SYNTHESIS OF NOVEL ORGANIC CONDUCTORS AND PHYSICAL AND CHEMICAL INVESTIGATION OF SOME CYCLIC SYSTEMS

by

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SUMMARY

Different aromatic systems have been synthesised with the aim of generating new conducting organic molecules. These molecules either incorporate heterocyclic atoms, sulphur or selenium, or are based on a donought shaped system. Both systems depend on extensive delocalisation to facilitate, with or without d- orbital enhancement, the electron movement.

To investigate the alpha effect the synthesis of an oxetane was attempted using various routes and strategies. The initial Diels- Alder reactions led to various attempts to synthesise the key intermediate, 7,7-dimethylnorbornadiene.

Artemisinin is an antimalarial drug, effective against *Plasmodium falciparum,* that chemically combats the the parasite in a different mode from traditional drugs. The synthesis of simple analogues was investigated to show that the activity was attributed to the peroxide bridge and that other functionalities present served to enhance this property.

As a result of NMR studies on various Schiff's Base systems it was shown that the formation of a molecular complex, as reported by the authors, was incorrect and a Schiff's Base reaction had occurred between the solute and acetone.

The influence of electron withdrawing substituents on the chemical shift of 4- substituted camphors has been investigated and the results reported.

Acknowledgements

Firstly, I wish to thank Dr. Morris for his support and enthusiasm during this period of research. Thanks also to Mum and Ann Marie, for putting up with me the past three years, and to the other internees: Gary, Greg, Dr. Koh and all in my year.

Finally I would like to thank the NMR, IR, Mass Spec. and Micro staff for their patience and Mrs June Anthony for typing the thesis. I would also like to thank SERC for funding the research.

INTRODUCTION

The possibility that organic solids might exhibit electrical conductivity, comparable to that of metals, was suggested over eighty years ago by McCoy and Moore who concluded "that it is possible to prepare composite metallic substances from non-metal constitutional elements."[1] Presently, the vast majority of organic crystals are electrical insulators at room temperature with a specific conductivity, σ_{RT}, of 10^{-9} - 10^{-14} Ω^{-1} cm^{-1}. A few organic systems are semiconductors, $\sigma_{RT} \approx 10^{-8}$ - 10^{-1} Ω^{-1} cm^{-1} including certain doped organic dyes. However, new organic materials with superior electrical properties have been synthesised recently and this growing number of organic materials are metallic in nature, $\sigma_{RT} \approx 10^{0}$ - 10^{2} Ω^{-1} cm^{-1}. Although metallic in nature, these materials have a low conductivity compared to metals such as copper, $\sigma_{RT} \simeq 10^{6}$ Ω^{-1} cm^{-1}. However, while some organic metals become superconducting *i.e.* absence of electrical resistance, at low temperatures, copper never does.

The organic metals fall into three classes:[2]

1) Polymeric Hydrocarbons
2) Charge Transfer Complexes
3) Graphite and its Intercalation Compounds

This introduction will consider only charge transfer complexes though with mention, where relevant, of the importance of the other classes indicated above, especially polymeric hydrocarbons, which have similar electrical properties to charge transfer complexes. In the conducting state both classes are ionic, electrical

conductivity is anisotropic (*i.e.* conductivity varies markedly along different crystal axes) with quasi one-dimensional properties.

Charge Transfer Complexes[3]

There are three classes of highly conducting organic charge transfer solids, classified according to the dependence of their conductivity with temperature[4,5] (Fig. 1).

Temperature-dependence of conductivity for some highly-conducting organic solids.

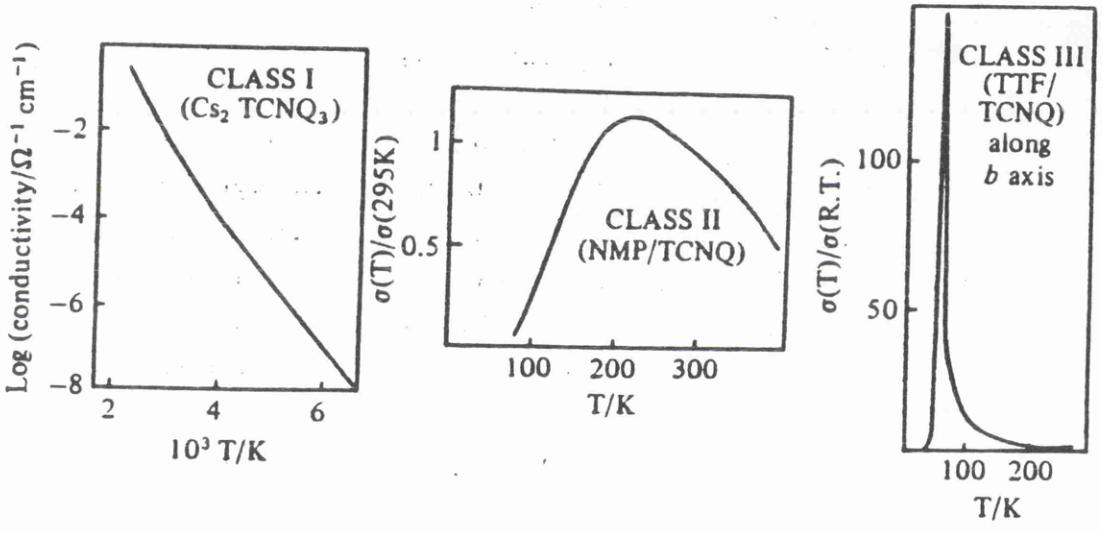


Figure 1

These categories can be indicated as follows:

1) Conductivity increases with temperature.

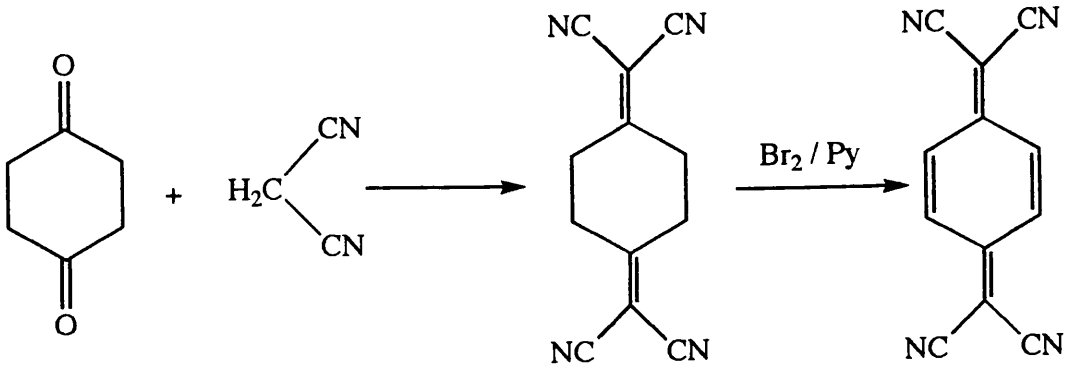
2) Conductivity of the organic metal gradually increases with temperature passing through a broad maximum, at low temperatures, then decreasing as room temperature is approached.

3) Organic metals whose conductivity increases as the temperature is reduced, reaching a sharp maximum at very low temperatures, then rapidly declining at temperatures below which maximum conductivity occurs.

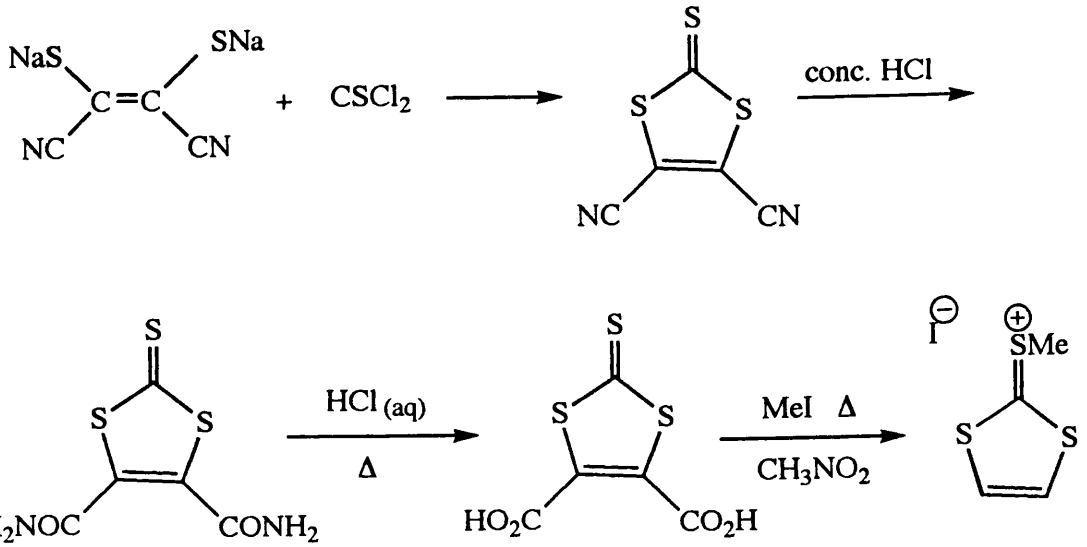
A stable charge transfer complex is formed by the partial transfer of an electron from a π-donor molecule (high HOMO energy) to a π^*-acceptor molecule (low LUMO energy) to form an ionic crystal in which either the cation or the anion (or both) are chemical groups of some complexity. Familiar donors include: alkali metals (often used in graphite intercalation compounds), amines, electron rich alkenes, heterocycles and aromatic molecules. Familiar acceptors include: halogen atoms, quinones, electron deficient alkenes, heterocycles and aromatic molecules.

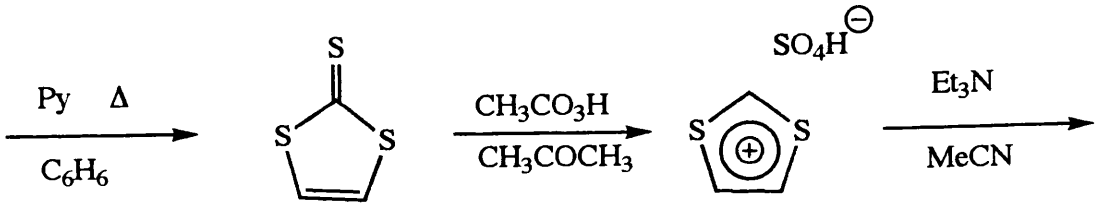
The earliest organic molecules which conducted electricity were based on tetracyano *para* quinodimethane (TCNQ see Fig. 2). Research into organic materials that conducted electricity received a dramatic impetus in 1972 when the powerful π-acceptor molecule, TCNQ, (discovered in 1960)[6] and tetrathiafulvalene, (TTF see Fig. 2), a π-donor molecule (discovered in 1970),[7,8] were paired to form the π-donor/acceptor molecule complex TTF-TCNQ.[9] The Cowan and Ferraris group discovered the metallic conductivity of TTF-TCQ crystals, with a conductivity value

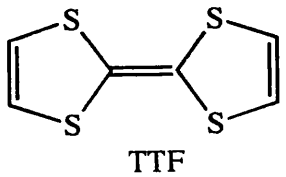
TCNQ SYNTHESIS



TTF







TTF

tetrathiafulvalene

Figure 2

σ_{RT} in the region of 500 Ω^{-1} cm^{-1}.

Since this discovery, a plethora of charge-transfer complexes has been prepared using TTF, TCNQ and their analogues, as well as other molecules and ions (Fig. 3).

Electrical Conductivity of Crystals (Fig. 4)

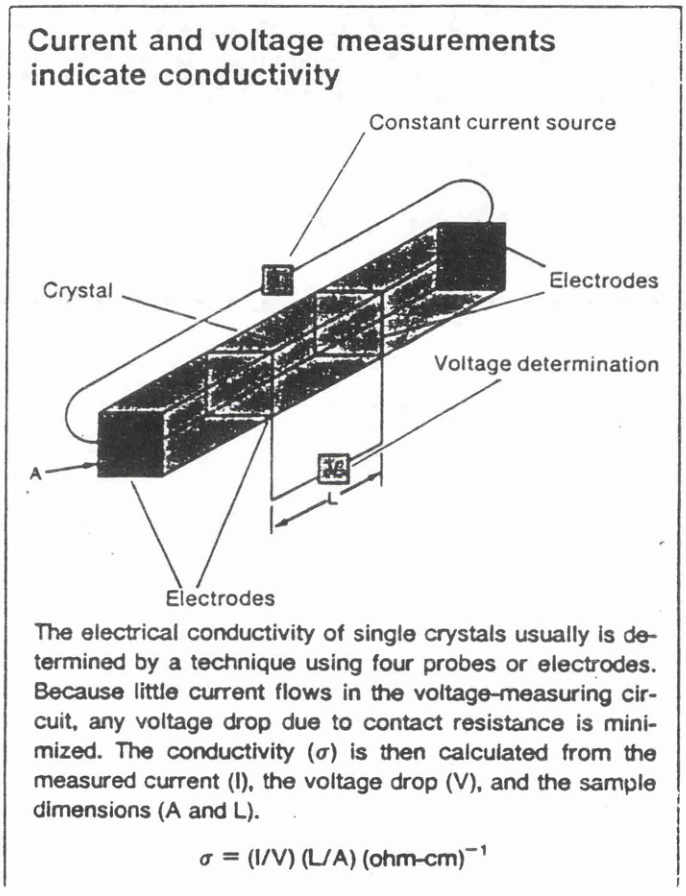
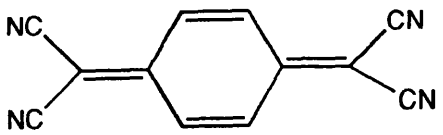


Figure 4

As previously stated, partial charge transfer is essential for organic conductivity as complete charge transfer would result in a fully ionic Mott-Hubbard insulator, in which both bands would be non-conducting *e.g.* HMTSF-$TCNQF_4$.

Molecules Involved In Charge Transfer Complexes

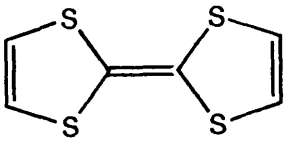
Acceptors (low LUMO, π^*)



TCNQ

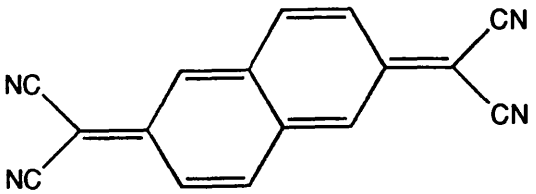
tetracyano- p- quinodimethane

Donors (high HOMO, π)



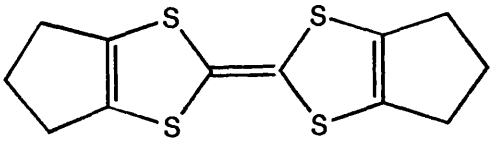
TTF

tetrathiafulvalene



TNAP

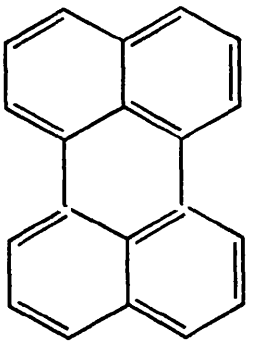
tetracyano- 2, 6- naphtho- quinodimethane



HMTTF

hexamethylenetetrathiafulvaene

PF_6^-



Perylene

Compound	Charge Transfer	σ_{RT} (Ω^{-1} cm $^{-1}$)	σ_{MAX} (Ω^{-1} cm $^{-1}$)	T_{max} (K)
TTF - TCNQ	0.59e	500	2×10^4	59
HMTTF - TCNQ	0.72e	500	2×10^3	75
(Perylene)$_2$ (PF_6)$_{1.1}$ *	0.55e	900	1×10^3	200

* only perylene participates in electrical conductivity

Figure 3

The basis for the electrical properties of TTF-TCNQ and other organic metals lies in the crystalline material, where donor and acceptor molecules form segregated stacks[11] (Fig. 5).

D = donor A = acceptor

D	A	D	A		D	A	D	A	
A	D	A	D		D	A	D	A	
D	A	D	A		D	A	D	A	
A	D	A	D		D	A	D	A	
D	A	D	A		D	A	D	A	

Mixed donor-acceptor stacks (heterosoric) (insulator)

Segregated donor & acceptor stacks (homosoric) (conductor)

Figure 5

Other stacking modes are also possible[12] though, without any obvious conduction bands, they are found to be insulators (Fig. 6).

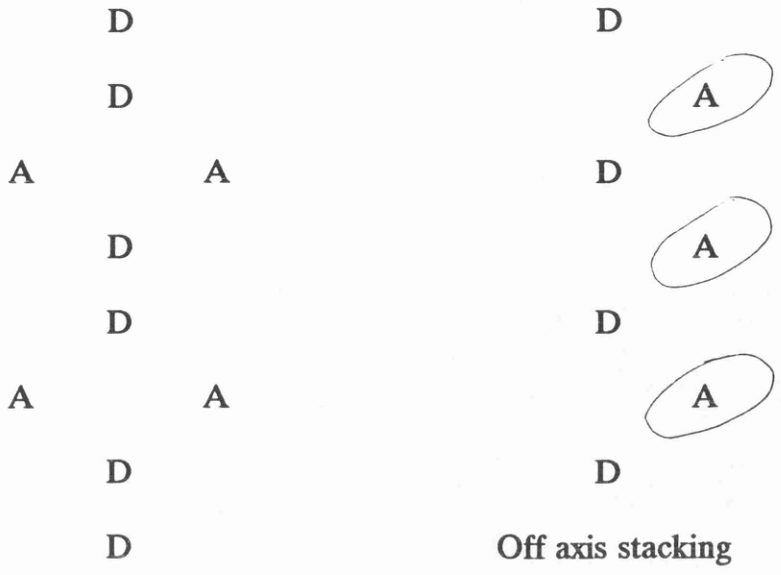


Figure 6

One example of homosoric stacking is TTF-TCNQ (Fig. 7).

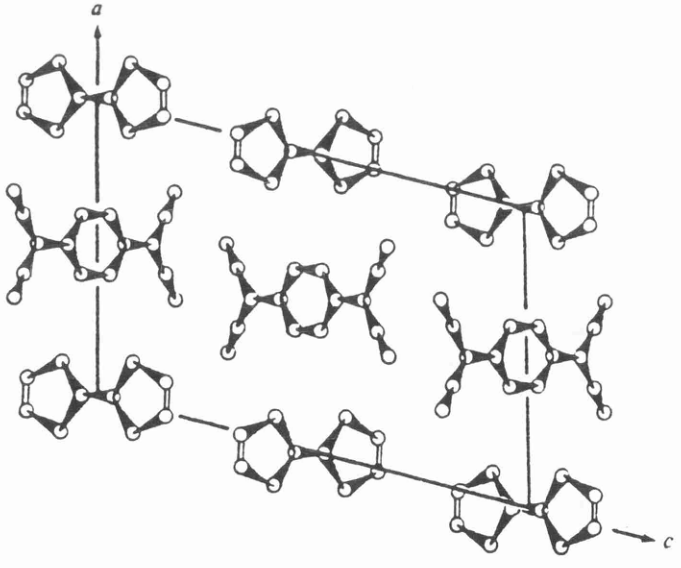
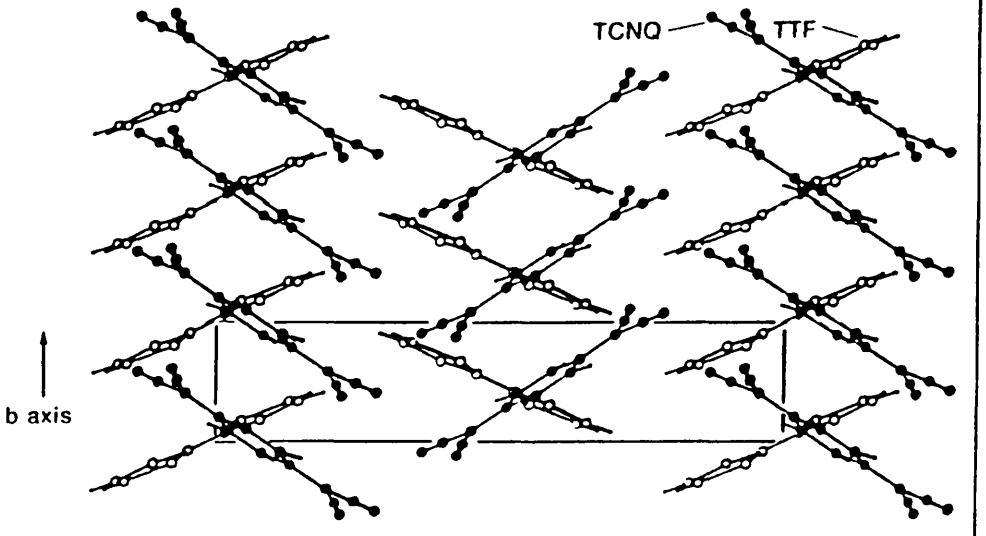


Figure 7



In the crystal structure of TTF-TCNQ, atoms represented by filled circles are in front of those represented by open circles. The TCNQ molecules (filled circles) are in one stack; the TTFs are behind them in a separate stack. The molecular planes are tipped with respect to the stacking direction (vertical or b axis). The tilt of the TCNQ molecular plane with respect to the b axis is 34.0° and in the opposite direction to the tilt of the TTF molecular plane (24.5°). The interplanar stacking distances are 3.17 Å for TCNQ and 3.47 Å for TTF. The direction of high electrical conductivity is along the b axis

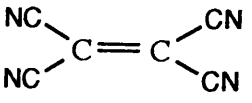
Figure 8

The direction of high conductivity in Figure 8 is along the b axis.

The majority of crystal structures in charge-transfer complexes between π-electron donors and acceptors are composed of heterosoric stacks as would be expected from electrostatic considerations. There are however two important interactions which favour homosoric formation:[5] i) donor-acceptor interaction between neutral D and $D^{\oplus}$ or neutral A and $A^{\ominus}$; ii) intermolecular attraction between the donor cation and acceptor anion, which favours edge contact rather than

face to face contact of the ions. In TCNQ the negative charges associated with the molecule are situated upon the electron withdrawing dicyanomethylene groups, $=C(CN)_2$, at the periphery of the molecule, thereby minimising any repulsion.

An example of the importance of such a charge separation is shown with the acceptor TCNE (tetracyanoethene). TCNE (Fig. 9) has a high electron affinity,



TCNE

tetracyanoethene

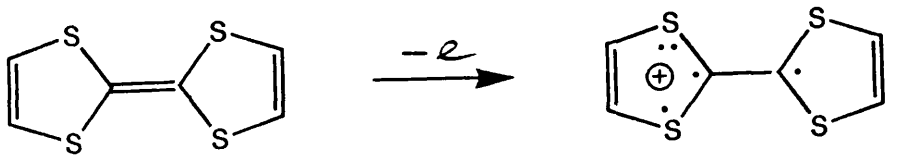
Figure 9

greater than TCNQ (2.84 eV, compared with 2.89 eV for TCNE), though it does not form conducting compounds. The comparatively small size of TCNE leads to high repulsion energies if a second electron is added, thereby disfavouring electric conduction.[13]

J.H. Perlstein proposed[14] that for one-dimensional stack conduction the generation of new aromatic sextets by one electron reduction or oxidation and their subsequent migration is an important factor (Fig. 10).

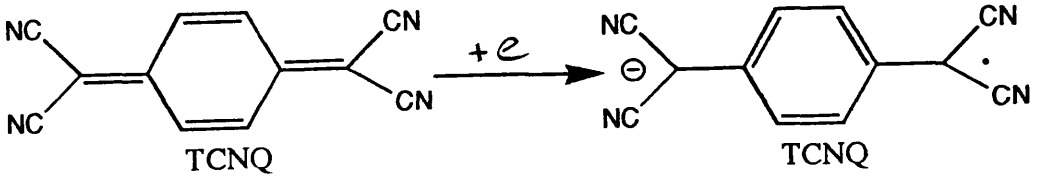
New aromatic sextets do not guarantee conductivity as exemplified with Weitz type radical donors.[15] This is due to inappropriate stacking arrangement causing steric repulsion and the reduction of overlap between molecules.

There are other equally important criteria to be met if an organic compound is to function as an organic metal:[2,10,16]



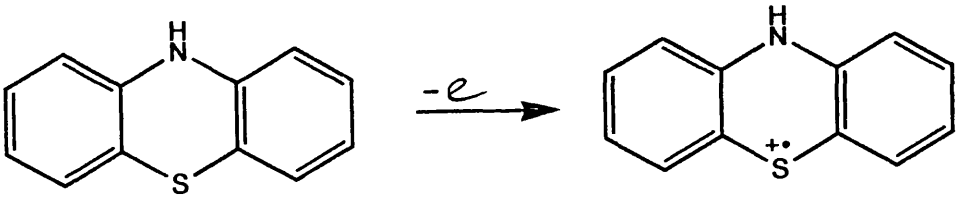
neutral donor radical cation

1 new aromatic sextet $500\ \Omega^{-1}\ cm^{-1}$ with TCNQ



TCNQ TCNQ

1 new aromatic sextet



0 new aromatic sextets $1.6 \times 10^{-7}\ \Omega^{-1}\ cm^{-1}$ with TCNQ

Figure 10

1. **Stable open-shell (free-radical) species in order to form a partially filled band.**
2. **Planar molecules with delocalised π molecular orbitals so that effective overlap of HOMO and/or LUMO can occur.**
3. **Inhomogeneous charge and spin distribution to reduce the repulsion when the charged molecules are stacked.**
4. **Segregated stacks of radical species; regardless of charge transfer a mixed stack will always have a completely filled band.**

5. No periodic distortions which inhibit electron movement between molecules *i.e.* intramolecular stack distance should be of a constant value.

6. Little or no disorder to reduce any local electrical potentials which inhibit electron movement between molecules.

7 Symmetrical molecular components of similar size (strengthens the crystal lattice).

8. Relatively strong interchain coupling to suppress phase transitions.

9. The ionisation potential/electron affinity values for the pair should favour incomplete charge transfer.

With TTF-TCNQ the above requirements are met. The interplanar distances for TCNQ is 3.17 Å and 3.47 Å for TTF, approximately sum of Van der Waals' radii, and so there is effective overlap. Nearest non-stacking neighbours are separated by 10-15 Å. With TCNQ there is a slipped stack system (Fig. 11) with ring over bond overlap along the stack (Fig. 12) (also true for TTF).

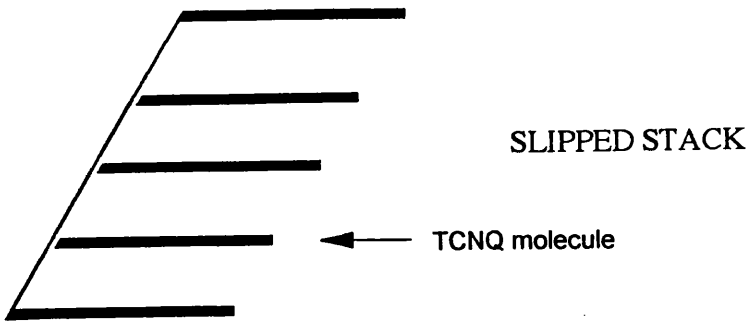


Figure 11

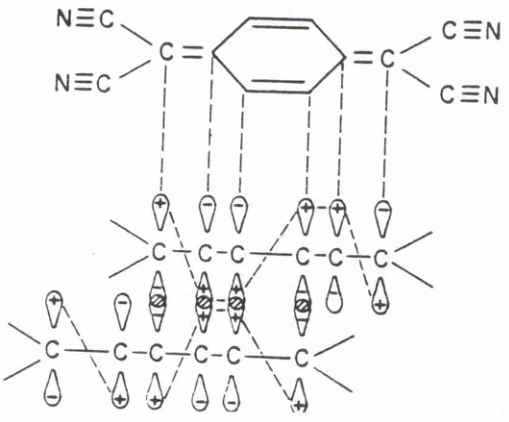
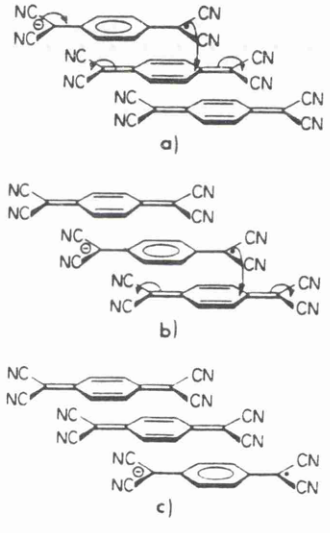


Figure 12

Electrical conduction is then possible, perhaps as Perlstein proposed, where migration of aromaticity accounts for conductivity (Fig. 13).



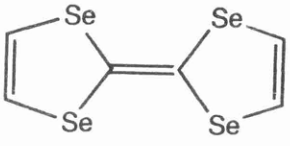
Stacking arrangement for mixed-valence TCNQ ions: a) $TCNQ^{\cdot}$ with aromatic sextet transfers charge to neutral TCNQ with no aromaticity resulting in b) and then again in c). Aromaticity migrates down the TCNQ stack along with the unpaired electron.

Figure 13

One method of satisfying condition 8 (p.10) is to enhance the degree of intermolecular orbital interaction. The introduction of selenium or tellurium, with their greater spatial orbital occupancy, rather than sulphur leads to more extensive

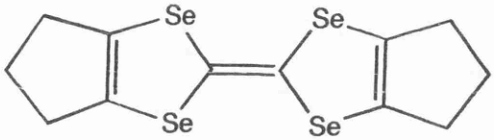
interactions of molecular orbitals along the stack and results in a greater band width (*i.e.* a wider range of allowed energies). This leads to a greater stability of the metallic state compared to the sulphur counterparts and the donor stack dominates the conduction process due to the presence of selenium d-orbitals. Examples of selenium based donors in charge transfer complexes are shown in Figure 14.

Selenium Based Donors



TSF

tetraselenofulvalene



HMTSF

hexamethylenetetraselenafulvalene

Compound	Charge Transfer	σ_{RT} (Ω^{-1} cm^{-1})	σ_{MAX} (Ω^{-1} cm^{-1})	T_{max} (K)
TSF - TCNQ	0.63e	800	1×10^4	40
TTF - TCNQ	0.59e	500	2×10^4	59
HMTSF - TCNQ	0.74e	2000	7×10^3	32
HMTTF - TCNQ	0.72e	500	2×10^3	75

Figure 14

In graph 3, Figure 1, it is noticeable that at a certain temperature there is a sudden collapse of the electronic conductive state and the complex regresses to that of an insulator.

Within such one-dimensional stack arrays there is a susceptibility to distortional instabilities which hinder electron motion within the stacks. Increasing the dimensionality of the stack *e.g.* exchange of S by Se introduces more interaction and helps to reduce the susceptibility to Peierls' distortion.[17]

Peierls' Distortion (Metal-Insulator Transition)

The anisotropy associated with homosoric charge-transfer salts arises from the large transfer integral (π overlap) value and such overlap of the molecular wave functions allows the electrons to move along the stack to generate a metallic state.

When degenerate unpaired electrons interact with the lattice vibrations (phonons) it becomes energetically favourable to lift the degeneracy and lower the electronic energy of the system. This distorts the molecular stack resulting in the formation of a weak dimer, as shown in Figs. 15a and 15b. The dimerisation caused by Peierls' distortion results in an insulator.

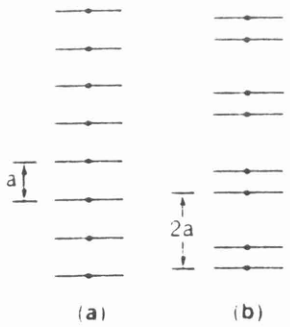


Figure 15a

a) Metal with uniform spacing

b) Dimerisation

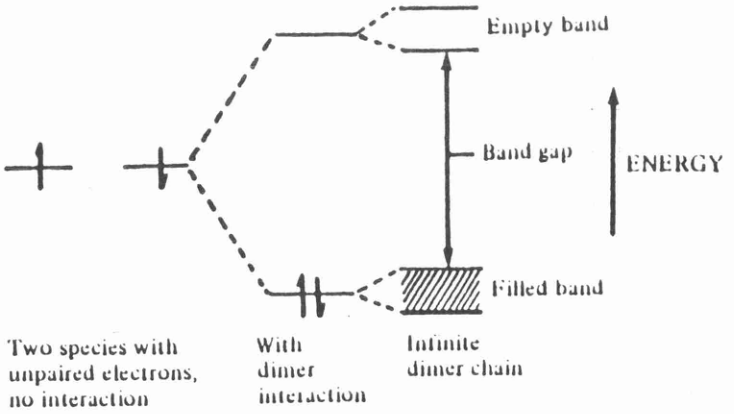


Figure 15b

The stack now possesses filled and empty bands and there are alternate short-long spacings; this lowers the electronic energy while increasing the electron repulsion. Overall a lower energy state prevails.

Above this transition temperature electrons can be thermally excited across the Peierls' band gap. However the promotion of electrons are to states that are higher in energy than the empty states of the undistorted lattice and the electronic energy advantage from the distorted lattice is reduced. A uniform lattice is retained until a temperature is reached at which it becomes energetically favourable for molecules to dimerise and form a distorted stack.

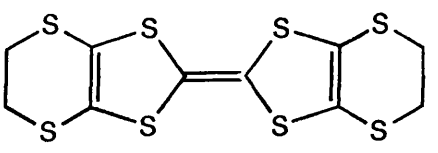
Organic Superconductors

"Superconducting metals have a transition temperature, T_c, usually a few degrees, above which they behave like normal metals. As the temperature is lowered below T_c, the electrical resistance disappears suddenly..... . Below the transition point the resistance appears to be zero, not merely very small."[17]

Superconductivity (the absence of electrical resistance) was first observed in 1911 by H.K. Onnes with mercury at liquid helium temperature.[18] Twenty six elements were known to become superconducting, ten more become more so under high pressure and over two thousand superconducting alloys were known.[19]

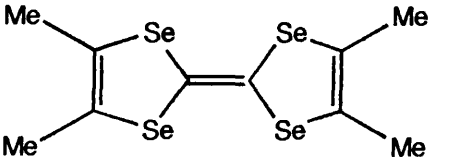
In 1980 the first organic superconductor was discovered, $(TMTSF)_2PF_6$, which required a pressure of 12 Kbar, with T_c at 1.0 K and in 1981 the first zero pressure organic superconductor, $(TMTSF)_2ClO_4$, (Fig. 16) was discovered. Much research is now concentrated on devising superconductors with a higher T_c, with (BEDT-

$TTF)_2I_3$, (Fig. 16), becoming superconducting.



BEDT

bis (ethylenedithio) tetrathiafulvalene



TMTSF

tetramethyltetraselenafulvalene

Figure 16

Superconductivity arises from the interaction between electrons and lattice vibrations (phonons) in the metal state.[20] It has been postulated[21] that the electrons in the metal conducting state are not free, as in normal metals, but are bound to one another in pairs, Cooper pairs; and secondly that the pairs form a condensate such that all the pairs are in the same quantum state. At low temperatures there is insufficient energy to hinder the motion of Cooper pairs (more energy is required to hinder Cooper pairs than normal state electrons); thus they are not scattered and electrical resistance disappears (Fig. 17).

O O O O

O O O O

O O O O

O O O O

O O O O

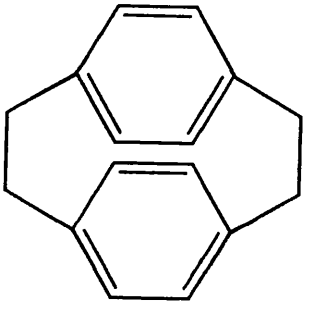
O O O O

Figure 17

As an electron moves through the lattice it interacts with the positive ions of the lattice which move towards the instantaneous position of the electron and produces a deformation in the lattice. A second electron is attracted to it and this results in electron pair movement.

Organic Conductors Based on Paracyclophanes

Cram and Steinberg synthesised (1) and in naming it [2,2]paracyclophane[22] coined the generic name for this type of compound.



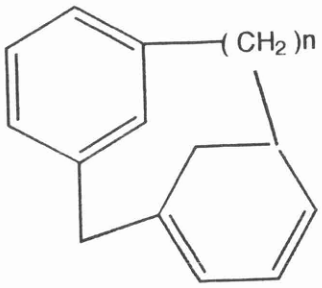
(1)

Other similar compounds had been known before Cram and Steinberg's preparation which now came under the same classification.[23] Cyclophanes are molecules with at least one aromatic ring bridged by at least one aliphatic n-membered bridge where $n \geq 0$.[24]

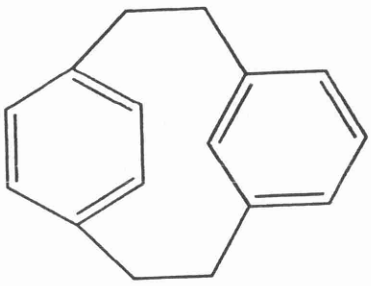
In this brief introduction only dibenzohydrocarbon cyclophanes are discussed (complete reviews of all cyclophanes and synthetic routes are illustrated in references 23, 24, and 25) of which there are many types, as shown in Figure 18.

With paracyclophanes as the basic structural unit in metal π sandwich complexes, it was envisaged that they would be employed to develop new organic conducting systems with potential for further development in the area of biosensors.

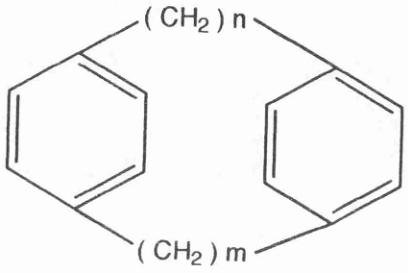
Ferrocene was the first sandwich complex,[26] discovered by Pauson and Miller in 1951, a serendipitous discovery, as they were trying to synthesise fulvalene.[27] Like most organometallic complexes it obeys the 18 electron rule (Fig. 19): transition



(1, n) metacyclophane



(2, 2) meta paracyclophane



(m, n) paracyclophane

Fig. 18

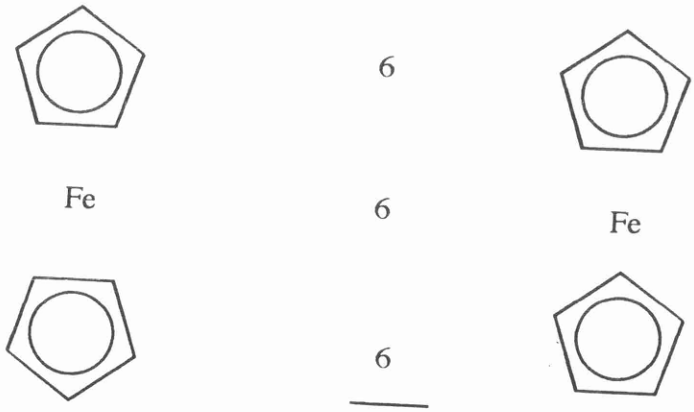


Fig. 19

metal atoms are most stable when surrounded by a full complement of 18 electrons. Ferrocene is an orange, air stable solid.

In a similar manner bis(benzene)chromium, (Fig. 20), also obeys the 18 electron rule and is a brown solid, m.p. 284°C, though it is air sensitive, with oxidation to the cation producing an air stable complex.

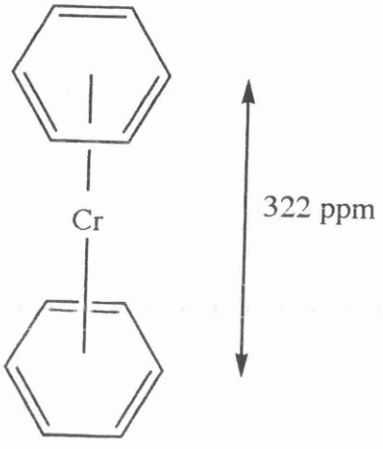


Figure 20

Variations on the theme are also well documented, the majority of such analogous compounds have been developed by Elschenbroich in a series of over forty papers concerned with metal π sandwich complexes.[28] The ninth paper of the series quoted the first chromocene complexes based on a paracyclophane[29] (Figs. 15, 18 and 21).

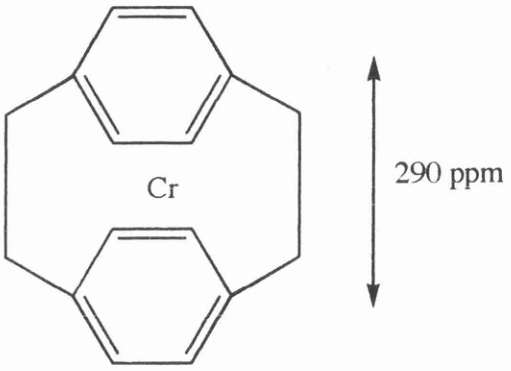


Figure 21

Since then many variations have appeared with some of the more relevant examples outlined below (Figs. 22 and 23).

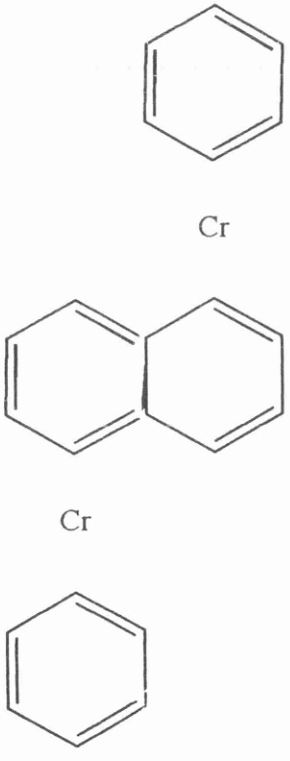


Figure 22[30]

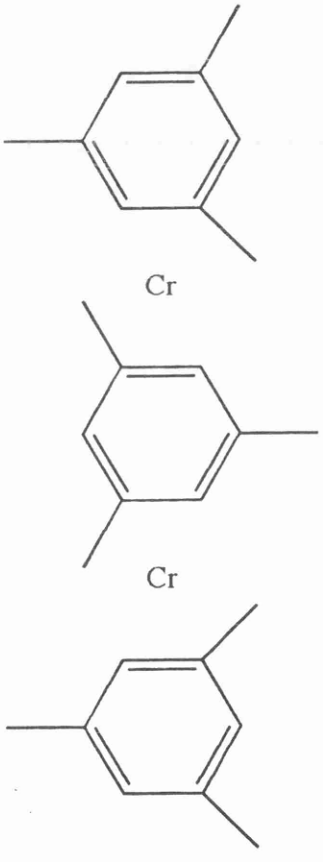


Figure 23[31]

From the examples illustrated it is possible to see the potential for monomeric units that can be used to construct stacks of chromocene complexes (Fig. 24).

