

ASPECTS OF THE PREPARATION AND PROPERTIES OF SOME
CONFORMATIONALLY BIASED DIHYDROAROMATIC COMPOUNDS

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by

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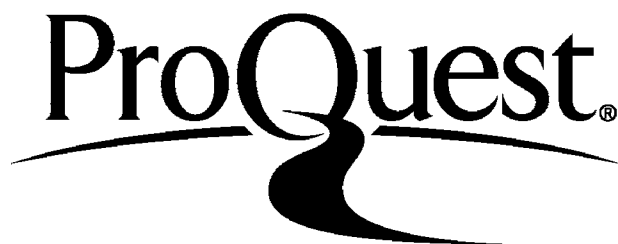
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ABSTRACT

The work described in this thesis is concerned with preparation and conformation of dihydroaromatic molecules. In part I the use of alkaline metal/liquid ammonia solutions in the preparation of dihydroaromatic compounds is reviewed; particular emphasis being placed on the effect of the substituent on the nature of the products obtained. The reduction of several benzoic acid and naphthoic acid derivatives has been investigated with a view to using the alkaline metal/liquid ammonia sequence to prepare sterically hindered dihydrobenzoic acids and dihydronaphthoic acids. 1,4-Dihydro-8-methyl-1-naphthoic acid and 1,4-dihydro-8-isopropyl-1-naphthoic acid have been successfully prepared by this method. In the course of this work the reduction of the lactones phthalide and naphthalide and their dimethyl analogues have been studied. In these cases, there is competition between reduction of the aromatic ring and of the ester formation. Factors which influence the competition between these two reaction pathways have been investigated.

In Part II evidence for the conformations of dihydroaromatic rings is reviewed and the effect of the substituents is discussed. Nuclear magnetic resonance (nmr) spectroscopic data for dihydroaromatic compounds prepared in Part I are analysed in detail; these data are then used to determine the conformations of these conformationally biased and conformationally locked dihydroaromatic rings.

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Aspects of the preparation and properties of some
conformationally biased dihydroaromatic compounds

CHAPTER 1
INTRODUCTION

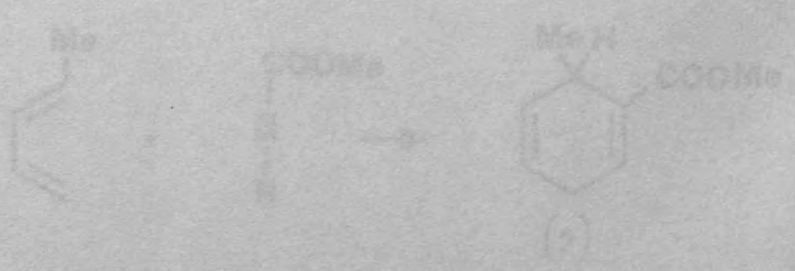
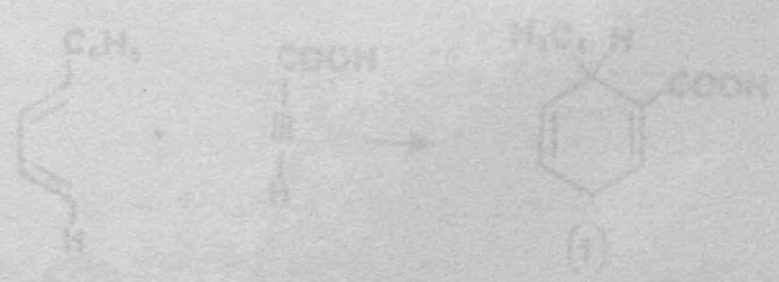
Cyclohex-1,4-dienes (1,4-dihydrobenzenes), 1,4-dihydronaphthalene, and 9,10-dihydroanthracene have been the subject of a considerable amount of study. Of particular interest has been the conformations adopted by these compounds and their derivatives^{1,2,3}.

1,4-Dihydroaromatic rings can be prepared by several synthetic routes. For example a Diels-Alder reaction⁴ between a diene and a dienophile leads directly to a 1,4-dihydroaromatic. Maleic acid and its methyl ester react with 1-phenyl-1,3-butadiene respectively

PART 1

THE PREPARATION OF DIHYDROAROMATIC COMPOUNDS

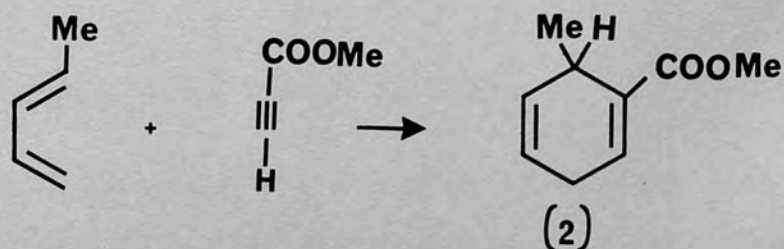
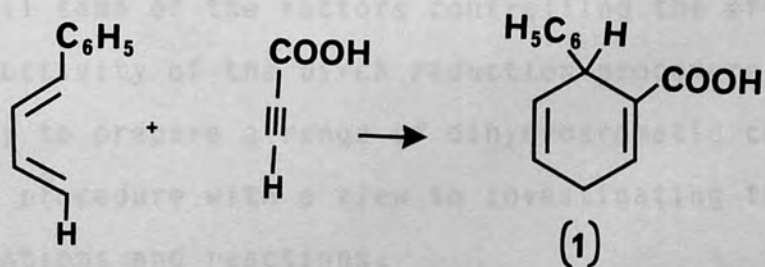
are also obtained from the thermal decomposition of azo compounds. For example, Hey, Perkins and Williams^{5,6}



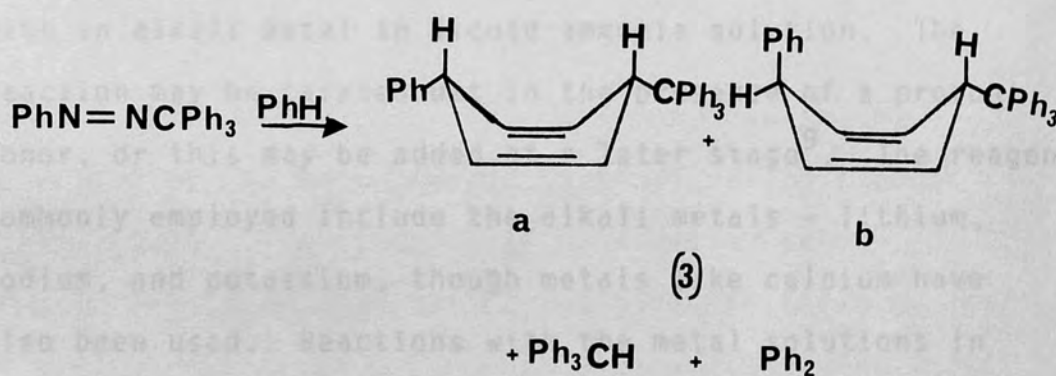
CHAPTER 1
INTRODUCTION

Cyclohexa-1,4-dienes (1,4-dihydrobenzenes), 1,4-dihydronaphthalenes, and 9,10-dihydroanthracenes have been the subject of a considerable amount of study. Of particular interest has been the conformations adopted by such compounds and their derivatives^{1,2,3}.

1,4-Dihydroaromatic rings can be prepared by several synthetic routes. For example a Diels-Alder reaction⁴ between a diene and acetylene leads directly to a 1,4-dihydrobenzene. Propiolic acid and its methylester react with 1-phenyl and 1-methylbutadiene respectively to give 1:1 adducts (1) and (2) [Scheme 1]. Such compounds are also obtained from the thermal decomposition of azo compounds. For example, Hey, Perkins and Williams^{5,6}



isolated cis- and trans- 1,4-dihydro-4-tritylbiphenyl (3) from the products of the decomposition of phenylazotriphenylmethane (PATM) in benzene [Scheme 2]. However the most convenient and general preparative route involves the reaction of aromatic compounds with alkali metals in liquid ammonia solution, the so-called Birch reduction^{7,8}.



The aims of this project are firstly to study in detail some of the factors controlling the efficiency and selectivity of the Birch reduction procedure and secondly to prepare a range of dihydroaromatic compounds by this procedure with a view to investigating their conformations and reactions.

CHAPTER 2

THE BIRCH REDUCTION AND RELATED PROCESSES

2.1. INTRODUCTION

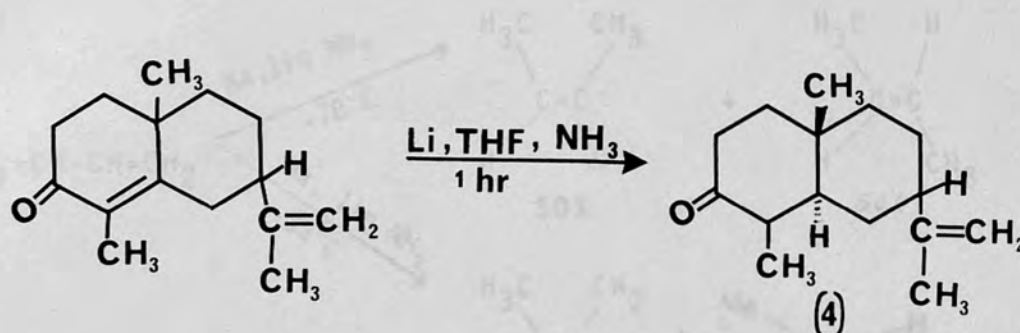
The Birch reduction is the name given to the process by which aromatic compounds are reduced to the non-conjugated dihydroaromatic derivatives upon treatment with an alkali metal in liquid ammonia solution. The reaction may be carried out in the presence of a proton donor, or this may be added at a later stage⁹. The reagents commonly employed include the alkali metals - lithium, sodium, and potassium, though metals like calcium have also been used. Reactions with the metal solutions in liquid ammonia often employ a cosolvent, such as ether, tetrahydrofuran, or 1,2-dimethoxyethane. These increase the solubility of the organic substrate in the reaction mixture¹⁰.

Other reactions in this category include the dissolving metal reductions of carbon-carbon double bonds conjugated with carbonyl groups, aromatic systems or other carbon-carbon multiple bonds. Dissolving metal reductions of aromatic systems can also lead to tetrahydro derivatives¹⁰.

(a) Reduction of carbon-carbon bonds

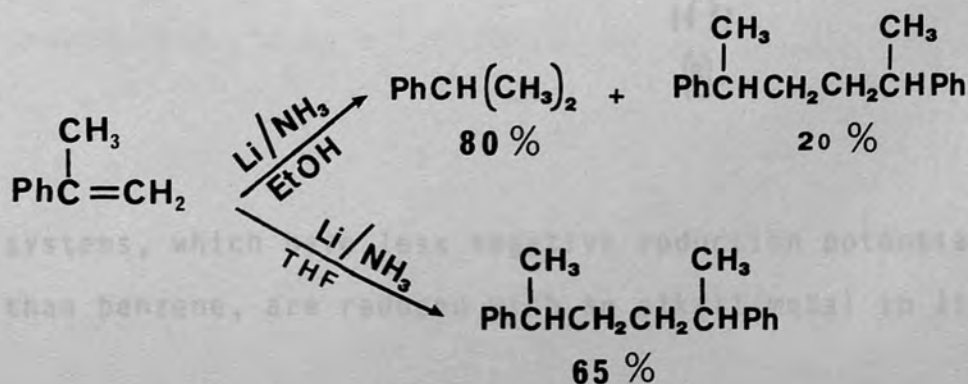
The metal ammonia solution is characterised by its ability to reduce conjugated carbon-carbon double

bonds to form unconjugated ketones selectively such as (4)¹¹. The reaction should be carried out relatively



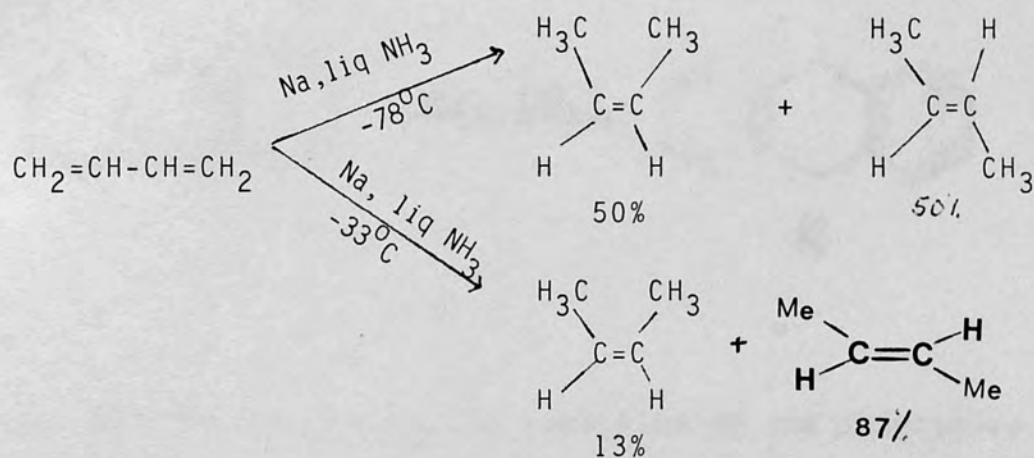
quickly since prolonged reaction times lead to the reduction of the unconjugated terminal carbon-carbon double bonds. The solution of unsaturated ketone is treated with more than two equivalents of sodium or lithium in liquid ammonia or a low-molecular-weight amine (the Benkeser reduction)¹².

Carbon-carbon double bonds conjugated with aromatic system or other multiple bonds may also be reduced under these conditions. In this reaction, excess of proton donor is required. In the absence of the excess proton donor dimerization of the initially formed anion radical is observed¹³ [Scheme 3]. The reduction of 1,3-dienes



(Scheme 3)

leads to the formation of cis-alkene at low temperatures or in non-polar media¹⁴.



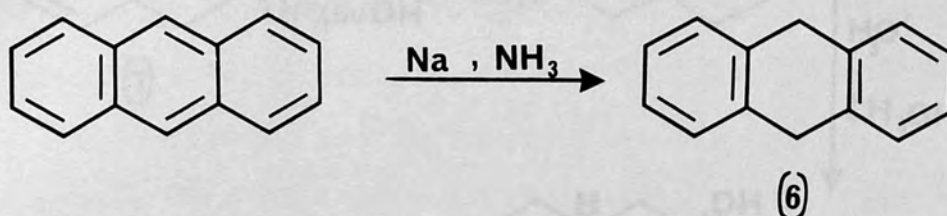
(b) Reduction of aromatic rings

The ability of alkali metals to partially reduce aromatic systems has proved especially useful in organic synthesis. The formation of 1,4-dihydrobenzenes shows that the metal-alcohol-ammonia reagent is powerful enough to reduce a benzene ring, but specific enough to add only two hydrogens^{7a} (5). A number of polycyclic aromatic



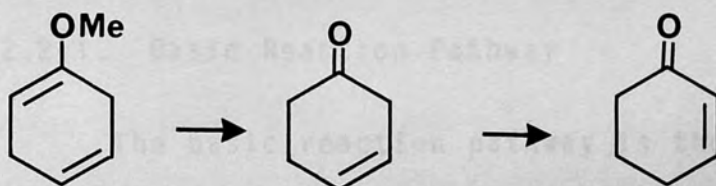
systems, which have less negative reduction potentials than benzene, are reduced with an alkali metal in liquid

ammonia in the absence of an alcohol, for example (6). With careful attention to the reaction conditions, it

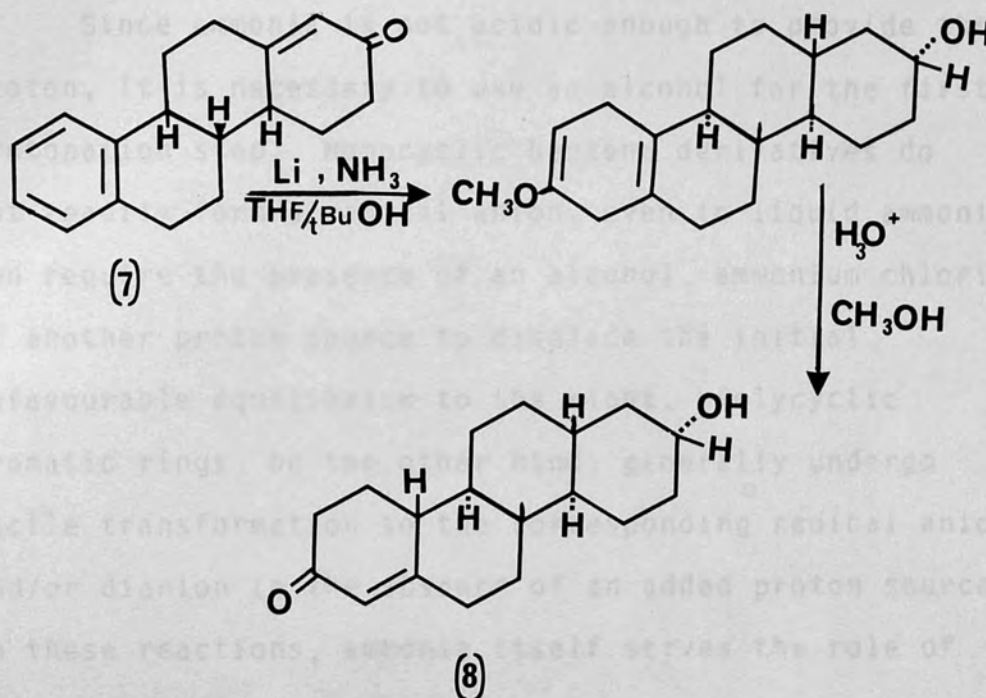


is possible to control the reduction of the polycyclic aromatic systems to dihydro-, tetrahydro-, and hexahydro- derivatives¹⁵.

The dihydrobenzenes are interesting because they can be converted into compounds inaccessible by other methods¹⁰.



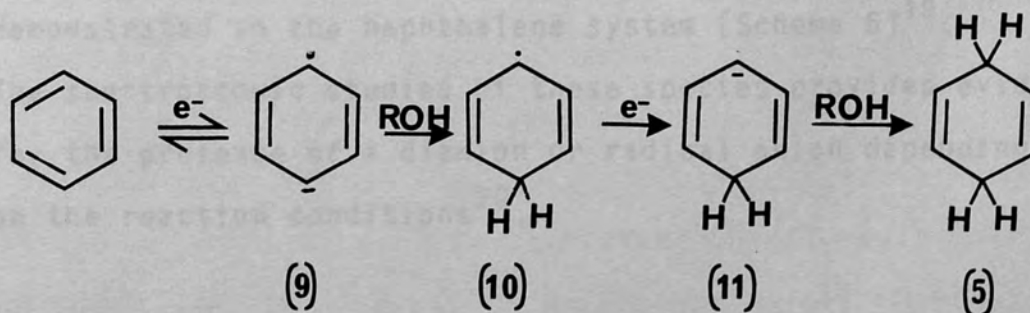
This reaction is of a particular importance in the synthesis of certain steroids since the process can be used, for example, in the conversion of an anisole ring (7) to a cyclohexenone (8)¹⁰.



2.2. MECHANISM OF THE BIRCH REDUCTION

2.2.1. Basic Reaction Pathway

The basic reaction pathway is thought¹⁶ to involve the addition of one electron to give a radical anion (9) which must be protonated (10) before addition of a second electron and proton can occur (11) [Scheme 4].

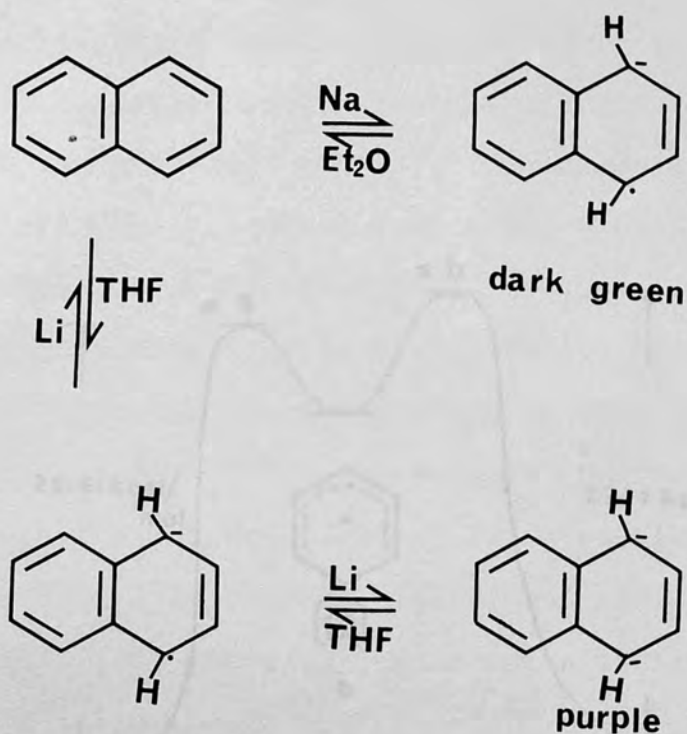


(Scheme 4)

Since ammonia is not acidic enough to provide the proton, it is necessary to use an alcohol for the first protonation step. Monocyclic benzene derivatives do not readily form a radical anion, even in liquid ammonia, and require the presence of an alcohol, ammonium chloride or another proton source to displace the initial unfavourable equilibrium to the right. Polycyclic aromatic rings, on the other hand, generally undergo facile transformation to the corresponding radical anion and/or dianion in the absence of an added proton source. In these reactions, ammonia itself serves the role of protonating agent.

Reduction of benzene provides the simplest example of the above process. Evidence in support of the mechanism is provided in the observation that C_6D_6 is converted into 1,4-dihydrohexadeuterobenzene (ca 1:1 cis:trans ratio) by Birch reduction¹⁷. Further, the presence of a radical anion containing an unpaired electron which interacts with the electrons of the conjugated system, has been established by measurement of the e.p.r. spectra of various radical anion solutions¹⁸.

Such radical anion intermediates have very characteristic colours. This has for example been demonstrated in the naphthalene system [Scheme 5]¹⁹. The spectroscopic studies of these species provides evidence for the presence of a dianion or radical anion depending on the reaction conditions²⁰.



(Scheme 5)

Bates and coworkers²¹ have observed that kinetically controlled protonation of a pentadienyl anion such as (12) leads to the non-conjugated diene (5) rather than its conjugated isomer (13). This is summarised in Fig. 1 and is typical of the behaviour observed in the kinetic protonation of pentadienyl anions of the type (14)^{21,22}.

In order to stop the reduction at the dihydro stage, it is necessary to prevent the initially formed non-conjugated diene (5) from reconvertng into the anion (11). This reversion would allow the diene (5) to be isomerised to its conjugated isomer which is susceptible to further reduction. Therefore, the second function of the alcohol is to prevent the accumulation of amide ion (NH₂⁻) which is a stronger base than alkoxide ion (R-O⁻), and facilitates this equilibration.

Correlation with experimental findings is generally high²³, despite the neglect of steric and solvation effects. Thus product formation is generally subject to kinetic rather than thermodynamic control. For example reduction of benzene produces 1,4-dihydrobenzenes rather than

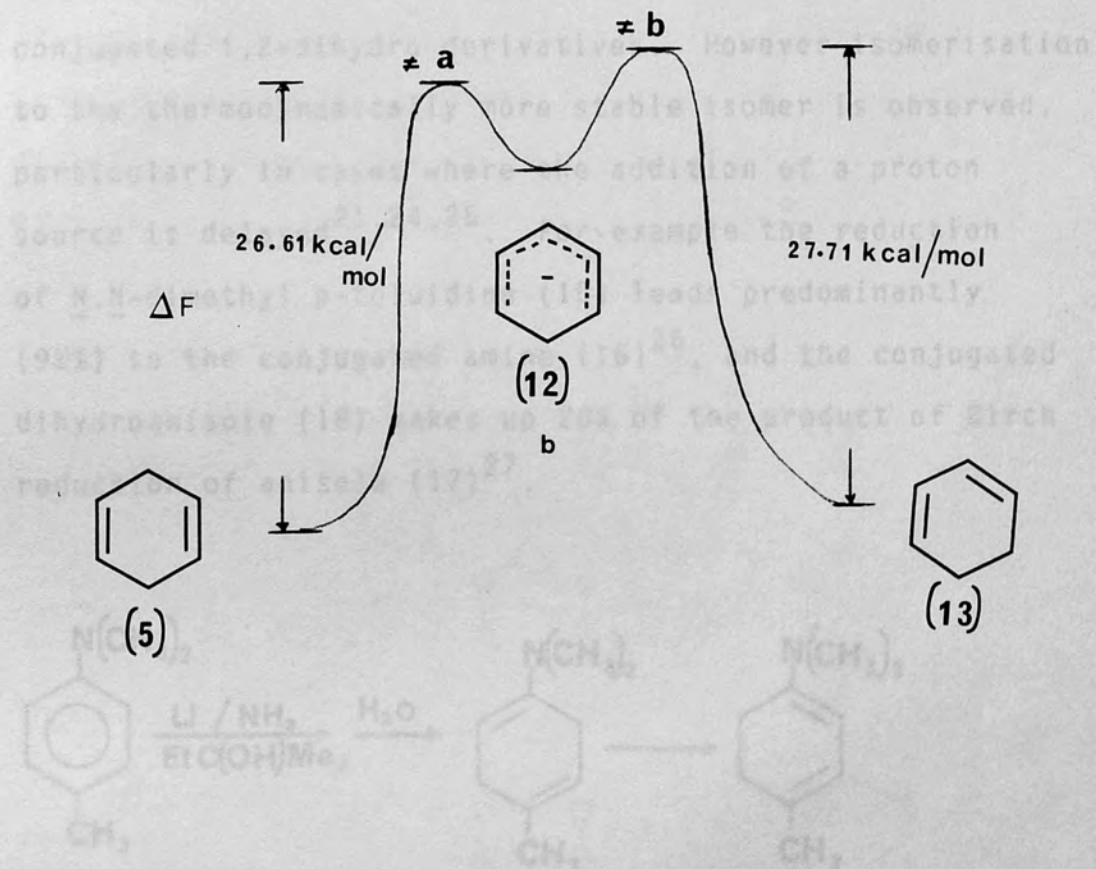
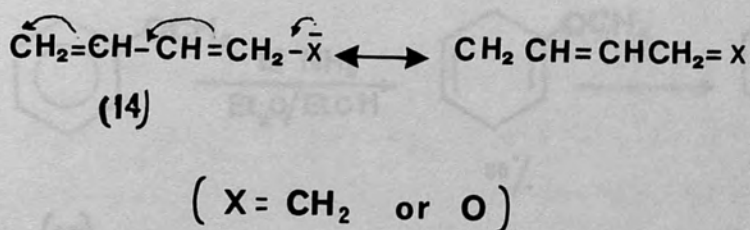
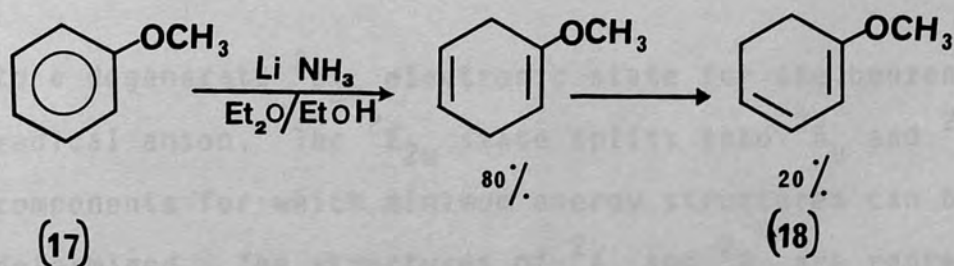
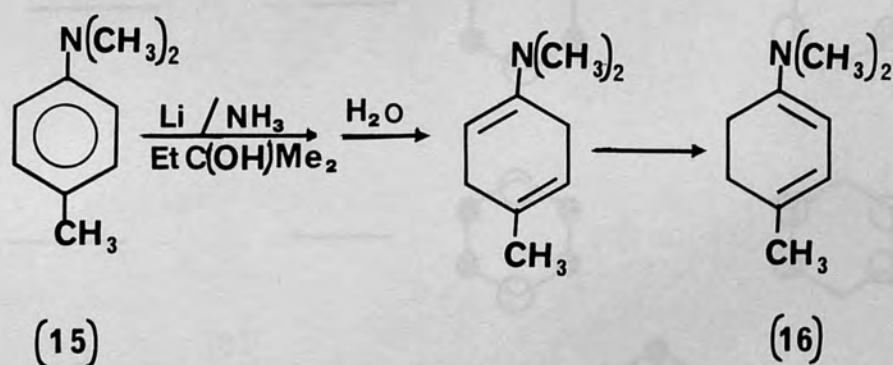


Fig. 1: Energy diagram for the interconversion of (5) and (13) at 95.0°C.



Correlation with experimental findings is generally high²³, despite the neglect of steric and solvation effects. Thus product formation is generally subject to kinetic rather than thermodynamic control. For example reduction of benzene produces 1,4-dihydrobenzenes rather than conjugated 1,2-dihydro derivatives. However isomerisation to the thermodynamically more stable isomer is observed, particularly in cases where the addition of a proton source is delayed^{21,24,25}. For example the reduction of *N,N*-dimethyl *p*-toluidine (15) leads predominantly (92%) to the conjugated amine (16)²⁶, and the conjugated dihydroanisole (18) makes up 20% of the product of Birch reduction of anisole (17)²⁷.

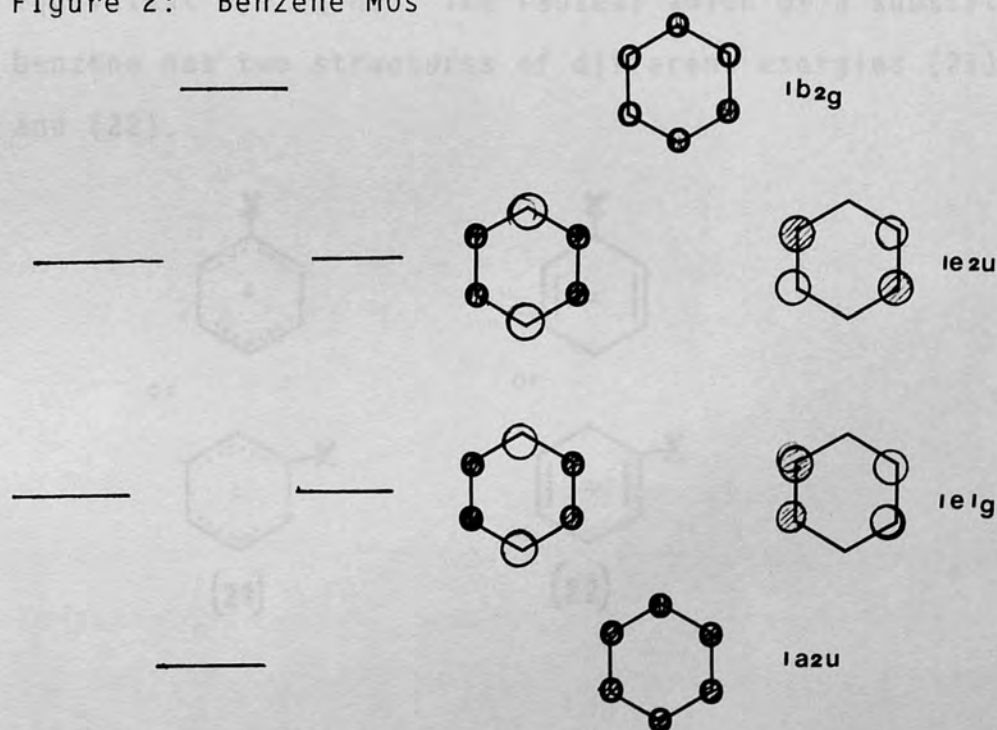


2.2.2. Theoretical Studies

(a) Introduction

Birch and coworkers²⁸ have studied the Birch reduction by a series of ab initio molecular orbital (MO) calculations on this reaction pathway. Examination of the π MO of benzene shows that the added electron can be accommodated in either one of the pair of degenerate e_{2u} orbitals (Figure 2). If D_{6h} symmetry is maintained, this leads

Figure 2: Benzene MOs



to a degenerate ${}^2E_{2u}$ electronic state for the benzene radical anion. The ${}^2E_{2u}$ state splits into 2A_u and ${}^2B_{1u}$ components for which minimum energy structures can be determined. The structures of 2A_u and 2B_u are represented as (19) and (20) respectively which have very similar

energies. Calculations suggest that the 2B_u structure (20) is more stable by less than 1 kJmol^{-1} but that the structures can freely interconvert as is required experimentally since an esr study²⁹ on PhH^\cdot shows 6



(19)

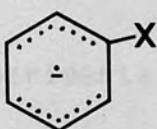


(20)

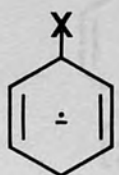
equivalent hydrogens. The radical anion of a substituted benzene has two structures of different energies (21) and (22).



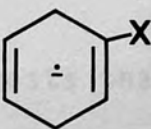
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(21)



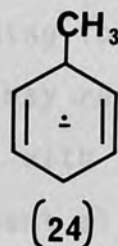
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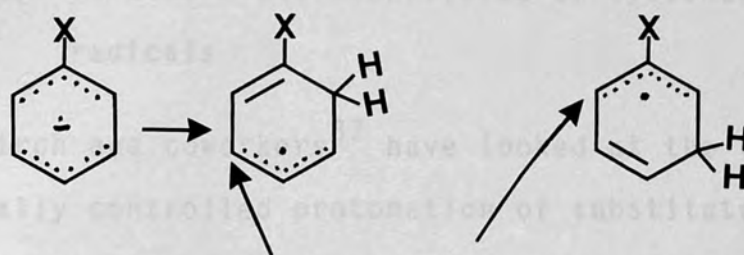
(22)

Such radical anions are important because of their involvement in the first stage of the Birch reduction. Calculations show that for π -bonding substituents ($X = \text{F}, \text{OH}, \text{NH}_2, \text{OCH}_3$) structure (21) is preferred with a 2A ground state whereas the π -accepting substituents ($X = \text{CH}_3, \text{COO}^-, \text{CF}_3, \text{CN}, \text{COOH}$, etc.) all preferred (22) with a 2B ground state and these are explained in terms

of the node properties. In the former case, i.e. π -donating substituents, the singly occupied MO (SOMO) has a node, and therefore zero electron density on the carbon adjacent to the substituent and is therefore favoured by π -electron donor substituents. Whereas in the latter case there is a large orbital coefficient at the ipso carbon atom, thus allowing charge transfer into the π -acceptor substituent. These preferred structures agree with the experimental e.s.r. data³⁰⁻³². However the preferred state of the toluene radical anion in solution is (23)³³, whereas Birch's calculations²⁸ suggest (24).



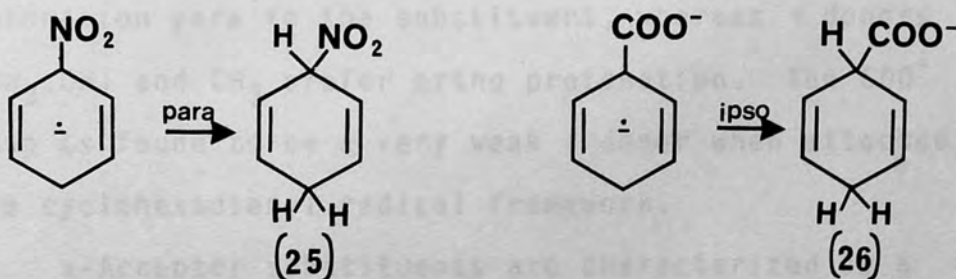
Experimental data suggests that the first steps in the Birch reduction involve reversible electron addition followed by irreversible protonation³⁴⁻³⁶. Therefore Birch and coworkers use the molecular electrostatic potential (MEP) to determine the path for protonation. But (MEP) does not take any account of cations (Li^+/Na^+) or solvent effects because the calculations have been carried out for gas phase ions. They also assume that no dianion is formed. For electron donor-substituents it is predicted that protonation should occur ortho or meta to the substituent [Scheme 6].



Second attack by H^+ should then be here after another electron addition.

(Scheme 6)

For electron-withdrawing substituents (π -acceptors) various results are obtained. For $C_6H_5NO_2^{\cdot-}$, protonation at para position affording (25) is favoured whereas for $C_6H_5COO^{2-\cdot}$ ipso protonation leading to (26) is predicted. The presence of the counterions may reverse the situation because they could be associated with the negative region around the oxygen atom. Attachment at the ipso position



is also preferred by CN^- and $COOH$ substituents. Some substituents however cannot survive the reduction conditions, NO_2 and CN^- for example being themselves reduced.

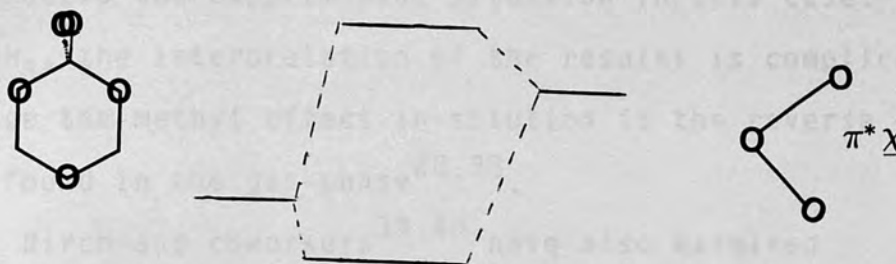
(b) Structure and Stabilities of cyclohexadienyl radicals

Birch and coworkers³⁷ have looked at the thermodynamically controlled protonation of substituted benzene radical anion. Although under the usual reaction conditions, this first protonation is thought to be irreversible and kinetically controlled. The ab-initio calculations were carried out on the parent cyclohexadiene and a number of substituted cyclohexadiene radicals, with substituents $X = \text{H}, \text{CH}_3, \text{CN}, \text{NO}_2, \text{COOH}$ etc. as examples of π acceptors and $\text{F}, \text{OCH}_3, \text{OH} \dots$ etc. as π -donor. The calculations were for isolated gas phase reactions and therefore no solvent effects were investigated.

The calculations predict the thermodynamically preferred protonation sites of substituted benzene radical anion. It is found that the π acceptors (CN, NO_2) favour protonation para to the substituent, whereas π donors (OCH_3, OH) and CH_3 prefer ortho protonation. The COO^- group is found to be a very weak π donor when attached to a cyclohexadienyl radical framework.

π -Acceptor substituents are characterized by a low lying antibonding LUMO (π^*X) which can interact with SOMO giving one electron stabilization. This interaction is strongest at the carbon-atom with the largest SOMO hence at C-3 and almost zero at C-2 (Figure 3).

fig. 3



Substituents which are π donors (F, OH, NH_2) are characterised by a high-energy doubly occupied p orbital which can interact with the SOMO to give a stabilizing three-electron interaction.

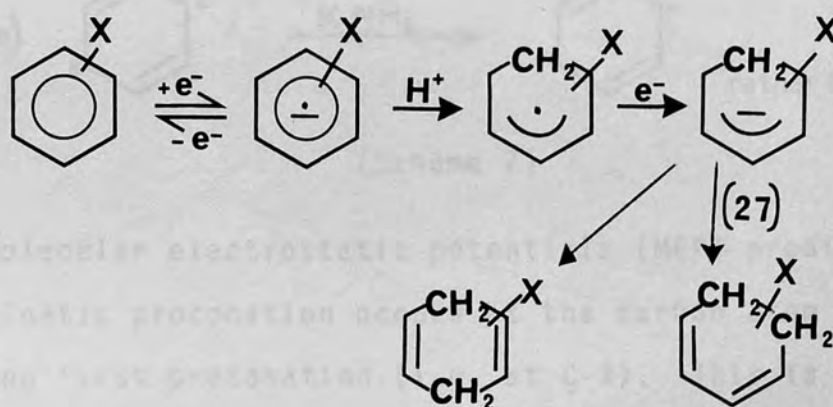
So these calculations suggest that π acceptors reduce ipso and/or para protonation under irreversible conditions and ortho/para protonations under equilibrium conditions. While π donors favour irreversible ortho or meta protonation and thermodynamically controlled ortho and para protonation.

(c) Relative reduction rates

Assuming that protonation takes place at the para position for π acceptors and at ortho position for π donors, the calculations suggest the greatest rate of reaction for π acceptors (CN , NO_2) and intermediate rate enhancement for π donors (OCH_3). These results are in qualitative agreement with experimentally observed rates³⁵. The experimental reduction of benzoic acid is very rapid, but of metal-ion association, and solvent effects, it

is not clear as to whether the substituent COOH or COO⁻ best models the experimental situation in this case. For CH₃, the interpretation of the results is complicated because the methyl effect in solution is the reverse of that found in the gas-phase^{28,38}.

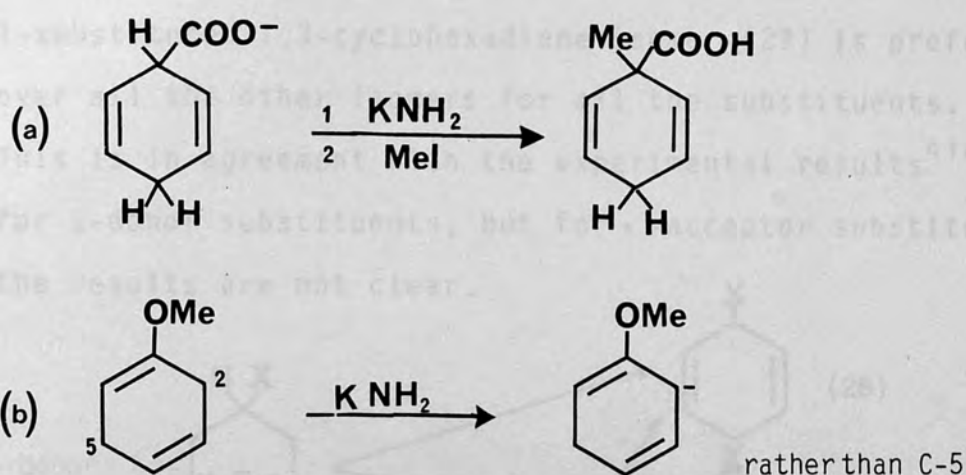
Birch and coworkers^{39,40} have also examined substituted cyclohexadienyl anions (27). These are stable in solution as salts involving the alkali metal cation⁴¹, and under certain conditions in liquid ammonia can be stored for several days⁴².



The second protonation step in the Birch reduction, i.e. protonation of (27) is known experimentally to occur predominantly para to the first protonation under irreversible conditions which is consistent with the theoretical result.

The equilibrium structure of the cyclohexadienyl anion has a planar ring. The relative isomer energies and stabilization energies of 1-,2-, and 3-substituted cyclohexadienyl anions are ordered in accordance with

the coefficients of the HOMO of cyclohexadienyl anion. Therefore π -donors favour the 6-substituted isomer and π acceptors favour the 3-substituted isomer [Scheme 7].

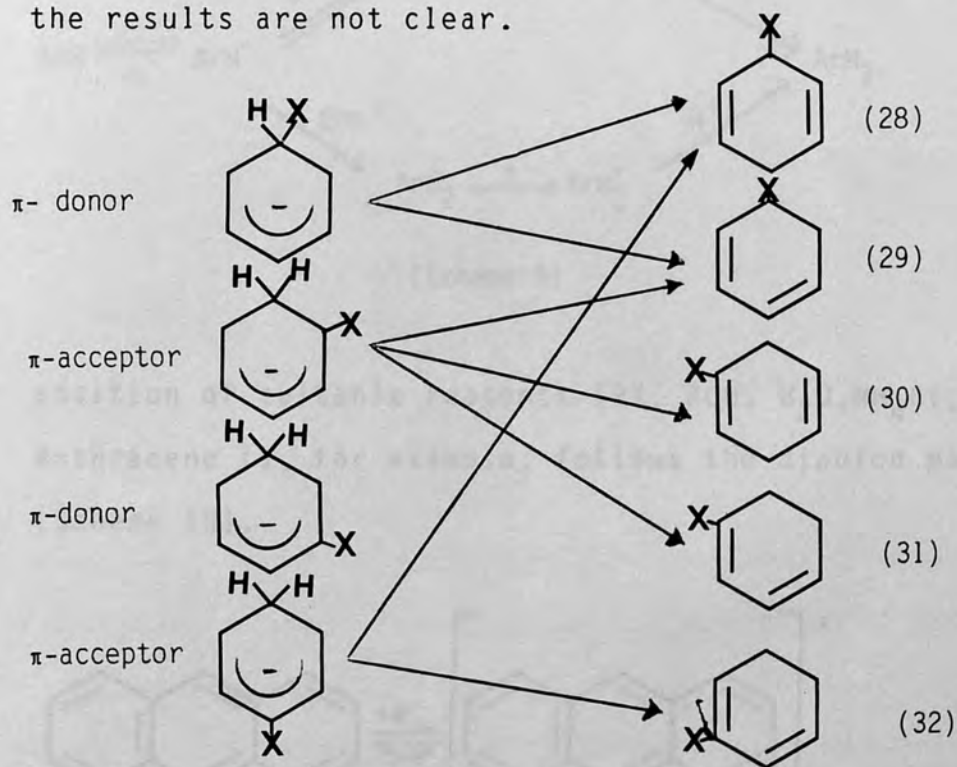


(Scheme 7)

Molecular electrostatic potentials (MEP) predict that kinetic protonation occurs at the carbon atom para to the first protonation (i.e. at C-2). This is so regardless of substituents or of substituent position. Protonation can also occur at the ortho carbons but at a slower rate.

The final step in the Birch reduction is the protonation of the cyclohexadienyl anion to form a 1,3-cyclohexadienes or 1,4-cyclohexadienes. Ab initio calculations⁴⁰ indicate 1,3-cyclohexadienes to be non-planar with C_2 symmetry while 1,4-cyclohexadienes are planar with D_{2h} symmetry. This is in agreement with the experimental results. The energies of 1,4-cyclohexadienes

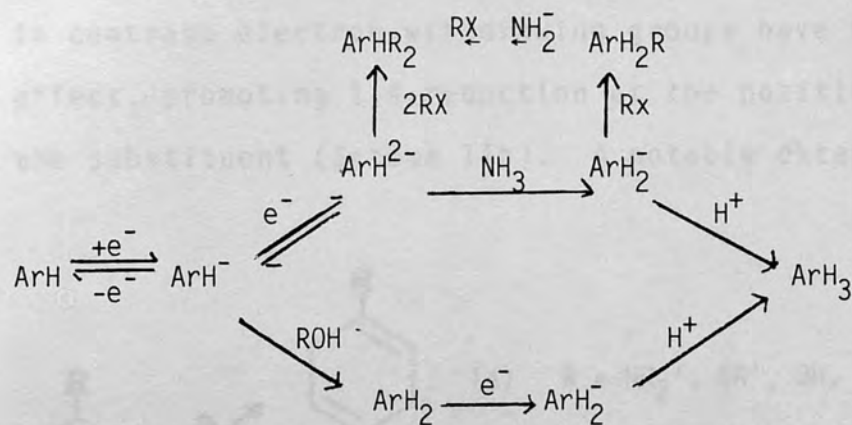
and 1,3-cyclohexadienes are found to be quite similar. Scheme 8 summarizes the five possible 1,3-cyclohexadienes and 1,4-cyclohexadienes isomers and the path by which they can be formed by initial protonation of the four substituted cyclohexadienyl anions isomers. The 1-substituted 1,3-cyclohexadiene isomer (29) is preferred over all the other isomers for all the substituents. This is in agreement with the experimental results^{41a} for π -donor substituents, but for π -acceptor substituents the results are not clear.



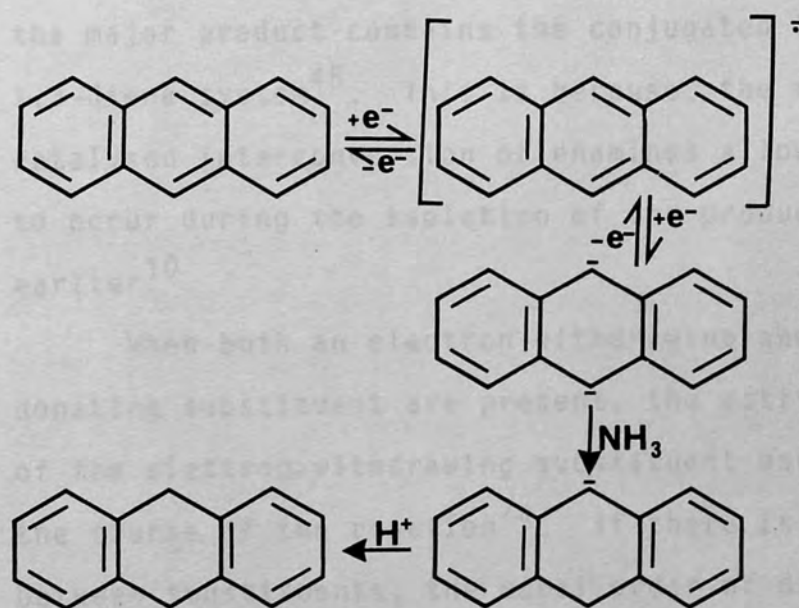
(Scheme 8)

In the above reaction mechanism of the Birch reduction, the initial electron addition produces a radical anion which requires the presence of proton source to shift the equilibrium to the right (see Scheme 4, p. 16). More recent work by Rabideau and coworkers⁴³ indicate that in some polynuclear compounds and some highly

activated benzenes, a second electron addition may take place to produce a dianion which is highly basic⁴⁴ and protonation by ammonia then takes place to produce a monoanion which is in most cases resistant to protonation by ammonia⁹ (Scheme 9) and can be alkylated or protonated by the

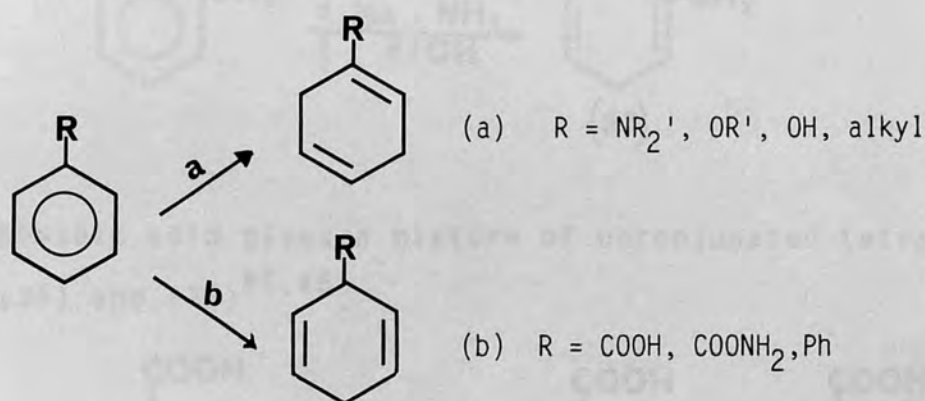


addition of suitable reagents (RX, ROH, H₂O, NH₄Cl, etc.). Anthracene is, for example, follows the dianion pathway (Scheme 10).



2.3. Experimentally Observed Substituent Effects

Experimentally observed substituent effects are in accord with the mechanism shown in (Scheme 11). Electron-releasing groups deactivate the ring and direct the protonation to unsubstituted 2,5-positions (Scheme 11a). In contrast electron-withdrawing groups have the opposite effect, promoting 1,4-reduction at the position bearing the substituent (Scheme 11b). A notable exception is

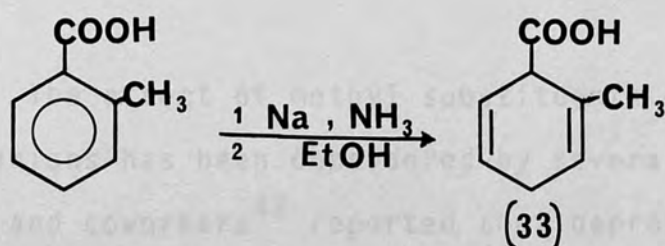


(Scheme 11)

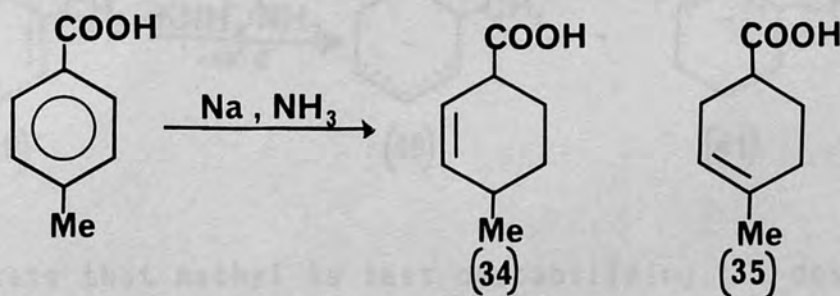
the reduction of N,N-dimethylaniline derivative where the major product contains the conjugated 1-(dimethylamino)-1,3-diene system⁴⁵. This is because, the ready acid-catalysed interconversion of enamines allows equilibrations to occur during the isolation of the product if not earlier¹⁰.

When both an electron-withdrawing and an electron-donating substituent are present, the activating effect of the electron-withdrawing substituent usually controls the course of the reaction^{7a}. If there is a competition between substituents, the usual order of directive priority

is: C=O > amino > alkyl. However many substituents, e.g. CH₂OH, COOMe* etc. do not survive the reduction conditions unaffected. The monoalkylbenzoic acids give an interesting illustration of some of the problems which one can see. Reduction of 2-methylbenzoic acid with sodium in liquid ammonia gives as expected, 2-methyl-1,4-dihydrobenzoic acid (33). Under the same conditions, however, 4-methyl-

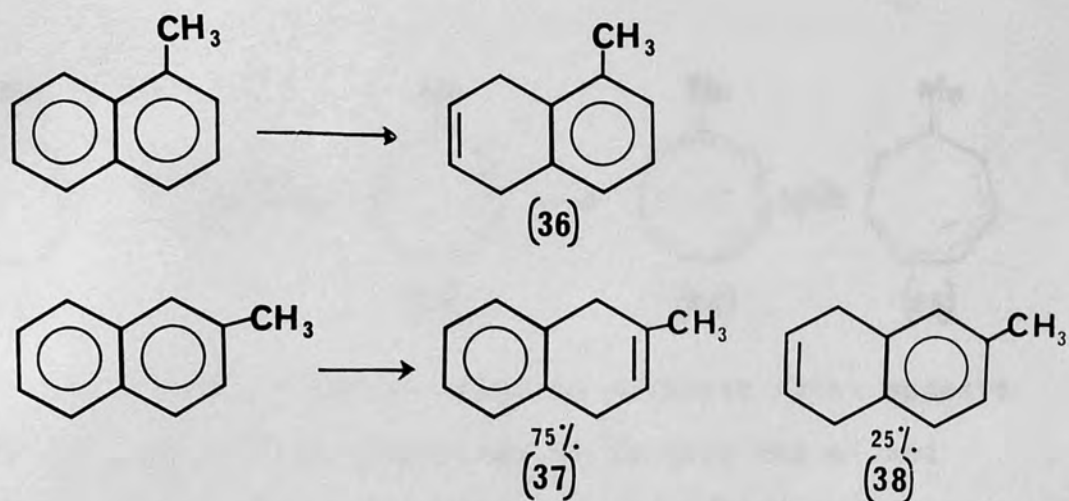


benzoic acid gives a mixture of unconjugated tetrahydroacids (34) and (35)^{45,46}.

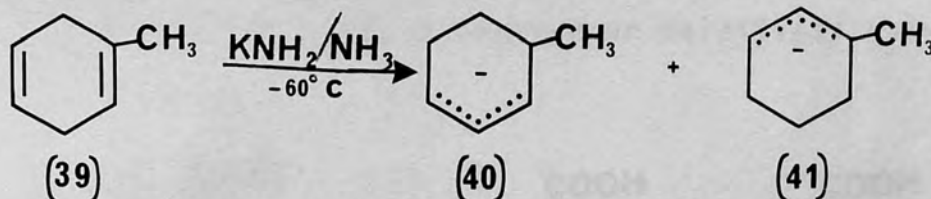


In the naphthalene skeleton, changing the position of the methyl substituent can markedly alter the course of the reaction. For example, whilst reduction of 1-methylnaphthalene only occurs in the non-methylated ring (36), 2-methylnaphthalene gives (37) as the major product³⁵ together with a significant amount of another isomer (38)⁴³.

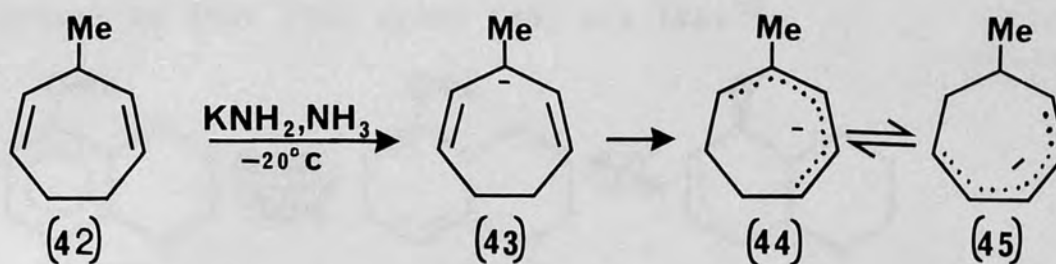
*See Chapter 3.



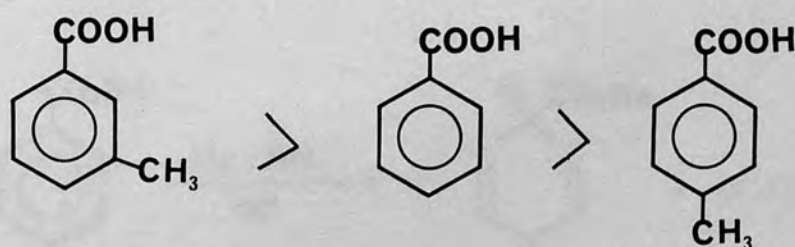
The effect of methyl substituents on delocalised carbanions has been considered by several investigators. Olah and coworkers⁴² reported that deprotonation of (39) leads to (40) and (41). The predominance of (41) may



indicate that methyl is less destabilizing (if destabilizing at all) when on a position which does not bear much negative charge in the delocalized anion. Staley⁴⁷ did in fact conclude that a methyl group is destabilizing on a charge-bearing carbon in anion (43) due to its rapid conversion to (44). The effect of a methyl group on a non-charge-bearing carbon during reduction in a biphenyl system will be discussed later (see page 37).



The effect of methyl group on relative rates appears relatively small from comparison of benzoic and *m*- and *p*-toluic acids. However, *m*-toluic acid was slightly more reactive than benzoic acid when reacted with a limited amount of sodium in ammonia in a competition experiment, while the *para* isomer was less reactive. Since the carboxylate group is known to be quite activating and produces 1,4-reduction, however, this does appear to confirm the differences in the effect of methyl with regard to its presence on a charge bearing or relatively non-charge-bearing carbon.

