CHEMISTRY OF 4aH-FLUORENES

A thesis presented by

DAVID NEUHAUS

in partial fulfilment of the requirements for

the award of the

DEGREE OF DOCTOR OF PHILOSOPHY,

UNIVERSITY OF LONDON.

Hofmann Laboratory,

Department of Chemistry,

Imperial College of Science and Technology,

London, SW7 2AY.   November, 1982.

for my parents.

FOREWORD

The work described in this thesis was carried out by the author at Imperial College of Science and Technology, and no part of it is concurrently being submitted for any other degree. The synthetic work was supervised by Professor C.W. Rees; the work on n.O.e. difference spectroscopy (Chapter Six), though connected, arose separately through the author's responsibility for the ^{1}H nmr service in this department.

I should like to thank my supervisor, Professor C.W. Rees, for his advice, encouragement and friendship throughout the project, and Dr. C.J. Moody, Dr. H.S. Rzepa, Dr. S.V. Ley and Mr. R.N. Sheppard for their many contributions and discussions. Thanks are also due to the Chemistry Department of Imperial College and its technical staff for their support, and, not least, to my mother for her patience while typing the manuscript. Finally, I should like to thank my many colleagues, especially those in the Hofmann Laboratory, who, through their help and friendship, provided such a pleasant environment in which to work.

D. Neuhaus

1982.

ABSTRACT

The literature concerning 3aH-indenes and their heterocyclic analogues as reactive intermediates is briefly reviewed, emphasising particularly work on 3aH-benzimidazole intermediates. Reactions potentially applicable to syntheses of 4aH-fluorenes, themselves of interest since they are benzo-fused 3aH-indenes, are discussed.

The structure, formation and chemistry of 4a-methyl-1,3,9-triphenyl-4aH-fluorene and its derivatives, the only previously known 4aH-fluorenes, are discussed, combining a review of the original work with results obtained by the present author.

Attempts to synthesise simple 4aH-fluorenes are then discussed. Several unsuccessful approaches, including decomposition of 3H-indazoles, direct and indirect Robinson annulation of 1,3-dimethylindan-2-one, and Friedel Crafts cyclisations of 4-(1,3-dimethylinden-1-yl)-4-oxobutanoic acid derivatives, are described, before dealing with the successful route to the skeleton via cyclisation of 4-(1,3-dimethylinden-1-yl)butyronitrile with polyphosphoric acid.

The transformation of the first-formed cyclisation product, 4a,9-dimethyl-2,3,4,4a-tetrahydrofluoren-1-one, into 4a,9-dimethyl-4aH-fluorene via dehydrogenation, reduction and dehydration is described, and the development of a parallel route from 2,3,4,9-tetrahydrofluoren-1-one to the monomethyl analogue, 4a-methyl-4aH-fluorene, is also discussed.

The reactions of these 4aH-fluorenes, particularly 4a-methyl-4aH-fluorene, are then described. Dimerisation via a [4+2] cycloaddition

leads to an unsymmetrical product, which rearranges to a symmetrical
dimer with Brønsted or Lewis acids; other [4+2] cycloadditions are
mentioned. Protic acids cause methyl shifts producing 4-methyl and
1-methyl-9H-fluorenes; 9-methyl-9H-fluorene results from flash vacuum
pyrolysis. Photolysis causes rearrangement to 9-methylcyclopenta[b]
naphthalene, among other products; the relationship of this rearrangement
to photolytic reactions of other 3aH-indenes is considered, and the
mechanism discussed.

The background and interpretation of nuclear Overhauser effect
(n.O.e.) difference spectroscopy, widely used to make structural
assignments in the foregoing work, are discussed. The potential of
the technique is further illustrated by elucidation of the regioisomerism,
stereoisomerism and solution conformation of repanduline, a macrocyclic
bisbenzylisoquinoline alkaloid. Finally, a method for largely
suppressing the unwanted consequences of scalar coupling during n.O.e.
difference experiments is described.

CONTENTS

of 4a,9-Dimethyl-4aH-fluorene and

4a-Methyl-4aH-fluorene.

1)   Synthesis of 4a,9-Dimethyl-4aH-fluorene.   99

2)   Oxidation of 4a-Methylhexahydrofluoren-1-one.   105

3)   Other Attempted Approaches to 4a-Methyl-4aH-fluorene.   113

4)   Synthesis of 4a-Methyl-4aH-fluorene.   116

CHAPTER FIVE   Chemistry of 4aH-Fluorenes.   120

1)   Properties.   120

2)   Dimerisation.   122

3)   Diels-Alder Reactions.   131

4)   Rearrangements   133

      i)   With acids.   133

     ii)   Thermolysis.   138

    iii)   Photolysis.   140

            a) 4a-Methyl-4aH-fluorene.   141

            b) 4a,9-Dimethyl-4aH-fluorene.   148

CHAPTER SIX   Nuclear Overhauser Effect Difference Spectroscopy.   151

1)   Introduction.   151

2)   Background.   152

3)   Interpretation.   154

      i)   N.O.e. enhancements.   154

     ii)   S.P.T. (Selective Population Transfer) effects.   156

    iii)   Saturation transfer.   157

CHAPTER ONE

CHAPTER ONE: Introduction.

The work on derivatives of 4aH-fluorene (1) presented in

this thesis forms part of a wider study of molecules related to

3aH-indene (2).   This introduction is therefore primarily intended

to set the present work in context by summarising the origins and

subsequent progress of this wider study.   Other literature references

to 3aH-indene analogues as transient intermediates will then briefly

be reviewed, before turning finally to a survey of reactions potentially

useful in synthesising the skeleton of 4a-methyl-4aH-fluorene (3).
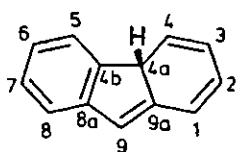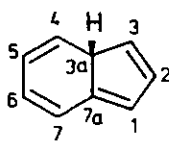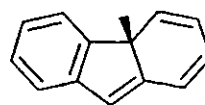
(1)   (2)   (3)

1)   3aH-Benzimidazoles from Imidoyl Nitrene Cyclisations.

Interest within this group in 3aH-indene analogues began

with the proposition that 3aH-benzimidazoles such as (9) were inter-

mediates in the photocyclisation of N-(N-arylimidoyl)sulphimides,

such as (4), to give 1H-benzimidazols.[1]   These cyclisations had

emerged during a systematic study of the sulphimides, which was intended

to determine the value of these reagents as nitrene precursors on the

one hand and as nucleophilic nitrogen species on the other.[1]   The

proposed mechanism of the cyclisation (Scheme 1) involved initial

formation of the imidoyl nitrene (8), followed by electrocyclic ring-closure and a [1,5] sigmatropic shift of the bridgehead proton in 3aH-benzimidazole (9) to give the product (10). It was noted in support of this mechanism that other nitrene precursors, e.g. (5)-(7), cyclised similarly to benzimidazoles on photolysis or thermolysis (Scheme 1).[2]
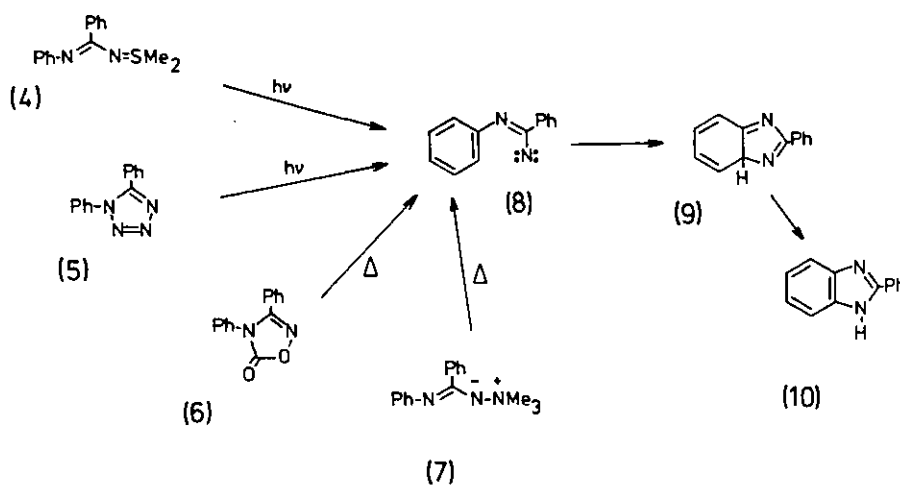
SCHEME 1

In order to test this mechanism, a number of ortho-blocked analogues of the nitrene precursors (4)-(6) were synthesised and their reactions investigated.[3,4] It was hoped that by arranging for a poor migrating group, such as methyl, to occupy the bridgehead position, the 3aH-benzimidazole intermediates might become sufficiently long lived to be trapped or even isolated. This approach had recently proved successful during a study of the related cyclisation of N-arylnitrosoimines. Thus generation of the unblocked nitrosoimine (11) led to 3-carbethoxy-7-chloro-1,2,4-benzoxadiazine (13) via cyclisation followed by a shift of the bridgehead proton in (12),[5] whereas generation of the ortho-blocked nitrosoimine (14) led to 3-carbethoxy-5,7,8a-trimethyl-1,2,4-benzoxadiazine (15), which could be isolated and did not undergo a methyl shift (Scheme 2).[6]
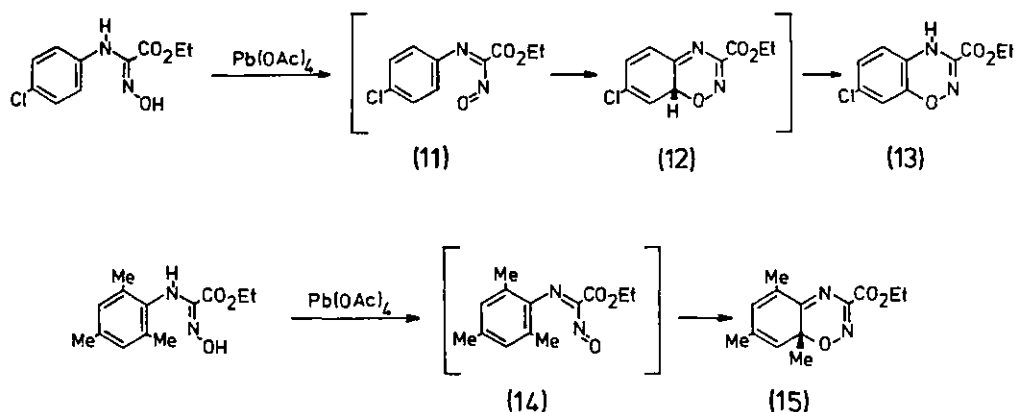
SCHEME 2

The ortho-blocked nitrene precursors, however, proved very
different in their behaviour. Relatively mild chemical methods
applicable to the synthesis of benzimidazoles from unblocked
N-arylbenzamidine derivatives failed to cyclise the corresponding
N-(2,6-dimethylphenyl)benzamidine derivatives;[3] such methods included
oxidation of the benzamidine with lead tetraacetate,[7] reaction of the
N-chlorobenzamidine with a base [8,9] and reaction of the amidoxime
with benzenesulphonyl chloride (Scheme 3).[10]

SCHEME 3

SCHEME 4

(16) a) $R_1 = Me, R_2 = H$

    b) $R_1 = R_2 = Me$

    c) $R_1 = Et, R_2 = H$

hv MeCN 254nm 4–10h

(17)   12%[a] 26%[b]   6%   18%

(18)   13%[a] 25%[b]   20%   7%

hv MeCN 254nm 4h

(16d)

(20) + (21)   (18)   (17)   FVP 600°C   (19)   hv MeCN 254nm 9–15h   (17) + (18)

10% (6%)[c]   3% (0%)[c]   46% (40%)

10%   8%   39%

a) $R_1 = Me, R_2 = H$ 1·5%   17%

b) $R_1 = R_2 = Me$ 0%   20%

(20a) + (21a)   (18a)   (17a)   FVP 600°C   (22)

4%   9%   24%
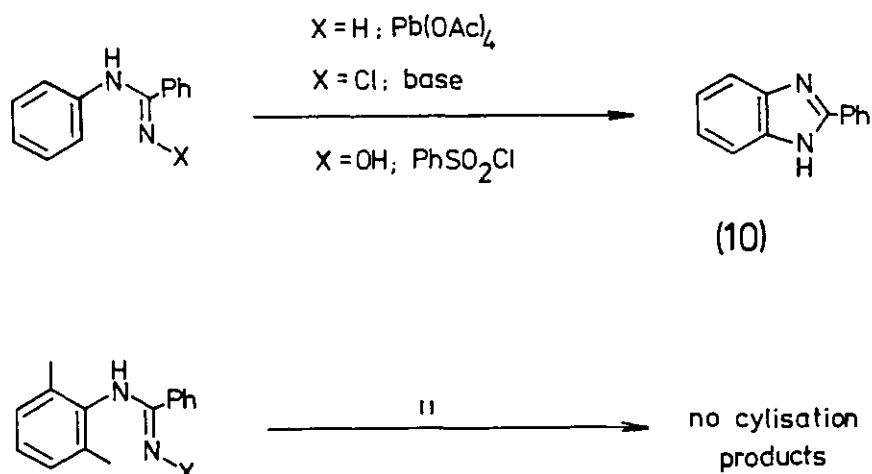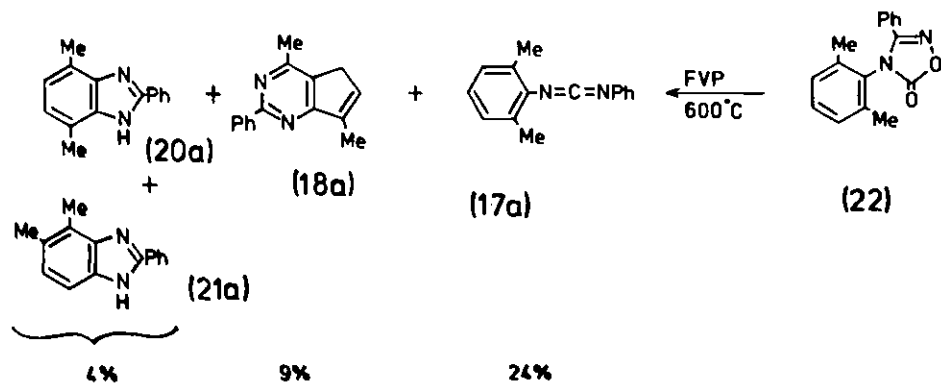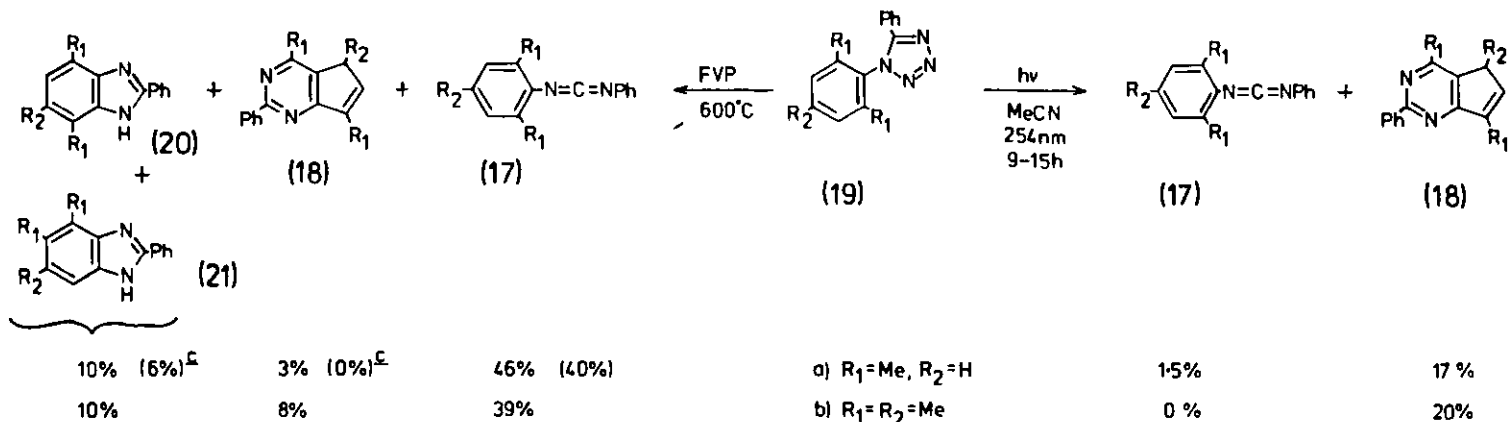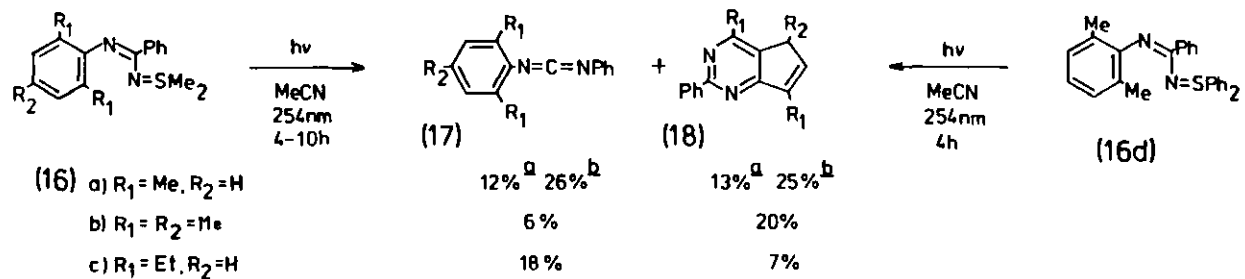
a — from SMe_2 compound

b — from SPh_2 compound

c — yields in brackets refer to FVP at 400°C; starting material (36%) was then also recovered.

In contrast, generation of the ortho-blocked nitrenes via

thermolysis or photolysis of suitable precursors (sulphimides,

tetrazoles or oxadiazolones) did lead to cyclisation, but the presumed

3aH-benzimidazole intermediates, far from being isolable, in turn gave

rise to a variety of further products depending on the reaction

conditions.   This high reactivity of the 3aH-benzimidazole intermediates

seemed surprising, especially since some of the products were totally

unexpected, and it was largely the attempt to understand these reactions

which led to the subsequent study of 3aH-indene analogues in general.

A short summary of these results will therefore be given.

Nitrene precursors were studied in which i) both blocking groups

were simple alkyl and ii) either or both groups were functionalised.

i)   Alkyl blocking groups (Scheme 4).[3]

Three types of product were isolated - carbodiimides (17),

benzimidazoles (20) and (21), and cyclopentapyrimidines (18).

Formation of the carbodiimides (via a [1,2] shift of the 2-phenyl

substituent, either concerted with decomposition of the precursor or,

later, in a nitrene intermediate) should be enhanced by the blocking

groups, since these presumably raise the activation barrier to competing

cyclisation processes.   This was observed;   the sulphimides (16a-d)

gave appreciable quantities of carbodiimide on photolysis,[3] whereas

unblocked sulphimides such as (4) give none.[1]   Similarly, even

photolysis of the tetrazole (19a) yielded a trace of carbodiimide,

despite the established strong preference for cyclisation of tetrazoles

on photolysis.[11,12]   On the other hand, the converse preference for

carbodiimide formation on thermolysis of tetrazoles, also previously

known[11,12,13], was not so strong as to prevent cyclisation altogether.

The other products were all rationalised by proposing electro-

cyclic ring closure of an intermediate nitrene followed by rearrangement

of the 3aH-benzimidazole so formed.   The interpretation suggested

in the original paper[3] is summarised in Scheme 5, using nitrene (23)

and 3aH-benzimidazole (24) as examples.
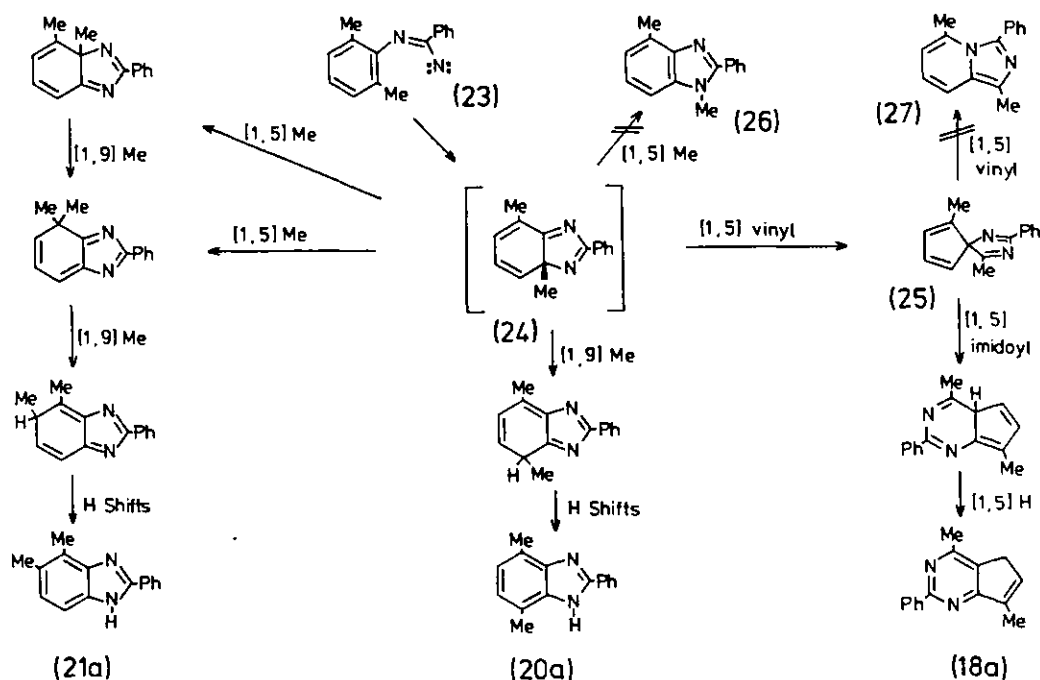
SCHEME 5

This network of sigmatropic shifts was devised largely on the

assumption that all the reactions of the 3aH-benzimidazole (24) were

thermal processes, which seemed reasonable since the photolysis

products of tetrazoles (19a-b) were also isolated from the thermolyses

(Scheme 4).   The [1,9] sigmatropic shifts invoked were amongst the

first reported.[14]   Evidence that cyclisation of the nitrene involves

a [1,5] electrocyclic process rather than insertion was provided by

photolysis of tetrazole (28), which gave no products derived from

closure to the unconjugated 8-position (Scheme 6).
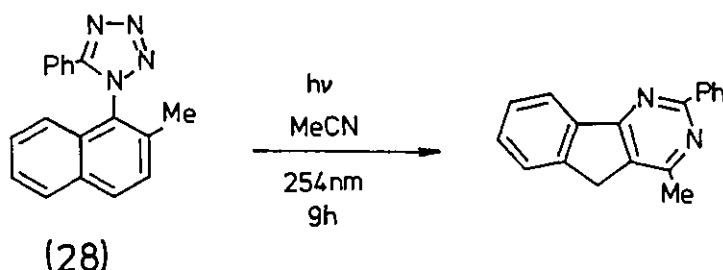
SCHEME 6

There are a number of difficulties with the reactions shown in Scheme 5, however. The failure of 3aH-benzimidazole (24) to undergo a [1,5] methyl shift to nitrogen to give benzimidazole (26) is remarkable, though not totally without precedent. A preference for poor migrating groups, such as alkyl, to migrate to carbon rather than nitrogen was previously observed in the competing [1,5] sigmatropic shifts undergone by 3H-pyrazoles; good migrating groups, such as acyl, showed the opposite tendency.[15] In the present case a blank experiment showed that N-methylbenzimidazole (26), if formed, would have been recognised.

Further, the explanation given for the formation of cyclopenta-pyrimidines to the exclusion of benzimidazoles on photolysis (Scheme 4) was that, since the former reaction proceeds via a [1,5] vinyl shift rather than a [1,5] or [1,9] methyl shift as the first step, it should be a lower energy pathway, favoured by a simple thermal selectivity at room temperature. Benzimidazole formation during FVP was thus supposed to be a consequence of reduced selectivity at higher temperatures, and the role of light in the photolyses was restricted

Scheme structures

(29) → hv / 254nm / MeCN / 11h → **(30)** 19% + **(31)** 16%

(32) → hv / 254nm / MeCN / 12h → **(33)** 19% + **(10)** 7% + 28% (CO_2Me) + starting material 32%

(34) → hv / MeCN / 254nm / 90h → **(35)** 16% (16%)[a] + starting material 23% (3·5%)[a]

(36) → hv / MeCN / 254nm / 7–9h → (X-benzimidazole) + **(10)**

a) X = $CONH_2$ 67%   0%
b) X = CON(pyrrolidine)   58% (63%)[a]   1·5% (1·1%)[a]
c) X = CN   59%   0%

(2,6-diOMe tetrazole) → FVP / 600°C → (2,6-diOMe-$N=C=N-Ph$) 44% + (OMe-benzimidazole) 6%

(2,6-diCl, N=SMe$_2$, Ph) → hv / MeCN / 254nm / 7h → (2,6-diCl-$N=C=N-Ph$) 34%
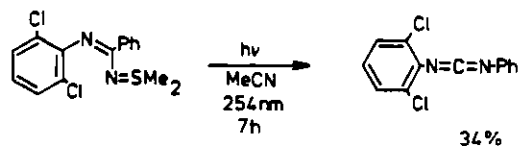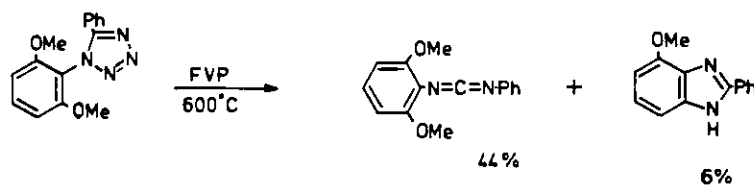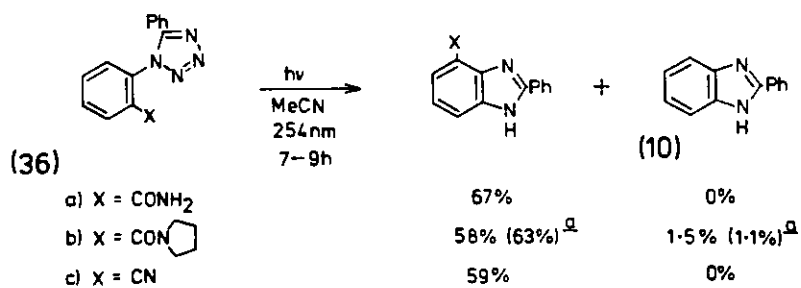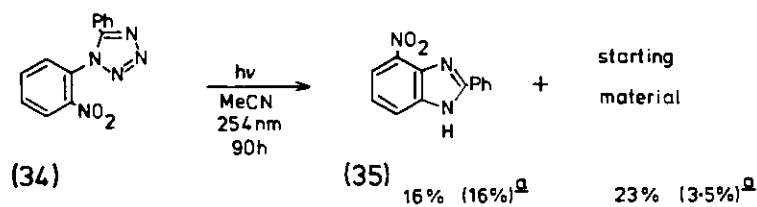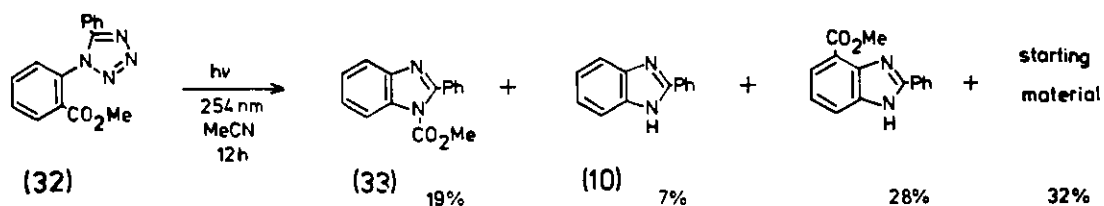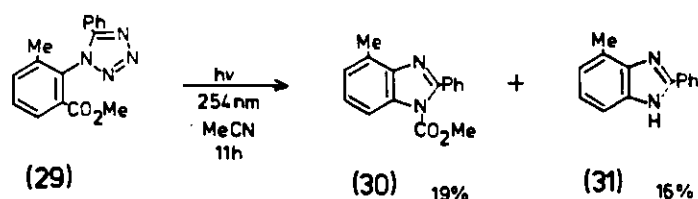
a   Yields in brackets were obtained when these experiments were repeated.[16]

SCHEME 7

to the initial generation of the nitrene from the precursor. Some of the FVP results contradict this, however, since in at least one case it appears that thermal formation of cyclopentapyrimidines is a <u>higher</u> energy process than benzimidazole formation.

Also puzzling is the implied total selectivity in the rearrangement of spiro-intermediate (25). There are a total of eight alternative [1,5] shifts which an unsymmetrical spiro[4.4]-nonatetraene could undergo. In this case these include not only the imidoyl shift proposed and regeneration of 3a<u>H</u>-benzimidazole (24), but also another [1,5] vinyl shift which would lead directly to the aromatic azaindolizine (27); there is some precedent that this latter might be the preferred process.[16]
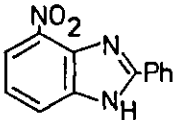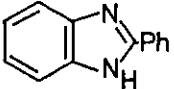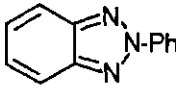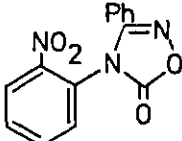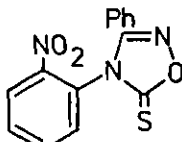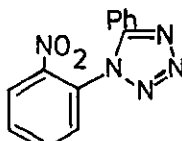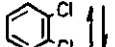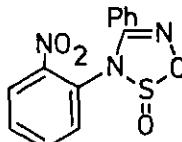
ii) <u>Functional blocking groups (Scheme 7)</u>.[4]

These experiments were prompted by the surprising observation that cyclisation of tetrazole (29) proceeded <u>via</u> closure of the nitrene exclusively to the ester-bearing carbon atom of the aryl ring. This strong directing effect was maintained even in tetrazole (32), in which competing closure to the unblocked position was no more efficient than closure to the ester-bearing position. Another feature of these results was that the methoxycarbonyl group in the presumed 3a<u>H</u>-benzimidazole intermediates (37a-b) apparently migrated exclusively to nitrogen, a very reasonable process, but one which the methyl analogue (24) completely failed to undergo (Section 1(i)). The de-esterified benzimidazoles (31) and (10) were assumed to arise <u>via</u> hydrolysis on
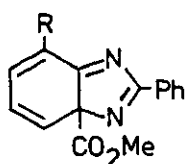
(37) a) R=Me
     b) R=H

TABLE 1

Substrate / Products	Conditions	(NO2 benzimidazole) 2-Ph, NH (35)	(benzimidazole) 2-Ph, NH (10)	(benzotriazole) N-Ph (41)
(38)	Ph₂O (210°C) 24 h	34 %	11 %	3 %
(39)	Ph₂O (210°C) 6 h	25 %	4 %	13 %
(34)	(185°C) 0·5 h	0 %	0 %	91 %
(40)	PhBr (165°C) 1 h	0 %	0 %	88 %

work up of the N-methoxycarbonylbenzimidazoles (30) and (33) respectively, this conclusion being supported by blank experiments.

No explanation has been found for the directing effect mentioned above, which further experiments (Scheme 7) suggest is a unique property of the methoxycarbonyl group; tetrazoles (34) and (36a-c) closed exclusively to the unblocked positions on photolysis, with the possible exception of (36b). Some evidence for a related effect involving the nitro group was found during solution thermolyses of oxadiazolone (38) and oxadiazolethione (39), however (Table 1).[17] Although the origin of the 2-phenylbenzimidazole (10) in these experiments is not certain, a blank experiment established that 4-nitro-2-phenylbenzimidazole (35) could not be the source, so suggesting that (10) might arise via closure to the nitro-bearing position. At the lower temperatures adequate for decomposition of tetrazole (34) and oxathiadiazole-2-oxide (40) a different reaction supervened leading to 2-phenylbenzotriazole (41). After intensive investigation it was established that this novel rearrangement was the result of an ortho-nitro interaction in the carbodiimide (42).[17,18]
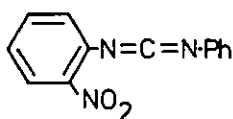
(42)

To summarise, these studies of ortho-blocked imidoyl nitrene cyclisations raised many mechanistic problems, and left the impression that the 3aH-benzimidazole system possessed intrinsically a strange pattern of reactivity. With the benefit of hindsight, and drawing on other results to be described in this thesis, this impression has since been somewhat modified. The high reactivity of the 3aH-benzimidazoles

in some of these experiments may now be viewed more as a consequence of
the methods by which they were formed, since closure of the thermally
or photochemically generated nitrenes would be expected to produce
3aH-benzimidazoles in highly excited states. The failure of the chemical
methods to effect similar cyclisation (Scheme 3) reflects the higher
activation barrier caused by the blocking groups, showing why more
energetic processes were needed.

The problem of the mechanism of cyclopentapyrimidine formation is a
complex one which will be referred to again in Chapter Five. For the
moment, suffice it to say that the results already described might
suggest, and are certainly consistent with, the operation of a photo-
chemical mechanism in the transformation of 3aH-benzimidazoles to cyclo-
pentapyrimidines during photolysis. The thermal formation of cyclopenta-
pyrimidines seems at first contradictory, but may be explained either by
the operation of a second mechanism, or by the rather broad statement
that for nitrene intermediates generated under the unimolecular conditions
of FVP experiments, the usual clear-cut distinctions between thermolytic
and photolytic pathways may to some extent be blurred due to the high
internal energy of these species.

2) Synthesis of 3aH-Indene Analogues.

The previous section having described why 3aH-indenes are of
interest, this section deals with their synthesis. The four classes of
target involved in this group's work have been i) 3aH-indenes themselves,
ii) 4aH-carbazoles, iii) 3aH-benzimidazoles and iv) 4aH-fluorenes. Of
these, 3aH-benzimidazoles have not yet been synthesised, although a
preliminary study was undertaken,[19] while 4aH-fluorenes form the subject
of this thesis. The remaining two catagories will now be discussed.

i) 3aH-<u>Indenes</u>.

Almost all the syntheses or attempted syntheses of 3aH-indenes under-
taken in this group have involved deprotonation of an appropriately bridge-
head substituted bicyclo[4.3.0]nonatrienone, followed by alkylation on
oxygen of the resulting anion. The syntheses of the various trienones
will not be discussed (although, naturally, these formed the bulk of the
synthetic work), but a comparison of the degree of success achieved in
converting each to a 3aH-indene is informative.

Trienones (43), (46) and (49) were available <u>via</u> literature procedures
or simple extensions.[20,21,22] Other methods for enolisation having proved
ineffectual, each was deprotonated at low temperature with potassium hydride
in dimethoxyethane containing the crown ether, 18-crown-6 (18-c-6), and the
resulting anion quenched by addition of freshly distilled methyl fluoro-
sulphonate (magic methyl). Attempts were then made either to isolate the
3aH-indene or to trap it with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)
(Scheme 8).[23]
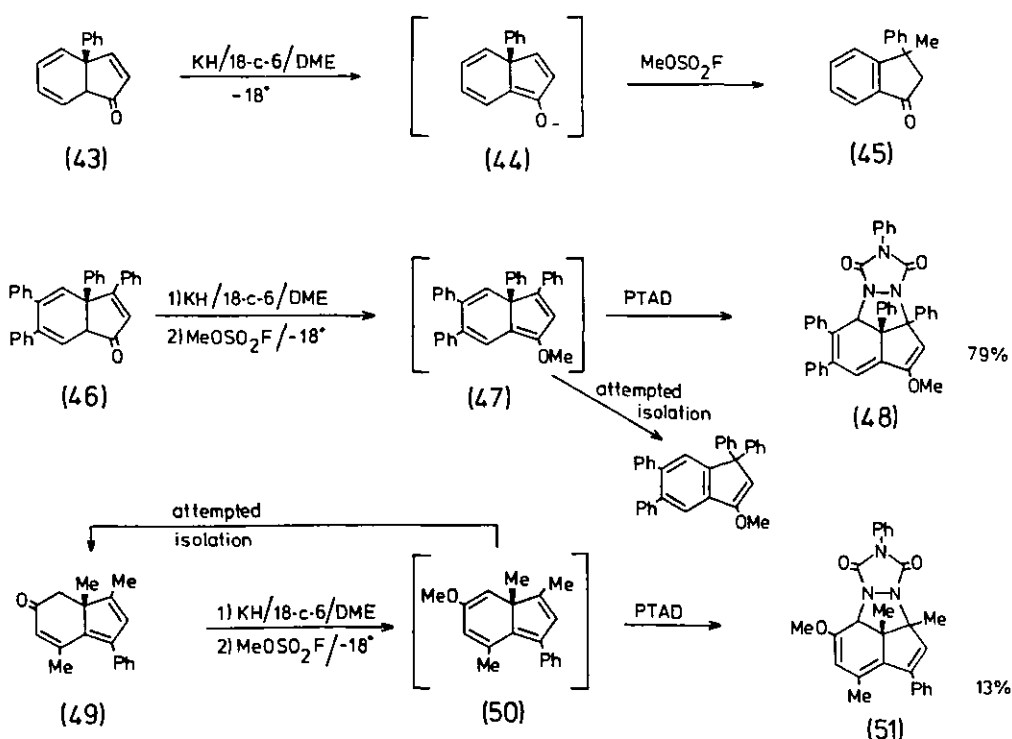
SCHEME 8

The products obtained in these reactions reflect the ease with which the bridgehead substituent of the 3a$\underline{H}$-indene generated can undergo a [1,5] sigmatropic shift to the adjacent five-ring position (C_3). Migration of the phenyl substituent in anion (44) was so facile that it was apparently complete before addition of the methylating agent; methylation therefore followed a different course to give the indanone (45). Although still rapid enough to frustrate attempted isolation, phenyl migration in enol ether (47) was sufficiently retarded by the presence of a second phenyl substituent at the migration terminus to allow trapping with PTAD to succeed, and the [8+2] adduct (48) was obtained. Migration of the bridgehead methyl group of enol ether (50) was evidently slower still, since attempted isolation, although it failed to yield the enol ether itself (due, presumably, to hydrolysis on work up) did show that migration had not been appreciable during the reaction period. This reflects both the much lower migratory aptitude of methyl groups relative to phenyl groups and the presence of a substituent at C_3. Adduct (51) was obtained from the corresponding trapping experiment.

Similar experiments were carried out using trienone (52), itself the product of considerable synthetic effort.[24,25] In this instance, however, a series of extended aldol condensations resulted in formation of the cage-like dimeric anion (53) before the monomer could be methylated or trapped (Scheme 9).[25]
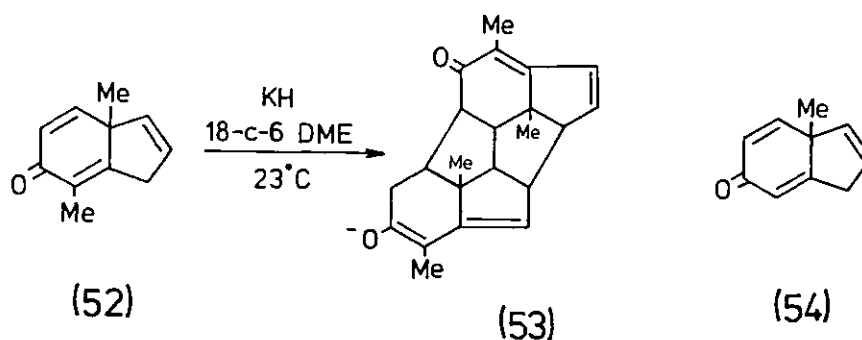
SCHEME 9

A parallel study of trienone (54) failed at the synthetic stage.[25]

These experiments notwithstanding, the most successful 3aH-indene precursor was trienone (56), from which was obtained the first isolable 3aH-indene. This synthesis of 3-methoxy-3a-methyl-3aH-indene (57), starting from 1-indanone, is summarised in Scheme 10.[26]

1) K / tBuOH / NH$_3$ / THF / -78°C
2) LiBr / THF / -78°C
3) MeI / THF / H$_2$O / -78°C

(55)

45%

1) LDA / THF / -78°C
2) Ph$_2$Se$_2$ / Br$_2$ / THF / -78°C
3) H$_2$O$_2$ / THF / 0°C

1) KH / 18-c-6 / DME / -20°C
2) MeOSO$_2$F / -20°C

(57)

36%

(56)
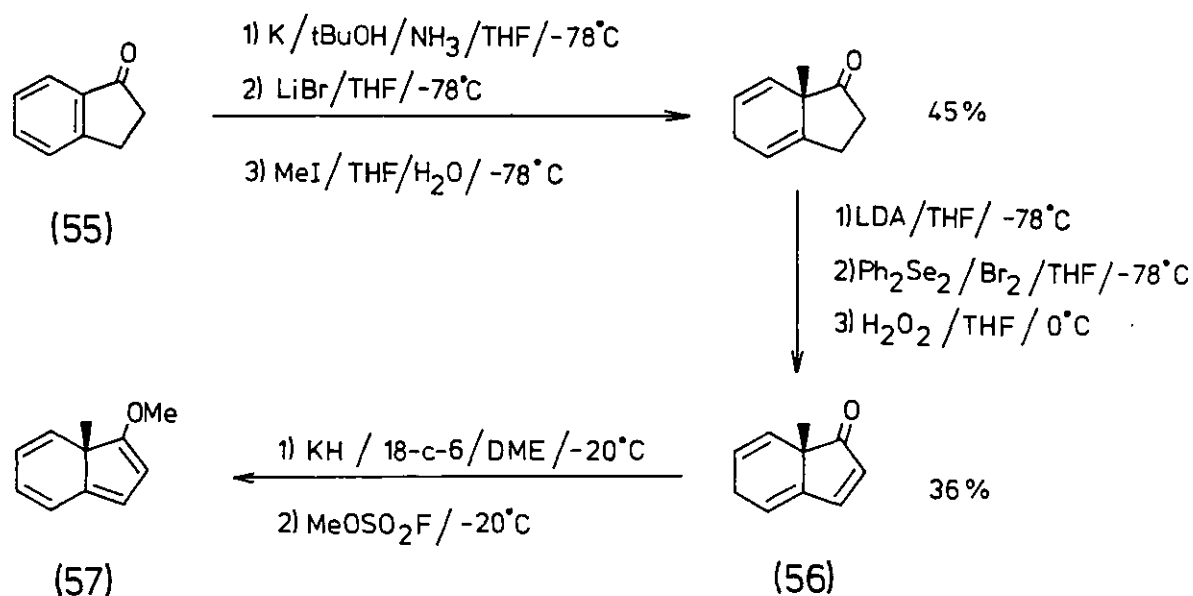
SCHEME 10

3aH-Indene (57) is an unstable yellow oil, isolable only in low yield. When neat it absorbs oxygen, even at reduced pressure, to give the cis-cinnamate ester (58), while on heating it aromatises via a [1,5] methyl shift to give 1H-indene (59); photolysis has not yet been investigated. Rearrangement via a [1,5] vinyl shift to give spiro[4.4]nonatetraene (60), or products derived from it, was never observed.

The majority of the known reactions of 3aH-indene (57), however, are cycloadditions. As in the cases discussed previously, there is a

marked preference for the formation of [8+2] adducts, these being

obtained with PTAD, diethyl azodicarboxylate and dimethyl acetylene-

dicarboxylate. Some suggestion that these adducts might be the result

of thermodynamic control is, however, provided by the isolation of

[4+2] adducts from reaction of 3aH-indene (57) with less reactive

dienophiles such as N-phenylmaleimide and maleic anhydride. The

first formed [4+2] adducts are converted into [8+2] adducts on therm-

olysis, most probably via a dissociation-recombination mechanism.[26,27]
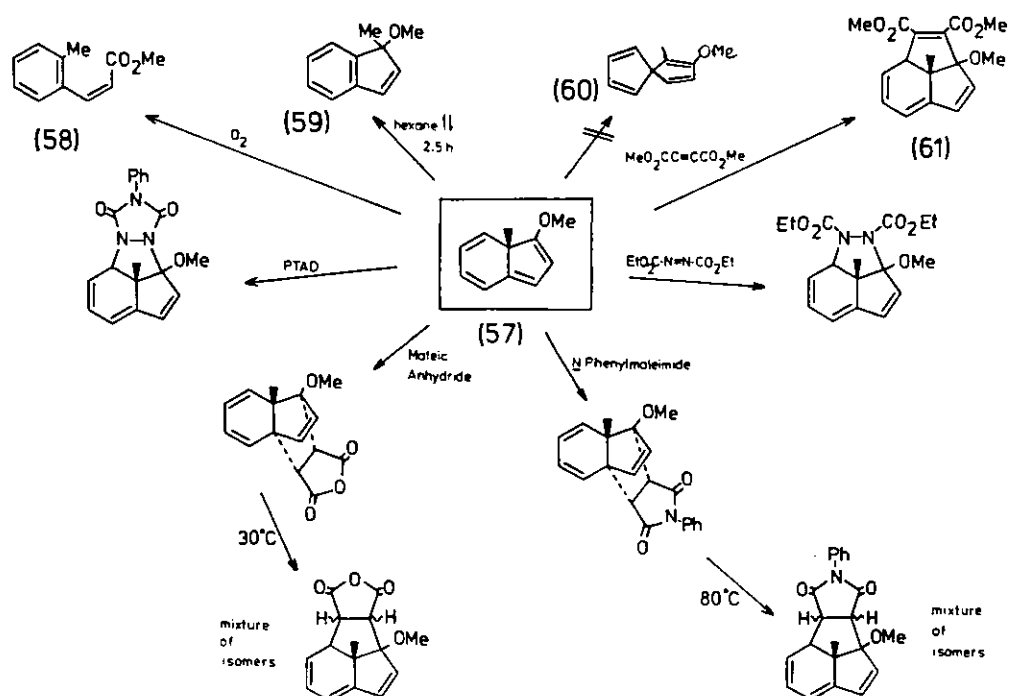
SCHEME 11

Adduct (61) was itself the starting point for another branch of

the study, since acid catalysed elimination of methanol provided access

to a new series of 10-annulenes. Diester (62) was the first example

of this series,[28] and hydrocarbon (64) is the parent, originally

obtained from decarbonylation of the dialdehyde (63) with Wilkinson's

catalyst.[29] An intensive investigation followed this discovery,

resulting in improved syntheses of the parent annulene; the best

of these avoids the labile 3aH-indene system altogether, forming the tricyclic skeleton by an internal aldol condensation of the 3-acetyldienone (65).[30] Annulenes bearing different bridgehead substituents (ethyl, benzyl and isopropyl) have been similarly prepared.[31]
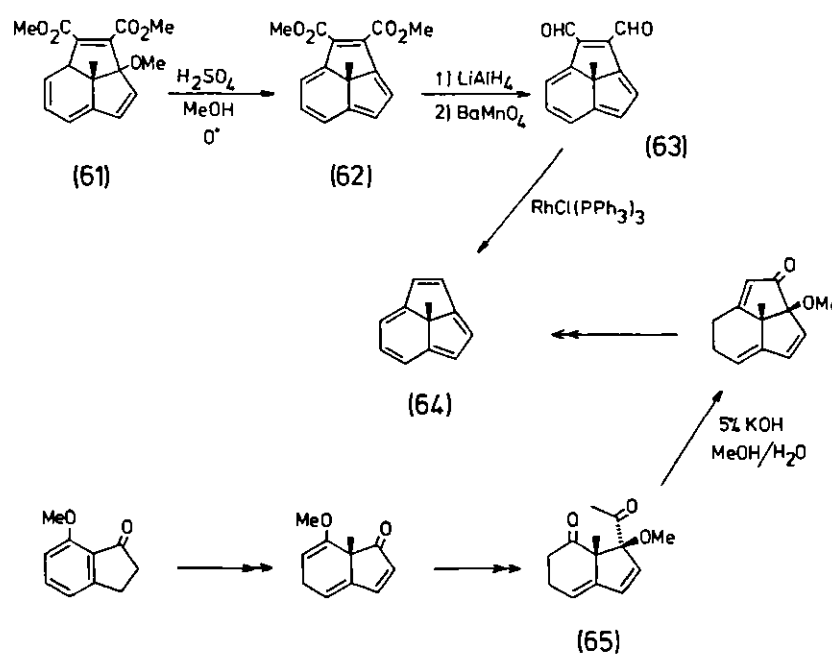
SCHEME 12

Although they are formally vinylidene-bridged 3aH-indenes, the theoretical interest of these annulenes lies in the fact that they are true 10π-aromatic systems; they have approximately equal bond lengths around the periphery and their central methyl groups resonate at high field (δ-2-⁻1) in the proton nmr.[28]

ii) 4aH-Carbazoles.

Two approaches have been followed in investigating the 4aH-carbazole system. In one, photolysis or thermolysis of 1-arylbenzotriazoles

bearing ortho-blocking groups on the aryl substituent generates the 4aH-carbazole molecule directly, but only as a transient intermediate. In the other, the aim is to create the system by conventional synthesis, the last step being sufficiently mild to allow the 4aH-carbazole to be isolated. These methods will now be considered separately.

a) Decomposition of benzotriazoles.[32]

The cyclisation of ortho-blocked 1-arylbenzotriazoles is an extension of the known formation of carbazole on thermolysis[33] or photolysis[34] of 1-phenylbenzotriazole, and bears an obvious relationship with the formation of 3aH-benzimidazoles from ortho-blocked 1-aryltetrazoles discussed earlier (Section 1). Photolysis or thermolysis of benzotriazoles (66a-c) leads to the products shown in Scheme 13. Although the 4aH-carbazoles (67a-c) were not isolated, the results are all consistent with their intermediacy.
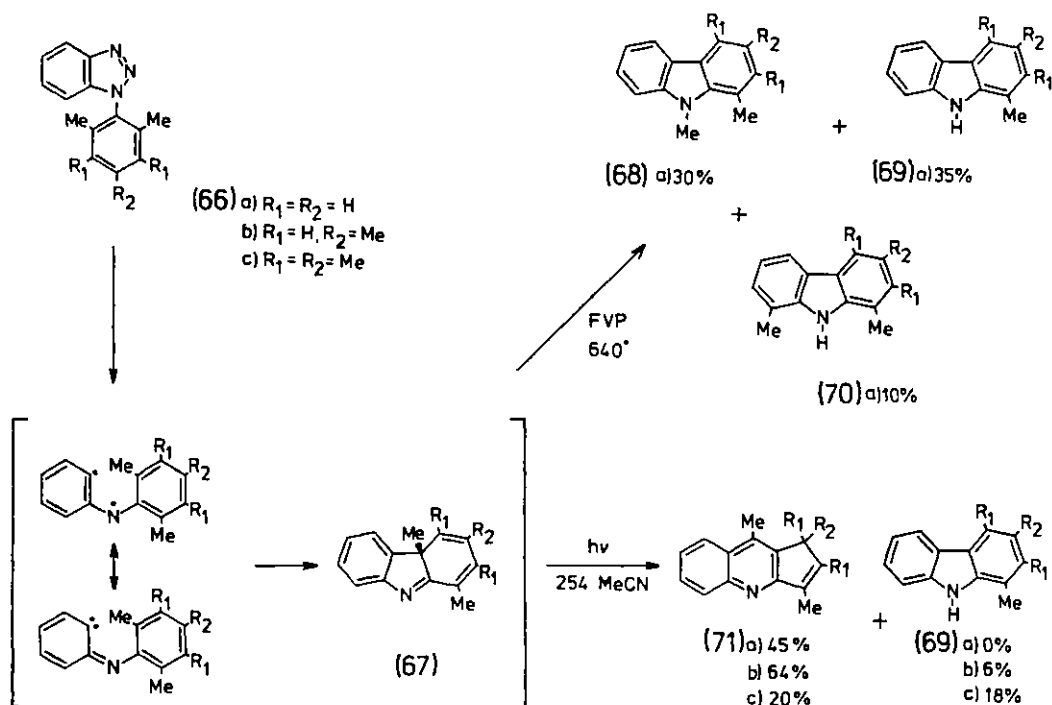
SCHEME 13

Thermolysis, as in the benzimidazole series, leads to aromatisation via methyl shifts. Unlike the benzimidazole results, however, this is the only thermolytic pathway observed; skeletal rearrangement to cyclopentaquinolines (71a-c) occurred only on photolysis (paralleling the formation of cyclopentapyrimidines on photolysis in the benzimidazole series). All but one of the sigmatropic methyl shifts required to account for the 9H-carbazole products (68), (69) and (70) are [1,5] shifts, but a final [1,9] shift may be involved in the formation of product (70). This is in marked contrast to the benzimidazole series, in which supposedly favourable [1,5] shifts to nitrogen were apparently avoided in favour of [1,9] or [1,5] shifts to carbon. Evidently this reluctance for migration to nitrogen is at least partially lost in the carbazole reactions, although the formation of demethylated carbazoles on either thermolysis or photolysis remains unexplained.

Some light was cast on the mechanism of the photolytic rearrangement by the trapping of an intermediate (72). When benzotriazole (66c)
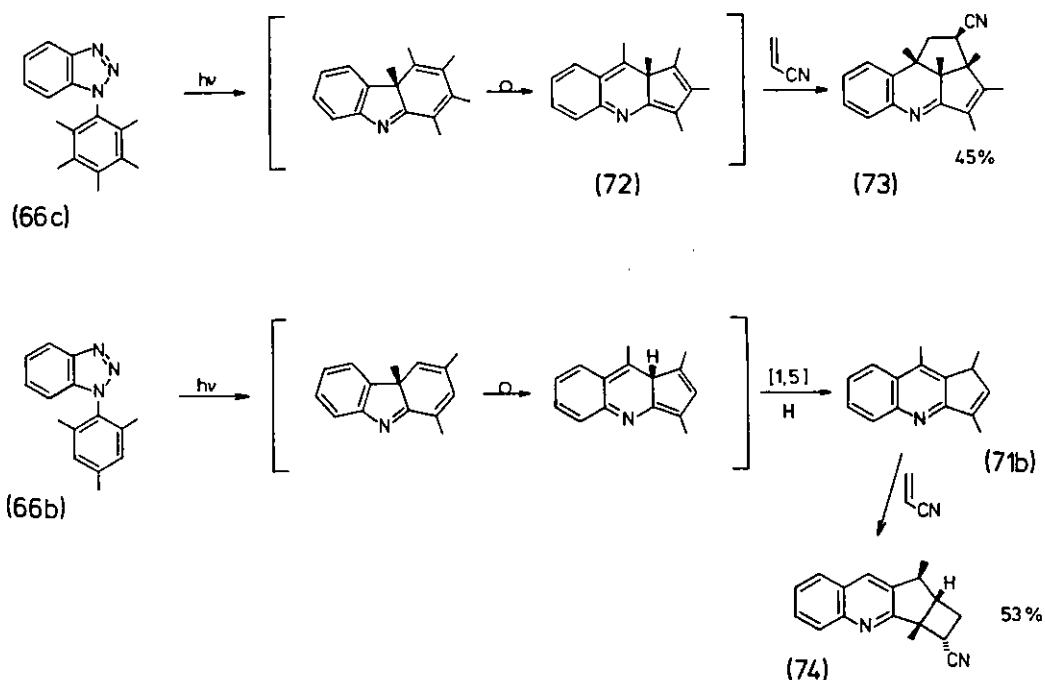
SCHEME 14

was photolysed in the presence of acrylonitrile, carbazole and cyclopentaquinoline formation were suppressed and adduct (73) formed. The corresponding intermediate from (66b) could not be intercepted, however, due to the much more rapid [1,5] sigmatropic shift of hydride, leading to cyclopentaquinoline (71b). Subsequent reaction of this with acrylonitrile then led to the [2+2] adduct (74) (Scheme 14).

b) Synthesis.[35]

An approach to the 4aH-carbazole system based on the Fischer-indole synthesis has been developed, and benzo-fused 4aH-carbazoles (75) and (76) have been prepared (Scheme 15). The route has also been applied to the parent system, but although the molecular skeleton was successfully synthesised, considerable difficulties in dehydrogenating the non-aromatic 6-ring have so far prevented completion of this work.
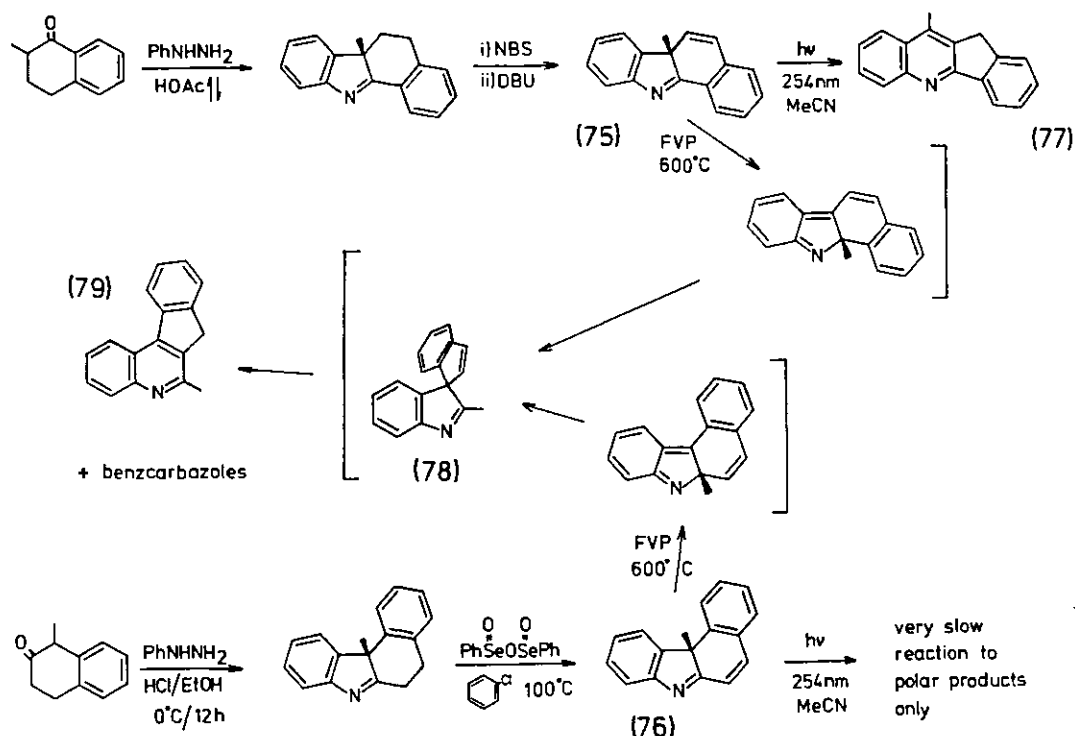
SCHEME 15

Investigation of the chemistry of benzcarbazoles (75) and (76)
is not yet complete, but two key results have emerged: i) only
compound (75) undergoes a photorearrangement to give an indenoquinoline
(77), while compound (76) is relatively unreactive, and ii) thermolysis
of either benzcarbazole (75) or (76) gives the same indenoquinoline
(79), an isomer of (77).   Consideration of the photochemical reaction
will be deferred until Chapter Five, since it forms a natural part of
the discussion of 4aH-fluorene photolyses.   The origin of indeno-
quinoline (79) is not certain, but it is tempting to suggest that it
arises in each case from a common spiro-intermediate (78) as shown
(Scheme 15).   If so, this would probably be the only genuine instance
of rearrangement via such a spiro-system encountered during this
group's study of 3aH-indenes.

3) 3aH-Indene Analogues as Reactive Intermediates.

In this section references to 3aH-indene analogues as reactive
intermediates are briefly reviewed, classifying the material according
to the type of reaction by which the intermediate is generated.

i) Cyclisations of nitrenes and carbenes onto adjacent aryl substituents.

The cyclisation of imidoyl nitrenes to 3aH-benzimidazoles
mentioned earlier is one of a group of related cyclisations of nitrenes
or carbenes linked to an aryl group via an olefinic or imidoyl double
bond (Scheme 16).

Reactions involving most of the possible permutations for X, Y
and Z have been described in the literature, although the 3aH-indene
intermediate is not always specifically mentioned.   If, as in Scheme 16,
the bridgehead substituent of the 3aH-indene analogue is a proton,

TABLE 2

	Reference
	36
FVP	37
FVP	37
FVP	38
FVP	39
Ph₃C-C≡C-OMe, hv, benzene	40a
Ph₃C-C≡C-Ph, hv	40a
Ph₃C-C≡C-CO₂Me, hv	40b
hv (80% + 20%)	41
Δ	41
200°C melt	42

products

(X,Y,Z = CH or N) ·

SCHEME 16

this invariably undergoes a [1,5] sigmatropic shift to the Z atom, giving the corresponding 1H-indene analogue; further proton shifts may then follow. In the case of other bridgehead substituents, a similar [1,5] shift usually occurs, although the 3a-methyl-3aH-benzimidazoles discussed earlier are an exception.

The nitrenes or carbenes may also close to the X atom, so forming a 3-membered ring (Scheme 17). Sometimes this process represents a pre-equilibrium which is tapped irreversibly to the fused product, while sometimes the 3-ring compound is the starting material from which the open-chain carbene or nitrene must be generated. In other cases the 3-ring system may not be involved.
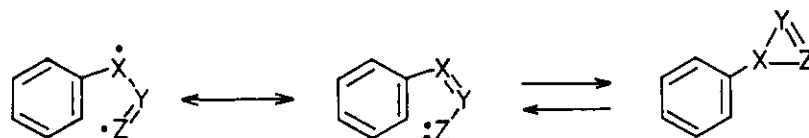
SCHEME 17

The carbenes or nitrenes may also be considered as diradicals; in either formulation there is a distinction between singlet and triplet species, but only rarely has it been determined which undergoes

cyclisation. Individual reactions are summarised in Table 2, excluding the benzimidazole forming reactions already discussed, and arbitrarily representing all the cyclisation precursors as nitrenes or carbenes.

In a few cases, the effect of methyl blocking groups has been investigated. On solution thermolysis, the vinyl azide (80) undergoes an insertion reaction leading to the isoquinoline (82) after oxidation (Scheme 18).[43] This is in marked contrast to the behaviour of the imidoyl nitrenes discussed previously, from which no insertion products were isolated. It is not possible to say, however, whether this difference is a consequence of the change from an imidoyl to a vinyl nitrene, of the change from phenyl to ethoxycarbonyl as the 2-substituent, or of the different reaction conditions. The probable formation of aziridine (81) may well be important. Efforts to generalise this synthesis of isoquinolines have resulted in the discovery of conditions which allow the insertion reaction to compete effectively even with cyclisation to an unblocked position.[44]
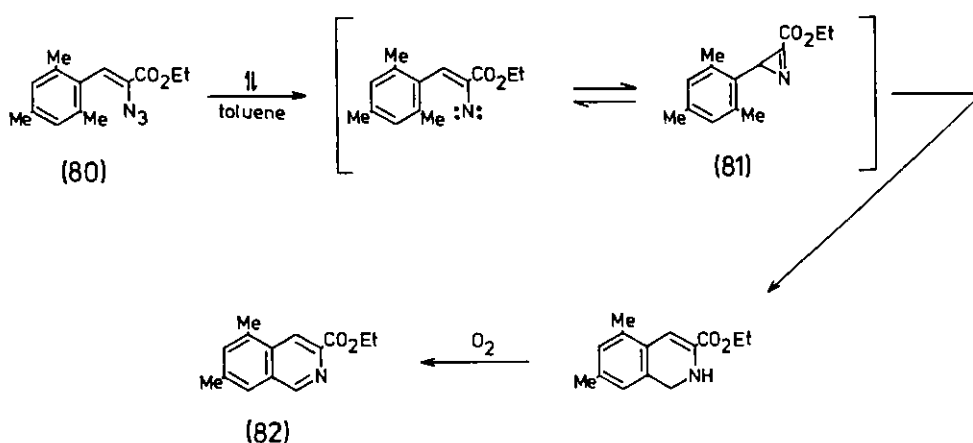
SCHEME 18

Melt thermolysis of the mesityltriphenylcyclopropene (83) has also been studied (Scheme 19).[42] No appreciable selectivity was observed between closure to the blocked and unblocked aryl substituents, and no insertion products were found. Not surprisingly, the 3a-methyl-3aH-indene

(83)

melt
190-200°C
2h

(84)
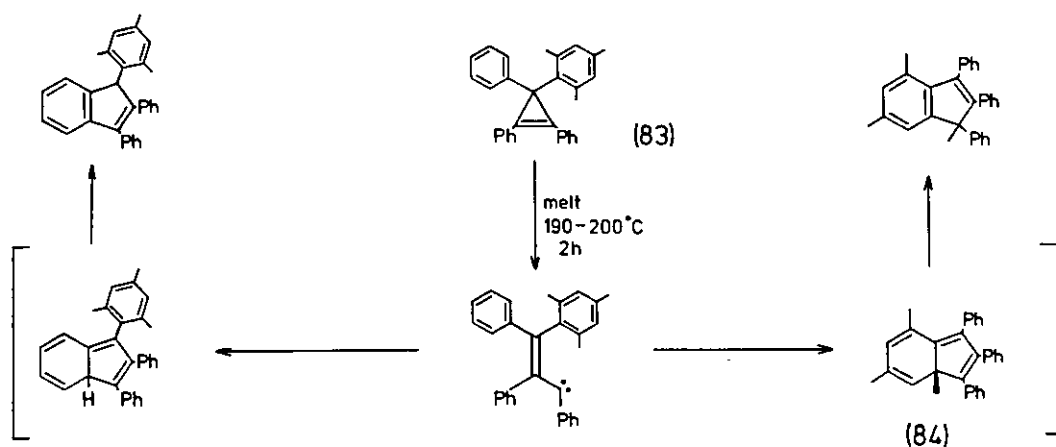
SCHEME 19

intermediate (84) rearranged under the reaction conditions.

Similar reactions which involve a second aryl ring and lead to a benzo-fused 3aH-indene analogue are also known. The Graebe-Ullmann synthesis of carbazole from 1-phenylbenzotriazole has already been discussed (Section 2(iia)). Cyclisation of 2-azidobiphenyl (85) on photolysis also gives carbazole, and the mechanism of this reaction has been intensively studied by flash photolysis. Lehmann and Berry[45] concluded that it was the free triplet nitrene which underwent cyclisation, but a later, more detailed study by Sundberg et.al.[46,47] excluded this possibility, and showed that it was the singlet nitrene which cyclised via an as yet unidentified intermediate (detected spectroscopically).

(85)   (86)

230°C
hexadecane
10 min

48%   Me 4·5%   NH2 29%

(87)
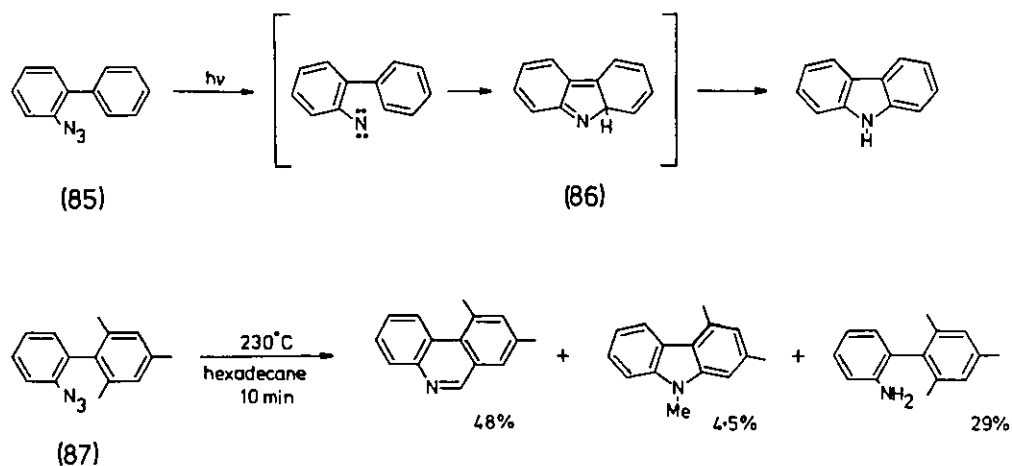
SCHEME 20

It was suggested that this intermediate was 9aH-carbazole (86). The
effect of methyl blocking groups on this reaction was investigated by
Smolinsky,[48] who found that azidotrimethylbiphenyl (87) underwent
predominantly an insertion reaction on thermolysis (Scheme 20).

The carbocyclic analogue of this cyclisation reaction is also known,
although in this case the carbene (89) is itself the product of prior re-
arrangement of the symmetrical carbene (88) (Scheme 21).[49] More complex
examples of the cyclisations shown in Schemes 20 and 21 are also known.[50]
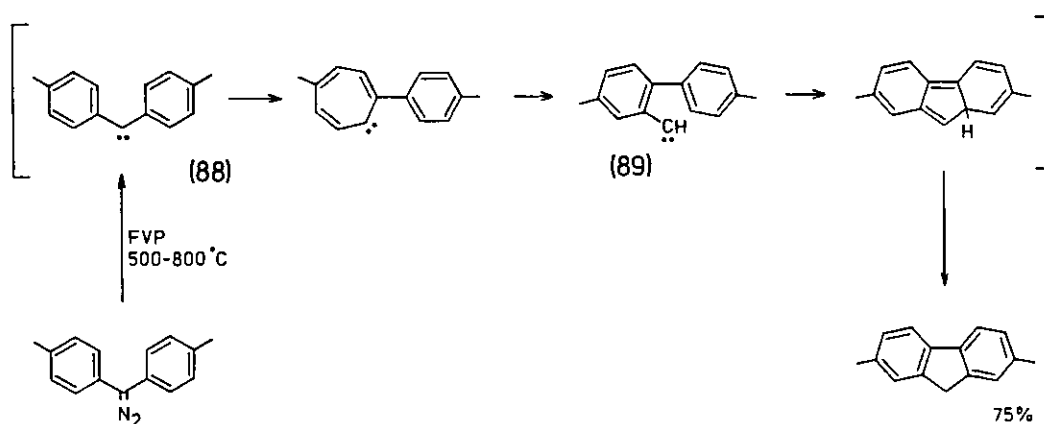
SCHEME 21

ii) Rearrangement of spiro[4.4]nonatetraenes.

Several reactions are known in which spiro[4.4]nonatetraenes
rearrange thermally to 1H-indenes, and in each case intermediacy of a
3aH-indene has been assumed. The first example of this reaction to
be discovered illustrates the mechanism (Scheme 22).[51] Spiro-compound
(91) undergoes a [1,5] vinyl shift leading to the 3aH-indene (92),
which in turn undergoes a [1,5] sigmatropic shift of the bridgehead
alkyl substituent to give the 1H-indene (93). The rearrangement took
place during gas liquid chromatography at high temperature.

In this instance the spirocycle was synthesised from tetrachloro-
diazocyclopentadiene (90) via reaction with a pre-formed palladium
complex of an alkyne (possibly a cyclobutadiene complex). Although
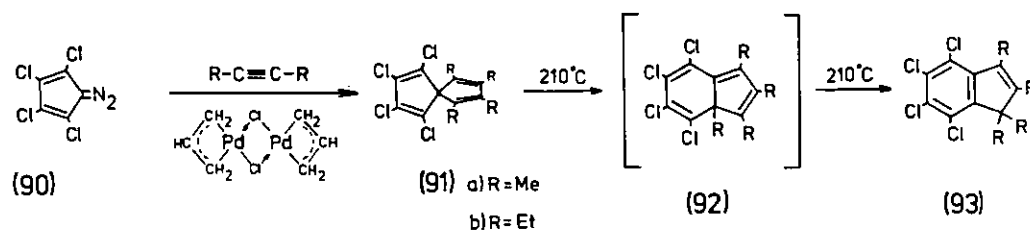
SCHEME 22

this synthesis gave only a poor yield ((91a), 16%; (91b), 10%), the rearrangement itself was quantitative.

The parent spirocycle (94) and its less unsaturated analogues (95), (96) and (97) were synthesised by Semmelhack as part of a general study of spiro-conjugation.[52] The expected rearrangement to
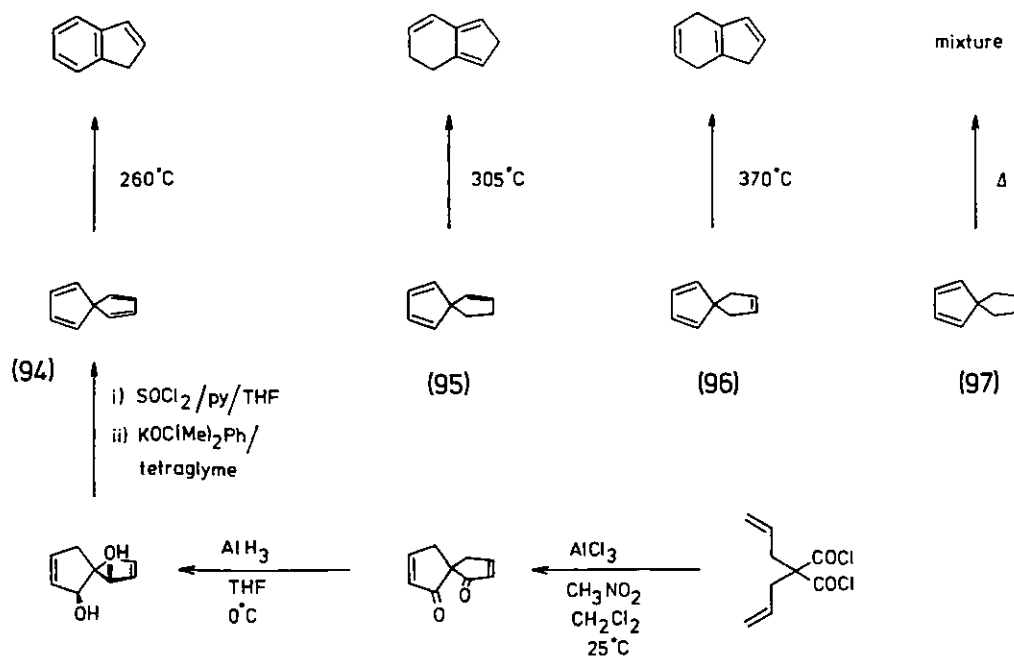
SCHEME 23

indene was observed at 260°C on flow pyrolysis,[53] and also at lower temperatures ($t_{\frac{1}{2}}$=65 minutes at 65°C) or on direct or sensitised irradiation (no details given).[54] Although compound (95) showed a similar reaction rate, the activation barriers determined for analogous rearrangement of compounds (96) and (97) were significantly higher.[53] This was explained in terms of a favourable secondary orbital interaction possible during a [1,5] vinyl shift but not during a [1,5] alkyl shift.

The synthesis (Scheme 23) and properties of spirocycle (94) form a parallel with those to be described for 4aH-fluorenes (Chapters Three, Four and Five). Hydrocarbon (94) is an oil which polymerises and oxidises when neat, undergoes Diels-Alder reactions with tetracyanoethylene and dimethyl azodicarboxylate, and forms a bis tricarbonyliron complex on reaction with diiron nonacarbonyl. Interestingly, dimerisation of compound (94) was anomalously fast relative to other Diels-Alder reactions, an observation which so far lacks an explanation.[52]

A series of spiro-pyrazoles was studied at length by Dürr and co-workers.[16,55,56] The compounds were generated in situ by cycloaddition of an acetylene to a diazocyclopentadiene. Although a few of the spiro-pyrazoles were stable, e.g.(99), most underwent one of two possible [1,5] vinyl shifts to give either an azaindolizine, such as (100), or a 3aH-indazole, such as (101), as the isolated product. The latter thus represent one of the very few types of isolable 3aH-indene analogues claimed in the literature prior to the synthesis of compound (57). The reactions shown in Scheme 24 are typical of the thirty or more which appear in the original papers.

Despite the large amount of data, it was not possible to reach many conclusions. Those spiro-pyrazoles which rearranged to 3aH-indazoles were, with one unexplained exception, all derived from tetrachlorodiazocyclopentadiene (90), while those which could be
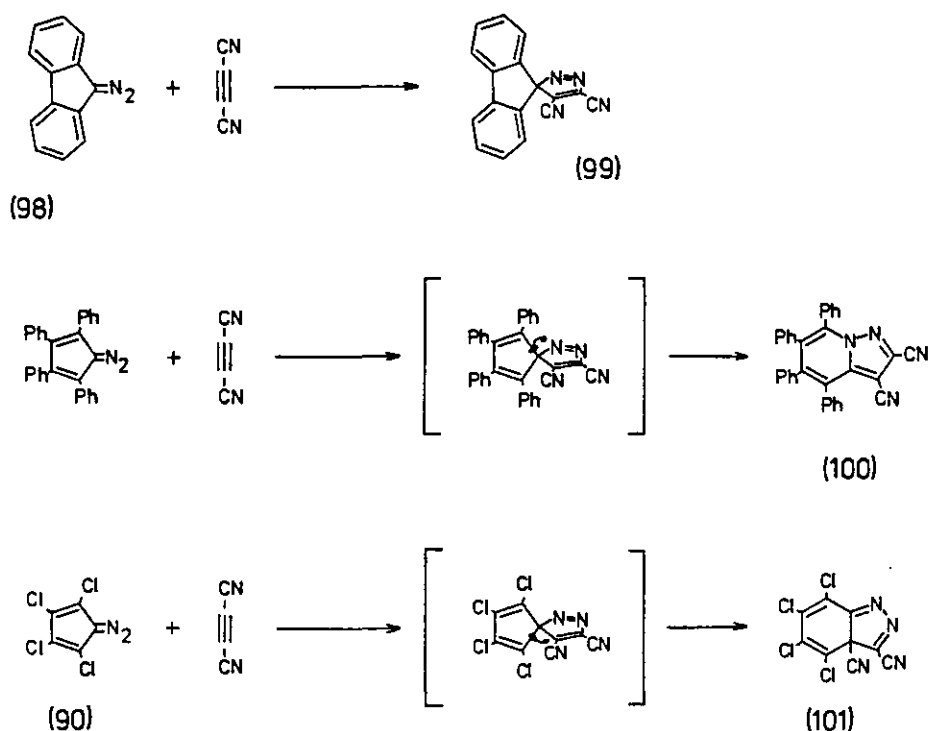
SCHEME 24

isolated in the spiro form were mostly, though not exclusively, derived
from 9-diazofluorene (98). Ring expansion apparently occurred
exclusively within the carbocyclic ring, although the authors'
structural assignments rest wholly on their assertion that the
alternative products, such as (102) and (103), would lose nitrogen
during mass spectrometry (which the products isolated did not).

