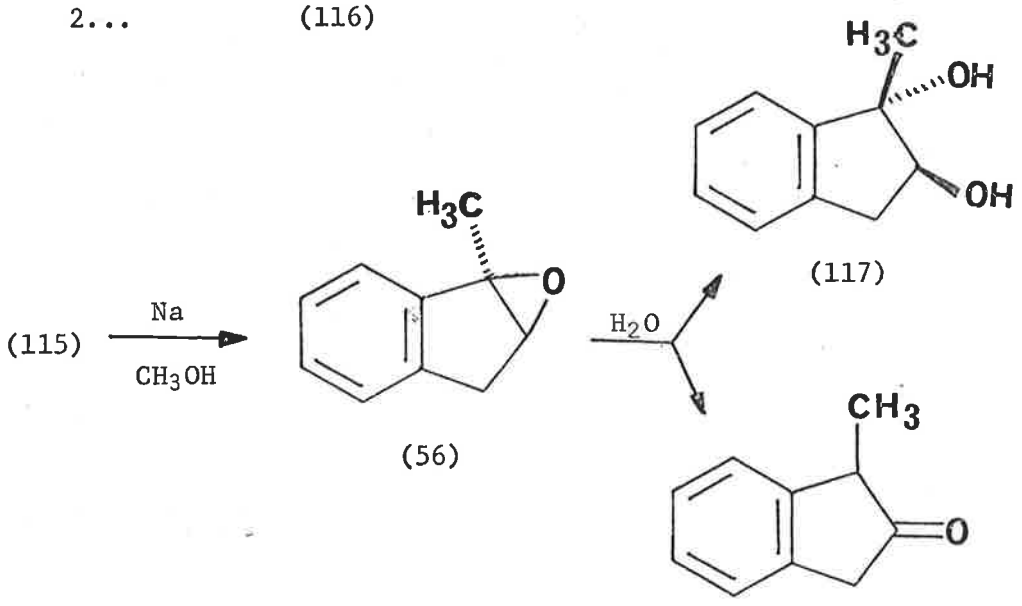
n = 1... (111) (113) (114)

2... (112) (96) (95)

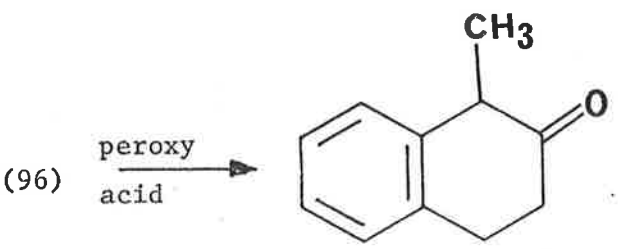


n = 1... (115) 64

2... (116)



(115) (56) (117) (118)

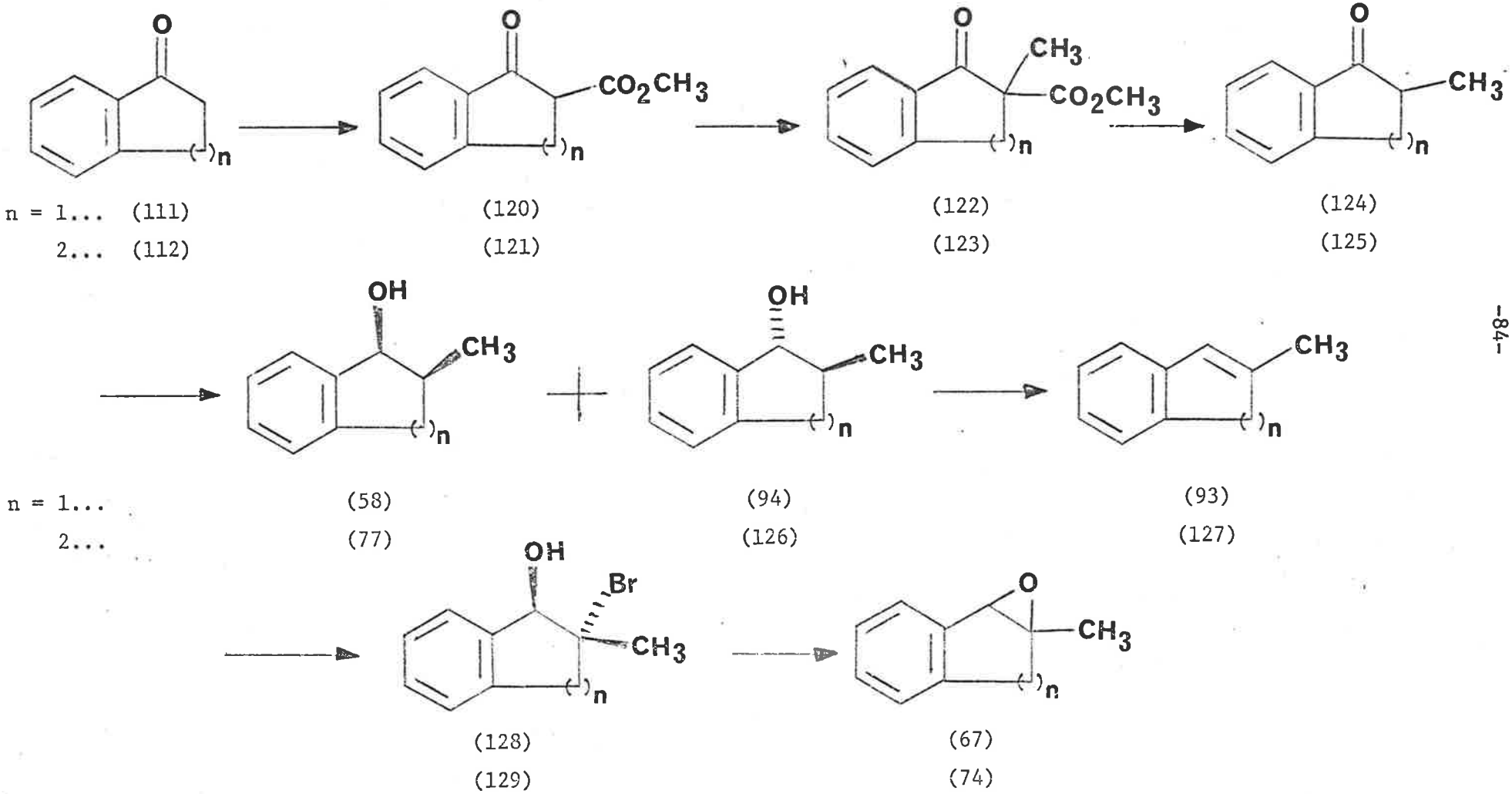


(96) (119)

Scheme 2.11

The syntheses of epoxides (67) and (74) were both achieved by the somewhat tedious route outlined in Scheme 2.12. Use of the carboxymethyl functionality as a "blocking" group[117] was necessary to attain selective monoalkylation of the ketones (111) and (112), despite literature reports to the contrary for the alkylation of (112).[118, 119] Concomitant hydrolysis and decarboxylation of the β-ketoesters (122) and (123) to give the ketones (124) and (125) respectively were accomplished with boiling acid[46b, 120] rather than under basic conditions which may have led to α-cleavage.[121] Elaboration to the epoxides (67) and (74) was achieved in a similar manner to that described for (56) and (64).

It had been claimed that reduction of (124) with sodium borohydride afforded the *cis*-alcohol (58) (m.p. 43-46°)[122] and that reduction with lithium aluminium hydride also gave (58) (m.p. 78-79°)[123] It was found, however, that reduction of (124) with borohydride yielded a *c.* 2 : 1 mixture of alcohols (58) and (94) respectively. Although these two alcohols could not be separated by normal chromatographic techniques, the benzylic protons adjacent to oxygen could be readily distinguished by p.m.r. spectroscopy, since an authentic specimen of the *trans*-alcohol (94) (m.p. 90-91) had been obtained separately by the hydroboration of 2-methylindene (Chapter 2.2). Similarly, the p.m.r. spectral data of (77) and (127) have already been published.[124]



n = 1... (111)
2... (112)

(120)
(121)

(122)
(123)

(124)
(125)

n = 1...
2...

(58)
(77)

(94)
(126)

(93)
(127)

(128)
(129)

(67)
(74)

Scheme 2.12

It is generally noted that the ylide from trimethylsulphonium iodide is potentially more reactive than the ylide derived from trimethyl-oxosulphonium iodide, as a reagent for the conversion of ketones to epoxides.[125, 126] It was proposed that treatment of benzocycloheptenone (104) with dimethylsulphonium methide would give the epoxide (80), since it was also known an analogous reaction was successful for the synthesis of (130) from 1-tetralone (112), albeit the experimental conditions were not stated (fig. 2.8).[127]

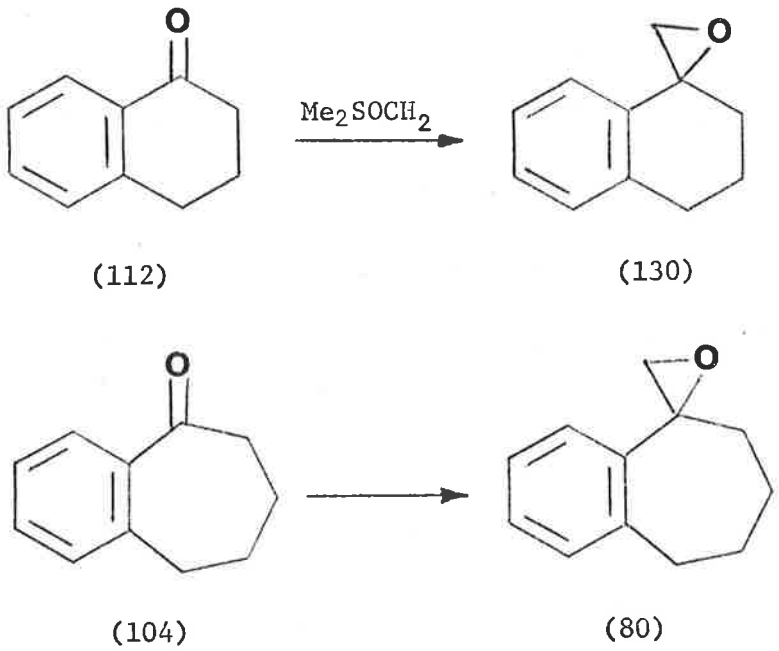


fig. 2.8

This reaction failed, however, under a variety of conditions, to afford even a fair yield of (80); instead ring expansion giving (105) and (132) was the preferred mode of reaction (fig. 2.9).

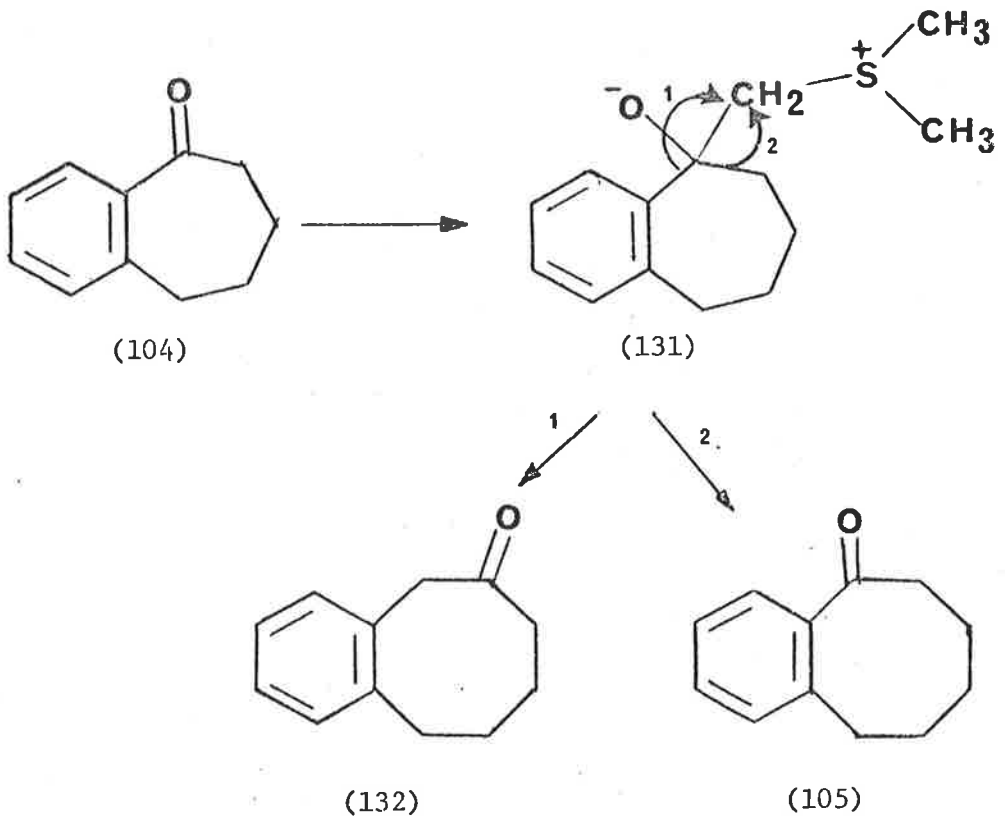
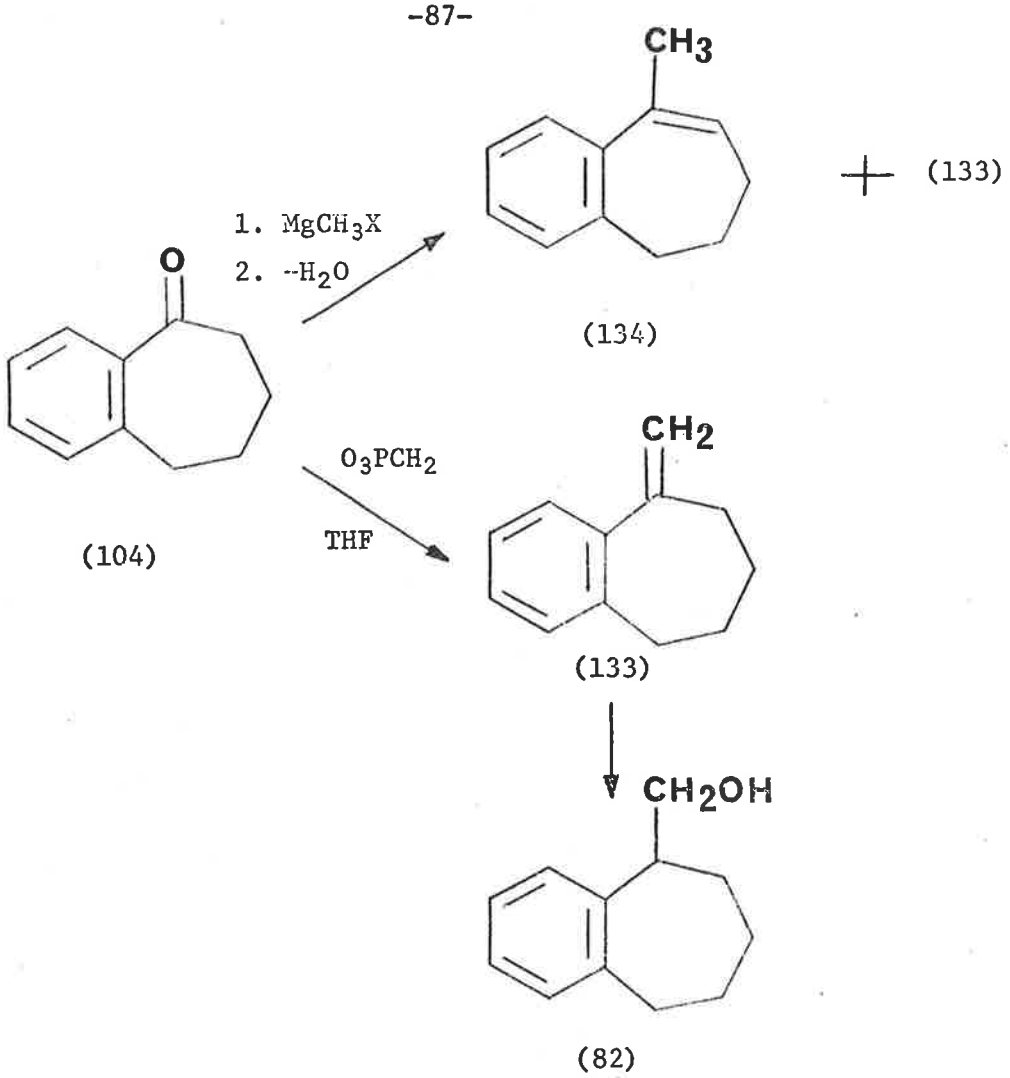


fig. 2.9

Although such competitive homologations are common using diazomethane,[128] reactions of this type are apparently unknown using sulphur ylides.[124b]

The independent synthesis of the alcohol (82), anticipated to be a product from the hydroboration of (80), was effected by hydroboration-oxidation of the exocyclic olefin (133), which had been prepared by a Wittig reaction between the ketone (104) and the appropriate ylide using tetrahydrofuran as a solvent (Scheme 2.13). An alternative method, viz., treatment of the ketone (104) with methylmagnesium iodide followed by dehydration, was considered unsuitable due to the concomitant formation of the endocyclic olefin (134) with (133).[129]

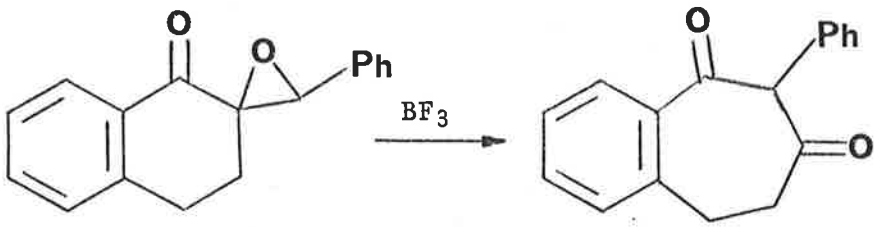


Scheme 2.13

A simple, efficient synthesis of 1,3-diols belonging to the general formula (43) was deemed valuable in authentication of any diols possibly obtained from the hydroboration-oxidation of benzocyclene oxides (30) (see Introduction). Although the synthesis of 5,6,7,8-tetrahydro-5H-benzocyclohepten-5,7-diol (135) (or (43), n = 3), has been described,[130] it was a clumsy and inefficient method; a general synthesis of the 1,3-diol (43) or a synthetic equivalent (e.g. the β-diketone (136)) was investigated.

The acid catalyzed rearrangement of some α, β-epoxyketones (137) has been shown to occur with simultaneous ring expansion to give the

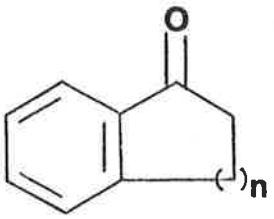
β-diketones (138) in reasonable yield (fig. 2.10).



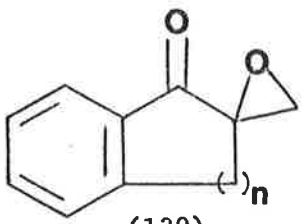
(137) (138)

fig. 2.10

It was thus envisaged that a similar reaction might be used to covert an analogous α,β-epoxyketone (139) to the β-diketone (136) which presumably could be converted to the 1,3-diol (135) by simple reductive procedures. A synthesis of the α,β-epoxyketone (139) (or (140), n = 2) was chosen as an experimental model due to the ready availability of the starting ketone (112) (Scheme 2.14).

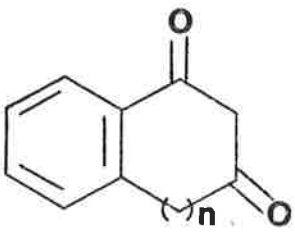


n = 2, (112)



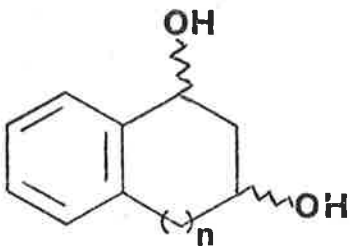
(139)

n = 2, (140)



(136)

n = 2, (141)



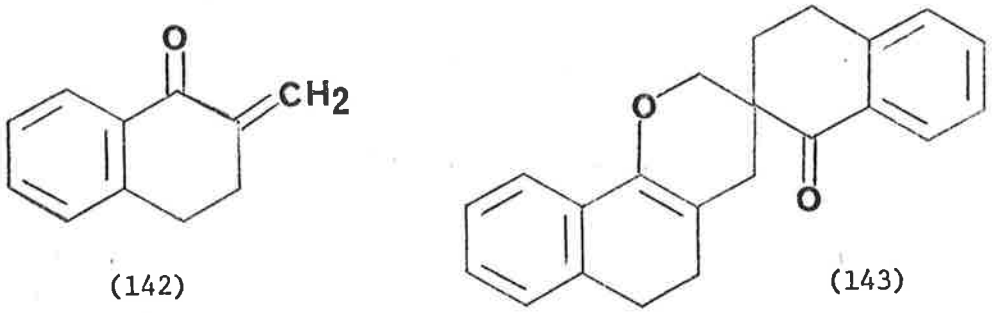
(43)

n = 2, (135)

Scheme 2.14

Although it was realized that the phenyl group on the oxirane ring assisted acyl migration in (137) by stabilization of the incipient positive charge, it was considered that strong acidic conditions might force rearrangement of (140) to the desired diketone (141) and hence (140) became a synthetic target molecule.

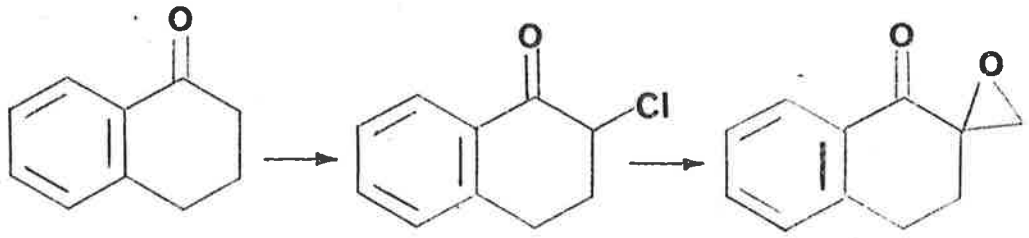
Attempted direct epoxidation of the α,β-unsaturated ketone (142) (prepared by the method of Mühlstadt[132]), under a variety of conditions was unsuccessful. In all conditions tried, a high yield of the dimeric Diels-Alder adduct (143) was obtained. The remarkable ease with which this dimerization occurs (fig. 2.11) has been observed unwittingly[133] and during an attempted *in situ* generation of (141) for Diels-Alder experiments.[134]



(142) (143)

fig. 2.11

An alternative approach to (140), based on a base-catalyzed Darzen's condensation[135] of 2-chloro-3,4-dihydronaphthalen-1-one (144) with paraformaldehyde afforded a moderate yield of the desired epoxyketone (140) (fig. 2.12)

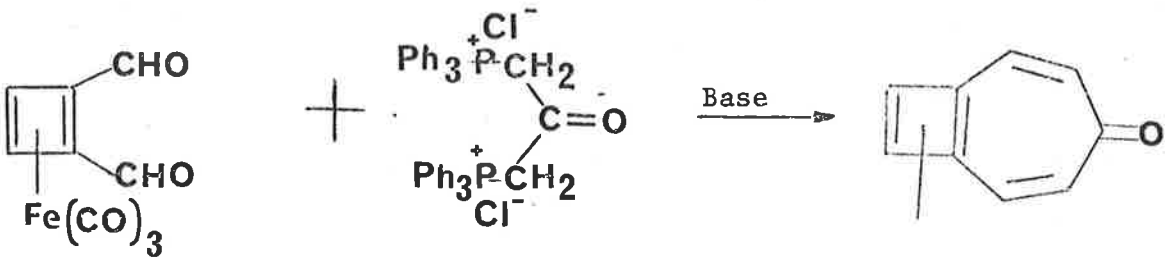


(112) (144) (140)

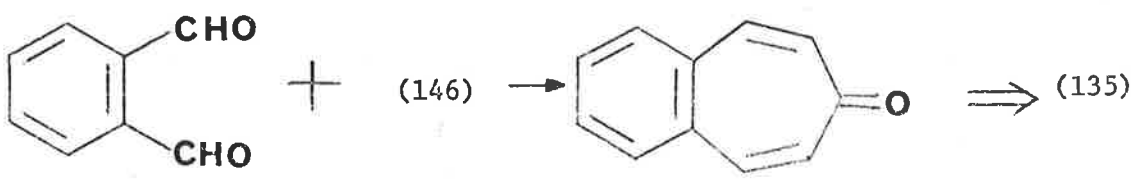
fig. 2.12

Once obtained, however, (140) failed to rearrange to the desired diketone (141), despite highly acidic conditions; either no reaction was detected, or polymerization with incorporation of solvent occurred and thus this approach to (43) was consequently abandoned.

It was reported recently[136] that a *bis*-Wittig reaction[137] between the dialdehyde (145) and the ylide derived from (146)[138] gave the adduct (147) in 8% yield. An analogous reaction using o-phthaldehyde (148) could conceivably produce the ketone (149) which should be able to be modified to the specific case of (43), viz., (135) (Scheme 2.15).



(145) (146) (147)

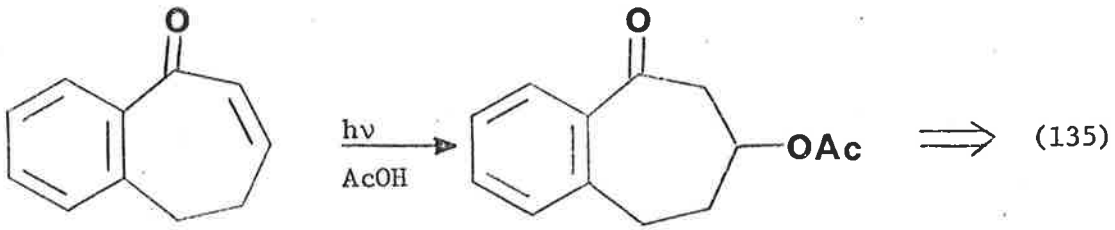


(148) (149)

Such a reaction realized, unfortunately, only a poor yield of severely contaminated (149), although considerable effort was extended to obtain an optimum yield. Since the unidentified contaminants could not be removed by normal methods, including extensive chromatography, this approach was also abandoned.

At this stage, it was considered more worthwhile to determine if hydrogen evolution did accompany the hydroboration of benzocyclene oxides (30) and whether 1,3-diols (43) would be obtained on oxidative workup. Neither of these events was observed and accordingly the pursuit of a novel synthesis of (43) was postponed.

