Intramolecular Radical Aromatic Substitution Reactions

A Thesis Presented by

Maria Lucília E. N. da Mata

In Partial Fulfilment of the Requirements for the Award of the Degree of

DOCTOR OF PHILOSOPHY

OF THE

UNIVERSITY OF LONDON

Department of Chemistry
University College London
20 Gordon Street
London

November 1994
Abstract

This thesis is divided into three chapters.

Chapter One presents a review on ipso substitution in aromatic and heteroaromatic rings, and is divided in two parts. The first is concerned with intermolecular ipso substitution reactions and the second describes the work that has been done on the intramolecular reactions.

Chapter Two describes the advances of an intramolecular free radical ipso substitution strategy which uses a sulfonyl moiety as an ipso nucleofuge. The reaction of an aryl radical with a sulfonyl substituted acceptor ring, with differing substituents on the acceptor ring and tethering chains of different nature and size, is discussed.

A strong effect on the promotion of ipso substitution was found with compounds where an ortho substituent to the sulfonyl substituted position was present. In the absence of an ortho substituent, preferential attack occurs in order to give the more stable radical.

The nature of the bridge between the two aromatic rings is also an important factor, and a slight change in the strain or conformation can change the course of the reaction. With simple chains was observed that in 1,5-ipso substitution reactions, a nitrogen atom is a more efficient ipso director than an oxygen atom, which in turn is better than a methylene unit.

1,6-Ipso substitution reactions were shown to be less efficient processes. Several linking chains, resulting from the combination of nitrogen, oxygen, methylene and carbonyl units were analysed, and in general ipso substitution products could be obtained, although, in some cases, only by the strategical introduction of ortho substituents.

A preliminary study on 1,5-ipso substitution reactions of α-carbonyl radicals was undertaken, in order to optimise the reaction conditions. Reactions involving tin compounds, transition metals and xanthates were studied. When tin hydride was used, the formation of indolone derivatives, by a sequential 1,5-ipso substitution / 1,5-addition of the intermediate amidyl radical to the aromatic ring was observed.

The temperature of the reaction was shown to be an important factor, as other competitive processes, such as reduction or β-scission can also occur.

Chapter Three provides a formal account of the experimental results and procedures.
<table>
<thead>
<tr>
<th>Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td>Contents</td>
<td>2</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>5</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>6</td>
</tr>
<tr>
<td>Stereochemical notation</td>
<td>8</td>
</tr>
<tr>
<td>Chapter One : Introduction</td>
<td>9</td>
</tr>
<tr>
<td>Radical <em>Ipso</em> Attack on Aromatic Compounds</td>
<td>10</td>
</tr>
<tr>
<td>1.1. Intermolecular Aromatic <em>Ipso</em> Substitution Reactions</td>
<td>11</td>
</tr>
<tr>
<td>1.1.1. Aromatic Halogen Displacement</td>
<td>11</td>
</tr>
<tr>
<td>1.1.1.1. Displacement by a Halogen</td>
<td>11</td>
</tr>
<tr>
<td>1.1.1.2. Displacement by a Phenyl Radical</td>
<td>13</td>
</tr>
<tr>
<td>1.1.1.3. Displacement by an Alkyl Radical</td>
<td>14</td>
</tr>
<tr>
<td>1.1.1.4. Displacement by Sulfur and Silicon Radicals</td>
<td>16</td>
</tr>
<tr>
<td>1.1.2. Aromatic Displacement with Cleavage of a Carbon-Nitrogen Bond</td>
<td>18</td>
</tr>
<tr>
<td>1.1.2.1. The Nitro Group</td>
<td>18</td>
</tr>
<tr>
<td>1.1.2.2. The Azo Group</td>
<td>20</td>
</tr>
<tr>
<td>1.1.3. Aromatic Displacement with Cleavage of a Carbon-Sulfur Bond</td>
<td>21</td>
</tr>
<tr>
<td>1.1.4. Aromatic Displacement with Cleavage of a Carbon-Oxygen Bond</td>
<td>21</td>
</tr>
<tr>
<td>1.1.5. Aromatic Displacement with Cleavage of a Carbon-Carbon Bond</td>
<td>23</td>
</tr>
<tr>
<td>1.1.5.1. Displacement of an Alkyl Group</td>
<td>23</td>
</tr>
<tr>
<td>1.1.5.2. Displacement of a Carboxy Group</td>
<td>23</td>
</tr>
<tr>
<td>1.1.6. Displacement Reactions on Heteroaromatic Rings</td>
<td>24</td>
</tr>
<tr>
<td>1.1.6.1. Furan and Thiophene Derivatives</td>
<td>24</td>
</tr>
<tr>
<td>1.1.6.2. Pyridine and Quinoline Derivatives</td>
<td>26</td>
</tr>
</tbody>
</table>
1.1.6.3. Benzothiazole Derivatives 28
1.1.6.4. Indole and Pyrrole Derivatives 29

1.2. Intramolecular Aromatic Ipso Substitution Reactions 31

1.2.1. Aromatic Displacement with Cleavage of a Carbon-Nitrogen Bond 31
   1.2.1.1. The Nitro Group 31
   1.2.1.2. The Amidyl Group 31
   1.2.1.3. The Diazo Group 33
   1.2.1.4. The Iminyl Group 34

1.2.2. Aromatic Displacement with Cleavage of a Carbon-Sulfur Bond 35

1.2.3. Aromatic Displacement with Cleavage of a Carbon-Carbon Bond 40

1.2.4. Aromatic Displacement with Cleavage of a Carbon-Oxygen Bond 44

1.2.5. Aromatic Displacement with Cleavage of a Carbon-Halogen Bond 47

1.3. Conclusions 47

References 49

Chapter Two: Results and Discussion 52

2.1. Introduction and Previous Work in These Laboratories 53

2.2. Steric and Electronic Effects on the Sulfonyl Substituted Acceptor Ring 56
   2.2.1. The Effect of an ortho Substituent 56
2.2.2. The Effect of a meta Substituent

2.2.3. The Effect of Multiple Substituents

2.3. The Nature of the Linking Chain in 1,5-Ipso Substitution vs 1,6-Addition

2.4. Strain and Ring Effects

2.5. The Nature of the Linking Chain in 1,6-Ipso Substitution vs 1,7-Addition

2.6. α-Carbonyl Radicals in Ipso Substitution Reactions

2.6.1. Reaction Under Atom Transfer Conditions

2.6.2. Reaction Using Copper (I)

2.6.3. Reaction Involving Xanthates

2.7. Conclusions and Perspectives

References

Chapter Three: Experimental

General Procedures

References

Appendix One: Selected nmr Data

Appendix Two: X-ray Data
Acknowledgements

I would like to thank my supervisor, Prof. W. B. Motherwell, for his constant flow of ideas, encouragement, guidance and friendship over the past three years.

I would like also to thank all the past and present members of the WBM group, who made these years so much enjoyable, in particular Herve, Fez and Lisa and my contemporaries Sheena, Donogh, Man-Tat and Lewis.

A very special acknowledgement to all the "eskimos" who proof read this thesis, Mark, Richard, Caroline, Tim, Alvin, Adrian, Donogh, Frederic, Mila, Peter, Phil, Sheena and Tania, Simon, Martin, Jean-Marc and Nadine, and also Eric for taking care of my bench.

This work would not have been possible without the support of the technical staff at Imperial College and University College London; especially Dick Sheppard, Paul Hammerton (IC) and Jill Maxwell (UCL) for high field nmr experiments, Geoff Tucker and John Barton (IC), Dr. J.A. Ballantine (SERC Mass Spectroscopy Centre, Swansea), Dr. M. Mruzek and John Hill (UCL) for the mass spectra. Also thanks to Dr. D. A. Tocher for the X-ray crystal structure, Alan Stones (UCL) for microanalyses Steven Corker for the HPLC and P. Leighton for help solving all the problems.

Outside the Chemistry Department, I would like to thank Ana and Barry for being good friends, Lena and Manel for the innumerable weekends they had to put up with me. A special acknowledgement to Luisa and Carlos for their friendship, and useful comments about my work. Also, to all my friends in Portugal, who did not forget me while I was away, and to all those who visited me in London, a big thank you.

For funding I am grateful to JNICT, Programa Ciência for very generous sponsorship.

Most importantly, I would like to thank my parents for their constant love and encouragement, and to my sisters, brothers, nephews and nieces, in particular to Paulina, who beat all the records in travelling to London.

Finally, I would like to thank Ian, for his love and support over the last two years.

I dedicate this thesis to my family.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Ad</td>
<td>Adamantane</td>
</tr>
<tr>
<td>AIBN</td>
<td>α,α'-Azoisobutyronitrile</td>
</tr>
<tr>
<td>Aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butoxycarbonyl</td>
</tr>
<tr>
<td>b.p.</td>
<td>Boiling point</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical ionization</td>
</tr>
<tr>
<td>conc.</td>
<td>Concentrated</td>
</tr>
<tr>
<td>conv.</td>
<td>Conversion</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DPDC</td>
<td>Di-isopropyl peroxydicarbonate</td>
</tr>
<tr>
<td>DTBP</td>
<td>Di-t-butyl peroxide</td>
</tr>
<tr>
<td>EI</td>
<td>Electron impact</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>FAB</td>
<td>Fast Atom Bombardment</td>
</tr>
<tr>
<td>hr</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>hv</td>
<td>Light</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>m</td>
<td>meta</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>min</td>
<td>Minute(s)</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>1H nmr</td>
<td>Proton nuclear magnetic resonance</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>P</td>
<td>Primary (α,n,m,n)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>py</td>
<td>Pyridine</td>
</tr>
<tr>
<td>q</td>
<td>Quartet ((^1)H nmr) or Quaternary ((^13)C nmr)</td>
</tr>
<tr>
<td>R</td>
<td>Unspecified carbon substituent</td>
</tr>
<tr>
<td>r.t.</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet ((^1)H nmr) or Secondary ((^13)C nmr)</td>
</tr>
<tr>
<td>sat.</td>
<td>Saturated</td>
</tr>
<tr>
<td>SET</td>
<td>Single electron transfer</td>
</tr>
<tr>
<td>t</td>
<td>Triplet ((^1)H nmr) or Tertiary ((^13)C nmr)</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-Tetramethylethylenediamine</td>
</tr>
<tr>
<td>Tol</td>
<td>p-Tolyl</td>
</tr>
<tr>
<td>tr.</td>
<td>Traces</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>vs</td>
<td>versus</td>
</tr>
<tr>
<td>X, Y</td>
<td>Unspecified groups</td>
</tr>
</tbody>
</table>
Stereochemical Notation

Throughout this thesis, the graphical representation of stereochemistry is in accord with the conventions proposed by Maehr. Thus, solid and broken wedges denote absolute configuration and solid and broken lines denote racemates. For the former, greater narrowing of both solid and broken wedges indicates increasing distance from the viewer.

Chapter One:

Introduction
Radical *Ipso* Attack on Aromatic Compounds

The displacement of groups other than hydrogen on an aromatic ring has been generally described as *ipso* substitution. The importance of this process is that it takes advantage of an existing group on the molecule to introduce a different one in its place.

Many examples of radical *ipso* substitution reactions have been described, and it is believed that they occur *via* an addition-elimination mechanism (Scheme 1.1). The radical $R^\ast$ attacks the aromatic ring at the same position as the leaving group $X$, leading to the formation of a $\sigma$-complex intermediate. The intermediate eliminates to afford the substituted aromatic ring and the radical $X^\ast$.

\[
\begin{align*}
R^\ast & \quad + \quad \text{Ar} \quad \rightarrow \quad \text{Ar}^\ast \quad \rightarrow \quad \text{Ar} & \quad + \quad X^\ast \\
\end{align*}
\]

*Ipso* attack is not the only process which can occur, since the addition to an unsubstituted position can of course be a competitive process.

There are several factors which control the selectivity of attack, either at the *ipso* carbon atom or another unsubstituted position. Thus, the nature of the attacking radical, the aromatic substrate, and the leaving groups may all be involved.

Such processes can occur either in the inter- or in the intramolecular mode.

The purpose of the present introduction, which is divided into two sections, is to provide some background information on radical *ipso* substitution reactions on aromatic rings. The first section is concerned with intermolecular reactions, while the second part will describe intramolecular *ipso* substitution reactions.
1.1. Intermolecular Aromatic *Ipso* Substitution Reactions

1.1.1. Aromatic Halogen Displacement

As the displacement of a halogen atom by another group through *ipso* substitution has been previously reviewed,\(^1\) this introduction will highlight only the more important aspects of each type of substitution.

1.1.1.1. Displacement by a Halogen

The first work involving radical *ipso* substitution reactions dates from 1890, when Srpek\(^1\) reported that chlorination of *p*-bromotoluene at room temperature gave an inseparable mixture of products with chlorine and bromine substituents in both the ring and the side chain (Scheme 1.2). Since then, several workers have described the displacement of a halogen atom by another one, but, in general, even with simple monosubstitution (Scheme 1.3) the reaction has been found to be unselective.

\[\begin{array}{c}
\text{Br} & \rightarrow & \text{Cl} & \text{Cl} & \text{Cl} & \text{Br} \\
\text{Br} & & 22-30\% & 2\% & 38-53\% & 11-18\%
\end{array}\]

Reagents: SO\(_2\)Cl\(_2\), benzoyl peroxide.\(^2\)

![Scheme 1.2](image)

\[\begin{array}{c}
\text{Br} & \rightarrow & \text{Cl} & \text{Cl} & \text{Cl} & \text{Cl}
\end{array}\]

\[\begin{array}{c}
28\% & 17\% & 17\%
\end{array}\]

Reagents: Cl\(_2\), light.\(^1\)

![Scheme 1.3](image)
The presence of additional electron withdrawing substituents decreases reactivity, and in the case of \( p \)-bromonitrobenzene the reaction fails.\(^3\) The same result is observed in the gas phase chlorination of a number of substituted benzenes.\(^4\)

The displacement of an iodine atom was reported some time later.\(^5\) Since chlorine itself reacts with iodobenzene to form iodobenzene dichloride, the reaction was performed using sulfuryl chloride and a peroxide initiator (Scheme 1.4).

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
& \quad \text{Cl}_2 \\
\text{I} & \quad \text{SO}_2\text{Cl}_2 \\
& \quad \text{BzOOBz} \\
\text{Cl} & \quad \\
\end{align*}
\]

A lack of selectivity was again observed, with formation of a mixture of chlorobenzene, \( p \)-dichlorobenzene (traces), and diiodobenzene. Competitive displacement of iodine and bromine by chlorine atoms showed that iodine is displaced 2.3 times as rapidly as bromine.

The substitution of a halogen by another of higher atomic number is a process that is contrary to expectations, based on bond energy data. Nevertheless bromination of chlorobenzene proceeds in the gas phase, to give low yields of dichlorobenzenes, dibromobenzenes and bromochlorobenzenes.\(^4\)

Photo-initiated chlorination of \( p \)-chloronitrobenzene at room temperature gives mainly \( p \)-dichlorobenzene, with traces of 1,2,4-trichlorobenzene.\(^6\) However, when the substrate is \( p \)-bromonitrobenzene, chlorodebromination and chlorodenitration are competitive processes. The increasing concentration of chloronitrobenzene before its conversion to dichlorobenzene, shows a preference for initial attack at the halogen substituent (Scheme 1.5).
1.1.1.2. Displacement by a Phenyl Radical

The displacement of a halogen atom by a phenyl radical is not a highly effective process, since the phenyl radical prefers to add to an unsubstituted position. However, an appreciable amount of biphenyl may be formed if iodobenzene is selected as substrate. In this case, iodine atom is lost 10 times more frequently than a hydrogen. A comparative study between the reactivity of fluoro and hydrogen substituents towards the attack of a phenyl radical has been made. When phenyl radicals react with a mixture of hexafluorobenzene and benzene, comparable reactivities were detected.¹

In a study of the relative reactivity of halogens towards displacement by the phenyl radical, a greater susceptibility of fluorine to be replaced was noted. Thus, chloropentafluorobenzene and bromopentafluorobenzene on reaction with phenyl radicals gave only displacement of fluorine (Scheme 1.6). The overall nature of the pentafluoroaromatic substrate may however play an important role in this instance.
The presence of electron withdrawing substituents on the aryl radical leads to a decrease in the yield of the reaction, as demonstrated by the reaction of hexafluorobenzene with substituted benzoyleperoxides (m-Me (55%), m-Cl (28%), m-Br (28%) and p-NO₂ (traces; reaction performed in a sealed tube)).

Further studies on the homolytic reactions of pentafluorobenzoyl peroxide show that the reaction with chlorobenzene and bromobenzene occurs before decarboxylation has occurred, and the phenyl ester is formed by displacement of the halogen. However, nitrobenzene exhibits different behaviour affording a mixture of biaryls and only traces of the phenolic ester are detected.

\[
\begin{array}{cccc}
\text{X} & \text{C}_6\text{F}_5\text{CO}_2\text{H} & \text{Biaryls} \\
\text{Br} & 51\% & \text{51\%} & 38\% & 0\% \\
\text{Cl} & 41\% & 28\% & 0\% \\
\text{NO}_2 & \text{tr.} & 41\% & 28\% \\
\end{array}
\]

Reagents: (C₆F₅CO₂)₂, 80°C. Yields based on peroxide consumed.

1.1.1.3. Displacement by an Alkyl Radical

The reaction of an alkyl radical with a halobenzene occurs to a limited extent via ipso substitution. Reaction of bromobenzene with the cyclohexyl radical, produced from cyclohexane and di-ter-butyl peroxide, gave the ipso substitution compound (17%) and a mixture of compounds resulting from attack at the ortho (48%), meta (26%) and para (8%) positions (Scheme 1.8).
A better selectivity for the substituted positions is observed on selection of ortho dihalobenzenes as substrates. The presence of the second electron attracting substituent on an adjacent position, the relief of steric and electronic repulsion when the radical adds to one of the carbons bearing the halogen and the ability of the halogen ortho to stabilise the cyclohexadienyl radical are all different factors which can influence this selectivity.12

The relative capacity for replacement of the halogens followed the unusual sequence of F>I>Br>Cl.12 The electronegativity and size of the fluorine atom may well explain such a preference for initial attack at the ipso site by the nucleophilic cyclohexyl radical.