(102)   (103)
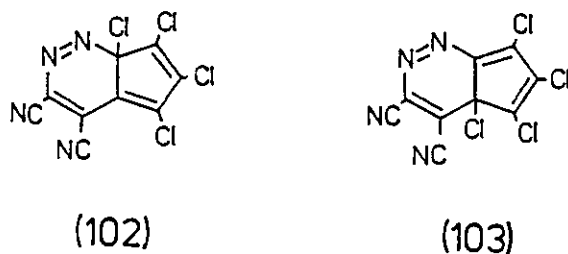
In general, the structure proof of many of these compounds was
not satisfactorily described. The carbon spectra of some twenty
compounds were fully assigned in one paper, in some cases distinguishing

between quaternary resonances separated by less than 1 ppm, but scarcely any justification was given for these difficult assignments.[56] In all, six 3a$\underline{H}$-indazoles were claimed, (101), (104a-d) and (105), although it is likely that (104c) and (104d) were in reality the same compound (some confusion having been caused by inconsistent numbering). A tantalising glimpse of a possible chemistry of the 3a$\underline{H}$-indazoles was given by the statement that, in two cases, "mass spectra could not be obtained due to the instability of these compounds"; no other details except melting points and spectral properties were given, however.[56]

(104) a) X=Y= CO$_2$Me

b) X=Y= COPh

c) X=COPh, Y=CO$_2$Me

d) X=CO$_2$Me, Y=COPh

(105)
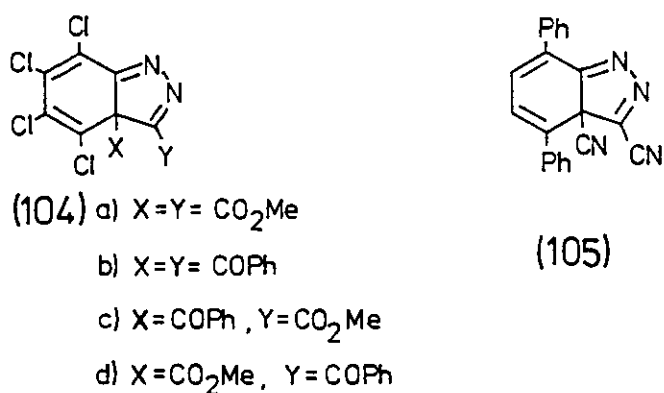
The closely related rearrangement of spiro-fluorene (106) is also known (Scheme 25).[57] Interestingly, in this case rearrangement appears to occur via a 7a$\underline{H}$-indole rather than an indolizine.
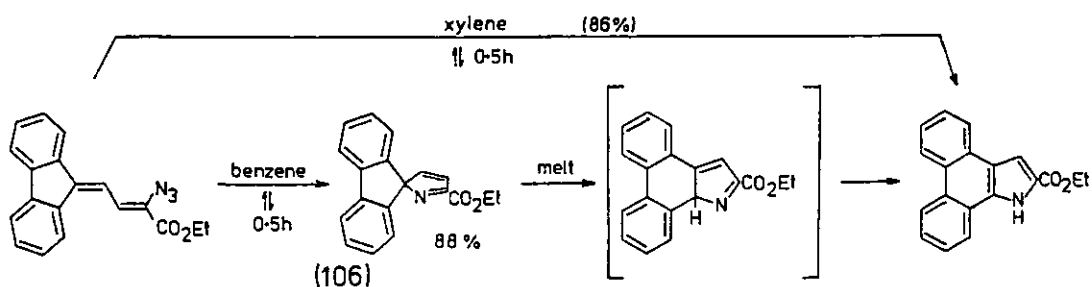
SCHEME 25

iii) Rearrangement of other bicyclic systems.

A number of reactions or reaction sequences are known in which bicyclononatriene derivatives, generally obtained from reaction of cyclooctatetraene or its dianion with electrophiles, undergo rearrangement

and elimination to give indenes. In a few cases a 3aH-indene inter-mediate is fairly clearly implicated, while in others a carbonium ion such as (107) may be involved. A 3aH-indene may then be formed, depending on the relative order of rearrangement and proton loss. If proton loss occurs first, this generates a 3aH-indene intermediate which rearranges in the usual way, but if rearrangement occurs in the carbonium ion, no such intermediate is required (Scheme 26). The order of these steps is, in general, unknown.
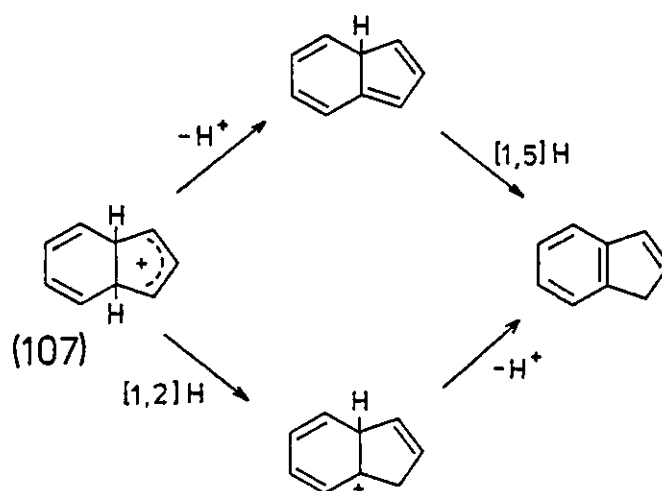
SCHEME 26

The rearrangements of bicyclononatrienes represent a mechanist-ically complex and, to some extent, unresolved area of chemistry, and a detailed discussion would be inappropriate. Instead a few representative mechanisms will be presented.

Bicyclo[4.2.1]nonatrienes such as (108) apparently rearrange via two alternative valence tautomers. These are illustrated for the case of carbonium ion (109), which is involved in several rearrangement reactions (Scheme 27).[58,59,20]
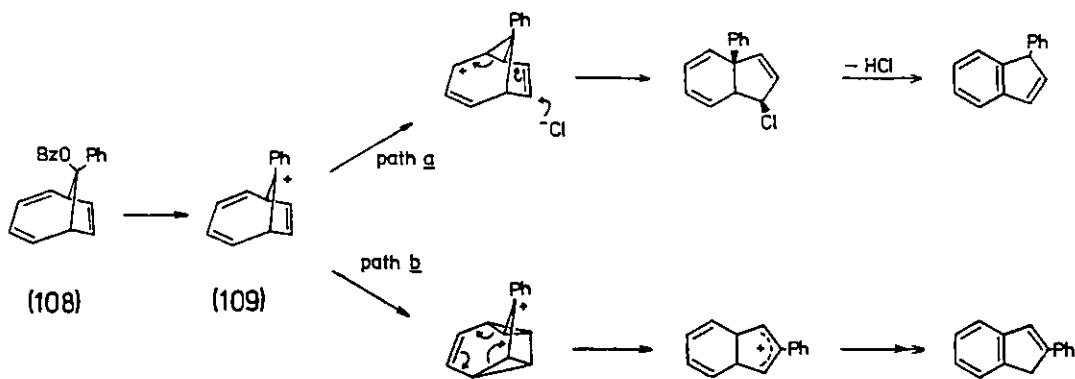
SCHEME 27

A mechanism similar to path a was also suggested for the rearrangements of ketone (110) and the carbene derived from its tosyl-hydrazone (111). In the former case 3a-hydroxy-3aH-indene (112) was proposed as an intermediate (Scheme 28).[60]
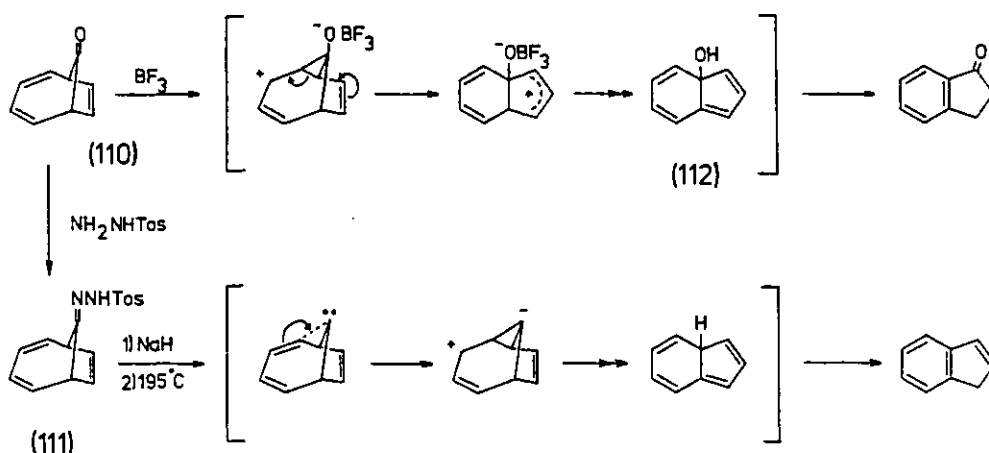
SCHEME 28

Bicyclo[6.1.0]nonatrienes such as (113) undergo a simpler valence tautomerism on heating, and, when possible, subsequent elimination leads to an indene.[58,59,61] Rearrangement of the corresponding carbene (114) probably follows an even more direct course, described by the authors as "an electron pusher's delight" (Scheme 29).[62]
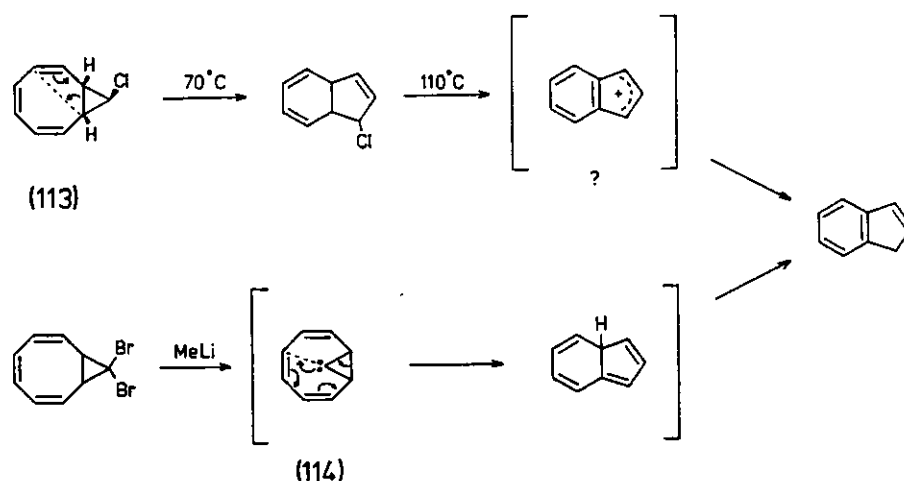
SCHEME 29

iv) 5H-Adenine.

5-Methyl-5H-adenine (116) was the subject of a recent study by Hosmane et.al.[63] The molecule was assumed to be formed by the reaction of the 4H-imidazole (115) with formamidine acetate, but it had only transient existence, the product isolated being the triazaindolizine (117) (Scheme 30).
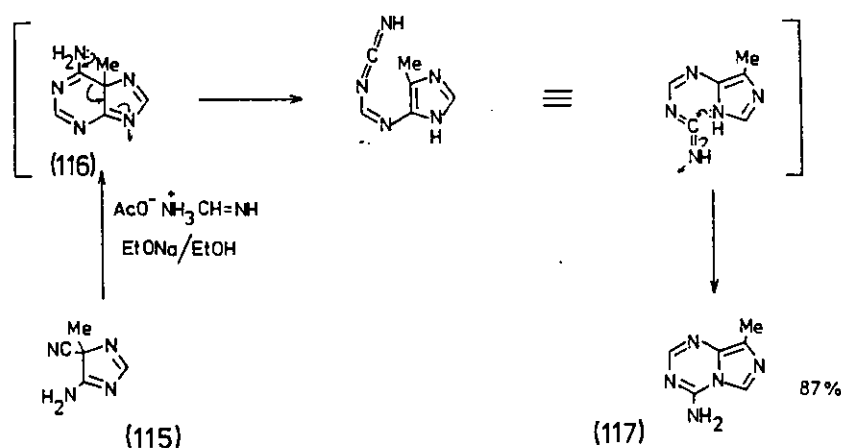
SCHEME 30

This mode of rearrangement is not observed for other 3aH-indene analogues, and is clearly only possible as a result of the arrangement of the heteroatoms in the adenine framework. The authors sought

further evidence for the intermediacy of the 5H-adenine (116) by

calculating the energetics of the proposed rearrangement using the

MINDO/3 method.   They found that the 5H-adenine system was severely

strained as a result of the opposing tendencies of the sp^3 carbon

atom to maintain tetrahedral geometry, and of the sp^2 periphery to

become planar to maximise conjugative overlap; the rearrangement was

thus explained in terms of the relief of this strain.

According to the above calculations, the strain in the 5H-

adenine system was accommodated mainly by distorting the peripheral

tetraene system, which was predicted to be puckered and to have a

considerable degree of bond alternation.   It is interesting to compare

these calculations with others for 3aH-indene (2) and 3a-methyl-3aH-

indene (118) made using the more recent MNDO method.   The distortion

in 3aH-indene (2) itself was predicted to be mainly of the sp^3 atom,

which was substantially flattened towards sp^2 geometry, while the

periphery resembled two independent butadiene moieties with a large angle

between their planes (torsion angle C_{3a}, C_{7a}, C_7, C_6 = 24.6°).[24,64] The

flattening of the bridgehead atom in this case, however, appears not to

be a consequence of strain in the periphery, but of steric compression

alone.   Analogous calculations for trimethylmethane (2-methylpropane)

revealed an almost identical flattening of the tertiary carbon caused by

steric congestion between the methyl groups.   As would be expected from

this explanation, the flattening was predicted to disappear when the

tertiary proton was replaced by a methyl group.   Thus 3a-methyl-3aH-

indene (118) was predicted to possess an almost exactly tetrahedral
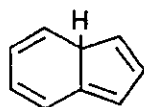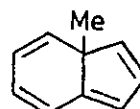
(2)   (118)

sp^3 atom and a puckered periphery, while tetramethylmethane

(2,2-dimethylpropane) is, of course, perfectly symmetrical.[64]

v) Isolable 3aH-indene analogues.

Prior to the synthesis of compound (57), only four types of

3aH-indene analogues appear to have been claimed in the literature as

isolable compounds. These were the 3aH-indazoles such as (101)

mentioned previously (Section 3(ii)), 4a-methyl-1,3,9-triphenyl-

4aH-fluorene (119) and a small group of its derivatives (discussion of

which is deferred until Chapter Two), and compounds (120) and (121a-d).
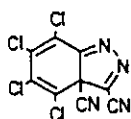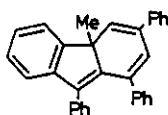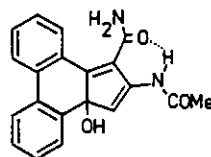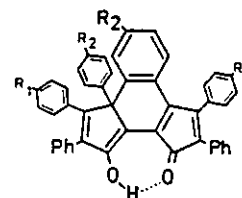
(101)　　　　　(119)　　　　　(120)　　　　　(121) a) $R_1 = R_2 = H$
　　　　　　　　　　　　　　　　　　　　　　　　　　　b) $R_1 = H, R_2 = OMe$
　　　　　　　　　　　　　　　　　　　　　　　　　　　c) $R_1 = OMe, R_2 = H$
　　　　　　　　　　　　　　　　　　　　　　　　　　　d) $R_1 = R_2 = OMe$

Bis-amide (120) was obtained during a study of ketones produced

by condensation of phenanthraquinone and ethyl acetoacetate (Scheme 31).[65]

The structures of the various products were carefully elucidated making

particular use of mass spectroscopy; nonetheless the alternative

structure (122), formally obtained by a [1,5] shift of hydroxyl, appears

not to have been specifically excluded. The product was a thermally

stable, sharp melting solid.

Compound (121a) was suggested to be the product of acid-catalysed

dehydration and oxidative dimerisation of 4-hydroxy-2,3,4-triphenyl-

2-pentenone (123a) (Scheme 32).[66] This product was also a thermally

stable, sharp melting, crystalline solid. The structure proof rested

largely on the demonstration, by ir, of the existence of a strong
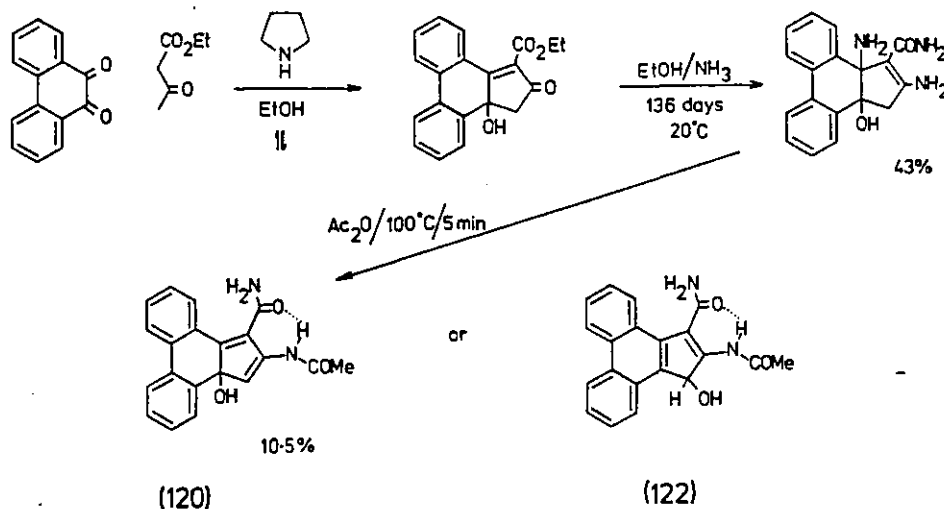
SCHEME 31

intramolecular hydrogen bond, which necessitates a head-to-head
dimerisation process. The possibility that a subsequent [1,5] phenyl
shift occurred, leading to structure (124a) as the isolated product,
was not considered at the time, but subsequent experiments lend some
support to this suggestion.[67] Thus the products of reaction of
hydroxycyclopentenones (123b) and (123c) both lost ·Ph and ·C_6H_4OMe
in roughly equal proportions during mass spectrometry, and the product
from reaction of hydroxycyclopentenone (123d) showed only three
separate methoxy resonances in its ^{1}H nmr spectrum (Scheme 32).
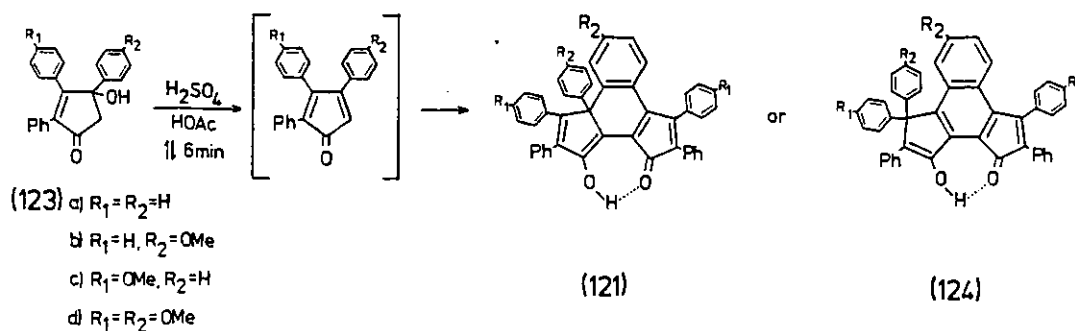
SCHEME 32

4) <u>Synthetic Approaches to the</u> 4aH-<u>Fluorene Skeleton</u>.

The principal goal at the outset of the work described in this thesis was the development of a rational route to simple 4aH-fluorenes. This section therefore presents the results of a literature survey of synthetic routes to hydrofluorene derivatives intended to identify those which might best be modified and extended to produce 4aH-fluorenes.

i) <u>Robinson annulation of indanones</u>.

There are many examples of Robinson annulation of indan-1-ones in the literature;[68-74] an indan-1-one chromium tricarbonyl complex has also been annulated.[75] These reactions could provide access to the 4a blocked fluorene skeleton provided that a suitable group could subsequently be delivered 1,4 to the enone component of products such as (125), for example by reaction with lithium dimethyl cuprate (Scheme 33).

(55)   (125)
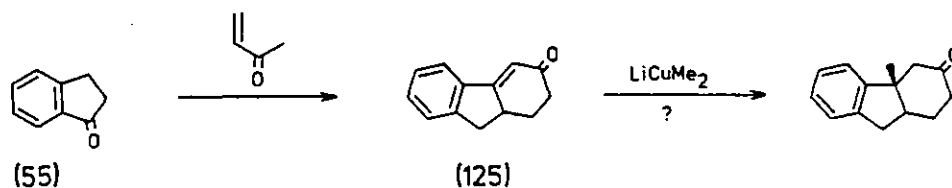
SCHEME 33

Robinson annulation of indan-2-one potentially provides more direct access to the 4a blocked fluorene skeleton, since the blocking group could, in principle, be present in the starting indanone. Such reactions of alkylated indan-2-ones are unknown, however, principally because there are scarcely any reports of suitable substrates. Precedent for Robinson annulation of other indan-2-ones exists, but is rare. Indan-2-one (126) itself has been annulated <u>via</u> its pyrrolidine

(126)   (128)

(127)
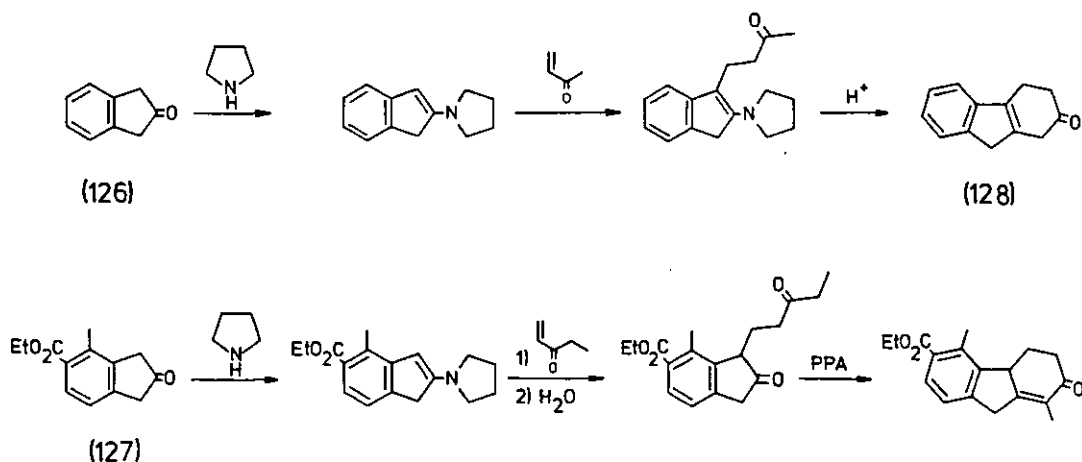
SCHEME 34

enamine,[76] as has 5-ethoxycarbonyl-4-methylindan-2-one (127)

(Scheme 34).[77]

The only indan-2-one to have been directly annulated is 1-ethoxy-carbonylindan-2-one (129).[78] In this case the selectivity observed is obviously due to activation of the 1-position by the ethoxycarbonyl group (Scheme 35).

(129)   17%   (128)
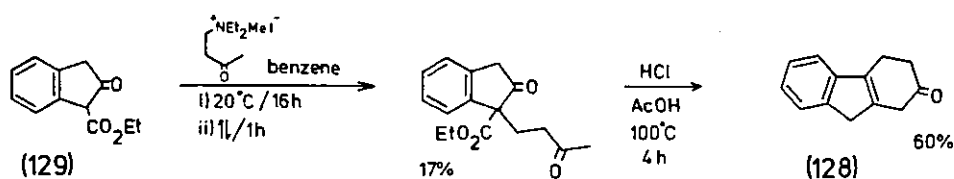
SCHEME 35

ii) Friedel Crafts cyclisations involving a phenyl group.

A variety of reactions are known in which a functionalised cyclohexane ring and a phenyl group interact to produce a hydrofluorene or hydrofluorenone. Usually these two components are joined in the starting material via a one atom bridge which becomes C_9 of the fluorene; in such cases it is the 4a-4b bond which is made on cyclisation. In
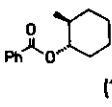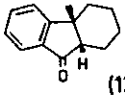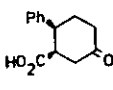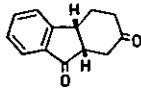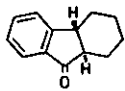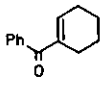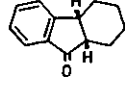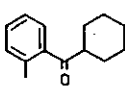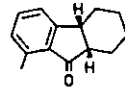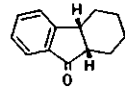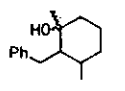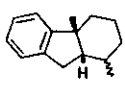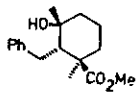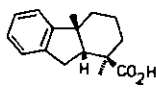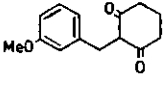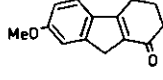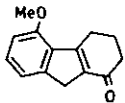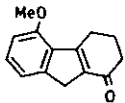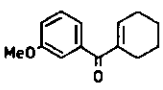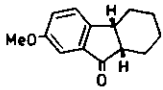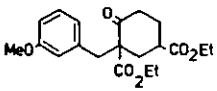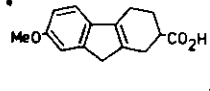
Substrate	Product	Reagent	Conditions	Yield	Ref.
(130)	(131)	PPA (91%)	$100^{\circ}C/0.5h$	64%	79
		PPA [a]	$80-85^{\circ}C/0.75h$	80%	80
		i) $SOCl_2$, then ii) $AlCl_3$	ii) $0^{\circ}C/1.5h$ then $25^{\circ}C/0.5h$	86%	81
		PPA	$100^{\circ}C/0.25h$	65%	82
		H_2SO_4	"steam bath" 0.1h	82%	83
$(PhCO)_2O$ +		PPA	$57^{\circ}C/0.5h$	41%	82
	[b]	PPA	$80^{\circ}C/1h$	80%	84
		PPA	$80-82^{\circ}C/1h$	50%[c]	85
		PPA	-	51% / 17%	86
		H_2SO_4	$60^{\circ}C/0.1h$	70-85%	87
		$HCl/AcOH/H_2O$	reflux 2h	47%	88

TABLE 3   a) PPA refers to commercial 82-85% material unless otherwise stated; b) 1:1 mixture of two isomers; c) after hydrolysis.

other cases the components are directly joined in the starting material, and either the 8a-9 or 9-9a bond is made on cyclisation. In still others, the components may be joined by a longer bridge which is partially lost on reaction, or they may not be joined at all; two bonds must then be made during cyclisation.

The cyclohexane component may be at various oxidation levels ranging from alcohols through enones to diones. Activation of the phenyl group by methoxy substituents is often present but is not vital. The most commonly used cyclising agent is polyphosphoric acid, but sulphuric acid, hydrochloric acid and aluminium chloride have also been used. Individual examples are summarised in Table 3.

A few of these reactions, especially the formation of compound (131) from the ester (130), could be directly incorporated into a 4aH-fluorene synthesis. Some of the others suggest simple extensions which would allow introduction of a 4a substituent into the product or the substrate, while the rest are not obviously applicable to the problem. The ready availability of 2-methylcyclohexyl benzoate (130) makes the first reaction far the most attractive in this group.

iii) Friedel Crafts cyclisations involving an indenyl group.

4-(Inden-3-yl)butanoic acid (134) and some of its derivatives have been cyclised to 2,3,4,9-tetrahydrofluoren-1-one (133) using a variety of cyclising agents. These reactions are summarised in Table 4; also shown is a cyclisation of 4-(indan-1-yl)butanoic acid (135) which, most surprisingly, gives (in part) the same product (133).

Tetrahydrofluorenones (125), (128) and (133) all have potential as substrates for 4aH-fluorene synthesis. Perhaps the most attractive is compound (133), since this combines a useful siting of the oxygen atom with the possibility of introducing a blocking group by 1,4
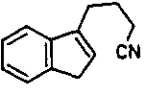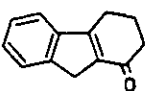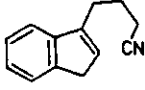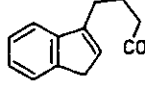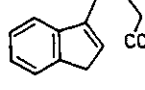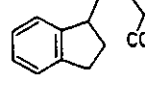
Substrate	Product	Cyclising Agent	Conditions	Yield	Ref.
(132)	(133)	PPA	120-130°C 0.5h	81.5%	89
CN	"	HCl/ZnCl$_2$/ Et$_2$O	20°C/2h then 0.25h	60%	90
(134) CO$_2$H	"	HF	20°C/overnight	67%	91
CO$_2$H	"	PCl$_5$	benzene 1.5h	45%	90
(135) CO$_2$H	"	PPA	90°C/1-2h	28%	92

TABLE 4

addition. Further, the reactions by which compound (133) is generated appear the most likely to bear extension to substrates already carrying blocking groups, given the ready availability of 1,3-dimethylindene (136) (see Page 82).
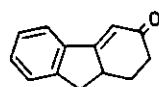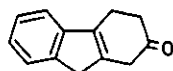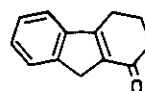
(125)   (128)   (133)   (136)

The only reported example of a blocked substrate undergoing a related reaction is the cyclisation of aldehyde (139), described by Field and Jones (Scheme 36).[93] Although this reaction produced the

very attractive 4aH-fluorene precursor (140), the substrate (139)

was itself the product of a long sequence of reactions, originally

necessary because compound (140) was required in an optically active

form. Nonetheless, if a shorter route to aldehyde (139) or some

similar molecule were available, such a cyclisation would become

most attractive. This point will be developed in Chapter Three.
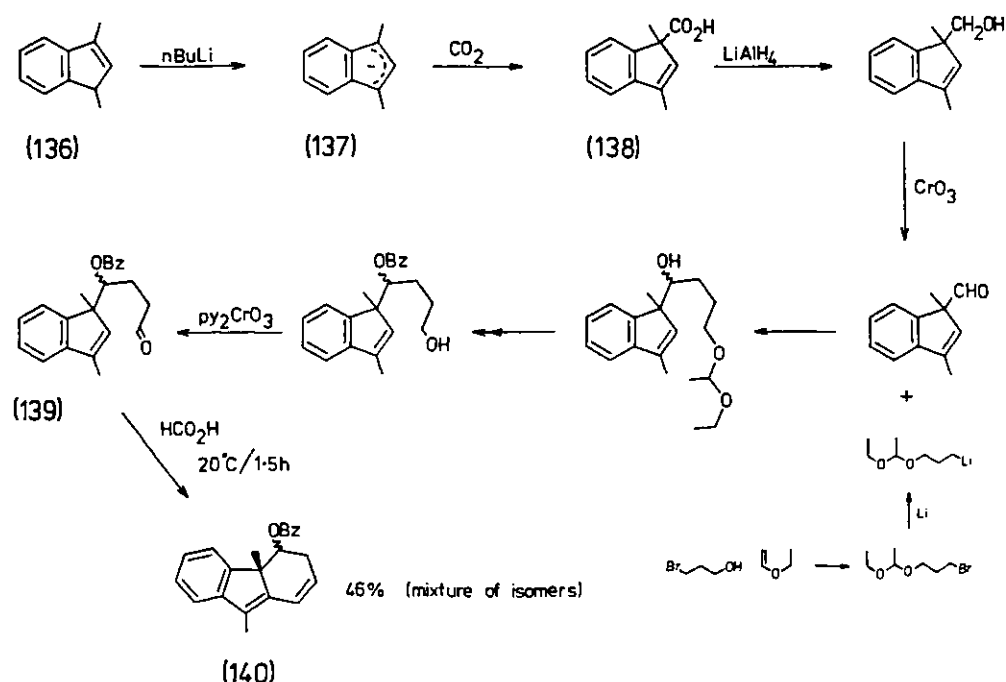
SCHEME 36

iv) Diels-Alder cyclisations.

Indene is known to undergo Diels-Alder reactions with many dienes,

including simple butadienes,[94] 1,1'-biscyclohexenyl (141a),[95] and

4,4'-dimethyl-1,1'-biscyclohexenyl (141b).[96] These are, however,

generally rather low yield reactions requiring forcing conditions.

The reaction may be made more facile if electron withdrawing

substituents are present. These may either be on the diene, in which

case the reaction is one with inverse electron demand, or on the indene,

in which case the reaction has normal electron demand. Examples of

27%

180°C
autoclave
16h

(146)

CO_2H
HO_2C (145)
neat 1l 75h

CO_2H
CO_2H

13%

R
R

(141) a)R=H
b)R=Me
a):80°C/20h

a) 35%

CO_2H
(144)
neat 1l 100h

CO_2H

24%

SO_2
(142)

(143)
neat 1l 48h
MeO OMe

CO_2H

4%

52%

(147)

CO_2Me
CO_2Me

180°C
autoclave
54h

H

MeO_2C CO_2Me

31%

(148)

O
O

180°C
autoclave
20h

O O

yield
not stated

(149)

CO_2Et
CO_2Et

benzene
1l 3h

CO_2Et
CO_2Et

70%

(136)

230-240°C
13h

16%

SCHEME 37
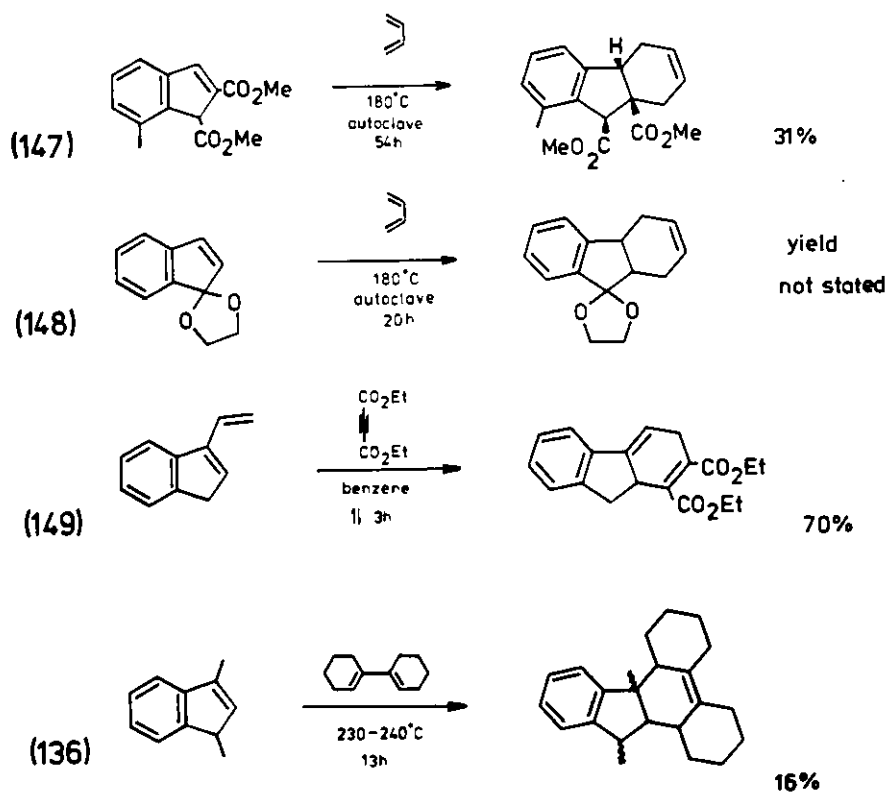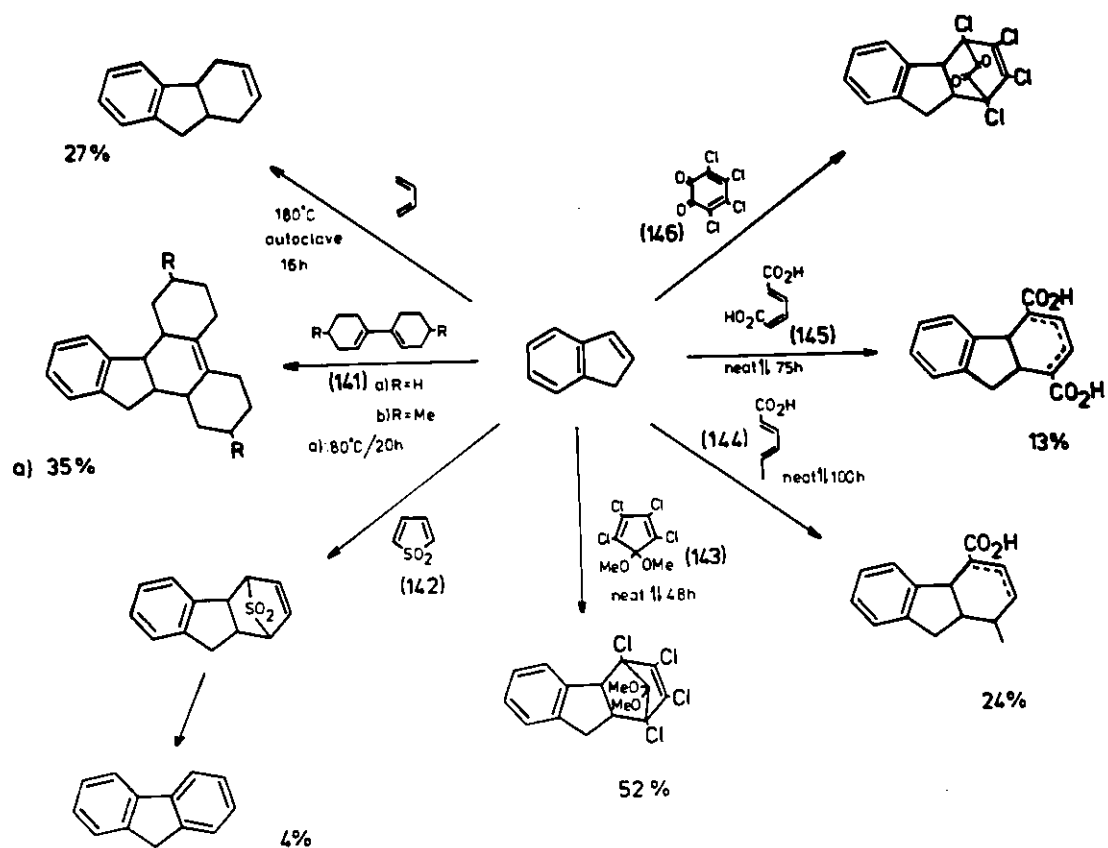
dienes used in the former approach are thiophene-1,1-dioxide (142),[97] 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (143),[98] sorbic acid (144),[99] muconic acid (145),[99] and 3,4,5,6-tetrachloro-1,2-benzoquinone (146);[100] most of these give highly substituted adducts, and many are prone to polymerise rather than react with indene.

The latter approach has been employed in the reaction of butadiene with 2-methoxycarbonylindenes such as 1,2-bismethoxycarbonyl-7-methyl-indene (147).[101] In addition, indenone ethylene ketal (148) has been used as a Diels-Alder component,[81b] while 3-vinylindene (149) has been used as a diene in a facile reaction with diethyl acetylene-dicarboxylate.[102] These reactions are summarised in Scheme 37.

The usefulness of most of these reactions for the synthesis of 4aH-fluorenes is limited by the high degree of substitution required, while the simpler cases are limited by their low yields and experimental inconvenience. The corresponding reactions of 3-methylindenes, which should give 4a-methyl substituted products, would be slower still, as evidenced by the relative slowness of the only reported Diels-Alder reaction of 1,3-dimethylindene (136) itself, that with 1,1'-biscyclo-hexenyl.[103]

v) Anionic cyclisations.

An interesting reaction complementary to the Friedel Crafts cyclisation of indenes mentioned previously is the ring closure of ethyl 4-(inden-2-yl)butanoate (150) by anionic intramolecular displacement (Scheme 38).[104]

(150)

NaH
Et₂O ||
2·5h

87·5%
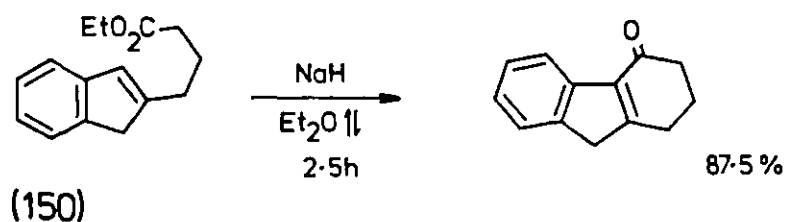
SCHEME 38

Superficially similar is the reaction of the indan-1-one derivative (151) (Scheme 39).[105]

(151)
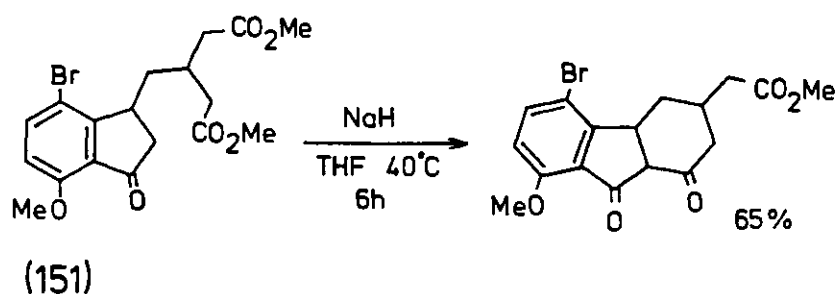
SCHEME 39

One further permutation (Scheme 40) is the culmination of an extremely laborious fabrication of the second 6-membered ring by successive ester condensations.[106]
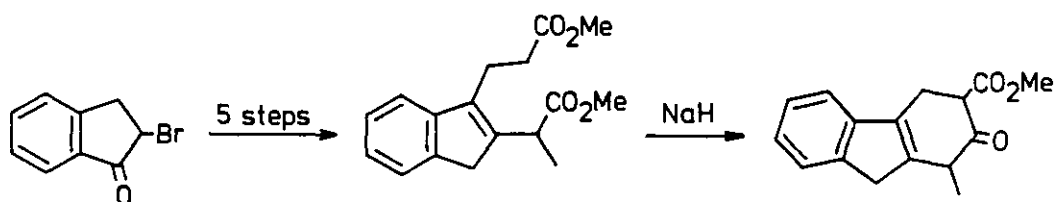
SCHEME 40

While these anionic reactions are all facile, their starting materials are not particularly accessible, nor are they particularly suited to elaboration to give 4a-methyl substituted products.

vi) Birch reduction of fluorene

According to one report, reductive methylation of fluorene with lithium metal in ammonia followed by methyl bromide yields 2,4a-dihydro-4a-methylfluorene (152).[107] Discussion of this reaction will be deferred until Chapter Three.
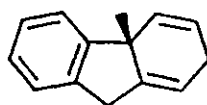
(152)

vii) 4a-Methylfluorenes from abietic acid

Abietic acid (153) is a cheap natural product isolated from pine rosin, and it is a source of the 1,4a-dimethylfluorene skeleton via the route shown in Scheme 41.[108,109]
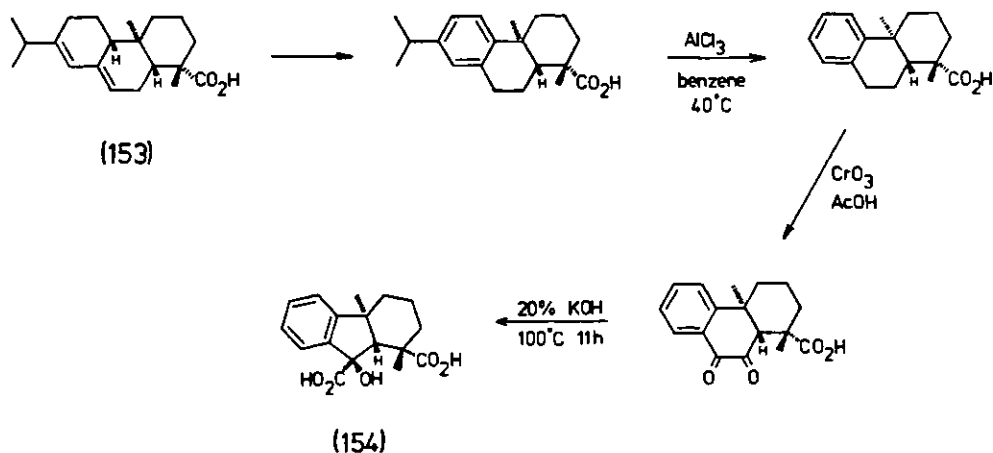
SCHEME 41

Diacid (154) is itself the starting point for a whole area of research into related hydrofluorenes, the importance of which lies in their varied modes of biological activity.[110] The sequence is also the basis of a commercial process, and is one source of gibberellins.[111] The large number of steps involved makes it uncompetitive for the synthesis of simple 4aH-fluorenes, however.

CHAPTER TWO

CHAPTER TWO: 4a-Methyl-1,3,9-triphenyl-4aH-fluorene.

In Chapter One, the somewhat surprising results of a study of ortho-blocked arylimidoylnitrenes were described.   It was proposed that most of their reactions proceeded via 3aH-benzimidazole intermediates, but the subsequent rearrangement of these species could not be easily rationalised.   The effort to understand these reactions better led to a wider study of 3aH-indene analogues, and the first stage of this was a search of the literature for reports of isolable compounds containing the 3aH-indene moiety or its analogues.

Very few such compounds were found.   A family of 3aH-indazoles (101), (104a-d) and (105) (Chapter One, Section 3 (ii)) were known, as was the bis-amide (120) (Chapter One, Section 3(v)).   A further report of a polyphenylated doubly-fused system (121) may well have been incorrect (Chapter One, Section 3(v)).

More significance, however, was attached to a series of papers concerning 4a-methyl-1,3,9-triphenyl-4aH-fluorene (119) and its derivatives.[112-116]   According to these, compound (119) was a stable, yellow, crystalline solid, isolated in low yield from the polyphosphoric acid induced self-condensation of acetophenone (Scheme 42).

SCHEME 42

(119)

15%
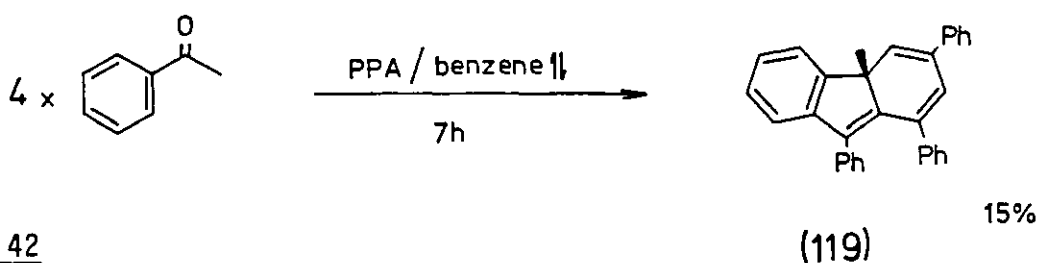
These reports suggested to us that the 4aH-fluorene system might be intrinsically more (kinetically) stable than the 3aH-indene system, due to the presence of the fused benzene ring: it was primarily this

possibility which prompted the present study of 4aH-fluorenes, and also
that of 4aH-carbazoles (Chapter One, Section 2(ii)).

The main purpose of the present work was thus to develop a synthesis
of simple 4aH-fluorenes (Chapters Three and Four) and to investigate
their chemistry (Chapter Five). Before attempting this, however, a
short study of 4a-methyl-1,3,9-triphenyl-4aH-fluorene (119) was undertaken.
In this chapter, the results of that study are presented, in conjunction
with a summary of the original work referred to above. For convenience,
compound (119) will be referred to as hydrocarbon "A"; this follows the
practice of other authors in this group and also of Snyder and coworkers
in their original papers.[112-116]

1) Structure.

Clearly, the most fundamental question concerning hydrocarbon "A"
was whether the proposed 4aH-fluorene structure (119) was correct.

Snyder established the molecular formula as $C_{32}H_{24}$ using
microanalysis and molecular weight determinations. His first step in
limiting the possible isomers of this formula was to rule out structures
containing condensed aromatic nuclei or lacking conjugated aliphatic
double bonds, on the grounds that these were not compatible with the
high reactivity (Section 3) and uv spectrum of hydrocarbon "A".

Treatment of hydrocarbon "A" with a mixture of hydrobromic and
acetic acids transformed it cleanly into an isomer, referred to by
Snyder as hydrocarbon "D". The chemical properties, uv and nmr spectra
of this substance strongly suggested that it was a methyltriphenyl-9H-
fluorene, which led Snyder to propose that hydrocarbon "A" itself was
a fluorene derivative in which the aromaticity of one ring was blocked
by a substituent. He suggested four possible structures; 1H-fluorene

(155), 3H-fluorene (156), and the two 4aH-fluorenes (157) and (119).

Structure (157) was discounted on the grounds that the nmr spectrum of

hydrocarbon "A" showed the methyl group probably not to be vinylic

(δ 1.71), while structure (156) was ruled out since it would not be

expected to form a monoadduct with maleic anhydride, as hydrocarbon "A"

was known to do (Section 3).

(155)   (156)   (157)   (119)
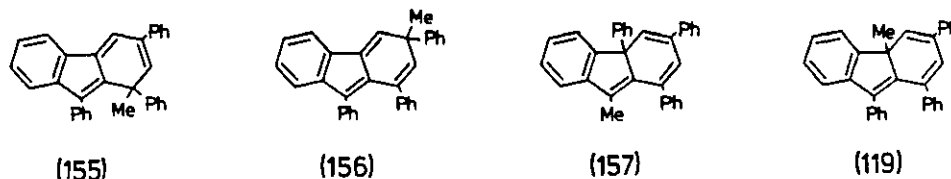
It now remained to distinguish between structures (155) and (119).

In the original paper, Snyder left this issue unsettled, although he did

present some rather contorted mechanistic speculation on the formation of

hydrocarbon "A", which he claimed supported the 4aH-fluorene structure

(119) (Section 2).[112]   In a later paper, however, he presented more

concrete evidence in that he established the structure of hydrocarbon "D"

(the rearrangement product of hydrocarbon "A") to be 4-methyl-1,3,9-

triphenyl-9H-fluorene (158).[113]   The all-important position of the methyl

group was proved by conversion of the fluorene into a phenanthridine by

oxidation followed by treatment with hydrazoic acid.   Comparison of the

nmr spectra of products (159) and (160) with those of model compounds,

particularly 2,4,6-triphenylphenanthridine (161), showed that, in each

product, only one of the bay positions (9 or 10) was occupied by a proton,

leading to the conclusion that the methyl group occupied the other

(Scheme 43).

While this convincingly established the position of the methyl group

in hydrocarbon "D" (158), Snyder's assignment of the structure of hydro-

carbon "A" rested wholly on his assertion that structure (119) was the

only possible precursor of structure (158) under the reaction conditions.

This seemed to us to be less than certain.   It is possible that structure
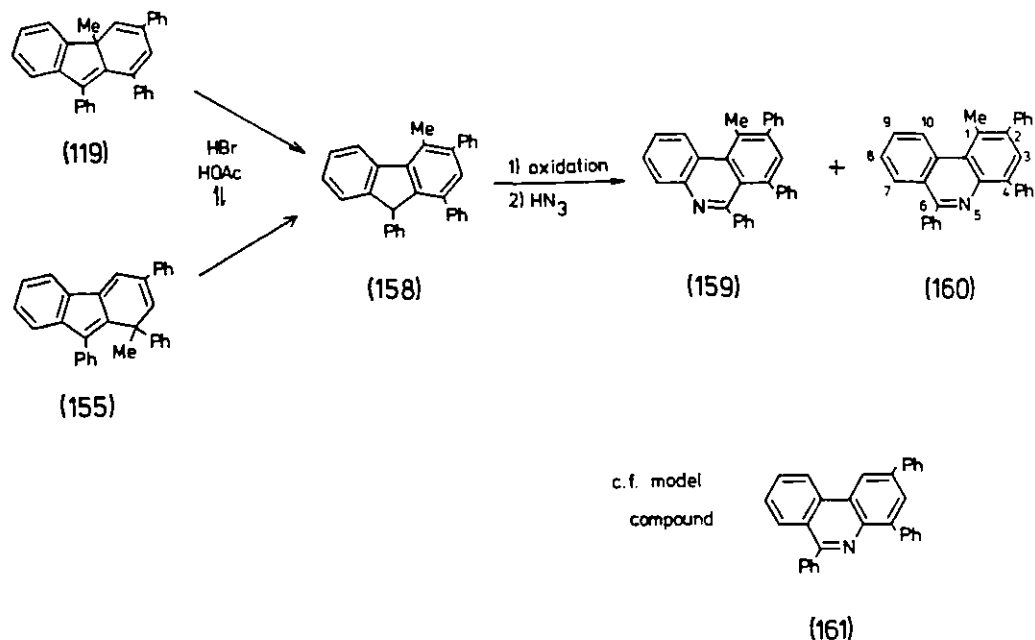
SCHEME 43

(158) might be the product of thermodynamic control, since the alternative product (162) would presumably be more sterically crowded. Further, structure (156) could also give rise to either of the possible products (158) and (162), and had only been discounted originally since it was thought impossible that it could form a monoadduct in Diels-Alder reactions.

For these reasons we undertook our own structural investigation of hydrocarbon "A". To emphasise the subtlety of the problem it may be pointed out that, if carbon-carbon connectivity alone is considered, the two most likely structures (119) and (155) may formally be interconverted

(119)   (155)
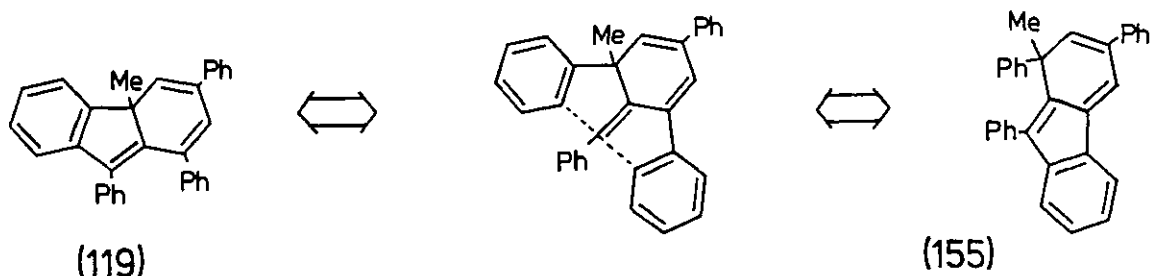
SCHEME 44

simply by exchanging two C-C connections (Scheme 44).

Chemical methods would clearly be severely taxed in resolving this problem; nonetheless, some attempt was made to use them. Oxidative degradation gave no useful results, but it was thought that a study of hydrogenated derivatives of hydrocarbon "A" might elucidate its structure, since it was hoped that the chemical and nmr properties of the various methine protons of the tetrahydro and hexahydro species might prove diagnostic (Scheme 45).

(119)

(155)
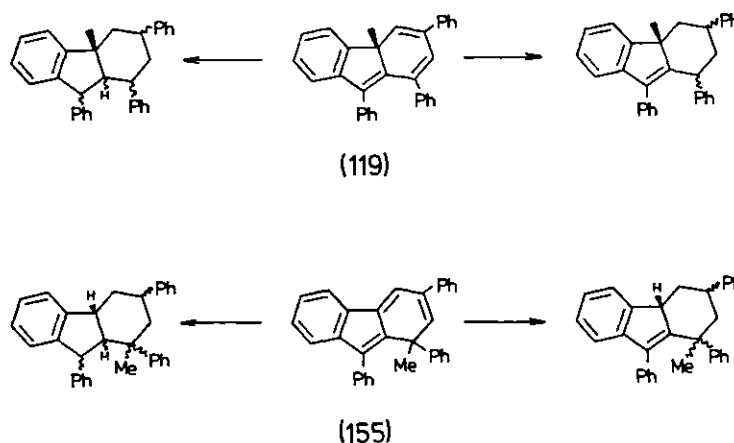
SCHEME 45

Snyder described preparations of dihydro, tetrahydro and hexahydro derivatives.[112] According to these reports, reduction of hydrocarbon "A" with lithium aluminium hydride or hydriodic acid gave a dihydro derivative, high pressure hydrogenation over Raney nickel gave a tetrahydro derivative, and reduction with sodium in liquid ammonia gave a hexahydro derivative.
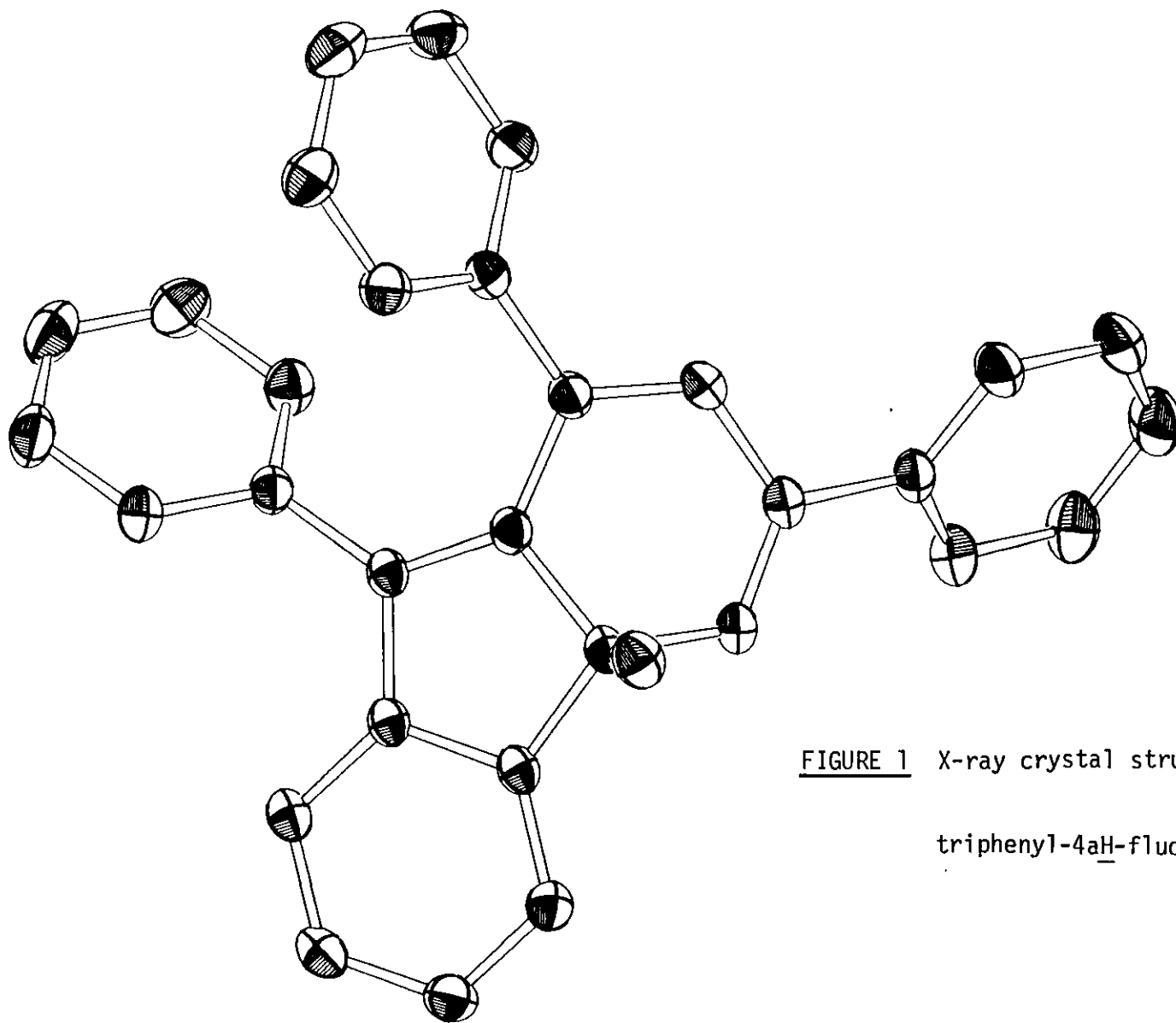
FIGURE 1 X-ray crystal structure of 4a-methyl-1,3,9-

triphenyl-4a_H_-fluorene (119).

The homogeneity of these products was not specified, however, and it seems likely that, even if the regioselectivity was complete, each reaction would generate more than one diastereomer. The hexahydro material in particular was noted to be very reluctant to crystallise, and probably contained many of the sixteen possible diastereomers.

Our attempts to avoid Snyder's rather inconvenient preparation of the tetrahydro derivative led only to the discovery that hydrogenation of hydrocarbon "A" at atmospheric pressure over palladium yielded a dihydro derivative. The stereochemical complexity of even this relatively simple reaction, although it was eventually unravelled (Section 3), caused us to abandon our planned investigation of the other reduced derivatives.

In view of the obvious difficulties in establishing the structure of hydrocarbon "A" by chemical means, a sample was submitted for X-ray crystallographic analysis. This showed directly that the 4a$\underline{H}$-fluorene structure (119) was indeed correct, and revealed several interesting features of its conformation (Figures 1 and 2).[117]

As in the calculated structure of 3a-methyl-3a$\underline{H}$-indene (118) (Chapter One, Section 3(iv)), the 3a$\underline{H}$-indene moiety of hydrocarbon "A" (C_1-C_{4b}, C_{8a}-C_{9a}) appeared to consist of two substantially independent diene fragments with a large dihedral angle between their (approximate) planes (torsion angle C_2, C_1, C_{9a}, C_{4a} = 30.0°). The sp^3 atom was, again, almost perfectly tetrahedral, while the five-membered ring was, as expected, almost perfectly coplanar with the fused benzo substituent. The phenyl groups at C_1 and C_9 were forced out of planarity with their respective diene fragments, presumably by steric congestion; that at C_3 was also twisted, though in this case packing forces may well be responsible. Such a conformation presumably results in reduced conjugative interaction between the 3- and 9- phenyl groups and the 4a$\underline{H}$-fluorene moiety, and also between the 1$\underline{H}$-indene moiety (C_{4a}-C_{9a})
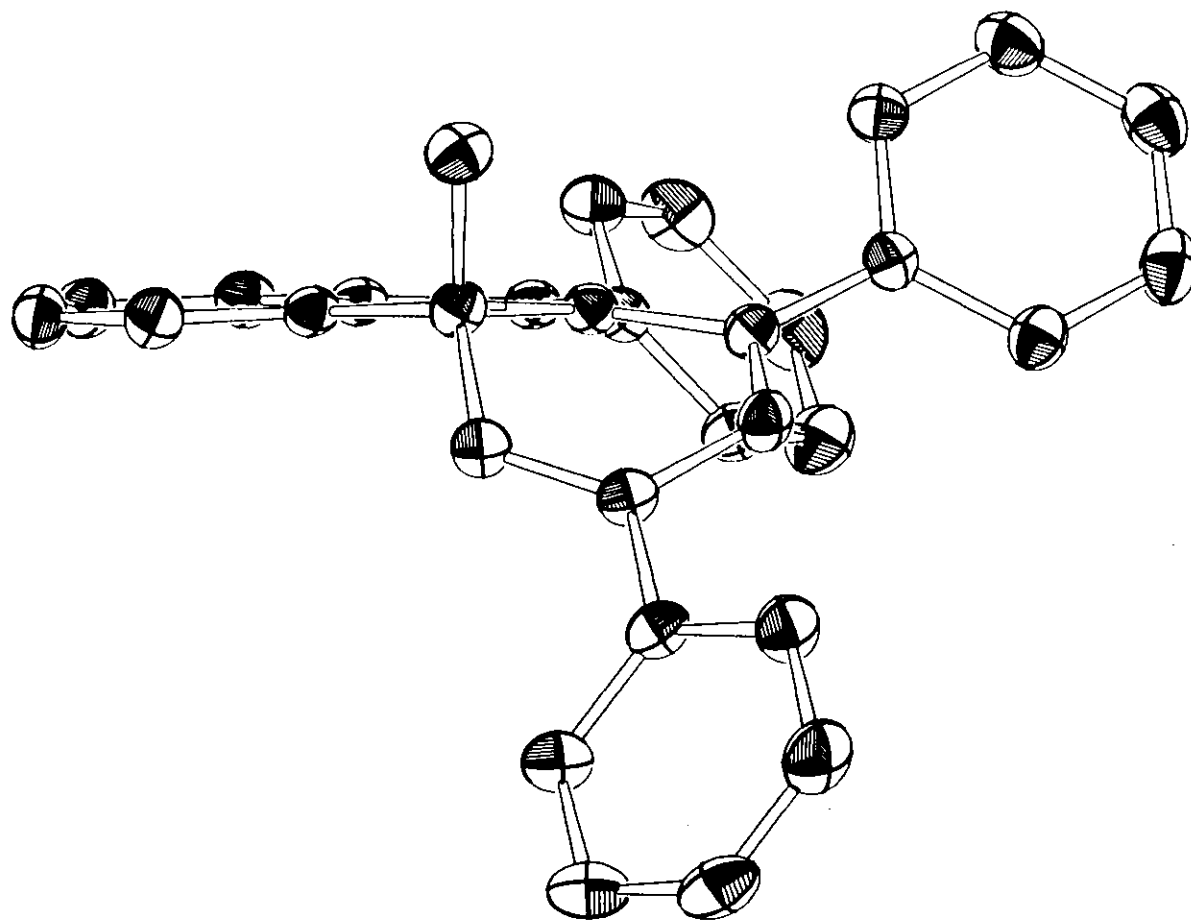
FIGURE 2 X-ray crystal structure of 4a-methyl-1,3,9-triphenyl-4aH-fluorene (119).

and the remaining diene fragment (C_1-C_4). Some twisting within this diene fragment was also found (torsion angle C_1, C_2, C_3, $C_4 = 17.4°$).
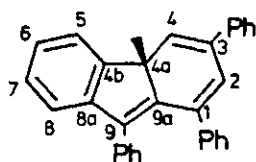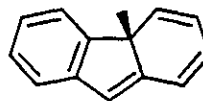
(119)   (3)

Calculations for 4a-methyl-4aH-fluorene (3), using the MNDO method, were also undertaken. The predicted geometry of this molecule matched the experimentally determined conformation of the 4aH-fluorene moiety in hydrocarbon "A" very closely.[64]

In summary, these results suggest that, structurally, the 4aH-fluorene system may best be regarded as a 1H-indene moiety imperfectly conjugated with a diene fragment.

2) Formation.

The formation of hydrocarbon "A" is obviously a very complicated reaction, and it is unlikely that a single mechanism operates or even predominates. Some important features may be deduced, however.

Obviously, four molecules of acetophenone must condense to form the final product. The first such condensation must be the formation of dypnone (163), but immediately there is an ambiguity. The next condensation might combine the enol of dypnone and the keto-form of acetophenone to give the dienone (164), or, conversely, the enol of acetophenone might react with the keto-form of dypnone. Although this latter process could involve a direct attack on the carbonyl group of

dypnone to yield the same product as before, Michael attack leading to the alternative trimer (165) is also a possibility. If all the possible modes of condensation are considered, three acyclic trimers (164)-(166) and five acyclic tetramers (167)-(171) of acetophenone are possible, assuming that dehydration always occurs to give maximum conjugation (Scheme 46; geometrical isomerism is depicted arbitrarily throughout). Some of the tetramers might also be formed by the self-condensation of dypnone (163).
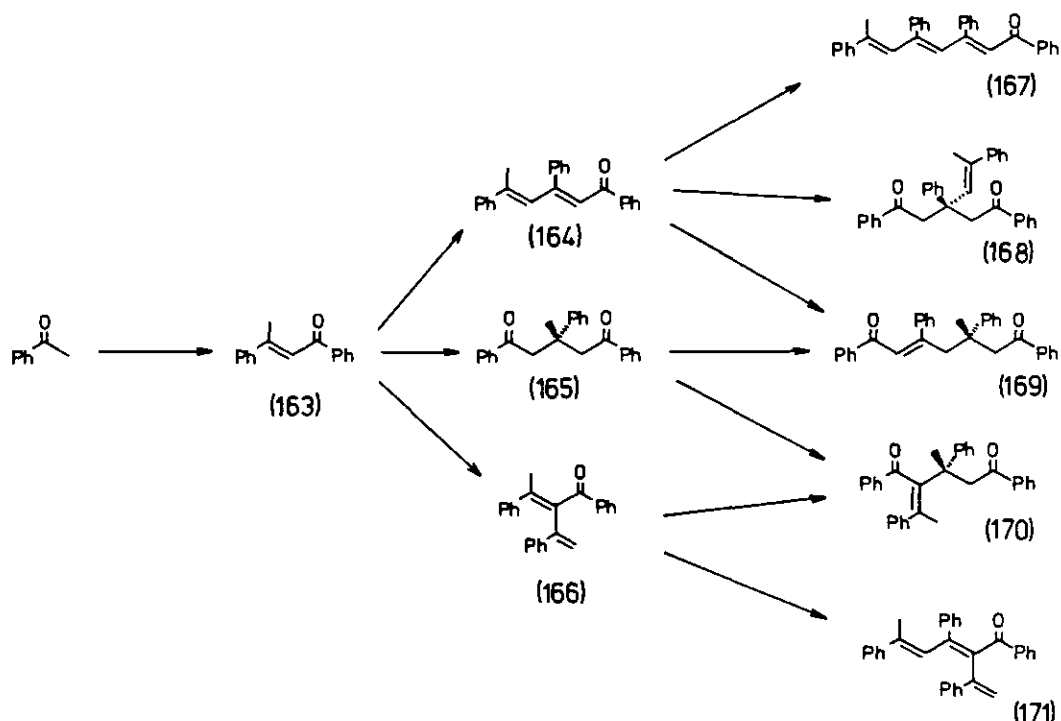
SCHEME 46

It is important to note that the structure of the final product is determined by which of these condensations occur; only trimers (164) and (165) or tetramer (169) possess the correct connectivity to give rise to hydrocarbon "A".

In addition to the condensation reactions, two rings must be formed during the overall reaction, and two closely related Friedel Crafts cyclisations are most probably responsible for this. The five membered ring is almost certainly formed first, by the interaction of a carbonyl group
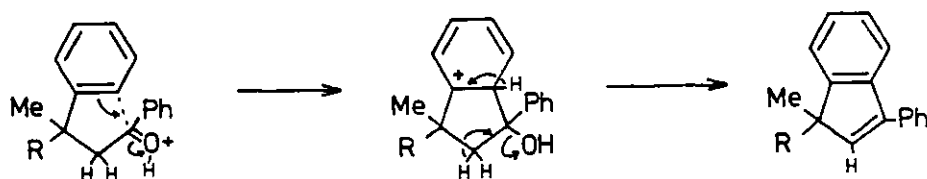
SCHEME 47

with a β phenyl substituent (Scheme 47).

The resultant indene, either immediately or after intermediate steps, then takes part in a further interaction with a carbonyl group in the side chain (Scheme 48).
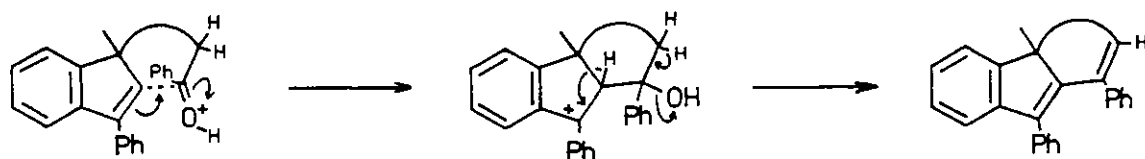
SCHEME 48

These processes are, of course, examples of the reactions previously considered for synthesis of the fluorene skeleton (Chapter One, Sections 4(ii) and 4(iii)).

A combination of these condensation and cyclisation processes leads to the overall sequence shown in Scheme 49. The apparent simplicity of this sequence is misleading, since only those reactions which can lead directly to hydrocarbon "A" are shown, and the intermediates are all depicted arbitrarily in their unprotonated forms. Many other reactions presumably compete at each stage, and a variety of other products may be expected.

Given the large number of alternative processes possible, one may reasonably ask why hydrocarbon "A" should be isolated in a yield as

(165)

PhAc

PhAc

PhAc

Ph

(163)

PhAc

PhAc

(169)

PhAc

Ph

(164)

(119)
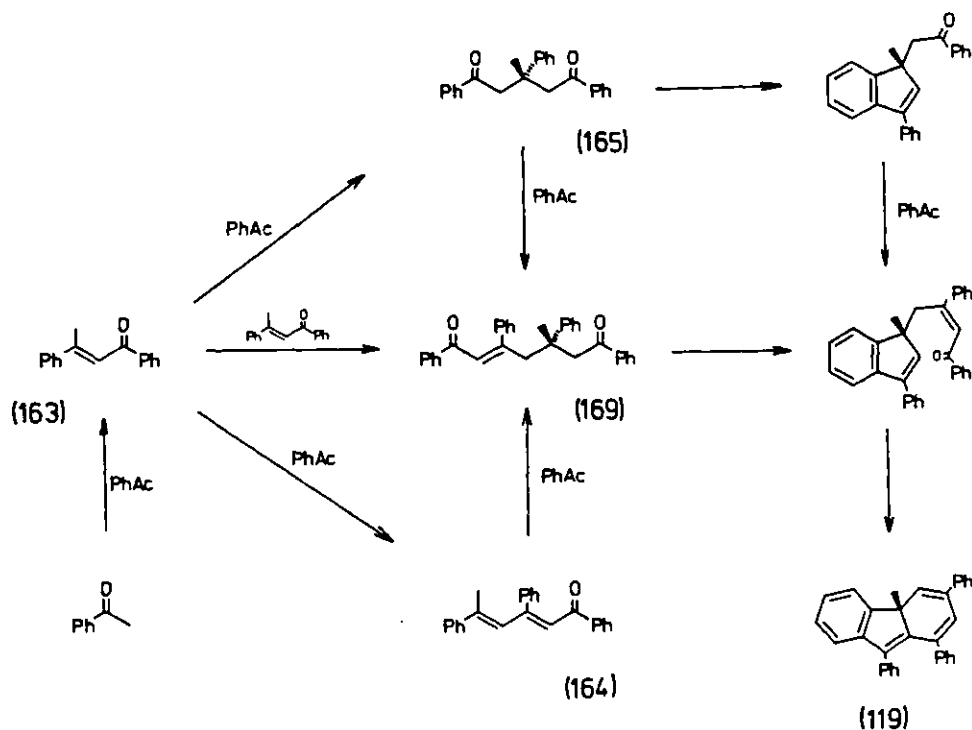
SCHEME 49

high as 15%. The most probable answer is that hydrocarbon "A" itself is not the true reaction product; rather it is its conjugate acid which accumulates in the reaction medium. Snyder's experiments showed that carbonium ion (172) is very highly stabilised, and may be isolated as its perchlorate, fluoroborate or even bromide salts.[114] The beautiful dark green colour of the polyphosphoric acid phase of the reaction mixture, which forms within minutes and persists until quenching, is most probably due to this species. Similar dark green solutions may be reversibly generated by dissolving hydrocarbon "A" in other strong acids, and a blank experiment showed that hydrocarbon "A" could be recovered quantitatively after treatment with polyphosphoric acid and refluxing benzene for 7h. The acidity of hydrocarbon "A" is so great that protonation even occurs on silica tlc plates, which develop a green spot on exposure to air if the hydrocarbon is present.

It is probable, therefore, that the carbonium ion (172) is the

product of thermodynamic control. In this context it may be noted that, of all the possible structures considered for hydrocarbon "A", only structure (119) can (at least formally) involve all the phenyl substituents in conjugative stabilisation of its conjugate acid.

(172)
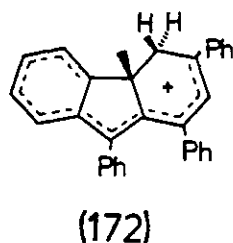
Brief mention should also be made of the other reaction products. Snyder only identified two of these, namely benzoic acid and dypnone (163), but he also claimed to have isolated two other pure materials, a higher-melting isomer of hydrocarbon "A" (referred to as "B") and an almost totally insoluble amorphous yellow substance (referred to as "C").[112] Isolation of the benzoic acid and "C" was trivial, while hydrocarbon "A" could, most conveniently, be precipitated in an almost pure state from a solution of the other products in benzene by trituration with petroleum ether. The separation of the remaining products was difficult, however. Snyder makes only passing reference to hydrocarbon "B", which he seems to have obtained in unspecified yield by combining material from many experiments.

On repeating Snyder's procedure, we obtained a similar yield of hydrocarbon "A" (16.5%), but nmr showed that the remaining mixture was very complex. The major materials present were acetophenone and dypnone (∿ 2:1), both of which could be removed on a small scale by washing with sulphuric acid, but the nmr spectrum of the residual material still showed at least six methyl groups resonating in the range 1-2 δ. Attempted concentration of the bulk material by distilling out the dypnone and

acetophenone at reduced pressure led to extensive resinification.