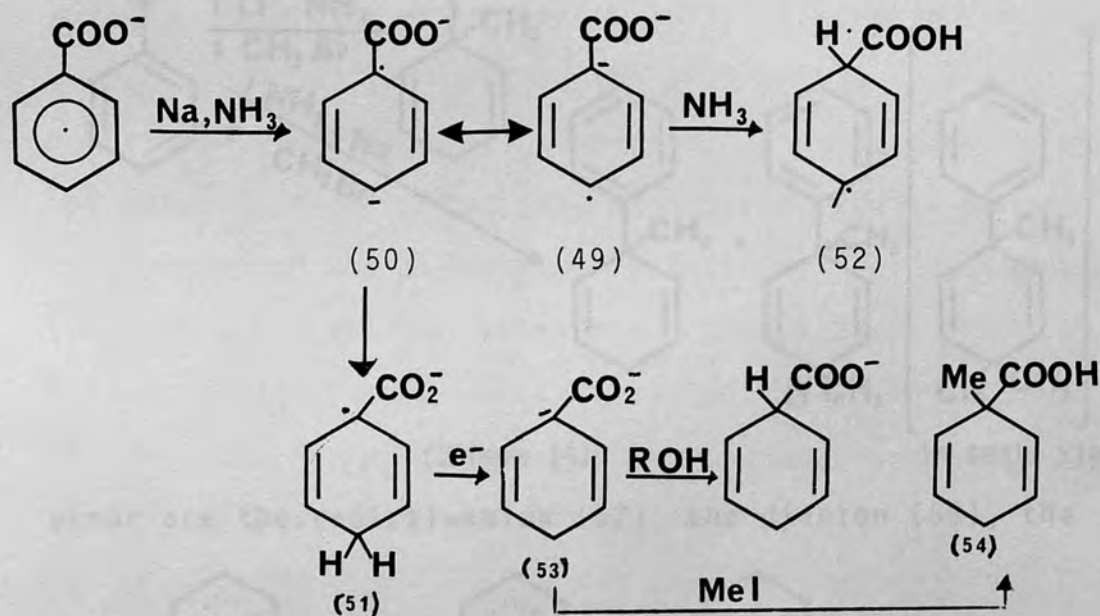


Therefore, we can conclude that the methyl substituent may not be simply categorized with regard to its effect on reactivity and regioselectivity in reduction reactions.

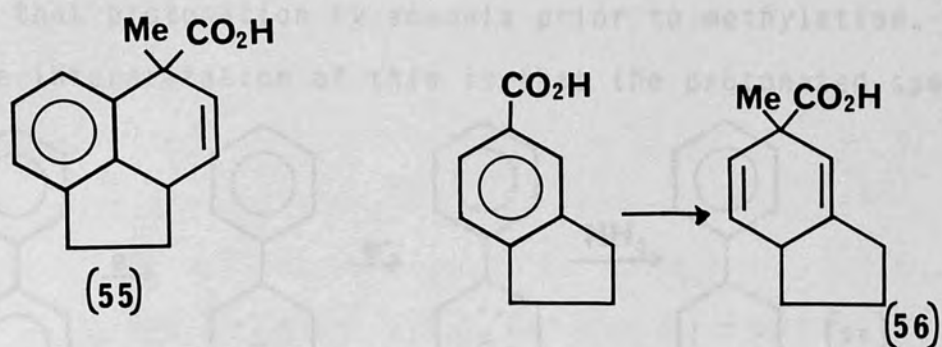
The reduction of anisole and aniline is a particularly useful synthetic route to cyclohexanones through hydrolysis of the dihydro intermediates. The directive effect of

2.4. REDUCTIVE ALKYLATION

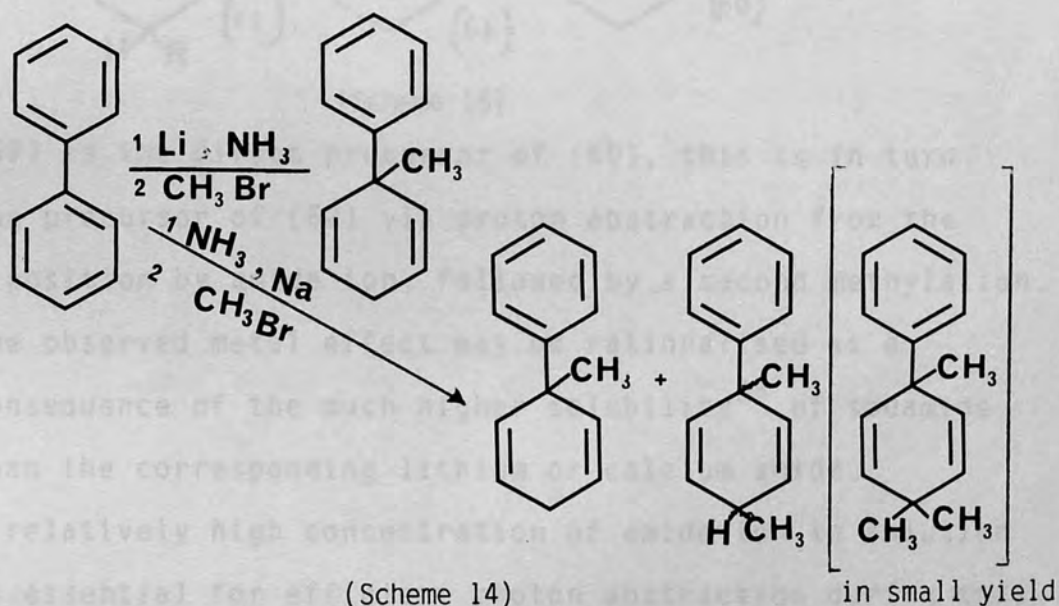
In this reaction, the cyclohexadienyl anion intermediate is trapped by an alkyl halide rather than being protonated. The site of the first protonation in a Birch reduction is often uncertain, e.g. in the case of benzoic acid (Scheme 13), protonation of 49 \longleftrightarrow 50 can lead either to (51) or to (52). Of course the final product (54) in either case is the same. However, there is evidence in favour of a route via (51) since the intermediate (53) can be methylated if a methyl halide is added to the reaction mixture.



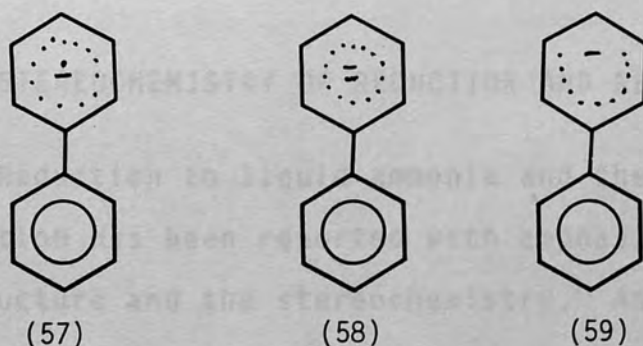
(Scheme 13)
Grossel and Hayward⁵¹ have also observed that the reductive methylation of 5-acenaphthoic acid gives a 2a,5-dihydro-5-methyl derivative (55) and that 6-indanoic acid gives 3a,6-hydro-6-methylindanoic acid (56), indicating that the final anionic site is situated by the carbonyl group.



The technique of reductive methylation is also helpful in the biphenyl system^{52,53}, which appears to give different intermediates with different alkali metals (Scheme 14). The species where the methylation could



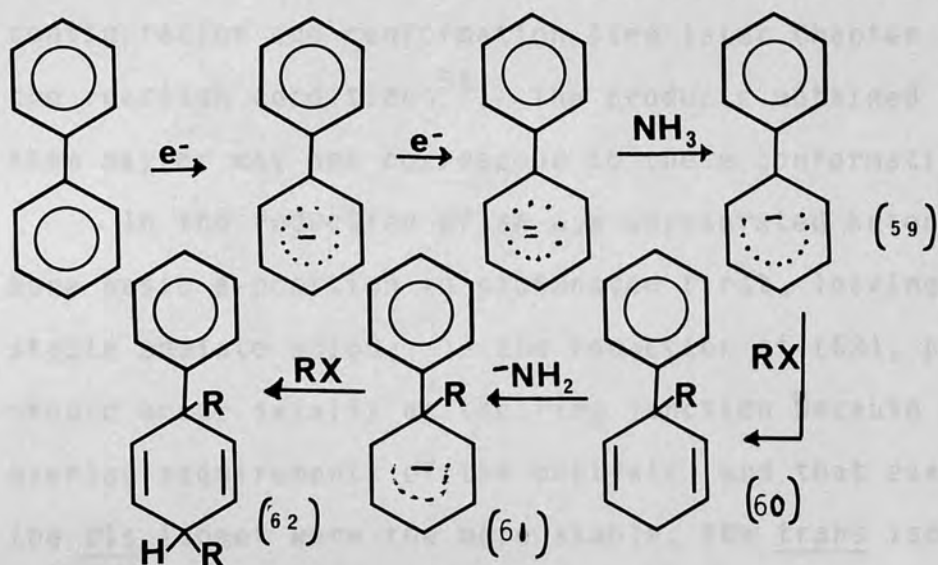
occur are the radical-anion (57), the dianion (58), the



protonated monoanion (59), and their respective ion pairs.

The proposed mechanism (Scheme 15) for the above methylation

is that protonation by ammonia prior to methylation. The interpretation of this is that the protonated species



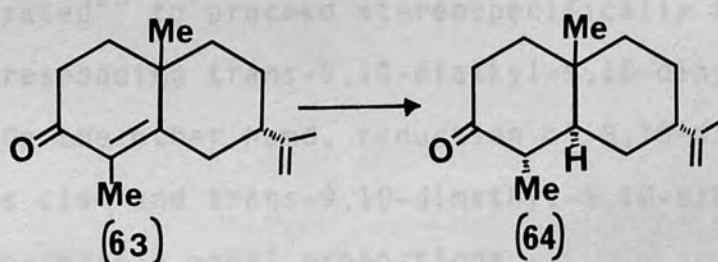
(59) is the direct precursor of (60), this is in turn the precursor of (62) via proton abstraction from the 4 position by amide ion, followed by a second methylation. The observed metal effect may be rationalised as a consequence of the much higher solubility⁵⁴ of sodamide than the corresponding lithium or calcium amide. A relatively high concentration of amide ion in solution is essential for efficient proton abstraction during this short time prior to second methylation.

2.5. STEREOCHEMISTRY OF REDUCTION AND REDUCTIVE ALKYLATION

Reduction in liquid ammonia and the related reductive alkylation has been reported with emphasis on the effects of structure and the stereochemistry. Any stereochemistry associated with reduction or reductive alkylation must result from the protonation or alkylation of the final monoanion⁵⁵. The intermediates should possess the ability

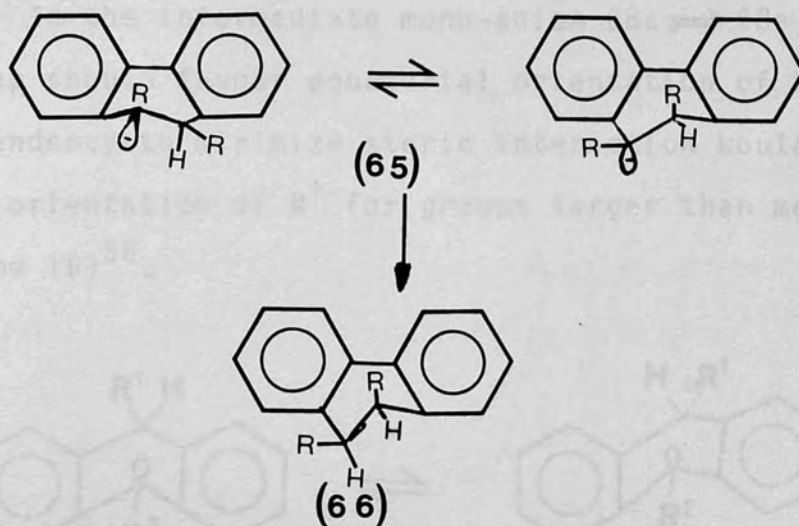
to invert at the charged centres, and should therefore be capable of adopting the sterically most stable configuration and conformation (see later Chapter 6) under the reaction conditions⁵⁶. The products obtained from them may or may not correspond to these conformations.

In the reduction of an α,β -unsaturated ketone, the more basic β -position is protonated first, leaving a more stable enolate anion. In the reduction of (63), protonation should occur axially at the ring junction because of the overlap requirements of the orbitals, and that even if the cis isomer were the more stable, the trans isomer should result. It was demonstrated that this is true of (63) which gives (64) although in this example despite

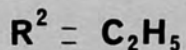
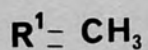
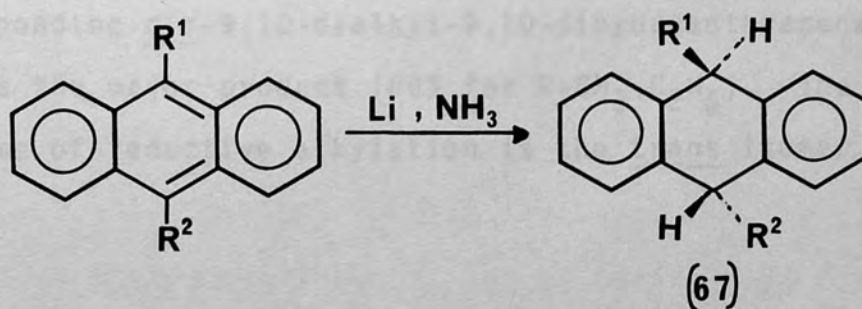


the fact that the latter is the less stable isomer formed from the less stable carbanion⁵⁷.

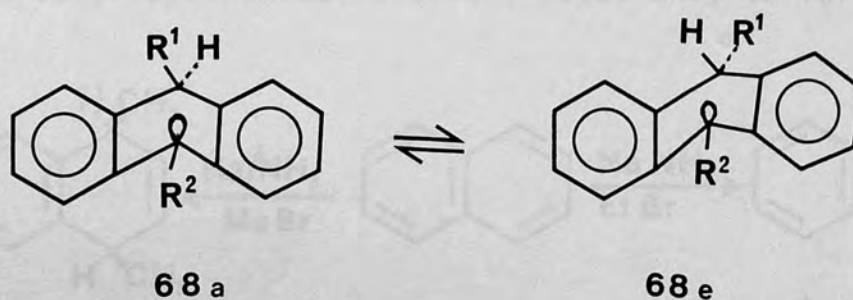
9,10-Dialkylphenanthrenes undergo stereospecific cis reduction at the 9,10-positions^{15b}, so that (65) gives (67) as sole product.



Reduction of 9,10-diethyl-, 9,10-dibutyl-, and 9-ethyl-10-methyl anthracene with lithium/liquid ammonia has been demonstrated²³ to proceed stereospecifically to provide the corresponding trans-9,10-dialkyl-9,10-dihydroanthracene (67). On the other hand, reduction of 9,10-dimethylantracene provides cis- and trans-9,10-dimethyl-9,10-dihydroanthracene in approximately equal proportions.

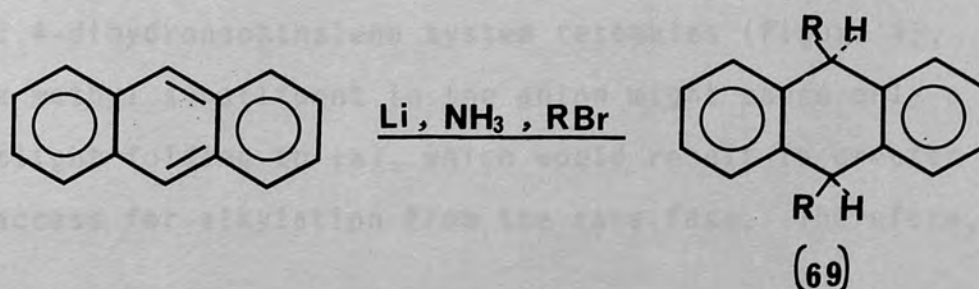


These observations are explicable by a mechanism in which product structure is determined during the final protonation step. In the intermediate mono-anion $68a \rightleftharpoons 68e$, orbital overlap should favour equatorial orientation of R^2 , and the tendency to minimize steric interaction would require axial orientation of R^1 for groups larger than methyl (Scheme 16)⁵⁸.

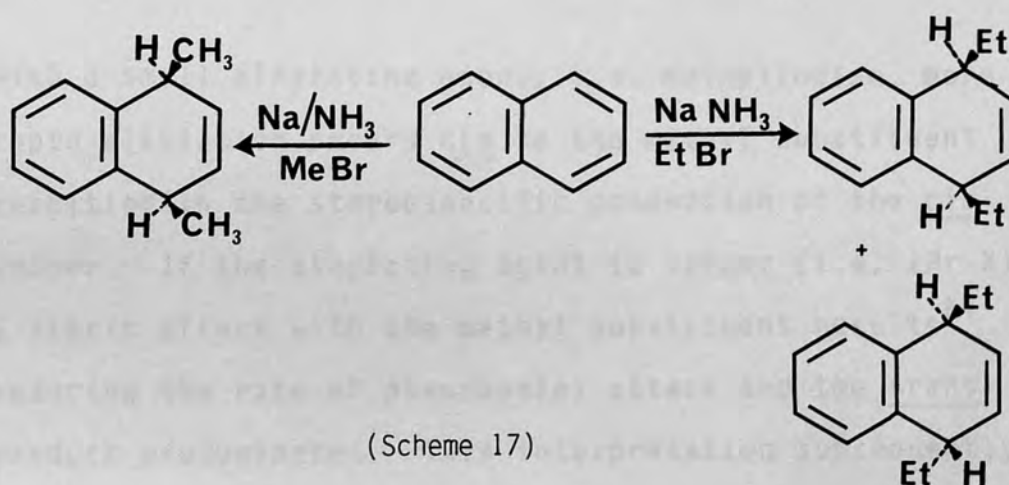


(Scheme 16)

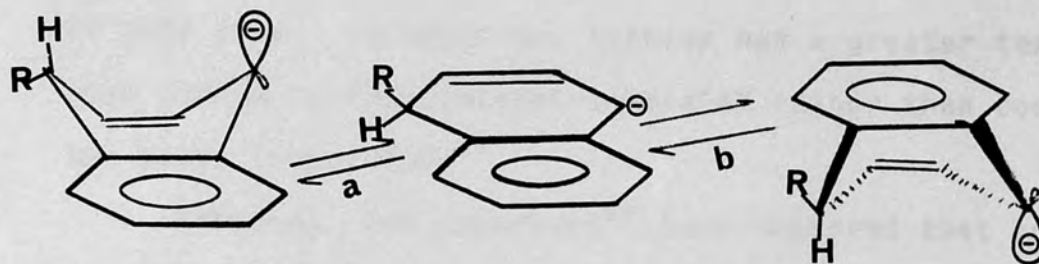
Analogous reductive alkylation of anthracene with lithium in liquid ammonia and alkylbromides also proceeds with high stereoselectivity⁵⁹, but provides the corresponding cis-9,10-dialkyl-9,10-dihydroanthracene (69) as the major product (80% for $R=CH_3, C_2H_5$). The minor products of reductive alkylation is the trans isomer.



In order to investigate further the stereochemistry of the reductive alkylation, Rabideau and coworkers⁵⁵ carried out the reductive ethylation of naphthalene and discovered that ethylation is less selective than methylation and results in a mixture of both cis and trans isomers (Scheme 17). In contrast, anthracene provides mainly the cis isomer. Reductive alkylation with isopropylbromide, however, leads only to formation



of the trans isomer, and this is similar to the behaviour of anthracene but is more selective. These results can be explained from the stereochemical requirement of the cyclohexadiene ring system⁶⁰. Derivatives of 1,4-cyclohexadienes have been shown to be planar and it was suggested that for 1,4-cyclohexadiene itself (Scheme 8) the planar form is an energy minimum. If the potential well for 1,4-dihydronaphthalene system resembles (Figure 4), a methyl substituent in the anion might cause only a slight folding to (a), which would result in greater access for alkylation from the same face. Therefore,



(Figure 4)

with a small alkylating agent, i.e. methyl iodide, more rapid alkylation occurs cis to the methyl substituent resulting in the stereospecific production of the cis isomer. If the alkylating agent is larger (i.e. $iPr-X$) a steric effect with the methyl substituent results⁶¹ reducing the rate of pseudoaxial attack and the trans product predominates. This interpretation subsequently has been modified (see p. 108).

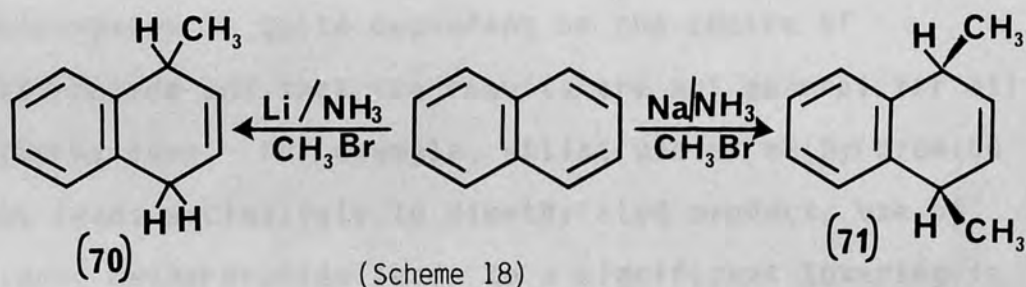
2.6. EFFECT OF CHANGING CONDITIONS OF BIRCH REDUCTIONS

2.6.1. Effect of Metals and Metals Concentration

The metals used in the Birch reduction are lithium, sodium and, to a lesser extent, potassium, magnesium and calcium. Use of lithium is preferred over that of sodium for three reasons:- (a) it has higher molar solubility and a higher reduction potential in ammonia²⁷ (-2.99 V at $-50^{\circ}C$) than sodium (-2.59 V at $-50^{\circ}C$); (b) the reactions

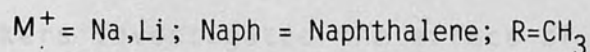
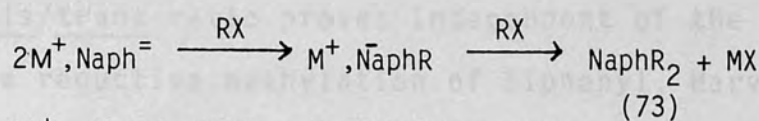
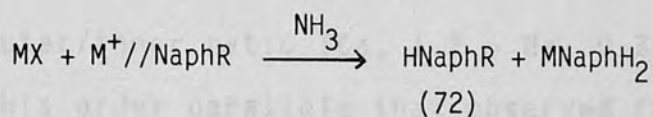
with lithium are cleaner than with heavier metals; and (c) the rate of decomposition of lithium salts to amides is very slow. In addition, lithium has a greater tendency than sodium to form solvent-separated rather than contact ion pairs in solution⁶³.

Rabideau and coworkers⁶³ have observed that in the reductive alkylation of naphthalene there is a substantial difference in behaviour between lithium and sodium metals (Scheme 19). Treatment of a solution of naphthalene in liquid ammonia/THF at -78° with lithium



followed by excess methyl bromide afforded 1-methyl-1,4-dihydronaphthalene (70) in good yield (95%). In contrast, similar reaction with sodium metal gave the dimethyl product, cis-1,4-dimethyl-1,4-dihydronaphthalene (71).

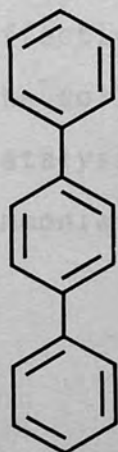
In this reaction, the monolithio anion ($\text{Li}^+ \|\ \bar{\text{N}}\text{CH}_3$) formed on initial alkylation of the dilithio dianion ($2\text{Li}^+, \text{N}^{2-}$) is solvent separated and susceptible to protonation by ammonia to form (72) (Scheme 19), whereas the corresponding monosodio anion exists as an intimate ion pair ($\text{Na}^+, \bar{\text{N}}\text{CH}_3$) able to persist in the medium sufficiently long enough to undergo a second alkylation, leading to formation of (73).



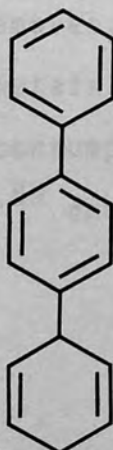
(Scheme 19)

More recently Rabideau has reported that this observation is quite dependent on the choice of alkyl halide and that the results are not general for all alkyl halides. For example, whilst use of methyl bromide gas leads exclusively to dimethylated product, use of liquid methyl bromide leads to a significant lowering in the extent of dimethylation.

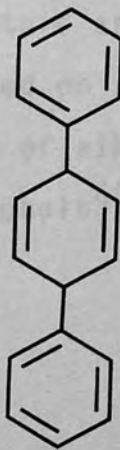
In reduction of p-terphenyl⁵³ (74), the nature of the metal employed influences the ratio of outer to inner ring reduction. Thus, use of lithium permits preferential inner ring reduction, whilst employment of calcium promotes outer ring attack. The nature of metal also influences



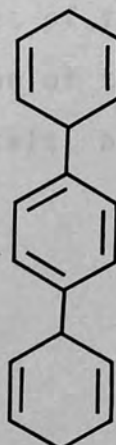
(74)



(75)



(76)

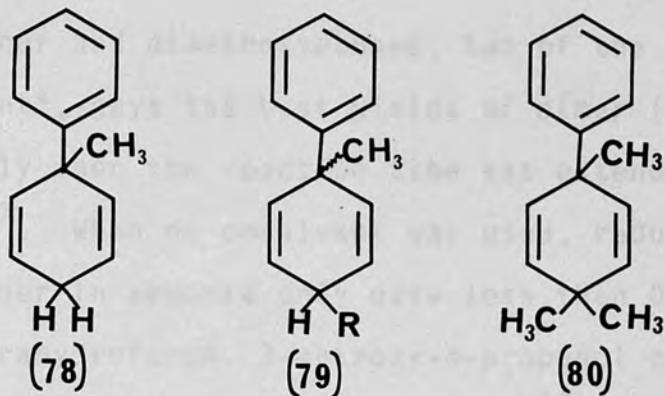


(77)

the outer/inner ratio (Ca, 1.2 > Na, 0.39 > Li, 0.24) and this order parallels that observed for reduction. The cis/trans ratio proves independent of the metal. In the reductive methylation of biphenyl, Harvey⁵² and coworkers investigated the effect of metal. Both lithium and calcium in ammonia and methylbromide gave (78) as the sole product. Analogous reaction with sodium gave as major products (78) and cis- and trans-1,4-dimethyl-1,4-dihydrobiphenyl (79) with minor amounts of 1,4,4-trimethyl-1,4-dihydrobiphenyl (80).

The concentration of the metal plays a significant role in the course of a reduction. Metal-ammonia solutions range from those containing essentially free solvated electrons at very high dilution (0.003 M) through salt-like intermediate states (0.003 to 1.0 M) to very highly concentrated salt solutions which have metallic properties^{15a}. A high concentration of metals favours anionic over radical intermediates.

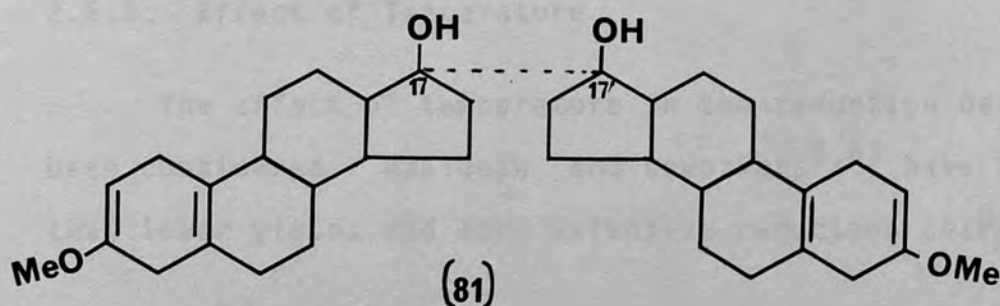
Impurities such as iron salts, water and peroxides may alter the course of reaction. Distillation of ammonia into the reaction vessel through a column of barium oxide, or from another vessel containing solvated electrons effectively removes moisture and traces of iron salts. The colloidal metals formed on reduction of the latter catalyse the consumption of alkali metals, both by ammonia^{15a,64,65} and alcohols⁶⁶.



2.6.2. Cosolvents

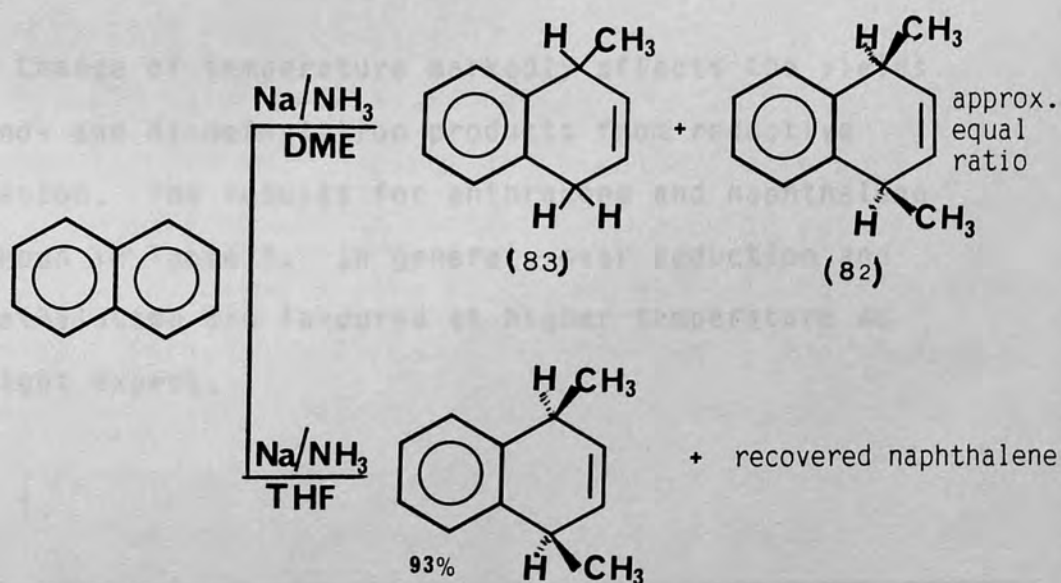
Many papers which study the Birch reduction stress the importance of the cosolvent, e.g., ether, tetrahydrofuran, dimethoxyethane or dioxane, in improving the poor solubility of the organic material in ammonia at -33°C . These agents have generally been considered inert and of no consequence to the course of the reaction.

The effect of cosolvent can be clearly seen in a reduction involving a carbonyl carbon. In this case, the nature of cosolvent can have a decisive influence on the composition of the reaction products⁶⁷. When the reduction of estronemethyl ether was conducted in a medium containing 10 parts of ammonia and 3 parts of ether there was isolated, in addition to the expected 3-methoxy $\Delta^{2,5}$ -estradiene-17 β -ol, a 30% yield of a more insoluble substance, the pinacol (81).



Ether and dimethoxyethane, two of the most popular "cosolvent", gave the best yields of dimer (7-10%) especially when the reaction time was extended to 1.5 hours^{9,67}. When no cosolvent was used, reduction of estrone methylether in ammonia only gave less than 0.5% of dimer. With tetrahydrofuran, 3-methoxy-n-propanol or dioxane dimerization amounted to less than 1%⁶⁷ (see discussion, p. 75).

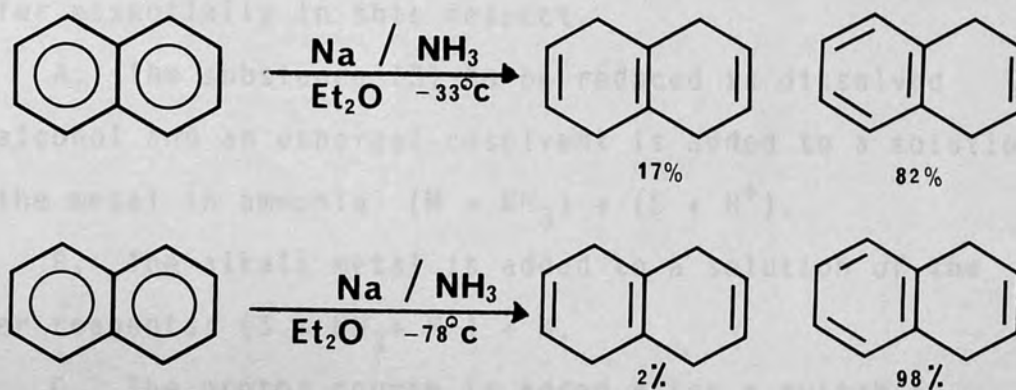
The solvating agents also affect the reductive methylation process⁶⁹. For example reductive methylation of naphthalene with sodium in ammonia-dimethoxyethane at -78° affords (82) and (83), whereas in THF (83) is the major product with no (82) being produced.



2.6.3. Effect of Temperature

The effect of temperature in the reduction has also been considered. Rabideau and coworkers^{9,63} have found that lower yields and more extensive reduction characterized

reactions performed at higher temperatures (-33°C). The reduction of naphthalene at -33°C gave more tetrahydro product than dihydro product, whereas at lower temperatures (-78°C) the dihydro product was favoured (Scheme 20).



Change of temperature markedly affects the yields of mono- and di-methylation products from reductive alkylation. The results for anthracene and naphthalene are shown in Table 1. In general, over reduction and polymethylation are favoured at higher temperature as one might expect.

TABLE 1.

Org. Compd.	R-X	Temp ^o C	alkali	quench process	ArH ₂ R ₁ %	ArHR ₂ %
Anthracene	MeBr	-78	Na	normal	15	80
	MeBr	-33	Na	normal	6	85
Naphthalene	MeI	-78	Na	normal	33	51
	MeI	-33	Na	normal	18	55

2.6.4. Quenching Procedure

The order of addition of reagents often dramatically influences product distribution⁵⁸, and is the most important single variable to consider in selecting a reaction procedure. The three techniques commonly employed differ essentially in this respect.

A. The substance (S) to be reduced is dissolved in alcohol and an ethereal cosolvent is added to a solution of the metal in ammonia: $(M + NH_3) + (S + H^+)$.

B. The alkali metal is added to a solution of the other reagents: $(S + NH_3 + H^+) + M$.

C. The proton source is added after a suitable interval to a solution of the other reagents: $(S + NH_3 + M) + (H^+)$.

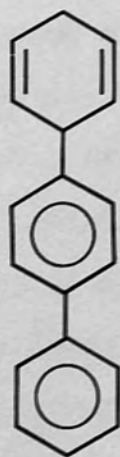
The choice of method is dependent upon the structure and properties of the compound to be reduced, and variations of these procedures are often advantageous for particular reactions. For example, the Wilds and Nelson²⁷ modification of Method A involves addition of a solution of the substance to one of the alkali metals in ammonia followed by addition of alcohol over a short period: $(M + NH_3) + (S) + (H^+)$. This technique has extensive application in the steroid field. Rabideau⁹ and Harvey⁵⁸ have found that the most successful method with polycyclic hydrocarbons is Method C in which the metal is added over a short period to a solution of the hydrocarbon in ammonia; after a suitable interval, reaction is rapidly quenched with water, alcohol or ammonium chloride (normal quench

technique). Simple reduction can be accomplished by rapid quenching with a strong proton source. In some cases, the monoanions produced by protonation of dianions by ammonia (see mechanism, p. 16) may be basic enough so as to be also protonated by the ammonia. This can lead to two results: (1) the compound produced (ArH_3) is resistant to further reduction, or (2) the compound may be reduced by other pathways. Therefore in case (2) the removal of the surplus metal becomes important.

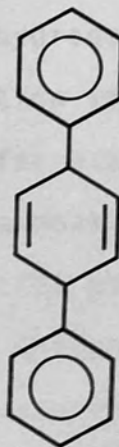
The reduction of anthracene to 9,10-dihydroanthracene involves the use of ferric chloride to reduce the surplus metal and decrease the over-reduction of anthracene and stopping the reaction at the dihydro stage. Since reductive methylation of anthracene proceeds via monoanion intermediates, the presence of ferric chloride is essential to consume the surplus metal. Use of ferric chloride involves long reaction time so an inverse quenching technique where the ammonia solution of the hydrocarbon can be poured into a large volume of saturated ammonium chloride or the alkylating agent is better and under these conditions the reduction or reductive alkylation proceeds smoothly and gives good yields.

The yield of dialkylation product from reduction of biphenyl after 0.5 minutes reduces on changing the metal from sodium to lithium from 95% to 10%⁵². An increased time interval between metal addition and methylation also resulted in a lower di- to monomethyl ratio; this time effect is quite interesting since it

would appear to indicate relatively slow protonation of a disodioanthracene dianion, this difference is consistent with the lower basicity expected of a dibenzylic vs. a diallylic anion. On the other hand, reaction with lithium proved time independent, so that protonation of the dilithio dianion must be relatively rapid. Rabideau reported⁵³ that an increase in the time interval before quenching leads to a higher proportion of (75) at the expense of (76).



(75)



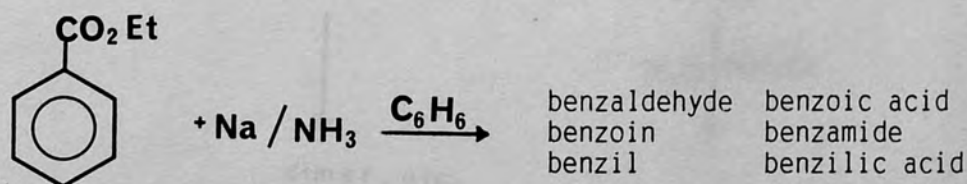
(76)

CHAPTER 3

REDUCTION OF CARBOXYLIC ACID DERIVATIVES

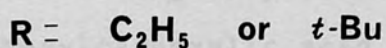
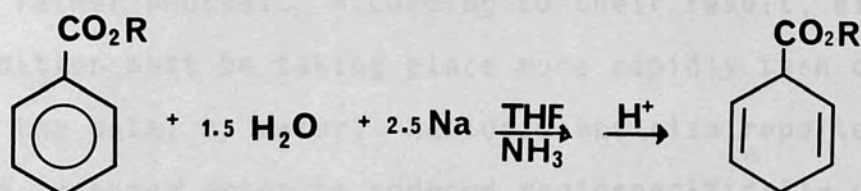
3.1. INTRODUCTION

The reduction of carboxylic acid derivatives, i.e., esters and amides, gives different products. The reduction of esters by sodium metal and alcohol in liquid ammonia to form an alcohol is known as the Bouveault-Blanc procedure⁴⁸. Esters can also be reduced with lithium aluminium hydride or catalytic hydrogenation with a copper chromic catalyst. If the reduction is carried out in the absence of a proton donor, for example, with sodium in xylene or sodium and liquid ammonia, dimerization takes place and this synthetically useful process is known as the acyloin condensation^{68,69}. Kharasch⁷⁰ investigated the reduction of ethyl benzoate with sodium/ammonia/benzene and found a wide variety of products depending on the reaction conditions (Scheme 21).



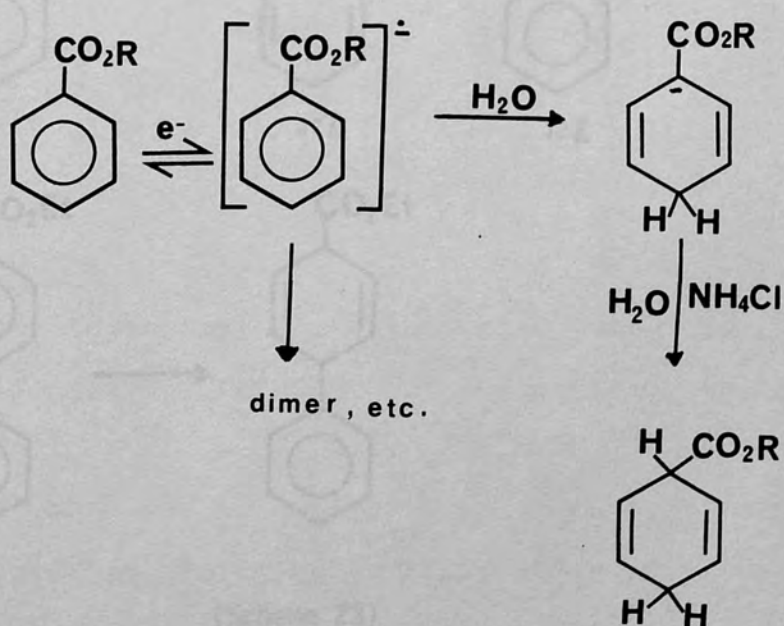
(Scheme 21)

In contrast, Rabideau⁷¹ has reduced alkyl benzoates to the corresponding 1,4-dihydro compounds in good yield by the addition of water prior to that of the metal (Scheme 22).

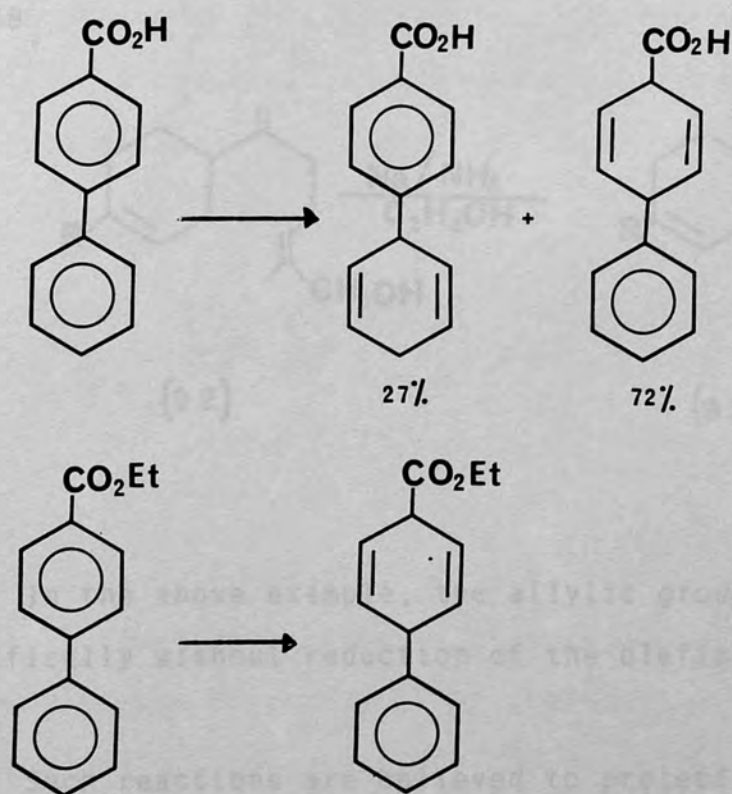


(Scheme 22)

Kharasch's conditions afford benzoin as the major product because no proton source is present prior to addition of the metal, but in Rabideau's procedure, water is acting to protonate the radical anion before dimerization takes place.



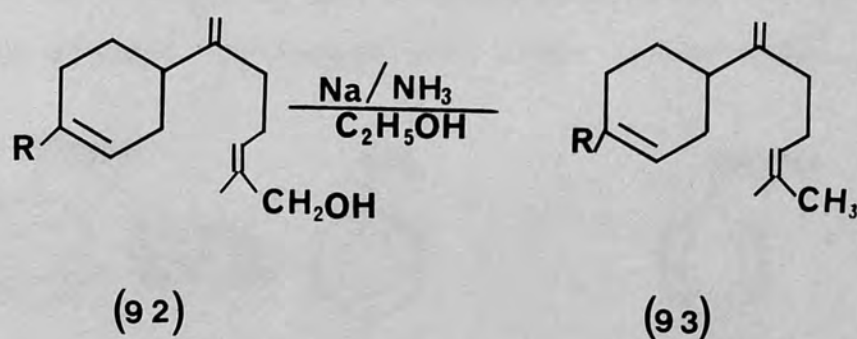
Rabideau and coworkers observed that reducing ester in the absence of water does not give the desired product. They found that although alcohols have been used to protonate radical anions and shift the initial equilibrium, the efficient use of water in this capacity appears to be rather unusual. According to their result, electron addition must be taking place more rapidly than destruction of the metal by water. Rabideau has also reported that the biphenyl ester is reduced regiospecifically under these conditions affording only a single product, although reduction of biphenylcarboxylic acid leads to two products⁷² (Scheme 23).



(Scheme 23)

3.2. REDUCTIVE FISSION

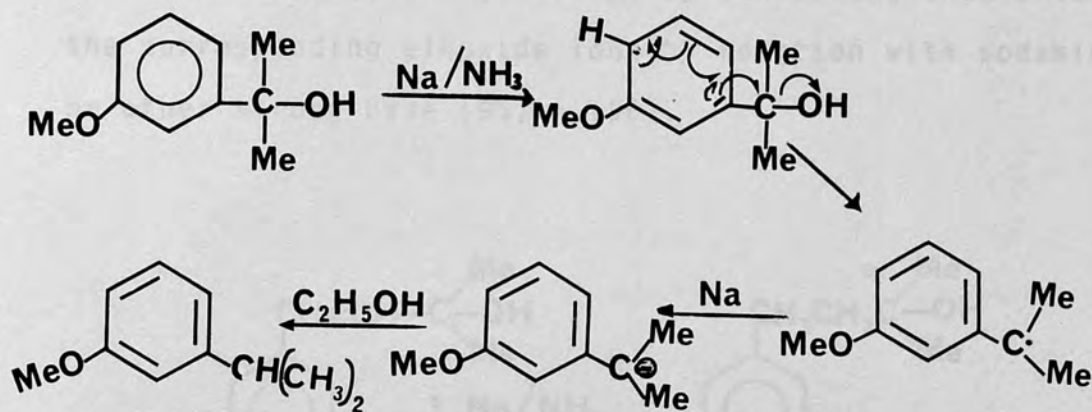
Metal-amine reducing agents and other dissolving metal systems can bring about a variety of reductive fission reactions which are useful in synthesis. Thus allyl or benzylalcohol are readily cleaved by metal-amine systems⁴⁸. These types of fission reactions have been widely used in structural studies and also for the reductive removal of unsaturated groups used as a protecting agent for amino, imino, hydroxyl and thiol groups. They have been of great assistance in the elucidation of the structures of a number of naturally occurring allyl and benzyl alcohols. Thus, the structure of the alcohol lanceol (92) was neatly confirmed by reduction with sodium and alcohol in liquid ammonia to the known sesquiterpene hydrocarbon bisabolene (93)⁴⁸.



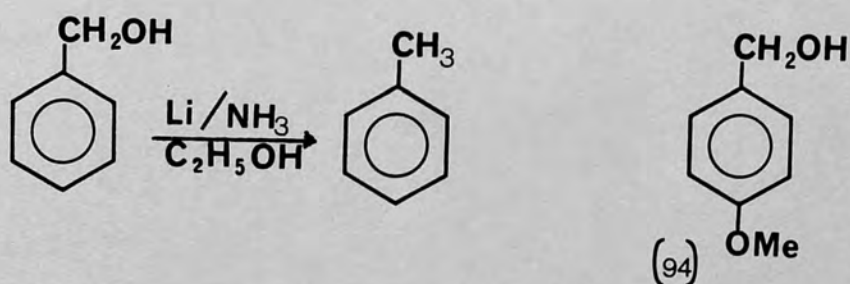
In the above example, the allylic group is cleaved specifically without reduction of the olefinic double bonds.

Such reactions are believed to proceed by formation of a radical anion followed by elimination of a stable

anion or some good leaving group¹⁰. Further reaction of the resulting radical with the metal and subsequent protonation give the product (Scheme 24)⁵⁶.



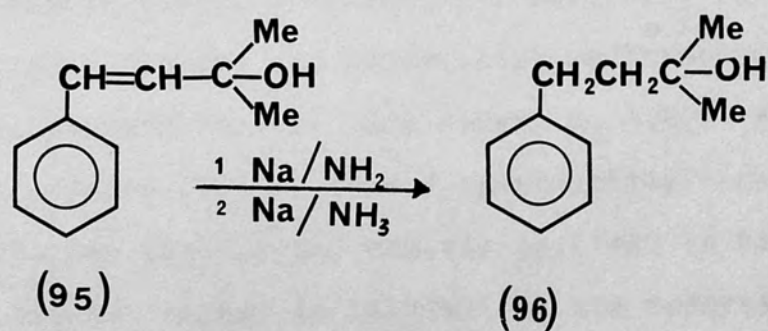
Allylic alcohols may be cleaved with varying degrees of ease depending on substitution. Benzyl alcohol is reducible to toluene⁵⁶, but p-methoxybenzylalcohol (94) undergoes minimal hydrogenolysis under appropriate



conditions and the ring is reduced instead. 4-Methylphenylmethylcarbinol can be made to undergo nuclear reduction in the presence of t-butanol by preliminary formation of the alkoxide, hydrogenolysis being inhibited by the charge on the oxygen^{73a}. For the same reason, treatment

of benzyl alcohol with lithium in ethylamine yields the tetrahydrobenzylalcohol, not the hydrocarbon⁷³.

The reductive fission of allyl or benzylalcohols can be prevented, if necessary, by converting them into the corresponding alkoxide ions by reaction with sodamide or other strong base (95) \rightarrow (96).



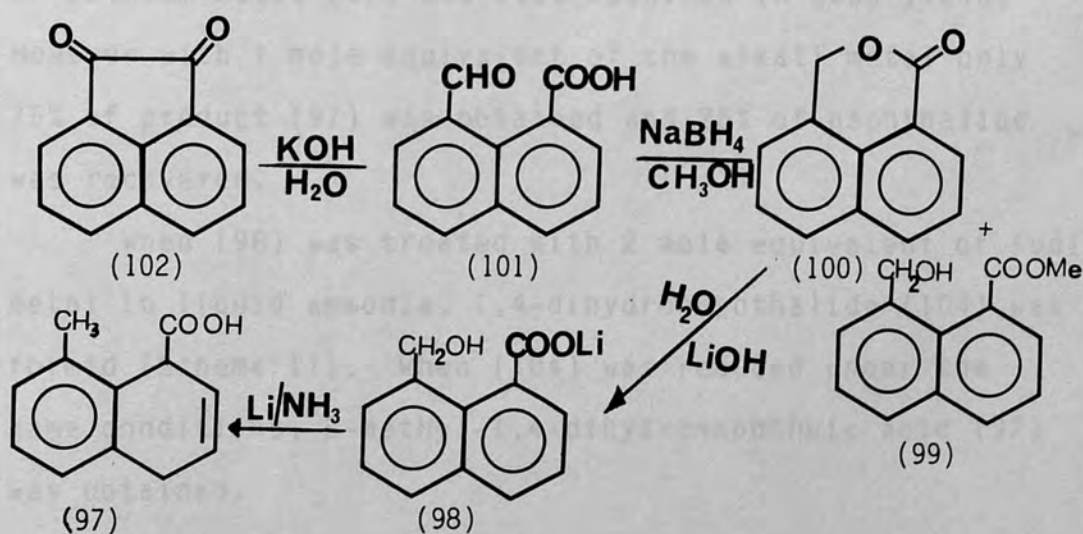
CHAPTER 4

RESULTS AND DISCUSSION

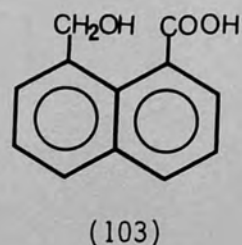
4.1. 8-METHYL-1,4-DIHYDRO-1-NAPHTHOIC ACID

4.1.1. Introduction

8-Methyl-1,4-dihydronaphthoic acid (97) is of interest as a crowded and potentially conformationally locked dihydronaphthalene (see later, p. 126). A logical route to prepare (97) is from 8-hydroxymethylnaphthoic acid (103) but this latter rapidly cyclises to naphthalide (100). Several routes to naphthalide are reported in the literature⁷³. The pathway chosen proved to be very satisfactory. The only difficulty in Scheme 25 arises from the formation of a mixture of (100) and the ester (99) this latter being isolated in the higher yield.



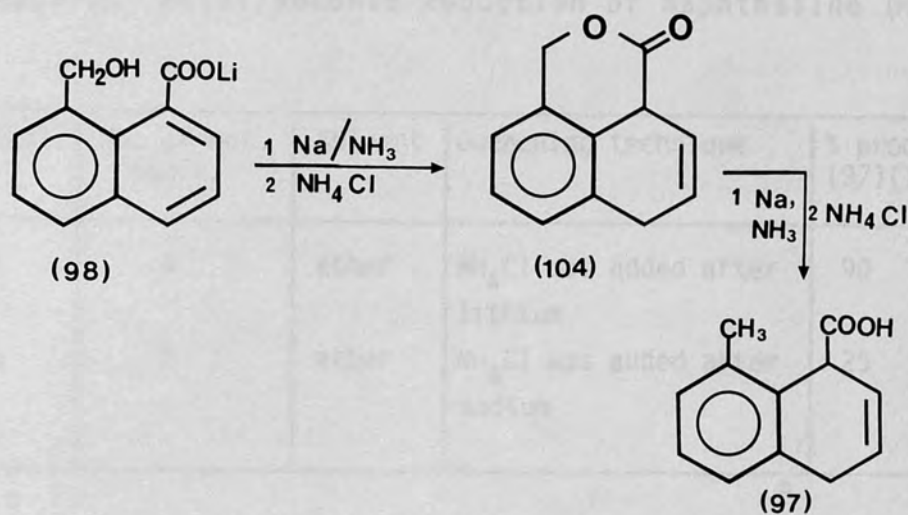
(Scheme 25)



4.1.2. Reduction of naphthalide

It was decided initially that the most efficient route to 8-methyl-1,4-dihydronaphthoic acid (97) would be from reduction of the salt lithium 8-(hydroxymethyl)-1-naphthoate (98), since reduction of naphthalide itself might result in a number of side reactions. Reduction of lithium 8-(hydroxymethyl)-1-naphthoate by lithium metal in ammonia solution afforded (97) in very good yield (90%). The effect of varying the reaction conditions on the reduction was also investigated (Table 2) in order to see whether 8-methylnaphthoic acid could be isolated as a reaction intermediate or to see whether conditions could be found which would afford 8-methylnaphthoic acid in good yield. With 4 mole equivalent of lithium, reduction of (98) gave 8-methyl-1,4-dihydro-1-naphthoic acid exclusively and no starting material was recovered. Using 2 molar equivalent of lithium metal (97) was also obtained in good yield. However with 1 mole equivalent of the alkali metal only 75% of product (97) was obtained and 25% of naphthalide was recovered.

When (98) was treated with 2 mole equivalent of sodium metal in liquid ammonia, 1,4-dihydronaphthalide (104) was formed (Scheme 11). When (104) was reduced under the same conditions, 8-methyl-1,4-dihydronaphthoic acid (97) was obtained.



(Scheme 26)

TABLE 2. Metal/Ammonia Reduction of Lithium 8-(hydroxymethyl)-1-naphthoate (98)

	Metal	No. of mol. equiv.	Solvent	Quenching technique	% prod. (97)(104)	% recovered naphthalide
1	Li	4	Et ₂ O	NH ₄ Cl added after lithium.	90 -	-
2	Li	2	Et ₂ O	"	82 -	-
3	Li	1	Et ₂ O	"	75 -	25
4	Na	2	EtOH	No NH ₄ Cl was added	92 -	-
5	Na	2	Et ₂ O	NH ₄ Cl was added after sodium.	- 94	-
6	Na	1	Et ₂ O	"	82	-
7	Na	2	EtOH	"	64	-
8	Na	2	Et ₂ O	Water was added before sodium	60 20	20
9	Na	2	Et ₂ O	NH ₄ Cl was added before sodium	90 -	-

TABLE 3. Metal/Ammonia Reduction of Naphthalide (100)

	Metal	No. of mol. equiv.	Solvent	Quenching technique	% product. (97)(104)	% recovered naphthalide
1	Li	4	ether	NH ₄ Cl was added after lithium	90 -	-
2	Na	2	ether	NH ₄ Cl was added after sodium	25 65	10

Subsequent investigation demonstrated that dihydronaphthalide (104) is not easily prepared unless the salt (98) is very dry (e.g., kept in a desiccator for not less than one week). When lithium 8-(hydroxymethyl)naphthoate is reduced by sodium metal (2 mole equivalent) in ammonia solution in the presence of added water, (97) is formed. It is interesting to note that Rabideau could only obtain ethyl-1,4-dihydrobenzoate from ethylbenzoate by reduction in the presence of water. Under anhydrous conditions dimeric products were isolated (see p. 53). Table 2 shows that 8-methyl-1,4-dihydronaphthoic acid (97) could be obtained in most cases; it was only when very dry salt and superdry solvent were employed that 1,4-dihydronaphthoic acid (104) could be obtained in very good yield. In some cases a mixture of (97) and (104) was formed which was very difficult to be separated.

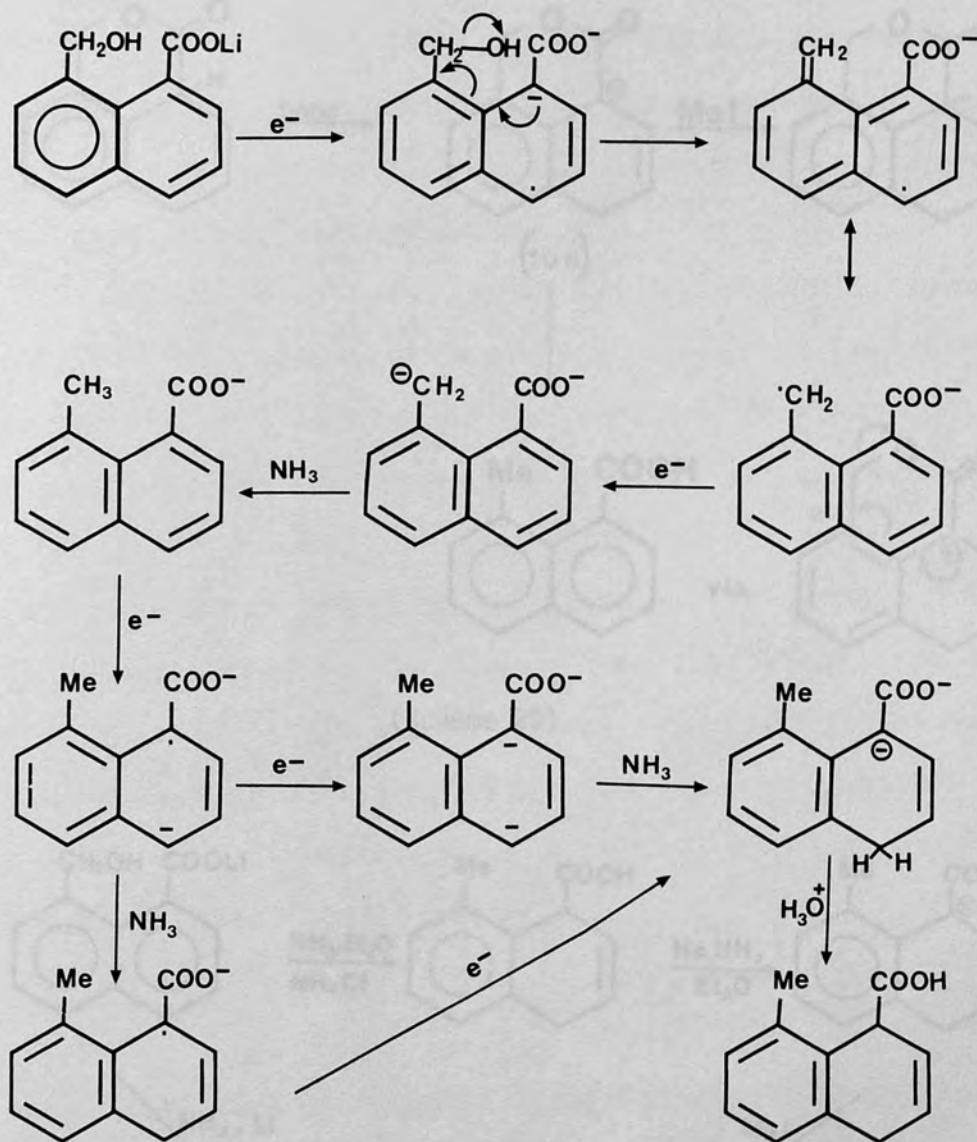
The reduction of naphthalide (100) itself was also attempted using 4 mol. equivalent of lithium metal; 8-methyl-1,4-dihydronaphthoic acid (97) was isolated in a good yield. Reduction of (100) with 2 mol. equivalent

of sodium gave a mixture of (97) and (104) which when further reduced with 2 mol. equivalent of sodium gave 8-methyl-1,4-dihydronaphthoic acid exclusively. The possible routes to 8-methyl-1,4-dihydronaphthoic acid may be envisaged in which benzylic-oxygen cleavage occurs either as the first (Scheme 27) or second step.