However, a different reactivity is observed when bromofluorobenzene and chlorofluorobenzene react with benzyl radicals. On the basis of the foregoing argument it would be expected that the displacement of the more electronegative halogen is the favoured reaction, but the loss of a fluorine atom was not observed. On the assumption that the addition of the benzyl radical is a reversible process, and that the carbon-fluorine bond is stronger than the carbon-chlorine bond, then intermediate 1 is more likely to proceed to product while intermediate 2 reverts to starting materials13(Scheme 1.9).

Reaction of the methyl radical, formed by pyrolysis of nitromethane, with benzene does not produce toluene but only biphenyl. The methyl radical therefore
prefers to abstract a hydrogen atom and form the phenyl radical, which can then react with another molecule of benzene. On the other hand, the reaction with hexafluorobenzene gives both methylpentafluorobenzene and pentafluorophenol, the latter product presumably derived by ipso attack of the nitro radical (Scheme 1.10).

![Scheme 1.10](image)

1.1.1.4. Displacement by Sulfur and Silicon Radicals

Only a few reports refer to the displacement of halogens by sulfur and silyl radicals. Benzenesulfenyl and benzenesulfonyl radicals react with chloro, bromo and iodobenzene to form products of dimerization and/or disproportionation as well as ipso substitution. A strong dependence on temperature was observed, with the ipso substitution products only being formed above 150 °C. At this temperature, the sulfur based dimerization products were unstable, and regenerated the free radicals (Scheme 1.11).

![Scheme 1.11](image)
A reactivity order for the tosyl radical was determined by a series of competition reactions with mixtures of labelled and unlabelled halobenzenes (Scheme 1.12). The results, obtained by determining the relative amounts of labelled (3) and unlabelled sulfone (4), were iodobenzene > bromobenzene > chlorobenzene in a ratio 18.6 : 6 : 1.

\[
p\text{-MeC}_6\text{H}_4\text{SO}_2^* + \text{C}_6\text{D}_2\text{Br} + \text{PhCl} \rightarrow p\text{-MeC}_6\text{H}_4\text{SO}_2\text{C}_6\text{D}_5 + p\text{-MeC}_6\text{H}_4\text{SO}_2\text{Ph}
\]

\[\text{Scheme 1.12}\]

The reaction of bromobenzene, either with benzenesulfonyl or benzenesulfenyl radicals, is facilitated by electron releasing substituents, as shown in Table 1.1.

<table>
<thead>
<tr>
<th>X</th>
<th>PhSO₂</th>
<th>PhS</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-OMe</td>
<td>8.78</td>
<td>60</td>
</tr>
<tr>
<td>p-Me</td>
<td>3.59</td>
<td>1.84</td>
</tr>
<tr>
<td>p-CO₂Me</td>
<td>0.27</td>
<td>---</td>
</tr>
<tr>
<td>p-NO₂</td>
<td>---</td>
<td>3.00</td>
</tr>
</tbody>
</table>

Table 1.1\(^4\)

Reactivities of substituted bromobenzenes towards phenylsulphonyl and phenylthio radicals (relative reactivities to bromobenzene = 1)

Trimethylsilyl and trichlorosilyl radicals undergo \textit{ipso} substitution on reaction with hexafluorobenzene (Scheme 1.13). Irradiation of trimethylsilane or trichlorosilane and hexafluorobenzene with UV light produces silyl radicals, which then attack the hexafluorobenzene nucleus. Although the reaction with trimethylsilyl radicals proceeds as expected, the reaction with trichlorosilyl radicals is further complicated by halogen exchange.\(^{15}\)
1.1.2. Aromatic Displacement with Cleavage of a Carbon-Nitrogen Bond

1.1.2.1. The Nitro Group

The displacement of a nitro group from an aromatic ring by *ipso* substitution has been extensively investigated.\textsuperscript{13,16,17} As we have noted earlier (Scheme 1.5), a nitro group may be replaced by a halogen atom. This was also observed\textsuperscript{4} in the gas phase at 375 °C on reaction of nitrobenzene with chlorine, to give chlorobenzene as the major product, together with chloronitrobenzene in a 45 : 2 ratio.

The pentafluorobenzoyl radical, generated by decomposition of dipentafluorobenzoyl peroxide, reacts with nitropentafluorobenzene, by displacement of the nitro group, to give mainly biaryls. In this instance, unlike the non fluorinated precursor (Scheme 1.7), the formation of esters was not observed.\textsuperscript{10} Some evidence for the replacement of nitro groups and sulfonyl groups during electrolytic oxidation has been reported, but the products were not isolated.\textsuperscript{1}

Tiecco\textsuperscript{18} has published an extensive study on the *ipso* substitution reaction of nitrobenzenes with alkyl radicals. This alkyl denitration was examined using primary, secondary and tertiary alkyl radicals. However, the best conversions were obtained with the adamantyl radical, produced from adamantane-1-carboxylic acid by persulfate oxidation. It was also noted that strongly electron deficient aromatic rings also favoured this process. Reaction of nitrobenzene, \(p\)-nitrotoluene, \(p\)-nitroanisole, \(o\) and \(m\)-dinitrobenzene and \(o\) and \(m\)-nitrotoluene did not produce *ipso* substitution products\textsuperscript{16} (Scheme 1.14).

The presence of additional electron withdrawing groups is obviously necessary in order to increase the yields of *ipso* substitution products. Thus, when more than one nitro group is present, only one is replaced and reactions do not proceed further.\textsuperscript{17}
It is of interest to note that the course of this reaction changes considerably when methyl or phenyl radicals are used, inasmuch as addition is favoured over *ipso* substitution\(^{17}\) (Scheme 1.15).

The difference of selectivity has been attributed to the different polarities of the radicals.\(^{13}\) The adamantyl radical, as a strong nucleophilic radical, adds at the most positive carbon atom, giving the *ipso* product. In this case, polar effects operate and the addition is governed by the local charge density at the ring positions.
On the other hand, with methyl and phenyl radicals, which can be considered electroneutral radicals, the polar effects are expected to be negligible and the regioselectivity is governed by the stability of the σ-complex (Scheme 1.16).

\[
\begin{align*}
\text{R} &= \text{Me, Ph} \\
\end{align*}
\]

\[\text{Scheme 1.16}\]

1.1.2.2. The Azo Group

In an interesting study, the reaction of a phenyl radical with an arylazo compound (5) has been shown to generate two different types of product; one from the process of addition / elimination at the nitrogen atom of the azo group, 6, and the other from ipso substitution on the aromatic ring (7)\(^9\) (Scheme 1.17).

\[\begin{align*}
\text{Me} \cdot \text{N= N} \cdot \text{Ph} & \rightarrow \text{Ph} \cdot \text{N}^\equiv \text{N} \cdot \text{Ph} \\
\text{X=CO, Y=H} & \rightarrow \text{X=CO, Y=NO}_2 \\
\text{X=CH}_2, \text{Y=H} & \\
\end{align*}\]

\[\text{Scheme 1.17}\]
These two competitive pathways may be channelled however, and there is an increase of \textit{ipso} substitution product (7) when an electron withdrawing substituent is present on the aromatic ring (Y = NO$_2$, 48%).

### 1.1.3. Aromatic Displacement with Cleavage of a Carbon-Sulfur Bond

Although there has been little published on the displacement of sulfonyl groups from an aromatic ring by intermolecular \textit{ipso} attack, it seems to be an efficient process.

The only example\textsuperscript{3} reports that photoinitiated chlorination of benzenesulfonyl chloride, p-bromobenzenesulfonyl chloride and diphenylsulfone produce nearly quantitative yields of chlorobenzene (97%), \textit{p}-dichlorobenzene (97%) and chlorobenzene, respectively. However, phenyl and methyl benzenesulfonates showed no displacement (Scheme 1.18).

![Scheme 1.18](image)

### 1.1.4. Aromatic Displacement with Cleavage of a Carbon-Oxygen Bond

The possible replacement of a methoxy group by an aryl radical was observed as the only product from the reaction of the triazine 8 with 1,2,3-trimethoxybenzene producing the biaryl 9, where the most sterically inaccessible group was remarkably replaced (Scheme 1.19). Other attempts to find further examples of methoxy replacement were unsuccessful; the reaction with dibenzoyl peroxide for example, resulting in the introduction of the benzoyloxy group on an unsubstituted position of the molecule as the major product.\textsuperscript{20}
On the other hand, reaction of dibenzoyl peroxide with anisole gave phenyl benzoate, formed by ipso attack, together with methoxybiphenyls in a 1:4 ratio. The same reaction with diphenyl ether gave similar results, but when para substituted aromatic peroxides (4-Cl, 4-MeO or 4-NO₂) were used only benzoates were observed²¹ (Scheme 1.20).

Reagents: Glacial AcOH, 100°C.

Scheme 1.19

Reagents: (ArCO₂)₂, 80°C, N₂. Yields based on peroxide used.

Scheme 1.20
1.1.5. Aromatic Displacement with Cleavage of a Carbon-Carbon Bond

1.1.5.1. Displacement of an Alkyl Group

The displacement of an alkyl group by *ipso* substitution was only observed to a minor extent when a phenyl radical, produced from pyrolysis of nitrobenzene, reacted with toluene. The major products were derived by hydrogen atom replacement either on the aromatic ring or the side chain^7 (Scheme 1.21).

![Scheme 1.21](image)

Reaction Conditions: nitrobenzene:toluene 0.05:0.25; 9.5 sec. contact time. Relative concentrations obtained from relative intensities in low voltage mass spectra.

1.1.5.2. Displacement of a Carboxy Group

The autoxidation of *p*-xylene to the correspondent terephthalic acid (10) or methyl terephthalate gives rise to two by-products, 11 and 12. The formation of 12 through an *ipso* intermediate was suggested, and a further experiment demonstrated that phenyl radicals, produced by decomposition of dibenzoyl peroxide, reacted with methyl terephthalate to give the same ratio of products^22 (Scheme 1.22).
1.1.6. Displacement Reactions on Heteroaromatic Rings

Radical ipso substitution reactions have been performed on several heteroaromatic rings with great success. Extensive studies on the type of attacking radical and leaving group have led to some useful conclusive results. In general, high yields were obtained with the strongly nucleophilic adamantyl radical and with strongly electron deficient substrates. When polar effects do not interfere with the course of the reaction, ipso substitution occurs to form the most stable σ complex.

1.1.6.1. Furan and Thiophene Derivatives

As it is known that, for furan and thiophene derivatives, radical addition occurs almost exclusively at the α-position, it is expected that 2,5-disubstituted substrates should give products derived from ipso attack.

On reaction of 5-nitro-2-furancarboxylic acid with hydroxyl radicals, ipso substitution of the nitro rather then carboxy group was observed. The same tendency has been observed to a lesser extent with the corresponding 5-bromo derivatives. 5-Nitro-2-carbomethoxyfuran (13) reacted in a similar way with methyl and adamantyl
radicals, to give a mixture of three products: two resulting from direct ipso substitution on both α-positions, and the third (16) derived from a rearrangement (Scheme 1.23). It is claimed that the isomerisation of the nitro group in intermediate 14 occurs to give nitrite 15, which subsequently fragments into nitric oxide and the lactone 16.

![Scheme 1.23](image)

The influence of the regiochemistry of the substituents on the molecule is well exemplified by the reaction of the two isomers 17 and 18 with methyl and adamantyl radicals (Scheme 1.24). While 3,5-dinitro-2-carbomethoxythiophene (17) gives the expected difference in reactivity with the methyl and adamantyl radicals, the 4,5-dinitro isomer (18) shows a similar reactivity towards both radicals, since ipso attack at the 5 position gives the more stable intermediate.  

![Scheme 1.24](image)
An unusual product was observed in the reaction of 2,5-thiophenedicarbaldehyde with the adamantyl radical\(^\text{13}\) (Scheme 1.25).

The major products formed were the ipso substitution product (19, 19%) and compound 20 (56%). The latter is thought to be formed from the common ipso intermediate as 19, followed by intramolecular migration of the aldehydic carbonyl.

\textbf{1.1.6.2. Pyridine and Quinoline Derivatives}

Nitrogen-containing heterocycles have been reported to undergo ipso substitution reactions, especially when the leaving group is an acyl or cyano group.

Monosubstituted protonated pyridines do not tend to undergo ipso substitution on reaction with alkyl radicals. 4-Cyano, 4-methoxycarbonyl, 4-chloro, 4-methyl and 4-methoxypyridines do not give any ipso substitution products. However, 2- (or 4-) acylpyridine undergo ipso substitution to a small extent, although the major product is formed by reaction at the unsubstituted position 4 (or 2)\(^\text{25}\) (Scheme 1.26).
In the case of 4-cyanopyridine, *ipso* substitution has been observed with hydroxyalkyl radicals, such as the hydroxy(diphenyl)methyl radical. With the hydroxy(phenyl)-(2,3,5,6-tetramethylphenyl)methyl radical however, substitution is not observed, probably as a result of steric hindrance\(^26\) (Scheme 1.27).

\[\text{Reagents: Irradiation at 350 nm in propan-2-ol/H}_2\text{O (3:1) containing 1M H}_2\text{SO}_4.\]

With quinolines, depending on the nature of the attacking radical, a different reaction course is observed (Scheme 1.28). Thus, photolysis of 2-substituted quinolines in the presence of an alcohol (ethanol, 1-propanol, 2-propanol or tert-butyl alcohol) gave exclusively the *ipso* substitution product. Better yields were obtained with an acidified solution (20-54%). A similar result was observed from irradiation in the presence of an ether which also gave good yields of the *ipso* substitution product (59% in the presence of acid). However, when the reaction was performed in the presence of a carboxylic acid, competition between *ipso* substitution and attack at an unsubstituted position was observed, yielding the two compounds in equivalent amounts.\(^27\)
A comparative study of the reaction of disubstituted pyridines, either protonated or unprotonated, has been published. In neutral pyridines, polar effects do not operate and substitution occurs on the position para to the electron withdrawing substituents. However, on protonation, polar effects intervene and substitution occurs at the most electronegative sites in the molecule (Scheme 1.29).

![Scheme 1.29](image)

1.1.6.3. Benzothiazole Derivatives

The reaction of benzothiazoles with alkyl radicals has been extensively studied. Again, better yields were obtained with the strongly nucleophilic adamantyl radical, and efficiency progressively decreased with isopropyl, n-propyl and methyl radicals.

An extensive study of the influence of the leaving groups on ipso substitution reactions, using the adamantyl radical, revealed the necessity for the presence of strong electron withdrawing substituents. A decrease in efficiency was observed when halogens or electron donating substituents were used (Table 1.2).

<table>
<thead>
<tr>
<th>X</th>
<th>NO₂</th>
<th>PhSO₂</th>
<th>PhSO₂</th>
<th>MeCO</th>
<th>F</th>
<th>Cl</th>
<th>Br</th>
<th>I</th>
<th>SMe</th>
<th>OMe</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Conv.</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>40</td>
<td>40</td>
<td>50</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>%Yield</td>
<td>95</td>
<td>80</td>
<td>80</td>
<td>70</td>
<td>50</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>
The effect of other substituents on ipso substitution was also considered (Table 1.3). The relative rates, obtained from the reaction with adamantyl radical, show that electron withdrawing substituents increase the rate of the reaction whereas electron donating substituents decrease it.

Table 1.3

Relative rates of the reaction of substituted benzothiazoles with adamantyl radical.

<table>
<thead>
<tr>
<th>X</th>
<th>6-CN</th>
<th>6-Cl</th>
<th>5-Cl</th>
<th>5-OME</th>
<th>H</th>
<th>5-Me</th>
<th>6-Me</th>
<th>6-OME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rel. rate</td>
<td>10.9</td>
<td>2.3</td>
<td>2.2</td>
<td>1.25</td>
<td>1</td>
<td>0.86</td>
<td>0.6</td>
<td>0.46</td>
</tr>
</tbody>
</table>

These results indicate once again, that the electron density at the ring position where attack occurs is very important in determining the reactivity of the substrate.

1.1.6.4. Indole and Pyrrole Derivatives

The ability of a heteroaromatic arenesulfonyl group to be transformed into the corresponding heteroaromatic stannane under free radical conditions has recently been demonstrated. Indole and pyrrole derivatives undergo a regiospecific and high yielding substitution reaction with nucleophilic organostannyl radicals\(^30\) (Scheme 1.29).
This strategy is a useful procedure for the introduction of trialkylstannyl groups into complex systems.
1.2. Intramolecular Aromatic *Ips*o Substitution Reactions

As we have shown in the previous section, there is a variety of groups which can act as leaving groups in an intermolecular aromatic *ipso* substitution reaction. In the present section we will describe the behaviour of different attacking radicals and leaving groups which have been used in intramolecular *ipso* substitution reactions.

1.2.1. Aromatic Displacement with Cleavage of a Carbon-Nitrogen Bond

1.2.1.1. The Nitro Group

The nitro group is a very effective leaving group towards the attack of a nucleophilic radical in intermolecular reactions. However, this potential ability has been explored to a much lesser extent in intramolecular processes. One of the few examples is the formation of 22 by the attack of an aryl radical, with extrusion of nitrogen dioxide, in the Pschorr reaction of 21 with copper in water\(^\text{31}\) (Scheme 1.30). Substitution of the carbonyl on the linking chain by a nitrogen (X=NMe) improved considerably the yield.

![Scheme 1.30](image)

1.2.1.2. The Amidyl Group

One of the most studied substituents in intramolecular *ipso* substitution reactions has been the amidyl group. Most of the work focuses on the displacement of the amidyl group by an aryl radical, with consequent formation of a biaryl.
The aryl radical, formed by the copper initiated electron transfer reaction of 23, can react via two different ways. Addition to an unsubstituted position of the phenyl ring affords 25, while attack at the substituted position, followed by cleavage of the carbon-nitrogen bond gives the ipso product (24)\(^2\) (Scheme 1.31).