To insert chromium, chromium wire is heated with an electric current which vapourises atoms which then react with the vapourised organic compound. In the case of Fig. 18, there is only a 5% yield, but 90% of starting material is recovered.

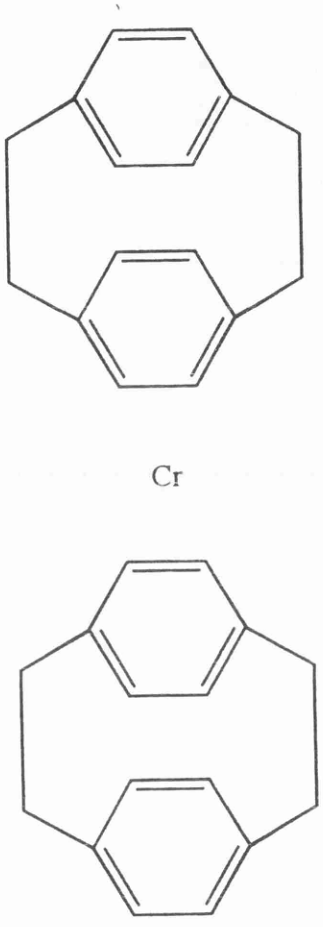
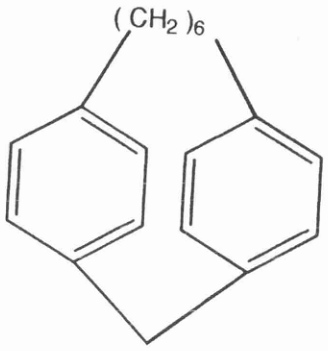


Figure 24

The present research conducted has centred on the synthesis of [1,6]paracyclophane (2) which could be employed in a stack-type arrangement, for



(2)

generation of a new type of conductor.

Firstly, steric considerations have to be clarified with respect to the para-cyclophane (2). If (2) were accurate, unfavourable steric interaction between the ortho/meta hydrogens would be expected. However, we expect the representation shown in Figure 25 to be the lowest energy conformation where the aromatic rings are essentially perpendicular to each other, thereby minimising any steric interaction.

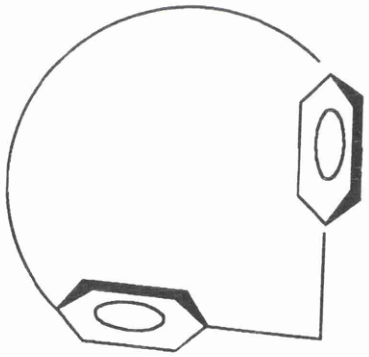
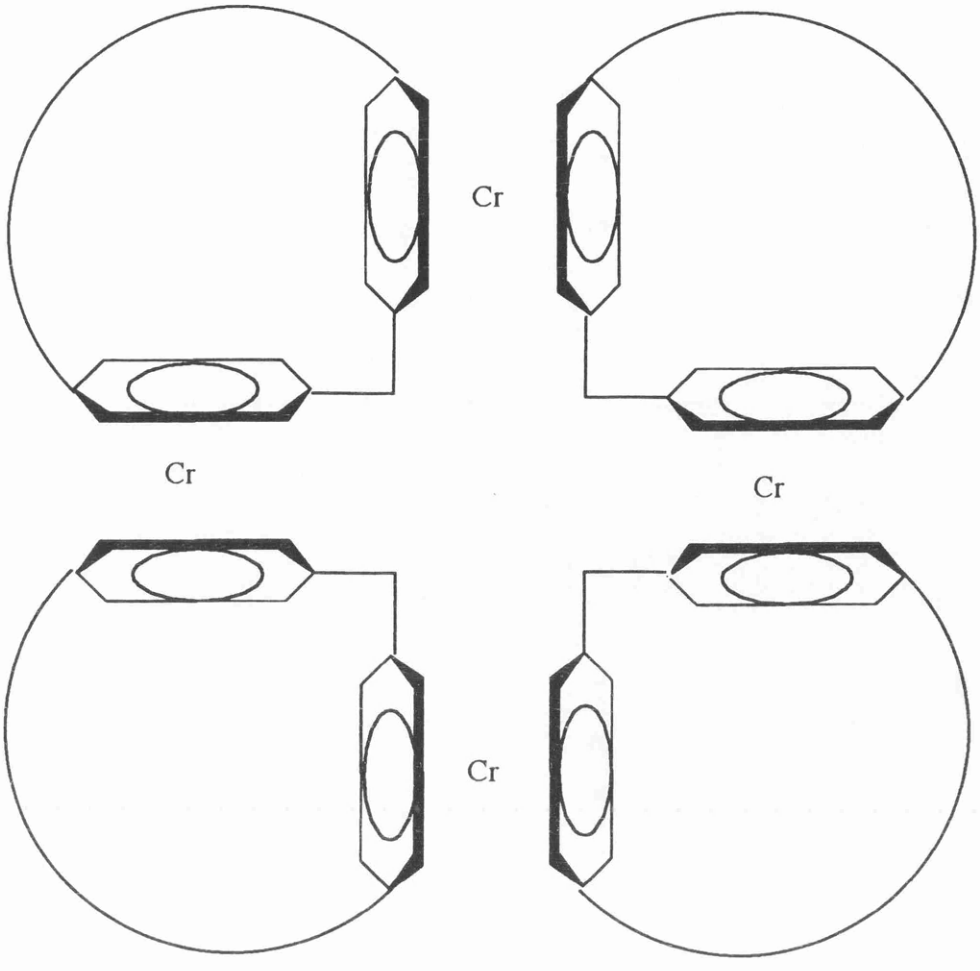


Figure 25

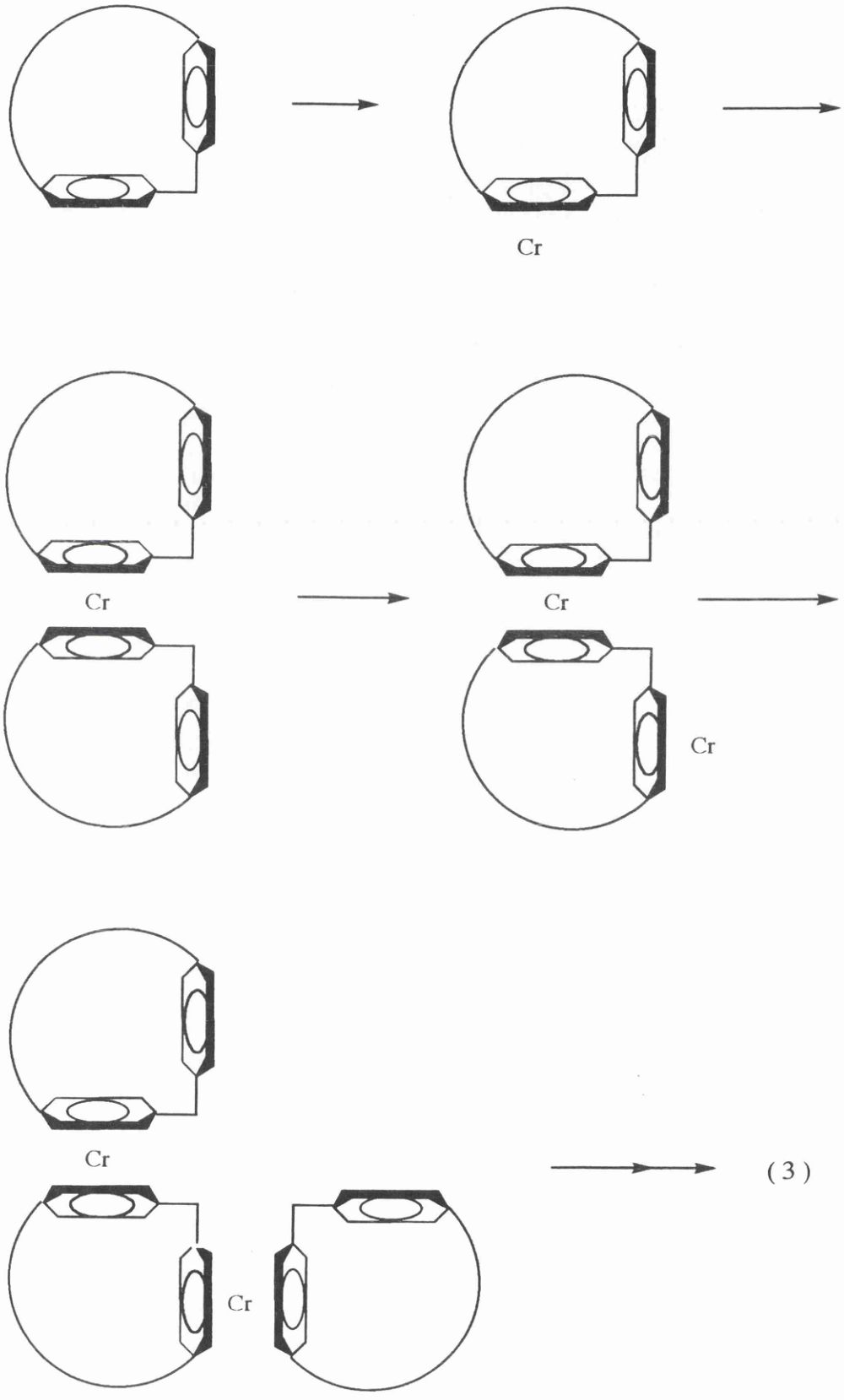
The perception of steric hindrance is important when the mechanism of formation of the new metallocene is investigated. The new metallocene towards which the synthesis is directed is shown below:



$= (CH_2)_6$

(3)

Mechanism of Formation (Fig. 26)



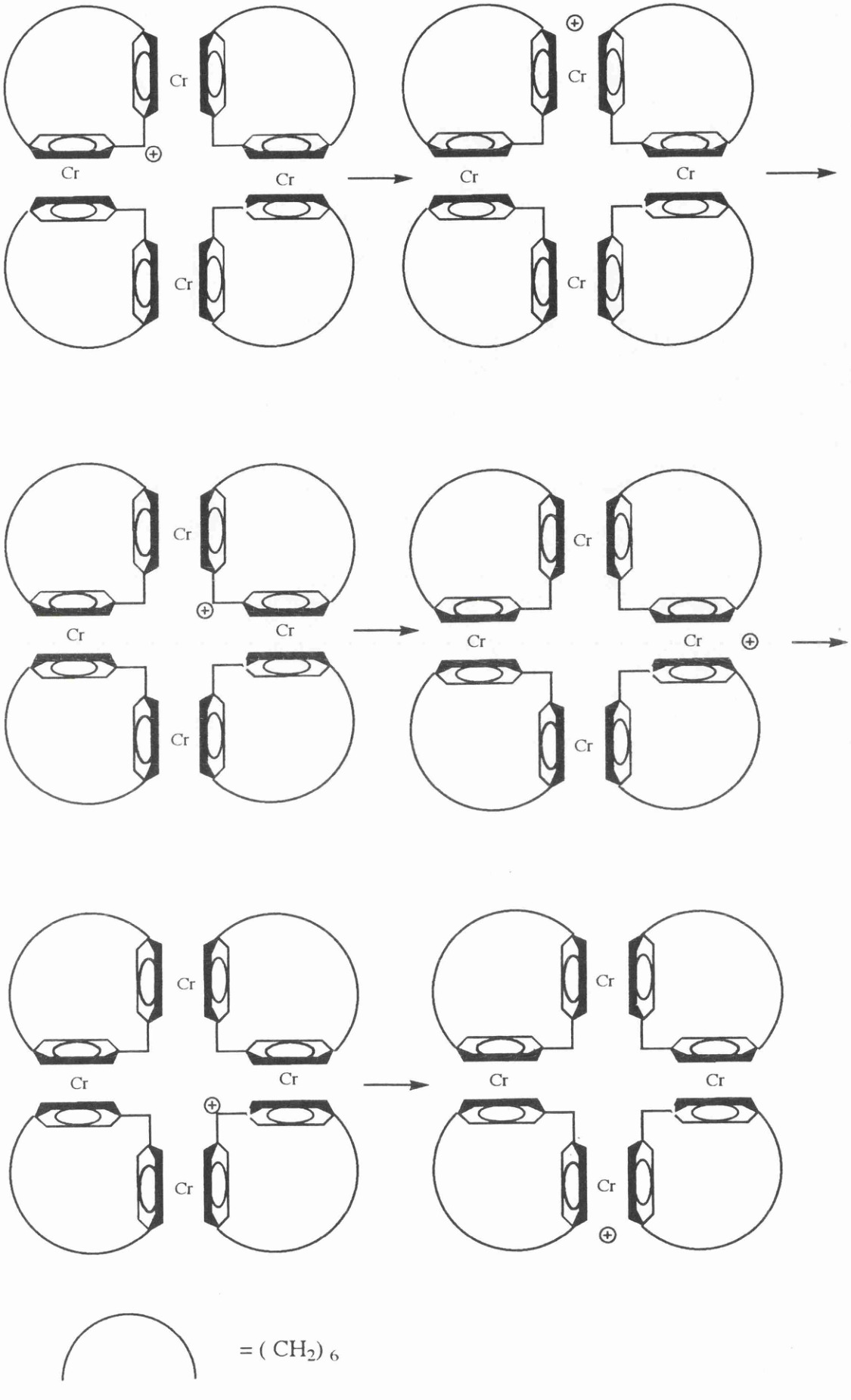
The presumption is that the complex will form a circular metallocene rather than a zig-zag type polymer, though the latter would be highly acceptable as a product, is based on an energetic preference. It will be energetically more favourable for the metallocene to form a doughnut complex as this will reduce steric interaction of aliphatic hydrogens (Fig. 26).

The conductivity interest arises in whether or not a cationic species ([2,2]-paracyclophane chromium (O) forms a cationic complex) which would allow a circular electrical movement as the charge jumps from one monomeric unit to another *via* the benzylic position (Fig. 27).

If this process is occurring very frequently we would effectively see a charge distribution throughout the whole complex. It would be of further interest to discover if a divalent cationic species could be generated.

One potential use for such a molecule may be in the area of biosensors. Presently there are ferrocene based biosensors (often disposable) which are used to test for organic molecules such as glucose and cholesterol[32] (Fig. 28).

Another family of biosensors has the redox material attached to the electrode rather than labile and employs porphyrin rings (Fig. 29). However, this tends to be a more direct reaction.


Cr
Cr
Cr
Cr
Cr
Cr
Cr
Cr
Cr
Cr
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Cr
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Cr
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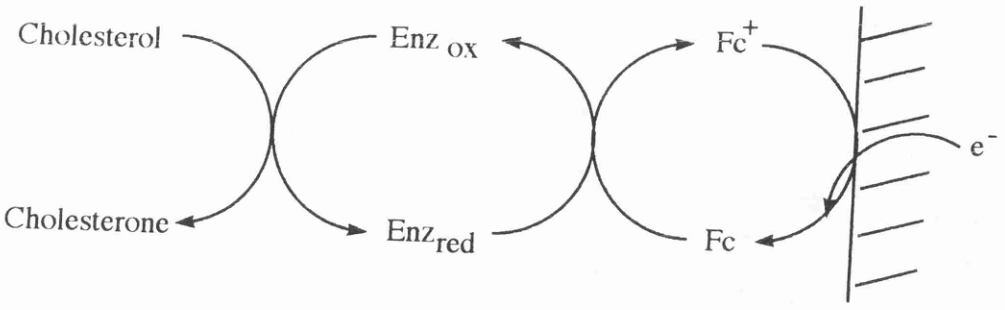
Cr
Cr
Cr
Cr
Cr
Cr
Cr
= (CH2) 6

Figure 27



$F_c \equiv$ ferrocene

Fig. 28

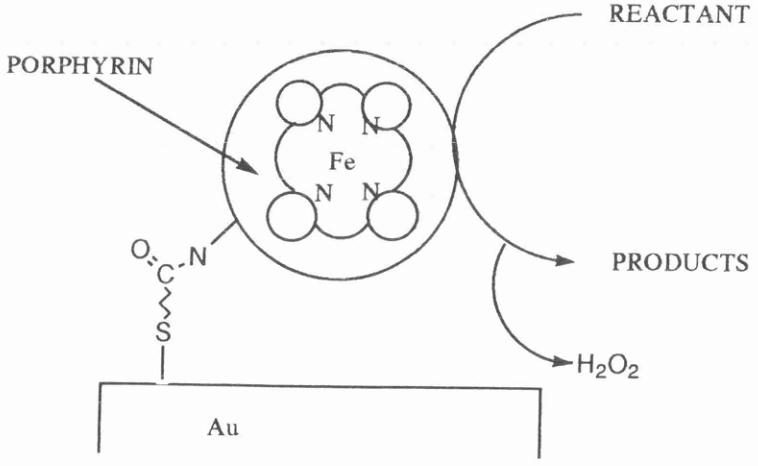
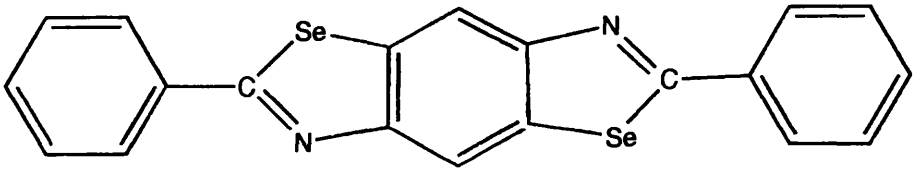


Fig. 29

RESULTS AND DISCUSSION

As described in the Introduction, charge transfer complexes consist of an acceptor and a donor molecule. Classical donors are based on TTF (tetrathia-fulvalene) and their analogues[33] although more extensive variations on TTF are now becoming more common.[34]

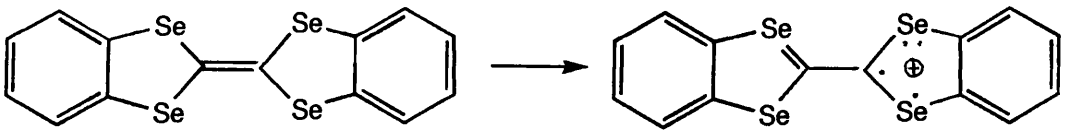
Compound (9), 2,2-diphenylbenzobis-selenazole follows the guidelines set out in the Introduction *i.e.* 2, 7, 8 (p.10). As well as having vacant d-orbitals on selenium, which would enhance interchain bonding, nitrogen, with its lone pair of electrons, is also present so adding to the dimensionality of the crystal.



(9)

Although in the radical cationic state there is no generation of a new aromatic sextet an extensive conjugation is present which should aid the stability of the cationic species and so favour conduction. Although organic donors based on sulphur tend to form a new aromatic cationic state, not all donors follow this strategy for conductivity. In the Introduction, perylene acts as a donor yet any electron loss will disrupt the aromatic sextet. However, only perylene participates in electrical conduction. Similarly, dibenzotetraselenafulvalene (DBTSF) has been found to form

conducting complexes, although not of the same magnitude as TTF-TCNQ, without the formation of a new aromatic sextet in the conducting state[35,36] (Figure 30).



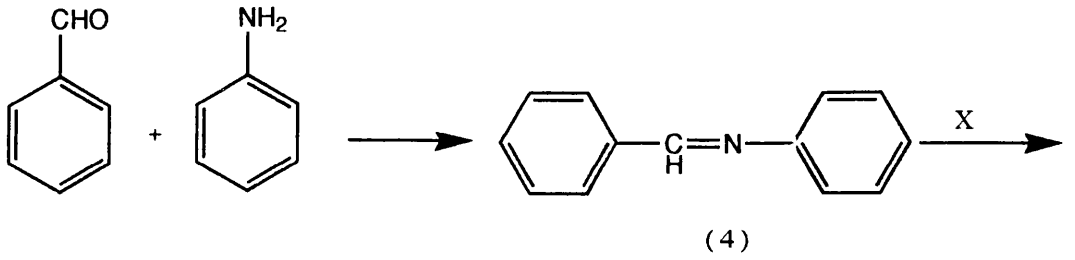
Zero new aromatic sextets

Figure 30

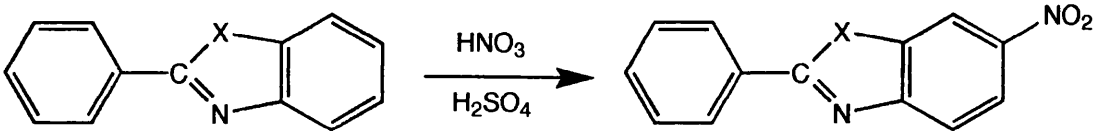
A final criterion for conductivity is the stacking system of any complex with (9). At the present stage of organic metal development it is almost impossible to influence the self-assembly process of donor and acceptor molecules as numerous variables influence the final stacking mode[12] *e.g.* van der Waals' forces, crystal growth kinetics, ionisation potential and electron affinity values.

The synthetic route to (9) is outlined overleaf (Scheme 1). The Schiff's base benzylidene aniline (4) was reacted with selenium powder to generate (5), 2-phenyl-benzoselenazole. Synthesis of (5) proved to be an arduous task and was satisfactorily accomplished when recycled selenium, from previous attempts, was employed and heated to 250-280°C for 72 hours. There are three allotropes of selenium at room temperature, but above 110°C only metallic (also known as grey, black or trigonal) selenium is present.

Some benzoselenazoles are known to be biologically active.[37] They have been used to treat *inter alia* pustular acne and seborrhoea and are generally applied as a

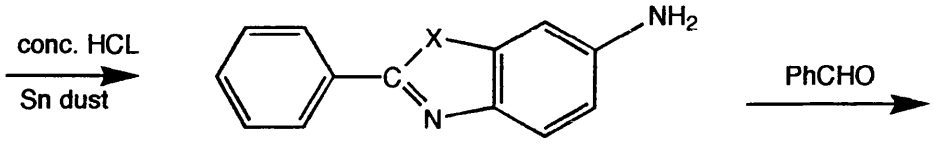


(4)

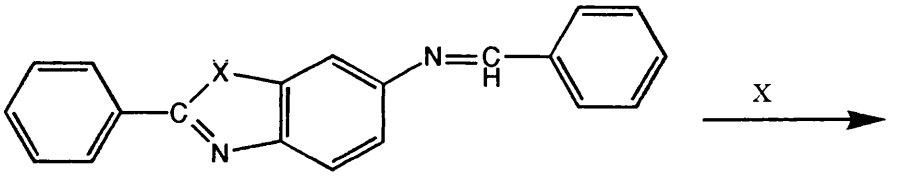


X = Se (5)
X = S (12)

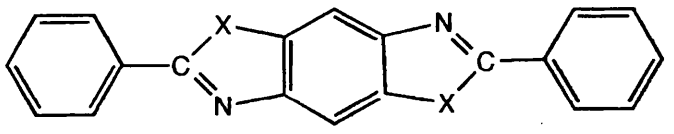
X = Se (6)
X = S (13)



X = Se (7)
X = S (14)



X = Se (8)
X = S (15)

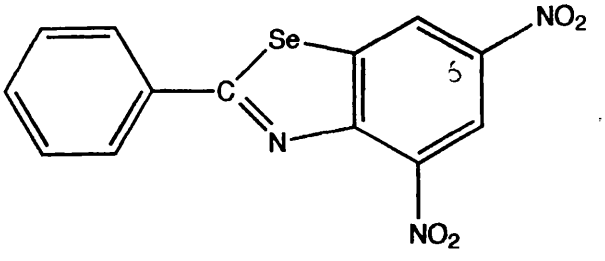


X = Se (9)
X = S (16)

Scheme 1

5% solution in an oily agent. It also possesses satisfactory local and general tolerance with very low acute toxicity.[38]

Subsequent nitration of (5) under literature conditions delivered mainly the dinitro derivative (10) rather than the mono-nitro counterpart.



(10)

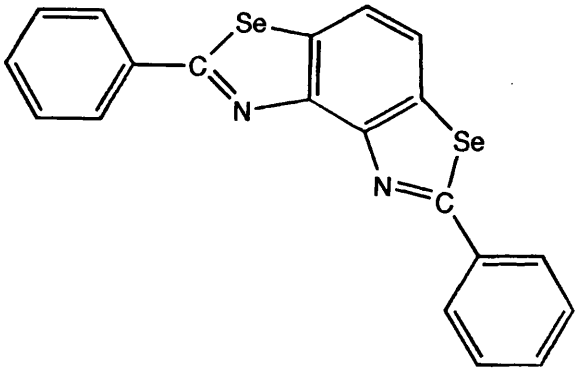
The first nitro group will attack at carbon six, as expected from the inductive effect of the nitrogen lone pair, with the second nitro group attacking ortho to N and meta to NO_2. The lone pairs of electrons on selenium will have unsuitably high energies to produce a significant effect by interaction *via* back donation with the aromatic system. Any heteroatom will have some electronic effect on the aromatic ring system although there may not be back bonding present. A suitable basis for comparison is chlorobenzene where there are lone pair resonance donations to the aromatic π-system, yet there is a deactivation of the aromatic system due to the inductive properties of chlorine. Selenium will also have an effect but to a lesser extent than chlorine.

Subsequent reduction in the experimental temperature for the nitration

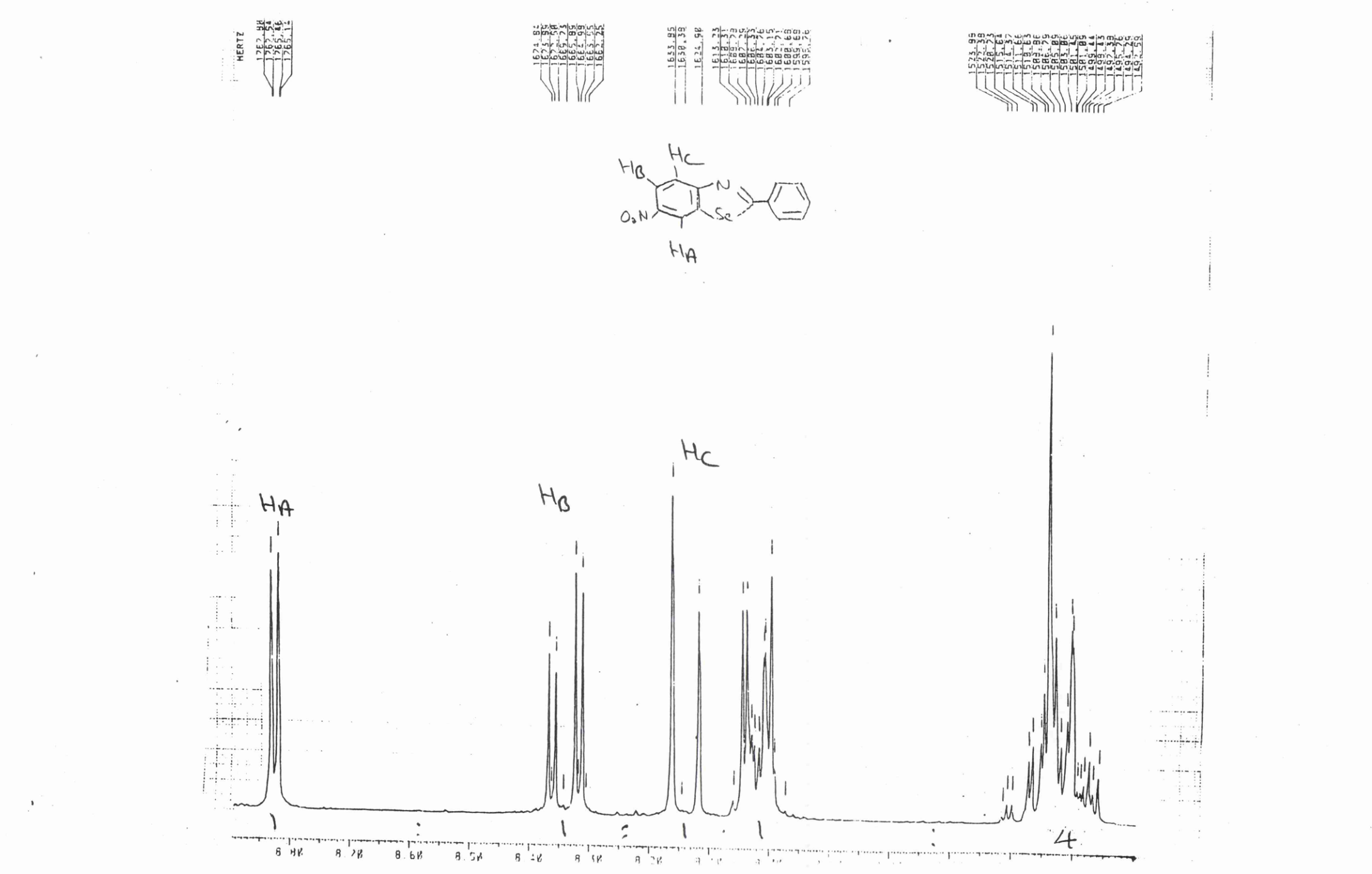
produced the mono nitro product. Bogert and Chen[39] reduced this mono nitro compound to the corresponding amine and reaction with KOH formed only benzene acid and no nitrobenzoic acid. They thus established the location of the nitro group on the benzo rather than the phenyl ring. The structure was also verified by 200 MHz ^{1}H NMR spectroscopy where protons H_4, H_5, and H_7 could be distinguished and their coupling values determined (see spectrum overleaf).

Reduction of (6) with powdered tin and conc. HCℓ produced the desired amine (7), where in the ^{1}H NMR spectrum protons H_4, H_5 and H_7 could be distinguished again. The penultimate step was analogous to the second stage in the reaction where the amine was reacted with benzaldehyde to produce the imine (8) which in turn is treated with powdered selenium to produce the final compound (9).

Originally intended for applications in charge transfer complexes it soon became apparent that any such use was severely limited. After the 200 MHz ^{1}H NMR spectrum had been determined and retrieval of the compound, a large proportion of the sample had decomposed with extrusion of selenium. Had the compound been produced in acceptable quantities, X-ray diffraction analysis would have pinpointed if (9) or (9b) was the actual structure.



(9b)


HERTZ
Hc
HB
N
O₂N
Se
HA
HA
HB
Hc
4

Either would have been suitable for organic charge transfer complexes.

Investigation of the literature showed that several organoselenium compounds extrude selenium.[40,41] Diselenides and polyselenides are also reported to extrude selenium,[42] with such reactions incorporated into the synthesis of molecules (Figure 31).

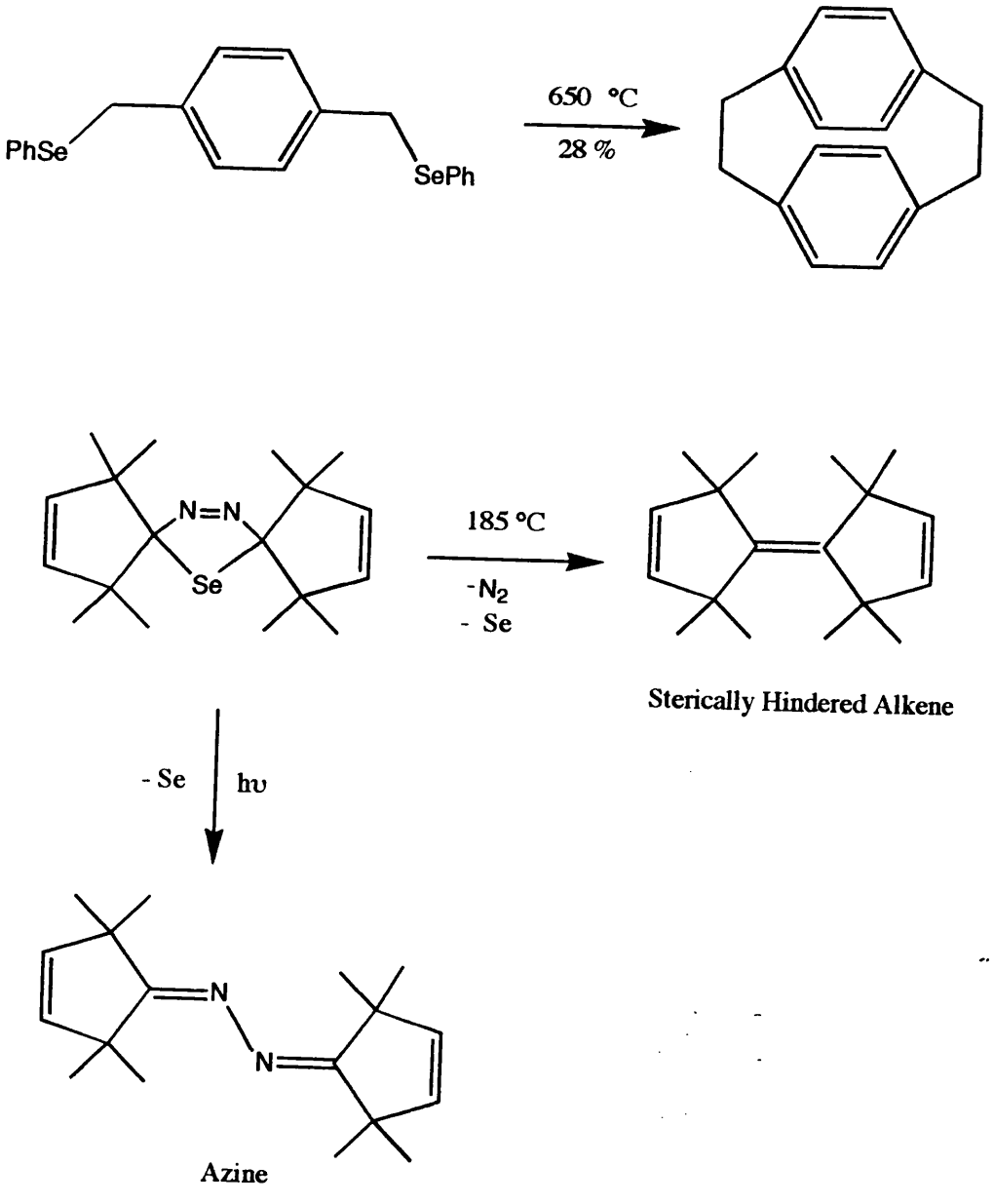
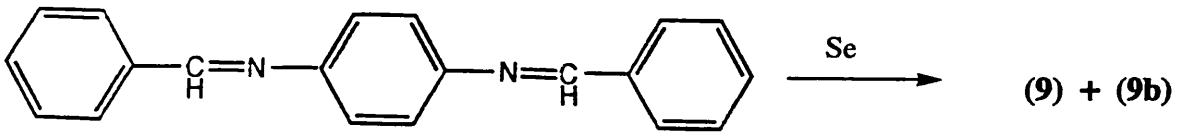


Figure 31

There was another route which involved only two steps to the final compound (1), that looked simple, but in our hands was unsuccessful. Dibenzal-p-phenylene diamine (11), synthesised from p-amino aniline and benzaldehyde, was reacted with selenium at high temperature (240-270°C) (Figure 32).



(11)

Figure 32

The observation of selenium extrusion led instead to the synthesis of the thio analogue (16) which should possess greater stability (extrusion of sulphur dioxide from sulphones is common but that of sulphur is, in general, rare) and although there would be less interchain coupling than the Se analogue, it may be an acceptable donor for charge transfer complexes (the majority of viable donors are based on sulphur heterocycles).

The synthetic route to (16) is outlined earlier, as cited by Bogert and Abrahamson[43] with slight variations in experimental procedure. In principle, one would expect the sulphur reaction with benzylidene aniline (4) to react faster than the selenium counterpart (sulphur m.p. 115°C *c.f.* selenium 221°C), hence the different reaction times of 3h for sulphur and 3 days for selenium. To prevent excess formation of sulphur dioxide, which consumes sulphur, a stream of dry

nitrogen, to exclude oxygen, is passed over the reaction and the resultant stream that contains hydrogen sulphide is passed through aqueous sodium hydroxide.

The next stage in the synthesis involved nitration of the benzo ring employing concentrated nitric and sulphuric acids at more elevated temperatures than usual, though below 40°C to ensure minimal formation of the dinitro product. The literature procedure[43] described produced significant proportions of the dinitro product. Initially this does not appear strange as sulphur is slightly more electronegative than selenium so it would deactivate while o, p directing (as with chlorobenzene), compared to selenium, thereby reducing the probability of dinitration.

If the degree of aromaticity in the heteroazole ring is considered then different results would be expected. There is a greater deshielding in the selenazole than in the thio counterpart. The authors conclude[44] that there is a greater charge density on the α carbons due to the d-orbitals on selenium accepting electrons from the benzo ring to a greater extent than sulphur (Figure 33).

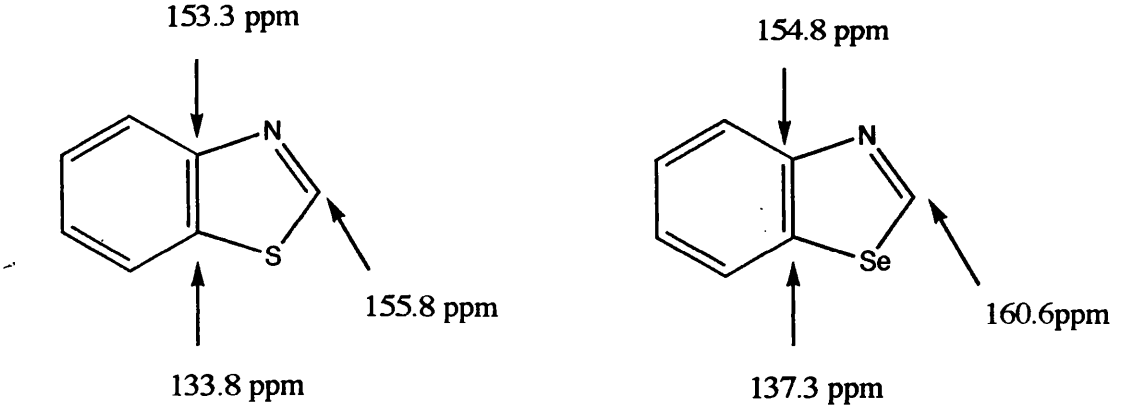


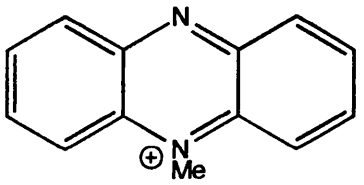
Figure 33

This explanation would lead to a reversal of the factors noted *i.e.* the thio analogue, with its more electron rich ring, would favour dinitration over the relatively electron deficient benzo ring of the seleno analogue, whereas experimentally nitration of the thio analogue requires higher temperature; this suggests that nitration (and also dinitration) would take place more readily in the seleno analogue.

Strongly exothermic reduction of the nitro derivative (13) with powdered tin and concentrated HCℓ produced the corresponding amine (14) which, after condensation with benzaldehyde, gave benzalaminophenylbenzothiazole (15). In the final stage, repeated attempts failed to produce enough of the material, (16), for purification. However, *via* 200 MHz ^{1}H, 50 MHz ^{13}C NMR and mass spectroscopy analysis, it is possible to detect the presence of the compound. As a result of the difficulty in the synthesis of the final product the synthesis was not pursued.

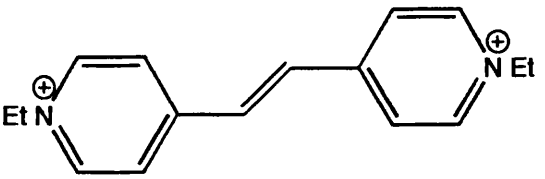
Further Work

To stabilise the final product it may be possible to alter the structure of the compound in a manner that would diminish degradation. One option applicable to both the seleno and the thio compound would be generation of a quaternary ammonium salt, as these are already known to participate in charge transfer complexes (Figure 34).



NMP

N - methylphenazinium



1, 2 diN- ethyl- 4- pyridiniumethene

Figure 34

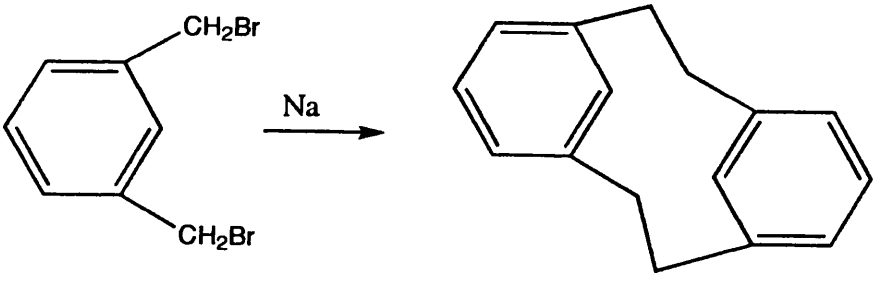
Organic Conductors Based on Paracyclophanes

There are two established methods of cyclophane/macrocycle synthesis:

Wurtz Coupling[45]

The best reported yield is 20% with a more realistic expectation of 3-4%.

e.g.