In another experiment, Snyder treated the cyclohexenol (173) with polyphosphoric acid and refluxing benzene, and found that it was apparently transformed entirely into substance "C".[112] The failure of this reaction to produce any hydrocarbon "A" is strange, and implies that formation of compound (173) by intramolecular aldol condensation of tetramer (169), although plausible, cannot be on the pathway to hydrocarbon "A" (Scheme 50).
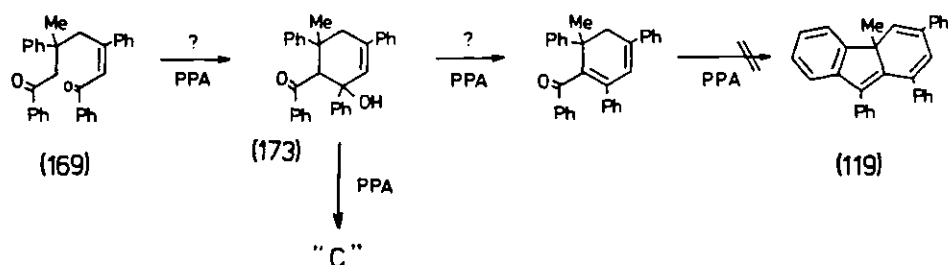
SCHEME 50

Snyder took this argument much further. He suggested that the isolation of "C" from the original acetophenone experiments indicated the intermediacy of cyclohexenol (173), and that this in turn probably arose from tetramer (169). Having thus implicated tetramer (169), he then suggested that it was also the precursor of hydrocarbon "A", so effectively assigning structure (119) to the latter.

Although this conclusion proved to be correct, none of the suggestions which led to it is necessarily true. The involvement of substance "C" in this reasoning is particularly unconvincing. It seems far from certain that the substance into which cyclohexanol (173) was transformed was genuinely identical to "C" as isolated from the acetophenone

experiments; this identity was only checked by ir spectroscopy.

Snyder does not comment on the nature of substance "C", which remains somewhat mysterious. It is a yellow solid (m.p. > 300°C), soluble in sulphuric or trifluoroacetic acids. Contrary to Snyder's implication that "C" is closely related to cyclohexanol (173), however, we found that its nmr spectra in CF_3CO_2H solution showed a fairly simple pattern of downfield aromatic protons only (δ 7.7-8.7), eleven ^{13}C resonances, all in the sp^2 region, and two broad ^{31}P resonances, both very close to δ 0 (referenced to H_3PO_4). It seems likely, therefore, that "C" exists in these solutions as a relatively simple ionic phosphate, or mixture of phosphates.

3) Chemistry.

i) Previous work.

Snyder's investigation of the chemistry of hydrocarbon "A" was mainly concerned with its ionic reactions. These were all dominated by the ability of the molecule to stabilise greatly a charge induced at C_3; the most obvious example, protonation, has already been mentioned (Section 2). In a separate paper, Snyder demonstrated that interconversion of hydrocarbon "A" (119) and carbonium ion (172) was a stereospecific process, the proton gained or lost being always on the face opposite to the methyl group, while the original proton at C_4 took no part in exchange.[114] In contrast, attack by other electrophiles was usually followed by loss of H_4, so that the overall reaction was one of substitution at C_4. Such reactions included bromination, chlorination, nitration and formylation (Scheme 51).[115]
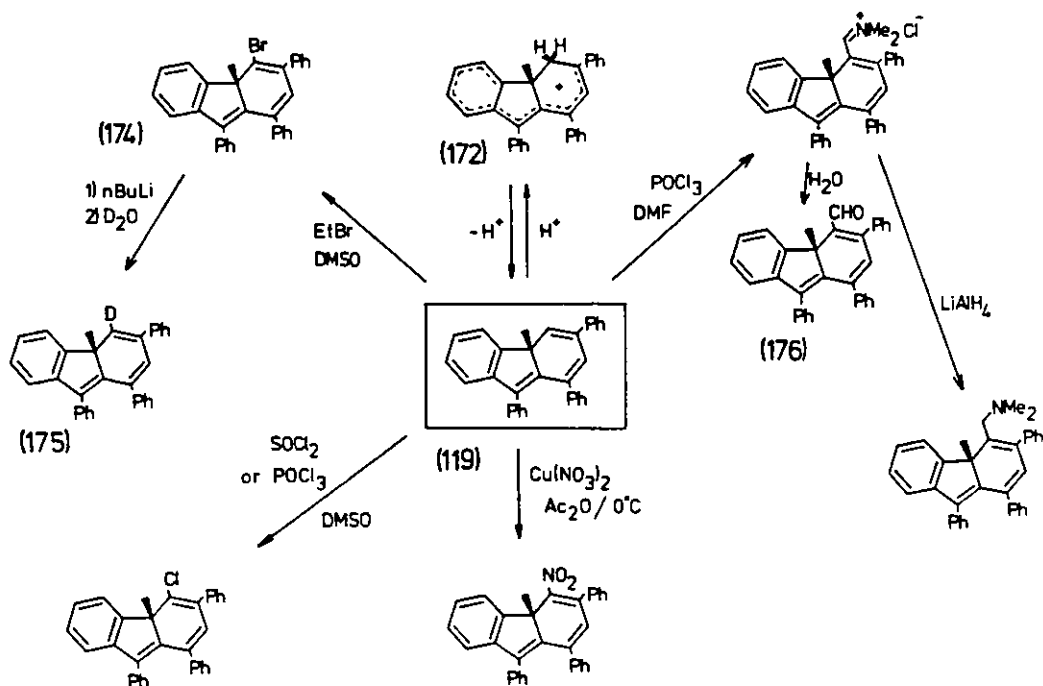
SCHEME 51

Snyder established the position of the deuterium atom in compound (175) by treating it with a mixture of hydrobromic and acetic acids. Since the product, previously identified as 4-methyl-1,3,9-triphenyl-9H-fluorene (158) (Section 1), had lost almost exactly one atom of deuterium during reaction, it was concluded that the deuteron must originally have been present at the site (C_4) to which the methyl group subsequently migrated. He then used this result to demonstrate the site of substitution in the other reactions, by showing that the 4-deutero-4aH-fluorene (175) similarly lost one atom of deuterium on either bromination or formylation. The reagents employed for the bromination and chlorination reactions emphasise the great reactivity of hydrocarbon "A"; in the former case this was the first example of bromination of a hydrocarbon under such conditions.

Snyder also treated hydrocarbon "A" with nucleophiles and found

it to behave analogously .[116]   On treatment with sodium cyanide in

dimethylsulphoxide or dimethylformamide, the dark green cyanocarbanion

(177) was formed.   Oxidation by air then led to isolation of the

substitution product (178), whereas quenching of the carbanion in the

absence of air allowed isolation of the addition product (179).   A

similar carbanion (180) was suggested to be present in the dark green

solution generated by addition of sodium methoxide to solutions of

hydrocarbon "A" in dipolar aprotic solvents (Scheme 52).   Treatment

of hydrocarbon "A" with n-butyllithium gave a butylated carbanion

which was quenched with solid carbon dioxide to give a carboxylic acid,

further characterised as its methyl ester.   Although the site of

attack by the butyl anion was presumably C_4, Snyder did not establish

either this or the site of carbonation experimentally.
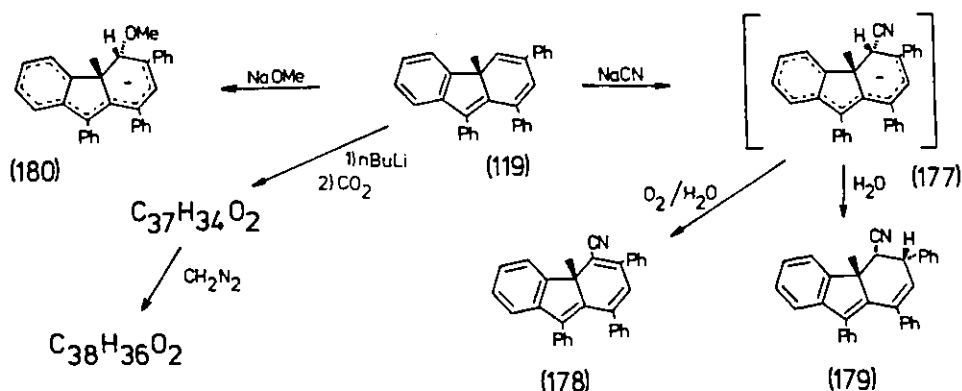
SCHEME 52

The acid-catalysed rearrangement of hydrocarbon "A" to give

9H-fluorene (158) has already been mentioned (Section 1).   Interest-

ingly, although Snyder found that the transformation was essentially

complete within 2h in a refluxing mixture of hydrobromic and acetic

acids, he found also that other reagents of comparable acidity

completely failed to bring it about;   such reagents included poly-

phosphoric acid, aluminium chloride and mixtures of sulphuric or hydrochloric acids in acetic acid.[112] The product (158) could be oxidised to the corresponding 9-fluorenol (181) using potassium permanganate, or N-bromosuccinimide followed by base hydrolysis. Alternatively, treatment of hydrocarbon "A" with hydrobromic acid in dimethylsulphoxide combined both transformations, yielding the 9-fluorenol (181) directly (Scheme 53).[113]

Snyder also investigated the rearrangement of the 4-substituted 4aH-fluorenes (174) and (176), which he found gave rise to the 9H-fluorene (158) on treatment with the hydrobromic-acetic acid reagent. He suggested that both these reactions proceded via initial formation of hydrocarbon "A" (119) from the protonated substrate, the former case involving loss of a positive bromine species while the latter involved loss of carbon monoxide (Scheme 53).[115]
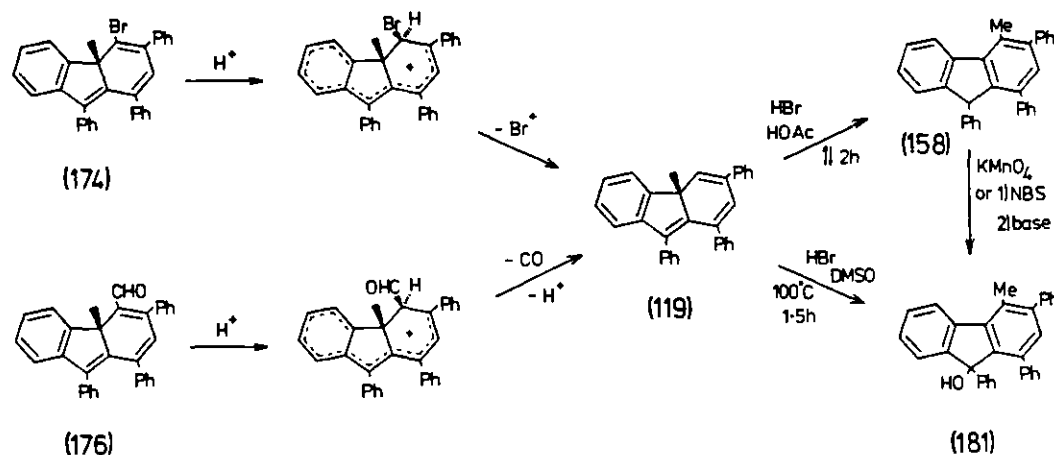
SCHEME 53

Cycloaddition and oxidation reactions were only touched on in Snyder's papers.[112] Reaction with maleic anhydride gave a monoadduct under normal conditions (reflux in benzene for 3h) or a tetraadduct under forcing conditions (160°C for 3h in the melt). The structures of these products were not elucidated, but he noted that the monoadduct readily reverted to starting materials on mild heating. Oxidation of

hydrocarbon "A" with refluxing dilute nitric acid for 4 days gave

benzoic and 4-nitrobenzoic acids together with an intractable oil,

while oxidation with chromic anhydride in refluxing acetic acid for

0.3h gave an unidentified acidic fraction mixed with a small amount

of unidentified, high melting, neutral material. Snyder also noted

that hydrocarbon "A" decolourised solutions of bromine or potassium

permanganate. The only other reactions he described were the various

reductions leading to the di-, tetra- and hexahydro derivatives already

mentioned (Section 1).

ii) Oxidation and Reduction.

Our own interest in hydrocarbon "A" was largely concerned with

its rearrangement reactions, but, as already mentioned, we also briefly

investigated its oxidation and reduction. Oxidation with the

Lemieux-Rudloff reagent[118] (sodium periodate and a catalytic amount of

potassium permanganate) was hampered by the difficulty of finding a

solvent system capable of holding both substrate and reagents simul-

taneously in solution without itself consuming the potassium permanga-

nate. Carefully purified aqueous sulpholane was found to meet these

requirements, but, although hydrocarbon "A" was fully consumed, none

of the products could be identified.

Catalytic hydrogenation at atmospheric pressure of a methanolic

solution of hydrocarbon "A" over palladium on charcoal gave a mixture

of two compounds, identified (below) as the two diastereomers of

4,4a-dihydro-4a-methyl-1,3,9-triphenyl-3H-fluorene, (182) and (183),

present in a ratio of $\sim$ 1:2. Compound (182) could be isolated by

washing the mixture with boiling ethanol, which selectively leached

out compound (183). Although the filtrate did not furnish a pure

sample of the other diastereomer (183), such a sample was obtained

on one occasion by slow crystallisation of the crude hydrogenation

product followed by mechanical separation of the larger crystals of compound (183) from the powdery crystals of compound (182).

The melting point (185-186°C) of compound (182), when pure, was identical to that of Snyder's dihydro derivative, prepared by reaction of hydrocarbon "A" with lithium aluminium hydride. We suspected, however, that there was no genuine diastereomeric selectivity during his reaction, since the work-up he described involved a wash with boiling ethanol, and on repeating his procedure we found, as expected, that compounds (182) and (183) were formed in approximately equal amounts. The diastereomeric selectivity shown during catalytic hydrogenation is presumably due to a more hindered approach to the catalytic surface when hydrocarbon "A" is in the orientation required to produce compound (182), while the failure of the reaction to produce more completely hydrogenated derivatives is probably due to steric hinderance from the C_1 and C_9 phenyl groups, which are severely twisted (Section 1).
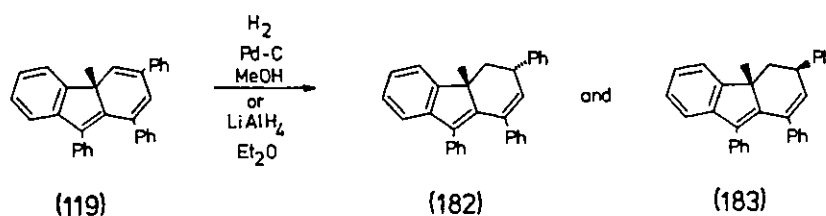
SCHEME 54

The structural assignments for these dihydro derivatives relied on an interpretation of their nmr spectra; spectral parameters for the non-aromatic protons of compounds (182) and (183) are shown in Tables 5 and 6 respectively. The pattern of coupling connectivities revealed by these data is clearly inconsistent with any regioisomeric structures derivable from hydrocarbon "A", this conclusion being supported by n.O.e. difference experiments (Figures 3 and 4; see Chapter Six for a more general discussion of the technique) which showed strong enhance-
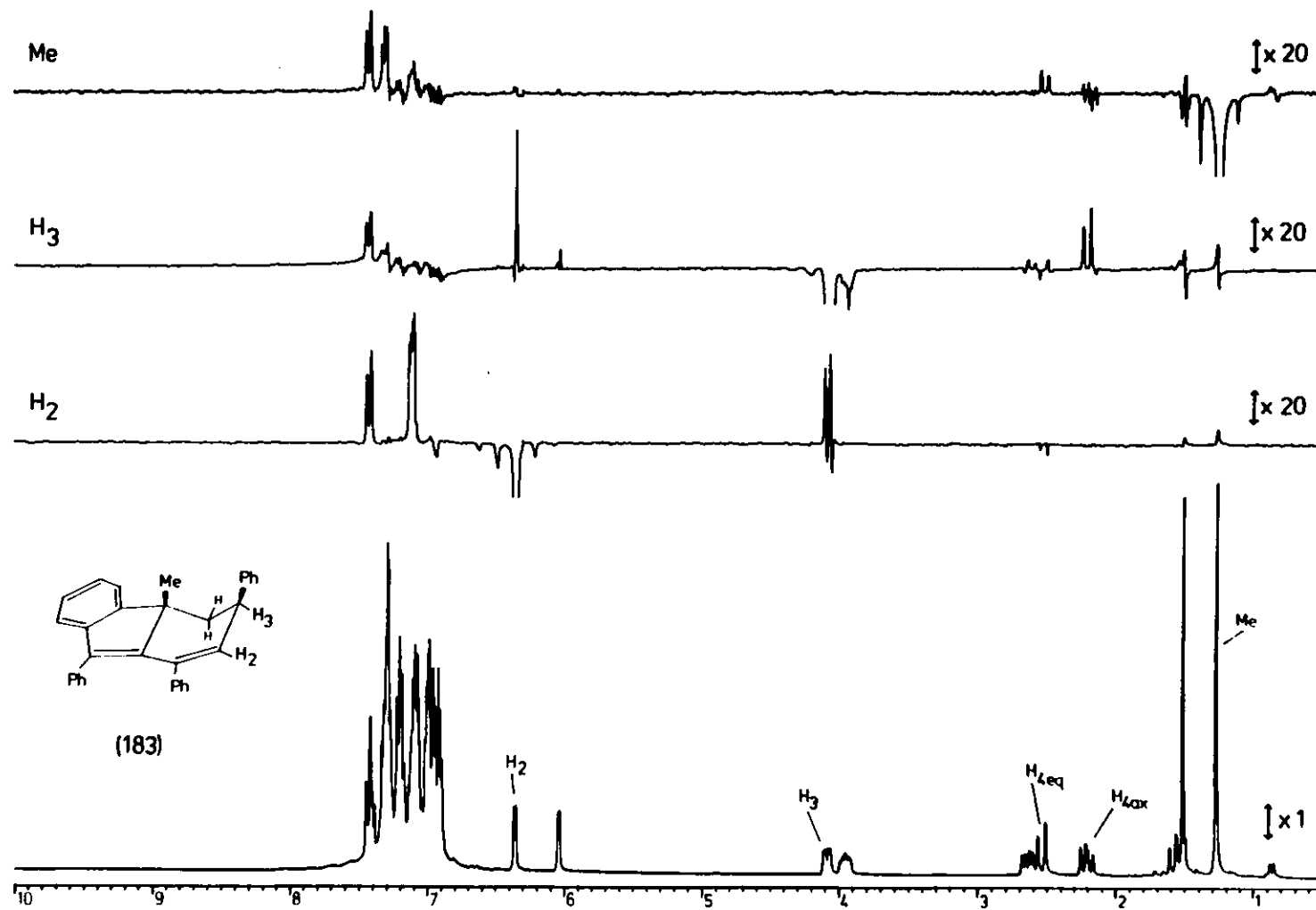
FIGURE 4 N.O.e. difference spectra of 4,4a-dihydro-4aβ-methyl-1,3β,9-triphenyl-3H-fluorene (183).
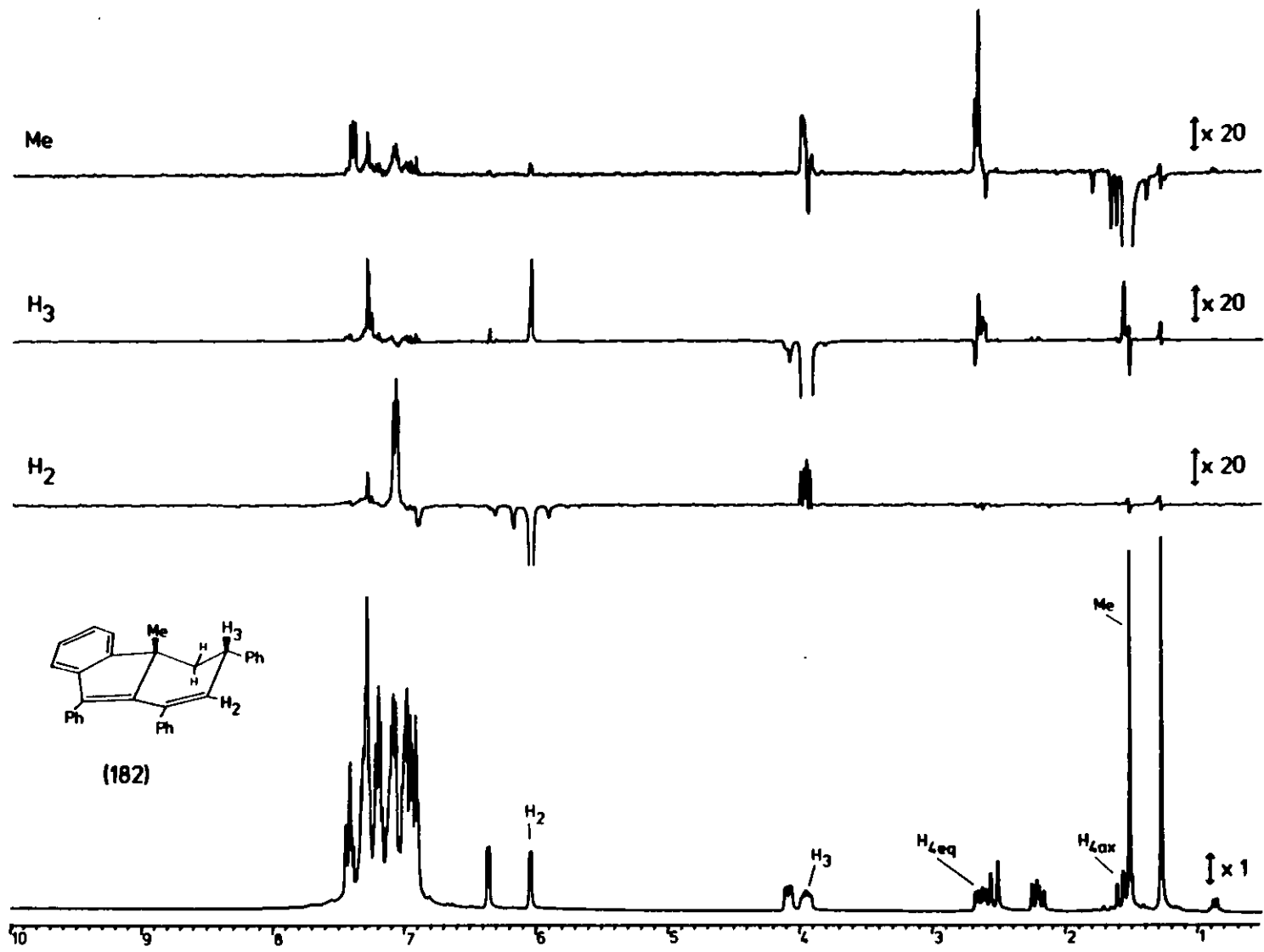
FIGURE 3 N.O.e. difference spectra of 4,4a-dihydro-4aβ-methyl-1,3α,9-triphenyl-3H-fluorene (182).

73

ments of $H_{4eq.}$ and H_2 on pre-irradiation of H_3 in compound (182)

(Figure 3), and of $H_{4ax.}$ and H_2 on pre-irradiation of H_3 in compound

(183) (Figure 4). These enhancements. together with the vicinal

couplings listed in Tables 5 and 6, clearly show that H_3 is axially

situated in compound (182) and equatorially situated in compound (183).

The absence of coupling between H_3 and $H_{4eq.}$ and the relatively small

enhancement of $H_{4eq.}$ on pre-irradiation of H_3 in compound (183)

(Figure 4) further suggest that, in this case, steric 1,3-diaxial

repulsion between the methyl group and the C_3 phenyl group distorts

the non-aromatic six-membered ring to the extent that the torsion

angle ($H_{4eq.}$, C_4, C_3, H_3) becomes $\sim 90°$; models show this to be

entirely reasonable. The proposed structures also account for the

greater shift difference between the methylene protons of compound (182)

than of compound (183), and the higher field methyl resonance of the

latter.

TABLE 5		
(Nmr of compound (182))		
Proton	δ	Couplings
H_2	6.04	$J_{2,3} = 3$ Hz
H_3	3.95	$J_{3,4ax.} = 9.5$ Hz
$H_{4eq.}$	2.65	$J_{3,4eq.} = 6$ Hz
$H_{4ax.}$	1.56	$J_{4eq.,4ax.} = 13$ Hz
Me	1.52	$J_{2,4eq.} = 0$ Hz
		$J_{2,4ax.} = 0$ Hz

TABLE 6		
(Nmr of compound (183))		
Proton	δ	Couplings
H_2	6.37	$J_{2,3} = 4$ Hz
H_3	4.09	$J_{3,4ax.} = 8.5$ Hz
$H_{4eq.}$	2.54	$J_{3,4eq.} = 0$ Hz
$H_{4ax.}$	2.21	$J_{4eq.,4ax.} = 14$ Hz
Me	1.29	$J_{2,4eq.} = 0$ Hz
		$J_{2,4ax.} = 0$ Hz

iii) Thermolysis and Photolysis.

Hydrocarbon "A" has a high degree of thermal stability, and was

recovered unchanged after extended periods in refluxing chlorobenzene

(132°C, 24h) or acetic acid (118°C, 48h). At the somewhat higher temperature of refluxing propanoic acid (141°C), very slow conversion to an unidentified product was observed, but this was relatively insignificant (< 10%) even after 48h; interestingly, the acidity of these solvents seemed not to affect the reaction.

On heating in the melt, however, hydrocarbon "A" was partially converted into complex mixtures of products within a few minutes. Since most of the products ran together on tlc, the composition of these mixtures was analysed directly by examining the methyl region of the crude nmr spectrum. The only material to be positively identified (below) was 9-methyl-1,3,9-triphenyl-9H-fluorene (184), which was the major product after heating at 210°C for 5 minutes. At least three other methyl containing products were detected, one of which was that previously observed in the propanoic acid experiment (methyl shift δ 1.80), while a peak at δ 5.14 suggested strongly the presence of 1,3,9-triphenyl-9H-fluorene (185); the absence of any sufficiently intense peak near δ 2.7 precluded the possibility that this peak was due to compound (158). At a slightly lower temperature (190°C) mixtures containing more of the unidentified components and much more starting material were obtained.
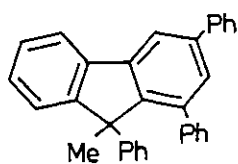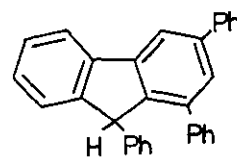
(184)   (185)

Flash vacuum pyrolysis of hydrocarbon "A" was also investigated, and found to give a good yield of fluorene (184) as the major product.[119] Subsequent chromatography and crystallisation allowed correlation with Snyder's products; the identity of compound (184) was confirmed by a comparison of the melting points (170-171°C, lit.[112] 171-172°C) and
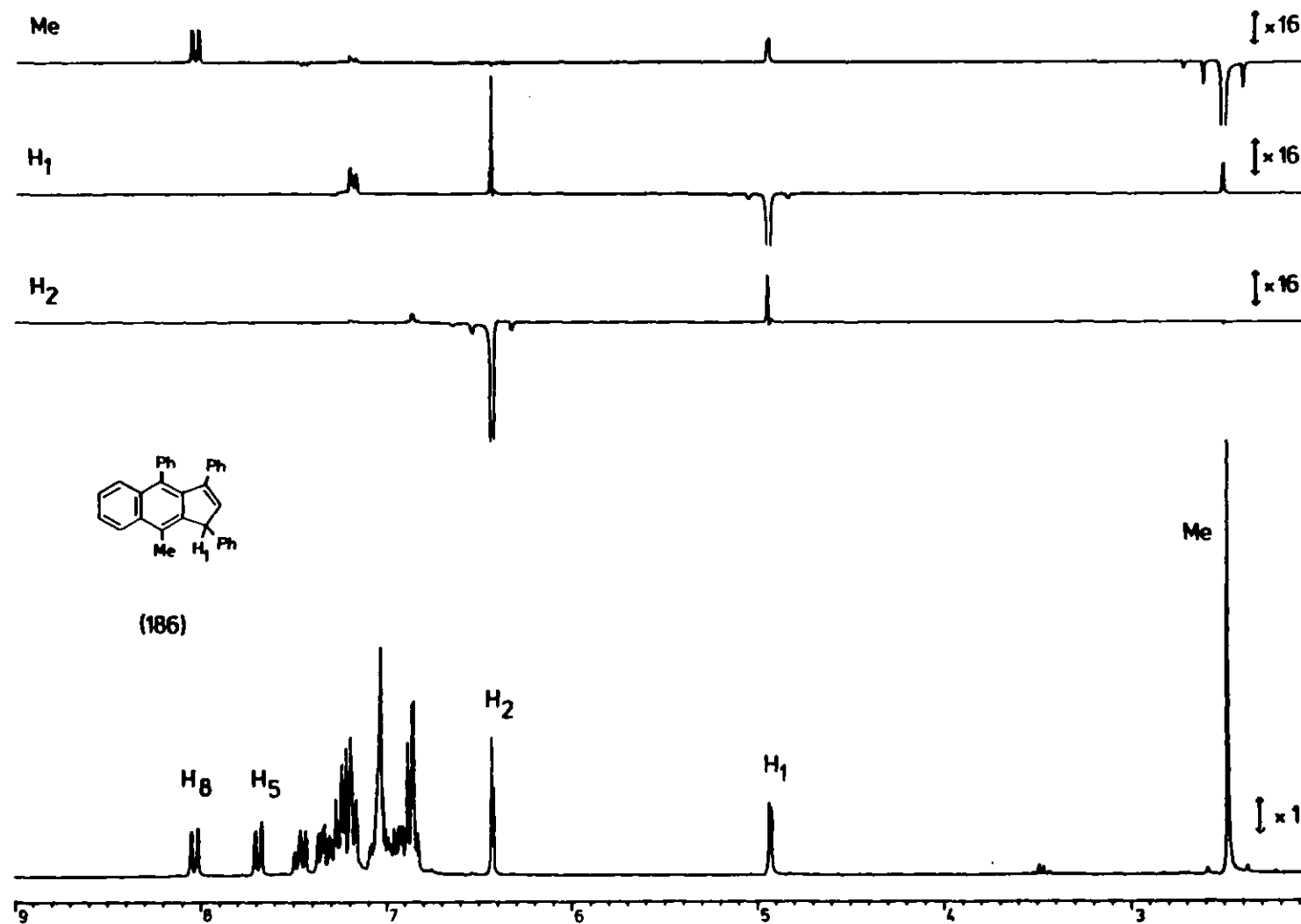
FIGURE 5 N.O.e. difference spectra of 9-methyl-1,3,4-triphenylcyclopenta[b]naphthalene (186).

the shifts of the methyl resonances in the nmr spectrum (δ 1.55; c.f.

δ 1.55 for 4,9-dimethyl-1,3,9-triphenyl-9H-fluorene[112]). Small amounts

of fluorenes (185) and (158) were also detected in the crude pyrolysate.

It must be noted, however, that the actual conversion of hydrocarbon

"A" to fluorene (184) probably occurred in the condensed phase, since

this had to be heated to nearly 300°C for several hours to induce

sublimation.

Photolysis of hydrocarbon "A" (irradiation at 254nm in aceto-

nitrile solution for 17h) followed an entirely different course to give

cyclopentanaphthalene (186) in good yield. Microanalysis showed that

the product was an isomer of the starting material; the simultaneous

presence of a methyl group attached to an aromatic ring, and the sub-

structure -CH(Ph)-CH=C- (both of which features were clear from the nmr

spectrum of the product) could then only reasonably be accommodated by

methyltriphenylcyclopentanaphthalene structures. The regioisomerism

of the product was unambiguously determined by n.O.e. difference

experiments (see Chapter Six), the results of which appear in Figure 5.

The enhancements of H_1 and H_8 on pre-irradiation of the methyl resonance

proved that the ring fusion was linear, and that H_1 was situated peri-

to the methyl group. Importantly, none of the alternative double-bond

isomer (187) was detected in the crude photolysate.
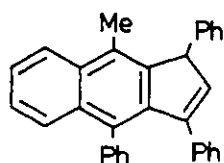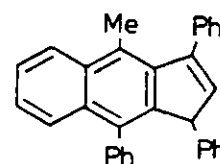
(186)   (187)

This reaction parallels the formation of cyclopentapyrimidines

on photolysis of ortho-blocked 1-aryltetrazoles (Chapter One, Section

1(i)), and of cyclopentaquinolines on photolysis of ortho-blocked

1-arylbenzotriazoles (Chapter One, Section 2(ii)), but there is a vital

difference. In the earlier cases, it was not possible to say whether

light was playing a role in the rearrangement of the presumed 3aH-
benzimidazole or 4aH-carbazole intermediates, since these were themselves
generated photochemically _in situ_.   In the present case, the 4aH-
fluorene system was the true starting material, and these results
establish clearly that the rearrangement _itself_ requires light; a blank
experiment showed that hydrocarbon "A" was recovered unchanged after
refluxing in acetonitrile for 12h.   Discussion of the mechanistic
implications of these findings is deferred until Chapter Five, Section 4 iii)
when analogous photorearrangements of simpler 4aH-fluorenes will also
be described.

CHAPTER THREE

CHAPTER THREE: Synthesis of the Ring System.

The investigation of 4a-methyl-1,3,9-triphenyl-4aH-fluorene

(hydrocarbon "A") (119), described in Chapter Two, revealed a number

of interesting reactions, and thus encouraged a widening of the present

study to include simpler 4aH-fluorenes.   It was clear, however, that

the reaction by which hydrocarbon "A" was formed was most unlikely to

be capable of extension to simpler cases, so a need arose to develop

a rational synthesis of the 4aH-fluorene system.

This chapter describes an investigation of several synthetic

approaches to the desired 4a-blocked fluorene ring system, while

Chapter Four will describe the methods used to introduce the necessary

unsaturation into the initial cyclisation products.

1)   3H-Indazoles.

As a logical extension of the previous work on ortho-blocked

1-aryltetrazoles (Chapter One, Section 1(i)) and ortho-blocked

1-arylbenzotriazoles (Chapter Two, Section 2(ii)), the decomposition

of ortho-blocked 3-aryl-3H-indazoles was considered first as a possible

method of generating the 4aH-fluorene system.   Loss of nitrogen from a

3H-indazole such as (188) would generate a diradical or carbene such as

(189), which could be expected to cyclise as shown in Scheme 55.

(188)   (189)   (190)
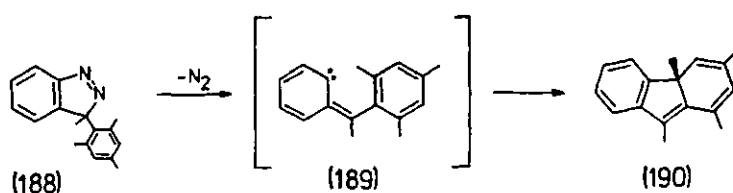
SCHEME 55

The presence of a blocking group at C_3 was considered necessary to lock the system as the 3H-isomer; structures bearing a hydrogen substituent in the five-membered ring would have to undergo an unfavourable tautomerisation from the aromatic 1H- to the 3H-tautomer before nitrogen loss could occur.

Although the previous work, referred to above, made it seem likely that such reactions would only generate the 4aH-fluorene as a transient intermediate, this was not thought a particular disadvantage, since it would allow a closer comparison with the 3aH-benzimidazole and 4aH-carbazole studies. Further, this approach was not considered in isolation; the usefulness of any such comparisons would be greatly enhanced if a more conventional, independent synthesis of the 4aH-fluorenes were also available, so that the reactions of the ground state, isolated system could be determined.

In the event, however, these plans were frustrated by the unavailability of the required 3H-indazoles. The planned route to indazole (188) involved synthesis of N-(benzotriazol-1-yl)-2,4,6-trimethyl-acetophenone imine (194) by condensation of 1-aminobenzotriazole (192) with 2,4,6-trimethylacetophenone (193), followed by decomposition with recyclisation as shown in Scheme 56.
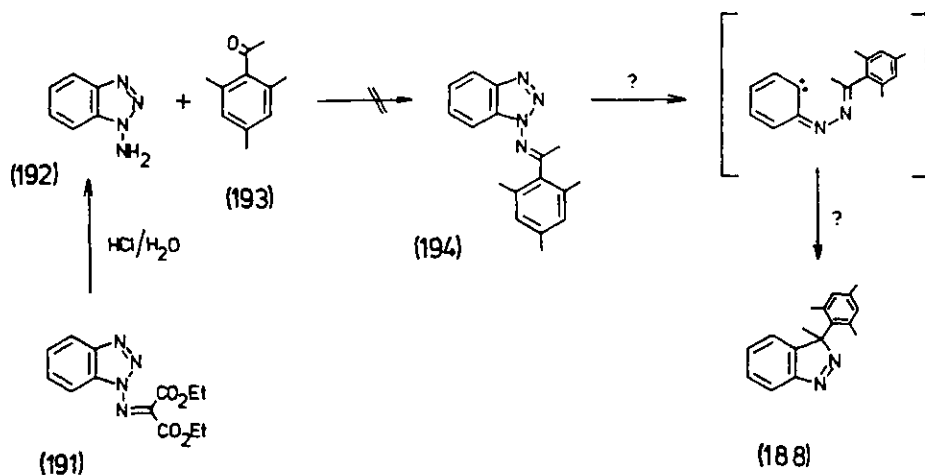
SCHEME 56

The ketone (193), however, could not be induced to condense with 1-aminobenzotriazole (192) under a wide variety of conditions; these included dehydration with 4A molecular sieves, refluxing with p-toluenesulphonic acid in benzene or toluene, refluxing with concentrated sulphuric or hydrochloric acids in ethanol, or refluxing in glacial acetic acid, all for extended periods. Variations of the desired condensation in which the oxime of ketone (193) was used, or diethyl N-(benzotriazol-1-yl)iminomalonate (191), the immediate precursor of 1-aminobenzotriazole,[120] was refluxed with ketone (193) and zinc chloride in o-dichlorobenzene, also failed.

In retrospect, these failures are not entirely surprising. 2,4,6-Trimethylacetophenone is an exceptionally hindered ketone, to the extent that the eventual preparation of its 2,4-dinitrophenylhydrazone (by refluxing the reagents in ethanol with concentrated sulphuric or hydrochloric acids) merited publication in its own right.[121,122] The ortho-methyl groups of ketone (193) presumably oblige the acetyl group to twist out of the plane of the aromatic ring, and in this conformation the approach of nucleophiles to the carbonyl group is almost completely blocked. It seemed unlikely that this hindrance, presumably associated with all such reactions α to a mesityl group, could be avoided in a synthesis of 3H-indazole (188), and consequently this approach was not pursued further.

2) Robinson Annulation of 1,3-Dimethylindan-2-one.

(195)   (196)   (197)
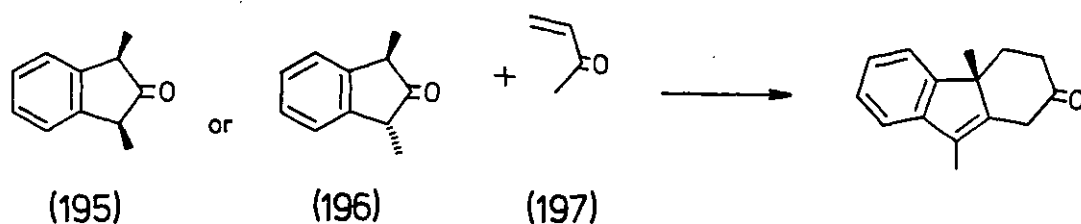
SCHEME 57

The formal reaction shown in Scheme 57 is, on paper, a most attractive

method of forming a 4a$\underline{H}$-fluorene precursor.   In practice, however, it proved less so.   The required synthesis of the 1,3-dimethylindan-2-ones (195) and (196), virtually unknown before the present work and non-trivial targets themselves, will be described first, followed by a brief account of subsequent attempts to annulate them.

i)   Synthesis of cis- and trans-1,3-dimethylindan-2-ones (195) and (196).

The only previous report of these ketones suggested, on the basis of nmr evidence alone, that they were present in the unstable mixture obtained by successive double methylation of 2-(1-pyrrolidyl)indene (198) via its anion, followed by hydrolysis (Scheme 58).[123]   This reaction seemed unsuitable for synthetic work not least because it generated a large quantity ($\sim$ 50%) of the unwanted 1,1-dimethyl regioisomer (199).
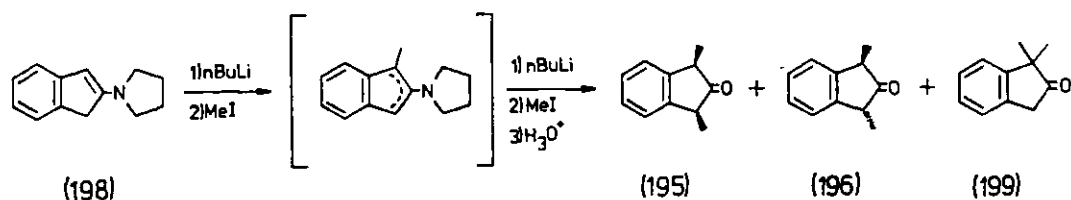
SCHEME 58

The best alternative seemed to be oxidation of 1,3-dimethylindene (136) using one of the many sequences known to convert indene into indan-2-one (126).   1,3-Dimethylindene was in turn available in large quantities via the Friedel Crafts reaction of benzene with crotonic acid,[124] followed by methylation and dehydration of the product (Scheme 59).[125]

Somewhat surprisingly, all the reactions referred to failed when applied to 1,3-dimethylindene, producing instead complex and unstable mixtures of many unidentified components.   These methods included oxidation with performic acid (followed by acid catalysed hydrolysis and dehydration to the ketone during steam distillation), oxidation to the epoxide with $\underline{m}$-chloroperbenzoic acid, either in a one phase system or a

two phase buffered system, and oxidation to the bromohydrin with hot aqueous bromine solution (Scheme 59). In each case, blank experiments confirmed the original literature reports that these reactions were successful when applied to indene itself.[126-129]
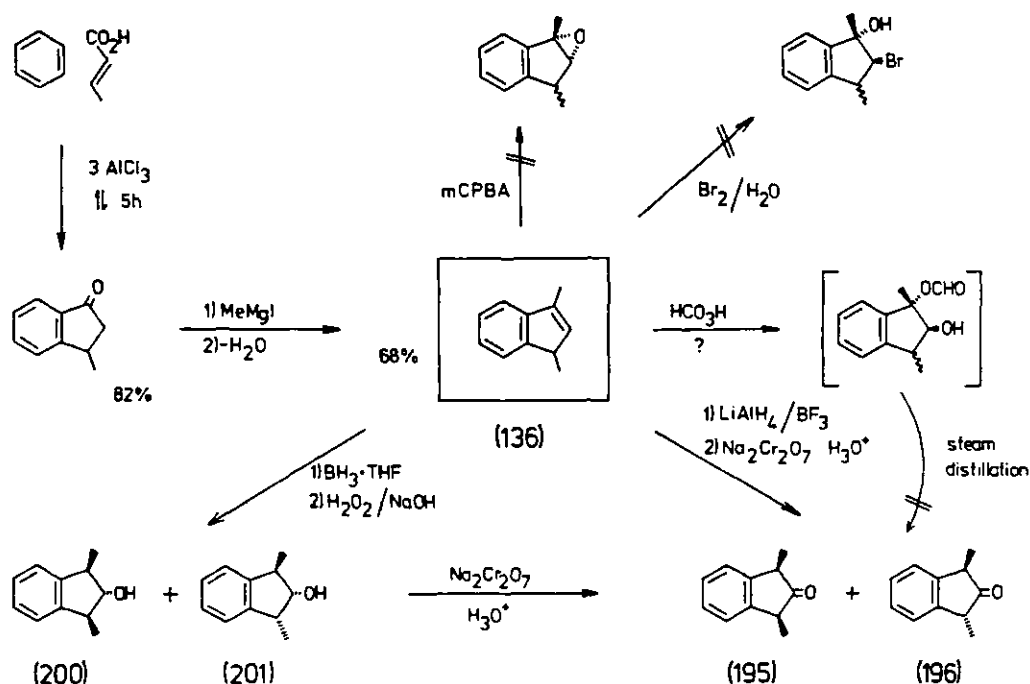
SCHEME 59

The most likely explanation for these differences in behaviour, also noted independently by Jones,[130] seemed to lie in the greater stability and potential for diversion of any benzylic carbonium ion intermediates produced during reactions in the 1,3-dimethyl series. A method which avoided such intermediates was therefore sought, the most attractive being hydroboration followed by oxidation.

This sequence proved to be the key. Direct conversion to a slightly impure diastereomeric mixture of ketones (195) and (196) (diastereomer ratio ∿ 1:4) in a one pot procedure was achieved in 50% overall yield after chromatography; since the ketones could not be stored, it was subsequently found more convenient to isolate and purify the crystalline mixture of alcohols (200) and (201) (diastereomer

ratio ∿ 4:1) which could then be used to generate an uncontaminated mixture of ketones (195) and (196) quickly as required. Both methods included the oxidation procedure due to Brown,[131] in which delicate oxidation substrates are protected from the worst effects of an aqueous oxidant solution by remaining largely in the ether phase of the heterogenous reaction mixture. In confirmation of the earlier report,[123] ketones (195) and (196) were found to be surprisingly unstable, deteriorating into an unusable mixture within a few hours. Still less expected was their unwelcome property of inducing a deep purple stain, persisting for several days, on even slight contact with the skin.

Separation of the diastereomeric ketones (195) and (196), or alcohols (200) and (201) was never observed, even on multiple-elution tlc, but this was thought unimportant in view of the nature of subsequent steps.

ii) **Attempted annulation.**

Previous results obtained with other indan-2-ones (Chapter One, Section 4(i)) suggested that annulation might best be achieved <u>via</u> reaction of methyl vinyl ketone (MVK) (197) with pyrrolidine enamine (202), the preparation of which was accordingly investigated. The reaction of a mixture of ketones (195) and (196) with pyrrolidine was found to be much slower than the corresponding reaction with indan-2-one (126), presumably due to steric hindrance from the methyl groups. Various catalysts were investigated, including p-toluenesulphonic acid,[132] titanium tetrachloride,[133] and calcium chloride,[134] but although these all gave excellent yields of the enamine (198) from indan-2-one (126), they did not improve the yield of 1,3-dimethyl-2-(1-pyrrolidyl)indene (202) from dimethylindan-2-ones (195) and (196). The cleanest procedure found involved refluxing ketones (195) and (196) with a large excess of pyrrolidine in benzene under nitrogen with azeotropic removal of water

overnight. The reaction was highly irreproducible; it regularly gave rise to an unidentified crystalline impurity, most probably a pyrrolidine salt, in varying amount, and sometimes reaction was incomplete. The product could be purified by column chromatography on basic alumina, but the yield was low, both the crude and purified products being very unstable towards atmospheric oxidation. The reaction of ketones (195) and (196) with morpholine was also investigated, and found to be less satisfactory still; scarcely any of the morpholine enamine (203) was produced under conditions similar to those of the pyrrolidine reaction.

(198)   (202)   (203)   (197)
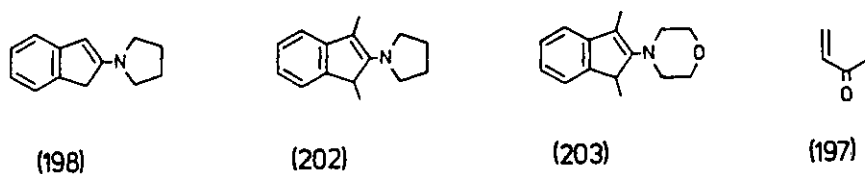
The reaction of crude dimethylenamine (202) with MVK (197) was next investigated. Conditions which brought about clean and complete reaction between enamine (198) and MVK, including standing at $2^{o}C$ in dry tetrahydrofuran for 3 days,[76] and refluxing in dry benzene, failed to do so between the dimethylenamine (202) and MVK. In refluxing benzene these latter components combined with the loss of approximately one mole of water to give mixtures exhibiting a peak (not due to water) at δ 5.12 in their nmr spectra, a shift characteristic of vinyl protons of enamines.

(202)   (204)

(206)   (205)
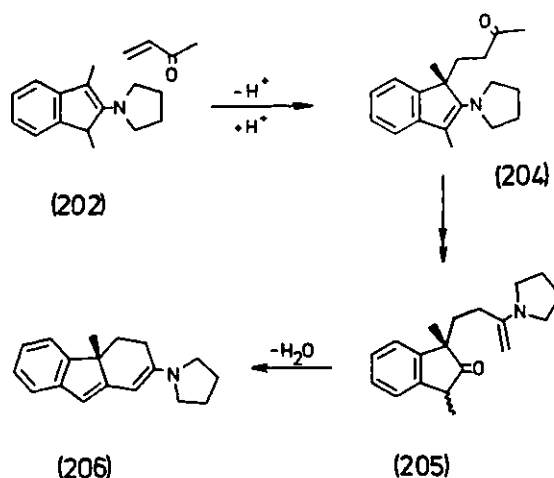
SCHEME 60

It was thought that the most likely process compatible with these results was the desired cyclisation itself (Scheme 60).

The conversion of ketoenamine (204) into the reversed ketoenamine (205) could involve trace amounts of water present in the reaction mixture, or could occur via a series of intramolecular nucleophilic displacements.

Attempted chromatography, however, led to the conclusion that the product mixtures contained, at best, little of the desired tricyclic enamine (206) or the ketoenamine (204), and their separation from the other unstable enamines present proved virtually impossible. The use of continuous dehydration techniques, intended to favour formation of the tricyclic enamine (206), resulted instead in still more complex mixtures.

Since it was thought that the temperature might be a major factor in producing these disappointing results, further experiments were carried out in benzene-tetrahydrofuran mixtures at $20^{o}C$. The results of these were inconclusive. The nmr spectra of the crude products suggested that the tricyclic enamine (206) was absent, but a moderate amount of the keto-enamine (204) may have been formed in at least one case, since the resonance of the C_1 methyl group (δ 1.22, d) in the starting enamine (202) was largely replaced by a singlet at δ 1.38. Extending the reaction time seemed to lead only to deterioration of the product mixture, the composition of which seemed also to depend on the solvent, best results being obtained with approximately 10% tetrahydrofuran in benzene. Only a brief study of this particular method was made, since, at the time, the tricyclic enamine (206) was thought a more valuable target.

Following the failure of the neutral dimethylenamine (202) to react cleanly with electrophiles, the formation and reactions of its anion (207) were investigated, but these reactions also were plagued by the irreproducibility of the preparation of the starting material (202). In one experiment, the anion (207) was methylated with methyl iodide

to yield the trimethylenamine (208); this compound was identified clearly in the nmr of the crude reaction mixture, but was not further characterised owing to its instability towards air and water. Attempts to reproduce this result failed, however, as did those to bring about any useful reaction between anion (207) and MVK (Scheme 61).
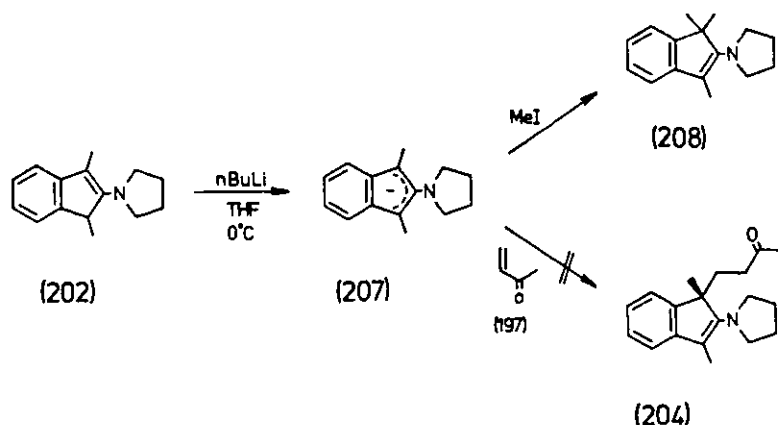
SCHEME 61

Although the presence of water in the MVK must have contributed to the failure of the anion experiments, the most fundamental and unavoidable problem in all these cases was the involvement of a long sequence of complex and irreproducible reactions via unstable intermediates which could not be isolated; the alkylation products discussed were, typically, the result of three or four consecutive steps without purification. These results are in marked contrast to the behaviour of 2-(1-pyrrolidyl)indene (198), mentioned previously, which is a relatively air-stable crystalline solid, reacts cleanly with MVK under mild conditions,[76] and can easily be alkylated via its anion.[123]

3) Attempted Synthesis of Robinson Annulation Intermediates.

The approach discussed in the previous section was eventually

abandoned, but the problems which caused this were connected with the instability of the 1,3-dimethyl-2-(1-pyrrolidyl)indene system rather than any failure of the cyclisation itself. It was hoped, therefore, that if diketone (209) (a formal intermediate in the Robinson annulation shown in Scheme 57) could be independently prepared, aldol cyclisation could subsequently be brought about, so bypassing the problems of the enamine route. As might be expected, direct treatment of 1,3-dimethyl-indan-2-ones (195) and (196) with MVK, even under mild conditions such as refluxing in dilute methanolic potassium hydroxide, led only to the dialkylation product (210).

(209)   (210)   (211)
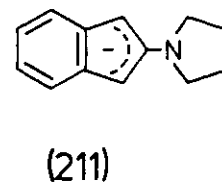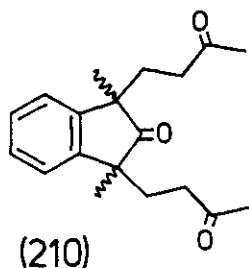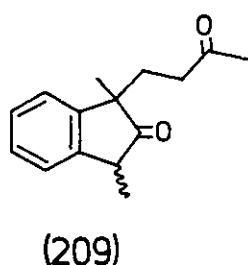
A possible synthetic approach to diketone (209) was suggested by the anion experiments involving 2-(1-pyrrolidyl)indene (198), referred to above.[123] Although the anion (211) could be considered as an enamine whose reactivity had been enhanced, the reactivity it possessed could perhaps be better described as that of the indenyl anion moiety alone, the pyrrolidyl substituent being relegated largely to the role of a protecting group. Consistent with this view, alkylations of indene via its anion are well known, and a series of papers by Jones and coworkers describes the facile deprotonation, alkylation and acylation of 1,3-dimethylindene (136).[93,135]

Since an efficient method for oxidising 1,3-dimethylindene to 1,3-dimethylindan-2-ones (195) and (196) (Section 2(i)) was now available, the possibility thus arose of introducing the 3-oxobutyl side-chain via alkylation of 1,3-dimethylindenyl anion (137), and then applying this oxidation procedure to the resultant indene (212), or (214), to give the diketone (209), or its protected analogue (215) (Scheme 62).
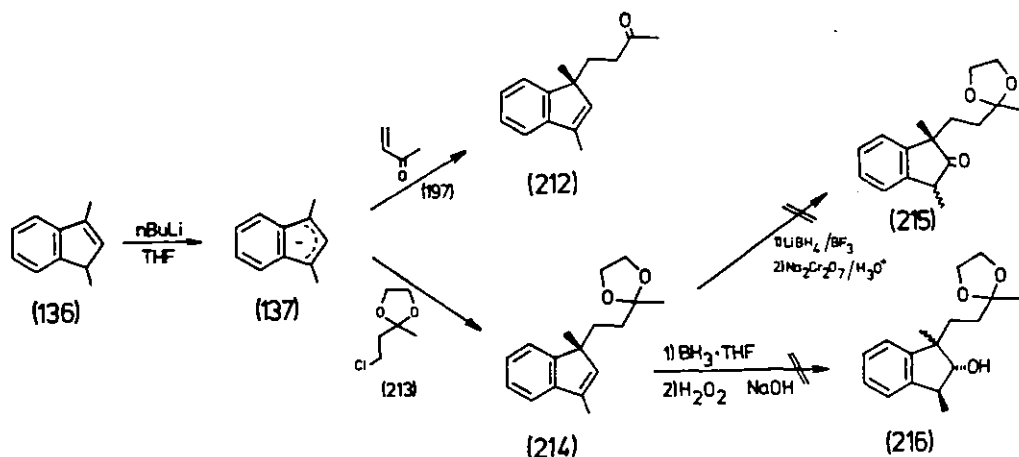
SCHEME 62

Alkylation of anion (137) with MVK (197) gave only a low yield (19%) of the required ketone (212). In contrast, reaction with the chloroketal (213) gave a high yield (87%) of the corresponding crystalline ketal (214). This discrepancy was probably due, at least in part, to the relative inefficiency of the drying procedures available for MVK.

The chloroketal reagent was prepared in 54% yield from the freshly distilled parent chloroketone[136] by refluxing in benzene containing 1.1 equiv. of ethylene glycol and a catalytic amount of p-toluenesulphonic acid, followed by distillation.[137] This appears to contradict the results of Kühn, who failed to obtain the same chloroketal using an almost identical procedure; this was probably due to his failure to purify the chloroketone, however, which was rather unstable, particularly when crude.[138]

As indicated in Scheme 62, however, these efforts were to be frustrated by the failure of the indene (214) to undergo oxidation to the ketones (215) or (209). Both of the procedures previously described (Section 2(i)), which had cleanly oxidised 1,3-dimethylindene (136) to 1,3-dimethylindan-2-ones (195) and (196), gave complex mixtures when applied to indene (214), from which neither ketone (215) nor alcohol (216) was isolated.

In an attempt to avoid this unsatisfactory reaction, the hydro-
boration of 1-methoxycarbonyl-1,3-dimethylindene (217), available from
the reaction of anion (137) with methyl chloroformate,[135] was examined.
It was thought that the intended product, 1-methoxycarbonyl-1,3-dimethyl-
indan-2-one (219), having only one enolisable proton, should undergo clean
monoalkylation with MVK; also subsequent cyclisation and manipulation
of the product (220) could give the hydroxyacid (221), which might serve
as a 4aH-fluorene precursor under mild conditions (Scheme 63).
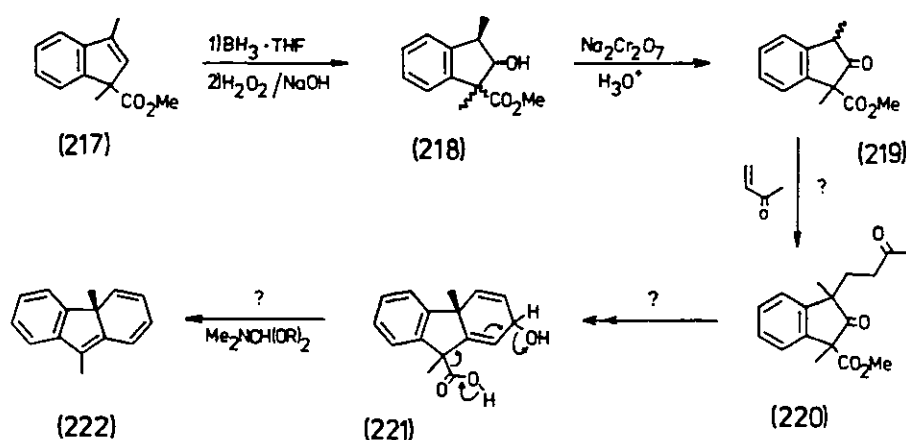
SCHEME 63

As in the previous case, a complex mixture resulted from attempted
hydroboration, but on this occasion a low yield (12%) of the desired
hydroxyester (218) could be isolated by column chromatography; nmr and
tlc suggested that this isolated yield represented approximately half of
the total of compound (218) formed. Despite several variations in the
reaction conditions, it was not possible to improve on this yield, and
the route was accordingly judged to be impractical. Nonetheless,
oxidation of the hydroxyester (218) was investigated, and found to proceed
smoothly under conditions identical to those employed in the oxidation of
the simpler indanols (200) and (201). The product (219), apparently a
single diastereomer, was identified clearly in the nmr, but was not further
characterised. Interestingly, the steric bulk of the ester group
retarded the reaction considerably; in the present case reaction required

6-7h, whereas the simpler case required only 0.3h.

It was thus the unsatisfatory hydroboration reactions of trisubstituted indenes which prevented the success of this approach. Somewhat surprisingly, the effect of the third substituent was not to prevent reaction, since the product mixtures contained very little starting material, but rather to divert it to unwanted, unidentified products.

4) Friedel Crafts Cyclisations of 1,3-Dimethylindenes.

Although it was not possible to prepare Robinson annulation intermediates using the approach described in the previous section, alkylation of 1,3-dimethylindenyl anion (137) had proved a very convenient method of introducing the four extra carbon atoms which would be required in any fluorene precursor. In order to make use of this, an alternative cyclisation was needed, and the most obvious choice was a Friedel Crafts cyclisation involving the indenyl double bond of some suitably alkylated 1,3-dimethylindene.

The most striking precedent for such a reaction lay in the work of Field and Jones, previously mentioned (Page 50, Scheme 36).[93] Their special requirement for optical activity, however, necessitated a rather uneconomical synthesis of the cyclisation substrate, aldehyde (139); we therefore sought a more direct approach to some closely related molecule.
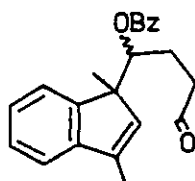
(139)

1,3-Dimethylindenyl anion (137) failed to react with γ-butyrolactone (223), but with the more reactive succinic anhydride (224), ketoacid (225) was obtained. The yield was not high (29%), but that was as much due to the difficulty of purifying the product as to the reaction itself. Various procedures for cyclising aromatic ketoacids were then applied to acid (225); these included refluxing in trifluoroacetic anhydride,[139] heating at 50°C in polyphosphoric acid,[140] and treatment with aluminium chloride-sodium chloride eutectic at 140°C for 2 minutes (Scheme 64).[141] All these reactions, however, repeatedly gave complicated mixtures of products which showed no evidence that the desired cyclisation had occurred to any appreciable extent.
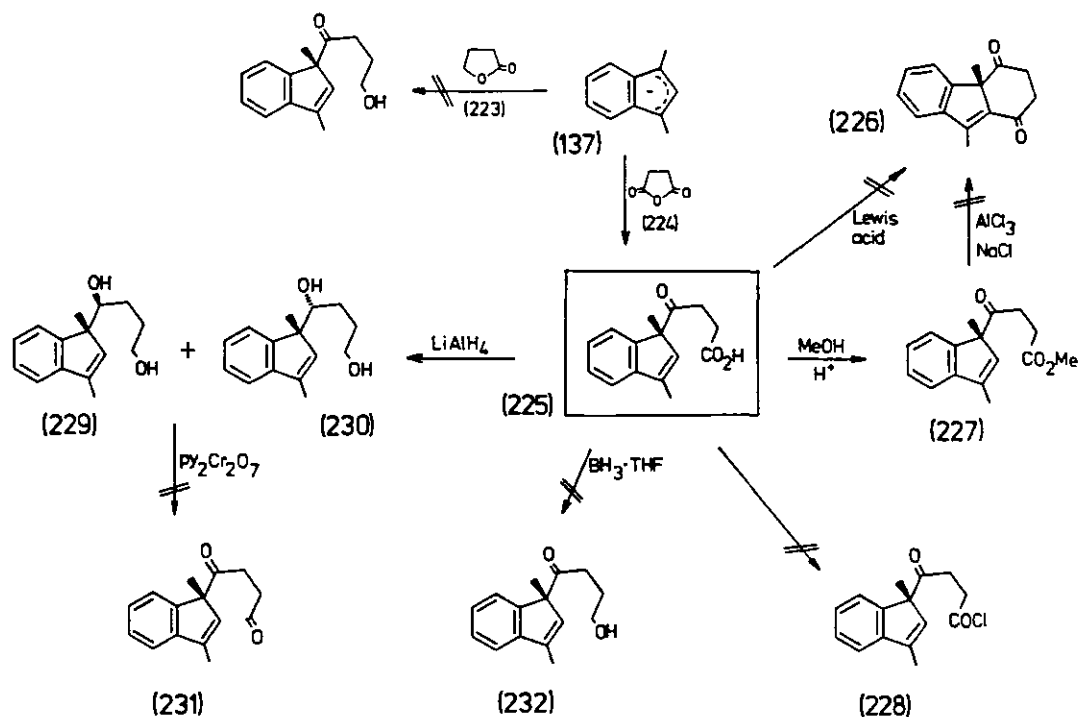
SCHEME 64

Following this, derivatives of the ketoacid (225) were investigated. On refluxing for 2h in methanol with a catalytic quantity of sulphuric acid, compound (225) was converted into its methyl ester (227). This material was unstable to chromatography on silica gel, but could be distilled in 50% yield. The distillate, which was almost pure by nmr

but was not characterised further, was then treated with aluminium chloride-sodium chloride eutectic at 120°C.[141] When the reaction was quenched after 2 minutes, the resultant mixture consisted mainly of starting material, but showed additional carbonyl peaks in the ir, possibly arising from a small amount of the desired tricyclic diketone (226). When the reaction was quenched after 10 minutes, however, a more complicated mixture was obtained, containing much starting material together with many other products, mostly retaining the proton at C_2 of the indene ring (by nmr), but no additional diketone (226) (by ir). It was concluded that this method was not capable of forming substantial quantities of the diketone (226), and that the milder alternative of cyclising the acid chloride (228) should be attempted.

Several methods of forming acid chlorides were therefore applied to the acid (225), including refluxing with thionyl chloride in benzene, stirring with phosphorus pentachloride in ether, and treatment with warm oxalyl chloride in benzene. In no case was there a clean yield of the chloride (228), and in all cases the 1'-keto group was at least partially destroyed.

Treatment of an ether solution of acid (225) with lithium aluminium hydride gave a roughly equimolar mixture of diols (229) and (230) in moderate yield after chromatography. This material was then treated with pyridinium dichromate in the hope of obtaining the corresponding ketoaldehyde (231) for use in a cyclisation analogous to that of aldehyde (139). In the event, however, the spectroscopic properties of the
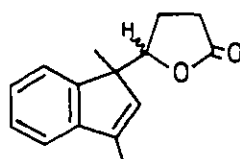
(233)

rather complex reaction mixture showed it to contain only a small
proportion of the desired aldehyde (231), together with a moderate
amount of a γ-lactone, presumably compound (233), identified by its
carbonyl absorption at 1780 cm^{-1} in the ir, and the presence of a proton
at δ 4.6 in the nmr.

In an attempt to circumvent these problems, the ketoacid (225)
was treated with 0.66mol of diborane in tetrahydrofuran. According to
the literature this electrophilic reducing agent reacts selectively with
carboxylic acids in the presence of keto groups,[142] but in this case no
such selectivity was observed, and the only products identified were
the diols (229) and (230).

It seems probable that most of these failures had a common cause,
namely ring-chain tautomerism of the side-chain. The literature
supports the view that the lactone (233) arises through oxidation of the
hydroxyaldehyde (234) (Scheme 65);[143] in fact, 1,4-diols are sometimes
employed as γ-lactone precursors in synthesis.[144]

(229) or (230)   (234)   (233)
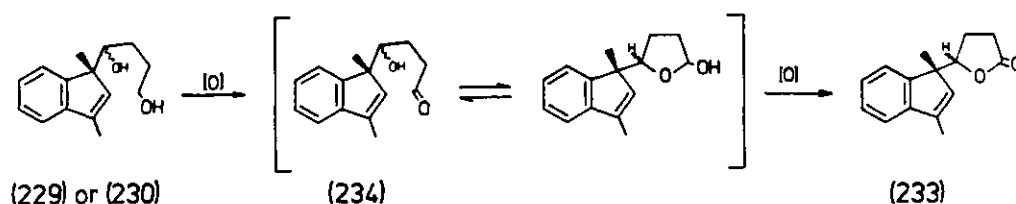
SCHEME 65

A similar tautomerism may be invoked to account for the behaviour
of ketoacid (225) (Scheme 66). The ring tautomer (235) might well be
diverted to unwanted products on treatment with Lewis acids, while the
loss of the 1'-keto group during attempted preparation of chloride
(238) might well be due to chlorination of the hydroxy group of the
ring tautomer (235), followed by nucleophilic attack of chloride ion
to form the C_{11} dichloride. Similarly, the tautomerism would lead to

(225) (235)
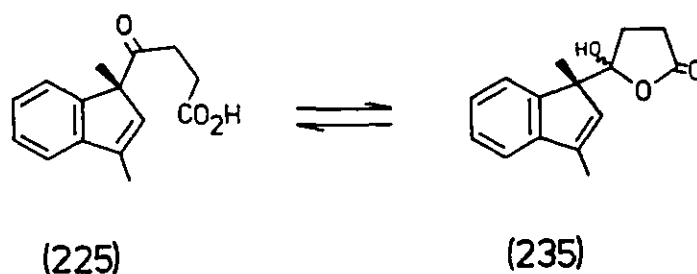
SCHEME 66

a loss of the distinction in nucleophilicity between the groups at C_1, and C_4, of ketoacid (225), resulting in the observed lack of regio-selectivity in its reaction with diborane.

The original motive for introducing difunctional side-chains as described was to provide some functionality in the saturated part of the intended cyclisation products, so as to facilitate later development of the required unsaturation. The failures just discussed, however, clearly demonstrated that this approach would have to be abandoned in favour of simpler alternatives in which difunctional systems were avoided. The most attractive of these was alkylation of the indenyl anion with 4-chlorobutyronitrile followed by cyclisation with polyphosphoric acid; this sequence has already been mentioned for the simpler case of indene itself (Chapter One, Section 4(iii)).[89] These reactions were therefore applied to 1,3-dimethylindene (136) (Scheme 67).

(136) (137) (237) (238)
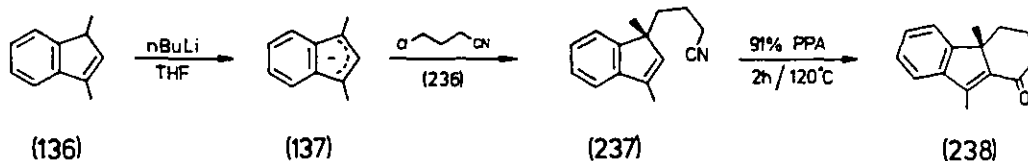
SCHEME 67

Alkylation of 1,3-dimethyl anion (137) with 4-chlorobutyronitrile

(236) gave a good yield (76%) of 4-(1,3-dimethylinden-1-yl)butyronitrile (237), despite some losses through polymerisation during distillation. Treatment of this material with 91% polyphosphoric acid then brought about the desired cyclisation, leading to a good yield (71%) of 4a,9-dimethyl-2,3,4,4a-tetrahydrofluoren-1-one (238), after acid hydrolysis of the first formed imine. The preparation of the 91% polyphosphoric acid reagent, although considerably more tedious than indicated in the original paper describing its use,[79] was justified by the higher yield relative to that obtained using commercial 83% polyphosphoric acid. Other cyclising agents, including sulphuric acid and a solution of phosphorus pentoxide in methanesulphonic acid, were also applied to this transformation, but the results were inferior.

This sequence thus provided a convenient entry into the required ring system, and further experiments showed it could be scaled up without loss in yield. Ketone (238) therefore became one starting point for the remaining phase of the synthetic work, described in Chapter Four.

5) Attempted Reductive Methylation of Fluorene.

According to Harvey et.al., treatment of fluorene with lithium metal in ether-liquid ammonia, followed by methylation with methyl bromide, gave 4a-methyl-4a,9-dihydro-2H-fluorene (152) (45%), 9-methyl-fluorene (239) (26%) and 9,9-dimethylfluorene (240) (13%).[107] In our hands, however, none of the 4a-methylated product (152) was detected, only the fully aromatic products (239) and (240) being obtained together with some starting material. Equally discouraging results were obtained when potassium was substituted for lithium.[145]

The reasons for this discrepancy are not clear. The original

report was detailed, and the product fully characterised, but the
authors did point out that the relative yield of compound (152)
depended markedly on experimental factors such as the order of addition
of reagents. In our case it seems that the only anionic species to
react was fluorenyl anion itself, but whether this was because no other
anions were present is not known.
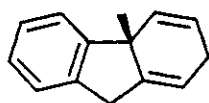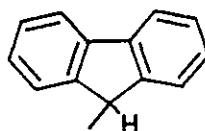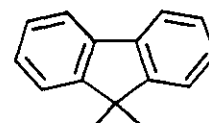
(152)   (239)   (240)

In view of these results, and also the availability of an
alternative route to the 4a-methylfluorene skeleton, this reaction
was not investigated further.

CHAPTER FOUR

CHAPTER FOUR: Oxidation of the Ring System: Syntheses of

4a,9-Dimethyl-4aH-fluorene and 4a-Methyl-4aH-fluorene.

As a result of the synthetic work described in Chapter Three, a synthesis of 4a,9-dimethyl-2,3,4,4a-tetrahydrofluoren-1-one (238) had been developed by analogy with the previously known synthesis of 2,3,4,9-tetrahydrofluoren-1-one (133) from indene (Scheme 68).[89] This chapter describes the conversion of these two tetrahydrofluorenones into 4a,9-dimethyl-4aH-indene (222) and 4a-methyl-4aH-fluorene (3) respectively.

(136)   (238)   (222)

(133)   (3)
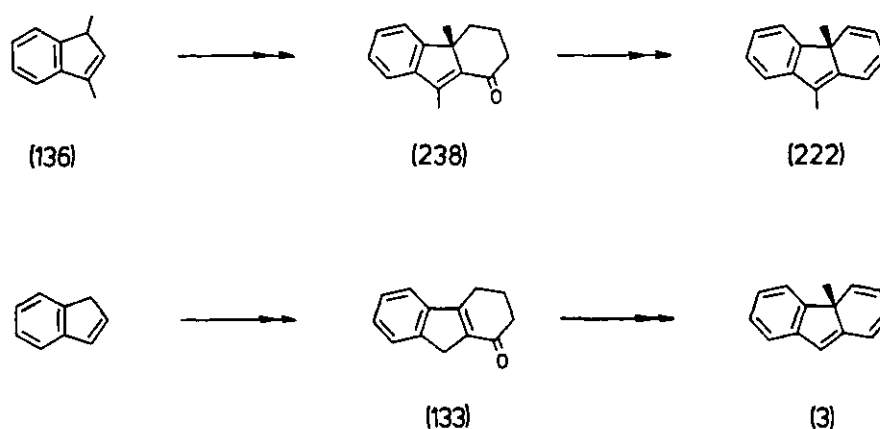
SCHEME 68

1) Synthesis of 4a,9-Dimethyl-4aH-fluorene.

Although the enone (238) is, formally, at the same oxidation level as the desired 4aH-fluorene (222), there was clearly no possibility of a direct conversion, so an indirect oxidation-reduction sequence was necessary. Dehydrogenation to the dienone (241) was considered to be the most attractive first step of such a sequence, since, of the three methylene groups which must ultimately be converted into olefinic methine groups, this reaction produces two directly and activates

(238)   (241)
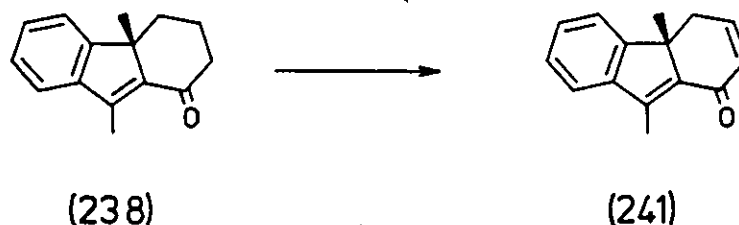
the third.

The direct dehydrogenation of ketones is a very important trans-
formation, particularly in the industrially important field of steroid
chemistry. Nonetheless, the reagents available for this transformation
remained, at least until recently, somewhat unsatisfactory. The
factors which control the applicability of these reagents to a given
dehydrogenation appear often to be finely balanced and somewhat ill-
understood; in the present case, not untypically, the most powerful
of the commonly used reagents, dichlorodicyanobenzoquinone (DDQ),
failed to give more than a small amount of dienone (241) from enone
(238).

Recent research by Barton, Ley and coworkers was aimed at over-
coming these difficulties, and led to the development of a new oxidant
for dehydrogenation of steroidal ketones.[146] The reagent, benzene-
seleninic anhydride (BSA) (242), is presumed to react with an enol to
give an α-selenoxyphenylketone which then undergoes a syn-elimination
(Scheme 69).

(242)
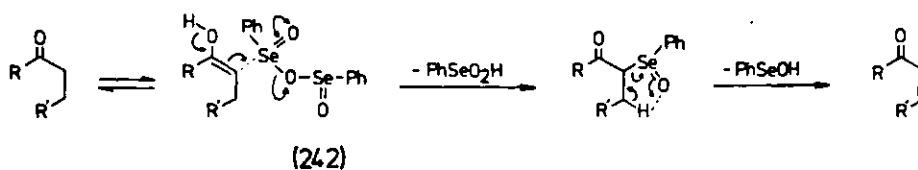
SCHEME 69

This single process represents a considerably more convenient method than its better known predecessor, the phenylselenation-oxidation sequence used, for example, in the synthesis of trienone (56) (Page 25, Scheme 10). The results of this research, as they became available, were therefore used extensively in the present work.

Treatment of enone (238) with a solution of BSA in chlorobenzene at $90^\circ C$ resulted in smooth, rapid oxidation to give dienone (241) in high yield (60-80%) (Scheme 70). This excellent reaction was marred only by the contamination of the product with a phenyl-selenated byproduct (243), which was barely separable by column chromatography. Some attempt was therefore made to optimise the reaction conditions, and this led to a number of interesting observations.
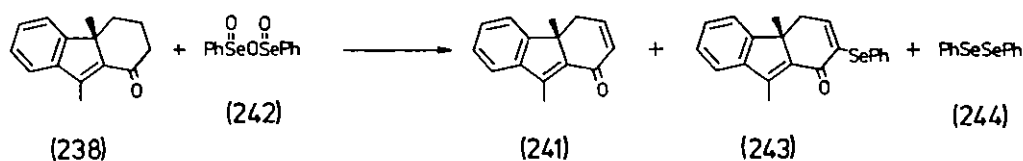
SCHEME 70

Variation of the reaction period showed that, although the conversion of enone (238) into products (241) and (243) was essentially complete after 0.2h at $90^\circ C$, any excess oxidant continued to be consumed after this period, until it had all been transformed into the reduction product, diphenyldiselenide (244). Although only one third of this quantity was formally required, one full mole of the reagent was usually employed per mole of substrate, implying that the unaccounted loss of oxidising power was considerable; thus, if the reaction was stopped after 0.2h, BSA was recovered in ∿ 50% yield, whereas after 1h no BSA was present. A marked decrease in yield, together with an increase

in phenylselenation, was observed either on reducing the excess of
reagent or on scaling up the quantities of reagent and substrate
without scaling up the volume of solvent in strict proportion. At
the higher temperature of refluxing chlorobenzene, no phenylselen-
ation was observed, but instead an over-oxidation product, the
aldehyde (245), was formed together with dienone (241).