Curiously, when one of the substituents on the nitrogen atom is changed from a phenyl to a methyl group, the spiro intermediate is generally trapped as a dimer.\(^3\) However, on further heating, the dimer dissociates and cleavage of the relatively weak carbon-nitrogen bond can then occur to permit subsequent recycclisation of the amidyl radical\(^4\) (Scheme 1.32).
Evidence for the "migration" of the nitrogen atom was found in a study of substituted aromatic rings, where the substituents on the product were not on the positions expected for a simple addition reaction (Scheme 1.33).

\[ \text{Scheme 1.33} \]

Identical results were observed when the same reaction was performed under electrochemical conditions. The reaction proceeds by two consecutive single electron transfers to afford a mixture of products resulting from ipso substitution, addition and direct reduction in a ratio of 33:13:54.36

### 1.2.1.3. The Diazo Group

Photolysis of compound 26 showed that the diazo group is also a good leaving group in ipso substitution reactions, which occur with extrusion of nitrogen (Scheme 1.34).

\[ \text{Scheme 1.34} \]

Reagents: Cyclohexane, hv (100W high-pressure mercury lamp), 48 hr.
When the reaction was carried out on a substrate with a phenyl group at the ortho position of the acceptor ring (27), the extra stabilisation of the intermediate radical favoured *ipso* attack. Subsequent cyclisation gave compound 28 as the major product in 46% yield (Scheme 1.35).

1.2.1.4. The Iminyl Group

N-Arylideneanilines (29) react with monosubstituted acetylenes in the presence of di-isopropylperoxydicarbonate (DPDC) to afford quinolines. The imidoyl radical initially formed reacts with the alkyne to give the intermediate vinyl radical 30 which, by an intramolecular process, forms quinolines in good yields (Scheme 1.36).

Reagents: i) DPDC, PhC≡CH, benzene, 60°C, N₂.
The "unexpected" position of the substituent in the major product 31 is indicative of an ipso cyclisation followed by cleavage of the carbon-nitrogen bond.

Reaction of the spirodienone 32 (Scheme 1.37), which was obtained from the imine 29 (X=Ph₃CO), with tri-n-butyltin hydride suggests that the rearrangement of the spiro radical might be a synchronous process or, if the iminyl radical is involved, ring closure is much faster than hydrogen atom abstraction from tri-n-butyltin hydride.

![Scheme 1.37](image)

**1.2.2. Aromatic Displacement with Cleavage of a Carbon-Sulfur Bond**

In contrast to the intermolecular case, intramolecular ipso substitution reactions with radical displacement of a sulfonyl group have received much attention, particularly in their reaction with alkyl radicals.

Initial work was carried out by Speckamp who noticed, in the course of a synthetic study, that an unexpected 1,4-aryl shift had occurred. This product was formed by ipso substitution attack on the sulfonyl position of the aromatic ring (Scheme 1.38).

![Scheme 1.38](image)
The reaction occurs with a wide variety of substituted aromatic\textsuperscript{40,41} and heteroaromatic\textsuperscript{42} derivatives, to give the addition products 33, the \emph{ipsos} substitution products 34 and the reduction products 35.

\begin{center}
\begin{tabular}{ccc}
R & 33 & 34 & 35 \\
a) R= Me & 45\% & 32\% & 23\% \\
b) OMe & 40 & 37 & 23 \\
c) CO$_2$Et & 27 & 53 & 20 \\
d) CN & 20 & 65 & 15 \\
\end{tabular}
\end{center}

Reagents: Bu$_3$SnH, AIBN, benzene, reflux.

\textbf{Scheme 1.39}

Further studies showed a temperature dependence on the ratio of products\textsuperscript{40} Thus, increasing the temperature leads to an increase in the 1,5-\emph{ipsos} substitution product, and consequently a decrease in 1,6-addition and reduced products (Scheme 1.40).

\begin{center}
\begin{tabular}{ccc}
Temp. & 33a & 34a & 35a \\
22\textdegree C & 68\% & - & 30\% \\
86\textdegree C & 46 & 30 & 23 \\
152\textdegree C & 30 & 56 & 13 \\
190\textdegree C & 26 & 64 & 9 \\
\end{tabular}
\end{center}

Reagents: Bu$_3$SnH, AIBN, anisole.

\textbf{Scheme 1.40}
Much more recently, and contemporaneous with our own studies in the biaryl area (vide infra), a similar rearrangement was observed during a radical cyclisation, where the by-product was formed by ipso substitution (Scheme 1.41).

![Scheme 1.41](image)

Reagents: Ph₃SnH / AIBN (slow addition), benzene, 80°C, 10 hr.

Thus, the initially generated radical 36 adds to the double bond and the resultant secondary alkyl radical is either reduced by the tri-phenyltin hydride to give 37 (61%), or undergoes ipso substitution, with extrusion of sulfur dioxide, to give 38 (18%). (Scheme 1.41).

Photolysis of conjugated enones substituted at the α-position by a group bearing an arylsulfonil substituent can lead to ipso substitution on the aryl ring (Scheme 1.42).

![Scheme 1.42](image)
When X=NR formation of the *ipso* substitution product 41 is in competition with hydrogen abstraction from the R group (R=Et, CH$_2$Ph, allyl) and subsequent addition to the ring (Scheme 1.43).

![Scheme 1.43](Image)

Reagents: EtOH or Et$_2$O, hv.

Compound 41 is the only product when R=CH(CH$_3$)$_2$ presumably since cyclisation to 39 or 40 is precluded for steric reasons.$^{44}$

When X=O the same desulfonation and migration of the aryl group is observed in good yields (45-63%).$^{45}$ Several aryl groups were tested, showing that the *ipso* product is favoured with electron rich aryl groups (3,4-dimethoxy; 90%).$^{46}$ This methodology was then successfully applied to the synthesis of isolaurene 42 (Scheme 1.44), where the key step involving *ipso* substitution occurred in 45%.$^{47}$

![Scheme 1.44](Image)

The displacement of a sulfonyl group by an aryl radical has also been observed$^{48}$ but will be discussed later, in the Results and Discussion chapter (Chapter 2), where it will be more appropriate.
Work in our own group also demonstrated that a vinyl radical can undergo efficient *ipso* attack with displacement of sulfur dioxide\(^{49}\) (Scheme 1.45).

\[
\begin{align*}
\text{O}_2S^- + X^- & \rightarrow \text{O}_2S^- + X^- \rightarrow \text{SO}_2^+ \rightarrow \text{R}^+ \\
R & \rightarrow \text{Y}^+ \\
\text{R}^+ & \rightarrow \text{R}^+ \\
\end{align*}
\]

**Scheme 1.45**

Although with sulfonamides (X=NMe, n=1, 2) the *ipso* attack was not observed, and with sulphones (X=CH\(_2\), n=1) only to a small extent (6%), more interesting results were obtained with the sulfonate group (X=O, n=1, 2) on the linking chain.

Sulfonate esters of propargyl alcohol showed good results when TsSePh was used as a radical source, with formation of the *ipso* product, which then underwent lactonization to give 43, in 55% (Scheme 1.46).

\[
\begin{align*}
\text{MeO}_2C\text{O}_2S^- & \rightarrow \text{TsSePh} \\
43 & \rightarrow \text{55%} \\
\end{align*}
\]

**Scheme 1.46**

An investigation of sulfonate esters of homopropargyl alcohol however, using tri-n-butyltin hydride as the radical source, led to the discovery of an unusual rearrangement reaction (Scheme 1.47).
As implied in the mechanism, the loss of sulfur dioxide is sufficiently slow to permit a further 6-endo addition-elimination sequence with expulsion of the tri-n-butylstannyl radical.\textsuperscript{50} The reaction occurs with a wide variety of aromatic substituents, where particularly good results are obtained with the carbomethoxy derivative (R=CO\textsubscript{2}Me, 61\%), and heterocyclic systems (14-74\%).

1.2.3. Aromatic Displacement with Cleavage of a Carbon-Carbon Bond

A process that involves \textit{ipso} substitution with cleavage of a carbon-carbon bond is the neophyl rearrangement. This is a 1,2 shift of a phenyl group, and is probably one of the best known radical rearrangements\textsuperscript{52} (Scheme 1.48).
When there is an extra carbon atom in the chain, as in compound 44, the acyl radical can undergo both *ipso* substitution (47) and addition (46) prior to decarbonylation, or to loose carbon monoxide to give 45\(^2\) (Scheme 1.49).

![Scheme 1.49]

A neophyl rearrangement was recently observed in the addition of an aryl radical to a double bond\(^5\) (Scheme 1.50).

![Scheme 1.50]
Kinetic studies\textsuperscript{54} of this reaction showed that the formation of compound 48 occurred both by 1,6 endo addition (path b) and also by sequential 1,5 exo addition followed by neophyl rearrangement (path a, c and d). The neophyl rearrangement is faster for radicals containing a naphthalene nucleus than for benzenoid radicals and is also facilitated by appropriately located electron withdrawing substituents.\textsuperscript{55}

The intramolecular \textit{ipso} substitution of an alkyl radical was confirmed by the use of deuterium labelled compounds\textsuperscript{55} (Scheme 1.51).

![Scheme 1.51 Image]

Radicals formed by decarboxylation of the parent acid with Pb(OAc)_4 in benzene, 50-60°C, 30 min and 24 hr reflux.

An attempted preparation of intermediate 49 for the synthesis of (+)Steganone 50, \textit{via} an intramolecular biaryl coupling with tri-n-butyltin hydride gave compound 51\textsuperscript{56} (Scheme 1.52).
The formation of compound 51 was explained via the spirocyclic intermediate formed by ipso attack, which then rearranged to the final product.

Another example of carbon-carbon bond cleavage can be found in a minor extension of the Pschorr cyclisation of 52 (Scheme 1.53).

Reagents: Cu, H₂SO₄/AcOH.
Compound 53 may be derived from 1,6 ipso substitution with displacement and elimination of the methylene group adjacent to the sulfonamide nitrogen.

The formation of the benzaldehydes 54 suggests that a 1,5-hydrogen atom transfer is involved, followed by hydrolysis (Scheme 1.54).

1.2.4. Aromatic Displacement with Cleavage of a Carbon-Oxygen Bond

The oxidation of 2'-substituted biphenyl-2-carboxylic acids with lead tetracetate\(^5\) or persulphate\(^6\) occurs via the intermediate carboxy radical, which can displace substituents on the 2' position. In lead tetracetate oxidation, the best results were obtained in the displacement of a methoxy group, which occurred in 68%. Other groups also underwent the displacement reaction but in lower yields (Scheme 1.55).
The persulphate oxidation was extended to substrates such as \( o \)-methoxycinnamic acid where the reaction proceeded with displacement of the methoxy group to give coumarin derivatives\(^6\) (Scheme 1.56).

![Scheme 1.56](image)

Reagents: potassium persulfate, NaOH, H\(_2\)O, reflux, 3 hr.

The displacement of a group involving the cleavage of a carbon-oxygen bond was reported in the reaction of compound 55 with tri-n-butyltin hydride\(^6\) (Scheme 1.57).

![Scheme 1.57](image)

Reagents: Bu\(_3\)SnH / AIBN, benzene, reflux.
Thus, in addition to the desired product 56 (9%), the lactone 58 (47%) was obtained as the major product.

The initial radical, formed by addition of the tri-n-butylstannyl radical to the thiocarbonyl sulfur atom is trapped in an intramolecular way by the double bond, to generate the benzylic radical. Two competitive processes can then occur: viz. the direct reduction or intramolecular *ipso* addition to the phenolic ring, followed by rearomatisation with loss of the tri-n-butylstannylthiyl radical and formation of lactone 58 (Scheme 1.57).

The isomerization of aryl ethers can also occur via an *ipso* process.\(^2\) \(^3\) Aryloxypropyl bromides in the presence of tri-n-butyltin hydride form the alkyl radical, which can either abstract a hydrogen atom from the stannane to form aryl propyl ethers, or add intramolecularly either to the *ortho* or *ipso* position of the aromatic ring (Scheme 1.58).

![Scheme 1.58](image)

Reagents: Bu3SnH / AIBN.

The preferred process is the *ipso* attack, and either electron withdrawing or electron donating substituents on the aryl ring promote the reaction. Curiously the best results were obtained when both electron withdrawing and electron donating substituents were present on the aromatic ring. The most important factor seems to be the stability of the intermediate spiro radical.
1.2.5. Aromatic Displacement with Cleavage of a Carbon-Halogen Bond

\( o-(2,4,6\text{-Trihalogenophenyl})\text{thiophenyl radicals were chosen to investigate the displacement of a halogen by intramolecular ipso attack of an aryl radical} \) (Scheme 1.59)

Products derived from addition of solvent (59), ipso substitution (60) and direct reduction (61; \( Y=H \)) were formed in different ratios according to the solvent and temperature used. In the above system when \( X=Br \), the use of a high boiling point solvent like \( o\)-dichlorobenzene, gave a mixture in which the ipso product (60) was present in 25% together with 59 (66%).

1.3. CONCLUSIONS

From the foregoing overview, it can be concluded that there are several factors which determine the selectivity towards ipso substitution or addition to an unsubstituted position both in intermolecular and intramolecular radical reactions.

It was observed that the polar character of the attacking radical and leaving group play an important role in selectivity for the intermolecular case.
When polar effects intervene, the attack of a nucleophilic radical species occurs on the most electron deficient position, favouring the displacement of electron withdrawing leaving groups.

If polar effects do not intervene the attack occurs on the position which will give the more stable intermediate.

Most of the work presented involved attack of nucleophilic intermediates on electron deficient aromatic rings. Under these conditions the nitro and sulfonyl groups were shown to be excellent leaving groups.

There is no rule which determines the direction of the reaction in the intramolecular case, since the nature of the linking chain is an extra factor which must be taken into consideration.

The best leaving groups are those whose displacement involves the cleavage of a carbon-nitrogen or carbon-sulfur bond. Curiously, in the carbon-nitrogen case, the intermediate nitrogen centred radical (amidyl or iminyl radicals) tends to cyclise again onto the aromatic ring.

The polar effect of the attacking group has not been thoroughly investigated, since most of the work presented deals with aryl, vinyl and alkyl radicals, which are mainly neutral or slightly nucleophilic.

The preferred length of the linking chain is that which allows the formation of 5 membered spirocyclic intermediates. We are tempted to suggest that introduction of an sp² centre encourages ipso substitution.
References


Chapter Two:

Results and Discussion
2.1. Introduction and Previous Work in These Laboratories

From the preceding chapter it is evident that *ipso* substitution is a powerful tool for the introduction of new groups to aromatic rings. This reaction is particularly attractive in the intramolecular mode, when it occurs between an aryl radical and an aryl acceptor ring which possesses a good radical leaving group, since a biaryl is formed (Scheme 2.1).

The importance of the biaryl framework, present in a vast number of natural products, led us to further explore the use of radical chemistry for the construction of this unit. Thus, a project involving radical *ipso* substitution reactions for the formation of biaryls, using the sulfonyl group as the leaving group, has been developed in these laboratories.

Although the use of alkyl radicals in *ipso* substitution reactions involving the displacement of an SO$_2$ moiety has received much attention (Chapter 1, Section 1.2.2), the same reaction with aryl radicals has not been the subject of such interest. Nevertheless, *ipso* substitution has been reported to occur$^1$, although only to a small extent, in the reaction shown in Scheme 2.2.
Compound 62 has two aromatic rings which can be attacked by the intermediate aryl radical. Thus, a mixture of products derived from addition and *ipso* substitution on both aromatic rings was obtained. Interestingly, *ipso* attack occurred with an almost equal facility for cleavage of either the carbon-carbon or the carbon-sulfur bonds and both biaryls isolated were formed in equivalent amounts.

Work previously carried out on this project\(^2\) had shown that the formation of a new carbon-carbon bond between two aromatic residues by such a radical *ipso* substitution reaction, involving displacement of a sulfonyl group, was a feasible process (Scheme 2.3). In the course of the preliminary study however, it was observed that both the nature of the tethering chain and the substituents around the aromatic acceptor ring exerted an influence on the nature and ratio of products formed. These influences were not clearly understood.

Thus for example, in the case of simple *para* toluenesulfonyl derivatives, the sulfonamide was clearly superior to the phenolic tosylate in terms of directing an *ipso* substitution pathway. Such an apparently inherent preference could however be moderated by "judicious" introduction of substituents around the sulfonyl acceptor ring. Nevertheless, in terms of developing a predictive rationale, the overall picture at this stage was extremely confusing, and highlighted the necessity for a systematic study of both:

a) the steric and electronic effect of substitution around the sulfonyl substituted acceptor ring and

b) the nature and number of atoms in the linking chain.
Results & Discussion

**Scheme 2.3**

Reagents: Bu$_3$SnH / AIBN (slow addition), benzene, reflux.
a) Isolated as the corresponding lactam. b) Isolated as the corresponding lactone.

It should be appreciated however that, throughout the course of the work described in this thesis both of these areas were under active study at the same time, and that additional work by my colleague Feroze Ujjainwalla on the arylation of heterocyclic systems was also contributing to the overall picture. Hence, the following section is not necessarily chronological.
2.2. Steric and Electronic Effects on the Sulfonyl Substituted Acceptor Ring

2.2.1. The Effect of an ortho Substituent

In the first instance, most of the work previously carried out on the influence of additional substituents on the acceptor aromatic ring had concentrated on their polarity. In this section the influence of a specifically located ortho substituent on the sulfonyl substituted aromatic ring on controlling the ratio of direct addition versus ipso substitution, and hence the nature of the products, was examined.

Thus, compound 65 was selected, and was prepared as outlined in Scheme 2.4. The required sulfonyl chloride (63) was prepared by standard procedures from o-toluidine. Coupling with o-iodo aniline followed by methylation gave the sulfonamide 65. It should be noted that additional protection of the nitrogen atom by further alkylation has been shown to be essential for success in these reactions, presumably because of the acidity of the parent sulfonamide.

![Scheme 2.4](image)

Reagents: i) HCl/AcOH, NaNO₂, -10°C, 30 min; ii) SO₂, CuCl, 10°C, 2 hr (62% over 2 steps); iii) Py, DMAP, r.t. (37%); iv) NaH, THF, MeI, r.t, (67%).