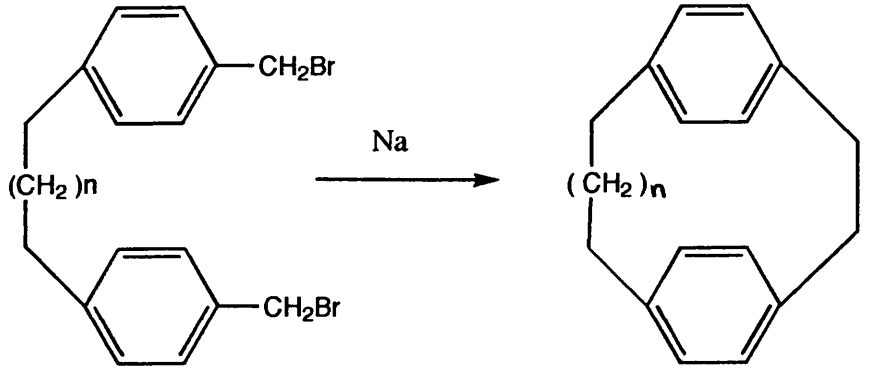


(2,2) METACYCLOPHANE

Figure 35

As a general rule, simple benzylic bromides are the best starting materials (Figure 35), since formation of oligomers and polymers is not extensive. As the complexity of the molecule increases so does the probability of side reactions. In their original paper[22] Cram and Steinberg successfully employed Wurtz coupling to generate the

coupling to generate the desired product ring structures, but in modest yield (Figure 36).



n = 2 2.1% yield

n = 3 4.6% yield

n = 4 0.48% yield

Figure 36

<u>Sodium Sulphide Method</u>[45]

This method is more suited for non-aromatic dibromides although benzylic bromides have been employed occasionally (Figure 37). The protocol outlined also has the disadvantages described for Wurtz coupling, which are especially prominent if the initial coupling reaction is inter- rather than intra-molecular. To suppress formation of oligomers and polymers the high dilution method used (this is further discussed later in the section).

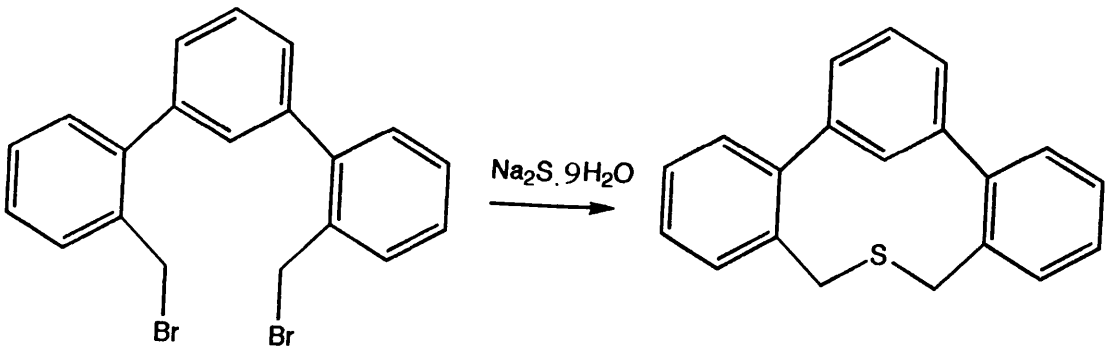
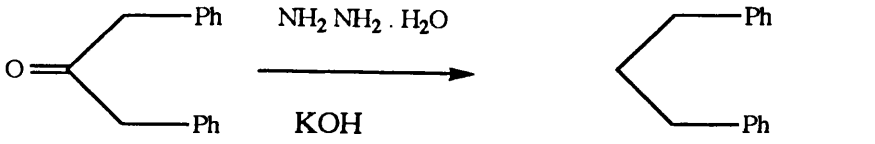


Figure 37

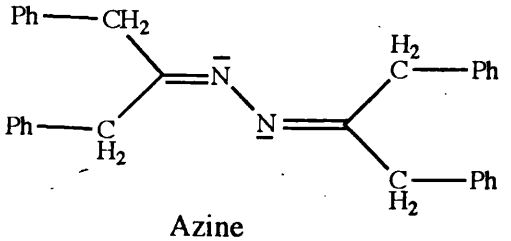
The initial aim of this part of the project was to synthesise a substituted aromatic compound which would then react to form a paracyclophane (Scheme 2).

From dibenzyl ketone, Wolff-Kishner reduction produced the desired hydrocarbon. Initial problems with the reaction centred on the production of the azine (Figure 38) as a by-product.



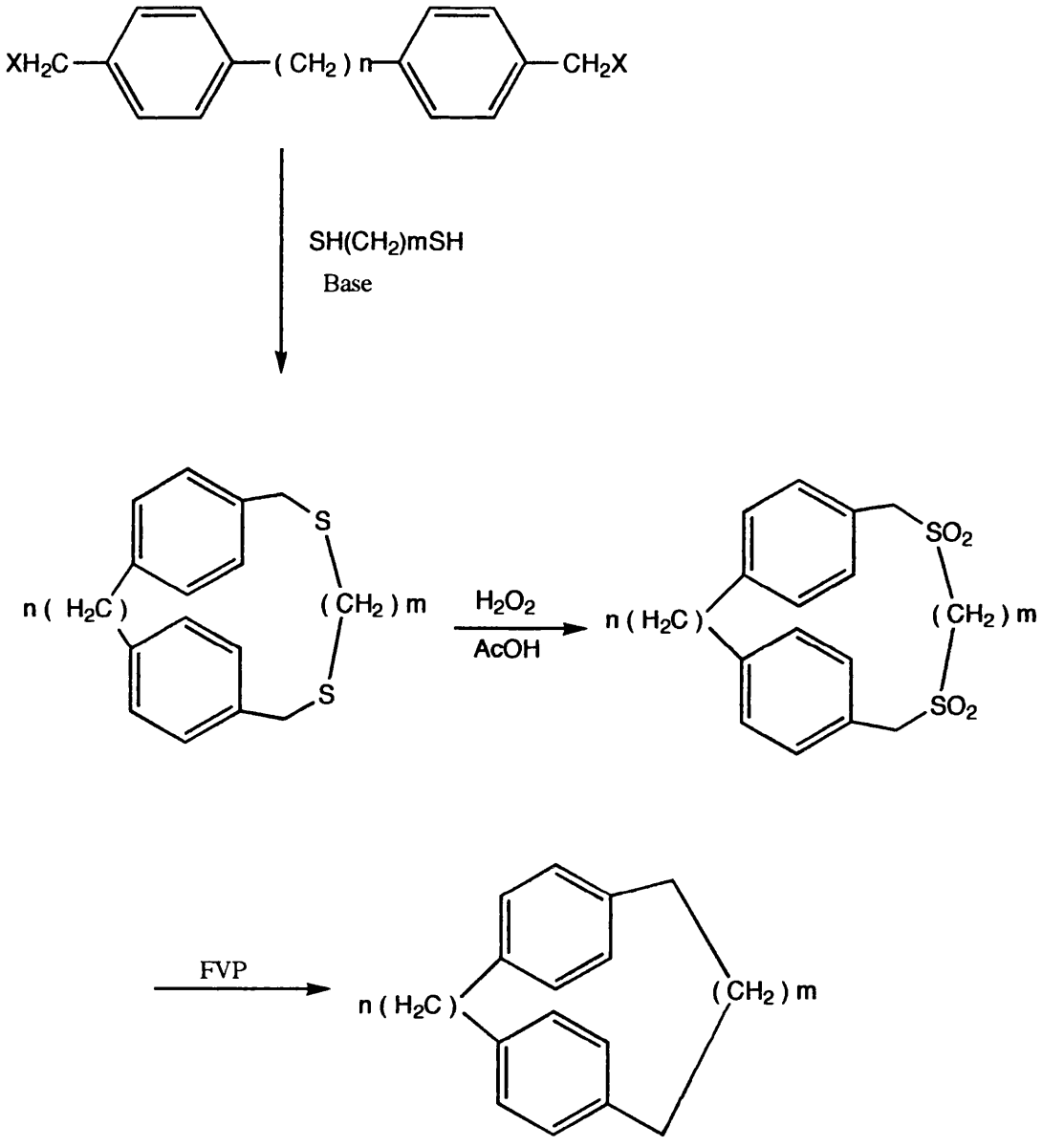
1,3 diphenylpropane

+



Azine

Figure 38



SCHEME 2

This problem was overcome by addition of the ketone to the basified hydrazine hydrate mixture rather than *vice versa*; thus hydrazine hydrate was always in excess. Formation of the azine did not interfere with purification of 1,3-diphenylpropane as the azine is a solid, whereas 1,3-diphenylpropane is a liquid.

The next stage of the synthesis was concerned with methods of attaching "ethyl carboxy" to the aromatic system, with ethyl chloroformate considered an appropriate reagent (Figure 39).

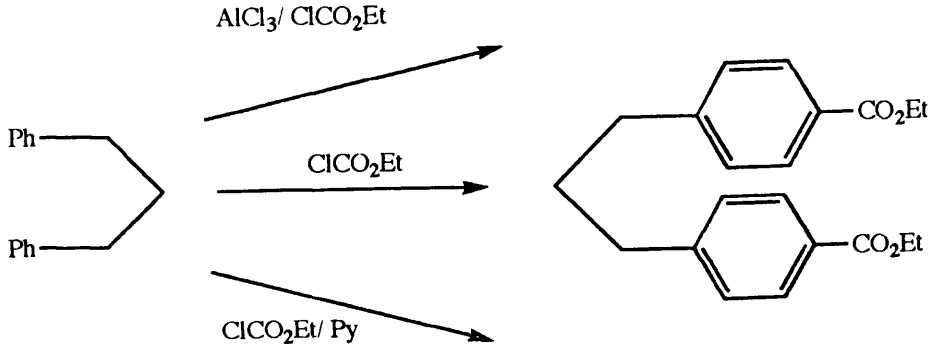


Figure 39

The projected sequence was to convert the ester to an alcohol, and thence to tosylate or to bromide.

Synthetic routes from diphenylmethane to 1,6-paracyclophane were considered. The first step in the investigation was the Friedel-Crafts acylation with acetic anhydride to generate 4,4′-diacetyl diphenylmethane which, in an iodoform reaction, was reacted with iodine and sodium hydroxide solution. In the iodoform reaction only the acetyl group is converted into a carboxylic acid group, with iodoform generated as a by-product. The mechanism is shown below (Figure 40).

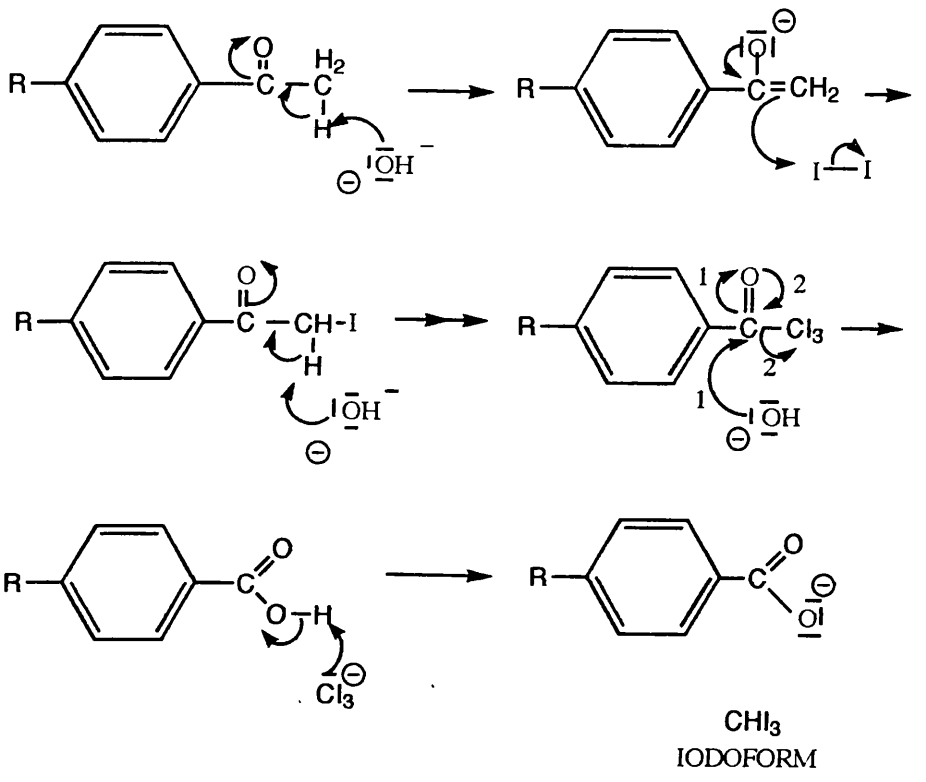


Figure 40

In this mechanism removal of subsequent protons becomes progressively easier as more electron withdrawing iodine atoms are attached to the relevant carbon. Therefore, the reaction has to be carefully monitored and in all attempts the exothermic reaction was extremely difficult to control and in the event furnished very little of the diacid product. The next step would have been the reduction of the diacid, *via* the methyl ester, to the diol and then transformation of this diol into the tosylate, or the bromide, for use in a coupling reaction with the thiol.

The lack of product from the iodoform reaction forced a new route to be followed which involved a one-step chloromethylation[46] (Figure 41) which would produce a compound suitable for cyclisation with a thiol.

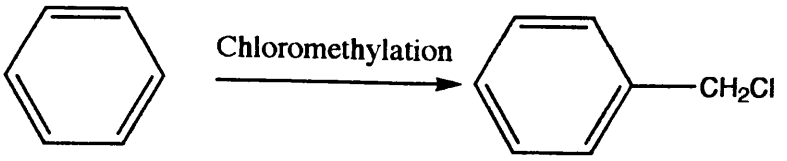
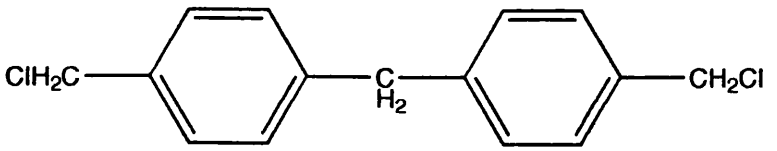


Figure 41

Generally, halomethylations involve passage of a continuous flow of $HX_{(g)}$ (X=Cℓ or Br) through the reaction mixture for several hours, often at elevated temperatures.[47,48] This is an extremely expensive route as use of dry $HBr_{(g)}$ for the reaction would be costly. With all cases suggested below the organic starting material was diphenyl methane (except where stated otherwise) and the desired product was:



(17)

Table 1

Reagents
1) paraformaldehyde, H_2SO_4, benzyl chloride
2) paraformaldehyde, $SnC\ell_4$
3) formaldehyde vapour, $SnC\ell_4$
4) paraformaldehyde, $SnC\ell_4$, HBr AcOH

In all but the first case there was no formation of products, and the first experiment produced only milligrammes. Production of the bromide would be preferred over the chloride as interconversion of chloride to bromide is rather difficult. The Finkelstein (S_N2) reaction is not applicable as in this reaction chlorides can be converted to iodides using sodium iodide, and this centres on the fact that sodium iodide is soluble in the solvent acetone, whereas neither the chloride nor the bromide are soluble.

Chloromethylation is performed by treatment of a suitable aromatic compound with formaldehyde, hydrogen chloride and zinc chloride.[49,50] A proposed mechanism is outlined in Figure 42.

It appears that the presence of the acid is solely to increase the concentration of the reactive species, $[CH_2OH]^+$, while $ZnC\ell_2$ acts as a catalyst and also sequesters water formed as a by-product in the reaction. Thus it may be possible to use highly concentrated acids instead of the hydrogen halide gas. Such reactions were

PROTIC CHLOROMETHYLATION

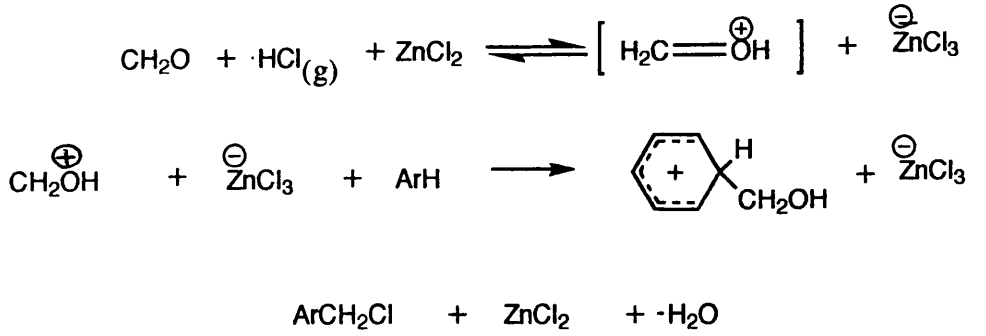


Figure 42

investigated with diphenyl methane as starting material, where reaction should occur at the para position as the ortho position will be sterically hindered.

Table 2

Reagents	Reference
1) $ZnC\ell_2$, paraformaldehyde	49, 50
2) $ZnC\ell_2$, paraformaldehyde, conc. $HC\ell$	
3) $ZnC\ell_2$, paraformaldehyde, HBr/AcOH	
4) $ZnC\ell_2$, paraformaldehyde, HBr/AcOH/LiBr	
5) $HC\ell O_4$, AcOH paraformaldehyde	51
6) paraformaldehyde, AcOH, conc. $HC\ell$, H_3PO_4 (Cambron's mixture)	46

None of the above experiments afforded any product, and starting material alone was recovered. The explanation for using concentrated acid has already been given; however, the idea of using hydrogen bromide in acetic acid was to try and eliminate any detrimental effects that water formed may have, and by use of bromide rather than chloride as the effective attacking species the more reactive benzyl bromide would be produced. The rationale for addition of lithium bromide was, firstly, that it would increase the concentration of bromide ion, so raising the probability of benzylic bromide formation, and secondly, the lithium ions would coordinate to the oxygen so driving the reaction towards the formation of products (Figure 43).

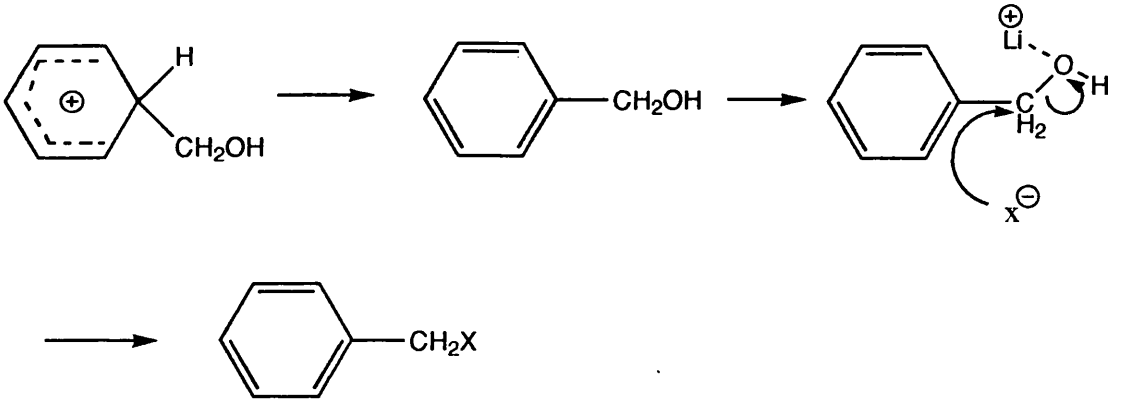
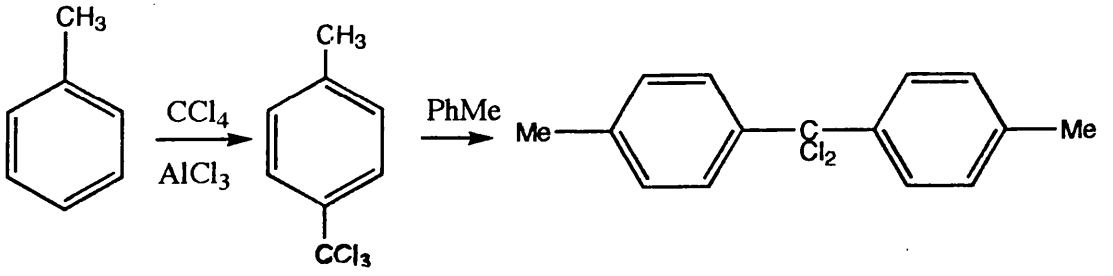


Figure 43

For entry 5, Table 2, it was hoped that the reaction could be stopped at the benzylic alcohol stage and so remove any need for a Lewis acid, and thereby avoid any complications with water and the Lewis acid reacting..

With the lack of success of this experiment we considered the proposed mechanism. The purpose of the Lewis acid is to increase the concentration of the reactive intermediate then other strong acids with nucleophilic anions would be expected to serve the same purpose; also, if water were the cause of any problems then use of HBr in acetic acid (AcOH) should obviate these.

One experiment which proved to be very fortuitous was a further Friedel-Crafts reaction, this time with carbon tetrachloride and toluene.[52,53] The expectation was that paratrichloroxylene (18) would be formed and then would undergo a similar reaction to generate 4,4'-dimethylphenyldichloromethane (19) (Figure 44).

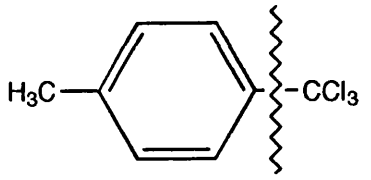


(18) (19)

Figure 44

Initial spectral results were misleading as the 90 MHz ^{1}H NMR spectrum of the product indicated an AA'BB' quartet in the aromatic region, characteristic of a para-substituted aromatic system; further upfield was a singlet at 2.3 ppm with intensities 4:3, respectively. This did not provide enough information to distinguish between (18) and (19). Mass spectral data showed a parent peak of *m/z* 210 with a base peak of *m/z* 119, and a strong peak at *m/z* 91. This points towards (18) with

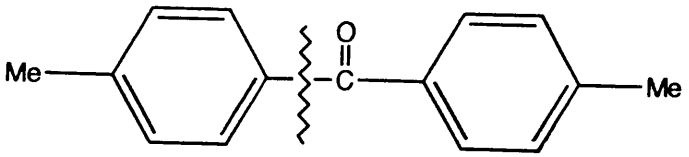
cleavage as shown in Figure 45.



C_7H_7	CCl_3
Mass = 91	Mass = 119 (2 x ^{35}Cl + 1 x ^{37}Cl)

Figure 45

However, there were no chlorine isotope peaks, which would have a ratio of 27:27:9:1, for three chlorine atoms with $^{35}C\ell$ 75% and $^{37}C\ell$ 25%, and be clearly indicative. Microanalysis confirmed the absence of chlorine in the compound and showed that the combined percentages of carbon and hydrogen were less than 100%; this suggested that the remainder of the atomic composition consisted of oxygen. The I.R. spectrum showed a characteristic strong absorption at 1650 cm^{-1}, a carbonyl group with extensive conjugation (a reference sample of benzophenone absorbed at 1645 cm^{-1}). Analysis by 200 MHz ^1H NMR spectroscopy and also by 50 MHz ^{13}C NMR spectrum clarified the structure. There was a quaternary ^{13}C absorption at 195 ppm which certainly is not consistent with $Ph^{13}CC\ell_2Ph$. It is noteworthy that the largest shift value for sp^3 carbons appears to be some ortho esters with values of *ca.* 120 ppm. The conclusion is that the product contains an sp^2 carbonyl carbon.



Mass = 210

C_7H_7 C_8H_7O

Mass = 91 Mass = 119 m/z

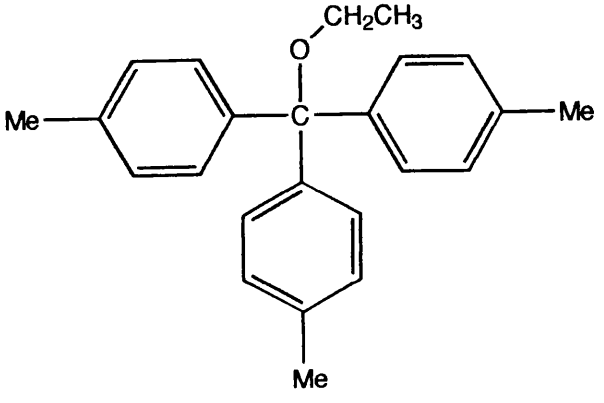
(20)

Figure 46

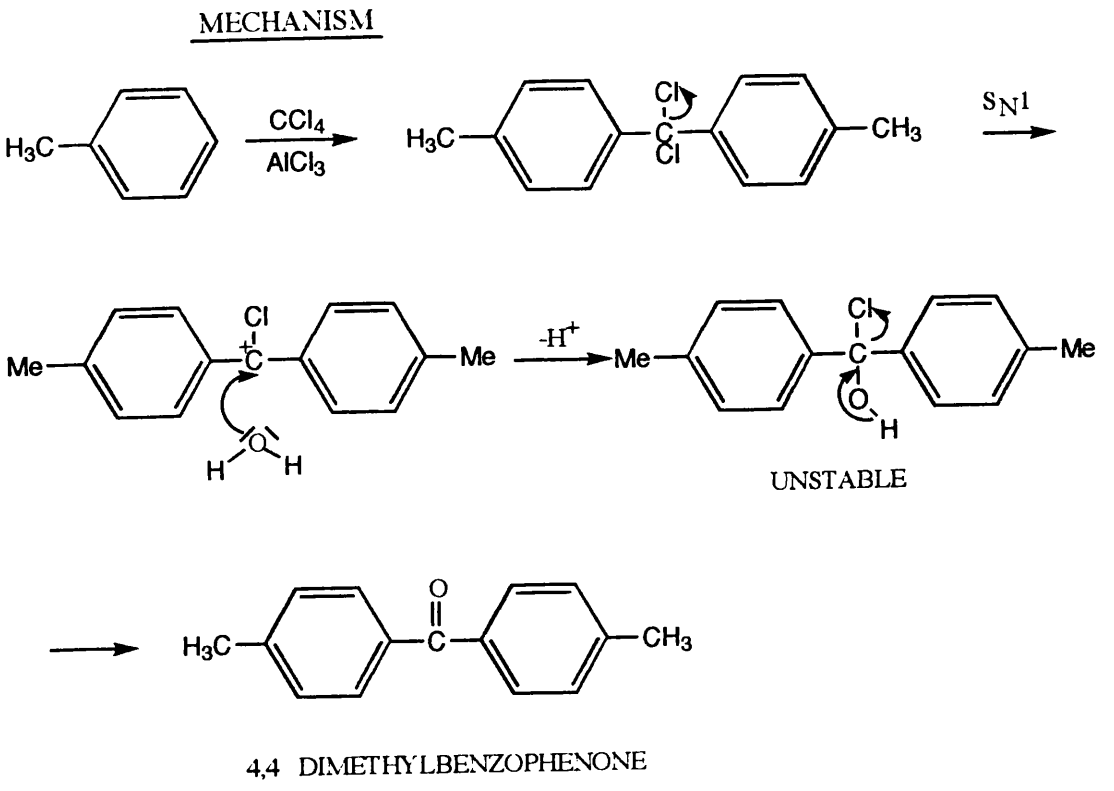
Cleavage of the bond indicated (Figure 46) accounts for the values given in the mass spectrum. The dimethylbenzophenone derivative (20) is formed by the hydrolysis of the dichloride (19) which is an intermediate to the final compound when the reaction mixture is poured onto iced water (Figure 47).

The first step in the hydrolysis would probably be an S_N1 reaction as, with two chlorine atoms and two phenyl groups attached to the central carbon, it would be sterically improbable that a nucleophile could attack.

An isolated by-product from this reaction was (21).



(21)



(20)

Figure 47

Although only produced in decigram quantities, compound (21) had strong fluorescent properties (Figure 48), which made for facile detection and isolation.

One advantage of a carbonyl group over the methylene group, as a bridge, is that bromination, using N-bromosuccinamide (NBS), will brominate the benzylic methyl groups only, the methylene group having been replaced. Although dibromination occurs (despite alteration of molar ratios to favour incomplete monobromination) this is not a major problem as the impurity, although not removable, was minimal (by ^1H NMR spectroscopic analysis) compared to the desired product.

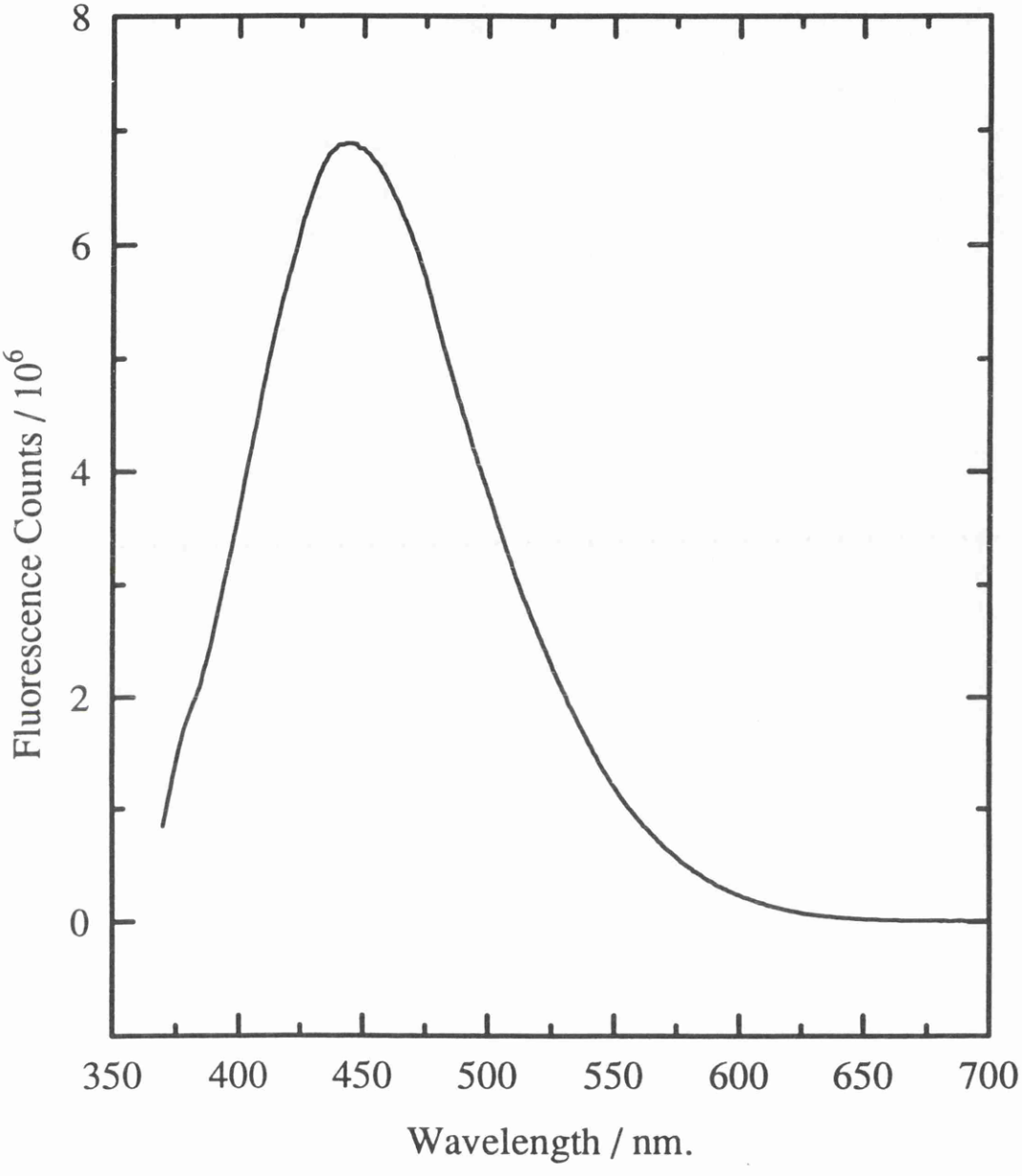

8
6
4
2
0
Fluorescence Counts / 10^6
350
400
450
500
550
600
650
700
Wavelength / nm.

Figure 48

Dilution Principle Reactions

The next stage of synthesis involved the important principle of high dilution.[45] This experimental methodology is often employed for cyclophane synthesis but can be applied for other types of macrocycles (Figure 49).[54]

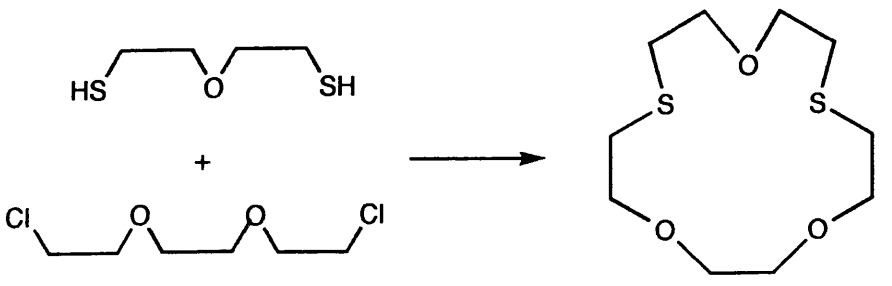
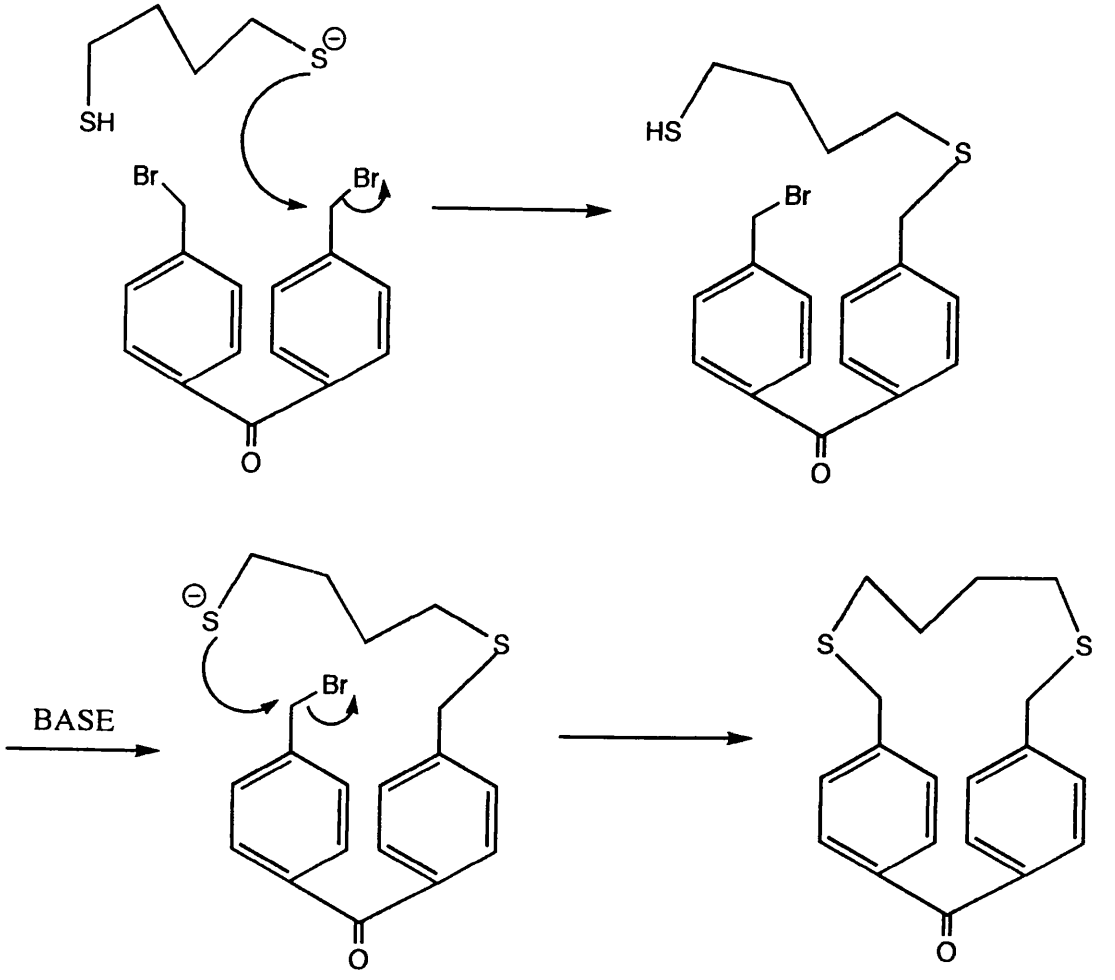


Figure 49

Starting materials for dilution principle reactions are generally compounds with two (or more) functional groups attached with the monomeric cyclisation product the compound normally desired, though other oligomers may be desired. To achieve optimum monomer formation, use of a large solvent volume and/or highly diluted reactants is highly advisable. However, in dilution principle reactions (not high dilution reactions) it is not the total amount of solvent that is crucial but the generation of a steady state concentration of reactants in the flask. This optimises monomeric cyclisation reactions thereby reducing the formation of oligomers.[55,56,57,58] Such a steady state concentration is possible not only with large solvent volumes but also small solvent volumes.

The dibromide (22), formed as previously described, was used in a dilution

principle reaction together with butane 1,4, dithiol (23) in an attempt to produce the thioether shown in Figure 50.



(24)

Figure 50

A base removes a thiol proton to leave the nucleophilic thiolate salt which attacks the benzylic bromide displacing a bromide ion to form a thioether which can then undergo either an inter- or an intra-molecular coupling. When the dilution principle is employed and the rate of feed is controlled to favour intramolecular

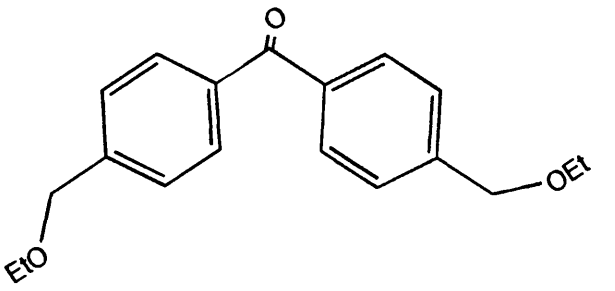
substitution then the cyclic thioether (24) should form. Numerous dilution principle experiments were run in ethanol, to synthesise (24), with variations in experimental conditions: concentration, addition time *etc.* Table 3 lists the experimental details.

Table 3

Experimental Details	Products	Reference
1) 2 days	SM* + ethyl ether	55
2) 30 h over 2 days	SM + ethyl ether	55
3) 2 days, NaOH mixed with thiol	SM + ethyl ether	56
4) 24 h over 2 days then 12 h reflux	SM + trace product/ polymer	56
5) 8 h and 4 h reflux	SM + product polymer	56
6) 8 h and 4 h reflux (x 4 dilution)	SM + ethyl ether + polymer	58
7) 40 h over 4 days (x 10 dilution)	SM + ethyl ether	58

* SM = starting material

The ethyl ether (25) produced will be a result of deprotonation of ethanol in the solvent mixture and the ethoxide ion, subsequently displacing the bromide ion to leave the relatively unreactive ether. Attempts to improve upon the yield of the product produced in reaction 4 failed to augment the amount of cyclised product.



(25)

For certain reactions yields had been improved by the "caesium effect",[59] where caesium carbonate, rather than other bases, is used as a base (Figure 51). Various systems have taken advantage of this effect, where carboxylates are used in the cyclisation process,[61] with benzylic halide systems where a one-step reaction with

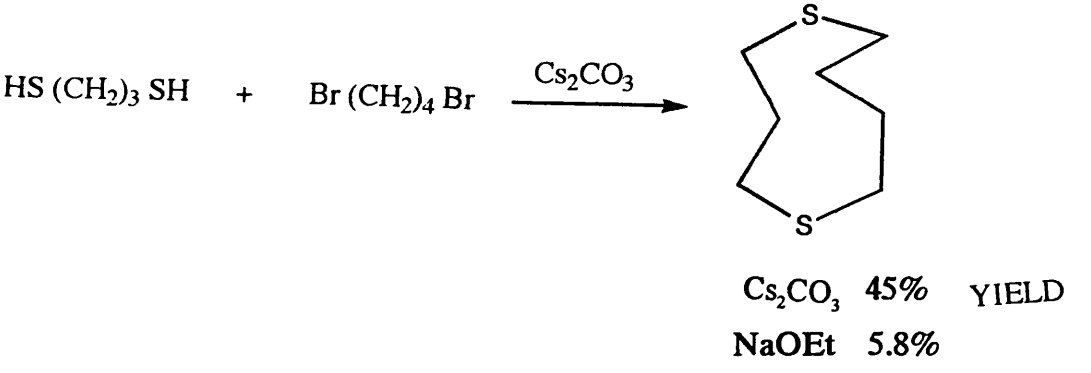


Figure 51[60]

caesium carbonate reduces the number of steps and increases the yield of a multi-bridged cyclophane.[62] It has also been employed in the synthesis of aza-macrocycles without using high dilution, but rather dilution principle techniques.[63]

There was no definitive explanation given in the relevant references although the advantages of caesium carbonate over its other, lower atomic number, alkali metal counterparts were stressed. One possibility is an interaction between the caesium cation and either the thiolate or the thio linkage in a chelating manner (Figure 52).