Since this work was concluded, it has been reported that irradiation of the α,β-unsaturated ketone (150) in acetic acid afforded the β-acetoxyketone (151).[139]



If necessary, the diol (135) could be easily derived from (151) by standard methods and no obvious problems present themselves for the extrapolation of this procedure to the syntheses of the homologous diols (43) (n = 4,5).

Miscellaneous alcohols necessary for the authentication of products derived from the hydroboration of olefins (Chapter 2.2) were generally obtained from their parent ketone by reduction with lithium aluminium hydride or by known synthetic procedures.

CHAPTER 3

RESULTS AND DISCUSSION

OTHER CYCLOADDITIONS

A comparison of the direction of addition in other cycloadditions to indene and 1,2-dihydronaphthalene, (the latter olefin conveniently representing the benzocyclenes (88) (n > 1)), was undertaken in an attempt to comprehend more fully the apparent anomaly in the direction of hydroboration of indene.

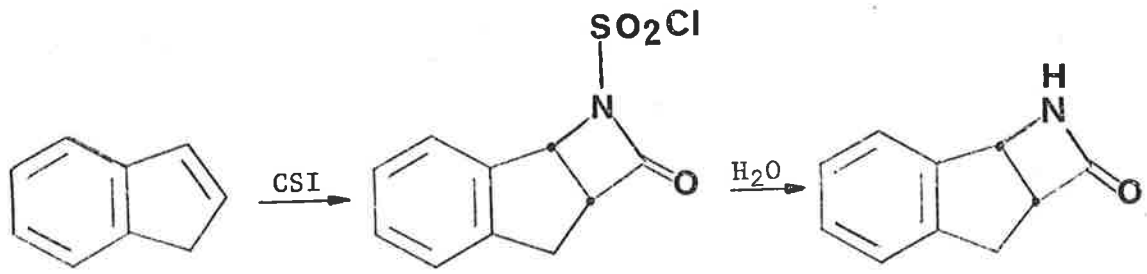
Generally speaking there are two categories of addition reactions, cyclic and noncyclic, according to the structure of the transition state or intermediate. A cyclic transition state or intermediate is involved in a cyclic addition and the stereochemistry of the product may be *cis* or *trans*, dependent on whether the reaction proceeds *via* one stage or two. The concept "cycloadditon" gives a formal description of an overall reaction but not a mechanistic interpretation. The hydroboration reaction, for example, is considered to be a cycloaddition proceeding through a cyclic, four-centred transition state[70, 75-83] in which the carbon-boron and carbon-hydrogen bonds are formed at the same or nearly same rate, i.e. the addition is approximately concerted.

It would thus seem logical that a comparable cycloaddition to hydroboration would need to fulfill the following requirements: (1), the addition should concerted or nearly concerted to afford products having a *cis* relationship between the new bonds formed; (2), a cyclic transition state of low steric demand would be required; and (3), the reaction should give products in which the direction of addition can be unambiguously assigned.

Cycloadditions proceeding through a six-membered transition state, exemplified by the Diels-Alder reaction,[140] were immediately discounted; in any case, indene and 1,2-dihydronaphthalene both react with (for example) α,β,γ,δ-unsaturated acids to give analogous products arising from the same orientation of addition of the diene moiety.[141]

According to Woodward and Hoffman rules,[142] concerted "2Π + 2Π" cycloadditions are forbidden in the ground state but permissable in the excited state,[142] and for this reason a comparison between thermal, ground-state hydroborations and photochemically induced, excited-state cycloadditions was considered of dubious value.

A promising analogy stemmed from the observation by Graf[143] that the addition of chlorosulphonylisocyanate (CSI) to olefins afforded the *cis*-adduct (152) (fig. 3.1),[145] after hydrolysis.



(85) (152)

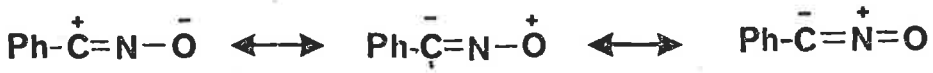
fig. 3.1

The reaction of CSI with 1,2-dihydronaphthalene failed, however, to give any required adduct but afforded a large amount of unidentified polymeric material.

Attention was focussed on 1,3-dipolar cycloadditions to carbon-carbon double bonds - an area enormously well served in the literature, especially by Huisgen.[146] Considerable debate is still being waged over the exact mechanism of these reactions, particularly between Huisgen, who

has advocated a concerted mechanism,[146] and Firestone[147] who has argued that the reaction involves a diradical intermediate.

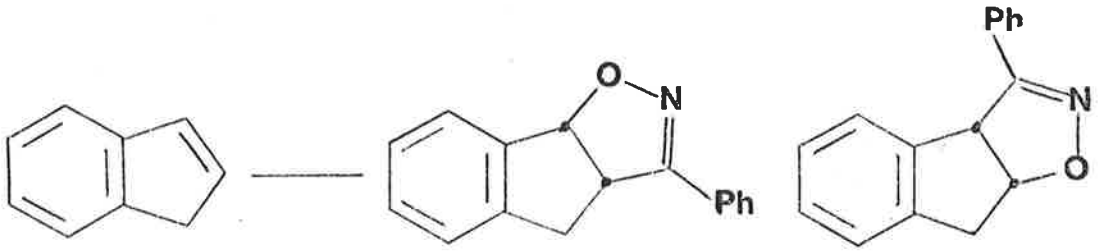
It is generally accepted, however, that the reaction essentially yields adducts having a *cis* relationship between the new bonds formed. An obvious problem in trying to compare a 1,3-cycloaddition to the hydroboration reaction is that unlike hydroboration, where the electron deficient boron is attracted to the nucleophilic end of the olefin, it not meaningful to assign a nucleophilic or an electrophilic end to a 1,3-dipole.[148] This is clearly illustrated with benzonitrile oxide (BNO).



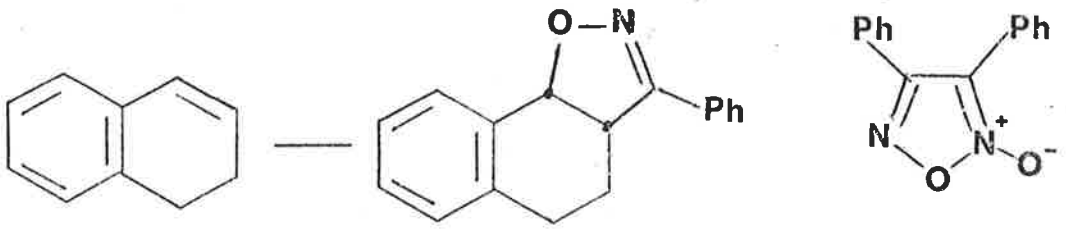
Benzonitrile Oxide (BNO)

Considerable effort has been extended to study the addition to substrates of BNO - a representative of a class of 1,3-dipoles which add preferentially to electron-rich and electron-deficient olefins,[149, 150] to give products which are generally crystalline and readily distinguishable by p.m.r. spectroscopy.[149]

The reaction of BNO with indene afforded a good yield of the adduct (153) together with a trace of (154).[150] Similarly, 1,2-dihydronaphthalene reacted with BNO to produce only a fair yield (43%) of the oxazole (155), the major product (156), however arising from the rapid dimerization of the reactive BNO - a problem noted by Hüisgen,[149d] (fig. 3.2) and others.[194]



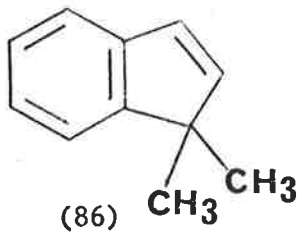
(85) (153), 98% (154), 2%



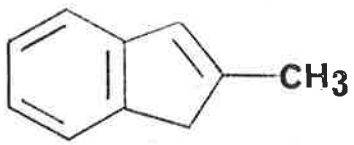
(90) (155) (156)

fig. 3.2

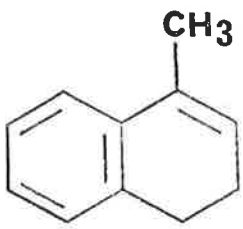
BNO failed to add, however, to the substituted olefins (86), (93), (96) and (111); the major product in each case was the BNO dimer (156). (fig. 3.3)



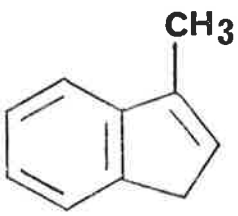
(86)



(93)



(95)



(111)

fig. 3.3

Since the addition of BNO to olefins appeared to be governed primarily by steric factors, an observation supported by other experimental evidence,[149] the addition of diazomethane, which would be less susceptible to steric influences, was considered.

Although it has been shown that diazomethane adds to styrene,[151, 152] no significant reaction could be detected (by thin layer chromatography) between indene and diazomethane, even after fourteen days at room temperature.

Seeing that 1,3-dipoles appeared reluctant to add to trisubstituted double bonds (unless in conjugation with a carbonyl group[153]) the use of this reaction as a comparison to hydroboration was dismissed.

From the cycloadditions to indene (85) and 1,2-dihydronaphthalene (90) discussed so far, indene was the more reactive species and higher yields of adducts were obtained. This appears general, and is borne out in other addition reactions to (85) and (90) using reagents such as iodine isocyanate[154] and diethylazodiformate.[155]

The cycloaddition of the reactive ketene, dichloroketene, to indene afforded only a 12% yield of adduct[156] and in view of the above observations, it was considered unlikely that an improved yield would be obtained using 1,2-dihydronaphthalene.

It is clear that extensive investigation in this area is required to find a suitable analogous reaction to hydroboration.

CHAPTER 4

EXPERIMENTAL

GENERAL

Infrared (i.r.) spectra were recorded with a Unicam SP200 or a Jasco IRA-1 grating infrared spectrophotometer, using the 1602 cm^{-1} band of polystyrene as a reference. The characteristics of the infrared bands are expressed in the text as follows: s, strong; m, medium; w, weak; sh, shoulder; b, broad.

Proton magnetic resonance (p.m.r.) spectra were recorded on a Varian T-60 or a Jeol PMX-60 spectrometer, operating at 60 MHz, using tetramethylsilane as an internal reference. Data are given in the following order: chemical shift in p.p.m. (δ), multiplicity, first order coupling constant (J) expressed in Hz, relative intensity as number of protons, assignment.

Mass spectra were recorded with a Hitachi Perkin-Elmer RMV-7D double focussing mass spectrometer operating at 70 eV. Spectral data are quoted in the following order: m/e value (assignment).

Melting points were determined using a Kofler hot-stage melting point apparatus under a Reichert microscope and are uncorrected.

Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

Gas liquid chromatographic (g.l.c.) analyses were carried out with a Pye 104 chromatograph using nitrogen as a carrier gas. The following columns, which were all constructed of glass, were used:

A. 1% FFAP on varaport (100/120), 2m x 6mm

B. 2% FFAP on varaport (100/120), 2m x 6mm

C. 5% Carbowax on varaport (100/120), 2m x 6mm

D. 5% OV17 on varaport (80/100), 2m x 6mm

E. 12.5% OV17 on varaport (70/80), 3m x 8mm

Columns A and B were treated with trimethylsilylchloride for 30 min, washed with 10% methanolic toluene and dried at 100° for 4 hr before packing. The carrier gas (nitrogen) flow rate for analytical columns A-D was 35ml/min and 65ml/min for the preparative column E.

Column chromatography was carried out on Spence alumina or Sorbsil silica gel. Preparative thin layer chromatography (t.l.c.) plates were prepared from a 50% mixture of Merck Kieselgel G and HF254 (35 g) applied to the glass plates (20cm x 20cm) as a suspension in water (95ml). After air drying for several days, the plates were heated in an oven at 110° for several hours. Initially, the analytical t.l.c. plates were prepared as above but were later purchased as a fine layer on aluminium foil from Merck.

All organic extracts were dried over anhydrous sodium sulphate unless otherwise stated. Redistilled solvents were used for extractions and chromatography. In this text, light petroleum refers to the hydrocarbon fraction of b.p. 60-70° and petroleum ether refers to the hydrocarbon fraction of b.p. 30-40°. Dry ether and tetrahydrofuran (THF) were obtained by redistillation from sodium wire and benzophenone immediately prior to use. All other solvents used were redistilled and the fractions corresponding to their literature boiling points were collected.[157*] Accurate masses were determined by Mr T. Blumenthal on a AEI-MS3074 mass spectrometer with a WF-028 peak matching unit and using perfluorokerosene as the standard.

---

* Reference 157 refers to Part II references.

WORK DESCRIBED IN PART I

PART A: WORK DESCRIBED IN CHAPTER 2.1

1,3-DIHYDRO-2H-INDEN-2-ONE (INDAN-2-ONE):

Initially, this compound (m.p. 56-57°; lit.[95] 57-58) was prepared according to the procedure of Horan and Schiessler.[95] In later runs, however, indan-2-one was purchased from Aldrich.

3-BROMO-1-(3H)-ISOBENZOFURANONE (3-BROMOPHTHALIDE):

This compound (m.p. 77-80°; lit.[96] 78-80°) was prepared in 78% yield by the method of Koten.[96]

ATTEMPTED CONDENSATION OF 1,3-DIHYDRO-2H-INDEN-2-ONE WITH 3-BROMO-1(3H)-ISOBENZOFURANONE:

To a solution of trimethylphenyllithium[64b] (2.0 mmol) in anhydrous THF (5ml) was added dropwise, under nitrogen, 1,3-dihydro-2H-inden-2-one (264mg; 2.0 mmol) in THF (3ml). The resultant mixture was cooled to 0° whereupon a solution of 3-bromo-1(3H)-isobenzofuranone (424mg; 2.0 mmol) in THF (5ml) was added. The mixture was then stirred at 0° for 2 h and hydrolyzed by the careful addition of water (1ml) followed by 10% hydrochloric acid (5ml). After stirring at room temperature for 15 min, the mixture was extracted with ether (3 x 25ml) and the combined organic layers were washed with water (2 x 20ml), dried and evaporated to give a dark yellow oil, titruation of which with light petroleum gave a yellow solid (974mg). Preparative t.l.c. of *c.* 300mg of this solid (using 20% ether/light petroleum as a developing solvent) afforded 4 major components characterized as follows:

Fraction 1: Base, dark brown solid (32mg) the .m.r. spectrum of which

showed the presence of a complex mixture which was not further characterized.

Fraction 2: Rf 0.2, off-white solid (47mg), which was identified as 3-bromo-1(3H)-isobenzofuranone (m.p. 78-80°, lit.[96] 78-80°).

Fraction 3: Rf 0.4, yellow oil (25mg), the p.m.r. spectrum of which did not indicate the presence of any of the desired compound and was not further characterized.

Fraction 4: Rf 0.9, white solid (148mg), triphenylmethane.

ATTEMPTED ENAMINE-ALKYLATION OF 1,3-DIHYDRO-2H-INDEN-2-ONE:

The method of Blomquist and Moriconi[68] was used to prepare 2-(N-pyrrolidyl)-1H-indene and was used immediately without further purification. To an ice-cooled solution of the enamine (1 mmol) thus prepared in benzene (10ml) was added a solution of 3-bromo-1(3H)-isobenzofuranone (212mg; 1 mmol) in benzene (2ml) and the resultant mixture was stirred at room temperature (*c.* 30°) for 2 h, then quenched by the addition of 10% hydrochloric acid (5ml). After stirring at room temperature for 30 min, the mixture was extracted with ether (2 x 30ml) and the combined organic extracts were washed with successive portions of 10% hydrochloric acid (2 x 10ml) and water (2 x 10ml), dried and evaporated to give a dark yellow oil (181mg). Analytical t.l.c. (25% methylene chloride/ light petroleum) of this oil indicated the presence of at least 6 components one of which (Rf 0.3) was consequently identified as 3-bromo-1(3H)-isobenzofuranone (*c.* 30% of product after preparative t.l.c.). The p.m.r. spectrum of the residue obtained above showed a complex mixture which did not appear to contain the desired compound and this reaction was not investigated further.

SYNTHESIS OF 1(3H)-ISOBENZOFURANONES, (PHTHALIDES):

6,7-Dimethoxy-1(3H)-isobenzofuranone:

This compound (m.p. 98-101°; lit.[43] 101-102°) was prepared in 34% yield by the method of Perkin *et al.*[43]

6-Methoxy-1(3H)-isobenzofuranone:

This compound (m.p. 118-120°; lit.[41] 120°) was prepared in 84% yield following the procedure of Chakravati and Perkin.[41]

SYNTHESIS OF 2-FORMYLBENZOIC ACIDS (PHTHALALDEHYDIC ACIDS):

5,6-Dimethoxy-2-formylbenzoic Acid, (Opianic Acid):

This compound was prepared by the method of Blair *et al.*[97] (m.p. 140-144°; lit.[43] 146°) in 88% yield.

2-Formyl-5-methoxybenzoic Acid:

This compound (m.p. 150°; lit.[97] 151-153°) was prepared by the method of Blair *et al.*[97]

6-Formyl-1,3-benzodioxole-5-carboxylic Acid, (2-Formyl-5,6-methylene-dioxybenzoic Acid):

This acid (m.p. 163-165°; lit.[98] 164-164.5°) was prepared according to the method of Ziegler and Fowler.[98] The precursor imine (2-formyl-1,3-benzodioxole cyclohexylimine, piperonal cyclohexylimine) (m.p. 65-66°, lit.[99] 65-66°) was prepared by the procedure of Baddar and Iskander[99] and had an identical p.m.r. spectrum with that published.[98]

CONDENSATION OF 1,3-DIHYDRO-2H-INDEN-2-ONES WITH 2-FORMYLBENZOIC ACIDS:

General Procedure:

In a typical experiment, a solution of the 1,3-dihydro-2H-inden-2-one (10 mmol) and the phthalaldehydic acid (10 mmol) in dry benzene (50ml) containing a crystal of *p*-toluenesulphonic acid was stirred under reflux and the water formed during the reaction was removed by means of

a Dean-Stark water separator. When analysis of the reaction mixture by t.l.c. no longer showed the presence of starting material (3-5 h), the mixture was cooled, stripped of solvent to give a (generally) viscous red oil which was (generally) titurated with ether to afford the desired product as an (often) yellow powder which could not be induced to crystallize. Attempted sublimation led to decomposition and it was found that chromatography of these compounds on silica or alumina was of little value. Attempted formation of derivatives (oximes, 2,4-dinitrophenylhydrazones and semicarbazones) invariably led to cleavage even under mild conditions; these trials were hampered by the extreme insolubility of the 1-(3'phthalidyl)-indan-2-ones in common solvents. The p.m.r. spectra were thus often obtained as dilute solutions in $CDCl_3$ and in some cases were poorly resolved. The following compounds were prepared by this general method:

(i) 3-(1',3'-Dihydro-1'(2'H)-inden-2-onyl) isobenzofuran-1(3H)-one (1-(3'phthalidyl)-indan-2-one) (12):

1,3-Dihydro-2H-inden-2-one (1.32g; 10 mmol) was treated with 2-formylbenzoic acid (1.4g; 10 mmol) in benzene (50ml) in the manner described above. The benzene was initially filtered to remove the precipitated solid (140mg)* and the filtrate was treated as described above to afford an off-white solid (2.2g; 72%) which had a m.p. 146-148°.

i.r. ν_{max} (nujol): 1765s, 1760s, 1755sh cm^{-1}.

p.m.r. ($CDCl_3$): δ 7.60, complex, 7H, Ar-*H*; 6.20, overlapping doublets, 2H, Ar-*H* and Ar-C*H*-O; 4.12 doublet, J = 3Hz, 1H, Ar-C*H*-CO; 3.60, singlet, 2H, Ar-CH_2-CO.

---

* This material (m.p. 235-238° (dec)) was obtained as a white insoluble powder and had an i.r. spectrum almost identical to (12). A suitable solvent could not be found for p.m.r. studies nor could the solid be induced to form a crystalline derivative; consequently its identity remains uncertain.

p.m.r. (benzene-d_6/CF_3CO_2H): δ 7.52, multiplet, 1H, Ar-*H* (C7-H); 7.0, complex, 6H, Ar-*H*; 5.83, doublet, J = 8Hz, Ar-*H*; δ5.58, doublet, J = 3Hz, 1H, Ar-C*H*-O; 3.55, doublet, J = 3Hz, 1H, Ar-C*H*-CO; 3.10, singlet, 2H, Ar-CH_2-CO.

Irradiation at: 420Hz caused the collapse of the doublet at δ5.83 to a singlet; 350Hz caused the collapse of δ3.55 to a singlet; 218Hz caused the collapse of δ5.58 to a singlet,

mass spectrum: m/e 264 (M^+ for $C_{17}H_{12}O_3$), 133 (M^+ - C_9H_7O).

This compound was characterized as the oxime (19) prepared according to the general method of Ruzicka *et al*,[100] which was recrystallized from acetone/light petroleum as colourless needles m.p. 193-195° (dec). (Found: C, 73.4; H, 4.8; N, 4.6. $C_{17}H_{13}NO_3$ requires C, 73.1; H 4.7; N 5.0%).

i.r. ν_{max} (nujol): 3350m, 1745s, 1610w, 740m cm^{-1}.

(ii) 6,7-Dimethoxy-3-(1',3'-dihydro-1'(2'H)-inden-2'-onyl)isobenzofuran-1(3H)-one (22):

Following an analogous procedure for the preparation of (12), using 1,3-dihydro-2H-inden-2-one (1.32g; 10 mmol) and 5,6-dimethoxy-2-formyl-benzoic acid (2.2g; 10 mmol), the ketone (22) was obtained as an off-white powder (695mg; 23%), m.p. 114-120°, and was charaterized as the 2,4-dinitrophenylhydrazone, m.p. 226-230° (dec). (Found: C,59.6; H, 4.2; N, 11.2. $C_{25}H_{20}O_8N_4$ requires C, 59.5; H 4.0; N, 11.1%).

The ketone (22) had the following spectral properties:

i.r. ν_{max} (nujol): 1750s, 1740s, 1015s, 765m, 750, cm^{-1}.

p.m.r. ($CDCl_3$): δ 7.30, complex, 5H, Ar-*H*; 6.20, doublet, J = 8Hz, Ar-*H*; 6.00, doublet, J = 3Hz, Ar-C*H*-O; 4.10-4.00, 2 singlets overlapping with a doublet, 7H, 2x CH_3O and Ar-C*H*-CO; 3.60, singlet, 2H, Ar-CH_2-CO.

mass spectrum: m/e 324 (M^+ for $C_{19}H_{16}O_5$), 193 (M^+ - C_9H_7O).

(iii) 6,7-Methylenedioxy-3-(1'3'-dihydro-1'(2'H)-inden-2'-onyl)isobenzofuran-1(3H)-one (23):

Using 1,3-dihydro-2H-inden-2-one (1.32g; 10 mmol) and 6-formyl-1,3-benzodioxole-5-carboxylic acid (2.04g; 10 mmol), the ketone (23) (3.06g, 99%) was obtained as a yellow insoluble powder (m.p. 107-113°). (Accurate mass 308.0684. $C_{18}H_{12}O_5$ requires 308.0685)

i.r. ν_{max} (nujol): 1765sh, 1760s, 1740s, 740m, 710m, 695m, cm^{-1}.

p.m.r. ($CDCl_3$): δ 7.42-6.85, complex, 5H, Ar-*H*; 6.23, singlet overlapping with 2 doublets, 4H, O-CH_2-O, Ar-*H*, and Ar-C*H*-O; 4.00, poorly resolved doublet, 1*H*, Ar-C*H*-CO; 3.21, singlet, 2H, Ar-CH_2-CO.

mass spectrum: m/e 308 (M^+ for $C_{18}H_{12}O_5$), 177 (M^+ - C_9H_7O).

(iv) 5,6-Dimethoxy-3-(1',3'-dihydro-1'(2'H)-inden-2'-onyl)isobenzofuran-1(3H)-one (24):

Using 1,3-dihydro-2H-inden-2-one (132mg; 1.0 mmol) and 4,5-dimethoxy-2-formylbenzoic acid,[101] (220mg; 1.0 mmol), the ketone (24) was obtained as a pale yellow powder (300mg, 92%), m.p. 132-138°. (Accurate mass 324.1001. $C_{18}H_{14}O_4$ requires 324.0998).

i.r. ν_{max} (nujol): 1760sh, 1752s, 1710sh, 740m, 720m cm^{-1}.

p.m.r. ($CDCl_3$): δ 7.27, complex, 5H, Ar-*H*; 6.40, doublet, J = 8Hz, Ar-*H*; 5.93, doublet, J = 3Hz, Ar-C*H*-O; 3.93, 2 singlets overlapping with doublet, 7H, 2xOCH_3 and Ar-C*H*-CO; 3.53, singlet, 2H, Ar-CH_2-CO.

mass spectrum: m/e 324 (M^+ for $C_{19}H_{16}O_5$), 193 (M^+ - C_9H_7O).

(v) 5-Methoxy-3-(1',3'-dihydro-1'(2'H)-inden-2'-onyl)isobenzofuran-1(3H)-one (25):

Using 1,3-dihydro-2H-inden-2-one (132mg; 1.0 mmol) and 2-formyl-5-methoxybenzoic acid (180mg; 1.0 mmol), the ketone (25) was obtained as a yellow gum (270mg; 89%). (Accurate mass 294.0884. $C_{18}H_{14}O_4$ requires 294.0892).

i.r. ν_{max} (nujol): 1760s, 1750s, 1740sh, 720s, 680m cm^{-1}.

p.m.r. ($CDCl_3$): δ 7.27, complex, 7H, Ar-*H*; 5.20, poorly resolved doublet, 1H, Ar-C*H*-O; 3.91, multiplet, 3H, Ar-CH_2-CO and Ar-C*H*-CO; 3.50, singlet, CH_3O.

mass spectrum: m/e 294 (M^+ for $C_{18}H_{14}O_4$), 163 (M^+ - C_9H_7O).

(vi) 3-(1',3'-Dihydro-5',6'-dimethoxy-2'H-inden-2'-onyl)isobenzofuran-1(3H)-one:

When 1,3-dihydro-5,6-dimethoxy-2H-inden-2-one (26) (47mg; 0.26 mmol) was treated with 2-formylbenzoic acid (40mg; 0.26 mmol) in benzene (5ml) containing a catalytic amount of *p*-toluenesulphonic acid, either at room temperature or at 80°, there was no evidence (by i.r. or p.m.r. spectroscopy) of any condensation product but only of involatile polymeric material.

(vii) 6,7-Dimethoxy-3-(1',3'-dihydro-5',6'-dimethoxy-2'H-inden-2'-onyl)isobenzofuran-1(3H)-one:

Treatment of 1,3-dihydro-5,6-dimethoxy-2H-inden-2-one (26) (94mg; 0.5 mmol) with 2-formyl-5,6-dimethoxybenzoic acid (1.1g; 0.5 mmol) in benzene (8ml) under the usual conditions (as above) afforded only starting compounds (by p.m.r. spectroscopy) with some polymeric material.