CHO
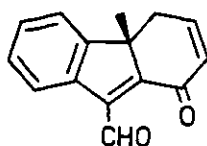
(245)

Barton and Ley observed similar trends in their own work on
steroids, from which they concluded that the reaction might best be
improved by finding some means of maintaining the various selenium
species at as high an oxidation state as possible.[147] It was thought
that the first-formed phenylselenenic acid (PhSeOH) was probably
responsible for the substitution side-reactions, and that the
suppression of these at higher temperatures was due to the then more
rapid disproportionation of the PhSeOH. The slow loss of oxidising
power was thought to reflect the existence of a complex set of rapid
oxygen-atom transfer equilibria between the many selenium containing
species formed, some of which presumably dissociated to give oxygen
gas (this was not proven, however). All of these problems, it was
argued, could thus be overcome by the presence of another oxidant
capable of rapidly re-oxidising any reduced selenium species as it
was formed, and the ideal choice for this other oxidant would be an
oxygen-atom transfer agent.   Such a scheme had the added advantage
that the relatively expensive BSA would then only be required as a
catalyst.

After some experimentation, iodylbenzene ($PhIO_2$) was found to meet these requirements, and a much improved procedure employing it as the bulk oxidant was published.[148]

When enone (238) was added to a refluxing solution of BSA (0.1mol) in dry benzene containing suspended iodylbenzene (1.2mol), smooth oxidation occurred to give a high yield (72%) of the dienone (241), uncontaminated by other materials after flash chromatography. Azeotropic removal of water served both to promote and monitor the reaction, which could be scaled up without loss in yield provided the volume of solvent was scaled up in strict proportion.

The next step chosen was the reduction of the keto group of dienone (241) to give dienol (248), which it was hoped would yield the target 4aH-fluorene (222) via an elimination step. A brief literature search showed that the reduction would require a careful choice of reagent, since the usual reducing agents caused at least partial saturation of αβ-unsaturated ketones; the two most satisfactory reagents described were diisobutylaluminium hydride (DIBAL)[149] and 9-borabicyclo[3.3.1]nonane (9-BBN).[150] The reaction of DIBAL with isophorone (246) was used to test the literature reports, and was indeed found to give the corresponding allylic alcohol (247) in high yield and free from saturated byproducts (Scheme 71).
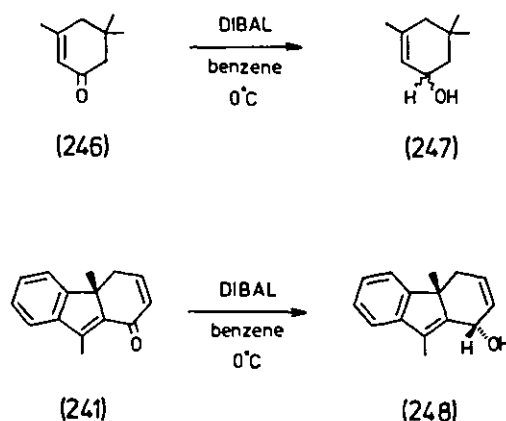
SCHEME 71
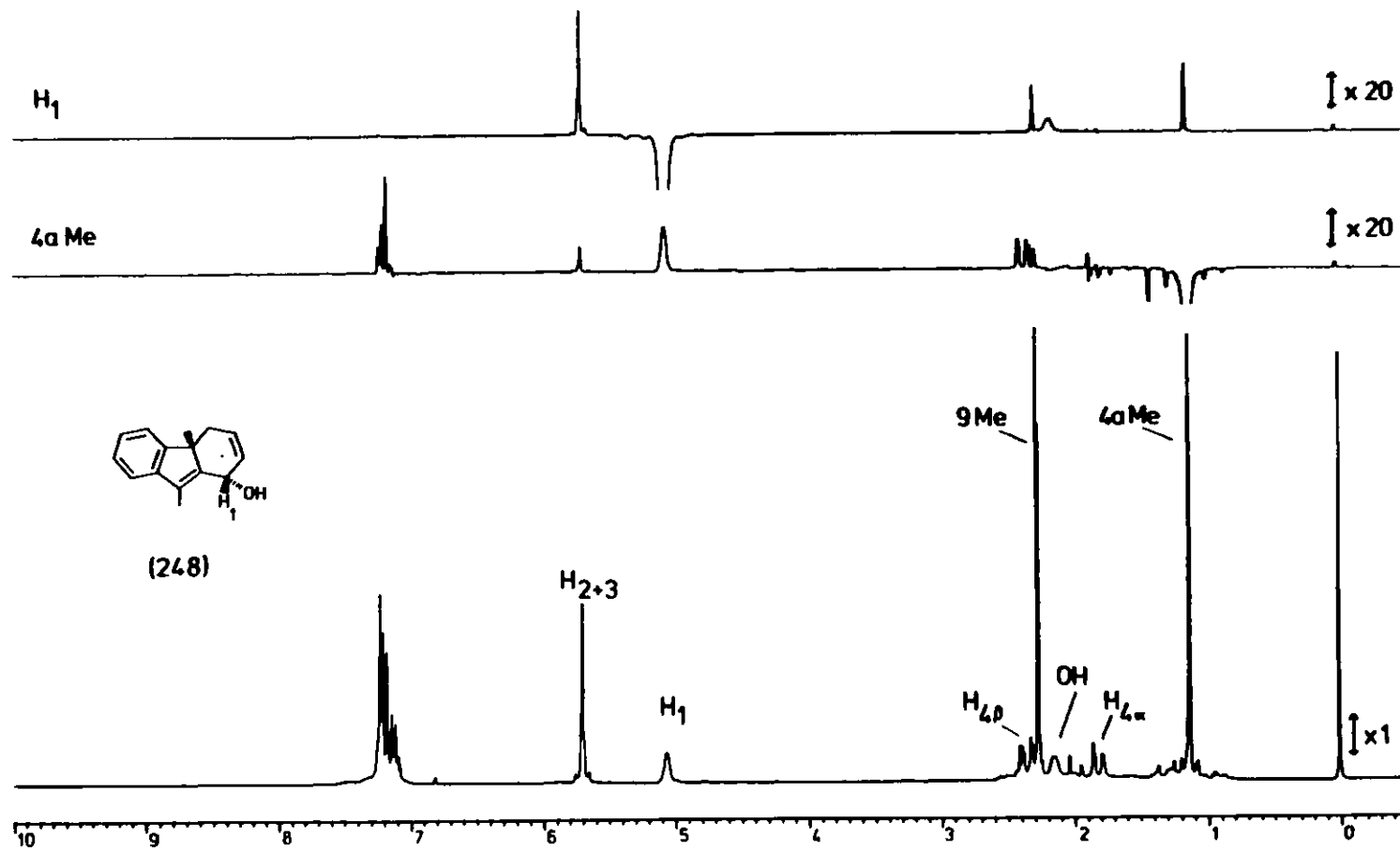
FIGURE 6 N.O.e. difference spectra of 4,4a-dihydro-4aβ,9-dimethyl-1H-fluoren-1α-ol (248).

The corresponding reduction of dienone (241) to dienol (248) (Scheme 71) was found to be a smooth, clean reaction, the crude product from which contained more than 95% of the required material. This was fortunate, since attempted purification led only to deterioration. Distillation or chromatography on silica gel caused almost complete destruction of the product, while even chromatography on alumina caused some decomposition and promoted aerial reoxidation to dienone (241). The reoxidation reaction necessitated storage under nitrogen, but with this precaution the compound could be stored for many days in solution at $0^{o}C$ without loss.

A curious feature of the dienol (248) is its stereochemistry, which was unambiguously established by an n.O.e. difference experiment, as shown in Figure 6 (see also Chapter Six). The relatively large enhancements between H_1 and the C_{4a} methyl group observed in both directions, clearly prove that the single diastereomer present is that in which the hydroxy and bridgehead methyl groups are on opposite faces of the molecule. This result implies that, during reaction, the reagent must have approached the carbonyl group of the dienone (241) exclusively from the same face of the molecule as occupied by the C_{4a} methyl group. It is not at all clear why this should be; models suggest that, if anything, this face is the more hindered of the two.

The final reaction required to produce the 4aH-fluorene (222) was a formal 1,4 elimination of water from dienol (248). A variety of possibilities exist for achieving this, but in the event the simplest, direct acid-catalysed dehydration, was tried first and proved successful. Thus, azeotropic removal of water from a refluxing benzene solution of crude dienol (248), acidified with p-toluene-sulphonic acid (10mol%), for 3h gave, after flash chromatography, the desired 4a,9-dimethyl-4aH-fluorene (222) in approximately 50% overall yield from dienone (241), and sufficient purity for immediate use in

(248)   pTSA
         benzene ↕   (222)
         0·3h
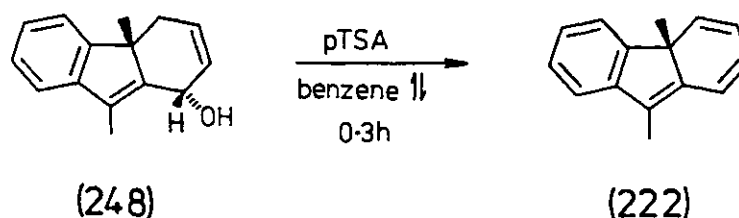
SCHEME 72

further reactions (Scheme 72).

Further discussion of this transformation is deferred until Section 4.

2) Oxidation of 4a-Methylhexahydrofluoren-1-one.

Given the success in synthesising 4a,9-dimethyl-4aH-fluorene (222) just described, it seemed wisest to attempt next a synthesis of the still simpler parent molecule, 4a-methyl-4aH-fluorene (3), since it was thought that if this were made available, an investigation of its chemistry would be of greater interest than one of the dimethyl derivative (222) alone.

The most attractive approach to a synthesis of 4aH-fluorene (3) was to prepare first 4a-methyl-2,3,4,4a-tetrahydrofluoren-1-one (250), the monomethyl analogue of enone (238), and then to apply to it the reactions described in the previous section. The problem thus became one of devising a route to enone (250), and given the previously known synthesis of enone (133) (Scheme 68),[89] the most economical route seemed to be via oxidation of 4a-methylhexahydrofluoren-1-one (249), itself obtained via conjugate methylation of enone (133) (Scheme 73).

FIGURE 7 N.O.e. difference spectra of cis-4a-methyl-hexahydrofluoren-1-one (249).
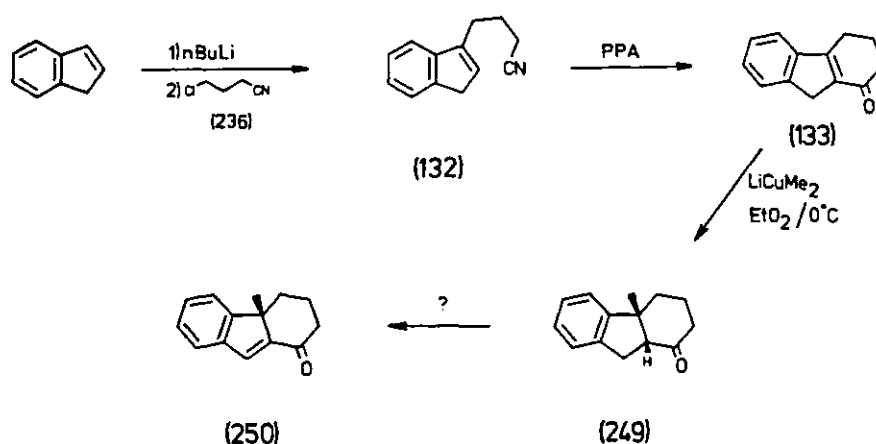
SCHEME 73

Methylation of eneone (133) was achieved using lithium dimethyl cuprate in ether solution at -20°C. It was found that this reaction was surprisingly slow, requiring a full 2h for completion. Work-up was also critical, since conventional quenching led to appreciable amounts of double addition and elimination products. By analogy with the literature, this problem was overcome using a reversed quench procedure in which the reaction mixture was added directly (but slowly!) to stirred 6M hydrochloric acid.[151] An attempt to use a copper catalysed Grignard reagent for this reaction gave two unidentified products in low yield, neither of which was the desired ketone (249).

An n.o.e. difference experiment, the results of which are shown in Figure 7, clearly showed that the hexahydrofluoren-1-one (249) had the expected cis-ring junction. The strong enhancements between the C_{4a} methyl group and $H_{9a\beta}$, observed in both directions, are unequivocal, and further effects involving $H_{9a\beta}$, $H_{9\beta}$ and $H_{9\alpha}$ provide a clear example of the distinction between S.P.T. effects (due to population redistribution) and n.o.e. enhancements (due to net population increase). This point will be developed in Chapter Six.

The last step now required to produce 4a-methyl-2,3,4,4a-tetra-hydrofluoren-1-one (250) was the dehydrogenation of 4a-methylhexa-hydrofluoren-1-one (249). Although this seems a favourable trans-formation on paper, the precursor having both ketonic and benzylic activation in useful positions, and the product being relatively stabilised by increased conjugation, it proved remarkably elusive in practice.

In view of the successful use of benzeneseleninic anhydride described in the previous section, much effort was expended in trying to apply the same reagent to the present dehydrogenation. A partic-ularly attractive feature seemed to be that, if the desired enone (250) were formed, it was likely that it would be further oxidised to dienone (252) in situ, so accomplishing two steps in one. The stoichiometric and catalytic reactions (Section 1) were both investi-gated, although less work was done on the latter since the method was not published until after our own study of the stoichiometric reaction was all but complete.

The stoichiometric reaction of 4a-methylhexahydrofluoren-1-one (249) with BSA was run using amounts of BSA somewhat in excess of two mols in various solvents at various temperatures. The desired dienone (252) could be recognised readily in the complex product mixtures since, like its dimethyl analogue (241), it gave a brilliant electric blue fluorescence on tlc plates when irradiated at 254nm Isolation of the corresponding fluorescent band by column chromatography gave only partial separation, however. This isolated "ketone fraction" generally contained the same compounds in differing proportions according to the experimental conditions, and nmr was used to analyse the product distribution directly. Further separation was only attempted once, and was found to be extremely difficult, even by multiple elution preparative thin layer chromatography. It was possible,

however, to confirm largely the nmr assignments.

A complex picture emerged of the response of the reaction to changing temperature and reaction period; the overall pattern of transformations is summarised in Scheme 74.
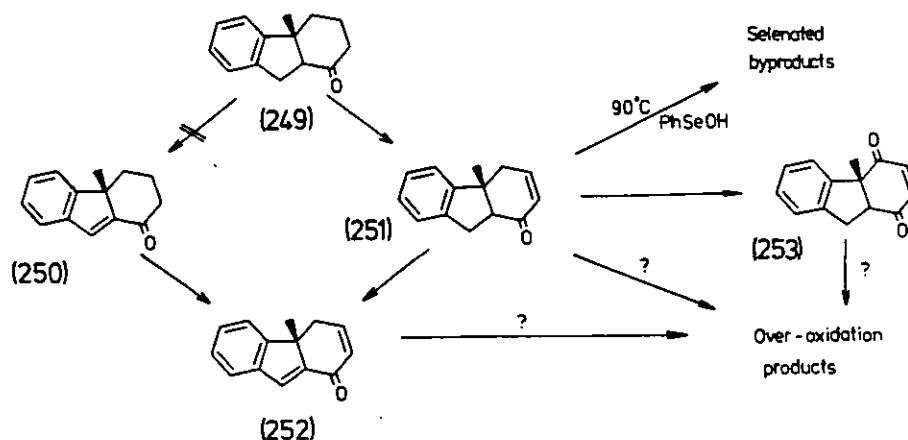
SCHEME 74

Initially the hexahydrofluorenone (249) underwent rapid oxidation to give the 2,3-dehydrogenated product (251). This reaction was complete after 0.3h in refluxing chlorobenzene, but about 20% of the starting material remained unchanged after 1.5h at $90^{o}C$ in the same solvent. Selenated byproducts were probably also produced in the lower temperature reaction, while, as expected (Section 1) they were consistently absent from the higher temperature experiments.

The initial product (251) was apparently resistant to further oxidation at $90^{o}C$, but reacted slowly at higher temperatures. The desired 9,9a-dehydrogenation did take place in refluxing chlorobenzene, but incompletely and in competition with another oxidation at a comparable rate. The product of the competing reaction was tentatively identified as the enedione (253) on the basis of mass-spectral and nmr evidence. Extending the reaction time led to a slightly improved

conversion of enone (251) into dienone (252), but only at the cost of a greater increase in production of the enedione (253). Increasing the proportion of oxidant from 2 to 3 mol resulted in an improved recovery of "ketone fraction" ($\sim$ 60% as opposed to $\sim$ 40%), but did not substantially affect the distribution of products within it.

Increasing the reaction temperature to reflux in bromobenzene resulted in a continuation of these trends. After 0.2h the enone (251) was, for the first time, absent from the product mixture, but the enedione (253) was present in almost equal proportion to the desired dienone (252). Further unidentified over-oxidation products were also present in the "ketone fraction", the yield of which was much reduced relative to the chlorobenzene experiments.

It was clear from this work that, at very best, the stoichiometric oxidation reaction could only give a 60% yield of an inseparable mixture containing approximately 50% of the required dienone (252). The catalytic oxidation method, using iodylbenzene as the bulk oxidant (Section 1), was also applied to this transformation, but although it led to a much improved material recovery the product distribution was substantially as it had been in the stoichiometric reactions. Thus the crude products from the catalytic reactions ($\sim$ 90% recovery) were typically of comparable purity to the separated "ketone fractions" from the stoichiometric reactions ($\sim$ 30-60% recovery), and although initial oxidation to the enone (251) was efficient, as before this material was transformed more rapidly into enedione (253) than into dienone (252).

The sluggish nature of the 9,9a-dehydrogenation reaction, which must have been the direct cause of all these disappointing results, is presumably the result of steric hindrance to the introduction of the bulky oxoselenophenyl group <u>cis</u> to the C_{4a} methyl group of molecules such as enone (251). In an attempt to force a selenophenyl group into

this crowded environment, the first-formed copper enolate derived from

tetrahydrofluorenone (133) on methylation (as described above) was

allowed to react with N-selenophenylphthalimide (254)[147] under non-

equilibrating conditions, but this gave rise only to a complex mixture

containing at least four major products; the reaction was not

investigated further.
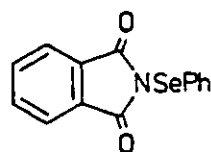
(254)

Following these failures with selenium reagents, the applicability

of other dehydrogenation agents to the oxidation of hexahydrofluorenone

(249) was investigated. Triphenylcarbenium trifluoroacetate

(generated in situ from triphenylmethanol) failed to give any reaction

at all with ketone (249) after refluxing for 9h in trifluoroacetic

acid. Reaction with DDQ, either in refluxing dioxan for 24h, or in

refluxing benzene for shorter times, gave only traces of oxidised

products inseparable from the starting material; these were not

identified.

Since these single step methods were of no avail, multi-step

alternatives, particularly bromination-dehydrobromination, were

considered. Such a sequence offered the attractive possibility of

placing a leaving group in the 9-position, rather than the 9a-

position as before. This would avoid steric crowding and favour a

base induced elimination step through activation of H_{9a} by the adjacent

carbonyl function. The necessary introduction of a leaving group at

C_9 also seemed favoured, since benzylic activation should direct

substitutions to the required position.

Bromine itself can be used as a radical bromination agent for ketones, provided any enol reactions are suppressed by the presence of an effective HBr trap, usually propylene oxide.[152] On irradiation with visible light, a solution of 4a-methylhexahydrofluoren-1-one (249), propylene oxide and bromine in carbon tetrachloride was rapidly decolourised at 20°C to give a complex mixture which decomposed slowly on attempted isolation. The crude product was treated directly with triethylamine in carbon tetrachloride for 14h at 20°C to give, in low yield, a mixture which seemed by nmr to consist largely of the diastereomeric bromides (255) and (256).
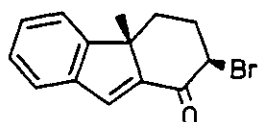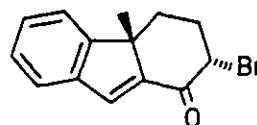
(255)   (256)

Clearly, a milder brominating agent was required, so the reaction of ketone (249) with N-bromosuccinimide (NBS) was investigated. No detectable reaction occurred at 20°C, but on refluxing a solution of ketone (249) in carbon tetrachloride containing suspended NBS, reaction was usually complete within ∿ 0.5h. Attempted isolation of the product led to rapid decomposition, accompanied by fuming, darkening and precipitation of tar; nonetheless, nmr suggested that the major material present before decomposition was a diastereomeric mixture of bromides (257) and (258). Direct dehydrobromination with triethylamine at 20°C for 20h, after removal of succinimide and oxidising impurities, was only partially successful, giving a complex mixture of the bromides (257) and (258), enone (250) and many minor products, but use of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) as the dehydrobrominating agent resulted in clean and complete elimination within 0.5h at reflux
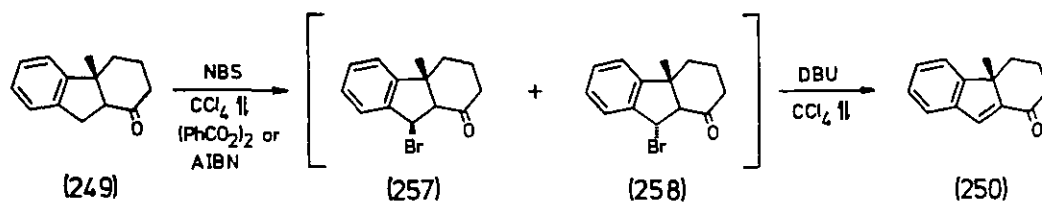
SCHEME 75

in carbon tetrachloride (Scheme 75).

Although this sequence proved to be the key, it was and remains somewhat unsatisfactory, particularly in terms of its reproducibility. Initiation of the reaction was found to be somewhat unreliable, with the result that, occasionally, only incomplete bromination occurred. This could not be detected at the intermediate stage, since the bromides were not isolable, but the consequences of using such a partially brominated mixture in the elimination step were severe, since the starting material (249) and product (250) were inseparable by column chromatography. After the experience of several runs, these problems were largely overcome by careful attention to the initiation, and by periodic addition of fresh initiator during the reaction. When N-chlorosuccinimide was used in place of NBS, the ketone (249) completely failed to react.

Thus, although this synthesis of enone (250) was used in the final route to 4a-methyl-4aH-fluorene (3) (Section 4), its unreliability motivated a brief investigation of other routes to the target which might avoid the difficult 9,9a-dehydrogenation reaction altogether (Section 3).

3) Other Attempted Approaches to 4a-Methyl-4aH-fluorene.

The route just described was developed by analogy with the previously described synthesis of 4a,9-dimethyl-2,3,4,4a-tetrahydro-fluoren-1-one (238) (Chapter Three, Section 4). A closer analogy, however, is provided by the reactions shown in Scheme 76, in which the 9,9a-dehydrogenation reaction is rendered unnecessary since the reductive methylation step of the route described above (Section 2) is avoided.
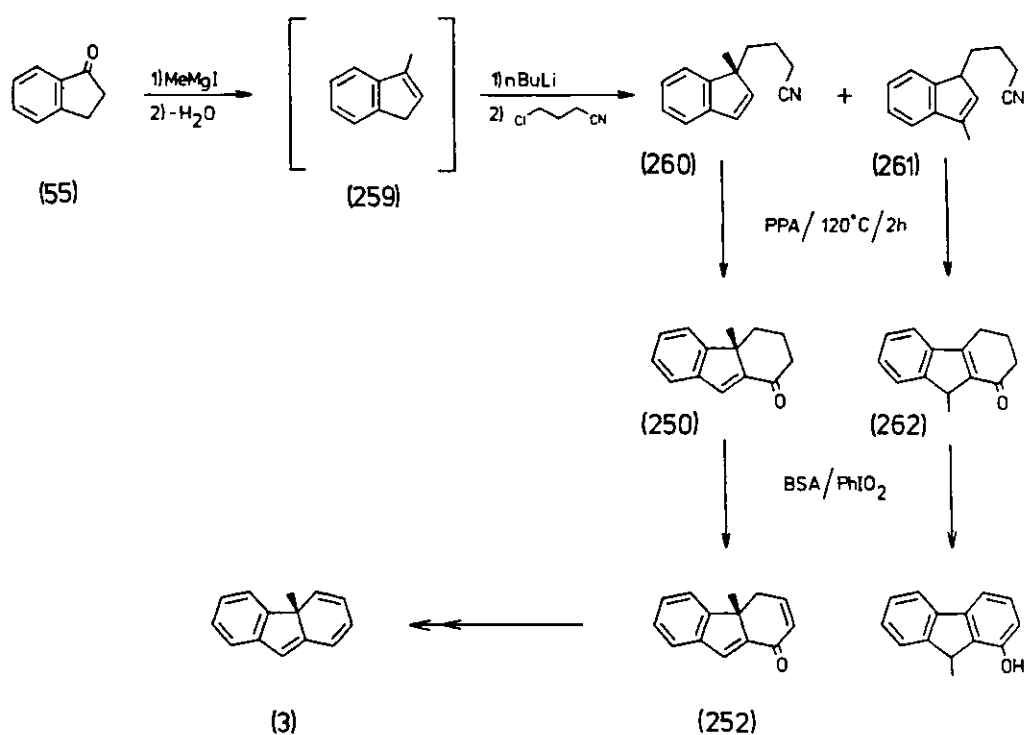
SCHEME 76

Although the analogy with the syntheses previously described appears close, these reactions proved very different experimentally.

3-Methylindene (259) could be prepared from indan-1-one (55) as shown, but, in marked contrast to indene and 1,3-dimethylindene, it was an extremely unstable material, reacting rapidly with air to form a black resin or, on the exclusion of air, with itself to form a polymer. It could not be stored even at $0^{\circ}C$ under nitrogen, and distillation

resulted in extensive loss through polymerisation (> 50%). Crude 3-methylindene (dried in ether solution over magnesium sulphate over-night) proved far too wet for the next reaction in the sequence, alkylation of its anion with 4-chlorobutyronitrile, to succeed. A compromise was therefore reached. Adequate dryness was achieved at the cost of only moderate polymerisation by refluxing the crude 3-methylindene (259) in benzene with azeotropic removal of water for 0.5h. Subsequent reaction with n-butyllithium in tetrahydrofuran, followed by 4-chlorobutyronitrile, gave a mixture of nitriles (260) and (261) in 50% combined yield after chromatography.

A very weak feature of this route is that it generates a parallel series of unwanted isomers having no bridgehead methyl group. In the event, very little regioselectivity was observed in the alkylation reaction, the product containing approximately 40% of the desired nitrile (260) and 60% of the unwanted nitrile (261); this pattern was virtually unchanged by reducing the reaction temperature from $+5^{o}C$ to $-60^{o}C$. Separation of the nitriles was impossible, even by multiple elution analytical tlc, but this further problem was not thought severe, since a facile separation was anticipated later in the route. Thus, on cyclisation and oxidation the unwanted nitrile (261) was to yield a phenol, which could be washed away with base, while the desired nitrile (260) was to yield the blocked dienone (252) which should remain with the neutral material.

Unfortunately, this hypothesis proved irrelevant, since the cyclisation of nitrile (260) failed. The mixture of nitriles (260) and (261) was treated with polyphosphoric acid at $125^{o}C$ for 2h, conditions identical with those used for cyclising 4-inden-3-ylbutyro-nitrile (132) and 4-(1,3-dimethylinden-1-yl)butyronitrile (237), but the only product which could be isolated from the complex product mixture which resulted was 9-methyl-2,3,4,9-tetrahydrofluoren-1-one (262).

The nitrile (260) disappeared, presumably to many minor products or polymers. The only plausible explanation for this frustrating difference in behaviour is that, whereas nitriles (132), (237) and (261) pass through tertiary benzylic carbonium ion intermediates (264), (265) and (266) respectively, nitrile (260) would have to pass through a less stable secondary benzylic carbonium ion intermediate (263) (Scheme 77).
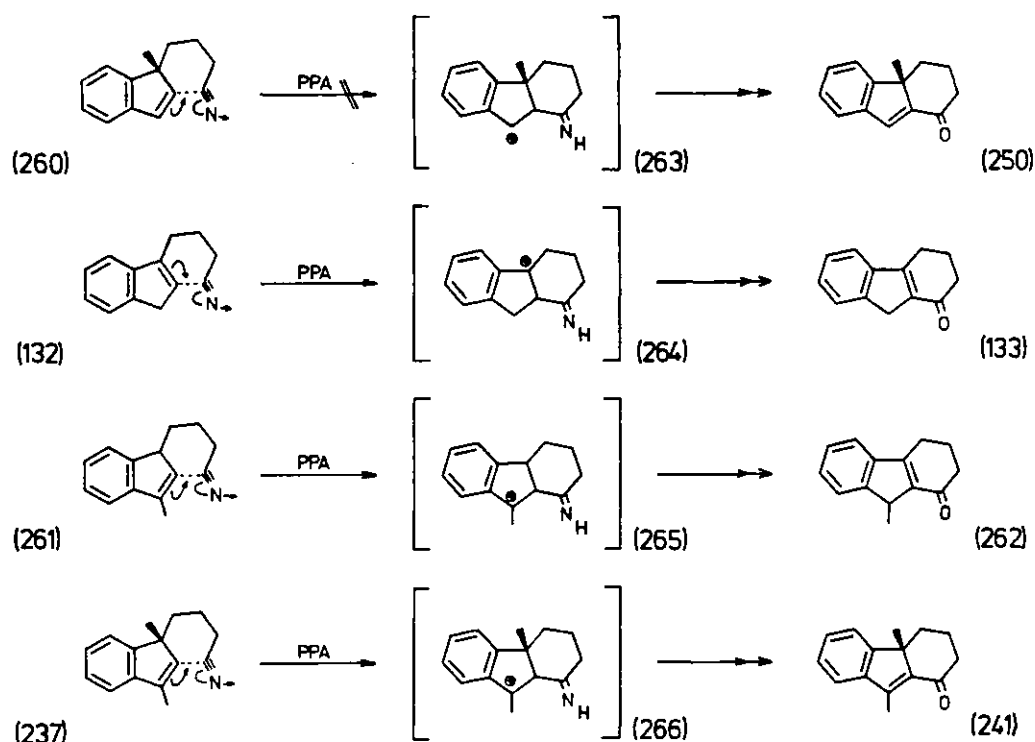
SCHEME 77

One other approach was investigated, based on the literature synthesis of 4a-methylhexahydrofluoren-9-one (131) (Chapter One, Section 4(ii)). The fluorenone (131) was prepared by the known route and treated with the BSA-iodylbenzene reagent in refluxing chloro-benzene. As anticipated, reaction was very slow due to the steric inaccessibility of the 9a position as previously discussed. The only material identified from the nmr of the crude product was 4a-methyl-2,3,4,4a-tetrahydrofluoren-9-one (267), and the mixture became
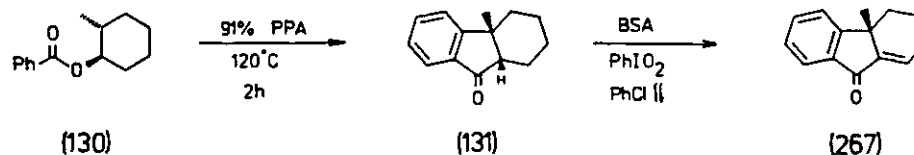
SCHEME 78

complex before adequate yields could be realised (Scheme 78).

4) Synthesis of 4a-Methyl-4aH-fluorene.

Following the development of a route to 4a-methyl-2,3,4,4a-tetrahydrofluoren-1-one (250), as described in Section 2, the remaining steps in the synthesis of 4a-methyl-4aH-fluorene (3) were expected to parallel exactly the closing steps of the synthesis of 4a,9-dimethyl-4aH-fluorene (222) (Section 1). This indeed proved to be the case (Scheme 79).
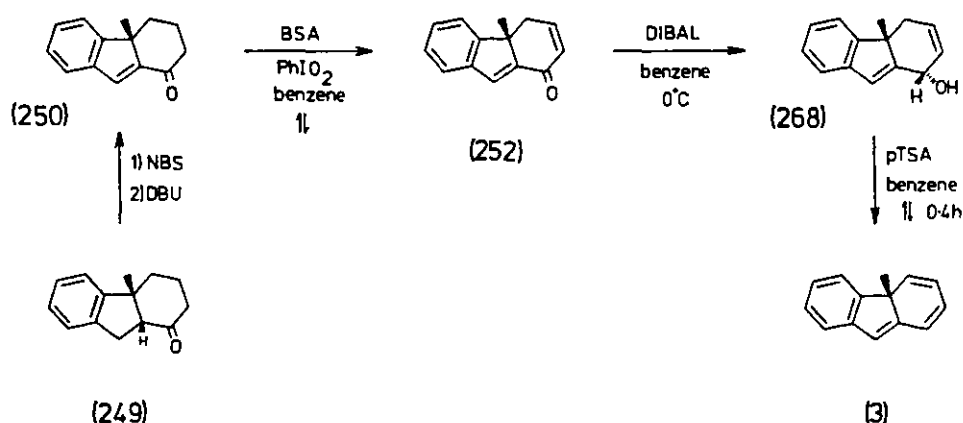
SCHEME 79

Oxidation of enone (250) with iodylbenzene-BSA in refluxing

benzene gave dienone (252) in 72% yield; normally the ketone (249) was subjected to the entire bromination-dehydrobromination-dehydrogenation sequence without isqlating the intermediates, giving an overall yield of 30-50% of dienone (252), dependent on the yield of the bromination step. Reduction with DIBAL then gave dienol (268), which was directly dehydrated as before to give the target 4a-methyl-4aH-fluorene (3) in 55% yield from dienone (252) and 17% overall yield from 2,3,4,9-tetrahydrofluoren-1-one (133). The stereochemistry of the DIBAL reduction was established by an n.O.e. difference experiment, and was identical to that in the dimethyl series.

The final dehydration reaction, common to both the monomethyl and dimethyl syntheses, requires some further comment; observations made for both sequences are grouped together for convenience. It is clearly vital that the final step of any 4aH-fluorene synthesis should generate the target system under conditions mild enough to allow it to survive. In the present case, the acid catalyst caused slight re-arrangement to an aromatic fluorene (< 5%) and some thermal dimerisation usually occurred (< 10%) (see Chapter Five for further discussion of these reactions), but careful attention to the quantity of catalyst used and the reaction time minimised these impurities, and flash column chromatography on silica gel then gave a hydrocarbon fraction containing > 90% of the desired product.

Some attempt was made to prepare a crystalline derivative of dimethyldienol (248) so as to provide a more convenient 4aH-fluorene precursor, but without success. Reaction of the dienol with either tosyl chloride or 3,5-dinitrobenzoyl chloride in the presence of pyridine or poly-4-pyridine resulted in complex mixtures including small amounts of the 4aH-fluorene (222) and a compound later identified as a symmetrical dimer of the 4aH-fluorene (see Chapter Five). It seems likely that elimination occurred via a first-formed tosylate or

3,5-dinitrobenzoate in each case, since treatment of the dienol (248) with poly-4-vinylpyridine hydrochloride alone resulted only in slow deterioration.

Other dehydration methods were applied to the monomethyldienol (268), but again without success. Treatment of the dienol with thionyl chloride in pyridine caused complete destruction of the material, while treatment with methyltriphenoxyphosphine iodide (MTPI) in hexamethyl-phosphoramide (HMPA), followed by 10% aqueous sodium hydroxide did give the required 4aH-fluorene, but only in 10% yield.

Finally, it may be noted that dienones (241) and (252) are themselves 4aH-fluorene precursors via their enol forms. To test the possibility of forming enol derivatives, the dimethyldienone (241) was treated with trimethylsilylchloride, sodium iodide and triethylamine in acetonitrile solution, and gave the O-trimethylsilyl enol ether (269) in low yield (10%) after distillation and flash chromatography on basic alumina (Scheme 80). No further investigation of this material was undertaken beyond the observation that it deteriorated into a complex mixture within a few days on standing in dilute $CDCl_3$ solution.

TMSCl
NaI
NEt₃
MeCN

(241)   (269)   10%
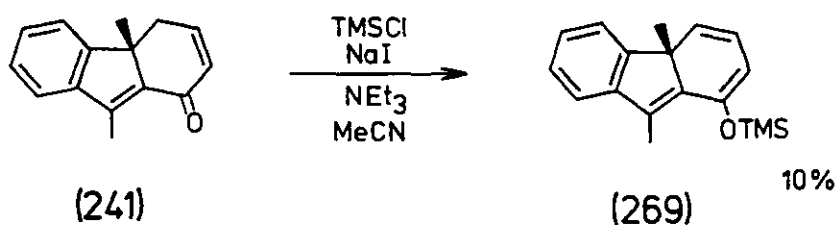
SCHEME 80

CHAPTER FIVE

CHAPTER FIVE: Chemistry of 4aH-Fluorenes.
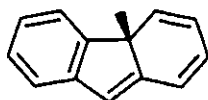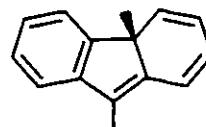
(3)   (222)

1) Properties.

4a-Methyl-4aH-fluorene (3), when prepared as described in the

previous chapter, is a pale yellow, mobile oil which polymerises and

oxidises rapidly when neat, but can be stored in dilute solution at

-20°C under nitrogen for a few days without loss.   The material was

fully characterised by the usual methods, although with some of these

the instability of the compound made some compromise necessary.   It

was not found possible, for instance, to obtain an analytical sample

free of oxidation products; freshly prepared material, isolated under

nitrogen and sealed for analysis within 5 minutes of chromatography,

was found to contain up to 8% of oxygen.   The ratio of carbon to

hydrogen was found to be correct, however, so this parameter

was used in the characterisation, not only of this material but also

of other oxidatively unstable hydrocarbons to be described in this

chapter.   In order to minimise deterioration, solutions were kept

dilute where possible; whenever concentrated or neat material was

re-diluted with light petroleum, traces of a flocculent white solid,

presumably the oxidised polymer, precipitated and were removed by

filtration.   4a,9-Dimethyl-4aH-fluorene (222) behaved similarly.

The spectral properties of 4aH-fluorenes (3) and (222) were, as

expected, very similar, and all were consistent with the proposed

structures. Their uv spectra, although less intense, were qualita-
tively similar to that of 4a-methyl-1,3,9-triphenyl-4aH-fluorene (119),
with the exception that the bands in the region 250-270nm due to the
phenyl substituents of the latter were absent from the spectra of the
former. The ir spectra of compounds (3) and (222) showed a pattern
in the aromatic C-H overtone region (2000-1600cm^{-1}) characteristic of
an o-disubstituted benzene, but were otherwise not useful except as
fingerprints. The mass-spectra were almost featureless, the only
major loss being that of methyl to give the base peak at 165mu for
compound (3), and 179mu for compound (222). The intensities of these
peaks clearly reflect the stability of the fluorenyl cations so formed;
a similar loss of methyl was observed during flash vacuum pyrolysis of
compound (3) (Section 4(ii)).

The ^{1}H nmr (CCl$_4$; 90 MHz) of the monomethyl compound (3) showed
a three proton singlet at δ 1.37 due to the methyl group, a complex
multiplet at δ 6.7-7.3 due to the aromatic protons, another at δ 5.7-
6.05 due to H$_2$ and H$_3$, while H$_1$, H$_4$ and H$_9$ were coincident at δ 6.4-6.55.
The dimethyl compound (222) differed only in that the resonance of H$_9$
was replaced by a three proton singlet at δ 2.11, while one of H$_1$ and
H$_4$, presumably H$_1$, resonated at slightly lower field than in compound
(3). Protons H$_1$ and H$_4$ of compound (222) thus appeared as slightly
broadened doublets (J = 9 Hz) at δ 6.57 and δ 6.46 respectively.

Little progress could be made in assigning the ^{13}C nmr spectra
of compounds (3) and (222). The compounds themselves dimerised
appreciably during the time required to collect the data, so compli-
cating the interpretation; nonetheless it was possible to distinguish
which lines arose from the monomer since they progressively decreased
in intensity as the data collection continued (Fig.33; facing p.226).
The shifts of the bridgehead methyl groups (δ 30.5 and δ 29.9 resp.) and
C$_{4a}$ (δ 54.5 and δ 53.6 resp.) were closely similar between compounds

(3) and (222), while the somewhat high field resonance of the C_9
methyl group of compound (222) (δ 10.2) is probably due to "γ-gauche"
interactions involving H_1 and H_8.[153]

2) Dimerisation.

On standing in neutral solution, 4a-methyl-4a$\underline{H}$-fluorene (3)
dimerises. The most convenient method of generating the dimer was to
leave a solution of 4a$\underline{H}$-fluorene (3) (1.5M in carbon tetrachloride)
to stand in an nmr tube at $60^\circ C$, monitoring the reaction by ^1H nmr.
After 18h, conversion was almost complete and preparative multiple
elution tlc then provided a pure specimen.

The structure of the dimer was established by a series of nmr
experiments. The normal spectrum (at 250 MHz in $CDCl_3$; Figures 9
and 10, base) clearly shows that the dimer is unsymmetrical, having two
methyl groups, four aliphatic protons, six olefinic protons of which
two, the original H_9 protons, are singlets, and eight aromatic protons.
Decoupling of all the aliphatic and olefinic multiplets revealed the
connectivity pattern summarised in Figure 8; protons are coded alpha-
betically in order of decreasing shift. This connectivity pattern
immediately suggests that the product is a [4+2] cycloadduct in which
H_G, H_D, H_E, and H_I originated from the 4π component, and H_B, H_F, H_H
and H_J from the 2π component; this would imply, however, that H_I and
H_J are vicinally related despite not showing a mutual coupling.

A series of n.O.e. difference experiments (Table 7 and Figures
9 and 10; see also Chapter Six) completed the structure proof.
Analysis of these results showed that only structure (270) is consistent
with all the enhancement data. In particular, the proximity of Me_B
to H_E and of Me_A to H_J showed that the original 4a$\underline{H}$-fluorene components
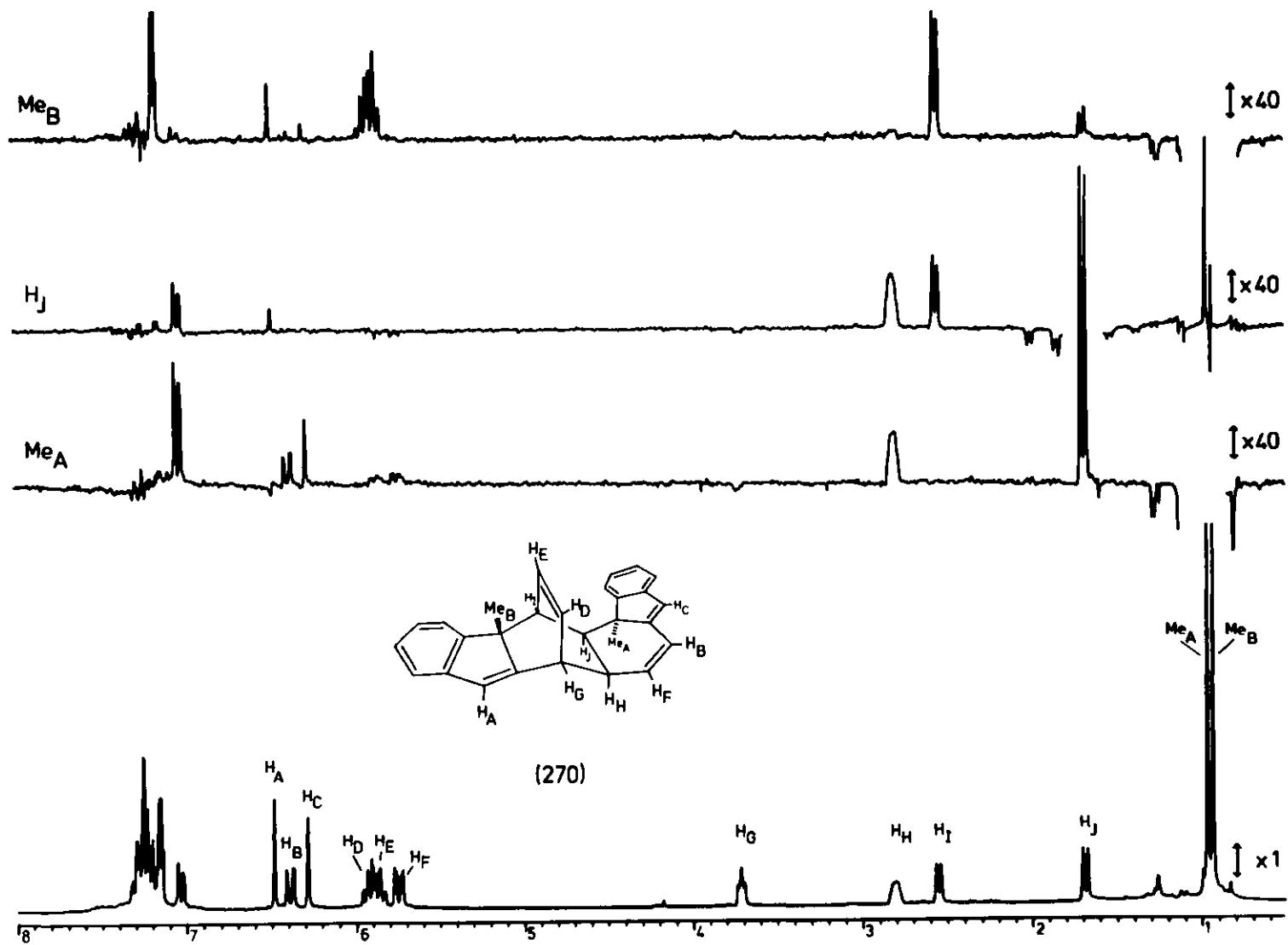
FIGURE 10 N.O.e. difference spectra of the unsymmetrical dimer (270).
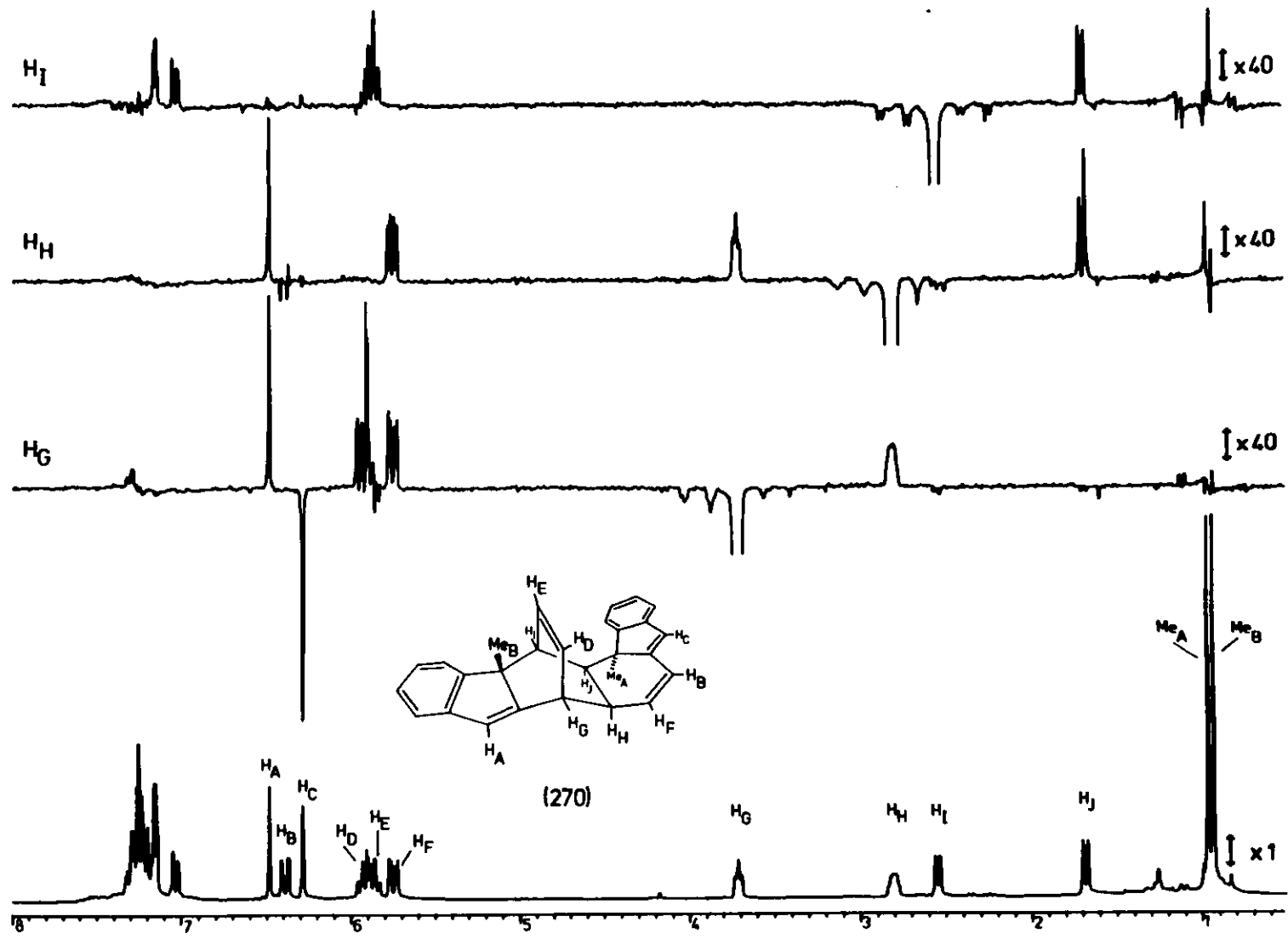
FIGURE 9 N.O.e. difference spectra of the unsymmetrical dimer (270).
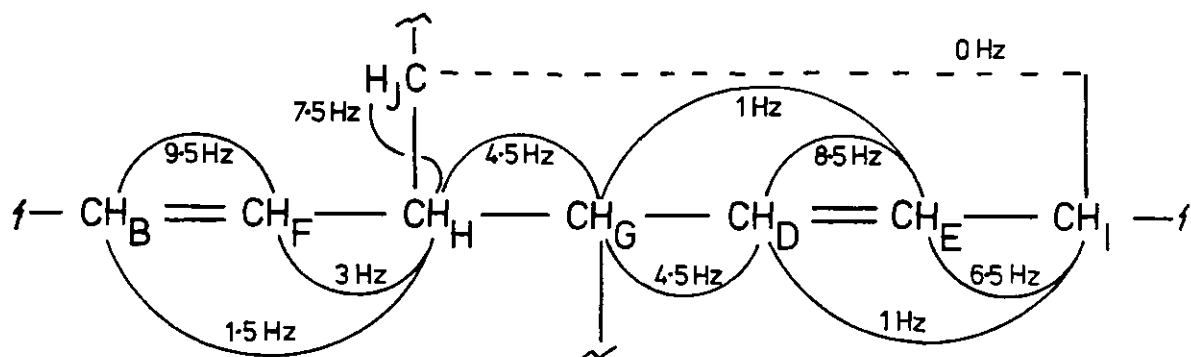
FIGURE 8
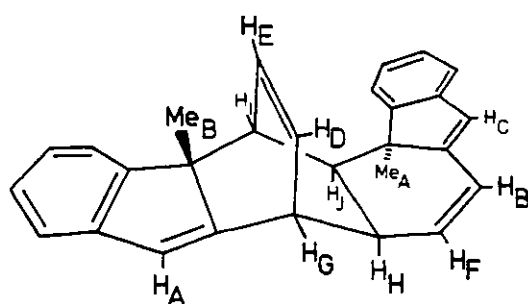
(270)

Pre-irradiate	Observe $\underline{a}$
H_G	$H_A(4.5\%)$, $H_D(8\%)$, $H_F(5\%)$, $H_H(4.5\%)$
H_H	$H_A(3.5\%)$, $H_F(4.5\%)$, $H_G(4.5\%)$, $H_J(5\%)$
H_I	$H_E(5.5\%)$, $H_J(3.5\%)$
H_J	$H_H(5.5\%)$, $H_I(4\%)$, $Me_A(1\%)$
Me_A	$H_B(2\%)$, $H_C(1.5\%)$, $H_H(6\%)$, $H_J(14.5\%)$
Me_B	$H_E(5\%)$, $H_I(7.5\%)$.

TABLE 7

$\underline{a}$ - enhancements quoted to the nearest 0.5%.

reacted in the orientation which would be expected on steric grounds, having both methyl groups as spatially remote from the sites of bond formation as possible. Also as expected, the 2π component was

provided by the terminal double bond of one triene system, resulting

in minimum loss of conjugation on reaction. A model of structure

(270) showed that the torsion angle (H_I, C, C, H_J) was close to 90° as

required by the coupling data; although it might at first appear that

symmetry would require this angle to be similar to torsion angle

(H_G, C, C, H_H), the model revealed that the bicyclo[2.2.2]oct-2-ene

moiety of hydrocarbon (270) was severely twisted as a result of the

fusion of the indene ring system to one face, so accounting for the

observed couplings.

This dimerisation in neutral solution was particularly clean, no

other products being detected; it is interesting to note that this

requires total enantioselectivity during the cycloaddition.

In the presence of Brønsted or Lewis acids a different dimer was

formed. As this new dimer was symmetrical, its structure was much more

difficult to elucidate, but the ^{1}H nmr (Figure 12, base) was particularly

informative. Decoupling experiments revealed the coupling connectivity

patterns summarised in Figure 11; protons are again coded alphabetically

in order of decreasing shift.
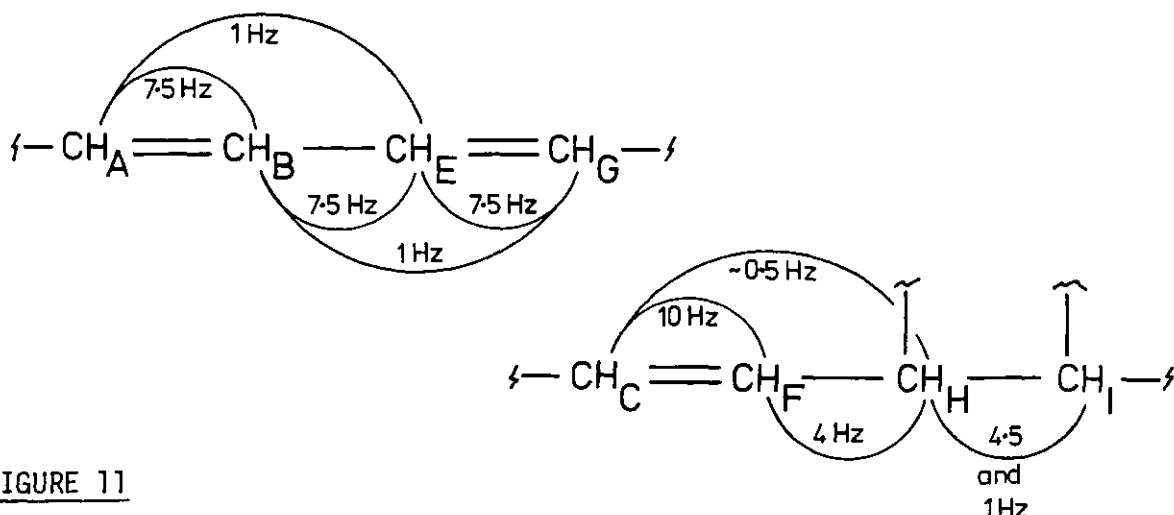
FIGURE 11

The most obvious feature of these data is that, of the four

olefinic protons of each original 4aH-fluorene component, two (H_H and

H_I) have become aliphatic in the symmetrical dimer, and their position
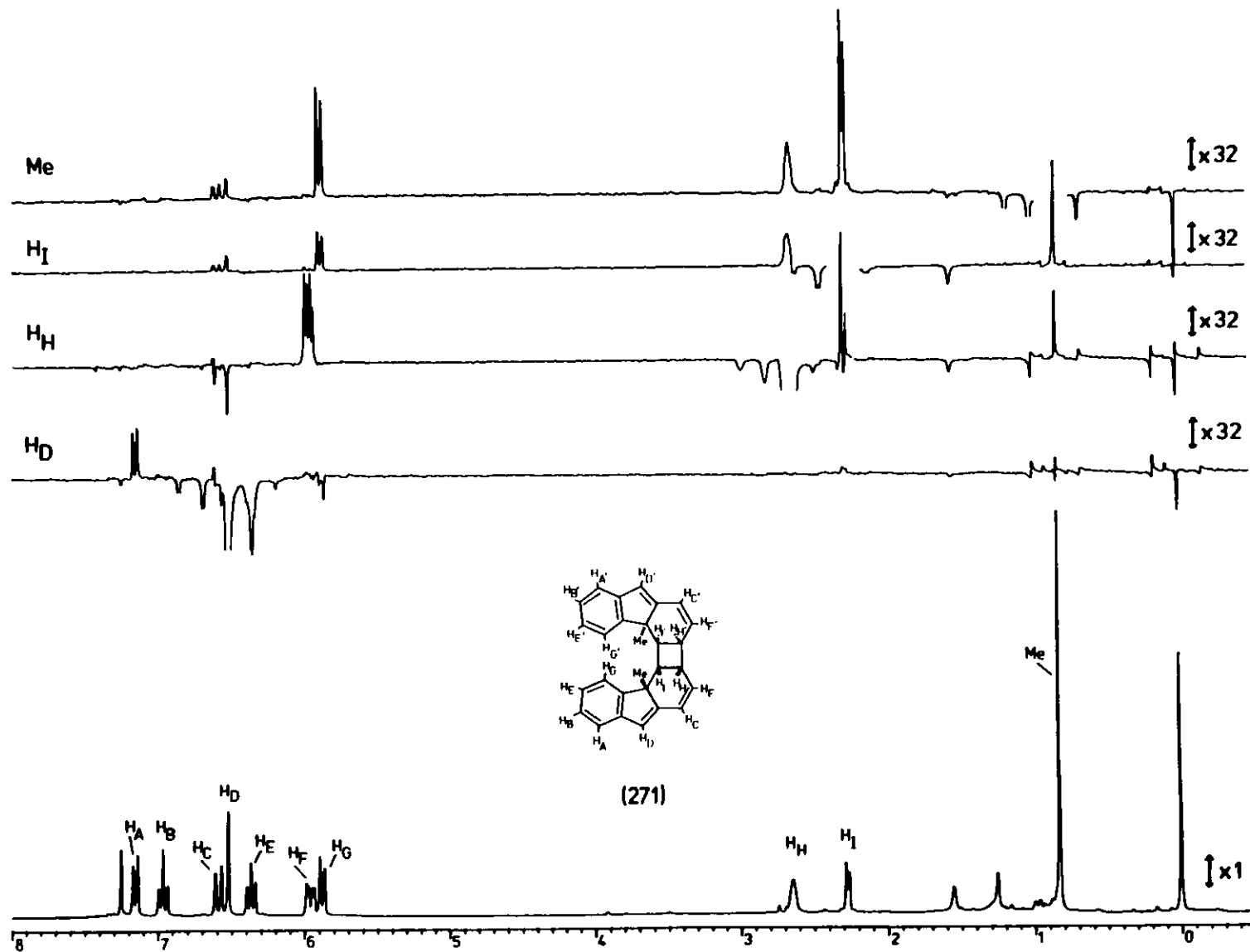
FIGURE 12   N.O.e. difference spectra of the symmetrical dimer (271).

within their coupling chain proves that the dimer must be a symmetrical
cyclobutane. Another very striking feature is the wide shift
dispersion of the four aromatic protons, H_A, H_B, H_E and H_G, which
resonate between δ 7.16 (H_A) and δ 5.88 (H_G). For comparison, protons
attached to the aromatic rings of 4aH-fluorene (3), its adducts
(Section 3), its precursors (Chapter Four), or the unsymmetrical dimer
(270), usually resonate as a highly complex second order pattern
occupying less than 0.4ppm at 250 MHz. Confirmation that these protons
are still attached to an aromatic ring in the symmetrical dimer is
provided by the magnitudes of their vicinal coupling constants
(Figure 11); the value of 7.5 Hz is typical for an aromatic C-C bond
length, and its constancy shows there to be no bond alternation.

The only plausible explanation for this unusual shift dispersion,
and particularly for the high field resonance of H_G, is that the two
symmetrically related aromatic rings of the dimer must be close to-
gether in space, and staggered so as to bring the H_G proton on each
ring into the deshielding region of the other. This condition limits
the possible structures for the symmetrical dimer to just one, cyclo-
butane (271).

All head-to-tail dimers are clearly excluded, since their aromatic
rings must be too far apart; a similar conclusion holds for head-to-
head structures in which the cyclobutane ring connects the original
C_1 and C_2 atoms of each component. The latter structures are still
more decisively eliminated by the observation of strong enhancements of
H_H and H_I on pre-irradiation of the methyl resonance (Figure 12).
This leaves only four possible symmetrical structures, (271)-(274).
Models clearly showed that structures (272) and (274) do not allow
close approach of the two aromatic rings, while in structure (273)
these rings are forced to occupy virtually the same space. In contrast,
structure (271) brings the two aromatic rings into exactly the relative

(271)

(272)

(273)

(274)
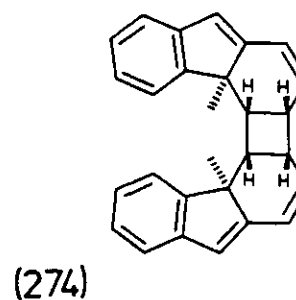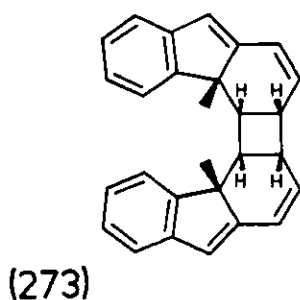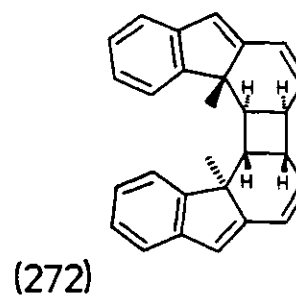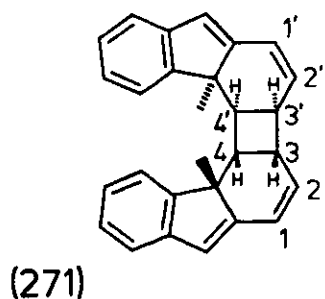
arrangement required to explain the shift data.

While this is, perhaps, short of a conclusive proof, it is at least very strongly suggestive that structure (271) is correct. Some further evidence for the cyclobutane ring was provided by the multiplicities of H_H and H_I. All the symmetrically related protons in structure (271), although chemically equivalent, are magnetically non-equivalent. Observable consequences of this would only be expected for the protons on the cyclobutyl ring, since the rest are too remote from their symmetrical partners for these pairs to share a coupling with any common proton. The cyclobutyl protons, however, should give rise to an AA'XX' sub-spectrum, and this was observed: although further couplings make the H_H resonance too complex to resolve, the pattern due to H_I was clearly a double doublet (J = 4.5 Hz and 1 Hz), and irradiation of H_H caused both couplings to collapse as required (Figure 13).

$J_{HI} = J_{H'I'} = 4 \cdot 5 \, Hz$

$J_{H'I} = J_{HI'} = 1 \, Hz$

$J_{HH'}$ and $J_{II'}$ not observed
due to equivalence
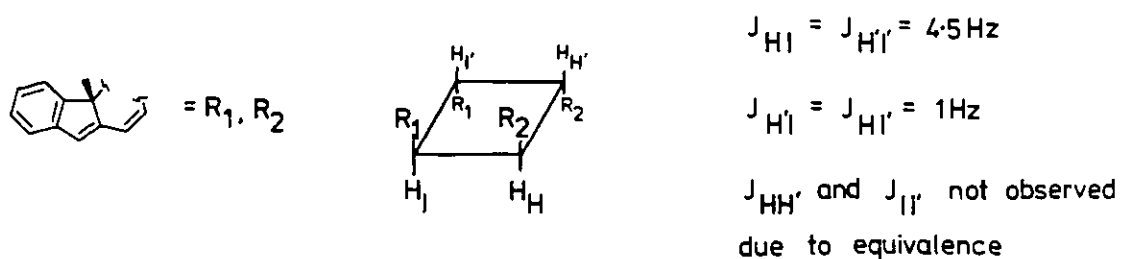
FIGURE 13

The origin of the symmetrical dimer remained obscure for some time. Small quantities of both the unsymmetrical (270) and symmetrical (271) dimers were formed during most reactions of 4a-methyl-4aH-fluorene (3), both being easily identifiable by their characteristic methyl resonances in the ^1H nmr. Their relative proportion appeared to depend mainly on the acidity of the reaction medium, higher acidity favouring compound (271). The highest yield of dimer (271) was formed during reaction of 4aH-fluorene (3) with N-chlorosulphonylisocyanate (CSI). Although intended as a dienophile, this reagent acted instead as a powerful dimerisation catalyst, dimers (270) and (271) being formed in roughly a 1:2 ratio (by nmr) after 0.6h at 20^0C in carbon tetrachloride, and dimer (271) being isolated in 24% yield. Other examples will be mentioned as they occur in subsequent sections.

It may be noted that structures (270) and (271) may be formally interconverted via a [1,3] shift of the $CH_G—CH_H$ bond in compound (270); this observation led us to consider whether the symmetrical dimer (271) originated, not from the monomer (3), but from the unsymmetrical dimer (270). To test this possibility, a sample of dimer (270) was left to stand in carbon tetrachloride-$[^2H_6]$acetone solution acidified with p-toluenesulphonic acid (0.7 equiv.), and the reaction monitored by ^1H nmr. It was found that almost complete conversion into dimer (271) occurred over a period of some days; the approximate progress of the

reaction, estimated using the change in intensity of the corresponding methyl resonances in the nmr, is summarised in Table 8. The process is evidently one of slow equilibration. The apparently greater stability of the cyclobutane (271) seems strange at first, but may reflect the severe twisting of the bicyclo[2.2.2]oct-2-ene moiety in dimer (270) already mentioned. Several minor products (each < 5%) were also formed, but were not identified.

Time	Conversion (± 5%)
0.6h	5%
13h	25%
20h	33%
42h	50%
110h	75%

TABLE 8

(270)   (275)   (271)
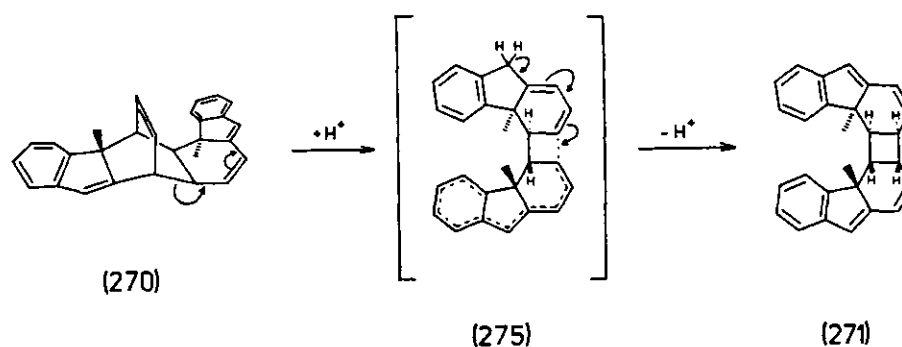
SCHEME 81

While it is possible that this reaction proceeds via the free monomer (3), the mechanism shown in Scheme 81 is perhaps more likely, especially in view of the absence of 4-methyl-9H-fluorene (281), the expected acid-rearrangement product of 4aH-fluorene (3). Some slight evidence in favour of the intermediacy of carbonium ion (275) was

provided by a small relative decrease ($\sim$ 20%) in the intensity of the

resonance of H_D (i.e. H_9 and $H_{9'}$) in the product (271) isolated from

this experiment. This might be due to specific deuterium incorporation

from the acid medium; almost all the hydroxyl protons in the system

exchanged with deuterons from the $[^2H_6]$acetone within the first few

hours of the experiment, as shown by the absence of the acid OH resonance

(previously at δ 7.6-8.1) and the marked increase in intensity of the

$[^2H_5]$acetone signal after this time, the medium thus becoming, in effect,

a deuterium acid.

Dimers of 4a,9-dimethyl-4aH-fluorene (222) were not investigated

as fully as those from the monomethyl series. Observation of the

characteristic high field methyl resonances expected for the correspond-

ing unsymmetrical (276) and symmetrical (277) dimers, however, showed

them to be formed under similar conditions to their monomethyl derived

analogues, although thermal formation of dimer (276) seemed slower than

that of dimer (270). Dimers (277) and, to a lesser extent, (276) were

minor products in the attempted derivatisations of dimethyldienol (248)

mentioned earlier (Chapter Four, Section 4); on one occasion dimer

(277) was isolated and shown to have an nmr spectrum exactly analogous

to that of dimer (271). Evidently the tosyl and 3,5-dinitrobenzoyl

chlorides used in these reactions were acting as Lewis acids in catalysing

formation of dimer (277), presumably via 4a,9-dimethyl-4aH-fluorene (222)

and dimer (276).
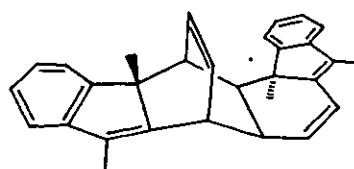
(276)
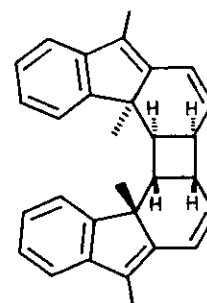
(277)
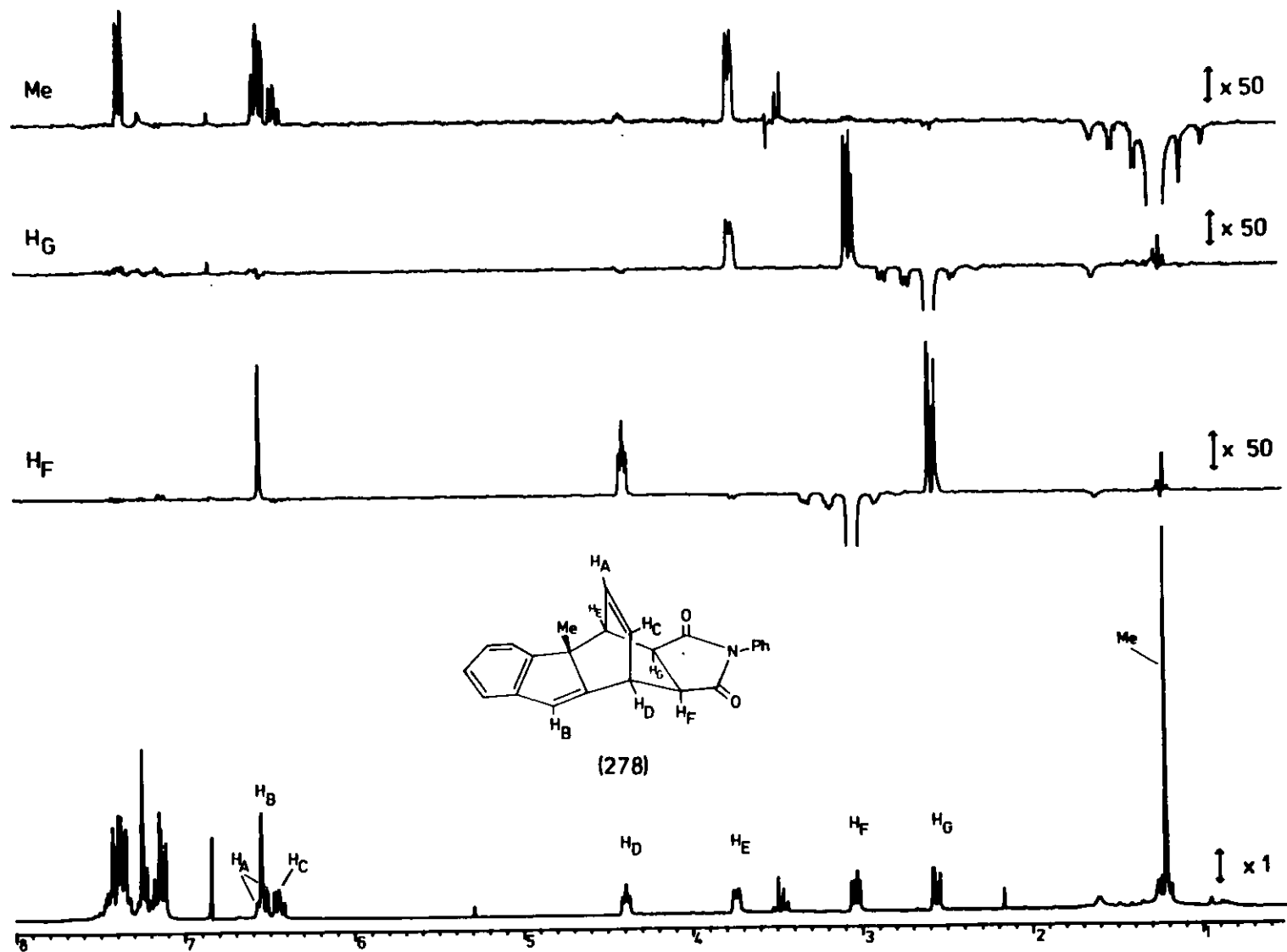
FIGURE 14   N.O.e. difference spectra of the N-phenylmaleimide adduct (278).

Some support for this suggestion comes from an experiment in the monomethyl series, in which 4a-methyl-4aH-fluorene (3) was left to stand with tosyl chloride (1 equiv.) in dichloromethane, resulting in conversion into a roughly equimolar mixture of dimers (270) and (271) over several days at $20^{\circ}C$. Treatment of 4aH-fluorene (3) with boron trifluoride etherate, however, resulted in an intractable mixture, even at $-40^{\circ}C$.

3) Diels-Alder Reactions.

Reactive dienophiles undergo cycloaddition reactions with 4a-methyl-4aH-fluorene (3) in a [4+2] sense. The stereoisomerism of the adduct obtained with N-phenylmaleimide was established by a series of n.O.e. difference experiments (Figure 14; see also Chapter Six); protons are coded as previously, and the assignments follow straight-forwardly from the enhancement data. The fact that pre-irradiation of H_F or H_G caused no enhancement of H_A or H_C shows that the product is an endo-adduct (with respect to the original 4π component), while the strong enhancement of H_A on pre-irradiation of the methyl signal shows that attack of the dienophile occurred from the face opposite to the methyl group; only structure (278) is compatible with these requirements. Twisting of the bicyclo[2.2.2]oct-2-ene moiety is evidently

(3)   (278)   + Dimer
                                                         (270)
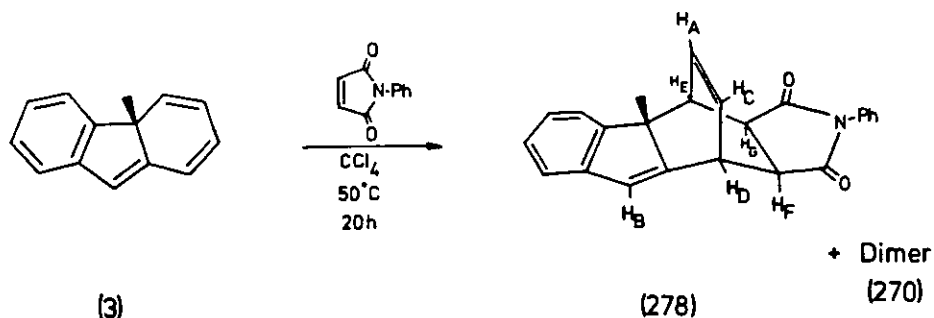
SCHEME 82

less severe in this adduct than in the unsymmetrical dimer (270),

since the spectrum of adduct (278) shows a non-zero value for $J_{E,G}$.

As in the case of the [4+2] dimerisation reaction, the adduct

is that expected on steric grounds and is the only stereoisomer

produced. The reaction was quite slow, however, and dimerisation of

the 4a$\underline{H}$-fluorene occurred at roughly the same rate; after 20h at

50°C an initially equimolar mixture of 4a$\underline{H}$-fluorene (3) and $\underline{N}$-phenyl-

maleimide was converted into approximately equal quantities of adduct

(278) and dimer (270), with some starting material remaining.

In contrast, 4-phenyl-1,2,4-triazoline-3,5,-dione (PTAD) reacted

almost instantly with 4a$\underline{H}$-fluorene (3), even at 0°C in dilute dichloro-

methane solution. The nmr spectrum of the crude product, if recorded

immediately after the reaction, was consistent with formation of the

expected adduct (279) in good yield, but, strangely, this substance

could not be isolated, and deteriorated into a complex mixture within

an hour or so.

(3)   (279)
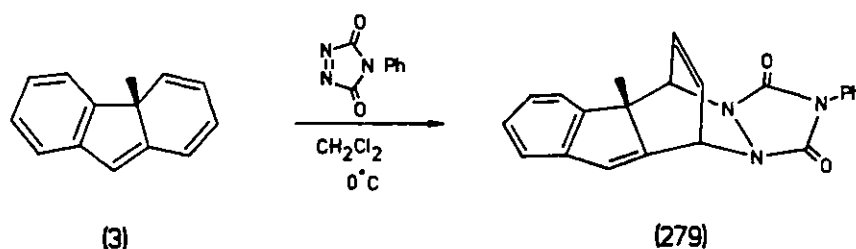
The reaction of PTAD with 4a,9-dimethyl-4a$\underline{H}$-fluorene (222) gave a more

complex mixture, but the major component could be separated by preparative tlc.