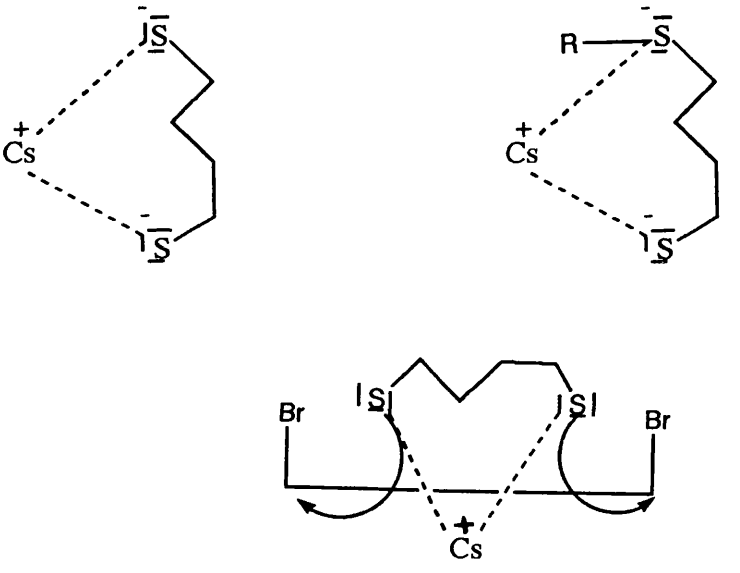


Figure 52

This would be acceptable as in both cases we have a favourable soft-soft interaction. A two-fold molar ratio of Cs_2CO_3 must be added to the reaction mixture as the corresponding bicarbonate, $[Cs^{\oplus}HCO_3^{\ominus}]$, is not sufficiently basic to remove protons from weakly acidic sources. The ideal combination of caesium ion and deprotonation would be caesium hydroxide. However, caesium hydroxide is only available as a 50% solution or as a hydrate and since water would be disadvantageous this method is not viable.

Such a chelation as depicted in Figure 49 would reduce the number of degrees of freedom and so increase the probability of intramolecular reaction. Disadvantages are apparent, exemplified by: i) the chelation to any thiolate which will reduce the nucleophilicity of the sulphur atom and ii) Cs_2CO_3 is a weak base which will result in less than 100% conversion of thiol to thiolate anion. This contradicts the assertion made by Blower and Cooper[64] who suggest that weak ion-pairing between $Cs^{\oplus}$ and $RS^{\ominus}$ generates an exceptionally nucleophilic thiolate anion which under high dilution conditions would favour intramolecular reaction, with the enhanced nucleophilic species. They did not make reference to the work of Vriesema, Buter and Kellog three years earlier,[63] in which high dilution techniques were not employed, though satisfactory yields were still obtained.

With this new technique various experiments were attempted in the pursuit of the elusive thioether, (24); ethanol was employed as solvent and caesium carbonate as base, as shown in Table 4.

In all the experiments detailed above, caesium carbonate did not dissolve completely; this would result in incomplete deprotonation of the thiol and diminish the concentration of the thiolate salt. The problems of dissolution of the caesium carbonate were tackled by the following step. It was hoped that such steps would afford realistic amounts of the thioether, (24), for use in later stages.

A standard method of generating thiolate salts is to use dimethylformamide (DMF) as solvent and sodium hydride (NaH) as base. DMF is a polar, high boiling (152-153°C) solvent which will effectively solvate both organic molecules and their

Table 4

Experimental Details	Products	Reference
1) 6 h and 6 h reflux	SM	57
2) 11 h	SM + trace product	57
3) 50 h over 5 days	SM + trace product	See exp.
4) 5 h	SM + other by-products	See exp.
5) 50 h, 60°C	SM	57
6) 70 h over 6 days	SM + ethyl ether + trace product	57

corresponding salts, especially the cations, thus the anion is more reactive, while also allowing an increased temperature with attendant increase in the reaction rate. DMF is also miscible with water which would allow the removal of trace amounts of DMF by an aqueous work-up. Sodium hydride is a powerful base and will drive the equilibrium of deprotonation in favour of the thiolate salt. Table 5 shows the experiments studied.

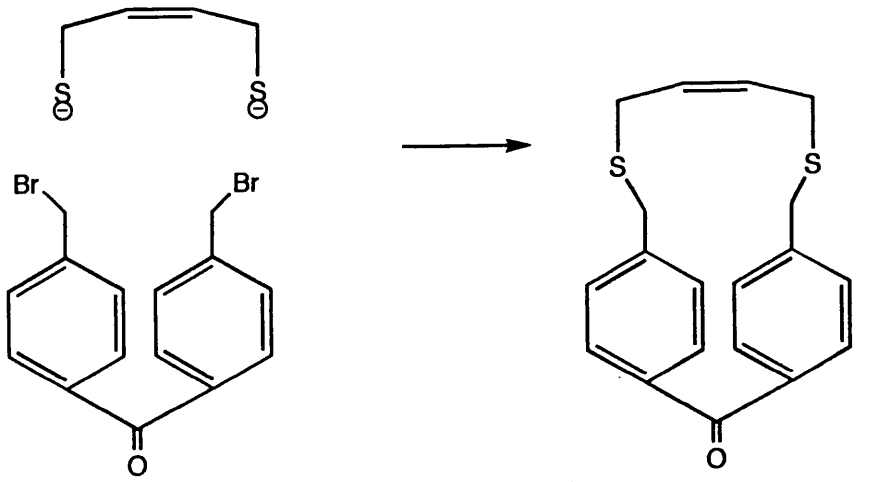
As with all previous attempts to attain a viable synthetic procedure to thioether (24) the DMF route proved unsuccessful. In the case of entry 1 the solution turned blue/violet as the mixtures were added to the flask. However, an important idea from our previous attempts was the seed for the next attempt at generating (26). If the number of degrees of freedom are reduced, as with the

Table 5

Experimental Details	Products	Reference
1) NaH, 80 h over 4 days	No SM or isolable products	
2) NaOH, 60 h over 3 days	"	
3) Cs_2CO_3, 50 h + 12 h reflux	"	64

caesium effect, such that the extent of "wandering" of the aliphatic chain is diminished, an intramolecular reaction should be favoured if the constraint does not interfere with each end of the molecule coupling together.

Instead of using 1,4 butane dithiol (23), 1,4-dithio-*cis*-but-2-ene (27) could be employed where the *cis* double bond would reduce the amount of rotation within the aliphatic chain and so effectively reduce the number of degrees of freedom (Figure 53).



(26)

Figure 53

From Figure 50 we can see that such a system would favour formation of the monomeric product rather than that of the dimer (or oligomer). The first step was the synthesis of the dithiol from *cis*-1,4-dichloro-but-2-ene, which could be performed in two ways:

i) Using thiourea (Figure 54)

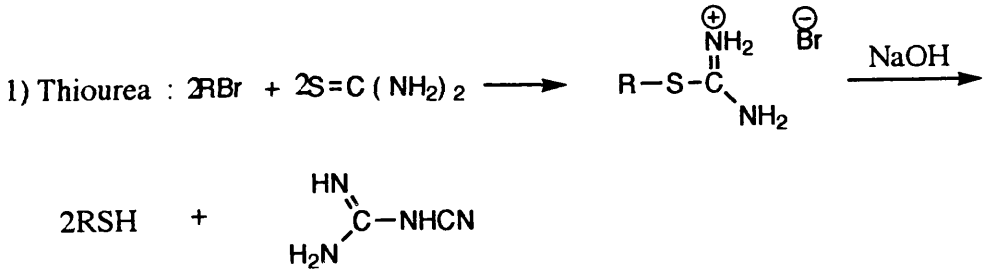


Figure 54

ii) Actual method chosen (Figure 55)

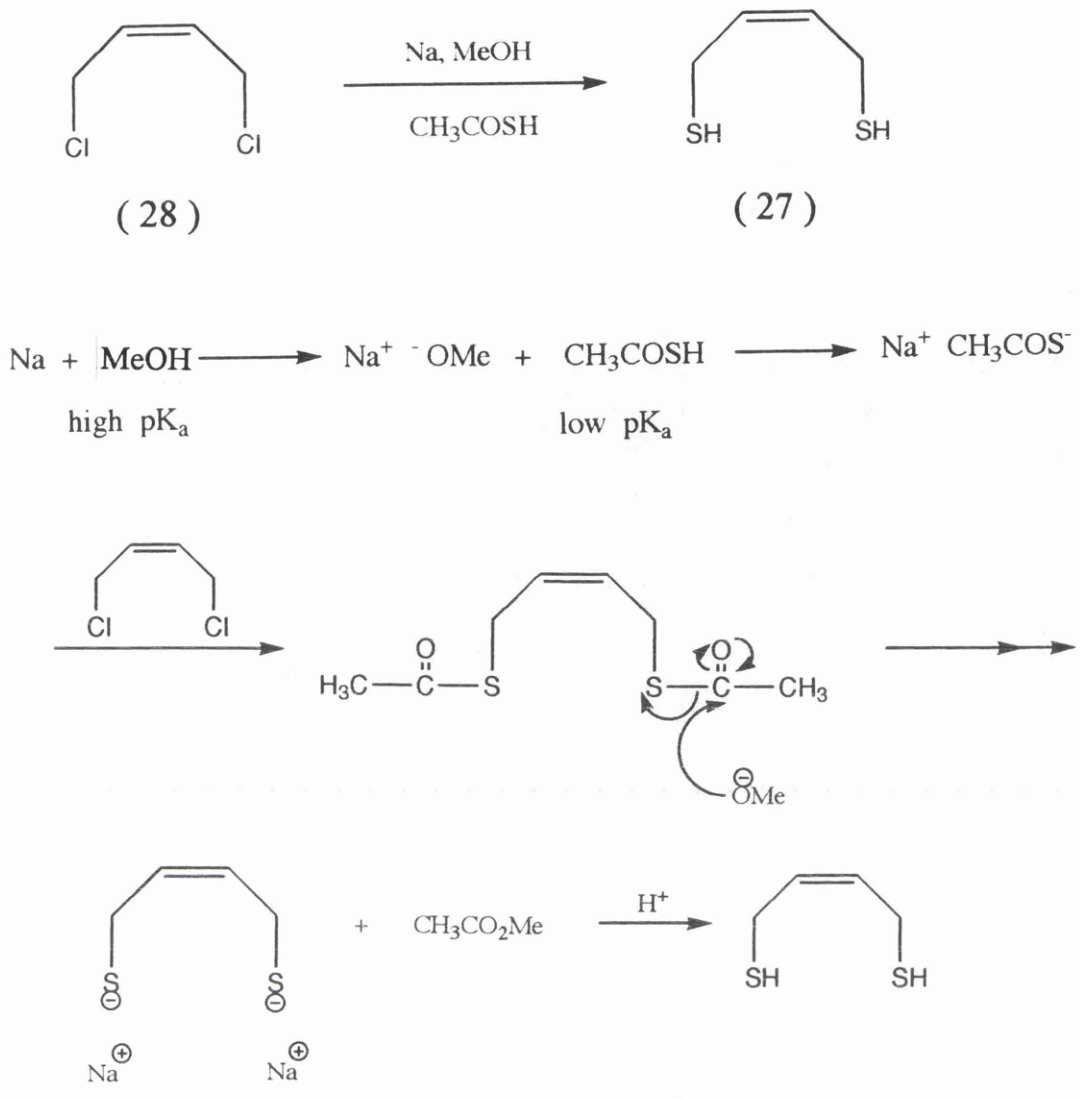


Figure 55

The dithiol (27) was extremely susceptible to degradation, either in air or thermally during distillation. Vacuum distillation proved to be the most effective purification method, though some degradation still occurred. The product was used in various experiments in an attempt to generate the unsaturated cyclic thioether (26) as shown in Table 6, with ethanol as solvent with different bases.

Table 6

Experimental Details	Products	Reference
1) NaOH, 24 h	SM + ethyl ether	55
2) Cs_2CO_3, 40 h	SM + ethyl ether	57
3) NaH, DMF, 20 h + 4 h reflux	No SM	
4) Cs_2CO_3, DMF, 20 h + 6 h reflux	No SM	64

However, as with all previous experiments to improve the yield, they proved to be unavailing. In a final series of experiments organometallic reagents[65] were employed in an attempt to synthesise the cyclophane (2) (Figure 56).

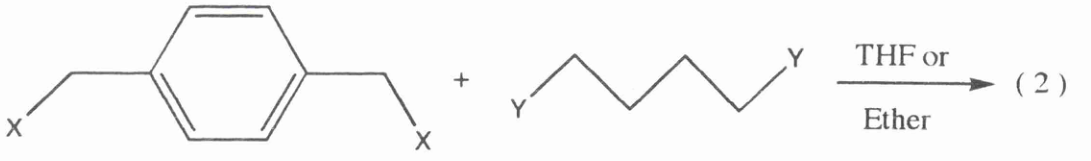


Figure 56

Table 7

Experimental Details	Products	Reference
1) X = Br Y = MgBr or MgCℓ	SM	66, 67
2) X = MgBr Y = Br	SM	—
3) X = Li Y = Br	SM	68
4) X = Br Y = Br	SM	69
5) X = Li (28)	Complicated NMR + SM	68

These procedures would eliminate any need for oxidation of sulphur to the sulphone, and its extrusion *via* flash vacuum pyrolysis (FVP). Thus, even if only small amounts of the cyclophane were obtained from each reaction, it would probably produce a similar yield but with fewer steps. We are effectively generating a reactive carbanion which would hopefully act as a nucleophile displacing bromine, as bromide, from the corresponding reactant to form a new σ C-C bond.

Problems in this method include the potential reaction of either organo-metallic reagent with the carbonyl group (although steric hindrance should reduce this possibility) and the possibility of Grignard exchange (Figure 57).

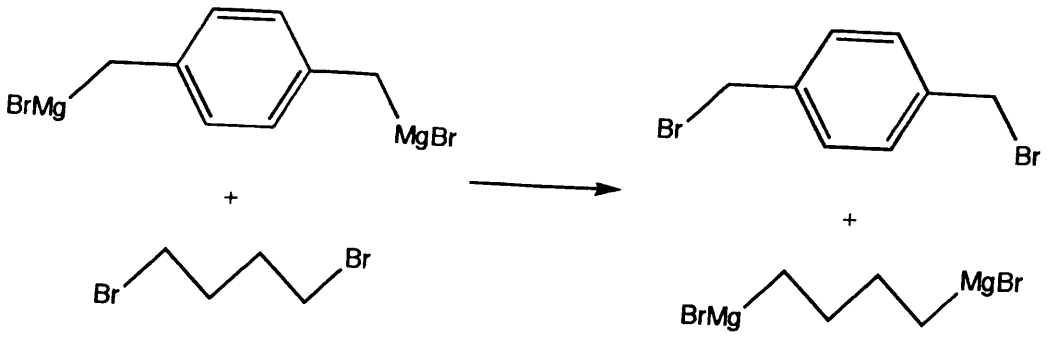


Figure 57

In all cases shown in Table 7, the organometallic reagent was added to diethyl ether or tetrahydrofuran solution of the corresponding dibromide *via* a cannula. The lithiated species of 1,4-*cis*-dichloro-but-2-ene, (28), cannot be made as it immediately undergoes 1,4 elimination to form butadiene. Thus only the lithiated species of the dibromide (22), [made using BuLi] is possible, and this was added to the reaction mixture that contained the *cis* dichloride, (28). In this experiment problems may have arisen due to the acidity of the ortho protons (relative to the carbonyl) which perhaps may be removed in significant quantities so diverting the reaction. In fact, from ^{1}H NMR spectroscopy and AA'BB' quartet is no longer present; however there are several signals upfield in the aliphatic region.

With the Grignard reactions a possible explanation would be that a constant Grignard exchange is occurring; quenching the reaction mixture accordingly produces only starting material.

Further Work

To reduce further the number of degrees of freedom, 1,4-chloro-but-2-yne, (29), could be used as a reagent for forming the thioether (24) (Figure 58).

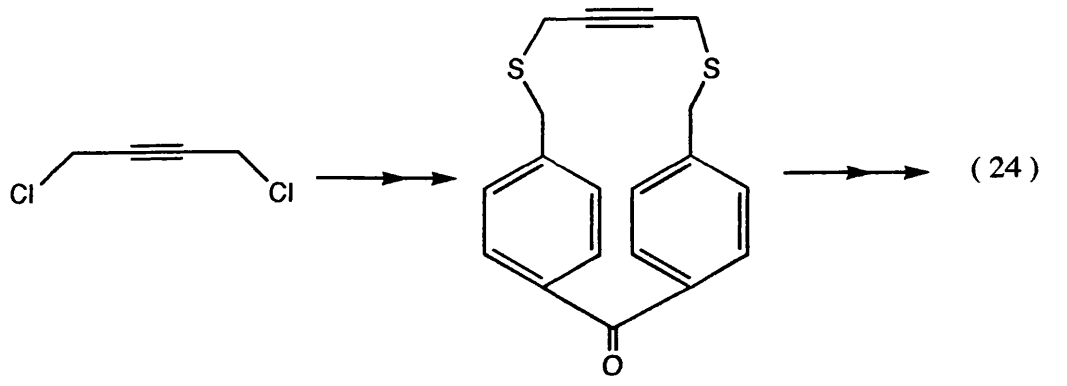


Figure 58

Another possibility would be to reverse the functionality of the molecules by means of an aliphatic dibromide reacting with an aromatic dithiol (Figure 59). From the intended synthetic route (Scheme 2) flash vacuum pyrolysis would be the final step in the synthesis. However with the carbonyl present, carbon monoxide may be extruded to leave a strained biphenyl system. However, conversion of the carbonyl to a methylene group *via* a Wolff-Kishner reduction would exclude this possibility.

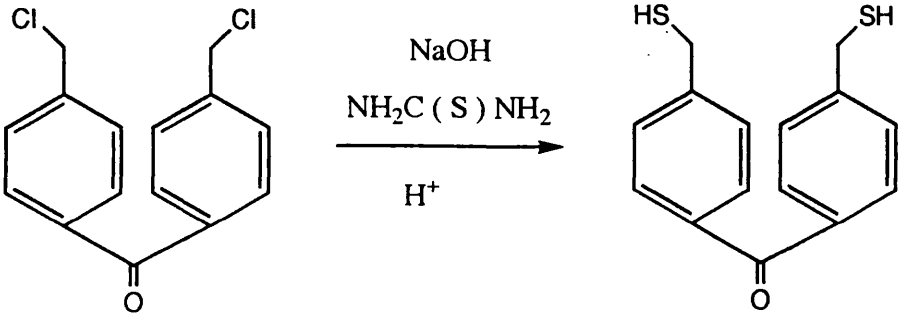


Figure 59[70,58]

This would have to take place at the thioether, (24), stage; if this transformation were performed at the sulphone stage it may deprotonate α to the sulphone and cause rearrangement analogous to the Ramberg-Bäcklund reaction,[71] which is often used to generate enediyne analogues[72] [although in our case an obvious leaving group is not present].

Flash vacuum pyrolysis and even reduction of the carbonyl moiety to methylene could be avoided by a separate method of sulphur extrusion. Photolysis in trimethylphosphite desulphurises thioethers (Figure 60).[58]

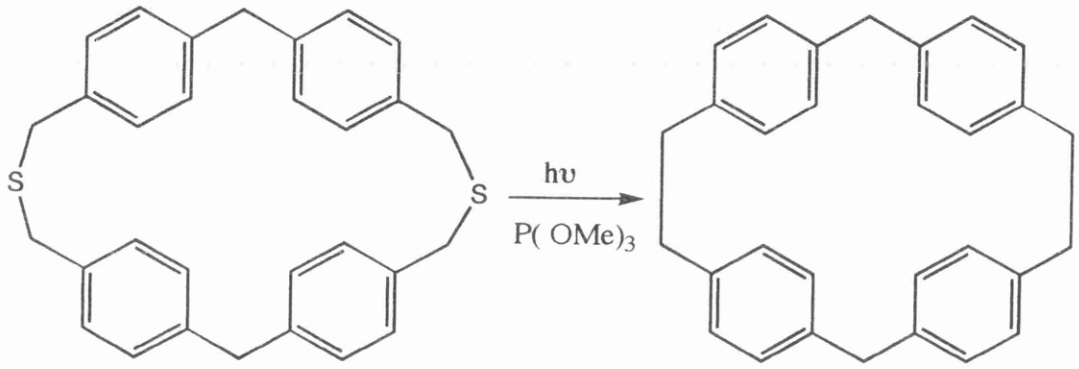


Figure 60

The reaction is generally associated with a low yield and has to be weighed against the combined yields of oxidation to sulphone and flash vacuum pyrolysis to the cyclophane.

A final method of coupling could be to use lithium dialkyl cuprates for coupling different halides together.[65]

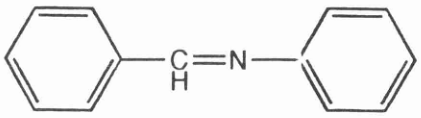
CHAPTER 1

GENERAL EXPERIMENTAL

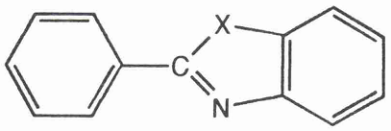
Low resolution mass spectra were determined using an up-dated VG MS 12 spectrometer with high resolution mass spectra determined on a modified Kratos MS 9 instrument (metastable peaks are marked *).

^{1}H NMR spectra were recorded on either a Perkin Elmer R32 spectrometer or a Varian T90 spectrometer, both operating at 90 MHz using deuteriochloroform solutions with tetramethylsilane as an internal standard (assignments are in ppm downfield from TMS) and/or a Bruker WP 200 SY spectrometer or a Bruker AM 200 spectrometer. ^{13}C NMR were recorded on the aforesaid Bruker instruments, both operating at 50.32 MHz. With the Bruker instruments spectra were recorded using deuteriochloroform as solvent. The following abbreviations are used: s - singlet, d - doublet, t - triplet, q - quartet and m - multiplet.

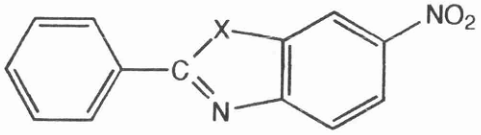
Infra red spectra were determined with either a Perkin Elmer 580 or 953 spectrometer. Melting points were determined on a Kofler hot stage melting point apparatus and are uncorrected.



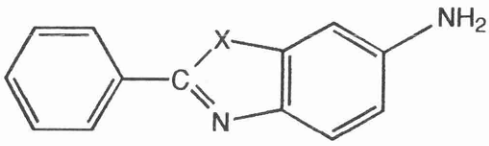
(4)



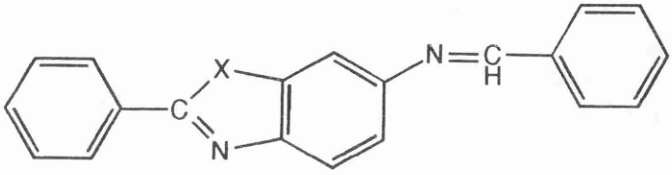
X = Se (5)
X = S (12)



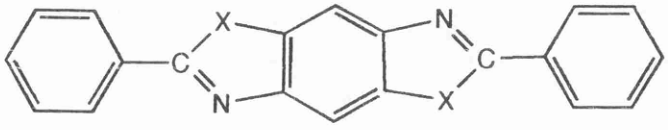
X = Se (6)
X = S (13)



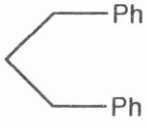
X = Se (7)
X = S (14)

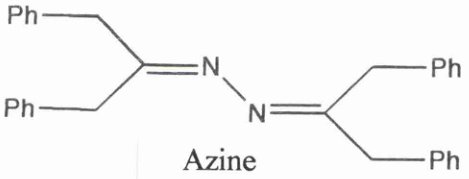


X = Se (8)
X = S (15)

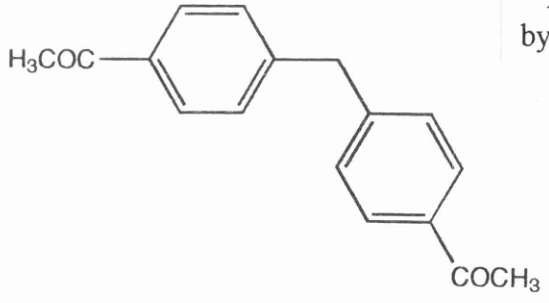


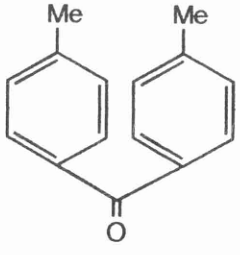
X = Se (9)
X = S (16)



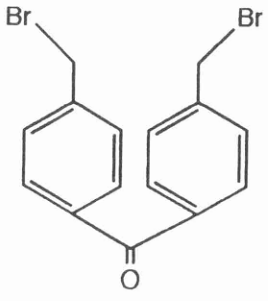


Azine
by-product

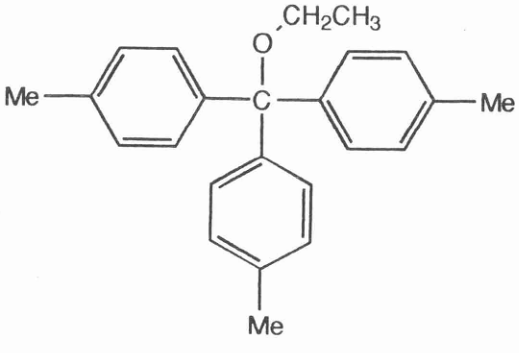




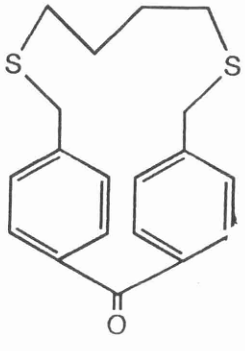
(20)



(22)



(21)



(24)

SECTION I

Benzylidene aniline (4)

53g (0.5 mol) of benzaldehyde was added directly to 46.5g (0.5 mol) of aniline, with stirring, to produce an immediate exothermic reaction. The resultant solid was recrystallised from ethanol to give 82.36g (91% yield); m.p. 49-50°C (lit.,[73] 48°C).

δ_H[74] (90 MHz): 6.9-7.6 (m, 8H), 7.6-8.0 (m, H), 8.40 (s, 1H).

δ_H (200 MHz): 6.92-7.28 (m, 3H), 7.28-7.62 (m, 5H), 7.67-8.05 (m, 2H), 8.40 (s, 1H).

δ_C (50 MHz): 120.941 (2CH), 125.997 (CH), 128.810 (2CH), 128.859 (2CH), 129.201 (2CH), 131.412 (CH), 136.252 (C), 152.114 (C), 160.399 (CH).

ν (cm^{-1}): 3441, 3059, 2365, 2345, 1626, 1591, 1577, 1483, 1451, 766, 694.

m/z: 181 (57.3*), 180 (69.4*), 104 (15.2*), 89 (11.9), 78 (20.3), 77 (100*), 63 (17.7), 51 (85.9), 50 (25.9), 39 (22.5).

Accurate Mass: Found 181.0872

$C_{13}H_{11}N$ requires 181.0889

2-Phenylbenzoselenazole (5)[39]

10.20g (0.056 mol) of benzylidene aniline (4) was mixed with 9g (0.114 mol) of grey selenium and, in a sand bath, heated with a Bunsen burner with overhead stirring for 3 days at 280-310°C resulting in gentle boiling (above 120°C all selenium allotropes give the same grey selenium form). The hot product was poured onto tin foil, crushed when cool then extracted with 400 ml of conc. HCl by refluxing for 3 h. Filtration through a hot sintered filter produced a cloudy solution which was

poured onto 1 litre of iced water and the resultant precipitate was filtered and washed until neutral. 1.63g (5) was recrystallised from ethanol to yield 1.28g (9% yield); m.p. 116-117°C (lit.[39] m.p. 117°C).

δ_H (200 MHz)[75]: 7.20-7.65 (5H, m), 7.85-8.25 (4H, m).

δ_C (50 MHz): 173.45 (C), 154.42 (C), 137.47 (C), 135.26 (C), 131.52 (CH), 129.18 (2CH), 128.18 (2CH), 126.69 (CH), 125.59 (CH), 124.80 (CH), 124.53 (CH).

^{77}Se (Ref. Me_2Se at $\delta 0$) ($CDCl_3$): δ616,78 (s).

ν_{max} (cm^{-1})[76]: 1655, 1580, 1553, 576, 546.

m/z[77]: 261 (18.2), 259 (100), 257 (50.5*), 256 (20.8), 255 (19.9), 179 (11.5), 158 (12.6), 156 (64.1), 152 (15.2), 129 (23.2), 128 (10.9), 74 (15.7), 63 (19.8), 51 (28.1), 50 (30.6), 39 (19.9).

Microanalysis: Found C, 60.48; H, 3.29; N, 5.44

$C_{13}H_9NSe$ requires C, 60.47; H, 3.49; N, 5.43

<u>6-Nitro-2-phenylbenzoselenazole (6)</u>

(1) 4g (1.55×10^{-2} mol) of (5) was reacted under literature conditions[39] with conc. HNO_3/conc. H_2SO_4 producing the dinitrated product (*m/z* 289).

(2) 3.4g (1.32×10^{-2} mol) of (5) was dissolved in 20 ml of conc. sulphuric acid and cooled to -12°C (ice/methanol bath changed every 10 min). A mixture of 0.91 ml of conc. nitric acid and 2 ml of conc. sulphuric acid, cooled to -12°C was added dropwise with stirring over 1½ h. The mixture was stirred for a further 2½ h at this temperature. The solution was then poured into 200 ml of iced water and the precipitate was filtered, washed with water until neutral, recrystallised from glacial

acetic acid and then n-propanol to give 2.72g (68% yield) of (6); m.p. 201-204°C (lit.,[39] 202.4°C).

δ_H (200 MHz): 7.40-7.65 (m, 4H), 7.90-8.08 (m, 1H), 8.10-8.20 (d, 2H), 8.30-8.40 (dd, 1H), 8.80-8.88 (d, 1H).

δ_C (50 MHz): 178.48 (C), 159.62 (C), 144.49 (C), 138.37 (C), 135.32 (C), 132.25 (CH), 129.32 (2CH), 128.33 (2CH), 124.67 (CH), 121.95 (CH), 121.17 (CH).

ν_{max} (cm^{-1}): 1522, 1323, 1338.

m/z: 304 (3.2), 274 (31.2), 258 (14.3), 246 (17.3), 63 (100).

Microanalysis: Found C, 51.35; H, 2.39; N, 9.24

$C_{13}H_8N_2O_2Se$ requires C, 51.49; H, 2.64; N, 9.24

6-Amino-2-phenylbenzoselenazole (7)

5.4g (1.78×10^{-2} mol) of (6) was added to a mixture of 8.5g (7.14×10^{-2} mol) of granular tin and 25 ml of conc. hydrochloric acid at 0°C with a further 75 ml of conc. hydrochloric acid being added. After the exothermic reaction had subsided the solution was heated at 80-90°C for 1 h then filtered while hot. The solution was basified to pH 14 with 4M sodium hydroxide solution, filtered and the precipitate was washed with the aforementioned solution then with water until neutral. Recrystallisation from n-propanol afforded 1.37g (28% yield); m.p. 201-203°C (lit.,[78] 201.2-202.3°C).

δ_H (90 MHz): 6.5-8.0 (m), δ 3.8 (s, D_2O exchange).

δ_H (200 MHz): 3.76-3.82 (b, 2H), 8.55-8.65 (dd, 1H), 8.14-8.17 (dd, 1H), 7.40-7.50 (m, 4H), 7.83-7.89 (dd, 1H), 7.90-8.00 (m, 1H).

δ_C (50 MHz): 167.58 (C), 149.01 (C), 144.52 (C), 139.94 (C), 136.34 (C), 130.29 (CH), 128.92 (2CH), 127.51 (2CH), 125.13 (CH), 115.21 (CH), 109.27 (CH).

ν_{max} (cm^{-1}): 3456, 3314, 3195, 1623, 1603, 1510, 1283, 1320.

m/z: 274 (100), 258 (0.5), 171 (22.9), 91 (37.1).

Microanalysis: Found C, 53.57; H, 3.26; N, 10.04

$C_{13}H_{10}N_2Se$ requires C, 57.14; H, 3.66; N, 10.25

6-Benzalamino-2-phenylselenazole (8)

1.12g (4.10×10^{-3} mol) of (7) was dissolved in 10 ml of propanol and reacted with excess benzaldehyde to produce crystals which were recrystallised from propanol to yield 1.31g (88%); m.p. 149-151°C (lit.[78] 156°C).

δ_H (200 MHz): 6.85-7.85 (m).

δ_C (50 MHz): 160.61 (CH), 154.22 (C), 149.33 (C), 139.18 (C), 136.14 (C), 136.08 (C), 131.58 (CH), 130.97 (CH), 129.67 (2CH), 128.89 (2CH), 128.84 (2CH), 127.89 (2CH), 124.98 (CH), 120.42 (CH), 116.62 (CH).

ν_{max} (cm^{-1}): 1624, 1508, 1482.

m/z: 361 (100), 181 (8.9), 257 (8.9), 103 (9.7), 63 (41.6).

Accurate: Found 362.0332

$C_{20}H_{14}N_2Se^{80}$ requires 362.0322

2,6-Diphenylbenzo-*bis*-selenazole (9)

1.03g (2.85×10^{-3} mol) of (8) was heated with 1g of grey selenium (1.27×10^{-2} mol) at 240-250°C in a sand bath for 24 h. The resultant molten product mixture

was pulverised as before and extracted with 75 ml of hot conc. hydrochloric acid, filtered while hot and poured onto 200 ml of iced water; this gave a small amount of precipitate which was carefully filtered off. There was no attempt at recrystallisation.

δ_H (200 MHz): 6.87-7.44 (m).

δ_C (50 MHz): 171.79 (2C), 153.08 (2C), 135.76 (2C), 133.97 (C), 131.16 (2CH), 129.13 (4CH), 127.45 (4CH), 122.89 (4CH).

δ^{77}Se (38.18 MHz) (Ref. Me_2Se at δ0 in $CDCl_3$): 640.19 (s).

m/z: 440* (63.1), 439* (100), 438* (86.2), 441* (22.1), 442* (4.8), 437* (67.4), 436* (29.5), 435* (48.8), 434 (4.1), 433 (14.3), 432 (4.7), 431 (3.1).

Synthetic procedures to 2,6-diphenylbenzo-*bis*-thiazole (16)

2-Phenylbenzothiazole (12)[39,78]

96g (0.53 mol) of (4) was added to 46g (1.44 mol) of sulphur and heated in a flask using a Bunsen burner. The reaction mixture became a brown refluxing oil with what appeared to be balls of sulphur smoking on the surface. After 1½ h heating the mixture was cooled to a solid and pulverised as before; the resultant fragmented solid was extracted twice with 200 ml aliquots of hot conc. hydrochloric acid. The solution obtained was filtered while hot and poured onto 3 L of ice water to produce 44g of crude precipitate which was washed until neutral, dried and recrystallised from n-propanol to afford 18.15g (16% yield) of product.

δ_H (200 MHz): 7.30-7.73 (m, 5H), 7.80-7.94 (dd, 1H), 7.95-8.30 (m, 3H).

δ_C (50 MHz): 121.62 (CH), 123.21 (CH), 125.18 (CH), 126.31 (CH), 127.54 (2CH), 129.01 (2CH), 130.97 (CH), 133.56 (C), 135.02 (C), 154.10 (C),168.08 (C).

ν_{max} (cm^{-1}): 1478, 1433, 1314, 1225, 965, 766, 760, 698, 686, 623.

m/z: 211 (42.7), 184 (12.2), 163 (17.0), 82 (51.1), 77 (26.0), 76 (32.3), 69 (100), 63 (60.3), 51 (49.0).

Accurate: Found 211.0455

$C_{13}H_9N_2S$ requires 211.0456

6-Nitro-2-phenylbenzothiazole (13)[39,78]

17.03g (8.1 mmol) of (12) was reacted with conc. nitric/sulphuric acid mixture according to literature procedure to yield 19.7g of crude material which was recrystallised from n-propanol to afford 16.82g (66% yield).

δ_H (200 MHz): 7.73-7.81 (t), 8.10-8.55 (m), 8.90-8.93 (d), 8.96-9.03 (t).

δ_C (50 MHz): 116.67 (CH), 120.74 (CH), 122.59 (CH), 122.92 (2CH), 127.14 (2CH), 131.79 (CH), 134.08 (C), 136.40 (C), 186.23 (C).

ν_{max} (cm^{-1}): 3441, 1516, 1476, 1443, 1342, 1333, 761, 685.

m/z: 256 (15.8), 226 (43.7), 210 (8.5), 198 (24.2), 77 (15.0), 76 (10.9), 63 (100), 51 (17.2).

Accurate: Found 256.0313

$C_{13}H_8N_2O_2S$ requires 256.0305

6-Amino-2-phenylbenzothiazole (14)[39,78]

15.03g (6.65 x 10^{-2} mol) of (13) was dissolved in 100 ml of conc. hydrochloric acid. Contrary to literature conditions the solution was cooled to 0°C before the addition of 24.2g tin powder (0.2 mol), carried out over 5 min. After a couple of minutes the reaction became extremely exothermically vigorous and began to overflow. After a further 5 min the reaction returned to a cooled state where only 20% of the reactant solution remained in the flask. The ice bath containing 80% of the solution was decanted into a 5L conical flask to which 700 ml of conc. hydrochloric acid was added. Approximately 10g of granular tin was placed in the flask and the reaction stirred for 1 h. Both reaction mixtures were then poured into 4L of iced water. The solution was filtered and made alkaline with solid sodium hydroxide and 4M aqueous sodium hydroxide. The resulting precipitate was collected, washed with water until neutral and then recrystallised from toluene to afford 1.97g (14%) of (14).

δ_H (200 MHz): 3.83 (br s, 2H), 1.61 (s, 1H), 6.66-6.89 (m, 1H), 7.09-7.53 (m, 4H), 7.74-7.89 (m, 1H), 7.97-8.08 (m, 1H).

δ_C (50 MHz): 105.71 (CH), 115.72 (CH), 127.10 (2CH), 128.93 (2CH), 129.86 (CH), 130.27 (CH), 144.44 (C).

ν_{max} (cm^{-1}): 3449, 3370, 3316, 3196, 2365, 2345, 1618, 1609, 1487, 1464, 1298, 1289, 835, 820, 689.

m/z: 226 (96.0), 123 (26.8), 96 (17.6), 79 (10.5), 52 (11.9).

Accurate: Found 226.0569

$C_{13}H_{10}N_2S$ requires 226.0566

6-Benzalamino-2-phenylbenzothiazole (15)

1.35g (6.0×10^{-3} mol) of (14) was reacted with benzaldehyde according to literature procedure and the product was recrystallised from n-propanol to produce 1.74g (93%) of (15).

δ_H (200 MHz): 7.28-7.60 (m, 8H), 7.70-8.18 (m, 5H), 8.51 (s, 1H), 8.57 (s, 0.1H).

δ_C (50 MHz): 167.24 (C), 161.16 (CH), 154.32 (C), 152.69 (C), 149.37 (C), 136.05 (C), 131.80 (CH), 131.21 (C), 129.02 (2CH), 128.86 (4CH), 128.47 (2CH), 123.39 (CH), 121.56 (CH), 120.62 (CH), 113.28 (CH).

ν_{max} (cm^{-1}): 3432, 3054, 3027, 2926, 2874, 2361, 2346, 1622, 1574, 1476, 1449, 1316, 968, 883, 841, 822, 756, 691, 600, 536.

m/z: 248, 242, 227, 202, 200, 198, 190, 184, 125, 123, 108, 106 (100), 69.

Microanalysis: Found C, 76.43; H, 4.45; N, 8.92

$C_{20}H_4N_2S$ requires C, 76.06; H, 4.57; N, 9.72

2,2-Diphenylbenzo-*bis*-thiazole (16)

1.23g (3.9×10^{-3} mol) of (15) was heated with 0.5g (1.57×10^{-2} mol) of sulphur with a Bunsen burner for 1 h and extracted as previously described. It was impossible to collect such a fine amount of precipitate so the solution was filtered through several layers of glass filter paper which was subsequently extracted with hot n-propanol to give 8 mg of yellow solid.

δ_H (200 MHz): 0.60-2.50 (m), 7.41-7.68 (m), 7.80-8.30 (m), 8.68 (s).

δ_C (50 MHz): 14.14 (CH), 22.69 (CH_2), 29.70 (CH_2), 56.78 (CH), 121.73 (2CH), 127.51 (4CH), 127.70 (4CH), 131.14 (CH), 133.26 (C).

m/z: 347 (100), 346 (27), 345 (15), 344 (3), 172 (18), 138 (12), 69 (18), 49 (18), 33 (19).

Accurate: Found 344.0465

$C_{20}H_{12}N_2S_2$ requires 344.0442

SECTION II

1.3-Diphenylpropane (see Fig. 38)

15g (0.071 mol) of dibenzyl ketone was reacted according to literature procedure[22,79] in 89% yield to produce 1,3-diphenylethane.

δ_H (90 MHz): 2.1-2.4 (m, 2H), 2.7-3.0 (t, 3H), 7.3-8.0 (m, 10H).

δ_H (200 MHz): 2.08-2.28 (quintet with 3 central peaks shouldered, 2H), 2.78-2.94 (t, 4H), 7.33-7.58 (m, 10H).

δ_C (50 MHz): 32.91 (CH_2), 35.36 ($2CH_2$), 125.68 (2CH), 128.17 (4CH), 128.24 (4CH), 142.14 (2C).

ν_{max} (cm^{-1}): 3091, 3063, 3030, 2939, 2858, 1496, 1452, 746, 700.

m/z: 196 (24.5), 105 (42.2), 104 (18.7), 103 (17.8), 91* (100), 85 (24.3), 83 (37.4), 79 (28.5), 78 (23.6), 77 (46.8), 65 (56.8), 63 (20.6), 51 (45.6), 50 (20.5), 47 (24.1), 39 (43.2).

Accurate: Found 196.1250

$C_{15}H_{16}$ requires 196.1252

Azine (see Fig. 38)

Produced as a by-product in the synthesis of 1,3-diphenylpropane.

δ_H (200 MHz): 3.66 (s, 4H), 3.78 (s, 4H), 7.00-7.19 (m, 4H), 7.20-7.46 (m, 16H).

δ_C (50 MHz): 35.92 ($2CH_2$), 42.66 (2CH), 126.26 (2CH), 126.52 (2CH), 128.43 (4CH), 128.49 (4CH), 129.27 (4CH), 129.32 (4CH), 136.92 (2C), 137.14 (2C), 165.014 (C).