The standard conditions adopted for the radical reactions consist of a slow addition of a solution of tri-n-butyltin hydride (1.3 eq.) and AIBN (0.7 eq.) in benzene to a refluxing solution of the sulfonamide in benzene. These conditions had earlier been
optimised, \(^3\) in order to minimise the concentration of tri-n-butyltin hydride, and thus avoid the formation of the simple reduction product. The large amount of AIBN used shows that the chain processes involved are extremely inefficient. When sulfonamide \(65\) was submitted to these conditions, a single product derived from a 1,5-\textit{ipso} substitution process (66) was obtained (Scheme 2.5).

\[
\text{Reagents: } \text{Bu}_3\text{SnH} / \text{AIBN (slow addition)}, \text{benzene, reflux.}
\]

\[\text{Scheme 2.5}\]

This is an intriguing result, since the equivalent para derivative had given\(^2\) a mixture of both 1,5-\textit{ipso} substitution (67) and 1,6-addition products (68) (Scheme 2.6).

\[
\text{Reagents: } \text{Bu}_3\text{SnH} / \text{AIBN (slow addition)}, \text{benzene, reflux.}
\]

\[\text{Scheme 2.6}\]

In terms of the electronic factor, both spiro intermediates \(69\) and \(70\) are "identically" stabilised by the alkyl substituent. Thus, the difference of selectivity observed for these two substrates suggests that the influence of the methyl group in the ortho position is to retard the 1,6-addition process, and thereby, by default, to favour \textit{ipso} substitution.
Some support for the "buttressing effect" of the ortho methyl group in directing 1,5-

The introduction of an additional methyl group in the classical 5-hexenyl radical ring closure has been shown to lead to a dramatic drop in the rate of the cyclisation reaction (Scheme 2.7).

\[
\begin{align*}
\text{\textbullet \text{CH}_2=CH_2} & \xrightarrow{K_1} \text{\textbullet \text{C}_5H_9} & K_1 = 2.3 \times 10^5 \text{s}^{-1} \\
\text{\textbullet \text{CH}_2=CH_2} & \xrightarrow{K_2} \text{\textbullet \text{C}_5H_9} & K_2 = 5.3 \times 10^3 \text{s}^{-1}
\end{align*}
\]

Scheme 2.7

Although this can explain why the addition does not occur at the substituted position of the aromatic acceptor ring, it is still not clear why it does not occur on the other possible site of reaction.

It had been noted in the initial study that a sulfonate ester in the linking chain favoured the 1,6-addition process over 1,5-ipso substitution. It was therefore of particular interest to examine the possibility that the presence of a simple ortho substituent would override this tendency and favour 1,5-ipso substitution. The combination of both of these effects was analysed using sulfonate 71 which was prepared by reaction of sulfonyl chloride 63 and o-iodophenol in pyridine. Reaction of 71 under the standard radical conditions afforded a mixture of products derived from both 1,5-ipso substitution (73, 23%) and 1,6-addition (72, 36%) pathways (Scheme 2.8).
Results & Discussion

Since the corresponding para derivative 74 gave the cyclic sultone 75 derived by 1,6-addition as the only product (Scheme 2.9), the effect of the substituent on the ortho position in the reaction of 71 is clearly revealed as an important contributor to the formation of 1,5-ipso substitution product 73 (Scheme 2.8).

While this work was in progress the preference for ortho substituted aryl ethers to undergo ipso substitution was also reported5 (Scheme 2.10).
R = o-CO₂Me / p-CO₂Me / o-MeO / p-MeO

53  24
25  65
53  21
24  61

Reagents: Bu₃SnH / AIBN (slow addition), benzene, reflux.

a) Isolated as the corresponding lactone.

Scheme 2.10

The same tendency was noted during parallel work in the heterocyclic series in our own group, where it was suggested that the excellent level of selectivity was not entirely electronic, but that retardation of the 1,6-addition process, as a consequence of the buttressing effect of the methyl group, was important (Scheme 2.11).

Reagents: Bu₃SnH/AIBN (slow addition), benzene, reflux.

Scheme 2.11

Thus, the dominant effect of an ortho substituent is probably due to steric hindrance, both in terms of disfavouring addition of the aryl radical to the ortho substituted carbon and also since unfavourable interactions can develop between the ortho substituent and the sulfonyl group in the alternative 1,6-addition intermediate (Figure 2.1). The ipso substitution process is accordingly favoured.
2.2.2. The Effect of a meta Substituent

Intramolecular reactions leading to the formation of aryl-aryl bonds are generally believed to be governed less by polar effects of the substituents than by ring strain. However, even in the early stages of this project polar effects have been found to have a marked influence on the outcome of the reactions, as for example in the comparison between the para toluene and the methoxyphenyl sulfonate esters of o-iodophenol (Scheme 2.3).

The presence of a carbomethoxy group on the ortho position of the aryl acceptor ring favours the formation of the ipso substitution product, probably both by an electronic stabilisation effect and by its location in the ortho position (c.f. Section 2.2.1).

It was therefore of interest to examine the influence of a meta carbomethoxy group, using compounds 79 and 84. (Scheme 2.13 and 2.14). Since the synthesis of these compounds required sulfonyl chloride 78, which was not commercially available, it was prepared by standard procedures from methyl benzoate, as shown in Scheme 2.12.

Reagents: i) H₂SO₄, HNO₃, 0-10°C, 1 hr (94%); ii) H₂, Pd/C, EtOH; iii) a) HCl/AcOH, NaNO₂, -10 °C, b) SO₂/AcOH, CuCl, 10 °C, 1 hr (67% overall).
Sulfonate 79 was then prepared by the standard reaction of the sulfonyl chloride 78 with o-iodophenol in pyridine. Reaction of the product under the usual standard radical conditions afforded only the 1,6-addition products in good yield. The addition occurred on the two possible positions, to give compounds 80 and 81 (Scheme 2.13).

![Scheme 2.13]

Reagents: Bu₃SnH/AIBN (slow addition), benzene, reflux.

The structure of 81 was only determined after a single crystal X-ray diffraction analysis had been carried out (Appendix 2).

Although this reaction, as expected, did not lead to ipso substitution, it is worthy of comment. The isolation of the "oxidised" fully aromatic 80 is a common phenomenon in the direct addition process even although the dihydroaromatic derivatives should be the anticipated products under reducing conditions. This aspect has been fully discussed by Bowman⁸ for other radical reactions. It is proposed that the oxidation of the radical formed upon 1,6-addition, occurs via a pseudo S₉N₁ mechanism (Scheme 2.14).

![Scheme 2.14]
In compound 81, it is clear that the oxidative process is more difficult. The observed regiochemistry of the carbomethoxy unit and the *cis* fused stereochemistry of the ring junction imply that although hydrogen atom capture from the stannane has occurred from the least hindered face, it is nevertheless apparently delivered adjacent to the bulky sulfonyl group. Although the favoured extended conjugation of the carbomethoxy unit is thus formed, it is nevertheless surprising.

The corresponding sulfonamide 84 was prepared in a similar fashion from the sulfonyl chloride 78 and *o*-iodoaniline followed by N-methylation with sodium hydride followed by methyl iodide. By way of contrast, reaction of this substrate under the standard tin hydride conditions, was less selective and both the formation of 1,5-*ipso* substitution product 85 and the 1,6-addition product 86, was observed (Scheme 2.15).

A dihydro compound was also isolated in minor amount, but complete structural elucidation was not possible, although the similarity of its $^1$H nmr spectrum with that of compound 81 is indicative of compound 87a. The $^1$H nmr spectra of compounds 81 and 87 are presented in Appendix 1.
These results may now be compared with those from the corresponding *ortho* derivative (Scheme 2.16).

From the results presented on Scheme 2.16, it can be seen that the presence of an oxygen atom in the linking chain favours the 1,6-addition mode. This effect is particularly noticeable when combined with the stabilisation of a *meta* carbomethoxy group, where formation of the *ipso* product is completely suppressed. It is nevertheless remarkable in the sulfonamide 84 that once again the nitrogen atom has allowed *ipso* attack to occur, even in the presence of an electronically "unfavoured" carbomethoxy substituent on the sulfonyl acceptor ring.

### 2.2.3. The Effect of Multiple Substituents

Until now, all of the work presented concerning *ipso* substitution has been carried out using compounds with a single substituent. The only reported example$^2$ with more than one substituent on the aromatic acceptor ring is the mesitylene derivative 89 (Scheme 2.17). In this case, both *ortho* positions are substituted, and thus only *ipso* substitution is observed. Curiously, under incomplete reaction conditions the product retained, to some degree, an iodine atom (91) (Scheme 2.17).
In our hands it was of course possible to eliminate the iodo derivative 91 by using a greater amount of tri-n-butylstannane, and hence to obtain the non halogenated ipso product 90 in 64% yield. Nevertheless, from the mechanistic viewpoint the formation of iodide 91 is interesting, as it formally appears to involve an iodine atom transfer reaction.\(^9\)

Thus, in principal, formation of the aryl radical, ipso substitution and loss of sulfur dioxide could occur in the standard fashion to give 93 (Scheme 2.18).

From the thermodynamic standpoint, it seems most unlikely that 93 is capable of iodine atom abstraction from the starting sulfonamide 89 to give the chain carrying aryl radical 92, in respect of whether iodination is finally achieved directly or via the
Orton rearrangement of an intermediate N-iodo derivative 94. This reaction is certainly worth of further investigation in its own right.

The corresponding sulfonate 95 was also prepared from o-iodophenol and 2,4,6-trimethylbenzenesulfonyl chloride in pyridine. Reaction using the usual radical conditions afforded the *ips* product 96 in 50% yield (Scheme 2.19), thereby contrasting with the simple *p*-toluenesulfonate 74 (Scheme 2.9) and reinforcing the idea of the importance of sterically buttressing substituents.

Reagents: Bu₃SnH / AIBN (slow addition), benzene, reflux.

**Scheme 2.19**

In order to examine the effect of two substituents on the acceptor ring, compounds 98 and 100 were prepared by the usual method, of coupling the correspondent sulfonyl chloride with o-iodoaniline in pyridine.

In both of these compounds, the presence of the *meta* methoxy group might be envisaged to encourage the direct 1,6-addition process, while, in electronic terms the *ortho* (98) and *para* (100) methoxy group should exert a favourable influence in *ips* substitution.
When compound 98 was submitted to the radical reaction conditions, only one product (101), resulting from *ipso* substitution, was detected (Scheme 2.20).

![Scheme 2.20](image)

Reagents: Bu₃SnH / AIBN (slow addition), benzene, reflux.

However, when compound 100 was submitted to the same conditions, it afforded a mixture of two compounds (4:1), inseparable by chromatography on silica gel, which could be resolved by HPLC to give the *ipso* substitution (103) and addition products (104) (Scheme 2.21).

![Scheme 2.21](image)

Reagents: Bu₃SnH / AIBN (slow addition), benzene, reflux.

The formation of a minor compound, 102, retaining an iodine atom, was also noticed (as reported before in Scheme 2.17).
Comparison of these two substrates (Scheme 2.20 and 2.21) clearly reveals that the location of an ortho methoxy group is, yet again, the dominant factor in directing the reaction pathway towards ipso substitution.

Following our studies, sulfonates 105 and 108 were also prepared. Thus, reaction of compound 105 under standard tin hydride conditions afforded the product from 1,5-ipso substitution, 106, and a minor product from direct 1,6-addition, 107. (Scheme 2.22).

![Chemical structure](image.png)

Reagents: Bu₃SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.22

Formation of the 1,6-addition product 107 to such a small extent can possibly be explained by a retardation of the addition process due to the presence of the methoxy group on position 2, since an ortho substituent favours ipso substitution.

In similar fashion to the case of the sulfonamide, compound 108 gives a mixture of both addition and ipso substitution products. Curiously, in contrast to the sulfonamide case (Scheme 2.21), addition products resulting from attack at both possible sites could be isolated (Scheme 2.23).
Thus, it can be observed that on sulfonate (108), addition to the less hindered position 6 (110, 24%) is favoured over position 2 (109, 10%). It is not at all clear however, why the corresponding sulfonamide 100 (Scheme 2.21) gave only the product of addition at the apparently more congested position 2.

In summary, at this stage, the most dominant substituent effect in terms of favouring a 1,5-ipso attack over a 1,6-addition process is the presence of at least one functional group located at the ortho position of the sulfonyl acceptor. Such a group may be either electron releasing or electron withdrawing. Electron donating substituents on the para position also favours 1,5-ipso substitution, this effect being stronger for better donating groups (p.e. R= OMe).

Finally, the presence of stabilising groups on the meta position favours 1,6-addition, in order to give the more stable radical intermediate.
2.3. The Nature of the Linking Chain in 1,5-\textit{Ips}o Substitution vs 1,6-Addition

Throughout this work on 1,5-\textit{ips}o substitution, we have noticed the importance of the nature of the linking chain X on the distribution of products resulting from 1,5-\textit{ips}o substitution and 1,6-addition (Figure 2.2).

![Figure 2.2](image)

Figure 2.2

While our studies on the effect of substituents R on the sulfonyl substituted acceptor ring provided valuable information in their own right, they also served, at the same time, to reinforce the inescapable conclusion that, for the simple series 1,5-\textit{ips}o substitution vs 1,6-addition reactions, an empirical rule could be clearly established viz., nitrogen is more efficient than oxygen in the linking chain in the promotion of 1,5-\textit{ips}o substitution.

With electron withdrawing groups at the \textit{meta} or \textit{para} positions of the acceptor aromatic ring, this rule was clearly observed as, with the oxygen linking chain, the \textit{ips}o substitution product was completely nonexistent (Table 2.1). Although for the \textit{meta} substituted compound, the addition product would be stabilised to a greater extent by the substituent, the nitrogen chain still shows some product from 1,5-\textit{ips}o substitution.

<table>
<thead>
<tr>
<th>$X=$</th>
<th>1,5-\textit{ips}o</th>
<th>1,6-add.</th>
<th>Start. Mat.</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMe</td>
<td>31%</td>
<td>44%</td>
<td>26%</td>
<td>3</td>
</tr>
<tr>
<td>O</td>
<td>---</td>
<td>50</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>NMe</td>
<td>28%</td>
<td>48%*</td>
<td>71*</td>
<td>Sec. 2.2.2.</td>
</tr>
<tr>
<td>O</td>
<td>--</td>
<td>71*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* combination of addition and dihydro products.
Even when an ortho group was introduced in the acceptor aromatic ring, and its effect analysed (Section 2.2.1), the same tendency was always observed (Table 2.2). Thus, although the ortho substituent itself tended to favour 1,5-ipso substitution, the oxygen atom in the linking chain, lead to a relative increase in the proportion of the 1,6-addition product, when compared with the nitrogen congener.

Table 2.2

<table>
<thead>
<tr>
<th></th>
<th>X=</th>
<th>1,5-ipso</th>
<th>1,6-add.</th>
<th>Start Mat.</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 1" /></td>
<td>NMe</td>
<td>57%</td>
<td>--</td>
<td>9%</td>
<td>Sec. 2.2.1.</td>
</tr>
<tr>
<td><img src="image" alt="Structure 2" /></td>
<td>O</td>
<td>23</td>
<td>36</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Structure 3" /></td>
<td>NMe</td>
<td>63%</td>
<td>--</td>
<td>23%</td>
<td>Sec. 2.2.3.</td>
</tr>
<tr>
<td><img src="image" alt="Structure 4" /></td>
<td>O</td>
<td>43</td>
<td>7%</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Structure 5" /></td>
<td>NMe</td>
<td>65%*</td>
<td>19%</td>
<td>11%</td>
<td>3</td>
</tr>
<tr>
<td><img src="image" alt="Structure 6" /></td>
<td>O</td>
<td>42@</td>
<td>21</td>
<td>37</td>
<td>3</td>
</tr>
</tbody>
</table>

* Isolated as the corresponding lactam.
@ Isolated as the corresponding lactone.

The presence of multiple substituents on the acceptor aromatic ring does, of course, present an extreme case, particularly when both addition sites are blocked, and thus, in this case, the addition product is not observed (Table 2.3). However, if these positions are not occupied, the same general trend is observed, with the addition products being formed in much higher yield when the oxygen link is used.
Thus, all our results confirm that a nitrogen atom in the linking chain is a better promoter for 1,5-\textit{ipso} substitution than an oxygen. For comparison with the sulfone case (X=CH_2) the preparation of compound 113 was deemed necessary (Scheme 2.21). This was accomplished by nucleophilic displacement of o-iodobenzyl chloride with thiophenoxide anion, which occurred in excellent yield, followed by oxidation with \textit{m}-CPBA which, although proceeding in poor yield, gave enough material to proceed with a reaction.

Reaction of 113 under standard radical conditions afforded the 1,6-addition adduct 116 as the major product, together with the 1,5-\textit{ipso} substitution product 114 and compound 115, as a result of direct reduction of the starting material. (Scheme 2.24).
Reagents: i) NaH, THF (91%); ii) m-CPBA, DCM, 0 °C, r.t. (17%); iii) Bu3SnH / AIBN (slow addition), benzene, reflux.

This is the first example in our 1,5-<i>ipso</i> substitution study where we observe the formation of the simple reduced product. Nevertheless, it is clear that the methylene chain favours the 1,6-addition step.