(viii) 3-(1'3'-Dihydro-1'-methyl-1'(2'H)-inden-2'-onyl)isobenzofuran-1(3H)-one (51):

1,3-Dihydro-1-methyl-2H-inden-2-one[102] (1.46g; 10 mmol) and 2-formylbenzoic acid (1.4g; 10 mmol) afforded a light brown powder (2.1g,

76%) which had the following spectral properties:

i.r. ν_{max} (nujol): 1760s, 1740s, 740w, 715s, 695m cm^{-1}.

p.m.r. ($CDCl_3$): δ 8.0-7.20, complex, 8H, Ar-*H*; 5.85, 5.73, 2x singlets, 1H, Ar-C*H*-O, 3.60, 3.58, 2x singlets, 2H, Ar-CH_2CO; 1.75, 1.63, 2xsinglets, -CH_3. The spectrum was therefore assumed to contain a *c.* 1:1 mixture of diastereoisomers (30).

mass spectrum: m/e 278 (M^+ for $C_{18}H_{14}O_3$), 133 (M^+ - $C_{10}H_9O$).

SCHMIDT REARRANGEMENT OF 3-(1',3'-DIHYDRO-1'(2H')-INDEN-2'-ONYL)ISOBENZOFURAN-1(3H)-ONE (12):

Method 1:

Sodium ozide (150mg) was added slowly to an ice-cooled, stirred solution of the ketone (12) (254mg; 1.0 mmol) in polyphosphoric acid (*c.* 5g). After addition, the mixture was stirred at room temperature overnight after which time it was quenched by the addition to ice-water. The resultant mixture was extracted with chloroform (3 x 50ml) and the combined extracts were washed with water (2 x 50ml), dried and evaporated to give 3-(1',4'-dihydro-1'(2H)-isoquinolin-3'-onyl)isobenzofuran-1(3H)-one (13) as a yellow solid m.p. 263-265° (203mg; 73%) which had the following spectral properties:

i.r. ν_{max} ($CDCl_3$): 3700w, 3400w, 3300w, 1765s, 1675m cm^{-1}.

i.r. ν_{max} (nujol): 1760s, 1660m cm^{-1}.

p.m.r. ($CDCl_3$): δ 8.0-6.6, complex, 8H, Ar-*H*; 5.80, doublet, J = 3.5Hz, 1H, Ar-C*H*-O; 5.21, multiplet (poorly resolved), 1H, Ar-C*H*-NHCO; 3.66, singlet, 2H, Ar-CH_2CO.

mass spectrum: m/e 279 (M^+ for $C_{17}H_{13}O_3N$), 133 (M^+ - C_9H_9NO).

Repetition of this experiment, however, under apparently identical conditions gave either polymeric tars or returned the starting ketone. Repetition, at higher temperatures, following the reaction by withdrawing aliquots at regular intervals and analysis (after hydrolysis and extraction into chloroform) by i.r. spectroscopy indicated that slow decomposition was occurring with no emergence of amide.

Method 2.

Sodium azide (650mg; 10 mmol) was added in portions to an ice-cooled, stirred solution of the ketone (12) (1.00g; 3.8 mmol) in trifluoroacetic acid (25ml). After addition, the solution was stirred at 0° for 30 min, 20° for 30 min and finally at 40° for 2 h during which time no significant evolution of nitrogen was noted but the solution became increasingly dark. The reaction mixture was hydrolyzed and extracted with chloroform as described above (Method 1.). Analysis of the crude dark brown residue by i.r. and p.m.r. spectroscopy indicated only a small amount (*c.* 10%) of the desired amide (13) and a complex mixture which was not further investigated.

Method 3.

Concentrated sulphuric acid (2.5ml) was added dropwise to an ice-cooled mixture of sodium azide (0.5g; 7.6 mmol) and the ketone (12) (1.00g; 3.8 mmol) in chloroform (8ml). After addition, the mixture was allowed to attain room temperature, during which time it formed a dark brown tar which was not further characterized.

ATTEMPTED BECKMANN REARRANGEMENT OF 3-(1',3'-DIHYDRO-1'(2'H)-INDEN-2'-OXIMINO)ISOBENZOFURAN-1(3H)-ONE (19):

Method 1.

This is based on a method of Paquette *et al.*[75b] A solution of the oxime (19) (250mg; 8.4 mmol) and *p*-toluenesulphonyl chloride (500mg;

17.5 mmol) in pyridine (8ml) was stirred under nitrogen for 15 min at 0° and for 3.5 h at room temperature. Ethanol (4ml) was added and the resulting solution was stirred at room temperature for 30 min. The mixture was neutralized with dilute sodium bicarbonate solution, extracted with methylene chloride (3 x 40ml) and the combined extracts were dried and evaporate to give a yellow solid (190mg) which had the following spectral properties:

i.r. ν_{max} (nujol): 1745s, 740w cm^{-1}.

p.m.r. ($CDCl_3$): δ 8.0-6.8, complex, 7H, Ar-*H*; 6.56, doublet, J = 8Hz, Ar-*H*; 5.91, doublet, J = 3Hz, 1H, Ar-C*H*-O; 4.66, doublet, J = 3Hz, Ar-C*H*- ; 3.63, singlet overlapping with a quartet, 4H, Ar-CH_2 and OCH_2CH_3; 1.23, 2x triplets, 3H, OCH_2CH_3. The complexity of the signal at δ1.23 suggested that this compound was a mixture of *syn*- and *anti*- 3(1',3'-dihydro-N-ethoxy-1'(2'H)-inden-2'-oximino)isobenzofuran-1(3H)-one (21) and not the desired 3-(1',4'-dihydro-3'-ethoxyisoquinolinyl)isobenzofuran-1(3H)-one (20) (see Chapter 2.1).

mass spectrum: m/e 133 (M^+ - $C_{11}H_{12}NO$).

Method 2.

This procedure was essentially the same as for Method 1 with the difference that water (3ml) was added instead of ethanol. An analogous workup afforded a pale yellow solid (97mg) which by analytical t.l.c. (50% ether/methylene chloride) indicated the presence of the starting oxime (19) together with 1(3H)-isobenzofuranone arising from cleavage of the oxime (19). Analysis by i.r. and p.m.r. spectroscopy did not indicate the presence of any of the desired amide (13).

Method 3.

A mixture of the oxime (19) and polyphosphoric acid (*c.* 10g) was

heated at 80° with occassional stirring for 30 min at which time the mixture became black. The reaction mixture was then poured onto ice (*c.* 20g), and extracted with chloroform (3 x 25ml). The combined organic layers were washed with water (2 x 20ml), dried and evaporated to give a dark yellow solid (65mg), t.l.c. analysis of which showed the presence of at least 6 compounds, 2 of which were identified as the starting oxime (19) and 1(3H)-isobenzofuranone. Analysis of the product by i.r. and p.m.r. spectroscopy did not indicate the presence of any of the desired amide (13). Tippett encountered analogous problems in the attempted Beckmann rearrangement of oximes of the phthalideketones belonging to the general structure (17) under similar conditions.[49]

ATTEMPTED SCHMIDT REARRANGEMENT OF 6,7-DIMETHOXY-3-(1'3'-DIHYDRO-1'(2'H)-INDEN-2'-ONYL)ISOBENZOFURAN-1(3H)-ONE (22):

Sodium azide (0.6g; 9 mmol) was added to an ice-cooled, stirred solution of the ketone (23) (1.5g; 4.6 mmol) in polyphosphoric acid (*c.* 15g). The resultant mixture was then stirred at room temperature overnight, hydrolyzed and worked up according to the procedure described for (12), to yield a viscous red oil (1.08g), analysis by t.l.c. (20% ethylacetate/light petroleum) of which showed the presence of 6,7-dimethoxy-1(3H)-isobenzofuranone and of at least 5 other more polar components. Analysis by i.r. and p.m.r. showed the product to be a complex mixture containing none of the desired amide and was not further characterized.

1H-INDENE-1,2(3H)-DIONE 2-OXIME:

Concentrated hydrochloric acid (3ml) was added slowly to a warm (50°) solution of 2,3-dihydro-1H-inden-1-one (5g) and *iso*-pentylnitrite

(6.5g) in methanol (15ml). After addition, the reaction mixture was cooled, and the product collected by vacuum filtration to give 1H-indene-1,2(3H)-dione 2-oxime (5.5g, 89%) as fine yellow needles (m.p. 205° (dec); lit.[103] 215° (dec)).

1,3-DIHYDRO-1-HYDROXY-2H-INDEN-2-ONE OXIME (27):

A mixture of sodium borohydride (0.1g; 25 mmol), 1H-indene-1,2(2H)-dione 2-oxime (1.0g; 6.2 mmol) in propan-2-ol (40ml) was stirred overnight during which time the reaction mixture changed from red to colourless. The solvent was removed *in vacuo* and the residue was treated with dilute hydrochloric acid (20ml) and extracted into methylene chloride (3 x 40ml). The combined organic extracts were washed with saturated brine, dried and evaporated to give (27) as a pale pink solid (960mg; 93%), m.p. 167-170° (dec). A small portion was recrystallized from acetone/light petroleum to give fine colourless needles (m.p. 168-170° (dec)). (Found: C, 66.0; H, 5.7; N 8.5. $C_9H_9NO_2$ requires C 66.2; H 5.6; N 8.6%).

i.r. ν_{max} (nujol): 3200s, 1610s, 740s cm^{-1}.

p.m.r. (CCl_4/$(CF_3CO)_2O$): δ 7.50, singlet, 4H, Ar-*H*; 6.87, singlet, 1H, Ar-C*H*-O; 4.23, doublet of doublets, J_{gem} = 14Hz, Ar-CH_2.

mass spectrum: m/e 163 (M^+ for $C_9H_9NO_2$).

ATTEMPTED CONDENSATION OF 1,3-DIHYDRO-1-HYDROXY-2H-INDEN-2-ONE OXIME (27) WITH 2-FORMYLBENZOIC ACID:

A solution of the oxime (27) (163mg; 1.0 mmol), and 2-formylbenzoic acid (140mg; 1.0 mmol) in benzene (5ml) containing a crystal of *p*-toluenesulphonic acid was stirred under reflux in an atmosphere of nitrogen for 18 h, during which time the mixture formed a black tar with no evidence

(by i.r. spectroscopy) of condensation to the required product. The black tar was shown (by t.l.c. analysis: ethylacetate) to consist of a complex mixture of polymeric material the identity of which was not pursued. When the oxime (27) was heated under the same conditions in the absence of 2-formylbenzoic acid a complex black tarry mixture was again obtained.

ATTEMPTED O-METHYLATION OF OXIME (27):

Method 1.

The oxime (27) (1.6g; 10 mmol) was added at 0° to a tenfold excess of freshly prepared ethereal diazomethane.[104] After stirring at room temperature for 18 h the ether was removed by careful distillation to afford a white solid (1.6g) which was shown by analytical t.l.c., i.r. spectroscopy, and m.p. to be the starting oxime (27).

Method 2.

A solution of the oxime (27) (163mg; 1 mmol) in methanol (5ml) was added to an ice-cooled, stirred solution of sodium methoxide (from 100mg of sodium; 4.3mg atm) in methanol (5ml) whereupon the solution became red. Iodomethane (5ml) was added under nitrogen and the mixture immediately became black. The mixture was stirred for a further 15 min, water (5ml) was added and the resultant black solution was extracted with ether (3 x 20ml). The combined organic extracts were washed with water (10ml), 10% hydrochloric acid, again with water (10ml) dried and evaporated to give a tarry residue, analysis of which showed the absence of starting oxime (27) but only a complex mixture of polymeric material.

Method 3.

As for Method 1 but the anion from (27) (163mg; 1.0 mmol) was generated at 0°, in tetrahydrofuran (10ml), using sodium hydride (100mg of a 50% dispersion in oil; 2 mmol). Iodomethane (2ml) was added at 0° under

nitrogen whereupon the mixture again turned dark. An analogous workup to Method 1 above afforded a red oil, (108mg) p.m.r. spectroscopy of which indicated that the starting oxime was present to the extent of *c.*50% of an otherwise complex mixture. Analysis by t.l.c. showed the presence of at least 5 other compounds which were not further identified.

PART B: WORK DESCRIBED IN CHAPTER 2.2

1-CHLORO-1,3-DIHYDRO-2H-INDEN-2-ONE:

This compound was prepared by the method of Kummler and coworkers[105] and gave a p.m.r. spectrum identical to that previously published.[105]

ATTEMPTED PREPARATION OF 1-(1,3-DIHYDRO-2H-INDEN-2-ONYL)TRIPHENYLPHOSPHONIUM CHLORIDE (32):

Method 1.

A mixture of 1-chloro-1,3-dihydro-2H-inden-2-one (100mg; 0.6 mmol) and triphenylphosphine (160mg; 0.61 mmol) in dry 1,2-dimethoxyethane (10ml) was boiled under reflux for 2 h. Removal of the solvent afforded a red oil (260mg) which was a *c.* 2:1 mixture (by p.m.r. spectroscopy) of 1,3-dihydro-2H-inden-2-one and 1-chloro-1,3-dihydro-2H-inden-2-one.

Method 2.

Triethylamine (*c.* 5 drops) was added to a stirred suspension of triphenylphosphine (1.6g; 6.1 mmol) and 1-chloro-1,3-dihydro-2H-inden-2-one (1.0g; 6 mmol) in 1,2-dimethoxyethane (20ml) whereupon the mixture immediately formed an intractable black tar.

Method 3.

A mixture of 1-chloro-1,3-dihydro-2H-inden-2-one (100mg; 0.6 mmol) in dry benzene (10ml) was boiled under reflux for 3 h. Removal of the

solvent afforded a yellow oil (250 mg) which slowly solidified. Examination of chloroform soluble material by p.m.r. spectroscopy only indicated the presence of 1,3-dihydro-2H-inden-2-one.

Method 4.

Triethylamine (*c*. 5 drops) was added to a mixture of 2-chloro-1,3-dihydro-2H-inden-2-one (100g; 0.6 mmol) and triphenylphosphine (160mg; 0.61 mmol) in dry benzene (10ml) whereupon the reaction proceeded to an intractable black tar.

ATTEMPTED PREPARATION OF (E)- AND (Z)- 3-(1'3'-DIHYDRO-2'-OXO-1'(2'H)-INDENYLIDINE)ISOBENZOFURAN-1(3H)-ONE (31) AND (30):

3,3-Dichloro-3(1H)-isobenzofuranone:

This compound (m.p. 84-87; lit.[106] 87-89°) was prepared according to a published method.[106]

Method 1.

A solution of 3,3-dichloro-3(1H)-isobenzofuranone (203mg; 1.0 mmol) and 1,3-dihydro-2H-indan-2-one (132mg; 1.0 mmol) in benzene (5ml) containing a crystal of *p*-toluenesulphonic acid, was heated under reflux for 6 h. Removal of the solvent afforded a yellow solid which appeared to be only the starting materials by p.m.r. spectroscopy.

Method 2.

As for Method 1 but with the omission of solvent; the mixture was heated at 120° for 10 min at which time analysis by t.l.c. showed only starting materials were present. The mixture was then heated at 120° for a further 30 min during which time a black tar was formed.

Method 3.

A solution of 3,3-dichloro-1(3H)-isobenzofuranone (203mg; 1.0 mmol) in methanol (1ml) and benzene (10ml), containing a catalytic amount of *p*-toluenesulphonic acid, was refluxed for 10 min, the formation of hydro-

gen chloride gas being noted. 1,3-Dihydro-2H-inden-2-one (132mg; 1.0 mmol) was added and the solution was boiled for 6 h. Removal of solvent afforded a red oil, analysis of which by t.l.c. showed the presence of 1,3-dihydro-inden-2-one together with polymeric material.

Method 4.

A mixture of 1,3-isobenzofurandione (phthalic anhydride) (148mg; 1.0 mmol), 1,3-dihydro-2H-inden-2-one (132mg; 1.0 mmol) and *p*-toluene-sulphonic acid (crystal) was heated at 120° for 20 min during which time the mixture deteriorated to an intractable black tar. (These results are summarized in Table 2.1 in Chapter 2.1).

Method 5.

A mixture of 3-(1',3'-dihydro-1'(2'H)-inden-2-onyl)isobenzofuran-1(3H)-one (12) (264mg; 1.0 mmol) and N-bromosuccinimide (180mg; 1.0 mmol) in carbon tetrachloride (25ml) was boiled under reflux in an atmosphere of nitrogen whilst being irradiated by a 100 watt globe placed *c*. 15 cm away. After 0.5 h, analysis by p.m.r. spectroscopy indicated only starting ketone (12) and the mixture was heated for a further 1.5 h at which stage the p.m.r. spectrum showed a complex mixture which did not appear to contain any of the desired compound.

PART C: WORK DESCRIBED IN CHAPTER 2.3

The preparation of 3,4-dihydroxybenzyl diazomethyl ketone has been adapted from the procedure of Mander.[88a]

3,4-DIHYDROXYPHENYLACETIC ACID:

A mixture of 3,4-dimethoxyphenylacetic acid (5g; .03 mmol) and pyridine hydrochloride [107] was heated at 180° (oil bath temperature) under an atmosphere of nitrogen for 5 h. Upon cooling, water (40ml) was added and the solution was extracted thoroughly with ethyl acetate (4 x

50ml). The combined organic extracts were washed with water, dried and evaporated to give a yellow gum which was crystallized from benzene to give 3,4-dihydroxyphenylacetic acid (4.05g; 96%) as colourless needles (m.p. 126-127°; lit.[108] 127°).

3,4-DIACETOXYPHENYLACETIC ACID:

A solution of 3,4-dihydroxyphenylacetic acid (14g; 0.08 mol) and anhydrous sodium acetate (17g; 0.2 mol) in distilled acetic anhydride (300ml) was stirred overnight at room temperature. Water (140ml) was added carefully and the solution was again stirred at room temperature for 1 h at which time water (100ml) followed by methylene chloride (200ml) was added. With the aid of saturated brine (100ml) the layers were separated and the aqueous layer was further extracted with methylene chloride (4 x 100ml). The combined organic layers were washed with water (2 x 100ml), dried and stripped of solvent to yield a yellow oil (18.4g) which was chromatographed on silica (*c.* 400g). Elution with 40% ethyl-acetate/ether gave 3,4-diacetoxyphenylacetic acid as an off-white solid (m.p. 89-90°; lit.[108] 89-90°).

3,4-DIACETOXYBENZYL DIAZOMETHYL KETONE:

A solution of 3,4-diacetoxyphenylacetic acid (1.26g; 5 mmol) and pyridine (0.8g; 5.1 mmol) in anhydrous benzene (5ml) was added dropwise, under nitrogen, to a well-stirred solution of oxalyl chloride (1g; 7.8 mmol) in benzene (10ml). After stirring at room temperature for 30 min the mixture was filtered and the filtrate was carefully concentrated under reduced pressure to afford a pale yellow oil (1.46g), 3,4-diacetoxyphenylacetyl chloride which was usedimmediately without further purification.

i.r. ν_{max} (film): 1810sh, 1770s, 690s cm^{-1}.

A solution of the acid chloride thus obtained in benzene (5ml) was added dropwise with stirring to an ice-cooled solution of freshly prepared ethereal diazomethane[104] (fivefold excess). After the solution was stirred at 0° for 30 min and at 25° for 30 min, the solvent was removed by careful distillation to afford 3,4-diacetoxybenzyl diazomethyl ketone as a yellow gum (1.37g; 93%) which was used immediately.

i.r. ν_{max} (film): 2120m 1770s, 1640m cm^{-1}.

3,4-DIHYDROXYBENZYL DIAZOMETHYL KETONE (34):

The diazoketone obtained above was dissolved in methanol (25ml) and treated with a solution of sodium bicarbonate (3g) and sodium carbonate (2.6g) in water (30ml). The mixture was stirred at room temperature for 1 h, poured onto ice-water and adjusted to pH 7-8 by the careful addition of cold, dilute aqueous oxalic acid. The resultant solution was extracted with ether (3 x 20ml) and the combined extracts were washed with water (2 x 15ml), dried and evaporated to give a yellow oil, 3,4-dihydroxybenzyl diazomethyl ketone (34) (0.83g; 87%) which decomposed rapidly on standing and was therefore used immediately.

i.r. ν_{max} (film): 3200b, 2120m, 1640m cm^{-1}.

ATTEMPTED CYCLIZATION OF 3,4-DIHYDROXYBENZYL DIAZOMETHYL KETONE (34):

These methods are adapted from those of Mander.[81]

Method 1.

A solution of the phenolic diazoketone (34) (450mg; 2.5 mmol) in methylene chloride (20ml) was added slowly (over 15 min) to cold (-20°) vigorously-stirred trifluoroacetic acid (40ml). After stirring for 15 min at -20° and for 15 min at 0°, the mixture was diluted successively with methylene chloride (40ml) and water (100ml). The organic layer was separated, washed with saturated sodium bicarbonate solution (20ml),

water (20ml), dried and evaporated to give a dark brown oil (80mg), which contained at least 5 compounds by analytical t.l.c. The p.m.r. spectrum also showed the oil to be a complex mixture of products and did not indicate the presence of any 1,3-dihydro-5,6-dihydroxy-2H-inden-2-one.

Method 2.

Boron trifluoride etherate (1 drop) was added, under nitrogen at 25°, to a stirred solution of the diazoketone (34) (100mg; 0.57 mmol) in nitromethane (15ml). After stirring at room temperature for 15 min, water (5ml) was added and the mixture was extracted with methylene chloride (3 x 20ml). The combined extracts were washed with water (2 x 10ml), dried and evaporated to give a dark brown residue (54mg). Analysis by t.l.c. and p.m.r. spectroscopy showed the residue to be an extremely complex mixture which was not further characterized; none of the desired product appeared to be present.

3,4-DIMETHOXYBENZYL DIAZOMETHYL KETONE (35):

This compound was prepared in an analogous manner to that described for the diazoketone (34) in 94% yield from 3,4-dimethoxyphenylacetic acid and was used immediately without further purification.

i.r. ν_{max} (film): 2150s, 1640s, 700s cm^{-1}.

REACTION OF 3,4-DIMETHOXYBENZYL DIAZOMETHYL KETONE (35) WITH TRIFLUOROACETIC ACID.

A solution of the diazoketone (35) (1.0g; 4.5 mmol) in methylene chloride (50ml) was added dropwise to cold (-20°), stirred trifluoroacetic acid. After addition, the mixture was stirred at -20° for 10 min and at 0° for 15 min. The mixture was then diluted with methylene chloride (100ml) and washed with water (2 x 100ml) dried and evaporated to give a reddish oil (0.8g), which appeared to be a 2:1 mixture of

3-(3',4'-dimethoxyphenyl)-2-oxo-1-propyl trifluoroacetate (36) and 1,3-dihydro-5,6-dimethoxy-2H-inden-2-one (26).

i.r. ν_{max} (film): 1795s, 1740s, 1240s, 1160s, 700s cm^{-1}.

p.m.r. (CCl_4): δ 6.85, 2x singlets, Ar-*H*; 4.92, singlet, 2H, $Ar\text{-}CH_2COCH_2OTFA$*; 3.85, singlet, CH_3O-; 3.67, singlet, 2H, $Ar\text{-}CH_2\text{-}CO\text{-}CH_2OTFA$; 3.52, singlet, $Ar\text{-}CH_2CO$ [from (26)].

Later Mander independently obtained a similar result (by p.m.r. spectroscopy).[83]

ATTEMPTED REACTION OF 1,2-DIMETHOXYBENZENE WITH 1,3-DICHLOROPROPAN-2-ONE:

General Procedure:

In a representative experiment, 1,2-dimethoxybenzene (1.38; 10 mmol) was added to an ice-cooled, stirred suspension of the Lewis Acid (4 mmol) and 1,3-dichloropropan-2-one (1.2g; 11 mmol) in the appropriate solvent. After stirring at 0° for 1 h, an aliquot was removed and analyzed by t.l.c., the remainder was stirred at the required temperature for 2 h, at which time the reaction was quenched by the addition of water (20ml) and precipitated salts were removed by vacuum filtration. The filtrate was extracted with methylene chloride (3 x 20ml) and the combined extracts were washed with brine, dried, evaporated and the residue was examined by analytical t.l.c. and p.m.r. spectroscopy. The results are listed below.

---

* TFA = trifluoracetate.

SOLVENT	LEWIS ACID	TEMPERATURE (C°)	RESULT
nitrobenzene	$ZnCl_2$	0,25	no reaction [A]
nitrobenzene	$AlCl_3$	0,25	no reaction [A]
benzene	$AlCl_3$	25	no reaction [A]
1,2-dichloroethane	$AlCl_3$	0,25	no reaction [A]
1,2-dichloroethane	$AlCl_3$	60	polymer

A: No reaction as detected by t.l.c. or p.m.r. spectroscopy.

5,6-DIMETHOXY-1H-INDENE :

This compound was prepared in the following sequence:

(i) 3-(3,4-Dimethoxyphenyl)-2-propenoic Acid

This acid (m.p. 178-181°; lit.[109] 180°) was prepared in 87% yield according to the method of Haworth *et al.*[109]

(ii) 3-(3,4-Dimethoxyphenyl)propionic Acid

This compound (m.p. 91-93°; lit.[110] 94°) was prepared according to the method of Horning[111] in quantitative yield, using dioxan instead of acetic acid as the solvent.

(iii) 2,3-Dihydro-5,6-dimethoxy-1H-inden-1-one (37)

The method of Koo[112] was used to prepare this compound (m.p. 117-119°; lit.[112] 117-119°) in 65% yield.

(iv) 2,3-Dihydro-5,6-dimethoxy-1H-inden-1-ol

This compound was prepared by an analogous method to Lukes and Ernest[113] using refluxing THF (3 h) instead of ether. This afforded the above alcohol as colourless needles (m.p. 122-123°; lit.[113] 120°) in 98% yield.

(v) 5,6-Dimethoxy-1H-indene

A solution of 2,3-dihydro-5,6-dimethoxy-1H-inden-1-ol (10.2g) in dimethylsulphoxide (100ml) was heated at 180° under an atmosphere of nitrogen for 6 h. Upon cooling, the mixture was poured onto ice (*c.* 250g) and extracted with ether (4 x 150ml). The combined ether extracts were washed with water (6 x 50ml), dried and evaporated to give a red oil (8.45g) which was chromatographed on silica (*c.* 200g). Elution with methylene chloride gave the olefin as a white solid (m.p. 69-70°; lit.[114] 71°).

p.m.r. (CCl_4): δ 6.90, singlet, 1H, CH-*H*, 6.83, singlet, 1H, C7-*H*; 6.75, multiplet, 1H, Ar-C*H*=CH; 6.35, doublet of triplets, 1H, Ar-CH=C*H*; 3.75, singlet, 6H, 2x CH_3O-; 3.20, singlet, 2H, Ar-CH_2.