ν_{max} (cm^{-1}): 3080, 3050, 3028, 2924, 1629, 1598, 1493, 1453, 1432, 754, 751.

m/z: 417 (13.9), 326* (21.3), 206 (3.9), 117 (4.4), 92 (9.2), 91 (100), 65 (17.1).

Microanalysis: Found C, 86.44; H, 6.84; N, 6.67

$C_{30}H_{28}N_2$ requires C, 86.53; H, 6.73; N, 6.73

4,4'-Diacetyl diphenyl methane

4.2g of diphenyl methane (0.025 mol) was dissolved in 25 ml of CCl_4 with 14g (0.1 mol) of $AlCl_3$ and cooled to 0°C. 5.1g (0.05 mole) of acetic anhydride was added dropwise over 30 min with overhead stirring. On completion of the addition the temperature was raised to 60-70°C for 1 h. The solution was then cooled and poured onto 500 ml of iced water. A dark oil was obtained after extraction with Et_2O and was flash chromatographed on silica to produce 4.13g (66% yield).

δ_H (90 MHz): 2.5 (s, 6H), 4.05 (s, 2H), 7.1-7.3 (d, 4H), 7.7-8.0 (d, 4H).

δ_H (200 MHz): 2.44 (s, 6H), 3.95 (s, 2H), 7.13-7.18, 7.75-7.80 (AB quartet, 4H).

δ_C (50 MHz): 26.54 ($2CH_3$), 41.70 (CH_2), 128.71 (4CH), 129.08 (4CH), 155.37 (2C), 145.62 (2C), 197.62 (2C).

ν_{max} (cm^{-1}): 1678, 1670, 1600, 1411, 1359, 1270, 961, 825.

m/z: 252 (31.7), 237* (100), 209 (2.0), 195 (9.6), 165 (42.3), 139 (9.0), 115 (7.9), 89 (14.8), 63 (11.9), 51 (7.2), 43 (93.9), 32 (40.0).

Microanalysis: Found C, 80.84; H, 6.42%

$C_{17}H_{18}O$ requires C, 80.95; H, 6.32%

4,4'-Dimethylbenzophenone (20)

(1)[52] Toluene (9.2g, 0.1 mol) was added dropwise to a solution of aluminium chloride, 13.3g (0.1 mol) in 30.8g (0.2 mol) of carbon tetrachloride at < 10°C during which time the reaction mixture turned purple. After addition the mixture was allowed to rise to room temperature and was stirred for a further 2 h with an overhead mechanical stirrer. The solution was then poured into 500 ml of iced water and extracted with chloroform. The solvent was removed and after several days crystals appeared; these were recrystallised from ethanol to give 1.07g (5% yield).

(2)[53] 27g (0.2 mol) of aluminium chloride was stirred, using an overhead mechanical stirrer in 60 ml of carbon tetrachloride at 0°C. To this, toluene (50 ml, 0.48 mol) mixed with 20 ml of carbon tetrachloride was added dropwise, the reaction mixture turning russet in colour. The mixture was allowed to rise to room temperature after addition was completed. It was then poured into one litre of iced water and vigorously stirred for 1 h. Repeated extractions with ether and subsequent removal of solvent *in vacuo* left a dark green/brown liquid. After 4 days no crystals appeared so the sample was subjected to flash column chromatography by elution with ether; repetition produced a yellow/green oil. Purification by column chromatography on neutral alumina with 10% Et_2O/90% petroleum ether 40-60° as eluent afforded 2.14g (2% yield).

δ_H (90 MHz): 2.5 (s, 6H), 7.1-7.8 (2d, 8H).

δ_H (200 MHz): 2.42 (s, 6H), 7.24-7.28, 7.67-7.71 (AA'BB' quartet, 8H).

δ_C (50 MHz): 21.56 ($2CH_3$), 128.82 (4CH), 130.10 (4CH), 135.10 (2C), 142.84 (2C), 196.17 (C).

ν_{max} (cm^{-1}): 1643, 1603, 1311, 1297, 1278, 1175, 976, 752.

m/z: 210 (26.1), 195 (14.9), 165 (8.5), 120 (8.4), 119 (100), 91 (93.9), 90 (15.0), 89 (26.4), 63 (30.7), 51 (15.5), 39 (40.0).

Accurate: Found 210.1038

$C_{17}H_{18}O$ requires 210.1041

Microanalysis: Found C, 85.68; H, 6.82%

$C_{17}H_{18}O$ requires C, 85.71; H, 6.67

By-product (21)

The early fractions eluted from the gravity column purification of (20) experiment (2) were combined and recolumned on an alumina gravity column with 1% Et_2O/99% petroleum ether 40-60° as eluent. This afforded a white powder which was recrystallised from dioxan giving white needles; m.p. 109°C (lit. 111°C).

δ_H (90 MHz): 1.1-1.3 (t, 3H), 2.3 (s, 9H), 2.9-3.2 (q, 2H), 6.9-7.3 (AA'BB' quartet, 12H).

δ_H (200 MHz): 1.18, 1.22, 1.25 (t, 3H), 2.31 (s, 9H), 3.02-3.13 (q, 2H), 7.06/7.10 - 7.29/7.33 (AA'BB' quartet, 12H).

δ_C (50 MHz): 15.34 (CH_3), 21.00 ($3CH_3$), 59.21 (CH_2), 114.75 (C), 128.38 (6CH), 128.49 (6CH), 136.21 (3C), 141.94 (3C).

ν_{max} (cm^{-1}): 3022, 2974, 2919, 2872, 1501, 1180, 1113, 1080, 826, 812, 803, 783.

m/z: 330 (4.0), 315 (0.6), 285 (28.6), 270 (1.2), 271 (16.4), 229 (2.0), 211 (6.4), 193

(21.8), 179 (17.0), 119* (100), 92 (14).

Microanalysis: Found C, 87.81; H, 7.94

$C_{24}H_{26}O$ requires C, 87,27; H, 7.88

4,4-'*bis*(Bromomethyl)benzophenone (22)

(1)[58] 5g (0.024 mol) of (20) was dissolved in 125 ml of dry carbon tetrachloride and 8.5g (0.048 mol) of N-bromosuccinimide (NBS), recrystallised from water, was added. A 160W lamp illuminated the reaction solution for 3 h with the temperature retained below 40°C; the solution was then heated at 60°C for 30 min, after which time succinimide was floating in the reaction vessel. Filtration and reduction *in vacuo* of the solution left 8.3g of crude material, recrystallised from carbon tetrachloride to afford 6.05g (69%) of (22); m.p. 120-124°C (lit.,[58] 121°C).

(2) Compound (20) 5.2g (2.48×10^{-2} mol) and NBS, 9.1g (5.1×10^{-2} mol) were dissolved in 150 ml of freshly distilled carbon tetrachloride to which a small spatula of benzoyl peroxide had been added as radical initiator. The reaction was heated at 60°C for 12 h then refluxed for 2½ days. Filtration of the cooled solution removed succinimide; reduction of the filtrate *in vacuo* afforded 10.1g of crude material. Double recrystallisation from carbon tetrachloride produced 5.12g (56%) of pale yellow crystals of (22); m.p. 120-123°C.

δ_H (200 MHz): 4.53 (s, 4H), 6.69 (s, $CHBr_2$, 0.15H), 7.46/7.52 - 7.74/7.79 (AA'BB' quartet, 8H).

δ_C (50 MHz): 32.31 ($2CH_2$), 129.01 (4CH), 130.50 (4CH), 137.11 (2C), 142.27 (2C), 195.19 (C).

ν_{max} (cm^{-1}): 3447, 2419, 2361, 1649, 1603, 1412, 1279, 1179, 928, 689, 612.

m/z: 368 (5.5), 366 (10.7), 289 (3.9), 287 (4.4), 285 (1.2), 260 (11.4), 259 (16.2), 258 (11.2), 257 (12.5), 181 (11.9), 180 (58.2), 91 (11.9), 90 (89.2), 89* (100), 39 (21.8).

Accurate: Found 365.9229

$C_{15}H_{12}O^{79}Br_2$ requires 365.9255

Compound (24)

(1) Compound (22), 1.47g (4.0 mmol), in 200 ml of toluene and butane-1,4-dithiol (23), 0.488g (4.0 mmol) in 200 ml of ethanol with Cs_2CO_3, 1.44g (4.0 mmol), of which approximately 90% dissolved, were added separately *via* dropping funnels, under nitrogen, into a flask containing 600 ml of refluxing ethanol. After 11 h approximately 50-60% of the solutions had been added. The addition and heating were stopped overnight, but next morning all the thiol solution had leaked into the reaction flask. The resultant solution was heated and the solution of dibromide (22) was quickly added (20 min), then refluxed for 6 h. As the reaction mixture cooled it began to turn cloudy. Reduction of the solvent *in vacuo*, extraction with dichloromethane, washing with water, reduction *in vacuo* of the dichloromethane layer followed by gravity column chromatography (alumina prestirred with Et_3N in petroleum ether) with 30% EtOAc/70% petroleum ether 40-60° afforded white crystals; m.p. 199-202°C.

(2)[57] Compound (22), 0.736g (2 mmol), compound (23), 0.244g (2 mmol) together in toluene, 100 ml, were added dropwise to 300 ml of refluxing ethanol containing caesium carbonate, 0.72g (2.0 mmol) (with 90% dissolved). After 50 h of addition

(10 h per day for 5 days) a solid residue and yellow nodules had formed around the side of the flask. Reduction of the solvent volume *in vacuo* followed by extraction with dichloromethane, washing with water and reduction *in vacuo* produced a yellow oil which later hardened. This was purified by gravity column chromatography with 40% Et_2O/40% petroleum ether 40-60°/20% EtOAc as eluent. The product so obtained showed

δ_H (90 MHz): 1.4-1.8 (m, 4H), 2.1-2.5 (m, 4H), 3.7 (s, 4H), 7.2-7.9 (AA'BB' quartet, 8H).

δ_H (200 MHz): 1.44-1.69 (q, 4H), 2.22-2.43 (t, 4H), 3.72 (s, 4H), 7.31/7.41 - 7.70/7.74 (AA'BB' quartet, 4H).

δ_C (50 MHz): 27.82 ($2CH_2$), 30.48 ($2CH_2$), 35.96 ($2CH_2$), 128.72 (2CH), 130.31 (2CH), 136.21 (C), 143.60 (2C), 195.67 (C).

ν_{max} (cm^{-1}): 3434, 2917, 1645, 1605, 1410, 1316, 1306, 1277, 1177, 934, 720, 685.

m/z: 658 (2.3, dimer), 656 (5.9), 655 (11.6), 567 (3.0), 450 (4.6), 416 (11.2), 329 (4.8), 65 (13.9), 59 (9.2), 46 (8.6).

Accurate Mass: Found 329.1005

$^{13}C^{12}C_{18}H_{20}OS_2$ requires 329.0985

CHAPTER 2

INTRODUCTION

Normally the α-effect is said to be operative if a nucleophile whose nucleophilic atom has adjacent, or α to it, an atom that carries a lone pair of electrons *e.g.* NH_2NH_2 as compared to NH_3. The α-effect manifests itself as a kinetic effect *i.e.* NH_2-NH_2 reacts faster than NH_3 with a given substrate. Another example is H_2O_2 compared to H_2O. The effect is operative towards sp^3, sp^2 or sp hybridised carbons.

To understand the increased rate of reaction, when the α atom has a lone pair of electrons, consideration of the molecular orbital energy diagram must be given. When a filled molecular orbital interacts with an empty molecular orbital then an overall lowering of energy is observed (Fig. 2.1).

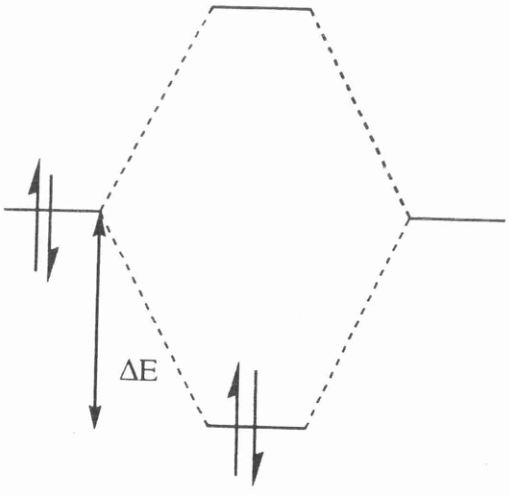


Figure 2.1

However, when two filled molecular orbitals interact then there is no overall lowering of energy, in fact the higher energy molecular orbital formed from the

interaction is now a full energetic species that will react rapidly in an attempt to lower its energy (Fig. 2.2).

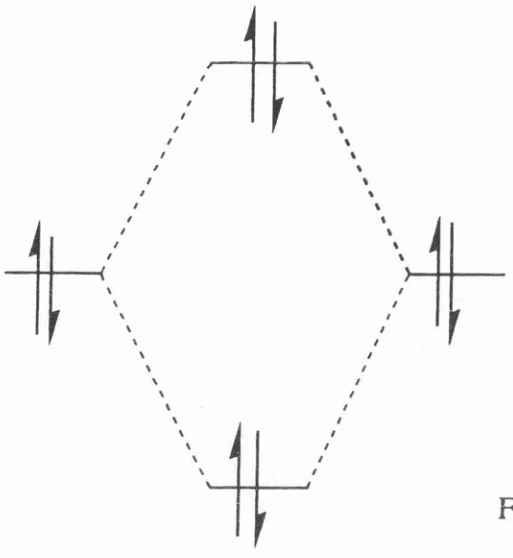
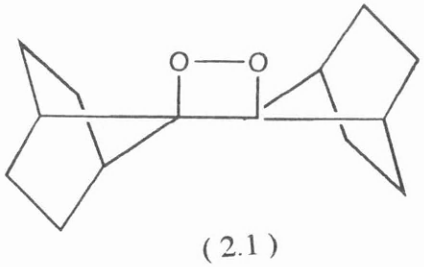


Figure 2.2

This area of research was concerned with the synthesis of a compound which should exhibit the α-effect, namely 7,7-dinorbornyl oxetane (2.1).

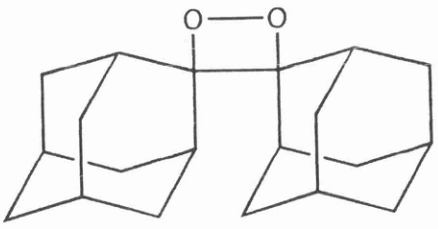


(2.1)

This compound would be studied for the α-effect on basicity,and equilibrium position , in the gas phase *i.e.* without the influence of solvent, by Dr. J.-F. Gal, University of Nice, France.

Previously 1,1-diadamantyl oxetane (2.2) had been studied but was found to be too involatile for measurements in the ion cyclotron resonance spectrometer since it decomposed in the inlet manifold when being heated in order to gain a working

vapour pressure.

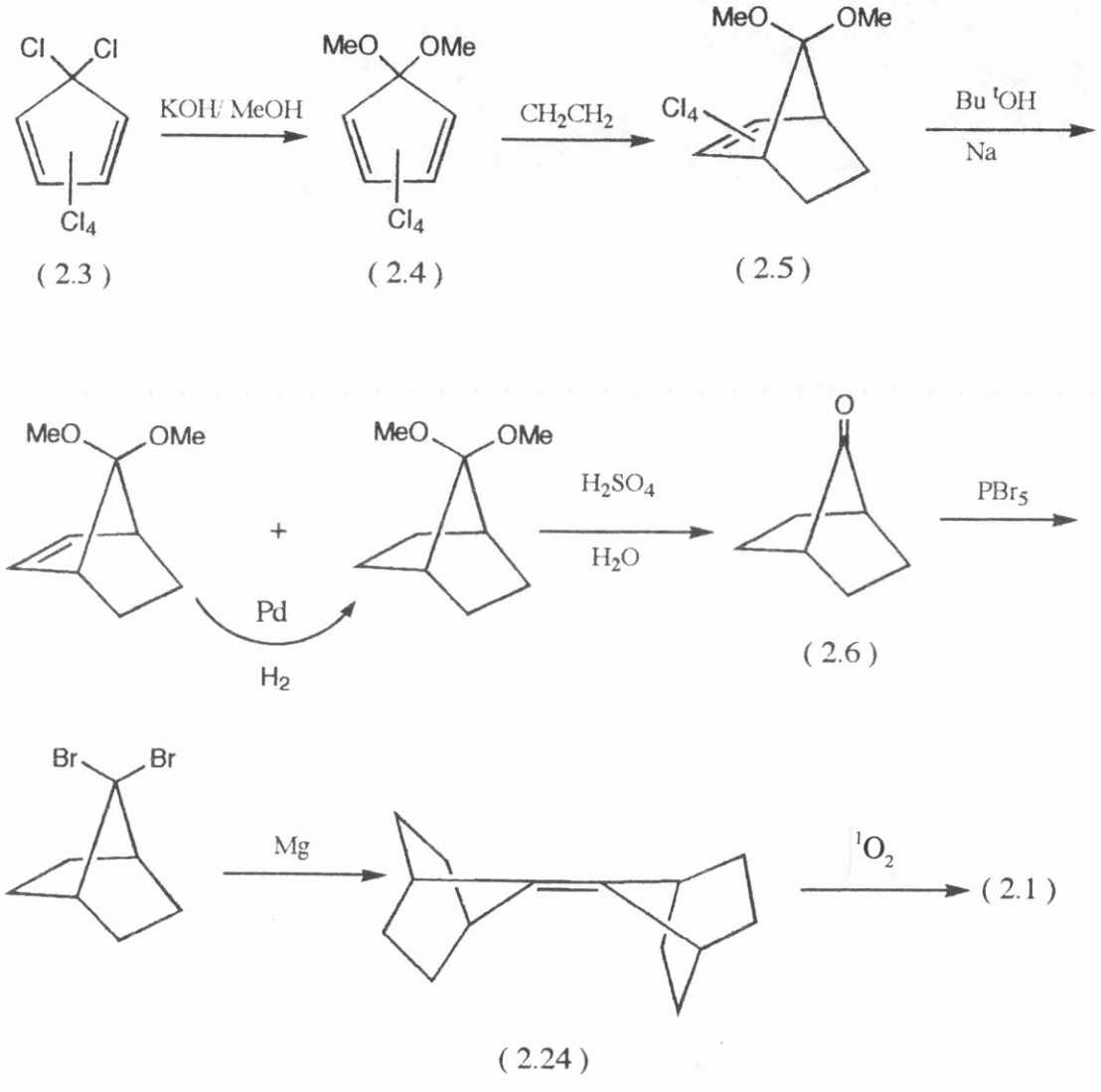


(2.2)

Accordingly we sought to make the norbornyl analogue which, having six carbons fewer, would possess a greater vapour pressure. Only a very limited number of stable dioxetanes are known.

RESULTS AND DISCUSSION

7,7-Dinorbornyl oxetane (2.1) has been synthesised previously by the route outlined below (Scheme 2.1).



(2.3) (2.4) (2.5) (2.6) (2.1)

(2.24)

Scheme 2.1

5,5-Dimethoxytetrachlorocyclopentadiene (2.4) was prepared from hexachloro-cyclopentadiene (2.3) and methanolic potassium hydroxide although small amounts of other methoxy products were also formed which could not be separated by either vacuum distillation or gravity column chromatography.

Literature[88] suggests the use of ethene for the next stage which proved to be unsuitable on two accounts: ethene is bubbled continuously through (2.4) for 6 h which would require large quantities of expensive ethene, secondly, the reaction temperature is 200°C and a lack of suitable apparatus prevented this approach.

Instead, maleic anhydride (2.7) was employed as the dienophile, which is a reactive dienophile, in a Diels-Alder reaction with (2.4).

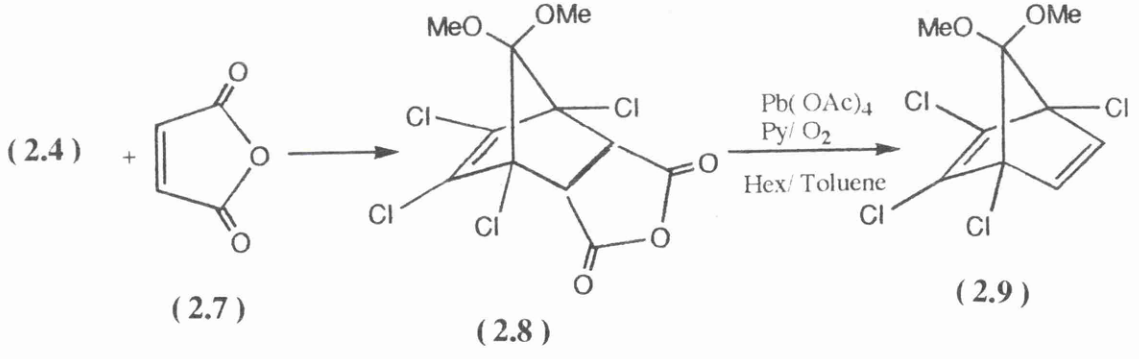


Fig 2.3

Oxidative decarboxylation of the anhydride (2.8)[83,84] with recrystallised lead tetra-acetate, $Pb(OAc)_4$, would then produce the diene which could be used as an intermediate in the synthesis of (2.1). However various reaction conditions afforded no products. From the review by De Lucchi and Modena[83] it may be expected that

a lactone would form if the anhydride was in the *endo* position (Fig. 2.4).

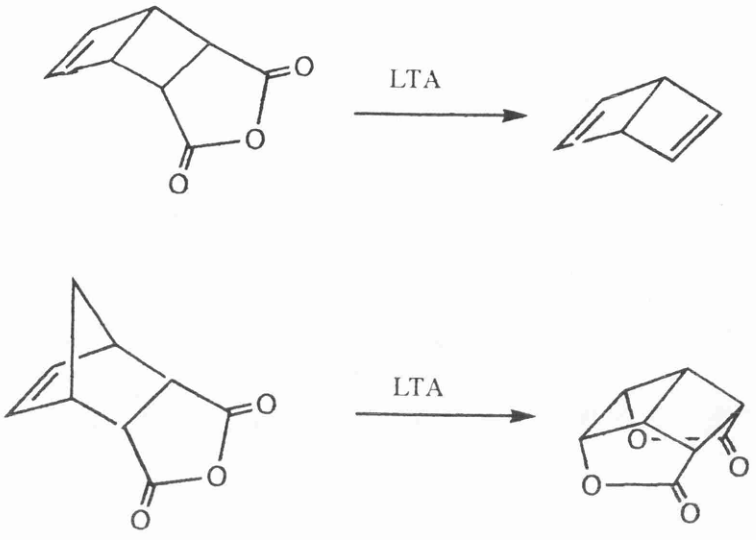
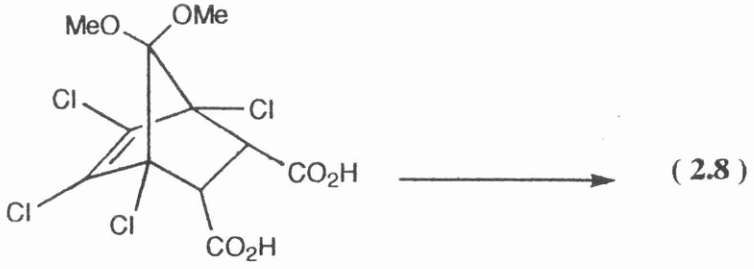


Fig 2.4

It was hoped however that the presence of the four chlorine atoms would reduce this possibility by sterically hindering lactone formation and by reducing the alkene reactivity. Therefore the diene would be the main product. As stated, no products or any isolable material was recovered and so a different route was studied.

The anhydride was converted into the diacid by means of hydroxide ion and subsequent acidic work-up. The diacid (2.10) was then subjected to various



(2.10) (2.8)

oxidative decarboxylation conditions with the alkene as desired product.

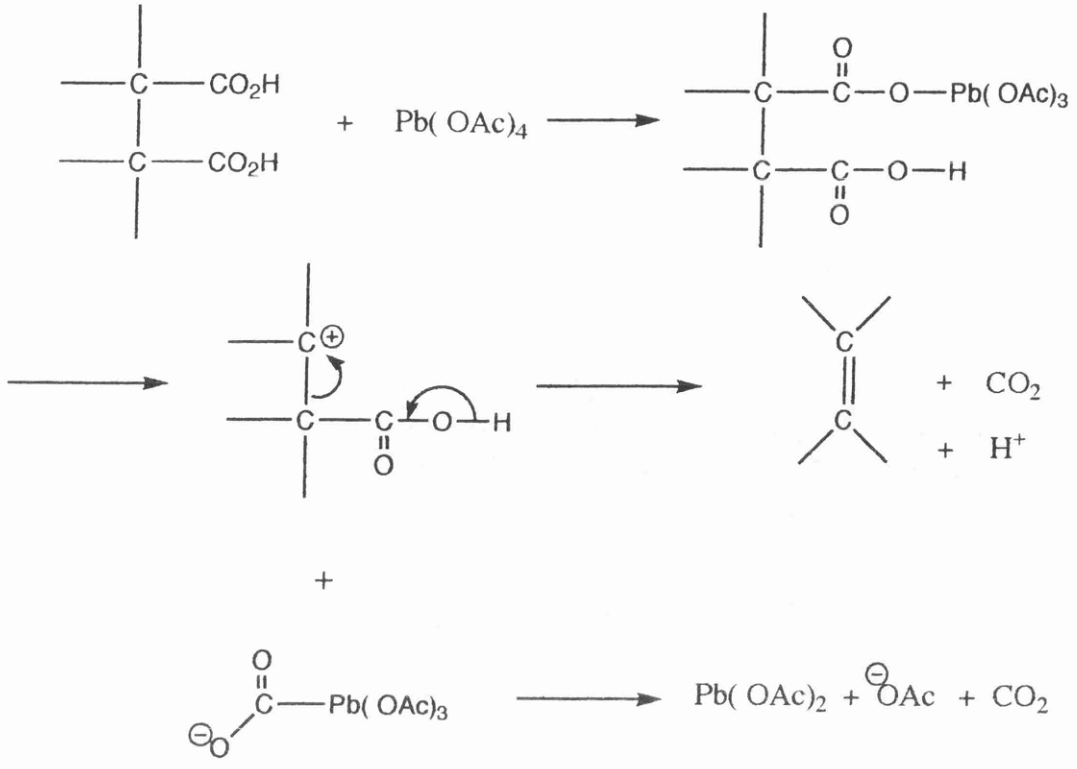


Fig 2.5

De Lucchi and Modena[83] suggested that attempts to decarboxylate an *endo* dicarboxylic acid led to lactone formation *via* an electrophilic interaction between the lead tetra-acetate and the double bond, except where the double bond is an integral part of an aromatic sextet. However the presence of four chlorine atoms may interfere with any such electrophilic interaction especially as the chlorine atom situated on the double bond will pull electrons away from the π-system leaving it less prone to electrophilic attack.

Due to a lack of success a new route was developed; again we started with compound (2.4) as a diene in a Diels-Alder reaction (Fig. 2.6).

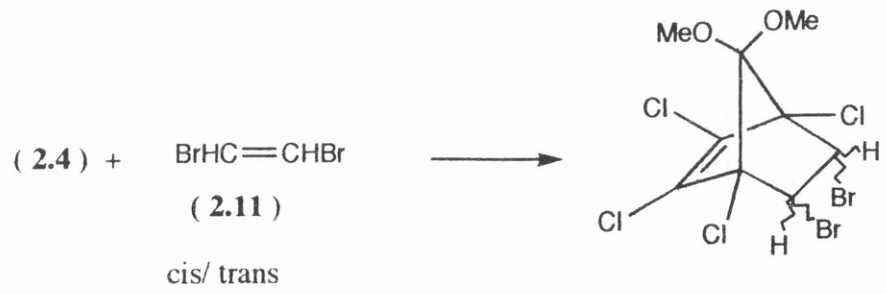
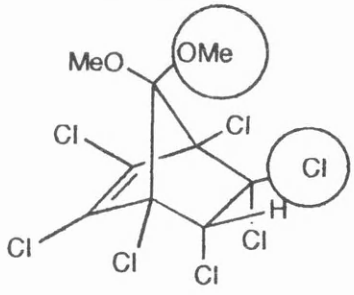


Fig 2.6

Previously the dienophile employed had been 1,1,2-trichloroethene. This is inexpensive, a liquid (unlike ethene) and reactive, due to the electron-withdrawing effect of three chlorine atoms which lowers LUMO. However repeated attempts at Diels-Alder addition proved unavailing. One explanation is that there is exceptional steric hindrance between an *exo* chlorine and a bridge methoxy group (2.12).



(2.12)

The desired compound was produced, as depicted in Figure 2.6, from a mixture of *cis/trans*-dibromoethene as the dienophile. From the crystals obtained a ^{1}H NMR spectrum was obtained and subsequently an NOE (Nuclear Overhauser Enhancement) was taken in order to determine whether or not the bromine atoms were *endo* or *exo* (Fig. 2.7).[85]

In the NOE experiment one of the protons is irradiated at its resonance frequency and the signal of the second proton, with which the first is interacting across space, is detected as an intenser or weaker signal. The difference between the irradiated and unirradiated spectra are calculated by computer, then printed as an NOE difference spectrum.

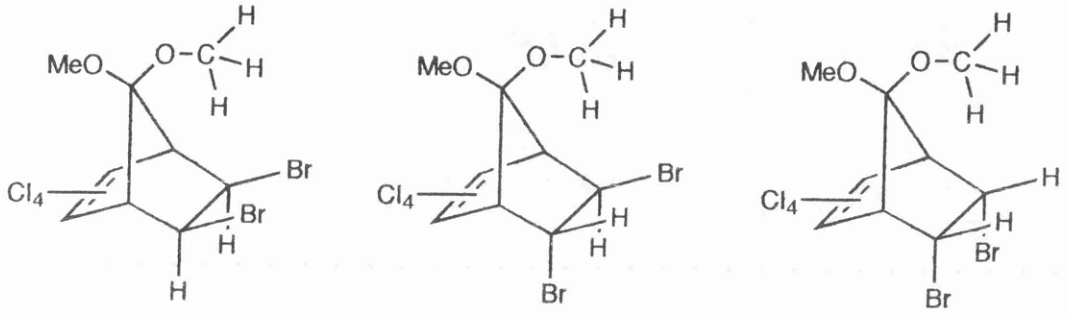
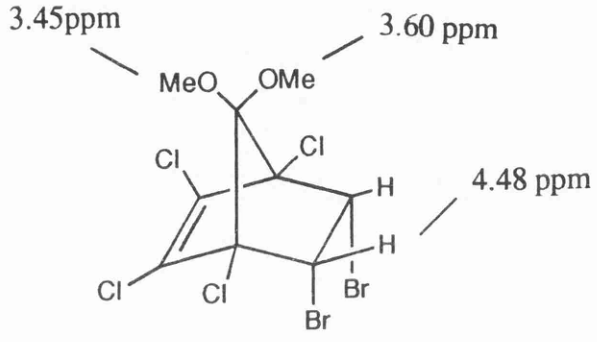


Fig 2.7

The methoxy protons of (2.13) absorb at δ 3.54 and δ 3.60 while the protons geminal to bromine absorb at δ 4.84. The methoxy methyl groups are non-equivalent as they lie above chemically non-identical parts of the molecule resulting in a small chemical shift difference. If the signal at δ 4.84 is irradiated then from the NOE difference spectrum a 2% enhancement of the signal at δ 3.60 was detected. When the signal at δ 3.60 was irradiated a 3% enhancement of the signal at δ 4.84 was detected. Finally when the methoxy methyl group at δ 3.54 was irradiated there was no enhancement of the signal at δ 4.84.

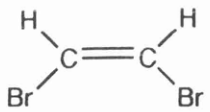
This evidence suggests that the protons of the dienophile are now in an *exo* position. We can now also identify each methoxy group with the -OMe group protons lying over the double bond resonating at δ 3.54 while the -OMe group protons lying above the *exo* protons are at δ 3.60 (Fig. 2.8).



(2.13)

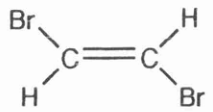
Figure 2.8

It is also possible to verify that it is only the *cis* isomer that reacts with the diene and not the *trans* isomer. The method involved looking at the kinetic change in the ratio of integrals between the *cis* and *trans* isomers as the reaction progresses. Firstly, however, we have to determine which NMR signal is attributable to each isomer. If the spectrum baseline is expanded and amplified it is possible to observe numerous peaks due to isotopomers containing carbon-13. The two isomers A and B (Fig. 2.9) produce the main ^{1}H absorptions at δ 6.62 and δ 7.00. However if there is one carbon-13 atom present then new possibilities arise (Fig. 2.9).



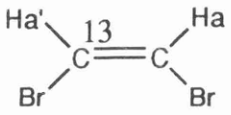
(2.14)

A

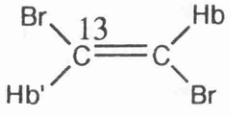


(2.15)

B



C



D

Figure 2.9

In isotopomer C both protons are still chemically equivalent but are magnetically non-equivalent. Thus proton $H_{a'}$ is coupled to ^{13}C which produces a doublet and the doublet is now further split by coupling to H_a. A similar scenario occurs with the *trans* isomer and proton $H_{b'}$ (Fig. 2.10).

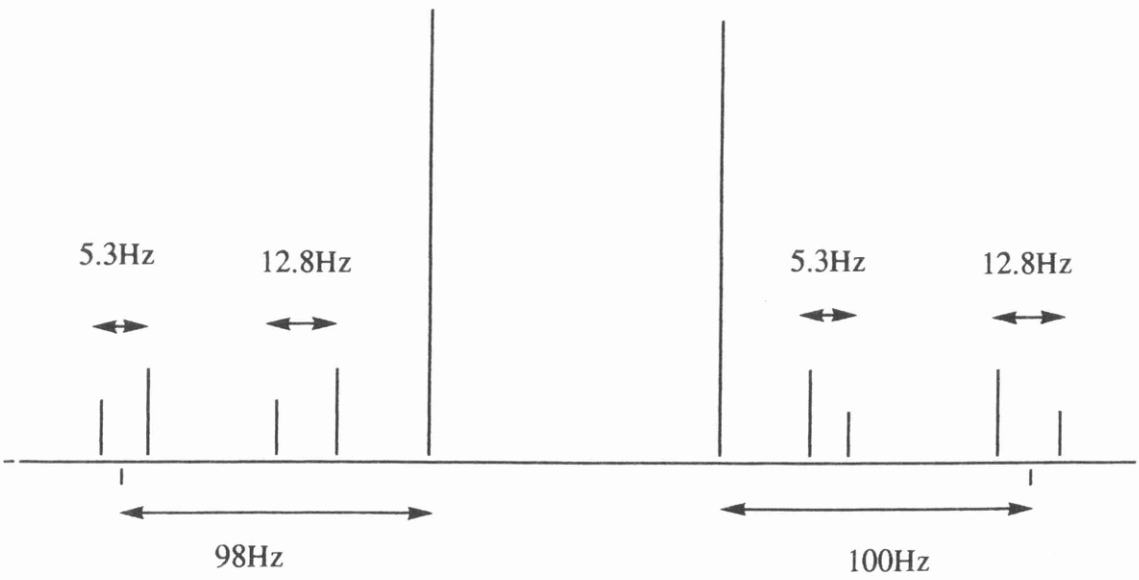
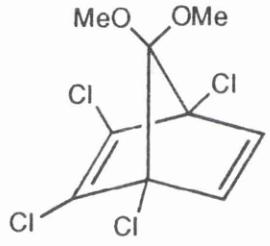


Figure 2.10

From the spectrum it is possible to determine that the signal at δ 6.63 is the *trans* signal as the satellites have a splitting of 12.8 Hz comparable to 5.3 Hz for *cis* coupling. Hence the *cis* isomer produces the signal at 7.02 ppm.

When samples from the reaction are taken at regular intervals it is possible to observe by ^{1}H NMR spectroscopy an overall decrease in the percentage of *cis* isomer during the reaction. As stated in the experimental section hydroquinone was added; this inhibits any addition polymerisation that may occur with dibromoethylene.

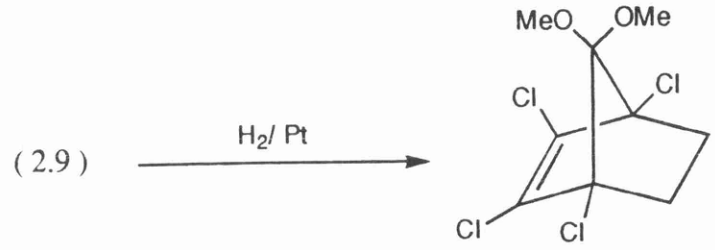
Compound (2.13) was debrominated with zinc and acetic acid to furnish 1,2,3,6-tetrachloro-7,7-dimethoxynorbornadiene (2.9).



(2.9)

Dechlorination with sodium and t-butanol destroyed the majority of the compound with only small amounts of starting material isolated from the reaction mixture, with no alkene ^{1}H NMR signals from the expected product.

Hydrogenation of (2.9) with Pd/C catalyst did not produce any of the expected product, believing that only the unsubstituted double bond would be reduced (Fig. 2.11) with steric hindrance preventing reduction at the other double bond. Extensive heating should be avoided as this can cause decomposition to aromatic chloro-hydrocarbons[86,87]

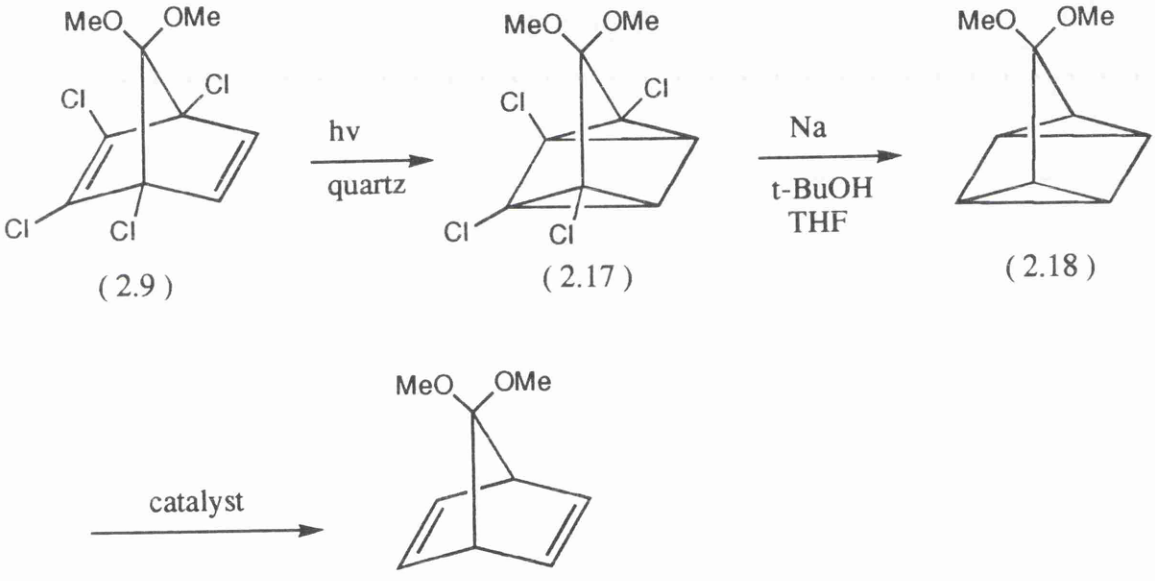


(2.9)

(2.16)

Figure 2.11

In a paper by Bicker, Kempf and Kessler[88] compound (2.9) was used in the synthesis of 7,7-dimethoxynorbornadiene (Fig. 2.12).



(2.9)

(2.17)

(2.18)

7,7 dimethoxynorbornadiene

Figure 2.12

Thus (2.9) was photolysed to produce the quadricyclene (2.17). As the double bonds were isolated and not conjugated short UV wavelengths *i.e.* high energy, are required to activate the double bonds and so quartz must be used as

Pyrex glass absorbs the shorter, more energetic, wavelengths. As with the previous route the next stage involved dechlorination using Na OBu^t. However various attempts to dechlorinate (2.17) provided no product for use in the next stage.

Two problems with the first step in the synthetic route (Scheme 2.1) followed are that some of the products *e.g.* (2.4) are liquids and so are often difficult to purify, due to similar polarity, and that impurities such as (2.4a) are carried through the reaction scheme producing corresponding impurities. One procedure to overcome such a problem is to use ethylene glycol as the initial reactant (Fig. 2.13).

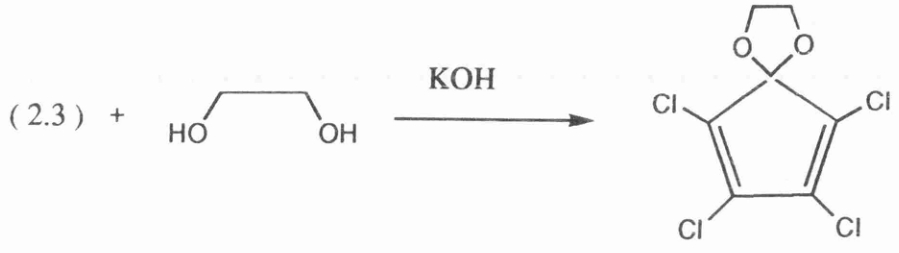


Figure 2.13

The acetal product is a solid and ethylene glycol is more liable to react at the five position, rather than any of the double bond positions, so reducing the chance of any impurities.

The acetal so produced was then subjected to a similar procedure (Fig. 2.14).