For simple <i>para</i> substituted compounds with electron donating groups the empirical rule for nitrogen and oxygen is also observed (Table 2.4), and it is possible to envisage an extension to the methylene substituted linking chain. Although on the <i>p</i>-toluenesulfonyl derivative both oxygen and methylene chains give exclusively 1,6-addition, when the <i>para</i> substituent is a methoxy group, the methylene group is even more efficient in promoting the 1,6-addition pathway.
Table 2.4

<table>
<thead>
<tr>
<th>X=</th>
<th>1,5-\textit{ipso}</th>
<th>1,6-add.</th>
<th>Start. Mat.</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMe</td>
<td>46%</td>
<td>25</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>O</td>
<td>--</td>
<td>63</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>CH₂</td>
<td>--</td>
<td>40</td>
<td>40</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>X=</th>
<th>1,5-\textit{ipso}</th>
<th>1,6-add.</th>
<th>Start. Mat.</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMe</td>
<td>29</td>
<td>10</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>O</td>
<td>18</td>
<td>24</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>CH₂</td>
<td>10</td>
<td>45</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

In summary, it has been demonstrated that another important factor in the direction of attack in a 1,5-\textit{ipso} substitution vs 1,6-addition reaction is the nature of the linking chain. An empirical rule is postulated where the efficiency on the promotion of the \textit{ipso} attack decreases from a nitrogen to oxygen, and then to a methylene group of the linking chain.
2.4. Strain and Ring Effects

All of the examples which we have discussed this far in the sulfonamide series have had the nitrogen atom on the linking chain substituted by a methyl group. To extend the range of this reaction we therefore decided to incorporate the nitrogen atom into a ring. Hence, compound 120 was prepared by a known sequence of protection, halogenation and deprotection\textsuperscript{10} followed by coupling with the sulfonyl chloride (Scheme 2.25).

\begin{align*}
\text{i)} & \quad (\text{MeOOC})_2\text{O}, \text{THF, r.t.} \\
\text{ii)} & \quad \text{a) TMEDA, 5BuLi, THF, \text{-78 }^\circ\text{C, } 1 \text{ hr, b) I}_2, \text{ ether, } 45 \text{ min;}} \\
\text{iii)} & \quad \text{DCM, TFA, } 5 \text{ hr; iv) Py, DMAP, methyl 2-(chlorosulfonyl) benzoate, r.t., } 20 \text{ hr.}
\end{align*}

Reagents: i) (\text{BuOCO})_2\text{O, THF, r.t.; ii) a) TMEDA, 5BuLi, THF, -78 \text{ }^\circ\text{C, } 1 \text{ hr, b) I}_2, \text{ ether, } 45 \text{ min;}} \\
\text{iii) DCM, TFA, } 5 \text{ hr; iv) Py, DMAP, methyl 2-(chlorosulfonyl) benzoate, r.t., } 20 \text{ hr.}

\textbf{Scheme 2.25}

For this experiment, the selection of o-carbomethoxy sulfonyl chloride was made, since it had been shown to be a particularly good \textit{ipsos} director (Scheme 2.16), and also to undergo subsequent lactamization. Most of all however, we were inextricably lured by the appeal of total synthesis, since such a process would lead to the skeletal framework of the pyrrolophenthridone alkaloids.\textsuperscript{11} These compounds have significant biological activity and some examples of this family of alkaloids are Hippadine (121), which was shown to reversibly inhibit fertility in male rats, Kalbretorine (122) which exhibits antitumor activity and Ungeremine (123) which has been known to be active against some type of carcinoma.
The synthetic strategy used by Meyers\textsuperscript{11} for the construction of these alkaloids and which inspired us to undertake the study is shown in Scheme 2.26. It involves the coupling of oxazoline 124 with the aryl Grignard, to give the corresponding biaryl 125. Hydrolysis of the oxazoline 125 to the aminoester 126 followed by trans-esterification to the methyl ester 127 and hydrogenation, affords Oxassoanine 128, \textit{via} spontaneous lactamization of the free amine.

\textbf{Scheme 2.26}

Comparison of this synthesis with the hypothetical \textit{ipso} substitution and trans-lactamization process outlined in Scheme 2.27 reveals that such a sequence would provide a remarkably short and efficient entry to this alkaloid skeletal type.
In the event however, the *ipso* substitution product 129, although present in the reaction mixture, was formed in only 13%, and the major product of this reaction was as a result of the 1,6-addition process (130, 39%) (Scheme 2.28).

Moreover, the lactamization step, which had presumably occurred during the basic fluoride anion work up, was not observed, presumably since it would lead to an even more strained compound.

Although the desired compound 129 was formed in minor amount, this was nevertheless an interesting example, since it reveals that the additional conformational restrictions and the strain created by incorporation of the nitrogen atom in a ring, can effectively block the progress of the reaction, even when the starting material 120 contains not only the favoured sulfonamide linkage, but also an *ortho* substituent, to facilitate *ipso* substitution.
At the same time, another system for *ipso* substitution reactions, derived from saccharine, was analysed (Scheme 2.29).

![Scheme 2.29](image)

We envisaged, that in this system suitable adjustment of the chain length should lead to intramolecular displacement of the sulfonyl group by *ipso* substitution, and hence to the creation of macrocyclic molecules.

In order to find the size of chain necessary to "curl" over the molecule and reach the sulfonyl substituted position of the aromatic ring, a series of compounds of increasing chain length, as represented in scheme 2.30, was prepared. Although all experiments were performed under the standard radical conditions, at extremely low concentrations of tri-n-butylstannane, only reduced product was formed in every case. Although by analysis of the crude $^1$H nmr spectrum a small signal at 2.6 ppm could be seen, which was indicative of the presence of benzylic protons, no product arising from *ipso* was ever present in sufficient quantity to be isolated.

![Scheme 2.30](image)

$n= 2, 3, 4, 5, 9$

Reagents: Bu$_3$SnH / AIBN (slow addition), benzene, reflux.
It should be noted that the saccharine molecule is essentially planar\(^{12}\) and that the narrow C-S-N angle (92.2°) in the five membered ring could be responsible for strain and angular distortions. In order to relieve this strain, the carbonyl group on the ring was therefore reduced, and the benzisothiazole derivative 145 was prepared. The 10 membered chain was then selected, since it should lead to a 14 membered macrocycle (Scheme 2.31).

\[
\begin{array}{c}
\text{Reagents: i) } \text{PCI, 175-180°C, 90 min; ii) } \text{NaBH}_4, \text{THF, 0°C; iii) } \text{NaH, DMF, Br(CH}_2)_1\text{OBr, r.t.; iv) } \text{Bu}_3\text{SnH / AIBN (slow addition), benzene, reflux.}
\end{array}
\]

However, reaction of compound 145 again afforded only the reduced product 146. From the analysis of these results it is clear that the probability of the radical to adopt the required conformation is very small, and that hydrogen abstraction is the preferential pathway.

Another interesting case to be compared is that of Speckamp,\(^{13}\) who had shown that the reaction of a primary radical with a sulfonyl substituted aromatic ring afforded 1,6-addition (147), 1,5-\textit{ipso} substitution (148) and direct reduction products (149) (Scheme 2.32).
However, in contrary to these results, when we examined the less rigid system 151, the *ipso* substitution product was not formed, and only 1,6-addition (153) and direct reduction (152) products were observed (Scheme 2.33).

Once again in this section, despite the fact that the selection of sulfonamide derivatives with a supposed predisposition for 1,5- *ipso* substitution was made, the overall subtlety of conformational, strain and entropic effects engendered in the linking chain, combined to frustrate us. Nevertheless they did reveal that the optimal geometry for *ipso* substitution is indeed a delicate balance.
2.5. The Nature of the Linking Chain in 1,6-\textit{ips}o Substitution vs 1,7-Addition

By increasing the size of the connecting chain between the aryl radical and the acceptor ring, so that the reaction can occur either by a 1,6-\textit{ips}o substitution or by a 1,7-addition process, the \textit{ips}o substitution would be generally predicted to be the favoured process, since a 6-membered ring transition state is favoured over the 7-membered ring. However, as we have seen in the case of 1,5-\textit{ips}o substitution vs 1,6-addition, the nature of the linking chain can have an important role in directing the reaction pathway. Therefore, it seemed necessary a similar study with different combinations of X and Y groups (Scheme 2.34), as well as continuing and reinforcing our studies on the effect of substituents on the acceptor ring.

Preliminary work in this area\textsuperscript{3} showed that the insertion of an additional carbonyl group into the sulfonamide chain, as in compounds 154 and 155, led under standard radical conditions, to complex reaction mixtures.
Nevertheless, contemporaneous work on the heterobiaryl series\(^6\) showed that the same linking chain could lead to \textit{ipso} substitution products albeit in relatively low yields. Interestingly, in the case of the pyridine derivative \textbf{156} a tandem 1,6-\textit{ipso} substitution / cyclisation occurred, with formation of \textbf{157} (Scheme 2.35).

\begin{equation}
\begin{array}{c}
\text{MeS} \quad \text{arrow} \quad \text{MeHN} \\
\text{O} \quad \text{O} \\
\text{Me} \quad \text{NHMe} \\
\text{O} \quad \text{O} \\
\text{N} \quad \text{NHMe} \\
\end{array}
\end{equation}

Reagents: Bu\textsubscript{3}SnH / AIBN (slow addition), benzene, 80°C, 18 hr.

\textbf{Scheme 2.35}

In order to encourage \textit{ipso} substitution in the biaryl series compound \textbf{159} was selected. In this substrate, the high electron density on the acceptor ring, and even more particularly, the presence of the \textit{ortho} substituent, was predicted to favour the formation of the desired product. Preparation of this compound was achieved by an established method,\(^3\) affording \textbf{159} in good yield. Although it is not clear whether sulfonylation occurs on the oxygen atom...
or the nitrogen atom, and by spectroscopic mean it is not easy to clarify this doubt, we accepted that the conditions used would favour reaction through the nitrogen atom, and structure 159 was tentatively adopted (Scheme 2.36).

![Scheme 2.36](image)

Reagents: i) MeNH₂, NaOH (aq) (82%); ii) NaH, THF, r.t., 25 hr (96%); iii) Bu₃SnH / AIBN (slow addition), benzene, reflux.

However, treatment of compound 159 under the usual tin hydride conditions did not give any product from ipso substitution or addition, and the only identifiable compounds in the reaction mixture were benzamide 160 and starting material (Scheme 2.36). The formation of the benzamide 160 had also been noted in the heterobiaryl series. An intermolecular ipso attack of the tri-n-butylstannyl radical at the sulfonyl substituted carbon atom has previously been reported to occur. However, it seems strange that this intramolecular displacement is observed on this particular substrate, since compound 159 has one of the most electron rich aromatic rings used, and the stannyl radical has a nucleophilic character.

Compound 161, prepared in a similar way, but differing in the methoxy substitution pattern, was also studied, and when exposed to standard radical conditions, afforded compounds 162 and 163 (Scheme 2.37).
The mechanism for the formation of 163 involves a 1,6-\textit{ipso} attack with extrusion of sulfur dioxide affording the amidyl radical, which then adds \textit{via} a 1,6-addition process to the aromatic ring (Scheme 2.38). This second cyclisation is probably favoured, since amidyl radicals are electrophilic species, and the aromatic ring has an electron donating group on the position \textit{para} to the site of attack.
The formation of an amidyl radical via ipso substitution had already been seen, either in our own work in the heteroaromatic series\(^6\) (Scheme 2.35) and also in the intramolecular attack of an aryl radical on to an aromatic residue with cleavage of a carbon-nitrogen bond\(^1\) (cf. Section 1.2.1.2). Amidyl radical additions to aromatic rings has been the subject of a study,\(^1\) but the formation of mixtures of phenanthridones and spiro compounds has always been observed (Scheme 2.39).

Reagents: \(\text{\textsuperscript{1}}\text{BuOCl, I}_2, \text{tBuOH, tBuOK, hv (1000W tungsten lamp)}, \text{r.t., 5 hr.}\)^\(1\)
The second product formed in the reaction, 162, has an unusual feature, inasmuch as the sulfonyl group is separated from the nitrogen atom by a methylene group. A possible mechanism for the formation of this compound is represented in Scheme 2.40.

The proposed mechanism involves a 1,5-hydrogen atom abstraction from the methyl group on the nitrogen atom, with formation of the primary radical, followed by elimination of the sulfonyl group which is a good radical leaving group. Recombination of the two species in a cage can then occur to give 164.

A recombination of two radical species is observed in the photo-Fries rearrangement of sulfonamides and sulfonates. The accepted mechanism for this rearrangement is represented on Scheme 2.41, where irradiation of compound 165 affords a radical pair which, by recombination within a solvent cage, gives the migration products 166 and 167.
From the results presented above, and those in the heterobiaryl series\(^6\) (Scheme 2.31), we were convinced that this type of linking chain favoured ipso substitution. This had also been observed in our first reaction of the \(p\)-toluenesulfonyl derivative 168 which had been reported\(^3\) to give the 1,6-ipso substitution product (37\%) and the 1,7-addition product (8\%). However, when we reinvestigated this reaction, the latter compound was obtained as the sole product. This discrepancy led us to re-examine and carefully analyse the spectroscopic data and it is now clear that the original assignment as a 1,7-addition product was incorrect. The product which is in fact isolated in this reaction is compound 169 (Scheme 2.42) formed by the tandem 1,6-ipso substitution / 1,6-addition process, as described before (Scheme 2.38).
In continuation of our study of the nature of the linking chain, we then decided to add a methylene to the sulfonamide chain. Thus, compounds 170 and 172 were prepared from the corresponding sulfonyl chloride, via the methyl sulfonamide, followed by deprotonation with sodium hydride in THF and addition of o-bromobenzyl bromide (Scheme 2.43 and 2.44).

![Scheme 2.43](image)

Reagents: i) MeNH₂, NaOH, 23 hr, r.t. (83%); ii) NaH, THF, 20 hr, r.t. (93%).

However, both compound 170 and 172, under standard radical conditions, afforded extremely complex mixtures. This suggests that the substrate underwent decomposition, perhaps by a process again involving a 1,5 hydrogen atom abstraction from the methyl group on the nitrogen atom, and subsequent elimination of the sulfonyl group (Scheme 2.45).

![Scheme 2.44](image)

Reagents: i) MeNH₂, NaOH, 23 hr, r.t. (82%); ii) NaH, THF, 20 hr, r.t. (91%).
Substitution of the methyl group on the nitrogen by an alternative functionality could provide a solution to this problem, since the Pschorr cyclisation of compound 173, bearing a phenyl group on the nitrogen atom, has been reported to give the product from direct 1,7-addition \(174^2\) (Scheme 2.46).

This result is in a way unexpected, since in the heterobiaryl series this type of chain reaction had given addition products in good yields (Scheme 2.47).
More interesting results were obtained when the benzylic sulfonate was used instead of the sulfonamide. Thus, compound 175 was prepared as shown (Scheme 2.48).

When sulfonate 175 was submitted to the standard tin hydride conditions, the only isolable product was that derived from 1,7 addition, 176. Although this reaction proceeded with a very poor mass balance, it was performed with other substituents on the acceptor aromatic ring. Thus, compound 177 was prepared (Scheme 2.49).
Reaction under standard tin hydride conditions afforded, as in the previous case, the addition product 178, and once again a dihydro product was isolated. Although its structure could not be fully determined, the presence in the $^{13}$C nmr spectra of a secondary carbon at $\delta = 72.3$ ppm allowed us to propose the two possible structures shown in Scheme 2.50.

The differentiation of these two compounds by simple $^1$H nmr is not a trivial exercise. Nevertheless we consider that compound 179 is the more probable structure, since one of the protons of the methylene group in the ring ($\delta = 3.23$ ppm) is coupled with the proton at $\delta = 4.15$ ppm, which can be attributed to the benzylic proton.

The results presented above suggest that aryl sulfonation of benzylic alcohols leads to a chain which favours 1,7-addition over 1,6-ipsos substitution, and this is in agreement with prior studies in this group on the heterobiaryl series.$^6$ However, when other factors intervene in the reaction, such as the presence of ortho substituents, this selectivity can be completely changed, as was shown by the following reactions.
The preparation of compound 180 caused some problems, probably as a result of the capacity of the sulfonate to act as a leaving group under the reaction conditions. Although we had to repeat the reaction, it was possible to get enough material to proceed with the radical reaction. Gratifyingly, submitting sulfonate 180 to the standard radical conditions afforded two products, both formed via 1,6-ipso substitution, in excellent overall yield, with the major product (181) being formed by subsequent lactonization (Scheme 2.51).

Reagents: i) NaH, THF, 24 hr, r.t. (21%); ii) Bu$_3$SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.51

The lactonization of related compounds with an ortho carbomethoxy substituent had been seen before, and it was suggested that this process could occur during the basic fluoride anion work up. However, examination of the $^1$H nmr spectrum of the crude reaction mixture, even before work up, showed that compound 182 was already present. The lactonization step must therefore occur under the reaction conditions, and transesterification processes may possibly involve organotin reagents.

The related mesitylene derivative, prepared the usual way, and with both ortho positions blocked, also gave the ipso substitution product obtained in moderate yield (Scheme 2.52).
Thus, the course of the reaction could be completely reversed from 1,7-addition to 1,6-\textit{ipso} substitution, when \textit{ortho} substituents were present in the acceptor aromatic ring, and these examples were also therefore contributing valuable knowledge to the overall picture summarised earlier in section 2.2.

The effect of two methylene groups on the linking chain was then examined using compound 186, which was prepared in several steps, as shown in Scheme 2.53.

![Scheme 2.52](image_url)

Reagents: i) NaH, THF, 24 hr, r.t. (76%); ii) Bu$_3$SnH / AIBN (slow addition), benzene, reflux.

![Scheme 2.53](image_url)

Reagents: i) NaHCO$_3$, Me$_2$SO$_4$, H$_2$O (81%); ii) nBuLi, THF, -70$^\circ$C (46%).
Thus, methylation of sodium p-toluenesulfinate with dimethyl sulfate, followed by deprotonation with butyl lithium and reaction with o-iodobenzyl chloride afforded sulfone 186.

In this case, reaction of 186 under the usual tin hydride conditions afforded a mixture of products from 1,6-\textit{ipso} substitution (187), 1,7-addition (189) and direct reduction (188), as shown in Scheme 2.54.

\begin{center}
\begin{tikzpicture}
\node [draw] (1) {186};
\node [draw, right of=1, xshift=2cm] (2) {187 \(14\%\)};
\node [draw, right of=2, xshift=2cm] (3) {188 \(26\%\)};
\node [draw, right of=3, xshift=2cm] (4) {189 \(22\%\)};
\node [draw, right of=4, xshift=2cm] (5) {Dihydro Compound \(3\%\)};
\draw [->] (1) -- (2);
\draw [->] (2) -- (3);
\draw [->] (3) -- (4);
\draw [->] (4) -- (5);
\end{tikzpicture}
\end{center}

Reagents: \textit{Bu}_{3}\text{SnH} / AIBN (slow addition), benzene, reflux.