HYDROBORATION OF 5,6-DIMETHOXY-1H-INDENE:

A solution of diborane in THF (2ml of 1.5M; 3 mmol) was added, under nitrogen, to an ice-cooled, stirred solution of 5,6-dimethoxy-1H-indene (200mg; 1.14 mmol) in THF (5ml). When the mixture had been stirred at 0° for 15 min and at 20° for 45 min, water (3ml) was cautiously added to the recooled (0°) mixture to destroy excess diborane. The mixture was diluted with ether (10ml) and the reaction was oxidized with aqueous sodium dichromate according to the general method of Brown.[86] The mixture was then extracted with ether (2 x 20ml) and the combined extracts were washed with water (10ml), saturated sodium bicarbonate solution (2 x 10ml) and with more water (20ml), dried and evaporated to afford a yellow solid (184mg, 96%) which on recrystallization from light petroleum afforded 2,3-dihydro-5,6-dimethoxy-1H-indan-1-one (37) (m.p. 117-119°; lit.[112] 117-119°) as colourless needles. Analysis of the crude product by p.m.r. spectroscopy indicated the presence of 1,3-dihydro-5,6-dimethoxy-

2H-inden-2-one (26). The ratio of (26):(37) was *c.* 15:85 by integration.

REACTION OF 5,6-DIMETHOXY-1H-INDENE WITH N-BROMOSUCCINAMIDE:

A mixture of 5,6-dimethoxy-1H-indene (100mg; 0.56 mmol) and N-bromosuccinimide (106mg; 0.6 mmol) in water (2ml) was stirred at room temperature for 1 h, after which time the mixture was extracted with methylene chloride (3 x 10ml). The combined organic layers were dried and evaporated to afford a green gum (63mg). Analysis of the residue by t.l.c. indicated the presence of at least 6 new compounds which were not further characterized.

ETHYL 3,4-DIMETHOXYPHENYLACETATE (43):

A solution of 3,4-dimethoxyphenylacetic acid (5g) in ethanol (30ml) containing a few drops of concentrated sulphuric acid was boiled under reflux for 2 h, at which time the solution was concentrated under reduced pressure to *c.* 10ml. The concentrate was diluted with methylene chloride (60ml), washed with saturated brine, water, dried and evaporated to give 5.36g (94%) of a faint yellow oil (b.p. 110-112°/0.25mm; lit.[115] 191°/25mm).

REACTION OF ETHYL 3,4-DIMETHOXYPHENYLACETATE WITH DIMSYL ANION:

This is an adaptation of the method of Oikawa and Yonemitsu.[88] The anion of dimethylsulphoxide (dimsyl anion) (5 mmol) was prepared by the method of Corey and Chaykovsky[116] using sodium hydride (0.24g of a 50% dispersion in oil; 5 mmol) and dimethylsulphoxide (5ml). To the solution thus prepared, was added under nitrogen a solution of ethyl 3,4-dimethoxyphenylacetate (1.2g; 5 mmol) in THF (5ml) and after addition the reaction was stirred at room temperature for 2 h* and at 70° for 2 h.

---

* Workup at this stage indicated only starting ester (43).

The mixture was then poured onto ice, acidified to pH 3 with hydrochloric acid and extracted with methylene chloride (4 x 30ml). The combined extracts were washed with water (3 x 30ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure to afford a yellow oil (0.95g); which had identical spectral properties with 3,4-dimethoxyphenylacetic acid.* Tituration of the oil with light petroleum afforded the acid as a white solid (m.p. 98-100°; lit.[117] 98-99°).

REACTION OF 3,4-DIMETHOXYPHENYLACETYL CHLORIDE WITH DIMSYL ANION:

A solution of 3,4-dimethoxyphenylacetyl chloride (0.91g; 5 mmol) in benzene (5ml) was treated with dimsyl anion (5 mmol) in an analogous manner to that described above. After stirring at room temperature for 1.3 h a similar workup gave a red oil (0.57g) which had identical spectral properties to 3,4-dimethoxyphenylacetic acid.

REDUCTION OF 1H-INDENE-1,2-(3H)-DIONE (49) WITH DIBORANE:

(i) The diketone (49) (m.p. 98-103° (dec); lit.[118] 95-105° (dec)) was prepared in near quantitative yield according to the method of Perkin *et al.*[118]

(ii) An aunthentic sample of *trans*-2,3-dihydro-1H-inden-1,2-diol (50) (m.p. 161-165°; lit.[92] 160-163°) was prepared by the method of Rosen *et al.*[92]

(iii) A solution of the diketone (49) (200mg; 1.4 mmol) in anhydrous THF (10ml) was added slowly under nitrogen to an ice-cooled, stirred solution of diborane in THF (1ml of 2.0M solution; 2 mmol). After addition, stirring was continued at room temperature until the canary yellow solution became colourless (2-3 h). After cooling the solution to 0°, water (5ml) was added cautiously followed by concentrated sulphuric acid (*c.* 2-3

---

* If an acid workup was not used then the starting ester (43) was returned.

drops) and stirring was maintained for a further 30 min to ensure hydrolysis. The layers were separated with the aid of saturated brine and the aqueous layer was extracted further with ether (3 x 10ml). The combined organic layers were washed with saturated brine (10ml), dried and evaporated under reduced pressure to give 202mg (99%) of *trans*-2,3-dihydro-1H-inden-1,2-diol (50) (m.p. 161-163°; lit.[92] 160-163°) which had an identical p.m.r. spectrum with an authentic sample.

5,6-DIMETHOXY-1H-INDENE-1,2(3H)-DIONE 2-OXIME:

This compound (m.p. 230-232° (dec); lit.[119] 240° (dec)) was prepared by the method of Perkin and Robinson[119] in 93% yield.

5,6-DIMETHOXY-1H-INDENE-1,2(3H)-DIONE (47):

The diketone (47) (m.p. 165-167°; lit.[94] 166°) was prepared in near quantitative yield according to the method of Perkin *et al.*[94]

HYDROBORATION OF 5,6-DIMETHOXY-1H-INDENE-1,2(3H)-DIONE (47):

A solution of the diketone (47) (2.04g; 10 mmol) in dry THF (50ml) was added, under nitrogen, to a ice-cooled, stirred solution of diborane (10ml of 2M solution; 20 mmol). After addition, the canary yellow solution was stirred at room temperature until the solution became colourless (*c.* 18 h). An analogous workup procedure to that described for the reduction of (49) afforded 1.91g (92%) of *trans*-2,3-dihydro-5,6-dimethoxy-1H-inden-1,2-diol (48) as an off-white solid (m.p. 186-188°) which discoloured on standing.

i.r. ν_{max} (nujol): 3350s, 1605w, 770 cm^{-1}.

p.m.r. ($CDCl_3$): δ 6.93, 6.80, 2 singlets, 2H, Ar-*H*; 5.03, doublet, J = 5.0Hz, Ar-C*H*-O; 4.46, doublet of doublets of doublets, 1H, Ar-CH_2-C*H*-O; 3.90, singlet, 6H, 2x CH_3O; 3.20, doublet of doublets, 2H, Ar-CH_2; 2.67, broad singlet, D_2O exch., 2H, 2x -O*H*.

mass spectrum: m/e 192 ($M^+ - H_2O$).

REARRANGEMENT OF DIOL (48) TO 1,3-DIHYDRO-5,6-DIMETHOXY-2H-INDEN-2-ONE (26):

General Procedure:

A solution of the diol (48) (50mg) in the solvent indicated in the table below (5ml) containing, where applicable, a catalytic amount of acid was stirred at the indicated temperature for a noted period of time, the reaction being monitored by analytical t.l.c. (4% ethyl acetate/ methylene chloride). Whenever the emergence of non polar products was observed or if the reaction became discoloured, the reaction was extracted with methylene chloride (2 x 10ml). The combined extracts were then dried, stripped of solvent and examined by p.m.r. spectroscopy. The reaction conditions are summarized in the table below and relevant experiments are expanded there after.

EXPERIMENT	SOLVENT	ACID	TEMP (°C)	TIME (h)	YIELD (%)	RESULT
1	benzene	TosOH [A]	25	48	95	isomeric diols
2	benzene	TosOH	40	2	65	(26)
3	benzene	TosOH	80	1	65	(26)
4	water	H_2SO_4	60	1		polymeric tar [B]
5	20% EtOH/H_2O	H_2SO_4	60	1		polymeric tar
6	DMSO	none	160-180	3.5	<1	unidentified
7	benzene	H_2SO_4	20	1	48	(26)
8	10% oxalic acid		60	1	71	(26)
9	10% oxalic acid		40	2	90	no reaction [B]

A: TosOH = *p*-toluenesulphonic acid

B: no significant reaction as detected by analytical t.l.c. and p.m.r. spectroscopy.

Experiment 1:

A pale yellow solid which had the following spectral properties was obtained:

i.r. ν_{max} (nujol): 3150s, 3250s, 1610w, 770w, 730w cm^{-1}.

p.m.r. ($CDCl_3/D_2O$): δ 6.95, multiplet, 2H, Ar-*H*, 4.83, complex, 1H, Ar-C*H*-O; 4.57, complex, 1H, Ar-CH_2-C*H*-O; 3.93, 3.83, 2 singlets, 6H, 2x CH_3O; 3.20, complex, Ar-CH_2.

The mixture thus appeared a *c.* 1:1 mixture of *cis*- and *trans*-2,3-dihydro-5,6-dimethoxy-1H-inden-1,2-diol.

Experiment 8:

The crude red oil obtained from workup was chromatographed on silica (preparative t.l.c. using 12% ethyl acetate/chloroform as a developing solvent) to afford 56mg (71%) of 1,3-dihydro-5,6-dimethoxy-2H-inden-2-one (26) as an off-white solid. A small portion was recrystallized from ethanol to give colourless needles (m.p. 136-137°; lit.[82] 137-139°).

i.r. ν_{max} (nujol): 1740s, 1605w, 760w cm^{-1}.

p.m.r. ($CDCl_3$): δ 6.80, singlet, 2H, Ar-*H*; 3.83, singlet, 6H, 2x CH_3O; 3.47, singlet 4H, 2x Ar-CH_2.

mass spectrum: m/e 192 (M^+ for $C_{11}H_{12}O_3$).

WORK DESCRIBED IN PART II

PART A: WORK DESCRIBED IN CHAPTER 2.1

HYDROBORATION OF EPOXIDES - A GENERAL PROCEDURE:

All reactions were carried out under an atmosphere of nitrogen and all solutions were transferred by hypodermic syringes. In a typical experiment, a solution of diborane in THF (1.6 M; 1-10 mmol) was introduced to a round bottom flask connected to a gas burette and having a side arm capped by a rubber septum. A solution of the epoxide (1-10 mmol) in dry THF (1ml per mmol of epoxide) was then added. In all cases a very slight excess of diborane (1.05 equivalents of BH_3) to epoxide was used.

Whenever the reaction was to be monitored by g.l.c., at suitable time intervale aliquots were withdrawn, diluted with ether, quenched by the addition of 3M aqueous sodium hydroxide and analyzed. A solution of aqueous 9M hydrogen peroxide was also added to the aliquot whenever it was desirable to analyze the reaction mixture after it had been oxidized. Qualitative indentifications were made initially by comparing the retention times of the components with those of authentic samples (where available), and then by the technique of peak enhancement ("spiking"). The relative yields of the components were determined by the area of peaks. Responses (to the detector in the g.l.c. apparatus) of the authentic samples with respect to a standard were determined in triplicate and where the response ratio could not be assessed directly, the average response ratio of other compounds of its type was assumed.

The syntheses of the epoxides and alcohols obtained from the hydroboration of the benzocyclene oxides (30) will be subsequently described.

HYDROBORATION OF 6,7-DIHYDRO-5H-BENZOCYCLOHEPTENE OXIDE (44):

The epoxide (44) (160mg; 10 mmol) was treated with diborane in the manner just described. No significant evolution of hydrogen was noted. Analysis of the hydrolyzed reaction mixture after 24 h by g.l.c. (column B, 150°) indicated the presence of 4 components having retention times (min. sec): 5.48, 2%, unidentified; 7.02, 5% (44); 10.24, 92%, 6,7,8,9-tetrahydro-5H-benzocyclohepten-6-ol (46); 11.28, 1%, 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (47),

Analysis of the reaction mixture after addition of 9M hydrogen peroxide showed no change (by g.l.c.) in the product composition.

The reaction mixture was diluted with ether (30ml), washed with saturated brine, dried and evaporated to give 170mg of a colourless oil. Preparative t.l.c. using 30% ether/light petroleum afforded the alcohol (46) as a white solid (143mg, 88%) which had identical spectral properties with an authentic sample.

HYDROBORATION OF 5,6,7,8-TETRAHYDRO-5H-BENZOCYCLOOCTENE OXIDE (49):

The epoxide (49) (174mg; 10 mmol) was treated in an analogous manner to that described for (44). No significant evolution of hydrogen was observed. Analysis of the hydrolyzed reaction mixture by g.l.c. (column B, 150°) after 24 h indicated the presence of 5 components having retention times: 4.57, 64%, (49); 6.42, 8%, unidentified; 12.27, 27%, 5,6,7,8,9,10-hexahydro-5H-benzocycloocten-6-ol (50); 14.12, 1%, 5,6,7,8,9,10-hexahydro-5H-benzocycloocten-5-ol (51). No difference was observed (by g.l.c.) after treatment of the hydrolyzed reaction mixture with hydrogen peroxide.

An analogous workup procedure to that described for (44) gave a 24% yield of (50) after preparative t.l.c. (30% ether/light petroleum), which had identical spectral properties to an authentic specimen.

HYDROBORATION OF (Z)-6,7,8,9-TETRAHYDRO-5H-BENZOCYCLONONENE OXIDE (52):

The epoxide (52) (188mg; 10 mmol) was treated with diborane in an analogous manner to that described for (44). No significant evolution of hydrogen was observed. Analysis of the hydrolyzed reaction mixture by g.l.c. (colum B, 175°) after 36 h indicated the presence of 4 components having retention times: 1.40, 8%, (52); 6.04, 31%, 6,7,8,9,10,11-hexahydro-5H-benzocyclononen-5-ol (54); 8.32, 58%, 6,7,8,9,10,11-hexahydro-5H-benzocyclononen-6-ol (53) 15.00, 3%, unidentified. No difference was observed (by g.l.c.) after oxidation with hydrogen peroxide. An analogous workup to that described for (44) afforded 172mg which was chromatographed (using 40% ether/light petroleum as a developing solvent) to afford 65mg (34%) of (53) and 41mg (21%) of (54) each of which had identical spectral properties with an authentic sample.

HYDROBORATION OF 3-METHYL-1H-INDENE OXIDE (56)

The epoxide (56) (0.9g; 6.14 mmol) was treated with diborane under the conditions described for (44). A rapid evolution of hydrogen (114ml; 84% of the theoretical) accompanied the addition of the epoxide. After 24 h the reaction mixture was ice-cooled, and aqueous 3M sodium hydroxide (4ml), followed by 9M hydrogen peroxide (4ml) were added. Stirring was continued at room temperature for 1 h. The mixture was extracted

with ether (4 x 20ml) and the combined organic extracts were washed with brine (20ml), dried and evaporated to dryness to afford a pink oil (0.92g). Analysis of the crude product by p.m.r. spectroscopy showed the presence of *cis*-2,3-dihydro-2(1H)-methylinden-1-ol (58) indicated by a doublet, J = 5Hz at δ1.33 and *trans*-2,3-dihydro-1-hydroxy-1H-indene-2-methanol (60) in a ratio of *c*. 15:85. Preparative t.l.c. of a sample (260mg) (using 5% ethyl acetate (ether as a developing solvent) gave a sample (30mg) (Rf 0.5) of the alcohol (58) which had the following spectral properties:

i.r. ν_{max} (film): 3460s, 1370s, 1200s, 1080s, 730s cm^{-1}.

p.m.r. ($CDCl_3$): δ 7.20, singlet, 4H, Ar-*H*; 4.20, quarlet, 1H, C*H*-OH; 3.18, complex, 3H, Ar-CH_2 and Ar-C*H*; 2.0, broad singlet, D_2O exch. 1H, O-*H*; 1.33, doublet, J = 5Hz, CH-CH_3.

mass spectrum: m/e 148 (M^+ for $C_{10}H_{12}O$).

A pure sample of the diol (60) was obtained by distillation b.p. 100-105° (block)/0.01mm (Found: C, 73.1; H, 7.4. $C_{10}H_{12}O_2$ requires C, 73.1; H, 7.4%).

i.r. ν_{max} (CCl_4): 3380s, 2950s, 1060s, 1020s cm^{-1}. The position of the O-H stretching frequency was unaffected by the concentration of (60) in CCl_4.

p.m.r. ($CDCl_3$): δ 7.00, singlet, 4H, Ar-*H*; 4.57, multiplet, 1H, C*H*-OH; 4.20-3.60, complex, 3H, 1 proton D_2O exch. simplifying signal to doublet J = 8Hz, CH_2-OH and O-*H*; 3.2-2.9, complex, 3H, Ar-CH_2 and Ar-C*H*.

mass spectrum: m/e 164 (M^+ for $C_{10}H_{12}O_2$)

A sample of the diol (60) (170mg; 1.03 mmol) was dissolved in acetone (2ml) containing 2,2 dimethoxypropane (0.2ml) and a crystal of

p-toluenesulphonic acid. After standing at room temperature overnight, the mixture was diluted with ether (20ml) and washed with 5% sodium bicarbonate solution (5ml), water (5ml) and dried over anhydrous potassium carbonate. Removal of the solvent afforded a red oil (115mg; 31%) which was distilled (b.p. 80-83° (block)/0.2mm) to give a colourless oil, bis (trans-2,3-dihydro-1-hydroxy-1H-indene-2-methano) ether (see Chapter 2.1) (Found: C, 74.5; H, 7.5. $C_{23}H_{28}O_4$ requires C, 74.9; H, 7.5%).

i.r. ν_{max} (film): 3450s, 2950s, 1100s, 745m cm^{-1}.

p.m.r. (CCl_4): δ 7.00, singlet, 8H, Ar-*H*; 4.63, doublet of triplets, 2H, C*H*-OH; 4.00, multiplet, 4H, CH_2-OH; 3.00, complex, 6H, Ar-*CH* and Ar-CH_2; 2.02, broad, 1H, O-*H*; 1.57 and 1.44, 2 singlets, 6H, 2 x CH_3.

HYDROBORATION OF 3,4-DIHYDRO-1-METHYLNAPHTHALENE OXIDE (64):

The epoxide (64) (1.40g; 10 mmol) was treated with diborane in an analogous manner to that described for (56). A rapid evolution of hydrogen (225ml; 100%) accompanied the addition of (64). A similar work-up procedure to that described for (56) gave a pale pink oil (1.5g) 1,2,3,4-tetrahydro-2-hydroxy-1-naphthalenemethanol (66) which crystallized from light petroleum as colourless cubes m.p. 72-75° (Found: C, 74.2; H, 8.1. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%).

i.r. ν_{max} (film): 3350s, 2900s, 1450m cm^{-1}.

p.m.r. ($CDCl_3/D_2O$): δ 7.00, singlet, 4H, Ar-*H*, 4.53-3.80, complex, 3H, CH_2-OH and C*H*-OH; 3.20, multiplet, 1H, Ar-C*H*; 2.87, multiplet, 2H, Ar-CH_2; 2.03 multiplet, 2H, —CH_2—.

mass spectrum: m/e 178 (M^+ for $C_{11}H_{14}O_2$).

HYDROBORATION OF 2-METHYL-1H-INDENE OXIDE (67)

The epoxide (67) (0.73g; 5 mmol) was treated with diborane in an analogous manner to that described for (44). A slow evolution of hydrogen (34ml; 30%) was observed after the addition of (67). After 24 h, analysis of the hydrolyzed reaction mixture by g.l.c. (column A, 145°) indicated the presence of 6 components having retention times: 1.25, 4%, 2-methylindene; 2.25, 50%, (67); 4.42, 6%, 2,3-dihydro-2-methyl-1H-inden-2-ol (69); 5.12; 36%, 2,3-dihydro-2-methylnaphthalene as an internal standard, this represented *c*. 70% of the product. Analysis of the oxidized reaction mixture by g.l.c. (column D, 160°) indicated the presence of 2,3-dihydro-1-hydroxy-1H-indene-2-methanol (71), 28%, with a retention time of *c*. 15 min.

HYDROBORATION OF 3,4-DIHYDRO-2-METHYLNAPHTHALENE OXIDE (74)

The epoxide (74) (320mg; 20 mmol) was treated with diborane in an analogous manner to that described for (56). A small amount (2.5ml, 4%) of hydrogen evolution was observed. Analysis of the hydrolyzed reaction mixture by g.l.c. (column A, 160°) indicated the presence of 4 major compounds having retention times: 1.50, 12%, 1,2-dihydro-3-methylnaphthalene (127); 3.24, 24%, (74); 4.12, 12%, 1,2,3,4-tetrahydro-2-methylnaphthalen-2-ol (78). Workup of the reaction mixture as described previously afforded a colourless oil, (300mg; 91%) the spectra of which were consistent with the alcohol (78) as the major component.

i.r. ν_{max} (film): 3440m, 2950s, 1020m, 1060m, 820m, 750s, 740s, 720s cm^{-1}.

p.m.r. (CCl_4/D_2O): δ 6.92, complex, 4H, Ar-*H*; 2.33, complex, 4H, Ar-CH_2; 1.67, complex, 2H, $-CH_2-$; 1.20, singlet, 3H, $-CH_3$.

mass spectrum: m/e 162 (M^+ for $C_{11}H_{14}O$, 10%) 144 (M^+-H_2O, base peak).

Due to the facile elimination of water from (78), an analysis was not obtained.

PART B: WORK DESCRIBED IN CHAPTER 2.2

HYDROBORATION OF BENZOCYCLENES - A GENERAL PROCEDURE

The synthesis of the olefins and of authentic samples of the alcohols (where appropriate) from the hydroborations will be subsequently described.

A. WITH DIBORANE:

All reactions were carried out under nitrogen and all solutions were transferred by means of hyperdermic syringes. In a typical experiment, a solution of the olefin (1-10 mmol) in dry THF (1ml per mmol of olefin) was added to an ice-cooled solution of diborane in THF (1.0 equivalents of BH_3). Stirring was maintained at 0° for 0.5 h and at room temperature (20-25°) for 2.5 h. The reaction was again cooled to 0°, 3M sodium hydroxide and 9M hydrogen peroxide were added. After stirring at room temperature for 30 min, a standard for g.l.c. analysis was added and an aliquot of the organic layer was examined by g.l.c. in a similar manner to that previously outlined for the benzocyclene oxides. The workup procedure for the isolation of the product(s) was analogous to that described for the hydroboration of 3-methylindene oxide (56).

B. WITH THEXYLBORANE:

Thexylborane was freshly prepared, as required, according to the method of Zweifel and Brown.[89] The hydroboration of the olefins was then performed in a similar fashion to that described (using 1.0 equivalents of thexylborane) for diborane.

HYDROBORATION OF INDENE (85):

A. WITH DIBORANE:

Indene (1.32g; 10 mmol) was treated with diborane in the manner previously outlined. Analysis of the oxidized reaction mixture by g.l.c. (column B, 142°) showed the presence of 3 compounds having retention times: 10.37, 14%, 2,3-dihydro-1H-inden-1-ol (40); 13.09, 86%, 2,3-dihydro-1H-inden-2-ol (38); 17.20, reference, 1,2,3,4-tetrahydronaphthalen-1-ol (41).

B. WITH THEXYLBORANE:

Indene (1.32g; 10 mmol) was treated with diborane the manner previously described. Analysis of the oxidized reaction mixture by g.l.c. (column B, 142°) indicated the presence of 3 compounds having retention times: 10.37, *c.* 1%, (40); 13.09, *c.* 99%, (38); 17.20, reference, (41).

HYDROBORATION OF INDENE AT -78°

A solution of indene (1.16g; 10 mmol) in dry THF (10ml) was added all at once, to a stirred solution of diborane (2.5ml of 1.5M; 0.4 equivalents of BH_3) in tetrahydrofuran cooled to -78°; an aliquot was removed and immediately oxidized with alkaline hydrogen peroxide as described previously. Analysis by g.l.c. (column B, 142°) did not indicate any significant change in the product composition from that

obtained when the hydroboration of indene was performed under "normal" conditions, as described previously.

HYDROBORATION OF 1,2-DIHYDRONAPHTHALENE (90):

A. WITH DIBORANE:

The olefin (90) (160mg; 1o mmol) was treated with diborane in an analogous manner described for indene. Analysis of the reaction mixture by g.l.c. (column B, 151°) showed the presence of 3 major components having retention times: 5.32, reference, (40); 8.49, 92%, 1,2,3,4-tetrahydronaphthalen-1-ol (41); 11.58, 8%, 1,2,3,4- tetrahydronaphthalen-2-ol (39).

B. WITH THEXYLBORANE:

Analysis of the oxidized reaction mixture by g.l.c. (column B, 151°), after treatment of the olefin (90) with thexylborane and consequent oxidation in the manner previously described, showed the presence of 3 components having retention times: 5.32, reference (40); 8.49, 90%, (41); 11.58, 10% (39).

HYDROBORATION OF 6,7-DIHYDRO-5H--BENZOCYCLOHEPTENE (90):

A. WITH DIBORANE:

The olefin (90) (60mg, 0.42 mmol) was treated with diborane in an analogous manner described for indene. Analysis by g.l.c. (column B, 155°) indicated the presence of 3 major components having retention time: 3.54, reference (40); 8.57, 6%, 6,7,8,9-tetrahydro-5H-benzocycloheptene-6-ol (46); 10.37, 94%, 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (47).

B. WITH THERXYLBORANE:

Analysis of the reaction mixture by g.l.c. (column B, 155°) indicated the presence of 3 major components having retention times: 3.54, reference,

(40); 8.57, 12%, (46); 10.35, 88% (47).

HYDROBORATION OF 7,8,9,10-TETRAHYDRO-5H-BENZOCYCLOOCTENE (91):

A. WITH DIBORANE:

The olefin (91) (59mg; 0.5 mmol) was treated as before with diborane. Analysis of the reaction mixture by g.l.c. (column B, 155°) indicated the presence of 4 components having retention times: 1.35, trace, (91); 9.45, reference, (47); 11.51, 14%, 5,6,7,8,9,10-hexahydro-5H-benzocycloocten-6-ol (50); 14.17, 86%, 5,6,7,8,9,10-hexahydro-5H-benzocycloocten-5-ol (51).