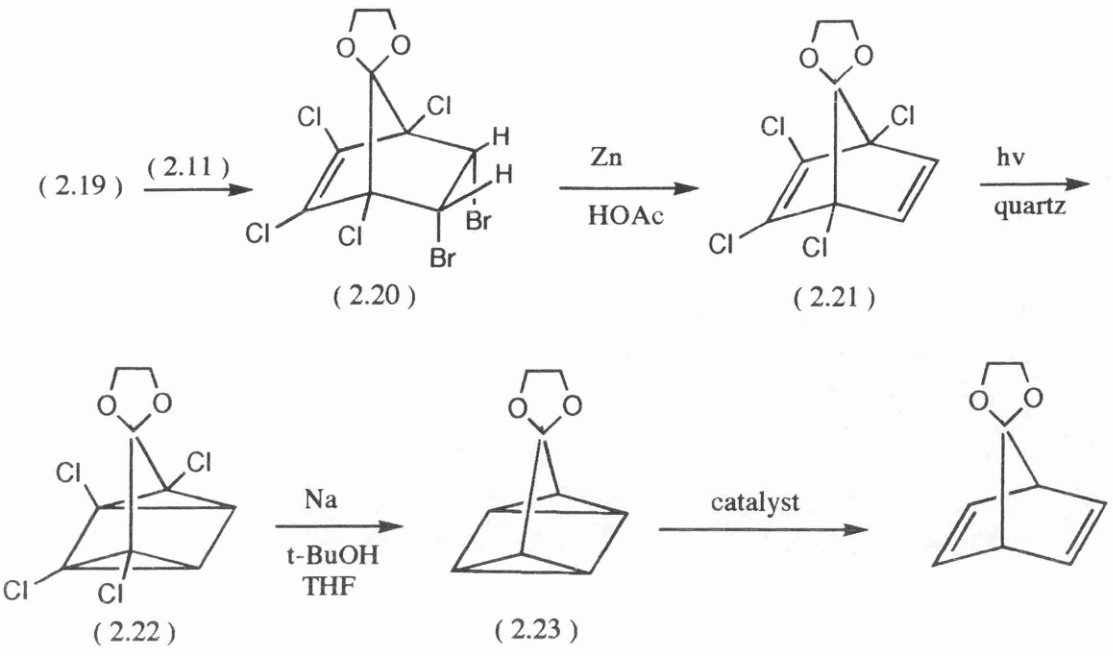


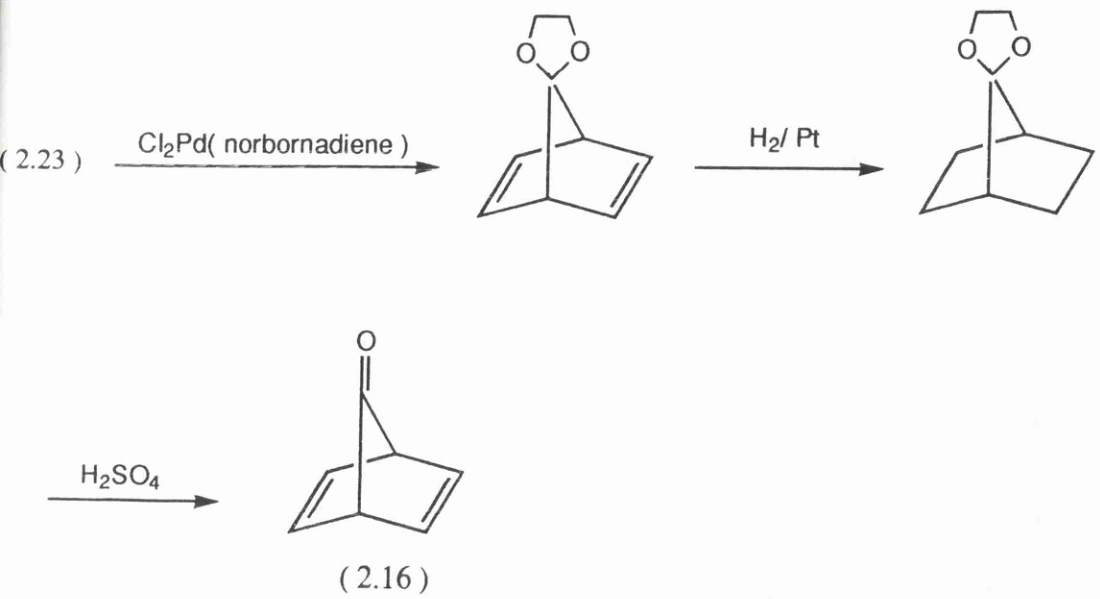
Figure 2.14

Debromination and photolytic cyclisation each afforded solids which were easily purified. However, as before, dehalogenation did not afford sufficient amounts of the desired product.

Further work would look at viable ways of dechlorinating the quadricyclene to the corresponding compound. A palladium catalyst would then be used to convert this compound to the norbornadiene derivative (Fig. 2.15).

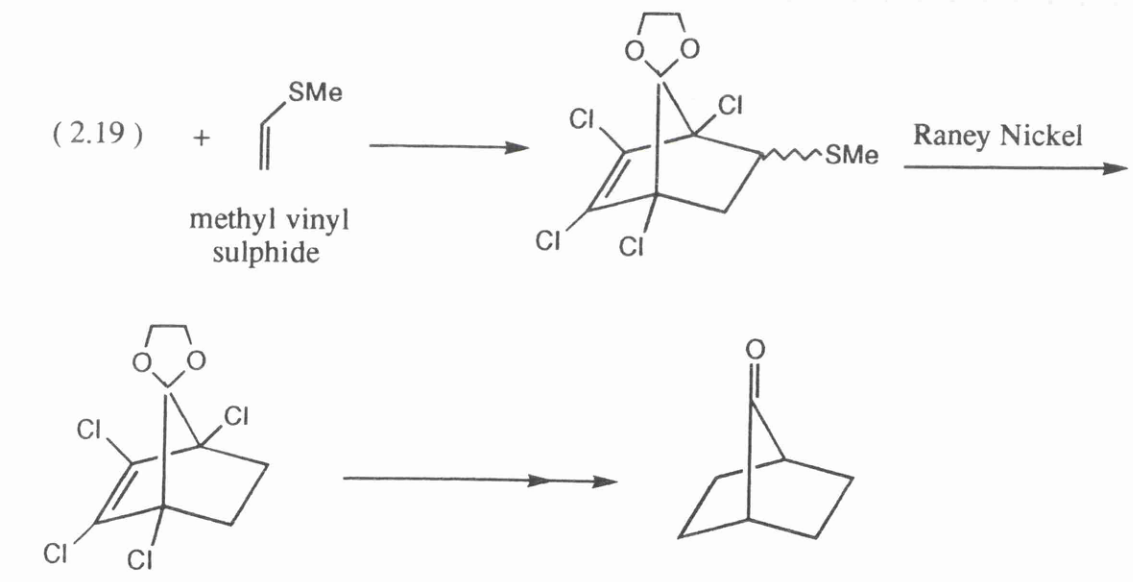
Another possible route to compound (2.6) is shown in Figure 2.16.

Phenyl vinyl sulphoxides can be used as acetylene equivalents in Diels-Alder reactions as the primary cycloadducts may spontaneously extrude sulphuric acid.[90] However, the majority require heating (Figure 2.17).



(2.16)

Figure 2.15



(2.6)

Figure 2.16

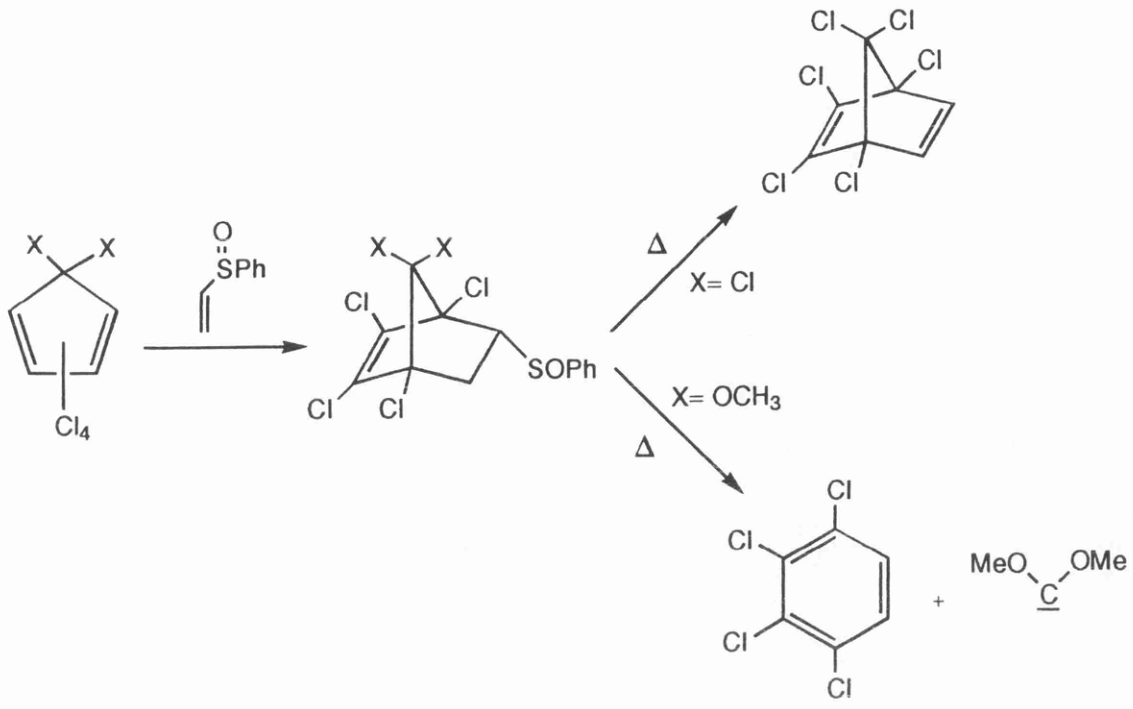


Figure 2.17

From the work of Paquette and Magnus[91] there seems to be little future for the use of phenyl vinyl sulphoxides in this synthesis.

Phenyl vinyl sulphones are known to be good dienophiles (Fig. 2.18) and reactions with cyclopentadiene are known to produce 100% yield.[92]

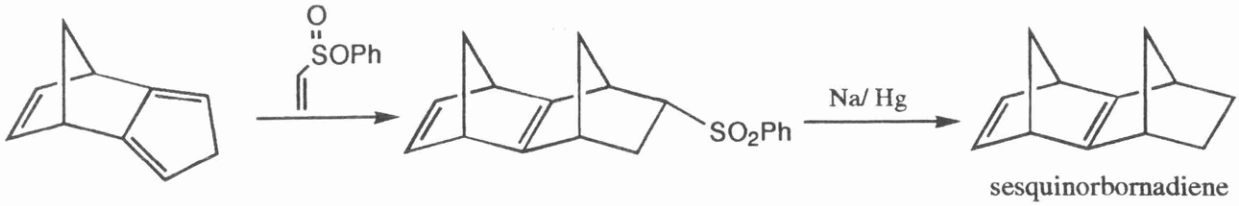
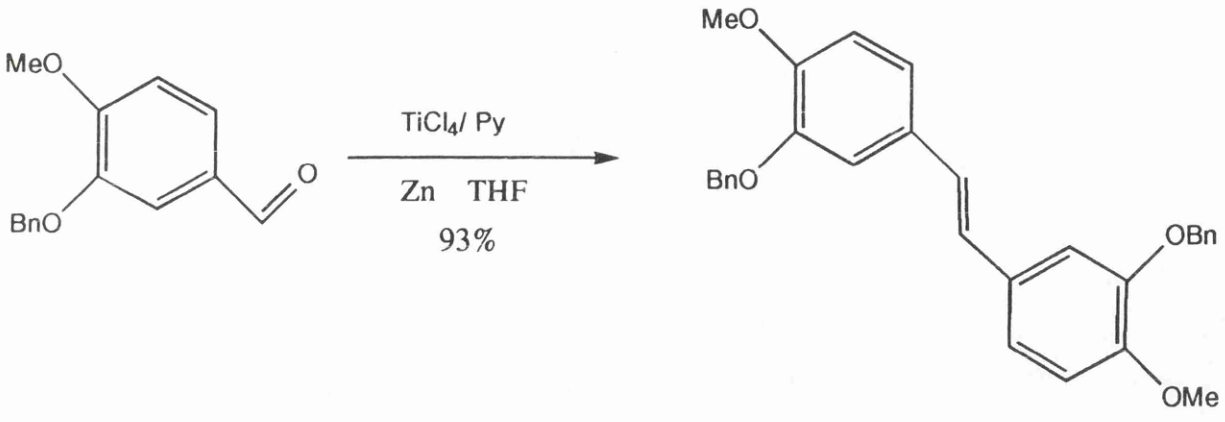
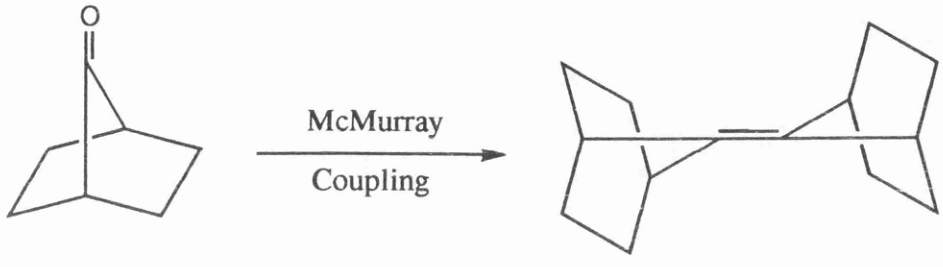


Figure 2.18

A short step to compound (2.24) from the ketone (2.6) could be to perform a McMurray coupling (Fig. 2.19)



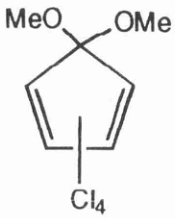
c.f.



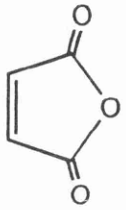
(2.24)

Figure 2.19

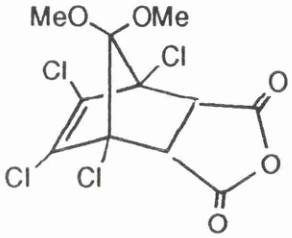
(2.3)



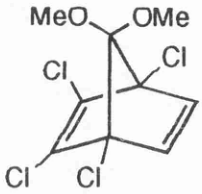
(2.4)



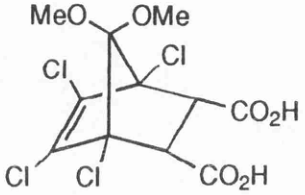
(2.7)



(2.8)

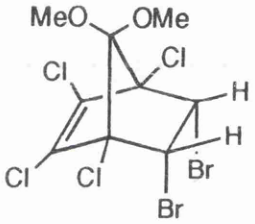


(2.9)

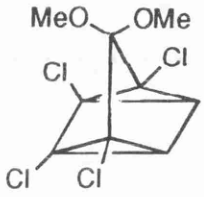


(2.10)

(2.11)

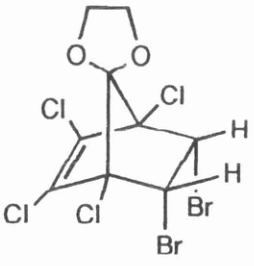


(2.13)

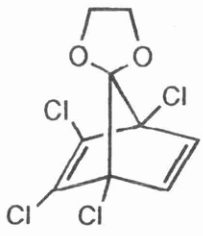


(2.17)

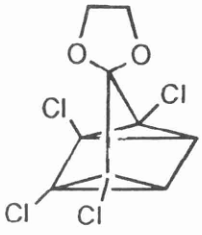
(2.19)



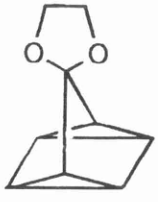
(2.20)



(2.21)



(2.22)



(2.23)

EXPERIMENTAL

5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (2.4)

Hexachlorocyclopentadiene (85g, 0.31 mol) was reacted with methanolic potassium hydroxide according to literature procedure.[80] The product was distilled using water pressure vacuum (oil bath 160°C, vapour 136°C) to yield 69.67g of product (86%).

δ_H (90 MHz): 3.3 ppm (s), 4.2 (s) (impurity).

δ_H (200 MHz): 3.29 ppm (s, 6H), 4.16 (s, 0.5H).

δ_C (50 MHz): 51.62 (CH_3), 59.36 (CH_3 impurity), 104.47 (C), 128.36 (2C), 129.14 (2C).

ν (cm^{-1}): 3008, 2952, 2941, 2738, 1648, 1616, 1455, 1444, 1317, 1242, 1210, 1172, 1141, 1126, 1100, 1069, 983, 781, 762, 664.

M.S. (*m/z*): 270 (0.9), 268 (3.0), 266 (7.4), 264 (13.7), 262 (10.8), 249 (15.2), 233 (30.4), 231 (35.3), 229 (39.9), 277 (43.3), 221 (25.2), 220 (22.0), 219 (22.0), 218 (45.0), 216 (40.7), 214 (19.3), 212 (20.0), 190 (31.1), 188 (24.9), 183 (21.6), 181 (22.3), 155 (35.0), 153 (33.4), 120 (43.9), 118 (69.1), 111 (21.0), 87 (19.9), 59 (25.2), 32 (20.3), 29 (21.9), 28 (100), 15 (42.5).

Accurate: Found 261.9121

$C_7H_6O_2{}^{35}Cl_3$ requires 261.9122

1,2,3,4-Tetrachloro-7,7-dimethoxynorbor-2-ene anhydride (2.8)

Maleic anhydride (5.0g, 0.051 mol) was added to 18.51g (0.07 mol) of (2.4) in 50 ml of chlorobenzene. The reaction mixture was stirred with heating to 160-170°C for 2 h then distilled to remove chlorobenzene solvent. Filtration and washing with cool pet. ether (40-60°) removed excess (2.4) and crystallisation from ethyl acetate produced 17.30g (94%) m.p. 200-202°C (lit.,[95] 192°C, lit.,[96] 184-185.5°C).

δ_H (90 MHz): 3.5 (s, 3H), 3.55 (s, 3H), 3.9 (s, 2H).

δ_H (200 MHz) (d_6-DMSO): 3.49 (s, 3H), 3.57 (s, 3H), 3.96 (s, 2H).

δ_C (50 MHz) (d_6-DMSO): 51.97 (CH_3), 52.51 (CH_3), 53.27 (2CH), 74.02 (2C), 114.64 (C), 128.90 (2C), 166.17 (2C).

ν (cm^{-1}): 2994, 2957, 2849, 1856, 1791, 1787, 1784, 1598, 1258, 1238, 1193, 1130, 1076, 1001, 939, 930, 901, 840, 695.

m/z: 328 (3.7), 259 (10.0), 257 (36.3), 218 (12.0), 216 (18.1), 214 (12.1), 211 (23.0), 183 (13.1), 181 (33.6), 179 (33.7), 159 (11.8), 145 (22.1), 144 (14.3), 143 (25.2), 111 (13.9), 109 (28.6), 108 (20.6), 84 (13.3), 74 (30.3), 73 (16.4), 59 (93.5).

No identifiable peak in accurate *m/z*.

1,2,3,4-Tetrachloro-7,7-dimethoxy-norbor-2-ene-5,6-dicarboxylic acid (2.10)

In a procedure analogous to the literature[97] 5.00g (1.52 x 10^{-2} mol) of anhydride (2.8) was refluxed in 50 ml of 1.5M NaOH for 5 h. The solution was acidified with 2M HCl to produce a white precipitate which was filtered and washed with water until neutral then dried to afford 3.76g (72%) of (2.10)[95] m.p. 194-197°C (lit. 196-197°).

δ_H (200 MHz) (d_6-DMSO): 3.43 (s, 3H), 3.53 (s, 3H), 3.75 (s, 2H), 12.89 (s, 2H).

δ_C (50 MHz) (d_6-DMSO): 51.89 (CH_3), 52.39 (CH_3), 54.50 (CH), 75.71 (2C), 112.75 (C), 129.01 (2C), 168.85 (2C).

ν (cm^{-1}): 3426, 2990, 2953, 2847, 2739, 2635, 2552, 1727, 1604, 1439, 1422, 1219, 1192, 1154, 1136, 992.

m/z: 331 (2.9), 329 (23.7), 327 (70.9), 325 (73.1), 257 (34.6), 255 (94.3), 216 (16.2), 214 (11.0), 211 (21.5), 209 (68.8), 207 (72.4), 183 (12.3), 181 (32.1), 179 (30.9), 159 (11.5), 145 (21.1), 144 (14.1), 143 (24.2), 111 (14.4), 109 (29.4), 107 (21.6), 84 (15.6), 73 (21.1), 18 (23.2).

Microanalysis: Found C: 36.96; H, 3.04

$C_{11}H_{12}O_6Cl_4$ requires C: 34.76; H, 2.63

<u>*cis*-endo-2,3-Dibromo-1,4,5,6-tetrachloro-7,7-dimethoxynorborn-5-ene (2.13)</u>

(1) Compound (2.4) (13.20g, 0.05 mol) and 18.6g (0.1 mol) of *cis/trans*-dibromoethene mixture were heated together with a few crystals of hydroquinone at 140°C-170°C for 50 h during which time the reaction mixture turned dark brown. The reaction mixture was cooled and washed with cold petroleum ether (40-60°) to remove excess starting materials, with the resulting solid recrystallised from petroleum ether (60-80°).

(2)[67] Compound (2.4) (6.61g, 0.025 mol) and 10g (0.054 mol) of (2.11) were mixed in a sealed tube with several crystals of hydroquinone and heated to 150°C for 3 days in a Carins oven. An almost black liquid was formed. On decantation the liquid solidified. The product was purified on an alumina (Grade O - neutral) gravity

column with 10% diethyl ether/90% petroleum ether (40-60°) as eluent to produce a white solid with approximately 1g of each starting material recovered. The dark colouration did not move on the column: m.p. of (2.13) 106-107° (lit.,[96] 108-109°C).

δ_H (90 MHz): 3.5 (s, 3H), 3.55 (s, 3H), 6.85 (2H).

δ_H (200 MHz): 3.57 (s, 3H), 3.60 (s, 3H), 3.79 (s, 0.5H, impurity), 4.84 (s, 2H), 4.87 (s, 0.4H).

δ_C (50 MHz): 52.12 (CH_3), 53.14 (CH_3), 56.46 (2CH, impurity), 57.69 (2CH), 78.48 (2C), 110.59 (C), 130.72 (C).

ν (cm^{-1}): 3004, 2986, 2948, 2843, 1604, 1451, 1438, 1270, 1256, 1232, 1215, 1185, 1156, 1135, 1009, 989, 974, 913, 767, 729, 612.

m/z: 448 (0.4), 446 (0.8), 449 (0.9), 442 (0.3), 370 (13.6), 368 (14.9), 288 (13.5), 286 (11.9), 255 (21.1), 253 (25.0), 215 (11.2), 208 (18.6), 206 (18.1), 180 (14.0), 178 (15.0), 145 (12.5), 143 (13.6), 111 (32.2), 109 (100), 108 (12.4), 74 (21.4).

Microanalysis: Found C, 24.16; H, 1.64; Cl, 31.70; Br, 35.57%

$C_9H_{10}O_2Br_2$ requires C, 24.00; H, 1.77; Cl, 31.55; Br, 35.55%

1,2,3,4-Tetrachloro-7,7-dimethoxynorborna-2,5-diene (2.9)[97,87]

Compound (2.13) (11.7g, 0.026 mol) was dissolved to saturation in 40 ml of glacial acetic acid and to which 3g (0.052 mol) of Zn dust was added in three portions over 20 min. Any undissolved (2.13) was subsequently dissolved and the reaction mixture was heated to 50°C (to avoid decomposition[96] the mixture was not allowed to rise above 50°C) and then cooled to room temperature. After stirring for a further 2 h the solution was filtered and the filtrate reduced *in vacuo*; the solid

was taken up in ether, washed repeatedly with H_2O then dilute $NaHCO_3$ solution. The ether extract was dried with anhydrous Na_2SO_4, filtered, reduced *in vacuo* and the residue distilled (oil bath 105-115°C, vapour temperature 65-80°C, 0.17 torr) to produce 6.49g liquid (86%) which solidified; m.p. 51-53°C (lit.[87] 54-55°C).

δ_H (90 MHz): 3.50 (s, 3H), 3.48 (s, 3H), 6.45 (s, 2H).

δ_H (200 MHz): 3.51 (s, 3H), 3.53 (s, 3H), 6.50 (s, 2H).

δ_C (50 MHz): 52.97 (CH_3), 53.01 (CH_3), 78.78 (C), 128.87 (2C), 135.41 (2C), 139.43 (2CH)

ν (cm^{-1}): 3136, 3090, 2980, 2943, 2840, 1603, 1455, 1445, 1438, 1285, 1210, 1185, 1157, 1125, 1066, 1050, 1028, 995, 885, 840, 782, 695, 591.

m/z: 259 (5.5), 257 (21.8), 255 (55.3), 253 (59.5), 220 (3.9), 218 (18.4), 216 (39.1), 214 (31.5), 213 (4.2), 211 (30.2), 209 (88.4), 207 (100), 183 (10.0), 181 (33.0), 179 (33.1), 147 (5.7), 145 (16.3), 143 (20.2), 109 (22.3), 108 (17.4), 74 (22.2), 59 (70.2), 15 (39.1).

Microanalysis: Found C, 37.24; H, 2.82%

$C_9H_{10}O_2Cl_4$ requires C, 37.24; H, 2.76%

1,2,3,4-Tetrachloro-7,7-dimethoxytetracyclo[3.2.0.0.0]heptane (2.17)[87,88]

Compound (2.9) (10.71g, 11 mmol) was dissolved in 500 ml of anhydrous dichloromethane and was photolysed for 5 h at room temperature with an Hanovian one litre UV photochemical reactor (125W), after which time the reaction mixture was light brown and acidic in nature. The solvent was removed *in vacuo* to leave 10.23g of crude product which was purified by flash column chromatography (Silica GF_{256}) to leave 9.43g of product (88% yield).

δ_H (90 MHz): 2.7 (s, 2H), 3.5 (s, 3H), 3.7 (s, 3H).

δ_H (200 MHz): 2.74 (s, 2H), 3.50 (s, 3H), 3.73 (s, 3H), 5.98 (s, 0.5H).

δ_C (50 MHz): 33.29 (2CH), 52.16 ($2CH_3$), 52.73 (C), 54.90 (C), 105.70 (C).

ν (cm^{-1}): 3088, 2951, 2843, 1721, 1460, 1325, 1302, 1260, 1202, 1184, 1147, 1123, 1084, 1013, 816, 802.

m/z: 304 (4.0*), 302 (4.1*), 300 (3.9*), 298 (2.1*), 149 (96.7), 127 (11.0), 115 (14.9), 91 (14.7), 79 (17.5), 77 (21.5), 75 (22.1), 74 (23.4), 73 (23.5), 63 (27.7), 59 (93.0), 57 (85.7), 55 (55.8), 43 (100), 36 (57.4).

No identifiable peak in accurate *m/z*.

1,2,3,4-Tetrachloro-5,5-ethylene-dioxycyclopentadiene (2.19)

Hexachlorocyclopentadiene (2.3) (25g, 0.092 mol) was stirred with 37 ml of distilled ethylene glycol and reacted with potassium hydroxide in ethylene glycol according to literature method.[87] The resultant precipitate was washed with water until neutral to give 20.1g yellow solid, taken up in diethyl ether, dried with anhydrous sodium sulphate, filtered, reduced *in vacuo* to a solid and recrystallised from petroleum ether (60-80°C) giving 11.45g (49%) white crystals; m.p. 64-67°C (lit.[87] 65-67°C).

δ_H (90 MHz): 4.2 (s).

δ_H (200 MHz): 4.32 (s).

δ_C (500 MHz): 67.16 ($2CH_2$), 108.39 (C), 128.41 (C), 129.78 (C).

ν (cm^{-1}): 3447, 3004, 2949, 2895, 2361, 2344, 1620, 1252, 1202, 1059, 1030, 995, 951, 804, 752.

m/z: 266 (4.7), 264 (22.8), 262 (45.5), 260 (36.6), 229 (31.6), 227 (95.3), 225 (98.5), 220 (6.9), 218 (14.1), 216 (10.8), 210 (10.6), 208 (49.1), 206 (100.0), 204 (81).

Microanalysis: Found C, 32.23; H, 1.53; Cl, 54.37

$C_9H_6O_2Cl_4$ requires C, 32.06; H, 1.53; Cl, 54.20

cis endo-2,3-Dibromo-1,4,5,6-tetrachloro-7,7-ethylene-dioxynorborn-5-ene (2.20)

In a slight variation from literature procedure[87] 10.35g (0.04 mol) of (2.19) was mixed with 22.02g (0.12 mol) of (2.11) and heated at 100°C in a sealed tube, with a few crystals of hydroquinone, for 17 h. The product was distilled to remove excess dibromoethylene (2.11) (11.84g). The solid was then rinsed with cold petroleum ether (40-60°C) to remove any (2.19) that remained. The produce was recrystallised from petroleum ether (40-60°) giving an off-white solid; m.p. 169-171°C (lit.[87] 169-170°C).

δ_H (90 MHz): 4.25 (m, 4H), 4.70 (s, 2H).

δ_H (200 MHz): 4.09-4.45 (m, 4H), 4.85 (s, 2H).

δ_C (50 MHz): 56.78 (2CH), 67.34 (CH_2), 68.47 (CH_2), 77.15 (C), 118.99 (C), 130.50 (C).

ν (cm^{-1}): 2990, 2963, 2901, 1603, 1271, 1231, 1217, 1202, 1119, 1024, 1001, 953, 810, 718, 629.

m/z: 419 (1.0), 417 (1.8), 415 (1.9), 413 (2.6), 411 (3.0), 253 (28.5), 251 (29.9), 243 (22.2), 216 (36.1), 214 (29.4), 211 (29.3), 209 (66.8), 207 (70.6), 183 (20.5), 146 (22.3), 145 (32.3), 144 (36.5), 143 (47.5), 111 (20.6), 109 (78.0), 107 (100), 74 (55.6), 63 (43.3).

Accurate: Found 412.7746

$C_9H_6{}^{35}Cl_3{}^{81}Br_2$ requires 412.7760

Microanalysis: Found C, 24.94; H, 1.38; Cl, 31.76; Br, 35.81

$C_9H_6O_2Br_2$ requires C, 24.11; H, 1.34; Cl, 31.70; Br, 35.71

1,2,3,4-Tetrachloro-7,7-ethylene-dioxynorborna-2,5-diene (2.21)

Compound (2.20) 6.73g (0.015 mol) was reacted with zinc according to literature procedure.[87] The product was purified by an alumina (grade 'O') gravity column with 5% Et_2O/95% petroleum ether (40-60°) as eluent to produce 2.97g (69%) white crystals; m.p. 45-47°C (lit.[87] 43-45°C).

δ_H (90 MHz): 4.17 (s, 4H), 6.50 (s, 2H).

δ_H (200 MHz): 4.22 (s, 4H), 6.55 (s, 2H).

δ_C (50 MHz): 67.37 ($2CH_2$), 77.64 (C), 134.32 (C), 137.45 (C), 138.37 (2CH).

ν (cm^{-1}): 3007, 2993, 2905, 1597, 1289, 1215, 1167, 1109, 1026, 959, 891, 828, 812, 756.

m/z: 290 (2.8), 288 (6.3), 286 (8.5), 253 (2.6), 251 (3.2), 210 (22.6), 208 (72.0), 206 (74.7), 182 (11.0), 180 (34.2), 178 (35.2), 144 (18.0), 142 (29.3), 74 (31.9), 57 (52.0), 55 (33.8), 43 (65.8), 41 (30.1), 28 (100).

Accurate: Found 250.9447

$C_9H_6{}^{35}Cl_3$ requires 250.9434

1,2,3,4-Tetrachloro-7,7-ethylene-dioxytetracyclo[3.2.0.0.0]heptane (2.22)

Compound (2.21) (2.99g, 1.04 x 10^{-2} mol) was dissolved in 350 ml of distilled dichloromethane and photolysed for 3 h (see preparation of (2.17)). Nitrogen was bubbled through the solution for 30 min to remove all traces of HCl. The solvent was removed *in vacuo* to produce 3.08g of crude product. This was chromatographed on an alumina (grade 'O') gravity column with 10% dichloromethane/90% petroleum ether (40-60°) to afford 2.71g (91%) of white crystals; m.p. 57-61°C.

δ_H (200 MHz): 2.75 (s, 2H), 4.35 (s, 4H).

δ_C (50 MHz): 34.03 (2CH), 53.45 (C), 54.30 (C), 67.12 (CH_2), 67.45 (CH_2), 114.90 (C).

ν (cm^{-1}): 3094, 3000, 2957, 2905, 1304, 1279, 1152, 1053, 1014, 947, 804, 637.

m/z: 210 (22.1), 206 (74.1), 180 (46.8), 178 (45.8), 108 (26.9), 74 (38.0), 73 (25.1), 28 (100*).

Accurate: Found 250.9444

$C_9H_6{}^{35}Cl_3$ requires 250.9434

Microanalysis: Found C, 37.53; H, 2.06; Cl, 48.52%

$C_9H_6Cl_4$ requires C, 37.50; H, 2.08; Cl, 49.31%

7,7-Ethylene-dioxytetracyclo[3.2.0.0.0]heptane (2.23)

Compound (2.22) (285 mg, 1 mmol) was dissolved in 20 ml of tetrahydrofuran and 1 ml of t-butanol with 3g (26 mmol) of potassium t-butoxide added and refluxed for 16 h under dry nitrogen. The solution was cooled, diluted with 100 ml of diethyl ether and shaken with water. The organic layer was dried with anhydrous sodium

sulphate then reduced *in vacuo* to give 210 mg of crude dark brown product.

δ_H (200 MHz): 1.25 (s, Bu^{t}OH), 2.76 (s, 1H), 4.16 (s, 2H), 4.35 (s, 2.5H), 6.55 (s, 1H).

δ_C (50 MHz): 29.65 (CH_2), 34.01 (CH), 53.42 (C), 54.26 (C), 67.12 (CH_2), 67.39 (CH_2), 67.45 (CH_2), 77.64 (C), 134.31 (C), 137.45 (C), 138.37 (CH).

CHAPTER 3

INTRODUCTION

Malaria parasites are thought to have first infected *Homo erectus* one million years ago in the forests of South East Asia; infection spread westwards into Africa and Europe and followed Columbus to the New World. Roughly 90% of all malaria cases occur in Africa with the incidence of infection in developed countries less than 0.5%; throughout the world about 300 million people are infected each year. Once infected the sufferer, if he or she survives, can be afflicted by months or even years of anaemia and periodic fever. In 10-30% of the indigenous population of Central and Western Africa (and areas in the Mediterranean) a natural immunity is carried,[99] even against the virulent malaria form, in the guise of a sickle cell trait in red corpuscles. Immunity to all types of malaria is eventually acquired over a number of years as a result of frequent attacks.

Although developed countries are now largely free of malaria it was not until the middle of the nineteenth century that the disease was eradicated in London when the Thames embankment was built in 1864 and flooding was controlled; Rome suffered until Mussolini had the Pontine marshes drained.

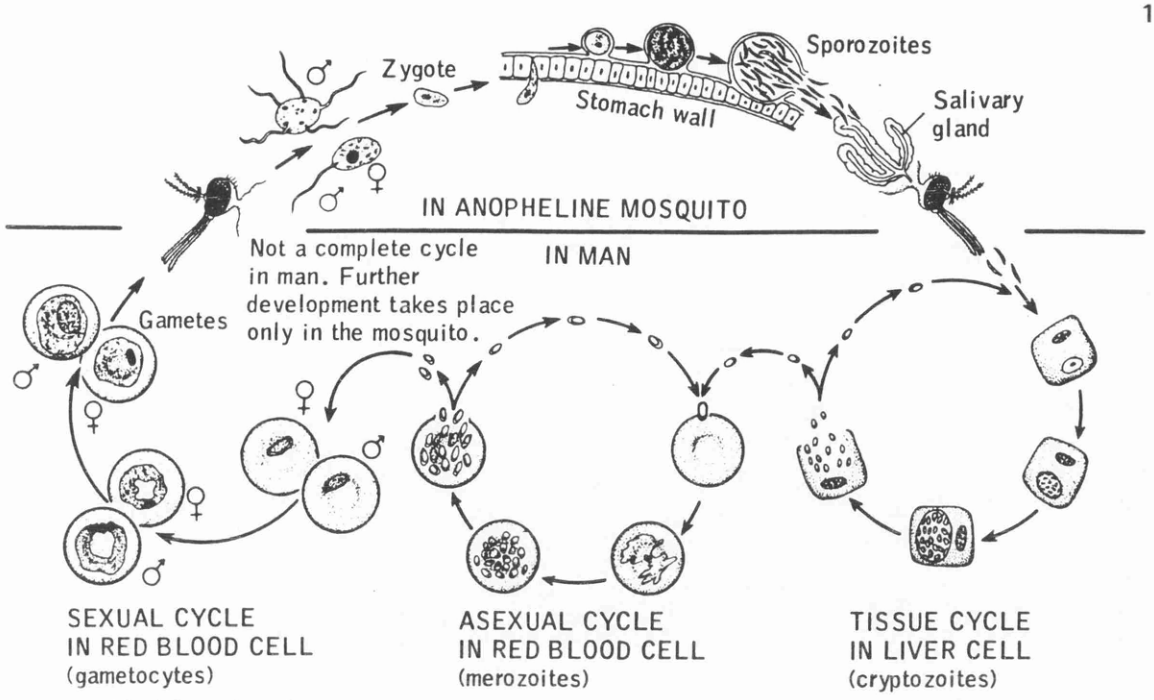
Malaria comes from Latin "bad air" and the disease was originally thought to arise from the "bad air" of swamps and marshes. Although malaria had been recognised for centuries its source remained a mystery until 1880 when Charles Laveran, a French Army physician in North Africa, observed a strange microbe in the

blood of afflicted patients; other researchers traced the web linking the parasite to the mosquito in 1887 and its breeding ground in stagnant pools.

It is now known that there are four species of malarial parasite with *Plasmodium vivax* the commonest and *Plasmodium falciparum* the deadliest. In the "milder" forms of *Plasmodium* red blood cells are destroyed in peripheral capillaries and anaemia results. *Plasmodium falciparum* causes red blood cells to become sticky and form clumps in the capillaries in the deep organs of the body causing micro-circulatory arrest. If this happens in the brain delirium, coma, convulsions and ultimately death can occur.

All four *Plasmodium* species are transmitted by the female Anopholes (Gr: harmful) mosquito, as only the female feeds to generate food for her egg production. The mosquito is therefore the vector for malaria. A vector is an animal that carries a parasite, acting as a host, with no adverse effect on itself *e.g.* tsetse fly is the vector for African sleeping sickness. When an anopholene mosquito starts to take blood it releases saliva that contains an anti-coagulant and often *Plasmodium* cells at the sporozite stage (see Figure 3.1).

The sporozites are carried by the blood stream to the liver where they invade liver cells and grow for 5-15 days where they further develop by asexual reproduction through multiple fission. These daughter cells invade other liver cells in their turn and continue to reproduce (not true for *Pl. falciparum*). In the next stage of the life cycle merozoites are released by the liver cells and they penetrate red blood corpuscles where they reproduce asexually generating more merozoites. The



The life cycles of *Plasmodium* in a mosquito and in man. Reinvasion of liver cells in the tissue cycle does not occur in *Plasmodium falciparum*. (Redrawn and modified from Blacklock and Southwell.)

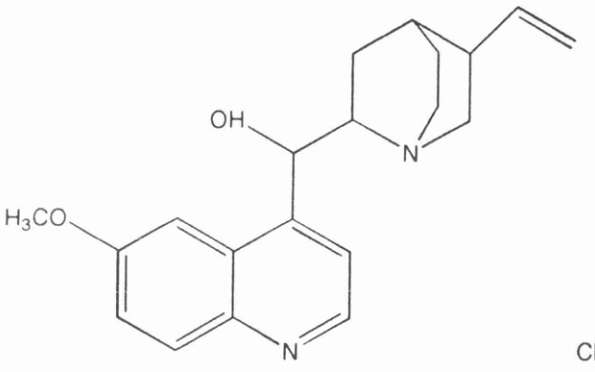
Figure 3.1

merozoite liberation and reinvasion are not continuous but occur simultaneously from all infected red blood cells. The timing of the event depends on the period of time required to complete the development cycle within the cell of the host. In cases with *Pl. vivax* the red corpuscles rupture every 48 hours and release toxins, as well as merozoites, which cause the fevers typical of malaria. Eventually some of the merozoites develop into special sexual cells and become either male or female gametes. If an anopholine mosquito takes up the gametocyte, with a blood meal, it then completes development in the mosquito midgut. Fertilisation produces a zygote which penetrates the stomach wall, encysts and ultimately produces sporozoites. These are released when the cyst ruptures and migrate to the salivary gland and are then introduced to the human host when the mosquito feeds.

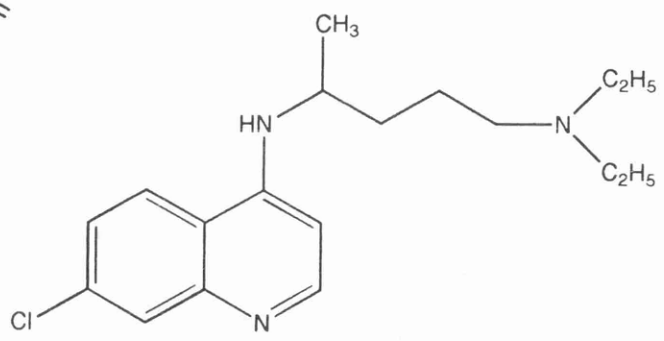
Prevention of malaria can be attempted in two ways. Eradication of the mosquitoes' habitat is effective but is too expensive for implementation in Third World Countries. Alternatively eradication of mosquitoes using insecticides such as DDT has been employed, but toxic side effects of DDT and DDT-resistant mosquitoes has negated this strategy. Cure rather than prevention is the main route now being followed by most organisations and this involves drugs that can combat the malarial parasite.