As previously, this material was unstable and eluded characterisation; the

available evidence, however, strongly suggests that it is the $\underline{bis}$-adduct (280).

Thus the material showed an N-H stretching band (ir), and nmr resonances

consistent with the presence of one methyl group only, an $\underline{exo}$-methylene group,

and two new phenyl groups. Perhaps most convincing, the mass-spectrum was

dominated by the fragmentation shown (Scheme 83), which would have been

blocked had the "ene" reaction not removed the indenyl double bond.

(280)
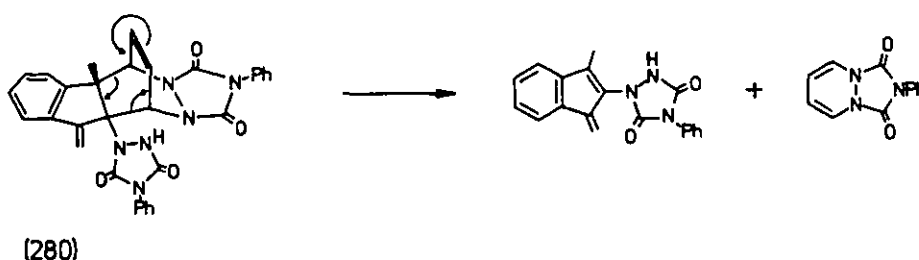
SCHEME 83

The only other dienophile studied was N-chlorosulphonylisocyanate (CSI) and, as previously mentioned (Section 2), this failed to give an adduct.

These experiments largely confirm in chemical terms that which physical measurements and calculations had earlier suggested (Chapter Two, Section 1), namely that the 4aH-fluorene system behaves as a 1H-indene unit conjugated to a diene unit. The [8+2] cycloadditions observed with non-fused 3aH-indenes (Chapter One, Section 2) are, as would be expected, totally supressed by the fused benzo substituent in 4aH-fluorene (3). In an effort to demonstrate further this diene reactivity of the non-aromatic six membered ring, and also to parallel the known formation of an iron tricarbonyl complex of hydrocarbon "A" (119),[25] 4a-methyl-4aH-fluorene (3) was treated with diiron nonacarbonyl and 4-methoxybenzylideneacetone in dry benzene at 55°C under nitrogen, but the only reaction observed after 7h was decomposition of the iron reagent.

4) Rearrangements.

i) With acids.

The effect of Lewis acids on 4a-methyl-4aH-fluorene (3) has

already been described (Section 2). Their overall effect was to transform the 4aH-fluorene into a mixture of the unsymmetrical dimer (270) and the symmetrical dimer (271), the former being a probable intermediate in the formation of the latter. The rate of reaction depended markedly on the strength of the acid; the weakest, tosyl chloride, took days to bring about reaction, while CSI required only 0.6h and boron trifluoride etherate rapidly brought about complete decomposition.

The same reactions were observed with protic acids but here a second type of reaction also became important, namely aromatisation via methyl shifts. Thus, on refluxing for 1h in benzene containing p-toluenesulphonic acid (1 equiv.), 4a-methyl-4aH-fluorene (3) was converted into a mixture of the symmetrical dimer (271) (15%), unsymmetrical dimer (270) (< 5%), and two fully aromatic methylfluorenes (combined yield 30%; isomer ratio 10:1). The poor recovery was probably due to competing polymerisation processes; on another occasion evaporation of a crude, freshly prepared solution of 4aH-fluorene (3) without prior removal of the acid catalyst caused complete polymerisation of the solute, yielding a film resembling cellophane.

The substitution patterns of the two aromatic fluorenes were established by a series of n.O.e. difference experiments, which, since the fluorenes were inseparable, were run using a purified mixture of both (Figures 15 and 16; see also Chapter Six). The major component of the mixture was clearly 4-methyl-4aH-fluorene (281) (Figure 15). Pre-irradiation of the methyl group caused enhancements of two doublets in the aromatic region, one of which, H_3, was relatively strongly enhanced ($\sim$ 12%), the other, H_5, less so ($\sim$ 6%), while pre-irradiation of the methylene group caused roughly equal enhancements ($\sim$ 4%) of two aromatic doublets, H_1 and H_8; no enhancements (within experimental error) were observed between the methyl and methylene groups. These
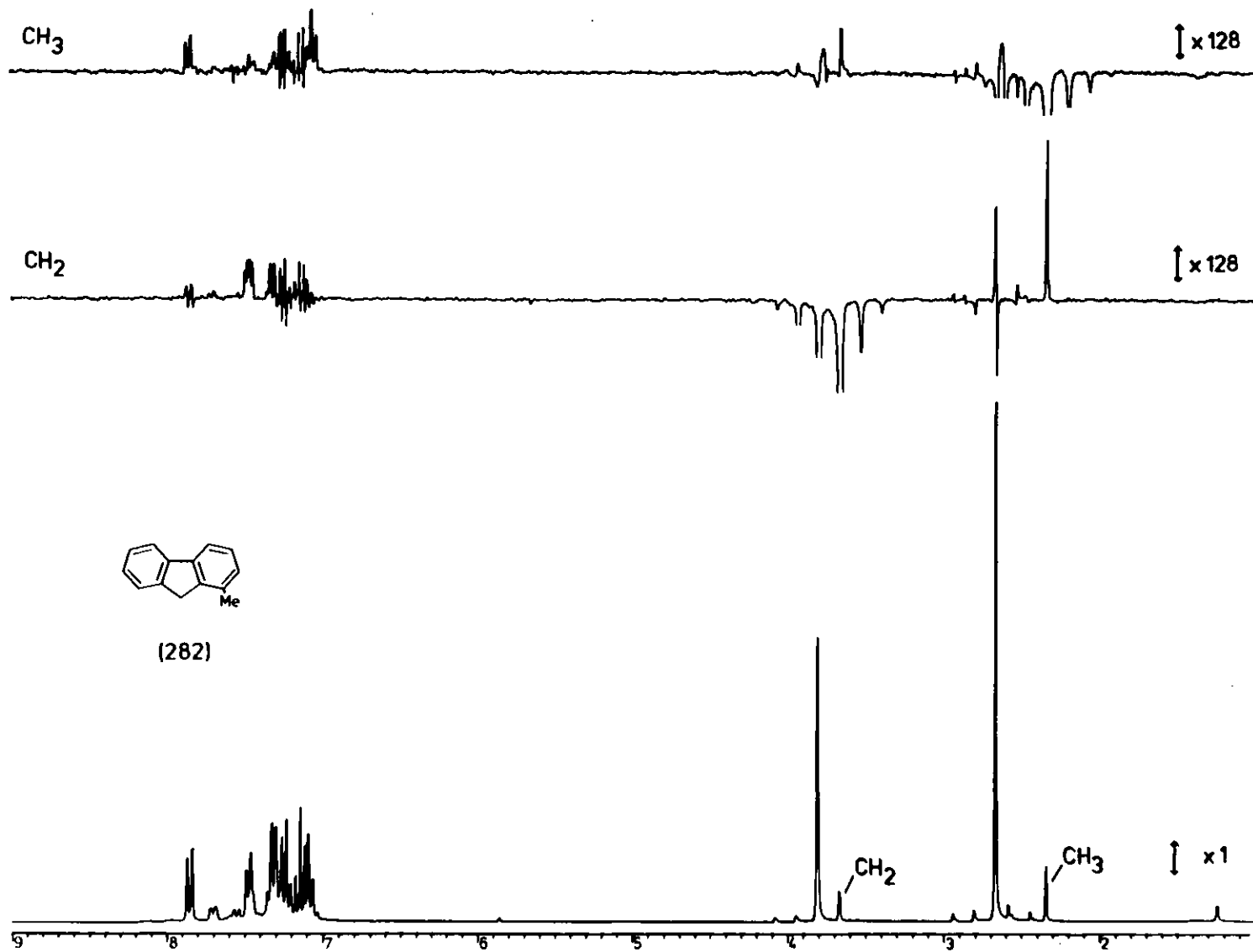
FIGURE 16 N.O.e. difference spectra of 1-methyl-9H-fluorene (282).
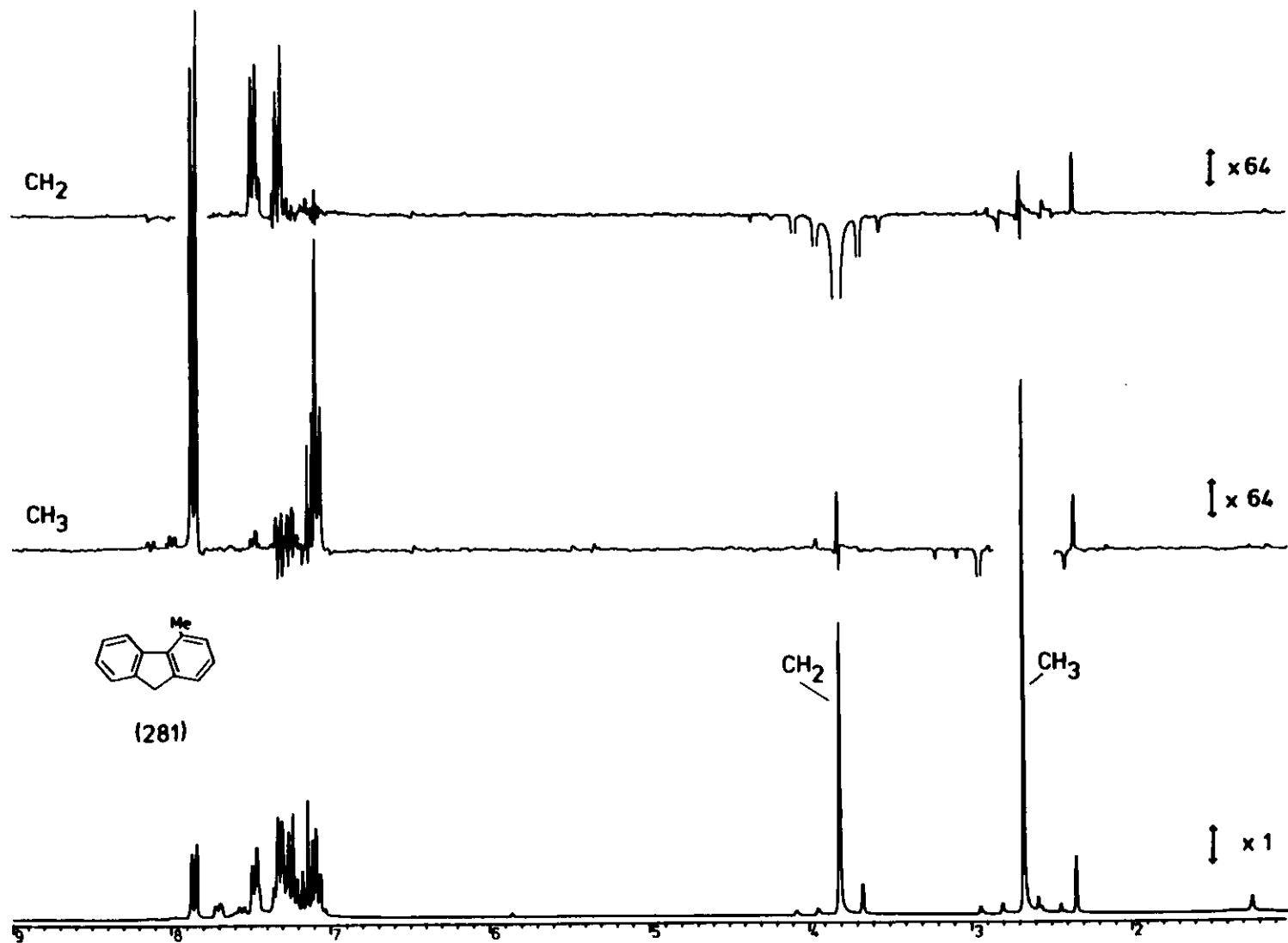
FIGURE 15   N.O.e. difference spectra of 4-methyl-9H-fluorene (281).

H_5 H_3

H_8 H_1

(281)

H_8 H_2
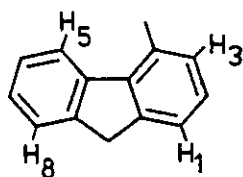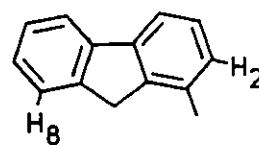
(282)

data are not consistent with any other methylfluorene structure.

The identification of the minor component as 1-methyl-9H-fluorene (282) is less secure, however. This is because the n.O.e. technique was here required to detect, selectively, modest enhancements of initially weak signals from within an envelope of other signals ten times as intense. As will be made clear in Chapter Six, this stretches the technique to its limit, but nonetheless some conclusions were possible.

Pre-irradiation of the minor methyl resonance (Figure 16) caused an enhancement ($\sim 5\%$) of one aromatic doublet, H_2, only. Although there were simultaneous very small enhancements of H_3 ($\sim 0.04\%$) and H_5 ($\sim 0.02\%$) in compound (281), caused by an unwanted slight saturation of the major methyl resonance, these could be distinguished by an accurate comparison of shifts (H_3 in compound (281) resonates at δ 7.08, H_2 in compound (282) at δ 7.04). In the case of pre-irradiation of the minor methylene group (Figure 16), interference from enhancements occurring in the major compound created more difficulty, owing to an exact overlap, but the quite different pattern of the multiplet enhanced at δ 7.48 in this experiment (Figure 16), compared to that previously observed at the same shift (Figure 15), suggested that a different proton was responsible in each case. This led to the conclusion that the multiplet enhanced at δ 7.48 in Figure 16 (middle trace) was due to H_8 in compound (282). Perhaps the most convincing evidence in favour of structure (282) is that none of the minor aromatic resonances enhanced in Figure 16 was a singlet, so excluding 2-methyl and 3-methylfluorene

from consideration. The mutual enhancements observed between the methyl and methylene resonances of the minor component (Figure 16) might seem more convincing, but the apparent enhancements (probably artefacts) of the minor methyl resonance during supposedly unrelated experiments (Figure 15) are disconcerting and remain unexplained.

Some further corroboration for these assignments comes from the literature nmr data in Table 9.

	Methyl	Methylene	Ref.
1-methylfluorene	δ 2.41	δ 3.76	154
2-methylfluorene	δ 2.36	δ 3.76	154
3-methylfluorene	δ 2.44	?	155
4-methylfluorene	δ 2.72	?	155

TABLE 9

In contrast with the above reaction involving p-toluenesulphonic acid, treatment of 4a-methyl-4aH-fluorene with a refluxing mixture of hydrobromic and acetic acids caused virtually no dimerisation, the substrate being instead rapidly converted into a mixture (60%) of fluorenes (281) and (282) in the same proportions as before. This result is reminiscent of Snyder's findings with hydrocarbon "A" (119) (Chapter Two, Section 3), which could only be rearranged using the hydrobromic-acetic acid mixture.[112]

The mechanisms of these methyl shifts are not entirely clear. Snyder's results imply that the thermodynamically favoured 4-protonated cation is probably not involved, since although acids other than hydrobromic did convert hydrocarbon "A" into such a cation (172), it then failed to rearrange. What evidence there is seems instead to suggest a specific involvement of the counterion, at least in the case
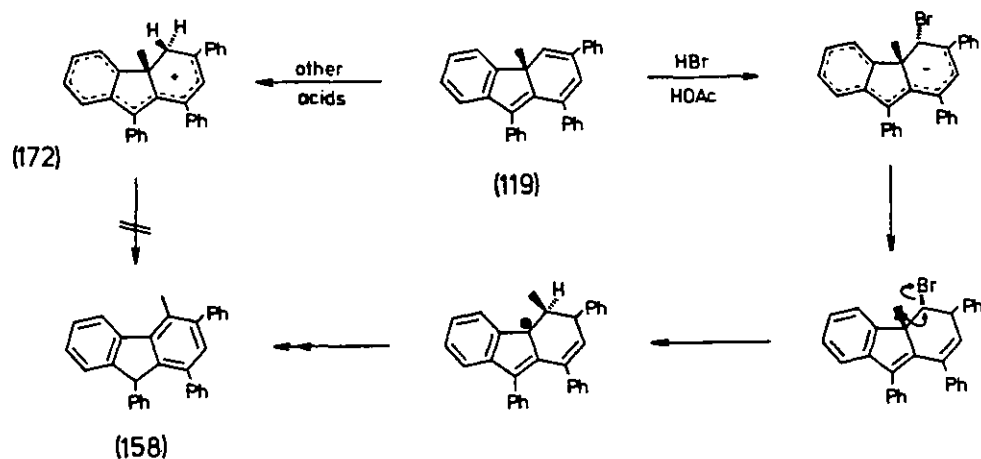
SCHEME 84

of hydrocarbon "A" (Scheme 84).

Similar mechanisms could apply to the unsubstituted 4aH-fluorene (3); formation of the 1-methyl isomer (282) in this case presumably occurs via carbonium ion (283), in which the alternative possibility of a shift to the 9-position is disfavoured by prior protonation at that site (Scheme 85).
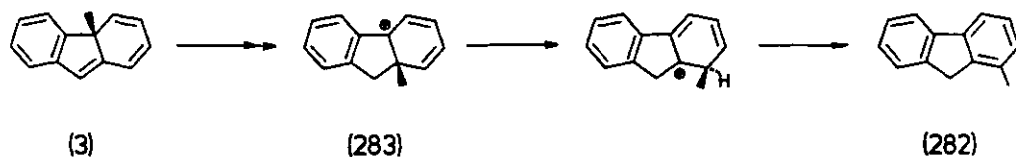
SCHEME 85

ii) Thermolysis.

Mild solution thermolysis of 4a-methyl-4aH-fluorene (3), as previously discussed (Section 2), gave the [4+2] cycloaddition dimer (270).

In contrast, flash vacuum pyrolysis at 650°C and 0.02-0.03mmHg led predominantly to aromatisation via methyl shifts. The products

obtained from the pyrolysate comprised a mixture of aromatic fluorenes

(50%), 9,9'-bifluorenyl (284) (28%), and an uncharacterised gum (20%),

apparently polymeric. The isomeric methylfluorenes could not be sep-

arated, but the composition of the mixture was assessed by nmr, and

found to include 9-methylfluorene (239), 4-methylfluorene (281) and

1-methylfluorene (282) in an approximate ratio of 60:3:2; these assign-

ments were made using data discussed in Section 3. The identity of

the 9,9'-bifluorenyl was established from its nmr spectrum, and confirmed

by a comparison of its melting point with the literature value (246°C).[156]

This reaction clearly parallels the pyrolysis of hydrocarbon "A"

(Chapter Two, Section 3), with the exception that no analogue of 9,9'-

bifluorenyl (284) was found in the latter reaction, presumably since

such a product would be prohibitively crowded. All the methylfluorene

products may be rationalised via a series of [1,5] and [1,9] sigmatropic

shifts (Scheme 86).
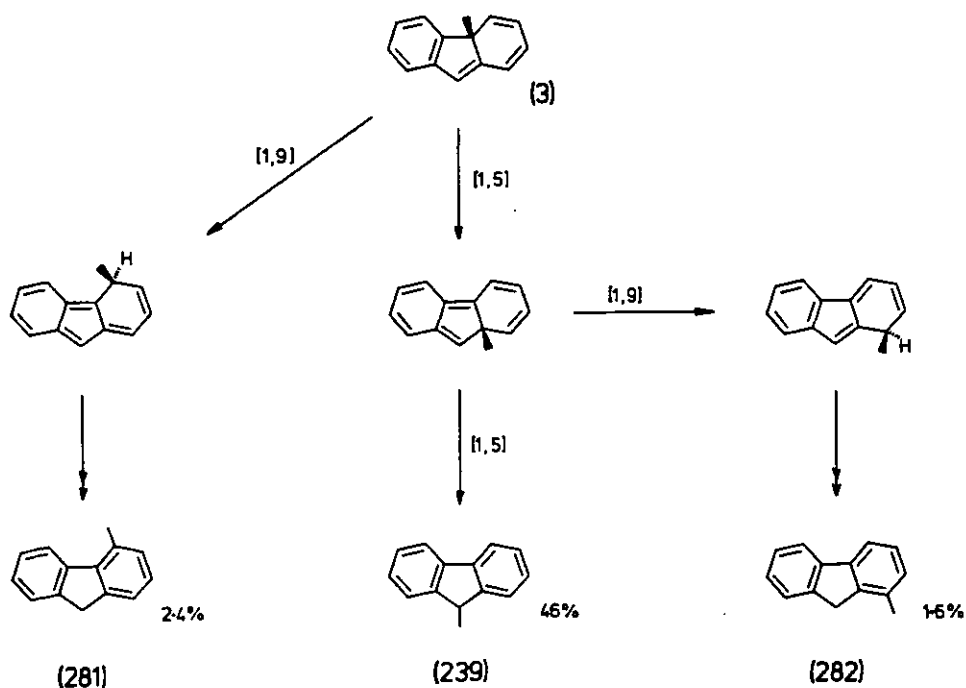
SCHEME 86

Analysis of the residual material from the sublimation flask

after FVP of 4aH-fluorene (3) showed that ∿ 30% of the substrate had

failed to sublime, and had been transformed, in the condensed phase,

into a mixture of the unsymmetrical dimer (270), the symmetrical dimer

(271) and 9,9'-bifluorenyl (284) in approximately equimolar proportions.

Consistent with the earlier discussion of its formation (Section 2),

formation of the symmetrical dimer (271) was cut by more than half when

the sublimation flask was washed with base immediately before the

experiment.

The presence of 9,9'-bifluorenyl (284) in the oven residues

strongly suggested that this material was formed in the condensed phase

and subsequently sublimed unchanged; a possible mechanism, especially

favourable in view of the facile loss of methyl observed in the mass

spectrum of 4aH-fluorene (3), is shown in Scheme 87.

(3)   (284)
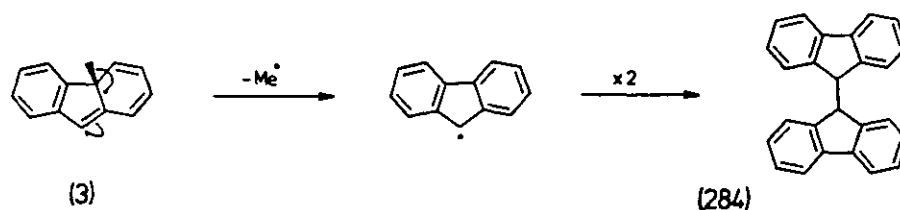
SCHEME 87

iii) Photolysis.

One of the intriguing reactions discovered during the earlier

studies of 3aH-benzimidazole and 4aH-carbazole intermediates was their

photolytic rearrangement to cyclopentapyrimidines and cyclopenta-

quinolines (Chapter One, Sections 1(i) and 2(ii)) respectively. The

transformation of hydrocarbon "A" (119) into cyclopentanaphthalene (186)

demonstrated that the reaction was paralleled in the 4aH-fluorene

series, and, importantly, that the rearrangement itself required light

(Chapter Two, Section 3(iii)).   It was of some interest, therefore, to determine the behaviour of the simpler 4a$\underline{H}$-fluorenes (3) and (222) on photolysis in the hope of discovering a general mechanism for this rearrangement.

a) 4a-Methyl-4a$\underline{H}$-fluorene (3).

Irradiation of 4a-methyl-4a$\underline{H}$-fluorene (3) at 254nm in hexane for 1h gave the mixture of compounds summarised in Scheme 88.
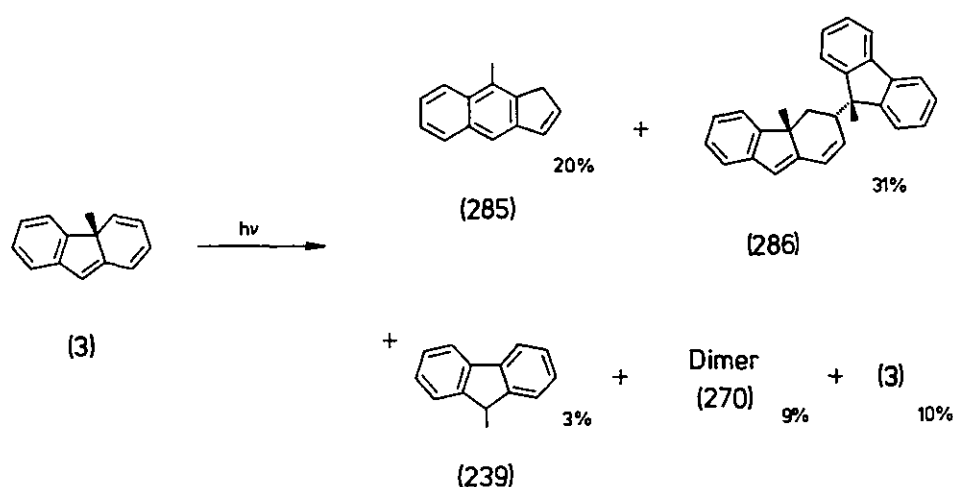
SCHEME 88

The structures of the two new compounds (285) and (286) were established spectroscopically.

The nmr spectrum of compound (285) (Figure 17, base) shows resonances due to a methyl group attached to an aromatic nucleus (δ 2.65), one isolated aromatic proton (δ 7.68), four other aromatic protons and the sub-structure —CH_2—CH=CH—; decoupling of the methylene resonance (δ 3.45) caused the expected simplification of the vinyl   resonances (δ 6.62 and δ 6.97) (Figure 17, inset i)).   As the compound is an isomer of the starting material (3), only cyclopentanaphthalene structures are compatible with these data.   The regioisomerism of the molecule was established by a series of n.0.e. difference experiments (Figure 17; see
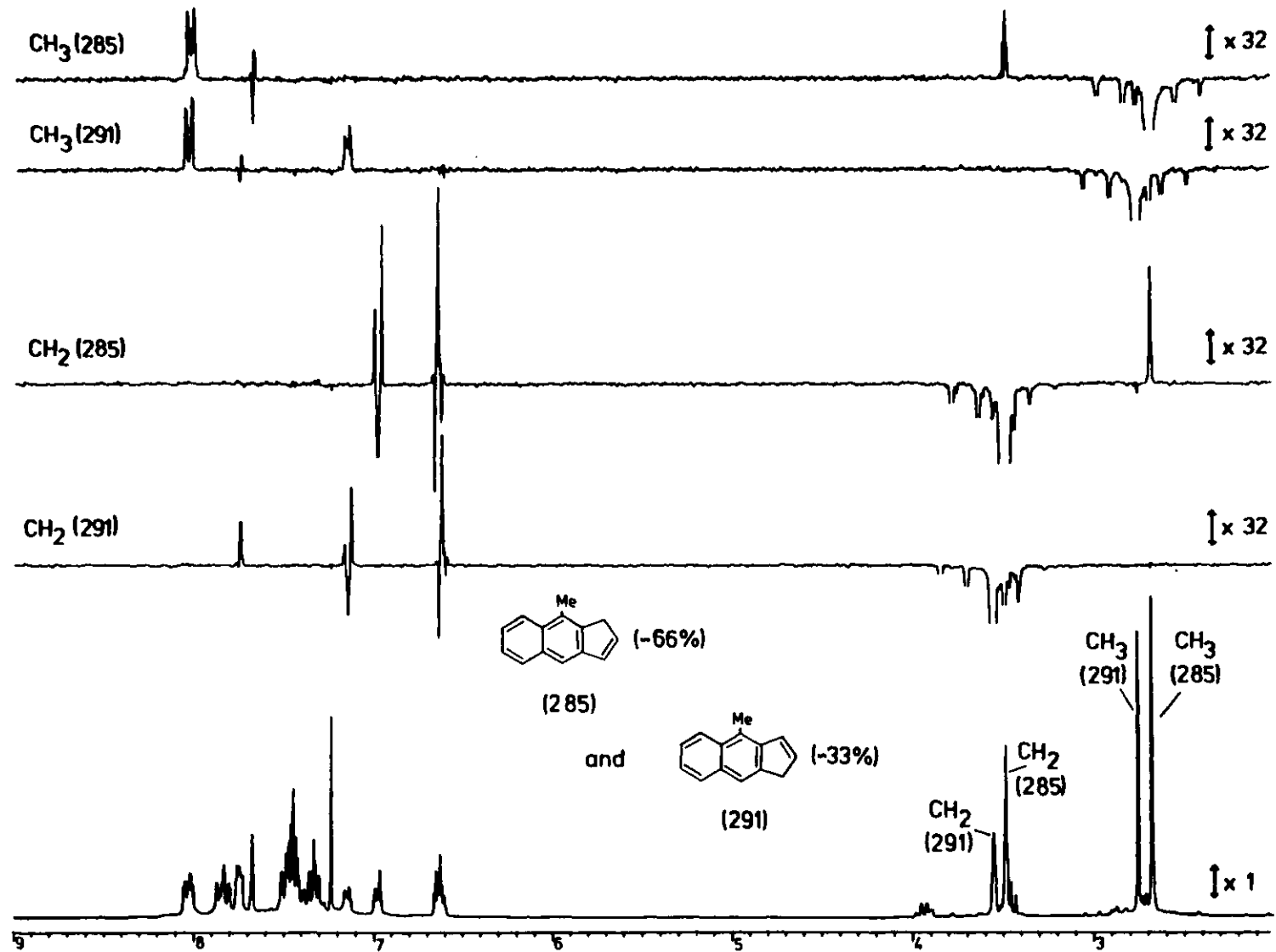
FIGURE 19   N.O.e. difference spectra of 9-methyl and 4-methylcyclopenta[b]naphthalenes, (285) and (291).
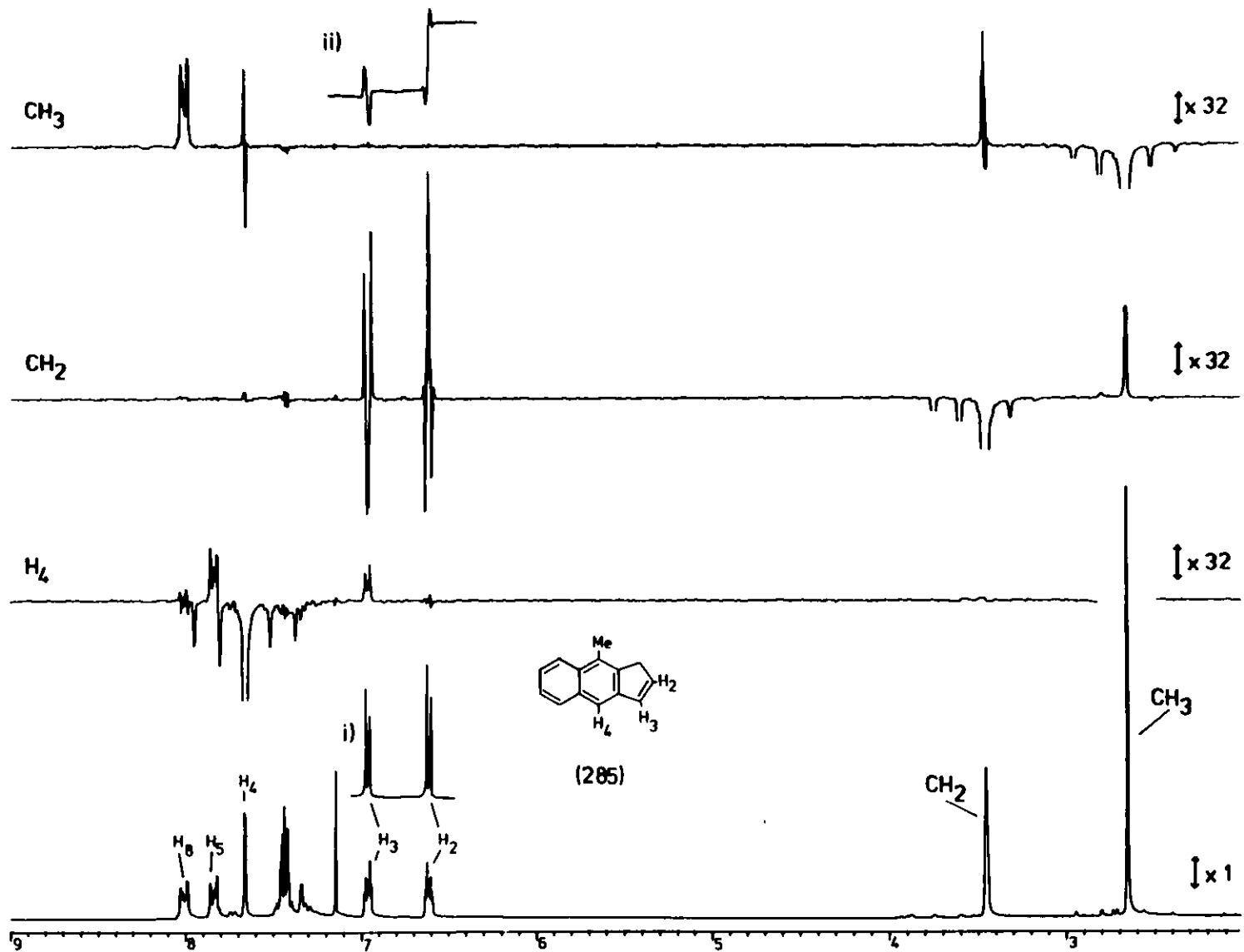
FIGURE 17   N.O.e. difference spectra of 9-methyl-cyclopenta[b]naphthalene (285).

also Chapter Six). The enhancements of H_8 and the methylene resonance on pre-irradiation of the methyl resonance can only be accommodated by structure (285), which is further supported by the enhancements of H_3 and H_5 on pre-irradiation of the H_4 resonance, and of the methyl resonance on pre-irradiation of the methylene resonance. Inset ii) in Figure 17 shows the integral trace for the patterns due to H_2 and H_3 on pre-irradiation of the methylene resonance; as expected, although both protons show large S.P.T. effects, only H_2 shows a net n.O.e. enhancement (overall positive integral; see Chapter Six for discussion).

Decoupling of the nmr spectrum of compound (286) revealed the coupling connectivity pattern summarised in Figure 18.
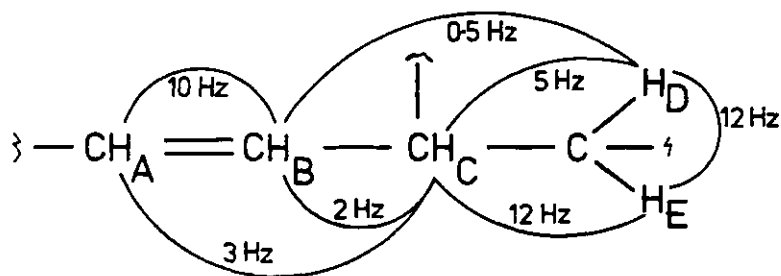
FIGURE 18
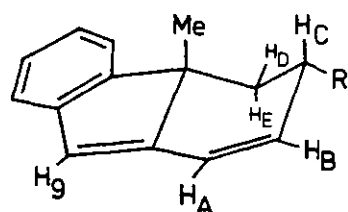
(286)

Assignments for (286)			
H_1	δ 6.49	$H_{4ax.}$	δ 0.75
H_2	δ 5.91	H_9	δ 6.26
$H_{3ax.}$	δ 3.21	$C_{4a}Me$	δ 1.12
$H_{4eq.}$	δ 1.88	$C_{9,}Me$	δ 1.61

TABLE 10

These data, together with the methyl singlet at δ 1.12 and the olefinic singlet at δ 6.26 (H_9), strongly suggest the presence of a 4a-methyl-4,4a-dihydro-3H-fluorene moiety equatorially substituted

at C_3. The presence of twelve aromatic protons and a methyl singlet at δ 1.61 further suggest that the C_3 substituent is a 9-methylfluoren-9-yl group, so accounting for the shifts of the $C_{9'}$ methyl group and $H_{4ax.}$. Further evidence for structure (286) was provided by the mass spectrum which included a weak molecular ion at 360mu and strong peaks at 181mu and 179mu.

Of the products of this reaction (Scheme 88), dimer (270) is presumably formed thermally, while 9-methylfluorene (239) is probably the result of a concerted, photo-allowed [1,3] sigmatropic shift of the methyl group, given the high energy requirement for a two-step thermal migration (Section 4(ii)). The origin of the photodimer (286) is not certain, but it seems likely that it arises via hydrogen abstraction from 9-methylfluorene (239) by 4a$\underline{H}$-fluorene (3), followed by collapse of the radical pair so formed (Scheme 89).

(3)   (239)   (286)
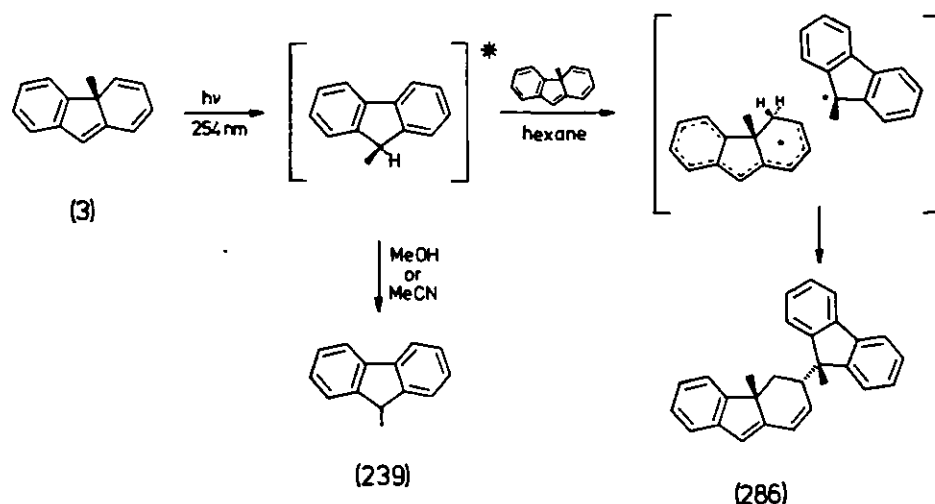
SCHEME 89

For this to occur, one of the reacting molecules (239) or (3) must presumably be in a photoexcited state; it is tempting to suggest that the 9-methylfluorene reacts rapidly in the excited state in which it is formed, since so little 9-methylfluorene was isolated. Consistent

with this view, in other solvents such as methanol or acetonitrile formation of the photodimer (286) was completely suppressed, its place in the reaction mixture being taken by an approximately equivalent amount of 9-methylfluorene (239), while the yields of other products remained substantially unaltered. Presumably these solvents differ from hexane in that they can themselves deactivate the photoexcited precursor of photodimer (286).

This leaves only the central question of the mechanism by which cyclopentanaphthalene (285) is formed. Three changes at least must occur during reaction: a new bond must be formed from C_{9a} to C_4, the original C_{9a}—C_{4a} bond must be broken and H_4 must migrate to C_3 (using the numbering of the original fluorene). It seems most probable that migration of the proton occurs last, implying that 9-methyl-9a$\underline{H}$-cyclopenta[b]naphthalene (288) is an intermediate. Many pathways to this molecule may be considered, but of these only the two shown in Scheme 90 seem likely. Path $\underline{a}$ is analogous to the mechanism previously suggested for the photorearrangement of ortho-blocked 1-aryltetrazoles (Chapter One, Section 1(i)),[3] while path $\underline{b}$ is a modification of the di-π-methane rearrangement.[157]
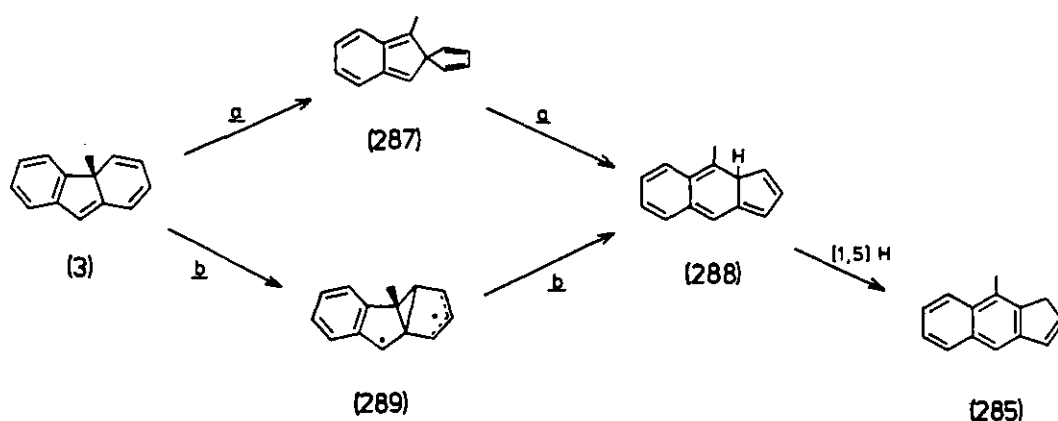
SCHEME 90

The fact that this rearrangement requires light is strong circumstantial evidence in favour of pathway b, since the di-π-methane rearrangement is a well known photoreaction, whereas both the steps of path a are thermal [1,5] shifts. In view of the original proposal of path a in the tetrazole series,[3] and the subsequent widespread invocation of spiro-intermediates similar to (287) to rationalise related reactions, however, more concrete evidence was sought.

As was previously mentioned (Chapter One, Section 1(i)), a fully unsymmetrical spiro[4.4]nonatetraene can undergo any one of eight different [1,5] shifts, but in all the photorearrangements of 3aH-analogues studied so far, only one ring-permuted product was detected in each case. In the earlier examples, such a selectivity could be reconciled with the involvement of a spiro-intermediate since the possible [1,5] shifts were very different from each other, and arguments could be found which favoured that shift required to form the observed product. In the case of 4aH-fluorenes (3) and (119), however, this selectivity seems more surprising; to avoid formation of the alternative double bond isomers (291) and (187), the rearrangements of spiro-intermediates (287) and (290) must proceed exclusively as shown in Scheme 91.

(291)   (287)   (285)

(187)   (290)   (186)
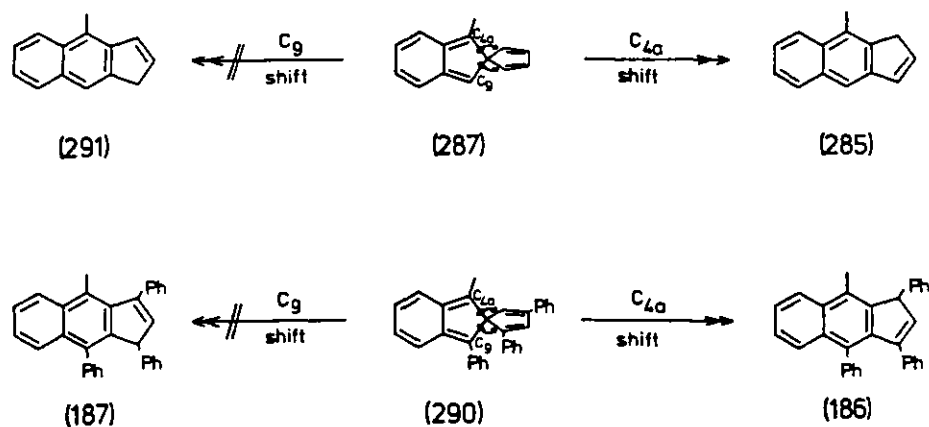
SCHEME 91

Such a selectivity could only be caused by remarkably strong substituent effects. In particular, the absolute preference for migration of a methyl bearing atom over migration of either a hydrogen bearing or a phenyl bearing atom seems so contradictory as to virtually rule out path a (Scheme 90).

To be sure of this argument, however, it was necessary to establish that the alternative double bond isomers (291) and (187) were stable to the reaction conditions. Cyclopentanaphthalene (285) was therefore converted into its anion using n-butyllithium and quenched to give a mixture of double-bond isomers (285) and (291) (ratio, ∿ 2:1). The identities of the components of this mixture were checked using n.O.e. difference experiments (Figure 19; see also Chapter Six); compound (285) gave the same results as previously (c.f. Figure 17), while compound (291) showed the expected enhancements of H_3 and H_5 on pre-irradiation of the methyl resonance, and of H_9 on pre-irradiation of the methylene resonance. This experiment illustrates well the potential of n.O.e. difference spectroscopy for analysing mixtures.

Irradiation of this mixture at 254nm in hexane for 1h caused some losses due to polymerisation and coating of the apparatus, but the material recovered (∿ 50%) consisted of cyclopentanaphthalenes (285) and (291) in an unaltered ratio, so establishing that compound (291) was definitely not produced during the photolysis of 4aH-fluorene (3). A similar experiment involving cyclopentanaphthalene (186) was inconclusive, since none of the double-bond isomer (187) was formed on quenching the corresponding anion. This may be because compound (187) would be disfavoured thermodynamically by steric compression between the methyl group and the C_3 phenyl group; the corresponding peri- interaction in compound (186) is probably reduced by rotation of the C_3 and C_4 phenyl groups, as in hydrocarbon "A" (Chapter Two, Section 1).

Although not a complete proof, the balance of the evidence thus

overwhelmingly supports path $\underline{b}$ (Scheme 90) as the correct mechanism

for this photolysis. It accounts for the data presented largely

because it preserves the original C_4—C_{4a} bond intact, so excluding

the wider possibilities open to spiro-intermediate (287). It seems

probable also that analogous mechanisms operate in the other related

photorearrangements discussed; such has already been suggested in the

4a$\underline{H}$-carbazole series.[32]

b) 4a,9-Dimethyl-4a$\underline{H}$-fluorene (222).

The photolysis of 4a-methyl-4a$\underline{H}$-fluorene (3) just discussed was

unique within this series of photorearrangements in that the ring-

permuted product, cyclopentanaphthalene (285), was not the major one.

Comparison with the rest of the series suggests that this is because

the [1,3] methyl shift involved in the competing reactions was at its

most favoured in compound (3), being then a carbon to carbon migration

unopposed by steric crowding at the terminus. It might be expected,

therefore, that photolysis of 4a,9-dimethyl-4a$\underline{H}$-fluorene (222) would

lead to a higher yield of the corresponding cyclopentanaphthalene (292),

since the competing [1,3] methyl shift would be somewhat retarded

sterically, and, once formed, any 9,9-dimethylfluorene (240) could not

consume further substrate in a photodimerisation analogous to that of

4a$\underline{H}$-fluorene (3).

This was found to be true. Irradiation of the 4a$\underline{H}$-fluorene

(222) at 254nm in hexane for 2h gave a mixture cyclopentanaphthalene

(292) ($\sim$ 40%), 9,9-dimethylfluorene (240) ($\sim$ 5%) and starting material

($\sim$ 10%) (Scheme 92).

At this point a correlation with the literature became possible,

as the dihydrocyclopentanaphthalene (293) had previously been reported

by Field and Jones.[93] Hydrogenation of our cyclopentanaphthalene (292)

over a palladium-charcoal catalyst in methanol gave the symmetrical
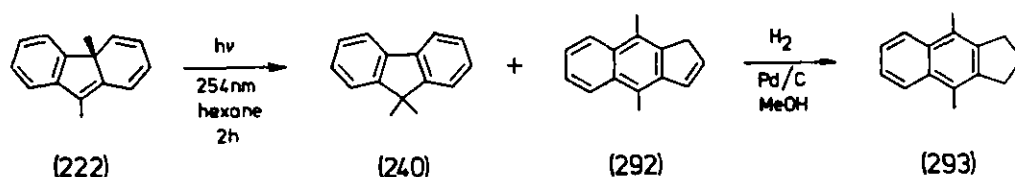
SCHEME 92

dihydro derivative (293), and a comparison of spectral data revealed
this to be identical to Jones' material. It may be noted in passing
that the original paper included a slip in describing the nmr spectrum
of compound (293); the resonance of the C_2 methylene group is in fact
a quintet (J = 7 Hz),[130] not an AB quartet as first reported.[93]

The only remaining problem was the origin of compound (293)
during Jones' work; it was obtained in low yield (17%) when olefin
(294) was heated at 250°C, neat, under nitrogen in a sealed tube for
14h. The mechanism remains obscure, but an attractive possibility is
that the necessary loss of methylene occurs from intermediate (295),
itself formed by a pathway similar to either a or b in Scheme 90.
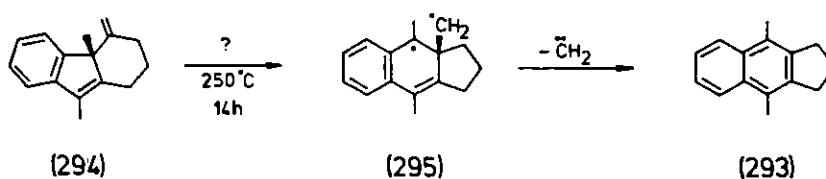
SCHEME 93

CHAPTER SIX

CHAPTER SIX: Nuclear Overhauser Effect Difference Spectroscopy.

1) Introduction.

The work presented in previous chapters, particularly Chapter Five, draws heavily on the results of nuclear Overhauser effect difference experiments to make difficult structural assignments.   One purpose of this chapter therefore is to provide sufficient background discussion of this recent pulsed nmr technique to justify and reinforce the brief explanations of individual results given earlier.   The main emphasis of the chapter, however, is on work into more demanding applications of the technique, since these illustrate more fully the very considerable potential of n.O.e. difference spectroscopy in organic structural and conformational studies.

Much of this work concerned repanduline, a bisbenzylisoquinoline alkaloid isolated from the bark of a north Queensland monimiaceous tree, Daphnandra repandula.   Several structural details of this alkaloid had not been resolved before the present work, and its macrocyclic molecule and reasonably dispersed nmr spectrum provided an ideal testing ground for the n.O.e. technique.   As with other substrates to be mentioned, the present study of repanduline began as a result of its submission, by other workers, to the 250 MHz ^{1}H nmr service in this department, for which the author was responsible.

The applications of n.O.e. difference spectroscopy discussed in this and earlier chapters are mainly concerned with elucidation of the three-dimensional layout of molecules, that is with stereochemical problems.   It is worth noting, however, that the technique is also particularly suited to the simpler task of determining aromatic substitution patterns; measurements of enhancements between protons and

substituents around the peripheries of these substantially flat molecules usually lead quickly to an unambiguous solution _via_ a minimum of inter-pretation. Examples from this thesis include the studies of cyclopenta-naphthalenes (186) and (285) (Figures 5, 17 and 19), and methylfluorenes (281) and (282) (Figures 15 and 16), while further successful applications of this approach involved substituted cyclopentaquinolines,[32] indoles,[158] thiophenes and pyrroles,[159,160] and a natural furanocoumarin. Other applications, which will not be discussed in detail, included determin-ations of the relative stereochemistries of a spiro-ketal,[161] dimers and trimers from the photolysis of certain azidocinnamate esters,[162] and several decalin natural products and their analogues.[163-166] A con-formational study of the macrocyclic antibiotic elaiophylin was also undertaken, and revealed an interesting and novel dependence of the sign of the n.0.e. on segmental motions within the molecule; this will not be discussed here, however.[167]

2) Background.

The n.0.e. is defined, in the inter-proton case, as the change in intensity of the multiplet due to one proton or group of protons (I) which occurs when another proton or group of protons (S) is saturated. Theoretical treatments are available elsewhere.[168] The effect is caused by dipole-dipole cross-relaxation between the I and S protons, and it is the relative contribution which this particular relaxation pathway makes to the total relaxation of the I proton(s) which determines the magnitude of the effect. This contribution depends in turn on the inverse sixth power of the distance between the I and S protons, $(r_{IS})^{-6}$, so that the relative magnitudes of enhancements reflect the spatial relationships of the protons involved. Measurements of n.0.e. enhancements have

therefore been much used as aids to spectral assignment, structural elucidation and in conformational studies.[168]

Until recently, n.O.e. enhancements could only be measured by careful integration of the I multiplet both with and without saturation of the S multiplet; this method resulted in a lower detection limit of ∿ 5%. N.O.e. difference spectroscopy avoids the problems of inaccurate integration by directly subtracting spectra within the spectrometer's computer. Thus, a control spectrum in which no n.O.e. enhancements are present is subtracted from a spectrum obtained while the S multiplet is saturated. The result is a difference spectrum which, ideally, consists entirely of changes caused by saturation of the S multiplet. The detection limit of this method depends only on the signal to noise ratio and the efficiency of subtraction (i.e. the extent to which unchanged signals are correctly nulled to give baseline in the difference spectrum).

An important feature of the difference method is that the saturating field (decoupler) is switched off a few milliseconds before data acquisition begins, with the result that only population effects, such as the n.O.e., persist at the moment of the observe pulse. This is because population effects build up and decay over several seconds at rates governed by spin-lattice relaxation processes, whereas decoupling effects and Bloch-Siegert shifts disappear essentially at the instant the decoupler is switched off. Interpretation of the difference spectrum is thereby greatly simplified, since the spectra subtracted differ only in the intensities of lines and not in their positions. A description of the method, due to Hall and Sanders,[169] which was used to acquire the difference spectra is given in Chapter Seven (Page 239).

3) Interpretation.

The main feature of each n.O.e. difference spectrum is a large negative signal, shown truncated in the Figures, corresponding to the pre-irradiated multiplet (S).   The intensity of this signal depends on the extent of saturation of the S multiplet in the pre-irradiated spectrum.   Generally, this is less than 100% because i) sub-saturating power levels were used to achieve adequate frequency selectivity, and ii) some slight recovery occurs during the short delay between pre-irradiation and the observe pulse.   In certain cases described later, much less than total saturation took place since only one component of a multiplet was being irradiated at a time.   Such partial saturation only excites approximately the corresponding fraction of any possible n.O.e. enhancement.

Other peaks in the difference spectrum arise through population disturbances induced by saturation of the S proton.   These can be of three types:

i) N.O.e. enhancements.

Protons close in space to the pre-irradiated proton generally receive an enhancement from it, and thus appear as positive signals in the difference spectrum.   It is important to note, however, that an enhancement is not itself a direct or quantitative measure of the distance between the pre-irradiated and observed protons;   rather, it measures the proportion of the total relaxation of the observed proton which is provided by cross-relaxation with the pre-irradiated proton. This distinction may be clarified by the hypothetical example shown in Figure 20, in which only four spins interact.   Pre-irradiation of H_C would cause an enhancement of H_D close to the theoretical homonuclear maximum (50%), since H_C is the only near neighbour of H_D.   Proton H_B,

conversely, although it is the same distance from H_C as is H_D, would

only receive a small enhancement $\left[f_B(C) = 2^{-6}/\ 2(1^{-6}+\ 2^{-6}+\ 4^{-6}) = 0.77\%\right]$,

because the vast majority of its own relaxation is provided by its much

nearer neighbour, H_A.[170]
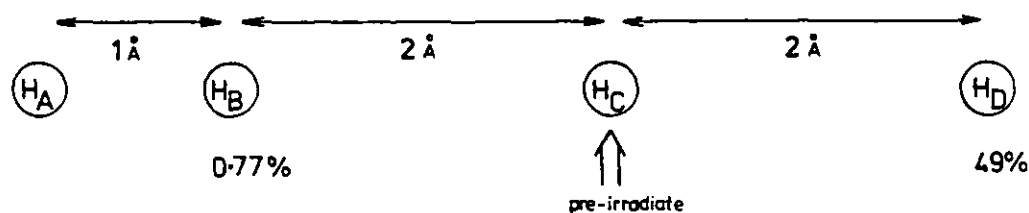
FIGURE 20

Equations are available which allow the calculation of inter-

nuclear distances from a suitable set of interrelated enhancement data;

this approach, which is fully discussed by Noggle and Schirmer,[168]

relies heavily on comparisons of enhancements of the same proton(s)

which occur when various neighbouring protons are separately irradiated.

The results of n.O.e. difference experiments are not well suited to such

an interpretation, mainly because the required comparisons between

different pre-irradiations cannot easily be quantified.   Instead, a

qualitative, or at most semi-quantitative approach was adopted in the

present work, discounting structures or conformations if they could not

account for the approximate relative magnitudes of particular observed

enhancements.

If a strongly enhanced proton (I) is itself close in space to a

third proton, their mutual cross-relaxation will cause a further trans-

mission of the original population disturbance to the third proton.

Under conditions which lead to direct enhancements being positive,

such a transmitted effect produces a small negative enhancement of the

third proton, provided this proton is sufficiently remote from the

pre-irradiated proton (S) that their direct cross-relaxation does not predominate. Such negative enhancements are known as three-spin effects,[168] and occur frequently in the present work.

It should also be mentioned that direct enhancements may themselves be negative if the solute molecules have a sufficiently long correlation time, caused by high solute molecular weight, high solvent viscosity or low temperature.[171] Although these conditions do not apply to the work presented here, some of the related work cited does involve such negative enhancements.[167,172]

ii) <u>S.P.T. (Selective Population Transfer) effects.</u>

These effects, which are the basis of the INDOR and FTINDOR experiments, occur whenever the component lines of a pre-irradiated multiplet are saturated to differing extents. S.P.T. then results in a <u>redistribution</u> of intensity between the component lines of other multiplets which share a scalar coupling with the pre-irradiated multiplet.

The relationship between the n.O.e. and S.P.T. effects is important, and is well illustrated by the experiments involving 4a-methylhexahydrofluoren-1-one (249) (Chapter Four, Figure 7, facing Page 106) and 9-methylcyclopenta[b]naphthalene (285) (Chapter Five, Figure 17, Page 142). The n.O.e., in isolation, enhances a whole multiplet evenly. Multiplets due to protons close to, but not coupled to, the pre-irradiated proton(s) therefore appear in the difference spectrum as they would in the normal spectrum (e.g. Figure 7, $H_{9a\beta}$ on pre-irradiation of the C_{4a} methyl, and Figure 17, H_8 on pre-irradiation of the C_9 methyl). Conversely, S.P.T., in isolation, produces no overall change in the intensity of the multiplet as a whole. Multiplets due to protons coupled to, but spatially remote from, the pre-irradiated proton(s) therefore appear in the difference spectrum as a series of positive and

negative lines whose summed intensities balance, the multiplet having

zero integral overall (e.g. Figure 7, $H_{9\alpha}$ on pre-irradiation of $H_{9\alpha\beta}$,

and Figure 17, H_3 on pre-irradiation of the C_1 methylene). If a proton

is both coupled to and close to the pre-irradiated proton(s), however,

both effects operate. Their relative contributions then depend on

i) the magnitude of the n.O.e. enhancement and ii) the extent and manner

in which the partial saturation of the pre-irradiated multiplet differs

between its components. The result is a pattern intermediate between

the extreme cases described above; that is, the appearance of the

multiplet in the normal spectrum will be distorted to a greater or

lesser extent in the difference spectrum as a result of S.P.T. Examples

of such patterns are, in Figure 9, H_J on pre-irradiation of H_H (slightly

distorted), in Figure 3, H_3 and $H_{4eq.}$ on pre-irradiation of $H_{4ax.}$, also

$H_{4ax.}$ on pre-irradiation of H_3 (considerably distorted), and in Figure 7,

$H_{9\beta}$ on pre-irradiation of $H_{9\alpha\beta}$, or Figure 17, H_2 on pre-irradiation of

the C_1 methylene group (grossly distorted).

As these examples show, substantial S.P.T. effects commonly do

occur in practice, as a result of the low pre-irradiation powers employed.

This is useful in some ways, since it reveals coupling connectivities,

but it can also complicate the detection of n.O.e. enhancements, and

some way of separating the two effects would be desirable. This point

will be developed in Section 5.

iii) Saturation transfer.

If the pre-irradiated proton undergoes chemical exchange at a

similar or faster rate than that of spin-lattice relaxation, saturation

will be "transported" by the exchanging proton, and resonances due to

protons at other exchange sites will appear partially saturated. This

important effect does not appear in the present work only because no

exchangeable protons were pre-irradiated.

PROTON	ASSIGNMENT		PROTON	ASSIGNMENT	
	(I) δ	(II) δ		(I) δ	(II) δ
H_1	2.9-3.0	2.80-2.88	$H_{2'''}$	7.37	7.23
$H_{3eq.}$	2.9-3.05	-	$H_{3'''}$	7.12	7.10
$H_{3ax.}$	2.4-2.6	-	$H_{5'''}$	6.92	7.00
$H_{4eq.}$	1.95-2.15	1.78-1.92	$H_{6'''}$	6.73	6.77
$H_{4ax.}$	2.3-2.5	-			
H_5	5.54	4.29	H_A	4.15	4.08
			H_B	3.88	3.78
$H_{1'}$	3.6-3.7	3.6-3.7	H_C	2.95-3.10	2.98-3.08
$H_{3'eq.}$	2.85-3.0	-	H_D	2.90-3.05	2.85-2.95
$H_{3'ax.}$	3.2-3.35	3.1-3.25	H_E	3.30-3.38	3.25-3.35
$H_{4'eq.}$	2.5-2.7	-	H_F	2.63-2.73	2.57-2.67
$H_{4'ax.}$	2.8-3.0	-			
$H_{5'}$	6.49	6.50	N_2Me	2.40	2.30
$H_{8'}$	5.11	5.13	$N_{2'}Me$	2.65	2.57
			OMe	3.62	3.32
$H_{2''}$	6.08	6.13	OCH_2O	5.92+5.97	5.71+5.75
$H_{6''}$	6.77	6.83			

TABLE 11. ^1H Assignments for repanduline in (I) $CDCl_3$ and (II) $[^2H_6]$benzene (20%) in $CDCl_3$.

4) Repanduline.

The aim of the present study was to resolve ambiguities left open by the original structural work on repanduline.[173,174] In particular, it was hoped to distinguish between the subtly related regioisomers (296) and (297), to determine the relative stereochemistry at all three chiral centres and to establish, as far as possible, the solution conformation.

(296)

(297)
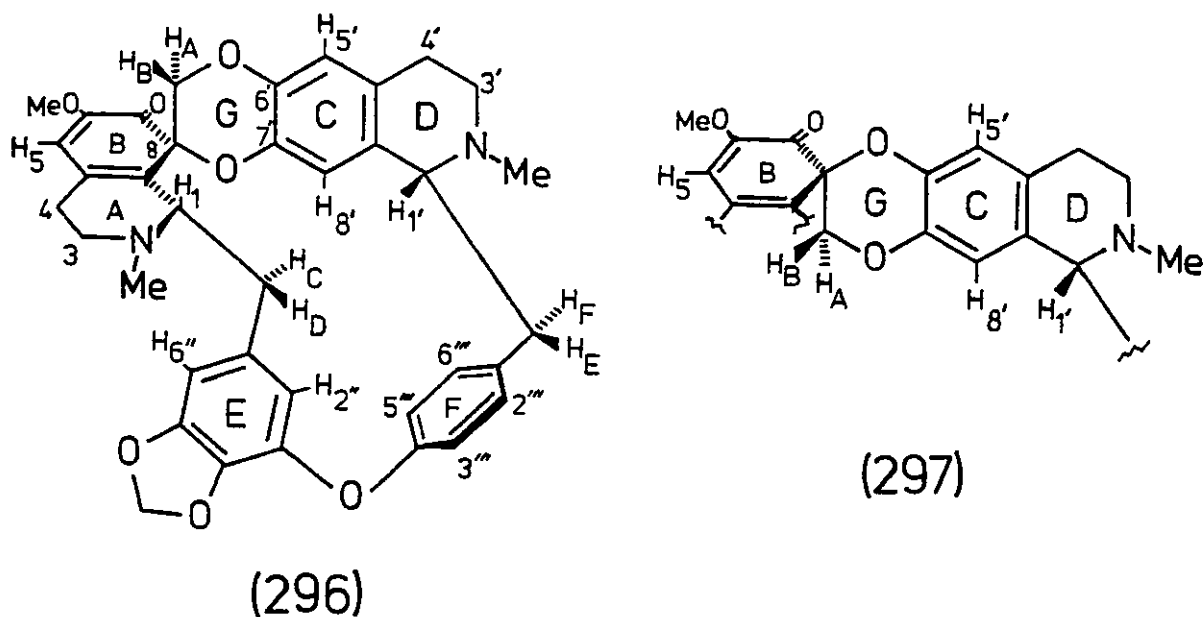
i) Assignments (summarised in Table 11).

The normal spectrum of repanduline in $CDCl_3$ is shown at the base of Figures 21-24. Assignments in the high field region (δ 1.8-3.5) clearly represent a considerable challenge, while the low field region (δ 3.5-7.5) consists of simple, well separated, first-order patterns. The low field region will be considered first, since its assignment is a pre-requisite for further discussion.

a) Low field region (δ 3.5-7.5).

A number of assignments were made immediately. The three proton singlet at δ 3.6 was assigned to the O-methyl group, the doublets at
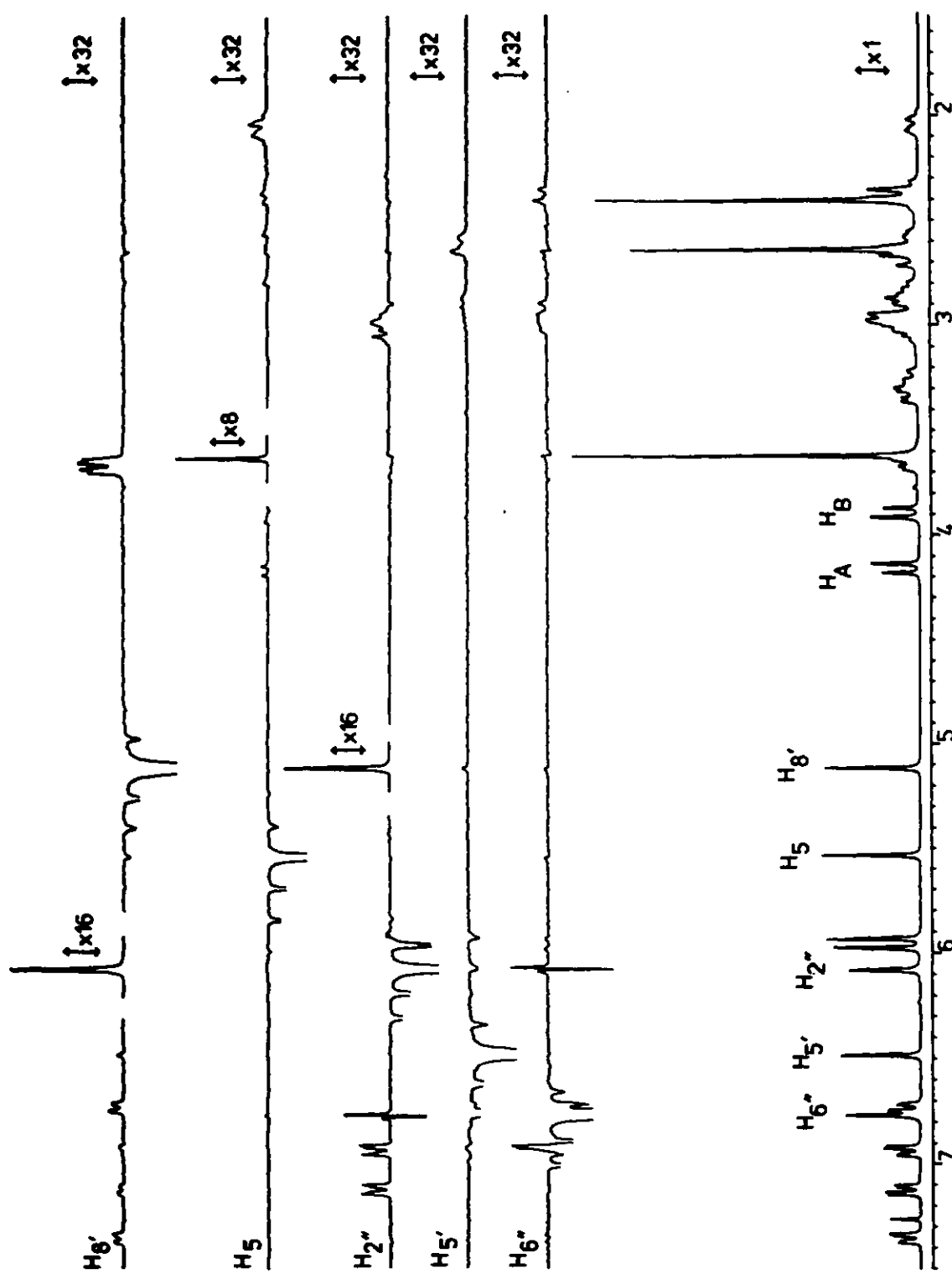
FIGURE 21   N.O.e. difference spectra of repanduline (296) in $CDCl_3$.
Pre-irradiation sites were $H_{6''}$, $H_{5'}$, $H_{2''}$, H_5 and $H_{8'}$.

δ 3.88 and 4.15 to the O-methylene group of ring G, and the four double

doublets at δ 6.73, 6.92, 7.12 and 7.37 to the aromatic protons of ring

F. Small couplings (more clearly resolved in other spectra) were used

to assign the peaks at δ 5.92 and 5.97 to the methylenedioxy group, and

those at δ 6.08 and 6.77 to the two aromatic protons of ring E

(J_m = 1.2 Hz). It then remained to assign the singlets at δ 5.11, 5.54

and 6.49 to $H_{5'}$, $H_{8'}$ and H_5, and also to make relative assignments

within the sets of signals already allocated to the protons of rings

E, F and G.

To resolve these ambiguities, a series of n.O.e. difference

experiments was carried out, the results of which appear in Figures 21

and 22. The simplest assignment was that of the peak at δ 5.54 (H_5),

pre-irradiation of which caused strong enhancement of the O-methyl

signal. Protons $H_{8'}$ and $H_{2''}$ were assigned on the basis of the strong

enhancements observed between them; molecular models very clearly

showed that no other pair of protons on rings C and E could be suffic-

iently close to each other. Assignments of $H_{5'}$ and $H_{6''}$ followed

automatically. The double doublet at δ 3.66 enhanced on pre-irradiation

of $H_{8'}$ was assigned to $H_{1'}$ and the double doublet enhanced on pre-

irradiation of $H_{1'}$ was assigned to $H_{2'''}$. Coupling connectivities from

$H_{2'''}$ then led automatically to assignment of the remaining ring F

protons. Confirmatory evidence for these was provided by the strong

enhancements of $H_{3'''}$ and $H_{5'''}$ on pre-irradiation of $H_{2''}$, and by the

enhancement of $H_{6'''}$ on pre-irradiation of H_F (next section).

The relative assignments of H_A and H_B (the methylene protons of

ring G) followed from the observation of an enhanced signal at δ 3.0

on pre-irradiation at δ 3.87 and 3.91 (data from two separate pre-

irradiations were summed in this case, so as to minimise S.P.T.; see

also Section 4 (ii) and Section 5). The enhanced signal can only be

due to one or more of the protons in the isolated three-spin system
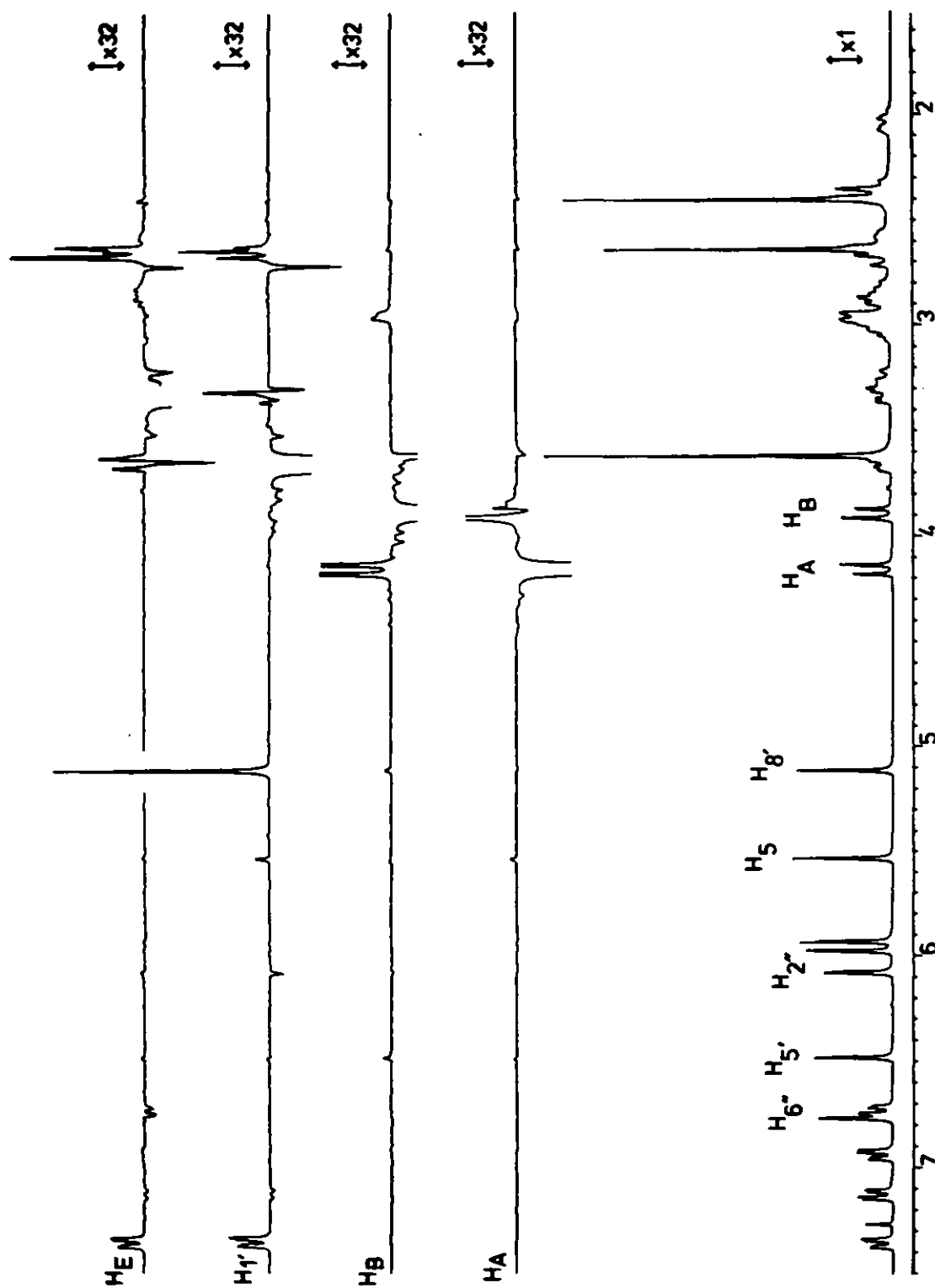
FIGURE 22   N.O.e. difference spectra of repanduline (296) in CDCl$_3$.
Pre-irradiation sites were H$_A$, H$_B$, H$_1$, and H$_E$.

comprised of H_1, H_C and H_D, implying that H_B was the proton pre-

irradiated. A detailed analysis of enhancements in this portion of

the molecule must include consideration of the relative stereochemistries

at C_1 and C_8, and such an analysis is given later; the relative

assignments of H_A and H_B, however, are independent of these considera-

tions.

b) High field region (δ 1.8-3.5).

The high field region of the repanduline spectrum is obviously

complicated and crowded. Nonetheless, one may assume that it consists,

in addition to the N-methyl singlets, of four superimposed sub-spectra

arising from isolated portions of the molecule. Of these sub-spectra,

two are three-spin systems (one consisting of H_1, H_C and H_D, the other

of H_1', H_E and H_F) while the remaining protons of rings A and D comprise

two four-spin systems. Although full spectral parameters of the three-

spin systems were required for the stereochemical assignments, it was

considered sufficient to characterise the four-spin systems only in

terms of chemical shift.

Several assignments were already obvious from the n.O.e.

difference experiments discussed in the previous section. Pre-

irradiation of H_1, revealed the multiplets due to H_E (δ 3.33) and H_F

(δ 2.68) through large S.P.T. effects. A simultaneous enhancement of

the singlet at δ 2.65 suggested that this be assigned to the N_2, methyl

group. Assignments for $H_{4eq.}$ (δ 1.95-2.15) and $H_{4'eq.}$ (δ 2.5-2.7)

were made on the basis of the expected enhancements of these protons

caused by pre-irradiation of H_5 and $H_{5'}$, respectively. The latter

experiment also revealed a weak enhancement of $H_{4'ax.}$ (δ 2.8-3.0).

To make the remaining assignments more n.O.e. difference experi-

ments were required, and the results of these are shown in Figure 23.