B. WITH THEXYLBORANE:

Analysis of the reaction mixture by g.l.c. (column B, 155°) showed the presence of 3 compounds having retention times: 1.35, trace, (91); 9.45, reference (47); 11.50, 25% (50); 14.17, 75% (51).

HYDROBORATION OF (Z)-8,9,10,11-TETRAHYDRO-5H-BENZOCYCLONONENE (92):

A. WITH DIBORANE:

The olefin (92) (81)mg; 0.5 mmol) was treated with diborane in a manner previously described. Analysis of the oxidized reaction mixture by g.l.c. (column C, 160°) showed the presence of 4 compounds having retention times: 8.35, < 1%, unidentified; 17.17, reference, alcohol (51); 29.15, 89%, 6,7,8,9,10,11-hexahydro-5H-benzocyclononen-5-ol (54); 32.45, 11%, 6,7,8,9,10,11-hexahydro-5H-benzocyclononen-6-ol (53).

B. WITH THEXYLBORANE:

Analysis of the reaction mixture by g.l.c. (column C, 160°) showed the presence of 4 compounds having retention times: 8.32, < 1%, unidentified; 17.20, reference, (51); 29.15, 62%, (54); 32.45, 38%, (53).

HYDROBORATION OF 2-METHYL-1H-INDENE (93):

A. WITH DIBORANE:

The olefin (130mg; 1.0 mmol) was treated with diborane in an analogous manner to indene described previously. Analysis of the oxidized reaction mixture by g.l.c. (column B, 145°) showed the presence of 4 compounds having retention times: 1.35, 2%, (93); 2.35, reference, 2-methylnaphthalene; 3.57, 2%, 2,3-dihydro-2-methylinden-2-ol (69); 4.54, 96%, *trans*-2,3-dihydro-2-methylinden-1-ol (94). Workup of the reaction mixture in a manner previously outlined afforded an oil (138mg; 98% based on indene) which was crystallized from light petroleum to give fine colourless needles m.p. 86-87°. (Found: C, 81.4; H, 8.4. $C_{10}H_{12}O$ requires C, 81.0; H, 8.2%).

i.r. ν_{max} (film): 3460m, 2950s, 1270s, 1200s, 1080s, 730s cm^{-1}.

p.m.r. ($CDCl_3$): δ 7.13, singlet, 4*H*, Ar-*H*; 4.67, doublet, J = 7Hz, 1H, C*H*-OH; 3.20-2.0, complex, 3H, C*H*-CH_3 and Ar-C*H*$_2$; 2.0, broad singlet, 1H, D_2O exch., *O-H*; 1.41, doublet, J = 7Hz, 3H, CH-*CH*$_3$.

mass spectrum: m/e 148 (M^+ for $C_{10}H_{12}O$).

B. WITH THEXYLBORANE:

Analysis of the oxidized reaction mixture by g.l.c. (column B, 145°) indicated the presence of 3 compounds having retention times: 1.35, *c.* 98% (93); 2.35, reference, 2-methylnaphthalene; 4.55, *c.* 2%, (94).

HYDROBORATION OF 3,4-DIHYDRO-1-METHYLNAPHTHALENE (95):

A. WITH DIBORANE:

The olefin (95) (1.44g; 10 mmol) was treated with diborane in a manner previously outlined. Analysis of the oxidized reaction mixture by g.l.c. (column B, 160°) showed the presence of 4 compounds having retention times: 1.55, 1%, (95); 3.52, reference, 2-methylnaphthalene; 8.42, 8%, 1,2,3,4-tetrahydro-1-methylnaphthalen-1-ol (96); 15.55, 91%, *trans*-1,2,3,4-tetrahydro-methylnaphthalen-2-ol (97). Workup of the reaction gave 1.52g (97% based on (95)), of a colourless oil. Preparative t.l.c. (using 40% ether/light petroleum as a developing solvent) of a sample (250mg) of the oil gave 224mg of the alcohol (97), b.p. 100-105° (block)/0.7mm. (Found: C, 81.5; H, 817. C H O requires C, 81.4; H 8.7%).

i.r. ν_{max} (film): 3400s, 2950s, 1020s, 750m, 720m cm^{-1}.

p.m.r. (CCl_4): δ 7.20, singlet, 4H, Ar-*H*; 3.67, approximating to a doublet of triplets, 1H, Ar-C*H*-OH; 2.77, multiplet, 2H, Ar-CH_2; 2.13, broad singlet, 1H, D_2O exch., O-*H*; 1.87, multiplet, 2H, —CH_2—; 1.27, doublet, J = 7Hz, 3H, CH-CH_3.

mass spectrum: m/e 162 (M^+ for $C_{11}H_{14}O$).

B. WITH THEXYLBORANE:

Analysis of the oxidized reaction mixture by g.l.c. (column B, 160°) showed the presence of 3 compounds having retention times: 1.55, trace, (95); 3.52, reference, 2-methylnaphthalene, 15.55, 98%, (97).

HYDROBORATION OF (Z)-1-PHENYLPROPENE (98):

A. WITH DIBORANE

The olefin (98) (60mg; 0.51 mmol) was treated with diborane in an analogous manner to that described for indene. Analysis of the oxidized reaction mixture by g.l.c. (column A, 80°), showed the presence of 3 compounds having retention times: 2.10, reference, *n*-dodecane; 10.49, 14%, phenylpropan-2-ol (15); 11.47, 86% phenylpropan-1-ol (16).

B. WITH THEXYLBORANE

Analysis of the reaction mixture by g.l.c. (column A, 80°) indicated the presence of 3 major compounds having retention times: 2.10, reference, *n*-dodecane; 10.49, 19%, (15); 11.47, 81%, (16).

PART C: WORK DESCRIBED IN CHAPTER 2.3

6,7,8,9-TETRAHYDRO-5H-BENZOCYCLOHEPTEN-5-ONE (104)

This compound (b.p. 90-93°/0.3mm; lit.[100] 141.5/14mm) was prepared according to the method of Caubere[100] in 67% yield.

6,7,8,9-TETRAHYDRO-5H-BENZOCYCLOHEPTEN-5-OL (47)

This alcohol (m.p. 101-102°; lit.[158] 102-103°) was prepared in 93% yield by the method of Treibs and Klinkhammer.[158]

6,7-DIHYDRO-5H-BENZOCYCLOHEPTENE (90)

The olefin (90) (b.p. 78-80°/2.5-3.0mm; lit.[159] 82-83°/3mm) was prepared in 97% yield by the method of Fujita[159] and had the following spectral properties.

i.r. ν_{max}(film): 2950s, 790s, 760s, 680s cm^{-1}.

p.m.r. (CCl_4): δ 7.00, singlet, 4H, Ar-*H*; 6.36, multiplet, 1H, Ar-C*H*=CH; 5.80, doublet of triplets, 1H, Ar-CH=C*H*; 2.94, doublet of doublets, 2H, Ar-CH_2, 2.00, multiplet, other *H*.

6,7-DIHYDRO-5H-BENZOCYCLOHEPTENE OXIDE (44)

A solution of the olefin (90) (3.25g; 0.023 mmol) in methylene chloride (10ml) was added to an ice-cooled suspension of *m*-chloroperoxybenzoic acid (4.67g as a 85% mixture with *m*-chlorobenzoic acid; (0.025 mmol), and sodium benzoate (3.5g; 0.025 mmol) in methylene chloride (20ml). The resultant mixture was kept at 0° overnight where upon it

was diluted with methylene chloride (100ml) and washed with 10% potassium carbonate solution (2 x 20ml), water (30ml) and dried. The solvent was removed under reduced pressure to afford a colourless oil (2.9g, 81%) (b.p. 70-72°/0.3mm; lit.[62] 96-98°/0.2mm).

p.m.r. (CCl_4): δ 7.60-6.95, complex, 4H, Ar-*H*, 3.84, doublet, J = 4Hz, Ar-C*H*(O)-CH; 3.21, doublet of triplets, 1H, Ar-CH(O)-C*H*; 2.80, multiplet, 2H, Ar-CH_2, 2.2-1.5, envelope, 4H, other H.

6,7,8,9-TETRAHYDRO-5H-BENZOCYCLOHEPTEN-6-OL (46):

This alcohol (m.p. 69-73°; lit.[62] 72-72.5°) was prepared by the method of Huisgen *et al.*[62]

7,8-BENZOBICYCLO[4.2.0]OCT-7-EN-1-OL (102):

The method of Caubere[100] was used to prepare this compound (m.p. 107-109°, lit.[160] 108-109°) in 53% yield.

7,8,9,10-TETRAHYDRO-5(64)-BENZOCYCLOOCTENONE (105):

This ketone (b.p. 102-104°/1.0mm; lit.[160] 148-148.5°/12mm) was prepared in near quantitiative yield according to the method of Thies and Shih.[161] It was subsequently found that sodium hydride could be substituted for potassium hydride in this reaction with no decrease in yield.

5,6,7,8,9,10-HEXAHYDRO-5H-BENZOCYCLOOCTEN-5-OL (51):

This alcohol (m.p. 78-79°; lit.[160] 78.5-79°) was synthesized by the procedure of Huisgen and Rapp[160] in quantitative yield.

7,8,9,10-TETRAHYDRO-5-BENZOCYCLOOCTENE (91):

The olefin (91) (b.p. 70-75° (block)/0.5-0.7mm; lit.[63] 107-109°/11mm) was made following the method of Huisgen *et al*[63] in 94% yield.

p.m.r. (CCl_4): δ 7.07; singlet, 4H, Ar-*H*, 6.40, multiplet, 1H, Ar-*CH*=CH; 5.84, doublet of doublets, 1H, Ar-CH=*CH*; 2.63, complex, 2H, Ar-CH_2; 2.17, complex, 2H, allylic CH_2; 1.60, envelope, 6H, other *H*.

7,8,9,10-TETRAHYDRO-5H-BENZOCYCLOOCTENE OXIDE (49):

This epoxide (b.p. 108-113° (block)/0.05mm; lit.[63] 95-99°/0.03mm) was prepared in 95% yield according to the method of Huisgen *et al*.[63]

5,6,7,8,9,10-HEXAHYDRO-5H-BENZOCYCLOOCTEN-6-OL (50):

The method of Huisgen *et al*[63] was used to prepare this alcohol (b.p. 120-130° (block)/0.5-0.6mm; lit.[160] 104-108°/0.01mm) in 76% yield.

8,9-BENZOBICYCLO-[5.2.0]NON-8-EN-1-OL (103):

This compound (m.p. 94-96°; lit.[100] 96°) was synthesized according to the method of Caubere.[100]

6,7,8,9,10,11-HEXAHYDRO-5H-BENZOCYCLONONEN-5-ONE (106):

A solution of the alcohol (103) (10g; 0.057 mol) in dry THF (100ml) was added to a stirred suspension of sodium hydride (10g as a 40% dispersion in oil; 0.15 mol) in light petroleum (150ml). After addition the mixture was refluxed under nitrogen for 1 h, cooled, and water (50ml) was cautiously added. The mixture was then vigorously stirred at room temperature for 0.5 h to complete the protonation. The layers

were separated and the aqueous layer was extracted with light petroleum (2 x 100ml). The combined organic layers were washed with saturated ammonium chloride solution (2 x 100ml), dried over anhydrous magnesium sulphate and stripped of solvent to yield 10.0g (100%) of an almost colourless oil which was characterized as its 2,4-dinitrophenylhydrazone (m.p. 148-151°; lit.[162] 151-151.5) prepared in the normal manner.[163a]

i.r. ν_{max} (film): 1700s, 1670s cm^{-1}.

6,7,8,9,10,11-HEXAHYDRO-5H-BENZOCYCLONONEN-5-OL (54):

A mixture of the ketone (106) (10g; 0.057 mol), and lithium aluminium hydride (2g) in dry ether (300ml) was refluxed under an atmosphere of nitrogen for 2 h. The mixture was cooled to 0° and water (2ml) followed by 10% sodium hydroxide solution (2ml) and water (6ml) were added. After stirring the mixture for 0.5 h at room temperature, the precipitated salts were removed by vacuum filtration and the filtrate was concentrated under reduced pressure to give a colourless oil (9.2g; 88%). Crystallization from light petroleum afforded large colourless prisms (m.p. 58-59°; lit.[164] 58.5-59°).

REACTION OF ALCOHOL (54) WITH POLYPHOSPHORIC ACID:

A solution of the alcohol (54) (1.1g) in polyphosphoric acid (*c.*15g) was stirred at 80° (water bath temperature) for 0.5 h. The resultant bright orange mixture was poured onto ice (*c.*50g) and extracted with ether (4 x 50ml). The combined ether layers were washed with 10% potassium carbonate solution (20ml), water (20ml) and dried. The ether was removed by careful distillation to give a pale yellow liquid, 2,3,3a, 4,5,6-hexahydro-phenalene (107) (0.8g; 81%), (b.p. 110°-125° (block)/ 3.0-4.5mm; lit.[102] 95-105° (block)/0.05 mm).

i.r. ν_{max} (film): 2900s, 1440s, 820m, 770m, 750s, 720m cm^{-1}.

p.m.r. (CCl_4): δ 6.80, broad singlet, 3H, Ar-*H*, 2.77, complex, 5H, Ar-C*H*; 2.3-1.0, envelope, 8H, other *H*.

mass spectrum: m/e 172 (M^+ for $C_{13}H_{16}$).

Analysis of the crude product by g.l.c. (column E, 190°) indicated the presence of 4 compounds having retention times: 7.25, 1%, unidentified; 8.50, 5%, unidentified; 10.1, 2%, unidentified; 11.39, 91% (107). The first 3 fractions were subsequently identified as the hydrocarbons (92), (109) and (110) by "spiking" the reaction product with authentic samples.

REACTION OF THE ALCOHOL (54) WITH BORIC ACID:

A mixture of the alcohol (54) (5g; 0.026 mol) and boric acid (1.86g; 0.03 mol) was heated at 180° for 1 h. After cooling, water (10ml) was added and the suspension was extracted with ether (4 x 25ml). The combined organic extracts were washed with 10% sodium hydroxide solution (20ml), water (10ml) and dried.

The ether was removed by careful distillation to give a pale yellow residue which was distilled (b.p. 102-104°/2.5mm) yielding a colourless oil. Analysis of the distillate by g.l.c. (column D, 150°) indicated the presence of 4 compounds which were separated and collected by preparative g.l.c. (column E, 165°) and identified as follows:

Fraction 1: retention time 14.20, 23%, (Z)-8,9,10,11-tetrahydro-5H-benzocyclonene (92). This olefin had identical spectral properties and g.l.c. retention time with an authentic sample independently prepared.

Fraction 2: retention time 17.0, 13%, E-8,9,10,11-tetrahydro-5H-benzocyclononene. (Found: C, 90.9; H, 9.1, $C_{13}H_{16}$ requires C, 90.6; H 9.4%).

i.r. ν_{max} (film): 2950s, 780m, 720s cm^{-1}.

p.m.r. (CCl_4): δ 6.93, complex, 4H, Ar-*H*; 6.0-5.16, complex 2H, Ar-C*H*=CH and Ar-CH=C*H*; 2.53, complex, 4H, Ar-CH_2 and allylic CH_2; 2.40-1.60, complex, 6H, other H.

mass spectrum: m/e 172 (M^+ for $C_{13}H_{16}$).

Fraction 3: retention time 20.0, 40%, (Z)-6,7,8,11-tetrahydro-5H-benzocyclononene (110). (Found: C, 91.0; H, 9.1. $C_{13}H_{16}$ requires C, 90.6; H, 9.4%).

i.r. ν_{max} (film): 2950s, 1410m, 760s, 730s cm^{-1}.

p.m.r. (CCl_4): δ 6.83, singlet, 4H, Ar-*H*; 5.33, complex, 2H, olefinic-*H*; 3.33, doublet, J = 7Hz, Ar-CH_2-CH=CH; 2.60, complex, 4H, Ar-CH_2 and allylic-CH_2; 1.57, complex, 2H, other *H*.

mass spectrum: m/e 172 (M^+ for $C_{13}H_{16}$).

Fraction 4: retention time 25.0, 24%, (107). This hydrocarbon had identical spectral properties and g.l.c. retention time as the hydrocarbon (107) obtained from the reaction of (54) with polyphosphoric acid discussed previously.

(Z)-8,9,10,11-TETRAHYDRO-5H-BENZOCYCLONONENE (92):

A solution of the alcohol (54) (0.5g; 2.7 mmol) in dimethylsulphoxide (20ml) was heated at 180° in an atmosphere of nitrogen for 4 h. The solution was poured onto ice (*c.* 50g), extracted with ether (4 x 30ml) and the combined organic extracts were washed with water (5 x 10ml), and dried. The ether was removed to give a dark red oil which was purified by preparative t.l.c. (using light petroleum ether as a developing solvent) and yielded a colourless oil (350mg; 79%) (b.p. 95-105° (block)/

0.4mm; lit.[102] 135-142°/15mm).

i.r. ν_{max} (film): 2950s, 1450m, 785m, 740s, 720s cm^{-1}

p.m.r. (CCl_4): δ 7.05, complex, 4H, Ar-*H*; 6.65, doublet, J = 11Hz, Ar-C*H*=CH; 5.80, doublet of doublet of doublets, 1H, Ar-CH=C*H*; 2.7, multiplet, 2H, Ar-CH_2; 2.2-1.2, envelope, other *H*.

mass spectrum: m/e 172 (M^+ for $C_{13}H_{16}$).

(Z)-8,9,10,11-TETRAHYDRO-5H-BENZOCYCLONONENE OXIDE (52):

A mixture of the olefin (92) (1.62g; 10 mmol), *m*-chloroperoxybenzoic acid (2.03g of a 85% mixture with *m*-chlorobenzoic acid; 10 mmol) in chloroform (25ml) was kept at 0° for 24 h. The mixture was then diluted with chloroform (20ml), washed with 10% potassium carbonate solution (10ml) dried and evaporated to give a colourless liquid which was chromatographed on alumina (preparative t.l.c. using 10% ether/light petroleum as a developing solvent) to give the epoxide (52) as a colourless oil (1.4g; 80%) (b.p. 115-120° (block)/0.9mm). (Found: C, 83.0; H, 8.6. $C_{13}H_{16}O$ requires: C, 82.6; H, 8.7%).

i.r. ν_{max} (film): 2960s, 1450m, 1210m, 910m, 750s cm^{-1}.

p.m.r. (CCl_4): δ 7.20, complex, 4H, Ar-*H*, 3.93, doublet, J = 4Hz, Ar-C*H*(O)-CH; 3.00, complex, 3H, Ar-CH_2 and Ar-CH(O)-C*H*; 2.4-1.0, envelope, 8H, other H.

mass spectrum: m/e 188 (M^+ for $C_{13}H_{16}O$).

6,7,8,9,10,11-HEXAHYDRO-5H-BENZOCYCLONONEN-6-OL (53):

A mixture of the epoxide (52) (210mg; 1.12 mmol) and lithium aluminium hydride (60mg; 1.5 mmol) in ether (10ml) was stirred with

refluxing for 1 h. Upon cooling, an analogous workup procedure to that described for the preparation of (54) was applied and gave 186mg of a colourless oil which was chromatographed on silica (using 35% ether-light petroleum as a developing solvent) to afford 39mg (21%) of the alcohol (53) (b.p. 110-120° (block)/0.01mm; lit.[102] 95-105/0.005mm), together with 105mg of unchanged epoxide (52). The alcohol had the following spectral properties.

i.r. ν_{max} (film): 3440m, 2950s, 1440s, 1020m, 770m, 730s cm^{-1}.

p.m.r. (CCl_4): δ 7.00, complex, 4H, Ar-*H*; 3.60, complex, 1H, C*H*-OH; 3.00, doublet, J = 7Hz, 2H, Ar-C*H*$_2$-CHOH; 2.73, complex, 2H, Ar-C*H*$_2$; 2.2-1.0, envelope, 8H, other *H*.

2,3-DIHYDRO-1-METHYLINDEN-1-OL (113):

This compound was prepared by the reaction of 2,3-dihydroinden-1-one (111) with methylmagnesium iodide according to the method of Paice[88] and was used without further purification.

i.r. ν_{max} (film): 3340s, 1170s, 1070s, 760s, 750s cm^{-1}.

3-METHYL-1H-INDENE (114):

The alcohol (113) (10g; 0.67 mol) was dissolved in benzene containing a crystal of *p*-toluenesulphonic acid. The solution was boiled until no more water was removed by azeotropic distillation. The benzene was removed under reduced pressure and the residue was distilled (b.p. 74°/1.0mm; lit.[165] 90°/17mm) to give the olefin (114) (7.1g, 81%) as a colourless oil.

2-BROMO-2,3-DIHYDRO-1-METHYL-1H-INDEN-1-OL (115):

This method is an adaptation from the preparation of (116).[166]

A solution of N-bromoacetamide (1.4g; 10 mmol) in water (10ml) containing *t*-butyl alcohol (2ml) and concentrated sulphuric acid (*ca* 4-5 drops) was added dropwise to an ice-cooled, vigorously stirred solution of the olefin (114) (1.3g; 10 mmol) in *t*-butyl alcohol (5ml) and water (2ml). When addition was complete the resultant emulsion was stirred at room temperature for 15 min and then thoroughly extracted with ether (5 x 20ml). The combined ether extracts were washed with water (3 x 10ml), dried and stripped of solvent to afford a pale yellow oil (1.4g, 58%) which crystallized from ether/pentane as large colourless prisms (m.p. 57-58°). Found: C, 52.7; H, 4.9. $C_{10}H_{11}OBr$ requires C, 52.9; H, 4.9%).

i.r. ν_{max} (film): 3450s, 1090s, 760s, 720s, 680m cm^{-1}.

p.m.r. (CCl_4): δ 7.33, complex, 4H, Ar-*H*; 4.38, doublet of doublets, C*H*-Br; 3.30, doublet of doublets of doublets, 2H, Ar-C*H*$_2$; 2.98, broad singlet, D_2O exch., O-*H*; 1.58, singlet, 3H, -C*H*$_3$.

mass spectrum: m/e 240, 242 (M^+ for $C_{10}H_{11}OBr$).

3-METHYL-1H-INDENE OXIDE (56):

Method 1:

This method is an adaptation from the preparation of (64).[166] A solution of the bromohydrin (115) (1.4g; 6.2 mmol) in methanol (5ml) was added to an ice-cooled, stirred solution of potassium hydroxide (350mg) in methanol (5ml). After addition, the solution was stirred at room temperature for 30 min and diluted with dry ether. The precipitated

salts were removed by vacuum filtration and the filtrate concentrated under reduced pressure to give a yellow oil, analytical t.l.c. of which showed the presence of at least 3 new compounds. The i.r. of the oil had ν_{max}: 3420s, 1740w cm^{-1}.

Preparative t.l.c. of *c.* 250mg of the oil (using 30% ether/light petroleum as the developing solvent) afforded 2 major fractions characterized as follows:

Rf. 0.2: (142mg), viscous oil; *trans*-2,3-dihydro-1-methyl-1H-inden-1,2-diol (117):

i.r. ν_{max} (film): 3420s, 1155m, 1085s, 760s, 730s, 680s cm^{-1}.

p.m.r. (CCl_4): δ 6.60, multiplet, 4H, Ar-*H*; 4.36, triplet, J = 6Hz, 1H, ArC*H*-OH; 3.20, doublet, J = 6Hz, 2H, Ar-CH_2; 2.67, broad singlet, D_2O exch., O-*H*; 1.50, singlet, 3H, $-CH_3$.

mass spectrum: m/e 164 (M^+ for $C_{10}H_{12}O_2$).

The oil could not be induced to crystallize and attempted distillation resulted in the facile formation of (118); an analysis was not obtained.

Rf. 0.5: (117mg) 1,3-dihydro-1-methyl-2H-inden-2-one (118), (m.p. 64-66°, lit.[167] 63-65°).

i.r. ν_{max} (nujol): 1740 cm^{-1}.

Method 2:

This method was based on a modification of method 1 using potassium *t*-butoxide in *t*-butyl alcohol[168] instead of potassium hydroxide in methanol. Essentially the same result was obtained as method 1.

Method 3:

A solution of the bromohydrin (115) (1.87g; 8.23 mmol) in freshly distilled anhydrous[163b] methanol (5ml) was added dropwise, under dry

nitrogen, to an ice-cold solution of sodium methoxide (from 200mg sodium, 8.6mg atm) in methanol (15ml), care being taken to exclude moisture from the reaction. After addition of (115), the reaction mixture was stirred at room temperature for 15 min and concentrated under reduced pressure. The gummy residue was taken up in light petroleum, the insoluble salts were removed by filtration and the filtrate was concentrated under reduced pressure to give the epoxide (56) (1.0g, 88%), Rapid distillation (b.p. 75-80° (block)/0.2mm) gave an analytically pure sample. (Found: C, 82.1; H 6.9. $C_{10}H_{10}O$ requires: C, 82.2; H, 6.9%).

i.r. ν_{max} (film): 2950s, 820m, 760s, 740m, 710m cm^{-1}.

p.m.r. ($CDCl_3$): δ 7.33, singlet, 4H, Ar-*H*; 3.95, doublet, J = 2Hz, 1H, Ar-C*H*-CH and Ar-C*H*$_2$; 1.77, singlet, 3H, —C*H*$_3$.

mass spectrum: m/e 146 (M^+ for $C_{10}H_{10}O$).

Attempted chromatography of (56) on silica resulted in the formation of (117) and (118).

1,2,3,4-TETRAHYDRO-1-METHYLNAPHTHALEN-1-OL (96):

This compound (m.p. 87.5-89°; lit.[169] 89°) was prepared in 85% yield by the method of Hückel.[169]

3,4-DIHYDRO-1-METHYLNAPHTHALENE (95):

Method 1:

The procedure of Garbisch[170] afforded the desired olefin (95) which was heavily contaminated with 1-methylnaphthalene and 1,2,3,4-tetrahydro-1-methylnaphthalene. A 98% yield of the combined olefins which distilled at 57-59°/0.5mm, was obtained.

Method 2:

The method of Hückel[169] afforded a 96% yield of (95) (b.p. 58-51°/0.2mm; lit.[169] 100-102°/14mm) from the alcohol (96).