The first recorded breakthrough came in the seventeenth century when European missionaries learned that the bark of the South American cinchona trees contained the potent, but toxic, remedy now known as quinine[99] (3.1). During the Second World War new drugs were required to protect soldiers fighting in malaria infested areas of the Far East as the supply of cinchona bark from Java had been cut off by the Japanese. Chloroquine was introduced in 1943 by the U.S. military and was as potent as quinine with the advantages of being longer lasting, less expensive and so well tolerated that people no longer had to wait passively for malaria to strike but could take the drug before they were in an infected area.

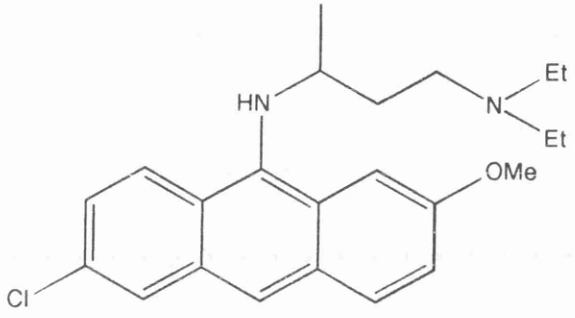
After the Second World War pharmaceutical companies still produced vast amounts of anti-malarial drugs other than chlorquine (3.2), such as pamaquin (3.3). These were distributed to tropical countries who used them in vast amounts which led to the development of resistant strains in the 1950's. Resistance has been attributed to various factors such as enzyme mutation so that drugs no longer blocked the enzyme.[100]



(3.1)
QUININE

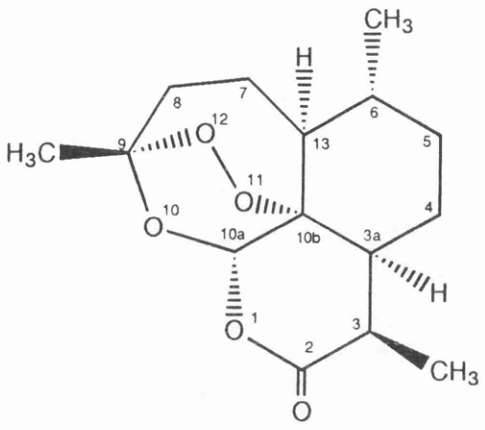


(3.2)
CHLORQUINE



(3.3)
PAMAQUIN

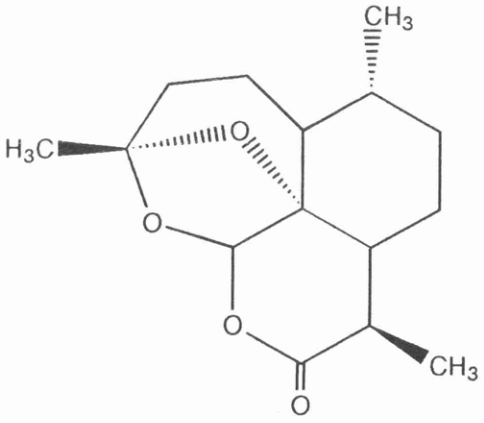
Many drugs used to treat malaria are derivatives of quinoline and none is particularly effective against *Pl. falciparum*. Recently a new compound has appeared which is not based on quinoline and is also active against *Pl. falciparum*. This new compound was isolated from the dried leaves of *qinghao*, a Chinese plant that had been used in ancient remedies to treat malaria. Artemisinin (3.4) has the structure shown below, 3,6,9-trimethyl-9-10-b-epidioxyperhydropyrano[4,3,2-jk]benzoxepin-2-one



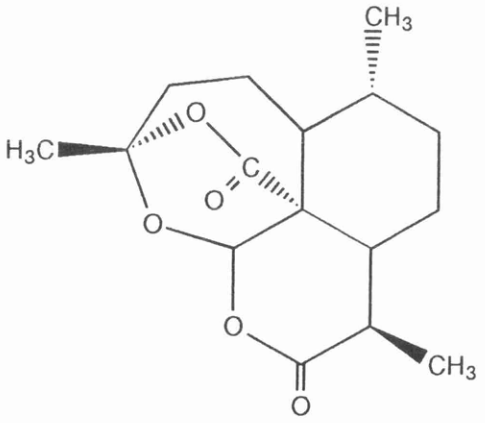
(3.4)
ARTEMESININ

The action of artemisinin appears to be different from that of chlorquine and may explain its effectiveness against chlorquine resistant parasites (both drugs accumulate in infected corpuscles).

Artemisinin has been synthesised in several ways and its analogues have been studied for antimalarial activity.[101,102,103,104]



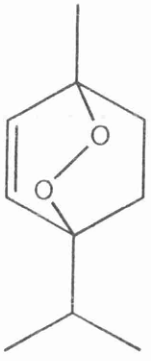
(3.5)
DEOXYARTEMESININ



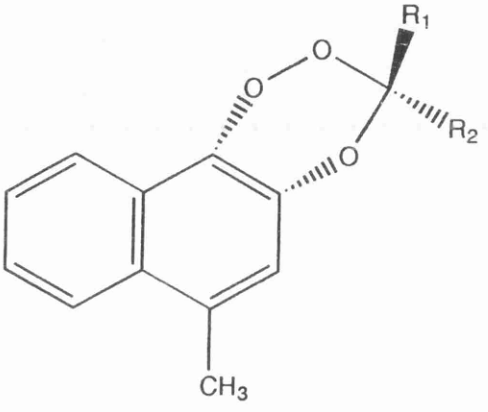
(3.6)

Neither (3.5) nor (3.6) have any antimalarial activity while (3.7), ascaridole, is an antimalarial agent *in vitro* but *in vivo* there is no activity against *Pl. falciparum*. This suggests that the peroxide bridge is an intrinsic factor in the activity of artemisinin and that the rest of the molecule is vitally important in transport to the infected red blood corpuscle.

Synthesis of trioxane ring systems *e.g.* (3.8) have also been investigated[105] in an attempt to clarify the important features concerning the peroxide bridge.



(3.7)
ASCARIDOLE



(3.8)

The authors concluded that the trioxane ring is a necessary, but not sufficient, condition to ensure activity as the most active compounds were at least one order of magnitude less potent than artemisinin, but were more active than ascaridole (3.7), which possesses only a peroxide bridge with no third oxygen atom, which showed no *in vivo* activity at the maximum tolerated dose.

The current trend in research appears to be directed towards synthesis of

various analogues and derivatives of artemisinin with increased solubility, hydrophilicity and stability to overcome the shortcomings of artemisinin itself: low solubility in oil and water, minimal absorption by oral or rectal routes, attendant problems in administration by injection in Third World Countries and, additionally, a high rate of recrudescence is noted.

RESULTS AND DISCUSSION

Butler and Wu[99] suggest that the peroxide bridge is broken due to an electron transfer with the generation of an oxygen centred radical which would be responsible for the destruction of the membranes of *Plasmodium* species. However, a vital point seems to have been overlooked concerning the 3-dimensional stereochemical arrangement of the oxygen atoms around the peroxide bridge. From molecular models it is easy to see the arrow pushing cascade that produces a peroxide anion which is the basis for antimalarial activity (Fig. 3.2).

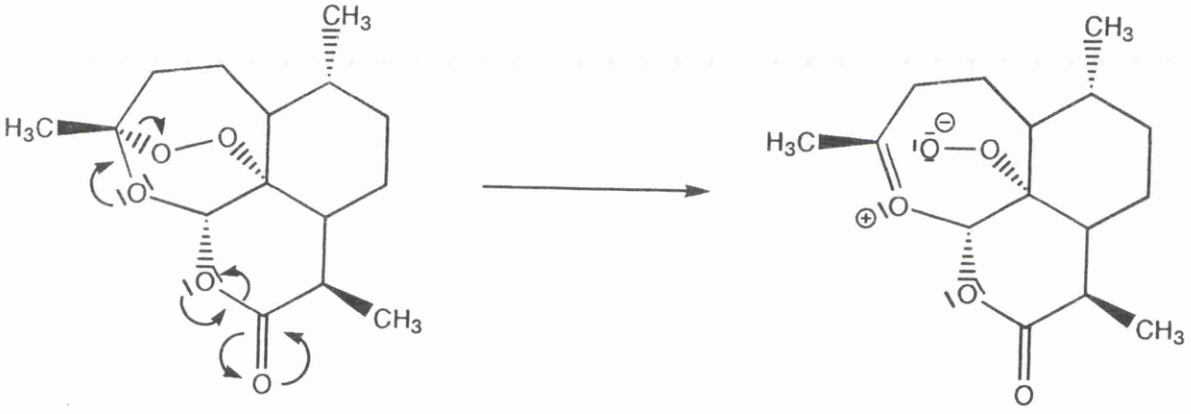


Figure 3.2

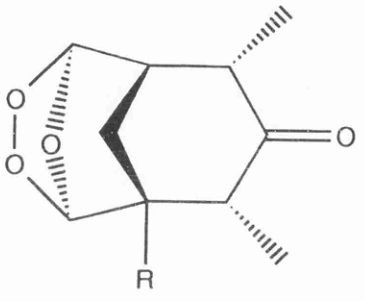
By studying similar peracetal systems and relevant papers concerned with analogues of artemisinin there are five reasons why the above mechanism is correct.

i) The Necessity for a Third Oxygen Atom

The paper by Jefford's group[105] showed that for *in vivo* activity the third oxygen atom is necessary.

ii) Oxygen Lone Pair Orientation

In a recent paper[106] stable synthesised ozonides showed antimalarial activity and the structure is shown below (3.9). If the molecular model is constructed a rigid ring system is apparent in which oxygen ( ) lone pair is in the optimum antiperiplanar arrangement for initiating peroxide ion formation.



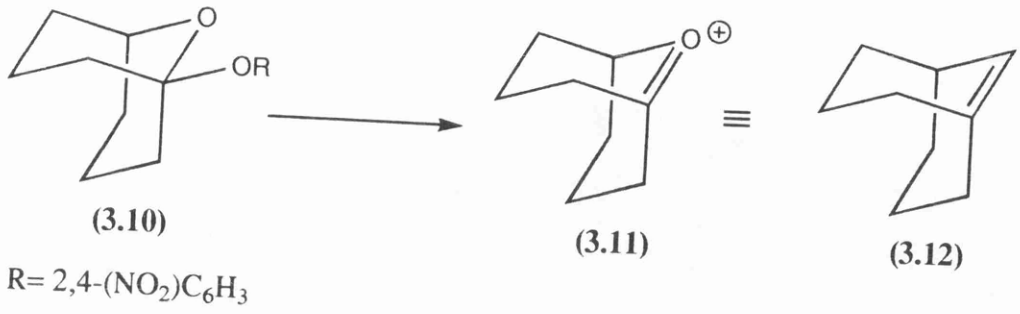
(3.9)

In fact of all the reported compounds tested it was found that the basic structure alone provided the greatest antimalarial activity although they are at least fifty times less potent than artemesinin itself.

iii) Stereoelectronic Effect of Oxygen in Acetals

In a series of concurrent papers (the last being Ref. 107) A.J. Kirby *et al.* showed that cleavage of a C-O acetal bond occurs readily when it is antiperiplanar to one of the non-bonding electron lone pairs on the other oxygen atom either in the most stable or a readily accessible conformation.[108] In the final paper of the series they prepared an extremely rigid acetal which would be converted to the oxocarbenium ion on loss of $RO^{\ominus}$. The corresponding hydrocarbon compound (3.12) has the highest olefinic strain known[109] on the basis of strain calculations (Fig.

3.3).



(3.10)

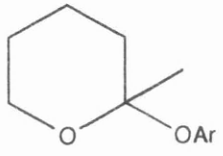
R= 2,4-$(NO_2)C_6H_3$

(3.11)

(3.12)

Figure 3.3

The simplest appropriate axial compound for comparison is the corresponding 2-aryloxy-2-methyltetrahydropyran (3.13). Here the lone pairs on the endocyclic



(3.13)

oxygen atom cannot assist is C-OAr cleavage and so (3.10) is hydrolysed *ca.* 10^{13} slower than (3.13) (which includes a subtraction of stereoelectronic barrier considerations, explained in the text) where suitable alignment of lone pairs can occur.

In artemisinin we have such an alignment with O(10) and O(12), thereby allowing cleavage with formation of a peroxide.

iv) Generation of a Peroxide

Nucleophilic attack by peroxy anions on the partially positive acyl carbon of a substrate is an equilibrium process[110] (Fig. 3.4).

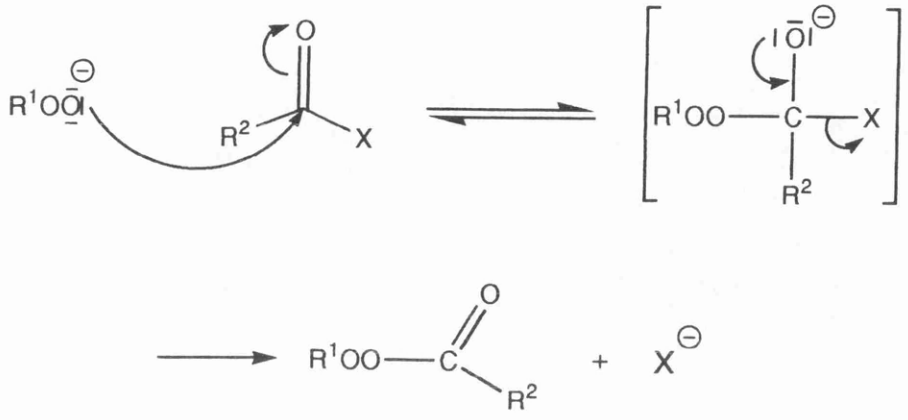


Figure 3.4

The intermediate formed is related to that present around the peroxy bridge of artemisinin itself (Fig. 3.5).

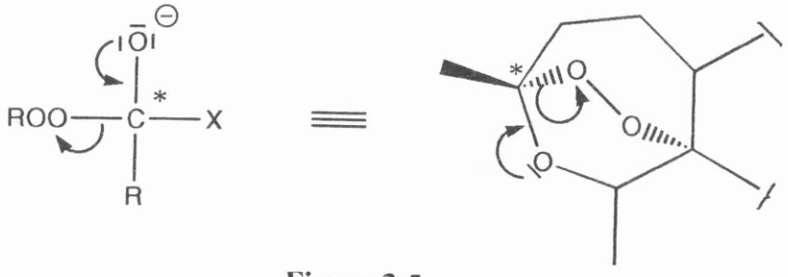
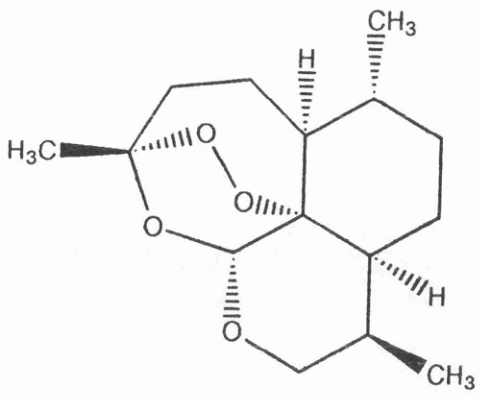


Figure 3.5

This reaction provides precedent for the formation of a peroxide anion.

v) Augmentation of the Cascade

Jung, Bustas, El Sohly and McChesney[111] have prepared artemisinin derivatives that show interesting antimalarial activity which can be explained by considering the theory that is being proposed.



(3.5)

Deoxoartemisinin (3.5) possesses eight times the antimalarial activity of artemisinin *in vitro*; this suggests that the carbonyl group is relevant in the activity of artemisinin. With reference to the original arrow pushing diagram (Fig. 3.2) it is possible to focus on oxygen (1). With molecular models it is possible to orientate a lone pair of electrons antiperiplanar to O(10), which would add further conjugative driving force to the original arrow pushing mechanism (Fig. 3.2). If the carbonyl group were present it would withdraw electrons from the oxygen with which it forms the lactone so decreasing its ability to donate electrons into the cascade that leads to the peroxide anion.

When the carbonyl group is removed the conjugative electron release from oxygen (1) enhances the drive for formation of the peroxide anion and accordingly the antimalarial activity is increased eight-fold (Fig. 3.6).

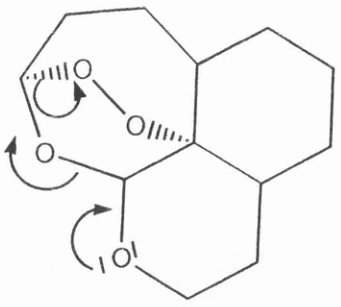


Figure 3.6

A final augmentation to the cascade would be to substitute an oxygen, so allowing further conjugative arrow pushing power. Similar cascade type reactions include Grob fragmentation and Eschenmoser-Tanabe ring cleavage (Fig. 3.7).

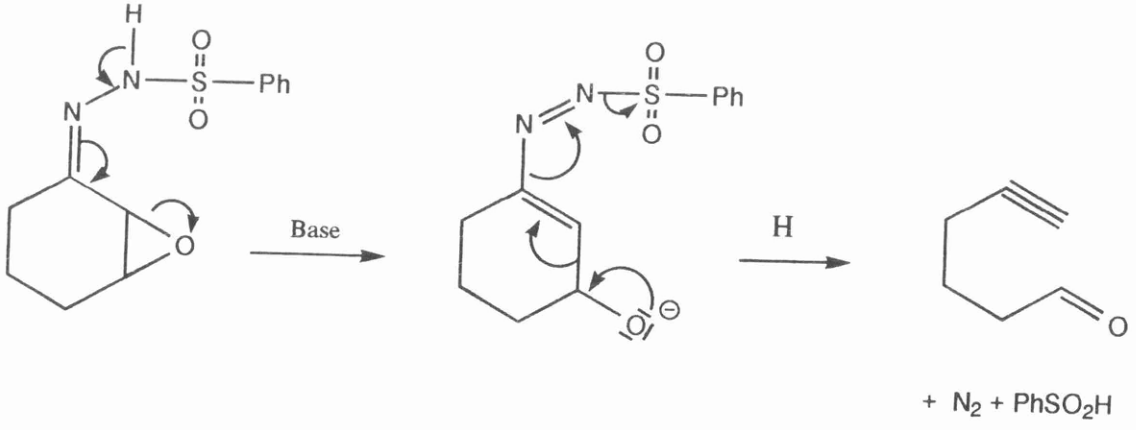
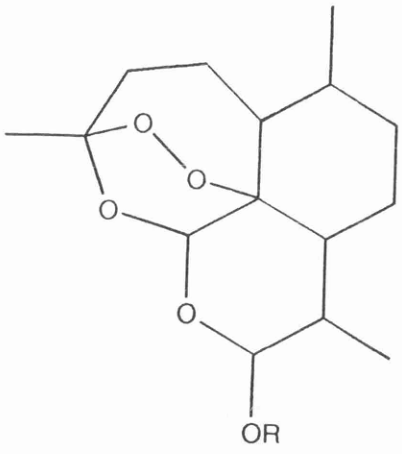


Figure 3.7

The lactol (3.14) produced by $NaBH_4$ reduction is chemically unstable but has greater antimalarial activity than artemisinin as does the ethyl ether (3.15) which is currently under commercial development.

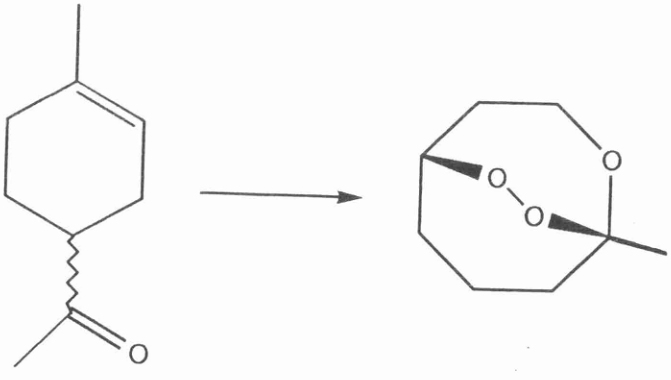


(3.14) R=H

(3.15) R=Et

The research carried out looked at compounds with an alignment, as previously discussed, and possessing antimalarial activity as well as molecules which have the augmentated cascade but with variations of conjugative arrow pushing power.

The first aim was to generate a simple peroxide compound with the third oxygen atom present. Using 4-acetyl-1-methylcyclohex-1-ene (3.16) as a starting material the synthesis of (3.17) was undertaken.



(3.16) (3.17)

Figure 3.8

The oxygen atom denoted has one lone pair approximately 30° off antiperiplanar arrangement and the whole structure is very rigid. Since it is not completely antiperiplanar we would not expect a high degree of antimalarial activity. A simple one-stage synthetic route was originally pursued (Fig. 3.9).

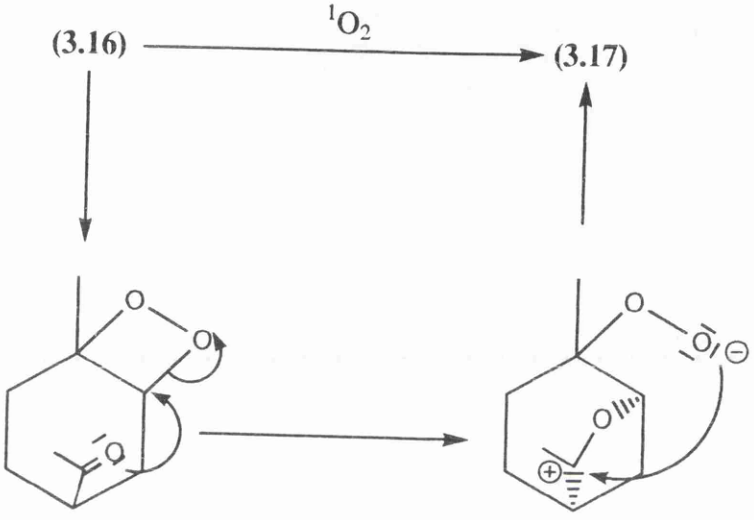


Figure 3.9

However if the 3-dimensional mechanism is analysed difficulties are apparent (Fig. 3.10).

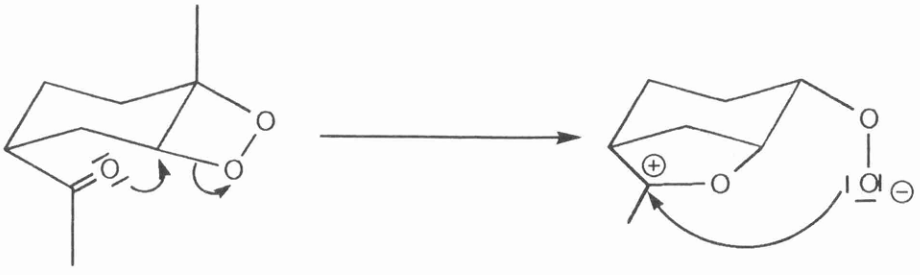


Figure 3.10

It is now impossible for the peroxide to link to the carbonium ion due to steric effects. This is true for both enantiomers of (3.16) although twistane, a hydrocarbon analogue is known.

In the final steps of artemisinin synthesis singlet oxygen is employed where an alcohol with a double bond present in the structure reacts under the conditions shown to form artemisinin (Fig. 3.11).[112]

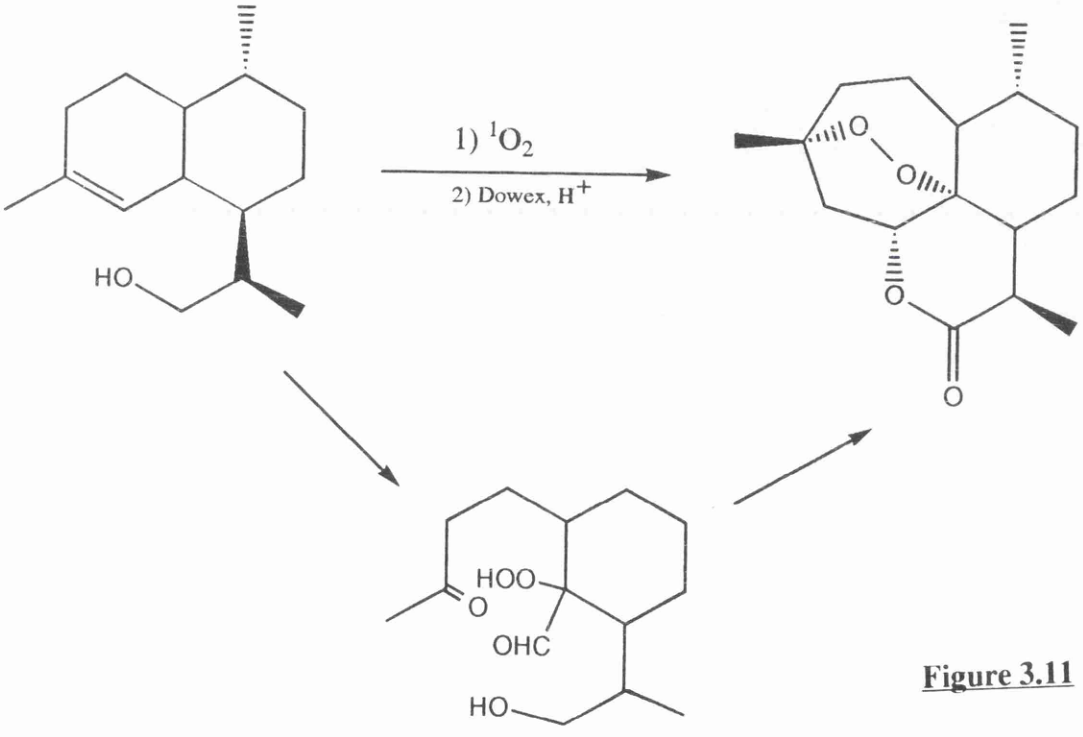
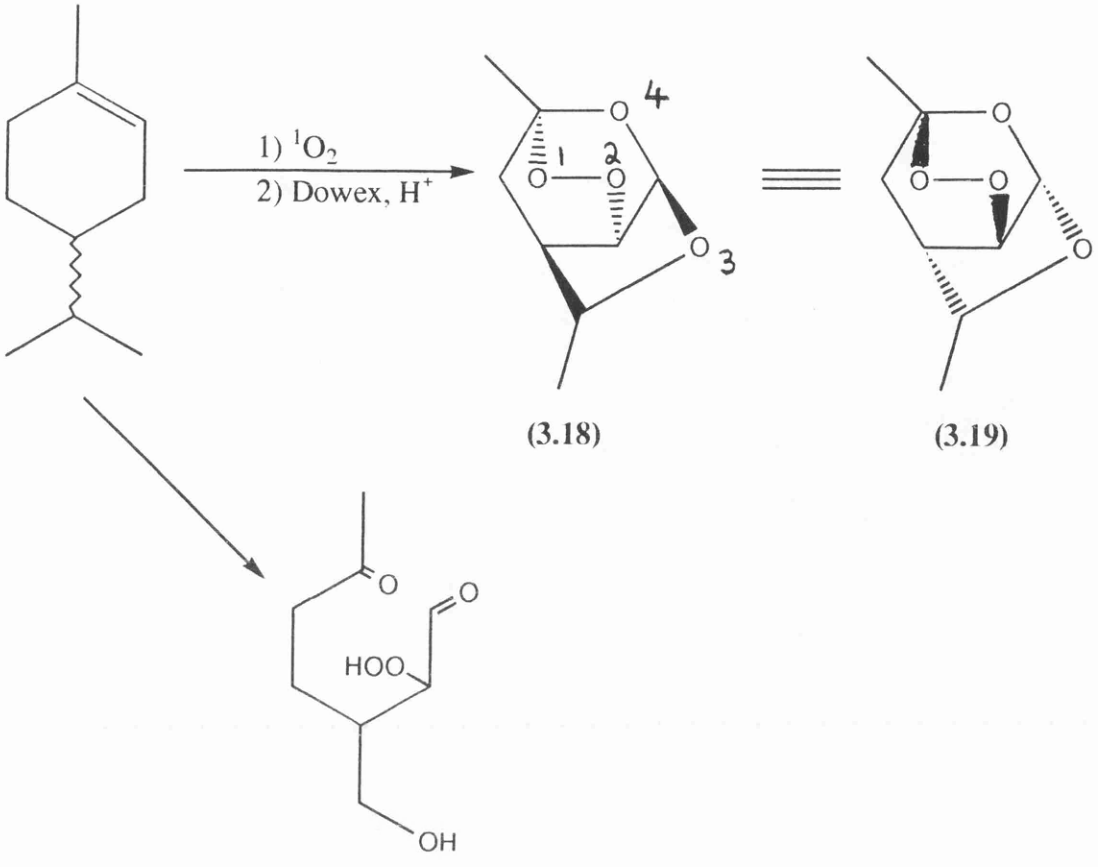


Figure 3.11

Similarly it may be possible to produce compound (3.18) in a similar type reaction. Unlike Figure 3.10 there is no ring constraint to prevent reaction occurring and so we would expect compound (3.18) to be generated.



(3.18) (3.19)

Figure 3.12

Compound (3.18) is fairly flexible and by varying the conformations the arrangement of the oxygen (4) lone pair varies from skew in one perspective to skew in another perspective to antiperiplanar in another while the lone pair of oxygen (3) varies from skew to antiperiplanar depending on the conformations of the rings *i.e.* boat or chair. Since there is a possibility of aligning oxygen (4) in an antiperiplanar arrangement with the peroxide bridge (while oxygen (3) is 30° skew) compound (3.18) should exhibit antimalarial activity.

Three reactions were studied using a racemic mixture of the alcohol and each of the enantiomers (Fig. 3.13).

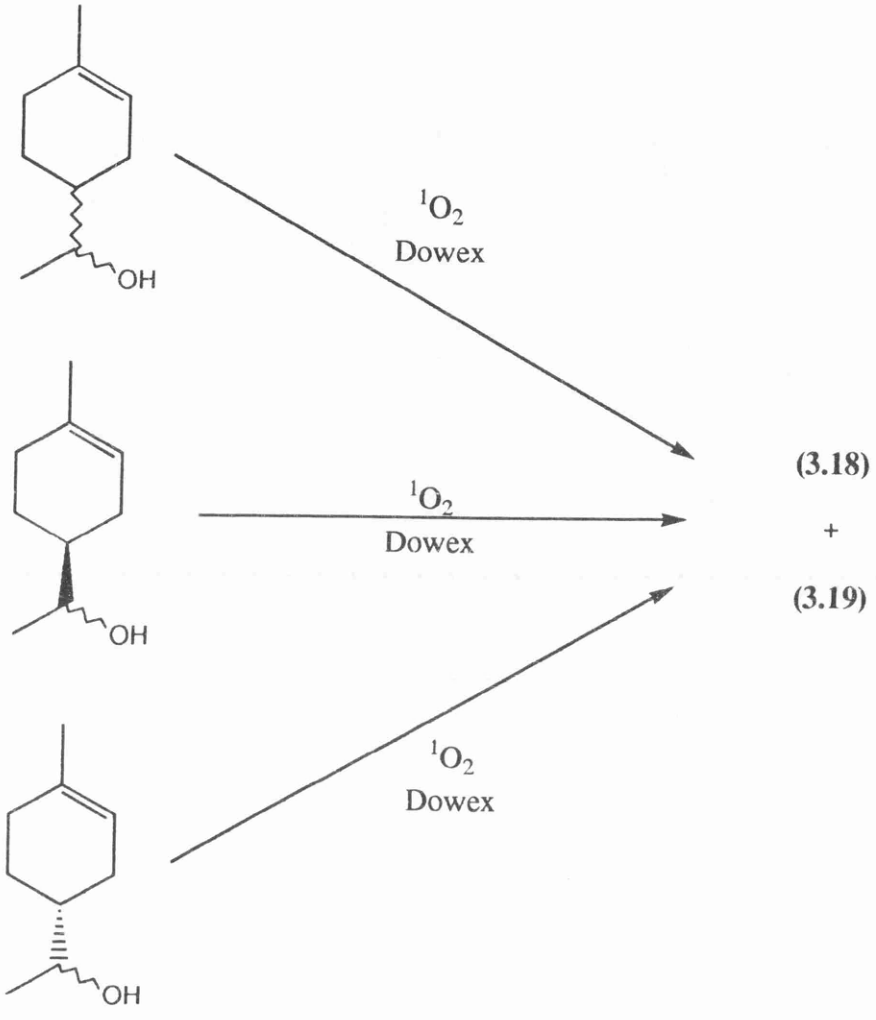
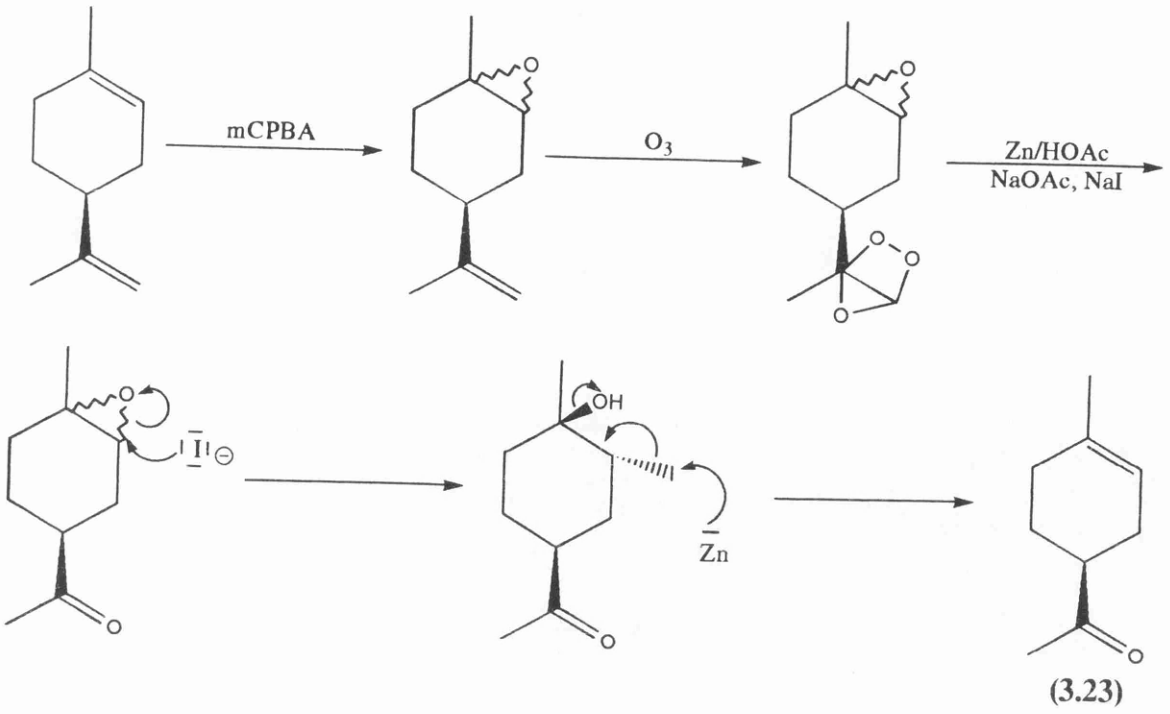


Figure 3.13

The racemic mixture (3.16) is readily available but the enantiomers had to be prepared from the corresponding limonene enantiomers (Fig. 3.14).



(3.23)

Figure 3.14

The initial step is protection of the endocyclic double bond by epoxidation. As it is the more electron rich double bond it will be epoxidised before the exocyclic double bond. However diepoxidation occurs to a significant degree and lowering the temperature results in the solution turning solid *i.e.* precipitation of meta chlorobenzoic and perbenzoic acid. Thus the reaction temperature is held at lowered temperature with mechanical overhead stirring and subsequently purified. In the one-step reduction of the ozonide and epoxide sodium acetate acts as a buffer to increase the yield of olefin.[113] Lithium aluminium hydride reduces the ketones to the corresponding alcohols. Finally the alcohol is treated with singlet oxygen in an attempt to produce the desired compound.

Analysis of the 200 MHz ^{1}H NMR and 50 MHz ^{13}C NMR produced from (3.21,3.22) reaction with singlet oxygen showed no starting alcohol present although

there is at least one new alcohol present, also detected by IR spectroscopy. Neither the starting olefin signal at δ 5.37 nor the methyl signal at δ 1.64 is present in the final reaction mixture. At low fields there is a ^{13}CH present which suggests that it is attached to electronegative elements such as oxygen. The NMR must be considered carefully as there are two pairs of enantiomers present in the starting mixture *i.e.* four diastereomers. In the ^{13}C NMR diastereomers have different chemical shifts so double the number of signals can be expected where we have such a presence. Similarly, with IR and mass spectroscopy data analysis it was difficult to elucidate any structure, although it was proposed to test the mixture for antimalarial activity. A similar situation with the diastereomeric pairs was observed.

By more careful examination of the final step in artemisinin synthesis it is possible to break down the whole molecule into a simple fragment that undergoes reaction with singlet oxygen (Fig. 3.15).

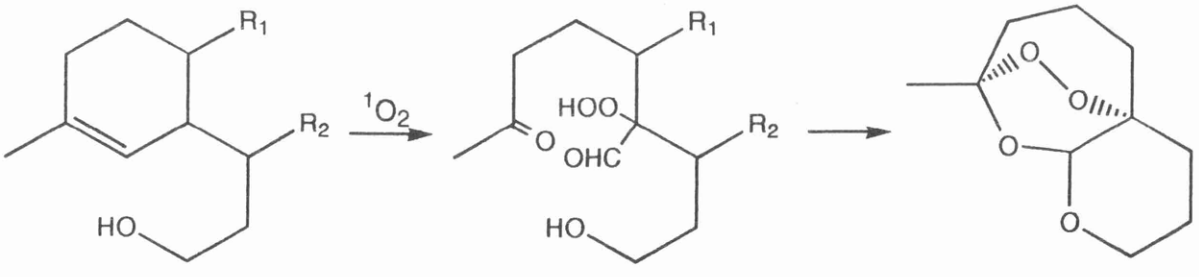
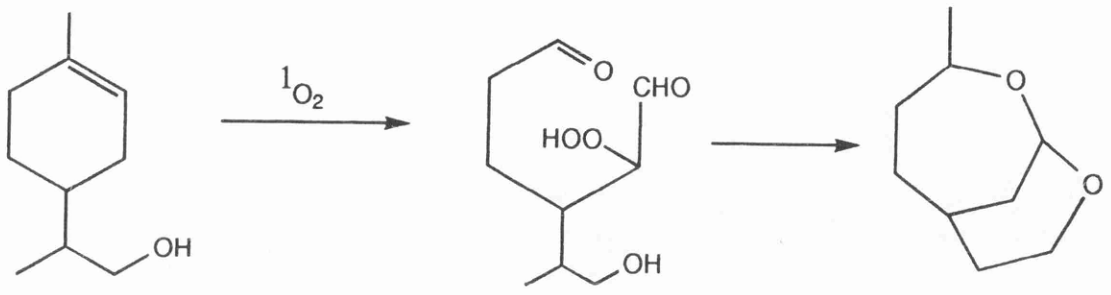


Figure 3.15

An analogous structure is seen in (+)-p-menth-1-en-9-ol (3.24) (Fig. 3.16).



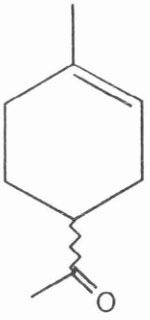
(3.24)

Figure 3.16

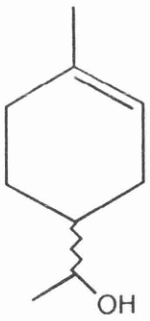
Comparison of the artemisinin fragment with the product from (3.24), the reaction with singlet oxygen shows many similarities. We have a 3.2.1 ring system with the 2 bridge a peroxide bridge. Oxygen (1) has a lone pair antiperiplanar to oxygen (2) which has a lone pair antiperiplanar to oxygen (3), all of which favour peroxide formation.

Preliminary TLC results show the formation of a less polar compound, which the product would be, although only in a small proportion compared to (3.24) and other polar products which remain at the bottom of the TLC plate.

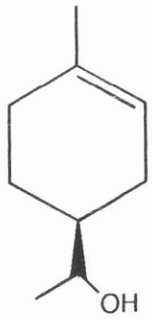
Further work would involve purification of the aforesaid compound and attempts at increasing the yield of the product should it prove to be the desired compound.



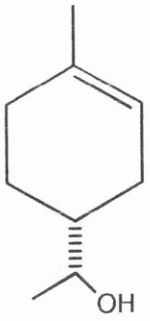
(3.16)



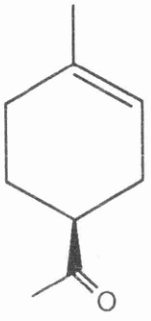
(3.20)



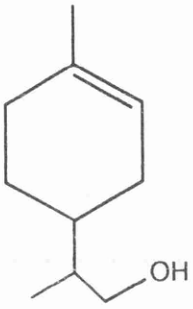
(3.21)



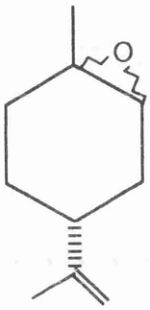
(3.22)



(3.23)

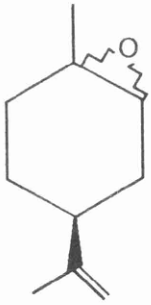


(3.24)

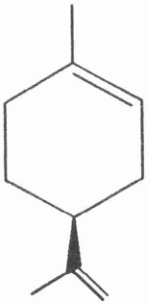


(3.25)

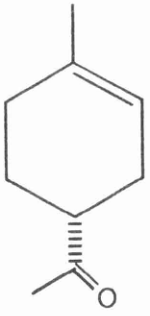
(3.26)



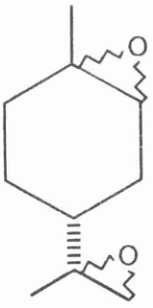
(3.27)



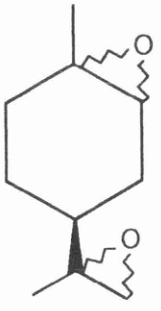
(3.28)



(3.29)



(3.30)



(3.31)

EXPERIMENTAL

4R 1,2-Epoxy-p-menth-8-en (3.25)

Compound (3.25) was prepared according to literature procedure[114] from (3.26) R-limonene, with column chromatography purification, rather than vacuum distillation, with 20% diethyl ether/80% light petroleum ether as eluent.