The pre-irradiation frequencies used are indicated in the normal spectrum;
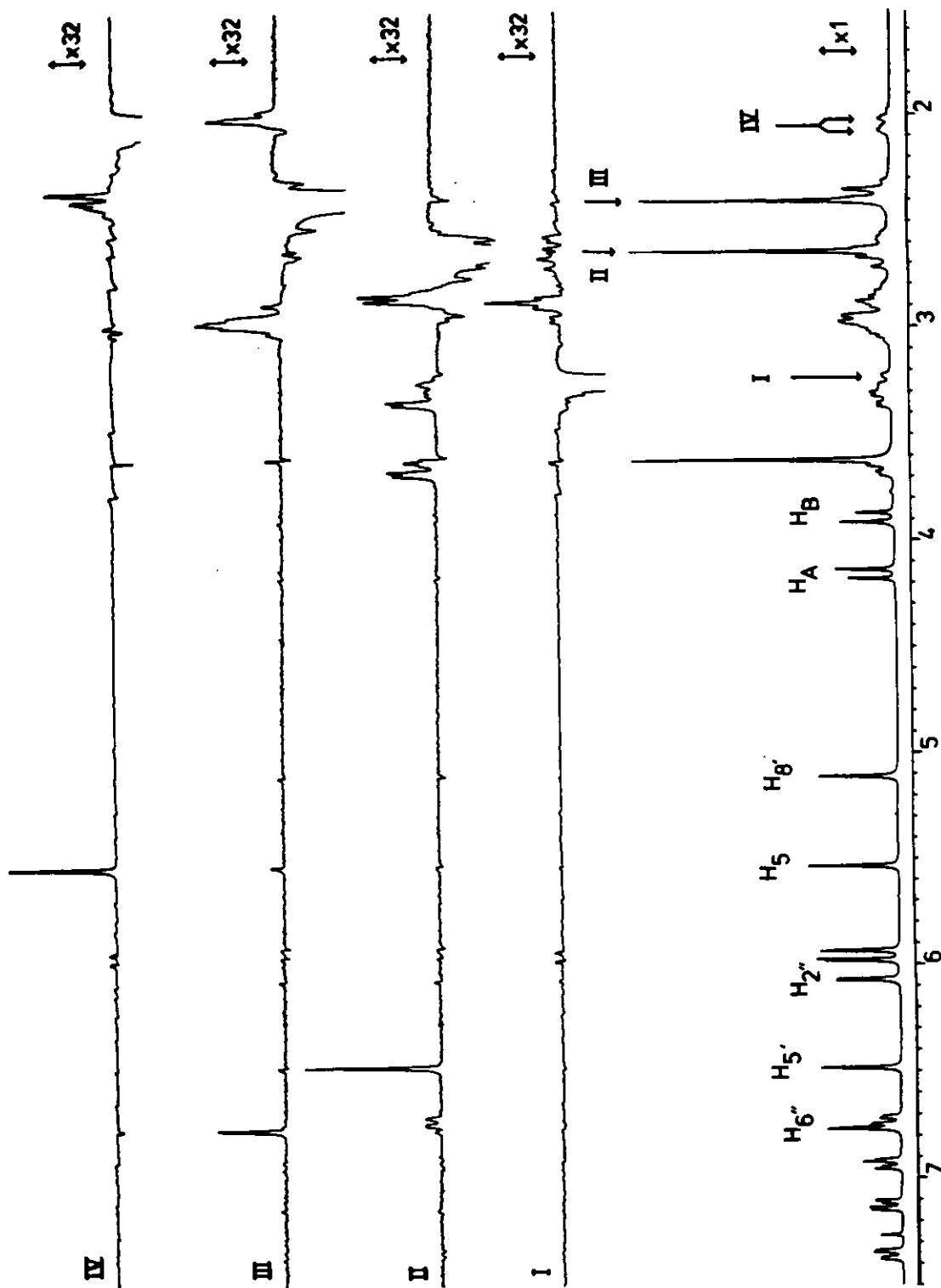
FIGURE 23   N.O.e. difference spectra of repanduline (296) in $CDCl_3$.
Pre-irradiation sites are referenced in the text.

since three of these are in regions of spectral overlap, it is important to consider how many protons are likely to be saturated by each pre-irradiation. Integration of the normal spectrum clearly shows that there are two protons resonating in the region δ 3.2-3.4, six in the region δ 2.8-3.1, two each in the regions δ 2.55-2.75 and δ 2.3-2.5 (excluding the two $\underline{N}$-methyl singlets) and one at δ 1.95-2.15. Thus pre-irradiation site I corresponds to a single proton partially overlapped with H_E, site II to an $\underline{N}$-methyl group overlapped only with H_F and $H_{4'eq.}$, site III to an $\underline{N}$-methyl group overlapped with two protons, and site IV to $H_{4eq.}$ only.

Pre-irradiation of $H_{4eq.}$ (site IV) led only to one major enhancement, that of $H_{4ax.}$ (δ 2.3-2.5). The assignments for $H_{4ax.}$ and $H_{4'ax.}$, and also the relative assignments of the $\underline{N}$-methyl singlets were confirmed by experiments II and III. Pre-irradiation at site II caused the expected strong enhancement of $H_{4'ax.}$ (saturation of $H_{4'eq.}$) together with others of $H_{2'''}$ (saturation of H_F), $H_{5'}$ (saturation of $H_{4'eq.}$), $H_{1'}$ and H_E (saturation of the $N_{2'}$ methyl group and H_F) and S.P.T. effects. Pre-irradiation at site III caused the expected strong enhancement of $H_{4eq.}$ among others.

A coupling from $H_{4eq.}$ to a multiplet at δ 2.9-3.05 was revealed by the S.P.T. effect observed in experiment IV, and was confirmed by difference decoupling. Since $H_{4ax.}$ had already been located, this multiplet was assigned to one of $H_{3ax.}$ or $H_{3eq.}$. The multiplet corresponding to site I was assigned to one of $H_{3'eq.}$ or $H_{3'ax.}$ since (i) it was too complex (8 lines) to form part of a three-spin system, and (ii) pre-irradiation of the multiplet caused strong enhancement of another multiplet at δ 2.85-3.0 (presumably the geminal partner) which was not that previously shown to be coupled to $H_{4eq.}$.

Assignments were now lacking only for H_1, H_C, H_D and one of $H_{3ax.}$ or $H_{3eq.}$. The integral data discussed earlier, in conjunction with

those assignments already made, showed that one of these resonances was overlapped with $H_{4ax.}$ and the N_2 methyl group at δ 2.4-2.6, while the other three were virtually coincident near δ 3. This coincidence, and the still unknown relative stereochemistry at C_1 and C_8, precluded any further assignments using the existing data. A further experiment, however, avoided these difficulties by using $[^2H_6]$benzene to induce differential solvent shifts which removed the coincidences. The stereo-chemistry and the remaining assignments were all deduced from this experiment, which is discussed in Section 4(iv).

ii) Long range n.O.e. difference spectroscopy.

One of the principal aims of the present work was to establish the substitution pattern in rings B and C of repanduline. In particular, it was hoped to distinguish between the two most likely regioisomers (296) and (297), which differ only in the relative positions of the spiro-link and the methylene group in ring G. A choice of (296) was made on purely biogenetic grounds in the original papers.[173,174]

A possible approach to this problem was suggested by our recent work on the closely related alkaloid, dihydrodaphnine diacetate (298),[172] in which the position of the ring C methoxy group was established by measuring its enhancements on separate pre-irradiation of $H_{5'}$ and $H_{8'}$. While the relative proximity of $H_{5'}$ and the protons of the 6'-methoxy group of daphnine made this experiment relatively simple, conformational constraints imposed by the presence of ring G obviously make the analogous experiment for repanduline much more difficult. Examination of models of structures (296) and (297) clearly showed that H_A was always significantly closer to one of the aromatic protons of ring C than to the other, but that even the shorter distance was in excess of 4 Å. Nonetheless, it was hoped that pre-irradiation of H_A might
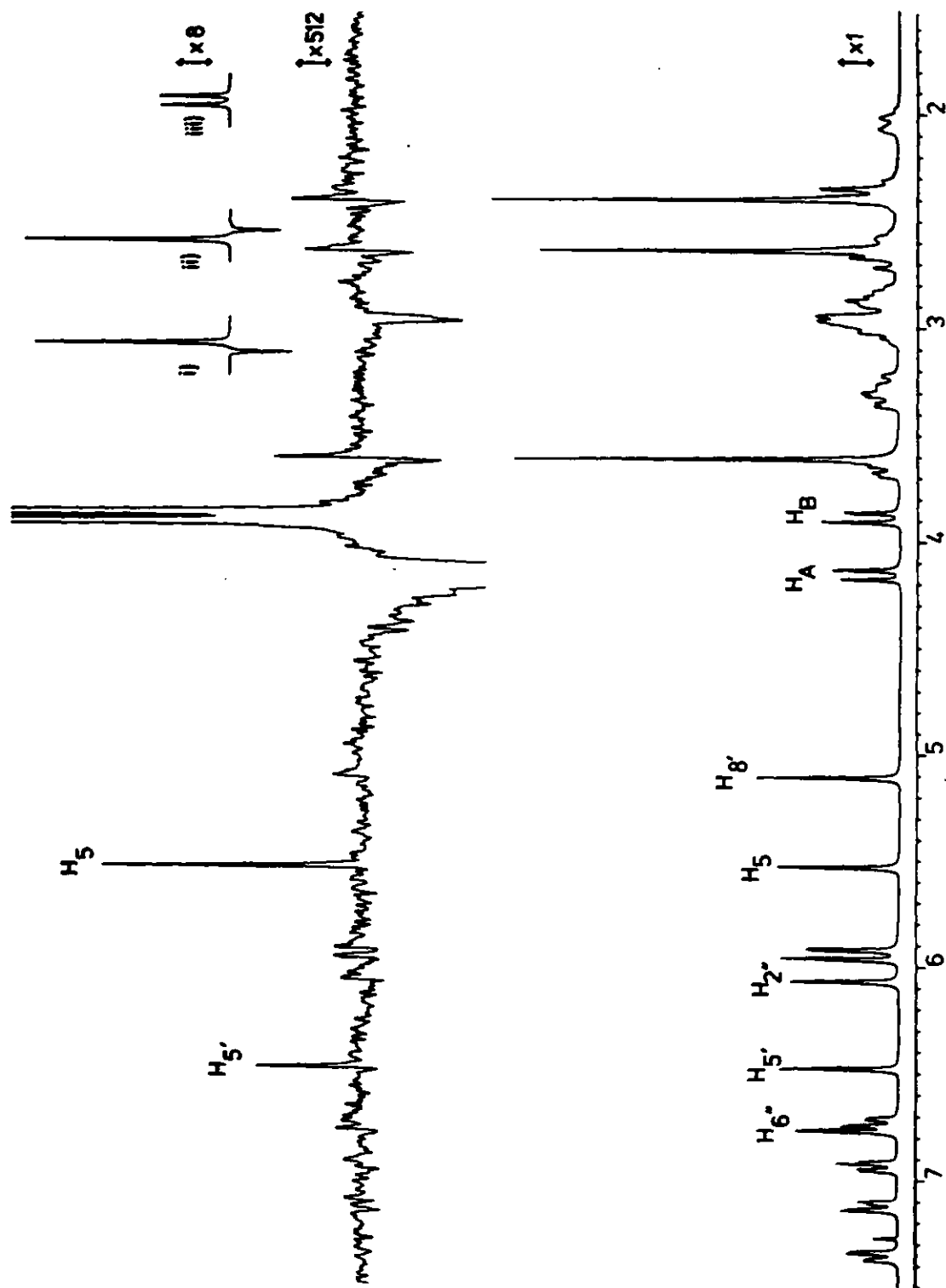
FIGURE 24   Long range n.O.e. difference experiment in which H_A of
repanduline was pre-irradiated.   The insets show the
pattern of H_B on pre-irradiation of (i) the downfield com-
ponent of H_A, and (ii) the upfield component of H_A, while
(iii) shows the sum of (i) and (ii).   The solvent was $CDCl_3$.

cause a detectable enhancement of either $H_{5'}$ or $H_{8'}$, and hence show which was the closer to the $\underline{O}$-methylene group.

(298)
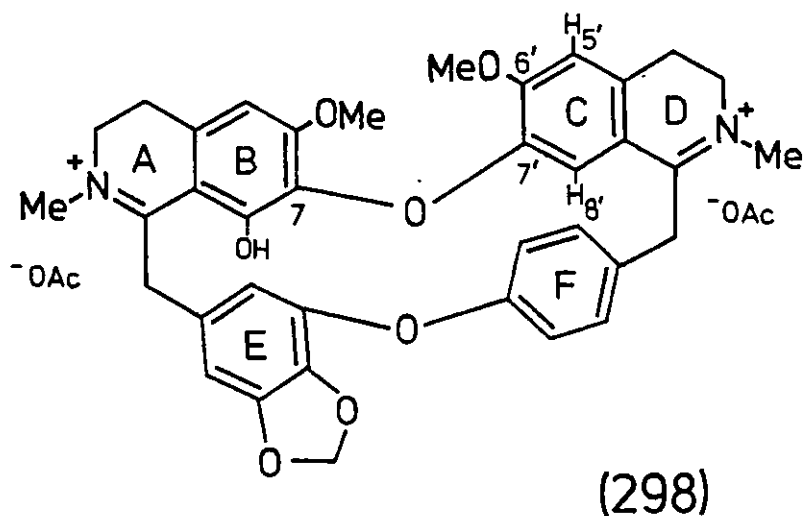
The result of this crucial experiment is shown in Figure 24; there is a clear enhancement of $H_{5'}$ (0.18%) but essentially none of $H_{8'}$ (< 0.04%). This very strongly suggests that $H_{5'}$ is the closer to H_A, and therefore that (296), rather than (297), is the correct structure of repanduline. To be completely sure of this, however, it was necessary to rule out the possibility that structure (297) could give rise to the observed enhancements. For it to do so, $H_{5'}$ would have to receive its 0.18% enhancement from H_A across 6 $\overset{o}{A}$, while $H_{8'}$, which is only 4.5 $\overset{o}{A}$ from H_A in structure (297), would have to be massively relaxed by other pathways to avoid showing a similar (or larger) enhancement itself. Such a drastic difference in relaxation behaviour between $H_{5'}$ and $H_{8'}$ seems most unreasonable. Final confirmation was given by approximate calculations of the enhancements expected for each structure on the basis of distances measured on molecular models. These results are summarised in Table 12.

Other peaks in the difference spectrum are enhancements of H_5 (0.42%), H_B (14%, shown truncated) and a three-spin effect at δ 2.97 (due to H_1). Enhancements of H_A on pre-irradiation of $H_{5'}$ or $H_{8'}$

DISTANCE (Å)	MODEL	X-RAY	DISTANCE (Å)	MODEL	X-RAY
$H_A - H_{5'}$	4.5	4.45	$H_B - H_{5'}$	4.4	4.09
$H_A - H_{8'}$	5.8	5.50	$H_B - H_{8'}$	4.8	4.64
$H_A - H_5$	3.8	3.56	$H_B - H_5$	5.4	4.77
$H_A - H_1$	3.8	3.43	$H_B - H_1$	2.6	2.44
$H_A - H_B$	1.8	1.57	$H_B - H_E$	4.0	3.80
			$H_B - H_F$	5.2	4.71
$H_{5'} - H_{4'eq.}$	2.4	2.56			
$H_{5'} - H_{4'ax.}$	3.4	2.86			
$H_{8'} - H_{1'}$	2.6	2.51			
$H_{8'} - H_{2''}$	2.8	2.59			

TABLE 12   Selected interproton distances in repanduline.

The distances measured on the model were used in the following

equation due to Noggle and Schirmer,[168] for the fractional enhancement

$(f_d(s))$ of a proton d on saturation of a proton s:

$$f_d(s) = \tfrac{1}{2} \frac{\rho ds}{R_d} - \tfrac{1}{2} \sum_n \frac{\rho dn \ f_n(s)}{R_d}$$

where ρds is the cross-relaxation between d and s, proportional to $(r_{ds})^{-6}$

R_d is the total direct relaxation rate of d, proportional to $(r_{ds})^{-6} + (r_{dn})^{-6}$

and $\sum_n$ represents a summation over all protons other than d and s.

It was assumed:

i) the term $\tfrac{1}{2} \sum_n \frac{\rho n \ f_n(s)}{R_d}$ may be neglected when calculating $f_B(A)$,

ii) H_B is relaxed only by H_A, H_1, $H_{5'}$ and $H_{8'}$;   iii) $H_{5'}$ only by H_A, H_B,

$H_{4'eq.}$ and $H_{4'ax.}$;   iv) $H_{8'}$ only by H_A, H_B, H_1 and $H_{2''}$.

This led to the calculated enhancements below, which are in good agreement

with the experiment, allowing for the effects of partial saturation and

dissolved oxygen: $f_B(A) = + 0.45$ (+ 45%); $f_{5'}(A) = + 0.0047$ (+ 0.47%)

$f_{8'}(A) = - 0.0001$ (-0.01%).

were undetectably small, presumably due to efficient relaxation of H_A by H_B. When a degassed solution of repanduline was used, the enhancement of H_5, on pre-irradiation of H_A, determined identically, increased to 0.26%, so providing independent evidence that the observed effect was a genuine n.O.e.

The very small size of the enhancement of H_5, on pre-irradiation of H_A calls for some comment since, as far as we are aware, there is no precedent for using such small enhancements in structural elucidation. The principal requirements for the detection of any n.O.e. enhancement by difference spectroscopy are that unenhanced peaks be nulled to a sufficiently low level and that the residual signal due to the n.O.e. be clear of the baseline noise. It is clear from Figure 24 that these conditions were both met in the present experiment. Nulling was effective to within ± 0.04% at worst, and the signal to (baseline) noise ratio was about 5:1 for H_5,. This was achieved by prolonged accumulation; a total of 32,000 transients was collected over one weekend (60h). For comparison, other experiments in this study used only 500-2000 transients from each pre-irradiation site and yielded a detection limit of $\sim$ 0.2-0.1% for most protons.

Satisfactory nulling of unenhanced signals is clearly a vital consideration in n.O.e. difference experiments, particularly since, unlike signal to noise ratio, nulling is not improved on raising the sample concentration. As we have shown, it is most important that a sufficiently large number of transients be collected. Prolonged repetition of the experimental cycle always progressively improves the nulling quality, although the rate at which it does so depends in some complex way on the relative values of the carrier and decoupler frequencies. Individual difference spectra from an automated multiple experiment thus commonly show significantly different degrees of nulling, despite the fact that all the data is effectively averaged over the

same period. This observation, together with the characteristic dispersion-like shape of the signals which result from incomplete nulling, suggests that its main cause is instrumental frequency instability.[175] Other factors which we find influential are use of a sufficiently low pre-irradiation power and an adequate delay between pre-irradiation and the observe pulse (see also Chapter Seven, Page 239).

Another feature of this experiment which requires comment is the method used to pre-irradiate H_A. When the decoupler was placed centrally between the two components of the H_A doublet, high power levels were required to produce adequate saturation. This was unsatisfactory since it caused poor nulling and, more significantly, an unwanted enhancement of H_B, via slight saturation of H_1. When the decoupler was placed on one of the components of the H_A doublet, however, lower power levels were sufficient to saturate that component, and both problems were avoided. Although H_A was only approx. 50% saturated, the resulting partially excited enhancements could still be detected more clearly than in the higher power experiments.

In order to suppress the very large S.P.T. effect at H_B caused by unsymmetrical partial saturation of H_A, two such difference spectra were accumulated, in each of which a different component of the H_A doublet was pre-irradiated. The asymmetry of the saturation (and hence of the S.P.T.) was approximately equal and opposite between these spectra, so that addition of the two during data processing resulted in cancellation of the asymmetry giving a combined spectrum in which the S.P.T. effect was suppressed (Figure 24)(see also Section 5).

iii) Long range $^{13}C\{^1H\}$ specific decoupling.

The long range n.O.e. experiment described in the previous

section establishes quite definitely that (296), not (297), is the correct substitution pattern for ring C of repanduline. Nonetheless, since an important objective of the experiment was to set a precedent for the use of very small enhancements in structural work, we felt an independent proof of this conclusion was still desirable. This was obtained from $^{13}C\{^1H\}$ specific decoupling experiments.

Although specific decoupling of ^{13}C from directly bound protons is commonplace, relatively little use has been made of specific long range $^{13}C\{^1H\}$ decoupling;[176] this is principally due to the difficulty of interpreting fully coupled ^{13}C spectra, which usually requires computer analysis.[177] For carbon atoms weakly coupled only to well separated protons, however, the relevant ^{13}C satellites in the ^1H spectrum are first-order, and a simple interpretation based on line separations in the carbon spectrum is appropriate. These conditions are met by $C_{6'}$, $C_{7'}$ and C_7 of repanduline, which couple only with $H_{5'}$, $H_{8'}$, H_A, H_B and H_5. In order to assign the couplings involving these atoms, ^{13}C spectra were accumulated in which $H_{5'}$ and $H_{8'}$ were separately decoupled at very low power. The results of these experiments are summarised in Table 13.

$|J|$ (Hz)	$H_{5'}$	$H_{8'}$	H_A	H_B
$C_{6'}$ (δ 140.2)	3.7	6.7	6.7	-
$C_{7'}$ (δ 139.6)	7.5	4.3	-	-

TABLE 13

Consideration of model compounds,[178] [6,7-dimethoxy-1-(4-methoxy-benzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline and 1-(4-methoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline], multi-

plicities and the changes caused by decoupling $H_{5'}$, H_5 and $H_{8'}$ led straightforwardly to identification of the multiplets due to $C_{6'}$, $C_{7'}$ and C_7. The relative assignment of $C_{6'}$ and $C_{7'}$ was made by comparing the couplings involving these atoms and $H_{5'}$ and $H_{8'}$. It is known that three-bond couplings, $^3J(C,H)$, are generally ~~smaller~~ larger than two-bond couplings, $^2J(C,H)$, in substituted benzenes; although $(^{13}C,^1H)$ couplings of 4.3 Hz and 3.7 Hz are not so small as to be inconsistent with a three-bond coupling path, values of 6.7 Hz and 7.5 Hz are too large to correspond to a two-bond coupling path.[177] This leads to the assignments given in Table 13. The remaining coupling from $C_{6'}$ is to H_A, and for this to be as large as 6.7 Hz, it must follow a three-bond rather than a four-bond path. The conclusion from this must again be that (296), not (297), is the correct structure of repanduline.

No other specific ambiguities of regioisomerism were left open by the original work on repanduline.[173,174] It is interesting to note, however, that the entire substitution pattern can be independently deduced from the ^1H n.O.e. difference spectra presented here, assuming only the presence of two tetrahydroisoquinoline skeletons. Without describing this process in detail one point may be mentioned, namely the relative positions of the spiro-link and the carbonyl group in ring B. This problem was originally resolved by chemical degradation; treatment of repanduline with potassium in liquid ammonia produced hemi-repanduline (299), the structure of which was confirmed by synthesis.[179] In view of the recent discovery of an unprecedented 7-7' ether link in the very closely related alkaloid daphnine (298),[180] and also the possibility that the hemi-repanduline was actually derived from an impurity, we wished to obtain direct physical evidence from repanduline itself.

(299)
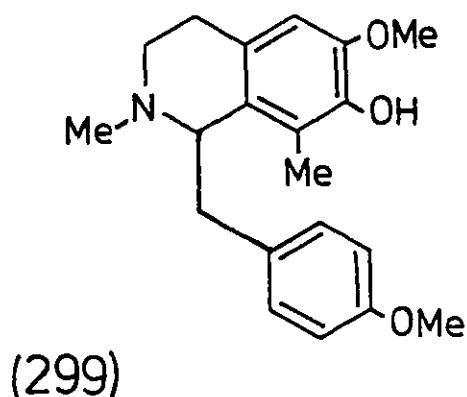
A further ^{13}C experiment in which H_5 was selectively decoupled provided this. The relatively large coupling ($|J|$ = 8.5 Hz) found between H_5 and the carbonyl carbon (δ 194.1) must follow a three-bond path,[177] so discounting structures such as (300). Also, models clearly showed that only in structures having the spiro-link at C_8 could $H_{2''}$ and $H_{8'}$ or H_B and H_1 be sufficiently close to explain the strong ^{1}H n.O.e. enhancements observed between them.

(300)
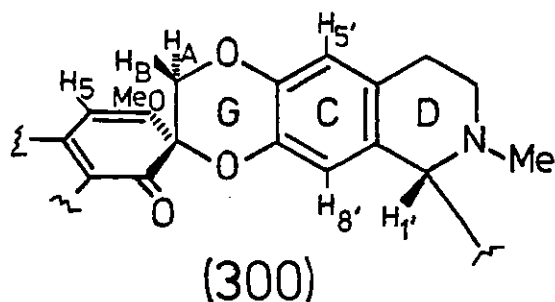
iv) Stereochemistry and conformation.

With the regioisomerism of repanduline fully defined, the remaining structural possibilities now comprised only the four diastereomers differing in relative configuration at C_1, C_8 and $C_{1'}$. Clearly, the stereochemistry at $C_{1'}$ is the least accessible to investigation by nmr, being relatively remote from the other chiral centres. We therefore first tackled the problem of the relative configuration of C_1 and C_8.
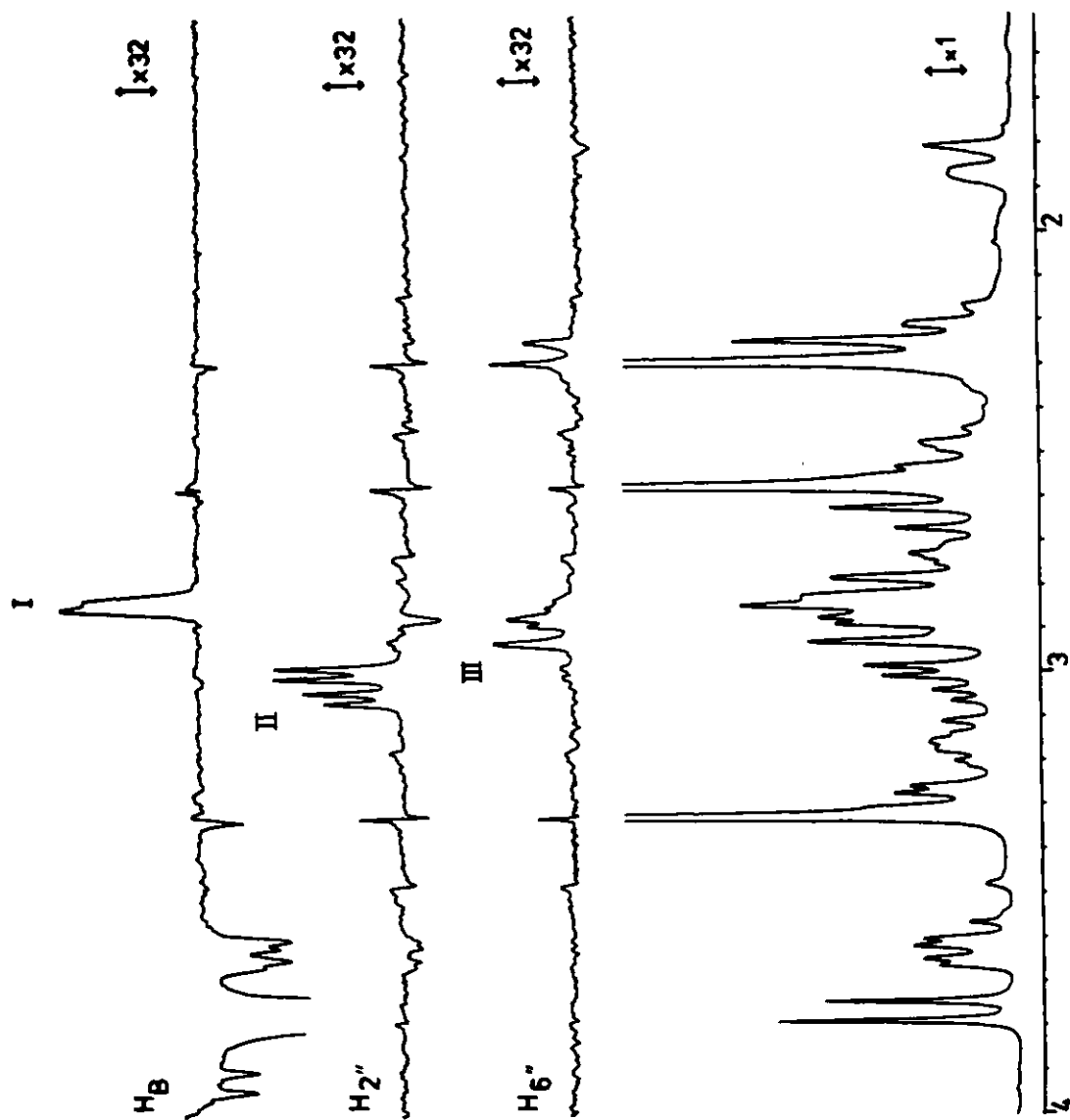
FIGURE 25   N.O.e. difference spectra of repanduline (296) in $CDCl_3$
containing $[^2H_6]$benzene (20%).   Pre-irradiation sites
were $H_{6''}$, $H_{2''}$ and H_B.

H_A H_5' H_B O MeO O H_5 B G C D N—Me N H_C $H_{8'}$ $H_{1'}$ Me H_1 H_D
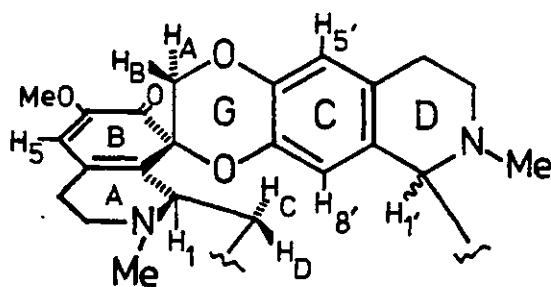
(301)

A distinction between diastereomers (296) and (301) requires

mainly a knowledge of the spatial relationships of H_1, H_C and H_D with

their neighbours H_B, $H_{2''}$ and $H_{6''}$.   In the original experiments, pre-

irradiation of H_B, $H_{2''}$ and $H_{6''}$ all caused enhancements at virtually the

same shift;   these coincidencies prevented assignment of the enhanced

multiplets and no structural conclusions could be drawn.   On repeating

the experiments after the addition of $\left[^2H_6\right]$benzene (20%) to the solution,

however, the coincidencies were removed and assignments became obvious

(Figure 25).   Multiplet II, which is enhanced by $H_{2''}$ and possesses a

geminal coupling ($|J|$ = 14 Hz) to multiplet III, must be due to H_C.

Multiplet I, since it is the only proton within the three-spin system

to lack a geminal coupling, can only correspond to H_1, and its

enhancement on pre-irradiation of H_B necessarily implies that dia-

stereomer (296) is the correct one.   Pre-irradiation of $H_{6''}$ also

caused enhancements of the N_2 methyl group and H_{4ax}.

The more difficult problem of the stereochemistry at C_1, could

not be so directly solved.   Diastereomers (296) and (302) would only

be expected to show relatively subtle differences in nmr properties

arising from their different overall conformations.   Distinguishing

between them was thus unavoidably linked with the final part of this

work, elucidation of the solution conformation of repanduline.   The

strategy adopted was to use the large amount of qualitative data

already obtained to specify as many details of the conformation as

possible, and then to incorporate these into a model of the whole molecule. Accurate Dreiding models were used throughout this work; less accurate models did not allow conformational energy minima to be recognised, and showed significantly different inter-proton distances in some cases. In the event, sufficient detail was available not only to establish almost completely the conformation of the macro-ring, but also to rule out diastereomer (302), since it could not simultaneously accommodate all the conformational requirements described below.

The result of this strategy was the proposed conformation shown in Figure 26; this drawing was traced from a photograph of a Dreiding model. The enantiomer shown was chosen only because it most resembles the conventional planar representation of repanduline.[173,174] No assignment of the absolute configuration was made. The evidence on which this proposed conformation is based is given below, considering each flexible portion of the macro-ring in turn.

a) Ring G.

Ring G is evidently fairly rigid, with H_A pseudo-equatorial and H_B pseudo-axial. This may be deduced from the following: i) H_A gives an enhancement to $H_{5'}$ but not to $H_{8'}$, ii) pre-irradiation of H_B enhances $H_{5'}$ and $H_{8'}$ to roughly equal extents, iii) H_A gives a modest enhancement to H_5 (0.42%), while H_B gives none, and iv) the proton-carbon coupling data suggests that $C_{6'}$ is anti-periplanar with H_A while C_7 is anti-periplanar with H_B (a Karplus dependence of $^3J(C,H)$ on dihedral angle has been established[177]). If ring G were not rigid, H_B would spend some time in a pseudo-equatorial position, and H_A in a pseudo-axial one, so that these clear distinctions would be lost.

b) Ring B.

Ring B spends most time in the conformation shown, in which the

H_5—C bond is roughly parallel to the H_A—C bond ($r_{H_AH_5} \simeq 3.8$ Å), and the carbonyl oxygen in "down" relative to the ring G methylene group. The only alternative arrangement for ring B suggested by the model would be obtained by "depressing" C_{4a}, C_5 and C_6 until the H_5—C bond is roughly perpendicular to the H_A—C bond, with the carbonyl oxygen now "up" relative to the ring G methylene group. In this conformation $r_{H_AH_5}$ would be ~ 5.8 Å, which is clearly inconsistent with the observed enhancement of (0.42%) of H_5 on pre-irradiation of H_A.

c) Rings A, E and the C_α link.

The positions of H_1, H_C and H_D may be specified in some detail. H_1 must be relatively close to H_B but distant from $H_{2''}$ and $H_{6''}$, while H_C and H_D are remote from H_B but relatively close to $H_{2''}$ and $H_{6''}$ respectively (Figures 25 and 26). Most significantly, the couplings involved reveal that the torsion angle (H_1, C_1, C_α, H_D) is close to 90° ($J_{H_1H_D} \simeq 0$ Hz), while the angle (H_1, C_1, C_α, H_C) is close to 30° ($J_{H_1H_C} \simeq 5$ Hz). The position of ring E is further evidenced by the large enhancement of $H_{2''}$ on pre-irradiation of H_8, (and vice-versa). The proposed conformation accounts for these data, and is also consistent with the observed enhancement of the N_2 methyl group and $H_{4ax.}$ on pre-irradiation of $H_{6''}$.

d) Rings C, D, F and the $C_{\alpha'}$ link.

Several observations lead to the conclusion that $H_{1'}$ is pseudo-equatorial: i) pre-irradiation of H_8, strongly enhances $H_{1'}$ but does not affect either H_E or H_F, ii) pre-irradiation of $H_{1'}$ does not affect $H_{3'ax.}$ and iii) pre-irradiation of either $H_{1'}$ or H_E causes strong enhancement of $H_{2'''}$. The large coupling between $H_{1'}$ and H_F ($J \simeq 12$ Hz) suggests that these protons spend most time in an anti-periplanar arrangement, while the chemical shift of H_F (δ 2.68 as opposed to δ 3.33
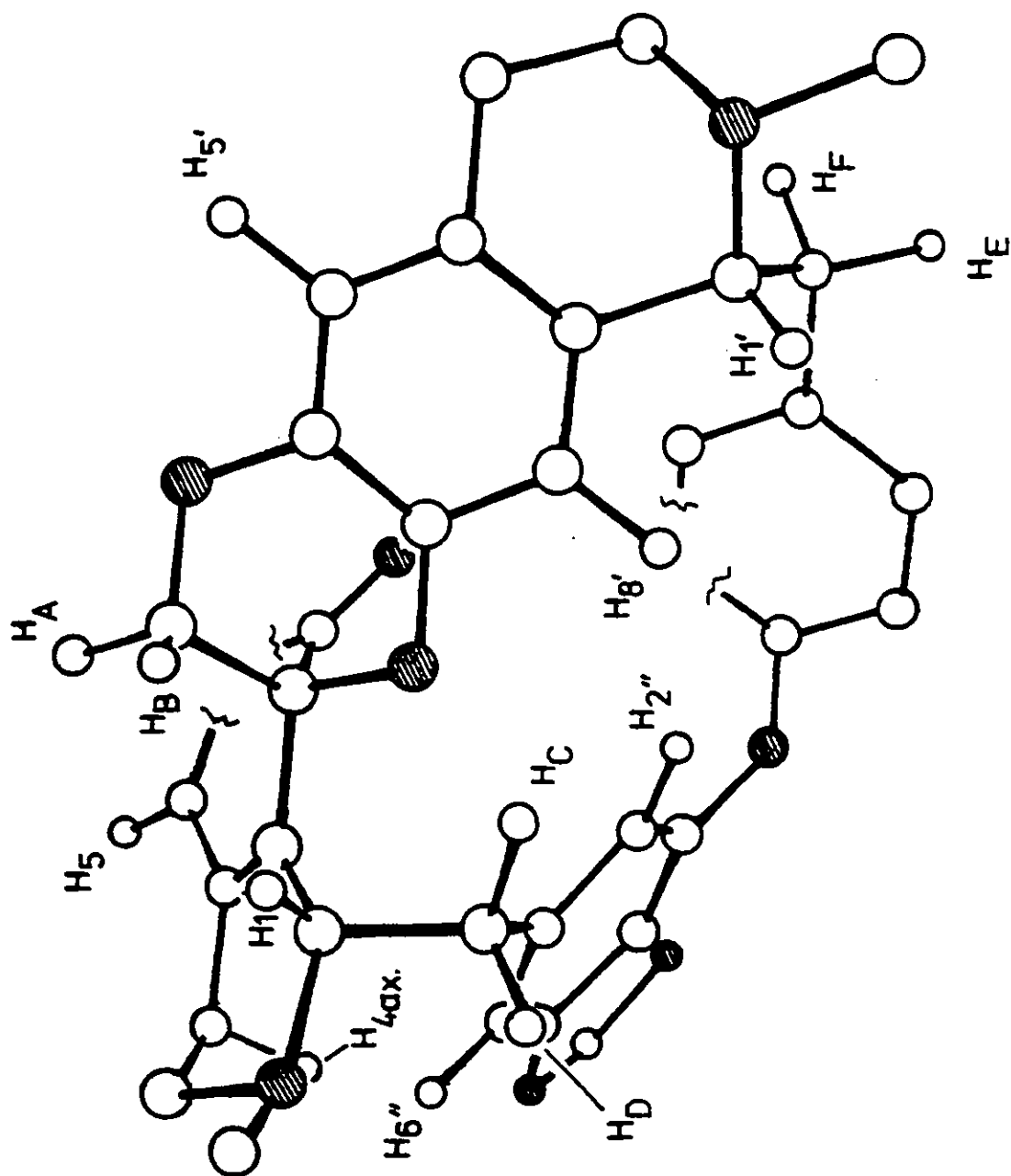
FIGURE 26   Proposed solution conformation of repanduline (296).
This drawing was   traced from photographs of a Dreiding
model (see text).   The enantimer shown was chosen only
because it most resembles the conventional planar repre-
sentation of repanduline.   No assignment of absolute con-
figuration was made.   Atoms C_6, $C_{5'''}$ and the methoxy group
are ommitted for clarity;   selected protons are shown.

for H_E) suggests this proton is shielded by ring C. The proposed conformation is also consistent with the unexpectedly high shifts of $H_{8'}$ (strongly shielded by ring F), $H_{2''}$ (shielded by rings C and F), $H_{5'''}$ and $H_{6'''}$ (shielded by ring C) and perhaps H_5 (slightly shielded by ring E).

Exhaustive examination of a molecular model showed that imposition of all these details specified the overall conformation of repanduline quite closely. The most demanding constraint was that the torsion angle (H_1, C_1, C_α H_D) be close to 90°; in practice this meant that the plane of ring E had to be "bent back" towards that of rings A and B, as in Figure 26. When the relative positions of H_A and H_5 were also constrained as described, this left very little option for the remainder of the molecule. In particular, these two requirements could not be simultaneously met by diastereomer (302).

(296)   (302)
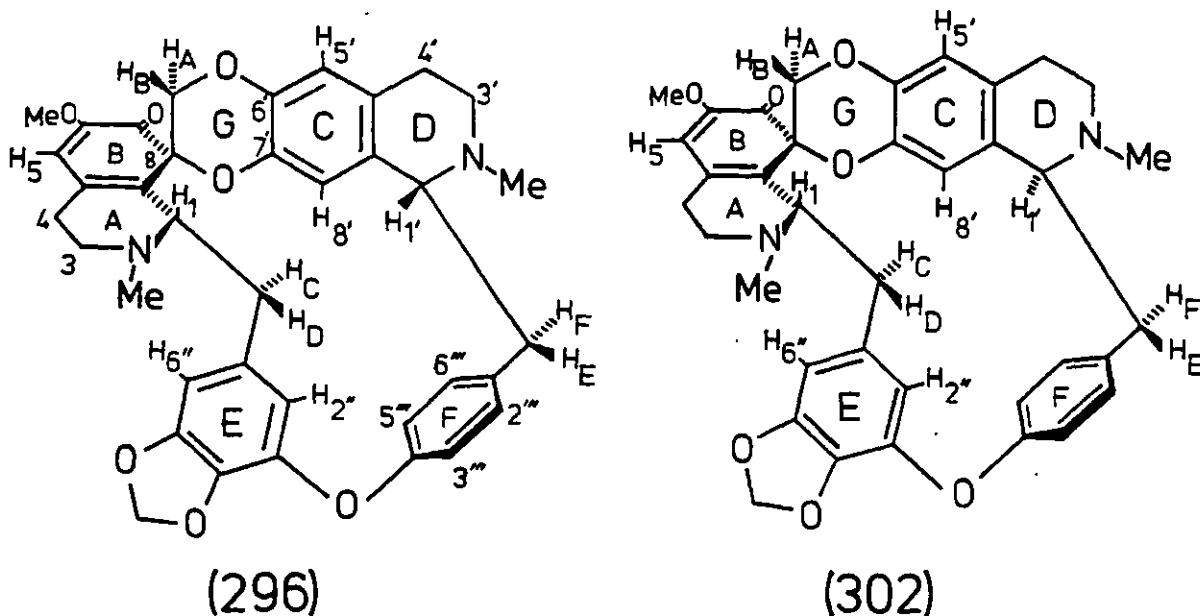
In conjunction, the model and enhancement data suggested that there is not much flexibility in the repanduline molecule. Apart from the (presumably) mobile methoxy group, the only significant conformational motions seemed to be a restricted rotation of ring F about its $C_{1'''}$ —$C_{4'''}$ axis, and a "flexing" of ring E, involving mainly movement about the C_α —$C_{1''}$ and $C_{3''}$ —O bonds, with some concomitant movement of

ring F and the C_α, link.

Finally, it must be emphasised that Figure 26 is merely a representation of one conformation which fits the available evidence. It is in no way intended to be a map of the actual average atomic positions, but may instead be taken to represent one point in the "conformational space" occupied by the real molecule. Strictly, the results apply only to the conformation in $CDCl_3$ containing $[^2H_6]$ benzene (20%), since the solvent shifts imparted by the benzene may be due in part to slight conformational changes (critical experiments originally run in $CDCl_3$ were repeated in the mixed solvent where necessary). Nonetheless, the similarity of the enhancement data obtained in the two solvent systems suggests that the proposed conformation is valid in $CDCl_3$ also, at least within the level of approximation of this qualitative interpretation.

v) Conclusion; X-ray crystal structure of repanduline.

These experiments illustrate the considerable power of n.O.e. difference spectroscopy, which seems to be still largely unrealised. In each of the traditional areas of application of inter proton n.O.e. measurements, problems which would have been completely beyond the scope of older methods succumbed to the difference technique. It was possible to measure reproducibly enhancements near the 0.1% level, and to show that they provided reliable structural information. While such long range experiments are no less prone to problems of interpretation than were previous n.O.e. studies, this ability to "see" protons over longer distances, in the present case as far as 4.5 Å, should allow many previously intractable problems to be solved. Enhancements induced within regions of overlap revealed vital and otherwise inaccessible spectral details; this use of the technique to render visible specific multiplets from within a complex envelope
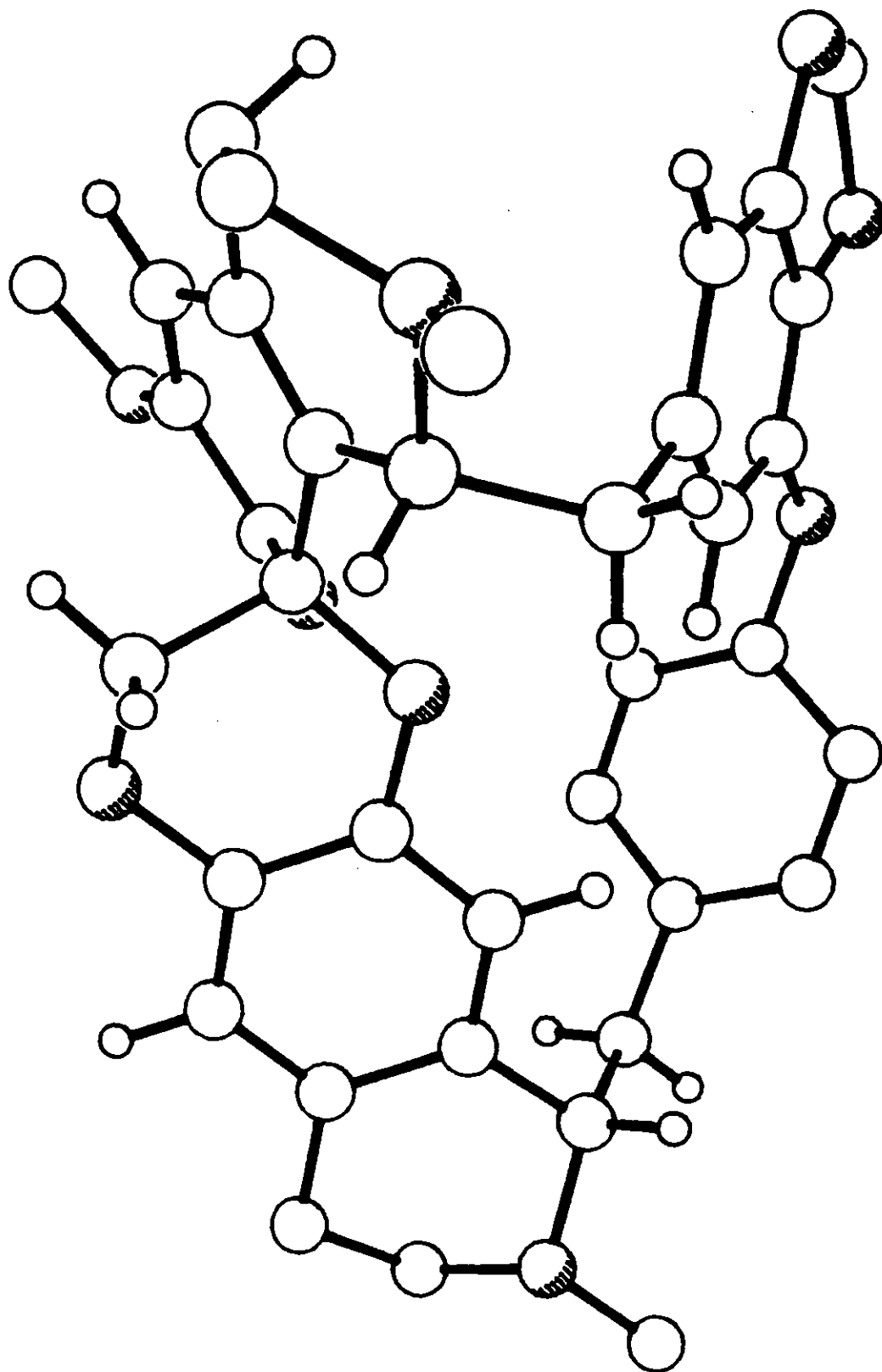
FIGURE 27   X-ray crystal structure of repanduline (296).

clearly offers considerable possibilities, particularly since the multiplets so revealed can often be assigned using a knowledge of the spatial relationships simultaneously determined.

The picture of the repanduline molecule which had emerged by the end of this nmr study (effectively summarised in Figure 26) was quite detailed, and invited comparison with X-ray crystallography. Repanduline had eluded X-ray analysis for many years since its crystals were unsuitable; the present work, however, led to the accidental discovery that useable crystals of a $CDCl_3$ solvate could be grown by evaporating the nmr sample. A suitable crystal was selected and subjected to a single-crystal X-ray study by Dr. D.J. Williams of this department; the results of this are summarised as the projection shown in Figure 27.

The X-ray study revealed that the absolute chirality of repanduline was opposite to that arbitrarily chosen when constructing Figure 26. This "discrepancy" is left uncorrected in this text, however, since it underlines the fact that the conclusions from the nmr study were all made before the X-ray result was available.

Comparison of Figures 26 and 27 shows how remarkably close the nmr predictions were; all the important features of the two conformations are essentially identical. The more demanding test (Table 12) of comparing inter-proton distances measured on the model with those determined in the crystal gives some idea of the accuracy of the results, although this is probably as much a test of the Dreiding models as of the nmr experiments. Obviously, the nmr-derived data can only be regarded as, at best, semi-quantitative, but for many chemical purposes this is sufficient, and the nmr results have the considerable advantage that they are obtained from solution.

5) Suppression of S.P.T. during n.O.e. difference experiments.

As was discussed in Section 3(ii), a complicated relationship exists between the n.O.e. and S.P.T. as they are encountered in n.O.e. difference experiments. Although S.P.T. is itself a useful phenomenon, being the object of study in the INDOR and FTINDOR experiments,[181] its occurrence during n.O.e. difference experiments can greatly complicate their interpretation. Some method of obtaining n.O.e. difference spectra free of the effects of S.P.T. would thus clearly be desirable.

S.P.T. occurs whenever the lines of a multiplet are saturated to differing extents, as inevitably happens when low power single frequency pre-irradiation is applied to multiplets during n.O.e. difference experiments. The consequences of this are apparent in many of the figures in this and previous chapters; they are clearly illustrated in Figure 28, which shows difference spectra obtained from 3β-acetoxy-5β-acetoxymethyltetrahydrofuran-2-one (303).[182] Single frequency pre-irradiation of the multiplets due to H_A, H_E and H_F, in each case setting the irradiation frequency to that of a central line in the multiplet, caused complicated intensity changes in multiplets coupled to the target.

Incomplete saturation has traditionally been avoided during n.O.e. experiments by using a sufficiently high pre-irradiation power to saturate even the outermost lines of an irradiated multiplet.[168] This approach, however, sacrifices much of the advantage of the difference technique, particularly its selectivity. More sophisticated methods for pre-irradiation, such as multiple resonance, narrow-band noise modulation, or tailored excitation,[183] might provide a general solution, but the necessary facilities are only available on a minority of spectrometers.

In the method proposed here, the position of every line of a
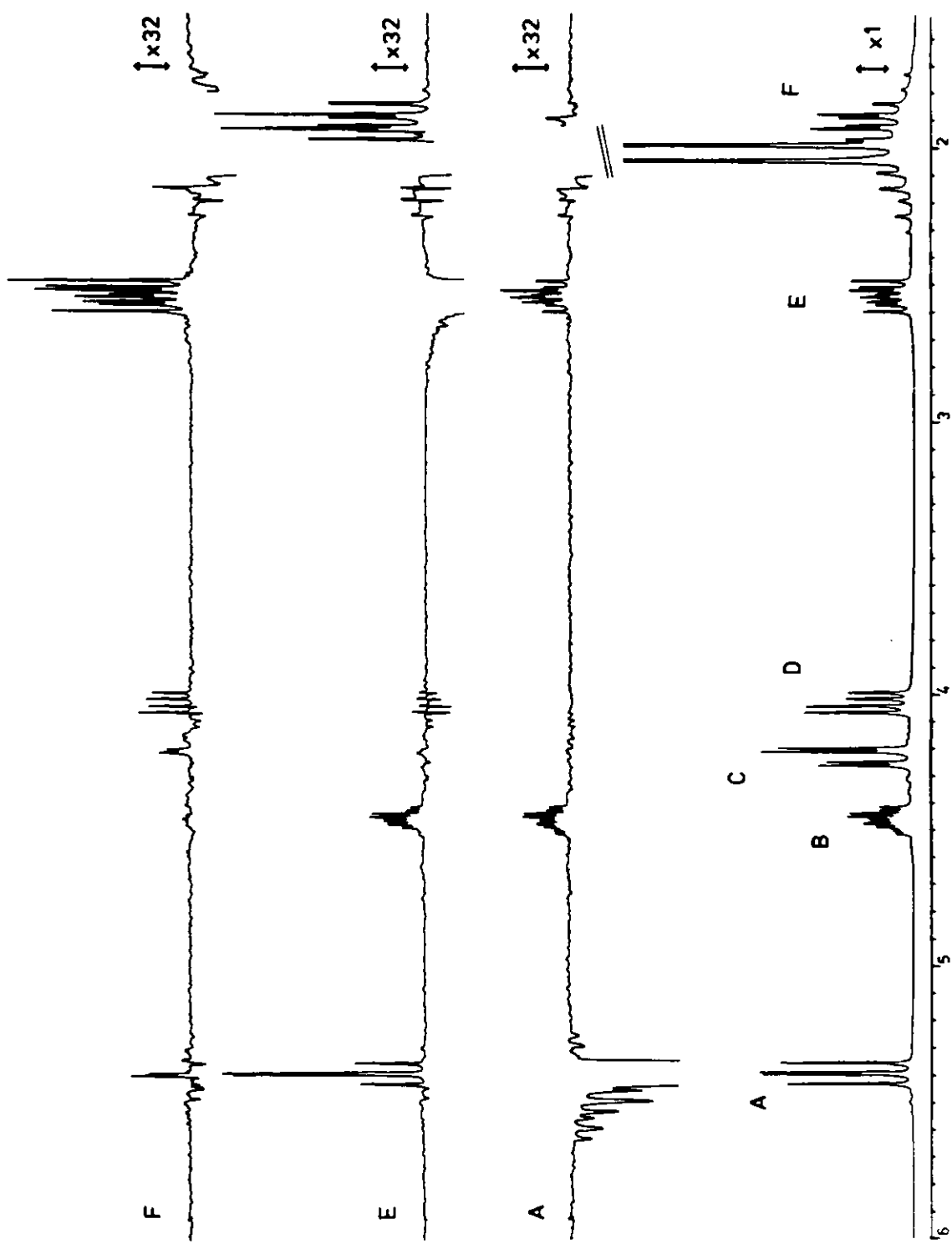
FIGURE 29 S.P.T. suppressed n.O.e. difference spectra of compound (303).
Dispersion artefacts in the region δ 1.9-2.1, resulting from incomplete
nulling of the intense acetoxy singlets and their side-bands, are omitted
for clarity.
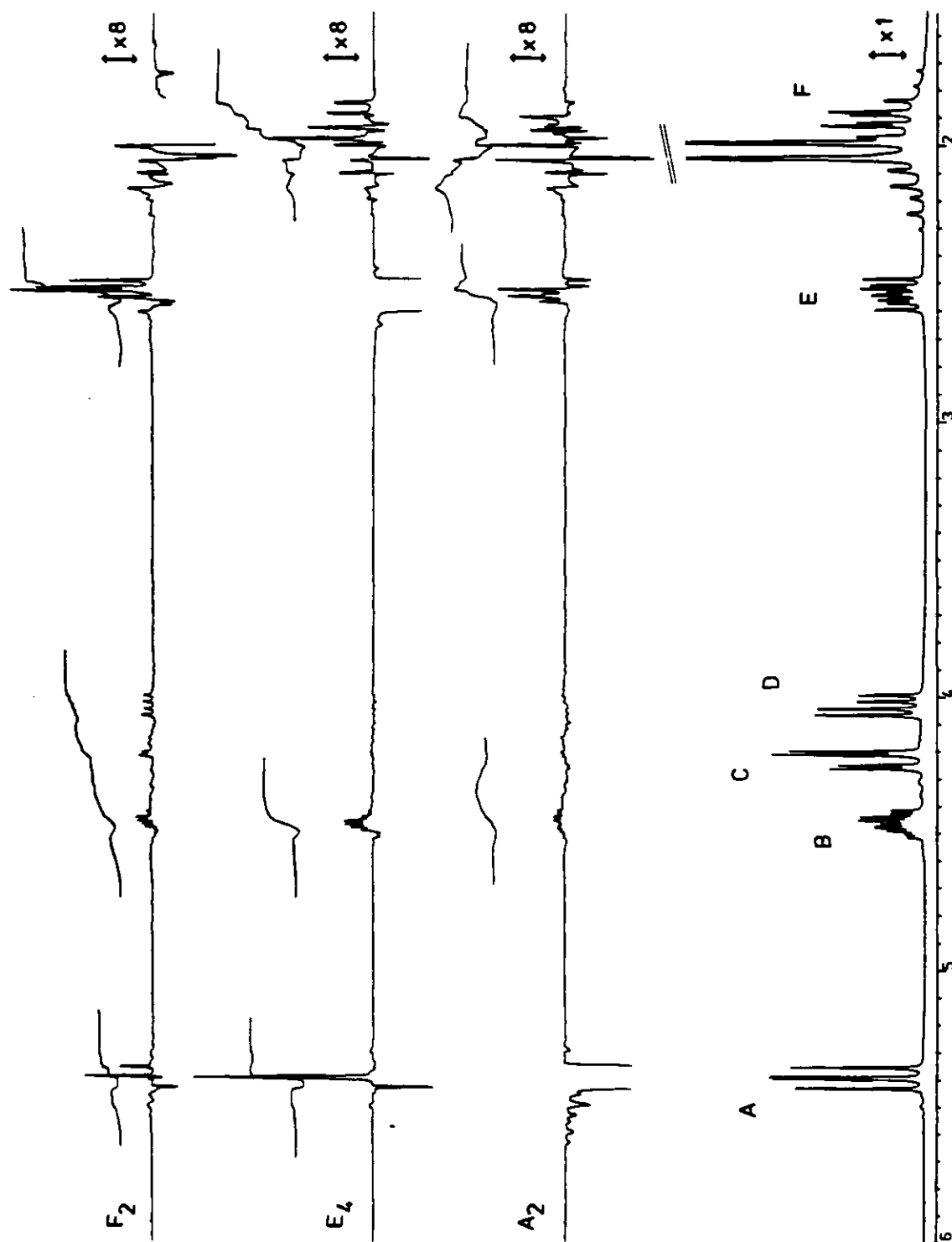
FIGURE 28 N.O.e. difference spectra of compound (303). Trace A_2 corresponds to pre-irradiation of line A_2, trace E_4 to line E_4, and trace F_2 to line F_2. These difference spectra are plotted at one quarter the vertical amplitude of those in Figure 29 to accommodate the large intensity fluctuations caused by S.P.T.

target multiplet is included in the frequency list for an automatic
n.0.e. difference sequence (see Chapter Seven), and an equal number
of transients collected at each line in the usual way. All the data
from pre-irradiation of these lines are then summed during processing;
this has the effect of cancelling out the individual S.P.T. contri-
butions from each line, leaving, after subtraction of an appropriately
weighted control spectrum, a difference spectrum in which only those
multiplets enhanced by the n.0.e. appear. This is illustrated in
Figure 29, which shows the results obtained when the previous experi-
ments were repeated using this suppression technique. Thus, trace A
is a summation of data from all four lines of multiplet A (due to H_A),
trace E results from pre-irradiation of all eight lines of multiplet E
(due to H_E), and trace F from the six lines of multiplet F (due to H_F).
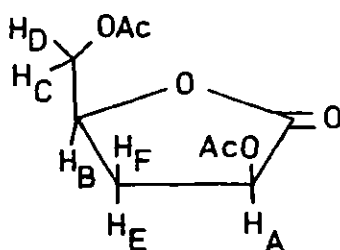
(303)

It is clear that the desired effect was largely achieved.
Multiplets due to protons coupled to, but remote from, the pre-
irradiated proton do not appear in the difference spectrum, while
those multiplets enhanced by the n.0.e. are only moderately distorted
relative to their appearance in the normal spectrum. The addition
process is illustrated in Figure 30, which shows how the final pattern
of multiplet E in trace A is built up from the contributions of lines
A_{1-4} (lines within a multiplet are numbered from left to right, i.e.
in decreasing order of frequency, throughout). Figure 30 also makes
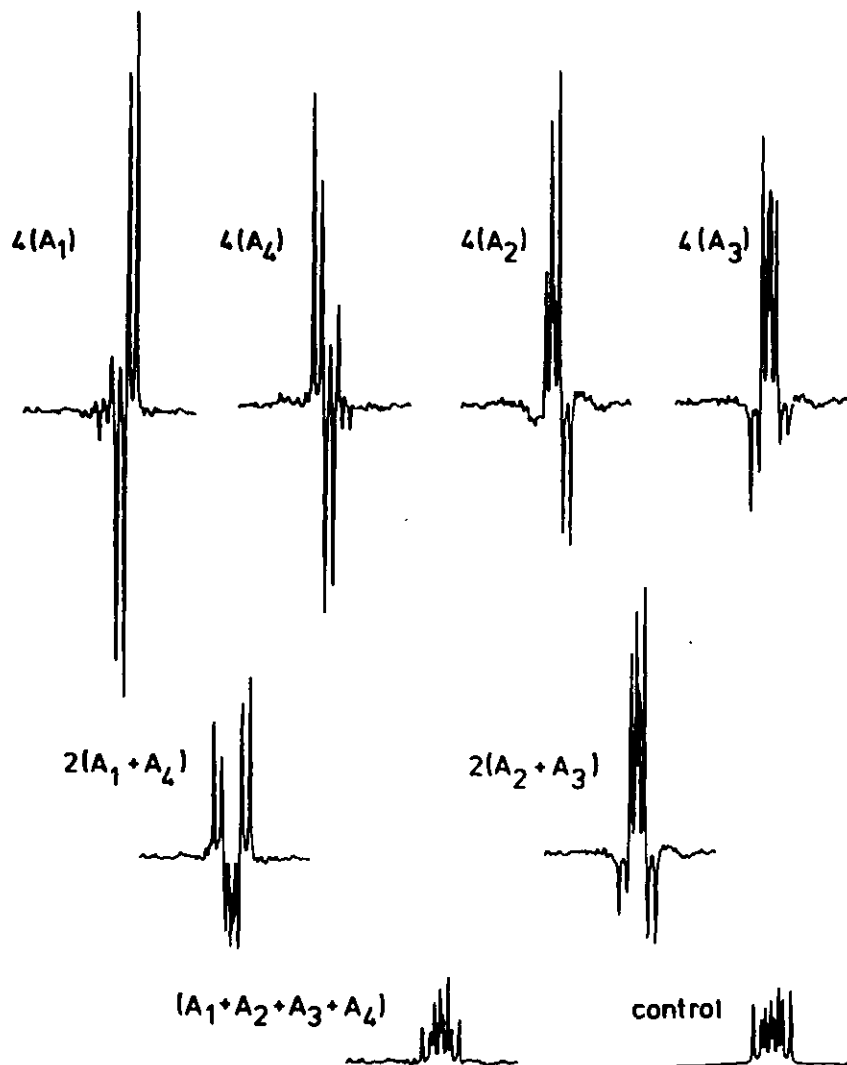
FIGURE 30 Stages in the addition of data from multiplet E on pre-irradiation of A (compound 303). The factors of 2 and 4 are necessary to allow direct comparison of all the difference traces with the same control. Difference traces are plotted at 32 times the vertical intensity of the control.
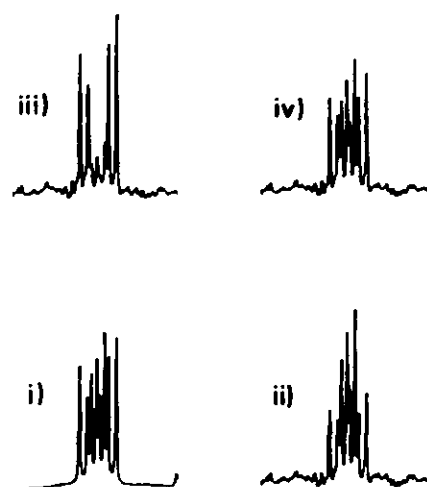
FIGURE 31 Weighted addition of the data from pre-irradiation of multiplet A. The traces correspond to i) control, ii) $(A_1 + A_4) + 1 (A_2 + A_3)$, iii) $(A_1 + A_4) + 0.5 (A_2 + A_3)$ and iv) $(A_1 + A_4) + 0.8 (A_2 + A_3)$.

clear the origin of the residual distortion in this case; too high a proportion of the contributions from lines A_2 and A_3 have been included, making lines E_{3-6} too intense at the expense of lines E_{1-2} and E_{7-8}. Since the same number of transients was collected at every pre-irradiation frequency, the real cause of this must be the narrow separation of lines A_2 and A_3. Pre-irradiation of either causes partial saturation of the other, with the result that both receive more than their correct "share" of the total saturation.

Figure 31 shows how this distortion may be corrected by weighting the contributions from lines A_2 and A_3 during addition. The correct weighting factor must lie between unity, corresponding to complete selectivity between saturation of A_2 and A_3, and 0.5, corresponding to no selectivity. As shown, a good match was obtained using a weighting factor of 0.8, which still represents excellent decoupler selectivity given that lines A_2 and A_3 are only 2 Hz apart. Such weighting would probably be an unnecessary refinement for most applications, and is only required at all in cases of near overlap; if overlap is complete, only one entry will appear for the coincident transitions in the frequency list, and the correct proportionality results automatically.

Since a target multiplet is only ever partially saturated, the n.O.e. enhancements measured by this method are correspondingly reduced in intensity. This loss is less than might be expected, however, since relaxation of protons coupled to that irradiated has the effect of spreading the saturation into other components of the target multiplet during pre-irradiation; the target multiplets in Figure 2, for instance, all showed >50% saturation in the final traces. Nor does this reduction imply any loss of information; percentage n.O.e. enhancements measured by difference are usually considered too experimentally variable to be treated as semi-quantitative molecular parameters in the way that conventional n.O.e. data used to be (Section 3(i)).[169]
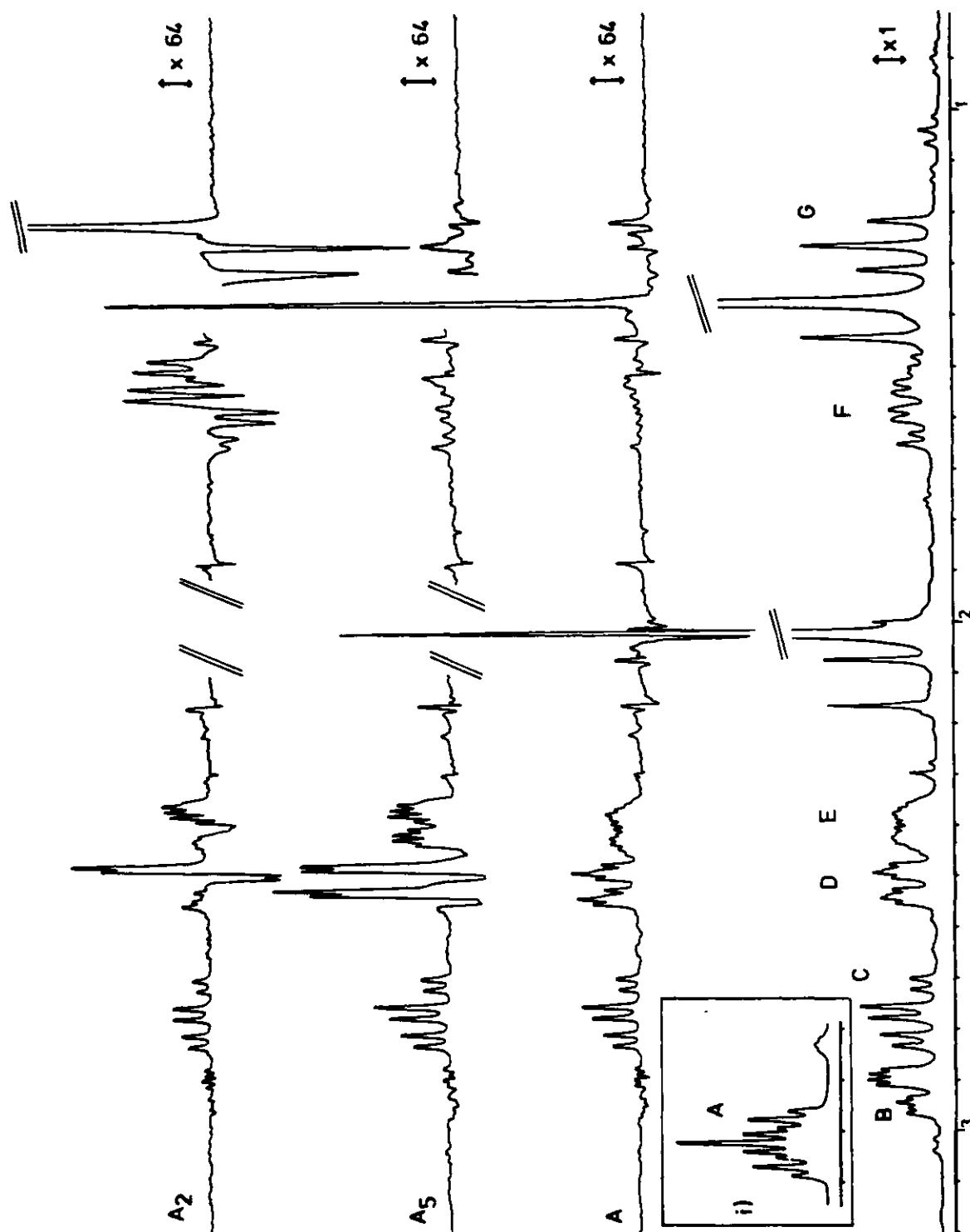
FIGURE 32 N.O.e. difference spectra of compound (304) (high field region only). Trace A is an S.P.T. suppressed spectrum obtained by sequentially pre-irradiating all nine lines of the multiplet due to H_A (inset (i) δ 5.32). Trace A_5 corresponds to pre-irradiation of line A_5 only, and trace A_2 to pre-irradiation of line A_2 only. Trace A clearly shows enhancements of the Me singlet and multiplets C, D and E, while traces A_5 and A_2 show distortions due to S.P.T.
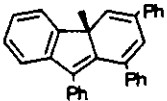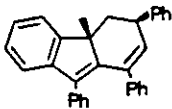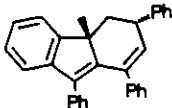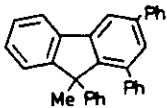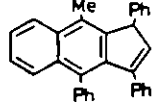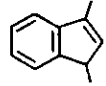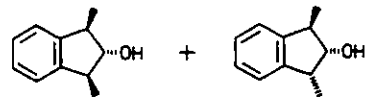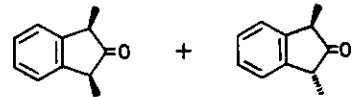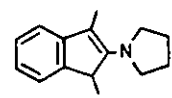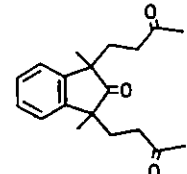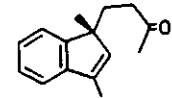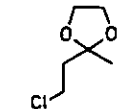
The method has been used, and gave comparable or better results, in a number of other instances. These included the remaining multiplets in the spectrum of compound (303),[184] the methine proton of tetrahydrocarbazole (304) (see Figure 32), protons in the AMX system of a monosubstituted spiro-cyclopropane derivative, and doublets in the spectra of numerous other molecules (including, of course, repanduline (296), Section 4(ii)). The only disadvantages of the method are its increased need for data storage and processing (both of which can be avoided by automating the addition during the experiment, if the individual data sets are not required) and a loss of conceptual simplicity, but these are more than compensated by the considerable simplification produced in the resulting spectra.
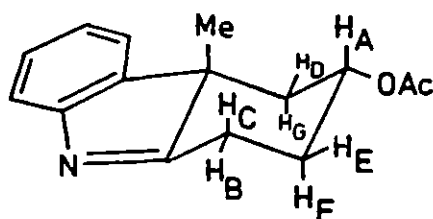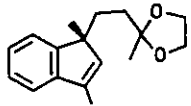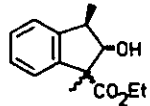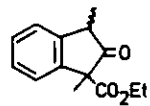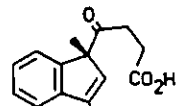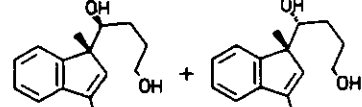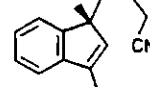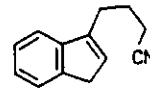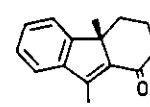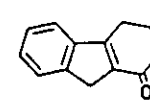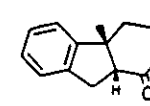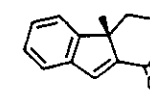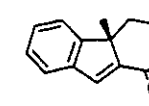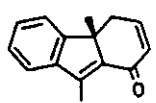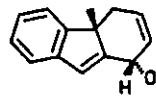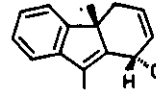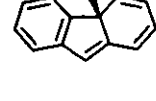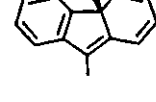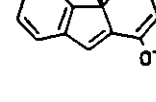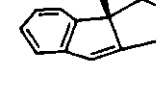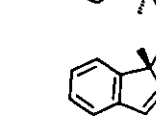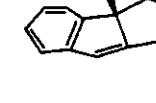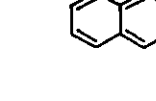
(304)

CHAPTER SEVEN

COMPOUND INDEX

CHAPTER SEVEN: Experimental

1) General

i) Solvents and reagents.

Light petroleum refers throughout to the fraction b.p. 40-60°C, unless otherwise stated, which was slowly distilled through a good fractionating column before use, collecting only that material which boiled over a 10-15° range.   Two such distillations were used when the solvent was required for purification of analytical samples of hydrocarbons.

Tetrahydrofuran and dioxan were distilled from sodium wire and benzophenone ketal under nitrogen, and were stored under nitrogen over 4A molecular sieves in darkened bottles.

Chlorobenzene was dried by distillation from calcium hydride, discarding a forefraction of ∿ 10%.

Ether (refers to diethyl ether throughout) and benzene were dried by standing over sodium wire, and were stored in darkened bottles.

Dry ethanol and methanol were prepared by distillation from their respective magnesium alkoxides, and were stored over 3A molecular sieves.

Dry pyridine was prepared by distillation from potassium hydroxide and was stored over 4A molecular sieves.

Sulpholane was purified as follows: sulpholane (500ml), de-ionised water (500ml) and concentrated sulphuric acid (10ml) were cautiously mixed and left to stand over potassium permanganate (25g) for 14h.   Sodium metabisulphite was added to give a clear solution, which was washed with dichloromethane (3x300ml).   The dichloromethane extracts were combined, dried over magnesium sulphate and distilled to

give pure sulpholane (b.p. 172-178°C/40mmHg).

Indene was slowly distilled and stored over 4A molecular sieves in a darkened bottle.

Cuprous bromide-dimethylsulphide complex was prepared as follows: sodium bromide (23.3g, 0.23mol) in water (40ml) was added to cupric sulphate pentahydrate (40g, 0.16mol) in water (180ml) at ∿ 50°C, and the mixture stirred during the addition of sodium sulphite heptahydrate (25g, 0.10mol) in warm water to discharge the green colour. The pale green precipitate was collected, washed repeatedly with water then dried over phosphorus pentoxide at 1mmHg for 90h. The resulting white solid was dissolved in dimethylsulphide, filtered, reduced to ∿ 50ml, then light petroleum (150ml) added, the white precipitate collected, washed several times with light petroleum and dried to give the complex (29.1g, 88.4%). It was stored in a darkened bottle in a desiccator.

Benzeneseleninic anhydride (BSA) was prepared as follows: concentrated nitric acid (20ml) was added dropwise to a stirred suspension of diphenyldiselenide[185] (20g, 64mmol) in water (20ml) at 60-65°C, and the mixture stirred 1h at 60°C. On cooling to 2°C for 3h, the nitric acid complex precipitated and was collected. The complex was heated at 110-120°C and 1-2mmHg for 80h; the crystals first melted, evolved fumes of nitric acid, then re-solidified after ∿ 20h to give an amorphous white mass which was periodically ground with a pestle and mortar. The resultant BSA (20.0g, 87.1%), m.p. 163-167°C (lit.[186] 165°C), was stored in a desiccator.

Iodylbenzene was prepared by the method of Sharefkin and Saltzman,[187] and its purity checked by iodometric titration. N-Phenylmaleimide was prepared by the method of Cava et.al.[188] 4-Phenyl-1,2,4-triazoline-3,5-dione (PTAD) was prepared by the method of Cookson et.al.[189] and was purified by vacuum sublimation. Other solvents and reagents were used as supplied. Alkyllithium reagents

were standardised in the usual way.[190]

ii) <u>Chromatography</u>.

Column chromatography employed silica gel 60H (Merck Art.7736), silica gel H (Rose Chemicals), alumina 60H (Typ E; Merck Art.1085) or basic alumina (B.D.H., 60-120 mesh), as indicated in the text. Most columns were run under pressure from hand-bellows; an electric pump was used for larger columns (> 20g adsorbant). Samples were applied as a dry pre-absorbed mixture with a small amount of absorbant, or as a solution in the minimum amount of suitable solvent in the case of unstable substrates.

Analytical thin layer chromatography employed aluminium-backed silica plates cut to size (Merck, Kieselgel 60 F_{254} Art.5554) or glass plates dipped into a slurry of chloroform and alumina 60H (Typ E; Merck Art.1085), then dried. Plates were visualised under uv light at 254nm and 306nm.

Preparative thin layer chromatography employed silica gel mixed with gypsum binder (Merck, Kieselgel Typ 60, GF_{254} Art.7730) applied to glass plates (20 x 20cm) in an even layer as a slurry with water, then dried. After elution, the appropriate band was separated and thoroughly washed, usually with ether, to extract the required material. Up to 100mg of sample was used with each plate.

iii) <u>Spectra</u>.

Infrared (ir) spectra were recorded in the range 600-4000 cm^{-1} using a Perkin Elmer 257 grating spectrometer and were calibrated against polystyrene (1603cm^{-1}). Sodium chloride plates or solution cells were used to contain the sample. The following abbreviations are used: strong (s), medium (m), weak (w), broad (br).

Ultraviolet (uv) spectra were recorded in the range 200-450 nm using a Pye Unicam SP800 recording spectrophotometer. ϵ max values are quoted in units of $1000cm^2.mol^{-1}$; shoulders are abbreviated (sh).

Proton nuclear magnetic resonance (^1H nmr) spectra were recorded using a Perkin Elmer R32 instrument operating at 90 MHz, Varian EM360 or T60 instruments operating at 60 MHz or a Bruker WM250 instrument operating at 250 MHz. All spectra included tetramethylsilane (TMS) as an internal standard; most of those run at 90 MHz employed a homonuclear lock (TMS) and all of those run at 250 MHz employed a heteronuclear lock (deuterium of the solvent). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), etc. Further experimental details of the more sophisticated nmr techniques are given in Section 5.