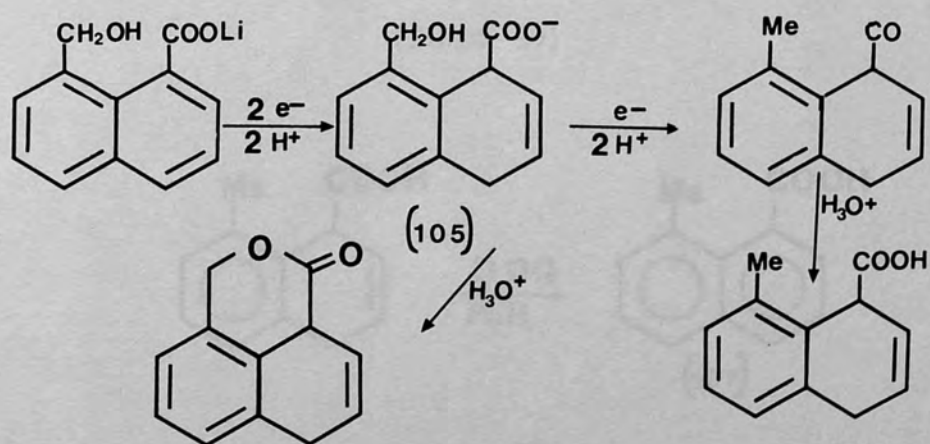
The formation of 1,4-dihydronaphthalide would seem to suggest that reduction of the carboxyl substituted ring is the first step in the reduction of naphthalide derivatives and that benzylic-oxygen cleavage occurs at a later stage. 1,4-Dihydronaphthalide is probably formed via the intermediate (105) [Scheme 28].

This observation is particularly important since it explains our inability to detect 8-methylnaphthoic acid in product mixtures from these reactions.

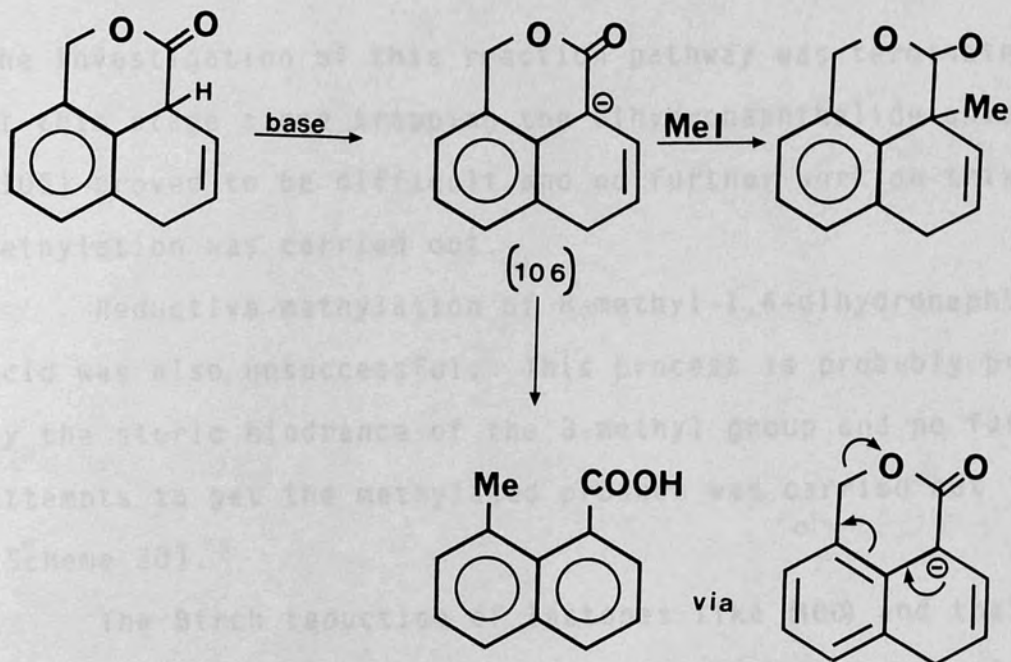
An attempt was therefore made to trap the intermediate anion (106) in order to investigate the mechanism in more detail. 1,4-Dihydronaphthalide was reacted with sodamide in liquid ammonia to generate anion (106) which might fragment to 8-methylnaphthoic acid [Scheme 29] or be captured by methyl iodide. However only naphthalide was recovered which probably formed by oxidation of (104) since 1,4-dihydronaphthalide itself is not very stable and readily aromatizes to naphthalide if not kept under nitrogen. Treatment of 1,4-dihydronaphthalide with butyllithium in tetrahydrofuran and then quenching of the reaction mixture with methyl iodide did not produce the desired alkylated product, but instead gave naphthalide together with a very small amount of 8-methylnaphthoic acid (107) (10%).



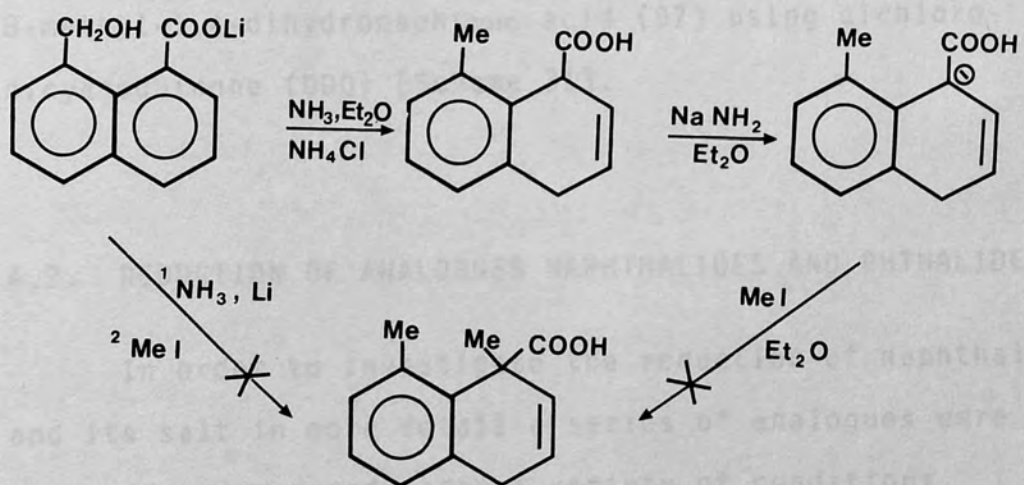
(Scheme 27)



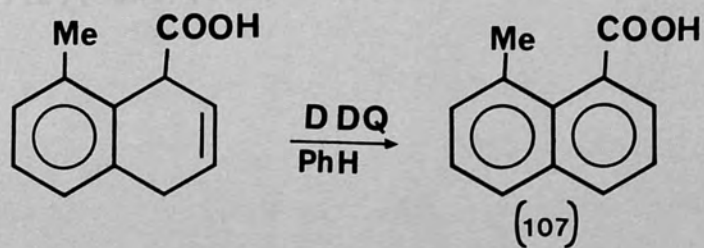
(Scheme 28)



(Scheme 29)



(Scheme 30)



(Scheme 31)

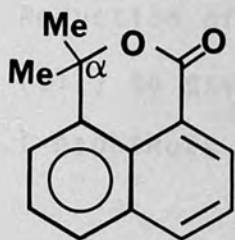
The investigation of this reaction pathway was terminated at this stage since trapping the dihydronaphthalide anion (106) proved to be difficult and no further work on this methylation was carried out.

Reductive methylation of 8-methyl-1,4-dihydronaphthoic acid was also unsuccessful. This process is probably prevented by the steric hindrance of the 8-methyl group and no further attempts to get the methylated product was carried out [Scheme 30].

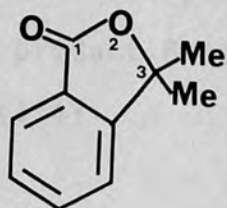
The Birch reduction of lactones like (100) and their derivatives does not provide a direct synthetic route to 8-allyl-1-naphthoic acid. 8-Methyl-1-naphthoic acid (107) can however be prepared by subsequent oxidation of 8-methyl-1,4-dihydronaphthoic acid (97) using dichlorodicyanoquinone (DDQ) [Scheme 31].

4.2. REDUCTION OF ANALOGUES NAPHTHALIDES AND PHTHALIDES

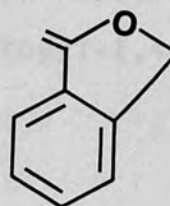
In order to investigate the reduction of naphthalide and its salt in more detail a series of analogues were prepared and reduced under a variety of conditions. These included: 3,3-dimethylnaphthalide (108), 3,3-dimethylphthalide (109), phthalide (110) and their salts (111), (112), and (113) respectively.



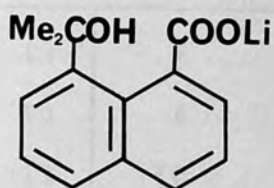
(108)



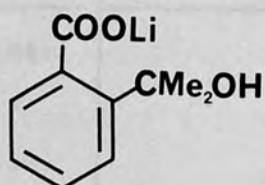
(109)



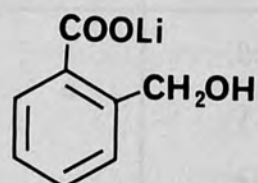
(110)



(111)



(112)



(113)

4.2.1. α,α -Dimethylnaphthalide

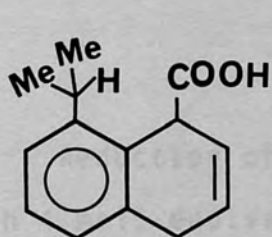
α,α -Dimethylnaphthalide was prepared as described by Bauer⁷⁵, but in poor yield and it proved difficult to separate (108) from naphthoic anhydride. Lithium 8-(2-hydroxypropyl)naphthoate (111) was then prepared from (108) by the same method as had been used for lithium 8-(2-hydroxymethyl)naphthoate (98). Metal/ammonia reduction of this material (111) was then carried out under a variety of conditions (Table 4).

8-Isopropyl-1,4-dihydro-1-naphthoic acid (114) was obtained in all cases but only in very low yield. From the table below it was obvious that the use of more lithium gave a better yield of (114) and less starting material was recovered. The only problem with this reduction was the difficulty of separating the product from the starting

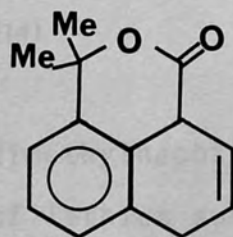
TABLE 4. Reduction of lithium 8-(2-hydroxypropyl)naphthoate (111) to give the product 8-isopropyl-1,4-dihydro-1-naphthoic acid (114)

Metal	mole equivalent	Solvent	Product (114) %	*SM %
Li	2	ether	6	85
Li	4	"	23	77
Li	10	"	55	40
Na	2	ether	20	70

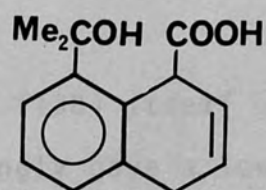
*(SM) is the starting material recovered which was a mixture of 8-(2-hydroxypropyl)-1-naphthoic acid (117) and α,α -dimethylnaphthalide (108).



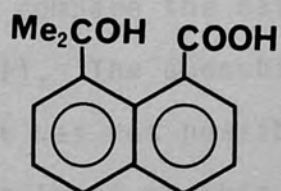
(114)



(115)

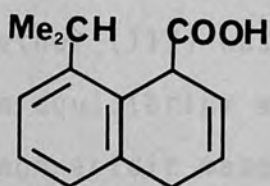


(116)



(117)

material. Purification by crystallisation proved unsatisfactory and the crystalline material sought for microanalysis was initially purified by plc eluting the mixture on silica gel. The use of 2 mol. equivalent of sodium gave better yield of 8-(isopropyl)-1,4-dihydro-1-naphthoic acid (114) than 2 mol. equivalent of lithium. This is probably due to the greater tendency of sodium to form contact ion pairs rather than solvent-separated ion pairs in solution in ammonia solution. The difficulty of reducing (111) was attributed to the crowded alkyl group in the 8-position which makes reduction more difficult than for (98).



(114)

Reduction of α,α -dimethylnaphthalide (108) itself with 4 mol. equivalent of lithium surprisingly gave a low yield (20%) of (114) similar to that obtained from reduction of (111). This reduction was carried out only once in order to compare the ease of reduction of (108) with that of (111). The quenching technique was the same in all cases. It was not possible to examine the effect of changing the solvent on this reduction even though ether is not a good solvent for α,α -dimethylnaphthalide.

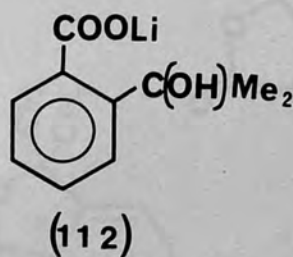
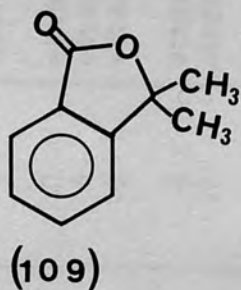
The ^1H nmr spectrum of 8-isopropyl-1,4-dihydro-1-naphthoic acid (114) has been fully analysed in order to see the effect of the 8-allyl group on the ring conformation (see later, p. 126).

In addition to 8-isopropyl-1,4-dihydro-1-naphthoic acid, some non-acidic material was recovered and in some cases this was the major product. Thin layer chromatography (tlc) showed two products, the nmr spectra of which showed no protons in the olefinic region but other peaks at δ (CDCl_3): 7.3-7.1 (ArH,m); 3.5 (broad H); 1.6 (CH_3 ,s); 1.7 (CH_3 ,s). IR shows peaks at 3400 (OH), 1710 ($\text{C}=\text{O}$) cm^{-1} . From these data it was thought that some of the dimethylnaphthalide (108) and 8-(2-hydroxypropyl)-1-naphthoic acid (117) were extracted in the non-acidic solution. It was not known whether (117) was formed after extraction or whether it was in equilibrium with (108), this latter being extracted as non-acidic material. In order to investigate this matter further, the non-acidic extracts were refluxed with 10% sodium hydroxide for one hour and the mixture was then extracted with ether to give non-acidic material which was found (nmr) to be exclusively dimethylnaphthalide (IR shows no alcoholic band). Therefore in the reduction process, not all of lithium 8-(2-hydroxypropyl)-1-naphthoate was reduced but some of the starting material was recovered either as α,α -dimethylnaphthalide or as 8-(2-hydroxypropyl)-1-naphthoic acid. For this reason excess lithium metal was used in the reduction of the salt (111) in the hope of improving the yield of reduced product, as was indeed observed. Neither 8-(2-hydroxypropyl)-

1,4-dihydro-1-naphthoic acid (116) nor 1,4-dihydrodimethyl-naphthalide (115) have been detected amongst the reduction products. The low conversion observed from reduction of (111) may well reflect the insolubility of this material under the reaction conditions.

4.2.2. 3,3-Dimethylphthalide

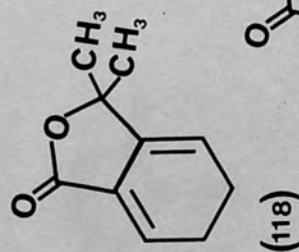
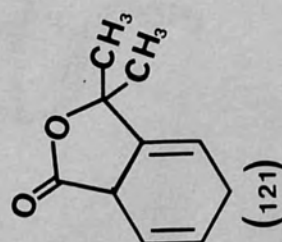
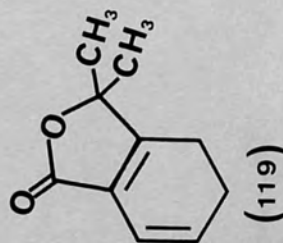
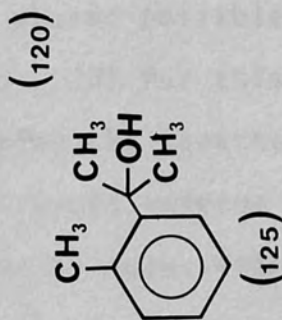
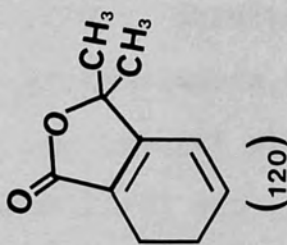
3,3-Dimethylphthalide (109) was initially prepared using the method of Eisner and coworkers⁷⁵, but the yield obtained was very poor. A better yield was obtained by using phthalic anhydride and the procedure described by Bauer⁷⁴ and isolation of the product in this case was easier. Lithium 2-(2-hydroxypropyl)benzoate (112) was then prepared by refluxing (109) with lithium hydroxide in water.



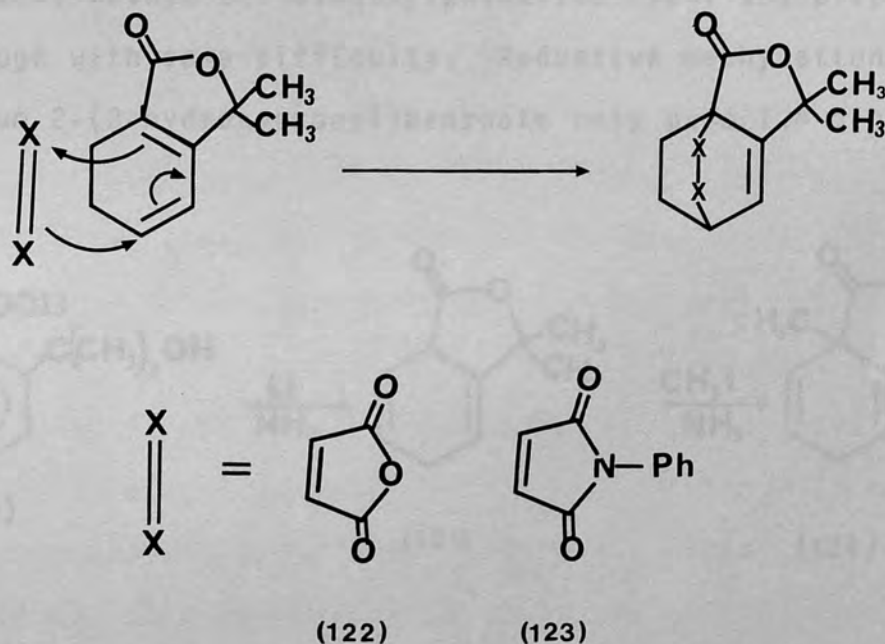
Reduction of lithium 2-(2-hydroxypropyl)benzoate was carried out under a variety of conditions (see Table 5). The reduction gave a number of interesting results. Reduction of (109) with 4 mol. equivalent of lithium gave an acidic material as white crystals which had δ (CDCl₃): 6.3-5.8 (2H, q, CH=CH); 2.5 (4H, s, CH₂); 1.5 (6H, s, CH₃). The infra-red of this material shows

TABLE 5. Reduction of (112)

Starting Material	Metal	Mol. equiv.	Solvent	Quenching Method	Product% (120)(121)(125)	Recovered S.M.
Lithium 2-(2-hydroxy- propyl)benzoate	Li	4	ether	NH ₄ Cl added after Li	95	-
"	Li	10	ether	"	90	-
"	Li	4	ethanol	"	70	-
"	Li	10	ethanol	"	80	-
dimethylphthalide	Li	4	ether	"	45	-
"	Li	10	ether	"	55 87	-



a peak at $1740 \text{ (C=O) cm}^{-1}$. The above product was obtained pure and in high yield and was not contaminated either by starting material or by non-acidic product. Spectroscopic data point to a dihydroaromatic material which could have the possible structure (118) - (120). Structure (118) can be excluded since olefinic protons would not be mutually strongly coupled. It has not yet proved possible to distinguish between structures (119) and (120) for this material. One possible method for identifying the structure of this compound would be to see whether it would undergo a Diels-Alder reaction (Scheme 32) with, for example, either (122) or (123).

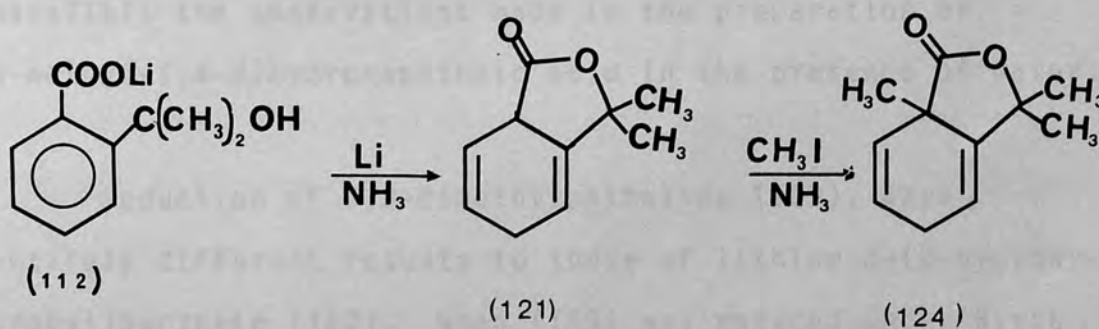


(Scheme 32)

When lithium 2-(2-hydroxypropyl)benzoate was reduced with 10 mol. equivalent of lithium metal a different product was formed. This was identified as 1,4-dihydro-

3,3-dimethylphthalide (121) on the basis of its ^1H nmr spectrum. This compound is rather unstable (perhaps as a result of strain) and all attempts to purify it failed. If (121) (which is an oil) is left to stand for 24 hours below 0°C in air it aromatizes. It can, however, be stored for several days under nitrogen. Attempts to distil (121) under reduced pressure (10 mm) result in decomposition.

Therefore all the analyses of (121) were carried out on the crude material without further purification. It was thought that methylation of 1,4-dihydro-3,3-dimethylphthalide would give more stable compound which could not aromatize or isomerize readily. Thus 1,4-dihydro-1-methyl-3,3-dimethylphthalide (124) was prepared, although with some difficulty. Reductive methylation of lithium 2-(2-hydroxypropyl)benzoate only gave 1,4-dihydro-



3,3-dimethylphthalide (121) or the dihydro isomer (120) together with recovered starting material. However (124) was successfully prepared from the reaction of (121) with sodamide in ammonia followed by addition of methyl iodide. 1,4-Dihydro-1-methyl-3,3-dimethylphthalide (124) is more

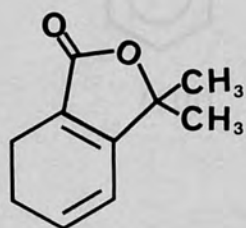
stable than (121). It is an oil which could not be readily purified by crystallisation or distillation (because of aromatization) but a pure sample was isolated by plc for the spectroscopic analyses.

Changing the solvent gave different results for when lithium 2-(2-hydroxypropyl)benzoate (112) was reduced with 4 mol. equivalent of lithium in ether as a cosolvent, the sole product obtained was (119) or (120), but in super dry ethanol 1,4-dihydro-3,3-dimethylphthalide (121) was formed. Reduction with 10 mol. equivalent of lithium metal in ethanol gave the same product, i.e. (121), but in no better yield. Rabideau has suggested that the presence of water is an essential prerequisite for the formation of dihydro products, a proposal supported by the above observations.

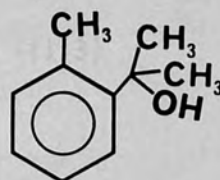
No other solvents have yet been employed in an attempt to investigate these effects in more detail but this result parallels the observations made in the preparation of 8-methyl-1,4-dihydronaphthoic acid in the presence of water.

Reduction of 3,3-dimethylphthalide (109), gave entirely different results to those of lithium 2-(2-hydroxypropyl)benzoate (112). When (109) was reduced under Birch conditions, no dihydroaromatic compounds were formed but a product was obtained which by nmr shows no olefinic protons but only aromatic protons. The ^1H nmr spectrum of this material is rather simple having $\delta(\text{CDCl}_3)$: 7.4-7.1 (4H, m, ArH); 2.5 (3H, s); 1.6 (1H, s, OH) exchanges with D_2O ; 1.5 (6H, s). Infrared shows no carbonyl absorption but a peak at 3400 cm^{-1} . This product has

been assigned the structure (125) on the basis of these data.



(120?)



(125)

This product arises from reduction of the ester carbonyl group rather than the aromatic ring. Reduction of 3,3-dimethylphthalide with 4 mol. equivalent of lithium metal in ammonia gave two products, the dihydro isomer (120) 45% and (125) 50%. Use of 10 mole equivalent of lithium metal afforded (125) as the sole reaction product.

Thus Birch reduction of the lithium salt (112) leads to aromatic ring-reduced product. In contrast, under these conditions the lactone dimethylphthalide undergoes the reduction of the ester group. These results contrast markedly with those found for phthalide itself, as reported in the next section.

4.2.3. Phthalide and its Salt

Lithium 2-(hydroxymethyl)benzoate (113), which was prepared from the reaction of phthalide with lithium hydroxide in water, was reduced by alkali/metal liquid ammonia solutions.

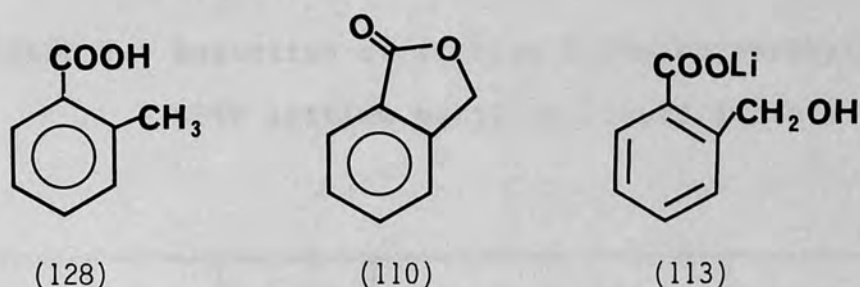


Table 6 summarizes the various reduction conditions used. Reduction of lithium 2-(hydroxymethyl)benzoate (113) with 10 mole equivalent of lithium metal in ammonia afforded an acidic product in a good yield (80%). (No non-acid product(s) were isolated.) NMR, ir, ms, and combustion analyses were all consistent with the formation of 1,4-dihydro-2-(hydroxymethyl)benzoic acid (126). From the nmr data, it was clear that the reduction occurred in the aromatic ring but not in the alcoholic function. The reaction mixture was clean and easy to work up. No starting material could be detected in the product mixture. For comparison, the reduction of o-toluic acid (128) was also investigated. In this case under the same conditions, a good yield of 1,4-dihydro-o-toluic acid (129) was isolated together with a negligible amount of non-acidic material which was identified as 2,2'-dimethylbibenzyl (127). Comparison of the reduction of (98) shows that (98) can be reduced both in the aromatic ring and at the benzylic position easily (even with 1 mol equivalent of lithium metal) whilst (113) is not easily reduced in the side chain. This is probably because of the hydroxyl leaving group in anion (130), requiring an unsatisfactory 1,3-elimination pathway, is positioned γ relative to the

TABLE 6. Reduction of lithium 2-(hydroxymethyl)benzoate with lithium metal in liquid ammonia.

Metal	Mole equiv.	Solvent	Quenching method	Acidic* prod.%	Non- ⁺ acidic%	S.M. ⁺⁺
Li	10	ether	NH ₄ Cl was added at the end	80	-	-
Li	4	ether	"	70	23	-
Li	2	ether	"	90	-	-
Li	10	ether	NH ₄ was added first	50	-	30
Li	10	ether	H ₂ O was added first	80	-	15

*Acidic product is 1,4-dihydro-2-hydroxymethylbenzoic acid

⁺2,2'-bibenzyl

⁺⁺Phthalide

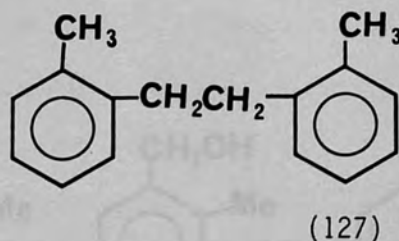
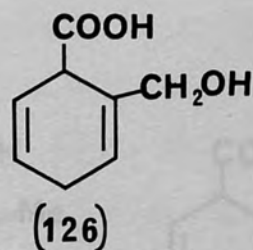
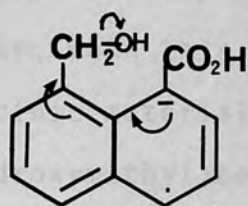


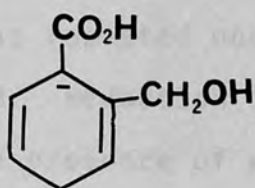
TABLE 7. Reduction of phthalide with metal/ammonia

Metal	Mole equiv.	Solvent	Quenching method	Acidic %	Non-acidic* %	S.M. %
Li	10	ether	NH ₄ Cl was added at the end	-	64	36
Li	5	ether	"	-	60	36

*non-acidic is the dimer 2,2'-dimethylbibenzyl.



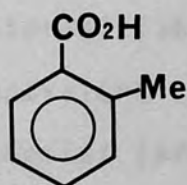
(130)



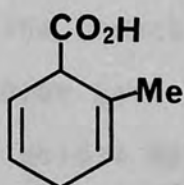
(131)

charge centre whereas in (131) it is in a β position.

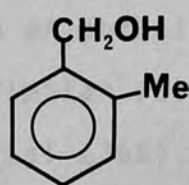
In order to investigate further the products obtained from metal/ammonia reduction of lithium 2-(hydroxymethyl)benzoate, the acid function of *o*-toluic acid (128) and of 1,4-dihydro-*o*-toluic acid (129) were each readily reduced by lithium aluminium hydride to give as products α -hydroxymethyl xylene (132) and 1,4-dihydro- α -hydroxymethyl xylene (133) respectively in high yield. No evidence was found for



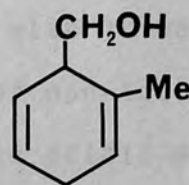
(128)



(129)



(132)



(133)

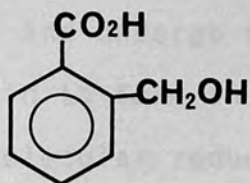
the formation of any of the products (128) - (133) in the reduction of (113). Only a small quantity of non-acidic material was observed which was identified as resulting from acyloin condensation (see later, p. 80).

Reduction of lithium 2-(hydroxymethyl)benzoate (113) with 4 mol. equivalent of lithium metal in ammonia solution gave some of the non-acidic material (23%) and acidic material (70%), the latter being identified as

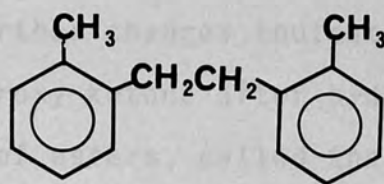
1,4-dihydro-2-(hydroxymethyl)benzoic acid (129).

However, when this experiment was repeated once more, no non-acidic material was observed. Reduction of lithium 2-(hydroxymethyl)benzoate in the presence of water (the conditions used by Rabideau for the preparation of dihydro compounds) or ammonium chloride did not change the course of the reaction or improve the yields. In fact the salt (113) could be reduced readily even with 2 mole equivalent of lithium metal. No attempts were carried out to use sodium metal and investigate the difference between the two metals, since the priority was given to solving the problem of the origin of the non-acidic material.

When phthalide (110) was reduced using 5 molar equivalents of lithium, the major product was the non-acidic material obtained above (60%) with some of acidic material (36%). The reduction of phthalide with 10 molar equivalent of lithium gave a similar ratio of non-acidic material (64%) to acidic material (36%). The acidic material was not very pure and was shown spectroscopically (ir, nmr) to consist of a mixture of the starting material (110) and 2-(2-hydroxymethyl)benzoic acid (134). The major component of the non-acidic fraction was purified by distillation to give a compound which has very simple ^1H nmr spectra $\delta(\text{CDCl}_3)$ 7.2 (8H, s, ArH); 2.9 (4H, s, CH_2); 2.3 (6H, s, CH_3). Infra-red spectroscopy showed no C=O or OH bands and a very small peak at 1700 cm^{-1} which was thought to be impurity. The mass spectrum showed major peaks at m/e 210, 195, 119 and 105. From these data it

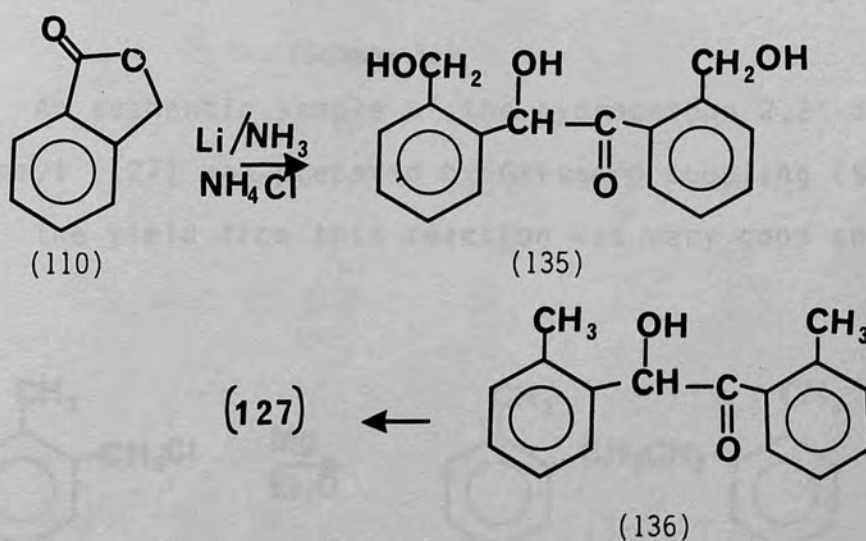


(134)



(127)

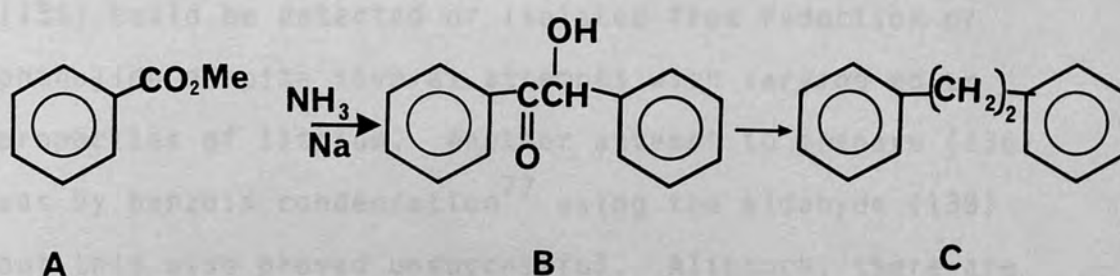
was suggested that the product might be a dimer for which the structure (127) was proposed. This is consistent with the mass spectral and nmr data. The hydrocarbon (127) could have arisen through acyloin dimerization followed by reduction (Scheme 33):



(Scheme 33)

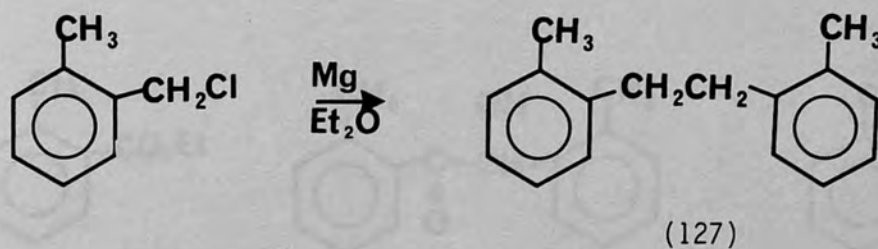
Such a pathway would not be unreasonable for a lactone under these conditions, there being precedents for the acyloin reaction in alkali metal/liquid ammonia solutions (Scheme 33)⁷⁰. If a sufficient excess of alkali metal was present, product (B) might then be reduced to the hydrocarbon (C) (Scheme 34). The reduction of esters to alcohols is carried out in the presence of a proton donor

through an initially formed anion radical. In the absence of a proton donor, the metal cation-radical anion pairs dimerize and undergo the further changes indicated at the side chain to form an α -hydroxy ketone after hydrolysis¹⁰. This bimolecular reduction of esters, called the acyloin reaction⁷⁶, has proved of special value for the preparation of medium and large rings.



(Scheme 34)

An authentic sample of the hydrocarbon 2,2'-dimethyl-bibenzyl (127) was prepared by Grignard coupling (Scheme 35). The yield from this reaction was very good and a

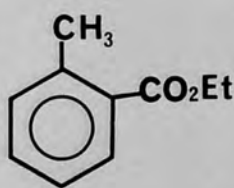


(Scheme 35)

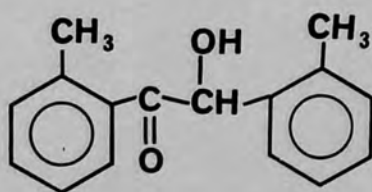
pure sample of (127) was obtained by distillation. This material had spectral properties and physical data identical with that found for the compound isolated from the reduction of phthalide.

In order to investigate further the pathway by which 2,2'-dimethylbibenzyl is formed, attempts were made to prepare *o,o'*-toluin (2,2'-dimethylbenzoin) (136) (See Appendix C) which was believed to be the intermediate which would lead to the formation of the dimer (127).

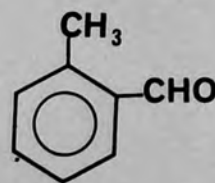
Preparation of *o,o'*-toluin (136) through acyloin condensation using the ester ethyl 2-methylbenzoate (137) with sodium in liquid ammonia failed. No acyloin adduct (136) could be detected or isolated from reduction of phthalide despite several attempts with varying molar properties of lithium. Another attempt to prepare (136) was by benzoin condensation⁷⁷ using the aldehyde (138) but this also proved unsuccessful. Although, there are many reviews in the literature^{78,79,80,81} for the preparation of compounds like *o,o'*-toluin (136) none of the methods described proved to be satisfactory. In some cases ironically, the dimer 2,2'-dimethylbibenzyl was isolated instead of *o,o'*-toluin.



(137)



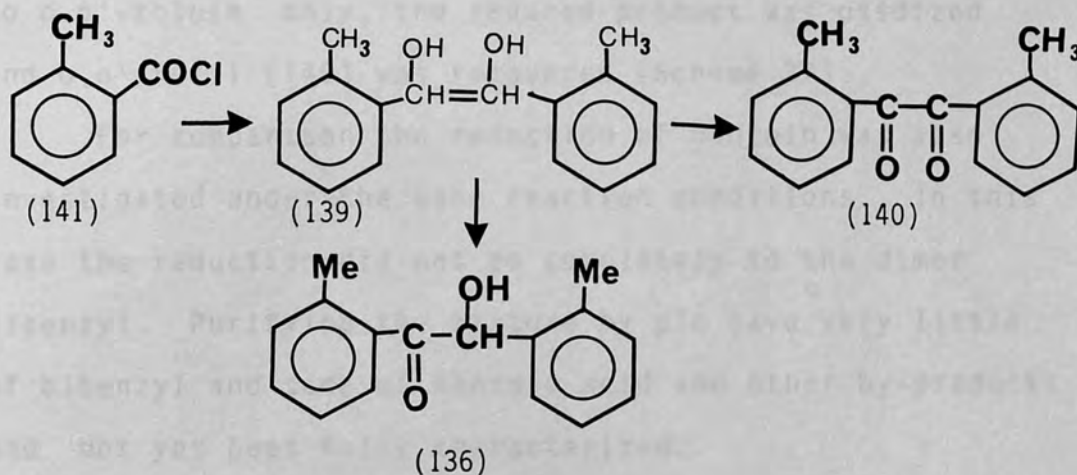
(136)



(138)

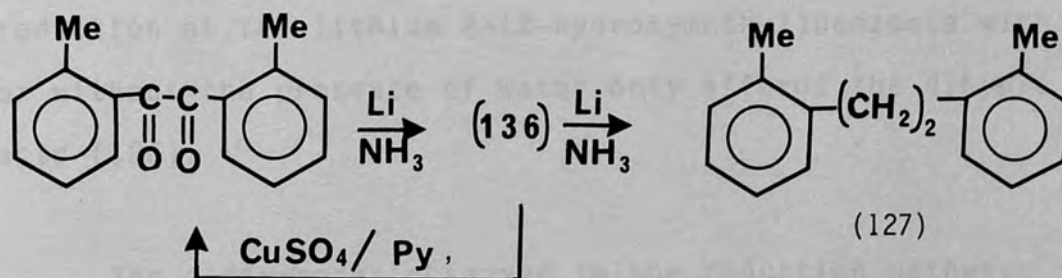
Finally, a route to *o,o'*-toluin was found which involved reduction of acid chloride (141) with Mg/MgI₂. The problem with this procedure is the low yield of the benzoin product (13%) due to the instability of the enediol

(139) which oxidizes readily. Therefore the reduction must be carried out as fast as possible to minimize the formation of oxidized material (Scheme 36).



(Scheme 36)

The benzoin (136) was then reduced under the same condition previously employed for reduction of phthalide. The product obtained from this reduction was the dimer 2,2'-dimethylbibenzyl (127) in very good yield (94%). No evidence being obtained for any by-products.



(Scheme 37)

The ease of this reaction suggests that detection of intermediates like (136) during the reduction of phthalide or the ester (137) would probably be very

difficult. However when *o,o'*-tolil (140) was reduced it gave *o,o'*-toluin (136) but not 2,2'-dimethylbibenzyl (127). To make sure that the reduction of *o,o'*-tolil led to *o,o'*-toluin only, the reduced product was oxidized and *o,o'*-tolil (140) was recovered (Scheme 37).

For comparison the reduction of benzoin was also investigated under the same reaction conditions. In this case the reduction did not go completely to the dimer bibenzyl. Purifying the mixture by plc gave very little of bibenzyl and some of benzoic acid and other by-products had not yet been fully characterized.

Unfortunately, lack of time did not permit the preparation of 2,2'-(hydroxymethyl)benzoin which could fit nicely with the scheme proposed for the reduction of phthalide. But it would appear that 2,2'-dimethylbibenzyl is formed by a pathway involving *o,o'*-toluin as an intermediate. The reduction of phthalide to the dimer (127) requires dry conditions. On the other hand, reduction of the lithium 2-(2-hydroxymethyl)benzoate with or without the presence of water only affords the dihydro acid (126).

The differences observed in the reduction pathways for phthalide and 3,3-dimethylphthalide may well reflect steric hindrance to dimerization of the initially ester radical anion in the latter compound which would prevent acyloin condensation. In the latter compound therefore simple reduction of the ester function becomes the dominant reaction pathway. In contrast reduction of the lithium salts of these compounds leads to dihydroaromatic derivatives.

CHAPTER 5

CONFORMATION OF 1,4-DIHYDROAROMATIC RINGS

5.1. INTRODUCTION

The conformation of 1,4-dihydroaromatics (5) and its derivatives have been studied for many years. Recently, largely due to the continued development of new spectroscopic techniques, investigators such as Flint, Roberts and others have investigated a variety of conformational problems.³² The cyclohexa-1,4-diene ring system occurs in three types of compounds: 1,4-dihydro-

PART II

A STUDY OF SOME CONFORMATIONALLY BIASED AND LOCKED DIHYDROAROMATIC COMPOUNDS

For many years, the 1,4-dihydroaromatic ring system was generally considered to favour a boat-like conformation (141).³³ However, a recent study³⁴ has suggested in 1953 on the basis of an analysis of vibrational spectra, absorption bands, and infrared electron absorption³⁵ and the study of the conformational energy of the 1,4-dihydroaromatic ring system. Some reports suggested a slight preference for the chair conformation (142).



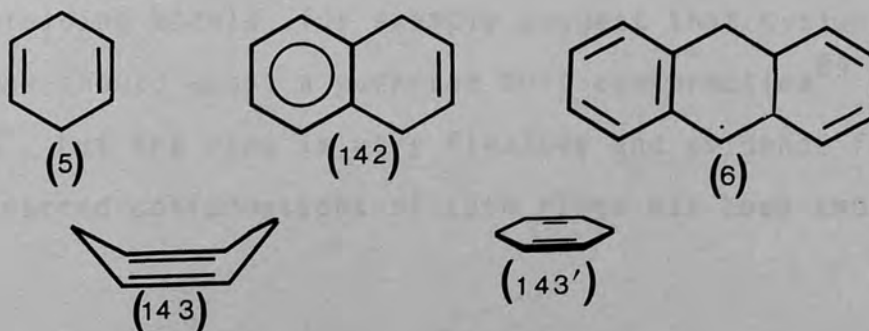
CHAPTER 5

CONFORMATION OF 1,4-DIHYDROAROMATIC RINGS

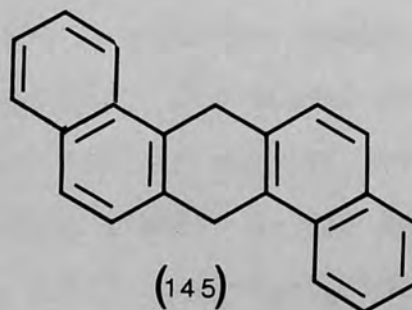
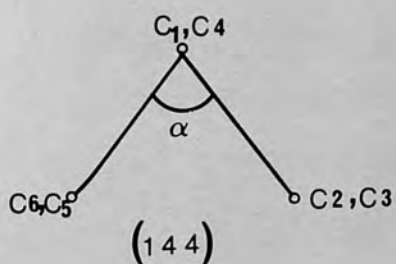
5.1. INTRODUCTION

The conformation of 1,4-dihydrobenzene (5) and its derivatives have been studied for many years. Recently, largely due to the continued development of nmr spectroscopic techniques, investigators such as Finet, Roberts and others have investigated a variety of conformational problems⁸². The cyclohexa-1,4-diene ring moiety occurs in three types of compound: 1,4-dihydrobenzenes (5), 1,4-dihydronaphthalenes (142) and 9,10-dihydroanthracene (6). For each of these systems there has been considerable controversy concerning some aspects of its stereochemistry⁶⁰.

For many years, the 1,4-cyclohexadiene ring system was generally considered to favour a boat-shaped conformation (143)⁸³ even though a planar structure was suggested in 1949 on the basis of an analysis of vibrational spectra¹. Subsequently Raman² and infrared³, electron diffraction⁸⁴ and nmr studies¹⁷ were carried out. Some reports suggested a planar geometry for the parent compound (143').



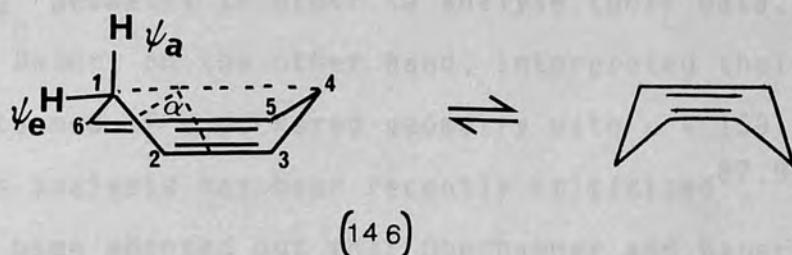
In 1959, Herbstein⁸⁵ predicted from semi-empirical calculations that for cyclohexa-1,4-diene the stable conformation has a dihedral angle of about $\alpha = 140^\circ$ (144) with a potential barrier for the inversion of the molecule from the "folded" to the "reverse folded" structure of about $1.5 \text{ kcal mol}^{-1}$. For 9,10-dihydroanthracene a dihedral angle of about 150° with a potential barrier for boat inversion of about $0.8 \text{ kcal mol}^{-1}$ was deduced. He also reported that the strain-energy curves obtained for (145) indicate the planar conformation as the more stable in good agreement with experiment.



Laane and Lord⁸⁶ subsequently noted that force field calculations favour a planar energy minimum. More recent ab initio⁸⁷ calculations have supported this view. These latter also predict $\Delta E = 0.95 \text{ eV}$ for the energy splitting in the photoelectron spectrum (Experimental $\Delta E = 1.0 \text{ eV}$)⁸⁸ with the first ionization potential at 9.0 eV (Experimental 8.9 eV).

Dreiding Models, for example suggest that cyclohexa-1,4-diene should adopt a puckered boat conformation⁸⁹ (146) $\alpha = 145^\circ$, but the ring is very flexible and evidence for the preferred conformations of such rings has been ambiguous.

A variety of techniques have been employed to this end, and whilst the situation now appears to be resolved for



the parent, the effect of substituents about the cyclohexa-1,4-diene ring remains uncertain, as does the interpretation of some of the spectroscopic data.

Directly related to (5) are 1,4-dihydronaphthalenes (70) and 9,10-dihydroanthracenes (6). The degree of puckering of the dihydroaromatic ring in each of these cases will be defined by the angle α which is the angle between the planes $C_1-C_2-C_3-C_4$ and $C_{1ax}-C_6-C_5-C_6$ in (146).

5.2. DIFFRACTION METHODS

Since these allow direct determination of the structure of the molecule they would seem to provide direct insight into the conformations of dihydroaromatic rings.

There have been two electron diffraction studies of cyclohexa-1,4-diene (5) itself^{84,89}. From the earlier of these⁸⁴ it was concluded that a planar conformation (D_{2h}) was present in the gas phase, although the authors did not exclude the presence of small amounts of other

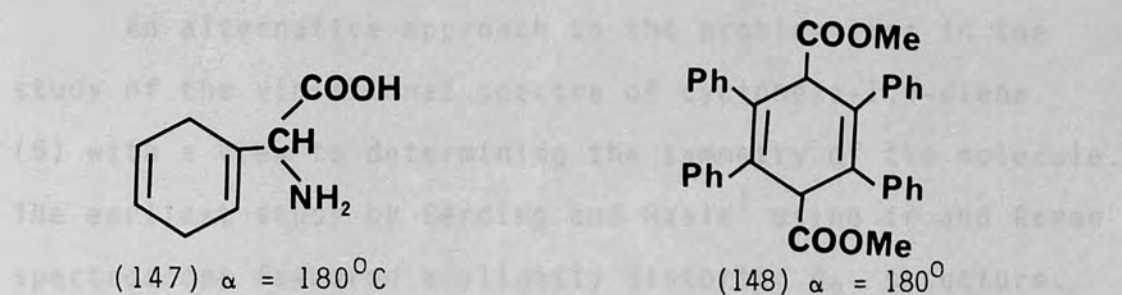
conformations. In a later study, by Oberhammer and Bauer⁸⁹, it was suggested that Dallinga and Toneman had assumed a D_{2h} geometry in order to analyse their data. Oberhammer and Bauer, on the other hand, interpreted their own data in terms of a puckered geometry with $\alpha = 159.3^\circ$. However, this analysis has been recently criticised^{87,90} since it has been pointed out that Oberhammer and Bauer neglected to allow for shrinkage effects arising from rapid vibrational motions of wide amplitude - the evidence for the latter being provided by infrared studies (see p. 92). It is notable that Oberhammer and Bauer's geometry does require a rather long C=C bond cf. the 'normal' bond length found by Dallinga (Table 8).

TABLE 8. C-C bond length in cyclohexa-1,4-diene from electron diffraction data

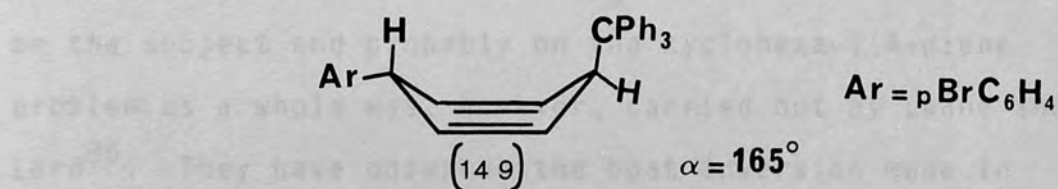
	Oberhammer	Dallinga
C ₁ -C ₂	1.511	1.496 Å ^o
C ₂ -C ₃	1.347	1.334 Å ^o

Attempts have been made to carry out an X-ray diffraction of cyclohexa-1,4-diene at low temperature (-49°C) but it has not yet proved possible to satisfactorily show these data⁹¹. However, the structures of several derivatives have been reported. For example, both cyclohexa-1,4-dienyl-1-glycine (147)⁹² and dimethyl 2,3,5,6-tetra-phenylcyclohexa-1,4-diene-1,4-dicarboxylate (148)⁹³ have

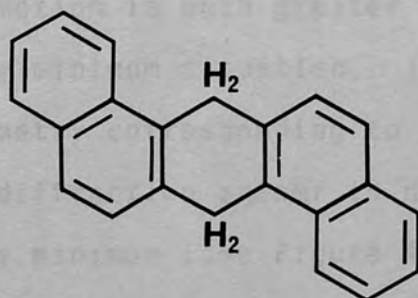
5.3. VIBRATIONAL SPECTROSCOPY



planar cyclohexa-1,4-diene rings. Early work on 4'-bromo-trans-1,4-dihydro-4-tritylbiphenyl (149) suggested a puckered ring with $\alpha = 165^\circ$ ⁹⁴. A more recent study suggests that



the dihydroaromatic ring is almost planar here⁹⁵. The interpretation of these data must, however, be treated with caution since the effect of lattice forces on conformation is uncertain. Indeed it has been found that whilst X-ray crystallography shows that 9,10-dihydroanthracene (6) is highly puckered ($\alpha = 145^\circ$)⁹⁶, 9,10-dihydro-1,2:5,6-dibenzanthracene (145) is planar ($\alpha = 180^\circ$)⁹⁷, possibly a consequence of lattice effects.

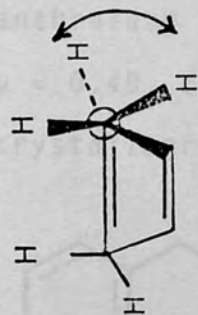
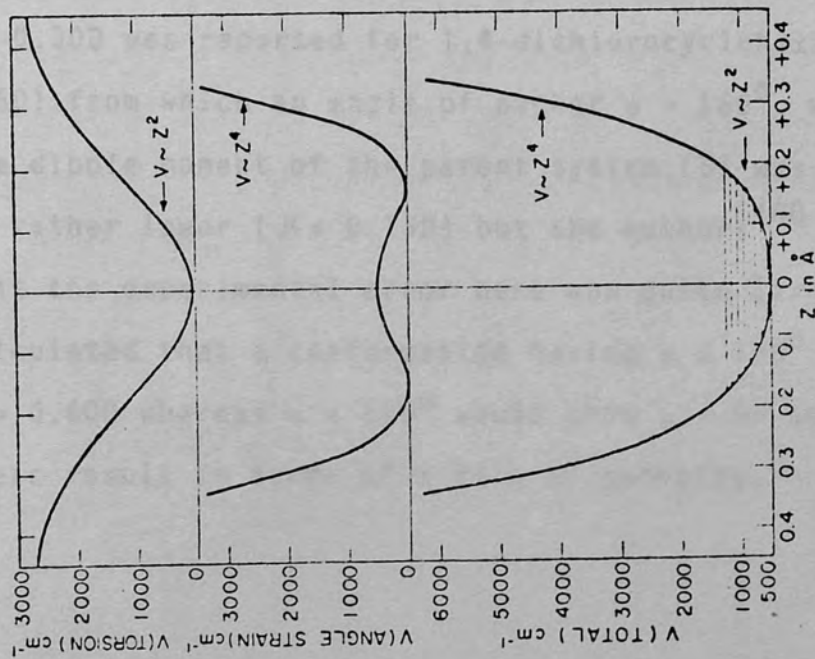


(145)

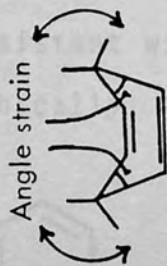
5.3. VIBRATIONAL SPECTROSCOPY

An alternative approach to the problem lies in the study of the vibrational spectra of cyclohexa-1,4-diene (5) with a view to determining the symmetry of the molecule. The earliest study by Gerding and Haale¹ using ir and Raman spectroscopy favoured a slightly distorted D_{2h} structure. Similar conclusions were subsequently drawn from a further study⁹⁷ of the pure rotational Raman spectrum of cyclohexa-1,4-diene (5) and comparison³ of the ir and Raman spectra of (5) and cyclohexa-1,4-diene- d_6 . The definitive work on the subject and probably on the cyclohexa-1,4-diene problem as a whole was, however, carried out by Laane and Lord⁸⁶. They have observed the boat inversion made in the far-infrared spectrum of 1,4-dihydrobenzene itself. The spectrum has been analysed in terms of a potential well with a flattened base, but having an energy minimum corresponding to the planar structure. However, it is suggested that vibrational quantum levels as high as the fifth, which has an amplitude corresponding to an oscillation from $\alpha = 155^\circ$ to $\alpha = -155^\circ$, would be significantly populated [ca. 10%] at room temperature. In such a deformation the time spent near the extremities of the vibrational motion is much greater than that spent close to the energy minimum situation. It follows that a time-averaged geometry corresponding to $\alpha = \text{ca. } 160^\circ$ as measured by electron diffraction and nmr is not consistent with a planar energy minimum (see Figure 4).

FIGURE 4. Far Infrared for Cyclohexa-1,4-diene

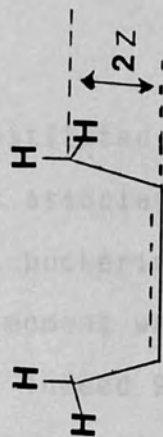


Torsional strain about C-C single bonds. This is maximum when C-H bonds eclipse each other; i.e. when $Z = \pm 0.55 \text{ \AA}$.



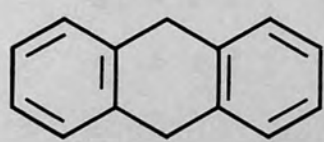
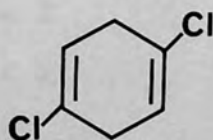
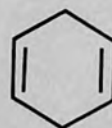
A tetrahedral geometry for the CH_2 group occurs when $Z = \pm 0.174 \text{ \AA}$ (for double bond angles of 120°).

Overall effect



5.4. DIPOLE MOMENT STUDIES

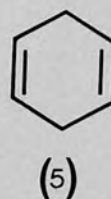
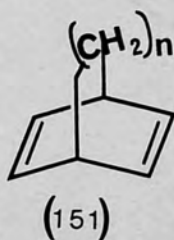
Whilst in a symmetrically substituted planar dihydroaromatic system, the dipoles associated with the various substituents should cancel, puckering of the molecule should introduce a dipole moment which should increase with increased puckering. Indeed 9,10-dihydroanthracene has been found⁹⁸ to have a dipole moment $\mu = 0.4\text{D}$, consistent with the puckered geometry observed crystallographically.

(6) $\mu = 0.4\text{ D}$ (150) $\mu = 0.3\text{ D}$ (5) $\mu = 0.13\text{ D}$

Two cyclohexa-1,4-dienes have been studied. A value of 0.30D was reported for 1,4-dichlorocyclohexa-1,4-diene (150) from which an angle of pucker $\alpha \approx 166^\circ$, was deduced⁹⁹. The dipole moment of the parent system (5) was found to be rather lower ($\mu = 0.13\text{D}$) but the authors¹⁰⁰ suggested that the experimental error here was quite large. They calculated that a conformation having $\alpha = 155^\circ$ would show $\mu = 0.60\text{D}$ whereas $\alpha = 180^\circ$ would show $\mu = 0\text{D}$ and interpreted their result in terms of a ring of geometry.