δ_H (90 MHz): 1.3 (s), 1.0-2.3 ppm (m), 2.3-2.6 (m), 2.8-3.1 (m), (total 14H), 4.6-4.8 (m, 2H).

δ_H (200 MHz): 1.30 (s), 1.32 (s), 0.99-2.31 (m, 14H), 2.90-3.09 (m, 1H), 4.63-4.76 (m, 2H), 7.34 (s, 0.5).

δ_C (50 MHz): 20.10 (CH_3), 20.97 (CH_3), 22.98 (CH_3), 24.17 (CH_3) 24.17 (CH_2), 25.77 (CH_2), 28.48 (CH_2), 29.74 (CH_2), 30.60 (CH_2), 36.07 (CH), 40.60 (CH), 57.14 (C), 57.33 (C), 59.08 (CH), 60.34 (CH), 108.98 (CH_2) 148.74 (C), 148.97 (C).

ν (cm^{-1}): 3083, 2971, 2932, 2861, 1645, 1451, 1435, 1379, 1181, 1121, 1040, 887, 843, 760.

m/z: 152 (4.0), 137 (4.8), 109 (11.3), 108 (5.5), 95 (8.7), 94 (5.3), 93 (7.8), 81 (15.2), 67 (18.2), 55 (10.9), 47 (15.1), 43 (17.4), 39 (11.9), 32 (20.3), 28 (100).

Accurate: Found 152.1201

$C_{10}H_{16}O$ requires 152.1213

4S 1,2-Epoxy-p-menth-8-ene (3.27)

See preparation of (3.25) except (3.28) S-limonene was used.

δ_H (200 MHz): 1.21 (s), 1.23 (s), 0.89-2.30 (m, 13H), 2.84-2.97 (m, 1H), 4.54-4.66 (m, 2H).

δ_C (50 MHz): 20.21 (CH_3), 21.06 (CH_3), 23.08 (CH_3), 24.26 (CH_3), 24.33 (CH_2), 25.91 (CH_2), 28.60 (CH_2), 29.90 (CH_2), 30.75 (CH_2), 36.21 (CH), 40.72 (CH), 57.08 (C), 57.28 (C), 59.04 (CH), 60.31 (CH), 109.14 (CH_2), 148.70 (C), 148.92 (C).

ν (cm^{-1}): 2971, 2932, 1645, 1451, 1435, 1379, 1215, 1040, 1015, 887, 843, 760.

m/z: 152 (1.2), 137 (9.1), 137 (9.1), 111 (1.1), 109 (17.3), 108 (17.3), 95 (15.0), 94 (19.1), 93 (30.5), 91 (22.0), 81 (26.2), 79 (35.6), 77 (17.3), 67 (59.1), 55 (23.5), 53 (24.9), 43 (100), 41 (63.0), 39 (56.9).

Accurate: Found 152.1205

$C_{10}H_{16}O$ requires 152.1213

4R Acetyl-p-menth-8-ene (3.29)

Compound (3.29) was prepared according to literature method from (3.25) with flash column purification rather than vacuum distillation.

δ_H (90 MHz): 1.1-2.7 (m, 15H), 2.1 (s), 5.2-5.35 (m, 1H).

δ_H (200 MHz): 1.40-1.71 (m, 4H), 1.83-2.22 (m, 9H), 2.40-2.59 (m, 1H), 5.31-5.41 (m, 1H).

δ_C (50 MHz): 23.14, 24.66 (CH_2), 26.79 (CH_2), 27.64 (CH_3), 29.25 (CH_2), 46.83 (CH), 119.09 (CH), 133.40 (C), 211.16 (C).

ν (cm^{-1}): 2964, 2924, 2857, 2836, 1709, 1453, 1439, 1377, 1352, 1167.

m/z: 139 (3.7), 138 (37.4), 123 (27.8), 105 (16.8), 95 (66.5), 94 (11.8), 93 (19.4), 91 (20.1), 79 (35.8), 77 (27.7), 67 (82.3), 43 (100), 39 (43.3).

Accurate: Found 138.1035

$C_9H_{14}O$ requires 138.1045

4S Acetyl-p-menth-8-ene (3.23)

Preparation identical to (3.29) except (3.27) was used rather than (3.25).

δ_H (200 MHz): 1.49-1.71 (m, 4H), 1.86-2.25 (m, 8H), 2.43-2.64 (m, 1H), 5.32-5.45 (m, 1H).

δ_C (50 MHz): 23.43 (CH_3), 24.94 (CH_2), 27.08 (CH_2), 27.96 (CH_3), 29.53 (CH_2), 47.23 (CH), 119.32 (CH), 133.79 (C), 211.78 (C).

ν (cm^{-1}): 3403, 3048, 3011, 2965, 2924, 2859, 2836, 2728, 1705, 1455, 1439, 1377, 1352, 1225, 1167, 1156, 800.

m/z: 139 (4.5), 138 (43.2), 123 (32.7), 105 (17.6), 95 (74.3), 93 (20.1), 91 (21.8), 79 (37.1), 77 (28.0), 67 (80.2), 55 (28.6), 43 (100), 39 (43.4).

Accurate: Found 138.1048

$C_9H_{14}O$ requires 138.1045

4R 1,2:8,9-Diepoxy-p-methane (3.30)

Compound (3.30) was extracted as a by-product from the synthesis of compound (3.25) on gravity column chromatography using neutral alumina with 50% diethyl ether/50% petroleum ether (40-60°) as eluent.

δ_H (200 MHz): 0.87-2.24 (m, 13H), 1.28 (s), 2.46-2.68 (m, 2H), 2.98-3.10 (m, 1H).

δ_C (50 MHz): 17.33 (CH_3), 18.04 (CH_3), 18.51 (CH_3), 19.97 (CH_3), 21.05 (CH_2), 21.18 (CH_2), 22.79 (CH_3), 23.16 (CH_2), 23.39 (CH_2), 24.08 (CH_3), 24.17 (CH_3), 26.26 (CH_2), 26.42 (CH_2), 27.46 (CH_2), 27.52 (CH_2), 28.23 (CH_2), 28.56 (CH_2), 29.94 (CH_2), 30.04 (CH_2), 34.68 (CH), 35.19 (CH), 39.02 (CH), 39.66 (CH), 52.36 (CH_2), 52.53 (CH_2), 52.78 (CH_2), 52.99 (CH_2), 56.95 (C), 57.00 (C), 57.33 (C), 57.40 (C), 58.30 (CH), 58.39 (CH), 58.66 (C), 59.72 (CH), 60.11 (CH).

ν (cm^{-1}): 3040, 2975, 2930, 2865, 1437, 1381, 1358, 1348, 1211, 1125, 1107, 1069, 1038, 1022, 903, 853, 837, 799, 764, 550.

m/z: 168 (1.6), 137 (3.6), 123 (3.1), 122 (4.9), 121 (4.9), 111 (8.6), 110 (9.2), 109 (9.0), 107 (15.5), 95 (23.1), 93 (26.5), 81 (34.6), 79 (32.4), 55 (37.7), 43 (100), 39 (44.4).

Accurate: Found 168.1158

$C_{10}H_{16}O_2$ requires 168.1150

<u>4S 1,2:8,9-Diepoxy-p-methane (3.31)</u>

Compound (3.31) was obtained *via* the flash column chromatography purification of (3.27).

δ_H (200 MHz): 0.51-1.85 (m, 13H), 0.93 (s), 2.05-2.28 (m, 2H), 2.52-2.70 (m, 1H).

δ_C (50 MHz): 17.02 (CH_3), 17.65 (CH_3), 17.72 (CH_3), 18.14 (CH_3), 20.70 (CH_2) 20.83 (CH_2), 22.45 (CH_3), 22.81 (CH_2), 23.05 (CH_2), 23.73 (CH_3), 23.83 (CH_3), 25.91 (CH_2), 26.07 (CH_2), 27.08 (CH_2), 27.18 (CH_2), 27.88 (CH_2), 28.23 (CH_2), 29.60 (CH_2), 29.71 (CH_2), 34.37 (CH), 34.84 (CH), 38.62 (CH), 39.26 (CH), 51.94 (CH_2), 52.05 (CH_2), 52.31 (CH_2), 52.53 (CH_2), 56.52 (C), 56.57 (C), 56.91 (C), 56.98 (C), 57.88 (CH),

57.96 (CH), 58.02 (C), 58.23 (C), 59.29 (CH), 59.678 (CH).

ν (cm^{-1}): 3503, 2974, 2932, 2867, 1721, 1449, 1437, 1381, 1358, 1213, 1125, 1071, 903, 853, 837, 799, 762, 669, 550.

m/z: 168 (0.6), 153 (0.9), 135 (1.7), 123 (3.4), 107 (10.8), 95 (15.7), 93 (17.6), 81 (16.1), 79 (21.5), 77 (12.8), 55 (26.2), 43 (100*).

Accurate: Found 168.1140

$C_{10}H_{16}O_2$ requires 168.1150

Preparation of (3.20)

1.38g of (3.16) (0.01 mole) was dissolved in 2 ml of dry THF and added to a stirred suspension of 750 mg (0.02 mol) of lithium aluminium hydride in 30 ml of THF with strong effervescence as each drop was added. The solution was stirred overnight at room temperature then quenched with saturated sodium sulphate solution, filtered, extracted with diethyl ether then washed with water. The diethyl ether solution was dried over anhydrous sodium sulphate, filtered, reduced *in vacuo* to produce 1.12g of (3.20), (80%). Purification by column chromatography on neutral alumina gave 1.01g of (3.20).

δ_H (90 MHz): 0.8-2.4 (m, 16H), 1.5 (s), 1.65 (s), 1.8 (s), 3.3-3.9 (br m, 1H), 5.2-5.5 (br s, 1H).

δ_H (200 MHz): 1.03-2.23 (m, 14H), 1.16 (s), 1.17 (s), 1.19 (s), 1.20 (s), 1.64 (s), 3.44-3.74 (octet, 1H), 5.37 (br s, 1H).

δ_C (50 MHz): 20.59 (CH_3), 20.77 (CH_3), 23.53 (CH_3), 25.02 (CH_2), 25.35 (CH_2), 27.17 (CH_2), 27.91 (CH_2), 30.14 (CH_2), 40.97 (CH), 41.15 (CH), 71.47 (CH), 71.62

(CH), 120.15 (CH), 120.32 (CH), 133.86 (C), 134.18 (C).

ν (cm^{-1}): 3356 (br), 2965, 2915, 2890, 2834, 1439, 1375, 1132, 1078, 1017, 947, 799, 666.

m/z: 140 (5.8), 125 (1.0), 122 (26.9), 107 (34.2), 95 (15.8), 94 (23.0), 93 (100), 91 (30.9), 79 (46.8), 77 (24.7), 67 (43.3), 39 (27.2), 28 (48.4).

Accurate: Found 140.1187

$C_9H_{16}O$ requires 140.1201

Preparation of (3.22)

Identical to preparation of (3.32) except (3.29) was reduced.

δ_H (200 MHz): 0.95-2.43 (m, 14H), 1.15 (s), 1.16 (s), 1.18 (s), 1.19 (s), 1.64 (s), 2.62-3.10 (br d, H), 3.42-3.70 (octet, H), 5.36 (br s, 1H).

δ_C (50 MHz): 20.36 (CH_3), 20.55 (CH_3), 23.35 (CH_3), 24.96 (CH_2), 25.16 (CH_2), 27.13 (CH_2), 27.76 (CH_2), 30.01 (CH_2), 40.80 (CH), 40.98 (CH), 71.18 (CH), 71.36 (CH), 120.07 (CH), 120.27 (CH), 133.63 (C), 133.98 (C).

ν (cm^{-1}): 3355 (br), 2965, 2915, 2834, 1439, 1375, 1132, 1117, 1078, 1016, 947, 914, 874, 799.

m/z: 140 (10.8), 125 (1.5), 123 (5.6), 122 (44.3), 107 (37.6), 95 (15.0), 94 (19.2), 93 (100), 91 (16.2), 79 (27.5), 74 (46.9), 67 (25.2), 59 (69.5), 55 (17.3), 53 (8.5).

Accurate: Found 140.1187

$C_9H_{16}O$ requires 140.1197

Preparation of (3.21)

Identical to preparation of (3.32) except (3.23) was reduced.

δ_H (200 MHz): 1.05-2.21 (m, 14H), 1.14 (s), 1.15 (s), 1.17 (s), 1.19 (s), 1.64 (s), 2.98 (br s, 1H), 3.45-3.69 (octet, 1H), 3.70-3.77 (m, 0.2H), 5.36 (br s, 1H).

δ_C (50 MHz): 20.33 (CH_3), 20.52 (CH_3), 23.28 (CH_3), 24.97 (CH_2), 25.15 (CH_2), 27.14 (CH_2), 30.02 (CH_2), 40.79 (CH), 40.96 (CH), 71.14 (CH), 71.31 (CH), 120.08 (CH), 120.29 (CH), 133.61 (C), 133.95 (C).

ν (cm^{-1}): 3353 (br), 2967, 2917, 2834, 1439, 1375, 1310, 1152, 1132, 1078, 1032, 1016, 947, 914, 874, 799.

m/z: 140 (4.7), 138 (2.5), 125 (5.5), 123 (12.8), 122 (27.9), 107 (85.5), 95 (24.9), 94 (33.7), 93 (100), 91 (19.3), 81 (17.1), 79 (35.6), 77 (15.1), 67 (25.9), 55 (18.8).

Accurate: Found 140.1202

$C_9H_{16}O$ requires 140.1201

Reaction of (3.24) with singlet oxygen[115]

420 mg of (3.24) (3 mmol) was dissolved in 200 ml of distilled CH_2Cl_2 and the solution saturated, at -78°C, with oxygen. 30 mg of Methylene blue was added and stirred, to aid dissolution, with 2 x 500W tungsten lamps shining on the reaction flask (ozonolysis flask) with oxygen bubbled through continuously for 1¾ h. As the reaction came to room temperature 4g of acidic Dowex resin (50W x 4) was added and stirred for a further 30 min until room temperature was attained. The solution was reduced *in vacuo* and purified by column chromatography with 60% Et_2O/40% petroleum ether 40-60 as the eluent. Fraction twelve was analysed.

δ_H (200 MHz): 1.00-2.71 (m, 38.5H), 1.11 (s), 1.15 (s), 1.18 (s), 3.41-3.90 (m, 5H), 4.27-4.61 (m, 1.5H), 4.72-4.88 (d, 1H), 4.90-5.05 (s, 2H).

δ_C (50 MHz): 19.24 (CH_3), 19.88 (CH_3), 20.47 (CH_3), 20.98 (CH_3), 28.82 (CH_2), 29.22 (CH_2), 29.61 (CH_2), 30.14 (CH_2), 32.69 (CH_2), 33.44 (CH_2), 33.76 (CH_2) 37.87 (CH), 38.42 (CH), 42.95 (CH), 43.06 (CH), 70.97 (CH), 71.15 (CH), 71.59 (CH), 84.66 (CH), 105.79 (CH_2), 106.67 (CH_2), 145.52 (C), 146.39 (C), 146.74 (C).

ν (cm^{-1}): 3378, 2973, 2936, 2251, 1707, 1655, 1449, 1443, 1377, 1113, 1072, 911, 733, 648.

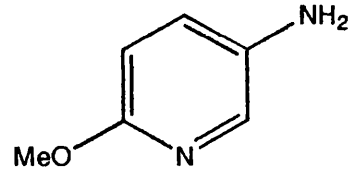
m/z: 233 (0.2), 180 (0.2), 165 (0.1), 156 (0.3), 154 (0.9), 138 (2.8), 123 (7.6), 110 (10.2), 109 (24.1), 95 (29.2), 94 (16.4), 93 (16.8), 91 (14.6), 84 (100*), 81 (25.2), 70 (44.3), 67 (22.5), 55 (32.5), 45 (34.7), 28 (37.1).

CHAPTER 4

INTRODUCTION

F. Ortiz and co-workers, continuing their work on methoxy pyridines, reported the formation of a molecular complex, long lived on the NMR timescale, between 3-amino-6-methoxy pyridine (4.1) and acetone.[116] The complex was formed when specific interactions take place between the solute (4.1) and acetone, the solvent, and could be recognised by use of NMR spectroscopy.

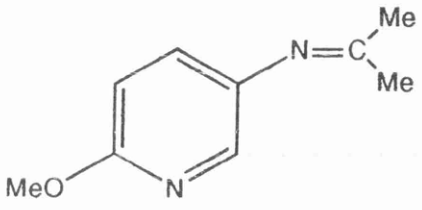
The authors proposed three possible causes for the molecular complex, but ruled out the presence of a chemical reaction and the co-existence of two different tautomeric forms in favour of the formation of a molecular complex, recognised by its ^{1}H and ^{13}C NMR spectra.



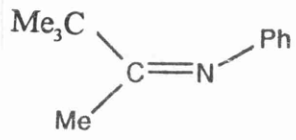
(4.1)

RESULTS AND DISCUSSION

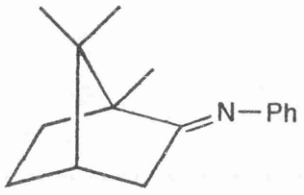
In F. Ortiz' paper it seemed more likely that a Schiff's base had been formed between the reaction of acetone and (4.1) and not a molecular complex as suggested. The synthesis of the Schiff's base (4.2) was undertaken along with other Schiff's bases (Figure 4.1) to prove the absence of a molecular association and the presence of the imine.



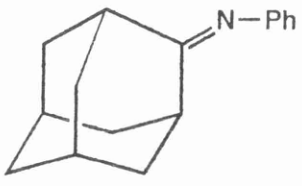
(4.2)



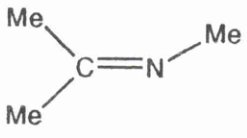
(4.3)



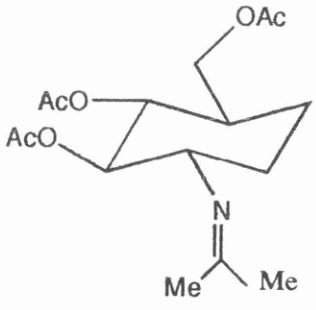
(4.4)



(4.5)



(4.6)



(4.7)

Figure 4.1

One indicative result would be to compare ^{13}C values for not only the imino carbon but also for the methyl carbons of the compounds.

Table 4.1 (values in ppm)

Compound	Imino Carbon	Methyl Carbons
4.2[116]	171.3	28.8, 20.6
4.3[117]	177.0	14.9
4.4[116]	184.3	-
4.5[118]	181.2	-
4.6[119]	168.0	29.1, 18.0
4.7[120]	171.7	29.4, 19.5

The imino carbons and the methyl signals absorb in the same region and if the ^{13}C spectra in the original paper is closely examined it is possible to detect the imino carbon which the authors have labelled as CO' (primed) *i.e.* the corresponding acetone carbonyl carbon in the molecular complex. It is also possible to see the two methyl carbons labelled in the original paper as CH_3'. Extrapolation of the spectra on the original paper gives rough values for not only the imino carbon but also for the methyl carbons:

Molecular Complex	Imino Carbon	Methyl Carbon
Figure 3 in original paper	173	21, 29

In the original paper exclusion of a chemical reaction was based on the removal of the acetone (as solvent) and then taking the solute up in carbon tetrachloride to show only 3-amino-5-methoxy pyridine (4.1). However, when water is removed azeotropically with the solvent and the resultant oil is dissolved in deuterochloroform the NMR spectra still show signals due to the imine (Figures 4.2 and 4.3).

A known reaction of imines is aqueous hydrolysis to the corresponding amine and carbonyl starting compounds. Thus when water is added to the deuterochloroform solution of imine there is a loss of virtually all signals due to the imine resulting in only acetone and (4.1) signals (Figures 4.2 and 4.3).

In a final series of tests it was possible to follow the formation of the imine and the extent of formation by using ^{1}H (200 MHz) spectrum integrals. By comparison of the developing imine signals with those of the primed spectra (in the original paper) it is obvious that they correspond exactly.

From the results given it is possible to conclude that Ortiz and co-workers were wrong in their paper title: "A Long-Lived Molecular Association between acetone and 2-methoxy-5-amino pyridine (≡ 3-amino-6-methoxy pyridine)".

EXPERIMENTAL

Camphor anil (4.4)[116]

Camphor (3g, 0.02 mol) was refluxed with 15 ml of aniline and 15 ml toluene in a Dean Stark apparatus for 18 h at 160°C with pTSA catalyst. The solvent was reduced *in vacuo* and the remaining oil was vacuum distilled to produce a yellow oil, 2.3g (52%) of (4.4).

δ_H (90 MHz): 0.90 (s, 3H), 1.00 (s, 3H), 1.10 (s, 3H), 0.6-2.5 (m, 7H), 6.70-7.50 (m, 5H).

δ_H (200 MHz): 0.86 (s, 3H), 0.96 (s, 3H), 1.09 (s, 3H), 1.13-1.33 (m, 1H), 1.40-1.60 (m, 1H), 1.62-2.00 (m, 4H), 2.05-2.30 (dt, 1H), 6.65-6.78 (dd, 2H), 6.85-7.10 (m, 1H), 7.15-7.32 (m, 2H).

δ_C (50 MHz): 11.06 (CH_3), 18.86 (CH_3), 19.37 (CH_3), 27.25 (CH_2), 31.87 (CH_2), 35.97 (CH_2), 46.91 (C), 53.68 (C), 119.19 (2CH), 122.80 (CH), 128.67 (2CH), 152.08 (C), 184.30 (C).

ν (cm^{-1}): 3020, 2970, 2880, 1680, 1600, 1488, 1449, 1392, 1068, 715, 705, 660.

m/z: 227 (39.7), 212 (8.7), 156 (11.6), 144 (30.2), 119 (39.4), 118 (23.8), 117 (15.3), 95 (34.9), 77 (81.7), 67 (21.2), 55 (21.7), 51 (41.1), 41 (46.2), 39 (28.9), 18 (100).

Microanalysis: Found C: 84.43; H, 9.40; N, 6.45

$C_{16}H_{21}N$ requires C: 84.58; H, 9.25; N, 6.16

Adamantylidene aniline (4.5)[118]

1-Adamantanone, 3g (1.33×10^{-2} mole), was refluxed with 1.9g (0.02 mole) of aniline in 35 ml of toluene with catalytic pTSA. The mixture was heated at 160°C overnight and water droplets were produced. The supernatant was removed and the residue vacuum distilled four times to produce (4.5).

δ_H (90 MHz): 1.9 (br s), 2.1 (br s) (total 10.5H), 2.7 (br s, 3.5H), 6.6-7.6 (m, 5H).

δ_H (200 MHz): 1.6-1.9 (br s, 6.25H), 1.9-2.2 (m, 6.25H), 2.68 (s), 2.69 (s) (total 1.5H), 6.50-6.80 (m, 2H), 6.80-7.10 (m, 1H), 7.10-7.40 (m, 2H).

δ_C (50 MHz): 27.35 ($2CH_2$), 34.86 (CH), 36.17 (CH_2), 38.68 ($2CH_2$), 38.94 ($2CH_2$), 42.72 (CH), 119.42 (2CH), 122.54 (CH), 128.50 (2CH), 150.41 (C), 181.23 (C).

ν (cm^{-1}): 2924, 2918, 2852, 1664, 1590, 1481, 1450, 1074, 789, 771, 715, 700.

m/z: 225 (97.8*), 146 (18.5), 130 (16.2), 117 (15.2), 106 (32.8), 93 (18.5), 91 (26.5), 77 (37.1), 77 (100*), 51 (45.9), 39 (36.9).

Accurate: Found 225.1521

$C_{16}H_{19}N$ requires 225.1513

Pinacolone imine (4.3)[117]

5g of Pinacolone (0.04 mole) was heated overnight with 4.7g (0.05 mole) of aniline in 35 ml of toluene with catalytic pTSA in a Dean-Stark apparatus. Toluene was removed *in vacuo* and the remaining oil was vacuum distilled. The third fraction was redistilled under vacuum to produce (4.3).

δ_H (90 MHz): 1.20 (s, 9H), 1.65 (s, 3H), 6.6-6.8 (m, 2H), 6.9-7.5 (m, 5H).

δ_H (200 MHz): 1.24 (s, 9H), 1.74 (s, 3H), 6.58-6.70 (dm, 2H), 6.95-7.06 (tm, 1H),

7.20-7.38 (tm, 2H).

δ_C (50 MHz): 14.94 (CH_3), 27.60 ($3CH_3$), 118.74 (2CH), 122.32 (CH), 128.63 (CH), 151.99 (C), 176.98 (C).

ν (cm^{-1}): 3020, 2980, 2939, 2910, 2879, 1658, 1600, 1487, 1479, 1453, 1371, 1245, 1241, 1148, 810, 713, 711, 700.

m/z: 175 (8.5), 160 (3.0), 133 (9.8), 119 (9.1), 118 (100), 77 (49.1), 51 (15.6), 28 (17.5).

Accurate: Found 175.1351

$C_{12}H_{17}N$ requires 175.1357

Schiff's base (4.2)[116]

2.5g (0.02 mole) of (4.1) was stirred overnight with 20 ml of anhydrous acetone with 10g of activated 4Å molecular sieves (activated by heating at 300°C under vacuum). The solution was decanted and vacuum distillation afforded the imine (4.2).

δ_H (90 MHz): 1.9 (s, 3H), 2.2 (s, 3H), 3.9 (s, 3H), 6.7 (s), 6.8 (s) (total 1H), 7.0 (d), 7.1 (d) (total 1H), 7.6 (d, 1H).

δ_H (200 MHz): 1.86 (s, 3H), 2.20 (s, 3H), 3.92 (s, 3H), 6.69-6.70, 6.73-6.74 (dd, 1H), 7.02-7.03, 7.06-7.08 (dd, 1H), 7.59-7.60, 7.60-7.61 (dd, 1H).

δ_C (50 MHz): 20.6 (CH_3), 28.8 (CH_3), 53.3 (CH_3), 110.6 (CH), 131.6 (CH), 137.0 (CH), 141.2 (C), 160.7 (C), 171.3 (C).

ν (cm^{-1}): 3355, 3208, 2940, 1662, 1602, 1486, 1469, 1431, 1379, 1301, 1283, 1255, 1031, 841, 776, 741.

m/z: 164 (24.7), 149 (73.8), 121 (15.7), 118 (14.7), 108 (20.1), 95 (14.1), 94 (54.6), 93 (29.1), 81 (40.3), 80 (34.8), 77 (31.5), 66 (40.5), 54 (64.5), 53 (63.8), 52 (84.7), 42 (38.9), 41 (70.7), 39 (100), 38 (48.7).

Accurate: Found 164.0953

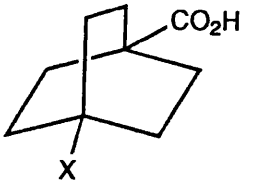
$C_9H_{12}N_2O$ requires 164.0947

CHAPTER 5

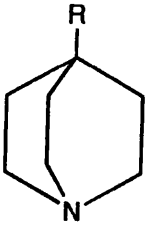
INTRODUCTION

In order to analyse the influence of a substituent on a spectroscopic property at a given site in a series of otherwise identical molecules, two main conditions must be fulfilled: a constant spatial relationship must exist between site and substituent and no steric interaction between the pair should occur.

The essentially rigid nature of certain alicyclic fused ring compounds, typically bicyclic or tricyclic, provides the framework for such investigations. Such a framework was first exploited by Roberts' group[122] who measured the dissociation constants of a series of 4-substituted bicyclo[2.2.2]octane carboxylic acids (4.1). Other relevant studies have involved measurements of equilibrium constants, reaction rates and spectroscopic properties. More recently, Grob[123,124,125] and Palacek[126,127] have measured the basicities of a series of 4-substituted quinuclidines (4.2).



(4.1)



(4.2)

Substituent constants have been determined from these, and other, studies and collations of the obtained values have been given by Charton[128] and by Hansch, Leo and Taft.[129]

To monitor the influence of substituents on the ^{13}C NMR chemical shifts of the carbonyl group, 4-substituted camphors have been used in two different solvents.[130] The present NMR measurements were carried out on significantly more dilute solutions (*ca.* 0.1 mol dm^{-3}) than previously[131] and from a more extended list of 4-substituted camphors (1)-(18). The significantly lower concentration of ketone appreciably diminishes any intermolecular interactions.

RESULTS AND DISCUSSION

Tables 4.1 and 4.2 show the ^{13}C chemical shift data for the substituted camphors (1)-(18) in $CDCl_3$ and CCl_4, respectively. There is a linear response in the chemical shift of the carbonyl carbon, C2, to the electronic character of the substituent. Such regular behaviour is not reproduced here, or in general, by the chemical shifts of sp^3 hybridised carbons.

The ^{13}C shifts of carbon 2 in (1)-(18) in $CDCl_3$ can be expressed by equation (1)

$$\delta_{CO}^{CDCl_3} = 219.458 - 13.179\,\sigma_F \qquad (1)$$

$r = 0.9890$ (correlation coefficient), $s = 2.739$ (standard deviation), $n = 18$

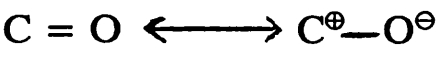
The corresponding relationship for carbon-2 chemical shifts in CCl_4 is given by equation (2)

$$\delta_{CO}^{CCl_4} = 214.128 - 10.239\,\sigma_F \qquad (2)$$

$(r = 0.9806)$, $(s = 2.146)$, $n = 18$

Both equations are accurate and indicate that field effects of the substituent are primarily responsible for the chemical shift variation. The electron-withdrawing substituents at carbon-4 of the camphor skeleton bring about shielding of the carbonyl carbon, carbon-2, so there is a greater influence of the canonical form a

over the dipolar form b, in Figure 4.1, with such electron-withdrawing substituents.



a **b**

Figure 4.1

Comparison of the respective carbonyl carbon, C2, chemical shifts in Tables 1 and 2 show a significant trend, outlined in Table 3. In $CDCl_3$ the C2 carbon is always more deshielded than in CCl_4 for a given substituent and the solvent induced chemical shift difference $\Delta\delta^{CDCl_3}_{CCl_4}$ is not constant but is a linear function of the electron-withdrawing character of the substituent, expressed by equation 3.

$$\Delta\delta^{CDCl_3}_{CCl_4} = 5.3423 - 2.9841\,\sigma_F \qquad (3)$$

$$(r = 0.9466)\ ,\ (s = 0.6479)\ ,\ n = 18$$

$\Delta\delta^{CDCl_3}_{CCl_4}$ is more than 2 ppm with the greatest value shown by neutral or weakly electron releasing substituents, as shown in Table 3.

These small solvent induced chemical shift differences arise from hydrogen (deuterium) bonding of the C2 oxygen to deuterium in $CDCl_3$ (although there may be a small factor due to the small polarity differences between solvents). In 4-nitro-camphor (18) the ability to hydrogen bond is least; this reflects the decreased

basicity of the carbonyl oxygen lone pair due to the electron-withdrawing properties of the nitro group. This, to our knowledge, represents the first demonstration of the dependence of the H-bonding carbonyl basicity on the substituent in an aliphatic system.

Table 1. 13C Chemical shifts (ppm) of 4 - substituted camphors (1) - (18) as 0.1 mol dm-3 solutions in deuteriochloroform.

	Substituent	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Other carbons	
1	$CO\bar{N}\text{-}\dot{N}Me_3$	60.39	220.05	46.38	55.38a	30.48	29.80	49.80	18.77	17.59	9.73	55.38,	174.33
2	$CO\bar{N}\text{-}\dot{S}Me_2$	60.44	218.78	46.66	56.19	31.03	29.67	50.29	18.5	17.40	9.69	31.85,	182.78
3	Et	59.76	219.29	46.10	48.44*	31.16	29.29	49.19*	17.59	16.03	9.89*	9.97*	23.23
4	Me	59.68	219.32	48.96	48.12*	34.27	29.58	47.57*	17.46	15.80*	10.03	15.43*	
5	H	57.69	219.75	43.28	43.01	27.02	29.88	46.78	19.76	19.13	9.24		
6	$CH=CH_2$	59.91	218.13	45.98	52.15	31.78	29.46	49.34	17.73	16.30	9.80	115.99,	137.42
7	C_6H_5	61.05	217.95	47.03	53.17	32.24	29.34	50.73	18.07	16.78	10.14	126.63	127.28
8	CH_3O	57.93	214.86	44.76	84.22	27.85	29.16	48.40	17.27	15.52	9.65	53.44	
9	C=CH	58.26	216.02	48.20	43.52	33.85	29.02	50.37	18.03	16.75	9.97	71.40	83.71
10	CO_2Me	60.15	216.09	45.48	54.78	30.38	29.07	50.67	18.32	17.21	9.51	51.77,	172.02
11	OCOMe	56.6	213.95	46.10	84.06	29.97	28.53	48.78	17.27	15.59	9.58	21.29,	170.71
12	COMe	60.62*	215.85	45.36	60.52*	30.56	29.33	49.73	18.27	17.29	9.30	29.27	208.62
13	$NHOO_2Et$	61.53	215.19	48.83	60.82	32.32	28.47	47.01	17.52	15.81	9.74	14.52	58.13
14	I	54.25	214.61	54.74	44.97	40.15	30.32	51.87	19.08	18.51	10.40		156.14
15	Cl	57.9	213.26	50.70	69.67	36.11	28.42	50.48	17.16	15.68	10.20		
16	Br	56.81	213.58	52.06	64.06	37.41	29.19	51.04	17.89	16.72	10.37		
17	CN	57.88	212.20	45.82	42.37	31.83	28.57	50.96	18.11	17.15	9.53	119.74	
18	NO_2	60.32	210.13	45.93	91.04	31.05	27.62	51.87	17.48	16.71	9.63		

[a]assumed to be coincident with the Me_3N (+)signal; * assignments may be reversed.

Table 2. 13C Chemical Shifts (ppm) of 4 - substituted camphors (1) - (18) as 0.1 mol dm -3 solutions in Carbon tetrachloride.

	Substituent	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Other Carbons	
1	$CO\bar{N}\text{-}\dot{M}Ne_3$	59.52	215.49	45.86	54.81a	30.48	29.51	49.15	18.66	17.53	9.73	54.81,	174.05
2	$CO\bar{N}\text{-}\dot{S}Me_2$	59.64	214.59	46.22	55.68	30.99	29.39	49.64	18.48	17.32	9.71	31.50	181.68
3	Et	58.89	213.89	45.40	47.89*	31.16	28.87	49.19*	17.43	15.92	9.74*	9.79*	23.19
4	Me	58.78	213.88	48.34	45.06*	34.32	29.15	47.57*	17.31	15.41*	10.00	10.00	15.69*
5	H	56.88	214.37	42.74	42.99	27.04	29.69	46.25	19.66	10.10	9.23		
6	$CH=CH_2$	59.07	213.03	45.28	51.81	31.77	29.08	48.86	17.58	16.20	9.78	115.68	137.39
7	$C_6\text{-}H_5$	60.20	213.03	46.44	52.82	32.19	28.98	50.18	17.89	16.65	10.12	126.23	126.87
8	MeO	57.14	210.35	44.12	83.76	27.59	29.11	48.01	17.11	15.37	9.65	52.75	
9	C = CH	57.44	211.49	47.54	43.20	33.72	28.78	49.01	17.85	16.62	9.94	71.27	83.54
10	CO_2 Me	59.28	211.68	44.73	54.25	30.32	28.75	50.02	18.13	17.04	9.47	51.01	171.37
11	OAc	55.91	209.58	45.51	83.66	29.89	28.23	48.24	17.11	15.49	9.56	20.68	168.44
12	COMe	59.64*	211.64	44.85	60.08	30.49	28.90	49.73	18.04	16.98	9.24	28.51	205.26
13	CO_2 Et	57.44	211.26	46.44	61.23	32.15	28.18	48.34	17.31	15.64	9.74	14.50	59.89
14	I	53.50	210.37	54.27	44.62	40.08	30.01	51.41	18.87	18.39	10.35		154.70
15	Cl	57.16	209.07	50.34	69.67	36.19	28.25	50.09	17.09	15.65	10.26		
16	Br	56.08	209.40	51.60	63.60	37.37	28.91	50.56	17.69	16.59	10.31		
17	CN	57.10	208.78	45.25	42.08	31.62	28.33	50.36	17.89	16.93	9.50	118.73	
18	NO_2	59.59	206.80	45.42	90.25	31.12	27.37	51.11	17.28	16.11	9.54		

[a]assumed to be coincident with the $Me_3N(+)$ signal; * Assignments may be reversed.

Table 3. Chemical shift differences ($\Delta\delta$) of the carbonyl carbons C(2) of 4 - substituted camphors (**1**) - (**18**) induced by solvent change $CDCl_3$ to CCl_4

Compound	Substituent	$\Delta\delta$ ($CDCl_3$ - CCl_4)	σF[a]
1	$CO\bar{N}\text{-}\dot{N}Me_3$	4.56	-
2	$CO\bar{N}\text{-}\dot{S}Me_2$	4.19	-
3	Et	5.41	-0.01
4	Me	5.44	-0.01
5	H	5.38	0.00
6	$CH{=}CH_2$	5.10	0.11
7	C_6H_5	4.92	0.12
8	CH_30	4.50	0.30
9	$C{\equiv}CH$	4.52	0.29
10	CO_2 Me	4.41	0.30
11	OCOMe	4.37	0.38
12	COMe	4.21	0.30
13	$NHCO_2Et$	3.93	0.28
14	I	4.45	0.40
15	Cl	4.07	0.47
16	Br	4.18	0.47
17	CN	3.42	0.57
18	NO_2	3.32	0.67

[a] σ F values are taken from M. Charton, Prog. Phys. Org. chem. 1981, 13, 119; see also C. Jansch, A Leo and R.W. Taft, chem. Rev. 1991, **91**, 165.

Experimental

4-Iodocamphor (14)

Jones oxidation of 4-iodoisoborneol[132] gave 4-iodocamphor which was recrystallised from ethanol, m.p. 157-159°C.

^{1}H (200 MHz): 0.79 (s, 3H), 0.88 (s, 3H), 0.99 (s, 3H), 1.34-1.48 (m, 1H), 1.58-1.72 (m, 1H), 1.93-2.05 (m, 1H), 2.28-2.49 (m, 2H), 2.66-2.76 (m, 1H).

ν (cm^{-1}) (KBr): 3478, 2962, 2924, 2868, 1748, 1444, 1390, 1372, 1320, 1280, 1068, 1026, 916, 880, 858.

m/z: 279 (0.6), 278 (5.3), 152 (3.5), 151 (31.9*), 124 (10.0), 123 (100), 95 (12.9), 93 (18.0), 91 (15.1), 81 (75.8*), 79 (16.4*), 77 (13.9*), 69 (18.6), 67 (25.5), 55 (19.4), 41 (46.6), 39 (30.9).

Accurate mass: Found 278.0156

$C_{10}H_{15}I^{127}O$ requires 278.0166

4-Cl Camphor (15)

Jones oxidation of 4-chloroisoborneol[133] gave 4-chlorocamphor.

^{1}H (200 MHz): 0.81 (s, 3H), 0.92 (s, 6H), 1.32-1.43 (m, 1H), 1.60-1.75 (m, 1H), 1.81-1.94 (m, 1H), 2.07-2.21 (m, 1H), 2.29-2.38 (m, 1H), 2.50-2.61 (d, d, 1H).

ν (cm^{-1}) (KBr): 3482, 2966, 2930, 2872, 1752, 1446, 1416, 1392, 1374, 1326, 1216, 1074, 1032, 972, 944.

m/z: 188 (4.4), 186 (13.8), 151 (6.8), 129 (27.5), 123 (32.0*), 122 (100*), 107 (59.2*), 93 (20.1), 91 (26.7*), 83 (52.6), 81 (25.6), 79 (22.8*), 77 (22.9), 69 (34.3), 67 (32.4), 55 (47.7), 53 (27.8), 41 (83.4), 39 (60.9).

Accurate mass: Found 186.0820

$C_{10}H_{15}Cl^{35}O$ requires 186.0811

4-Br Camphor (16)

Jones oxidation of 4-bromoisoborneol[134] gave 4-bromocamphor (16).

^1H (200 MHz): 0.82 (s, 3H), 0.92 (s, 3H), 0.95 (s, 3H), 1.31-1.45 (m, 1H), 1.60-1.75 (m, 1H), 1.88-2.06 (m, 1H), 2.15-2.44 (m, 2H), 2.60-2.73 (m, 1H).

ν (cm^{-1}) (KBr): 3446, 2966, 2926, 1750, 1392, 1282, 1073, 1018, 913, 890.

m/z: 232 (4.5), 230 (4.6), 217 (0.2), 215 (0.2), 151 (10.4), 123 (100), 122 (16.7), 107 (18.7), 93 (13.3), 91 (15.5), 83 (14.5), 81 (54.8), 79 (16.0), 69 (29.9), 67 (28.9), 55 (24.3), 41 (53.8), 39 (36.1).

Accurate mass: Found 232.0286

$C_{10}H_{15}{}^{79}BrO$ requires 232.0288

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