Carbon nuclear magnetic resonance spectra (^{13}C nmr) were recorded using a Bruker WM250 spectrometer operating at 62.9 MHz, with broadband decoupling. Abbreviated multiplicities, when given, refer to off-resonance spectra.

Mass spectra (ms) were recorded at low resolution using A.E.I. MS 12 and VG Micromass 7070B instruments. High resolution spectra were obtained on the VG Micromass 7070B instrument. Samples were mostly recorded at 70eV using a direct insertion probe.

iv) Other data.

Melting points were determined using a Kofler Hot Stage apparatus, and are uncorrected.

Microanalyses were carried out by Mr. K.I. Jones of this department.

v) Techniques.

All reactions involving extremely air or moisture sensitive materials (particularly alkyl lithium reagents) were carried out in a

flame-dried apparatus under a slow stream of nitrogen, and materials were transferred by syringe or catheta through suba-seals.

Photolyses were carried out in a Rayonet photochemical reactor using lamps of 254nm wavelength. The reaction vessel consisted of a quartz tube fitted with a glass frit at its base, through which a slow stream of nitrogen was passed to keep the reaction mixture agitated and de-oxygenated throughout the irradiation period.

The apparatus used for flash vacuum pyrolysis (FVP) comprised a quartz tube fitted with a carbon dioxide condensor and a connection to a high vacuum system at the upper end, and a 50ml flask containing the sample at the lower end. During each experiment, the sample was heated (using a Kugelrohr oven) until it sublimed through the quartz tube, which was independently pre-heated at $650^{o}C$. When sublimation was complete, the pyrolysate was collected from the condensor and worked up conventionally. Further details of the technique are available elsewhere.[191]

2,4-Dinitrophenylhydrazones of delicate ketones were prepared by stirring a solution of the ketone, 2,4-dinitrophenylhydrazine (0.8 equiv.) and p-toluenesulphonic acid monohydrate (0.1 equiv.) in ethanol at $50^{o}C$ for 48h. Evaporation and column chromatography on basic alumina using chloroform (20% in light petroleum (b.p. $40-60^{o}C$)) as eluent, followed by recrystallisation then gave the required derivative.

2) Preparation and Reactions of 4a-Methyl-1,3,9-triphenyl-4aH-fluorene (119).

i) Preparation.[112]

Polyphosphoric acid (85%; 425g), acetophenone (197g, 1.64mol) and benzene (240ml) were refluxed together at $90^{\circ}C$ for 7h with mechanical stirring. A dark green colour appeared 0.2h after reflux commenced, and persisted throughout the reaction. The hot mixture was then cautiously poured into ice-water (1 litre) with stirring to yield a brown benzene layer, a very pale blue-green aqueous layer, and an insoluble yellow solid ("C") at the interface between them. The solid "C" was collected by filtration, then the benzene layer of the filtrate was separated, washed with dilute sodium hydroxide solution (2M; 2x200ml), dried over sodium carbonate and thoroughly evaporated to give an oil which was crystallised from light petroleum (1 litre). The resultant yellow solid was recrystallised from a mixture of benzene and light petroleum (b.p. $60-80^{\circ}C$) to give 4a-methyl-1,3,9-triphenyl-4aH-fluorene (119) (27.6g, 16.5%), m.p. $181-182^{\circ}C$ (lit.[112] m.p. $180-181^{\circ}C$).

ν_{max} (nujol) 3015 (w), 1600 (w), 1500 (m), 782 (m), 768 (m), 759 (s), 737 (m), 700 (m) cm^{-1}.

λ_{max} (EtOH) 415 (ϵ 2400, sh), 393 (4200), 373 (4200), 347 (4300, sh), 286 (24500, sh), 273 (30300, sh), 265 (34000), 262 (33000, sh), 258 (31300, sh), 241 nm (28200).

δ_{1H} (CCl_4; 90 MHz) 1.71 (3H, s, Me), 6.65-6.75 (2H, ABq, H_2 and H_4), 7.8-7.9 (19H, m, aromatic protons).

δ_{13C} ($CDCl_3$; 62.9 MHz) 27.3 (Me), 55.3 (C_{4a}), 121.5, 125.8 (x2), 125.9, 126.0, 126.8, 126.9, 127.1, 127.3, 127.4 (x2), 127.5 (x2), 127.6 (x2), 128.5 (x2), 129.2 (x2), 133.4, 135.0, 136.3, 137.1, 138.0, 140.1, 140.4, 143.8, 146.9, 150.2.

m/e 408 (100%, $\underline{M}^+$), 393 (74%, $\underline{M}^+ - {}^\bullet CH_3$), 331 (14%, $\underline{M}^+ - {}^\bullet Ph$),
315 (15%, $\underline{M}^+ - {}^\bullet C_7H_9$).

The filtrate from the original crystallisation was evaporated to
give a brown oil, which nmr showed to be a complex mixture. A small
sample was redissolved in benzene, washed with concentrated sulphuric
acid (3x20ml), then water (20ml), dried ($MgSO_4$) and evaporated to give
a pale brown resinous oil. Nmr showed that only acetophenone and
dypnone had been removed from the original mixture. The remainder of
the evaporated filtrate (150g approx.) was distilled to yield aceto-
phenone (15g) (b.p. 30-40°C/0.35mmHg), a mixed fraction (5g) (b.p. 40-
155°C/0.35mmHg) and dypnone (163) (20g) (b.p. 157-164°C/0.35mmHg).

Substance "C" was purified by washing with hot acetone.

Found: C, 55.62; H, 4.01%.

ν_{max} (nujol) 1625 (s), 1595 (m), 1580 (w), 1495 (s), 1250 (m),
1160 (m, br), 995 (w), 780 (w), 762 (m), 715 (w), 678 (m) cm^{-1}.

δ_{1H} (CF_3CO_2H; 90 MHz) 7.7-8.1 (100%, m), 8.15-8.35 (25%, m),
8.35-8.55 (50%, m), 8.70 (25%, s).

δ_{13C} (CF_3CO_2H; 62.9 MHz) (ref. DSS in D_2O; ext.) 116.5 (45%, d),
130.3 (100%, d), 130.7 (25%, s), 131.0 (46%, d), 132.6 (96%, d),
132.7 (46%, d), 134.9 (9%, s), 138.2 (26%, d), 138.4 (43%, d),
170.0 (10%, s), 174.3 (20, s).

δ_{31P} (CF_3CO_2H; 101.3 MHz) (ref. H_3PO_4; ext.) - 8.1 (21%, $\Delta\nu\frac{1}{2}$ht.
615 Hz), 4.9 (100%, $\Delta\nu\frac{1}{2}$ht. 175 Hz).

In a further experiment, polyphosphoric acid (25g), compound (119)
(1.75g, 4.29mmol) and benzene (30ml) were refluxed together at 90°C for
7h with mechanical stirring. The hot mixture was then poured into
ice-water (100ml) and the benzene layer separated, washed with dilute
sodium hydroxide solution (2M; 2x200ml), dried (Na_2CO_3) and evaporated
to give unchanged (119) (1.45g, 82.8%). The base extracts were
neutralised then washed with ether (3x100ml). The ether extracts were

dried (MgSO₄) and evaporated; no material was recovered from these extracts.

ii) Oxidation and Reduction.

Oxidation of 4a-methyl-1,3,9-triphenyl-4aH-fluorene (119). —
Sodium metaperiodate (12g, 56mmol) and potassium permanganate (0.6g, 3.8mmol) were dissolved in a mixture of freshly distilled, pure sulpholane (Section 1(i)) (120ml) and de-ionised water (40ml) at 70°C. Sodium hydroxide solution (10%) was added to bring the pH to 7.5, then compound (119) (0.43g, 1,1mmol), as a slurry in the sulpholane-water mixture (50ml), was added and the mixture stirred at 60-70°C for 14h. Solid sodium metabisulphite was added until the purple colour was discharged, then water (1.5 litres) was added and the mixture washed with ether (3x250ml). The ether extracts were combined, reduced, washed repeatedly with dilute hydrochloric acid, dried (MgSO₄) and evaporated to give a semi-solid brown oil (0.4g). Tlc and nmr showed that starting material was absent, but preparative tlc yielded no identifiable materials. The majority of the product mixture was highly polar.

Hydrogenation of 4a-methyl-1,3,9-triphenyl-4aH-fluorene (119). —
A solution of compound (119) (0.41g, 1mmol) in cyclohexane (50ml) was hydrogenated at atmospheric pressure and 20°C for 14h in the presence of 10% palladium on charcoal (0.1g). The mixture was filtered (celite) and evaporated to give a yellow oil which nmr showed to contain compounds (182) and (183) in an approximate ratio of 1:2. Crystallisation from glacial acetic acid-methanol and slow recrystallisation from hexane gave a mixture of large prisms and a fine powder. Mechanical separation of the prisms followed by washing with hexane and drying gave 4,4a-dihydro-4aβ-methyl-1,3β,9-triphenyl-3H-fluorene (183),

m.p. 136-141°C.

δ_{1H} (CCl$_4$; 90 MHz) 1.29 (3H, s, Me), 2.21 (1H, dd, $\underline{J}$, 14 and 8.5 Hz, H$_{4\alpha}$), 2.54 (1H, d, $\underline{J}$, 14 Hz, H$_{4\beta}$), 4.09 (1H, dd, $\underline{J}$, 8.5 and 4 Hz, H$_3$), 6.37 (1H, d, $\underline{J}$, 4 Hz, H$_2$), 6.8-7.55 (19H, m, aromatic protons).

In a further experiment, an identical crude product mixture (2g), obtained as before, was crystallised from light petroleum (7ml) and recrystallised from acetic acid. Short path column chromatography on silica 60H (10g), eluting with light petroleum, followed by a further recrystallisation from light petroleum gave a mixture of compounds (182) and (183) in a roughly equimolar ratio. This material was used in the n.O.e. difference experiments shown in Figures 3 and 4.

Reaction of 4a-methyl-1,3,9-triphenyl-4aH-fluorene (119) with lithium aluminium hydride. — Lithium aluminium hydride (0.125g, 3.29mmol) was added in small portions to a stirred solution of compound (119) in dry ether (30ml) at 20°C under nitrogen, and the resultant dark green solution stirred for 6h. Water was cautiously added, followed by concentrated hydrochloric acid until the inorganic salts had dissolved. The ether layer was separated, washed with dilute hydrochloric acid (20ml) and water (20ml), dried (MgSO$_4$) and evaporated to give a pale yellow oil which nmr showed to contain roughly equal amounts of compounds (182) and (183). This oil was washed with boiling ethanol and filtered while hot to give a yellow solid which was re-crystallised twice from glacial acetic acid to give 4,4a-dihydro-4aβ-methyl-1,3α,9-triphenyl-3H-fluorene (182) (0.170g, 33.8%), m.p. 184-186°C (lit.[112] m.p. 185-186°C).

Found: C, 93.52; H, 6.32. Calc. for C$_{32}$H$_{26}$: C, 93.62; H, 6.38%.

ν_{max} (nujol) 1605 (w), 1595 (w), 767 (m), 750 (s), 729 (m), 694 (s) cm^{-1}.

δ^1H (CCl$_4$; 90 MHz) 1.52 (3H, s, Me) superimposed on 1.56

(1H, dd, $\underline{J}$, 13 and 9.5 Hz, H$_{4\alpha}$), 2.65 (1H, dd, $\underline{J}$, 13 and 6 Hz, H$_{4\beta}$),

3.95 (1H, ddd, $\underline{J}$, 9.5, 6 and 3 Hz, H$_3$), 6.04 (1H, d, $\underline{J}$, 3 Hz, H$_2$),

6.8-7.6 (19H, m, aromatic protons).

iii) Thermolysis and Photolysis.

Thermolysis of 4a-methyl-1,3,9-triphenyl-4aH-fluorene (119). —

Compound (119), either neat or in a solvent, was heated for the times

and at the temperatures specified in Table 14.   The reaction mixtures

were analysed by tlc and nmr.

Solvent	Temperature ^{o}C	Time h	Methyl peaks in crude nmr spectrum δ (very approximate relative intensity)
MeCO$_2$H	118	24	1.71 (100%)
PhCl	132	48	1.71 (100%)
EtCO$_2$H	141	48	1.80 (20%), 1.71 (70%), 1.60 (<5%) 1.55 (<5%)
-	190	0.03	1.80 (5%), 1.71 (95%)
-	185	0.25	1.80 (20%), 1.71 (60%), 1.60 (10%) 1.55 (10%)
-	210	0.08	2.07 (10%), 1.80 (10%), 1.71 (20%) 1.60 (10%), 1.55 (40%), 1.32 (5%)

TABLE 14

Flash vacuum pyrolysis of 4a-methyl-1,3,9-triphenyl-4aH-fluorene

(119). — Compound (119) (130mg, 0.32mmol) was vaporised at 200-300°C

and 0.03mmHg, and the vapour passed through a quartz tube at 650°C as

described in Section 1.   Preparative tlc of the pyrolysate (100mg) on

silica, eluting with dichloromethane (20% in light petroleum) gave a

gum (71mg) which nmr showed to consist almost exclusively of compound (184), though additional small peaks at δ 2.70 and δ 5.14 were present. Crystallisation from a mixture of ether and light petroleum gave 9-methyl-1,3,9-triphenylfluorene (184) (28mg) as colourless prisms, m.p. 170-171°C (lit.[112] m.p. 171-172°C).

δ_{1H} (CCl$_4$; 90 MHz) 1.55 (3H, s, Me), 6.50-7.90 (20H, m) and 7.94 (1H, d, $\underline{J}$, 1.5 Hz) (aromatic protons).

Photolysis of 4a-methyl-1,3,9-triphenyl-4aH-fluorene (119). — A saturated solution of compound (119) (370mg, 0.9mmol) in dry aceto-nitrile (100ml) was photolysed at 254nm for 17h, during which period the original yellow colour faded and white crystals precipitated. The mixture was evaporated and washed with acetone to remove unconsumed starting material. The crude solid (151mg), which nmr showed to consist very largely of compound (186), was recrystallised from a mixture of ethanol and benzene to give 9-methyl-1,3,4-triphenylcyclo-penta[b]naphthalene (186) as colourless prisms (88mg), m.p. 227-229°C.

Found: C, 94.26; H, 5.96. $C_{32}H_{24}$ requires C, 94.08; H, 5.92%.

ν_{max} (nujol) 3060 (w), 3030 (w), 1605 (m), 1070 (m), 1028 (m), 1010 (w), 915 (w), 862 (m), 770 (m), 760 (s), 752 (s), 730 (m), 695 (s) cm^{-1}.

λ_{max} (cyclohexane) 349 (ϵ 1200, sh), 333 (2500, sh), 315 (16200), 303 (17000), 293 (13200, sh), 275 (22000), 261 (29510, sh), 247 (41700), 226 nm (38900).

δ_{1H} (CDCl$_3$; 250 MHz) 2.48 (3H, s, Me), 4.93 (1H, d, $\underline{J}$, 2 Hz, H$_1$), 6.42 (1H, d, $\underline{J}$, 2 Hz, H$_2$), 6.8-7.5 (17H, m, aromatic protons), 7.69 (1H, d, $\underline{J}$, 8 Hz, H$_5$), 8.04 (1H, d, $\underline{J}$, 8 Hz, H$_8$).

A second crop (38.5mg) was also obtained; the acetone washings yielded more crude product (36mg).

In a further experiment, compound (119) was recovered unchanged

after refluxing in acetonitrile for 12h.

3) Synthesis of 4aH-fluorenes (Chapters Three and Four).

Attempted reaction of 1-aminobenzotriazole and 2,4,6-trimethyl-acetophenone. — In a series of experiments, 1-aminobenzotriazole (192) (0.50g, 3.7mmol), prepared by the method of Campbell and Rees,[120] and 2,4,6-trimethylacetophenone (193) were subjected to a variety of reagents and conditions as specified in Table 15, but in none of these was there any evidence that the required ketimine (194) had been formed.

Equiv-alents of (193)	Other Reagents	Reaction Conditions	Reaction Time	Work Up
1	4A molecular sieves (2.24g)	$Et_2O/25^{\circ}C$	18h	Filtered then evaporated
1	pTSA (0.1g)	benzene ⫯ with Dean and Stark trap	5h	Filtered then evaporated
1	pTSA (trace)	toluene ⫯ with Dean and Stark trap	10h	Filtered then evaporated
0.79	conc.H_2SO_4 (2ml)	dry EtOH ⫯	6h	Quenched in four fold excess of water, then extracted into ether. Aqueous layer neutral-
1.21	conc.HCl (3.7ml) H_2O (3.7ml)	EtOH ⫯	10h	ised, then second ether extract made.
1	glacial AcOH	⫯	65h	Evaporated then $CHCl_3$ added, and filtered.

TABLE 15

In another experiment, a solution of 1-aminobenzotriazole (192)

(0.50g, 3.7mmol) and 2,4,6-trimethylacetophenone oxime (0.61g, 3.7mmol)

in dry toluene (30ml) was refluxed for 6h with azeotropic removal of

water, but no reaction occurred.   In a further experiment, diethyl

N-(benzotriazol-1-yl)iminomalonate (191) (0.50g, 1.7mmol), 2,4,6-tri-

methylacetophenone (193) (0.28g, 1.7mmol) and anhydrous zinc chloride

(0.01g, 0.07mol) were mixed with o-dichlorobenzene and refluxed for 2h.

Ir, nmr and tlc all showed that no reaction had occurred.

1,3-Dimethylindene (136).[125] — Magnesium (13.6g, 0.56mol)

was dried, placed in a flame-dried flask fitted with a mechanical

stirrer, and dry ether (30ml) added.   Methyl iodide (34.8ml, 0.56mol)

was added, cautiously at first to allow reaction to commence, and the

mixture stirred at 20°C until the magnesium had dissolved.   3-Methyl-

indan-1-one (74.2g, 0.51mol), prepared by the method of Koelsch,

Hochmann and LeClaire,[124] in dry ether (500ml) was then added slowly,

keeping the mixture just below reflux.   Stirring was continued for 1h

after addition was complete, then water was cautiously added until a

distinct water layer was observed.   The ether layer was separated,

washed with hydrochloric acid (2M, 2x100ml) and sodium hydroxide

solution (2M, 2x100ml), dried (MgSO$_4$) and evaporated to yield a light

brown oil from which water slowly separated over several days.   The

oil was re-dried over magnesium sulphate acidified with two drops of

hydrochloric acid, and distilled to give 1,3-dimethylindene (136)

(50.2g, 68.5%)as a pale yellow oil, b.p. 110-115°C/40mmHg (lit.[125]

b.p. 86-88°C/11mmHg).

ν_{max} (liq. film) 2963 (s), 1620 (w), 1460 (m), 1383 (m), 1173 (m),

1020 (m), 810 (m), 783 (m), 759 (s), 743 (s), 732 (s) cm^{-1}.

δ_{1H} (CCl$_4$; 90 MHz) 1.22 (3H, d, C$_3$ Me), 2.04-2.14 (3H, m, C$_1$ Me), 3.15-

3.53(1H, m, H$_1$), 6.00-6.10 (1H, m, H$_2$), 7.05-7.38 (4H, m, aromatic protons).

Oxidation of 1,3-Dimethylindene (136).

i) with performic acid. — 1,3-Dimethylindene (11.1g, 77.3mmol) was added dropwise to a stirred mixture of formic acid (90%; 70.6ml, 1.66mol) and hydrogen peroxide (30%; 15ml, 0.13mol) at $35^{o}C$ and the mixture stirred for 2h at $35^{o}C$ then 16h at $20^{o}C$. Residual peroxides were destroyed by addition of ferrous sulphate solution, then the mixture was evaporated at $50^{o}C$ to one third its volume. The resultant semi-solid was added to a mixture of sulphuric acid (26.5ml) and water (176ml) at $95^{o}C$, and the mixture immediately steam distilled until 2 litres of distillate had collected. Extraction of the distillate with dichloromethane yielded an oil (3.38g) which contained ∿ 50% of indanones (195) and (196) together, but these could not be isolated.

ii) with m-chloroperbenzoic acid. — m-Chloroperbenzoic acid (85%; 2.03g, 10mmol) was added in small portions to a rapidly stirred mixture of 1,3-dimethylindene (136) (1.44g, 10mmol) in dichloromethane (10ml) and sodium bicarbonate (1.26g, 15mmol) in water (30ml) at $20^{o}C$. Starch-iodide paper was used to test for the absence of m-chloroperbenzoic acid before each addition. Stirring was continued for 2h after addition was complete, then the dichloromethane layer was separated, washed with sodium bicarbonate solution (0.5M; 30ml), dried ($MgSO_4$) and evaporated to give a colourless oil (1.8g). Nmr, ir and tlc showed this to be a complex mixture probably containing little or none of the desired epoxide; equally useless mixtures were obtained on extending the reaction period to 14h or on repeating the experiment in the absence of the aqueous buffer phase. A blank experiment showed that indene was converted into 1,2-epoxyindan under identical conditions.[128b]

iii) with aqueous bromine. — 1,3-Dimethylindene (136) (1.0g, 6.9mmol) was stirred vigorously with water (10ml) at $75^{o}C$ during the addition of bromine (0.37ml, 7.2mmol) in small portions, each dissolved in potassium bromide solution (10%). The mixture was cooled, the products extracted

into ether, dried ($MgSO_4$) and evaporated to give a brown oil (1.5g) which nmr and ir showed to be a complex mixture, and which could not be induced to crystallise.   A blank experiment showed that indene was converted into trans-2-bromoindan-1-ol under identical conditions.[129]

1β,3β-Dimethylindan-2α-ol (200) and 1α,3β-Dimethylindan-2α-ol (201). — Diborane-tetrahydrofuran complex (1M; 69ml, 69mmol) was added dropwise via a pressure-equalising dropping funnel to a stirred solution of 1,3-dimethylindene (136) (10.0g, 69.0mmol) in dry tetrahydrofuran (40ml) at 20°C under nitrogen and the mixture stirred 1h. The mixture was cooled to 10°C, sodium hydroxide solution (2M; 10.5ml, 21mmol) added dropwise, stirred 0.5h, then hydrogen peroxide (30%, 8.3ml, 73mmol) was added dropwise and stirred 0.3h.   The product was extracted into ether, washed with a solution of ferrous sulphate (2M; 2x50ml) and hydrochloric acid (2M; 3x50ml), dried ($MgSO_4$) and evaporated to give a brown oil (12.12g).   Gradient elution column chromatography on basic alumina, eluting with chloroform-light petroleum mixtures, gave a 4:1 mixture of 1β,3β-dimethylindan-2α-ol (200) and 1α,3β-dimethylindan-2α-ol (201) (6.94g, 61.7%) as a yellow crystalline solid, m.p. 45-58°C.   A centre cut was taken and prepared for analysis by distillation at reduced pressure.

Found: C, 80.61; H, 8.58. $C_{11}H_{14}O$ requires C, 81.44; H, 8.70%.

ν_{max} (nujol) 3300 (br), 3200 (br), 1067 (s), 1010 (m), 931 (w), 771 (m), 733 (s) cm^{-1}.

δ_{1H} (CDCl$_3$; 250 MHz) Compound (200) (∿ 80%) 1.33 (6H, d, J, 6 Hz, C$_1$ and C$_3$ Me), 2.85 (2H, broadened quintet, H$_1$ and H$_3$), 3.39 (1H, t, J, 8 Hz, H$_2$), 3.9-4.0 (OH), 6.95-7.15 (4H, m, aromatic protons). Compound (201) (∿ 20%) 1.18 (3H, d, J, 7 Hz) and 1.24 (3H, d, J, 6 Hz) (C$_1$ and C$_3$ Me), 3.00 (1H, broadened quintet) and 3.11 (1H, broadened quintet) (H$_1$ and H$_3$), 3.9-4.0 (m, superimposed on OH of (200), OH and H$_2$),

6.95-7.15 (4H, m, aromatic protons).

$\underline{m/e}$ 162 (51%, $\underline{M}^+$), 147 (25%, $\underline{M}^+-$ ˙CH$_3$), 144 (14%, $\underline{M}^+-$ H$_2$O), 133 (100%, $\underline{M}^+-$ ˙CHO), 129 (29%, $\underline{M}^+-$ ˙CH$_3$ and ˙OH), 115 (25%, $^+$C$_9$H$_7$).

cis and trans-1,3-Dimethylindan-2-ones (195) and (196)

i) from 1,3-dimethylindene (136). — Boron trifluoride etherate (45% in ether; 2.4ml, 14mmol) was added slowly to a stirred suspension of lithium borohydride (0.228g, 10.4mmol) in a solution of 1,3-dimethyl-indene (136) (2.00g, 13.9mmol) in dry ether (20ml) at 20°C. Stirring at 20°C was continued for 3.5h, then water (2ml), followed by a solution of sodium dichromate dihydrate (4.14g, 13.9mmol) in sulphuric acid (3M; 10ml) was added dropwise. After stirring for 0.3h at 20°C, the product was extracted into ether, washed with hydrochloric acid (2M; 3x20ml) and sodium hydroxide solution (2M; 3x20ml), dried (MgSO$_4$) and evaporated to give a yellow oil. Rapid gradient elution column chromatography on basic alumina, eluting with light petroleum followed by ether-light petroleum mixtures, gave, after removal of a small hydrocarbon fraction, a mixture of cis and trans-1,3-dimethyl-indan-2-ones (195) and (196) (1.102g, 49.6%) as a pale yellow oil; an unidentified impurity (∿ 5%) was also present.

ii) from 1β,3β-Dimethylindan-2α-ol (200) and 1α,3β-Dimethylindan-2α-ol (201). — A solution of sodium dichromate dihydrate (0.92g, 3.1mmol) in sulphuric acid (3M; 10ml) was added to a solution of alcohols (200) and (201) (0.250g, 1.54mmol) in ether (10ml) and the mixture stirred 0.3h. The product was extracted into ether, washed with hydrochloric acid (2M; 3x5ml) and sodium hydroxide solution (2M; 3x5ml), dried (MgSO$_4$), evaporated and re-evaporated from carbon tetrachloride to yield a mixture of cis and trans-1,3-dimethylindan-2-ones (195) and (196) (0.197g, 79.8%) as a pale yellow oil.

ν_{max} (liq. film) 3030 (w), 2970 (m), 2935 (m), 1755 (s),

1482 (m), 1458 (m), 1375 (w), 1195 (w), 780 (m), 760 (w), 740 (m) cm^{-1}.

δ_{1H} (CCl$_4$; 90 MHz) Major isomer ($\sim$ 75%) 1.33 (6H, d, $\underline{J}$, 7 Hz,

C$_1$ and C$_3$ Me), 3.39 (2H, q, $\underline{J}$, 7 Hz, H$_1$ and H$_3$), 7.22 (4H, s, aromatic

protons). Minor isomer ($\sim$ 25%) 1.33 (6H, d, $\underline{J}$, 7 Hz, C$_1$ and C$_3$ Me),

3.34 (2H, q, $\underline{J}$, 7 Hz, H$_1$ and H$_3$), 7.22 (4H, s, aromatic protons).

$\underline{m/e}$ 160.0892 ($\underline{M}^+$; C$_{11}$H$_{12}$O requires 160.0888).

1,3-Dimethyl-2-(1-pyrrolidyl)indene (202). — cis and trans-

1,3-dimethylindan-2-ones (195) and (196) (1.102g, 7.65mmol) and

pyrrolidine (5.0ml, 60mmol) in benzene (40ml) were refluxed for 18h

under nitrogen with azeotropic removal of water. The mixture was then

evaporated to yield a brown semi-crystalline oil (1.62g). Column

chromatography on basic alumina, eluting with ether (10% in light petrol-

eum), gave 1,3-dimethyl-2-(1-pyrrolidyl)indene (202) (0.56g, 34%) as

a pale yellow oil which darkened rapidly on exposure to air.

ν_{max} (liq. film) 2960 (m), 2865 (m), 1590 (s), 1470 (s), 1398 (m),

1357 (m), 1017 (m), 756 (m), 742 (m) cm^{-1}.

δ_{1H} (CCl$_4$; 90 MHz) 1.22 (3H, d, C$_1$ Me), 1.60-1.85 (4H, m,

$\overline{NCH_2\underline{CH_2}\underline{CH_2}CH_2}$), 2.08 (3H, s, C$_3$ Me), 3.10-3.70 (5H, m, $\overline{N\underline{CH_2}CH_2CH_2\underline{CH_2}}$

superimposed on H$_1$), 6.6-7.3 (4H, m, aromatic protons).

In practice the crude product was used without purification;

it then contained both starting materials and an unidentified crystalline

impurity (which showed only pyrrolidyl protons in its nmr spectrum).

Although the presence of these contaminants could not be controlled,

their amount was often acceptably small. In other experiments ketones

(195) and (196) and pyrrolidine in benzene were stirred with titanium

tetrachloride or calcium chloride. In neither case was the crude

product any purer than that described above; blank experiments showed

that all these methods were capable of forming 2-(1-pyrrolidyl)indene (198)

from indan-2-one (126) in good yield. When ketones (195) and (196)

(0.197g, 1.23mmol) and morpholine (2.5ml, 28mmol) were refluxed in ben-

zene (15ml) for 5h under nitrogen with azeotropic removal of water, nmr

and ir showed that the inhomogeneous brown oil obtained after evaporation

six times from carbon tetrachloride contained no significant amount of

the desired morpholine enamine (203), and that considerable deterior-

ation of the ketones had occurred.

Attempted reaction of 1,3-dimethyl-2-(1-pyrrolidyl)indene (202)
with methyl vinyl ketone (197).

i) Cold. — Equimolar mixtures of crude (202) and methyl vinyl ketone

were made up as specified in the solvent systems listed in Table 16 and

allowed to stand under nitrogen. The mixtures were then filtered

(experiment 1 only) and evaporated to yield brown oils.

Experiment	1	2	3
Solvent Composition	THF(15ml)	benzene (20ml)	benzene (7.5ml) + THF (1ml)
Reaction temperature	2°C	20°C	20°C
Reaction time	2 days	1 day	1 day
Mass of crude (202) used	0.98g (4.6mmol)	∿ 0.7g (3.3mmol)	∿ 0.7g (3.3mmol)
Volume of (197) used	0.38ml (4.6mmol)	0.27ml (3.3mmol)	0.27ml (3.3mmol)
Recovery	1.11g	∿ 0.9g	∿ 0.9g
Estimated extent of alkylation (very approximately)	30%	50%	80%

TABLE 16

The products were complex, air-sensitive mixtures, but their nmr

spectra suggested that the starting enamine had been partially alkylated.

This was inferred from the partial replacement of the doublet at δ 1.23

(C_1 Me of (202)), by a singlet at δ 1.38 (probably due to C_1 Me of (204)),

which also gave a very approximate measure of the extent of reaction.

A solid isolated from experiment 1 remains unidentified; its nmr

spectrum showed only multiplets at δ 2-2.3, δ 3.1-3.6 and a broad

singlet at δ 6.7-7.8.

ii) <u>Hot</u>. — A solution of crude 1,3-dimethyl-2-(1-pyrrolidyl)indene

(202) (1.91g, 8.97mmol) and methyl vinyl ketone (0.48ml, 5.8mmol) in

benzene was refluxed for 5h under nitrogen and the mixture evaporated

to give a brown inhomogeneous oil (2.5g), which ir and nmr and tlc

showed to be extremely complex. Similar mixtures were obtained when

a Dean and Stark trap was used to remove water azeotropically, or the

distillate was returned <u>via</u> 4A molecular sieves. Column chromatography

on basic alumina gave only a slight separation of the many materials

present, none of which could be identified, and all of which rapidly

darkened and decomposed in air. Treatment of these mixtures with an

aqueous dioxan-acetic acid buffer led to intractable tarry mixtures.

iii) via <u>The anion</u>. — <u>n</u>-Butyllithium (1.6M in hexane; 1.4ml, 2.2mmol)

was added dropwise to a stirred solution of crude 1,3-dimethyl-2-

(1-pyrrolidyl)indene (202) (0.40g, 1.9mmol) in dry tetrahydrofuran (5ml)

at 20°C under nitrogen. After stirring for 1h, the mixture was cooled

to 0°C, methyl vinyl ketone (0.18ml, 2.2mol) added dropwise, stirred

0.6h, water (2ml) added, stirred 0.2h, then the organic layer was

separated, dried ($MgSO_4$), evaporated and re-evaporated from carbon

tetrachloride to yield a brown tarry oil (0.67g) which ir and nmr

showed to be a complex mixture containing little or no 1-alkylated

material.

The experiment was repeated substituting methyl iodide (0.14ml,

2.3mmol) for methyl vinyl ketone; on this occasion the crude product, a

brown oil (0.4g), contained 2-(1-pyrrolidyl)-1,1,3-trimethylindene (208).

ν_{max} (liq. film) 2960 (m), 2865 (m), 1595 (s), 1472 (s), 1395 (m), 1357 (m), 1096 (w), 1017 (m), 785 (s), 755 (s) cm^{-1}.

δ_{1H} (CCl$_4$; 90 MHz) <u>inter alia</u> 1.32 (6H, s, C$_1$ Me x2), 1.52-2.1 (4H, m, $\overline{\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2}$), 1.98 (3H, s, C$_3$ Me), 3.2-3.7 (4H, m, $\overline{\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2}$), 6.6-7.3 (4H, m, aromatic protons).

<u>Reaction of cis and trans-1,3-dimethylindan-2-ones (195) and (196) with methyl vinyl ketone.</u> — A solution of <u>cis</u> and <u>trans</u>-1,3-dimethyl-indan-2-ones (195) and (196) (0.52g, 3.2mmol), methyl vinyl ketone (0.26ml, 4.3mmol) and potassium hydroxide (∿ 15mg) in methanol (15ml) was refluxed for 2h and then evaporated to yield a yellow oil (0.91g); column chromatography on basic alumina, eluting with chloroform, followed by distillation at 0.1mmHg gave 1,3-dimethyl-1,3-di-(3-oxo-butyl)indene (210) (77mg, 8%) as a yellow oil.

ν_{max} (liq. film) 2970 (m), 2930 (m), 1745 (s), 1720 (s), 1455 (m), 1365 (m), 1165 (m), 765 (s) cm^{-1}.

δ_{1H} (CCl$_4$; 90 MHz) 1.29 (6H, s, C$_1$ and C$_3$ Me), 1.4-2.3 (8H, m, $\underline{\text{CH}_2\text{CH}_2}\text{COCH}_3$), 1.97 (6H, s, $\text{CH}_2\text{CH}_2\text{COC}\underline{\text{H}}_3$), 7.0-7.4 (4H, m, aromatic protons).

<u>m/e</u> 300 (14%, $\underline{M}^+$), 230 (46%, $\underline{M}^+$– CH$_2$=CHCOCH$_3$), 159 (85%, $\underline{M}^+$– CH$_2$=CHCOCH$_3$ and $^\cdot$CH$_2$CH$_2$COCH$_3$), 71 (35%, $^+$CH$_2$CH$_2$COCH$_3$), 43 (100%, $^+$COCH$_3$).

<u>1,3-Dimethyl-1-(3-oxobutyl)indene (212)</u>. — <u>n</u>-Butyllithium (1.5M in hexane; 1.2ml, 1.8mmol) was added dropwise to a stirred solution of 1,3-dimethylindene (136) (0.250g, 1.74mmol) in dry tetra-hydrofuran (4ml) at 0°C under nitrogen. After 0.3h, a solution (previously dried over magnesium sulphate) of methyl vinyl ketone (1.6M in benzene; 1.5ml, 2.1mmol) was added dropwise at 0°C, stirred 1.5h, water added and stirred 0.2h. The product was extracted

into ether, dried (MgSO$_4$), evaporated and re-evaporated twice from carbon tetrachloride to give a mobile yellow oil (0.43g). Gradient elution column chromatography on silica gel 60H eluting with ether-light petroleum mixtures gave, after elution of unchanged 1,3-dimethyl-indene, 1-(3-<u>oxobutyl</u>)-1,3-<u>dimethylindene</u> (212) (69mg, 19%) as a colourless oil.

Found: C, 83.62; H, 8.71. C$_{15}$H$_{18}$O requires C, 84.07; H, 8.47%).

ν_{max} (liq. film) 2955 (m), 2918 (m), 1718 (s), 1618 (w), 1470 (m), 1360 (m), 1162 (m), 1107 (w), 1017 (w), 752 (s) cm^{-1}.

δ_{1H} (CCl$_4$; 90 MHz) 1.27 (3H, s, C$_1$ Me), 1.65-2.2 (4H, m, C$\underline{H}_2$C$\underline{H}_2$COCH$_3$), 1.82 (3H, s, CH$_2$CH$_2$COC$\underline{H}_3$), 2.12 (3H, d, $\underline{J}$, 1.5 Hz, C$_3$ Me), 5.88 (1H, q, $\underline{J}$, 1.5 Hz, H$_2$), 7.18 (4H, s, aromatic protons).

2-(2-<u>Chloroethyl</u>)-2-<u>methyl</u>-1,3-<u>dioxolane (213)</u>.[137] — A solution of freshly distilled 4-chloro-2-butanone, prepared by the method of Smith and Sprung,[136] (6.9g, 65mmol), ethane-1,2-diol (4.4g, 71mmol) and p-toluenesulphonic acid monohydrate (80mg, 0.42mmol), in benzene (40ml) was refluxed for 3.5h with azeotropic removal of water. The solution was evaporated, dissolved in ether, washed with saturated calcium chloride solution (3x10ml), dried (MgSO$_4$) and evaporated to give a brown liquid. This was distilled using a 10cm Vigreux column to give 2-(2-chloroethyl)-2-methyl-1,3-dioxolane (213) (5.33g, 54.6%) as a colourless liquid, b.p. 40-50°C/20mmHg (lit.[137] b.p. 50-55°C/11mmHg). The product was stored for several days over 4A molecular sieves before further use.

1,3-<u>Dimethyl</u>-1-(3,3-<u>ethylenedioxybutyl</u>)<u>indene (214)</u>. — n-Butyllithium (1.4M in hexane; 18.7ml, 26.2mmol) was added dropwise to a solution of 1,3-dimethylindene (136) (3.44g, 23.9mmol) in dry

tetrahydrofuran (20ml) at 20°C under nitrogen, and the solution stirred

0.3h.   2-(2-Chloroethyl)-2-methyl-1,3-dioxolane (213) (3.27g, 21.7mmol)

was added dropwise, stirred 1.8h, water (5ml) added, stirred 0.1h, the

product extracted into ether, dried ($MgSO_4$) and evaporated to give a

yellow oil (6.35g).   This was distilled at reduced pressure to give

1,3-dimethyl-1-(3,3-ethylenedioxybutyl)indene (214) (4.90g, 89.4%)

as a pale yellow oil which crystallised slowly on standing.   A sample

was prepared for analysis by gradient elution column chromatography on

silica gel 60H eluting with ether-light petroleum mixtures, followed by

redistillation to yield compound (214) as a white crystalline solid,

m.p. 51-55°C.

Found: C, 78.64; H, 8.81. $C_{17}H_{22}O_2$ requires C, 79.03;

H, 8.58%.

ν_{max} (liq. film) 2955 (s), 1620 (w), 1460 (m), 1385 (m), 1058 (m),

1042 (m), 1020 (w), 947 (m), 857 (s), 750 (s) cm^{-1}.

δ_{1H} (CCl_4; 90 MHz) 1.13 (3H, s, $CH_2CH_2\overline{C(CH_3)OCH_2CH_2O}$), 1.28

(3H, s, C_1 Me), 0.95-1.55 (2H, m) and 1.70-1.95 (2H, m)

($\overline{CH_2CH_2C(CH_3)OCH_2CH_2O}$), 2.12 (3H, d, $\underline{J}$, 1.8 Hz, C_3 Me), 3.7-3.85

(4H, m, $CH_2CH_2\overline{C(CH_3)OCH_2CH_2O}$), 5.96 (1H, q, $\underline{J}$, 1.8 Hz, H_2), 7.18

(4H, s, aromatic protons).

m/e 258 (14%, $\underline{M}^+$), 243 ($\underline{M}^+$– $^{\cdot}CH_3$), 156 (100%, $\underline{M}^+$– $^{\cdot}CH_3$ and

$^{\cdot}\overline{C(CH_3)OCH_2CH_2O}$), 143 (21%, $\underline{M}^+$– $^{\cdot}CH_2CH_2\overline{C(CH_3)OCH_2CH_2O}$), 142 (12%),

141 (22%, 156– $^{\cdot}CH_3$), 128 (22%, 143– $^{\cdot}CH_3$), 115 (17%, $^+CH_2CH_2\overline{C(CH_3)OCH_2CH_2O}$

and $C_9H_7^+$).

Attempted oxidation of 1,3-dimethyl-1-(3,3-ethylenedioxybutyl)-

indene (214). — Compound (214) (0.250g, 0.97mmol) was treated with

boron trifluoride etherate (45% in ether; 0.2ml, 1.3mmol) and lithium

borohydride (30mg, 1.4mmol) followed by sodium dichromate dihydrate

(0.49g, 1.9mmol) in sulphuric acid (3M; 10ml) following the procedure

described for the synthesis of ketones (195) and (196) from dimethyl-indene (136) (Page 200). The product, a colourless semi-crystalline oil (0.136g), contained no starting material and showed a peak at 1755 cm^{-1} in its ir spectrum, but was very complex and unpromising by nmr.

Reaction of 1,3-dimethyl-1-(3,3-ethylenedioxybutyl)indene (214) with diborane-tetrahydrofuran complex. — Compound (214) (1.17g, 4.5mmol) was treated with diborane-tetrahydrofuran complex (2M; 2.5ml, 5mmol) followed by sodium hydroxide solution (2M; 0.70ml, 1.4mmol) following the procedure described for the synthesis of alcohols (200) and (201) from 1,3-dimethylindene (136) (Page 199). The product, a colourless oil (0.59g) which was complex by nmr, was dissolved in a mixture of water (5ml), dioxan (10ml) and concentrated hydrochloric acid (0.5ml) stirred for 16h then isolated as usual to give a pale yellow oil (0.53g). Prolonged gradient elution chromatography on basic alumina gave a very low total recovery (68mg) distributed over many fractions.

1,3-Dimethyl-1-methoxycarbonylindan-2-ol (218). — 1,3-Dimethyl-1-methoxycarbonylindene (217) (0.75g, 3.7mmol), prepared by the method of Jones and Kneen,[135] was treated with diborane-tetrahydrofuran complex (1M; 3.50ml, 3.50mmol) followed by sodium hydroxide solution (2M; 0.50ml, 10mmol) following the procedure described for the synthesis of alcohols (200) and (201) from 1,3-dimethylindene (136) (Page 199) to give a yellow oil (0.619g). Gradient elution column chromatography on basic alumina, eluting with ether-light petroleum mixtures gave, after removal of starting material (43mg), crude 1,3-dimethyl-1-meth-oxycarbonylindan-2-ol (218) (0.101g, 12.3%) apparently as a single diastereomer, a yellow oil.

ν_{max} (liq. film) 3650-3200 (br), 2960 (m), 1732 (s), 1455 (m), 1258 (m), 1212 (m), 1118 (m), 1088 (m), 750 (s) cm^{-1}.

δ_{1H} (CDCl$_3$; 250 MHz) 1.36 (3H, s, C$_1$ Me), 1.39 (3H, d, $\underline{J}$, 5.5 Hz, C$_3$ Me), 2.93 (1H, distorted quintet, $\underline{J}$, 5.5 and 8.5 Hz, H$_3$), 3.67 (4H, distorted singlet, simplified and reduced to 3H on D$_2$O exch., CO$_2$Me superimposed on OH), 4.32 (1H, d, $\underline{J}$, 8.5 Hz, H$_2$), 6.98-7.32 (4H, m, aromatic protons). These assignments were confirmed by decoupling H$_2$ and H$_3$.

m/e 220 (24%, $\underline{M}^+$), 202 (39%, $\underline{M}^+$– H$_2$O), 161 (100%, $\underline{M}^+$– $^{\cdot}$CO$_2$Me), 143 (70%, $\underline{M}^+$– H$_2$O and $^{\cdot}$CO$_2$Me), 128 (24%, $^+$C$_{10}$H$_9$), 115 (17%, $^+$C$_9$H$_7$).

Further elution gave mixed fractions (0.10g) containing more alcohol (218) and an unidentified product, the nmr of which precluded its being the expected second diastereomer. In other experiments, a longer reaction time and a lower temperature were employed, but no increase in yield resulted.

1,3-Dimethyl-1-methoxycarbonylindan-2-one (219). —
1,3-dimethyl-1-methoxycarbonylindan-2-ol (218) (0,10g, 0.45mmol) was treated with sodium dichromate dihydrate (0.50g, 1.7mmol) in sulphuric acid (3M; 10ml) for 7.5h at 20°C following the procedure described for the synthesis of ketones (195) and (196) from alcohols (200) and (201) (Page 200) to give crude 1,3-dimethyl-1-methoxycarbonylindan-2-one (219) as a yellow oil.

ν_{max} (liq. film) 2970 (w), 2870 (w), 1763 (s), 1740 (s), 1480 (w), 1455 (w), 1238 (m), 1114 (m), 785 (s), 760 (s) cm^{-1}.

δ_{1H} (CCl$_4$; 90 MHz) 1.47 (3H, d, $\underline{J}$, 8 Hz, C$_3$ Me), 1.52 (3H, s, C$_1$ Me), 3.2-3.65 (1H, m, H$_3$), 3.61 (3H, s, CO$_2$Me), 6.95-7.6 (4H, m, aromatic protons). Further peaks in the nmr suggested that related impurities ($\sim$ 10%) were also present.

4-(1,3-Dimethylinden-1-yl)-4-oxobutanoic acid (225). — n-Butyl-lithium (1.3M in hexane; 53ml, 70mmol) was added dropwise to a stirred solution of 1,3-dimethylindene (10.0g, 69.4mmol) in dry tetrahydrofuran at 0°C under nitrogen, and the mixture stirred 0.3h. A solution of succinic anhydride (freshly recrystallised from acetic anhydride; 6.92g, 69.2mmol) in dry tetrahydrofuran (90ml) was added dropwise, stirred 1h, then water was added (dropwise at first) and the acidic fraction isolated via extraction into base, acidification and re-extraction into ether, drying ($MgSO_4$) and evaporation. The resultant orange oil was dissolved in hot carbon tetrachloride, filtered (celite), evaporated and distilled at reduced pressure (0.06mmHg) to yield 4-(1,3-dimethylinden-1-yl)-4-oxobutanoic acid (225) (4.95g, 29.2%) as yellow oily crystals which slowly turned dark blue-green on exposure to air. A sample was prepared for analysis by recrystallisation (charcoal) from light petroleum (b.p. $60-80^{o}$C) containing a small amount of benzene to give colourless crystals, m.p. $91-95^{o}$C (with previous softening).

Found: C, 73.19; H, 6.58. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60%.

ν_{max} (nujol) 3500-2500 (w), 1707 (s), 1242 (m), 1225 (m), 1155 (w), 1067 (w), 1005 (w), 761 (w), 750 (m) cm^{-1}.

δ_{1H} (CDCl$_3$; 250 MHz) 1.46 (3H, s, C_1 Me), 2.0-2.5 (4H, m, COCH$_2$CH$_2$CO$_2$H), 2.23 (3H, d, J, 1.8 Hz, C_3 Me), 6.09 (1H, q, J, 1.8 Hz, H$_2$), 7.20-7.45 (4H, m, aromatic protons).

When the experiment was repeated substituting γ-butyrolactone (redistilled) for succinic anhydride, only starting materials were recovered after 18h.

Attempted cyclisations of 4-(1,3-dimethylinden-1-yl)-4-oxobutanoic acid (225) and its derivatives.

i) With trifluoroacetic anhydride. — Crude 4-(1,3-dimethylinden-1-yl)-4-oxobutanoic acid (225) (200mg, 0.82mmol) was treated with trifluoroacetic anhydride at reflux for 2.5h or 6h, or at 20°C for 18h, and the neutral fraction of the product isolated in 50%, 36% and 23% yields respectively. In all three cases the product was a brown oil, complex by tlc and containing little or none of the desired diketone (226) by ir.

ii) With polyphosphoric acid. — A mixture of crude 4-(1,3-dimethylinden-1-yl)-4-oxobutanoic acid (225) (0.20g, 0.82mmol), polyphosphoric acid (1g) and benzene (5ml) was heated at 70°C for 3h with magnetic stirring. After quenching in ice-water, the product was extracted into ether, washed with potassium carbonate solution, dried ($MgSO_4$) and evaporated to give a yellow oil (63mg) containing little or none of the desired diketone (226) by ir and nmr. Similar results were obtained when the benzene was omitted.

iii) Via the methyl ester (227). — A solution of 4-(1,3-dimethylinden-1-yl)-4-oxobutanoic acid (225) (0.50g, 2.0mmol) and concentrated sulphuric acid (2 drops) in methanol (8ml) was refluxed 4h, then the neutral fraction of the product isolated; dried over magnesium sulphate and evaporated to give a brown oil (0.47g). Distillation then gave methyl 4-(1,3-dimethylinden-1-yl)-4-oxobutanoate (227) (0.286g, 54.1%).

v_{max} (liq. film) 2955 (w), 2935 (w), 1747 (s), 1716 (s), 1440 (m), 1370 (m), 1210 (m), 757 (m) cm^{-1}.

δ_{1H} (CCl_4; 90 MHz) 1.41 (3H, s, C_1 Me), 1.8-2.6 (4H, m, $COCH_2CH_2CO_2Me$), 2.22 (3H, d, J, 1.8 Hz, C_3 Me), 3.56 (3H, s, CO_2 Me), 6.09 (1H, q, J, 1.8 Hz, H_2), 7.15-7.4 (4H, m, aromatic protons).

A portion of this material (0.10g, 0.39mmol) was added to a molten mixture of aluminium chloride (0.83g, 6.2mmol) and sodium chloride (0.17g, 2.9mmol) at 130°C, maintained at that temperature for 0.03h then allowed to cool and quenched in ice. The product was extracted into ether, the neutral fraction isolated, dried (MgSO$_4$) and evaporated to yield a brown oil (77mg). Although this consisted largely of starting material, its ir spectrum showed a new carbonyl band at 1660 cm^{-1}.

The experiment was repeated using 243mg of ester (227) and a reaction time of 0.17h. On this occasion the yield was lower (73mg) and, although the mixture contained much starting material, ir and nmr showed it to be extremely complex, the band at 1660 cm^{-1} being no stronger than previously.

When 4-(1,3-dimethylinden-1-yl)-4-oxobutanoic acid (225) (200mg, 0.82mmol) was subjected to identical conditions for 0.03h, a brown oil (11mg) was obtained which nmr showed to be extremely complex.

iv) Via the acid chloride. — 4-(1,3-dimethylinden-1-yl)-4-oxobutanoic acid (225) was treated with various chlorinating agents as specified in Table 17.

Reagent	Solvent (dried)	Quantities		Temperature	Time	Yield
		(225)	Reagent			
SOCl$_2$	benzene (15ml)	0.2g (crude)	2ml	reflux	2h	∿0.2g
PCl$_5$	ether (15ml)	0.2g (crude)	0.18g	20°C	18h	0.17g
PCl$_5$	ether (15ml)	0.2g (crude)	0.25g	20°C	2h	∿0.2g
(COCl)$_2$	benzene (10ml)	0.2g (distilled)	0.15ml	50°C	3h	∿0.2g
(COCl)$_2$	benzene (10ml)	0.2g (distilled)	0.3ml	40°C	4h	∿0.2g

TABLE 17

Reaction with thionyl chloride gave a complex mixture which showed a very strong carbonyl absorption at 1810 cm^{-1}, but only a relatively weak one at 1710 cm^{-1} (the position expected for absorption due to the C_1-keto group of chloride (228)). Base hydrolysis yielded another complex mixture.

Reaction with phosphorus pentachloride was cleaner, but the product again showed loss of carbonyl absorption at 1710 cm^{-1} at the expense of new bands at 1810 cm^{-1} and 1760 cm^{-1}.

Reaction with oxalyl chloride gave an apparently simple mixture, but again the only strong carbonyl band was at 1810 cm^{-1}. This mixture was completely unaffected by treatment with aluminium chloride in carbon tetrachloride at $50^{\circ}C$ for 3h.

1-(1β,4-Dihydroxybutyl)-1β,3-dimethylindene (229) and 1-(1α,4-dihydroxybutyl)-1β,3-dimethylindene (230). — Lithium aluminium hydride (1.60g, 42mmol) was added in small portions to a stirred solution of 4-(1,3-dimethylinden-1-yl)-4-oxobutanoic acid (225) (1.94g, 7.9mmol) and the resulting slurry stirred 18h. Water followed by concentrated hydrochloric acid was cautiously added until the salts were dissolved, then the product was extracted into chloroform, dried ($MgSO_4$) and evaporated to give a brown oil (1.81g). Gradient elution column chromatography on silica gel 60H, eluting with ether-light petroleum mixtures, gave an approximately equimolar mixture of 1-(1β,4-dihydroxybutyl)-1β,3-dimethylindene (229) and 1-(1α,4-dihydroxybutyl)-1β,3-dimethylindene (230) (1.00g, 65.7%) as an oil which crystallised on standing. A centre cut was taken for analysis.

Found: C, 77.60; H, 8.83. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68%).

ν_{max} (nujol) 3300 (br), 1057 (m), 970 (m), 823 (w), 758 (m), 752 (m) cm^{-1}.

δ_{1H} (CDCl$_3$; 250 MHz) 1.31 (3H, s) and 1.33 (3H, s) (C$_1$ Me x2),

1.40-1.85 (8H, m, CH(OH)CH$_2$CH$_2$CH$_2$OH x2), 2.10 (6H, d, J, 1.8 Hz, C$_3$ Me x2),

2.70-2.85 (4H, br s, OH x4), 3.39-3.66 (4H, m, CH(OH)CH$_2$CH$_2$CH$_2$OH x2), 3.81

(1H, q) and 3.85 (1H, q) (CH(OH)CH$_2$CH$_2$CH$_2$OH x2), 5.97 (1H, q, J, 1.8 Hz) and

6.06 (1H, d, J, 1.8 Hz) (H$_2$ x2), 7.10-7.40 (8H, m, aromatic protons).

Reaction of 1-(1,4-dihydroxybutyl)-1,3-dimethylindenes (229) and

(230) with chromium trioxide. — Chromium trioxide (1.01g, 9.6mmol)

was added to a solution of pyridine (1.60g, 20.3mmol) in dichloromethane

(50ml), stirred 0.3h, then a solution of alcohols (229) and (230)

(0.195g, 0.84mmol) in dichloromethane (5ml) was added and stirred 0.3h.

The product was extracted into ether, washed with sodium bicarbonate

solution (2M; 2x20ml), hydrochloric acid (2M; 2x20ml) and sodium

bicarbonate solution (2M; 2x20ml), dried (MgSO$_4$), filtered (celite)

and evaporated to give a brown oil (0.142g). The nmr spectrum of the

product showed a minor aldehyde proton (δ 9.58), at least three types

of vinyl proton, a proton at δ 4.6 and a complicated methyl region,

while the ir showed peaks at 1710 and 1780 cm^{-1}.

Reaction of 4-(1,3-dimethylinden-1-yl)-4-oxobutanoic acid (225)

with diborane-tetrahydrofuran complex. — Diborane-tetrahydrofuran

complex (2M; 0.27ml, 0.54mmol) was added dropwise to a stirred solution

of acid (225) (0.20g, 0.82mmol) in dry tetrahydrofuran (4ml), and the

mixture stirred 0.3h. Water was added, the product extracted into

ether, washed with potassium carbonate solution (2M; 2x5ml), dried

(MgSO$_4$) and evaporated to yield a viscous colourless oil (0.123g).

Gradient elution column chromatography on silica gel H, eluting with

ether-light petroleum mixtures, gave only one major fraction (43mg),

identified as a mixture of alcohols (229) and (230) by comparison

with authentic material.

Attempted reductive methylation of fluorene. — Lithium metal

(0.2g, 0.03mol) was added to liquid ammonia at -78°C to give a dark

blue solution. Fluorene (2.0g, 0.012mol) in dry ether (50ml) was

immediately added, stirred 0.2h, then methyl iodide (3ml, 0.05mol)

followed after 60s by ammonium chloride (20g) were added. Water and

ether were added and the product, after evaporation of the ammonia,

was extracted into ether, dried ($MgSO_4$) and evaporated to give a

colourless oil (2.05g) which crystallised on standing. Nmr showed

this to be a mixture of fluorene ($\sim$ 20%), 9-methylfluorene ($\sim$ 70%) and

9,9-dimethylfluorene ($\sim$ 10%).

4-(1,3-Dimethylinden-1-yl)butyronitrile (237). — n-Butyllithium

(1.4M in hexane; 27.0ml, 37.8mmol) was added dropwise to a solution of

1,3-dimethylindene (136) (5.00g, 34.7mmol) in dry tetrahydrofuran (40ml)

at 20°C under nitrogen, and the brown solution stirred 0.5h. A solution

of 4-chlorobutyronitrile (236) (3.5ml, 37mmol) in dry tetrahydrofuran

was added dropwise, stirred 1h, water (10ml) added dropwise, stirred

0.2h then the product extracted into ether, dried ($MgSO_4$) and evaporated

to give a yellow oil (8.08g) which was distilled at reduced pressure

to yield 4-(1,3-dimethylinden-1-yl)butyronitrile (237) (5.58g, 76.2%)

as a very viscous oil which turned light orange on standing, b.p.

108-114°C/0.2mmHg. A centre cut was taken and redistilled for analysis.

Found: C, 85.46; H, 8.40: N, 6.67. $C_{15}H_{17}N$ requires

C, 85.26; H, 8.11; N, 6.63%.

ν_{max} (liq. film) 2970 (s), 2875 (s), 2255 (m), 1620 (w), 1470 (s),

1380 (m), 1110 (w), 1020 (m), 825 (m), 758 (s) cm^{-1}.

δ_{1H} (CCl$_4$; 90 MHz) 0.9-2.1 (6H, m, $\underline{CH_2CH_2CH_2}$CN), 1.27 (3H, s,

C_1 Me), 2.09 (3H, d, $\underline{J}$, 1.6 Hz, C_3 Me), 5.93 (1H, q, $\underline{J}$, 1.6 Hz, H_2),

7.20 (4H, s, aromatic protons).

δ_{13C} (CDCl$_3$; 62.9 MHz) 12.7 (q, C_3 Me), 17.5 (t), 21.1 (t),

24.0 (q, C_1 Me), 37.5 (t, $C_{3'}$), 51.4 (s, C_1), 119.3 (d), 119.6 (s, CN),

121.0 (d), 125.3 (d), 126.7 (d), 137.7 (s), 139.2 (d), 144.8 (s),

151.7 (s).

m/e 211 (64%, $\underline{M}^+$), 196 (66%, $\underline{M}^+-{}^{\bullet}CH_3$), 157 (100%, $\underline{M}^+-{}^{\bullet}CN$ and

C_2H_4), 143 (93%, $\underline{M}^+-{}^{\bullet}CH_2CH_2CH_2CN$), 128 (89%, $143-{}^{\bullet}CH_3$), 115 (48%, ${}^+C_9H_7$).

Crude 3-methylindene (259), prepared by treatment of indan-1-one

(55) (2.0g, 15mmol) with methyl magnesium iodide (from magnesium (0.4g,

16mmol) and methyl iodide (1.04ml, 16mmol) was dried by azeotropic

removal of water from benzene solution for 0.5h, and then subjected to

the procedure just described to give a crude mixture of 4-(1-methylinden-

1-yl)butyronitrile (260) and 4-(3-methylinden-1-yl)butyronitrile (261)

(1.49g, 49.8%; isomer ratio $\sim$ 1:2), contaminated with 4-chlorobutyro-

nitrile, after column chromatography on silica gel H (20g), eluting with

chloroform (20% in light petroleum).

δ_{1H} (CCl_4; 90 MHz) Compound (260) ($\sim$ 33%) 1.25 (3H, s, C_1 Me),

1.0-2.2 (m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CN$), 6.22 (1H, d, $\underline{J}$, 6 Hz, H_2), 6.65 (1H, d, $\underline{J}$, 6 Hz,

H_3), 6.9-7.4 (4H, aromatic protons). Compound (261) ($\sim$ 66%) 2.10

(3H, t, $\underline{J}$, 1.5 Hz, C_3 Me), 1.0-2.2 (m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CN$), 3.2-3.5 (1H, m, H_1),

6.08 (1H, quintet, $\underline{J}$, 1.5 Hz, H_2), 6.9-7.4 (4H, m, aromatic protons).

4a,9-Dimethyl-2,3,4,4a-tetrahydrofluoren-1-one (238). — Ortho-

phosphoric acid (40ml, 0.72mol) was added at once to phosphorus pentoxide

(145g, 1.02mol) in an open cylindrical flask (500ml) (EXOTHERMIC) and

the mixture mechanically stirred at 130°C until homogeneous (20h).

4-(1,3-dimethylinden-1-yl)butyronitrile (237) (15.62g, 74mmol) was

added, the mixture stirred 2h, quenched in water while still hot and

basified with solid potassium hydroxide. The product was thoroughly

extracted into chloroform, the residual aqueous phase further washed

with ether, then the organic phases were combined, dried (MgSO$_4$) and

evaporated to yield a brown oil (17.3g). This was distilled to give

4a,9-<u>dimethyl</u>-2,3,4,4a-<u>tetrahydrofluoren</u>-1-<u>one</u> (238) as a pale yellow

oil (12.26g, 78.1%) which crystallised on standing for 10 months,

b.p. 112-116°C/0.25mmHg.   A centre cut was taken for analysis.

Found: C, 85.23; H, 7.54. $C_{15}H_{16}O$ requires C, 84.87;

H, 7.60%.

ν_{max} (liq. film) 2945 (m), 1670 (s), 1600 (m), 1576 (m), 1379 (m),

1321 (m), 1192 (m), 933 (m), 752 (s) cm^{-1}.

λ_{max} (EtOH) 305 (ϵ 20300), 241 (11000, sh), 234 nm (12900).

δ_{1H} (CDCl$_3$; 250 MHz) 1.23 (3H, s, C_{4a} Me), 1.25-1.45 (1H, m, $H_{4\alpha}$?),

1.9-2.4 (4H, m) and 2.55-2.73 (1H, m) (H_2 x2, H_3 x2, $H_{4\beta}$), 2.32 (3H,

s, C_9 Me), 7.28-7.38 (3H, m) and 7.41-7.48 (1H, m) (aromatic protons).

δ_{13C} (CDCl$_3$; 62.9 MHz) 11.5 (q, C_9 Me), 20.2 (t), 22.0 (q,

C_{4a} Me), 33.6 (t), 40.9 (t), 52.4 (s, C_{4a}), 121.5 (d), 121.9 (d), 127.1

(d), 127.9 (d), 142.1 (s), 142.3 (s), 145.4 (s), 153.7 (s), 200.2

(s, C_1).

<u>m/e</u> 212 (94%, $\underline{M}^+$), 197 (47%, $\underline{M}^+$− ˙CH$_3$), 156 (100%, $\underline{M}^+$− C_2H_4

and CO), 141 (55%, 156−˙CH$_3$), 128 (21%), 115 (38%, $^+C_9H_7$).

2,4-<u>Dinitrophenylhydrazone</u>, m.p. 172-176°C (Found: C, 64.17;

H, 5.11; N, 14.23. $C_{21}H_{20}N_4O_4$ requires C, 64.28; H, 5.14; N, 14.28%).

Similarly prepared was 2,3,4,9-tetrahydrofluoren-1-one (133)

(23.5g, 37.3% over two steps).[89]   Indene (78.9ml, 0.68mol) was treated

with <u>n</u>-butyllithium (1.45M in hexane; 258ml, 0.37mol) followed by

4-chlorobutyronitrile (32.5ml, 0.34mol) according to the procedure

described for the synthesis of nitrile (237) from 1,3-dimethylindene

(136).   The crude nitrile (132) was treated directly with poly-

phosphoric acid from phosphorus pentoxide (195g, 1.37mol) and ortho-

phosphoric acid (96ml, 1.73mol) and the ketone (133) purified by crystall-

isation from light petroleum (b.p. 80-100°C) (charcoal).

λ_{max} (EtOH) 304 (ϵ 16600), 239 (8300), 231 (8400), 225 nm

(5900, sh).

δ_{1H} (CCl$_4$; 90 MHz) 2.0-2.9 (6H, m, H$_2$ x2, H$_3$ x2, H$_4$ x2),

3.52 (2H, t, J, 2.5 Hz, H$_9$ x2), 7.2-7.6 (4H, m, aromatic protons).

When the mixture of nitriles (260) and (261) (0.74g, 3.8mmol), prepared as described previously, was treated with polyphosphoric acid from phosphorus pentoxide (4.0g, 28mmol) and orthophosphoric acid (1.5ml, 27mol), and the crude product purified by column chromatography on silica gel 'H', eluting with chloroform (20% in light petroleum), the only product isolated was 9-methyl-2,3,4,9-tetrahydrofluoren-1-one (262) (0.21g, 28.2%), a low-melting brown crystalline solid.

δ_{1H} (CCl$_4$; 90 MHz) 1.41 (3H, d, J, 7.5 Hz, C$_9$ Me) 2.0-2.9 (6H, m, H$_2$ x2, H$_3$ x2, H$_4$ x2), 3.45-3.85 (1H, m, H$_9$), 7.2-7.6 (4H, m, aromatic protons).

When nitrile (237) (0.44g, 2.1mmol) was treated with phosphorus pentoxide (2.26g, 16mmol) in methanesulphonic acid (freshly distilled; 16ml) at 100°C for 0.5h, nmr showed the product to be an umpromising mixture. Only starting material was recovered when the nitrile (237) (0.25g, 1.2mmol) was heated in sulphuric acid (5ml) at 100°C for 0.3h.

cis-4a-Methylhexahydrofluoren-1-one (249). — Methyllithium-lithium bromide complex (1.3M in ether, 53ml, 68mmol) was added drop-wise to a stirred suspension of cuprous bromide-dimethylsulphide complex (freshly recrystallised; 7.4g, 36mmol) in dry ether (80ml) at −25°C under nitrogen to give first a yellow suspension then a tan solution. A solution of 2,3,4,9-tetrahydrofluoren-1-one (133) (4.0g, 22mmol) in dry ether (20ml) was added dropwise and the mixture stirred 2h keeping the temperature between −10 - 0°C throughout. The resulting yellow slurry was then transferred directly, in small aliquots, into vigorously stirred hydrochloric acid (6M; 150ml). The product was extracted into ether, dried (MgSO$_4$) and evaporated to give a brown oil. Column chromatography on silica gel 'H' (50g) under nitrogen pressure,

eluting with ether (10% in light petroleum), gave a fast running impurity (0.39g) then cis-4a-methylhexahydrofluoren-1-one (249) (3.30g, 75.9%) as a pale yellow oil.

ν_{max} (liq. film) 2940 (m), 1710 (s), 1480 (m), 1460 (m), 1320 (m), 755 (s) cm^{-1}.

λ_{max} (EtOH) 303 (ε 400), 291 (430), 280 (630, sh), 273 (1680), 266 (1990), 260 (1750), 252 nm (1250, sh).

δ_{1H} (CDCl$_3$; 250 MHz) 1.32 (3H, s, Me), 1.55-2.05 (4H, m, H$_3$ x2, H$_4$ x2), 2.2-2.45 (2H, m, H$_2$ x2), 2.67 (1H, dd, $\underline{J}$, 7.5 and 6 Hz, H$_{9a\beta}$), 3.02 (1H, dd, $\underline{J}$, 15.5 and 7.5 Hz, H$_{9\beta}$), 3.31 (1H, dd, $\underline{J}$, 15.5 and 6 Hz, H$_{9\alpha}$), 7.0-7.4 (4H, m, aromatic protons).

δ_{13C} (CDCl$_3$; 62.9 MHz) 21.5 (t), 27.6 (q, Me), 32.8 (t, C$_9$), 35.0 (t), 39.4 (t), 50.7 (s, C$_{4a}$), 60.1 (d, C$_{9a}$), 121.5 (d), 124.9 (d), 126.8 (d x2), 141.2 (s), 149.8 (s), 212.9 (s, C$_1$).

2,4-Dinitrophenylhydrazone, m.p. 160-175°C (Found: C, 62.95; H, 5.26; N, 14.53. C$_{20}$H$_{20}$N$_4$O$_4$ requires C, 63.15; H, 5.30; N, 14.73%).

When this procedure was repeated with the exception that N-selenophenylphthalimide (254) (2 equivalents) in dry tetrahydrofuran was added and stirred 1h at $^-$30 - $^-$20°C prior to quenching as described previously, a complex mixture was obtained; nmr showed at least four major methyl singlets.

When the reaction was repeated using methyl magnesium iodide and cuprous cyanide in place of LiCuMe$_2$ as the methylating reagent, a complex mixture was obtained. Column chromatography on silica gel 'H' furnished two unidentified products only, in low yields; nmr showed the major product (35%) to contain a tertiary methyl [δ 1.12 (d, $\underline{J}$, 7 Hz)]. and the minor (13%) a quaternary methyl [δ 1.23 (s)].

4a-Methyl-2,3,4,4a-tetrahydrofluoren-1-one (250). — N-Bromo-

succinimide (1.50g, 8.4mmol), followed by benzoyl peroxide (∿ 10mg), was added to a solution (previously dried azeotropically) of 4a-methyl-hexahydrofluoren-1-one (249) (1.66g, 8.3mmol) in carbon tetrachloride (200ml), and the suspension refluxed 0.6h, making fresh additions of initiator periodically. On cooling no solid denser than the solution was observed; in other experiments, if such solid (unreacted NBS) was observed reflux was extended as required after addition of fresh NBS and initiator. The suspension was filtered to remove succinimide, washed with sodium thiosulphate solution (∿ 20%; 2x50ml), dried ($MgSO_4$), then 1,8-diazobicylo[5.4.0]undec-7-ene (DBU) (1.8ml) was added and the mixture refluxed 0.5h. The mixture was filtered, washed with hydrochloric acid (6M; 4x50ml), dried ($MgSO_4$) and evaporated to give a brown oil. This crude product was normally used directly in the next step, but purification by column chromatography on silica gel 'H', eluting with chloroform (12.5% in light petroleum) gave a clean sample of 4a-methyl-2,3,4,4a-tetrahydrofluoren-1-one (250) (0.82g, 50%) as low-melting yellow crystals.

ν_{max} (nujol) 1680 (s), 1608 (w), 1590 (m), 936 (m), 837 (s), 753 (s) cm^{-1}.

λ_{max} (EtOH) 300 (ε 8900), 233 nm (7000).

δ_{1H} ($CDCl_3$; 250 MHz) 1.27 (3H, s, Me), 1.25-1,45 (1H, m, $H_{4\alpha}$?), 1.9-2.35 (4H, m) and 2.57-2.73 (1H, m) (H_2 x2, H_3 x2, $H_{4\beta}$), 7.12 (1H, s, H_9), 7.21-7.38 (3H, m) and 7.41-7.49 (1H, m) (aromatic protons).

δ_{13C} ($CDCl_3$; 62.9 MHz) 19.9 (t), 21.2 (q, Me), 33.3 (t), 40.1 (t), 52.9 (s, C_{4a}), 121.5 (d), 123.9 (d), 126.9 (d), 127.4 (d), 131.0 (d), 139.8 (s), 152.4 (s), 154.3 (s), 199.2 (s, C_1).

2,4-Dinitrophenylhydrazone, m.p. 140-145°C (Found: C, 63.55; H, 4.67; N, 14.77. $C_{20}H_{18}N_4O_4$ requires C, 63.49; H, 4.79; N, 14.81%).

When triethylamine was substituted for DBU in the second step a complex mixture resulted after 20h at 20°C, and when N-chloro-succinimide was substituted for NBS in the first step, no reaction occurred.

4,4a-Dihydro-4a-methylfluoren-1-one (252). — Iodylbenzene (2.42g, 10.2mmol) was added to a solution of benzeneseleninic anhydride (0.35g, 0.97mmol) in refluxing benzene (200ml), and the suspension dried azeotropically for 0.5h before the addition of crude 4a-methyl-2,3,4,4a-tetrahydrofluoren-1-one (250) [1.0g; prepared from ketone (249) (1.03g, 5.15 mmol)] in benzene (10ml). The suspension was refluxed for 2h, filtered, washed with potassium carbonate solution (∿ 20%; 3x50ml), dried (MgSO$_4$) and evaporated to yield a brown oil [the iodylbenzene recovered (∿ 50%) could be re-used after washing with chloroform]. Column chromatography on silica gel 'H', eluting with chloroform (20% in light petroleum) gave 4,4a-dihydro-4a-methylfluoren-1-one (252) (0.53g, 53% over two steps) as a pale yellow oil.

δ_{1H} (CCl$_4$; 90 MHz) 1.34 (3H, s, Me), 2.12 (1H, ddd, $\underline{J}$, 18, 3 and 2 Hz, H$_{4\alpha}$), 2.81 (1H, dd, $\underline{J}$, 18 and 6 Hz, H$_{4\beta}$), 6.20 (1H, dd, $\underline{J}$, 10 and 3 Hz, H$_2$), 6.98 (1H, ddd, $\underline{J}$, 10, 6 and 2 Hz, H$_3$), 7.2-7.6 (5H, m, aromatic protons and H$_9$).

δ_{13C} (CDCl$_3$; 62.9 MHz) 22.8 (q, Me), 37.0 (t, C$_4$), 53.0 (s, C$_{4a}$), 121.9 (d), 124.5 (d), 127.5 (d), 127.8 (d), 131.7 (d), 132.6 (d), 140.8 (s), 149.2 (d, C$_3$), 149.8 (s), 154.1 (s), 186.1 (s, C$_1$).

2,4-Dinitrophenylhydrazone, (Found: C, 63.24; H, 4.26; N, 14.63. C$_{20}$H$_{16}$N$_4$O$_4$ requires C, 63.83; H, 4.28; N, 14.89%).

Similarly prepared was 4,4a-dihydro-4a,9-dimethylfluoren-1-one (241) (0.92g, 73%), a pale yellow oil, starting from ketone (238) (1.27g, 6.0mmol), iodylbenzene (3.26g, 13.8mmol) and benzeneseleninic anhydride (0.48g, 1.3mmol).

ν_{max} (liq. film) 2935 (w), 1650 (s), 1598 (m), 1383 (m),

1245 (m), 1159 (w), 956 (w), 850 (w), 820 (m), 755 (m) cm^{-1}.

λ_{max} (EtOH) 335 (ε 12600), 243 nm (14700).

δ_{1H} (CCl$_4$; 90 MHz) 1.38 (3H, s, C$_{4a}$ Me), 2.18 (1H, ddd, $\underline{J}$,

18, 3 and 2 Hz, H$_{4\alpha}$), 2.44 (3H, s, C$_9$ Me), 2.75 (1H, dd, $\underline{J}$, 18 and

6 Hz, H$_{4\beta}$), 6.18 (1H, dd, $\underline{J}$, 10 and 3 Hz, H$_2$), 6.93 (1H,

ddd, $\underline{J}$, 10, 6 and 2 Hz, H$_3$), 7.1-7.6 (4H, m, aromatic protons).

δ_{13C} (CDCl$_3$; 62.9 MHz) 11.8 (q, C$_9$ Me), 23.1 (q, C$_{4a}$ Me), 37.3

(t, C$_4$), 52.5 (s, C$_{4a}$), 121.7 (d), 122.3 (d), 127.4 (d), 128.1 (d),

132.6 (d), 142.3 (s), 143.3 (s), 144.8 (s), 147.7 (d, C$_3$), 153.3 (s),

187.7 (s, C$_1$).

m/e 210 (41%, $\underline{M}^+$), 195 (50%, $\underline{M}^+$- $^{\cdot}$CH$_3$), 167 (45%, $\underline{M}^+$- C$_3$H$_2$O),

115 (24%, $^+$C$_9$H$_7$), 43 (100%, $^+$C$_3$H$_2$O).

2,4-Dinitrophenylhydrazone, m.p. 219-222°C (Found: C, 65.23;

H, 4.77; N, 14.16. C$_{21}$H$_{18}$N$_4$O$_4$ requires C, 64.61; H, 4.65;

N, 14.35%).

When this reaction was carried out in the absence of iodyl-

benzene, using ketone (238) (0.10g, 0.47mmol) and benzeneseleninic

anhydride (0.17g, 0.47mmol) in dry chlorobenzene (10ml) at 95°C for

0.2h, dienone (241) was formed in comparable yield but contaminated

with 4,4a-dihydro-4a,9-dimethyl-2-selenophenylfluoren-1-one (243)

($\sim$ 13mg).

ν_{max} (liq. film) 2930 (w), 1640 (s), 1600 (m), 1580 (m),

1380 (m), 1345 (m), 1215 (m) 1020 (w), 927 (w), 875 (m), 825 (m),

690 (m) cm^{-1}.

δ_{1H} (CCl$_4$; 90 MHz) 1.40 (3H, s, C$_{4a}$ Me), 1.95-2.85 (2H, m,

H$_4$ x2), 2.50 (3H, s, C$_9$ Me), 6.32 (1H, dd, $\underline{J}$, 7.5 Hz and 2.5 Hz, H$_3$),

7.1-7.75 (4H, m, aromatic protons).

m/e 366 (39%, Se pattern, $\underline{M}^+$), 351 (4%, Se pattern, $\underline{M}^+$- $^{\cdot}$CH$_3$),

314 (7%, Se$_2$ pattern, PhSeSePh), 210 (56%, $\underline{M}^+$ of (241)), 195 (56%,

$\underline{M}^+$ of (241) — $^\bullet CH_3$), 181 (39%), 145 (78%), 43 (100%).