2-BROMO-3,4-DIHYDRO-1(2H)-METHYLNAPHTHALEN-1-OL (116):

This compound (m.p. 51-53°; lit.[166] 53-54°) was prepared in 92% yield by the method of Stille.[166]

3,4-DIHYDRO-1-METHYLNAPHTHALENE OXIDE (64):

Method 1:

A solution of the olefin (95) (144mg; 1 mmol) in dry chloroform (5ml) was added to an ice cooled mixture of *m*-chloroperoxybenzoic acid (203mg of an 85% mixture with *m*-chlorobenzoic acid; 10 mmol) in chloroform (5ml). After standing at 0° overnight, the mixture was diluted with methylene chloride (20ml) and washed with 10% potassium carbonate solution (5ml) dried and evaporated to give 3,4-dihydro-1-methylnaphthalen-2-one (119) (b.p. 90-95° (block)/0.5mm; lit.[170] 134°/14mm).as a colourless oil (107mg; 67%).

i.r. ν_{max} (film): 1720s, 765m, 760s, 720m cm^{-1}.

English had also noted this product from the treatment of (119) with peroxybenzoic acid.[107]

Method 2:

This is an adaptation of Anderson's method.[108] Solid *m*-chloroperoxybenzoic acid (203mg of an 85% mixture with *m*-chlorobenzoic acid; 1 mmol) was added slowly to a stirred mixture of the olefin (95) (144mg; 1 mmol), methylene chloride (20ml) and 0.5M aqueous sodium bicarbonate solution

(3ml). After addition, stirring of the reaction mixture was maintained for a further 2 h. The layers were separated and the organic layer was washed with water and dried. Removal of the solvent under reduced pressure gave the ketone (119) (120mg; 75%) which had identical spectral properties to that obtained previously by the peroxidation of (95).

i.r. ν_{max} (film): 1720 cm^{-1}.

Method 3:

The method of Stille[166] was used to prepare the epoxide (64) from the bromohydrin (116) in 87% yield. Chromatography on alumina afforded a colourless oil which slowly solidified at 0° (m.p. 30-35°; lit.[166] 34-36°). Attempted distillation of (64), however, resulted in isomerization to the ketone (119).

METHYL 2,3-DIHYDRO-3-OXO-1H-INDENE-2-CARBOXYLATE (120):

This compound (b.p. 110-121°/0.5mm; lit.[117] 109-111°/0.1mm) was prepared according to the method of House and Hudson[117] and had identical spectral properties with those reported.[117]

METHYL 2,3-DIHYDRO-2-METHYL-3-OXO-1H-INDENE-2-CARBOXYLATE (122):

The β-ketoester (120) (15.7g; .083 mol) was added to an ice-cooled solution of sodium methoxide (from 2.0g sodium; .086g atm) in dry methanol (300ml). The system was flushed with nitrogen and iodomethane (15g) was added dropwise. After addition, the mixture was stirred under reflux for 1.5 h, cooled to 0° and saturated sodium sulphate solution (20ml) was added. The mixture was extracted with 50% ether/light petroleum (4 x 100ml) and the combined organic extracts were washed with saturated brine (2 x 50ml), water (100ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure to afford the ester (122) as a pale yellow liquid (16.8g, 99%) which slowly solidified

on standing. A small sample was recrystallized from pentane to give fine colourless needles, m.p. 58-59°. (Found: C, 70.6; H, 6.0. $C_{12}H_{12}O_3$ requires: C, 70.6; H 5.9%).

i.r. ν_{max} (film): 1740s, 1700s, 1600m, 1260m, 1190s, 720s cm^{-1}.

p.m.r. ($CDCl_3$): δ 7.53, complex, 4*H*; Ar-*H*; 3.66, singlet, 3H, OCH_3; 3.80 and 3.18 as an AB quartet, J = 17Hz, 2H, Ar-CH_2; 1.53, singlet, 3H, $-CH_3$.

mass spectrum: m/e 204 (M^+ for $C_{12}H_{12}O_3$).

2,3-DIHYDRO-2-METHYL-1H-INDEN-1-ONE (124):

A mixture of the ketoester (122) (15g; 0.073 mol), hydrochloric acid (100ml) and water (200ml) was stirred under reflux for 4 h. Upon cooling, the mixture was extracted with light petroleum (3 x 100ml) and the combined organic layers were washed with dilute sodium bicarbonate solution (2 x 50ml), saturated brine (100ml) and dried over anhydrous magnesium sulphate to give the ketone (124) as a yellow oil (6.2g, 58%) (b.p. 80-82°/2mm; lit.[171] 125-126°/18mm).

i.r. ν_{max} (film): 1720, 1700 cm^{-1}.

p.m.r. (CCl_4): δ 7.41, complex, 4H, Ar-*H*; 3.48, doublet of quartets; 1H, C*H*-CO; 2.71, multiplet, 2H, Ar-CH_2; 1.25, doublet, J = 7Hz, CH-CH_3.

CIS and *TRANS*-2,3-DIHYDRO-2-METHYL-1H-INDEN-1-OL (68) and (94):

Sodium borohydride (500mg; 13 mmol) was added to a stirred solution of the ketone (124) (1.56g; 10 mmol) in methanol (50ml). After addition, the resultant suspension was stirred at room temperature for 2 h. Dilute hydrochloric acid (20ml) was added and the solution was extracted with ether (3 x 50ml). The combined organic extracts were washed with

brine (3 x 20ml), dried and concentrated *in vacuo* to afford a yellow solid (160mg; 100%). Recrystallization from light petroleum afforded fine colourless needles m.p. 66-82°. Sam and Thompson[122] had reported that the reduction of (124) with sodium borohydride afforded *cis*-2,3-dihydro-2-methyl-1H-inden-1-ol (68) m.p. 43-46°. On the other hand Baddeley *et al*[123], reported that reduction of (124) with lithium aluminium hydride also gave (68), m.p. 78-79°.

Examination of the p.m.r. spectra of the alcohol obtained above (m.p. 66-82°) showed the alcohol to be a mixture of *cis: trans* isomers, *ca* 2:1 (note that the hydroboration of the olefin (93) gave *trans*-2,3-dihydro-2-methyl-1H-inden-1-ol (94)).

p.m.r. ($CDCl_4$): δ 7.13, singlet, 4H, Ar-*H*; 4.93, doublet, J = 6Hz, Ar-C*H*(OH)-CH (*cis*); 4.67, doublet, J = 6.5Hz, Ar-C*H*(OH)-CH (*trans*); (δ 4.93 and 4.67 accounted for 1H), 3.16-2.37, multiplet, 3H, Ar-CH_2 and C*H*-CH_3; 1.26, broad singlet, 1H, D_2O exch., O-*H*; 1.66, doublet, J = 7Hz, CH-CH_3.

2-METHYL-1H-INDENE (93):

A solution of the isomeric alcohols (68) and (94) (2g; 13.5 mmol) in dimethylsulphoxide (30ml) was heated under an atmosphere of nitrogen at 180° (oil bath temperature) for 4 h. Upon cooling, the reaction mixture was poured onto ice (*c.* 20g) and extracted with petroleum ether (4 x 30ml). The combined organic extracts were washed with water (3 x 20ml) and saturated brine (50ml), dried and the solvent was removed under reduced pressure to afford a red oil (2.1g) which was chromatographed on silica (*c.* 50g). Elution with light petroleum gave the olefin (93) as a colourless liquid (1.6g; 91%) which had identical p.m.r. spectral properties to those previously described.[172]

2-BROMO-1,3-DIHYDRO-2(2H)METHYLINDEN-1-OL (128):

The olefin (93) (2.6g; 20 mmol) was suspended in a mixture of *t*-butyl alcohol (10ml) and water (2ml) and treated with a solution of N-bromoacetamide (2.8g; 10 mmol) in *t*-butyl alcohol (30ml) and water (10ml) containing a few drops of concentrated sulphuric acid in an analogous manner to that described for the bromohydrin (115). A similar workup afforded (128) as a yellow oil (3.6g; 75%) which was crystallized from pentane to give colourless needles (m.p. 66-67°). (Found: C, 52.8; H, 4.8. $C_{10}H_{11}OBr$ requires C, 52.9; H 4.9%).

i.r. ν_{max} (film): 3400s, 1200s, 920m, 730, 710

p.m.r. ($CDCl_3/D_2O$): δ 7.27, singlet, 4H, Ar-*H*; 5.33, singlet, 1H, Ar-C*H*-O; 3.40, centre of an AB quartet, J = 16Hz, 2H, Ar-CH_2; 1.83, singlet, 3H, CH_3.

mass spectrum: m/e 240, 242 (M^+ for $C_{10}H_{11}OBr$)

2-METHYL-1H-INDENE OXIDE (67):

A solution of the bromohydrin (128) (2.27g; 9.4 mmol) in anhydrous methanol (10ml) was dripped into an ice-cold solution of sodium methoxide (from 230mg; 10mg atm of sodium) in methanol (10ml). Stirring was continued at 0° for 30 min and at room temperature for 1 h. The solution was carefully concentrated, and the concentrate was treated in an analogous manner described for the epoxide (56) to afford (67) as a pale yellow oil (1.36g, 100%) (b.p. 65-68° (block)/0.4mm). (Found: C,82.0; H, 7.0. $C_{10}H_{10}O$ requires C, 82.2; H, 6.9%).

i.r. ν_{max} (film): 3040m, 2850m, 1400s, 1215m, 810s, 765s, 710s cm^{-1}.

p.m.r. (CCl_4): δ 7.26, multiplet, 1H, Ar-*H*; 7.06, singlet, 3H,

Ar-*H*; 3.90, singlet, 1H, Ar-C*H*O, 2.90, centre of an AB quartet, J = 18Hz, Ar-C*H*$_2$; 1.57, singlet, 3*H*, C*H*$_3$.

mass spectrum: m/e 146 (M^+ for $C_{10}H_{10}O$).

2,3-DIHYDRO-1-HYDROXY-1H-INDENE-2-METHANOL (71):

A mixture of the keto-ester (122) (250mg; 1.3 mmol), and lithium aluminium hydride (100mg; 2.5 mmol) in dry THF was stirred under a nitrogen atmosphere for 18 h. Following an analogous workup to that described for the preparation of alcohol (54), the diol (71) was obtained as a colouless viscous oil (198mg, 94%), (b.p. 115-120° (block)/0.5mm). (Found: C, 73.5; H 7.3. $C_{10}H_{12}O_2$ requires C, 73.1; H, 7.4%).

i.r. ν_{max} (film): 3400s, 1040m, 730s cm^{-1}.

p.m.r. (CCl_4/D_2O): δ 7.00, multiplet, 4H, Ar-*H*; 4.77, multiplet, 1H, Ar-C*H*-OH; 3.30, multiplet, 2H, CH-C*H*$_2$OH; 2.73, multiplet, Ar-C*H*$_2$; 2.20, complex, 1H, C*H*-CH$_2$OH.

mass spectrum: m/e 164 (M^+ for $C_{10}H_{12}O_2$).

METHYL 3,4-DIHYDRO-1-OXO-2(1H)-NAPHTHALENECARBOXYLATE (123):

To a stirred suspension of sodium hydride (10g of a 40% dispersion in oil; 0.16 mol) in dry benzene (200ml) was added 3,4-dihydro-1(2H)-naphthalenone (112) (22g; 0.15mmol). Dimethylcarbonate (90g; 1 mol) was added and stirring was maintained at room temperature for 30 min and at 80° for 30 min whenupon the mixture became a light-brown solid mass. After cooling the reaction to 0°, glacial acetic acid (50ml) was cautiously added. The mixture was extracted with ether (4 x 100ml) and

the combined extracts were washed with 10% potassium hydroxide until neutral to litmus (*ca* 200ml), saturated brine, and dried. Evaporation of the solvent afforded a red oil (27g) the p.m.r. spectrum of which indicated that the starting ketone (112) was present to the extent of *c*. 60%. Fractional distillation afforded 8.2g (27%) of the ketoester (123) (b.p. 130-134°/0.7mm). A small sample was crystallized from acetone/light petroleum to give fine colourless needles (m.p. 82-84°; lit.[173] 84.5-86.5).

METHYL 3,4-DIHYDRO-2-METHYL-1-OXO-2(1H)-NAPHTHALENECARBOXYLATE (123):

This compound (m.p. 56-57°; lit.[173] 56-57.5°) was prepared in 97% yield by the method of Bachmann and Thomas.[173]

3,4-DIHYDRO-2-METHYL-1(2H)-NAPHTHALENONE (125):

A mixture of the β-ketoester (123) (4g; 0.02 mol) and concentrated hydrochloric acid (100ml) was stirred under reflux for 24 h. Upon cooling, the mixture was extracted with ether (3 x 60ml) and the combined ether extracts were washed with water, saturated brine, dried and evaporated under reduced pressure to afford (125) as a yellow oil (2.6g, 88%) (b.p. 70-80° (block)/0.4mm; lit.[119] 84-86°/0.8mm).

i.r. ν_{max} (film): 1680s, 1260s, 760s, 720s cm^{-1}.

p.m.r. (CCl_4): δ 7.87, multiplet, 1H, Ar-*H* (*peri* H); 2.95, complex, 2H, Ar-C*H*$_2$; 2.07, complex, 3H, Ar-COC*H* and —C*H*$_2$—; 1.17, doublet J = 7Hz, CH-C*H*$_3$.

The method of Hattersley *et al*[119] was found to give not the desired ketone (125) but a *c.* 1:1 mixture (by p.m.r.) of 3,4-dihydro-2,2-dimethyl-1(2H)-naphthalenone and the starting ketone (3,4-dihydro-1(2H)-naphthalenone) (112). Following the procedure of Spencer *et al*,[118] only the starting material (2-bromo-3,4-dihydro-1(2H)-naphthalenone[174]) was recovered.

CIS AND *TRANS*-1,2,3,4-TETRAHYDRO-2-METHYL-NAPHTHALEN-1-OL (77) AND (126):

A solution of the ketone (125) (2.4g; 15 mmol) in ether was treated with lithium aluminium hydride (0.2g; 5 mmol) in an analogous manner described for the reduction of (106). Workup gave a mixture of the *cis* and *trans* alcohols, (77) and (126) respectively, in a ratio of 35:65 (by p.m.r. spectroscopy). The p.m.r. spectrum of the mixture was consistent with that previously described for (77) and (126) by Mitsui *et al*.[124]

3,4-DIHYDRO-2-METHYLNAPHTHALENE (127):

A solution of the isomeric alcohols (77) and (126) (1.62g; 10 mmol) obtained above in dimethylsulphoxide (20ml) was heated at 180° (oil bath temperature) for 3 h. After cooling to room temperature, the mixture was poured onto ice (*c.* 10g) and extracted with ether (4 x 25ml). The combined ether extracts were washed with water (3 x 20ml) dried and stripped of solvent to afford the olefin (127) (1.54g, 96%) as a red oil (b.p. 120-130° (block)/18mm, lit.[175] 105-106°/13mm).

2-BROMO-3,4-DIHYDRO-2(2H)-METHYLNAPHTHALEN-1-OL (129):

A solution of the olefin (1.5g; 9.3 mmol) in *t*-butyl alcohol (10ml) and water (5ml) was treated with a solution of N-bromoacetamide (1.5g; 10 mmol) in *t*-butyl alcohol (10ml) and water (10ml) containing concentrated sulphuric acid (4-5 drops) in a similar manner described for the preparation of the bromohydrin (115). An analogous workup afforded a colourless oil (2.1g; 93%) which crystallized from pentane to give a low melting solid and which decomposed on prolonged exposure to air.

i.r. ν_{max} (film): 3460s, 2950s, 1200s, 910s, 800w, 720s cm^{-1}.

p.m.r. ($CDCl_3$): δ 7.13, complex, 4H, Ar-*H*; 4.80, singlet, 1H, Ar-C*H*-O; 2.87, multiplet, 2H, Ar-CH_2; 2.30, multiplet, 2H, $-CH_2-$; 2.0, broad singlet, D_2O exch., 1H, O-*H*; 1.23, singlet, 3H, $-CH_3$.

mass spectrum: m/e 224, 226, (M^+ for $C_{11}H_{13}OBr$)

3,4-DIHYDRO-2-METHYLNAPHTHALENE OXIDE (74):

A solution of the bromohydrin (129) (1.0g; 4.64 mmol) in anhydrous

methanol (5ml) was added, under nitrogen, to a stirred, ice-cooled solution of sodium methoxide (from 110mg of sodium; 4.78mg atm) in methanol (10ml). Stirring was maintained at 0° for 30 min, and the mixture was concentrated under reduced pressure. Ether was added to the concentrate and the precipitated salts were removed by vacuum filtration. The filtrate was concentrated to afford 420mg (58%) of the epoxide (74) (b.p. 78-80° (block)/0.5mm). (Found: C. 82.7; H, 8.0. $C_{11}H_{12}O$ requires 82.4, H, 7.7%).

i.r. ν_{max} (film): 2950s, 880s, 770s, 740s cm^{-1}.

p.m.r. (CCl_4): δ 7.17, complex, 4H, Ar-*H*, 3.47, singlet, 1H, Ar-C*H*-O, 2.47, multiplet, 2H, Ar-CH_2; 2.0 complex, 2H, —CH_2—; 1.51, singlet, 3H, —CH_3.

mass spectrum: m/e 160 (M^+ for $C_{11}H_{12}O$).

ATTEMPTED PREPARATION OF 6,7,8,9-TETRAHYDRO-5-EPOXYMETHYLENE-5H-BENZOCYCLOHEPTENE (80):

Trimethylsulphonium Iodide:

Iodomethane (71g; 0.5 mol) and dimethylsulphide (31g; 0.5 mol) were allowed to stand at room temperature for 24 h. The resultant product was recrystallized from ethanol to give trimethylsulphonium iodide (100g; 98%) as prismatic needles m.p. 186-189°, with decomposition.[176]

Method 1:

Dimethylmethylenesulphurane was prepared by the method of Corey and Chaykovsky[125] from sodium hydride (70mg of a 40% dispersion in oil; 1.6 mmol), trimethylsulphonium iodide (230mg; 1.1 mmol) in dimethylsulphoxide (2ml). A solution of the ketone (104) (160mg; 1.0 mmol) in dimethylsulphoxide (1ml) was added and the mixture was stirred at room temperature for 30 min. The reaction mixture was cooled, poured onto ice (*c.* 5g),

extracted with ether (3 x 10ml) and the combined organic extracts were washed with water (2 x 10ml), dried, and evaporated to give a brown oil (106mg), which was shown by analytical t.l.c. and comparison of spectral data with an authentic sample to be the starting ketone (104).

Method 2:

A solution of *n*-butyllithium (0.4ml of a 1.4M solution in pentane; 0.5 mmol) was added to a suspension of trimethylsulphonium iodide (105mg; 0.5 mmol) in dry THF (2ml). To this mixture was added a solution of the ketone (104) (80mg; 0.5 mmol) in THF (1ml), and the resultant precipitate was stirred at room temperature. An analogous workup procedure previously described (Method 1) yielded 62mg (76%) of yellow oil which had identical spectral properties to the starting ketone (104).

Method 3:

The same procedure as described for Method 2 was employed with the modification that after the addition of the ketone (104) (500mg; 3.13 mmol) the reaction mixture was stirred under reflux for 15 h. A similar workup afforded 606mg of a dark red oil, 200mg of which was chromatographed on silica (preparative t.l.c. using 30% methylene chloride/light petroleum as the developing solvent).

The major fraction (95mg) had the following spectral properties:

i.r. ν_{max} (film): 1740sh, 1720sh, 1680s, 1440s, 760s, 740s cm^{-1}.

p.m.r. (CCl_4): δ 7.15, complex, 4H, Ar-*H*, 2.76, complex, 2.5-1.3, envelope. The resonances between 2.76 and 1.3 accounted for *c*. 10H.

mass spectrum: m/e 174 (M^+ for $C_{12}H_{14}O$).

Analysis of the other fractions did not show any evidence of the required epoxide (80).

6,7,8,9-TETRAHYDRO-5-METHYLENE-5H-BENZOCYCLOHEPTENE (133):

Triphenylphosphonium methide was prepared by the addition of potassium *t*-butoxide (112mg; 1.0 mmol) to a suspension fo methyltriphenylphosphonium iodide (404mg; 1 mmol) in dry THF (20ml) and was used immediately. A solution of the ketone (104) (160mg; 1.0 mmol) in dry THF (1ml) was dripped onto the ice-cooled, stirred, orange suspension and the reaction mixture became yellow. The reaction mixture was allowed to attain room temperature whereupon it was stirred for a further 2 h. Water (10ml) was then added and the layers separated. The aqueous layer was further extracted with light petroleum (3 x 10ml) and the combined organic layers were washed with water (10ml), methanol/water (10ml), water and dried. The solvent was removed under reduced pressure to afford a pale yellow oil (243mg) which partially solidified. Preparative t.l.c. on silica (using light petroleum as the developing solvent) afforded the olefin (133) (68mg; 43%) as a colourless oil (b.p. 68-73° (block)/0.3mm; lit.[177] 122°/15mm). (Found: C, 90.8; H, 8.9. $C_{12}H_{14}$ requires C, 91.1; H, 8.9%).

p.m.r. (CCl_4): δ 7.10, complex, 4H, Ar-*H*; 5.00, multiplet, 2H, $C{=}CH_2$; 2.90, multiplet, 2H, Ar-CH_2; 2.35, multiplet, 2H, allylic CH_2; 1.75, complex, 4H, other *H*.

6,7,8,9-TETRAHYDRO-5H-BENZOCYCLOHEPTENE-METHANOL (82):

The olefin (133) (55mg; 0.35 mmol) was treated with diborane in an analogous manner described previously. Workup afforded 97mg of a colourless oil which, after preparative t.l.c. (using 15% light petroleum/methylene chloride as the developing solvent), afforded 48mg (79%) of the alcohol (82) (b.p. 85-90° (block)/0.2mm; lit.[178] 113-115°/.001mm). (Found: C, 81.8; H, 8.9. $C_{12}H_{16}O$ requires C, 81.8, H, 9.2%).

i.r. ν_{max} (film): 3400s, 1080s, 740s, 710s cm^{-1}.

p.m.r. (CCl_4): δ 7.00, singlet, 4H, Ar-*H*; 3.83, multiplet, 2H, CH_2-OH; 2.83, complex, 3H (1H D_2O exch.), Ar-CH_2 and O-*H*; 1.70, envelope, 6H, other *H*.

mass spectrum: m/e 176 (M^+ for $C_{12}H_{16}O$).

3,4-DIHYDRO-2-METHYLENE-1(2H)-NAPHTHALENONE (142):

This compound was prepared in 80% yield by the method of Mühlstadt and Gensrich[132] and was characterized as the semicarbazone[163c] (m.p. 198-202°; lit.[132] 200-202°). The precursor salt, 2-(dimethylaminomethyl)-3,4-dihydro-1(2H)-naphthalenone[179] (m.p. 142-144°, lit.[179] 146°) was prepared according to the method of Mannich and coworkers.[179] The p.m.r. spectrum of (142) was identical to that published.[132]

ATTEMPTED EPOXIDATION OF (142):

Method 1:

A solution of 15% sodium hydroxide (2.5ml) was added slowly to a stirred solution of hydrogen peroxide (2.5ml of 30%) and the methylene-ketone (142) (1.58g; 10 mmol) in methanol (100ml). The solution was stirred for a further 3 h during which time a white solid precipitated. This was collected by vacuum filtration to yield 1.07g and concentration of the filtrate gave a further 0.44g; total yield was 1.51g (98%) (m.p. 105-107°; lit.[133] 105-106°) of 3,4-dihydro-2-methylene-1(2H)-naphthalenone dimer (143).

Method 2:

A solution of 15% hydrogen peroxide (2ml) and 10% sodium hydroxide was added to a solution of the ketone (142) (2g; 12.6 mmol) in ethanol (10ml). The resultant solution was stood overnight, diluted with water (10ml) and extracted with ether (3 x 20ml). The combined ether layers

were washed with brine, dried and evaporated to give a dark brown solid (0.84g). Recrystallization from ether/light petroleum gave the dimer (143), identical to that previously obtained.

Method 3:

A solution of the methylene ketone (142) (1.58g; 10 mmol) in methylene chloride (10ml) was added to an ice-cooled suspension of *m*-chloroperoxybenzoic acid (2.03g of an 85% mixture with *m*-chlorobenzoic acid; 10 mmol) and sodium benzoate (1.44g; 10 mmol) in methylene chloride (20ml). The reaction was kept cold for 2 h and an analogous workup described for the preparation of (44) afforded 1.5g (95%) of the dimer (143), identical to that previously isolated.

2-CHLORO-3,4-DIHYDRO-1(2H)NAPHTHALENONE (144):

A solution of chlorine in carbon tetrachloride (60ml of *c*. 1.6M) was added dropwise to a stirred solution of 3,4-dihydro-1(2H)-naphthalenone (112) (20g; 0.14 mol) in methylene chloride (100ml) After addition, the reaction was stirred at room temperature for 30 min and washed with water (50ml), 5% sodium carbonate solution (50ml), dried, filtered through celite and the solvent removed under reduced pressure to give 22g of a pale yellow oil. The oil was taken up in light petroleum (30ml) and cooled to -80°. The solid thus obtained was collected by vacuum filtration to give the chloroketone (144) (11.6g, 47%) (m.p. 40-44°, lit.[180] 44-44.5°).

3,4-DIHYDRO-2-EPOXYMETHYLENE-1(2H)-NAPHTHALENONE (140):

A solution of potassium hydroxide (2.6g; .046 mol) in methanol (20ml) was added, with swirling, to a solution of the chloroketone (144) (8.2g; .045 mol) and, aqueous paraformaldehyde (10ml of 38%) in methanol (30ml).

The mixture was then kept at room temperature for 1 h whereupon it was neutralized with concentrated methanolic oxalic acid, concentrated under reduced pressure and diluted with methylene chloride (150ml). The organic solution was washed with water (20ml), and saturated brine (50ml), then dried. The solvent was removed under reduced pressure to afford a red oil which was chromatographed on silica (500g). Elution with 30% ether/light petroleum yielded the epoxyketone (140) (4.7g; 59%) as a white solid. Recrystallization from light petroleum gave colourless needles, m.p. 65.5-66°. (Found: C, 76.0; H, 5.8. $C_{11}H_{10}O_2$ requires C, 75.8; H, 5.8%).

i.r. ν_{max} (nujol): 1705s, 900m, 750s, 710s cm^{-1}

p.m.r. ($CDCl_3$): δ 8.05, approximating to a doublet of doublets, J_{meta} = 2Hz, 1H, Ar-*H* (*peri* H); δ 7.42, complex, 3H, Ar-*H*; 2.13, 2.60, 2 x doublet of triplets, J_{gem} = 14Hz, $Ar\text{-}CH_2\text{-}CH_2$; 3.00, 3.13, 2 x doublets, 2H, $C(=O)\text{-}CH_2$; 3.20, doublet of triplets, 2H, $Ar\text{-}CH_2$.

mass spectrum: m/e 164 (M^+ for $C_{11}H_{10}O_2$).