5.5. PHOTOELECTRON SPECTROSCOPY

Heilbronner^{101,102} has studied the photoelectron spectra of a series of 3,6-bridged cyclohexa-1,4-dienes (151) and of cyclohexa-1,4-diene (5) itself.



a, $n = 1$; c, $n = 3$

b, $n = 2$; d, $n = 4$

The interaction of two π -bonds with each other will result in a splitting of levels (Figure 5) leading to two occupied energy levels, the energy difference between the two occupied levels (ΔE) reflecting the extent of this interaction. This phenomenon is a purely through space effect (152), but superimposed upon it will be a through 6 bond effect. In cyclohexa-1,4-diene this can be

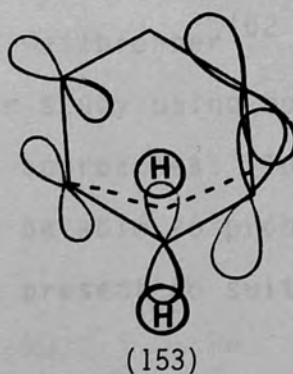
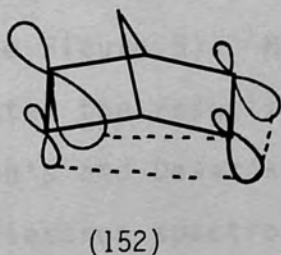
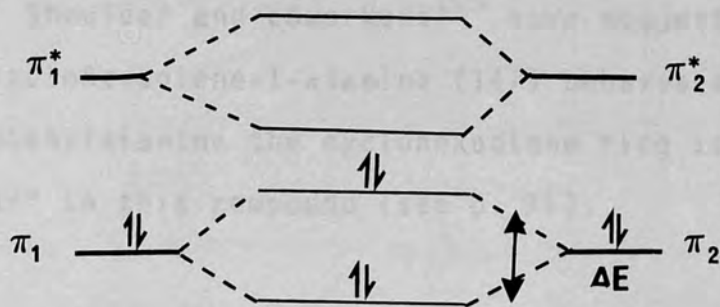


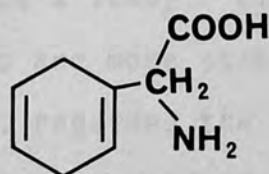
FIGURE 5.



considered to involve the C-H bonds of the methylene groups e.g. (153) and has been described as a hyperconjugation interaction. Hofmann¹⁰³ and Dewar have shown that these two interactions occur in opposite senses and are very geometrically dependent. In the planar conformation the hyperconjugative interaction is found to dominate. In Figure 5 Hofmann's¹⁰³ full interaction diagram is presented. For cyclohexa-1,4-diene two π -electron levels are indeed observed at 8.8 eV and 9.8 eV (i.e. $\Delta E = 1.0$ eV). For a planar ring (5), Hofmann calculates $\Delta E = 0.65$ eV. Dewar¹⁰⁴ on the other hand, using the geometry of Oberhammer and Bauer⁸⁹ (i.e. $\alpha \approx 160^\circ$) predicts $\Delta E = 1.0$ eV. Dewar¹⁰⁴ has determined the conformational dependence of ΔE (see Figure 5). More recently Heilbronner¹⁰² has presented the results of a similar study using both Hofmann's and Dewar's theoretical approaches. In principal photoelectron spectroscopy should be able to probe the ring conformation but there is at present no suitable reference point.

5.6. OTHER APPROACHES

Shoulder and coworkers¹⁰⁵ have suggested that since 1,4-cyclohexadiene-1-alanine (147) behaves as an antagonist for phenylalanine the cyclohexadiene ring is "essentially planar" in this compound (see p. 91).



(147)

5.7. STRUCTURAL CALCULATIONS

The earliest conformational calculations were performed by Herbstein⁸⁵ and have already been discussed. These suggested that cyclohexa-1,4-diene itself is folded ($\alpha = 140^\circ$) with $E_a^{\text{flip}} \approx 1.5 \text{ kcal mol}^{-1}$.

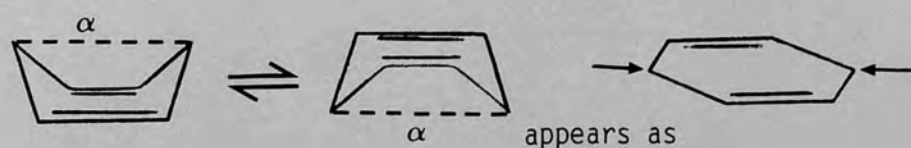
More sophisticated calculations by Dashevskii and coworkers¹⁰⁶ predicted an energy minimum for $\alpha = 158.5^\circ$ in very close agreement with Oberhammer and Bauer's electron diffraction data⁸⁹ ($\alpha = 159.3^\circ$) even though these latter results were not available at the time. However, the calculations indicated that a planar geometry is only $0.13 \text{ kcal mol}^{-1}$ higher in energy, leading the authors to suggest that whilst the equilibrium conformation is non-planar, there should normally be a considerable population of the planar form. Herbstein's conformation was, however, found to be several kcal mol^{-1} higher in energy. These

calculations also predicted a value for the heat of hydrogenation of $52.26 \text{ kcal mol}^{-1}$ in close agreement with the reported value ($53.9 \text{ kcal mol}^{-1}$). Strain energy calculations carried out by Oberhammer and Bauer⁸⁹ using geometries (both planar and puckered) derived from their own electron diffraction data and the planar geometry proposed from Dallinga's study⁸⁴ clearly showed that the planar geometries are more stable by $6\text{-}10 \text{ kcal mol}^{-1}$. The authors, however, regarded the calculations as unreliable since these appeared unable to satisfactorily predict the heat of isomerisation to the 1,3-isomer (although they here assumed that cyclohexa-1,3-diene was non-planar. For planar cyclohexa-1,3-diene $\Delta H_{\text{isom}} = 3.14 \text{ kcal mol}^{-1}$ cf. $12.7 \text{ kcal mol}^{-1}$ which they claim since ΔH_{isom} was expectedly quite small).

Allinger and Sprague¹⁰⁷ found that force field calculations clearly favoured a planar energy minimum in a shallow potential well as indicated by Laane and Lord's data. The optimised geometry was close to that reported by Dallinga and Toemann and the calculated heat of formation ($24.22 \text{ kcal mol}^{-1}$) was close to the expected value ($26.3 \text{ kcal mol}^{-1}$). They concluded that the potential well indicates that the molecule is planar on the average but oscillating between boat forms. They comment that the boat geometry proposed by Bauer from electron diffraction work took no account of the possibility that rapid molecular vibrations would lead to an apparent band shortening similar to that expected for the puckered structure¹⁰⁷.

Self-consistent force field calculations of Ermer and Lifson¹⁰⁸ also predicted a planar energy minimum for (5). Once again it was found that whilst angle strain favours a puckered geometry, torsional strain, i.e., the rotation barrier about a C-C single bond, favours planarity. In cyclohexa-1,4-diene (5) the torsional strain factors dominate, leading to a preference for a planar geometry. Rotational barriers about C-aryl bonds in 9,10-dihydroanthracene (6) are much lower, and thus this latter favours a puckered conformation to minimise angle strain. It is pointed out here that Herbstein's calculations did not consider torsional strain.

Both Ermer¹⁰⁸ and Allinger¹⁰⁷ have criticised Oberhammer and Bauer's⁸⁹ electron diffraction study committing that these authors have misinterpreted the short C_3-C_6 bond length in terms of puckered geometry, for rapid vibrations will reduce the measured C_3-C_6 distance, i.e., one sees a projection of a puckered ring on a plane.



Ahlgren and others⁸⁷ have reported ab initio calculations on cyclohexa-1,4-diene (5). They have compared planar (Dashevstii) and puckered (Oberhammer and

Bauer) ($\alpha = 159.3^\circ$) geometries, using Oberhammer and Bauer's bond length data⁸⁹ in both cases. These calculations indicate that the planar conformation has the lower energy by $7.4 \text{ kcal mol}^{-1}$. For both conformations the separation of the two occupied π -electron levels is found to be ca. 0.95 eV (cf. 1.00 eV expectedly¹⁰²).

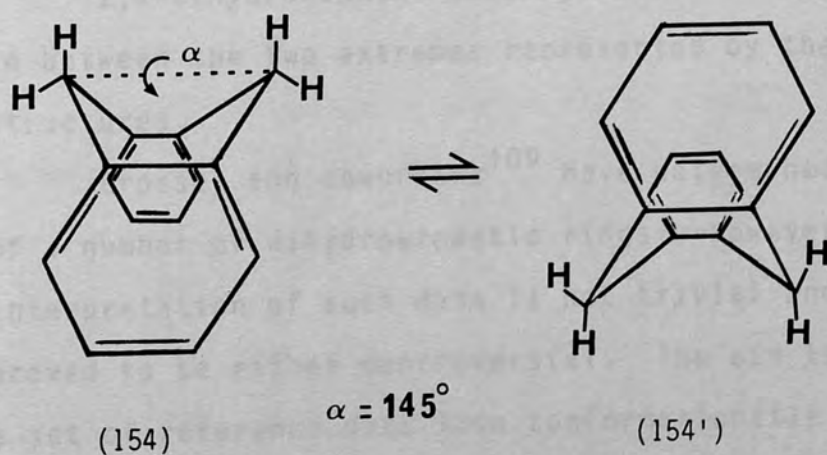
CHAPTER 6

CONFORMATIONALLY LOCKED AND CONFORMATIONALLY FLEXIBLEDIHYDROAROMATIC RINGS

6.1. INTRODUCTION

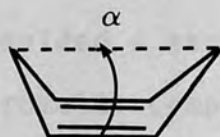
Since the first part of this project is concerned with the mechanism of the Birch reduction and the effect of structural modification on the course of the reaction, it is clearly important to investigate the reduction of a wide range of aromatic acids with different substitution patterns. This is also of interest to us since much time and effort has been spent elucidating the conformations of 1,4-dihydrobenzenes, 1,4-dihydronaphthalenes, and 9,10-dihydroanthracenes.

9,10-Dihydroanthracenes are apparently folded (into a geometry similar to that suggested by Drieding models) and rapidly invert, in the absence of other substituents (154) and (154').



1,4-Dihydrobenzenes behave rather differently, for there are two competing effects which control the conformation (see Figure 6). Bond angle strain favours a double minimum potential energy well since the tetrahedral bond angles are most readily accommodated in a boat geometry whereas torsional interactions about the C_1-C_2 , C_3-C_4 , C_4-C_5 , and C_6-C_1 bonds favour a planar ring conformation. These two interactions are of similar magnitude in 1,4-dihydrobenzene (cyclohexa-1,4-diene) itself and there is

FIGURE 6.



α = angle of folded

evidence that this molecule lives in a very shallow vibrational potential energy well which allows rapid vibrational flexing about a planar energy minimum geometry.

1,4-Dihydronaphthalenes appear to adopt conformations in between the two extremes represented by the other structures.

Grossel and coworkers¹⁰⁹ have determined conformations of a number of dihydroaromatic rings. However, the interpretation of such data is not trivial and has indeed proved to be rather controversial. The aim is to derive a set of reference data from conformationally rigid

structures and then to extrapolate these results to the flexible systems. They have carried crystallographic structure determinations (X-ray) of selected structures to provide further information on the conformations of the rigid systems and to examine the effect of the crystal lattice forces on the molecular conformations of flexible structures.

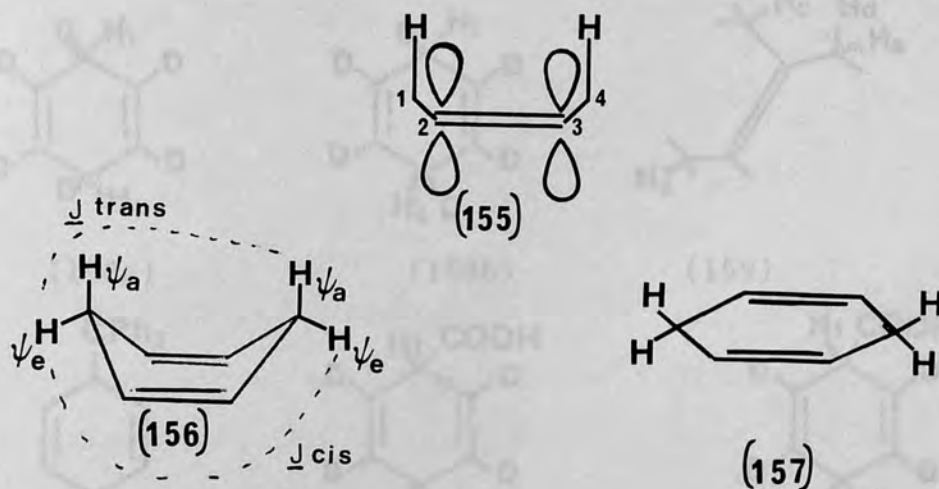
6.2. NUCLEAR MAGNETIC RESONANCE (NMR) STUDIES

6.2.1. 1,4-Dihydrobenzenes

NMR studies provided a sensitive probe into the geometry of dihydroaromatic compounds. Although 1,4-dihydrobenzene is a relatively simple molecule, the determination of the ring conformation by spectroscopic means (e.g. ^1H nmr) has proved particularly difficult. Problems which arise are due to: (i) identical chemical shifts for non-equivalent protons which are often observed in derivatives of (155); (ii) unusually large couplings (8-10 Hz) which were measured across the ring from one allylic proton to the other. Such large couplings arise because the methylene C-H bonds (at C-1 and C-4) are able to interact through the double bonds (157) - such an interaction being called homoallylic coupling (Figure 7). The planar conformation, (155) has two coupling constants [$^5J_{\text{trans}}$ and $^5J_{\text{cis}}$] (157), but in a puckered ring the situation is different. The methylene protons occupy either a pseudoaxial (ψ_a) or a pseudoequatorial (ψ_e) position

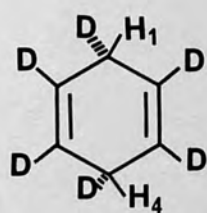
and therefore ${}^5J_{\text{trans}}$ must involve a pseudoaxial and a pseudoequatorial proton (${}^5J_{\psi_a/\psi_e}$), whereas ${}^5J_{\text{cis}}$ may result from pseudoaxial-pseudoaxial (${}^5J_{\psi_a/\psi_a}$) or pseudoequatorial-pseudoequatorial (${}^5J_{\psi_e/\psi_e}$) interactions. Garbisch and Griffith¹⁷ prepared the two isomers (158a) and (158b) and measured the two homoallylic coupling

FIGURE 7.

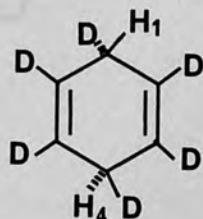


constants: ${}^5J_{\text{cis}} = 9.63$, and ${}^5J_{\text{trans}} = 8.04$ Hz. Karplus¹¹⁰ predicted that for a planar situation (159) ${}^5J_{\text{cis}}$ should equal ${}^5J_{\text{trans}}$ in a generalised system; but Atkinson and Perkins⁹⁴ concluded from the spectra of the dihydrobiphenyls (160) that the trans coupling ${}^5J_{\text{trans}}$ might be greater than the cis coupling ${}^5J_{\text{cis}}$ by as much as 25%. Since then there have been many studies concerning the relationship between homoallylic coupling constants and the geometry. Perkins and coworkers^{94,111} observed long-range couplings in several 1,4-dihydrobenzene derivatives. For example, in (158a) and (158b) ${}^5J = 11$ and 7.5 Hz respectively. They suggested that ${}^5J_{\text{cis}}$ may be smaller than ${}^5J_{\text{trans}}$ for a planar ring and therefore that (158)

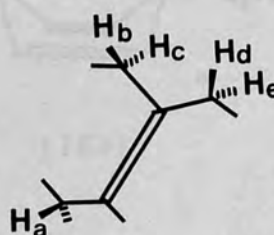
must be puckered. Marshall and coworkers¹¹² prepared (161a) and (161b) and found that the homoallylic coupling constants were nearly identical for these stereoisomers. Therefore they predicted that $\frac{{}^5J_{\text{cis}}}{{}^5J_{\text{trans}}}$ ratio gave only rough approximation to the puckering and the substituents on (161) caused the puckering.



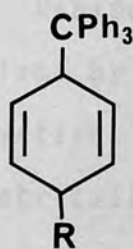
(158a)



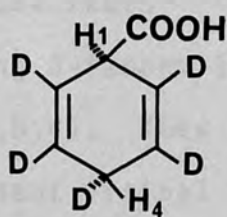
(158b)



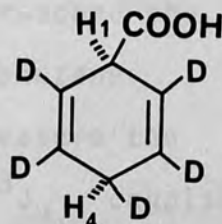
(159)



(160)



(161a)



(161b)

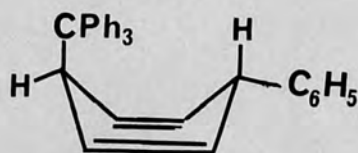
Then they concluded that (158) and (161) are both puckered. More recently these authors have changed their interpretation of these data and now they propose that (161) is essentially planar.

In recent studies of substituted cyclohex-1,4-dienes, Grossel and coworkers^{113,114} have investigated differently substituted cyclohexa-1,4-dienes. They reported¹¹⁴ ^1H nmr and crystallographic studies of trans-1,4-dihydro-4-tritylbiphenyl (163) suggests¹¹⁴ that this compound favours planar conformation having $\alpha \approx 171.8^\circ$ in the crystal.

The isomer cis-1,4-dihydro- 4-tritylbiphenyl (162) also adopts a solid state geometry in which the dihydroaromatic ring is almost planar.

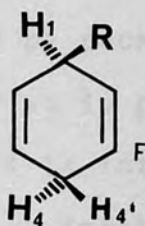


(162)



(163)

Rabideau and coworkers^{60,115,116} approached the problems by preparing 3-fluoro-1,4-dihydrobenzene derivatives (164, a,b,c). They tried to measure the geometrically dependent vicinal $^3J_{\text{H}_4\text{F}}$ and $^3J_{\text{H}_4\text{F}}$ couplings in order to define the stereochemistry of the entire ring. They expected this to be a particularly informative approach for determining ring conformation since proton-fluorine coupling is generally much larger than proton-proton coupling. Further, replacement of hydrogen with fluorine - a very electronegative substituent - should resolve the accidental chemical shift equivalences of H_4 and H_4 . In the event this proved not to be so and they could not obtain analysable nmr data because of chemical shift equivalences. Useful nmr results were, however, obtained from the compounds (164d) and (165) indicating a planar conformation in each case.

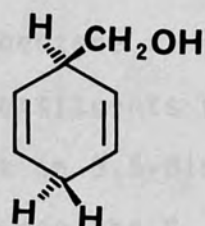


(164)

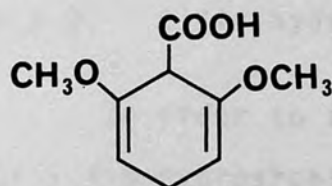
(a), R = Si(CH₃)₃

(b), R = m-FPh

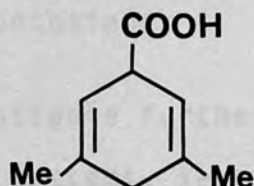
(c), R = COOH

(d), R = CH₂OH

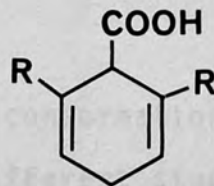
(165)



(166)



(168)

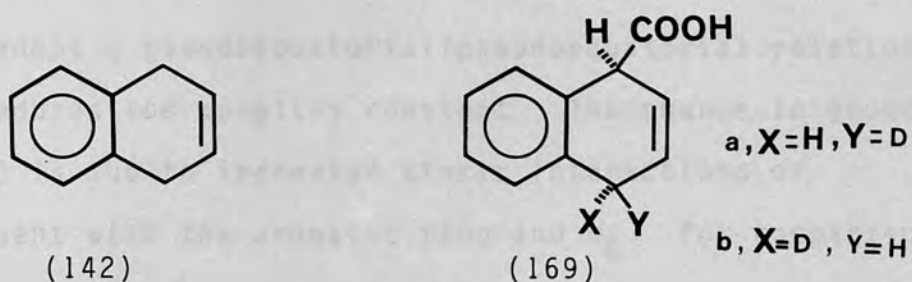
(a), R = CH₃(167) (b), R = CD₃

Rabideau¹¹⁷ also re-investigated the conformational geometry of (166) and (167), and in contrast to the earlier suggestion of Grossel and Perkins¹¹⁸ that these are planar (on the basis of homoallylic coupling constants), he proposed that both compounds are slightly puckered and that alkyl-substituents have little effect on the magnitude of the homoallylic coupling constants. More recently, Grossel and coworkers¹¹⁹ have determined the solid state conformation of 2,6-(167) and 3,5-dimethyl-1,4-dihydrobenzoic acid (168), the former is indeed puckered ($\alpha = 171.6^\circ$) as suggested by Rabideau whereas the latter is planar. Clearly steric interference between the carboxyl substituent and neighbouring methyl group is

relieved by puckering of the dihydrobenzene ring in such a manner as to place the carboxyl substituents pseudo-pseudo axial; it is interesting to note that in 3,5-dimethyl derivative torsional interaction between the C₄-H and C-methyl bonds are minimized in the planar ring. In this case therefore the alkyl substituents favour a planar ring and may well steepen the side of the vibrational potential energy well.

6.2.2. 1,4-Dihydronaphthalenes

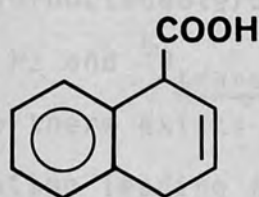
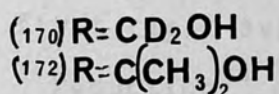
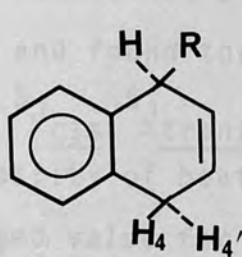
In order to investigate further the conformation of 1,4-dihydroaromatic systems, several different studies have been carried out on the conformation of 1,4-dihydronaphthalenes in the hope of gaining more insight into the controversy. Marshall and Folsom¹¹² investigated the nmr spectrum of 1,4-dihydronaphthoic acid (142) and deduced that the structure is boat-shaped on the basis of the magnitude and vicinal and allylic coupling constants. Later, as a result of values obtained for the homoallylic couplings they preferred a planar conformation. However, more recent work involving the measurement of three-bond carbon-carbon couplings about (142)¹²⁰ and the homoallylic carbon-carbon coupling about (169a) and (169b)¹²¹ together with a theoretical prediction that J_{-cis}/J_{-trans} (≈ 1.2 Hz) for a planar dihydrobenzene ring^{117,122} have led to the conclusion that (142) and its simple derivatives are somewhat puckered. Further support¹⁰⁹ for this view comes



from X-ray study of (169, X=Y=H) which shows a folded ring $\alpha = 169.2^\circ$, however the conformation of (169) may well be influenced by steric interference between the carboxyl group and H_8 .

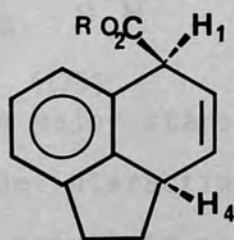
Rabideau and coworkers^{60,123} have prepared several 1,4-dihydronaphthalenes in an attempt to resolve the controversy concerning its conformation. They prepared compound (170) and analysed its ^1H nmr spectrum using shift reagents and triple irradiation. Comparison of the data for (170) with that for 1,4-dihydronaphthoic acid (171), revealed that the homoallylic coupling constants are smaller for (170) ($J_{1,4} = 3.8$ Hz) than (171) ($J_{1,4} = 3.5$ Hz), furthermore the $\frac{{}^5J_{\text{cis}}}{{}^5J_{\text{trans}}}$ ratio is similar for both compounds. They therefore concluded that both of them have a similar geometry. Introduction of a large substituent provides a different result and (172) was prepared as a representative of a highly puckered mono substituted 1,4-dihydronaphthalene. Such a conformation is supported by the fact that the cis homoallylic coupling constant ($J_{1,4}$) has dropped to 1.8 Hz. This is reasonable

since as the substituent becomes pseudoaxial protons H_1 and H_4 adopt a pseudoequatorial/pseudoequatorial relationship, which reduces the coupling constant. The change in geometry of (172) is due to increased steric interactions of substituent with the aromatic ring and H_8 . For comparison



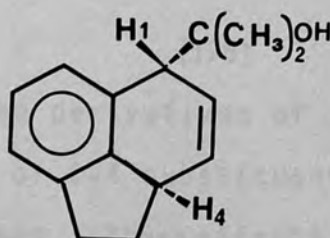
(171)

of the above geometry with a rigid boat shaped model compound, the ester (173) and alcohol (174) were prepared both of which require a locked boat shaped dihydronaphthalene ring. Homoallylic coupling constants of 8.5 Hz for ν_{ax}/ν_{ax} relationship and 3.2 Hz for ν_{ax}/ν_{eq} coupling were found. Grossel and coworkers⁵¹ have previously prepared 2a,5-dihydro-acenaphthoic acid (173b) and observed a similar value for $^5J_{cis}$. They later reported¹²⁴ an X-ray structural analysis which shows $\alpha = 146.5^\circ$ for the dihydronaphthalene ring.



a, $R = Me$
 b, $R = H$

(173)

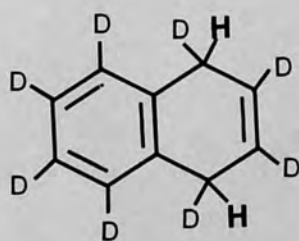


(174)

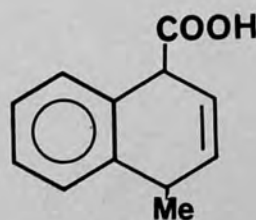


It would therefore seem that a single large substituent such as $C(CH_3)_2OH$ forces the 1,4-dihydronaphthalene ring into a boat conformation. On the other hand, smaller groups such as CO_2H and CD_2OH lead to only a slight degree of puckering. There is no evidence for a planar structure in substituted dihydronaphthalenes. In support of this view Grossel has prepared 1,4-dihydrooctadeuteronaphthalene¹²⁵ (175) and found that ${}^5J_{\text{cis}} = 7.15 \text{ Hz}$ and ${}^5J_{\text{trans}} = 4.55 \text{ Hz}$ (i.e. ${}^5J_{\text{cis}}/{}^5J_{\text{trans}} = 1.57$). Here there exists the possibility of boat-boat equilibration leading to a time averaged value for ${}^5J_{\text{cis}}$. These couplings appear to provide the first clear evidence for a boat geometry.

Reduction⁵¹ of 4-methyl-1-naphthoic acid affords two isomers of 1,4-dihydro-4-methyl-1-naphthoic acid (176). The spectra of the product mixture may be interpreted in terms of unequal proportions of cis and trans isomers. It is suggested that the coupling values reflect a slightly greater puckering as a result of steric interactions between methyl group and C-5 aromatic proton.



(175)

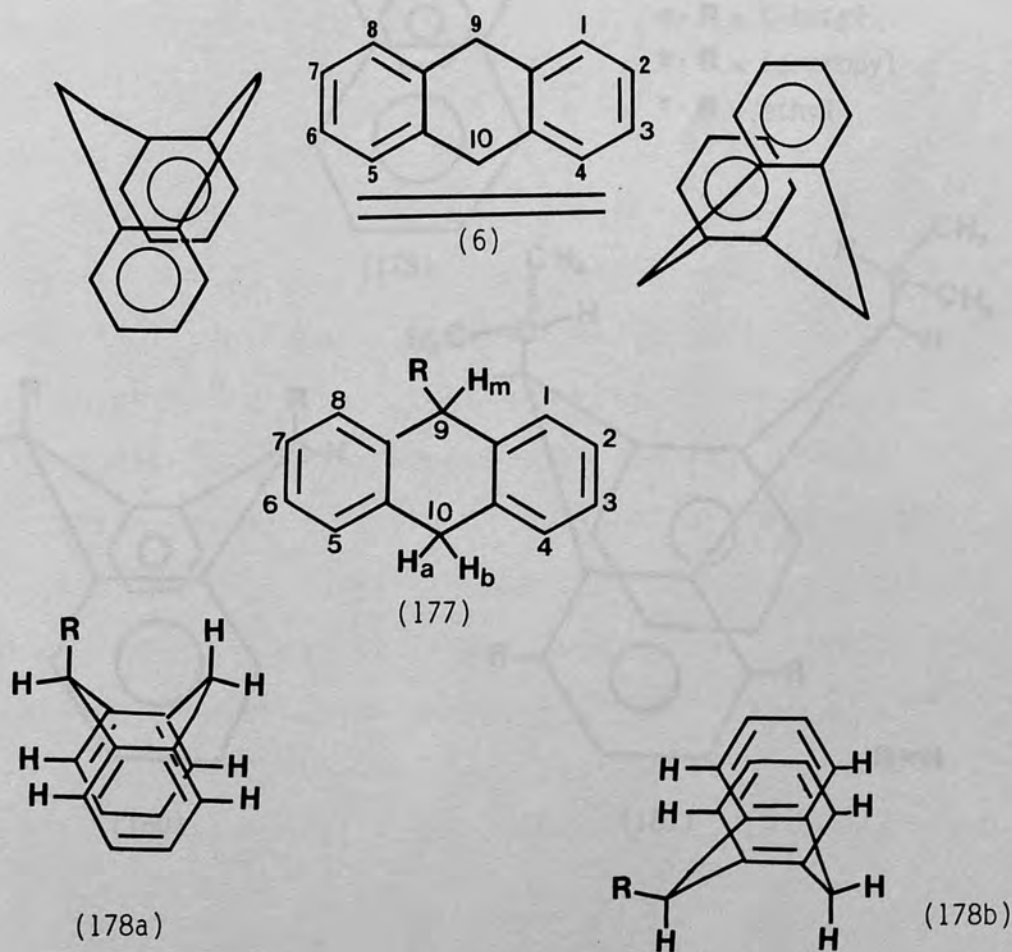


(176).

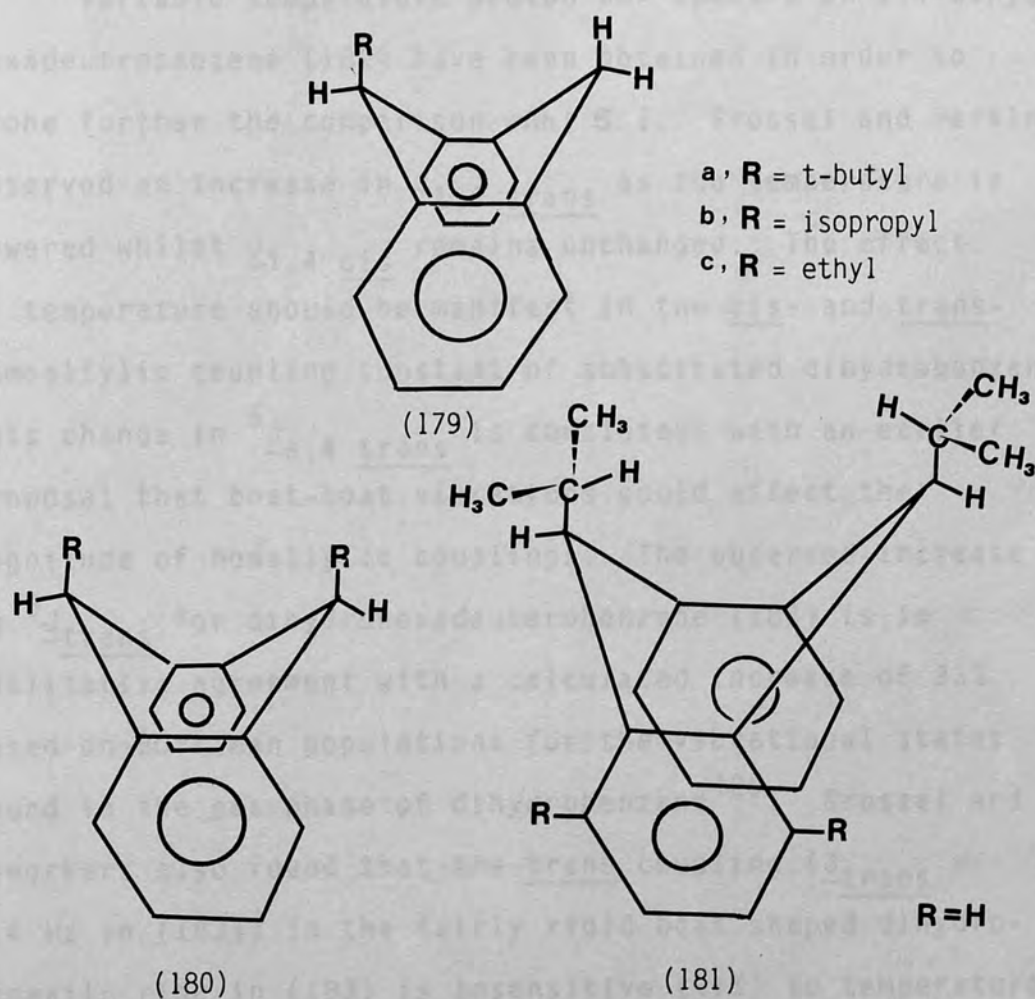
The major steric factors in the derivatives of (142) arise from interaction of large C-1 or C-4 substituents with the proximate *peri*-hydrogen atoms. These effects are minimized by puckering of the 1,4-dihydronaphthalene ring.

6.2.3. 9,10-Dihydroanthracenes

9,10-Dihydroanthracene (6) has been shown by X-ray diffraction⁹⁶ to be non-planar ($\alpha = 145^\circ$) and is presumed to undergo rapid boat-to-boat ring inversion even at low temperatures¹⁰⁵. There is general agreement that the central ring of 9,10-dihydroanthracene exists in a boat conformation. In contrast the preferred conformations of 9-substituted derivatives have been a matter of some controversy. While R=H in (177) undoubtedly inverts rapidly between equivalent boat conformers^{126,127}, the presence of a 9-substituent can shift the equilibrium to favour one of the two forms (178a) in which R is pseudoaxial or (178b) where R is pseudoequatorial.



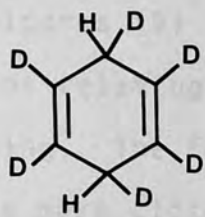
Rabideau and coworkers¹²⁷ have prepared a series of 9-alkyl(phenyl)-9,10-dihydroanthracenes and the substituents were shown to prefer a pseudoaxial location. These results which contradict earlier reports show that 9-*t*-butyl (179a), 9-isopropyl (179b) and 9-ethyl groups (179c) favour a pseudoaxial orientation. However in the case of the 9-methyl and 9-phenyl derivatives there is some population of the other conformer at equilibrium. For the disubstituted derivatives, it was found that cis-9,10-dialkyl-9,10-dihydroanthracene (180) favours an orientation in which the alkyl groups are dipseudoaxial, whereas the trans-isomers undergo rapid boat-boat inversion.



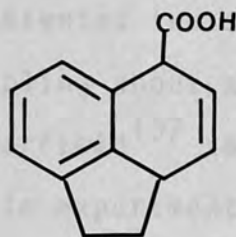
Homoallylic coupling constants were measured in an attempt to resolve the dispute about the conformations of mono substituted 9,10-dihydroanthracenes. Rabideau and coworkers⁶⁰ found that cis-9,10-tert-butyl-10-ethyl-9,10-dihydroanthracene (180) has a large (for dihydroanthracenes) homoallylic coupling constant of 1.3 Hz as compared with the more normal value of 0.3 observed with cis-9-isopropyl-10-ethyl-9,10-dihydroanthracene (181).

6.3. VIBRATIONAL EFFECTS VS. BOAT-BOAT INVERSION

Variable temperature proton nmr spectra of 1,4-dihydrohexadeutrobenzene (182) have been obtained in order to probe further the comparison with (5). Grossel and Perkins¹²⁸ observed an increase in $\underline{J}_{1,4 \text{ trans}}$ as the temperature is lowered whilst $\underline{J}_{1,4 \text{ cis}}$ remains unchanged. The effect of temperature should be manifest in the cis- and trans-homoallylic coupling constant of substituted dihydrobenzenes. This change in $\underline{J}_{a,4 \text{ trans}}$ is consistent with an earlier proposal that boat-boat vibrations could affect the magnitude of homallylic couplings. The observed increase in $\underline{J}_{\text{trans}}$ for dihydrohexadeutero benzene (182) is in qualitative agreement with a calculated increase of 23% based on Boltzman populations for the vibrational states found in the gas phase of dihydrobenzene¹²⁹. Grossel and coworkers also found that the trans coupling ($\underline{J}_{\text{trans}} = 3.4 \text{ Hz}$ in (183)) in the fairly rigid boat shaped dihydroaromatic ring in (183) is insensitive (<1%) to temperature over a 120° range.



(182)



(183)

6.4. THEORETICAL DEPENDENCE OF COUPLING ABOUT A DIHYDRO-AROMATIC RING

A number of attempts have been made to predict theoretically the dependence of the various interpretation coupling constants with conformation. Grossel and coworkers have used various literature data to predict the variation of vicinal, allylic and homoallylic couplings about a dihydroaromatic ring with conformation. These data have been compared with experimental values both to provide insight into the conformations of the dihydroaromatic derivatives and to assess the precision of calculation.

In Figure (8), is presented the variation of vicinal coupling with ring conformation based on calculation of Pople and coworkers¹³⁰. For a planar ring the vicinal coupling to pseudoaxial and pseudoequatorial protons should of course be identical. As the ring puckers coupling to the pseudoaxial proton decreases in magnitude as overlap between the C-H bonds diminishes and passes through a minimum value ca. 2.5 Hz for $\alpha = 160^\circ$. In contrast coupling to the pseudoequatorial proton increases with increased ring puckering.

In Figures (9) and (10) are presented two sets of calculations relating to allylic coupling about a dihydro-aromatic ring. The former, due to Barfield¹³⁷ seems to approximate more closely the available experimental data. For example, allylic coupling to a pseudoaxial proton decreases from ≈ -1.5 Hz in a planar ring to ca. 3.0 Hz when $\alpha = 140^\circ$. The largest experimental values for this interaction are ca. ≈ -3.2 Hz. The other calculations due to Marshall¹²² suggest a similar geometric dependence but passes through a minimum value of ca. -4 Hz. Coupling to the pseudoequatorial proton passes through 0 and becomes positive as ring puckering increases.

The conformational dependence of homoallylic coupling has been the subject of much controversy. In Figure (11) are compared calculations of Grossel and Perkins, and Marshall and coworkers. It is not clear whether J_{cis} or J_{trans} should be the greater in the planar dihydrobenzene ring. However it is clear that as the ring folds, cis dipseudoaxial coupling increases in magnitude reaching a maximum value for $\alpha \approx 145^\circ$. Cis dipseudoequatorial coupling rapidly decreases to a very low value when $\alpha \approx 140^\circ$. The trans coupling also decreases as ring puckering increases but at less rather than slower rate.

Grossel has compared these calculations and has argued that Marshall's data overestimate homoallylic coupling by a factor of 2. He notes, as is shown in Figure (11) that if this factor is taken into account the two sets of calculations predict an essentially similar geometric dependence for the homoallylic couplings.

This is further emphasised by a comparison of the geometric dependence of the homoallylic constant ratio $\frac{J_{\text{cis}}}{J_{\text{trans}}}$ in Figure (12).



FIGURE 12.

Vicinal coupling ($J_{1,2}$) in puckered cyclohexane-1,4-diene

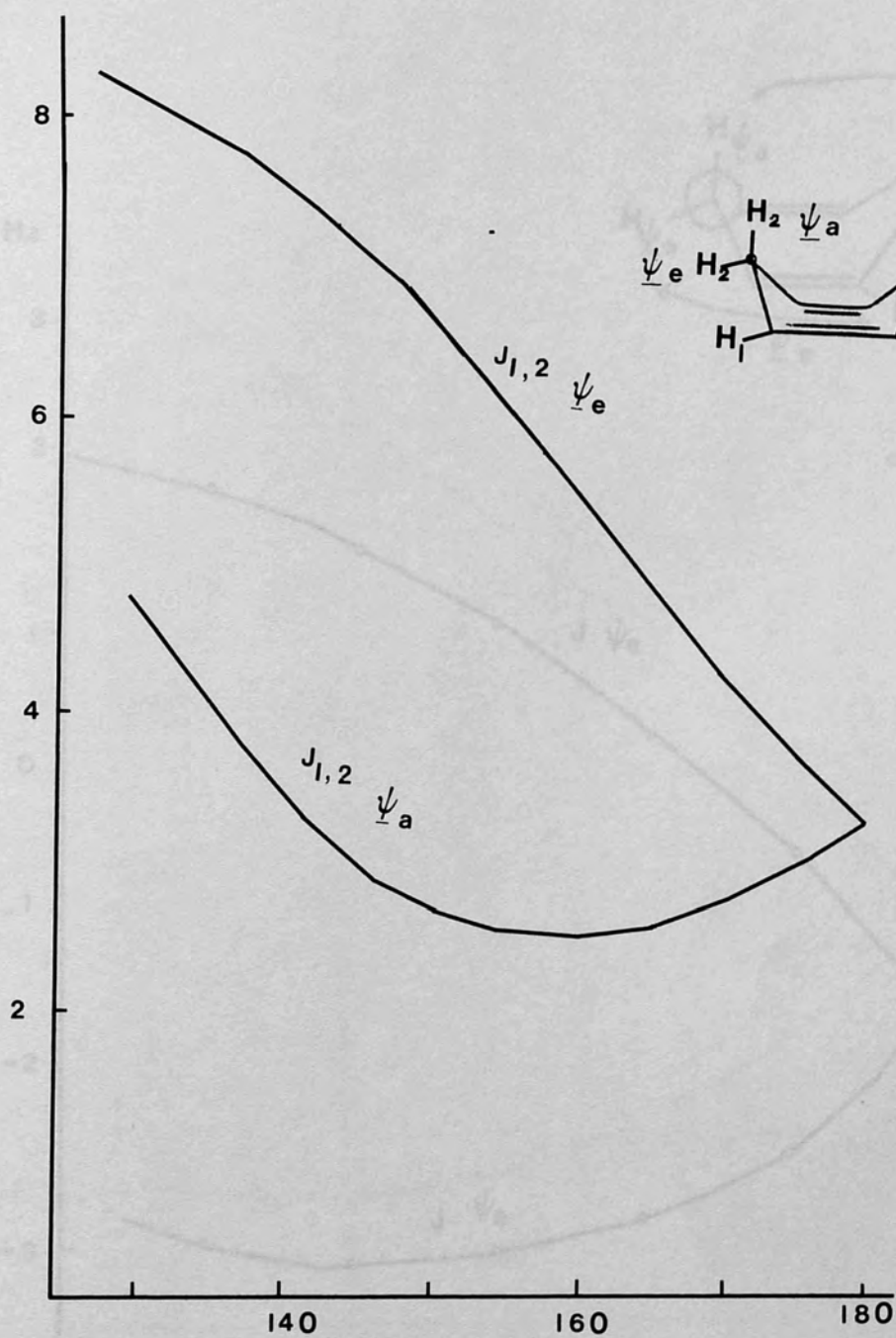


FIGURE 8.

Vicinal coupling ($J_{1,2}$) in puckerd cyclohexa-1,4-diene¹³⁰

FIGURE 9.

Allylic coupling in cyclohexa-1,4-diene as a function of ring pucker¹³¹

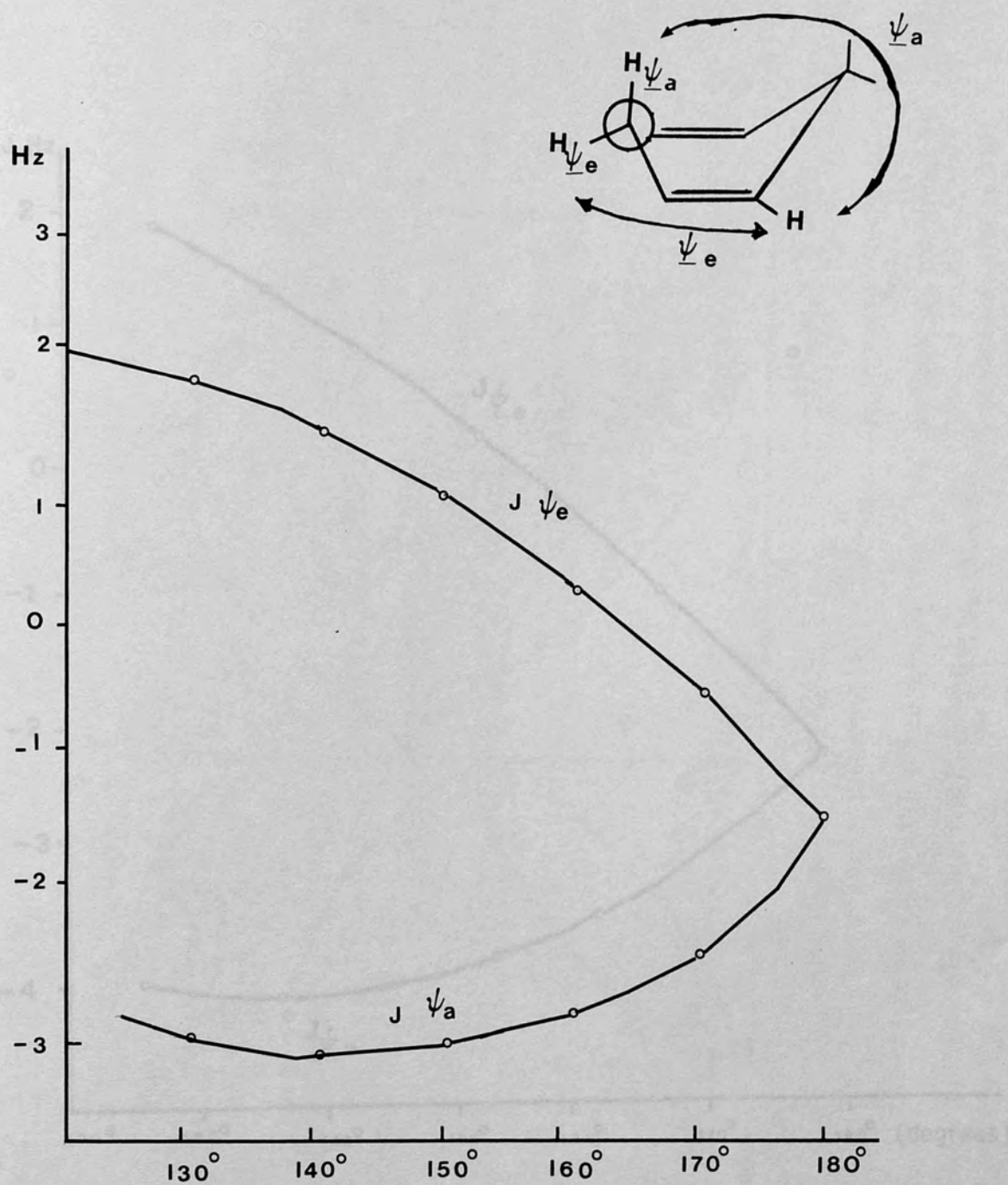


FIGURE 9.
Allylic coupling in cyclohexa-1,4-diene as a function of
ring pucker¹³⁷

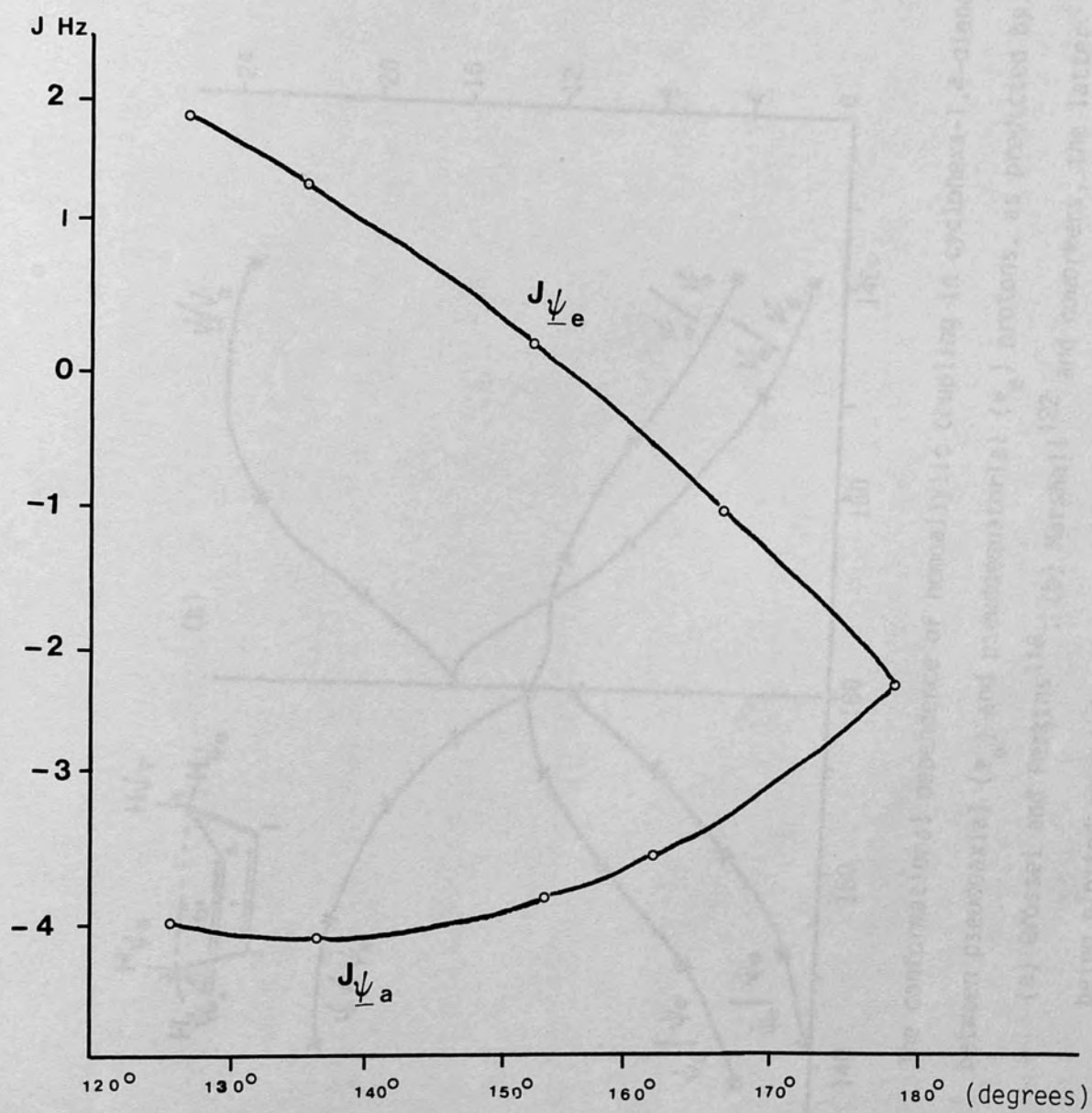


FIGURE 10.

INDO calculations for cyclohexa-1,4-diene after Marshall and coworkers showing allylic coupling values.¹²²

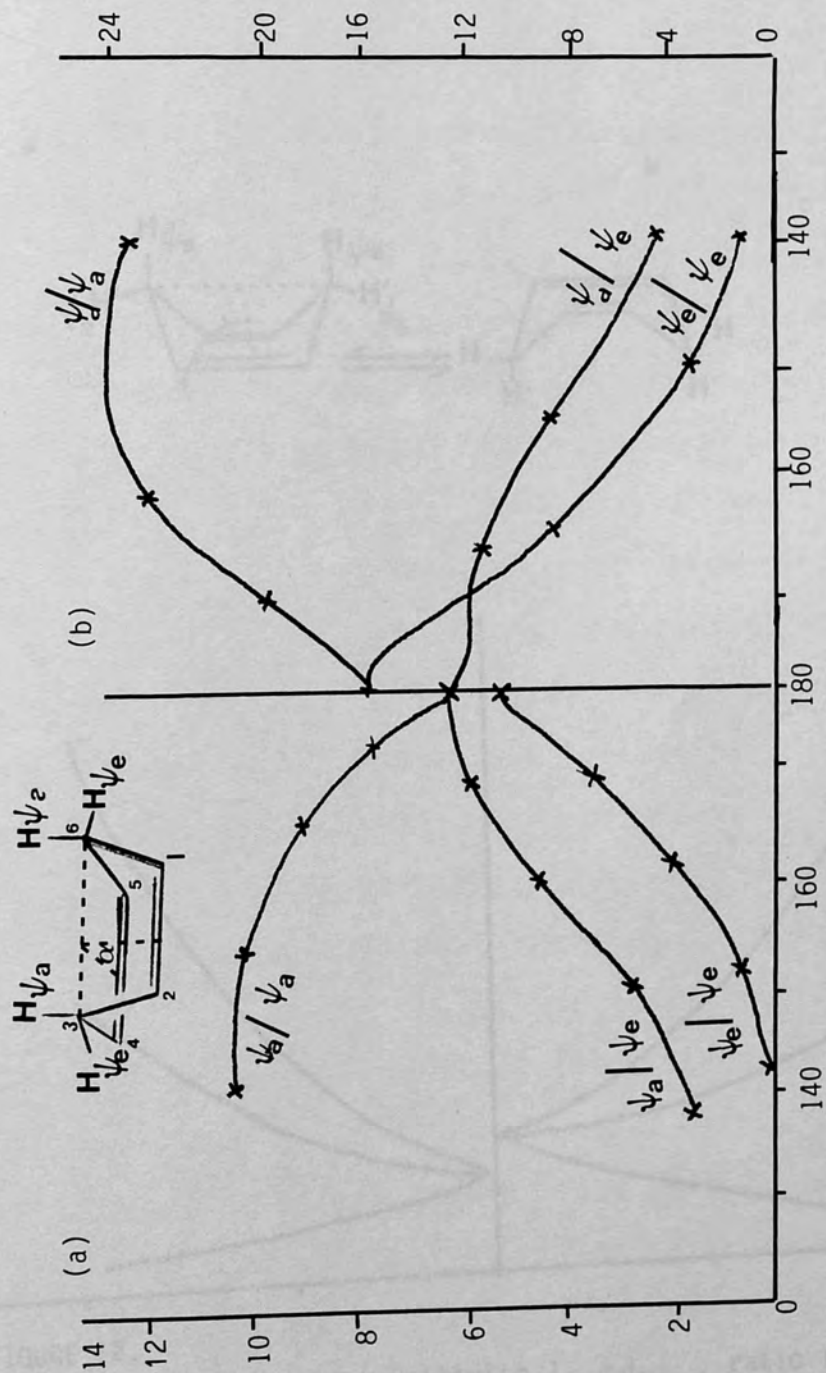


FIGURE 11. The conformational dependence of homoallylic coupling in cyclohexa-1,4-diene between pseudoaxial (ψ_a) and pseudoequatorial (ψ_e) protons, as predicted by: (a) Grosse and Perkins¹¹⁸; (b) Marshall¹²² and coworkers, the latter being plotted on a halved scale.

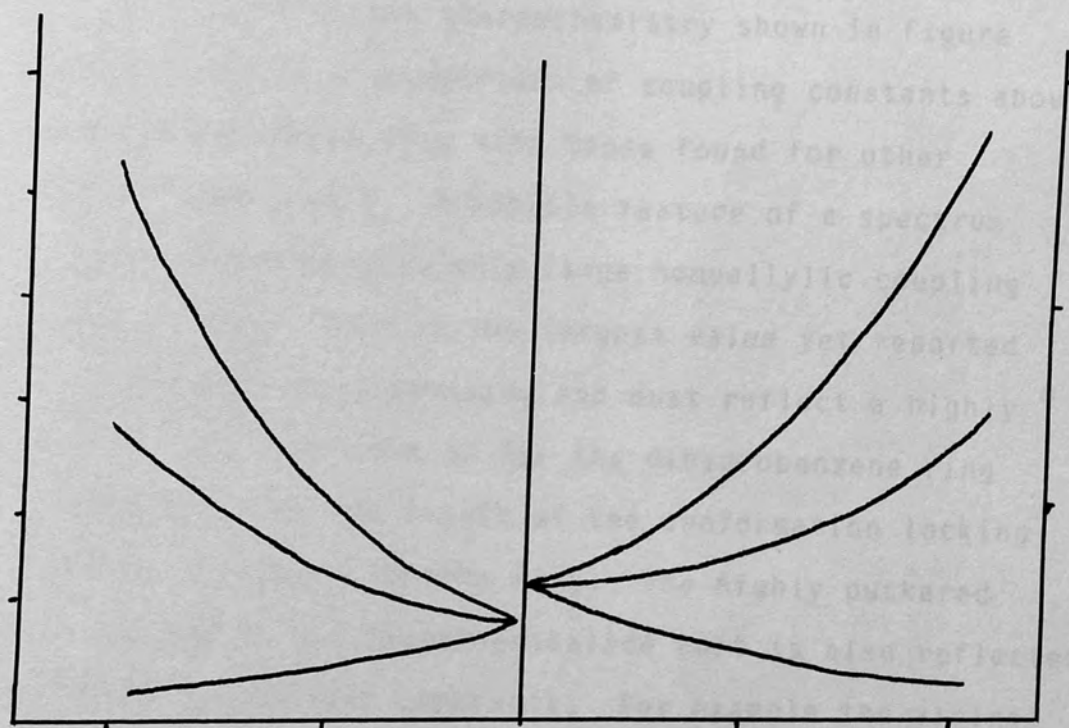
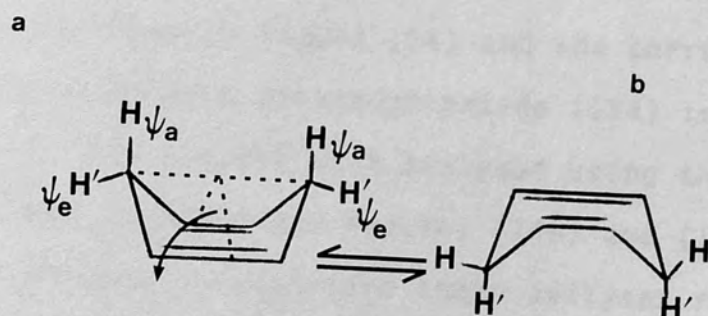


FIGURE 12.
 Geometric dependence of homoallylic $J_{\text{cis}} : J_{\text{trans}}$ ratio in cyclohexa-1,4-diene. (a) Grossel and Perkins¹¹⁸
 (b) Marshall and coworkers¹²²

CHAPTER 7

RESULTS AND DISCUSSION

7.1. 1,4-DIHYDROPHthalIDES

^1H NMR spectrum of 1,4-dihydro-3,3'-dimethylphthalide (121) is shown in Figure (14) and the corresponding spectra of the methylated dihydrophthalide (124) is shown in Figure (15). These spectra were analysed using the spin simulation programme (ITACAL) and Figures (14A) and (15A) include the simulated spectra from these analyses respectively.

In Table 9 are listed the coupling constants obtained from analysis of the ^1H nmr of (121) and (124). The protons have been assigned the stereochemistry shown in Figure (13) as a result of comparison of coupling constants about the dihydroaromatic ring with those found for other dihydroaromatic acid. A notable feature of a spectrum of (121) is the particularly large homoallylic coupling $J_{1,4} = 13.7$ Hz. This is the largest value yet reported for cyclohomomoallylic coupling and must reflect a highly puckered boat conformation for the dihydrobenzene ring in (121) which is the result of the conformation locking effect of the fused lactone ring. The highly puckered conformation of the dihydrophthalide unit is also reflected in the other coupling constants. For example the vicinal coupling between pseudoaxial protons H-1 and H-4, and the vicinal neighbours H-2, H-3 and H-6 are all relatively small lying in the range 2.1-2.5 Hz. The slight difference

TABLE 9. Frequencies and coupling constants for the ring protons in 1,4-dihydro-3,3-dimethylphthalide (121) and 1,4-dihydro-1-methyl-3,3-dimethylphthalide (124) as obtained by computer simulation of their 400 MHz spectra in CDCl_3 .