When the reaction was repeated in refluxing chlorobenzene for 0.5h, none of the selenophenylketone (243) was formed. Instead, an inseparable mixture of dienone (241) and 4,4a-dihydro-9-formyl-4a-methylfluoren-1-one (245) was formed.

δ_{1H} (CDCl$_3$; 250 MHz) inter alia 1.33 (3H, s, C$_{4a}$ Me), 2.12 (1H, ddd, $\underline{J}$, 18, 3 and 2 Hz, H$_{4\alpha}$), 2.71 (1H, dd, $\underline{J}$, 18 and 6 Hz, H$_{4\beta}$), 6.20 (1H, dd, $\underline{J}$, 10 and 3 Hz, H$_2$), 6.88 (1H, ddd, $\underline{J}$, 10, 6 and 2 Hz, H$_3$), 7.1-7.4 (m, aromatic protons), 8.25-8.35 (1H, m, H$_8$), 10.52 (1H, s, C$\underline{H}$O).

m/e inter alia 224 ($\underline{M}^+$).

When ketone (238) (0.13g, 0.61mmol) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.33g, 1.45mmol) and glacial acetic acid (1ml, 17mmol) in refluxing benzene for 4h, the neutral fraction of the product (35mg) was found to contain <20% of dienone (241).

Other oxidations with benzeneseleninic anhydride.

— 4a-Methylhexahydrofluoren-9-one (131) (1.0g, 0.52mmol), prepared by the method of Ng et.al.,[79] was treated with iodylbenzene (0.40g, 1.7mmol) and benzeneseleninic anhydride (38mg, 0.10mmol) in refluxing benzene for 1h as described under the synthesis of 4,4a-dihydro-4a-methylfluoren-1-one (252) to give a mixture (0.11g) comprising 20-40% 4a-methyl-2,3,4,4a-tetrahydrofluoren-9-one (267).

δ_{1H} (CCl$_4$; 90 MHz) inter alia 1.27 (3H, s, Me), 0.75-2.5 (m, H$_2$ x2, H$_3$ x2, H$_4$ x2), 6.63 (1H, t, $\underline{J}$, 4 Hz, H$_1$), 7.0-7.9 (m, aromatic protons).

4a-methylhexahydrofluoren-1-one (249) (0.10g, 0.50mmol) was added to a refluxing solution of benzeneseleninic anhydride (0.50g, 1.40mmol) in PhCl, and the mixture refluxed 0.5h with azeotropic removal of water. The cooled solution was diluted with chloroform, washed with

sodium carbonate solution (20%; 3x25ml), dried (MgSO$_4$) and evaporated to give a brown oil. Column chromatography on silica gel 'H', eluting with chloroform (20% in light petroleum), gave, after removal of chlorobenzene and diphenyldiselenide, one major fraction (64mg) which was further purified by preparative tlc on silica, eluting four times with progressively more polar chloroform-light petroleum mixtures. Two fractions were obtained; the more polar (24mg) consisted predominantly of enone (251), the less polar (19mg) of dienone (252), but both were contaminated with enedione (253). Data for (251) appear below:

δ_{1H} (CCl$_4$ + C$_6$D$_6$; 250 MHz) inter alia 1.32 (3H, s, Me), 2.26 (1H, ddd, J, 19, 4.5 and 2 Hz, H$_{4\alpha}$), 2.45 (1H, ddd, J, 19, 4 and 2.5 Hz, H$_{4\beta}$), 2.65 (1H, t, J, 8 Hz, H$_{9\alpha}$), 3.03 (1H, dd, J, 16 and 7.5 Hz) and 3.16 (1H, dd, J, 16 and 8 Hz) (H$_9$ x2), 5.93 (1H, dt, J, 10.5 and 2 Hz, H$_2$), 6.64 (1H, ddd, J, 10.5, 4.5 and 4 Hz, H$_3$), 6.96-7.2 (m, aromatic protons). These assignments were confirmed by decoupling.

In another experiment, ketone (249) (0.10g, 0.50mmol) was treated with iodylbenzene (0.39g, 1.7mmol) and benzeneseleninic anhydride (36mg, 0.10mmol) in refluxing dry chlorobenzene (40ml) for 0.5h, the crude product washed with sodium carbonate (20%, 3x50ml), dried (MgSO$_4$), evaporated and re-evaporated repeatedly from carbon tetrachloride to give a mixture of compounds (251), (252) and (253) in an approximate ratio of 1:1:2. Data for (253) appear below:

δ_{1H} (CDCl$_3$; 250 MHz) inter alia 1.58 (3H, s, Me), 3.25 (1H, dd, J, 7.0 and 6.5 Hz, H$_{9a}$), 3.37 (2H, d, J, 6.5 Hz, H$_9$ x2), 6.72 (2H, s, H$_2$ and H$_3$?), 7.1-7.45 (m, aromatic protons).

m/e inter alia 212 (17%, M$^+$), 197 (8%, M$^+$– ˙CH$_3$), 183 (42%, M$^+$– ˙CHO), 130 (100%, M$^+$– O=C=CHCH=C=O).

In other experiments, ketone (249) was treated with various

Reagents		Solvent	Temp.	Reaction Period (h)	Recovery %	Approximate product ratios (from crude nmr)			
BSA (equiv.)	PhIO$_2$ (equiv.)					(251)	(252)	(253)	Other
2.2	-	PhCl	90°C	1.5	35	1	-	-	> 80%
2.2	-	PhCl	↑↓	0.3	45	5	4	1	< 10%
2.8	-	PhCl	↑↓	0.5	65	4	3	1	10-20%
3.1	-	PhBr	↑↓	0.25	40	trace	4	3	∿ 50% ?
0.2	3.3	PhH	↑↓	24	85	6	3	1	< 10%
0.2	3.3	PhCl	↑↓	0.2	80	3	1	trace	< 10%
0.2	3.3	PhCl	↑↓	0.5	90	1	1	3	< 10%
0.2	3.3	PhCl	↑↓	2.5	90	-	trace	1	> 80%
2	3.3	PhCl	↑↓	0.05	> 90	4	1	trace	∿ 50% ?
2	3.3	PhCl	↑↓	0.25	> 90	3	2	2	∿ 50% ?

TABLE 18

amounts of benzeneseleninic anhydride (BSA), with or without iodyl-
benzene, and the proportions of products (251), (252) and (253)
estimated (very approximately) from the total nmr spectrum; these
results are summarised in Table 18. Experiments not involving
iodylbenzene were worked up by column chromatography on silica gel
'H', which always yielded only one major mobile fraction (other than
diphenyldiselenide), a mixture of compounds (251)-(253) among others.
The crude products of the experiments with iodylbenzene were analysed
directly.

Other oxidations of 4a-methylhexahydrofluoren-1-one (249).
Treatment of ketone (249) with excess 2,3-dichloro-5,6-dicyano-1,4-
benzoquinone (DDQ) (2-4.5 equivalents) in either refluxing benzene
for 1h or refluxing dioxan for 24h gave unchanged (249) with only
traces of unidentified oxidation products. No reaction at all occurred
when ketone (249) (0.10g, 0.5mmol) was treated with triphenylmethanol
(0.14g, 0.55mmol) in refluxing trifluoroacetic acid (10ml) for 10h.

In a further experiment, ketone (249) (0.12g, 0.6mmol), propylene
oxide (46µl, 1mmol) and bromine (31µl 0.6mmol) in dry carbon tetra-
chloride (30ml) were irradiated with a tungsten lamp for 0.2h at $20^{o}C$.
The solution was washed with sodium thiosulphate solution (20%;
3x10ml), dried (MgSO$_4$), then triethylamine (1ml) added and the mixture
left for 20h at $20^{o}C$. Removal of triethylamine hydrobromide followed
by column chromatography on silica gel 'H', eluting with chloroform
(20% in light petroleum) gave only one major fraction (36mg), probably
a mixture of bromides (255) and (256).

δ_{1H}(CDCl$_3$; 250 MHz) Major isomer [∿ 75%; (255)] 1.15 (3H, s, Me),
1.75-2.17 [m, including 1.82 (td, J, 13 and 3.5 Hz) and 1.99 (dt, J, 13
and 3 Hz)] and 2.38-2.55 (m) (H$_3$ x2, H$_4$ x2), 4.38-4.44 (1H, m, H$_{2eq.}$),
7.13 (1H, s, H$_9$), 7.15-7.28 (m) and 7.30-7.39 (m) (aromatic protons).

[Minor isomer ∿ 25%; (256)] 1.21 (3H, s, Me), 1.75-2.17 (m) and

2.38-2.55 (m) (H_3 x2, H_4 x2), 4.22 (1H, dd, $\underline{J}$, 10.5 and 7.5 Hz, $H_{2ax.}$),

7.02 (1H, s, H_9), 7.15-7.28 (m) and 7.30-7.39 (m) (aromatic protons).

4,4a-Dihydro-4aβ-methyl-1H-fluoren-1α-ol (268). — Diisobutyl

aluminium hydride (1M in hexane; 2.3ml, 2.3mmol) was added dropwise

to a stirred solution of 4,4a-dihydro-4a-methylfluoren-1-one (252)

(0.18g, 0.92mmol) in dry benzene (6ml) and light petroleum (2ml) at

0^oC under nitrogen. After stirring 2h, methanol (2ml) was added drop-

wise and the mixture allowed to warm to 20^oC over 1h. The resultant

gel was mixed with celite and very thoroughly washed with hot methanol.

The washings were evaporated, dissolved in carbon tetrachloride,

filtered (celite) and re-evaporated to give crude 4,4a-dihydro-4aβ-methyl-

1H-fluoren-1α-ol (268), a yellow oil (0.18g), which was stored in

dilute CCl_4 solution at 0^oC under nitrogen and used without further

purification.

δ_{1H} (CDCl$_3$; 250 MHz) 1.25 (3H, s, Me), 1.89 (1H, m, $H_{4\alpha}$),

2.38 (very concentration dependent) (1H, br s, OH), 2.52 (1H, dd, $\underline{J}$, 15 and

4 Hz, $H_{4\beta}$), 5.02 (1H, m, H_1), 5.75-5.88 (2H, m, H_2 and H_3), 6.61 (1H,

d, $\underline{J}$, 2 Hz), 7.1-7.4 (4H, m, aromatic protons).

Similarly prepared was crude 4,4a-dihydro-4aβ,9-dimethyl-1H-fluoren-

1α-ol (248) (0.17g) from 4,4a-dihydro-4a,9-dimethylfluoren-1-one (241)

(0.18g, 0.85mmol) and diisobutylaluminium hydride (1M in hexane;

2.3ml, 2.3mmol).

ν_{max} (liq. film) 3600-3200 (br), 3030 (m) 2960 (m) 1595 (w),

1380 (m), 1070 (m), 1040 (m), 990 (m), 870 (m), 750 (s) cm^{-1}.

δ_{1H} (CDCl$_3$; 250 MHz) 1.15 (3H, s, C_{4a} Me), 1.82 (1H, m, $H_{4\beta}$),

2.17 (very concentration dependent) (1H, br s, D_2O exch., OH), 2.29

(3H, d, $\underline{J}$, 1.5 Hz, C_9 Me), 2.37 (1H, dd, $\underline{J}$, 15 and 4 Hz, $H_{4\alpha}$), 5.08 (1H,

m, H_1), 5.65-5.80 (2H, m H_2 and H_3), 7.08-7.30 (4H, m, aromatic protons).
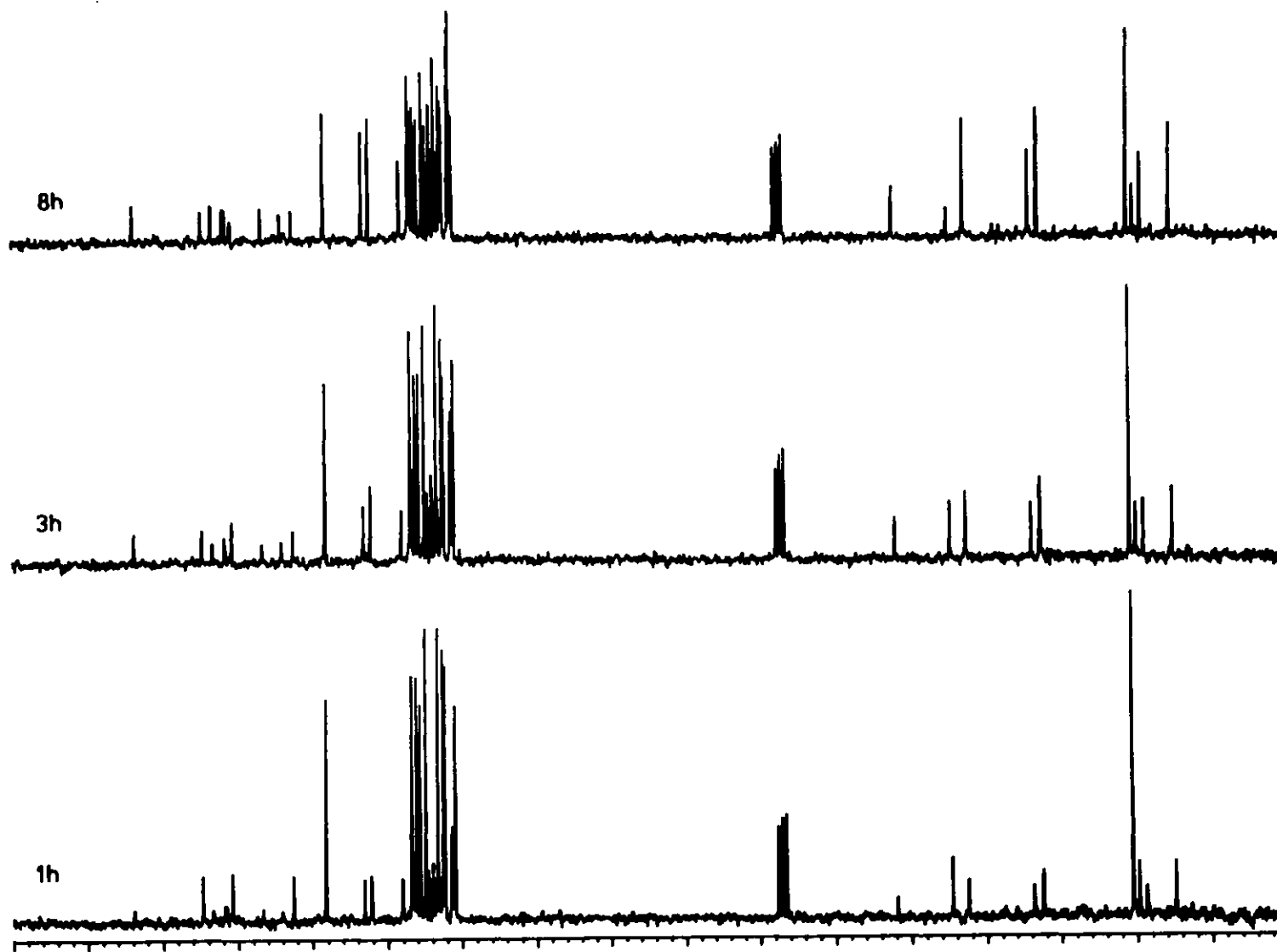
FIGURE 33 ^{13}C spectra showing the partial conversion of 4a-methyl-4a$\underline{H}$-fluorene (3) into its symmetrical dimer (270).

When isophorone (246) (0.54ml, 3.6mmol) was similarly treated

with diisobutylaluminium hydride (1M in hexane; 3.6ml, 3.6mmol),

∿ 90% conversion to 3,5,5-trimethylcyclohex-2-enol (247) occurred.

δ_{1H} (CCl$_4$; 90 MHz) <u>inter alia</u> 0.84 (3H, s) and 0.95 (3H, s)

(C$_5$ Me x2), 1.0-2.2 (4H, m, H$_4$ x2 and H$_6$ x2), 1.62 (3H, s, C$_3$ Me),

4.15 (2H, s, H$_1$ and OH), 5.42 (1H, m, H$_2$).

4a-<u>methyl</u>-4aH-<u>fluorene</u> (3) — A solution of crude 4,4a-dihydro-

4αβ-methyl-1<u>H</u>-fluoren-1α-ol (268)[∿ 0.16g; from dienone (252) (0.166g,

0.85mmol)] and <u>p</u>-toluenesulphonic acid monohydrate (10mg, 0.05mmol)

in dry benzene (40ml) was refluxed with azeotropic removal of water

for 0.4h, cooled to 20°C, washed with sodium hydroxide solution

(2M; 2x10ml), dried (MgSO$_4$), evaporated and immediately subjected to

very rapid column chromatography on silica gel 'H' (4g), eluting with

light petroleum. Evaporation of the first ∿ 50ml of eluent only

gave 4a-<u>methyl</u>-4aH-<u>fluorene</u> (3) (96mg, 55% over two steps), a pale

yellow mobile oil.

Found: C, 87.38; H, 6.50 (ratio C/H = 13.44). C$_{14}$H$_{12}$ requires

C, 93.29; H, 6.71% (ratio C/H = 13.90).

ν_{max} (liq. film) 2970 (s), 2920 (s), 1609 (w), 1565 (w),

1528 (m), 1462 (s), 1371 (m), 1345 (m), 1208 (m), 1015 (m), 870 (s),

861 (m), 845 (s), 750 (s), 710 (s), 670 (s) cm^{-1}.

λ_{max} (EtOH) 394 (ϵ 2700, sh), 371 (4900), 358 (4700), 333 (3200,

sh), 318 (2700, sh), 303 (2400, sh), 292 (2200, sh), 244 nm (17000).

δ_{1H} (CDCl$_3$; 250 MHz) 1.42 (3H, s, Me), 5.84-6.01 (2H, m, H$_2$ and

H$_3$), 6.46-6.54 (3H, m, H$_1$, H$_4$ and H$_9$), 7.0-7.35 (4H, m, H$_{5-8}$).

δ_{13C} (CDCl$_3$; 62.9 MHz) 30.5 (Me), <u>54.5</u> (C$_{4a}$), 120.9, 122.4,

122.6, 123.3, 125.0, 125.7, 126.2, 126.8, 138.2, <u>142.5</u>, <u>150.8</u>, <u>154.7</u>.

Quaternary carbons underlined.

m/e 180 (92%, $\underline{M}^+$), 165 (100%, $\underline{M}^+- \ ^{\cdot}CH_3$), 152 (5%, $\underline{M}^+- \ C_2H_4$)

Found: $\underline{M}^+$, 180.0943. $C_{14}H_{12}$ requires $\underline{M}^+$, 180.0939.

Similarly prepared was 4a,9-<u>dimethyl-4aH-fluorene</u> (222) (55% over two steps) from 4,4a-dihydro-4aβ,9-dimethyl-1$\underline{H}$-fluoren-1α-ol (248).

ν_{max} (liq. film) 2960 (s), 2920 (s), 1638 (w), 1598 (w), 1526 (w), 1470 (s), 1387 (s), 1015 (m), 767 (m), 751 (s), 715 (s), 670 (s) cm^{-1}.

λ_{max} (EtOH) 396 (ε 2300, sh), 373 (3800), 358 (3600), 335 (2200, sh), 319 (1800, sh), 303 (1700, sh), 288 (1700, sh), 245 nm (13500).

δ_{1H} (CDCl$_3$; 250 MHz) 1.40 (3H, s, C_{4a} Me), 2.11 (3H, s, C_9 Me), 5.96-6.00 (2H, m, H_2 and H_3), 6.46 (1H, dt, $\underline{J}$, 8.5 and 1Hz, H_4), 6.57 (1H, br d, $\underline{J}$, 9 Hz, H_1), 7.07-7.35 (4H, m, H_{5-8}).

δ_{13C} (CDCl$_3$; 62.9 MHz) 10.2 (C_9 Me), 29.9 (C_{4a} Me), <u>53.6</u> (C_{4a}) 120.0 120.7, 121.2, 123.5, 124.4, 125.2, 126.7, <u>134.5(?)</u>, 138.0, <u>144.4</u>, <u>147.3</u>, <u>150.8</u>. Quaternary carbons underlined.

m/e 194 (84%, $\underline{M}^+$), 179 (100%, $\underline{M}^+- \ ^{\cdot}CH_3$). Found: $\underline{M}^+$, 194.1093. $C_{15}H_{14}$ requires $\underline{M}^+$, 194.1095.

In a further experiment, alcohol (268) (0.25g, 1.3mmol) was treated with methyltriphenoxyphosphine iodide (MTPI) (0.95g, 2.1mmol) in hexamethylphosphoramide (HMPA) (10ml) for 0.6h, the mixture quenched in sodium hydroxide solution (10%), and the product extracted into light petroleum; column chromatography as described above gave 4a-methyl-4a$\underline{H}$-fluorene (3) (22mg, 9.5%). When thionyl chloride (0.5ml, 6.9mmol) was added dropwise to a solution of alcohol (268) (0.19g, 0.96mmol) in dry pyridine, the black mixture stirred 3.5h at 20°C then quenched in water and washed with ether, only hydrocarbon residues (17mg) were recovered.

In another experiment, a solution of dimethylalcohol (248) (0.213g, 1.00mmol), tosyl chloride (0.225g, 1.18mmol), pyridine (0.2ml,

2.4mmol) and 4-dimethylaminopyridine (10mg, 0.08mmol) in dichloromethane (5ml) was stirred 20h at $20^{\circ}C$, then quenched in water and the products extracted into ether. Column chromatography on silica gel 'H', eluting with light petroleum, gave tosyl chloride (59mg) and two mixed fractions which were analysed by nmr. The first (22mg) contained 4a$\underline{H}$-fluorene (222) ($\sim$ 80%) and its symmetrical dimer (277) ($\sim$ 20%), while the second (67mg) contained mostly dimer (277) and tosyl chloride together with many unidentified minor products (unsymmetrical dimer (276) was assumed to be one of these since there were minor methyl peaks at δ 0.85 and δ 0.88). Similar results were obtained when 3,5-dinitrobenzoyl chloride was used in place of tosyl chloride, while treatment of alcohol (248) with poly-4-vinylpyridine hydrochloride in carbon tetrachloride at $0^{\circ}C$ resulted only in slow decomposition. During one preparation of 4a$\underline{H}$-fluorene (222), a pure specimen of symmetrical dimer (277) (5mg) was isolated.

δ_{1H} ($CCl_4 + C_6D_6$; 250 MHz) 0.79 (6H, s, C_{4a} and $C_{4a'}$ Me), 2.12 (6H, s, C_9 and $C_{9'}$ Me), 2.20 (2H, dd, $\underline{J}$, 4.5 and 1.5 Hz, H_4 and $H_{4'}$), 2.57 (2H, m, H_3 and $H_{3'}$), 5.81 (2H, br d, $\underline{J}$, 7.5 Hz, H_5 and $H_{5'}$), 5.83 (2H, dd, $\underline{J}$, 10 and 4 Hz, H_2 and $H_{2'}$), 6.37 (2H, td, $\underline{J}$, 7.5 and 1 Hz, H_6 and $H_{6'}$), 6.58 (2H, dd, $\underline{J}$, 10 and 0.5 Hz. H_1 and $H_{1'}$), 6.94 (2H, td, $\underline{J}$, 7.5 and 1 Hz, H_7 and $H_{7'}$), 7.05 (2H, br d, $\underline{J}$, 7.5 Hz, H_8 and $H_{8'}$). These assignments were confirmed by decoupling.

$\underline{m/e}$ 388 (4%, $\underline{M}^+$), 194 (100%, $\frac{1}{2}\underline{M}^+$), 179 (62%, $\frac{1}{2}\underline{M}^+ - \cdot CH_3$).

4a,9-Dimethyl-1-trimethylsilyloxy-4aH-fluorene (269).

— Trimethylsilylchloride (0.13ml, 1.0mmol) was added to a stirred suspension of sodium iodide (0.144g, 0.96mmol) in dry acetonitrile (2ml) at $20^{\circ}C$ under nitrogen. After 0.03h, a solution of 4,4a-dihydro-4a-9-dimethylfluoren-1-one (241) (0.165g, 0.79mmol) and triethylamine (0.14ml, 1.0mmol) was added dropwise and the bright yellow suspension

stirred 1.5h. The products were extracted into light petroleum

to give a yellow oil (98mg). Bulb-to-bulb distillation (0.02mmHg)

followed by rapid column chromatography on alumina 'H', eluting with

chloroform (20% in light petroleum), gave 4a,9-dimethyl-1-trimethyl-

silyloxy-4aH-fluorene (269) (22mg, 10%) as a yellow oil.

ν_{max} (liq. film) 2970 (m), 1600 (w), 1485 (m), 1255 (br),

1228 (br), 1140 (br), 1110 (br), 910 (s), 850 (s br) cm^{-1}.

λ_{max} (EtOH) 368 (ε 4700), 319 (4900, sh), 306 (5600), 292

(4800, sh), 250 (13900), 231 (10300, sh), 224 nm (9000, sh).

δ_{1H} (CDCl$_3$; 250 MHz) 0.30 (9H, s, OTMS), 1.43 (3H, s, C$_{4a}$ Me),

2.31 (3H, s, C$_9$ Me), 5.27 (1H, d, $\underline{J}$, 6 Hz, H$_2$), 5.78 (1H, dd, $\underline{J}$, 9 and

6 Hz, H$_3$), 6.12 (1H, dd, $\underline{J}$, 9 and 0.5 Hz, H$_4$), 7.1-7.35 (4H, m,

aromatic protons).

m/e 282 (8%, $\underline{M}^+$), 226 (100%). Found: $\underline{M}^+$– $^{\cdot}CH_3$, 267.1199

$C_{17}H_{19}OSi$ requires $\underline{M}^+$– $^{\cdot}CH_3$, 267.1205.

4) Chemistry of 4aH-Fluorenes.

4,4a-Dihydro-1α,4α-(4,4a-dihydro-4aα-methyl-3H-fluoren-3β,4β-ylene)-
4aβ-methyl-1H-fluorene (270). — A solution of 4a-methyl-4aH-fluorene

(3) (freshly prepared; 83mg, 0.46mmol) in carbon tetrachloride (0.5ml)

was left to stand for 20h at 55-60°C. Preparative tlc on silica,

eluting with light petroleum (x2), gave the unsymmetrical dimer (270)

(58mg, 64%) as a semi-crystalline glass (m.p. >310°C; decomp.) after

prolonged drying at 40°C/0.2mmHg.

Found: C, 88.33; H, 6.35 (ratio C/H = 13.91). $C_{28}H_{24}$ requires

C, 93.29; H, 6.71% (ratio C/H = 13.90).

ν_{max} (nujol) 1610 (w), 1018 (w), 870 (w), 850 (m), 750 (s) cm^{-1}.

λ_{max} (EtOH) 328 (ε 8600, sh), 313 (13700), 301 (14100), 292

(14800, sh), 284 (15200), 245 (15800, sh), 237 (19100), 230 nm (18900).

δ_{1H} (CDCl$_3$; 250 MHz) 0.93 (3H, s, C$_{4a}$ Me), 0.97 (3H, s, C$_{4a'}$ Me),

1.68 (1H, d, $\underline{J}$, 7.5 Hz, H$_{4'}$), 2.56 (1H, br d, $\underline{J}$, 6.5 Hz, H$_4$), 2.81

(1H, m, H$_{3'}$), 3.72 (1H, br t, $\underline{J}$, 4.5 Hz, H$_1$), 5.76 (1H, dd, $\underline{J}$, 9.5

and 3 Hz, H$_{2'}$), 5.87 (1H, ddd, $\underline{J}$, 8, 6.5 and 1 Hz, H$_3$), 5.94 (1H, ddd,

$\underline{J}$, 8, 4.5 and 1 Hz, H$_2$), 6.38 (1H, s, H$_{9'}$), 6.39 (1H, dd, $\underline{J}$, 9.5 and

1.5 Hz, H$_{1'}$), 6.49 (1H, s, H$_9$), 7.0-7.07 (1H, m) and 7.12-7.35 (7H, m),

(aromatic protons). These assignments were confirmed by decoupling

and n.O.e. difference experiments (Pages 122-4).

δ_{13C} (CDCl$_3$; 62.9 MHz) 24.8, 28.7, 42.4, 42.5, 43.7, 52.4 (x2?),

$\underline{61.8}$, 121.2 (x2), 121.4 (x2), 122.3, 123.2, 123.9, 123.95, 124.5, 126.6,

126.65, 128.1, 132.2, 133.2, $\underline{144.1}$, $\underline{146.7}$, $\underline{151.5}$, $\underline{151.8}$, $\underline{153.4}$, $\underline{163.7}$.

Quaternary carbons underlined.

$\underline{m/e}$ 360 (8%, $\underline{M}^+$), 180 (100%, $\frac{1}{2}\underline{M}^+$), 165 (10%, $\frac{1}{2}\underline{M}^+$- $^\bullet$CH$_3$).

4,4a-$\underline{Dihydro}$-3α,4α-(4,4a-$\underline{dihydro}$-4aα-$\underline{methyl}$-3H-$\underline{fluoren}$-3β,4β-$\underline{ylene}$)-
4aβ-$\underline{methyl}$-3H-$\underline{fluorene}$ (271). — A solution of unsymmetrical dimer

(270) (40mg, 0.11mmol) and $\underline{p}$-toluenesulphonic acid monohydrate (15mg,

0.08mmol) in $\left[^2H_6\right]$ acetone (50% in carbon tetrachloride) was left to

stand at 20°C in an nmr tube, and the reaction monitored by ^{1}H nmr

(Page 128). After 110h, the solution was diluted with carbon tetra-

chloride, washed with sodium hydroxide solution (2M; 2x10ml), dried

(MgSO$_4$) and evaporated. Preparative tlc on silica, eluting with light

petroleum (x2), followed by vacuum sublimation then gave a pure sample

of the $\underline{symmetrical\ dimer}$ (271) (4mg, 10%), a waxy crystalline solid,

m.p. 150-180°C.

Found: C, 89.71; H, 7.24 (ratio C/H = 12.39). C$_{28}$H$_{24}$ requires

C, 93.29; H, 6.71% (ratio C/H = 13.90).

ν_{max} (CCl$_4$) 2930 (s), 1622 (w), 1610 (w), 1465 (s), 1370 (m),
1320 (w), 1130 (w), 930 (w), 910 (w), 872 (s), 850 (s), 652 (s) cm^{-1}.

λ_{max} (EtOH) 325 (ε 2300, sh), 310 (4000, sh), 295 (7900), 286
(7100, sh), 273 (4600, sh), 245 (6200), 237 (7800), 231 nm (7300, sh).

δ_{1H} (CDCl$_3$; 250 MHz) 0.83 (6H, s, Me x2), 2.28 (2H, dd, $\underline{J}$, 4.5
and 1 Hz, H$_4$ and H$_{4'}$), 2.65 (2H, m, H$_3$ and H$_{3'}$), 5.89 (2H, br d,
$\underline{J}$, 7.5 Hz, H$_5$ and H$_{5'}$), 5.96 (2H, dd, $\underline{J}$, 10 and 4 Hz, H$_2$ and H$_{2'}$),
6.38 (2H, td, $\underline{J}$, 7.5 and 1 Hz, H$_6$ and H$_{6'}$), 6.52 (2H, s, H$_9$ and H$_{9'}$),
6.59 (2H, d, $\underline{J}$, 10 Hz, H$_1$ and H$_{1'}$), 6.97 (2H, td, $\underline{J}$, 7.5 and 1 Hz,
H$_6$ and H$_{6'}$), 7.15 (2H, dd, $\underline{J}$, 7.5 and 1 Hz, H$_8$ and H$_{8'}$). These
assignments were confirmed by decoupling and n.O.e. difference
experiments (Pages 125-8).

m/e Found: $\underline{M}^+$ = 360.1868. C$_{28}$H$_{24}$ requires $\underline{M}^+$, 360.1878.

3β,4β-(4,4a-Dihydro-4aβ-methyl-1H-fluoren-1α,4α-ylene)-1-
phenylsuccinimide (278). — A solution of 4a-methyl-4aH-fluorene (3)
(freshly prepared; 50mg, 0.28mmol) and N-phenylmaleimide (48mg, 0.28mmol)
in carbon tetrachloride (5ml) was heated at 50-55°C for 20h, then
evaporated and subjected to preparative tlc on silica, eluting (x4)
with a mixture of ether (10%), chloroform (20%) and light petroleum
(70%), to give a hydrocarbon fraction [15mg; (270) ∿ 60%, (3) ∿ 30%]
and the adduct (278) (17mg, 18%) as a semi-crystalline glass resistant
to sublimation.

ν_{max} (CHCl$_3$) 1615 (s), 1600 (w), 1496 (m), 1456 (w), 1380 (s),
1290 (w), 1170 (m) cm^{-1}.

δ_{1H} (CDCl$_3$; 250 MHz) 1.22 (3H, s, Me), 2.57 (1H, dd, $\underline{J}$, 8 and
2.5 Hz, H$_2$), 3.03 (1H, dd, $\underline{J}$, 8 and 4 Hz, H$_3$), 3.74 (1H, br d, $\underline{J}$, 6 Hz,
H$_{4'}$), 4.39 (1H, br t, $\underline{J}$, 5 Hz, H$_{1'}$), 6.45 (1H, ddd, $\underline{J}$, 8, 6 and 1.5 Hz,
H$_{2'}$), 6.66 (1H, ddd, $\underline{J}$, 8, 6 and 1.5 Hz. H$_{3'}$), 6.66 (1H, s, H$_{9'}$),
7.10-7.30 (2H, m) and 7.32-7.50 (2H, m) (aromatic protons).

m/e 353 (10%, M$^+$), 180 (100%, M$^+$– $\overline{\text{COCH=CHCONPh}}$), 165 (58%,

M$^+$– $\overline{\text{COCH=CHCONPh}}$ and $^\bullet$CH$_3$). Found: M$^+$, 353.1411. C$_{24}$H$_{19}$NO$_2$

requires M$^+$, 353.1416.

Reactions of 4aH-fluorenes with other dienophiles.

i) 4-Phenyl-1,2,$\cancel{\beta}$,4-triazoline-3,5-dione (PTAD): — A solution of

PTAD (20mg, 0.11mmol) in dichloromethane (5ml) was added dropwise to

a stirred solution of 4a-methyl-4aH-fluorene (3) (freshly prepared;

23mg, 0.13mmol) in dichloromethane (5ml) at 0°C to give a pale yellow

solution. After 0.2h, this was evaporated and subjected to column

chromatography on silica gel 'H', eluting with methanol (10% in ethanol),

to give crude 1,2-dihydro-1,2-(4,4a-dihydro-4aβ-methyl-1H-fluoren-1α,4α-

ylene)-4-phenyl-1,2,4-triazoline-3,5-dione (279) as a white semi-

crystalline solid (26mg, 57%) which rapidly deteriorated into a complex

mixture, even in dilute solution.

δ_{1H} (CDCl$_3$; 90 MHz) 1.27 (3H, s, Me), 5.56 (1H, dd, J, 4 and 3.5

Hz) and 5.77 (1H, dd, J, 4 and 3.5 Hz) (H$_1$, and H$_4$,), 6.75-7.10 (3H, m,

H$_2$,, H$_3$, and H$_9$,), 7.2-7.7 (~9H, m, aromatic protons).

When 4a,9-dimethyl-4aH-fluorene (222) (freshly prepared; 35mg,

0.18mmol) was similarly treated with PTAD (30mg, 0.17mmol) and the

product subjected to preparative tlc on silica gel, eluting (x4) with

progressively more polar mixtures of ethyl acetate and light petroleum,

one major fraction (24mg) was obtained; this showed an NH stretch (ir)

and other data consistent with structure (280):

δ_{1H} (CDCl$_3$; 90 MHz) 1.52 (3H, s, Me) 4.93 (1H, dd, J, 5.5 and

2 Hz) and 5.82 (1H, m) (H$_1$, and H$_4$,), 5.51 (1H, s) and 5.93 (1H, s)

(exo-CH$_2$), 6.6-7.0 (2H, m, H$_2$, and H$_3$,), 7.1-7.7 (~14H, m, aromatic

protons).

m/e 554 (3.8%, M⁺), 368 (7.6%, M⁺– ˙NNHCON(Ph)CO), 317 (10.3%,

M⁺– ˙CH=CHCH=CHNCON(Ph)CON), 227 (100%, ⁺CH=CHCH=CHNCON(Ph)CON),

177 (84%).

ii) N-Chlorosulphonylisocyanate (CSI): — CSI (freshly distilled;

33μl, 0.34mmol) was added to a solution of 4a-methyl-4aH-fluorene (3)

(freshly prepared; 62mg, 0.34mmol) in carbon tetrachloride (10ml)

at 20°C under nitrogen.   After 0.6h, a solution of sodium sulphite

(0.5g) and sodium hydrogen carbonate (0.5g) in water (5ml) was added,

stirred 1.5h, then the products were extracted into carbon tetrachloride,

dried (MgSO₄) and evaporated.   Nmr showed the resultant gum (56mg) to be a

mixture of hydrocarbons (3), (270) and (271) in an approximate molar

ratio of 2:1:3; preparative tlc gave a pure sample of (271) (15mg).

iii) Diiron nonacarbonyl: — Diiron nonacarbonyl (0.22g, 0.61mmol)

was added to a solution of 4a-methyl-4aH-fluorene (3) (freshly prepared;

0.10g, 0.56mmol) in dry de-gassed benzene under nitrogen, and the

mixture heated at 55°C for 4h.   Since tlc showed no reaction,

4-methoxybenzylideneacetone (0.10g, 0.56mmol) was added and the mixture

heated at 55°C a further 3h.   Column chromatography of the resultant

brown suspension gave only starting materials.

Reaction of 4a-methyl-4aH-fluorene (3) with acids.

i) Hydrobromic acid: — 4a-Methyl-4aH-fluorene (3) (freshly prepared;

98mg, 0.54mmol) in carbon tetrachloride (∿ 5ml) was added at once to a

solution of hydrobromic acid (45% in acetic acid; 1ml, 5.6mmol) in glacial

acetic acid (10ml), and the solution refluxed at 100-105°C for 0.6h.

The mixture was quenched in water, the products extracted into carbon

tetrachloride, washed with sodium hydroxide (2M; 4x10ml), dried (MgSO₄)

and evaporated to give a light brown oil (108mg).   Preparative tlc on

silica gel, eluting (x2) with light petroleum, gave a mixture (58mg,

59%) of 4-methyl and 1-methylfluorenes (281) and (282), in an approximate

ratio of 10:1 (Page 134).

ii) p-Toluenesulphonic acid: — A solution of 4a-methyl-4aH-fluorene (3) (freshly prepared; 96mg, 0.53mmol) and p-toluenesulphonic acid monohydrate (103mg, 0.54mmol) in dry benzene (30ml) was refluxed with azeotropic removal of water for 1h. Preparative tlc on silica gel, eluting (x2) with light petroleum gave the same mixture of fluorenes (281) and (282) (29mg, 30%), and a mixed fraction (14mg, 14%) containing dimer (271) and fluorenes (281) and (282) in an approximate molar ratio of 30:10:1.

Flash vacuum pyrolysis of 4a-methyl-4aH-fluorene (3).

— 4a-Methyl-4aH-fluorene (3) (freshly prepared; 83mg, 0.46mmol) was vaporised at 85-90°C and 0.02mmHg, and the vapour passed through a quartz tube at 650°C as described in Section 1. Preparative tlc of the pyrolysate (54mg, 65%) on silica gel, eluting (x2) with light petroleum, gave a mixture (27mg, 33%) of 9-methyl, 4-methyl and 1-methylfluorenes (239), (281) and (282), and 9,9'-bifluorenyl (284) (15mg, 20%) [needles from ethanol-benzene m.p. 246-247°C (lit.[156] 246°C)] . Preparative tlc of the oven residues (25mg, 30%) as above gave the symmetrical dimer (271) (5mg), the unsymmetrical dimer (270) (9mg), and 9,9'-bifluorenyl (284) (13mg). The fluorenes were identified by a comparison of nmr data (Page 137); data for 9,9'-bifluorenyl appear below:

δ_{1H} (CCl$_4$; 90 MHz) 4.80 (2H, s, H$_9$ and H$_{9'}$), 6.8-7.4 (12H, m, H$_{1-3}$, H$_{6-8}$, H$_{1'-3'}$ and H$_{6'-8'}$), 7.63 (4H, dd, J, 7 and 1.5 Hz, H$_4$, H$_5$, H$_{4'}$ and H$_{5'}$).

m/e 330 (13%, M$^+$), 165 (100%, ½M$^+$).

Photolysis of 4a-methyl-4aH-fluorene (3). —

Solutions of 4a-methyl-4aH-fluorene (3) in the specified solvents were photolysed at 254 nm to give the products summarised in Table 19.

Expt.	Solvent	Time	Very Approximate product ratios (crude nmr)				
		h	(285)	(286)	(239)	(270)	(3)
1	petrol$\underline{a}$	1	3	2	1	1	3
2	petrol$\underline{a}$	1.5	3	4	1	3	3
3	petrol$\underline{a}$	3.5	2	3	2	?	-
4	acetonitrile	1.3	3	-	2	2	2
5	acetonitrile	2.5	3	-	2	-	-
6	methanol	1.2	3	-	4	2	2

TABLE 19 $\underline{a}$ petrol = light petroleum (b.p. 40-60°C)

Preparative tlc on silica gel, eluting (x2) with light petroleum, gave the following isolated yields —

Experiment 1, from (3) (96mg): i) a mixed fraction (14mg) of (3), (285) and (239), ratio $\sim$ 6:2:1; ii) (285) (17mg); iii) (270) (9mg); iv) (286) (30mg).

Experiment 2, from (3) (108mg): i) a mixed fraction (15mg) of (285) and (239), ratio $\sim$ 2:1; ii) (285) (8mg); iii) (286) (41mg).

Experiment 3, from (3) (70mg): i) a mixed fraction (10mg) of (285), (239) and (270), ratio $\sim$ 6:4:1; ii) (286) (16mg).

Experiment 4, from (3) (92mg): i) a mixed fraction of (3) and (239) (18mg); ii) a mixed fraction of (285) and (239) (18mg), ratio $\sim$ 6:1; iii) (270) (9mg).

Experiment 6, from (3) (92mg): i) a mixed fraction of (285), (239) and (3) (16mg), ratio $\sim$ 1:6:4; ii) a mixed fraction of (285) and (239), ratio $\sim$ 1:1; iii) (270) (17mg).

Data for the new compounds appear below.

9-Methylcyclopenta[b]naphthalene (285). — Pale yellow, low melting crystals.

Found: C, 92.89; H, 6.70 (ratio C/H 13.86). $C_{14}H_{12}$ requires C, 93.29; H, 6.71 (ratio C/H 13.90).

ν_{max} (CCl$_4$) 2935 (m), 1382 (m), 950 (m), 922 (m), 878 (m), 672 (m) cm^{-1}.

λ_{max} (EtOH) 306 (ε 10000), 303 (8600, sh), 293 (11900), 281 (8800), 271 (6500, sh), 254 (29300), 245 (38000), 240 (37900), 232 nm (30400, sh).

δ_{1H} (CDCl$_3$; 250 MHz) 2.67 (3H, s, Me) 3.48 (2H, t, $\underline{J}$, 2 Hz, C$\underline{H}_2$), 6.64 (1H, dt, $\underline{J}$, 5.5 and 2 Hz, H$_2$), 6.98 (1H, dt, $\underline{J}$, 5.5 and 2 Hz, H$_3$), 7.3-7.5 (2H, m, H$_6$ and H$_7$), 7.68 (1H, s, H$_4$), 7.82-7.88 (1H, m, H$_5$), 7.98-8.05 (1H, m, H$_8$).

m/e 180 (100%, $\underline{M}^+$), 165 (98%, $\underline{M}^+$- $^{\cdot}$CH$_3$). Found: $\underline{M}^+$, 180.0938. $C_{14}H_{12}$ requires $\underline{M}^+$, 180.0939.

4,4a-Dihydro-4aβ-methyl-3α-(9-methyl-9H-fluoren-9-yl)-3H-fluorene (286). — Off-white crystals, m.p. 130-160°C, prepared for analysis by double sublimation (180°C/0.2mmHg, then 125°C/10^{-4}mmHg).

Found: C, 89.68; H, 6.55 (ratio C/H = 13.69). $C_{28}H_{24}$ requires C, 93.29; H, 6.71 (ratio C/H = 13.90).

λ_{max} (EtOH) 320 (ε 9400, sh), 304 (20700), 293 (16900), 281 (15800, sh), 276 (17400, sh), 269 (18800), 265 (18300, sh), 258 (16400, sh), 244 (14800), 235 (16000), 222 nm (18900, sh).

δ_{1H} (CDCl$_3$; 250 MHz) 0.75 (1H, t, $\underline{J}$, 12 Hz, H$_{4\alpha}$), 1.12 (3H, s, C$_{4a}$ Me), 1.61 (3H, s, C$_9$, Me), 1.88 (1H, ddd, $\underline{J}$, 12, 5 and 0.5 Hz, H$_{4\beta}$), 3.21 (1H, m, H$_3$), 5.91 (1H, br d, $\underline{J}$, 10 Hz, H$_2$), 6.49 (1H, dd, $\underline{J}$, 10 and 3 Hz, H$_1$), 6.95-7.45 (10H, m) and 7.58-7.68 (2H, m)(aromatic protons). These assignments were confirmed by decoupling experiments (Page 143).

δ_{13C} (CDCl$_3$; 62.9 MHz) 23.1, 24.6, 33.8, 43.5, 49.0, 53.2, 119.7, 119.9, 121.2, 121.3 (x2), 123.0, 123.7, 123.9, 124.4, 126.7, 127.1 (x3), 127.3, 130.8, 140.2, 140.4, 143.4, 150.4, 151.1, 153.0 (x2). Quaternary carbons underlined.

m/e 360 (1%, $\underline{M}^+$), 181 (100%, $\underline{M}^+$- $^{\cdot}C_{14}H_{13}$), 179 (24%, $\underline{M}^+$- $^{\cdot}C_{14}H_{11}$), 165 (5%, $^+C_{13}H_9$).

Reaction of 9-methylcyclopenta[b]naphthalene (285) with n-butyl-lithium. — n-Butyllithium (1.5M in hexane; 0.3ml, 0.45mmol) was added to a solution of compound (285) (23mg, 0.13mmol) in dry tetra-hydrofuran (2ml) and the purple mixture stirred 0.3h at 20°C. Water was added dropwise, the products extracted into ether, dried (MgSO$_4$), evaporated and subjected to preparative tlc to give a mixture of 9-methyl and 4-methylcyclopenta[b]naphthalenes (285) and (291) (isomer ratio ~ 2:1) (19mg, 83%). Data for compound (291) appear below.

δ_{1H} (CDCl$_3$; 250 MHz) inter alia 2.77 (3H, s, Me), 3.56 (2H, t, J, 2 Hz, CH$_2$), 6.62 (1H, dt, J, 5.5 and 2 Hz, H$_2$), 7.15 (1H, dt, J, 5.5 and 2.2 Hz, H$_3$), 7.3-7.5 (2H, m, H$_6$ and H$_7$), 7.73 (1H, s, H$_9$), 7.77-7.85 (1H, m, H$_8$), 8.0-8.08 (1H, br d, J, 7 Hz, H$_5$).

This mixture was recovered unchanged (9mg, 47%) after irradiation at 254nm for 1h in light petroleum. In another experiment, 9-methyl-1,3,4-triphenylcyclopenta[b]naphthalene (186) was treated with n-butyl-lithium in dry tetrahydrofuran as described above, but only starting material was recovered on quenching the purple solution.

Photolysis of 4a,9-dimethyl-4aH-fluorene (222).

— A solution of 4a,9-dimethyl-4aH-fluorene (222) (105mg, 0.54mmol) in light petroleum was irradiated at 254nm for 2h. Column chromato-graphy on silica gel, eluting with light petroleum, gave a mixture (45mg) of cyclopentanaphthalene (292), 9,9-dimethylfluorene (240) and

starting material (222) (ratio ∿ 8:1:2), which was separated by
preparative tlc on silica gel, eluting (x2) with light petroleum, to
give 4,9-dimethylcyclopenta[b]naphthalene (292) (27mg, 26%). A
sample was prepared for analysis by sublimation (100°C/0.2mmHg) to give
pale yellow waxy crystals, m.p. $109-119^{\circ}$C.

Found: C, 89.44; H, 7.01 (ratio C/H = 12.76). $C_{15}H_{14}$
requires C, 92.74; H, 7.26 (ratio C/H = 12.77).

ν_{max} (nujol) 1612 (w), 1020 (w), 950 (m), 918 (w), 750 (s),
733 (s), 670 (m) cm^{-1}.

λ_{max} (EtOH) 313 (ε 8200), 300 (9700), 289 (7100), 277 (4500, sh),
257 (28100, sh), 252 (32400), 248 (32200), 245 (31400), 238 (27500, sh),
234 nm (24400, sh).

δ_{1H} (CCl_4; 90 MHz) 2.57 (3H, s, C_9 Me), 2.68 (3H, s, C_4 Me),
3.38 (2H, t, $\underline{J}$, 2 Hz, $C\underline{H}_2$), 6.52 (1H, dt, $\underline{J}$, 5.5 and 2 Hz, H_2), 7.09
(1H, dt, $\underline{J}$, 5.5 and 2 Hz, H_3), 7.25-7.5 (2H, m, H_6 and H_7), 7.8-8.05
(2H, m, H_5 and H_8).

m/e 194 (84%, $\underline{M}^+$), 179 (100%, $\underline{M}^+- \, ^{\bullet}CH_3$).

Hydrogenation of 4,9-dimethylcyclopenta[b]naphthalene (292).
— A mixture of compounds (292) and (240) (20mg, ratio ∿ 1:2) in
methanol (10ml) was hydrogenated over a palladium-charcoal catalyst
(50mg) for 1h at 20°C. The mixture was filtered (celite) and evaporated,
then preparative tlc on silica, eluting (x2) with light petroleum, gave
a mixture (6mg) of 2,3-dihydro-4,9-dimethylcyclopenta[b]naphthalene
(293) and 9,9-dimethylfluorene (240). Data for compound (293) appear
below.

δ_{1H} ($CDCl_3$; 250 MHz) inter alia 2.12 (2H, quintet, $\underline{J}$, 7 Hz,
H_2 x2), 2.58 (6H, s, Me x2), 3.08 (4H, t, $\underline{J}$, 7 Hz, H_1 x2 and H_3 x2),
7.42-7.48 (2H, m, H_6 and H_7), 7.97-8.02 (2H, m, H_5 and H_8).

5) N.O.e. Difference Spectroscopy.

Repanduline (296) was purified by six recrystallisations from methanol and was dissolved in $CDCl_3$ containing TMS as internal standard. For some experiments, $[^2H_6]$ benzene was also added. A moderately concentrated solution (0.26M) was used in a high quality 5mm o.d. tube. On one occasion only, the sample was degassed using a repeated freeze-pump-thaw cycle, and then closed under nitrogen (suba-seal). Other samples were prepared as described in earlier sections.

Spectra were obtained at 250 MHz (^1H) and 62.9 MHz (^{13}C), without temperature regulation, using a Bruker WM250 spectrometer operating under ASPECT 2000 control. For most ^1H experiments a spectral width of 3 KHz was used with 8K data points (for convenience in data processing), resulting in an acquisition time of 1.36s and a digital resolution of 0.73 Hz per point. For the long range experiment, a spectral width of 4.5 KHz was used with 8K data points giving an acquisition time of 0.91s and a digital resolution of 1.1 Hz per point. Single phase detection was employed with phase cycling. The decoupler attenuation was set at 30L (HD mode); the actual decoupler power output was not calibrated.

N.O.e. difference experiments were run automatically using the method of Hall and Sanders.[169] This works by repetition of the basic sequence pre-irradiation (5s), delay (50ms), pulse and acquire one transient. When four transients had been so collected using one pre-irradiation frequency, the summed data were stored, the pre-irradiation frequency changed, and four transients collected using the new frequency. In this way the pre-irradiation frequency was cycled through all the required positions, always adding the four new transients to the data accumulated using the same pre-irradiation frequency on previous passes round the cycle. An off-resonance pre-irradiation frequency was

included to provide the control spectrum.   After N passes around the full cycle, each data file (corresponding to one particular pre-irradiation frequency) contained 4N transients; for large N, long term variations in temperature, field etc. affected each file identically. Typically, N was set to reach 100-500, but in the long range experiment a value of 2000 was used.

After the experiment, difference spectra were generated by subtracting the control file from each individual pre-irradiation file in turn.   Data were subtracted in the form of FID's, and the resulting difference spectra phased identically using constants derived for the control spectrum.   No line broadening was used.

The $^{13}C\{^1H\}$ specific decoupling experiments were run using low power (28H) single frequency irradiation during acquisition and high power (4H) noise irradiation during the relaxation delay (2s); the actual decoupler power output was not calibrated. In this way, some of the extra sensitivity due to the $^{13}C\{^1H\}$ n.O.e. was retained.   A spectral width of 15.15 KHz was used with 32K data points, giving an acquisition time of 1.08s and a digital resolution of 0.92 Hz per point. Quadrature detection was used with phase cycling.

REFERENCES

REFERENCES

1. T.L. Gilchrist, C.J. Moody and C.W. Rees, J. Chem. Soc., Perkin Trans.1, 1975, 1964.

2. P.N. Preston, Chem. Rev., 1974, 74, 279 and references therein.

3. T.L. Gilchrist, C.J. Moody and C.W. Rees, J. Chem. Soc., Perkin Trans.1, 1979, 1871.

4. T.L. Gilchrist, P.F. Gordon, D.F. Pipe and C.W. Rees, J. Chem. Soc., Perkin Trans.1, 1979, 2303.

5. T.L. Gilchrist, M.E. Peek and C.W. Rees, J. Chem Soc., Chem. Commun., 1975, 912.

6. T.L. Gilchrist, M.E. Peek and C.W. Rees, J. Chem. Soc., Chem. Commun., 1975, 914.

7. R.L. Ellsworth, D.F. Hinkley and E.F. Schoenewaldt, Fr. P. 2,014,324 (Chem. Abs., 1971, 74, 87,975).

8. V.J. Grenda, R.E. Jones, G. Gal and M. Sletzinger, J. Org. Chem., 1965, 30, 259.

9. E. Haruki, T. Inaike and E. Imoto, Bull. Chem. Soc. Japan, 1968, 41, 1361.

10. Merck and C., Inc., B.P. 988,784 (Chem. Abs., 1965, 63, 16,357).

11. W. Kirmse, Angew. Chem., 1959, 71, 537.

12. R.M. Moriarty and J.M. Kliegman, J. Amer. Chem. Soc., 1967, 89, 5959.

13. P.A.S. Smith and E. Leon, J. Amer. Chem. Soc., 1958, 80, 4647.

14. a) T.L. Gilchrist, C.J. Moody and C.W. Rees, J. Chem. Soc., Chem. Commun., 1976, 414;
    b) R.M. Harrison, J.D. Hobson and A.W. Midgley, J. Chem. Soc., Perkin Trans.1, 1976, 2403.

15. M. Franck-Neumann and C. Dietrich-Buchecker, Tetrahedron Lett., 1976, 2069.

16. H. Dürr and W. Schmidt, Justus Liebigs Ann. Chem., 1974, 1140.

17. D.F. Pipe, PhD. thesis, University of London, 1980.

18. P.G. Houghton, D.F. Pipe and C.W. Rees, J. Chem. Soc.,
    Chem. Commun., 1979, 771.

19. M. Casey, personal communication.

20. A.S. Kende and T.L. Bogard, Tetrahedron Lett., 1967, 3383.

21. C.F.H. Allen and E.W. Spanagel, J. Amer. Chem. Soc., 1933,
    55, 3773.

22. a) J. Mellor and C. Lam, J. Chem. Soc., Perkin Trans.1, 1975, 80;
    b) J.M. Mellor and P.A. Knott, J. Chem. Soc.(C), 1971, 670;
    c) J.M. Mellor and C. Lam, J. Chem. Soc., Perkin Trans.2, 1975, 412.

23. T.L. Gilchrist, C.W. Rees and D. Tuddenham, J. Chem. Soc.,
    Perkin Trans.1, 1981, 3221.

24. C.W. Rees, Pure and Appl. Chem., 1979, 51, 1243.

25. S.J. Foster, PhD. thesis, University of London, 1981.

26. T.L. Gilchrist, C.W. Rees and D. Tuddenham, J. Chem. Soc.,
    Perkin Trans.1, 1981, 3214.

27. R. McCague, personal communication.

28. T.L. Gilchrist, C.W. Rees, D. Tuddenham and D.J. Williams,
    J. Chem. Soc., Chem. Commun., 1980, 691.

29. T.L. Gilchrist, D. Tuddenham, R. McCague, C.J. Moody and C.W. Rees,
    J. Chem. Soc., Chem. Commun., 1981, 657.

30. Z. Lidert and C.W. Rees, J. Chem. Soc., Chem. Commun., 1982, 499.

31. H.C. Gibbard, personal communication.

32. J.J. Kulagowski, C.J. Moody and C.W. Rees, J. Chem. Soc.,
    Chem. Commun., 1982, 548.

33. W. Freudenberg, Heterocycl. Comp., 1952, 3, 298.

34. E. M. Burgess, R. Carithers and L. McCullagh, J. Amer. Chem. Soc.,
    1968, 90, 1923.

35. J.J. Kulagowski, personal communication.

36. K. Isomura, S. Kobayashi and H. Taniguchi, Tetrahedron Lett.,
    1968, 3499.

37. T.L. Gilchrist, C.W. Rees and C. Thomas, J. Chem. Soc.,
    Perkin Trans.1, 1975, 8.

38. T.L. Gilchrist, C.W. Rees and C. Thomas, J. Chem. Soc., Perkin Trans.1, 1975, 12.

39. C. Wentrup, A. Damerius and W. Reichen, J. Org. Chem., 1978, 43, 2037.

40. a) B. Halton, M. Kulig, M.A. Battiste, J. Perreten, D.M. Gibson and G.W. Griffen, J. Amer. Chem. Soc., 1971, 93, 2327.
    b) J. W. Wilson and K.L. Huhtanen, J. Chem. Soc., Chem. Commun., 1968, 454.

41. A. Padwa, Acc. Chem. Res., 1979, 12, 310 and references therein.

42. M.A. Battiste, B. Halton and R.H. Grubbs, J. Chem. Soc., Chem. Commun., 1967, 907.

43. T.L. Gilchrist, C.W. Rees and J.A.R. Rodrigues, J. Chem. Soc., Chem Commun., 1979, 627.

44. D.M.B. Hickey, C J. Moody and C.W. Rees, J. Chem. Soc., Chem. Commun., 1982, 3.

45. P.A. Lehmann and R.S. Berry, J. Amer. Chem. Soc., 1973, 95, 8614.

46. R.J. Sundberg and R.W. Heintzelman, J. Org. Chem., 1974, 39, 2546.

47. R.J. Sundberg, D.W. Gillespie and B.A. DeGraff, J. Amer. Chem. Soc., 1975, 97, 6193.

48. G. Smolinsky, J. Amer. Chem. Soc., 1960, 82, 4717.

49. C. Wentrupp and K. Wilczek, Helv. Chim. Acta., 1970, 53, 1459.

50. C. Wentrupp, Adv. Heterocycl. Chem., 1981, 28, 231.

51. E.T. McBee, G.W. Calundann and T. Hodgins, J. Org. Chem., 1966, 31, 4260.

52. M.F. Semmelhack, J.S. Foos and S. Katz, J. Amer. Chem. Soc., 1973, 95, 7325.

53. M.F. Semmelhack, H.N. Weller and J.S. Foos, J. Amer. Chem. Soc., 1977, 99, 292.

54. C. Batich, E. Heilbronner, E. Rommel, M.F. Semmelhack and J.S. Foos, J. Amer. Chem. Soc., 1974, 96, 7662.

55. a) H. Dürr and R. Sergio, Chem. Ber., 1974, 107, 2027.
    b) H. Dürr and R. Sergio, Tetrahedron Lett., 1972, 3479.

56.   H. Dürr, H. Kober, R. Sergio and V. Formacek, <u>Chem. Ber.</u>, 1974, <u>107</u>, 2037.

57.   H. Hemetsberger, I. Spria and W. Schönfelder, <u>J. Chem. Res. (S)</u>, 1977, 247.

58.   T.S. Cantrell and H. Shechter, <u>J. Amer. Chem. Soc.</u>, 1967, <u>89</u>, 5868.

59.   D.C. Sanders and H. Shechter, <u>J. Amer. Chem. Soc.</u>, 1973, <u>95</u>, 6858.

60.   T.A. Antkowiak, D.C. Sanders, G.B. Trimitsis, J.B. Press and H. Shechter, <u>J. Amer. Chem. Soc.</u>, 1972, <u>94</u>, 5366.

61.   T.J. Katz and P.J. Garrett, <u>J. Amer. Chem. Soc.</u>, 1964, <u>86</u>, 5194.

62.   E.E. Waali and N.J. Allison, <u>J. Org. Chem.</u>, 1979, <u>44</u>, 3266.

63.   R.S. Hosmane, V. Bakthavachalam and N.J. Leonard, <u>J. Amer. Chem. Soc.</u>, 1982, <u>104</u>, 235.

64.   H.S. Rzepa, personal communication.

65.   L.A. Cort and A. Mahesar, <u>J. Chem. Soc., Perkin Trans.1</u>, 1979, 2034.

66.   R.S. Atkinson, <u>J. Chem. Soc. (C)</u>, 1971, 3524.

67.   R.S. Atkinson, personal communication.

68.   J. Davey, B.R.T. Keene and G. Mannering, <u>J. Chem. Soc. (C)</u>, 1967, 120.

69.   D. Bergmann, R. Ikan and H. Weiler-Feilchenfeld, <u>Bull. Soc. Chim. France</u>, 1957, 290.

70.   E. Broun, M. Ragault and J. Touet, <u>Bull. Soc. Chim. France</u>, 1971, 2195.

71.   E. Broun, J. Touet and M. Ragault, <u>Bull. Soc. Chim. France</u>, 1972, 292.

72.   H.J.E. Lowenthal and S. Schatzmiller, <u>Tetrahedron Lett.</u>, 1972, 3115.

73.   a) K. Mori, M. Matsui and Y. Sumiki, <u>Agric. Biol. Chem. (Japan)</u>, 1963, <u>27</u>, 537.
      b) K. Mori, M. Matsui and Y. Sumiki, <u>Agric. Biol. Chem. (Japan)</u>, 1964, <u>28</u>, 243.
      c) T. Ogawa and M. Matsui, <u>Agric. Biol. Chem. (Japan)</u>, 1967, <u>31</u>, 1327.

74.   J. Davey and B.R.T. Keene, <u>Chem. and Ind.</u>, 1965, 849.

75.   G. Jaouen and A. Meyer, <u>Tetrahedron Lett.</u>, 1976, 3547.

76. E.J. Corey, M. Narisada, T.Hiraoka and R.A. Ellison,
    J. Amer. Chem. Soc., 1970, 92, 396.

77. W.S. Johnson, J.M. Cox, D.W. Graham and H.W. Whitlock, Jr.,
    J. Amer. Chem. Soc., 1967, 89, 4525.

78. B.P. Sen, A. Chatterjee, S.K. Gupta and B.K. Bhattacharyya,
    J. Indian Chem. Soc., 1958, 35, 751.

79. K.S. Ng, J.L. Roberts, P.S. Rutedge, M.A. Wilson and P.D. Woodgate,
    Australian J. Chem., 1976, 29, 2683.

80. a) F.E. Ziegler and M.E. Condon, Tetrahedron Lett., 1969, 2315.
    b) F.E. Ziegler and M.E. Condon, J. Org. Chem., 1971, 36, 3707.

81. a) J.W. Cook and C.L. Hewett, J. Chem. Soc., 1936, 62.
    b) H.O. House, V. Paragamian, R.S. Ro and D.J. Wluka, J. Amer.
    Chem Soc., 1960, 82, 1457.

82. S. Dev, J. Indian Chem. Soc., 1957, 34, 169.

83. H.O. House, V. Paragamian and D.J. Wluka, J. Amer. Chem. Soc.,
    1960, 82, 2561.

84. a) U.R. Ghatak and J. Chakravarty, Tetrahedron Lett., 1966, 2449.
    b) J. Chakravarty, R. Dasgupta, J.K. Ray and U.R. Ghatak,
    Proc. Indian Acad. Sci., 1977, 86A, 317.

85. U.R. Ghatak, J. Chakravarty and A.K. Banerjee, Tetrahedron Lett.,
    1965, 3145.

86. H.J.E. Lowenthal and H. Rosenthal, Tetrahedron Lett., 1968, 3693.

87. H.O. House, T.M. Bare and W.E. Hanners, J. Org. Chem., 1969,
    34, 2209.

88. P.N. Chakrabortty, R. Dasgupta, S.K. Dasgupta, S.R. Ghosh and
    U.R. Ghatak, Tetrahedron, 1972, 28, 4653.

89. H.T. Nagasawa and H.R. Gutmann, J. Medicin. Chem., 1966, 9, 719.

90. F.H. Howell and D.A.H. Taylor, J. Chem. Soc., 1957, 3011.

91. C.C. Irving and R.F. Williard, J. Org. Chem., 1962, 27, 2260.

92. R. Gruber, P. Cagnaint and D. Cagnaint, Tetrahedron, 1974, 30, 3605.

93. D.J. Field and D.W. Jones, J. Chem. Soc., Perkin Trans.1, 1980, 1909.

94. K. Alder and H.F. Rickert, Chem Ber., 1938, 71, 379.

95. E. Bergmann and F. Bergmann, J. Amer. Chem. Soc., 1938, 60, 1805.

96. W. Ziegenbein, Chem. Ber., 1955, 88, 1787.

97. W.J. Bailey and E.J. Cummins, J. Amer. Chem. Soc., 1954, 76, 1940.

98. E.T. McBee, W.R. Dively and J.E. Burch, J. Amer. Chem. Soc., 1955, 77, 385.

99. N.C. Deno, J. Amer. Chem. Soc., 1950, 72, 4057.

100. L. Horner, Angew. Chem., 1949, 61, 442.

101. a) H.O. House, F.J. Sauter, W.G. Kenyon and J.J. Riehl, J. Org. Chem., 1968, 33, 957.
    b) H.O. House, J.K. Larsen and H.C. Muller, J. Org. Chem., 1968, 33, 961.
    c) H.O. House, C.B. Hudson and E.J. Rachah, J. Org. Chem., 1972, 37, 989.
    d) H.O. House, D.G. Meillo and F.J. Sauter, J. Org. Chem., 1973, 38, 741.

102. R. Bergamasco and Q.N. Porter, Austral. J. Chem., 1977, 30, 1061.

103. F. Bergmann and A. Wiezmann, J. Org. Chem., 1944, 9, 352.

104. a) D. Binder and C.R. Noe, Monatsh., 1976, 107, 1145.
    b) D. Binder and C.R. Noe, Monatsh., 1977, 108, 839.

105. V. Piskov, J. Org. Chem. U.S.S.R., 1967, 3, 1265.
    (translated from V. Piskov, Zh. Org. Khim., 1967, 3, 1304.)

106. a) B.K. Battacharyya, A.K. Bose, A. Chatterjee and B.P. Sen, J. Indian Chem. Soc., 1964, 41, 479.
    b) J. Roy, J. Indian Chem. Soc., 1967, 44, 91.
    c) K.D. Gupta, J. Indian Chem. Soc., 1969, 46, 415.

107. R.G. Harvey, P.P. Fu and P.W. Rabideau, J. Org. Chem., 1976, 41, 2706.

108. M. Ohta and L. Ohmori, Chem. Pharm. Bull. (Japan), 1957, 5, 91.

109. A. Tahara, Chem. Pharm. Bull. (Japan), 1961, 9, 252.

110. A. Tahara and Y. Ohtsuka, J. Chem. Soc., Perkin Trans.1, 1972, 320.

111. A. Tahara, Y. Ohtsuka, T. Nakata and S. Takada, Ger. Offen. 2,132,315 (Chem. Abstracts, 1972, 76, 85599).

112. R. W. Roeske, D.B. Bright, R.L. Johnson, W.J. DeJarlais, R.W. Bush and H.R. Snyder, J. Amer. Chem. Soc., 1960, 82, 3128.

113. H.W. Moore and H.R. Snyder, J. Org. Chem., 1963, 28, 535.

114. H.W. Moore and H.R. Snyder, J. Org. Chem., 1963, 28, 297.

115. H.W. Moore and H.R. Snyder, J. Org. Chem., 1964, 29, 97.

116. B.E. Galbraith and H.R. Snyder, J. Org. Chem., 1967, 32, 380.

117. I thank Prof. D. Rogers and M.A.A.F.C.T. Carrondo for this result.

118. a) R.U. Lemieux and E. von Rudloff, Can. J. Chem., 1955, 33, 1701.
      b) R.U. Lemieux and E. von Rudloff, Can. J. Chem., 1955, 33, 1710.
      c) E. von Rudloff, Can. J. Chem., 1956, 34, 1413.

119. I thank J.J. Kulagowski for this result.

120. C.D. Campbell and C.W. Rees, J. Chem.Soc. (C), 1969, 742.

121. J.C. Charlton and E.D. Hughes, J. Chem. Soc., 1954, 2939.

122. D.E. Pearson and F. Greer, J. Amer. Chem. Soc., 1955, 77, 1294.

123. H.W. Thompson and B.S. Huegi, J. Chem. Soc., Perkin Trans.1,
      1976, 1603.

124. C.F. Koelsch, H. Hochmann and C.D. LeClaire, J. Amer. Chem. Soc.,
      1943, 65, 59.

125. J.V. Braun and G. Kirschbaum, Chem. Ber., 1913, 46, 3041.

126. J.E. Horan and R.W. Schiessler, Org. Synth., 1973, Coll. Vol 5, 647.

127. J. Sam and T.C. Snapp, J. Pharm, Sci., 1965, 54, 756.

128. a) W.K. Anderson and T. Veysoglu, J. Org. Chem., 1973, 38, 2267.
      b) M. Imuta and H. Ziffer, J. Org. Chem., 1979, 44, 1351.

129. W.J. Pope and J. Read, J. Chem. Soc., 1912, 760.

130. D.W. Jones, personal communication.

131. H.C. Brown and C.P. Garg, J. Amer. Chem. Soc., 1961, 83, 2951.

132. S. Hünig, E. Lücke and W. Brenninger, Org. Synth., 1961,
      Coll. Vol. 5, 808.

133. W.A. White and H. Weingarten, J. Org. Chem., 1967, 32, 213.

134. E.P. Blanchard, Jr., J. Org. Chem., 1963, 28, 1397.

135. D.W. Jones and G. Kneen, J. Chem. Soc., Perkin Trans.1, 1977, 1313.

136. L.I. Smith and J.A. Sprung, J. Amer. Chem. Soc., 1943, 65, 1276.

137. L. Willimann and H. Schinz, Helv. Chim. Acta., 1949, 32, 2151.

138. M. Kühn, J. Prakt. Chem., 1940, 156, 103.

139. R.J. Ferrier and J.M. Tedder, J. Chem. Soc., 1957, 1435.

140. M.F. Ansell and S.S. Brown, J. Chem. Soc., 1958, 2955.

141. L.F. Fieser and M.A. Peters, J. Amer. Chem. Soc., 1932, 54, 4347.

142. H.C. Brown and W. Korytnyck, J. Amer. Chem. Soc., 1960, 82, 3866.

143. a) T. Suga and T. Matsuura, Bull. Chem. Soc. Jap., 1966, 39, 326.
     b) G.R. Robertson, Org. Synth., 1932, Coll. Vol. 1, 138.

144. V.I. Stenberg and R.J. Perkins, J. Org. Chem., 1963, 28, 323.

145. D. Tuddenham, personal communication.

146. a) D.H.R. Barton, D.J. Lester and S.V. Ley, J. Chem. Soc., Chem.
     Commun., 1978, 130.
     b) D.H.R. Barton, D.J. Lester and S.V. Ley, J. Chem. Soc., Perkin
     Trans.1, 1980, 2209.

147. S.V. Ley, personal communication.

148. a) D.H.R. Barton, J.W. Morzycki, W.B. Motherwell and S.V. Ley,
     J. Chem. Soc., Chem. Commun., 1981, 1044.
     b) D.H.R. Barton, C.R.A. Godfrey, J.W. Morzycki, W.B. Motherwell
     and S.V. Ley, J. Chem. Soc., Perkin Trans.1, 1982, 1947.

149. K.E. Wilson, R.T. Seidner and S. Masamune, J. Chem. Soc., Chem.
     Commun., 1970, 213.

150. S. Krishnamurthy and H.C. Brown, J. Org. Chem., 1977, 42, 1197.

151. E. Piers and R.J. Keziere, Can. J. Chem., 1969, 47, 137.

152. V. Calò and L. Lopez, J. Chem. Soc., Chem. Commun., 1975, 212.

153. H. Günther, "NMR Spectroscopy", John Wiley and Sons, Chichester,
     1980, pp 371-373.

154. A. Mathieu, Bull. Soc. Chim. Fr., 1971, 1533.

155. W. Carruthers and D. Whitmarsh, J. Chem. Soc., Perkin Trans.1,
     1973, 1511.

156. C. Graebe and H. Stindt, Justus Liebigs Ann. Chem., 1896, 291, 6.

157. S.S. Hixon, P.S. Mariano and H.E. Zimmerman, Chem. Rev., 1973,
     73, 531.

158. G. Nechvatal and D.A. Widdowson, J. Chem. Soc., Chem. Commun., 1982, 467.

159. C.J. Moody, C.W. Rees and S.C. Tsoi, J. Chem. Soc., Chem. Commun., 1981, 927.

160. S.C. Tsoi, Ph.D. thesis, University of London, 1982.

161. S.V. Attwood, A.G.M. Barrett and J.C. Florent, J. Chem. Soc., Chem. Commun., 1981, 556.

162. D.M.B. Hickey, C.J. Moody and C.W. Rees, J. Chem. Soc., Chem. Commun., 1982, 4.

163. S.V. Ley and M. Mahon, Tetrahedron Lett., 1981, 3909.

164. S.V. Ley and M. Mahon, Tetrahedron Lett., 1981, 4747.

165. S.V. Ley, N.S. Simpkins and A.J. Whittle, J. Chem. Soc., Chem. Commun., 1981, 1001.

166. S.V. Ley, D. Neuhaus, N.S. Simpkins and A.J. Whittle, J. Chem. Soc., Perkin Trans.1, 1982, 2157.

167. S.V. Ley, D. Neuhaus and D.J. Williams, Tetrahedron Lett., 1982, 1207.

168. J.H. Noggle and R.E. Schirmer, "The Nuclear Overhauser Effect", Academic Press, New York, 1971.

169. L.D. Hall and J.K.M. Sanders, J. Amer. Chem. Soc., 1980, 102, 5703.

170. I thank Dr. J.K.M. Sanders for this example.

171. a) J.D. Glickson, S.L. Gordon, T.P. Pitner, D.G. Agresti and R. Walter, Biochemistry, 1976, 15, 1521.

    b) M.P. Williamson and D.H. Williams, J. Chem. Soc., Chem. Commun., 1981, 165.

172. D. Neuhaus, H.S. Rzepa, R.N. Sheppard and I.R.C. Bick, Tetrahedron Lett., 1981, 2933.

173. J. Harley-Mason, A.S. Howard, W.I. Taylor, M.J. Vernengo, I.R.C. Bick and P.S. Clezy, J. Chem. Soc. (C), 1967, 1948

174. I.R.C. Bick, J.H. Bowie, J. Harley-Mason and D.H. Williams, J. Chem. Soc. (C), 1967, 1951.

175. a) "Aspect 2000 Software Manual 1981", Bruker Spectrospin, Part 6, p.24.

b) J.K.M. Sanders and J.D. Mersh, in preparation.

176. Y. Fujimoto, H. Tsunoda, J. Uzawa and T. Tatsuno, J. Chem. Soc., Chem. Commun., 1982, 83 and references therein.

177. P.E. Hansen, Progress in N.M.R. Spectroscopy, 1981, 14, 175 and references therein.

178. A.J. Marsaioli, E.M. Ruveda and F. de A.M. Reis, Phytochemistry, 1978, 17, 1655.

179. K. Aoki and J. Harley-Mason, J. Chem. Soc. (C), 1967, 1957.

180. J. Guilhem and I.R.C. Bick, J. Chem. Soc., Chem. Commun., 1981, 1007.

181. J. Feeney and P. Partington, J. Chem. Soc., Chem. Commun., 1973, 611.

182. I thank S.V. Attwood for a kind gift of this material.

183. H.D.W. Hill and B.L Tomlinson, J. Chem. Phys, 1973, 59, 1775.

184. I thank J.J. Kulagowski for kindly providing a sample of this material.

185. H.J. Reich, J.M. Renga and I.L. Reich, J. Amer. Chem. Soc., 1975, 97, 5434.

186. G. Ayrey, D. Barnard and D.T. Wooldridge, J. Chem. Soc., 1962, 2087.

187. J.G. Sharefkin and H. Saltzman, Org. Synth., 1973, Coll. Vol.5, 665.

188. M.P. Cava, A.A. Deana, K. Mulh and M.J. Mitchell, Org. Synth., 1973, Coll. Vol.5, 944.

189. R.C. Cookson, S.S. Gupta, I.D.R. Stevens and C.T. Watts, Org. Synth., 1971, 51, 121.

190. R.G. Jones, H. Gilman, Org. Reactions, 1951, 6, 353.

191. D.J. Anderson, D.C. Horwell, E. Stanton, T.L. Gilchrist and C.W. Rees, J. Chem. Soc., Perkin Trans.1, 1972, 1317.