This is the first example of an attempted 1,6-\textit{ipso} substitution reaction in which the direct reduction product (188) can be isolated, indicating that for this type of chain the cyclization step of the aryl radical competes with hydrogen atom abstraction.

As in the heterobiaryl series,\textsuperscript{6} although with less selectivity, this type of chain has favoured the 1,7-addition process. The formation of 187 involves an \textit{ipso} attack followed by 1,6-addition of the alkyl radical to the aromatic ring (Scheme 2.55).
Although there is not much work in the literature concerning the addition of alkyl radicals to aromatic rings, particularly when another aromatic ring is incorporated on the linking chain, this result is nevertheless consistent with the observations of Julia\textsuperscript{21} who studied the reactivity of naphthylbutyl radicals, and observed both addition and ipso substitution (Chapter 1, Scheme 1.50).

Finally, we decided to investigate the effect of having both a carbonyl group and a methylene spacer in the linking chain. Accordingly, the β-ketosulfone 1\textsuperscript{91} was prepared, and we found that both compounds isolated (1\textsuperscript{92} and 1\textsuperscript{93}) were formed via ipso substitution (Scheme 2.56).
Reagents: i) BuLi, THF, -78°C (73%); ii) Bu₃SnH / AIBN (slow addition), benzene, reflux.

The intermediate α-carbonyl radical, formed as a result of ipso substitution followed by the loss of sulfur dioxide, undergoes either hydrogen abstraction to give 192, or further cyclization leading to the phenanthrene derivative 193 (Scheme 2.57).
Again, there is not much work concerning the intramolecular addition of \( \alpha \)-carbonyl radicals to aromatic nuclei particularly when they are connected by an all carbon linking chain. However, macrocyclization of compound 194 has been observed\(^{22} \) under photolytic conditions (Scheme 2.58).

By way of summary, in this section we can see that once again, although the nature of the linking chain by itself can control the products formed, the effect of the substituents can never be forgotten, especially when they are on the ortho position.

Moreover, as shown in Table 2.5, the following general trends can be discerned, for the different chains which were studied:
Table 2.5

<table>
<thead>
<tr>
<th>X-Y in</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂NMe</td>
<td>Decomposition. Probably a 1,5 hydrogen abstraction is a competitive process</td>
</tr>
<tr>
<td>CH₂O</td>
<td>When there is a para-substituent it is formed exclusively 1,7-addition; Although, when the substituent is in the ortho position exclusive 1,6-ipso substitution takes place.</td>
</tr>
<tr>
<td>CH₂CH₂</td>
<td>A mixture of reduced, 1,6-ipso substitution and 1,7-addition products is observed, although 1,7-addition is preferred to 1,6-ipso substitution.</td>
</tr>
<tr>
<td>COCH₂</td>
<td>Exclusive 1,6-ipso substitution.</td>
</tr>
<tr>
<td>CON</td>
<td>Exclusive 1,6-ipso substitution.</td>
</tr>
</tbody>
</table>
2.6. α-Carbonyl Radicals in \textit{ipso} Substitution Reactions

2.6.1. Reaction Under Atom Transfer Conditions

Proceeding with our studies on \textit{ipso} substitution we turned our attention to a different radical species, the α-carbonyl radical, which could be formed from compounds like 194, by halogen abstraction (Scheme 2.59). The radicals formed in this way, can undergo \textit{ipso} substitution or addition, and it was our aim to examine these possibilities.

\[ \begin{align*}
\text{O}_2\text{S}^- \cdot \text{X} \rightarrow \\
\text{O}_2\text{S}^- \cdot \text{X} \rightarrow \\
\text{O}_2\text{S}^- \cdot \text{X} \rightarrow \\
\text{O}_2\text{S}^- \cdot \text{X} \\
\end{align*} \]

Scheme 2.59

α-Carbonyl radicals are very stable species, which in general prefer to abstract a hydrogen atom, rather than undergo a cyclisation step. We thought that this problem could be overcome by using our standard radical conditions, where the concentration of tin hydride is minimised by slow addition and large amounts of AIBN are present.

Thus, compound 196 was selected for this preliminary study, and it was prepared from the corresponding methyl sulfonamide 150 by deprotonation with NaH in THF, followed by addition of chloroacetyl chloride and finally halogen exchange with NaI in acetone (Scheme 2.60).
When compound 196 was submitted to the standard tin hydride conditions the formation of reduced product 197 (29%), \textit{ipso} substitution product 199 (17%) and indol-2-one 198 (14%) was observed (Scheme 2.61). However, the addition product was not formed, which was indicative of the fact that the amidyl chain was a good promoter for \textit{ipso} substitution.

The large amount of reduced product 197 shows that, although the amount of tin hydride in solution was minimised by slow addition, it is still enough to interfere with the reaction. The formation of indol-2-one 198 seems particularly interesting, since it occurs via a sequential 1,5-\textit{ipso} substitution with loss of sulfur dioxide, followed by a 1,5-addition of the resultant amidyl radical on to the aromatic ring (Scheme 2.62). In this way, from a very simple precursor, annulation of the aromatic ring involving both a carbon-carbon and carbon-nitrogen bond formation can be achieved.
Curran,\textsuperscript{9} in his study on the effect of temperature on cyclization reactions, has observed that for simple amides the population of the \textit{syn} and \textit{anti} conformations at room temperature for amide 200 was 52:48. Based on this observation he explained why the yield of the radical cyclization of compound 200 increases from 39\% at 25\(^\circ\)C, to 87\% at 80\(^\circ\)C. Thus, by increasing the temperature the equilibrium between the two rotamers is faster, leading to an increase in the rate of conversion (Scheme 2.63).

\begin{center}
\textbf{Scheme 2.62}
\end{center}

The same principle can be applied to the reaction of 196, where both the carbonyl and the sulfonyl groups around the nitrogen atom can interfere with the conformation adopted (Scheme 2.64). Hence, an increase in temperature would increase the ratio of conversion, and consequently, \textit{ipso} substitution. Gratifyingly, when the reaction was performed in toluene at reflux (110\(^\circ\)C), the ratio between \textit{ipso} substitution / reduced product was increased from 31:29 to 64:7. Unexpectedly, however, the formation of compound 198 was not observed under this set of conditions.
Alternative methods for effecting radical annulations, which involve atom transfer propagation steps and avoid the formation of reduced product, have been developed by Curran. The use of photolytic conditions could be ideal, to avoid the formation of reduced product as well as inducing the second cyclization step to form indolones, since in general these are the conditions used for the cyclization of amidyl radicals. Under these conditions, once the α-carbonyl radical is formed it can only undergo ipso substitution with extrusion of sulfur dioxide and formation of the amidyl radical, or revert to starting material (201) (Scheme 2.65).
The amidyl radical 202 formed in this way was expected to cyclize via a 1,5-addition process, or capture an iodine atom from another molecule of starting material to form the N-iodo-amide which, under the reaction conditions, would revert to the amidyl radical 202.

When 196 was irradiated with UV light, in the presence of bis(tri-n-butyltin) and ethyl iodide in benzene, the ipso substitution product 199 was the only compound detected in the 1H nmr spectrum of the mixture. Under these conditions, the hydrogen abstraction by the amidyl radical appears to be faster than 1,5-addition to the aromatic ring. Ethyl iodide is used in these reactions as a source of iodine atoms, either towards the amidyl radical 202, or for the α-carbonyl radical, when the latter is not in the correct conformation for cyclisation.

As amidyl radicals are electrophilic species, the presence of electron donating groups on the aromatic acceptor ring could promote the second addition step. Thus, the dimethoxy substituted derivatives 204 and 209, which had given good results on promoting 1,5-ipso substitution in the biaryl series (section 2.2.3), were prepared. Deprotonation of sulfonamide 171 with sodium hydride followed by addition of chloroacetyl chloride afforded 203, which on further halogen exchange with sodium iodide in acetone, gave the desired product 204 (Scheme 2.66).

\[
\begin{align*}
\text{MeO} & \quad \text{O}_{2}S \quad \text{NHMe} \\
\text{Me} & \quad \text{Me} \\
\text{171} & \quad \text{203} & \quad \text{204}
\end{align*}
\]

Reagents: i) NaH, THF, $\text{ClCH}_2\text{COCl}$, 2 days (63%); ii) NaI, acetone, reflux (64%).

Reaction of 204 under standard tin hydride conditions (Scheme 2.67) afforded the ipso substitution product 206 in good yield (51%), together with some reduced product 205 (21%).
Acetamide 209 was also prepared, in a similar way to that described above for 204 (Scheme 2.66) and, when exposed to the usual radical conditions, the formation of three products in the same ratio, deriving from direct reduction, 210 (26%), and ipso substitution (211 and 211a), was observed (Scheme 2.68).

Our attention turned again to the formation of the indolone derivative 211 (21%), which had not been formed in the reaction of 204 (Scheme 2.67). Both substrates undergo ipso substitution, but only intermediate 213 (Scheme 2.69) favours the second cyclization to form the indolone derivative.
Both intermediates 212 and 213 have a methoxy group on the ortho or para positions, which can stabilise the radical formed by 1,5 addition of the electrophilic amidyl radical to the aromatic ring. However, while intermediate 212 has only one position available for the attack of the amidyl radical, intermediate 213 has both positions available and position 6, in particular, is less hindered than the other. It may well be that, although both situations are electronically favourable, the resultant outcome in this case is dictated by steric effects.

Most of synthetic radical reactions are based on tin hydride chemistry. The limitations of this method are obvious in this section, where an irreversible hydrogen atom transfer occurs, giving the reduced product. In the next sections, alternative ways of generating an α-carbonyl radical with the potential to retain or incorporate further functionality were investigated.

2.6.2. Reaction Using Copper (I)

Another approach to the ipso substitution reactions was the use of transition metals, which react via single electron transfer. Subsequent loss of iodide anion can then occur, to form the α-carbonyl radical (Scheme 2.70).
Preliminary experiments on 196 in the presence of catalytic copper (I) iodide in acetonitrile at reflux, yielded only starting material. Clearly, copper (I) iodide on its own, is not sufficiently powerful to deliver an electron to the starting iodide 196.

During the course of this work, the transition metal catalysed radical cyclization of N-substituted-N-allyltrichloroacetamides to give N-substituted trichlorinated γ-lactams at low temperatures in high yields was reported25 (Scheme 2.71).

The mechanism (Scheme 2.72) involves the coordination of electron donating amine ligands (bipyridine or TMEDA) to form complexes such as CuCl(bipyridine) or [Cu(bipyridine)2]+Cl-. This coordination facilitates abstraction of a chlorine atom from the N-allyltrichloroacetamide to form the N-allyldichloroacetamide radical.
This low temperature copper mediated reaction seemed a good method for *ipso* substitution and we hoped that by using it, the formation of the reduced product could be minimised.

Compound 214, prepared from the corresponding sulfonamide (150) and trichloroacetyl chloride, was submitted to the copper (I) conditions described above. When TMEDA was added to a solution of the substrate in dry DCM at r.t. in the presence of copper (I) chloride, there was a colour change to dark green, indicating the presence of copper (II) species in solution. Analysis of the reaction mixture showed that the major product formed was the sulfonamide 150 (39%), together with the *ipso* substitution product 216 (36%) and traces of 215 resulting from a reductive process (Scheme 2.73). Under these conditions however, further cyclisation to indolones was not observed.
It is interesting that *ipso* substitution can occur even at room temperature, although the major drawback of this method is the large amount of the sulfonamide 150 which was formed.

Although there are aspects of the mechanism of this reaction which are not clear, some different alternatives are presented in Scheme 2.74.

Abstraction of a chlorine atom or single electron transfer (SET) from 214 by the copper (I) complex occurs with the formation of the electrophilic dichloro radical. If the molecule adopts the conformation 217, the reaction can then proceed via *ipso* substitution and extrusion of sulfur dioxide, with formation of the amidyl radical. At this stage the pathway for further reaction is not very clear however, and two alternative routes can be considered:

A) a single electron transfer (SET) occurs with formation of the amidyl anion. Hence, consuming another molecule of Cu (I).

![Scheme 2.74](image-url)
B) chlorine atom transfer occurs with formation of the N-chloro amide derivative. This would involve a reduction of Cu (II), and thus, the completion of the catalytic cycle. The main disadvantage of this step is that it involves the combination of two electrophilic radical species.

Due to the low temperature of the reaction there must be a significant population of molecules which are in the 218 conformation. These cannot cyclise and, again two alternative pathways can be postulated:

C) a second electron is transferred to the electrophilic dichloro radical, with formation of the dichloroanion, which eliminates dichloroketene with formation of the sulfonamide anion. Hence, copper (I) is oxidised to copper (II), which breaks the catalytic cycle. The alternative chlorine atom transfer to the dichloro radical would revert to starting material.

D) as the dichloro radical can not cyclise, β-scission occurs, with formation of the sulfonamidyl radical, which is then oxidised by the copper species. However, to the best of our knowledge β-scission with formation of a sulfonamidyl radical has not been observed, although the amidyl group can act as a leaving group in ipso substitution reactions.

The mechanism discussed presumes that the copper-TMEDA complex can react either by single electron transfer or by chlorine atom transfer. However, those steps involving SET would break the cycle in a very early stage, which clearly does not occur, since 75% of the starting material is transformed.

An important factor in this reaction is the effect of the temperature. Thus, changing the solvent and increasing the temperature of the reaction would probably increase the conversion to the products of ipso substitution.

2.6.3. Reaction Involving Xanthates

An alternative way of forming a radical is the use of xanthates. This approach involves the generation of a radical R* from a xanthate 219 by either photochemical or chemical means26 (Scheme 2.75)
In the presence of olefinic compounds, $R^*$ can either add to the alkene or to the thiocarbonyl group of the starting xanthate (219) to give 220. If $R'$ is primary or aromatic, radical 220 can only fragment to give back $R^*$ and 219.

The extension of this approach to an ipso substitution process was envisaged and hence compound 221 was prepared from the iodide 196 by halogen substitution (Scheme 2.76).
Irradiation of 221 using a medium pressure mercury vapour lamp (125W) in benzene or toluene afforded indolone 198 and the amide 199 as shown in Scheme 2.77. Comparing these results with those obtained in the reaction of 196 with tin hydride, it can be seen that although the reduced product is not formed when photolytic conditions are used, the ratio between 198 and 199 is similar under both conditions.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Medium</th>
<th>Reaction</th>
<th>Indolone 198</th>
<th>Amide 199</th>
</tr>
</thead>
<tbody>
<tr>
<td>221</td>
<td>Benzene, hv</td>
<td></td>
<td>1.1</td>
<td>2.7 (27%)</td>
</tr>
<tr>
<td>221</td>
<td>Toluene, hv</td>
<td></td>
<td>1 (10%)</td>
<td>-</td>
</tr>
<tr>
<td>196, Bu3SnH, Benzene</td>
<td></td>
<td>1.2 (17%)</td>
<td>1 (14%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>196, Bu3SnH, Toluene</td>
<td></td>
<td>(64%)</td>
<td>--</td>
<td>(11%)</td>
</tr>
</tbody>
</table>

Recently, a different approach using tin xanthates as a source of stannyl radicals was reported.\(^{27}\) Once again, this methodology avoids the use of tin hydride and consequently the reduced product is not formed, even though, stannyl radicals are involved as the radical source. Thus, by irradiation with visible light, the reaction between the substrate (RX) and O-ethyl triphenyltin xanthate (222), proceeds through a chain as shown on Scheme 2.78. All the steps involving the xanthate group are reversible, hence there should not be any competitive process to the cyclization step.
When iodide 196 was submitted to these conditions, a different result was obtained. The major product formed was the xanthate 223 (77%) and the sulfonamide 150 (17%) (Scheme 2.79). This shows that the α-carbonyl radical is trapped by another molecule of the tin xanthate 222 before it is able to cyclise.
Slow addition of tin xanthate was used to minimise its concentration in solution, but this led only to the formation of the sulfonamide 150. Here again, formation of this compound is unexpected. Considering the discussion in the last section (Section 2.6.2), and since single electron transfer does not occur in the reaction conditions, the mechanism for this elimination must proceed via a free radical mechanism. As a result of the different character of the dichloro radical and the simple methylene radical, ipso substitution does not occur at all, and the only product obtained is that formed by β-scission.

In conclusion, we have seen that α-carbonyl radicals can undergo ipso substitution, and a second cyclization of the amidyl radical can also occur. Preliminary studies on the use of tin compounds, transition metals and xanthates have been made, but competitive reactions, like reduction or elimination, could not be suppressed. However, the importance of temperature in maximising the products of ipso substitution is now clear.
2.7. Conclusions and Perspectives

This work has demonstrated that the outcome of *ipso* substitution reactions is based on a delicate balance of substituents, linking chain, conformation and strain. All these factors have their own influence on the selectivity of a 1,5-*ipso* substitution vs 1,6-addition in the reaction between an aryl radical and a sulfonyl substituted acceptor ring.

It was found that the presence of a substituent *ortho* to the sulfonyl group in the acceptor ring, which can be either electron releasing or electron donating, has a significant effect of possible steric origin in promoting *ipso* substitution. It is still not immediately apparent however, why the presence of a single *ortho* substituent does not simply encourage 1,6-addition to the alternative ortho carbon atom adjacent to the sulfonyl group. At the same time, the *ortho* substituent increases the stabilisation of the radical formed, and even in the presence of other stabilising groups in other positions, this *ortho* effect is dominant and *ipso* substitution is favoured. Nevertheless, polar effects are also an important factor overall in *ipso* substitution reactions, with the position of the substituent playing an important role, since the attack occurs in order to form the most stabilised radical.

Throughout this work in 1,5-*ipso* substitution, it was noted that the nature of the linking chain also has a relevant role on the distribution of products. Thus, although the reasons are not very clear, it may be postulated that a nitrogen atom in the linking chain is more efficient in promoting *ipso* substitution than an oxygen atom, which in turn is more efficient than a methylene group. On the latter, much more work needs to be done, in order to confirm our predictions, that a methylene group is a more efficient promoter of 1,6-addition than an oxygen atom. It remains to be understood whether this factor is related to the geometry of the molecule, and thus, the angle of the chain and the distance between the position where the radical is formed and the site of attack.