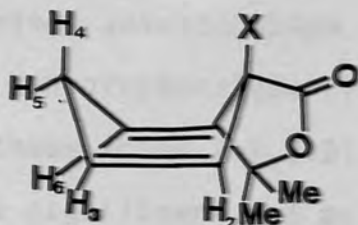
P.m.r. spectral parameters	1,4-dihydro-3,3-dimethylphthalide (121)	1,4-dihydro-1-methyl-3,3-dimethylphthalide (124)
(a) frequencies		
ν_1	1479.595	
ν_2	2419.902	2447.034
ν_3	2370.359	2359.342
ν_4	1088.354	1107.871
ν_5	1109.377	1079.322
ν_6	2306.775	2331.236
(b) coupling constants		
J(1,2)	2.466	
J(1,3)	-3.126	
J(1,4)	13.709	
J(1,5)	6.369	
J(1,6)	-3.143	
J(2,3)	9.734	9.252
J(2,4)	-2.957	-3.227
J(2,5)	-1.001	-0.604
J(2,6)	-0.012	-0.006
J(3,4)	2.328	1.911
J(3,5)	4.659	5.230
J(3,6)	1.184	1.038
J(4,5)	-21.938	-21.729
J(4,6)	2.111	1.794
J(5,6)	5.573	6.316

line width

0.5 Hz

0.5 Hz

FIGURE (13)

(121) $X = H_1$ (124) $X = Me$ 

between $J_{1,2}$ and $J_{3,4}$ on the one hand and $J_{4,6}$ on the other may reflect a substituent effect due to the alkyl group on the double bond bearing the latter proton. The allylic couplings $J_{1,3}$, $J_{1,6}$ and $J_{2,4}$ all have a magnitude greater than -3 Hz. These values are all once again consistent with interaction with pseudoaxial proton on a highly puckered dihydrobenzene ring (and should be negative). In contrast the vicinal couplings $J_{3,5}$ and $J_{5,6}$ are both relatively large suggesting that the C-H₃ and C-H₅ bonds are each almost coplanar. With C-H₆ the allylic coupling $J_{2,5}$ is very small as expected for a pseudoequatorial proton. The coupling $J_{3,6}$ is not normally measurable since the protons H-3 and H-6 are normally equivalent; the value of approximately 1 Hz observed for this coupling is similar to the only other values previously observed in a highly puckered ring (*cis*-2a,5-dihydrobenzocyclobutene-oic acid)¹³². An unusual aspect of the data for (121) lies in the relatively high value for the trans homoallylic coupling $J_{1,5}$ (6.4 Hz) which can be compared with the value of

(4.7 Hz) observed by Rabideau in numbers of dihydrotriptycene carboxylic acid¹³³. The interpretation of these values is not clear and may result from substituent effect and this will need further investigation. The coupling observed for the methylated dihydrophthalide (124) are similar but not identical to those found for (121). These differences are believed to be significant and may reflect different steric interactions resulting from introduction of the extra methyl substituent at C-1. It is hoped to obtain crystals of (124) suitable for X-ray structural analysis. Unfortunately (121) is probably too unstable to be suitable for this purpose.

7.2. 8-ALKYL-1,4-DIHYDRONAPHTHOIC ACID

In the course of this work two 8-substituted 1,4-dihydronaphthoic acid (97) and (114) have been prepared. Their ¹H nmr spectra have been analysed in detail and the results are presented in Figures 16 and 16A for (97), 17 and 17A for (114) and the coupling constants in Table (10). A notable feature of these data is that the coupling constants of (97) and (114), all are effectively the same. The vicinal coupling constants $J_{1,2}$ and $J_{3,4}$ are both large and of similar magnitude. These values suggest that H-1 and H-2 are effectively coplanar as are H-3 and H-4. It must therefore be concluded that H-1 and H-4 are cis to each other and pseudoequatorial. The observation that $J_{3,5}$ is much smaller than $J_{3,4}$ suggests that H-5 is

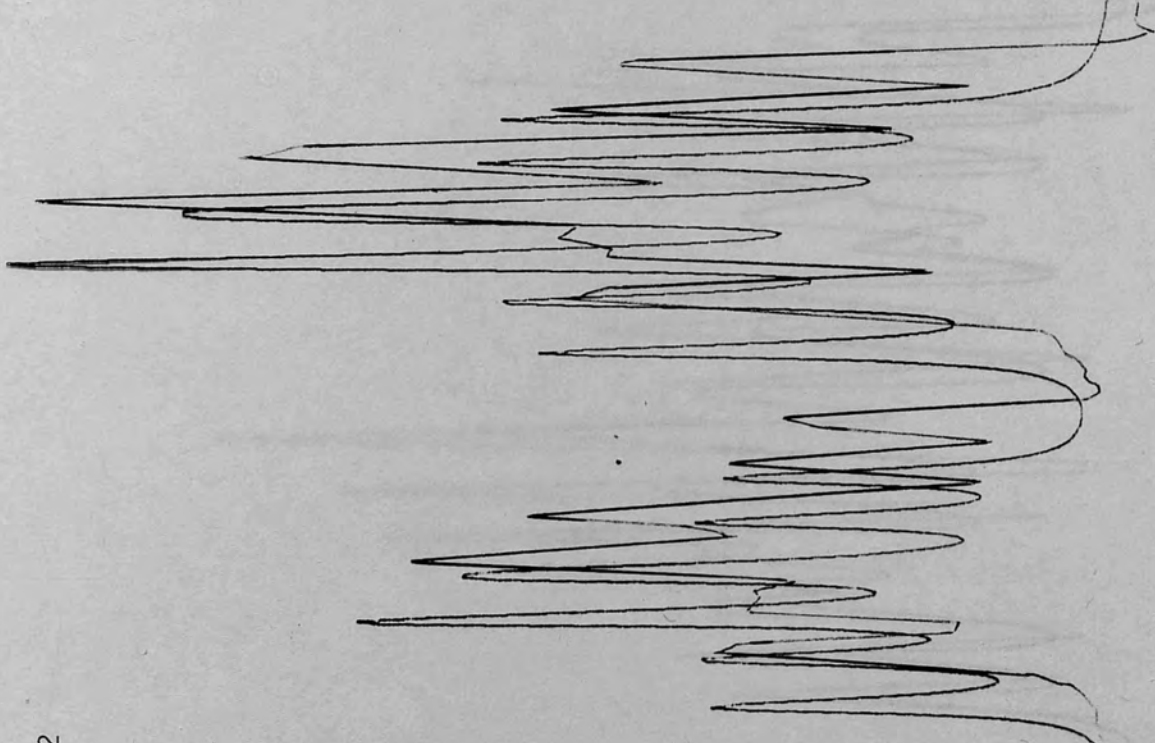
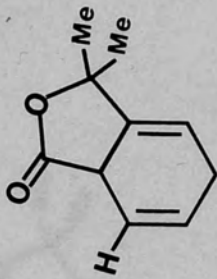


FIG. 14: H-2

fig. 14 A

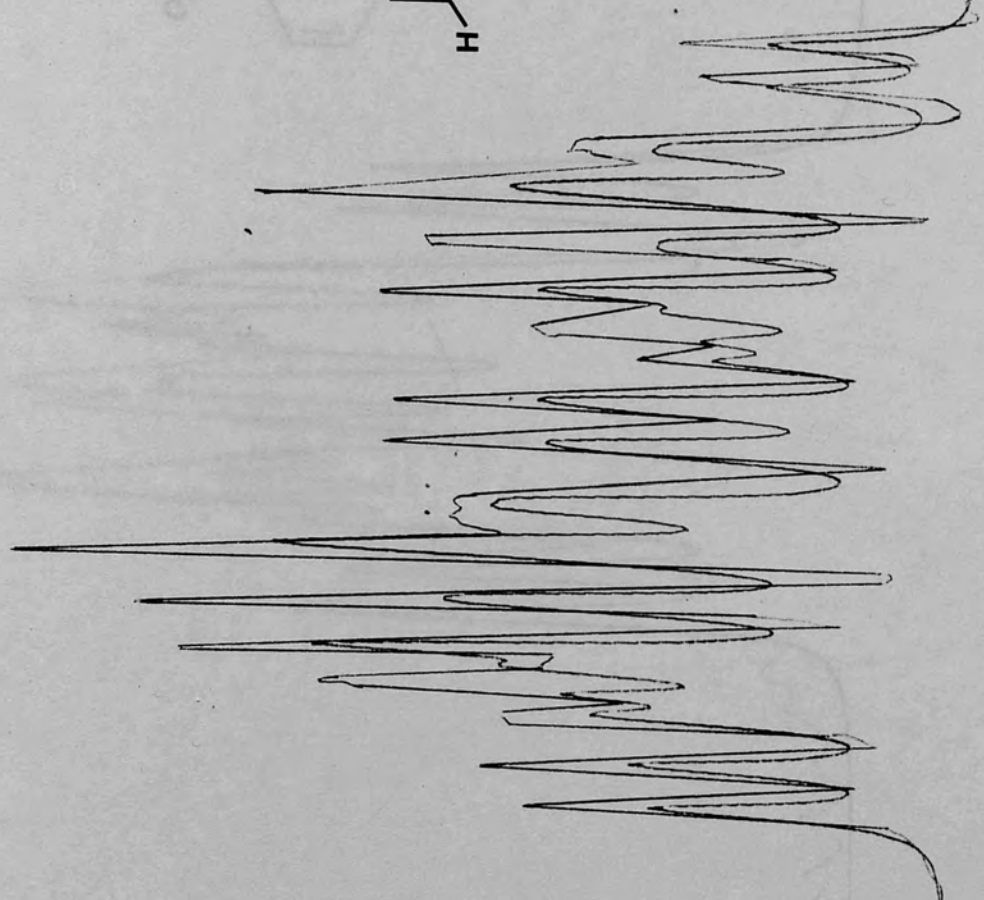
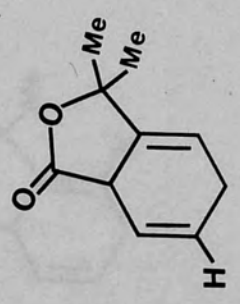


FIG. 14: H-3

fig 14 A

FIG. 14: H-6

fig 14A

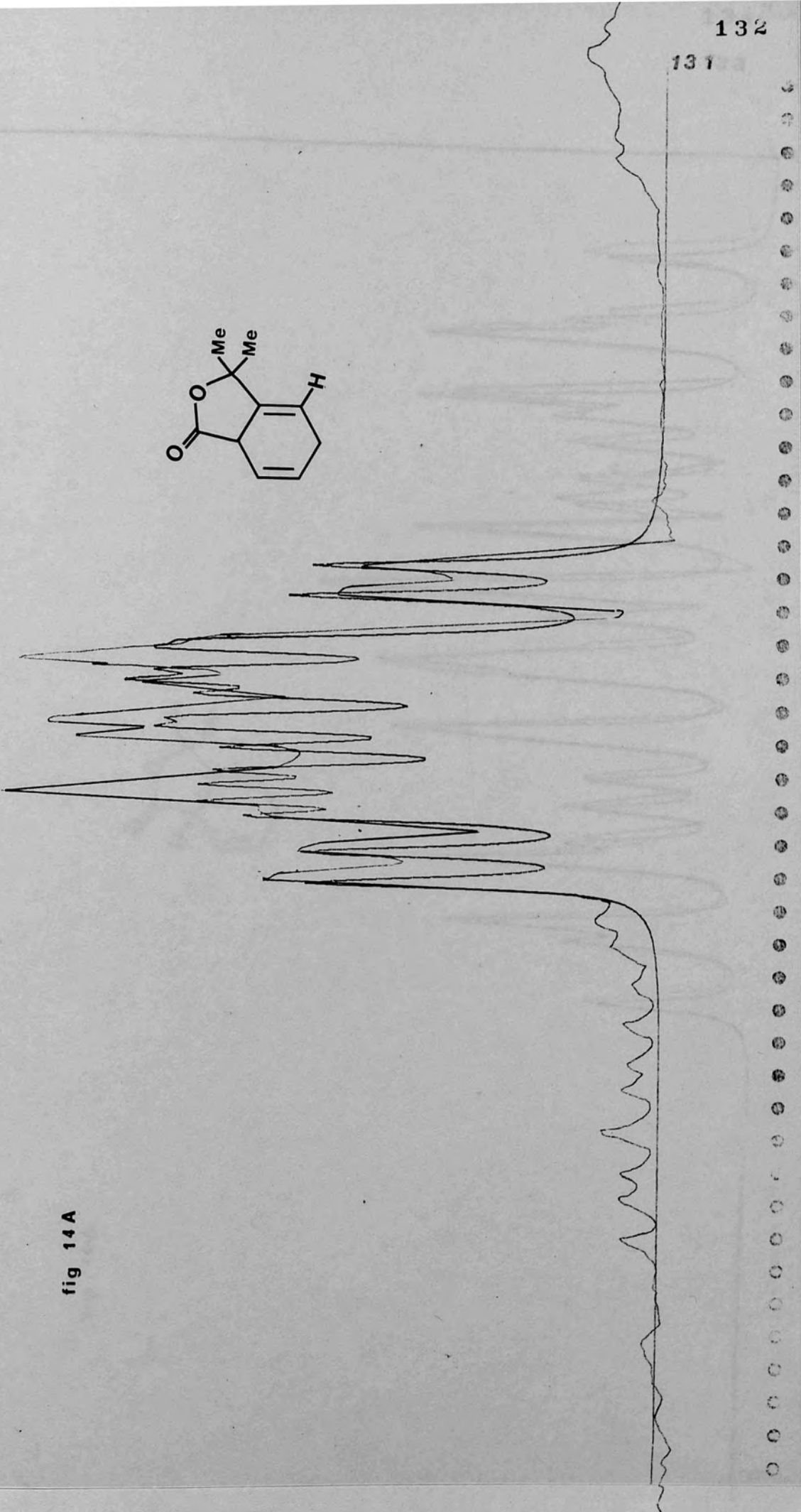
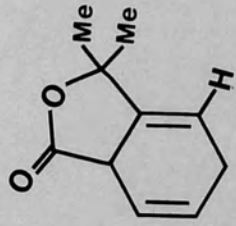
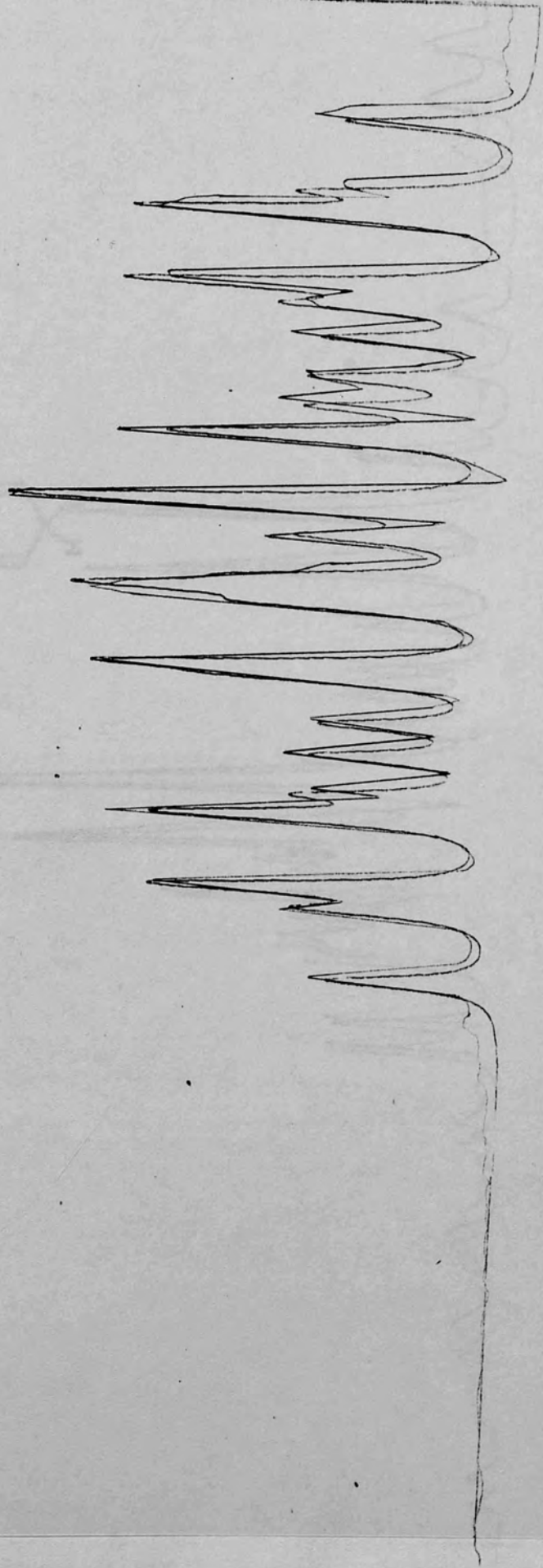
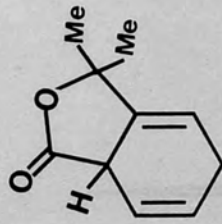


FIG. 14: H-1

fig 14 A



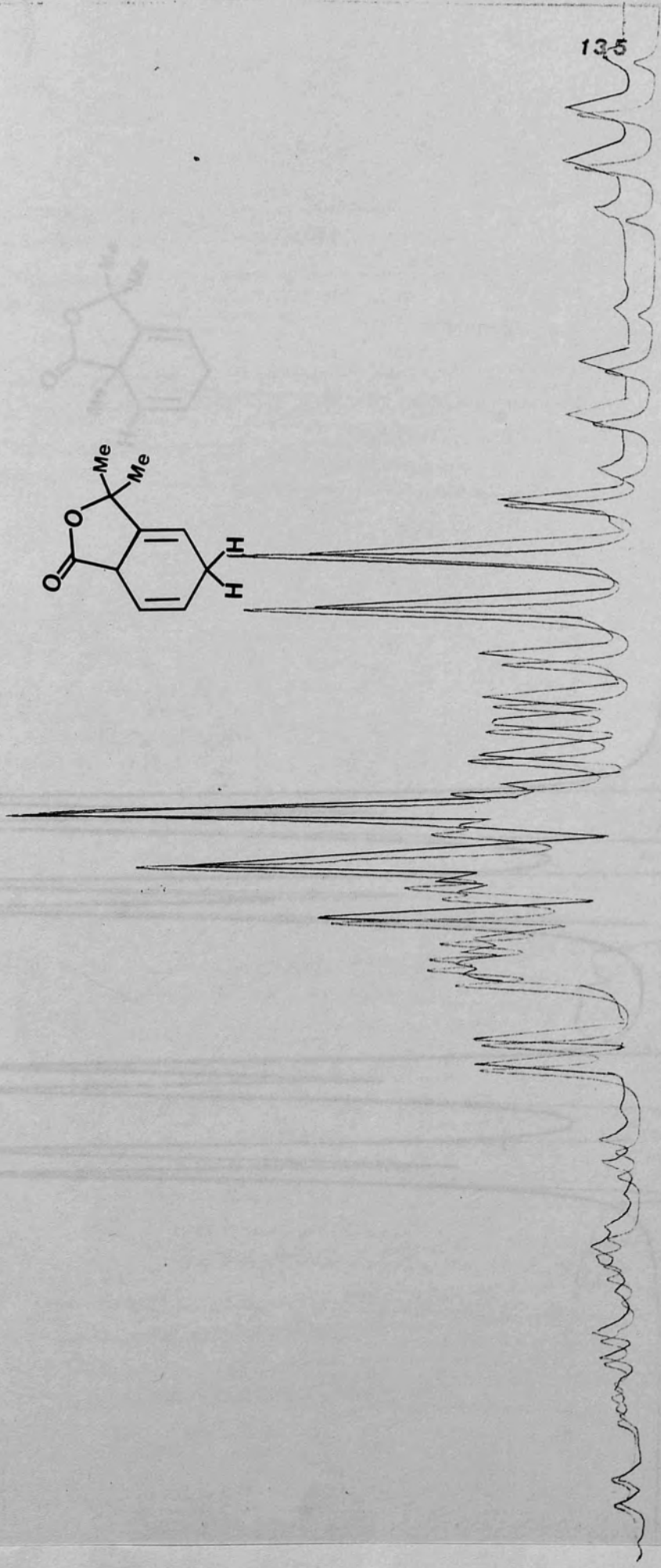
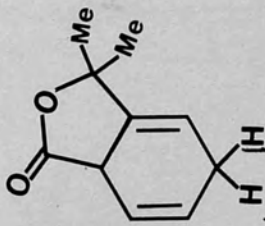


FIG. 14: H-4,5

fig 14 A

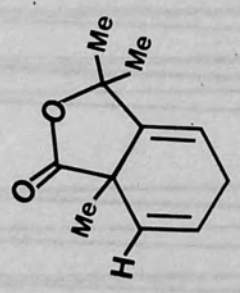


FIG. 15: H-2

fig 15A

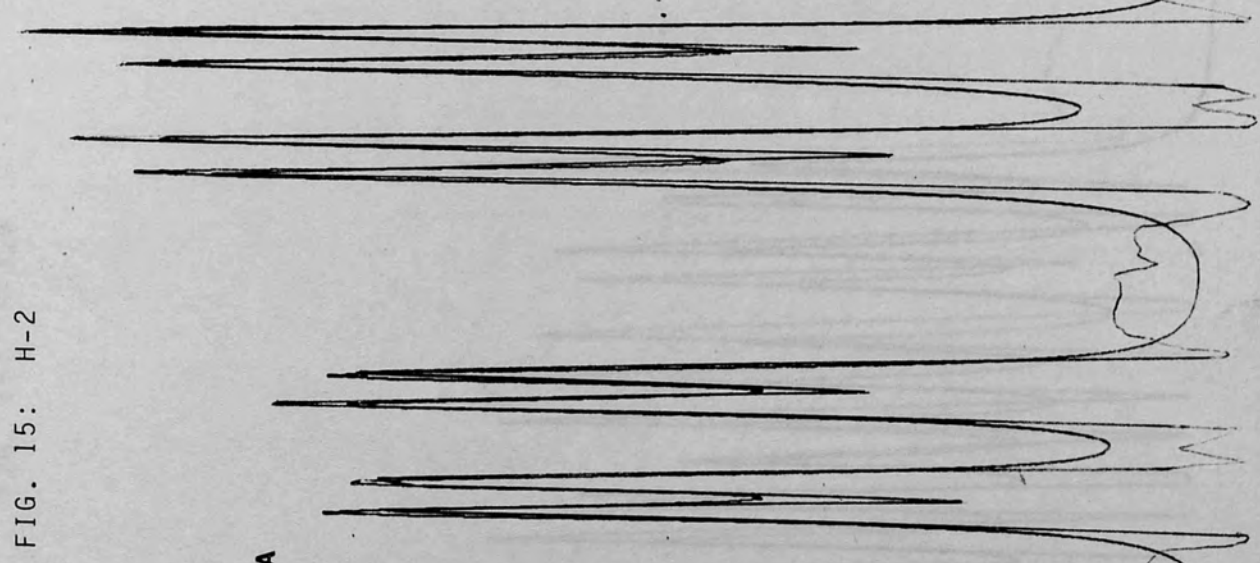
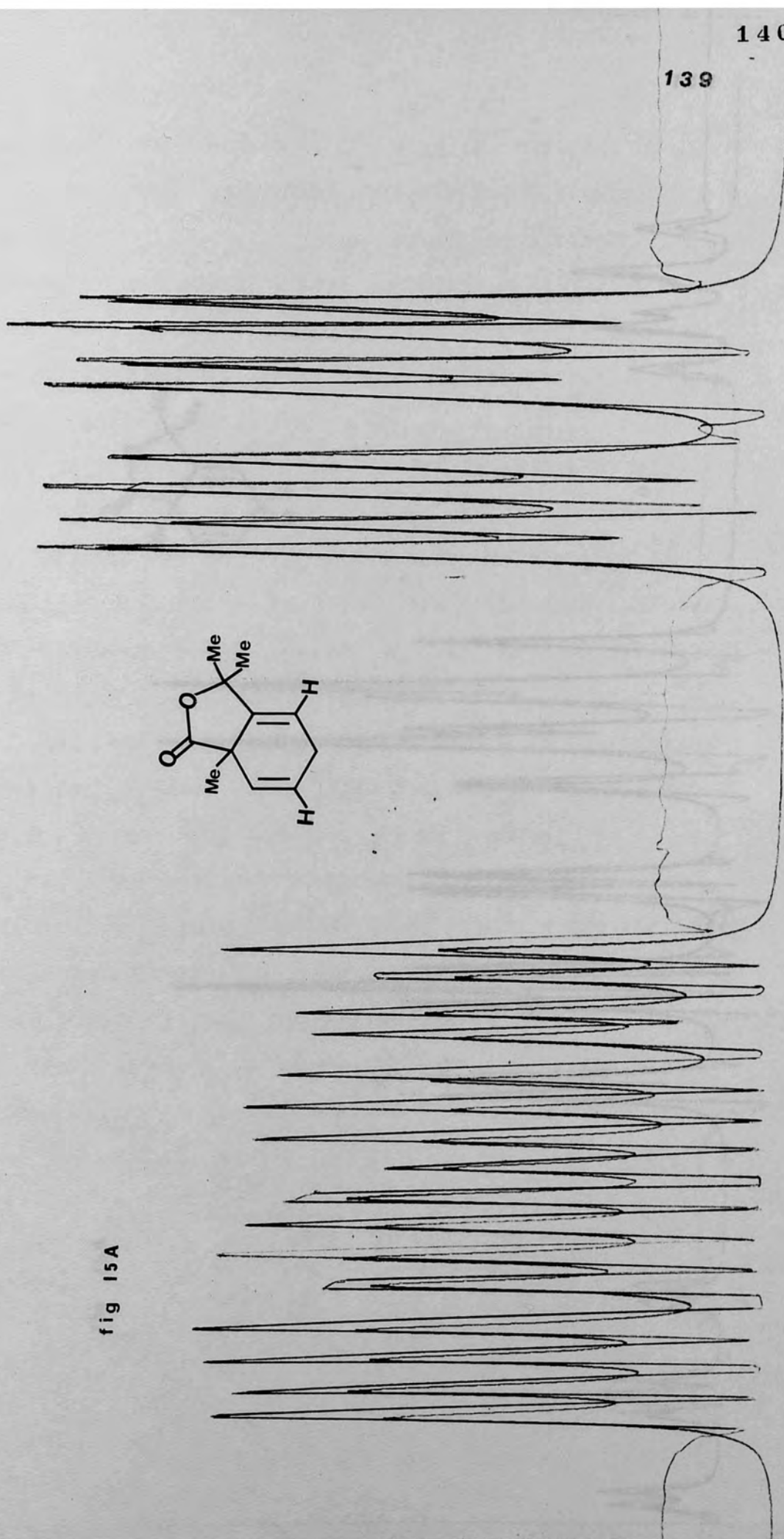
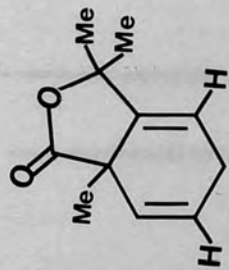
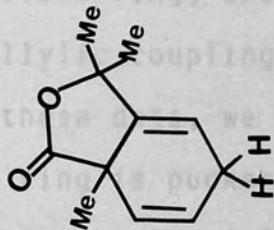


fig 15A



pseudoaxial. In the case of the allylic couplings $J_{1,3}$ and $J_{2,4}$ are small consistent with H-1 and H-4 being pseudoequatorial. $J_{2,5}$ is large suggesting a pseudoaxial location for H-5 and $J_{1,2}$ must therefore be cis-pseudoaxial pseudoequatorial homoallylic coupling across the dihydronaphthalene ring, whereas $J_{1,5}$ is the corresponding trans homoallylic coupling.

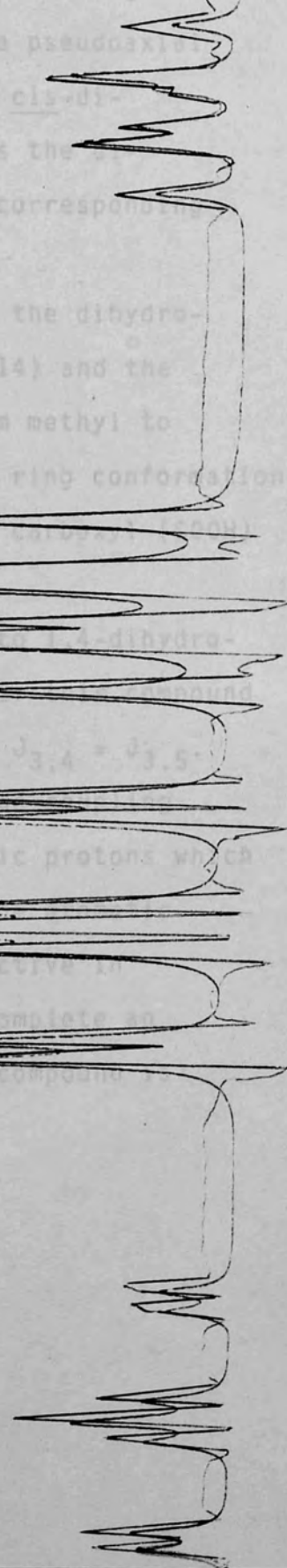


From these data we can conclude that the dihydronaphthalene ring is puckered in (97) and (114) and the effect of changing the C-8 substituents from methyl to isopropyl does not significantly affect the ring conformation which remains puckered in order to keep the carbonyl group away from the 8-alkyl substituent.

Table 10 shows the coupling constants for 1,4-dihydronaphthalene, vicinal and allylic couplings. The data suggest a planar ring since $J_{2,4} = J_{2,5}$ and $J_{3,4} = J_{3,5}$. Unfortunately there is significant distortion in the structure to the aromatic and benzylic protons which hampered further analysis. Decoupling of the aromatic protons in the spectrum has not proved effective in simplifying the data to be analysed and a complete and unambiguous solution of the spectrum of this compound is not yet available.

FIG. 15: H-4,5

fig 15A



pseudoaxial. In the case of the allylic couplings $J_{1,3}$ and $J_{2,4}$ are small consistent with H-1 and H-4 being pseudoequatorial; $J_{2,5}$ is large suggesting a pseudoaxial location for H-5 and $J_{1,4}$ must therefore be cis-di-pseudoequatorial homoallylic coupling across the dihydronaphthalene ring, whereas $J_{1,5}$ is the corresponding trans homoallylic coupling.

From these data, we can conclude that the dihydronaphthalene ring is puckered in (97) and (114) and the effect of changing the C-8 substituents from methyl to isopropyl does not significantly affect the ring conformation which remains puckered in order to keep the carboxyl (COOH) away from the 8-alkyl substituents.

Table 10 also includes data relating to 1,4-dihydronaphthalide, vicinal and allylic coupling for this compound suggest a planar ring since $J_{2,4} = J_{2,5}$ and $J_{3,4} = J_{3,5}$. Unfortunately there is significant long range coupling in the structure to the aromatic and benzylic protons which hampered further analysis. Decoupling of the aromatic protons in the spectrum has not proved effective in simplifying the data to be analysed and a complete unambiguous solution of the spectrum of this compound is not yet available.

TABLE 10. Frequencies and coupling constants for the ring protons in 1,4-dihydro-8-alkylnaphthoic acid (97) and (114) and 1,4-dihydro-naphthalide (104) as obtained by computer simulation of their 400 MHz spectra in CDCl_3 .

p.m.r. spectral parameter	1,4-dihydro-8-methyl-naphthoic acid (97)	1,4-dihydro-8-isopropyl-naphthoic acid (114)	1,4-dihydro-naphthalide (104)
(a) Frequencies			
ν_1	1814.168	1867.775	1640.00
ν_2	2425.129	2414.701	2450.00
ν_3	2492.967	2484.223	2513.00
ν_4	1369.741	1356.356	1375.00
ν_5	1432.135	1421.090	1378.00
(b) Coupling constants			
J(1,2)	5.386	5.500	4.0
J(1,3)	-1.123	-1.103	-2.4
J(1,4)	2.781	2.800	3.7
J(1,5)	4.018	4.000	3.0
J(2,3)	9.718	9.500	10.5
J(2,4)	-0.712	-.727	-3.5
J(2,5)	-3.241	-3.173	-3.5
J(3,4)	5.210	5.200	2.2
J(3,5)	2.226	2.180	2.2
J(4,5)	-21.550	-21.658	-21.00
line width	0.5 Hz	0.5 Hz	0.5 Hz

FIG. 16: H-2

fig 16A

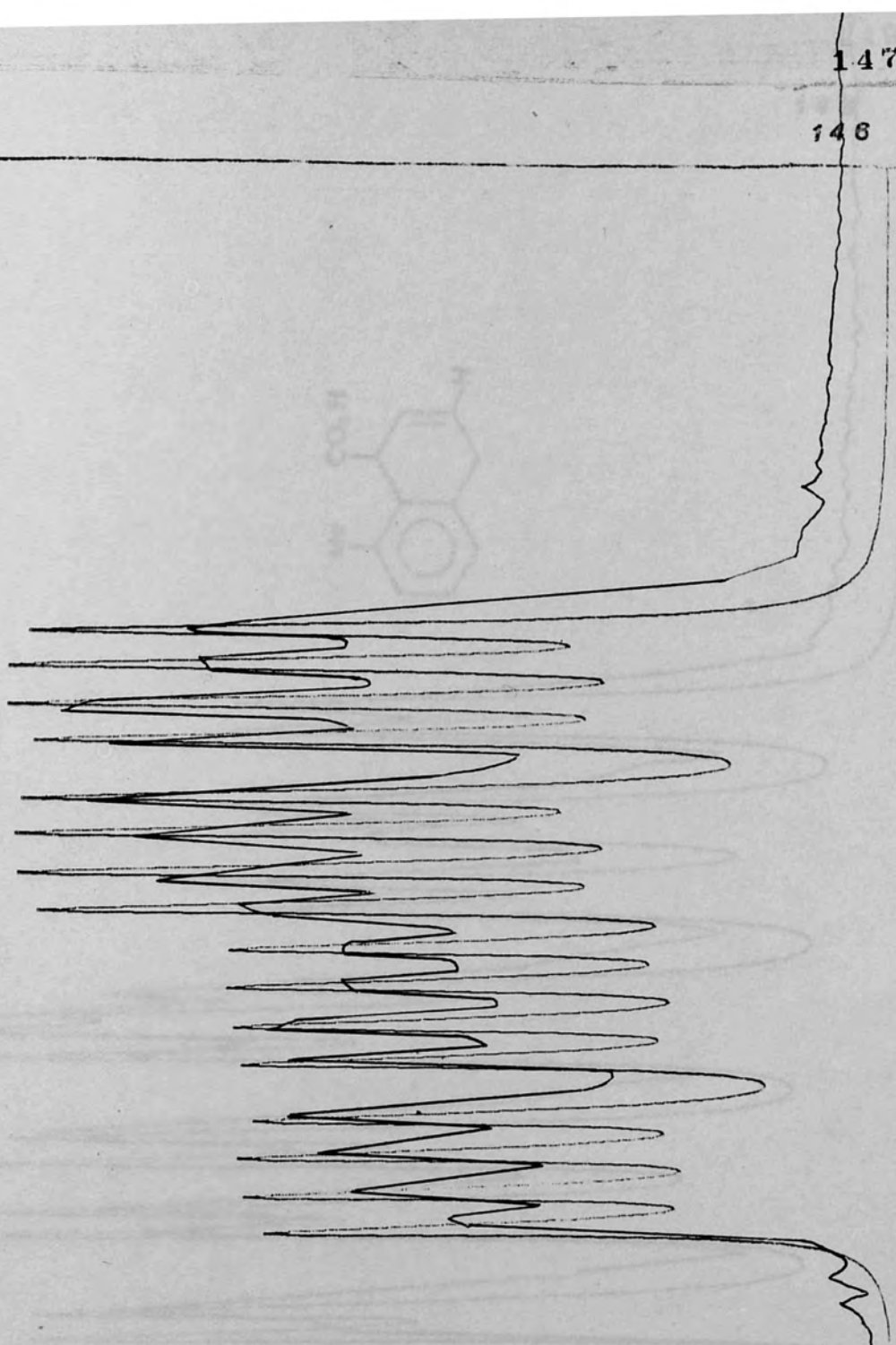
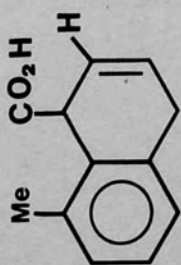
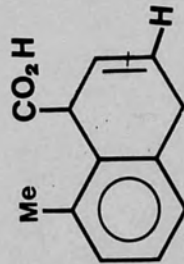


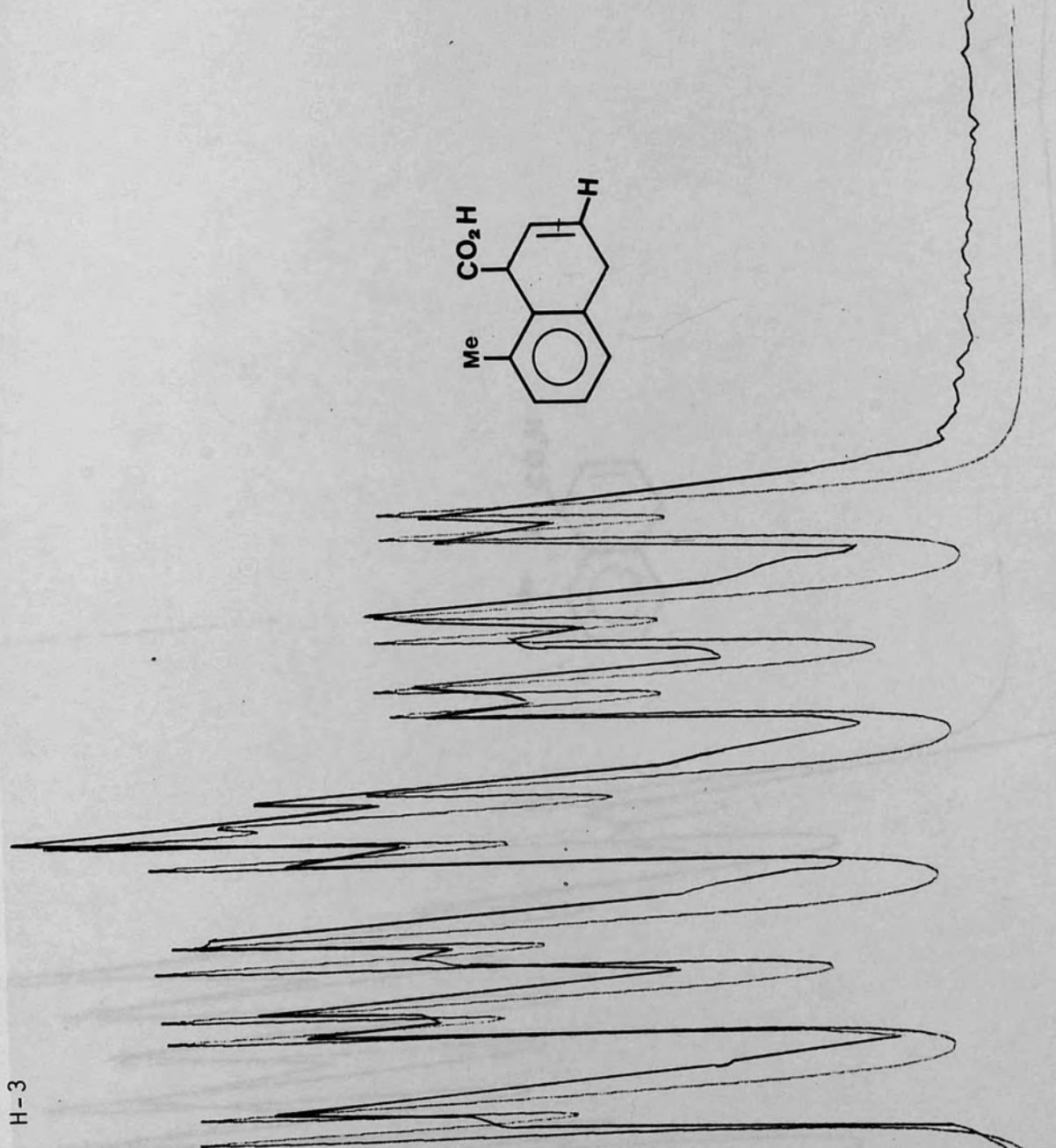
FIG. 16: H-3

fig 16A



149

149



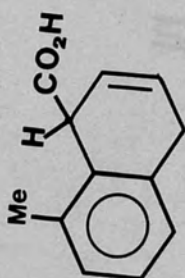


FIG. 16: H-1

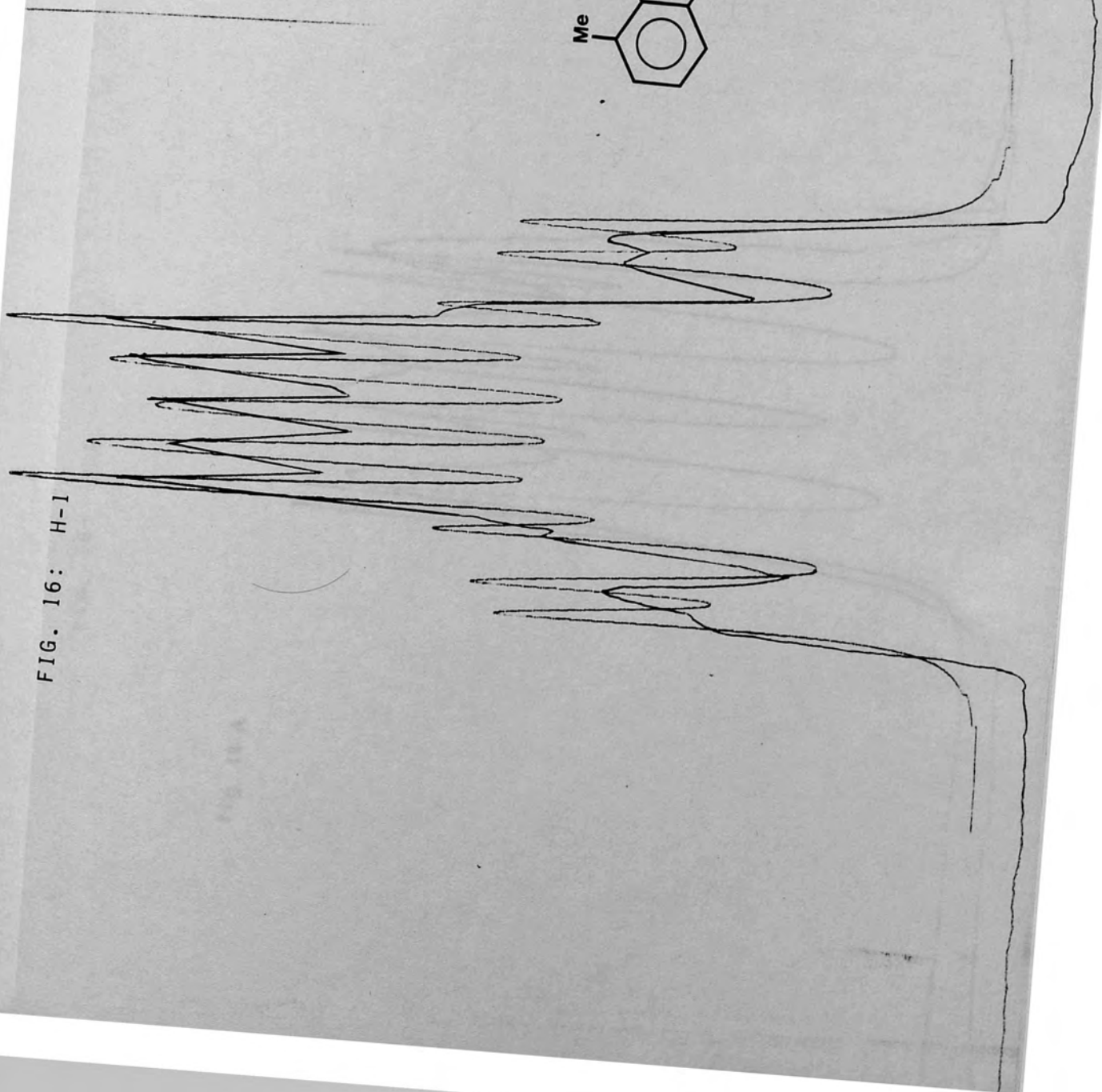


FIG. 16: H-4

fig 16 A

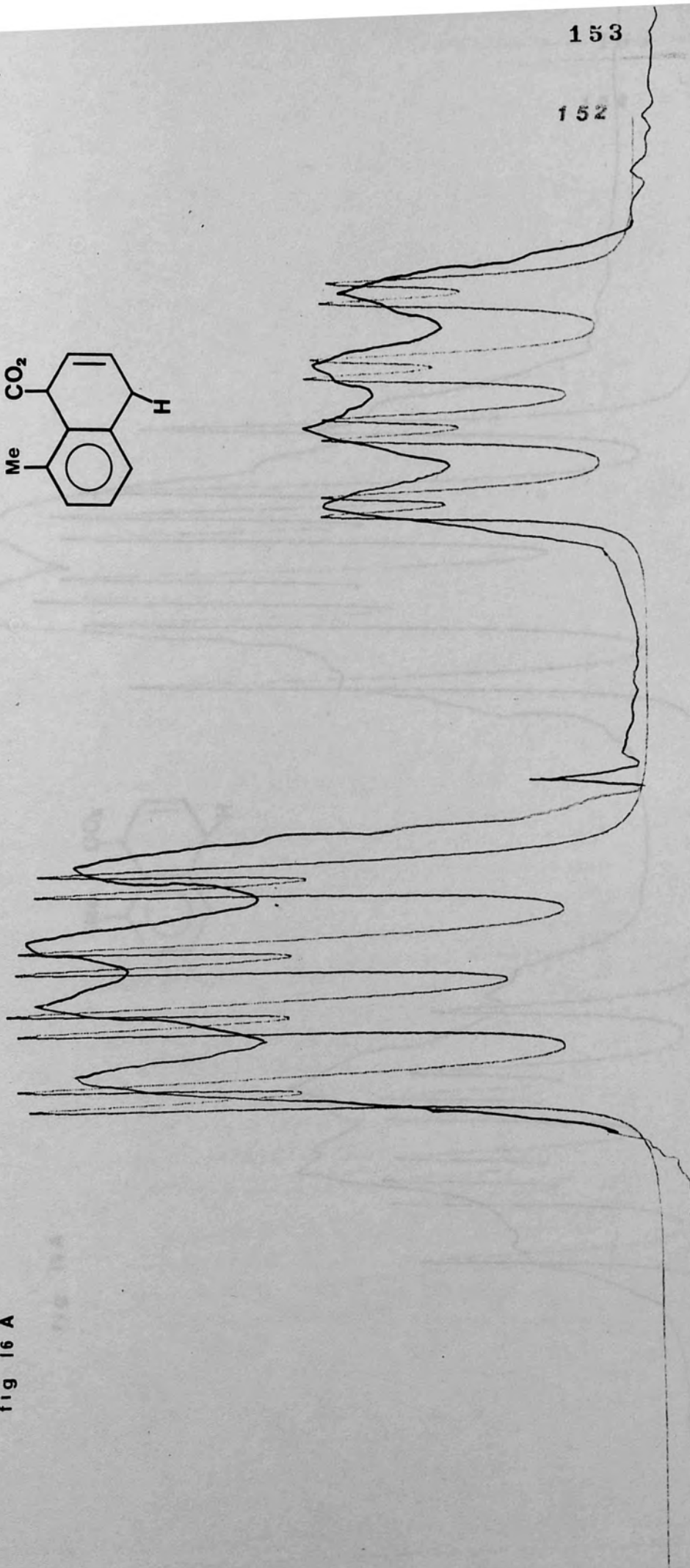
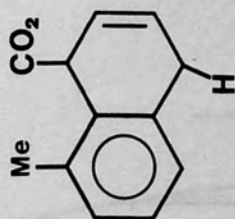


FIG. 16: H-5

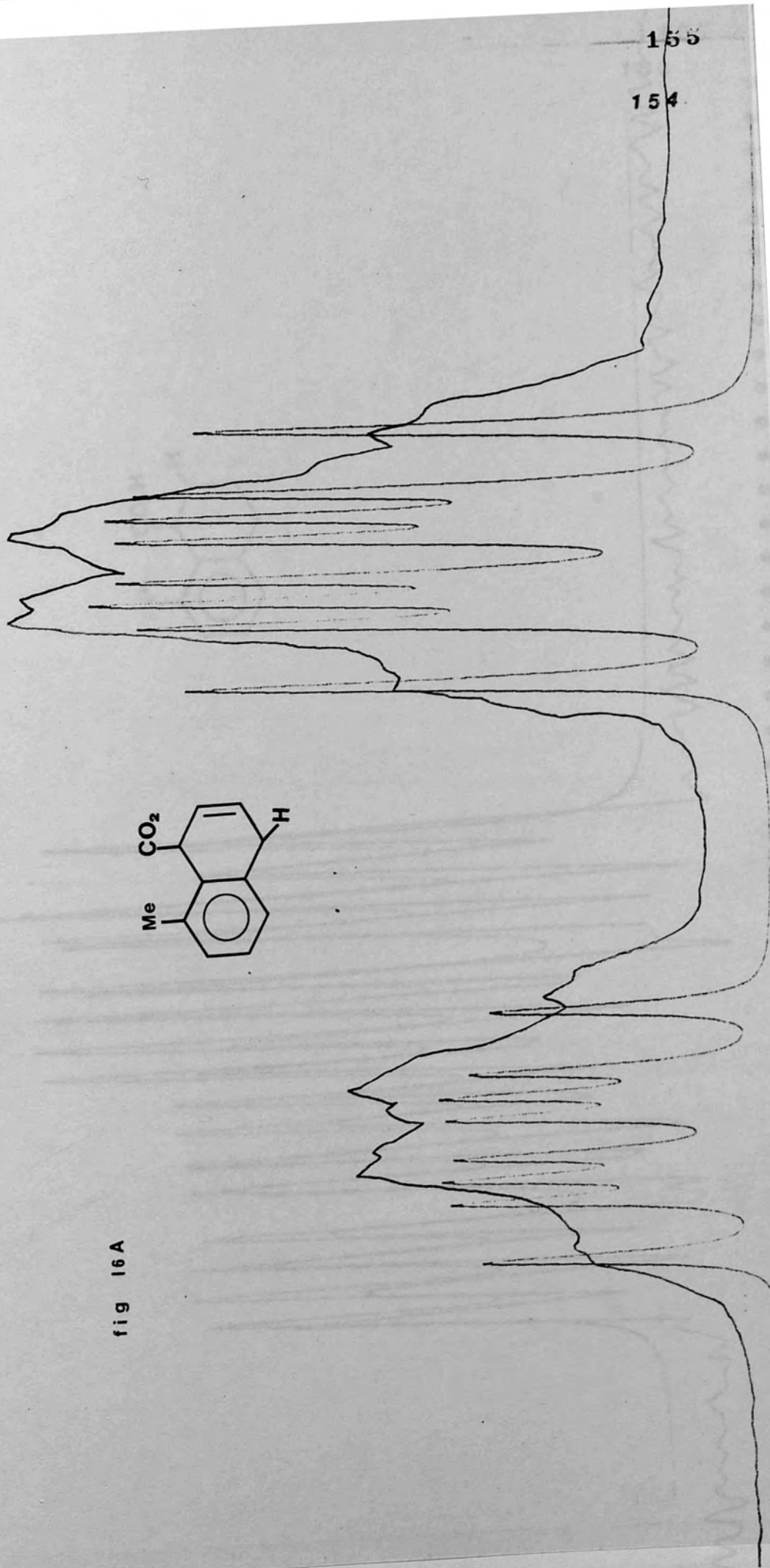
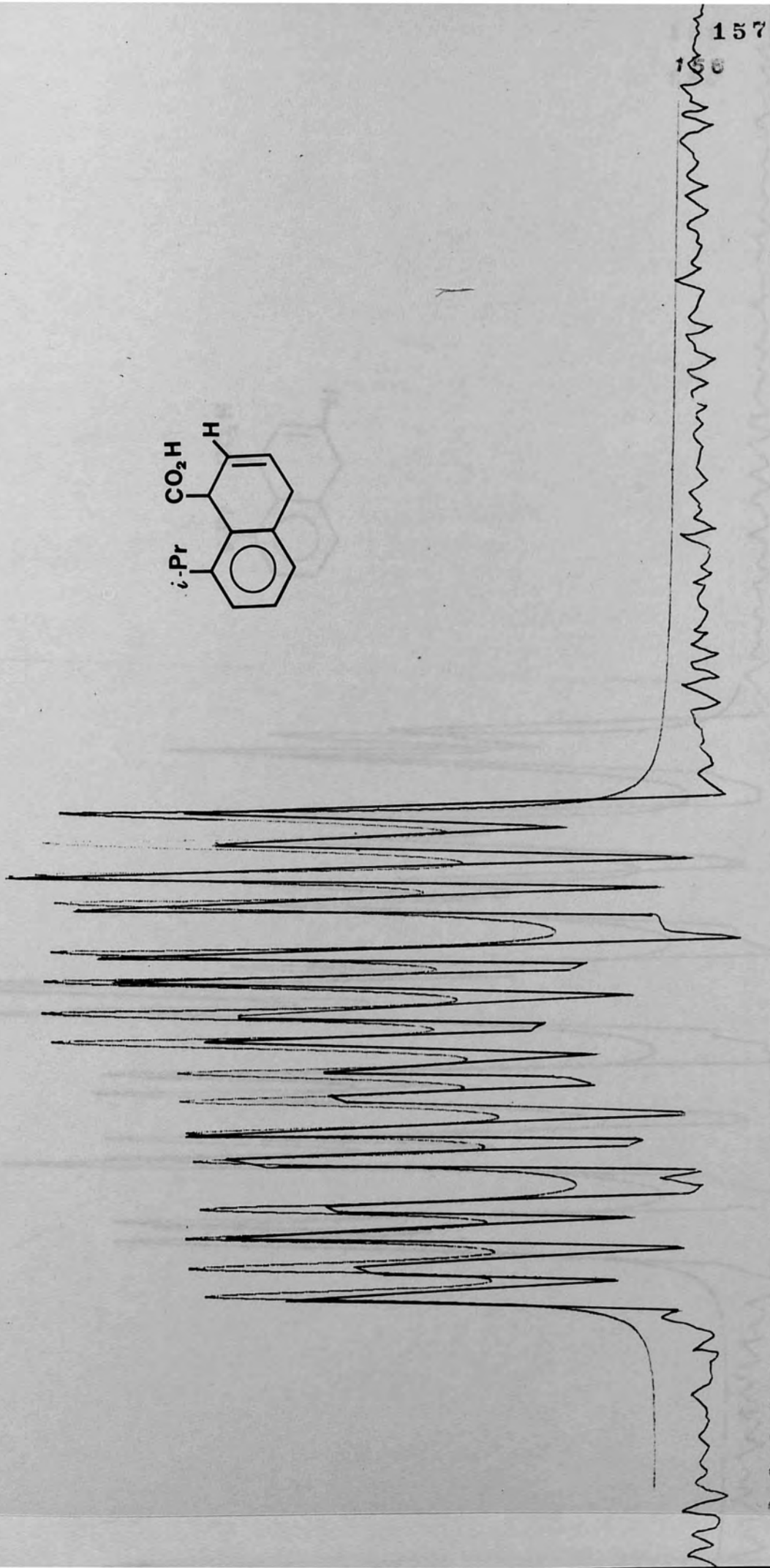
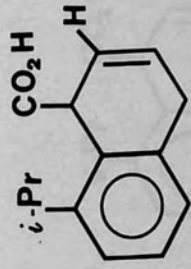


fig 16A

FIG. 17: H-2

fig 17A



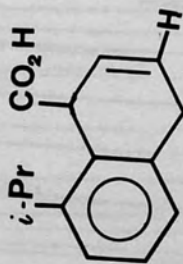


FIG. 17: H-3

fig 17 A

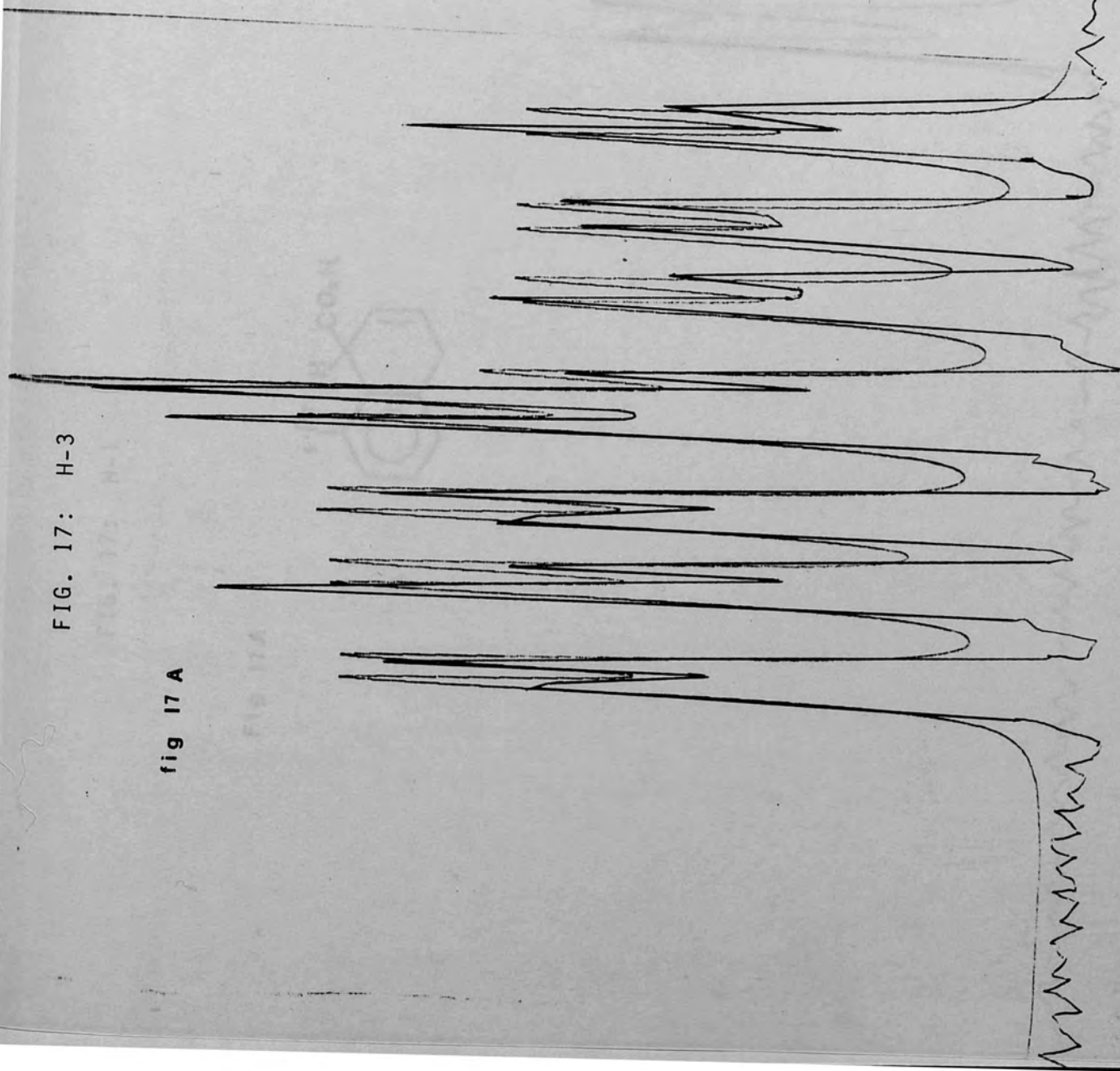
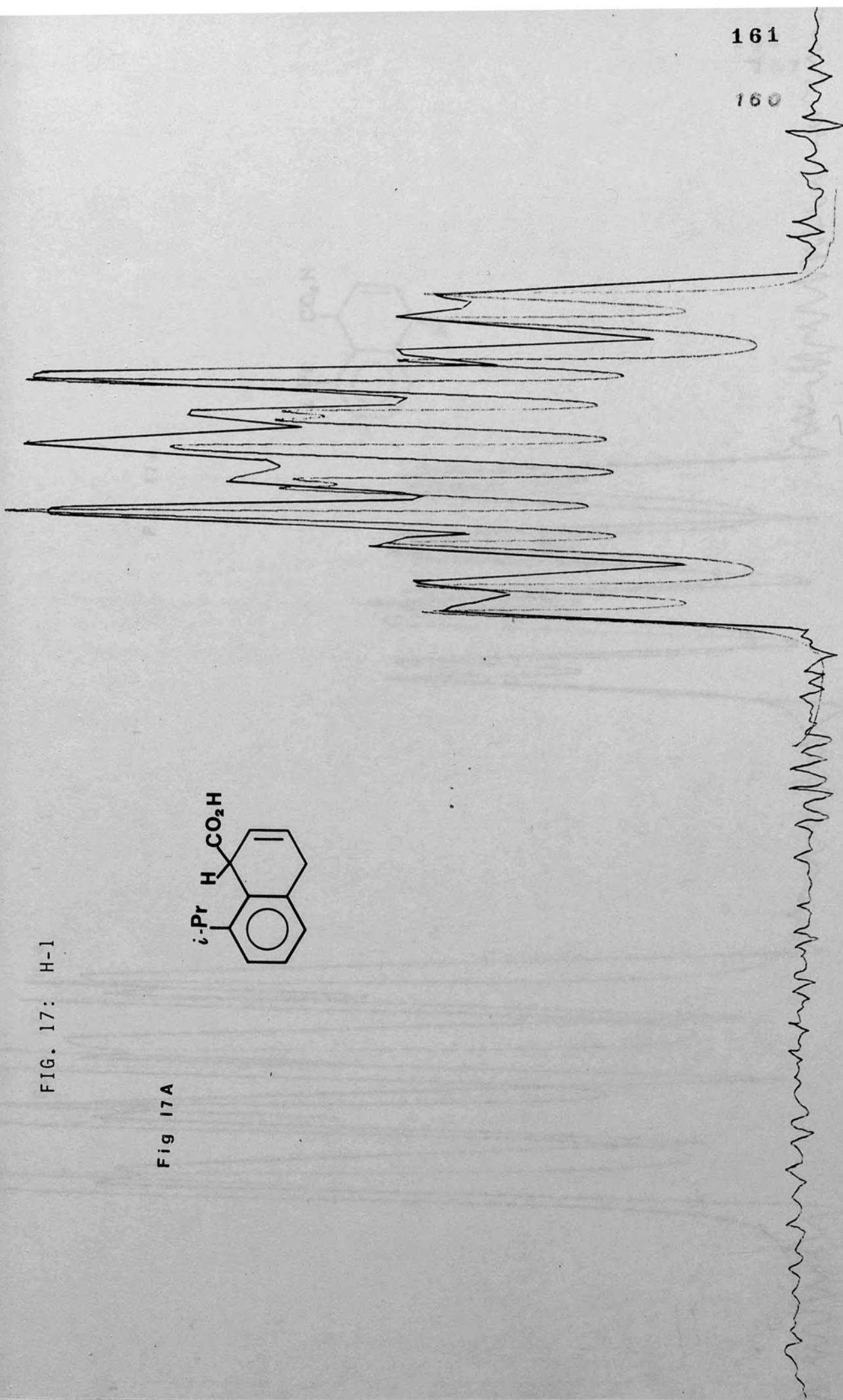
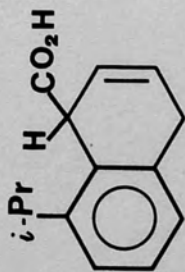


FIG. 17: H-1

Fig 17A



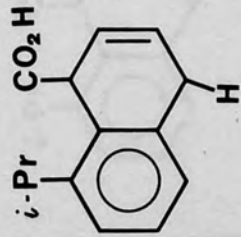
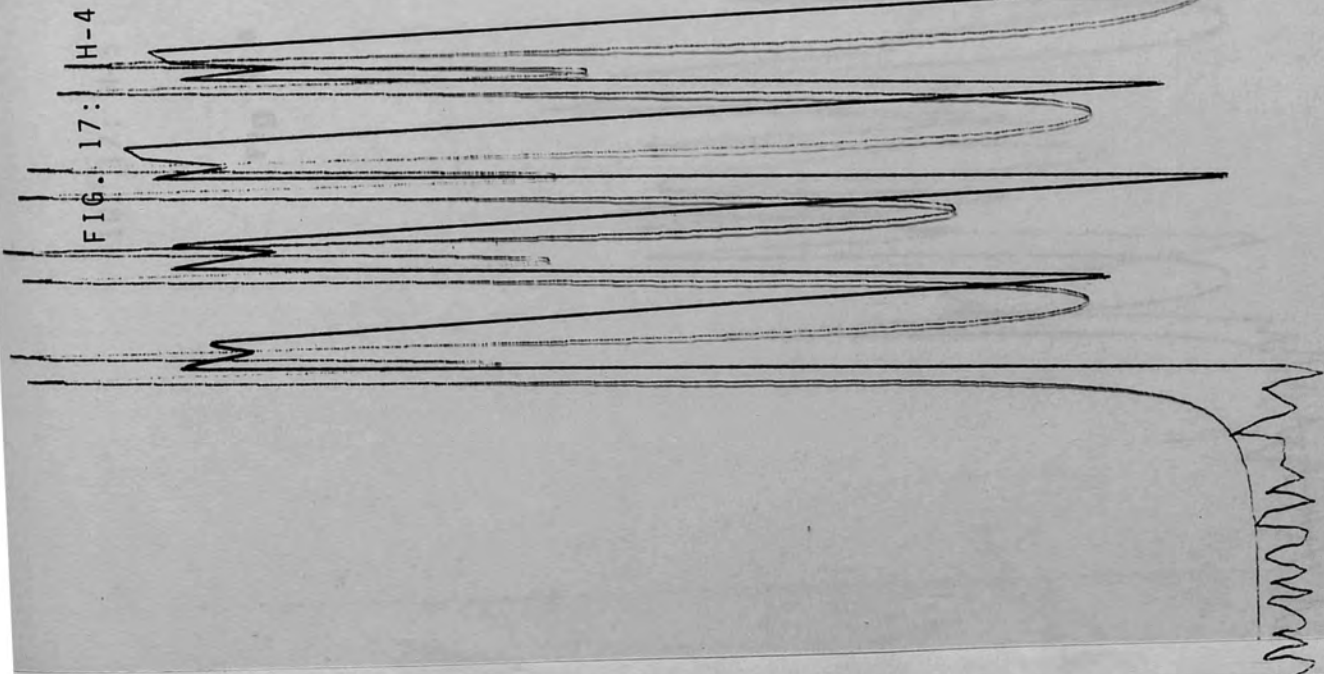


Fig 17A



1.3. SUBSTITUENT EFFECTS OF THE CONFORMATIONS OF
1,4-DIHYDRONAPHTHALENES

Further insight into the conformation of 5-methyl- and 8-isopropyl-1,4-dihydronaphthalene can be gained from a comparison of the coupling constants about the dihydroaromatic ring (171) and (172) with those of related structures. The available data are presented in Table (17).