ATTEMPTED REARRANGEMENT OF (140) TO 8,9-DIHYDRO-5H-BENZOCYCLOHEPTENE-5,7(6H)-DIONE (141):

General Procedure:

A solution of the epoxyketone (140) (*c.* 5mg) in solvent (2ml) was treated at 0° with boron trifluoride etherate (2-3 drops). The reaction mixture was kept at 0° for 0.5 h and at room temperature overnight; an aliquot (*c.* 1ml) was removed at regular intervals and analyzed by analytical t.l.c. (using 40% light petroleum/ether as developing solvent). The results are summarized in the following table below.

SOLVENT	REACTION TIME (h)	RESULT
benzene	0.5	polymeric tar
THF	1	THF:polymer
1% ether/benzene	24	no reaction*
5% ether/benzene	24	no reaction
10% ether/benzene	24	no reaction
50% ether/benzene	24	no reaction
ether	1	no reaction
ether	24	ether:polymer

* no detectable reaction (by t.l.c.)

Attempted Rearrangement of (140) to (141)

PROPAN-2-ONE-1,3-*BIS*(TRIPHENYLPHOSPHONIUM)CHLORIDE (146):

The salt (146) (m.p. 244-248° (dec); lit.[138] 260-261°) was prepared in 86% yield following the method of Denney and Song.[138]

7H-BENZOCYCLOHEPTEN-7-ONE (149):

Method 1:

This is an adaptation of the method of Cresp and Sargent.[137b] A solution of lithium ethoxide (from 14mg; 2.0mg atm) in ethanol (2ml) was added dropwise, under nitrogen to a hot (oil bath temperature 85%), stirred mixture of the phosphonium salt (146) (574mg; 1.0 mmol), in dimethylformamide (5ml). The colour changed from a canary yellow to dark green. The mixture was then stirred at 20-30° for 18 h, after which time water (1ml) was added. The resultant solution was extracted with ether (4 x 10ml) and the combined ether layers were washed with water (3 x 10ml), dried and evaporated to give a dark yellow oil (452mg). Preparative t.l.c. (60% ether/light petroleum) afforded 50mg of a yellow solid (Rf 0.2), consistent in part with (149).

p.m.r. (CCl_4): δ 7.57, broad singlet, 4H, Ar-*H*; 7.33, 6.33, an ABX system J_{AB} = 12Hz, 2H, Ar-C*H*=CH and Ar-CH=C*H* respectively. The spectrum also contained resonances at δ 5.00, quartet; 4.1-3.4 complex; 1.4, complex in a ratio of 1:2:8. Further preparative t.l.c. (twice, using ether) failed to remove the (assumed) contaminants.

Method 2:

As for method 1 but the ethanolic lithium ethoxide (2 mmol) added to the reactants (1 mmol) at room temperature. Examination of the product (142mg) from a similar workup by p.m.r. spectroscopy did

not show the presence of resonances at δ7.33 or δ6.33 but did show an increase of the unidentified resonances at δ4.1-3.4 and δ1.4.

Method 3:

A solution of *n*-butyllithium (1.7ml of 1.5M in hexane; 2 mmol) was added, under nitrogen, to an ice-cooled, stirred suspension of the salt (146) (574mg; 1 mmol) in dry THF (5ml). A solution of the dialdehyde (148) (134mg; 1 mmol) in THF (1ml) was then added. After attaining room temperature, the reaction was stirred overnight after which time water (1ml) was added. The solution was extracted with ether (3 x 15ml) and the combined organic layers were washed with water (3 x 5ml), dried and evaporated to afford a viscous red oil (494mg). Preparative t.l.c. (40% ether/light petroleum) afforded a yellow solid (22mg) consistent in part with (149)..

p.m.r. (CCl_4): δ 7.57, broad singlet, 4H, Ar-*H*; 7.33, 6.33 an ABX system (poorly resolved). The spectrum was severely contaminated with complex resonances at δ5.0, 4.1-3.4, 1.4.

This reaction was not further investigated, nor were the contaminants identified.

2,3-DIHYDRO-1H-INDEN-1-OL (40):

The alcohol (40) was obtained as colourless needles (m.p. 50-55°, lit.[181] 54°) in near quantitative yield by the reduction of 2,3-dihydro-1H-inden-1-one (111) with lithium aluminium hydride in an analogous manner to that described for the preparation of (54).

2,3-DIHYDRO-1H-INDEN-2-OL (38):

This alcohol (38) (m.p. 67.5-69°; lit.[182] 68-69°) was prepared in similar manner to that described for (40); a near quantitative yield

was achieved.

1,2,3,4-TETRAHYDRONAPHTHALEN-1-OL (41):

This alcohol (b.p. 88-89°/0.3mm; lit.[183] 132-134°/12-13mm) was prepared in 92% yield by a similar method to that described for (40).

1,2-DIHYDRONAPHTHALENE (89):

This compound (b.p. 67-68°/3mm; lit.[183] 77°/15mm) was prepared by the method of Chivhevskaya and Idelchik[183] in 62% yield.

p.m.r. (CCl_4): δ 7.00, singlet, 4H, Ar-*H*; 6.41, doublet of triplets, 1H, Ar-C*H*=CH; 5.87, doublet of triplets, 1H, Ar-CH=C*H*; 2.86, complex, 2H, Ar-CH_2; 2.67, complex, 2H, —CH_2—.

3,4-DIHYDRO-2(1H)-NAPHTHALENONE:

This ketone (b.p. 71-74°/0.3mm; lit.[184] 92°/2mm) was prepared in 60% yield following the procedure of Cornforth.[184]

1,2,3,4-TETRAHYDRONAPHTHALEN-2-OL (39):

This alcohol (82-85°/0.3mm; lit.[185] 141°/17mm) was prepared in 92% yield by the lithium aluminium hydride reduction of 3,4-dihydro-2(1H)-naphthalenone in a similar manner described for the synthesis of (54).

(Z)-1-PHENYLPROPENE (98):

The olefin (b.p. 60-65° (block)/16mm; lit.[186] 175-176°) was prepared in 81% yield by the Wittig reaction between benzaldehyde and

ethyltriphenylphosphonium bromide[187] according to the procedure of Schlosser *et al.*[188]

1-PHENYLPROPAN-1-OL (16):

A solution of benzaldehyde (5.3g; 0.05 mol) in dry ether (20ml) was added dropwise to a stirred, ice-cooled solution of methylmagnesium iodide (from 1.2g; 0.05g atm of magnesium and 7.8g; 0.07 mol of bromoethane). After completion of addition, the reaction was stirred at room temperature for 2 h. Saturated ammonium chloride was added and the layers were separated. The aqueous layer was further extracted with ether (2 x 20ml) and the combined ether layers were washed with water (10ml), dried and evaporated to yield the alcohol (16) as a colourless oil (6.8g, 100%) (b.p. 52-53°/0.3mm; lit.[189] 108-110°/14mm).

1-PHENYLPROPAN-2-OL (15):

A suspension of 1-phenylpropan-2-one (6.7g; 0.05 mol) and lithium aluminium hydride (200mg; 0.05 mol) in dry ether (60ml) was boiled under reflux for 3 h. Upon cooling, workup in the manner prescribed for (54) afforded the alcohol (16) as a colourless oil (6.7g; 98%) (b.p. 66-68°/1.5mm; lit.[190] 64-65°/0.7mm).

PART D: WORK DESCRIBED IN CHAPTER 3

REACTION OF (89) WITH CHLOROSULPHONYLISOCYANATE:

This is an adaption from the addition of chlorosulphonylchloride to indene;[145] an equivalent yield was obtained on repetition.

A solution of 1,2-dihydronaphthalene (89) (2.64g; 20 mmol) in anhydrous ether (5ml) was added dropwise, under nitrogen, to a cold (-50°), stirred solution of chlorosulphonylisocyanate (3.2g; 22 mmol) in ether (5ml). After stirring at -50° for 15 min, the reaction was allowed to attain room temperature. As analysis by t.l.c. only showed the presence of starting olefin (89), the reaction was further stirred for 45 min at room temperature, during which time the solution became dark. Removal of the solvent gave a dark brown tar which was not further characterized.

3,3-DIMETHYL-1H-INDENE (86):

A solution of 3,3-dimethyl-2,3-dihydro-1H-inden-1-ol[191] (1g; 6.2 mmol) in dimethylsulphoxide (20ml) was heated at 180° (oil-bath temperature) for 4 h. An analogous workup as described for the preparation of (92) afforded the olefin (86) (0.82g; 93%) which had a similar p.m.r. spectrum to that published.[192]

BENZALDOXIME:

The oxime (b.p. 131-132°/23mm; lit.[163c] 122-124°/12mm) was prepared in 56% yield according to the procedure of Vogel.[163c]

BENZOHYDROXAMOYL CHLORIDE:

This compound (m.p. 46-49°; lit.[193] 48-52°) was prepared in 58% yield following the published method.[193]

ADDITION OF BENZONITRILE OXIDE (BNO) TO OLEFINS:

A General Procedure:

This is based on the addition of BNO to indene;[150a] on repetition a similar yield and result was achieved. A solution of distilled triethylamine[157a] (0.62g; 6 mmol) in dry ether (2ml) was slowly dripped (over 30 min), under nitrogen, into an ice-cooled, stirred mixture of the olefin (10 mmol) and benzohydroxamoyl chloride (1g; 6 mmol) in ether (25ml). When addition was complete the mixture was stirred at 0° for 2 h and at room temperature (*c.* 20°) overnight. The resultant precipitate was removed by vacuum filtration and washed with anhydrous ether. The filtrate was concentrated under reduced pressure and the residue was analyzed by t.l.c. and p.m.r. spectroscopy.

REACTION OF BNO WITH 1,2-DIHYDRONAPHTHALENE (89):

The olefin (89) was treated with BNO in a manner just described and afforded, on workup, 1.4g of a pale yellow oil, 500mg of which was chromatographed on silica (preparative t.l.c. using 15% ethylacetate/light petroleum). The two major fractions were isolated and characterized as follows:

Fraction 1:

(Rf 0.8) (245mg) 3,5-diphenylfuroxane (156) m.p. 130° (dec); lit.[194b] 134°

Fraction 2:

Rf 0.4 (207mg; 43%), 2-phenyl-4,5[2,1-(1,2,3,4-tetrahydro-

naphthaleno)]-2-isoxazoline (154) as a white solid which recrystallized from ether/light petroleum as fine colourless needles (m.p. 93-94°). (Found: C, 82.1; H, 6.0; N, 5.5. $C_{17}H_{15}NO$ requires C, 81.9; H, 6.1; N, 5.6%).

i.r. ν_{max} (nujol): 1640w, 885s, 880s, 750s, 745s, 730s cm^{-1}.

p.m.r. ($CDCl_3$): δ 8.0-7.0, complex, 9H, Ar-*H*; 5.53, doublet, J = 10Hz, 1H, Ar-C*H*-O; 3.83, doublet of triplets, 1H, C*H*-C=N; 2.65, doublet of doublets, 2H, Ar-CH_2; 1.93, approximating to a triplet, 2H, -CH_2-.

mass spectrum: m/e 249 (M^+ for $C_{17}H_{15}NO$).

REACTION OF OLEFINS (86), (93), (96) and (111) WITH BNO:

The olefins (86), (93), (96) and (111) were individually treated with BNO in a manner previously described. In each case, analysis by p.m.r. and analytical t.l.c. of the concentrated filtrate only showed the presence of the starting olefin and of the BNO dimer, 3,5-diphenylfuroxane (156).

REACTION OF INDENE WITH DIAZOMETHANE:

Indene (1.16g; 0.01 mol) was added at 0° to a freshly prepared solution of ethereal diazomethane[163d] (0.59 mol). The reaction mixture was stood at room temperature for 14 days during which time the solution became dark. Analysis of an aliquot by analytical t.l.c. indicated the presence of indene and polymeric involatile material which was not further characterized.

PART I

REFERENCE

1. J. Stanek, R.H.F. Manske Ed;, "The Alkaloids," Vol 9, (Academic Press: New York 1967) p.117.
2. A.R. Pinder, *Chem.Rev.*, 64, 551 (1964).
3. M. Shamma, "The Isoquinoline Alkaloids," (Academic Press: New York 1972) p. 359.
4. R.H.F. Manske, *Can.J.Res.*, 7, 265 (1932).
5. R.H.F. Manske, *Can.J.Res.*, 8, 210, 407 (1933).
6. R.H.F. Manske, *Can.J.Res.*, 9, 436 (1933).
7. G.A.R. Johnston, P.M. Beart, D.R. Curtis, C.J.A. Game, R.M. McCulloch, R.M. MacLachlan, *Nature (London), New Biol.*, 240, 219 (1972).
8. D.R. Curtis, A.W. Duggan, D. Felix, and G.A.R. Johnston, *Brain Res.*, 32, 69 (1971).
9. S.F. Pong and L.T. Graham, *Brain Res.*, 42, 486 (1972).
10. J. Earl and W.A. Large, *J.Physiol.(London)*, 236, 113 (1974).
11. K. Krnjevic, *Nature (London)*, 228, 119 (1970).
12. D.R. Curtis, A.W. Duggan, D. Felix, and G.A.R. Johnston, *Nature (London)*, 226, 1222 (1970).
13. E.G. Steward, P.W. Borthwick, G.R. Clarke, and D. Warner, *Nature (London), New Biol.*, 256, 601 (1975).
14. J.F. Mitchell and V. Srinivasan, *Nature (London)*, 224, 633 (1969).
15. H.L. Holland, M.Curcumelli-Rodostamo, and D.B. Maclean, *Can.J.Chem.*, 54, 1472 (1976).
16. W.H. Perkin, Jr., and R. Robinson, *J.Chem.Soc.Proc.*, 26, 46 (1910).

17. W.H. Perkin, Jr., and R. Robinson, *J.Chem.Soc.Trans.*, 99, 775 (1911).

18. E. Hope and R. Robinson, *J.Chem.Soc.Proc.*, 26, 228 (1910).

19. D. Beke, *Adv.Heterocycl.Chem.*, 1, 167 (1963).

20. E. Hope and R. Robinson, *J.Chem.Soc.Trans.*, 99, 2114 (1911).

21. E. Hope and R. Robinson, *J.Chem.Soc.Trans.*, 105, 2085 (1914).

22. E. Hope, F.L. Pyman, F.G.P. Remfry, and R. Robinson, *J.Chem.Soc.*, 236 (1931).

23. P.W.G. Groenewoud and R. Robinson, *J.Chem.Soc.*, 199 (1936).

24. R.H.F. Manske, *Can.J.Res.*, 8, 210 (1933).

25. E. Hope and R. Robinson, *J.Chem.Soc.Trans.*, 99, 1153 (1911).

26. D.W. Hughes, H.L. Holland, and D.B. MacLean, *Can.J.Chem.*, 54, 2252 (1976).

27. S. Safe and R.Y. Moir, *Can.J.Chem.*, 42, 160 (1964).

28. M. Shamma and V.St. Georgiev, *Tetrahedron Lett.*, 2339 (1974).

29. M. Shamma and V.St. Georgiev, *Tetrahedron*, 32, 211 (1976).

30. T. Kametani, T. Honda, H. Inoue, and K. Fukumoto, *Heterocycles*, 3, 1091 (1975).

31. T. Kametani, T. Honda, H. Inoue, and K. Fukumoto, *J.Chem.Soc.Perkin Trans.1*, 1221 (1976).

32. R.D. Haworth and A.R. Pinder, *J.Chem.Soc.*, 1776 (1950).

33. V.P. Kerekes and R. Bognar, *J.Prakt.Chem.*, 313, 923 (1971).

34. W.M. Whaley and T.R. Govindachari, *Org.React.*, 6, 74 (1951).

35. V. Smula, N.E. Cundasawmy, H.L. Holland and D.B. MacLean, *Can.J.Chem.*, 51, 3287 (1973).

36. S. Teitel, J. O'Brien and A. Brossi, *J.Org.Chem.*, 37, 1879 (1972).

37. J.L. Moniot and M. Shamma, *J.Am.Chem.Soc.*, 98. 6714 (1976).

38. V.Gy. Gaal, P. Kerekes, and R. Bognar, *J.Prakt.Chem.*, 313, 935 (1971).

39. C.A. Buehler, T.A. Powers, and J.G. Michels, *J.Am.Chem.Soc.*, 66, 417 (1944).

40. J. Tirauflet, *Bull.Soc.Sci.Bretagne*, 26, 7 (1951).

41. S.N. Chakravarti and W.H. Perkin, Jr., *J.Chem.Soc.*, 196 (1929).

42. L.A. Duncanson, J.F. Grove, and J. Zealley, *J.Chem.Soc.*, 1331 (1953).

43. G.A. Edwards, W.H. Perkin, Jr., and F.W. Stoyle, *J.Chem.Soc.*, 127, 195 (1925).

44. S.N. Chakravarti, *J.Indian Chem.Soc.*, 17, 264 (1940).

45. V.F. Dallacker, K-W. Glombitza and M. Lipp, *Justus Liebigs Ann.Chem.*, 643, 67 (1961).

46. T. Fujisawa and K. Okada, *Yakugaku Zasshi*, 79, 772 (1959).

47. W.H. Perkin, Jr., and V.M. Trikojus, *J.Chem.Soc.*, 2925 (1926).

48. T. Ikeda, S. Kanahara, and T. Ujiie, *Kanazawa Daigaku Yakugakubu Kenkyu Nempo*, 8, 1 (1958); *Chem.Abstr.*, 53, 4287 (1959).

49. J.M. Tippett, Ph.D. Thesis, University of Adelaide, 1977.

50. H. Wolff, *Org.React*,, 3, 307 (1946).

51. P.A.S. Smith, *J.Am.Chem.Soc.*, 70, 320 (1948).

52. P.A.S. Smith, *J.Am.Chem.Soc.*, 72, 3718 (1950).

53. P.A.S. Smith and B. Ashby, *J.Am.Chem.Soc.*, 72, 2503 (1950).

54. L.G. Donaruma and W.Z. Heldt, *Org.React.*, 11, 1 (1960).

55. R.E. Lyle and D.A. Walsh, *Org.Prep.Proceed.Int.*, 5, 299 (1973).

56. R. Huisgen, J. Witte, and I. Ugi, *Chem.Ber.*, 90, 1844 (1957).

57. L.H. Briggs and J.W. Lyttleton, *J.Chem.Soc.*, 421 (1943).

58. L.H. Briggs and G.C.De Ath, *J.Chem.Soc.*, 456 (1937).

59. A-U-Rahman, A. Basha, N. Waheed, and S. Ahmed, *Tetrahedron Lett.*, 219 (1976).

60. F. H. Suydam, W.E. Greth, and N.R. Langerman, *J.Org.Chem.*, 34, 292 (1969).

61. D.J. Brown and K. Ienaga, *Aust.J.Chem.*, 28, 119 (1975).

62a R.N. Icke, and B.B. Wisegarver, *Org.Syn., Coll.Vol.*, 3, 723 (1955).

b R.F. Borch and A.I. Hassid, *J.Org.Chem.*, 37, 1673 (1976).

63. A.T. Nielsen and W.J. Houlihan, *Org.React.*, 16, 1 (1968).

64a P. Tomboulin, *J.Org.Chem.*, 24, 329 (1959).

b H. Gilman and B.J. Gai, *J.Org.Chem.*, 28, 1725 (1963).

65. A.G. Cook, Ed., "Enamines: Synthesis, Structure and Reactions," (Marcel Dekker: New York 1969) p. 347.

66. D.N. Mukherji, *Sci.Culture (Calcutta)*, 27, 405 (1961); *Chem.Abstr.*, 56, 3431c (1962).

67. V.S. Racine, *Justus Liebigs Ann.Chem.*, 239, 78 (1887).

68. A.T. Blomquist and E.J. Moriconi, *J.Org.Chem.*, 26, 3761 (1961).

69. B.L. Jensen and D.P. Michaud, *Synthesis*, 848 (1977).

70. B.A. Mooney and R.H. Prager, unpublished results.

71. D.D. Wheeler, D.C. Young, and D.S. Erley, *J.Org.Chem.*, 22, 547 (1957).

72. I. Heilbron and H.M. Bunbury, Ed., "Dictionary of Organic Compounds," Vol. 1, (Eyre and Spottiswoode: London 1953) p. 42.

73a R.F. Stockel and D.M. Hall, *Nature (London)*, 197, 787 (1963).

b H.R. Snyder and C.T. Elstron, *J.Am.Chem.Soc.*, 76, 3039 (1954).

c H.R. Snyder, C.T. Elston, and D.M. Kellom, *J.Am.Chem.Soc.*, 75, 2014 (1953).

d R.T. Conley, *Chem.Ind.(London)*, 438 (1958).

74. D.H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry" (McGraw Hill: London 1966) p. 84.

75a W.Z. Heldt, *J.Am.Chem.Soc.*, 80, 5880 (1958).

b L.A. Paquette, H.C. Berk, and S.V. Ley, *J.Org.Chem.*, 40, 902 (1975).

76. K.N. Carter, *J.Org.Chem.*, 31, 4257 (1966).

77a K-I. Morita, and Z. Suzuki, *J.Org.Chem.*, 31 233 (1966).

b A. Hassner and E.G. Nash, *Tetrahedron Lett.*, 525 (1965).

78a W. Flitsch and H. Peters, *Tetrahedron Lett.*, 1161 (1969).

b A.P. Gara, R.A. Massy-Westropp, and G.D. Reynolds, *Tetrahedron Lett.*, 4171 (1969).

79a K. Fukui, R. Sudo, M. Masaki, and M. Ohta, *J.Org.Chem.*, 33, 3504 (1968).

b I.J. Borowitz, K.C. Kirby, Jr., P.E. Rusek, and R. Virkhaus *J.Org.Chem.*, 33 3686 (1968).

80. H.O. House "Modern Synthetic Reactions," 2nd Edit., (W.A. Benjamin: Philippines 1972) (a) p. 698 (b) p. 494.

81a D.J. Beames and L.N. Mander, *Aust.J.Chem.*, 27, 1257 (1974).

b D.W. Johnson and L.N. Mander, *Aust.J.Chem.*, 27, 1277 (1974).

82. J.B. Taylor, J.W. Lewis, and M. Jacklin, *J.Med.Chem.*, 13, 1226 (1970).

83. L.N. Mander, Australian National University, private communication.

84. See Part II, Chapter 2.2 of this thesis.

85a H.C. Brown and G. Zweifel, *J.Am.Chem.Soc.*, 82, 4708 (1960).

b. H.C. Brown and R.L. Sharp, *J.Am.Chem.Soc.*, 88, 5851,(1966).

86. H.C. Brown and C.P. Garg, *J.Am.Chem.Soc.*, 83, 2951 (1961).

87. V.W. Treibs and W. Schroth, *Justus Liebigs Ann.Chem.*, 639, 204 (1961).

88a Y. Oikawa and O. Yonemitsu, *Tetrahedron*, 30, 2653 (1974).

b Y. Oikawa and O. Yonemitsu, *Tetrahedron Lett.*, 3393 (1972).

89. R.B. Woodward, A.A. Patchett, D.H.R. Barton, D.A.J. Ives, and R.B. Kelly, *J.Chem.Soc.*, 1131 (1957).

90. C.M. Suter and H.B. Milne, *J.Am.Chem.Soc.*, 62, 3473 (1940).

91. R. Criegee and K-H. Plate, *Ber.Dtsch.Chem.Ges.*, 72, 178 (1939).

92. W.E. Rosen, L. Dorfman, and M.P. Linfield, *J.Org.Chem.*, 29, 1723 (1964).

93. D. Taub, R.D. Hoffsommer, C.H. Kuo, H.L. Slates, Z.S. Zelawski, and N.L. Wender, *J.Chem.Soc. Chem.Commun.*, 1258 (1970).

94. W.H. Perkin, Jr., W.M. Roberts, and R. Robinson, *J.Chem.Soc.Trans.*, 105, 2405 (1914).

95. J.E. Horan and R.W. Schiessler, *Org.Syn., Coll.Vol.*, 5, 647 (1973).

96. I.A. Koten and R.J. Sauer, *Org.Syn., Coll.Vol.*, 5. 145 (1973).

97. J. Blair, J.J. Brown and G.T. Newbold, *J.Chem.Soc.*, 708, (1955).

98. F.E. Ziegler and K.W. Fowler, *J.Org.Chem.*, 41, 1564 (1976).

99. F.G. Baddar and Z. Iskander, *J.Chem.Soc.*, 209 (1954).

100. L. Ruzicka, M. Kobelt, O. Häfliger, and V. Prelog, *Helv.Chim.Acta*, 32, 544 (1949).

101. The author is grateful to Mr Tran Viet Hung for a sample of 4,5-dimethoxy-2-formylbenzoic acid.

102. For the synthesis of 1,3-dihydro-1-methyl-2H-inden-2-one, see Experimental Part II (Part C) of this thesis.

103. F.S. Kipping, *J.Chem.Soc.Trans.*, 65, 480 (1894).

104. A.I. Vogel "A Textbook of Practical Organic Chemistry," 3rd Edit., (Longmans: London 1956) p. 969.

105. W.D. Kumler, J.N. Shoolery, and F.V. Brutcher, Jr., *J.Am.Chem.Soc.*, 80, 2533 (1958).

106. E. Ott, *Org.Syn.*, 11, 88 (1931).

107. M.D. Taylor and L.R. Grant, *J.Chem.Educ.*, 32, 39 (1955).

108. A. Pictet and A. Gams, *Ber.Dtsch.Chem.Ges.*, 42, 2943 (1909).

109. R.D. Haworth, W.H. Perkin, Jr., and H.S. Pink, *J.Chem.Soc.*, 127, 1709 (1925).

110. K. Kindler and T. Li, *Ber.Dtsch.Chem.Ges.*, 74, 321 (1941).

111. E.C. Horning, J. Koo, and G.N. Walker, *J.Am.Chem.Soc.*, 73, 5826 (1951).

112. J. Koo, *J.Am.Chem.Soc.*, 75, 1891 (1953).

113. R. Lukes and I. Ernes, *Chem.Listy.*, 46, 361 (1952); *Chem.Abstr.*, 47. 6922c (1953).

114. V.M. Trikojus and D.E. White, *J.Proc.Roy.Soc.N.S.Wales*, 74, 82 (1940).

115. J.C. Cain, J.L. Simonsen, and C. Smith, *J.Chem.Soc.Trans*, 103, 1035 (1913).

116. E.J. Corey and M.Chaykovsky, *J.Am.Chem.Soc*., 87, 1345 (1965).

117. A. Pictet and M. Finkelstein, *Ber.Dtsch.Chem.Ges*., 42, 1979 (1909).

118. W.H. Perkin, Jr., W.M. Roberts and R. Robinson, *J.Chem.Soc.Trans*., 101, 232 (1912).

119. W.H. Perkin, Jr., and R. Robinson, *J.Chem.Soc.Trans*., 91, 1081 (1907).

REFERENCES

PART II

1. A. Stock and C. Massenez, *Ber.Dtsch.Chem.Ges.*, 45, 3539 (1912).
2. H.I. Schlesinger and A.B. Burg, *J.Am.Chem.Soc.*, 53, 4321, (1931).
3. H.I. Schlesinger, H.C. Brown, J.R. Gilbreath, and J.J. Katz, *J.Am.Chem.Soc.*, 75, 195 (1953).
4. H.C. Brown and R.L. Sharp, *J.Am.Chem.Soc.*, 90, 2915 (1968).
5. H.C. Brown, H.I. Schlesinger and A.B. Burg, *J.Am.Chem,Soc.*, 61, 673 (1939).
6. J.R. Elliott, W.L. Roth, G.F. Roedel, and E.M. Boldebuck, *J.Am.Chem.Soc.*, 74, 5211 (1952).
7. H.C. Brown, P. Heim, and N.M. Yoon, *J.Am.Chem.Soc.*, 92, 1637, (1970) and references cited therein.
8. H.C. Brown and B.C. Subba Rao, *J.Am.Chem.Soc.*, 82, 681 (1960).
9. H.C. Brown and R.M. Gallivan, Jr., *J.Am.Chem.Soc.*, 90, 2906 (1968).
10. H.J. Emelèus and K. Wade, *J.Chem.Soc.*, 2614 (1960).
11. H.C. Brown and P. Heim, *J.Am.Chem.Soc.*, 86, 3566 (1964).
12. H. Feuer, R.S. Bartlett, B.F. Vincent, Jr., and R.S. Anderson, *J.Org.Chem.*, 30, 2880 (1965).