Biaryl synthesis *via* 1,6-*ipso* substitution is however a less effective process. The analysis of several linking chains allows us to have a better knowledge of this subject, and to suggest a general pattern for these reactions. Thus, the presence of a carbonyl group in the sulfonamide or sulfone chains gives only *ipso* substitution products. However, the addition of a methylene spacer to the methyl sulfonamide chain leads to decomposition, the same spacer in a sulfone chain gives a mixture of products, while the selectivity of the related sulfonate chain is dependent of the position of the substituents. Hence, the presence of an *ortho* substituent shows again, a preponderant
influence on *ips*o substitution, as well as an increase in the efficiency of the reaction, while the *para* substituted rings give exclusively 1,7-addition product.

Another area for further investigation, is the effect of substituents other than a methyl on the nitrogen of the linking chain. Thus, selection of a bulky group on the nitrogen atom or methylene chain, which can dominate the conformation of the molecule in a more favourable position, will most probably enhance the likelihood of *ips*o substitution. Also, the effect of substituent groups on the ring where the aryl radical is formed could be an interesting area for further analysis.

We have also shown that α-carbonyl radicals can undergo *ips*o substitution, with displacement of a sulfonyl group. The influence of the temperature of the reaction on the ratio and nature of products was observed, however, further work is required, in order to optimise the conditions for the subsequent cyclisation with formation of indolone derivatives. The use of stannane compounds, transition metals and xanthates was analysed, but competitive reactions, such as reduction or elimination were also observed. The influence of the substituents on the aromatic ring was also investigated. Thus, both the *ips*o substitution as well as the formation of the indolone are more efficient when electron rich aromatic rings are used.

The introduction of other groups in the chain (p.e. CH₂), or use of analogues that show more reactivity than an α-carbonyl radical can be an area of further study. For example, the substitution of the carbonyl in the linking chain by an acetal, may avoid the reduction step.
References

Chapter Three:

Experimental
General Procedure:

\(^1\)H nmr spectra were recorded in CDCl\(_3\) at 200 MHz on a Varian XL-200, 270 MHz on a Joel GSX 270 and 400 MHz on a Varian VXR-400. \(^{13}\)C nmr spectra were recorded 68 and 100 MHz on a Joel GSX 270 and Varian VXR-400. Residual protic solvent, i.e. CHCl\(_3\) (\(\delta_H=7.26\) ppm; \(\delta_C=77.0\) ppm) was used as internal reference. Coupling constants were measured in hertz. Infrared spectra were recorded on a Perkin Elmer 983G and FT-IR 1600 spectrometers. Mass spectra and accurate mass measurements were recorded by EI on a VG 7070B instrument at Imperial College, on a VG 12 253 and VG ZAB-e instruments by the SERC mass spectrometry service and by EI and CI with NH\(_3\) carrier gas, and FAB, on a VG 7070 instrument at UCL. Melting points were determined on a Reichert hot-stage instrument. Microanalysis were performed at Imperial College Chemistry Department microanalytical laboratory and at UCL Chemistry Department microanalytical laboratory. HPLC separation was performed on a Partisil 5 silica gel column (250mm x 10mm), using a UV detector (254 nm) and a solvent mixture of 2% isopropanol in hexane, at a flow rate of 5.0 cm\(^3\)/min. Flash column chromatography was performed on Merck Kieselgel 60 (230-400 mesh) at low positive pressure. Preparative thin layer chromatography was performed on pre-coated glass plates (Merck Kieselgel 60 F\(_{254}\), 2mm) and visualised using ultraviolet light (245 nm). Analytical thin layer chromatography was performed on pre-coated glass backed plates (Merck Kieselgel 60 F\(_{254}\), 0.2 mm) and visualised using ultraviolet light (245 nm), potassium permanganate, acidic ammonium molybdate and iodine, as appropriate. "Petrol" refers to petroleum ether (b.p. 40-60 °C) which was distilled prior to use. Diethyl ether (referred as ether), tetrahydrofuran and benzene were distilled from sodium benzophenone ketyl; dichloromethane from phosphorous pentoxide and toluene from sodium. All free radical reactions were carried out in glassware oven dried, teflon sealed and degassed with dry argon or nitrogen for approximately 20 min, which was maintained for the entire period of the reaction.
Preparation of 2-methyl-benzenesulfonyl chloride (63)

\[
\text{NH}_2 \quad \rightarrow \quad \text{SO}_2\text{Cl} \\
\text{63}
\]

To a mixture of conc. HCl (16 ml) and glacial acetic acid (5 ml) was added o-toluidine (5.3 ml, 50 mmol) dropwise, and the hydrochloric salt precipitated. The flask was cooled in a dry ice-ethanol bath to -10°C, and a solution of sodium nitrite (3.8 g, 55 mmol) in water (5.5 ml) was added dropwise at such a rate that the temperature did not exceed -5 °C. The mixture was left under stirring at -10 to -5 °C for 30 min.

Meanwhile sulfur dioxide (SO2) was introduced to acetic acid (50 ml) by a tube immersed below the surface, over a period of 20 min CuCl (1.24 g) was added and the sulfur dioxide (SO2) bubbled through for a further 30 min. The mixture was cooled with ice to 10 °C and the diazonium salt added dropwise so as to maintain the temperature at 10 °C. After a further 2 hr at this temperature the mixture was warmed to r.t. and stirred overnight. Water was added (150 ml) and the mixture extracted with ether (3x75 ml), washed with aq. NaHCO3, water (50 ml), dried (MgSO4) and the solvent removed under reduced pressure to give the crude sulfonyl chloride 63 (5.9 g, 62%) as an oil; \( v_{\text{max}}(\text{film})/\text{cm}^{-1} \) 1494, 1371 (S=O), 1182 (S=O); \( \delta_H(200 \text{ MHz}; \text{CDCl}_3) \) 8.06 (1H, d, \( J \ 8.3 \), H-6), 7.61 (1H, t, \( J \ 7.5 \), H-4), 7.44-7.37 (2H, m, H-3 and H-5), (3H, s, ArCH3); which was used without further purification.
To 2-iodoaniline (1.1 g, 5.0 mmol) and DMAP (30 mg, 0.24 mmol) was added a solution of the crude sulfonyl chloride 63 (1.1 g, 6.0 mmol) in pyridine (10 ml), and the reaction mixture was stirred at room temperature for 2 days. The pyridine was removed in vacuo, the residue dissolved in DCM (25 ml) washed with sat. aq. CuSO₄ (2x20 ml) and water (20 ml), dried (MgSO₄), concentrated in vacuo and chromatographed (DCM/petrol 25-33 %) to give the sulfonamide 64 (682 mg; 37%) as white prisms, m.p. 58-59 °C (from ether-petrol); νₓ璜(film)/cm⁻¹ 3324, 1474, 1393, 1334 (S=O), 1161 (S=O); δₓ璜(400 MHz; CDCl₃) 7.96 (1H, dd, J 1.2 and 8.2, H-3' or H-6), 7.67 (1H, dd, J 1.3 and 7.9, H-3' or H-6), 7.47 (1H, dd, J 1.5 and 8.3, H-6'), 7.45 (1H, dt, J 1.3 and 7.5, H-5' or H-4), 7.30-7.26 (2H, m, H-3 and H-4 or H-5'), 7.21 (1H, dt, J 1.4 and 8.4, H-4'), 6.99 (1H, bs, NH), 6.77 (1H, ddd, J 1.5, 7.4 and 7.9, H-5), 2.68 (3H, s, ArCH₃); δₓC(CDCl₃) 139.2 (1C, t), 137.5 (1C, q), 137.4 (1C, q), 136.9 (1C, q), 133.4 (1C, t), 132.8 (1C, t), 130.1 (1C, t), 129.4 (1C, t), 126.2 (1C, t), 126.0 (1C, t), 120.2 (1C, t), 90.3 (1C, q, C-I), 20.8 (1C, p, CH₃); m/z 373 (M⁺), 218, 91 (100%); (Found: C, 41.5; H, 3.2; N, 3.6. C₁₃H₁₂INO₂S requires C, 41.8; H, 3.2; N, 3.75%).
Preparation of \(N,2\)-dimethyl-\(N\)-(2-iodophenyl)-benzenesulfonamide (65)

\[
\begin{align*}
\text{64} & \quad \longrightarrow \quad \text{65}
\end{align*}
\]

To a stirred suspension of NaH (60% dispersion in mineral oil; 125 mg, 3.1 mmol) in THF (3 ml) at room temperature was added a solution of the sulfonamide 64 (538 mg, 1.4 mmol) in THF (4 ml). Vigorous effervescence occurred. After 30 minutes methyl iodide (0.8 ml, 13 mmol) was added and the reaction mixture stirred for 24 hr. Water (25 ml) was added and the solution extracted with DCM (3x20 ml), dried (MgSO\(_4\)), the solvent removed \textit{in vacuo} and the residue chromatographed (DCM/petrol 40%) to give the \textit{methyl sulfonamide} 65 (375 mg, 67%) as white prisms, m.p. 102.5-104 °C (from DCM/petrol); \(v_{\text{max}}\) (film/cm\(^{-1}\)) 2924, 1468, 1347 (S=O), 1156 (S=O), 716; \(\delta_H\) (400 MHz; CDCl\(_3\)) 7.84 (1H, dd, \(J = 1.5\) and 8.0, H-6), 7.80 (1H, dd, \(J = 1.4\) and 7.9, H-3'), 7.43 (1H, dt, \(J = 1.4\) and 7.9, H-5'), 7.29-7.22 (4H, m, H-4', H-6', H-3 and H-4), 6.99 (1H, ddd, \(J = 1.8\), 7.2 and 8.0, H-5), 3.23 (3H, s, NCH\(_3\)), 2.50 (3H, s, ArCH\(_3\)); \(\delta_C\) (CDCl\(_3\)) 143.3 (1C, q), 140.3 (1C, t), 138.3 (2C, q), 137.3 (1C, t), 132.9 (1C, t), 130.4 (1C, t), 130.3 (1C, t), 129.8 (1C, t), 129.1 (1C, t), 126.1 (1C, t), 100.5 (1C, q, C-I), 39.3 (1C, p), 21.7 (1C, p); \(m/z\) 387 (M\(^+\)), 323 (M\(^+\)-SO\(_2\)), 260 (M\(^+\)-I), 232, 105 (100%); (Found: C, 43.3; H, 3.8; N, 3.3. \(C_{14}H_{14}INO_{2}S\) requires C, 43.4; H, 3.6; N, 3.6%).
Reaction of \(N,2\text{-dimethyl-N-(2-iodophenyl)-benzenesulfonamide} \ (65)\) with tri-n-butyltin hydride

![Chemical structure of 65 and 66]

To a stirred solution of the sulfonamide 65 (332 mg, 0.86 mmol) in benzene (17 ml) at reflux, was added a solution of tri-n-butyltin hydride (290 \(\mu\)l, 1.06 mmol) and AIBN (101 mg; 0.61 mmol) in benzene (4.5 ml) dropwise over 11 hr, \textit{via} a needle placed directly above the refluxing solution. After a further 2 hr the reaction mixture was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed \textit{in vacuo}, the residue dissolved in ethyl acetate (20 ml), sat. aq. KF (15 ml) added and vigorous stirring continued for 2 hr. The suspension was filtered, the organic layer washed with sat. aq. KF (15 ml) and water (15 ml) dried (MgSO₄), and concentrated under reduced pressure. The residue was chromatographed (DCM/petrol 50%) to give in order of elution \(N,2\text{-dimethyl-1',1'-biphenyl-2-amine} \ (66)\) (97 mg, 57%) and the sulfonamide 65 (31 mg, 9.5%).

\(N,2\text{-dimethyl-1',1'-biphenyl-2-amine} \ (66)\) as an oil; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3426 (NH), 2919, 1512, 742; \(\delta\)\(_{\text{H}}\) (400 MHz; CDCl₃) 7.29-7.21 (4H, m, ArH), 7.18-7.16 (1H, m, ArH), 6.97 (1H, dd, \(J\ 1.5\) and \(7.3\), H-6), 6.74 (1H, dt, \(J\ 1.1\) and \(7.4\), H-5), 6.67 (1H, d, \(J\ 8.2\), H-3), 3.40 (1H, bs, NH), 2.76 (3H, s, NCH₃), 2.11 (3H, s, ArCH₃); \(\delta\)\(_{\text{C}}\) (CDCl₃) 146.2 (1C, q), 138.5 (1C, q), 137.2 (1C, q), 130.3 (1C, t), 130.2 (1C, t), 129.5 (1C, t), 128.5 (1C, t), 127.6 (1C, t), 127.1 (1C, q), 126.2 (1C, t), 116.4 (1C, t), 109.4 (1C, t), 109.4 (1C, p, NCH₃), 19.6 (1C, p, ArCH₃); \(m/z\) 197 (M⁺, 100%), 182, 167; (Found: M⁺, 197.1204. C\(_{14}\)H\(_{15}\)N requires \(M\), 197.1204).
Preparation of (2-iodophenyl) 2-methylbenzenesulfonate (71)

To 2-iodophenol (1.1 g, 5.0 mmol) and DMAP (30 mg, 0.24 mmol) was added a solution of the crude sulfonyl chloride 63 (1.3 g, 6.0 mmol) in pyridine (10 ml). The mixture was left stirring overnight at r.t. The pyridine was removed in vacuo, the residue dissolved in DCM (25 ml), washed with sat. aq. CuSO4 (2x20 ml) and water (20 ml) dried (MgSO4), concentrated in vacuo and chromatographed (DCM/petrol 25%) to give an inseparable mixture of 2-iodophenol and the sulfonate 71. The mixture was dissolved in ether (5 ml), added to a suspension of sodium hydride (excess) in ether (5 ml) and filtered by cannula to give the sulfonate 71 (458 mg, 25%) as white prisms, m.p. 53-55 °C (DCM/petrol); νmax(film)/cm⁻¹ 1462, 1372 (S=O), 1199, 1174 (S=O); δH(400 MHz; CDCl₃) 7.89 (1H, d, J 8.1, H-3'), 7.80 (1H, dd, J 1.6 and 7.9, H-6), 7.58 (1H, dt, J 1.3 and 7.6, H-5'), 7.41 (1H, d, J 7.6, H-6'), 7.32 (1H, t, J 8.0, H-4'), 7.27 (1H, dt, J 1.5 and 7.4, H-4), 7.05 (1H, dd, J 1.4 and 8.2, H-3), 6.97 (1H, dt, J 1.4 and 7.4, H-5), 2.79 (3H, s, ArCH₃); δC(CDCl₃) 150.2 (1C, q), 140.2 (1C, t), 139.1 (1C, q), 135.1 (1C, q), 134.3 (1C, t), 132.8 (1C, t), 130.2 (1C, t), 129.4 (1C, t), 128.3 (1C, t), 126.3 (1C, t), 122.7 (1C, t), 90.1 (1C, q, C-T), 21.0 (1C, p, Ar CH₃); m/z 374 (M⁺), 155, 91 (100%); (Found: M⁺, 373.9474. C₁₃H₁₁I₁O₃S requires M, 373.9474).
Reaction of (2-iodophenyl) 2-methylbenzenesulfonate (71) with tri-n-butyltin hydride

To a stirred solution of the sulfonate 71 (336 mg, 0.90 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (106 mg; 0.65 mmol) in benzene (4.7 ml) dropwise over 11 hr, via a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed in vacuo, the residue dissolved in ethyl acetate (20 ml), sat. aq. KF (15 ml) added and vigorous stirring continued for 2 hr. The suspension was filtered, the organic layer washed with sat. aq. KF (15 ml) and water (15 ml) dried (MgSO₄), and concentrated under reduced pressure. The residue was dissolved in DCM (30 ml), washed with aq. NaOH (10%, 3x 20ml), the aq. layer acidified with conc. HCl to pH 1 and extracted with DCM (3x30 ml), dried (MgSO₄) and the solvent removed under reduced pressure to give 2'-methyl-1,1'-biphenyl-2-ol (73) (38 mg, 23%).

The organic layer was dried (MgSO₄), the solvent removed under reduced pressure and the residue chromatographed (DCM/petrol 30%) to give in order of elution the sulfonate 71 (28 mg, 8%) and 4-methyl-dibenzo[c,e]oxathiine-S,S-dioxide (72) (80 mg, 36%).

2'-methyl-1,1'-biphenyl-2-ol (73) as an oil; v_max(film)/cm⁻¹ 3501, 3434 (OH), 3060, 2922, 1472, 1185, 754; δ_H(400 MHz; CDCl₃) 7.60-7.49 (5H, m, ArH), 7.37 (1H, dd, J 1.4 and 7.3, H-3), 7.26-7.22 (2H, m, ArH), 5.06 (1H, bs, OH), 2.43 (3H, s, ArCH₃); δ_C(CDCl₃) 152.4 (1C, q), 137.4 (1C, q), 135.6 (1C, q), 130.6 (1C, t), 130.4 (1C, t), 130.1 (1C, t), 129.1 (1C, t), 128.5 (1C, t), 127.6 (1C, q), 126.4 (1C, t), 120.4 (1C, t), 115.2 (1C, t), 19.7 (1C, p, Ar CH₃); m/z 184 (M⁺, 100%), 169 (M⁺-Me); (Found: M⁺, 184.0900. C₁₃H₁₂O requires M, 184.0888).
4-methyl-dibenz[c,e]oxathiine-S,S-dioxide (72) as white needles, m.p. 119-121 °C (DCM/petrol); $\nu_{\text{max}}$(film)/cm$^{-1}$ 1367 (S=O), 1177 (S=O), 790, 757; $\delta_H$(400 MHz; CDCl$_3$) 7.86 (1H, dd, $J$ 1.5 and 7.9, H-10), 7.76 (1H, d, $J$ 8.1, H-1), 7.59 (1H, t, $J$ 7.8, H-2), 7.44 (1H, dt, $J$ 1.6 and 7.7, H-3), 7.38-7.34 (2H, m, H-3 and H-9), 7.30 (1H, dd, $J$ 1.3 and 8.0, H-7), 2.75 (3H, s, $A\text{CH}_3$); $m/z$ (El) 246 (M+, 100%), 181 (100%); (Cl) 263 (MNH$_4^+$, 100%); (Found: M+, 246.0351. C$_{13}$H$_{10}$O$_3$S requires $M^+$, 246.0351).