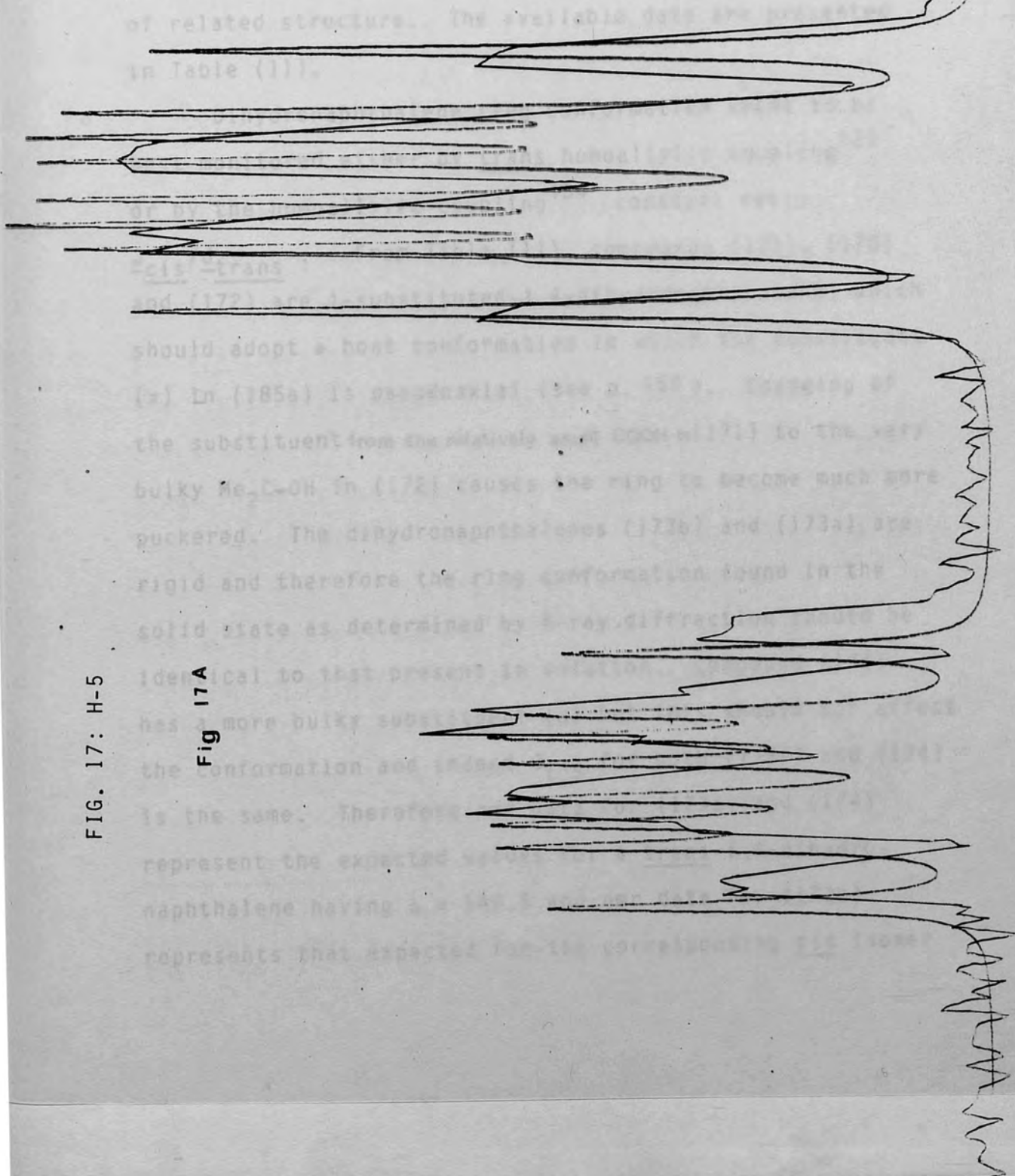
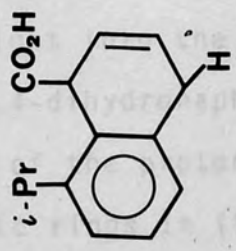


FIG. 17: H-5

Fig 17A

7.3. SUBSTITUENT EFFECTS OF THE CONFORMATIONS OF 1,4-DIHYDRONAPHTHALENES

Further insight into the conformation of 8-methyl and 8-isopropyl-1,4-dihydronaphthoic acids can be gained from a comparison of the proton coupling constants about the dihydroaromatic rings in (97) and (114) with those of related structure. The available data are presented in Table (11).

Dihydronaphthalene ring conformation seems to be best monitored either by trans homoallylic coupling¹²³ or by the homoallylic coupling¹³⁴ constant ratio $\frac{J_{cis}}{J_{trans}}$. From Table (11), compounds (171), (170) and (172) are 1-substituted-1,4-dihydronaphthalene, which should adopt a boat conformation in which the substituent (x) in (185a) is pseudoaxial (see p. 169). Changing of the substituent **from the relatively small COOH in (171) to the very bulky Me₂C-OH in (172)** causes the ring to become much more puckered. The dihydronaphthalenes (173b) and (173a) are rigid and therefore the ring conformation found in the solid state as determined by X-ray diffraction should be identical to that present in solution. Compound (174) has a more bulky substituent (x) but this should not affect the conformation and indeed $J_{1,5}$ for both (173a) and (174) is the same. Therefore nmr data for (173a) and (174) represent the expected values for a trans-1,4-dihydronaphthalene having $\alpha = 146.5$ and nmr data for (173b) represents that expected for the corresponding cis isomer

in which the substituent (x) is placed pseudoequatorial*. Examination of the data for (172) shows that all couplings about the dihydronaphthalene ring are similar to those for (174) except that $J_{3,5}$ is bigger for (172) and $J_{2,5}$ is smaller for (174). This discrepancy may mean that (172) is slightly less puckered than (174) or it may reflect substituent effect on the coupling constants.

The ratio of cis-homoallylic coupling/trans-homoallylic coupling seems to be the most reliable and least substituent sensitive indicator of dihydroaromatic ring conformation. Where appropriate values of this ratio have been calculated in Table (11). No values are included for (173a,b) and (174) because in these examples, the cis coupling is pseudoaxial-pseudoaxial whereas in all the other cases the cis coupling is pseudoequatorial-pseudoequatorial. The cis-/trans- J ratio homoallylic coupling constants calculated for (97) and (114) is significantly less than those found in the almost planar ring (171) and (170) but not as small as that determined for (172). It is therefore concluded that there is a significant puckering effect when a methyl or isopropyl substituents introduced at position -8 on the dihydronaphthalene skeleton. This relieves steric interference between the groups (R) and (x) in compound (185). However this effect is not as great as the steric interference between a H- atom at

*This cis-isomer cannot therefore be used as a model for cis-coupling in a flexible system where the substituent x in (174) is located pseudoaxial.

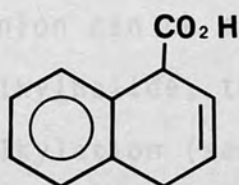
TABLE: 11

	J	(171)	(170)	(97)	(114)	(173b) (Me)	(173a)	(174)	(172)
v	1,2	4.6	3.8	5.4	5.5	1.9 (1.6)		5.0	5.2
a	1,3	-1.2	<1	-1.1	-1.1	-3.0 (2.8)		<1	<1
ch	1,4	3.8	3.5	2.8	2.8	8.45 (8.5)		-	1.8
th	1,5	4.4	3.7	4.0	4.0	-	3.3	3.2	3.0
v	2,3	9.6	9.9	9.7	9.5	10.1 (9.6)		9.5	9.6
a	2,4	-1.2	?	-0.7	-0.7	-3.2 (3.1)		-	<1
a	2,5	-3.0	?	-3.2	-3.1	-		2.8	2.0
v	3,4	4.6	3.7	5.2	5.2	1.8 (1.4)		-	5.0
v	3,5	2.4	2.1	2.2	2.1	-		1.2	2.0
g	4,5	-21.9	21.0	-21.5	-21.6	-		-	20.5
	*Jratio/ cis/trans	0.86	0.94	0.7	0.7				0.6
	α	169.2	-	-	-	146.5	146.5	146.5	
	source	ref(112)	ref 123	US	US	ref(109	109	123	123

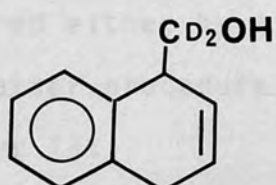
v = vicinal
a = allylic
h = homoallylic
c = cis
t = trans
g = geminal

$$* \frac{{}^5J_{\text{cis}}(\psi_e/\psi_e)}{{}^5J_{\text{trans}}}$$

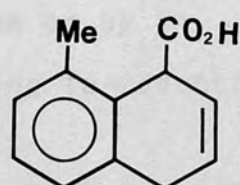
position -8 and a 2-hydroxy propyl substituent at position 1. An X-ray structural study of (97) is awaited which it is hoped to provide further insight into the dihydroaromatic ring conformation of this molecule. Meanwhile it is clear that the conformation of (97) and (114) are significantly non-planar.



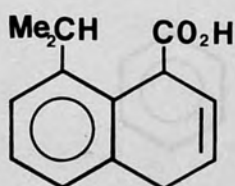
(171)



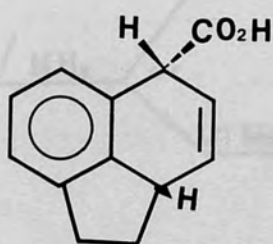
(170)



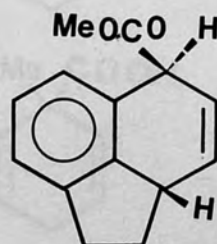
(97)



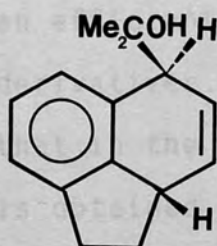
(114)



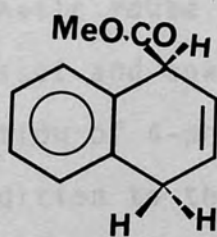
(173b)



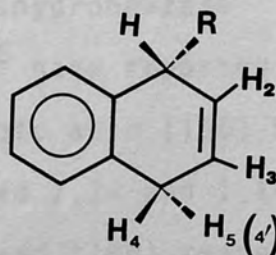
(173a)



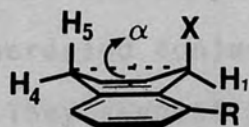
(174)



(172)



(184)

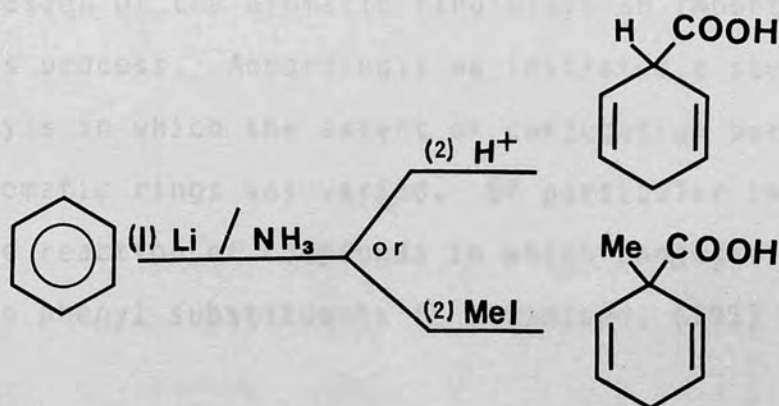


(185) a, R = H
b, R = alkyl

APPENDIX A

1. Unusual Birch Reduction Pathways

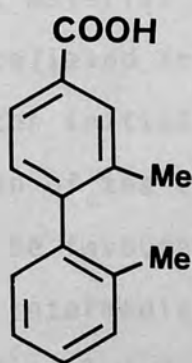
Dihydroaromatic compounds are conveniently prepared by reduction of the aromatic analogues using solutions of alkali metals in liquid ammonia. The intermediate anion can be captured either by a proton or by an alkylhalide, the latter procedure leading to reductive alkylation (see Part 1):



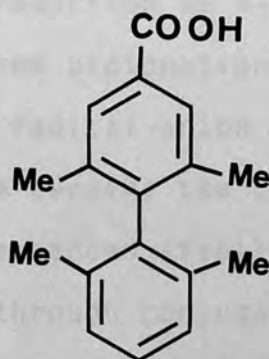
The Birch reduction, however, does not always provide an efficient synthetic route to 1,4-dihydrobenzene derivatives. Grossel and coworkers¹³⁵ have reported that in the reduction of 4-phenylbenzoic acid (186) there is obtained in addition to the expected 1,2- and 1,4-dihydro-4-phenylbenzoic acids (187), and (188) respectively, and recovered starting material, a 25% yield of a mixture of an alcohol (192) and a hydrocarbon (190). This is the result of increased conjugation in the reaction intermediates. They suggest that carboxy-function

reduction may be related to a variation in protonation sites owing to extended conjugation in this system.

Part of our work has therefore concentrated on the investigation of this unexpected process with the hope of determining what structural features and reaction conditions favour non-acidic products. Preliminary experiments suggest that aromatic carboxylic acids can be reduced in the presence of excess NH_4^+ ion and that under these conditions reduction of the side chain is favoured over reduction of the aromatic ring. Therefore, conjugation of the aromatic ring plays an important role in this process. Accordingly we initiated a study of biphenyls in which the extent of conjugation between the aromatic rings was varied. Of particular interest was the reaction of compounds in which conjugation between the two phenyl substituents is minimised, (193) and (194).



(193)



(194)

Franks¹³⁶ and Knutsen¹³⁷ devised synthetic routes to (193). Knutsen carried out a preliminary study of the reduction of (193) which suggest that very little non-acidic material was produced. He did not identify

the effect of modifying the reaction conditions on this process. It is clearly important, therefore, to prepare (193) and to carry out detailed investigation of this reaction.

This work has now been re-examined and Table 12 summarizes the percentage yield of acidic and non-acidic material under various reaction conditions. It will be seen that in each case the reduction of (186) produces a significant quantity of non-acidic material (20%) in addition to a mixture of dihydro-4-phenylbenzoic acid (80%). The non-acidic material is composed of a mixture of aldehyde, alcohol and hydrocarbon derived from reduction of the carboxyl group. The earlier workers¹³⁷ also detected traces (4%) of non-acidic material in the reduction of benzoic acid itself. These were identified as a mixture of benzaldehyde, benzyl alcohol and toluene and their dihydro derivatives. The increased yield of non-acidic material from the reduction of 4-phenylbenzoic acid was believed to result from protonation at different sites in the initially formed radical-anion or dianion. Protonation of the carbon atom bearing the carboxylate group may be favoured by the enhanced stability of the resulting intermediate (195) through conjugation of the cyclohexadienyl radical or anion, with the phenyl substituent.

TABLE 12. Birch reduction of 4-phenylbenzoic acid with lithium metal/NH₃

Mol.equiv.	Quenching technique	Acidic%	Non-acidic%
10	Lithium was added first	80	16
10	Lithium was added after NH ₄ Cl	80	20
4	Lithium was added first	80	20
4	Lithium was added later	66*	26

*This low yield is because of recovered starting material of 8%.

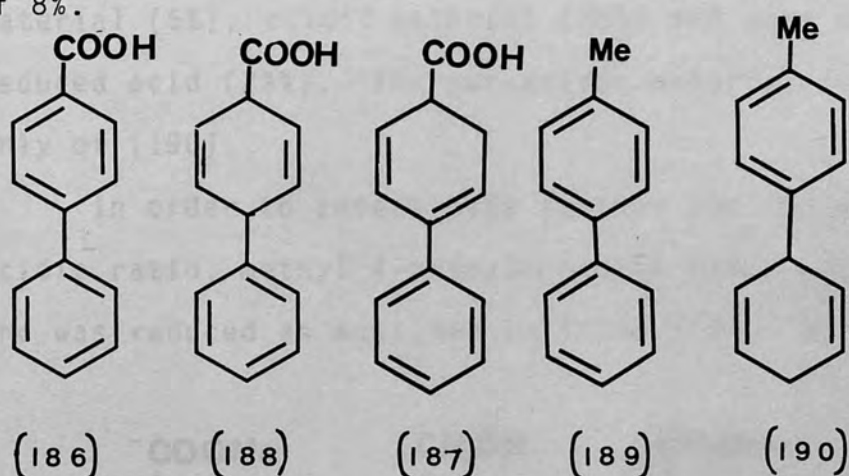
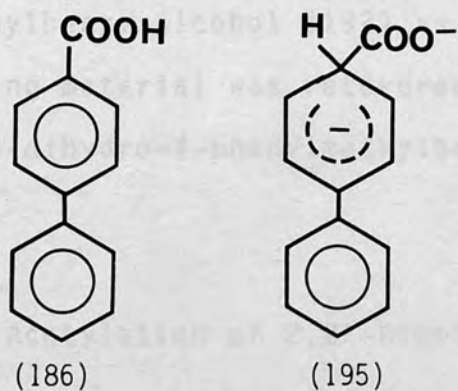


TABLE 13. Metal/Ammonia reduction of methyl 4-phenylbenzoate

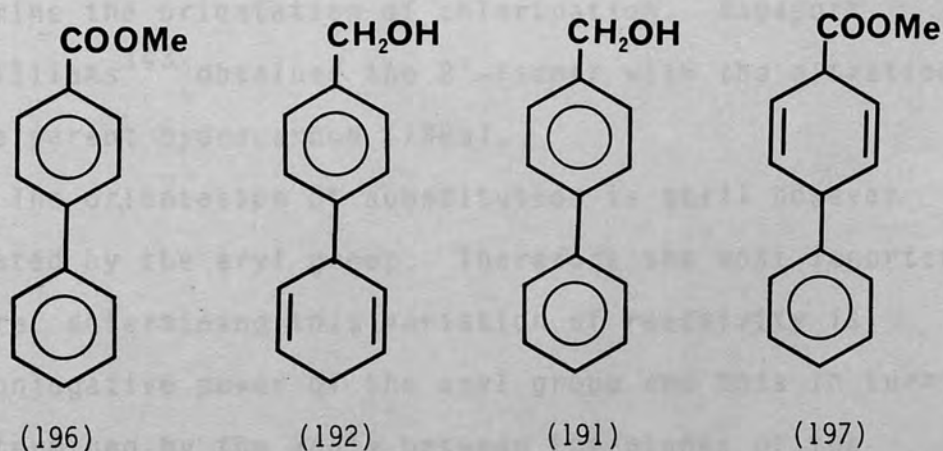
Mol.equiv.	Metal	Non-acidic**				Acidic
		(192)	(191)	(197)		
10	Li	45	39	16	100	-
4	Li	20	69	10	99	-
4	Na	20	74	6	100	-

**estimation by nmr.



In order to study this process further we have also reduced sodium 4-phenylbenzoate under the same conditions as used for 4-phenylbenzoic acid (10 mol. equiv. of Li/NH_3 , NH_4Cl). There was obtained non-acidic material (5%), acidic material (70%) and some of non-reduced acid (23%). The non-acidic material consisted only of (190).

In order to investigate further the non-acidic:acidic ratio, methyl 4-phenylbenzoate (196) was prepared and was reduced as outlined in Table (13). No acidic



material was isolated from any of the reactions. Almost all the product was non-acidic material (98%) and this contains 4-phenylbenzyl alcohol (191) and 1',4'-dihydro-

4-phenylbenzyl alcohol (192) as major components. No starting material was recovered and only a very low yield of 1,4-dihydro-4-phenylmethylbenzoate (197) was isolated.



2. Acetylation of 2,2'-Dimethylbiphenyl.

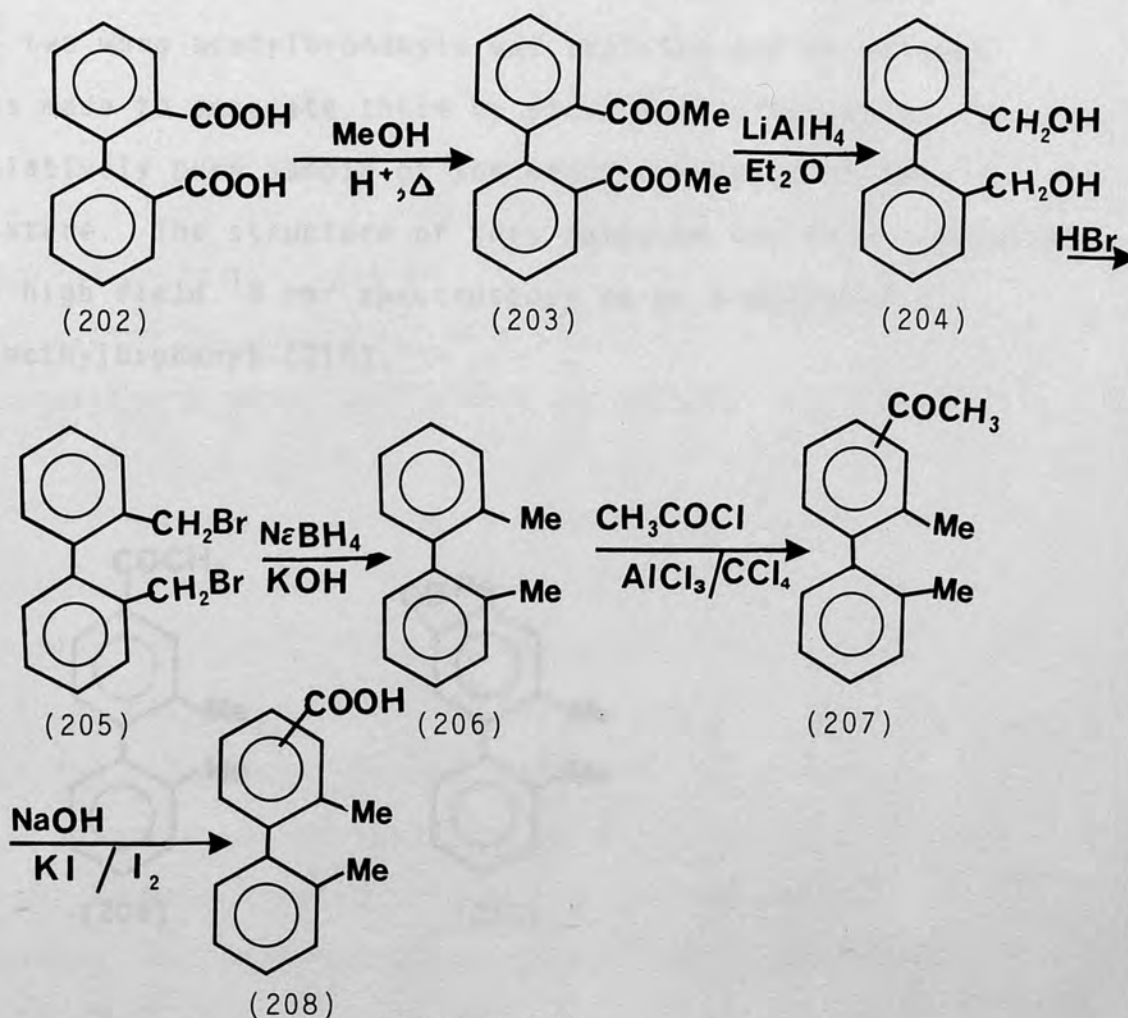
The acetylation of 2,2'-dimethylbiphenyl leads to the formation of a mixture of products. The study of the rate and the orientation of electrophilic substitution in biphenyls was pioneered by Brown^{138,139}, de la Mare^{140,141}, and Eaborn¹⁴². De la Mare and coworkers¹⁴⁰ concluded that the chlorination of 1,2,3,4-dibenzocyclohepta-1,3-diene (198) with molecular chlorine in acetic acid gave the 2'-chloro-derivative. Thus despite the large angle between the planes of the benzene ring (ca. 42° cf. 45° in biphenyl), the mesomeric electron release from the aryl group is still large enough to determine the orientation of chlorination. Rapaport and Williams¹⁴³ obtained the 2'-isomer with the nitration of the parent hydrocarbon (198a).

The orientation of substitution is still however dominated by the aryl group. Therefore the most important feature determining this variation of reactivity is the conjugative power of the aryl group and this in turn is determined by the angle between the planes of the aryl rings in the transition state. The effect of this steric inhibition of resonance, progressively increasing from fluorene (200) to 6,7-dimethyl-1,2:3,4-dibenzocyclo-

basis of the angles between the planes of the rings, and it was suggested that the reaction is significantly influenced by the inductive effects of the alkyl substituents.

From analysis of the rates of chlorination of substituted biphenyl, it appears that a meta-aryl group affects the rate of chlorination by a partial rate factor of 0.5-0.7. De la Mare suggested that for a hypothetical "perpendicular 2,2'-dialkylbiphenyl" where only the inductive effect of the aryl group is operative (no conjugation), this inductive effect is transmitted nearly equally to the meta- and para-positions, and he ascribes a factor of 0.5 to the influence of the constrained aryl group on the para-position.

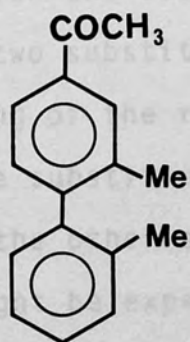
Despite these literature observations it was decided to investigate the preparation of acetylbitolyl by acetylation of 2,2'-dimethylbiphenyl. It was hoped that sufficient of the desired isomeric ketone would be obtained and that it could be separated from other products of the reaction. It was then intended to reduce bitolyl-4-carboxylic acid in order to investigate the effect of tilting the biphenyl ring on the Birch reduction pathways of biphenylcarboxylic acid. The proposed synthetic route is outlined in Scheme (38).



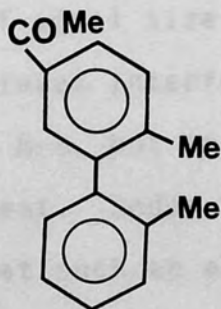
(Scheme 38)

In the event this preparative route was not particularly efficient. 2,2'-Dimethylbiphenyl (206) being obtained in approximately 20% overall yield. The subsequent acetylation afforded pure acetylbiphenyl in approximately 10% yield from (206). This process was hampered by the formation of two acetylbiphenyls (209), (210) and a bis-acetylated biphenyl (212). This latter (212) was the major product (78%) when the reaction was carried out in carbon tetrachloride (CCl₄). However the yield of monoacetyl derivative was greatly improved when nitrobenzene was used as a solvent, though subsequent separation

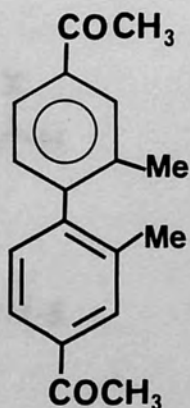
of the product was found to be difficult. A mixture of two mono acetylbiphenyls was isolated and an attempt was made to separate these by plc. This afforded a relatively pure sample of the major component of the mixture. The structure of this compound was then determined by high field ^1H nmr spectroscopy to be 4-acetyl-2,2'-dimethylbiphenyl (210).



(209)



(210)

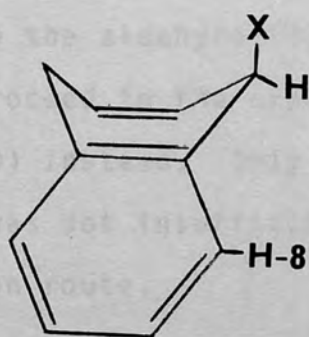


(212)

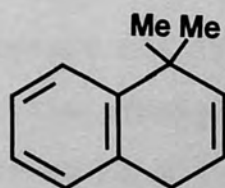
APPENDIX B

ATTEMPTED PREPARATION OF 1,1'-DIMETHYLNAPHTHALENE

1,4-Dihydro-1,1'-dimethylnaphthalene is of particular interest in the context of the conformations of dihydronaphthalene derivatives. In a 1-substituted 1,4-dihydronaphthalene steric interference between the substituent and H-8 leads to a preference for a boat conformation in which the substituent is located pseudoaxial (215). When two substituents of equal size are placed in C-1, folding of the ring relieves interference between one of the substituents and H-8, but increases interference with the other substituent. Under these circumstances it might be expected that such an effect would be minimized if the dihydroaromatic ring were to become planar. In order to test this hypothesis we have attempted a synthesis of (214).

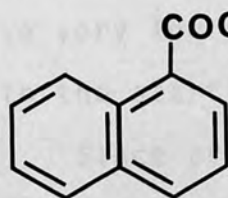


(215)

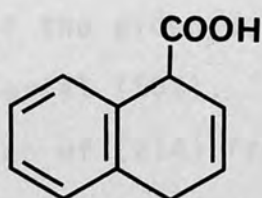


(214)

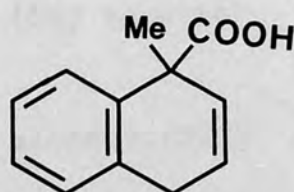
Birch reduction of naphthoic acid (216) gave 1,4-dihydro-1-naphthoic acid (171) in good yield (96%). Attempted reductive methylation of 1-naphthoic acid failed. 1,4-Dihydro-1-methyl-1-naphthoic acid (217) was subsequently prepared by the reaction of (171) with sodamide or



(216)

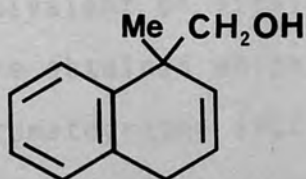


(171)

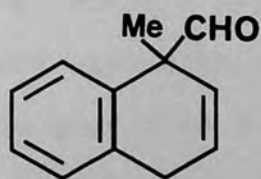


(217)

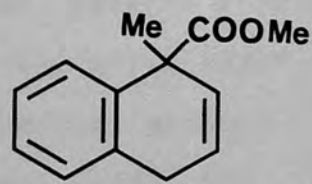
potassium amide in liquid ammonia. The reaction is very sensitive to water therefore it is necessary to dry and distill the ammonia prior to use. Preparation of (217) occurs in better yield when potassium amide is used than with sodamide. From (217) several attempts were made to synthesise 1,1'-dimethylnaphthalene (214). Reduction of (217) with lithium aluminium hydride gave (218) efficiently (97%) which was then oxidized in an attempt to prepare the aldehyde (219). However the reaction did not proceed to the expected product affording the ester (220) instead. Only very little aldehyde was obtained and this was not insufficient to carry on with this preparation route.



(218)



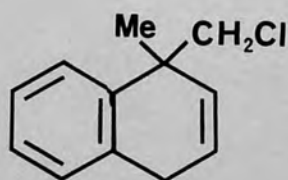
(219)



(220)

Two attempts were carried out to oxidize (218), both of which failed and gave back the alcohol (218). Oxidation with chromium trioxide in pyridine gave 90% of the starting material and no other product isolated. With p-toluenesulphonyl chloride and pyridine the oxidation gave very low yield of the aldehyde (219) (5%) together with the starting material (80%).

Since preparation of (214) from the alcohol (218) was found to be difficult a different reaction sequence via the chloride (221), was then investigated. 1-Methyl-1-chloromethyl-1,4-dihydronaphthalene (221) was prepared from the reaction of (218) with thionylchloride in quantitative yield. 1-Methyl-1-chloromethyl-1,4-dihydronaphthalene was then reduced with lithium aluminium hydride but no reaction occurred and the starting material was recovered. Reduction of (221) with tri-n-butyltinhydride in dry benzene did not work and the starting material



(221)

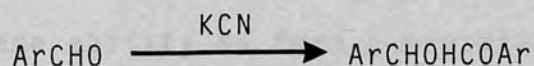
was isolated. When (221) was reduced with 4 molar equivalent of lithium in ammonia solution, several products were obtained which were separated by preparative layer chromatography (PLC) to give some over-reduced product (no olefinic hydrogen was observed in nmr) (15%), the

APPENDIX C

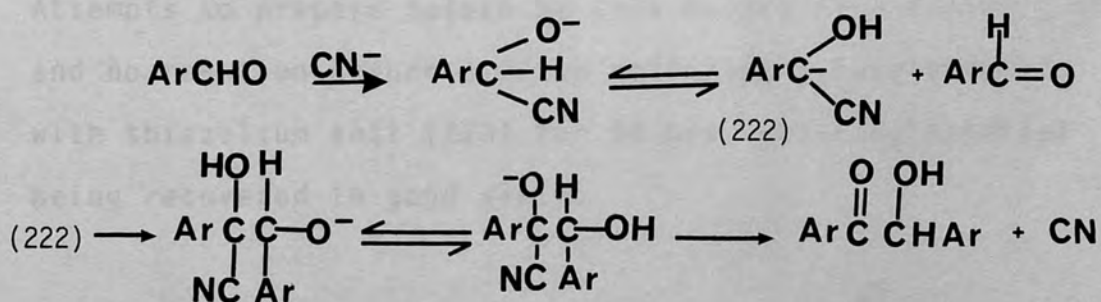
THE ACYLOIN REACTION. ATTEMPTS TO PREPARE 2,2'-
DIMETHYLBENZOIN (TOLUIN)

C.1. Benzoin Condensation

The first attempt to prepare 2,2'-dimethylbenzoin (toluin) by benzoin condensation. The benzoin condensation consists of the treatment of an aromatic aldehyde with potassium or sodium cyanide, usually in aqueous ethanolic solution⁷⁷. The mechanism of this condensation, in



which the cyanide ion is almost a specific catalyst, can be represented as follows¹⁴⁴:

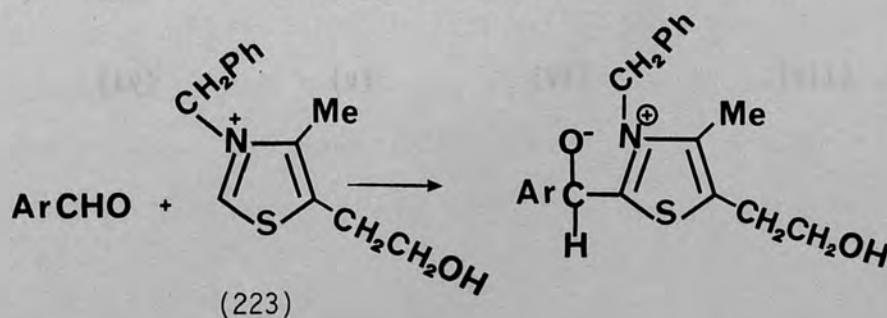


The catalyst must be able to add to the carbonyl group and activate the hydrogen so that the anion (222) is formed to add to a second molecule of aldehyde. Many benzoin derivatives have been prepared by this method. Benzoin itself has been prepared in good yield (90-92%)

from benzaldehyde and sodium cyanide in aqueous alcohol¹⁴⁵. Although 4,4'-dimethylbenzoin was prepared in good yield by the action of the cyanide ion on alcoholic solutions of 4-methylbenzaldehyde¹⁴⁶, all the attempts to prepare toluin from o-tolylaldehyde failed and o-tolylaldehyde was recovered in a good yield (98%).

C.2. Condensation of o-Tolylaldehyde with Thiazolium Salt.

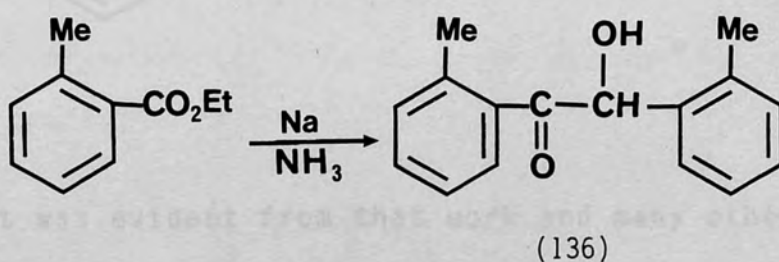
Thiazolium salts have been shown to act as efficient catalysts for the benzoin condensation¹⁴⁷. They have the same ability to form a benzylic anion intermediate with cyanide. This then condenses with a second aldehyde molecule. 4,4'-Dimethylbenzoin was formed easily¹⁴⁸ by the reaction of 4-methylbenzaldehyde and 3-benzyl-4-methyl-5-(2-hydroxyethyl)thiazolium chloride (223). Attempts to prepare toluin by this method have failed and no reaction occurred after refluxing o-tolylaldehyde with thiazolium salt (223) for 50 hrs, starting material being recovered in good yield.



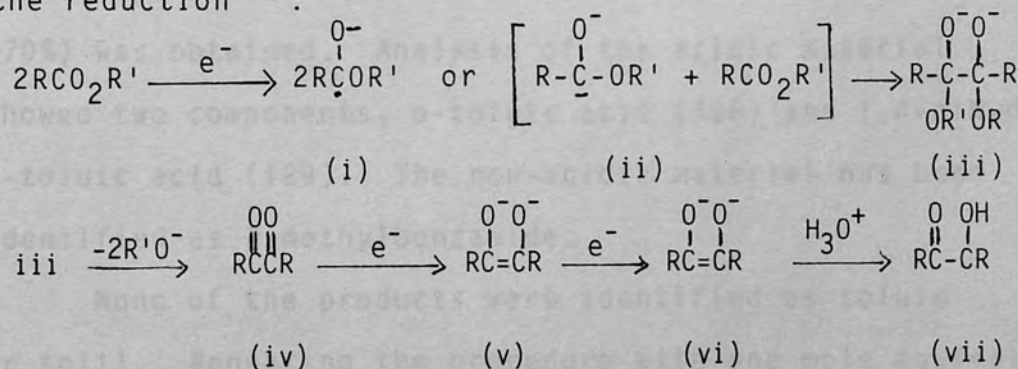
C.3. Reduction of ethyl *o*-toluate in alkali metal and ammonia.

Two attempts were carried out to prepare (136).

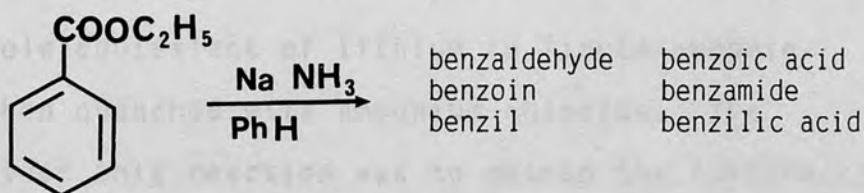
C.3.1. Reduction of ethyl *o*-toluate with 2 mol. equivalent of sodium metal in liquid ammonia.



The reduction of esters with sodium metal in liquid ammonia is generally known as Bouveault-Blanc reduction and it is widely applicable for preparation of the corresponding acyloins¹⁰. The mechanism suggested for the reduction¹⁴⁹:



Furthermore, Kharasch and coworkers⁷⁸ investigated the reduction of ethyl benzoate with sodium/ammonia/benzene and found a variety of products depending on reaction conditions.



It was evident from that work and many others^{79,80,81}, that acyloin condensation could be carried out with either one or two mole equivalent of sodium metal. Therefore we carried out the acyloin condensation with ethyl 2-methylbenzoate (137) in order to prepare or trap 2,2'-dimethylbenzoin (toluine) (136). When the reaction was worked up, acidic material (21%) and non-acidic material (70%) was obtained. Analysis of the acidic material showed two components, o-toluic acid (128) and 1,4-dihydro-o-toluic acid (129). The non-acidic material has been identified as 2-methylbenzamide.

None of the products were identified as toluin or tolil. Repeating the procedure with one mole equivalent of sodium metal gave the same products but with a high yield of 2-methylbenzamide (81%) and some acidic material (15%).

C.3.2. Reduction of ethyl-o-toluate with 10 mol. equivalent of lithium metal.

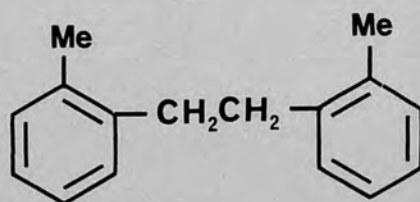
In order to trap or trace toluin or tolil, the reduction was carried out using the same conditions as for phthalide (see p. 76). Ethyl-o-toluate was reduced with 10 mole equivalent of lithium in liquid ammonia and was then quenched with ammonium chloride. The difficulty of this reaction was to obtain the satisfactory recovery of products. The reaction was carried out four times (see Table 14).

TABLE 14.

	no. of moles of (137) mole	Non-acidic %	Acidic %
1	0.018	33%	-
2	0.06	30%	6%
3	0.012	25%	11%
4	0.06	56%	14%

The increase of the acidic yield on the third time resulted from the evaporation of the aqueous layer. In the fourth experiment a different work-up procedure was employed. The ethereal solutions of acidic and non-acidic were distilled at atmospheric pressure. In the case of non-acidic material, the product was distilled

at atmospheric pressure to give a colourless oil which was shown to be o-xylene. The residue (4.00 g) was dark brown oil and did not boil over 220°C. The aqueous layer of the acidic material was extracted with ether which was then distilled off at atmospheric pressure to yield 0.36 g of white solid. Then the aqueous layer was extracted continuously with chloroform for 30 hrs and gave further 1.0 g of white solid which has the same nmr spectrum as the solid obtained from ethereal solution. Analysis of the acidic material showed this to contain both o-toluic acid and its 1,4-dihydro compound. From the non-acidic products of the second preparation the dimer (127) was isolated, and this was purified by plc to give small amounts of (127) 3% yield. In all these attempts, neither toluin nor tolil was isolated nor was any trace of these detected.



(127)

C.4. Claisen Condensation

When esters containing an α -hydrogen are treated with a strong base such as NaOEt, NaH etc., a condensation occurs to give a β -keto ester¹⁵⁰. We, therefore tried to prepare (224) by a Claisen condensation, followed

C.4.1. With sodium ethoxide

Super dry ethanol was used, but some hydrolysis still occurred and no reaction was detected when the two esters were refluxed for 10 hours. At the end of this time the esters were recovered together with *o*-tolylacetic acid.

C.4.2. With sodium hydride

Sodium hydride was used as the base for the Claisen condensation in dry dimethoxyethane. The two esters were left to reflux with sodium hydride for twenty-four hours. When the reaction was worked up, the acids of the esters and some of the ethyl-*o*-toluate were recovered and once again no reaction had occurred.

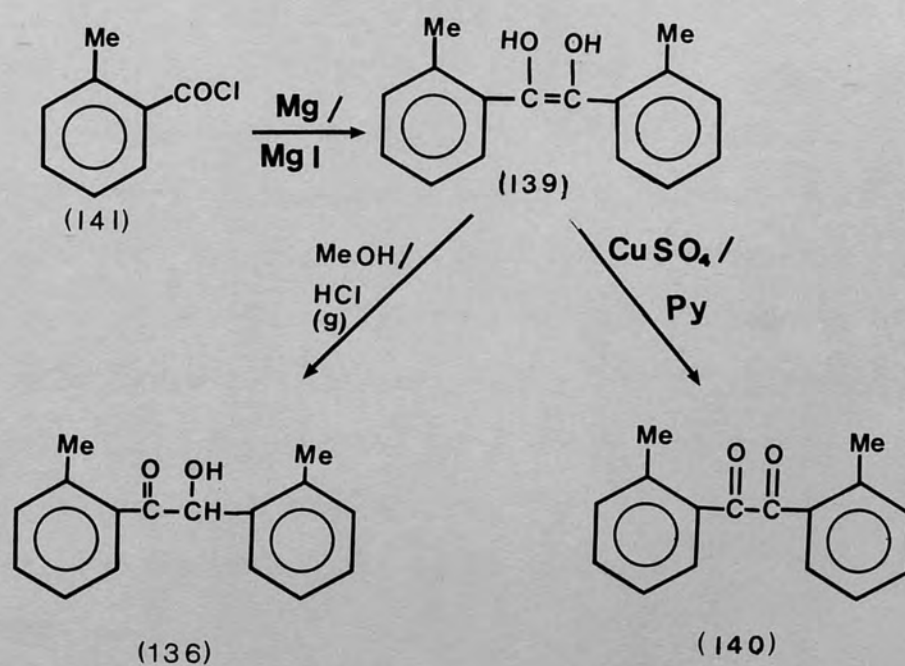
C.5. The Reduction of the Acid Chloride

The reduction of aromatic acids, their chlorides, esters, and peroxides can be accomplished by treatment with Mg/MgI₂ in a mixture of ether and benzene as solvents⁷⁷. With an acid chloride or ester the MgI₂ derivative of the enediol forms directly and is hydrolysed to the benzoin.

Following this procedure, toluin (136) and tolil (140) have been prepared in very low yield. 2-Methylbenzoylchloride (141) was prepared from the reaction of 2-methylbenzoic acid and thionyl chloride.

To 2-methylbenzoylchloride (141) was added Mg/MgI₂ and the mixture was refluxed for 24 hrs. Working up the reaction gave the enediol (139) which was oxidised with CuSO₄ to an oil (56.8%). This was distilled under reduced pressure to give (21%) of o-tolil which solidified on cooling. This was crystallised from EtOH to give pure yellow crystals.

O-toluin was prepared by reacting the enediol (139) with MeOH saturated with hydrogen chloride gas. Distillation of the mixture gave pure sample (13%). The enediol is unstable and is readily oxidised and this instability results in the low yield of toluin which is contaminated with tolil.



111. GENERAL DETAILS AND INSTRUMENTATION

Infrared Spectra (IR) were recorded on Perkin-Elmer 257 and 297 instruments. Solid samples were examined either between sodium chloride plates as a Nujol mull or as solutions in chloroform (0.1 M sodium chloride cells). Liquids were examined as thin films on sodium chloride plates. The abbreviations s, m, w are used for bands sharp, medium, and weak respectively.

Mass Spectra were recorded on VG 15F mass spectrometer with VG data system 2000 at Chelms College, the electron energy being 70 eV and 10 eV trap current 1A. source temperature ca. 200°C. Ionization voltage 2.1 kV.

PART III
EXPERIMENTAL PROCEDURE

Elemental Analysis: Some analyses required for the synthesis part of this work were carried out at the School of Chemistry, Perkin-Elmer elemental analyser. These proved to be reliable and as where necessary additional analyses were also determined at the School of Chemistry, 23b W. Subsequently microanalyses were carried out to Bullerworth Laboratories Ltd. and the Perkin-Elmer Perkin-Elmer elemental analyser 240. The results were satisfactory. However, microanalyses of samples on liquid methyl alcohol were unreliable and were carried out by service.

Nuclear Magnetic Resonance (NMR): Spectra were recorded out on a Perkin-Elmer 224, 225, 226 and 227 instruments operating at 60, 80, 100 and 100 MHz respectively.

III.1 GENERAL DETAILS AND INSTRUMENTATION

Infrared Spectra (IR) were recorded on Perkin-Elmer 257 and 297 instruments. Solid samples were examined either between sodium chloride plates as a Nujol mull or as solutions in chloroform in 0.1 mm sodium chloride cells. Liquids were examined as neat films on sodium chloride plates. The abbreviations b, s, m, w are used for broad, sharp, medium, and weak respectively.

Mass Spectra were recorded on VG 16F mass spectrometer with VG data system 2000 at Chelsea College, the electron energy being 70 eV and 18 eV, trap current μA , source temperature ca. 240°C and accelerating voltage 3.3 kV.

Elemental Analysis: Some analyses required on the early part of this work were carried out at Bedford College on Perkin-Elmer elemental analyser. These proved to be rather unreliable and so where necessary accurate mass measurements were also determined at the School of Pharmacy on V.G. Zab 1F. Subsequently microanalysis samples were sent to Butterworth Laboratories Ltd. and they were run on Perkin-Elmer elemental analyser 240, and more reliable results were obtained. However, microanalytical data on liquid samples proved to be unreliable from either service.

Nuclear Magnetic Resonance (nmr): Spectra were carried out on a Perkin-Elmer R 24, 32, 293A and Bruker WH 400 instruments operating at 60, 90, 200 and 400 MHz respectively.

400 MHz spectra were recorded at Queen Mary College under the direction of Dr. Hawkes whom I thank. Chemical shifts are reported relative to tetramethylsilane (TMS) $\text{Si}(\text{CH}_3)_4$ in CDCl_3 unless otherwise stated. The spectra were taken first on crude products as soon as practicable after isolation and before any purification to detect aromatization, isomerization, etc. occurring spontaneously or by purification techniques. The abbreviations b, s, d, t, q, m are used for broad, singlet, doublet, quartet, multiplet respectively.

Melting Points: An electrothermal melting apparatus with range selection guide for coarse and fine temperature control was used to determine melting points using open capillary tubes and are uncorrected. All temperatures are in degree Celsius.

Removal of solvents in vacuo was carried out using a Büchi rotary evaporator.

Unless otherwise stated all organic solutions were dried over anhydrous magnesium sulphate (MgSO_4).

Experiments which led to the recovery of starting material are not described.

All reagents were SLR grade. Light petroleum ether refers to that fraction which boils between 60 and 80^o unless otherwise stated.

Thin layer chromatography (tlc) was carried out on 20 x 5 cm glass plates covered with 0.25 mm aluminium oxide 60F₂₅₄ or 2.5 mm silica gel 60F₂₅₄. The plates were developed either under an ultraviolet lamp or in an iodine tank.

Preparative layer chromatography (PLC) was carried out on 20 x 20 cm glass plates covered with either 1 mm aluminium oxide 60F₂₅₄ or 2 mm silica gel 60F₂₅₄.

Column chromatography was carried out using silica gel 60 or aluminium oxide 60 supplied by Merk.

All Birch reductions were carried out distilling ammonia from the cylinder directly into the reaction vessel except when dry ammonia was required. In this case the ammonia was distilled from sodium metal.

Lithium lumps and sodium metals were freshly cut and washed free of oil with dry toluene before use.

Computer simulation of nmr spectra: Spectra were recorded at various frequencies and, if necessary, simplified by selective decoupling experiments. Approximate coupling constants and chemical shift values were then used to simulate the nmr spectrum by means of the program ITRCAL adapted for 1180 from the LACON3 supplied with a Nicolet NT200 model 293A. The parameters were then adjusted to obtain a "best-fit" spectrum, and these optimised values

were then used in conjunction with the program ITRCAL to obtain an iterated "best-fit" set of spectral data.

III.2 PURIFICATION OF THE SOLVENTS

All solvents were laboratory grade, except for the following:

III.2.1 Ammonia was condensed into a 1 ml 3-necked flask fitted with a Dewar condenser carrying a silica gel drying tube. When half of the reaction vessel was full, pieces of sodium metal (0.1 g) were carefully added and the solvent was left to stir for 10 minutes. Ammonia was then distilled into another reaction vessel and was used immediately.

III.2.2 Benzene was first treated with anhydrous calcium chloride, filtered and then distilled. The distillate was collected at 80-81°C and was stored over sodium wire.

III.2.3. Carbon tetrachloride (CCl₄): 500 ml of (CCl₄) was shaken with anhydrous calcium chloride and left to stand for 24 hours. The solvent was filtered and was distilled (the first 10 percent of the distillate being rejected until the distillate was clear. The fractions were collected at 77°C.

III.2.4 Chloroform: The chloroform was passed through a column of basic alumina (Grade 1; 5 g per 7 ml of solvent) and the eluate was used directly.

III.2.5 Dichloromethane: The commercial grade was purified by washing with 5 percent sodium carbonate solution, followed by water, and dried over anhydrous calcium chloride. It was then fractionally distilled, the fraction bp 40-41°C being collected.

III.2.6 Diethyl ether (ether): One litre of the commercial ether was refluxed over sodium for one hour. The solvent was then distilled collecting the fraction bp 35°C. Ether was stored over sodium wire and left for at least 24 hours prior to use.

III.2.7 Dimethoxyethane (DME): 200 ml of commercial DME was stored over potassium hydroxide pellets for 48 hours. The solvent was heated under reflux over sodium hydride for half an hour, and was then distilled into the reaction vessel, rejecting the first fraction and used immediately.