13a H. Feuer, B.F. Vincent, Jr., and R.S. Bartlett, *J.Org.Chem.*, 30,

b H. Feuer and D.M. Braunstein, *J.Org.Chem.*, 34, 1817 (1969).

14. H.C. Brown, P. Heim and N.M. Yoon, *J.Org.Chem.*, 37, 2942, (1972).
15. H.C. Brown, D.B. Bigley, S.K. Arora, and N.M. Yoon, *J.Am.Chem.Soc.*, 92, 7161 (1970).
16. H.C. Brown and W. Korytnyk, *J.Am.Chem.Soc.*, 82, 3866 (1960).

17a E. Schenker, *Angew.Chem.*, 73, 81 (1961).

b H.C. Brown, *Tetrahedron*, 12, 117 (1961).

18a P.M. Maitlis, *Chem.Rev.*, 62, 233 (1962).

b B.M. Mikhailov, *Usp.Khim.*, 31, 417 (1962).

19. G. Zweifel and H.C. Brown, *Org.React.*, 13, 1 (1963).

20. T. Onak, *Adv.Organomet.Chem.*, 3, 263 (1965).

21a H.C. Brown, *Acc.Chem.Res.*, 2, 65 (1969).

b A. Suzuki, *Yukagaku*. 18, 285 (1969).

c N.M. Yoon, *Hwahak Kwa Kongop Ui Chinbo*, 9, 191 (1969).

d I. Schikatanz, *Stud.Cercet.Chim.*, 17, 833 (1969).

e G.M.L. Cragg, *J.Chem.Educ.*, 46, 794 (1969).

22. D. Devapraphakama, S. Devadas, and S. Dalbir, *J.Sci.Ind.Res.*, 29, 280 (1970).

23. H.C. Brown, *Chem.Brit.*, 7, 458 (1971).

24. H.C. Brown and E. Negishi, *Pure Appl.Chem.*, 29, 527 (1972).

25. C.F. Lane, *Aldrichimica Acta*, 6, 21 (1973).

26. J. Weill-Raynal, *Synthesis*, 633 (1976).

27. H.C. Brown, "Hydroboration" (W.A. Benjamin: New York 1962).

28. H. Steinborg and R.J. Brotherton, "Organoboron Chemistry," Vol. 2 (Wiley-Interscience: New York 1966).

29. R.T. Holzmann, Ed., "Production of the Boranes and Related Research," (Academic Press: New York 1967).

30. H.C. Brown, "Boranes in Organic Chemistry," (Cornell Univ. Press: Ithaca, New York 1972).

31. G.M.L. Cragg, "Organoboranes in Organic Synthesis," (Marcel Dekker: New York 1973).

32. H.C. Brown "Organic Synthesis via Boranes," (Wiley-Interscience: New York 1975) (a) p. 18, (b) pp. 11-14.

33. T. Onak, "Organoborane Chemistry," (Academic Press: New York 1975).

34, A. Suzuki, N. Miyaura, M. Itoh, H.C. Brown, and P. Jacob, III, *Synthesis*, 305 (1973).

35a M. Zaidlewicz and A. Uzarewicz, *Rocz.Chem*., 47, 1433 (1973).

b M. Zaidlewicz and A. Uzarewicz, *Rocz.Chem*., 48, 467 (1974).

36a J. Klein and E. Dunkelblum, *Tetrahedron*, 24, 5701 (1968).

b E. Dunkelblum, R. Levene, and J. Klein, *Tetrahedron*, 28, 1009, (1972).

c H.C. Brown and K.A. Keplys, *J.Am.Chem.Soc*., 86, 1791 (1964).

d H.C. Brown and O.J. Cope, *J.Am.Chem.Soc*., 86, 1801 (1964).

e R. Murphy and R.H. Prager, *Aust.J.Chem*., 29, 617 (1976).

37. D.J. Pasto, C.C. Cumbo, and J. Hickmann, *J.Am.Chem.Soc*., 88, 2201 (1966).

38. H.C. Brown and N.M. Yoon, *J.Am.Chem.Soc*., 88, 1464 (1966).

39a Y. Bessiere-Chretien, C. Grisson, J.P. Montheard, F. Ovar, and M. Chatzopoulas, *Bull.Soc.Chim.Fr*., 4391 (1971).

b Y. Bessiere-Chretien and B. Meklati, *Tetrahedron Lett*., 621 (1971).

40a H.C. Brown and N.M. Yoon, *J.Am.Chem.Soc*., 90, 2686 (1968).

b I. Uzarewicz, A. Uzarewicz, and E. Zientek, *Rocz.Chem*., 46, 1189 (1972).

41. H.C. Brown and N.M. Yoon, *Chem.Commun*., 1549 (1968).

42. P.A. Marshall and R.H. Prager, *Aust.J.Chem*., 30, 141 (1977).

43. P.A. Marshall and R.H. Prager, *Aust.J.Chem*., 30, 151 (1977).

44. P.A. Marshall, B.Sc. Honours Thesis, University of Adelaide, 1974.

45. Von S. Kabuss, H. Friebolin, and H. Schmid, *Tetrahedron Lett*., 469 (1965).

46. H.O. House, "Modern Synthetic Reactions," 2nd Edit., (W.A. Benjamin: Philippines (1972) (a) p. 104, (b) p. 515.

47. E.R.H. Walker, *Chem.Soc.Rev*., 5, 23 (1976).

48. Y. Yamamoto, H. Toi, A. Sonoda, and S.I. Murahashi, *J.Chem.Soc. Chem.Commun*., 672 (1976).

49a N.M. Yoon and H.C. Brown, *J.Am.Chem.Soc.*, 90, 2927 (1968).

b H.C. Brown and B.C. Subba Roa, *J.Am.Chem.Soc.*, 78, 2582 (1956).

50. M. Lj. Mihailovic, V. Andrejevic, J. Milovanovic, and J. Jankovic, *Helv.Chim.Acta*, 59, 2305 (1976).

51. H.C. Brown, S. Krishnamurthy, and N.M. Yoon, *J.Org.Chem.*, 41, 1778 (1976).

52. E,M. Kaiser, C.G. Edmonds, S.D. Grubb, J.W. Smith, and D. Tramp, *J.Org.Chem.*, 36, 330 (1971).

53. H.C. Brown, S. Ikegami, and J.W. Kawakami, *J.Org.Chem.*, 35, 3243 (1970).

54. N. Neto, C. DiLauro, and S. Califano, *Spectrochim.Acta Part A.*, 26, 1489 (1970).

55. M. St.-Jacques and C. Vaziri, *Org.Magn.Reson.*, 4, 77 (1972).

56. N.L. Allinger and J.T. Sprague, *J.Am.Chem.Soc.*, 94, 5734 (1972).

57. G. Favini and A. Nava, *Theor.Chim.Acta*, 31, 261 (1973).

58. G. Favini and A. Nava, *Gazz.Chim.Ital.*, 104, 621 (1974).

59. G. Favini, G. Buemi, and M. Ramondi, *J.Mol.Struct.*, 2, 137 (1968).

60. S. Kabuss, H.G. Schmid, H. Friebolin, and W. Faisst, *Org.Magn.Reson.* 2, 19 (1970).

61. G. Bodennec and M. St.-Jacques, *Can.J.Chem.*, 55, 1199 (1977).

62. R. Huisgen, E. Rauenbusch, G. Seidl, and I. Wimmer, *Justus Liebigs Ann.Chem.*, 671, 41 (1964).

63. R. Huisgen, E. Rauenbusch and G. Seidl, *Chem.Ber.*, 90, 1958 (1958).

64. F.A.L. Anet and J.J. Wagner, *J.Am.Chem.Soc.*,93, 5266 (1971).

65. B.R. Brown and J.A.H. MacBride, *J.Chem.Soc.*, 3822 (1961).

66. J. March, "Advanced Organic Chemistry, Reactions, Mechanisms and Structure," (McGraw Hill: Kogakusha 1968) (a) p.316, (b) p. 585.

67. D.T. Hurd, *J.Am.Chem.Soc.*, 70, 2053 (1948).

68. H.C. Brown, K.J. Murray, L.J. Murray, J.A. Snover and G. Zweifel, *J.Am.Chem.Soc.*, 82, 4233 (1960).

69. H.C. Brown and B.C. Subba Rao, *J.Am.Chem.Soc.*, 81, 6428 (1959).

70. H.C. Brown and G. Zweifel, *J.Am.Chem.Soc.*, 82, 4708 (1960).

71. H.C. Brown and R.L. Sharp, *J.Am.Chem.Soc.*, 88, 5851,(1966).

72a G. Redeuilh, P. Rumf and C. Viel, *Bull.Soc.Chim.Fr.*, 2665 (1975).

b G. Redeuilh, P. Rumf, and C. Viel, *Bull.Soc.Chim.Fr.*, 2668 (1975).

73. J.M. Birchall, R.N. Hazeldine, and J.F. Marsh, *Chem.Ind.(London)*, 1080 (1961).

74. T.R. Phillips and F.G.A. Stone, *J.Chem.Soc.*, 94 (1962).

75. H.C. Brown and G. Zweifel, *J.Am.Chem.Soc.*, 81, 247 (1959).

76. H.C. Brown and G. Zweifel, *J.Am.Chem.Soc.*, 83, 2544 (1961).

77. W.J. Wechter, *Chem.Ind.(London)*, 294 (1959).

78. K.R. Varma and E. Caspi, *Tetrahedron*, 24, 6365 (1968).

79. S. Wolfe, M. Nussin, Y. Mazur, and F. Sondheimer, *J.Org.Chem.*, 24, 1034 (1959).

80. G. Zweifel and H.C. Brown, *J.Am.Chem.Soc.*, 86, 393 (1964).

81. H.C. Brown and K.-T. Liu, *J.Am.Chem.Soc.*, 93, 7335 (1971).

82. Y. Senda, S. Kamiyama, and S. Imaizum, *Tetrahedron*, 33, 2933 (1977).

83. J. Klein, E. Dunkelblum, and M.A. Wolff, *J.Organomet.Chem.*, 7, 377 (1967).

84. E.L. Allred, J. Sonnenberg, and S. Winstein, *J.Org.Chem.*, 25, 26 (1960).

85. A. Streitwieser, Jr., L. Verbit, and R. Bittman, *J.Org.Chem.*, 32, 1530 (1967).

86. P.R. Jones, *J.Org.Chem.*, 37, 1886 (1972).

87. D.J. Pasto, B. Lepeska, and T-C. Cheng, *J.Am.Chem.Soc.*, 94, 6083 (1972).

88. J.C. Paice, Ph.D. Thesis, University of Adelaide, 1968.

89. G. Zweifel and H.C. Brown, *J.Am.Chem.Soc.*, 85, 2066 (1963).

90. G.L. Larson, D. Hernandez, and A. Hernandez, *J.Organomet.Chem.*, 76, 9 (1974).

91. L.M. Jackman and S. Sternhill, "Aplications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd Edit. (Permagon: Oxford 1969) p. 83.

92. N.S. Bhacca, D.P. Hollis, L.F. Johnson, and E.A. Pier, "Varian NMR Spectra Catalog," (Palo Alto, California) Spectrum No. 227.

93. M.A. Cooper and S.L. Manatt, *J.Am.Chem.Soc.*, 91, 6325 (1969).

94. B. Tinland and C. Décoret, *Tetrahedron Lett.*, 3019 (1971).

95. S. Wold and G. Bergson, *Ark.Khem.*, 28, 245 (1967).

96. J.D. Quirk, *Diss.Abstr.Int.B*, 30, 4013 (1970).

97. L. Rosenblum, *J.Am.Chem.Soc.*, 77, 5016 (1955).

98a H.C. Brown and B.C. Subba Rao, *J.Am.Chem.Soc.*, 81, 6434 (1959).

b P.A. McCusker and J.H. Bright, *J.Org.Chem.*, 29, 2093 (1964).

99a H.C. Brown, M.V. Bhatt, T. Munekata, and G. Zweifel, *J.Am.Chem. Soc.*, 89, 567 (1967).

b H.C. Brown and G. Zweifel, *J.Am.Chem.Soc.*, 82, 1504 (1964).

c H.C. Brown and B.C. Subba Rao, *J.Org.Chem.*, 22, 1137 (1957).

100. P. Caubère, N. Derozier, and B. Loubinoux, *Bull.Soc.Chim.Fr.*, 302 (1971).

101. M.C. Carre, M.L. Viriot-Villaume, and P. Caubère, *Synthesis*, 48 (1977).

102. R. Huisgen and G. Seidl, *Tetrahedron*, 20, 231 (1964).

103. R.B. Woodward and T. Singh, *J.Am.Chem.Soc.*, 72, 494 (1950).

104. R. Baird and S. Winstein, *J.Am.Chem.Soc.*, 84, 788 (1962).

105. B. Capon, *Quart.Rev.*, 18, 45 (1964).

106. V.J. Traynelis, W.L. Hergensother, J.R. Livingston, and J.A. Valicenti, *J.Org.Chem.*, 27, 2377 (1962).

107. J. English, Jr., and G. Cavaglieri, *J.Am.Chem.Soc.*, 65. 1085 (1943).

108. W.K. Anderson and T. Veysoglu, *J.Org.Chem.*, 38, 2267 (1973).

109. R.G. Carlson and R. Ardon, *J.Org.Chem.*, 36, 216 (1971).

110. R.E. Parker and N.S. Isaacs, *Chem.Rev.*, 59, 737 (1959).

111. E. Glotter, P. Krinsky, M. Rejtö, and M. Wissenberg, *J.Chem.Soc. Perkin Trans.1*, 1442 (1976).

112. V.S. Joshi, N.P. Damadaran and Sukh Dev, *Tetrahedron*, 27, 459 (1971).

113. I.C. Nijam and L. Levi, *Can.J.Chem.*, 46, 1444 (1968).

114. M. Hudlicky, *J.Org.Chem.*, 39, 3460 (1974).

115. G.H. Posner and D.Z. Rogers, *J.Am.Chem.Soc.*, 99, 8208 (1977).

116. V.S. Joshi and Sukh Dev, *Tetrahedron*, 33, 2955 (1977).

117. H.O. House and C.B. Hudson, *J.Org.Chem.*, 35, 647 (1970).

118. T.A. Spencer, R.W. Britton, and D.S. Watt, *J.Am.Chem.Soc.*, 89, 5727 (1967).

119. P.J. Hattersley, L.M. Lockhart, and M. Wright, *J.Chem.Soc., C*, 217 (1969).

120. F. Elsinger, *Org.Synth.*, 45, 7 (1965).

121. R. Mayer in W. Foerst, Ed., "Newer Methods of Preparative Organic Chemisty, Vol. 2" (Academic Press: New York 1963). pp. 101-131.

122. J. Salm and A.C. Thompson, *J.Pharm.Sci.*, 52, 898 (1963).

123. G. Baddeley, J.W. Rasburn, and R. Rose, *J.Chem.Soc.*, 3168 (1958).

124a K. Hanaya, *Nippon Kagaku Zasshi (J.Chem.Soc. Japan, Pure Sect.)*, 87, 991 (1966).

b S. Mitsui, A. Kasahara, K. Hanaya, *Bull.Chem.Soc.Jap.*, 41, 2526 (1968).

125. E.J. Corey and M. Chaykovsky, *J.Am.Chem.Soc.*, 87, 1353 (1965).

126. B.M. Trost and L.S. Melvin, Jr., "Sulfur Ylides, Emerging Synthetic Intermediates," (Academic Press: New York 1975), (a) p. 23 (b) p. 128.

127. W.N. Speckamp, R. Neeter, P.D. Rademaker, and H.O. Huisman, *Tetrahedron Lett.*, 3795 (1968).

128a E.P. Kohler, M. Tishler, H. Potter, and H.T. Thompson, *J.Am.Chem. Soc.*, 61, 1057 (1939).

b G.B. Payne, *J.Org.Chem.*, 32, 3351 (1967).

129. H. Christol and F. Plenat, *Bull.Soc.Chim.Fr.*, 202 (1961).

130. S. Ebine, M. Horoshino, and K. Takahashi, *Bull.Chem.Soc. Japan*, 41, 2942 (1968).

131a G.L. Buchanan and D.B. Jhaveri, *J.Org.Chem.*, 26, 4295 (1961).

b N.H. Cromwell and R.E. Bambury, *J.Org.Chem.*, 26, 997 (1961).

c H.O. House and R.L. Wasson, *J.Am.Chem.Soc.*, 78, 4394 (1956).

132. M. Mühlstadt and H.J. Gensrich, *J.Prakt.Chem.*, 34, 139 (1966).

133. J. Kenner, W.H. Ritchie and F.S. Statham, *J.Chem.Soc.*, 1169 (1937).

134a M. Mousseron, R. Jacquier, and H. Christol, *Bull.Soc.Chim.Fr.*, 346 (1957).

b J. Brugidou and H. Christol, *Bull.Soc.Chim.Fr.*, 1693 (1966).

135a A. Hassner and N.H. Cromwell, *J.Am.Chem.Soc.*, 80, 893 (1958).

b E. Weitz and A. Scheffer, *Ber.Dtsch.,Chem.Ges.*, 54, 2327 (1921).

136. M.B. Stringer and D. Wege, *Tetrahedron Lett.*, 65 (1977).

137a K.P.C. Vollhardt, *Synthesis*, 765 (1975).

b T.M. Cresp and M.V. Sargent, *J.Chem.Soc. Perkin Trans.1*, 2961 (1973).

138. D.B. Denney and J. Song, *J.Org.Chem.*, 29, 495 (1964).

139. E. Dunkelblum and H. Hart, *J.Am.Chem.Soc.*, 99, 644 (1977).

140. H. Fujimoto, S. Inagaki and K. Fukui, *J.Am.Chem.Soc.*, 98, 2670 (1976).

141. R.B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry," (Academic Press: New York 1970).

142. N.C. Deno, *J.Am.Chem.Soc.*, 72, 4057 (1950).

143. R. Graf, *Chem.Ber.*, 89, 1071 (1956).

144a H. Ulrich, *Chem.Rev.*, 65, 369 (1965).

b H. Bestian, *Pure Appl.Chem.*, 27, 611 (1974).

145. E. Dunkelblum and A. Shaviv, *Isr.J.Chem.*, 10, 971 (1972).

146. R. Huisgen, *J.Org.Chem.*, 41, 403 (1976) and references therein.

147. R.A. Firestone, *Tetrahedron*, 33, 3009 (1977) and references therein.

148. R. Huisgen, *J.Org.Chem.*, 33, 2291 (1968).

149a K.Bast, M. Christl, R. Huisgen, W. Mack and R. Sustmann, *Chem.Ber.*, 106, 3258 (1973).

b M. Christl, R. Huisgen and R. Sustmann, *Chem.Ber.*, 106, 3275 (1973).

c R. Huisgen and M. Christl, *Chem.Ber.*, 106, 3291 (1973).

d K. Bast, M. Christl, R. Huisgen and W. Mack, *Chem.Ber.*, 106, 3312 (1973).

e M. Christl and R. Huisgen, *Chem.Ber.*, 106, 3345 (1973).

150a G. Bailo, P. Caramella, G. Cellerino, A.G. Invernizzi and P. Grünanger, *Gazz.Chim.Ital.*, 103, 47 (1973).

b G.W. Perold and F.V.K. Reiche, *J.S.African Chem.Inst.*, 10, 5 (1957); *Chem.Abstr.*, 54, 1145b (1958).

151. E. Oliveri-Mandala, *Gazz.Chim.Ital.,(I)*, 40, 117 (1910); *Chem.Abstr.*, 5, 1091 (1911).

152. P.K. Kadaba and T.F. Colturi, *J.Heterocycl.Chem.*, 6, 829 (1969).

153. T.V. Van Auken and K.L Rinehart, Jr., *J.Am.Chem.Soc.*, 84, 3736 (1962).

154. G. Drefahl and K. Ponsold, *Chem.Ber.*, 93, 519 (1960).

155a C.F. Huebner, E.M. Donoghue, C.J. Novak, L. Dorfman, and E. Wenkert, *J.Org.Chem.*, 35, 1149 (1970).

b R. Huisgen and H. Pohl, *Chem.Ber.*, 93, 527 (1960).

156. R.W. Turner and T. Seden, *Chem.Commun.*, 399 (1966).

157. D.D. Perrin, W.L.F. Armarego, and D.R. Perrin, "Purification of Laboratory Chemicals," (Permagon: Oxford 1966), (a) p. 273.

158. W. Treibs and H-J. Klinkhammer, *Chem.Ber.*, 83, 367 (1950).

159. T. Fujita, *Yakugaku Zasshi*, 79, 1192 (1959); *Chem.Abstr.*, 54, 3354a (1960).

160. R. Huisgen and W. Rapp, *Chem.Ber.*, 85, 826 (1952).

161. R.W. Thies and H.H.J. Shih, *J.Org.Chem.*, 42, 281 (1977).

162. R. Huisgen, I. Ugi, E. Ravenbusch, V. Vossius, and H. Oertel, *Chem.Ber.*, 90, 1946 (1957).

163. A.I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd Edit. (Longmans: London 1956) (a) p. 344, (b) p. 169, (c) p. 719, (d) p. 969.

164. G. Seidl, R. Huisgen, and J.H.M. Hill, *Tetrahedron*, 20, 633 (1964).

165. J. Colonge and P. Garnier, *Bull.Soc.Chim.Fr.*, 436 (1948).

166. J.K. Stille and C.N. Wu, *J.Org.Chem.*, 30, 1222 (1965).

167. O. Wallach and E. Beschke, *Justus Liebigs Ann.Chem.*, 336, 1 (1904).

168. W. Cocker and D.H. Grayson, *Tetrahedron Lett.*, 4451 (1969).

169. W. Hückel and E. Vevera, *Chem.Ber.*, 89, 2105 (1956).

170. E.W. Garbisch, Jr., *J.Org.Chem.*, 26, 4165 (1961).

171. A.F. Titley, *J.Chem.Soc.*, 2591 (1928).

172. M. Ohtsuru, K. Tori, and H. Wantanabe, *Chem.Pharm.Bull. (Tokyo)* 15, 1015 (1967).

173. W.E. Bachmann and D.G. Thomas, *J.Am.Chem.Soc.*, 63, 598 (1941).

174. A.L. Wilds and J.A. Johnson, Jr., *J.Am.Chem.Soc.*, 68, 86 (1946).

175. W. Hückel and R. Cramer, and S. Läufer, *Justus Liebigs Ann.Chem.*, 630, 89 (1960).

176. R. Kuhn and H. Trischmann, *Justus Liebigs Ann.Chem.*, 611, 117 (1958).

177. H. Christol, Y. Delhoste, and M. Mousseron, *Bull.Soc.Chim.Fr.*, 1238 (1959).

178. R. Huisgen and G. Seidl, *Chem.Ber.*, 96, 2740 (1963).

179. C. Mannich, F. Borkowsky, and W.H. Lin, *Arch.Pharm.*, 275, 54 (1937); *Chem.Abstr.*, 31, 3038[1] (1937).

180. R.L. Stevens, J.J. Beereboom, Jr., and K. Rutherford, *J.Am.Chem.Soc.*, 77, 4590 (1955).

181. R. Weissgerber, *Ber.Dtsch.Chem.Ges.*, 44, 1436 (1911).

182. J.F. Ford, R.C. Pitkethly, and V.O. Young, *Tetrahedron*, 4, 325 (1958).

183. I.T. Chizhevskaya and Z.B. Idelchik, *Zhur.Obschei.Khim.*, 27, 83 (1957).

184. J.W. Cornforth, R.H. Cornforth, and R. Robinson, *J.Chem.Soc.*, 689 (1942).

185. E. Bamberger and W. Lodter, *Ber.Dtsch.Chem.Ges.*, 23, 197 (1890).

186. G. Gelli, A. Maccioni, M. Secci, and V. Solinas, *Ann.Chim. (Rome)*, 54., 1143 (1964).

187. H.O. House and G.H. Rasmusson, *J.Org.Chem.*, 26, 4278 (1961).

188. M. Schlosser, G. Müller, and K.F. Christmann, *Angew.Chem.Ed.Engl.*, 5, 667 (1966).

189. A.A. Morton and J.R. Stevens, *J.Am.Chem.Soc.*, 53, 2244 (1931).

190. K. Auwers and O. Jordan, *Biochem.Z.*, 144, 31 (1921).

191. The author is grateful to Dr. G.E. Gream for a sample of 3,3-dimethyl-2,3-dihydro-1H-inden-1-ol.

192. A. Bosch and R. K. Brown, *Can.J.Chem.*, 42, 1718 (1964).

193. P. Rajagopalan, B.G. Advani, and C.N. Talaty, *Org.Synth.Coll.Vol.*, 5, 504 (1973);

194a A. Werner and H. Buss, *Ber.Dtsch.Chem.Ges.*, 27, 2193 (1894).

b H. Wieland, *Ber.Dtsch.Chem.Ges.*, 40, 1667 (1907).

c A. Dondini, A. Mangini and S. Ghersetti, *Tetrahedron Lett.*, 4789 (1966).