III.2.8 Ethanol (super dry): In dry 2-litre round-bottomed flask with a double surface condenser and a calcium chloride drying tube was placed 5 g of dry magnesium turnings and 0.5 g of iodine followed by 75 ml of commercial absolute ethanol. The mixture was warmed until the iodine had disappeared. The heating was continued

for half an hour and 900 ml of alcohol was then added and was refluxed for a further 30 minutes. Ethanol was distilled directly into the storage vessel containing Type 4 molecular sieve for protection from atmospheric moisture.

III.2.9 Pyridine: This was heated under reflux over potassium hydroxide and was then distilled with careful exclusion of moisture. The fraction at 115°C was collected and stored over potassium hydroxide pellets.

III.2.10 Tetrahydrofuran (THF): This was heated under reflux over lithium aluminium hydride (LiAlH_4) for half an hour. The solvent was then distilled, collecting the fraction bp $65\text{-}66^{\circ}\text{C}$. The distillate was kept over sodium wire.

III.2.11 Toluene: Toluene free from sulphur compounds, was distilled and the fraction bp $110\text{-}110.5^{\circ}\text{C}$ was collected and stored over sodium wire.

III.3. EXPERIMENTS : The structures are shown at the end

III.3.1 Preparation of Naphthalide (100)

i. Preparation of 1,8-naphthaldehydic acid (101)

1,8-Naphthaldehydic acid was prepared as previously described^{73b} to give white crystals which has m.p. 157-159°C (lit.¹⁵¹ 167°C). IR (Nujol) 1680. Subsequently this material was obtained commercially (Fluka).

ii. Reduction of naphthaldehydic acid with sodium-tetrahydroborate

1,8-Naphthaldehydic acid (10.13 g, 0.05 mol) was added to methanol (130 ml) to make a slurry. Sodium tetrahydroborate (2.26 g, 0.059 mol) was then added to the mixture in small portions. When half of NaBH_4 had been added, the reaction mixture became homogenous. After the addition was completed, the solution was left to stir for one hour and was then poured into water (300 ml). The mixture was acidified with concentrated hydrochloric acid, and was extracted with dichloromethane (4 x 150 ml). The combined extracts were dried (MgSO_4) and the solvent was evaporated to give a brown oily solid (10 g) which was crystallised from petroleum ether/benzene to give 1,8-naphthalide (100) as a yellow solid (2.5 g, 27%) m.p. 154-155°C (lit.¹⁵² 159-160°C). The solvent was evaporated from the mother liquor and further crystallisation of the residue gave more product (4 g, 43%) which had m.p. 153-155°C.

δ (CDCl₃): 7.3-8.6 (6H,m,ArH), 5.8-5.9 (2H,s,CH₂O) ppm
 ν_{\max} (Nujol): 2900, 1700 (s) (C=O), 1380, 750 cm⁻¹.

III.3.2. Preparation of lithium 8-(hydroxymethyl)-1-naphthoate (98)

1,8-Naphthalide (1.0 g, 0.005 mol) and lithium hydroxide (0.25 g, 0.005 mol) were refluxed in water until all the material had dissolved. The solvent was then evaporated under reduced pressure. Portions of benzene were then added and evaporated under reduced pressure. Portions of benzene were then added and evaporated to give (1.2 g) of a solid which was dried in a desiccator overnight. This crude material was used without further purification.

III.3.3. Reduction of lithium 8-(hydroxymethyl)-1-naphthoate (98) by lithium metal (4 mol. equivalent).

The above salt (98) (1.2 g, 0.005 mol) was added to dry ether (20 ml) and ammonia (350 ml) was condensed into the suspension. Lithium metal (0.15 g, 0.02 g-atom, 4 mol. equiv.) was added to the stirred solution. The solution which rapidly turned blue was stirred for a further half an hour and the reaction was then quenched by addition of portions of solid ammonium chloride (2.0 g, 4 mol. equiv.) over 5 min. until discharge of the deep colour occurred (caution: NH₄Cl should be added carefully in small portions). Ammonia was allowed to evaporate

overnight, and the solid residue was dissolved in water (200 ml). This solution was acidified with 3 N HCl which was then extracted with portions of ether (3 x 100 ml). The combined extracts were dried (MgSO_4) and the ether was evaporated under reduced pressure to give a white solid (0.9 g, 90%) which was crystallised from petroleum ether/ CHCl_3 affording 1,4-dihydro-8-methylnaphthoic acid (97) (0.85 g, 85%) as white crystals which had m.p. 154-156°C.

$\delta(\text{CDCl}_3)$: 7.1(3H,s,ArH), 6.1(2H,s,CH=CH), 4.5 (1H,d,H),
3.45(2H,s, CH_2), 2.25(3H,s, CH_3).

ν_{max} (Nujol): 3000 (b), 17000(s) (C=O), 1460 cm^{-1}

Required for $\text{C}_{12}\text{H}_{12}\text{O}_2$ C,76.50; H,6.30%,

Found: C,76.34; H,6.37%

m/e: 188(26%, m^+), 143(79%, $\text{m}^+ - \text{COOH}$), 142(100%,
 $\text{m}^+ - \text{H} - \text{COOH}$).

In view of the poor analysis figures obtained an accurate mass measurement of the product was carried out. This had m/e 188.0837 $\text{C}_{12}\text{H}_{12}\text{O}_2$ requires m/e 188.0837.

III.3.4. Reduction of lithium 8-(hydroxymethyl)-1-naphthoate by lithium metal (2 mol. equiv.)

The procedure described in (III.3.3) was followed, the salt (98) (2.0 g, 0.0096 mol.) being reacted with lithium metal (0.13 g, 0.018 g atom, 2 mol. equiv.) The reaction **was** quenched by addition of solid NH_4Cl over 5 minutes to discharge the deep blue colour. This gave 1,4-dihydro-8-methylnaphthoic acid (1.7 g) which

was crystallised from petroleum ether/chloroform as white crystals (1.4 g, 82%) which had m.p. 156-158^oC. The spectra of this material are identical with those obtained for (97) in (III.3.3).

III.3.5. Reduction of lithium 8-(hydroxymethyl)-1-naphthoate by lithium metal (1 mol. equiv.)

Following the same procedure as in (III.3.3), reaction of lithium 8-(hydroxymethyl)-1-naphthoate (2.0 g, 0.0096 mol) in dry ether (50 ml) with lithium metal (0.065 g, 0.096 g atom, 1 mol. equiv.) and quenching with ammonium chloride (2.0 g, 0.03 mol., 4 mol. equiv.) gave 1,4-dihydro-8-methylnaphthoic acid (97) (1.2 g, 75%, m.p. 156-158^oC) and recovered naphthalide (100) (25%) which was identified with authentic material as in (III.3.1,ii).

III.3.6. Reduction of lithium 8-(hydroxymethyl)naphthoate by lithium metal (2 mol. equiv.) in the presence of ammonium chloride.

A mixture of lithium 8-(hydroxymethyl)naphthoate (1.0 g, 0.0048 mol.) in dry ether (15 ml), and ammonia (200 ml) containing ammonium chloride (1.00 g, 2 mol. equiv.) was reduced with lithium (0.22 g, 2 g-atom, 2 mol. equiv.). Working up the reaction gave a white solid (0.7 g, 70%) which was shown by ¹H nmr spectroscopy to contain 1,4-dihydro-8-methylnaphthoic acid (97) and naphthalide (100) in the ratio of 2:3 respectively.

III.3.7. Reduction of lithium 8-(hydroxymethyl)-1-naphthoate with sodium metal (2 mol. equiv).

Ammonia (400 ml) was condensed into a suspension of lithium 8-(hydroxymethyl)-1-naphthoate (1.0 g, 0.004 mol) in dry ether (15 ml). Sodium metal (0.22 g, 0.009 g atom, 2 mol. equiv.) was added and the mixture turned dark red, the solution was stirred for 15 min and was then quenched by addition of solid ammonium chloride (0.5 g, 2 mol. equiv.) over 10 minutes to discharge the deep red colour. The reaction mixture was worked up as in procedure (III.3.3) to give a crude solid (0.84 g, 94%) which was crystallised from petroleum ether/ CHCl_3 to give 1,4-dihydronaphthalide (104) as yellow crystals (0.65 g, 73%) m.p. $93-94^\circ\text{C}$ which had:

$\delta(\text{CDCl}_3)$: 7.3-7.1(3H,m,ArH), 6.4-6.0(2H,m,CH=CH), 5.5-5.1(2H,q,CH₂), 4.15-4(1H,t,CH), 3.5-3.4(2H,d,CH₂).

$\nu_{\text{max}}(\text{Nujol})$: 1750(s)(C=O), 1470, 1150, 800 cm^{-1}

Required for $\text{C}_{12}\text{H}_{10}\text{O}_2$: C, 77.5; H, 5.3%

Found C 77.5; H, 5.3%

m/e: 186(100%, m^+), 184(68%, m^+-2H), 155(83%, $\text{m}^+-\text{CH}_2\text{OH}$), 142(83%, m^+-CO_2), 127(85%, $\text{m}^+-\text{CH}_3\text{OCO}$).

The mother liquor was found to be a mixture of 1,4-dihydronaphthalide and naphthalide in the ratio of 2:1.

This experiment was repeated a number of times and the results were found unreliable, the reaction either gave 1,4-dihydronaphthalide or 8-methyl-1,4-dihydronaphthoic

acid in addition to recovered starting material. Subsequent investigation revealed that 1,4-dihydronaphthalide was only obtained when the lithium salt had been properly dried (approximately two weeks in a vacuum desiccator).

III.3.8 Reduction of lithium 8-(hydroxymethyl)naphthoate with Na (1 mol. equiv.)

Following the procedure described in (III.3.7), the salt (97) (2.00 g, 0.0095 mol.) in dry ether (10 ml) and ammonia (300 ml) was reduced using sodium metal (0.22 g, 0.0095 g-atom., 1 mol. equiv.) and the reaction was subsequently quenched with solid ammonium chloride (0.5 g, 1 mol. equiv.) over 10 minutes period. This gave a white solid (1.47 g, 73.5%) which was crystallised from petroleum ether/ CHCl_3 to give 1,4-dihydro-8-methylnaphthoic acid (97) (0.70 g, 35%). Nmr spectrum of the mother liquor shows the presence of some naphthalide in the ratio of 1:1.5.

III.3.9. Reduction of lithium 8-(hydroxymethyl)naphthoate with sodium (2 mol. equiv.) in the presence of ethanol.

A solution of lithium 8-(hydroxymethyl)naphthoate (2.00 g, 0.0095 mol.) in ethanol (5 ml) and ammonia (300 ml) was reduced using sodium (0.44 g, 0.018 g-atom, 2 mol. equiv.), following the method outlined in (III.3.7). The crude solid (1.94 g, 97%) obtained was crystallised from petroleum ether/ CHCl_3 to give 8-methyl-1,4-dihydro-

naphthoic acid (97) (0.6 g, 30%). Removal of the solvent from the mother liquor gave a residue, the nmr spectrum of which revealed the presence of 8-methyl-1,4-dihydro-naphthoic acid and naphthalide in the ratio of 3:1.

III.3.10. Reduction of lithium 8-(hydroxymethyl)naphthoate with sodium (1 mol. equiv.) in the presence of ethanol.

Using the same procedure as in (III.3.7), a solution of lithium 8-(hydroxymethyl)naphthoate (2.00 g, 0.0095 mol.) in ethanol (5 ml) and ammonia (200 ml) was reduced with sodium metal (0.22 g, 1 mol. equiv) and the reaction was quenched with ammonium chloride (0.5 g, 1 mol. equiv) over 5 minutes. After working up the reaction there was obtained a solid (1.85 g, 92.5%) which was crystallised from petroleum ether/ CHCl_3 to give 8-methyl-1,4-dihydro-naphthoic acid (97) (0.7 g, 35%). Spectroscopic study of the mother liquor residues reveals the presence of some unreacted naphthalide (and another as yet unidentified material which would not be separated) in the ratio of 2:1:1.

III.3.11. Reduction of lithium 8-(hydroxymethyl)naphthoate with sodium (2 mol. equiv) in the presence of water

A solution of lithium 8-(hydroxymethyl)naphthoate (1.00 g, 0.004 mol) in a mixture of ether (15 ml), ammonia (200 ml), and water (1 ml) was reduced with sodium metal

(0.22 g, 0.008 g-atom, 2 mol.equiv.) and subsequently quenched with NH_4Cl (0.5 g, 2 mol.equiv.) over 10 minutes. Working up the reaction mixture gave a crude product (1.0 g, 100%) which was crystallized from petroleum ether/ CHCl_3 to give 8-methyl-1,4-dihydronaphthoic acid (97) (0.4 g, 40%). Analysis of the contents of the mother liquor showed that this contained 1,4-dihydronaphthalide (104), unreacted naphthalide (100) and 8-methyl-1,4-dihydronaphthoic acid (97) in a ratio of 1:1:3 respectively.

III.3.12. Reduction of naphthalide (100)

(i) With sodium metal (2 mol.equiv.)

Following the procedure outlined in (III.3.3), naphthalide (1.5 g, 0.008 mol.) in dry ether (20 ml) and ammonia (200 ml) was reduced with sodium (0.37 g, 0.016 g-atom, 2 mol.equiv.) and the reaction was then quenched with ammonium chloride (0.87 g, 2 mol.equiv) over 10 minutes. The reaction was worked up to give a brown oil (1.3 g, 87%), the ^1H nmr spectrum of which shows that it is a mixture of naphthalide (100), 8-methyl-1,4-dihydronaphthoic acid (97), and 1,4-dihydronaphthalide (104) in the ratio of 1:2:4.

(ii) With lithium metal (4 mol.equiv.)

Using the standard procedure of (III.3.3) naphthalide (2.0 g, 0.01 mol) in dry ether (20 ml) and ammonia (250 ml) was reduced by lithium metal (0.3 g, 0.04 g-atom,

4 mol equiv) and the reaction was quenched with ammonium chloride (2.5 g, 4 mol equiv) over 10 minutes. The crude product (1.8 g, 90%) obtained was identified as 1,4-dihydro-8-methylnaphthoic acid which has ^1H nmr identical to that of (97). This was crystallised from petroleum ether/ CHCl_3 to give white crystals (1.5 g, 75%) which had m.p. 155-157 $^\circ\text{C}$. No starting material was recovered.

III.3.13. 8-Methylnaphthoic acid (107)

1,4-Dihydro-8-methylnaphthoic acid (2.0 g, 0.01 mol) was dissolved in benzene (50 ml) and dichlorodicyano(-p-benzo)quinone (DDQ) (2.2 g, 0.011 mol, 1.1 mol equiv) was added to the solution. The mixture was left to stir at room temperature for three hours. Petroleum ether was added and thus dichlorodicyanohydroquinone which formed was filtered off. The solvent was evaporated from the filtrate and the solid residue which was obtained was washed several times with petroleum ether. This solid which was crystallised several times did not crystallise satisfactorily so it was purified by sublimation to give white crystals (1.8 g, 90%) which had a m.p. 129-130 $^\circ\text{C}$ (lit.³ 130-1 $^\circ\text{C}$) were identified as 8-methylnaphthoic acid (107).

$\delta(\text{CDCl}_3)$: 8.7(1H, s, COOH), 7.2-8(6H, m, ArH), 2.7(3H, s, CH₃)

ν_{max} (Nujol): 2900, 1700s(C=O)s, 1200, 780 cm^{-1}

m/e: 186(62%, m^+); 171(3%, $m^+ - \text{CH}_3$); 169(50%, $m^+ - \text{OH}$);
168(100%, $m^+ - \text{H}_2\text{O}$); 141(62%, $m^+ - \text{COOH}$)

m/e observed 186.0681 $\text{C}_{12}\text{H}_{10}\text{O}_2$ requires m/e 186.0681.

III.3.14. 8-methyl-1-methylnaphthoate (226)

To 8-methylnaphthoic acid (2.0 g, 0.01 mol) in water (30 ml) was added sodium carbonate (1.2 g). The mixture was warmed to 40°C and dimethylsulphate (1.5 g) was added. The mixture was left to stir for 45 minutes. Then a second portion of Me₂SO₄ (1.5 g) was added followed by Na₂CO₃ (1.2 g) and the mixture was left to stir for a further 30 minutes. After the addition of a final portion of Me₂SO₄ (1.0 g) followed by Na₂CO₃ (1.0 g), the mixture was left to stir for a further 15 min. The mixture was then cooled and was extracted with ether (3 x 100 ml). The combined extracts were dried (MgSO₄) and the solvent was evaporated to give an oily product (0.65 g, 30%) which was purified by column chromatography (alumina eluted with benzene). The purified product (0.4 g) was distilled under water pressure (10 mm) (bp of the oil at which the product distilled was 180-200°C), to give a pure sample of the ester (0.20 g).

δ (CDCl₃): 7.2-7.9(6H,m,ArH), 3.9(3H,s,COOCH₃), 2.5(3H,s,
-CH₃)

ν_{\max} (Nujol): 2950, 1720 s (C=O) cm⁻¹

Required for C₁₃H₁₂O₂: C, 78.0; H, 6.0%

Found: C, 78.2; H, 6.2%

m/e: 200(51%, m⁺); 185(2%, m⁺-CH₃); 170(8%, 2CH₃);
169(66%, m⁺-ome), 168(100%, m⁺-O₂), 141
(93%, m⁺-COOMe).

III.3.15. Reduction of 1,4-dihydronaphthalide with sodium metal

1,4-Dihydronaphthalide (1.0 g, 0.005 mol) in dry ether (20 ml) and ammonia (300 ml) was treated with sodium metal (0.24 g, 0.01 mol, 2 mol.equiv). The mixture was stirred for half an hour and the reaction was then quenched with ammonium chloride (1.5 g, 2 mol.equiv) over 10 minutes. Ammonia was allowed to evaporate overnight, and water (100 ml) was then added to the mixture. The solution was acidified with HCl (2 N) and was then extracted with ether (3 x 100 ml). The combined ether extracts were dried ($MgSO_4$) and the solvent was evaporated to give a white solid (0.8 g) which was crystallised from petroleum ether/ $CHCl_3$) to give 8-methyl-1,4-dihydronaphthoic acid (97) (0.5 g, 50%) which had mp 153-155°C. Evaporation of the solvent of the mother liquor gave a residue (0.26 g) which was found to contain by 1H nmr unreacted 1,4-dihydronaphthalide and 8-methylnaphthoic acid in the ratio of 1:3 respectively.

III.3.16. Reductive methylation of lithium 8-(hydroxymethyl)-1-naphthoate

Two procedures were followed in an attempt to prepare 1,4-dihydro-1,8-dimethylnaphthoic acid but neither gave the desired product.

(i) Dry ammonia (500 ml) was distilled into a 3-necked flask containing lithium 8-(hydroxymethyl)-1-naphthoate

(2.0 g, 0.009 mol) in dry ether (50 ml). Lithium metal (0.26 g, 0.03 mol, 4 mol.equiv.) was added and the solution turned blue. The solution was stirred for 15 minutes and then methyl iodide (MI) (3.8 g, 0.03 mol, 3 mol.equiv.) in ether (20 ml) was added and no change in the colour of the solution was observed, and the solution left to stir for half an hour and then ammonium chloride (1.5 g) was added and the mixture left to stir for a further 15 minutes. Ammonia was left to evaporate overnight and the work up of the reaction gave a crude product (1.7 g, 94%) which was identified as 1,4-dihydro-8-methylnaphthoic acid and which has identical ^1H nmr as that of (97) in (III.3.3). This was crystallised from petroleum ether/ CHCl_3 to give white crystals (1.5 g, 88%) m.p.156-158 $^\circ\text{C}$.

(ii) Another attempt was made to prepare 1,4-dihydro-1,8-dimethylnaphthoic acid following this procedure.

Dry ammonia (200 ml) was distilled into a 500 ml-3-necked flask, and anhydrous iron(III)chloride (FeCl_3) (50 mg) was added to the ammonia followed by potassium metal (0.41 g, 0.01 mol, 2 mol.equiv.). The reaction mixture was stirred until the blue colour had disappeared and then 8-methyl-1,4-dihydronaphthoic acid (1.0 g, 0.005 mol) in dry ether (20 ml) was added as gently as the reaction permitted and a yellow solution was obtained which disappeared immediately. The reaction was left to stir for 15 minutes, and methyl iodide (2.25 g, 0.01 mol, 3 mol.equiv.) was added and the mixture left to stir for a further 15 minutes. Ammonia was allowed to evaporate

overnight, and the solid residue was then dissolved in water (100 ml), the resulting solution was acidified with HCl (3 N) and extracted with ether (3 x 100 ml). The combined organic extracts were washed with aqueous sodium metabisulphite ($\text{Na}_2\text{S}_2\text{O}_5$) (3 x 100 ml). The ether extracts were dried (MgSO_4) and the solvent was evaporated to give a crude product (0.8 g, 80%) which was found by ^1H nmr and m.p. to be of 8-methyl-1,4-dihydronaphthoic acid (97). No trace of 1,4-dihydro-1,8-dimethylnaphthoic acid was observed. For changes of colour see page experiment (63).

III.3.17. Reaction of 1,4-dihydronaphthalide with sodamide in ammonia

To distilled ammonia (400 ml) was added FeCl_3 (50 mg) followed by sodium (0.2 g, 0.008 mol, 2 mol.equiv). The mixture was left to stir for 15 minutes until the blue colour had disappeared, leaving a grey suspension. A solution of 1,4-dihydronaphthalide (0.8 g, 0.004 mol) in dry ether (15 ml) was then added and the mixture was left to stir for half an hour. Ammonium chloride (0.5 g, 2 mol.equiv) was then added. The ammonia was left to evaporate overnight and the mixture was then worked up by dissolving the solid in water (100 ml) and the resulting solution was acidified with HCl (3 N) (50 ml). The acidic solution was extracted with ether (3 x 100 ml) and the combined extracts were dried (MgSO_4) and the solvent was evaporated under reduced pressure to give a brown solid (0.7 g, 88%). An nmr spectrum of this solid revealed that it was naphthalide (100).

III.3.18. Reaction of 1,4-dihydronaphthalide with butyllithium in THF

To 1,4-dihydronaphthalide (1.0 g, 0.005 mol) in dry THF (20 ml) was added n-butyllithium (nBuLi) (3.3 ml, 1.6 M in hexane, 0.005 mol). The mixture was stirred under N_2 at $\approx -70^\circ C$ for half an hour and was then stirred at room temperature for a further 15 minutes. Methyl iodide (1.5 g, 0.01 mol) in dry THF (5 ml) was added dropwise and the mixture was left to stir for a further 2 hrs. The reaction was then quenched by careful addition of water. The THF layer was separated and the aqueous layer was extracted with ether (3 x 100 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give non-acidic material (0.1 g), the nmr spectrum of which showed that it was naphthalide. The aqueous layer was acidified with 2 N HCl (20 ml) and the products were isolated by extraction with ether to give a brown oil (0.9, 90%). This acidic material was purified by PLC (silica gel eluted with toluene/ethyl acetate 2:1). This gave three major fractions: (1) white solid (10%), this had $\delta(CDCl_3)$: 7.2-7.9(ArH,m), 2.9(CH_3 ,s) ppm which corresponds closely to the spectrum of 8-methylnaphthoic acid (**107**). (2) An oil (50%) nmr of which is identical with naphthalide (100). (3) An oil (20%) nmr shows $\delta(CDCl_3)$ 7.2-7.3(ArH,m); 5-5.5(broad H); 2.3(s). This material had not been identified yet.

III.3.19. α,α' -Dimethyl-1,8-naphthalide (108)

Magnesium turnings (5.0 g, 2 mol.equiv.) were placed in a dry 3-necked flask fitted with a dropping funnel, condenser, drying tube and stopper, and dry ether (100 ml) was added. A solution of methyl iodide (28.5g, 10 ml, 2 mol.equiv.) in dry ether (100 ml) was then added slowly, and when the reaction had started the rest of MeI solution was added dropwise at a rate sufficient to maintain gentle refluxing of the solvent. The mixture was then heated for 15 min. To the cooled mixture naphthalic anhydride (20.0 g, 0.01 mol) was added as a fine powder whilst the mixture was cooled. The mixture was left to stir for one hour and then a water-ice slurry was added. The solid was filtered off and the filtrate was extracted with ether (3 x 300 ml). The ethereal solution was washed with 30% sodium hydroxide (3 x 200 ml), and dried (MgSO_4) and the solvent was evaporated to give a yellow solid (7.0 g, 33%) which was crystallised from petroleum ether to give dimethylnaphthalide (6.0 g, 28%) which had m.p. 90-92°C.

IR ν_{max} (Nujol): 1700, s(C=O), 1460, 1380, 1220 cm^{-1}
 $\delta(\text{CDCl}_3)$: 7.3-8.6 (6H, m, ArH), 1.8 (6H, s, CH_3)

III.3.20. Preparation of lithium 8-(2-hydroxypropyl)-1-naphthoate (111)

α,α' -Dimethyl-1,8-naphthalide (10.0 g, 0.05 mol) and lithium hydroxide (2.3 g, 0.053 ml) were refluxed in water until

all the material had dissolved. The solvent was then evaporated under reduced pressure. Portions of benzene were added and evaporated to give yellow solid of lithium 8-(2-hydroxypropyl)-1-naphthoate (11.0 g, wet) which was dried in a desiccator for five days to give (III) (10.2 g, 98%). This crude material was used without further purification.

III.3.21. Reduction of lithium 8-(hydroxypropyl)-1-naphthoate with 10 mol.equiv. of lithium metal

Following the same procedure as in (III.3.3), lithium 8-(2-hydroxypropyl)-1-naphthoate (1.0 g, 0.004 mol) in dry ether (10 ml) and ammonia (400 ml) were treated with lithium metal (0.3 g, 10 mol.equiv.). The reaction mixture turned blue and it was stirred for half an hour, and was then quenched with solid ammonium chloride (2.26 g, 10 mol.equiv.) over 10 minutes and the solution turned to yellow. Ammonia was allowed to evaporate overnight, and the solid residue was dissolved in water (100 ml). The aqueous solution was extracted with ether (3 x 100 ml), the combined extracts were dried (MgSO_4) and the ether was evaporated under reduced pressure to give a yellow solid (0.4 g, 40%) which was identified as α, α' -dimethylnaphthalide by comparison with authentic material. The aqueous layer was then acidified with 3 N HCl which was extracted with portions of ether (3 x 100 ml). The combined extracts were dried (MgSO_4) and the solvent was evaporated to give a yellow solid (0.6 g, 60%) which was crystallised from

carbon tetrachloride to give 1,4-dihydro-8-(2-propyl)-1-naphthoic acid (114) (0.5 g, 50%) as yellow crystals which had m.p. 235-237°C.

δ (CDCl₃): 10.2-9.6(1H,b,COOH); 7.4-7(3H,m,ArH);
6.3-6(2H,m,CH=CH); 4.8-4.6(1H,q,CH); 3.5-3.4
(2H,q,CH₂); 3.3-3.0(H,q,CH); 1.3(3H,d,CH₃);
1.2(3H,d,CH₃).

ν_{\max} (Nujol): 1700 s (C=O), 1470, 1380, 1270 cm⁻¹

m/e: 216(38%,m⁺), 173(2%), 171(21%), 129(100%).

Required for C₁₄H₁₆O₂: C, 77.77; H, 7.40%

Found: C, 77.78; H, 7.41%

III.3.22. Reduction of lithium 8-(2-hydroxypropyl)-1-naphthoate with 4 mol.equiv. of lithium metal

Following the procedure in (III.3.3), lithium 8-(2-hydroxypropyl)-1-naphthoate (1.0 g, 0.004 mol) in dry ether (10 ml) and ammonia (400 ml) was treated with lithium metal (0.11 g, 4 mol.equiv). The reaction mixture turned blue and it was stirred for half an hour, then was quenched with ammonium chloride (0.85, 4 mol.equiv.) over 5 minutes and the mixture turned to yellow. Working up the reaction as in (III.3.21) gave a yellow solid (0.70 g, 77%) of α,α' -dimethylnaphthalide which was identified with authentic material and acidic material as a yellow solid 0.2 g, 23%) which was crystallised from CCl₄ to give 1,4-dihydro-8-(2-propyl)-1-naphthoic acid (114) (0.15 g, 17%) which had m.p. 236-238°C and spectroscopic data identical to that found in (III.3.21).

III.3.23. Reduction of lithium 8-(2-hydroxypropyl)-1-naphthoate with 2 mol.equiv. of lithium metal

Following the procedure in (III.3.21), lithium 8-(2-hydroxypropyl)-1-naphthoate (1.0 g, 0.004 mol) in dry ether (10 ml) and ammonia (400 ml) was treated with lithium metal (0.05 g, 2 mol.equiv.) and the reaction mixture left to stir for half an hour and was then quenched with ammonium chloride (0.5 g, 2 mol.equiv) over 5 minutes. Following the procedure outlined in (III.3.21) working up of the reaction mixture gave: (1) a yellow solid (0.85 g, 85%) which by nmr was identified as a mixture of α,α' -dimethylnaphthalide and another hydroxylic-containing compound in the ratio 2:1 respectively. The mixture had $\delta(\text{CDCl}_3)$ (7.3-7.1(m,ArH);4.3,3.5(b,H), 1.6; 1.7(s,CH₃), 1.8(s,CH₃)) and IR ν_{max} (Nujol) (3400,1710; 1460,1300 cm^{-1}). In order to separate these, the non-acidic product (0.5 g) was refluxed with 10% aqueous sodium hydroxide (20 ml) for one hour until all the solid had dissolved. Water (50 ml) was added to the cooled mixture which was extracted with ether (3 x 50 ml). The combined extracts were dried (MgSO_4) and the solvent was evaporated to give yellow solid (0.40 g, 90%) which was identified with an authentic sample of α,α' -dimethylnaphthalide (III.3.19).

(2) The aqueous layer was then acidified with HCl and extracted with ether (3 x 100 ml). The combined extracts were dried (MgSO_4) and the solvent was evaporated to give

a brown solid (0.05 g, 6%) which had m.p. 233-238°C and it was identified as 1,4-dihydro-8-(2-propyl)-1-naphthoic acid (114) which had spectra identical to that of (III.3.21).

III.3.24. Reduction of lithium 8-(2-hydroxypropyl)-1-naphthoate with 2 mol. equiv. of sodium

Birch reduction to lithium 8-(2-hydroxypropyl)-1-naphthoate (1.0 g, 0.004 mol) in ether (10 ml) and ammonia (300 ml) was carried out using sodium metal (0.19 g, 2 mol.equiv.) and following the procedure (III.3.21), the reaction mixture was stirred for half an hour and was then quenched with ammonium chloride (0.5 g, 2 mol.equiv.) over 5 minutes. The reaction was worked up as in (III.3.21) to give yellow solid (0.7 g, 70%) which was identified as 8-(2-hydroxypropyl)-1-naphthoic acid which had $\delta(\text{CDCl}_3)$: 7.2-7.3(6H, m, ArH); 2.4(1H, b, OH); 1.8(3H, s, CH₃); 1.9(3H, s, CH₃) and ν_{max} (3400, 2250, 1720(C=O) cm⁻¹). The residual aqueous layer was then acidified with HCl to give a solid (0.2 g, 20%) which had spectral properties identical with 1,4-dihydro-8-(2-propyl)-1-naphthoic acid (114) together with some impurities.

III.3.25. Reduction of α, α' -dimethylnaphthalide with 4 mol.equiv. of lithium

Carrying out the procedure outlined in (III.3.3), α, α' -dimethylnaphthalide (1.5 g, 0.007 mol) in dry ether (25 ml) and ammonia (300 ml) was reduced with lithium (0.19 g, 4 mol.equiv.) and the reaction left to stir for half an hour and was then quenched with ammonium chloride

(1.5 g, 4 mol.equiv.) over 5 minutes. The reaction mixture was worked up following the procedure in (III.3.21) and gave a brown oil (1.3 g, 80%) which was identified as a mixture of 8-(2-hydroxypropyl)naphthoic acid which had identical spectral data with that of (III.3.24) and α,α' -dimethylnaphthalide which was identified with an authentic sample (III.3.19). Acidification of the aqueous layer afforded yellow solid (0.2 g, 20%) which was found to be 1,4-dihydro-8-(isopropyl)-1-naphthoic acid and which had m.p. 234-237°C and had identical spectral data as outlined in (III.3.21).

III.3.26. 1,4-Dihydro-o-toluic acid (129)

o-Toluic acid (5.0 g, 0.036 mol) was added to dry ether (40 ml) and ammonia (500 ml) was condensed into the suspension. Lithium metal (1.02 g, 0.1 mol, 4 mol.equiv.) was added to the stirred solution. The solution which rapidly turned blue was stirred for a further half an hour and the reaction was then quenched by the addition of portions of solid ammonium chloride (7.8 g, 4 mol.equiv.) over 15 minutes until the discharge of the deep colour. Ammonia was allowed to evaporate overnight, and the solid residue was dissolved in water (300 ml). The solution was acidified with 3 N HCl which was then extracted with portions of ether (3 x 150 ml). The combined extracts were dried (MgSO_4) and the ether was evaporated under reduced pressure to give a white solid which was identified as 1,4-dihydro-o-toluic acid (129) (4.9 g, 97%) which

crystallised from petroleum ether as white crystals (4.0 g, 80%) which had m.p. 70-72°C (lit.^{41b} 74-5°C).

δ (CDCl₃): 5.9-5.7(3H,m,CH=CH);3.8-3.6(1H,m,CH);2.8
(2H,s,CH₂),1.8(3H,s,CH₃),1.2(1H,s,COOH).

ν_{\max} (Nujol): 3000 b, 1700 s (C=O),1460,1380,1280,900 cm⁻¹.

Required for C₈H₁₀O₂: C,69.5;H,7.2%

Found: C,69.3;H,7.3%

m/e C₈H₁₀O₂ requires 138.0681 and found for C₈H₁₀O₂
138.0681.

III.3.27. 1,4-Dihydro- α -hydroxyxylene (133)

1,4-Dihydro-*o*-toluic acid (129) (2.0 g, 0.014 mol) in dry ether (50 ml) was added dropwise to a slurry of lithium aluminium hydride (1.10 g, 0.02 mol) in dry ether (70 ml). The mixture was left to stir for one hour. Water (200 ml) was then added cautiously followed by 4 N H₂SO₄ (150 ml). The ether layer was separated and the aqueous layer was extracted with another portion of ether (100 ml). The combined ether extracts were washed once with water (50 ml) and was dried (MgSO₄). The solvent was evaporated to give a colourless oil which was identified as 1,4-dihydro- α -hydroxyxylene (1.5 g, 84%). The oil was distilled under reduced pressure to give a pure sample of 1,4-dihydro- α -hydroxyxylene (133) (1.2 g, 67%) which had bp 69.5°C/10 mm.

δ (CDCl₃): 5.9-5.5(3H,m,CH=CH);3.7(1H,s,OH);2.7(2H,s,CH₂);
2.2(1H,s,CH₈);1.8(3H,s,CH₃).

ν_{\max} (film): 3350 b (OH),2900,1440,1380,1040,1000 cm⁻¹

m/e: 124(2%,m⁺);109(7%);107(32);105(21);93(46)

Required for C₈H₁₂O: 124.0888

Found: 124.0888

III.3.28. α -Hydroxy-*o*-xylene (2-methylbenzylalcohol) (132)

Following the procedure described in (III.3.27), *o*-toluic acid (3.0 g, 0.02 mol) in dry ether (100 ml) was reacted with a slurry of lithium aluminium hydride (1.62 g, 0.04 mol) in dry ether (70 ml). After the addition of water (100 ml) and extraction of the organic product gave a white solid α -hydroxy-*o*-xylene (2.1 g, 80%) which was crystallised from petroleum ether to give white crystals of α -hydroxy-*o*-xylene (132) (1.9 g, 73%) which had m.p 34-35°C (lit.¹⁵³ 37-39°C).

δ (CDCl₃): 7.1(4H,s,ArH);4.5(2H,s,CH₂);2.9(1H,s,OH);
2.2(3H,s,CH₃).

ν_{\max} (film): 3300 b (OH), 2900, 1600, 1460 cm⁻¹

m/e: 122(30%,m⁺);107(32),105(21);104(62);91(47).

III.3.29. 2,2'-Dimethylbibenzyl (127)

α -Chloro-*o*-xylene (10.0 g, 0.071 mol) in dry ether (100 ml) was added dropwise to a stirred solution of Mg turnings (0.85 g, 0.035 g-atom) in dry ether (50 ml). When the addition was complete, the mixture was left to stir

at room temperature for 2 hrs. Cold diluted hydrochloric acid was added and the organic layer was separated and dried (MgSO_4) and the solvent was removed under reduced pressure to give crude product of 2,2'-dimethylbibenzyl (127) (10.3,70%) which was distilled under reduced pressure to give a colourless liquid of 2,2'-dimethylbibenzyl (127) (7.0,47%) which had bp. $166-168^\circ\text{C}/15\text{ mm}$ (lit.¹⁵⁴ $177^\circ/20\text{ mm}$). This solidified on cooling m.p. $52-54^\circ\text{C}$.

$\delta(\text{CDCl}_3)$: 7.2(8H,s,ArH);2.9(4H,s, CH_2);2.3(6H,s, CH_3)

ν_{max} (Nujol): 2900, 1460, 1380, 760 cm^{-1}

m/e: 210(20%, m^+);105(100)

III.3.30. Preparation of lithium 2-(hydroxymethyl)benzoate (113)

Following the procedure outlined in (III.3.2), phthalide (10 g,0.07 mol) and lithium hydroxide (3.5 g, 0.08 mol) in water were refluxed for 2 hrs. Evaporation of the solvent gave white solid of lithium 2-(hydroxymethyl)benzoate (113) (11 g wet) which was dried in the desiccator for 3 days to give (10.0 g, 95%).

III.3.31. Reduction of lithium 2-(hydroxymethyl)benzoate with 10 mol equiv. of lithium metal

Ammonia was condensed in a flask containing lithium 2-(hydroxymethyl)benzoate (3.0 g, 0.018 mol) in dry ether (50 ml). Lithium metal (1.32 g, 0.18 mol) was added and the mixture was stirred for half an hour and then quenched

with ammonium chloride (0.90 g, 0.18 mol) over five minutes. The reaction was worked up following the procedure in (III.3.26) to give an acidic material as white solid of 1,4-dihydro-2-(hydroxymethyl)benzoic acid (134) (2.5 g, 87%) which was crystallised from chloroform to give white crystals of 1,4-dihydro-2-(hydroxymethyl)benzoic acid which had m.p. 118-120°C.

δ (CDCl₃): 5.8(3H,s,CH=CH);5.3(2H,s,CH₂);4.0(2H,s,CH₂);
3.7(1H,d,CH);2.7(2H,m,CH₂).

ν_{\max} (Nujol): 3520 b (OH);2960,1720 s (C=O),1540,1350,
1260 cm⁻¹

m/e: 136(8%,m⁺);134(31);105(100);91(28);77(63).

Required for C₈H₁₀O₂: C,62.3; H,6.4%

Found: C,62.5; H,6.5%

III.3.32. Reduction of lithium 2-(hydroxymethyl)benzoate with 4 mol equiv. of lithium metal

Following the procedure described in (31), lithium 2-(hydroxymethyl)benzoate (2.0 g, 0.013 mol) in dry ether (30 ml) and ammonia (250 ml) was treated with lithium metal (0.35 g, 4 mol.equiv.) and the reaction left to stir for 15 minutes. The reaction mixture was quenched with ammonium chloride (3.0 g, 4 mol.equiv.) over 5 minutes. Ammonia was evaporated and water was added to the solid residue which was extracted with ether (3 x 100 ml). The combined extracts were dried (MgSO₄) and the solvent was evaporated to give an oil of

2,2'-dimethylbibenzyl (127) (500 mg, 23%) which was solidified upon cooling which had m.p.49-52^oC and spectra identical to that of the authentic sample (111-3-29). The aqueous layer was then acidified with 3 N HCl and extracted with ether (3 x 100 ml). The solvent was dried (MgSO₄), and evaporated under reduced pressure to give white solid of 1,4-dihydro-2-(hydroxymethyl)benzoic acid (134) (1.32 g, 70%) which had m.p. 118-119^oC and nmr and IR spectra identical with that of authentic material (see Experiment 31).

III.3.33. Reduction of lithium 2-(hydroxymethyl)benzoate with 2 mol.equiv. of lithium metal

Following the procedure described in (III.3.31), lithium 2-(hydroxymethylbenzoate) (2.0 g, 0.013 mol), in dry ether (15 ml) and ammonia (300 ml) was reduced with lithium metal (0.17 g, 2 mol.equiv.). After stirring the reaction for 15 minutes, the reaction was quenched with ammonium chloride (2.8 g, 4 mol.equiv.). Working up the reaction as in (III.3.32), no non-acidic material was found. The acidic material which had m.p.115-118^oC was identified as 1,4-dihydro-2-(hydroxymethyl)benzoic acid (134) by spectral analyses (see experiment 31).

III.3.34. Reduction of lithium 2-(hydroxymethyl)benzoate with 10 mol.equiv. of lithium metal in the presence of ammonium chloride

To a mixture of lithium 2-(hydroxymethyl)benzoate (2.0 g, 0.013 mol) in dry ether (15 ml), ammonia (300 ml), and ammonium chloride (2.7 g, 4 mol.equiv.) was added lithium metal (0.88 g, 10 mol.equiv.). The reaction was left to stir for half an hour. Ammonia was allowed to evaporate overnight and water was added to the solid residue. The aqueous layer was extracted with ether (3 x 100 ml). The condensed extracts were dried (MgSO_4) and the solvent was evaporated to give a white solid (600 mg, 30%) which was identified as phthalide which had m.p. 70-73°C (lit.¹⁵⁵ 75°C). The aqueous layer was acidified and extracted with ether (3 x 100 ml) to give acidic material of white solid (1.0 g, 52%) which had an nmr spectrum identical with 1,4-dihydro-2-(hydroxymethyl)benzoic acid (134) and m.p. 114-117°C (See section III.3.31).

III.3.35. Reduction of lithium-2-(hydroxymethyl)benzoate with 10 mol equiv. of lithium metal in the presence of water.

Following the procedure in (31), to a mixture of lithium 2-(hydroxymethyl)benzoate (2.0 g, 0.013 mol) in dry ether (15 ml), water (1 ml), and ammonia (300 ml) was added lithium metal (0.88 g, 10 mol.equiv.). The reaction was stirred for half an hour and ammonium chloride

(2.7 g, 4 mol.equiv.) was then added. The reaction was worked up following the procedure in (31) to give only acidic material (1.7 g, 85%) which was crystallised from chloroform to give white crystals of 1,4-dihydro-2-(hydroxymethyl)benzoic acid (134) (0.7 g, 35%) which had m.p. 114-115°C and nmr spectra identical with authentic material (see 31). The mother liquors were evaporated to give a residue (1.0 g, 50%) which contain by nmr ($\delta(\text{CDCl}_3)$: 7.9-7.2, 5.9, 5.8, 4, 2.6, 2) 1,4-dihydro-2-(hydroxymethyl)benzoic acid (see 31) together with phthalide in the ratio of 1:1. These could not be separated.

III.3.36. Reduction of phthalide with 10 mol.equiv. of lithium metal.

To a solution of phthalide (3.0 g, 0.022 mol) in dry ether (30 ml) and ammonia (400 ml) was added lithium metal (1.56 g, 0.22 mol, 10 mol.eq.). The mixture was left to stir for half an hour and ammonium chloride (11.7 g, 0.22 mol) was then added over 10 minutes. The reaction was worked up following the procedure in (32) to give non-acidic material (1.6 g, 55%) as an oily product which was distilled under reduced pressure to give a colourless oil of 2,2'-dimethylbibenzyl (1.0 g, 35%) which had b.p. 122°C/10 mm. This had $\delta(\text{CDCl}_3)$: 7.1(8H, s, ArH), 2.9(4H, s, CH₂); 2.3(6H, s, CH₃). ν_{max} (Nujol): 2900, 1500, 1460, 1350, 1160, 760. The analyses were identical with the authentic sample (experiment 29). The aqueous layer was acidified with 3 N HCl and extracted with ether (3 x 100 ml).

The solvent was evaporated under reduced pressure to give a white solid (0.9 g, 30%) which had $\delta(\text{CDCl}_3)$: 7.9-7.3, 5.3, 3.5-2.5 (broad peak); ν_{max} (Nujol): 3400, 2900, 1700, 1430. This was believed to be a mixture of phthalide and 2-(hydroxymethyl)benzoic acid. All the attempts to separate them failed, (by tlc it was seen as only one spot).

III.3.37. Reduction of phthalide with 4 mol.equiv. of lithium metal.

Following the procedure in (36), phthalide (2.0 g, 6.01 mol) in dry ether (20 ml) and ammonia (300 ml) was reduced with lithium metal (0.4 g, 0.05 mol, 4 mol.equiv.). The reaction was stirred for 15 minutes and was then quenched with ammonium chloride (2.9 g, 6.05 mol., 4 mol.equiv.). The reaction was worked up following the procedure in (36) to give 2,2'-dimethylbibenzyl (1.2 g, 60%) as an oil which had identical spectra as the authentic material (see 29) and an acidic material (0.72 g, 36%) which was identified as the mixture of phthalide and 2-(hydroxymethyl)benzoic acid and had nmr and ir spectra identical with the mixture was obtained in (36).

III.3.38. Preparation of ethyl o-toluate (137)

A solution of o-toluic acid (50.0 g, 0.36 mol) in dry ethanol (150 ml) containing a few drops of concentrated sulphuric acid was refluxed for 15 hrs. The cooled reaction

mixture was then added to water (200 ml) and the solution was extracted with ether (3 x 200 ml). The extracts were washed once with 10% sodium hydroxide (100 ml) and once with water (100 ml). The ether layer was dried (MgSO_4) and the solvent was evaporated to give the crude ester (56.0 g, 93%) which was distilled under reduced pressure to give ethyl o-toluate (48.0 g, 80%) which had b.p. $83-86^\circ\text{C}/2\text{ mm}$ (lit.¹⁵⁶ $102-102.5^\circ\text{C}/13\text{ mm}$).

$\delta(\text{CDCl}_3)$: 8.0-7.2(4H,m,ArH); 4.4-4.2(2H,q, CH_2CH_3);
2.6(3H,s, CH_3); 1.4-1.2(3H,t, CH_2CH_3).
 ν_{max} (film): 2980,1740 s (C=O),1500,1360,1260,700 cm^{-1}
m/e: 164(51%, m^+),149(4),135(26),119(100),91(67).

III.3.39. Ethyl o-tolylacetate (225)

A mixture of o-tolylacetic acid (50.0 g, 0.3 mol) in super dry ethanol (200 ml) and concentrated sulphuric acid (5 ml) was refluxed for 4 hours. Water (300 ml) was added to the cooled mixture which was then extracted with ether (3 x 250 ml). The condensed ether extracts were washed with 10% sodium hydroxide (3 x 100 ml) and water (100 ml). The ethereal layer was dried (MgSO_4) and the solvent was then evaporated to give a colourless liquid (56.0 g, 95%) which was distilled under reduced pressure to give ethyl o-tolylacetate (53.0 g, 90%)
b.p. $115-117^\circ\text{C}/5\text{ mm}$.

$\delta(\text{CDCl}_3)$: 7.2(4H,s,ArH); 4.3-4.0(2H,q, $\underline{\text{CH}_2\text{CH}_3}$);
 3.6(2H,s, CH_2); 2.3(3H,s, CH_3); 1.3-1.1(3H,t, CH_2CH_3).
 ν_{max} (neat): 2910,1760 s (C=O), 1500,1360,1150,1060,750 cm^{-1}
 Required for $\text{C}_{11}\text{H}_{14}\text{O}_2$: C,74.15; H=7.86
 Found: C,74.20; H=7.66

III.3.40. 2-Methylbenzoylchloride (141)

A mixture of o-toluic acid (50 g, 0.36 mol) and thionyl chloride (90 ml, 0.75 mol) were stirred for 2 hours. Excess thionyl chloride was evaporated under reduced pressure and the residue was then distilled under reduced pressure to give the acid chloride (141) (50.4 g, 88%) which had b.p. 72-73°C/3 mm (lit.¹⁵⁷ 110-110°/29 mm; 99-100°/14 mm).

$\delta(\text{CDCl}_3)$: 8.2-7.2(4H,m,ArH); 2.5(3H,s, CH_3)
 ν_{max} (film.): 3060,2900,1780 s (C=O),1600,1480,1380,1210,
 870 cm^{-1}

III.3.41. Reaction of o-tolylbenzaldehyde with potassium cyanide.

To o-tolylbenzaldehyde (10.0 g, 0.08 mol) in water (10 ml) and ethanol (20 ml) was added with care potassium cyanide (1.6 g, 0.024 mol). The solution was refluxed for 3 hrs and then cooled and extracted with ether (3 x 100 ml). The ether extracts were washed with ferric chloride solution (4 x 100) and water (2 x 100). The organic layer was dried (MgSO_4) and the solvent was

evaporated to give back unchanged *o*-tolylbenzaldehyde (9.8 g, 98%) identical with an authentic sample.

III.3.42. Reaction of *o*-tolylaldehyde with 3-benzyl-5-(2-hydroxyethyl)-thiazolium chloride.

A mixture of *o*-tolylaldehyde (10.0 g, 0.08 mol) and 3-benzyl-5-(2-hydroxyethyl)-thiazolium chloride (1.2 g, 0.04 mol) in ethanol (100 ml) was stirred at room temperature under a nitrogen atmosphere for 15 min. Triethylamine (4.0 g, 0.04 mol) was then added and the mixture was left to stir for 50 hrs under N₂. At the end of this time no change could be detected by tlc (on silica gel eluted with petroleum ether:ethylacetate 2:1). The reaction was worked up (41) by the addition of water (100 ml) and the mixture was extracted with ether (3 x 100). The ethereal extracts were dried (MgSO₄) and evaporated to give unchanged aldehyde (9.5 g, 95%) which had spectra identical to that of authentic sample.

III.3.43. Reduction of ethyl *o*-toluate (137) with 10 mol. equiv. of lithium metal.

The reduction was carried out several times following the procedure outlined in (31), but consistent results could not be obtained (see Table 15).

To the ester (137) (10.0 g, 0.06 mol) in ether (30 ml) and ammonia (500 ml) was added lithium metal (4.26 g, 10 mol.equiv.). The mixture was left to stir

TABLE 15.

Reduction of ethyl-o-toluate (137) with 10 mol. equivalent of lithium metal.

NO. of mole of (137)	ACIDIC PRODUCTS			NON-ACIDIC PRODUCTS							Overall yield%
	Yield of (128)%	Yield of (129)%	Overall yield	Yield % (127)	Yield% (227) o-xylene	Yield% (136)	Yield% (132)	Yield% (133)	Yield% (137)		
1 0.010	(a) 1%	(a) 1	2	(b) 10	10	-	-	-	(b) 5	25	
2 0.020	(a) 3	-	3	(b) 10	(b) 12	(b) 10	-	-	-	33	
3 0.03	(b) 10	(b) 6	16	-	-	-	30	15	-	46	
4 0.06	(a) 2	(a) 4	6	5	-	-	(b) 15	(b) 10	-	30	
5 0.06	(b) 4	(b) 10	14	(b) 12	(c) 20	(b) 10	-	-	(b) 15	57	

(a) isolated by plc

(b) estimated for nmr data

(c) separated by distillation.

for half an hour. At the end of this time ammonium chloride (32 g, 10 mol.equiv.) was added and the mixture was then left to stir for a further half hour. Ammonia was allowed to evaporate overnight and water was added. Two different work-ups of the reaction mixture were followed.

(i) The work up of the reaction mixture for no.1,2, 3,4 (from the Table 15) was followed as in Section (26) Water was added to the solid residue which was extracted with ether (3 x 100 ml). The solvent was dried ($MgSO_4$) and evaporated to give an oil (the yield of the non-acidic material varies, see table below). From the table the five different products were detected from nmr and ir spectra. Thin layer chromatography shows between six and seven spots, therefore separation of these products could not be achieved by crystallisation or distillation. Separation by plc was successful in some instances and only in this case an isolated product was possible. The product(s) separation by plc were carried out on silica gel and eluted with EtOAc: Petroleum ether (1:2). To the aqueous layer, 3 N HCl was added and the acidic solution was extracted with ether (3 x 100 ml). The ether solution was dried and evaporated to give white solid which by tlc shows only two product(s). The mixture was separated (no.4, Table 15) by plc on silica gel and eluted with petroleum ether to give an isolated product of α -hydroxyxylene (15%) and 1,4-dihydro- α -hydroxyxylene (10%) which had identical nmr spectra with the authentic samples (see 27 and 28).

(ii) The second work up of the reaction was carried out in case 5 to detect any volatile materials not present in the previous mixture (i). Ammonia was evaporated overnight and to the solid mixture water (200 ml) was added which was extracted with ether (3 x 100 ml). The ether solution was dried (MgSO_4) and distilled at atmospheric pressure to give an oil (5.64 g). The oil residue was then distilled at atmospheric pressure to give two fractions (a) (1 g) bp 145-153°C which had nmr $\delta(\text{CDCl}_3)$: 7.1(4H,s,ArH), 2.2(6H,s, CH_3); (b) dark brown oil (4.00 g) which did not distil above 220°C atmospheric pressure and which had nmr $\delta(\text{CDCl}_3)$: 7.1 (broad) 4.8, 4.6, 3.9-3.7(q), 2.7, 2.8-2.3, 2.2, 1.3(t). The aqueous layer was then acidified with 3 N HCl and extracted with ether which was dried (MgSO_4) and distilled at atmospheric pressure to give white solid (0.36 g) which was crystallised from petroleum ether/chloroform to give white crystals of 1,4-dihydro-*o*-toluic acid which had identical nmr spectra (See 2.). The mother liquor shows some of *o*-toluic acid together with 1,4-dihydro-*o*-toluic acid in the ratio 1:3 respectively. The acidic layer then extracted continuously with chloroform for 30 hours to give further white solid (1.0 g) which was identified by nmr as a mixture of *o*-toluic acid and its 1,4-dihydro compound.

III.3.44. Reduction of ethyl o-toluate with 2 mol.equiv. of sodium metal.

Following the procedure in (31), ethyl o-toluate (5.0 g, 0.03 mol) in dry ether (30 ml) and ammonia (500 ml) was treated with sodium metal (1.4 g, 2 mol.equiv.) in portions and the reaction was left to stir for one hour. Ammonium chloride (3.2 g, 2 mol.equiv.) was then added over 10 minutes. The ammonia was evaporated and water (100 ml) was then added to the solid residue. The solution was extracted with ether (3 x 150 ml), the ether layer was dried (MgSO_4) and evaporated to give white solid (3.25 g, 65%) which had m.p. 118-125°C and nmr $\delta(\text{CDCl}_3)$: 7.8-7.1(m, ArH), 5.9-5.6, 4.9(s), 4.4-4.2(q), 3.5 (broad H), 2.6(s), 1.7(s), 1.6(s), 1.4-1.1(t). IR ν_{max} (Nujol): 3360 (s), 3180(b) 1700, and 1640 w cm^{-1} .

Crystallisation of the solid from chloroform gave white crystals (2.13 g) which had m.p. 120-127°C and identical spectra to the crude product. Tlc plates on silica gel eluting with ethylacetate: Toluene in the ratio 1:2 shows three spots. Therefore purifying the product by plc was carried out on 0.3 g scale to give three fractions:

(1) colourless liquid (0.05 g, 17%) which had nmr $\delta(\text{CDCl}_3)$: 7.3(ArH), 4.4-4.1(q), 2.6(s), 1.4-1.1(t), and this was identified with authentic material of ethyl o-toluate (137). (a) An oil (0.04 g, 13%) which had nmr $\delta(\text{CDCl}_3)$: 7.2(s), 4.3(m), 1.7(s), 1.6(s). This material could not be identified because of the small quantity which was obtained. (3) A white solid (0.18 g, 60%) which had

m.p. 140-144°C and this material was further crystallised from chloroform to give white crystals (0.14 g, 47%) which had nmr δ (CDCl₃): 7.3(4H,s,ArH);6.4-5.5(1H,broad,NH),2.6 (3H,s,CH₃). IR ν_{\max} (Nujol): 3380,3180,1700,1450, 1360 cm⁻¹. This material was identified as o-toluamide (228) which had m.p. 142-144°C (lit.¹⁵⁸ m.p. 147°C).

The aqueous layer was then acidified with 3 N HCl and extracted with ether (3 x 150 ml). The ether solution was dried (MgSO₄) and evaporated to give acidic material as white solid (1.01 g, 20%), which were identified spectroscopically as 1,4-dihydro-o-toluic acid (see nmr Section 26) and o-toluic acid (nmr δ (CDCl₃): 11.0 (1H, broad, COOH);8-7.2(4H,m,ArH);2.6(3H,s,CH₃), in the ratio of 1:1.

III.3.45. Condensation of ethyl o-tolyl acetate and ethyltoluate in the presence of sodium ethoxide.

Sodium metal (1.3 g, 0.05 g-atom) was added to a 'super dry' ethanol (30 ml) and the mixture was stirred until the sodium had dissolved. To this solution of sodium ethoxide was added ethyl-o-tolylacetate (5.0 g, 0.028 mol) and the mixture was refluxed for 5 minutes. Ethyltoluate (5.0 g, 0.03 mol) was then added and the mixture was left to stir for 10 hrs. No change was observed after this time so the reaction was left to stir under reflux for a further 40 hours. The mixture was cooled and water was added and acidified with 3 N HCl which was extracted with ether (3 x 200 ml). The ether solution was dried

(MgSO_4) and evaporated to give acidic product (2.35, 23%) which was identical with that of *o*-tolyl acetic acid. The acidic layer was basified with 10% NaOH and extracted with ether (3 x 100 ml). The ether extracts were dried and the solvent was evaporated to give non-acidic material (5.92, 60%) which was identified as a mixture of the starting materials (nmr identical to that of Section 31).

III.3.46. Condensation of *o*-tolylethylacetate and ethyl *o*-toluate in the presence of sodium hydride.

To sodium hydride (0.7 g, 50% dispersion in oil, 1 mol. equiv.) in dry dimethoxyethane (30 ml) was added ethyl-*o*-tolylacetate (5.5 g, 0.03 mol) and the mixture was left to stir for half a hour. Ethyl *o*-toluate (5.5 g, 0.03 mol.) was then added slowly and the mixture was left to stir for half an hour, then refluxed for 5 hours. During this time the colour of the solution changed to dark brown. The mixture was then left to stir overnight. Water was added to the cooled mixture and the solution was extracted with ether (3 x 150 ml). The extracts were dried (MgSO_4) and the solvent was removed to give non-acidic material (5.6 g, 56%) which had nmr $\delta(\text{CDCl}_3)$: 8.1-7.1(m, ArH), 4.5-4.1(q, CH_2CH_3), 2.6(s, CH_3), 1.5-1.3(t, CH_2CH_3) which is identical to that of ethyl *o*-toluate. The aqueous layer was acidified with 3 N HCl and extracted with ether. The extracts were dried (MgSO_4) and the solvent was evaporated to give acidic material (3.53 g, 35%) which had nmr $\delta(\text{CDCl}_3)$: 8.1-7.3(m), 7.2(s), 3.7(s),

2.6(s),2.3(s), which is identified as a mixture of o-toluic acid and o-tolylacetic acid in a ratio of 1:2 respectively.

III.3.47. Preparation of o-tolil (2,2'-dimethylbenzil) (140)

(i) To Mg (3.0 g, 0.12 g-atom), dry ether (60 ml), and dry benzene (120 ml) was added iodine (15.3 g, 0.06 mol) in several portions under nitrogen. When the reaction mixture had become almost colourless and had cooled to room temperature, a solution of 2-methyl benzoylchloride (10.0g, 0.064 mol) in dry ether (10 ml) was added over a period of 15 min. The mixture was then refluxed under nitrogen atmosphere for 18 hrs. The mixture was treated with ice-cold water (10 ml) and acetic acid (100 ml). The organic layer was separated and was washed successively with 5% sodiumthiosulfate solution (100 ml), 10% potassium bicarbonate solution (100 ml) and water (100 ml). After the solution had been dried ($MgSO_4$) the solvent was evaporated to give an oil (9.5 g, 95%) which was believed to be the unstable enediol (139).

(ii) To this oil was added a solution of hydrated $CuSO_4$ (5 g) in water (15 ml) and pyridine (10 ml). The mixture was heated under reflux with stirring for four hours. The cooled mixture was poured into water and the resulting solution was acidified to pH 3-4 and was then extracted with ether (3 x 150 ml). The combined extracts were dried

(MgSO₄) and the solvent was evaporated to give a dark red oil (8.7 g, 87%) which was distilled under reduced pressure to give as a yellow liquid of *o,o'*-bitolil (4.2 g, 30%) which had b.p. 172-74⁰C/2.5 mm. This solidified on cooling. The solid was crystallized from ethanol to give yellow needles of *o,o'*-bitolil (3.8 g, 25%) which had m.p. 91-92⁰C (lit.¹⁵⁹ 92-4⁰C). This had δ (CDCl₃): 7.7-7.2(8H,m,ArH),2.7(6H,s,CH₃). IR, ν_{\max} (Nujol): 2900,1670,1600,1450,1360,1200,900 cm⁻¹ m/e: 119(100%,m⁺-PhCO),91(38%,mePh).

III.3.48. *o,o'*-tolouin (2.2'-dimethylbenzoin) (136).

The preparation of enediol was followed as in (47i). To the brown syrup of enediol (139) (8.6 g, 86%) was added methanol (40 ml) which was saturated with HCl and the mixture was left to reflux for 45 minutes. The mixture was then cooled, and water (250 ml) was added. The methanol mixture was extracted with ether (3 x 150 ml). The combined ether extracts were dried (MgSO₄) and the ether was evaporated to give a brown thick syrup (8.0 g, 80%). All the attempts to crystallise this failed and the mixture was distilled under reduced pressure to give *o,o'*-tolouin (1.6 g, 11%) which had b.p.150-52⁰C/0.9 mm (lit.^{77,160} m.p. 79⁰C).

δ (CDCl₃): 7.1(8H,m,ArH);6(1H,s,OH);5.6(1H,s,CH);
2.2(6H,s,CH₃).

ν_{\max} (neat): 3450 b (OH),2900,1700 s (C=O),1600,1450,1300 cm⁻¹.

m/e: 222(4%,m⁺-H₂O);208(2),121(10),120(100),119(8).

III.3.49. Metal/Ammonia reduction of o,o'-tolouin (136).

To o,o'-tolouin (1.0 g, 0.004 mol) in dry ether (15 ml) and ammonia (200 ml) was added lithium metal (0.29 g, 10 mol.equiv.). The mixture was stirred for half an hour and the reaction was then quenched with ammonium chloride (2.2 g, 10 mol.equiv.). The mixture was left to stir for a further half an hour and ammonia was allowed to evaporate overnight. Water was added and the solution was extracted with ether (3 x 100 ml) to give a colourless liquid which solidified on cooling which had spectroscopic properties identical with 2,2'-dimethyl-bibenzyl (127) (0.82 g, 94%) m.p. 52-53⁰C. This had $\delta(\text{CDCl}_3)$: 7.1(8H,s,ArH); 2.8(4H,s,CH₂); 2.3(6H,s,CH₃) (see 29). The aqueous layer was acidified with 3 N HCl and extracted with ether (3 x 100 ml). The extracts were dried (MgSO₄) and the solvent was evaporated but no acidic material was found.

III.3.50. Metal/Ammonia reduction of o,o'-bitolil.

To o,o'-bitolil (1.1 g, 0.004 mol) in dry ether (15 ml) and ammonia (400 ml) was added lithium metal (0.3 g, 10 mol.equiv.) in small pieces, the reaction mixture turned red then blue and the mixture was left to stir for 15 minutes. It was then quenched with ammonium chloride (1.6 g, 10 mol.equiv.) over 10 minutes. The ammonia was allowed to evaporate overnight and water (100 ml) was then added. The solution was extracted with ether (3 x 100 ml) and the extracts were dried (MgSO₄).

The solvent was evaporated to give a non-acidic material (1.00 g, 90%), nmr analysis of which revealed the presence of a mixture of the dimer 2,2'-dimethylbibenzyl ($\delta(\text{CDCl}_3)$: 7.1(8H,s,ArH);2.8(4H,s,CH₂);2.3(6H,s,CH₃) and o,o'-tolouin ($\delta(\text{CDCl}_3)$:7.2(8H,s,ArH),5.9-5.5(1H,b,OH),4.5(1H,s,CH)2.2(6H,s,CH₃)) in the ratio of 1:3 respectively.

The aqueous solution was acidified with 3 N HCl and was then extracted with ether (3 x 100 ml). The ether extracts were dried (MgSO₄) and the solvent was then removed to give acidic material (0.1 g, 10%) which from nmr analysis is thought to be a mixture of o-toluic acid and 1,4-dihydro-o-toluic acid (see experiment 26 for nmr) in the ratio of 1:2 respectively.

III3.51. 3,3'-Dimethylphthalide (109)

Magnesium turnings (6.48 g, 0.27 g-atom) were placed in a dry 3-necked flask fitted with a dropping funnel, condenser, drying tube and stopper, To it was added dry ether (20 ml), a solution of methyl iodide (38.3 g, 0.27 mol, 2 mol.equiv.) in dry ether (70 ml) was then added dropwise at a rate sufficient to maintain a gentle reflux of the solvent. The mixture was stirred under reflux for 15 minutes. The mixture was then cooled and phthalic anhydride (20.0 g, 0.135 mol) was added as a fine powder in a small portion while the mixture was cooled. The reaction mixture was then left to stir at room temperature for one hour. Water (300 ml) was then added to the reaction mixture and the solution was acidified

with dil. HCl. The acidic solution was extracted with ether (3 x 200 ml) which was washed once with Na_2CO_3 (100 ml) and then with sodium metabisulfite (100 ml) and was then dried (MgSO_4). The solvent was evaporated to give brown solid of 3,3'-dimethylphthalide (15.05 g, 69%) which was crystallised from petroleum ether to give 3,3'-dimethylphthalide (10.0 g, 46%) as white crystals which had m.p. 65-66°C (lit.⁷⁴ 68°C).

$\delta(\text{CDCl}_3)$: 8.0-7.4(4H,m,ArH), 1.6(6H,s, CH_3).

ν_{max} (Nujol): 2900, 1780 s (C=O), 1460, 1380, 900 cm^{-1} .

III.3.52. Preparation of lithium 2-(2-hydroxypropyl)-benzoate (II2)

Following the procedure in (III.3.2), lithium 2-(hydroxypropyl)benzoate was prepared from dimethylphthalide (10.0 g, 0.06 mol) and lithium hydroxide (2.9 g, 0.067 mol.) in water (100 ml) and the mixture refluxed until all dimethylphthalide had dissolved. The water was evaporated and the mixture washed with portions of benzene to give white solid (11.0 g wet) which was dried in the dessicator for one week to give lithium 2-(2-hydroxypropyl)benzoate (10.3 g, 99%).

III.3.53. Reduction of lithium 2-(2-hydroxypropyl)benzoate
with 4 mol.equiv. of lithium metal.

Following the procedure in (III.3.3), lithium 2-(2-hydroxypropyl)benzoate (2.0 g, 0.01 mol) in dry ether (15 ml) and ammonia (300 ml) were treated with lithium metal (0.33 g, 4 mol.equiv.). The reaction was left to stir for half an hour and was then quenched with ammonium chloride (3.0 g, 4 mol.eq.) over five minutes. Ammonia was allowed to evaporate overnight and water was then added to the solid residue. The aqueous solution was acidified with dil. HCl and extracted with ether (3 x 100 ml) which was dried ($MgSO_4$). The solvent was evaporated to give white solid (1.9 g, 95%) which was crystallised from petroleum ether to give a dihydrophthalide (119) (1.6 g, 84%) as white crystals which had m.p. 59-61°C.

δ ($CDCl_3$): 6.3-5.8(2H, q, CH=CH); 2.5(2H, s, CH_2); 1.6(2H, s, CH_2);
1.5(6H, s, CH_3).

ν_{max} (Nujol): 2900, 1740 s (C=O), 1460, 1380, 110, 700 cm^{-1} .

m/e: 164(43%, m^+), 149(10), 121(100).

Required for $C_{10}H_{12}O_2$: C, 73.0; H, 7.3%

Found C, 73.0; H, 7.1%

III.3.54. Reduction of lithium 2-(2-hydroxypropyl)benzoate with 10 mol.equiv. of lithium metal.

Following the procedure in (III.3.3), lithium 2-(2-hydroxypropyl)benzoate (2.0 g, 0.01 mol.) in dry ether (15 ml) and ammonia (300 ml) was reduced with lithium metal (0.7 g, 10 mol.equiv.). The reaction was stirred for half an hour and was then quenched with ammonium chloride (2.1 g, 4 mol.equiv.) over five minutes. The reaction was worked up as in (53) to give 1,4-dihydro-3,3'-dimethylphthalide (121) (1.6 g, 90%) as an oil.

δ (CDCl₃): 6.0-5.7(3H,m,CH=CH);4-3.5(1H,m,CH);2.9-2.7(2H,m,CH₂);1.6(6H,s,CH₃).

ν_{\max} (neat): 229,1760 s (C=O),1300,1140,1020, and 860 cm⁻¹.

m/e: 164(38%,m⁺);149(9);121(100);106(1).

An attempt to crystallise the oil was carried out on 0.2 g scale with petroleum ether, solid formed immediately which was filtered off to give white crystals (0.1 g, 50%) which had m.p. 67-69°C and was shown by nmr spectra to be dimethylphthalide (109). The solvent of the mother liquor was evaporated and nmr analysis of the residue revealed the absence of any dihydro products and that only dimethylphthalide was present. Another attempt was carried out to purify 1,4-dihydro-3,3'-dimethylphthalide was by distillation under reduced pressure. The oil (1.0 g) was distilled under reduced pressure to

give an oil (0.7 g) which solidified on cooling. This material was shown by nmr and IR spectra to be the other dihydroisomer (53). Therefore no further attempt was carried out and the oil was stored under nitrogen in the fridge which was stable for a few days.

III.3.55. Reduction of lithium 2-(2-hydroxypropyl)benzoate with 4 mol.equiv. of lithium in the presence of dry ethanol.

Following the procedure in (53), lithium 2-(2-hydroxypropyl)benzoate (2.0 g, 0.01 mol) in super dry ethanol (5 ml) and ammonia (300 ml) were reduced with lithium metal (0.37 g, 4 mol.equiv.). The mixture was left to stir for half an hour and was then quenched with ammonium chloride (2.00 g, 4 mol.equiv.) over five minutes. Working up the reaction as in (53) gave an oil of 1,4-dihydro-3,3'-dimethylphthalide (1.4 g, 70%) which had identical spectral properties with (54).

III.3.56. Reduction of lithium 2-(2-hydroxypropyl)benzoate with 10 mol.equiv. of lithium in the presence of dry ethanol.

Following the procedure in (53), lithium 2-(2-hydroxypropyl)benzoate (2.0 g, 0.01 mol.) in super dry ethanol (5 ml) and ammonia (300 ml) were reduced with lithium metal (0.75 g, 10 mol.equiv.). The reaction was stirred for half an hour and was then quenched with ammonium chloride (5.00 g, 10 mol.equiv.). The reaction

was worked up as in (53) and gave an oil of 1,4-dihydro-3,3 -dimethylphthalide (1.6 g, 80%) which had identical spectra as in (54).

III.3.57. 1,4-Dihydro-1-methyl-3,3 -dimethylphthalide
(124).

Following the procedure in (III.3.16ii), to dry ammonia (400 ml) was added ferric chloride (ca. 100 mg) and potassium (0.7 g, 2 mol.equiv.). The mixture was left to stir until the blue colour had disappeared and then 1,4-dihydrodimethylphthalide (1.5 g, 0.009 mol) in dry ether (10 ml) was added and the reaction mixture turned to orange. The reaction was left to stir for 5 min and methyl iodide (3.8 g, 3 mol.equiv.) in dry ether (10 ml) was carefully added and the orange colour disappeared. The mixture was left to stir for a further half an hour. The reaction mixture was worked up as in (III.3.16ii) to give a colourless oil of 1,4-dihydro-1-methyl-3,3 -dimethylphthalide (1.3 g, 81%). The product was purified by plc on silica gel eluted with toluene:ethylacetate 10% on 0.3 g scale to give: (1) 1,4-dihydro-1-methyl-3,3 -dimethylphthalide (0.2 g, 66%).

$\delta(\text{CDCl}_3)$: 6.2-5.8(3H,m,CH=CH); 2.75-2.65(2H,m,CH₂);
1.6(3H,s,CH₃); 1.5(3H,s,CH₃); 1.4(3H,s,CH₃).

ν_{max} (neat): 3040,2990,1770 s (C=O),1450,1280,1090,
950 cm⁻¹.

m/e: 134(15%,m⁺-MeCOH); 119(100);91(12).

This compound proved to be unstable for satisfactory purification for microanalysis despite a number of attempts to do so.

(2) A mixture of 1,4-dihydro-1-methyl-3,3 -dimethylphthalide and dimethylphthalide (0.1 g, 30%) in a ratio, estimated by nmr, 1:2 respectively.

III.3.58. Reductive methylation of lithium 2-(2-hydroxypropyl)benzoate.

Following the procedure in (III.3.16i), lithium 2-(2-hydroxypropyl)benzoate (3.5 g, 0.02 mol) in dry ether (35 ml) and ammonia (400 ml) was reduced with lithium metal (1.6 g, 10 mol.equiv.). The reaction was left to stir for 15 minutes and methyl iodide (10.0 g, 3 mol.equiv.) in dry ether (25 ml) was then added. The mixture was left to stir for a further half an hour and was then worked up as in (III.3.16i) to give a brown oil (3.1 g, 89%). This oil (0.3 g) was purified by plc on silica gel eluted with toluene: EtOAc 10% to give three fractions:

(1) an oil of 1,4-dihydro-3,3 -dimethylphthalide (0.1 g, 33%) which had identical spectra as that of (45).

(2) White solid of the dihydrophthalide (119) (0.05g, 17%) which had identical spectra as in (55).

(3) Yellow solid of dimethylphthalide (0.1 g, 33%) which was identical with authentic material (Section 52).

III.3.59. Reduction of 3,3-dimethylphthalide with
4 mol.equiv. of lithium metal.

Following the procedure in (54), 3,3 -dimethylphthalide (2.0 g/0.12 mol) in dry ether (20 ml) and ammonia (300 ml) was treated with lithium (0.33 g, 4 mol.equiv.). The reaction was stirred for 15 min. and ammonium chloride (2.5 g, 4 mol.equiv.) was then added. The reaction was worked up as in (54) to give brown oil (1.8 g, 90%) which was distilled under reduced pressure affording two fractions: Fraction (1) by 82-88°C/10 mm (0.5 g, 27%) which by further purification by plc eluted with petroleum ether: EtOAc 2:1 on silica gel gave white solid of the dihydrophthalide isomer (119) (0.1 g, 20%) which had identical spectra as in (54) and m.p. 62-63°C. Fraction (2) b.p. 120-124°C/10 mm (0.6 g, 33%) which was further purified by plc on silica gel eluted with petroleum ether: EtOAc 2:1 to give an oil (0.3 g, 58%) which had $\delta(\text{CDCl}_3)$: 7.4-7.1(8H,m,ArH); 2.5(4H,s,CH₂); 1.6(2H,s,OH), 1.5 (12H,s,CH₃). ν_{max} (neat film): 3400 b (OH), 2990, 1400, 940, 760 cm^{-1} . This product was identified as 2-(2-hydroxypropyl)toluene (125).

III.3.60. Reduction of 3,3-dimethylphthalide with 10 mol.
equiv. of lithium.

Following the procedure in (59), phthalide (109) (2.0 g, 0.12 mol.) in dry ether (20 ml) and ammonia (300 ml) was reduced with lithium metal (0.84 g, 10 mol.equiv.). The reaction was stirred for half an hour and was then quenched

with ammonium chloride (2.5 g, 4 mol.equiv.). Working up the reaction as in (59) gave an oil (1.75 g, 88%) which was distilled to give an oil of 2-(2-hydroxypropyl)toluene (1.0 g, 50%) which had b.p.94-98°C/3 mm and which had spectra identical as that of (59,2).

III.3.61. 1,4-Dihydronaphthoic acid (171).

Naphthoic acid (5.0 g, 0.029 mol) was added to dry ether (100 ml) and ammonia (400 ml) was condensed into the suspension. Lithium metal (2.0 g, 0.28 mol, 10 mol. equiv.) was then added to the stirred solution in small pieces. The solution which rapidly turned blue and then dark green was stirred for a further half an hour and the reaction was then quenched with solid ammonium chloride (15.5 g, 10 mol. equiv.) over 10 minutes, and the reaction mixture was stirred for 15 minutes. Ammonia was allowed to evaporate overnight, and the solid residue was dissolved in water (200 ml). The solution was acidified with 3 N HCl which was then extracted with ether (3 x 200 ml). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give white solid of 1,4-dihydronaphthoic acid (5.0 g, 100%) which was crystallised from petroleum ether/toluene affording 1,4-dihydronaphthoic acid (171) (4.8 g, 96%) as white crystals which had m.p. 99-100°C (lit.¹⁶¹ 103°C). This had $\delta(CDCl_3)$: 7.2(4H,s,ArH);6.0(2H,s,CH=CH);4.34-4.3(1H,d,CH); 3.4(2H,s,CH₂),11.0(1H,s,COOH). ν_{max} (Nujol): 2950b, 1700 s (C=O),1460,1210 cm^{-1} .

III3.62. 1,4-Dihydro-1-methylnaphthoic acid.

Following the procedure in (III.3.16ii), dry ammonia (500 ml) was distilled into a 500 ml 3-necked flask, anhydrous iron (III)chloride (50 mg) was added to the ammonia followed by potassium metal (1.3 g, 0.034 mol, 2 mol.equiv.). The reaction mixture was stirred until the blue colour had disappeared and then 1,4-dihydronaphthoic acid (3.0 g., 0.017 mol) in dry ether (50 ml) was added as gently as the reaction permitted and a yellow solution was obtained. The reaction was left to stir for 15 min., and methyl iodide (7.2 g, 0.051 mol) was then added and the mixture was left to stir for a further 15 minutes. During this time the yellow solution disappeared. Ammonia was allowed to evaporate overnight and the solid residue was then dissolved in water (300 ml). The resulting solution was acidified with 3 N HCl and extracted with ether (3 x 200 ml). The combined extracts were washed with aqueous sodium metabisulphite (3 x 100 ml) and the ether solution was then dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give yellow solid (4.0 g) which was crystallised from petroleum ether affording 1,4-dihydro-1-methylnaphthoic acid (217) (3.0 g, 94%) as white crystals which had m.p. 114-116⁰C (lit.^{41b} 116-117⁰C).

δ ($CDCl_3$): 11.0(1H,s, \underline{COOH});7.3-7.1(4H,m,ArH);6-5.6(2H,m, $\underline{CH=CH}$);3.5(2H,s, $\underline{CH_2}$);1.6(3H,s, $\underline{CH_3}$).

ν_{\max} (Nujol): 3000 b, 1700 s (C=O), 1460, 1380, 740 cm^{-1} .

Required for $\text{C}_{12}\text{H}_{12}\text{O}_2$: C, 76.5; H, 6.3%

Found: C, 76.5; H, 6.4%

III.3.63. 1,4-Dihydro-1-methyl-1-(hydroxymethyl)naphthalene
(218).

1,4-Dihydro-1-methylnaphthoic acid (2.0 g, 0.01 mol) in dry ether (30 ml) was added dropwise to a slurry of lithium aluminium hydride (0.9 g, 0.02 mol) in dry ether (30 ml). This mixture was then refluxed for two hours. The cooled mixture was then hydrolysed by cautious addition of water (20 ml) followed by 20% sulphuric acid (100 ml). The aqueous layer was washed with ether (3 x 100 ml), the ethereal solution was dried (MgSO_4) and the solvent was evaporated to give an oil of 1,4-dihydro-1-methyl-1-(hydroxymethyl)naphthalene (218) (1.8 g, 97%) which was distilled under reduced pressure to give 1,4-dihydro-1-methyl-1-(hydroxymethyl)naphthalene (1.2 g, 70%) as a colourless oil which had b.p. $123^\circ\text{C}/10$ mm.

$\delta(\text{CDCl}_3)$: 7.1-7.3(4H, m, ArH); 5.5-6.2(2H, m, CH=CH);
3.3-3.7(4H, m, CH_2); 1.7(1H, s, OH); 1.2(3H, s, CH_3).

ν_{\max} (film): 3350 s (OH), 2950, 1500, 1040, 740 cm^{-1}

Required for $\text{C}_{11}\text{H}_{14}\text{O}$: C, 82.7; H, 8.0%

Found C, 82.6; H, 8.0%

III.3.64. 1,4-Dihydro-1-methylnaphthyl chloride (221).

1,4-Dihydro-1-methylnaphthoic acid (2.0 g, 0.01 mol) and thionyl chloride (1.25 g, 70% excess) were refluxed for half an hour. Excess thionyl chloride was evaporated to give 1,4-dihydro-1-methylnaphthyl chloride (2.0 g, 91%) as an oil which was used without purification.

δ (CDCl₃): 7.2(4H,s,ArH), 5.6-6.3(2H,m,CH=CH); 3.5
(2H,s,CH₂); 1.7(3H,s,CH₃).

ν_{\max} (film): 3000, 1800 s (C=O), 1500, 1440, 940 cm⁻¹.

III.3.65. 1,4-Dihydro-1-methylnaphthaldehyde (219).

1,4-Dihydro-1-methylnaphthoyl chloride (2.0 g, 0.01 mol) in acetone (100 ml) was added to triphenylphosphine (5.56 g, 0.02 mol). To this solution at room temperature, solid bis(triphenylphosphine) copper tetrahydroborate (6.02 g, 0.01 mol) was added and the reaction mixture became warm and some gas evolution was observed. The mixture was then stirred for two hours. The white precipitate, tris(tri-phenylphosphine)copper chloride (4 g) was removed by filtration and the acetone filtrate was evaporated to dryness. Ether was added to the residue and the insoluble material was removed by filtration. Ether solution was washed with 30% sodium hydroxide (3 x 100) and water (200 ml). The ether layer was evaporated and the residue was extracted with methanol. Methanol was evaporated to give brown oil (1.40 g) which by tlc contains two products. The crude product was

purified by column chromatography (on alumina eluted with toluene) to give:-

(1) an oil (0.3 g, 15%) which was distilled under reduced pressure to give a colourless oil of 1,4-dihydro-1-methylnaphthaldehyde (219) (0.15 g, 11%) (b.p. of the oil bath 120-140°C). This had:

$\delta(\text{CDCl}_3)$: 9.3(1H,s,CHO); 7.2(4H,s,ArH); 5.3-6.3
(2H,m,CH=CH); 3.5(2H,d,CH₂); 1.5(3H,s,CH₃).

$\nu_{\text{max}}(\text{oil})$: 3000, 1720, 1500, 1440, 760, and 740 cm⁻¹.

(2) An oil of methyl 1,4-dihydro-1-methylnaphthoate (220) (1.0 g, 50%) which had:

$\delta(\text{CDCl}_3)$: 7.1(4H,s,ArH), 5.7-6(2H,m,CH=CH); 3.4(3H,s,CH₃);
1.6(3H,s,CH₃).

$\nu_{\text{max}}(\text{film})$: 3000, 1720, 1500, 1420, 1440, 1220, 1100 and
740 cm⁻¹

m/e calculated for C₁₃H₁₄O₂: 202.0994 and found 202.0994.

Methyl 1,4-dihydro-1-methylnaphthoate (220)

(0.2 g, 0.009 mol) was dissolved in 30% sodium hydroxide (20 ml) and the mixture was refluxed for one hour.

Water was added and the mixture was acidified with

3 N HCl and extracted with ether (3 x 100 ml). The ether

solution was dried (MgSO₄). The solvent was then evaporated

to give white solid of 1,4-dihydro-1-methylnaphthoic acid

(0.15 g, 83%), which had m.p. 115-118°C and identified

with an authentic sample (62).

III.3.66. Oxidation of 1,4-dihydro-1-methyl-1-(hydroxymethyl)naphthalene with CrO_3 in pyridine.

Chromium trioxide (1.3 g, 0.01 mol) was added to a magnetically stirred solution of pyridine (1.6 g, 0.02 mol) in dichloromethane (50 ml). The deep burgundy solution was stirred for half an hour at room temperature. At the end of this period, a solution of 1,4-dihydro-1-methyl-1-(hydroxymethyl)naphthalene (3.0 g, 0.017 mol) in dichloromethane (50 ml) was added in one portion. The black deposit separated immediately. After stirring an additional one hour at room temperature, the solution was decanted from the residue. The solution was washed with 5% sodium hydroxide (3 x 100 ml), 3 N HCl (100 ml), 5% sodium hydrogen carbonate (100 ml) and water (100 ml). The organic layer was dried (MgSO_4) and the solvent was evaporated to give an oily material (2.7 g, 90%) which by tlc on silica gel eluted with EtOAc:toluene 1:3 and nmr spectrum was identified as 1,4-dihydro-1-methyl-1-(hydroxymethyl)naphthalene compared with an authentic sample (63).

III.3.67. Oxidation of 1,4-dihydro-1-methyl-1-(hydroxymethyl)naphthalene with p-toluenesulphonyl chloride.

To a solution of 1,4-dihydro-1-methyl-1-(hydroxymethyl)naphthalene (1.0 g, 0.005 mol) in pyridine (50 ml) was added with swirling p-toluenesulphonyl chloride (1.5 g, 0.007 mol). The tightly sealed mixture was allowed to

stand at 0.5°C for 7 days. The mixture was diluted with ether and washed with dil. HCl (100 ml), diluted NaHCO_3 (100 ml), and water (100 ml). The ether layer was separated and dried (MgSO_4). The solvent was evaporated to give brown oil (1.0 g, 100%). The crude product was purified by column chromatography on alumina eluting with petroleum ether $40-60^{\circ}\text{C}$ gave:-

Fraction 1: a colourless oil of 1,4-dihydro-1-methyl-naphthaldehyde (219) (0.05 g, 5%) which was identified with an authentic sample (65).

Fraction 2: an oil of 1,4-dihydro-1-methyl-1-(hydroxymethyl)naphthalene (218) (0.8 g, 80%) identical with an authentic material (63).

III.3.68. Preparation of 1-methyl-1-methylenechloride-1,4-dihydronaphthalene (221).

To 1-methyl-1-(hydroxymethyl)-1,4-dihydronaphthalene (2.0 g, 0.01 mol) in toluene (15 ml) was added dropwise thionyl chloride (1.8 g, 0.018 mol) and the mixture was left to reflux until the evolution of the gas had finished (approx. after 1 hr). Toluene and thionyl chloride were evaporated under reduced pressure to give an oil (2.0 g, 100%). The oil (0.5 g) was purified by plc on silica gel eluted with petroleum ether/EtOAc 2:1 which gave 1,4-dihydro-1-methyl-1-methylenechloridenaphthalene (221) (0.3 g, 60%).

δ (CDCl_3): 7.1(4H,s,ArH);5.6-6.5(2H,m,CH=CH);3(4H,s, CH_2);
2.4(3H,s, CH_3).

ν_{max} (film): 3000,1600 w, 1500,1480,1200,780 cm^{-1} .

III.3.69. Reduction of 1-methyl-1-methylchloride-1,4-dihydronaphthalene with lithium aluminium hydride.

To lithium aluminium hydride (0.8 g, 0.02 mol) in dry ether (20 ml) was added dropwise 1,4-dihydro-1-methyl-1-methylchloridenaphthalene (221) (2.0 g, 0.01 mol) in dry ether (20 ml). When the addition had finished, the reaction was refluxed for 3 hrs. Ice-water was added to the cooled mixture which was acidified with dilute sulphuric acid (20 ml). The aqueous solution was extracted with ether (3 x 100 ml). Ether layer was dried (MgSO_4) and the solvent was evaporated to give an oil of 1-methyl-1-methylchloride-1,4-dihydronaphthalene (221) (1.9 g, 95%) which was identified with an authentic sample (68).

III.3.70. Lithium/Ammonia reduction of 1,4-dihydro-1-methyl-1-methylchloridenaphthalene.

Following the procedure in (61), 1,4-dihydro-1-methyl-1-methylchloride naphthalene (221) (2.0 g, 0.001 mol) in dry ether (30 ml) and ammonia (300 ml) was added lithium metal (0.3 g, 4 mol.equiv.). The reaction mixture was left to stir for half an hour and ammonium chloride

(2.0 g, 4 mol.equiv.) was then added and the mixture was left to stir for a further half hour. Ammonia was allowed to evaporate and water was added to the solid residue which was extracted with ether (3 x 100 ml). The ether solution was dried (MgSO_4) and the solvent was evaporated to give an oil (1.7 g, 85%). A sample of the oil (0.4 g) was purified by plc on silica gel eluted with toluene affording three fractions:

(1) an oil (0.1 g, 25%) which was shown to be a mixture which had ($\delta(\text{CDCl}_3)$): 7.1, 5.5-6, 3.4, 3-2.6, 1.8(b), 1.4(s), 1.3(s)) and this mixture was purified once more by plc on silica gel eluting with petroleum ether: EtOAc 5% and gave two products: (a) an oil (0.06 g, 6%) which was identified as an over-reduced product where no olefinic was observed ($\delta(\text{CDCl}_3)$): 7.1, 3-2.6(b), 1.4(s), 1.3(s)). No further attempts were carried out to identify this product.

(b) an oil (0.04 g, 4%) which had $\delta(\text{CDCl}_3)$: 7.1(m), 5.5-6(m), 3.4-3, 2.8 and no methyl peak was observed and no further identification was carried out.

(2) an oil of 1-methyl-1-methylchloride-1,4-dihydro-naphthalene (0.03 g, 8%) which had identical spectra with an authentic material (68).

(3) an oil of 1,4-dihydro-1-methyl-1-(hydroxymethyl)-naphthalene (0.2 g, 50%) which was identified with an authentic material (63).

III.3.71. Methyl diphenate (203).

A solution of diphenic acid (50 g, 0.2 mol) in methanol (300 ml) containing concentrated sulphuric acid (5 ml) was refluxed overnight. The cooled reaction mixture was then added to water (500 ml) and the aqueous solution was extracted with dichloromethane (3 x 200 ml). The extracts were washed with 10% sodium hydroxide (2 x 100 ml) and once with water. The organic layer was dried (MgSO_4) and the solvent was evaporated to give the crude ester (49.0 g, 90%) which was crystallised from ether to give methyl diphenate (203) (42.0 g, 75%) as white crystals which had m.p. 76-78°C (lit. 74°C¹⁶²). These had $\delta(\text{CDCl}_3)$: 7.1-8.0(8H,m,ArH); 3.5(6H,s, CH_3).

ν_{max} (Nujol): 3000, 1720 (C=O), 1580, 1460, 1380, 1260, 1080, and 760 cm^{-1} .

III.3.72. 2,2'-bis(hydroxymethyl)biphenyl (204).

Methyl diphenate (203) (30 g, 0.11 mol) in dry ether (100 ml) was added dropwise to a slurry of lithium aluminium hydride (8.4 g, 0.22 mol) in dry ether (250 ml). The mixture was then refluxed for two hours. The cooled mixture was then hydrolysed by cautious addition of water (300 ml) followed by 20% sulphuric acid (100 ml). The aqueous layer was washed with ether (3 x 100 ml), the ethereal solution was dried (MgSO_4) and the solvent was evaporated to give white solid of 2,2'-bis(hydroxymethyl)-biphenyl (21.4 g, 90%) which was crystallised from benzene

to give 2,2'-bis(hydroxymethyl)biphenyl (18.0 g, 76%) as white crystals which had m.p. 108-110°C (lit.^{163,164} 111-112°C).

$\delta(\text{CDCl}_3)$: 7.0-7.5(8H,m,ArH), 4.28(4H,s,CH₂); 3.1(2H,s,OH).

ν_{max} (Nujol): 3500(OH), 1460, 1380, and 760 cm⁻¹.

III.3.73. 2-2'-bis(bromomethyl)biphenyl (205).

Hydrobromic acid (48%, 350 ml) was heated to 90°C with stirring and 2,2'-bis(hydroxymethyl)biphenyl (14.0 g, 0.065 mol) was added slowly. The solution was then heated for 30 minutes, and then the mixture was allowed to cool. The resultant aqueous/oil mixture was extracted with dichloromethane (3 x 150 ml) and the combined extracts were dried (MgSO₄). The solvent was evaporated to give white solid (19.0 g, 86%) which was crystallised from petroleum ether to give 2,2'-bis(bromomethyl)biphenyl (17.0 g, 77%) as white crystals which had m.p. 71-73°C.

$\delta(\text{CDCl}_3)$: 7.3-7.7(8H,m,ArH); 4.2(4H,q,CH₂).

ν_{max} (Nujol): 2900, 1460, 1380, 760 and 600 cm⁻¹.

III.3.74. o,o'-Bitolyl (206).

Dimethoxyethane (170 ml) was heated to 70°C with stirring, and sodiumborohydride (36.0 g, 0.95 mol) was added followed by a solution of potassium hydroxide (11.0 g) in water (100 ml). Finally 2,2'-bis(bromomethyl)-

biphenyl (16.0 g, 0.05 mol) was added and the mixture was stirred at 50°C for three hours. The cooled mixture was extracted with dichloromethane (3 x 200 ml) and the combined extracts were dried (MgSO₄). The solvent was evaporated to give liquid (8.4 g, 91%) which was distilled under reduced pressure to give o,o'-bitolyl (206) (4.3 g, 47%) as a colourless liquid which had b.p. 106-107°C/2 mm Hg. o,o'-Bitolyl (500 mg) was further purified by preparative layer chromatography (plc) on silica gel eluted with petroleum ether gave pure o,o'-bitolyl (0.3 g, 60%) of colourless liquid. This had:

δ (CDCl₃): 7.1-7.3(8H,m,ArH);2.0(6H,s,CH₃).

ν_{\max} (film): 3000,2910,1460,1110,760, and 730 cm⁻¹.

III.3.75. Acetylbitolyl

A. To o,o'-bitolyl (206) (6.0 g, 0.032 mol) in dry carbontetrachloride (180 ml) was added acetylchloride (2.5 g, 0.032 mol) followed by aluminium chloride (8.7 g, 0.065 mol) and the mixture left to stir overnight at room temperature, the mixture then refluxed for one hour. The mixture was cooled and water (200 ml) was added, followed by concentrated hydrochloric acid (50 ml). The organic layer was separated and washed with saturated sodiumbicarbonate (2 x 100 ml) and water (150 ml). The organic solution was dried (MgSO₄) and the solvent was evaporated to give brown oil (7.0 g **94%**) which was

distilled under reduced pressure to give acetylbitolyl (1.2 g, 16%) as a colourless liquid which had b.p. 96-99°C/0.8 mm. Further purification of the distillate (0.3 g) by plc on alumina eluted with petroleum ether gave two products:

(1) acetylbitolyl (210) (0.2 g, 60%) which had:

$\delta(\text{CDCl}_3)$: 7.1-7.9(7H,m,ArH); 2.55(3H,s,CH₃); 2.2(3H,s,CH₃);
2.0(3H,s,CH₃).

ν_{max} (oil): 2910,1680(C=O),1600,1480,1350,1260 and
740 cm⁻¹.

m/e: 224(80%,m⁺); 209(100%,m⁺-me); 181(5%,m⁺-COme).

(2) biacetylbitolyl (212) (0.1 g, 30%) which had:

$\delta(\text{CDCl}_3)$: 7.3-8(6H,m,ArH); 2.6(6H,s,CH₃); 2.1(6H,s,CH₃).

ν_{max} (oil): 1700(C=O),1670(C=O),1600,1350,900 cm⁻¹

m/e: 266(30%,m⁺); 251(100%,m⁺-me); 180(5%,m⁺-2COme).

The residue (5.0 g) was crystallised from methanol to give biacetylbitolyl (212), (4.4 g, 73%) as white crystals which had m.p. and nmr and ir identical to (2) in (III.3.75,2).

B. The above procedure was repeated using nitrobenzene (35 ml) as a solvent. The mixture of o,o'-bitolyl (2.0 g, 0.01 mol) in nitrobenzene (35 ml), acetylchloride (1.0 g, 6.01 mol) and aluminium chloride (2.9 g, 0.02 mol) was stirred overnight at room temperature. Water (100 ml) was added to the mixture followed by conc. HCl

(10 ml) and the mixture was extracted with dichloromethane (3 x 100 ml) which was washed with NaHCO_3 (2 x 100 ml) and water (100 ml). The organic solution was dried (MgSO_4) and the solvent was evaporated to give yellow oil (20 ml) which contains nitrobenzene. The mixture was steam distilled to give yellow liquid (3.0 g) which was further purified by plc (0.3 g) on alumina eluted with petroleum ether to give acetylbitolyl (210) (0.1 g, 30%) as a colourless liquid, this had nmr and ir identical to that product in (75,A1). The nmr spectrum of the mixture shows only acetyl product and no biacetylbitolyl was observed in this mixture.

III.3.76. o,o'-Bitolylcarboxylic acid (211).

To acetylbitolyl (1.0 g, 0.004 mol) in dioxane (30 ml) was added 2 N sodium hydroxide (10 ml) followed by a solution of potassium iodide (6.0 g, 0.036 mol) and iodine (3.0 g, 0.01 mol) in water (30 ml). The mixture was left to stir for four days at room temperature and for three hours at 70°C . The cooled mixture was acidified with conc. HCl (5 ml) and the aqueous solution was extracted with dichloromethane (4 x 50 ml). The combined extracts were washed with sodiummetabisulphite solution (50 ml) and water (50 ml). The organic layer was extracted into 10% sodium hydroxide (50 ml) and the basic solution was acidified with conc. HCl (5 ml) and extracted with dichloromethane (3 x 50 ml) which was dried (MgSO_4). The solvent was removed under reduced pressure to give

white solid (0.5 g, 50%) which was crystallised from ethanol to give *o,o'*-bitolylcarboxylic acid (0.1 g, 10%) as white crystals which had m.p. 169-170°C.

$\delta(\text{CDCl}_3)$: 11-11.4(1H, b, COOH); 7.1-8.1(7H, m, ArH);
2.15(3H, s, CH₃); 2.05(3H, s, CH₃).

ν_{max} (Nujol): 3300-3000 b (COOH), 2900, 1690 s (C=O),
1450, 1370, 710 cm⁻¹

m/e: 226(100%, m⁺); 211(14); 209(8); 193(1), 182(24).

III.3.77. Reduction of 4-phenylbenzoic acid with 10 mol equivalent of lithium metal.

4-Phenylbenzoic acid (5.0 g, 0.025 mol) was added to dry ether (30 ml) and ammonia (700 ml) was condensed into the suspension. Lithium metal (1.76 g, 0.25 mol) was added in small pieces to the stirred solution. The solution which rapidly turned blue was stirred for half an hour and the reaction was then quenched by addition of portions of solid ammonium chloride (13.37 g, 0.25 mol) over 5 minutes. The solution was left to stir for a further half an hour. Ammonia was allowed to evaporate overnight, and the solid residue was dissolved in water (200 ml) which was extracted with ether (3 x 200 ml) to give white solid (0.8 g, 16%) which was crystallised from petroleum ether to give 4-(1',4'-dihydrophenyl)toluene (190) as white crystals.

$\delta(\text{CDCl}_3)$: 7.1(4H,s,ArH);5.8(4H,s,CH=CH);4.0(1H,t,CH);
2.7-2.8(2H,d,CH₂);2.3(3H,s,CH₃).

ν_{max} (Nujol): 2910,1600,1460,1230,800, and 750 cm^{-1} .

The mother liquor was rich in 4-(1',4'-dihydrophenyl)toluene and 4-phenyltoluene (189) in the ratio of 5:1.

4-Phenyltoluene had

$\delta(\text{CDCl}_3)$: 7.1-7.4(9H,m,ArH),2.3(3H,s,CH₃).

ν_{max} (film): 3000,1500,800,660 cm^{-1} .

The aqueous solution was acidified with 3 N HCl and extracted with ether (3 x 100 ml). The combined extracts were dried (MgSO_4) and the solvent was removed under reduced pressure to give white solid (4.0 g, 80%).

NMR spectrum showed mainly 1,2-dihydro-4-phenylbenzoic acid (188) which had:

$\delta(\text{CDCl}_3)$: 11.4(1H,s,COOH);7.2(5H,s,ArH);5.9(1H,s,CH=CH);
6.0(2H,s,CH=CH);3.5-4(2H,m,CH₂);2.6-3(1H,t,CH);

and 1,4-dihydro-4-phenylbenzoic acid (187) m.p.102-104°C

which had

$\delta(\text{CDCl}_3)$: 11.4(1H,s,COOH);7.25(5H,s,ArH);5.18(4H,s,CH=CH);
2.7(2H,s,CH₂) and 4-phenylbenzoic acid

identical with authentic material. The ratio estimated by nmr was 4:1:1 respectively.

III.3.78. Reduction of 4-phenylbenzoic acid with 10 mol. equivalent in the presence of ammonium chloride.

Following the procedure in (77), 4-phenylbenzoic acid (5.0 g, 0.025 mol) in ether (30 ml), ammonia (600 ml) and ammonium chloride (13.37 g, 0.25 mol) was reduced with lithium metal (1.76 g, 0.25 mol) and the reaction left to stir for half an hour. The reaction was worked up as in (77) affording non-acidic material (1.0 g, 20%) which consisted of a mixture of 4-(1'-4'-dihydrophenyl)-toluene (190) and 4-phenyltoluene (189) in a ratio of 5:1 and had nmr spectra identical with the mixture prepared in (77). Acidic material (4.0 g, 80%) was found (nmr) to be a mixture of 4-phenylbenzoic acid, 1,4-dihydro-4-phenylbenzoic acid (187) and 1,2-dihydro-4-phenylbenzoic acid (188) in the ratio of 2:1:4.

III.3.79. Reduction of 4-phenylbenzoic acid with 4 mol equivalent of lithium metal.

Following the procedure in (77), 4-phenylbenzoic acid (5 g, 0.025 mol) in ether (30 ml) and ammonia (600 ml) was reduced with lithium metal (0.7 g, 4 mol. equiv.). The reaction mixture was left to stir for half an hour and was then quenched with ammonium chloride (6.0 g, 4 mol.equiv.). The reaction was worked up as in (77) to give non-acidic material (1.0 g, 20%) which was shown (nmr) to be a mixture of 4-(1',4'-dihydrophenyl)-toluene and 4-phenyltoluene in a ratio of 3:2 respectively

and acidic material (4.0 g, 80%) which contained (nmr) the same products as in (78) in a ratio of 1:1:5.

III.3.80. Reduction of 4-phenylbenzoic acid with 4 mol. equiv. of sodium metal.

Following the procedure in (77), 4-phenylbenzoic acid (5.0 g, 0.025 mol) in ether (100 ml) and ammonia (600 ml) was reduced with sodium metal (2.35 g, 4 mol. equiv.). The reaction was left to stir for half an hour and the reaction mixture was then quenched with ammonium chloride (6.0 g, 4 mol.equiv.). Working up the reaction mixture following the procedure in (77) gave

(1) a non-acidic material (1.32 g, 26%) [$\delta(\text{CDCl}_3)$: 7.1-7.4(m, ArH); 6(s, CH=CH); 4(1H, t, CH); 2.7-2.8(d, CH₂); 2.3(s, CH₃)]; and

(2) acidic material (3.3 g, 66%) [$\delta(\text{CDCl}_3)$: 11.4(H, s, COOH); 7.25(5H, s, ArH); 5.8(4H, s, CH=CH); 2.7(2H, s, CH)]

consistent with 1,4-dihydro-4-phenylbenzoic acid

(3) together with recovered starting material (0.4 g, 80%).

III.3.81. Reduction of sodium 4-phenylbenzoate with 10 mol.equiv. of lithium metal.

Following the procedure in (77), sodium 4-phenylbenzoate (5.0 g, 0.022 mol) in ether (100 ml) and ammonia (500 ml) was treated with lithium metal (1.54 g, 10 mol. equiv.) and the reaction mixture was left to stir for

half an hour and was then quenched with ammonium chloride (7.8 g, 10 mol.equiv.). Working up the reaction as in (77) gave non-acidic material (0.28 g, 5%) which had

$\delta(\text{CDCl}_3)$: 7.1(4H,s,ArH); 5.75(4H,s,CH=CH); 3.95(1H,t,CH);
2.7-2.8(2H,d,CH₂), 2.3(3H,s,CH₃)

and an acidic material (3.5 g, 70%) which is identical with 1,4-dihydro-4-phenylbenzoic acid. This had

$\delta(\text{CDCl}_3)$: 11.4(1H,s,COOH); 7.25(5H,s,ArH); 5.8(4H,s,CH=CH);
2.7(2H,s,2xCH)

and m.p. 102-104°C.

III.3.82. Preparation of methyl 4-phenylbenzoate (196).

A solution of 4-phenylbenzoic acid (40.0 g, 0.2 mol) in methanol (700 ml) containing conc. sulphuric acid (2 ml) was refluxed for three hours. The cooled reaction mixture was then added to water (300 ml) and the aqueous solution was extracted with dichloromethane (3 x 200 ml). The combined extracts were washed with 10% sodium hydroxide (3 x 50 ml) and once with water. The organic solution was dried (MgSO₄) and the solvent was evaporated to give yellow solid (41.5 g, 97%) which was crystallised from methanol affording methyl 4-phenylbenzoate (38.0 g, 89%) as white crystals which had m.p. 115-117°C (lit. 117-118°C¹⁶⁵).

$\delta(\text{CDCl}_3)$: 7.2-8.2(9H,m,ArH); 3.9(3H,s,CH₃).

ν_{max} (Nujol): 2920, 1710(C=O), 1460, 1370, 110 and 750 cm⁻¹.

III.3.83. Reduction of methyl 4-phenylbenzoate with
10 mol.equiv. of lithium metal.

Following the procedure in (77), methyl 4-phenylbenzoate (2.00 g, 0.009 mol) in dry ether (25 ml) and ammonia (300 ml) was treated with lithium metal (0.66 g, 10 mol. equiv.). The reaction was stirred for 15 minutes and was then quenched with ammonium chloride (5.0 g, 10 mol. equiv.). The reaction was worked up as in (77) to give non-acidic material (2.0 g, 100%) which consisted by tlc of three components.

[δ (CDCl₃): 8-7(m,ArH);5.8(m,CH=CH),3.9(b,OH);
3.7(m,CH₂),2.3(s,CH₃)]

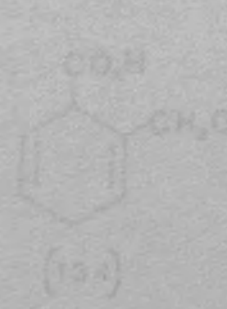
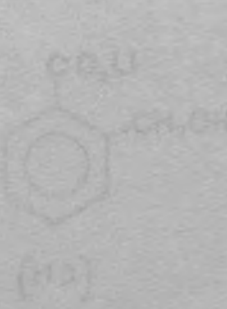
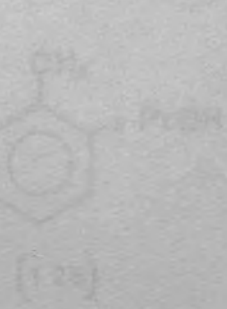
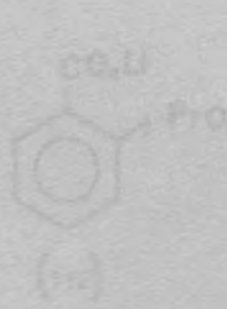
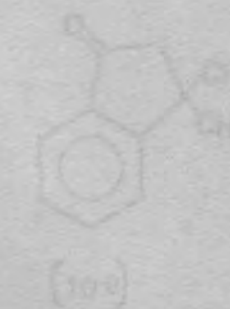
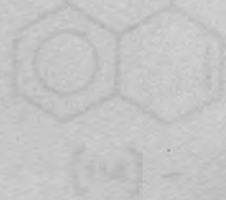
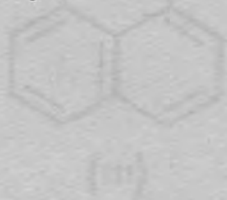
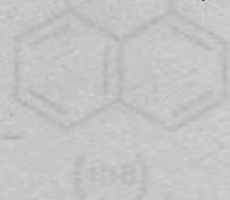
identified as 4-phenylbenzylalcohol (191), 1,4-dihydro-4-phenylbenzylalcohol (192) and methyl 1,4-dihydro-4-phenylbenzoate in the (197) ratio of 2:5:1 respectively.

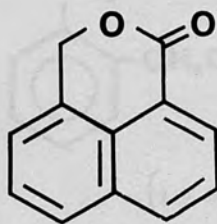
III.3.84. Reduction of methyl 4-phenylbenzoate with 4
mol.equiv. of lithium metal.

Following the procedure in (77), methyl 4-phenylbenzoate (2.0 g, 0.009 mol) in dry ether (20 ml) and ammonia (300 ml) was treated with lithium metal (0.26 g, 4 mol. equiv.). The reaction was left to stir for 15 min. and was then quenched with ammonium chloride (2.0 g, 4 mol. equiv.). The reaction was worked up as in (77) to give non-acidic material (1.9 g, 99%) which had nmr spectra identical with (83) and was a mixture of methyl 1,4-dihydro-4-phenylbenzoate, 1,4-dihydro-4-phenylbenzyl alcohol and 4-phenylbenzyl alcohol in a ratio of 1:3:6 respectively.

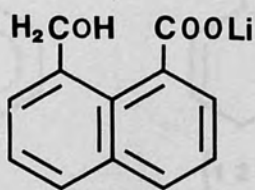
III.3.85. Reduction of methyl 4-phenylbenzoate with 4 mol.equiv. of sodium metal.

Following the procedure as in (77), methyl 4-phenylbenzoate (2.0 g, 0.009 mol) in dry ether (20 ml) and ammonia (300 ml) was treated with sodium metal (0.86 g, 4 mol.equiv.). The mixture was left to stir for 15 min. and was then quenched with ammonium chloride (2.0 g, 4 mol.equiv.). The reaction mixture was worked up as in (77) to give non-acidic material (2.0 g, 100%) which was found (nmr) to contain the same mixture as in (84), i.e., 1,4-dihydro-4-phenylmethylbenzoate, 1,4-dihydro-4-phenylbenzylalcohol and 4-phenylbenzyl alcohol in a ratio of 1:3:8 respectively.

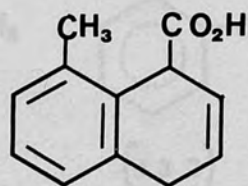




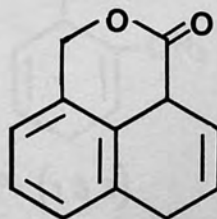
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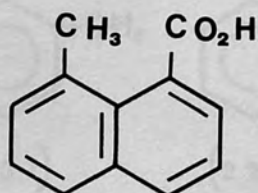
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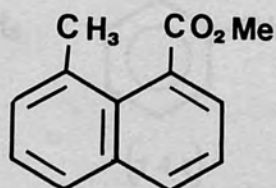
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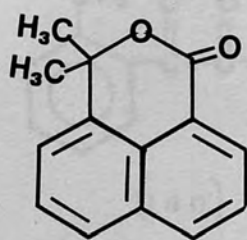
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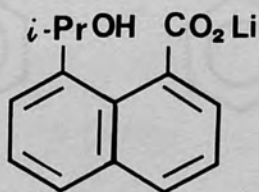
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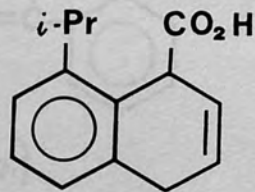
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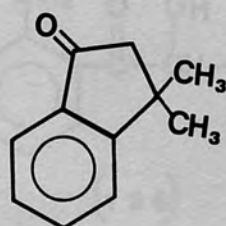
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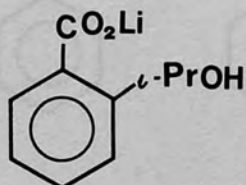
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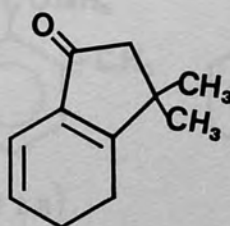
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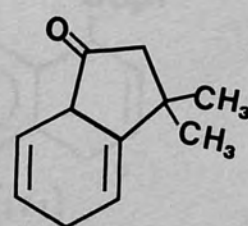
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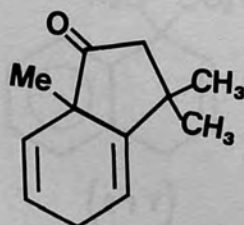
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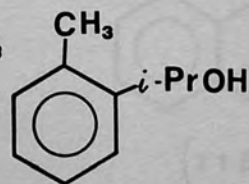
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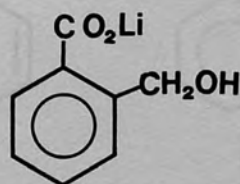
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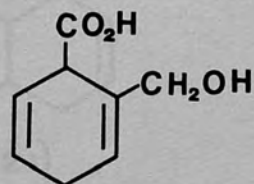
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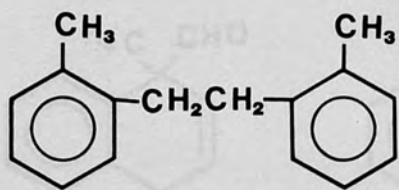
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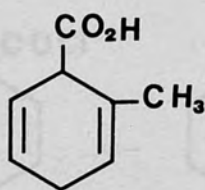
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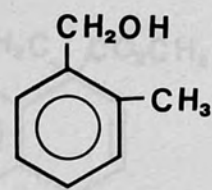
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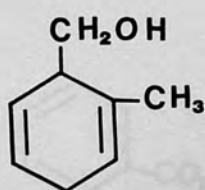
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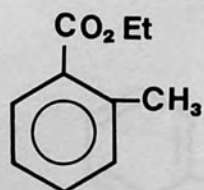
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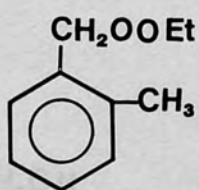
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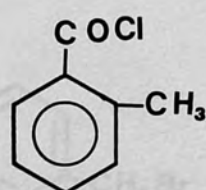
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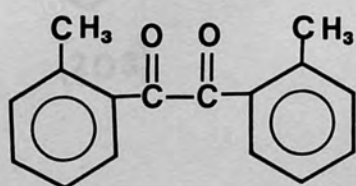
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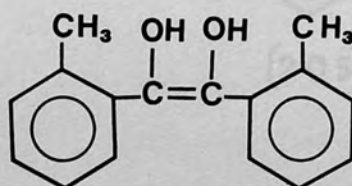
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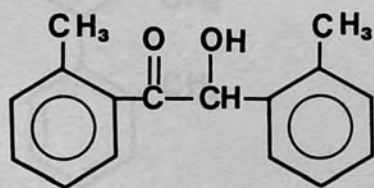
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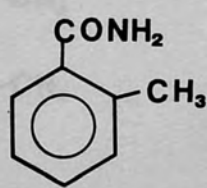
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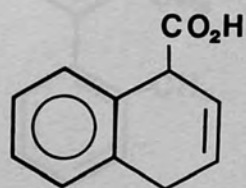
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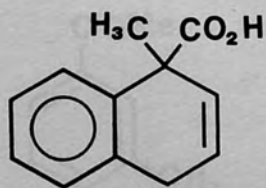
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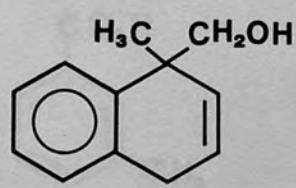
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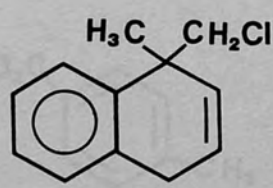
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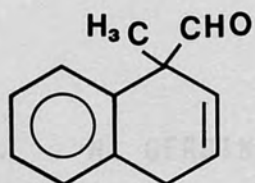
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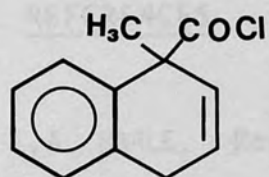
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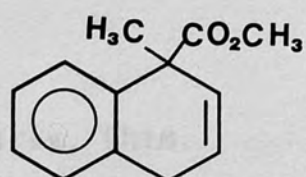
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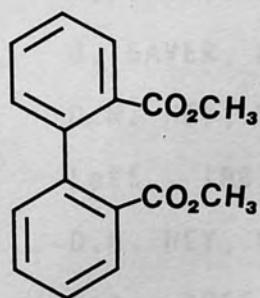
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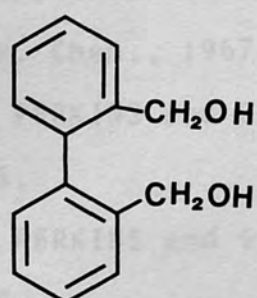
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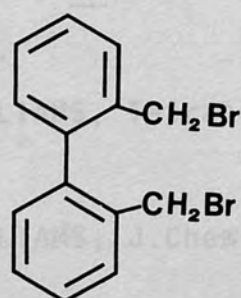
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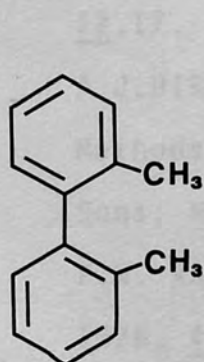
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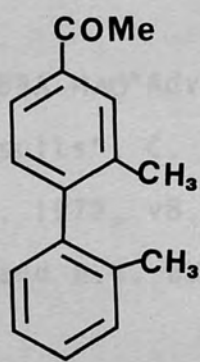
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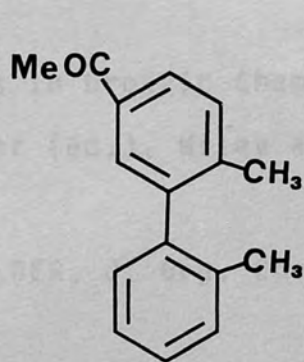
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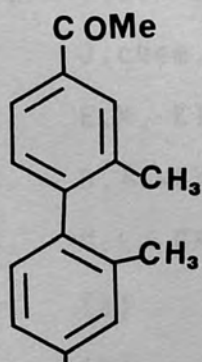
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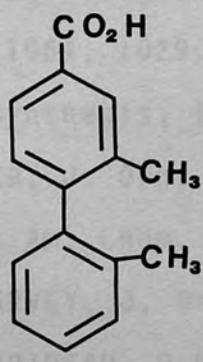
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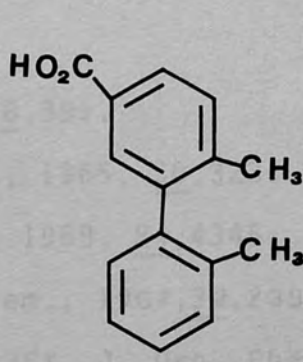
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