Preparation of methyl 3-nitrobenzoate (76)$^1$

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad\rightarrow\quad \text{NO}_2 \\
\text{CO}_2\text{Me} & \quad\text{76}
\end{align*}
\]

To the methyl benzoate (7.2 ml, 58 mmol) at 0 °C was added conc. H$_2$SO$_4$ (16 ml). Meanwhile, in another flask, HNO$_3$ (6 ml) was mixed with H$_2$SO$_4$ (6 ml), and the mixture cooled in an ice bath. This solution was added to the methyl benzoate solution, maintaining the temperature between 0-10°C, over 1 hr. After stirring for a further 10 min at r.t., the mixture was poured into ice and stirred until a granular precipitate was seen. The product was filtered and washed with water to give the benzoate 76 (9.8 g, 94%) as white prisms, m.p. 79-80 °C (Lit.$^1$ 78 °C); $\nu_{\text{max}}$(film)/cm$^{-1}$ 2958, 1713 (C=O), 1530 (NO$_2$), 1350 (NO$_2$); $\delta_H$(200 MHz; CDCl$_3$) 8.87 (1H, s, H-2), 8.39-8.34 (2H, m, H-4 and H-6), 7.65 (1H, dd, $J$ 7.9 and 8.2, H-5), 3.98 (3H, s, OCH$_3$).
Preparation of methyl 3-aminobenzoate (77)

![Chemical structure](image)

To a suspension of the benzoate 76 (8.8 g, 48.5 mmol) in ethanol (32 ml) was added Pd/C (230 mg) and the flask flushed with argon and then with hydrogen. After stirring vigorously for 2 days the mixture was filtered through a pad of celite, and the solvent removed in vacuo to give the aminobenzoate 77 which was used without further purification.

**methyl 3-aminobenzoate (77)** as an oil, (Lit.² m.p. 54 °C) \( v_{\text{max}} \) (film)/cm\(^{-1}\) 3374, (NH) 2951 (CH), 1709 (C=O), 1320 (C-N), 1242 (C-O), 1102 (C-O), 754; \( \delta_H \) (270 MHz; CDCl\(_3\)) 7.42 (1H, td, \( J \) 1.0 and 7.3, H-6), 7.34 (1H, t, \( J \) 2.0, H-2), 7.21 (1H, t, \( J \) 7.8, H-5), 6.85 (1H, ddd, \( J \) 1.0, 2.4 and 7.8, H-4), 3.88 (3H, s, OCH\(_3\)), 3.76 (2H, bs, NH\(_2\)); \( m/z \) 151 (M\(^+\)), 120 (M\(^+\)-OMe, 100%), 92 (M\(^+\)-CO\(_2\)Me).

Preparation of methyl 3-(chlorosulfonyl) benzoate (78)

![Chemical structure](image)

To a mixture of conc. HCl (16 ml) and glacial acetic acid (5 ml), was added the crude benzoate 77 (49 mmol). The flask was placed in a dry ice-ethanol bath and the temperature of the mixture lowered to -10°C. A solution of sodium nitrite (3.7 g, 53 mmol) in water (5.4 ml) was added dropwise, at such a rate so that the temperature did not exceed -5 °C. The mixture was left stirring at -10 to -5 °C, while the other solution was prepared.
Sulfur dioxide (SO\textsubscript{2}) was introduced into acetic acid (49 ml) by a tube immersed below the surface, over a period of 30 min. CuCl (1.35 g, 13.6 mmol) was added and SO\textsubscript{2} was kept bubbling for a further hour. The mixture was cooled with ice to 5 °C and the diazonium salt was added dropwise so as to maintain the temperature.

After the addition the mixture was allowed to warm to 10 to 15 °C and stirred for 1 hr. Ice was added and the mixture stirred until it melted, extracted with ether (3x120 ml) washed with NaHCO\textsubscript{3} (100 ml) dried (MgSO\textsubscript{4}) and the solvent removed in vacuo to give the benzoate 78 (7.7 g, 67%) as orange plates m.p. 64-66 °C (Lit.\textsuperscript{3} 68 °C); \nu_{\text{max}}(film)/\text{cm}^{-1} 3104, 2956, 1736 (C=O), 1435, 1368 (S=O), 1179 (S=O), 1124, 855, 750, 672, 657; \delta\textsubscript{H}(400 MHz; CDCl\textsubscript{3}) 8.67 (1H, dd, J 1.4 and 1.7, H-2), 8.39 (1H, ddd, J 1.2, 1.6 and 7.8, H-4 or H-6), 8.20 (1H, dddd, J 1.2, 2.0 and 7.9, H-4 or H-6), 7.72 (1H, t, J 7.8, H-5), 3.97 (3H, s, CO\textsubscript{2}Me); \delta\textsubscript{C}(CDCl\textsubscript{3}) 164.4 (1C, q, C=O), 144.7 (1C, q), 135.9 (1C, t), 132.0 (1C, q), 130.7 (1C, t), 130.0 (1C, t), 128.1 (1C, t), 52.9 (1C, p, CH\textsubscript{3}); m/z 236, 234 (M++2 and M+), 205, 203, (M+-OMe), 199, (M+-Cl), 135 (M+-SO\textsubscript{2}Cl, 100%);

Preparation of methyl 3-[(2-iodophenyl)oxysulfonyl]benzoate (79)

To 2-iodophenol (1.0 g, 4.7 mmol) and DMAP (40 mg) was added a solution of the benzoate 78 (1.5 g, 6.4 mmol) in pyridine (10 ml). The mixture stirred overnight at r.t. The pyridine was removed in vacuo, the residue dissolved in DCM (25 ml), washed with sat. aq. CuSO\textsubscript{4} (2x25 ml) and water (20 ml) dried (MgSO\textsubscript{4}), concentrated in vacuo and chromatographed (DCM/petrol 75%) to give the benzoate 79 (1.8 g, 91%) as an oil; \nu_{\text{max}}(film)/\text{cm}^{-1} 3072, 2955, 1730 (C=O), 1383 (S=O), 1202, 1173 (S=O); \delta\textsubscript{H}(270 MHz; CDCl\textsubscript{3}) 8.60 (1H, t, J 1.7, H-2), 8.34 (1H, td, J 1.5 and 7.8, H-4 or H-6), 8.08 (1H, td, J 1.5 and 8.1, H-4 or H-6), 7.72 (1H, d, J 7.3, H-3'), 7.63 (1H, dd, J 7.8 and 8.1, H-5), 7.35 (2H, d, J 3.9, H-5' and H-6'), 7.01-6.95 (1H, m, H-4'), 3.94 (3H, s,
Reaction of methyl 3-[(2-iodophenyl)oxysulfonyl]benzoate (79) with tri-n-butyltin hydride

![Chemical Structure](image)

To a stirred solution of the benzoate 79 (371 mg, 0.89 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 μl, 1.17 mmol) and AIBN (121 mg; 0.74 mmol) in benzene (4.6 ml) dropwise over 11 hr, via a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed in vacuo, the residue dissolved in DCM (20 ml), washed with sat. aq. KF (2 x 15 ml) and water (15 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%) to give, in order of elution, methyl dibenz[c,e]oxathiine-S,S-dioxide-3-carboxylate (80) (135 mg, 52%) and methyl (4aR,10bR)-4a,10b-dihydridobenz[c,e]oxathiine-S,S-dioxide-1-carboxylate (81) (50 mg, 19%);

*methyl dibenz[c,e]oxathiine-S,S-dioxide-3-carboxylate* (80) as white prisms, m.p. 183-185 °C (DCM/petrol); ν_max(film)/cm⁻¹ 2956 (CH), 1728 (C=O), 1377 (S=O), 1202, 1176 (S=O), 758; δ_H(400 MHz; CDCl₃) 8.65 (1H, d, J 1.7, H-4), 8.40 (1H, dd, J 1.7 and 8.3, H-2), 8.03 (1H, d, J 8.3, H-1), 7.98 (1H, dd, J 1.7 and 7.8, H-10 or H-7), 7.53 (1H, dt, J 1.7 and 8.1, H-10 or H-7), 7.44 (1H, dt, J 1.5 and 7.6, H-8 or H-9), 7.37 (1H, dd, J 1.2 and 8.1, H-8 or H-9), 3.99 (3H, s, CO₂CH₃); δ_C(CDCl₃) 164.7 (1C, q, C=O),
150.1 (1C, q), 135.4 (1C, q), 134.4 (1C, t), 132.3 (1C, t), 130.7 (1C, q), 126.9 (1C, t),
125.7 (2C, t), 125.1 (1C, t), 120.9 (2C, q), 120.2 (1C, t), 52.8 (1C, p, OCH3); m/z 290
(M+, 100%), 259, 195, 139; (Found: M+, 290.0238. O14H10O5S requires M, 290.0249).

(4aR,10bR)-4a,10b-dihydrodibenz[c,e]oxathiine-S,S-dioxide-1-carboxylate (81) as
white prisms, m.p. 125-126 °C (DCM/petrol); νmax(film)/cm⁻¹ 1710 (C=O), 1375
(S=O), 1227, 1156 (S=O); δH(270 MHz; CDCl3) 7.28-7.24 (2H, m, H-8 or H-9 and H-2), 7.13
(1H, dt, J 1.2 and 7.3, H-8 or H-9), 7.06 (1H, d, J 7.8, H-7 or H-10), 6.99 (1H, dd, J 1.2 and 8.3, H-7 or H-10), 6.81 (2H, d, J 7.9, H-3 and H-4), 4.83 (1H, d, J 7.3, H-10b), 4.37 (1H, d, J 7.8, H-4a), 3.93 (3H, s, CO2CH3); δC(CDCl3) 166.6 (1C, q, C=O),
150.9 (1C, q), 134.4 (1C, t), 129.1(1C, t), 128.5 (1C, q), 128.4 (1C, t), 128.1 (1C, t),
125.9 (1C, t), 125.2 (1C, t), 121.7 (1C, q), 118.6 (1C, t), 55.9 (1C, p), 52.6 (1C, t), 33.9
(1C, p, NCH3); m/z 292 (M+), 290, 196 (100%), 168; the X-ray of this compound is on
Appendix 2.

Preparation of methyl 3[(2-iodophenyl)aminosulfonyl] benzoate (83)

\[
\begin{align*}
\text{NH}_2 & \quad \text{SO}_2\text{Cl} \\
\text{I} & \quad \text{CO}_2\text{Me} \\
\text{I} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

To 2-iodoaniline (628 mg, 2.9 mmol) and DMAP (20 mg, 0.2 mmol) was added
a solution of the benzoate 78 (1.1 g, 4.5 mmol) in pyridine (6 ml), and the reaction
mixture was stirred at room temperature for 3 days. The pyridine was removed in
vacuo, the residue dissolved in DCM (25 ml) washed with sat. aq. CuSO4 (2x20 ml)
and water (20 ml), dried (MgSO4), concentrated in vacuo and chromatographed
(DCM/petrol 50-75%) to give the benzoate 83 (820 mg, 69%) as an oil; νmax(film)/cm⁻¹
3267 (NH), 1762 (C=O), 1471, 1342 (S=O), 1271, 1166 (S=O), 1125, 754; δH(270
MHz; CDCl3) 8.43 (1H, t, J 1.5, H-2), 8.21 (1H, ddd, J 1.2, 1.7 and 7.8, H-4 or H-6),
7.87 (1H, ddd, J 1.2, 2.0 and 7.8, H-4 or H-6), 7.65 (2H, m, H-3’ and H-6’), 7.50 (1H, t,
J 7.8, H-5), 7.33 (1H, dt, J 1.2 and 7.6, H-4’ or H-5’), 6.85 (1H, m, H-4’ or H-5’), 6.82
Preparation of methyl 3[(2-iodophenyl)methylaminosulfonyl] benzoate (84)

To a stirred suspension of NaH (60% dispersion in mineral oil; 160 mg, 3.9 mmol) in THF (3 ml) at room temperature was added a solution of the benzoate 83 (820 mg, 2.0 mmol) in THF (5 ml). Vigorous effervescence occurred. After 30 min methyl iodide (1.0 ml, 16 mmol) was added and the reaction mixture stirred for 24 hr. Water (25 ml) was added and the solution extracted with DCM (3x15 ml), dried (MgSO4), the solvent removed in vacuo and the residue chromatographed (DCM/petrol 75%) to give the benzoate 84 (337 mg, 40%) as white needles, m.p. 112-114 °C (DCM/petrol); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2952 (CH), 1728 (C=O), 1356 (S=O), 1271, 1157 (S=O), 705; $\delta_H$ (270 MHz; CDCl$_3$) 8.50 (IH, t, J 1.5, H-2), 8.28 (1H, ddd, J 1.2, 1.5 and 7.8, H-4 or H-6), 7.97 (1H, ddd, J 1.2, 1.5 and 7.8, H-4 or H-6), 7.90 (1H, dd, J 1.5 and 8.3, H-3'), 7.61 (1H, dt, J 0.5 and 7.8, H-5), 7.30 (1H, ddd, J 1.5, 7.6 and 8.6, H-5'), 7.07-7.01 (2H, m, H-4' and H-6'), 3.95 (3H, s, CO$_2$CH$_3$), 3.19 (3H, s, NCH$_3$); $\delta_C$(CDCl$_3$) 165.5 (1C, q, C=O), 143.3 (1C, q), 140.5 (1C, t), 139.6 (1C, q), 133.8 (1C, q), 132.1 (1C, t), 131.3 (1C, q), 130.1 (1C, t), 129.4 (1C, t), 129.2 (2C, t), 129.1 (1C, t), 101.0 (1C, q, C-I), 52.6 (1C, p, OCH$_3$), 38.9 (1C, p, NCH$_3$); m/z 431 (M$^+$), 400 (M$^+$-OMe), 304 (M$^+$-I), 232 (100%), 183, 105; (Found: M$^+$, 430.9688. C$_{15}$H$_{14}$INO$_4$S requires M, 430.9688).
Reaction of methyl 3[(2-iodophenyl)methylaminosulfonyl] benzoate (84) with tri n-butyltin hydride

To a stirred solution of the benzoate 84 (322 mg, 0.74 mmol) in benzene (15 ml) at reflux, was added a solution of tri-n-butyltin hydride (260 μl, 0.95 mmol) and AIBN (101 mg; 0.62 mmol) in benzene (3.8 ml) dropwise over 11 hr, via a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added, and stirring continued for a further hour. The solvent was removed in vacuo, the residue dissolved in DCM (20 ml), washed with sat. KF (2x15 ml) and water (15 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%, ethyl acetate/petrol 20%) to give in order of elution methyl (N-methyl-1',2'-biphenyl-2'-amine)-3-carboxylate (86) (50 mg, 28%), methyl 6-methyl-6H-dibenzo[c,e]thiazine-S,S-dioxide-3-carboxylate (85) (84 mg, 37%) and a dihydro compound 87 (28 mg, 11%).

*methyl* (N-methyl-1',2'-biphenyl-2'-amine)-3-carboxylate (85) as white prisms m.p. 93-95°C (DCM/petrol); ν max(film)/cm⁻¹ 3423 (NH), 2950 (CH), 1722 (C=O), 1511, 1462, 1305, 1260, 1231; δH (270 MHz; CDCl₃) 8.10 (1H, t, J 1.7, H-2), 8.02 (1H, td, J 1.7 and 7.8, H-4), 7.62 (1H, td, J 1.5 and 7.6, H-6), 7.51 (1H, t, J 7.6, H-5), 7.29 (1H, ddd, J 1.7, 7.8 and 8.5, H-4'), 7.08 (1H, dd, J 1.5 and 7.3, H-6'), 6.79 (1H, t, J 7.3, H-5'), 6.71 (1H, d, J 8.5, H-3'), 3.92 (3H, s, CO₂CH₃), 2.80 (3H, s, NCH₃); δC (CDCl₃) 166.8 (1C, q, C=O), 145.9 (1C, q), 139.7 (1C, q), 133.9 (1C, t), 130.7 (1C, q), 130.5 (1C, t), 129.9 (1C, t), 129.1 (1C, t), 128.9 (1C, t), 128.3 (1C, t), 126.4 (1C, q), 116.8 (1C, t), 109.9 (1C, t), 52.0 (1C, p, OCH₃), 30.7 (1C, p, NCH₃); m/z 367 (M⁺), 266, 241 (100%); (Found: M⁺, 241.1103. C₁₅H₁₅NO₂ requires M, 241.1103).

*methyl* 6-methyl-6H-dibenzo[c,e]thiazine-S,S-dioxide-3-carboxylate (86) as white prisms, m.p. 178-180 °C (DCM/petrol); ν max(film)/cm⁻¹ 1720 (C=O), 1292, 1166;
Experimental

δ_H(270 MHz; CDCl₃) 8.65 (1H, d, J 2.0, H-4), 8.33 (1H, dd, J 2.0 and 8.3, H-2), 8.04-8.00 (2H, m, H-1 and H-7), 7.54 (1H, dt, J 1.7 and 7.3, H-8 or H-9), 7.30-7.37 (2H, m, H-8 or H-9 and H-10), 3.97 (3H, s, CO₂CH₃), 3.46 (3H, s, NCH₃); δ_C(CDCl₃) 169.4 (1C, q, C=O), 139.9 (1C, q), 136.2 (1C, q), 134.2 (1C, q), 132.9 (1C, t), 131.4 (1C, t), 129.8 (1C, q), 126.0 (1C, t), 125.6 (1C, t), 124.8 (1C, t), 124.0 (1C, t), 123.2 (1C, q), 119.4 (1C, t), 52.5 (1C, p, OCH₃), 32.7(1C, p, NCH₃); m/z 303 (M⁺, 100%), 272, 238, 208, 180; (Found: M⁺, 303.0576. C₁₅H₁₃NO₄S requires M, 303.0565).

Dihydro compound 87 as a clear oil; ν_max(film)/cm⁻¹ 2948 (CH), 1707 (C=O), 1335 (S=O), 1138 (S=O); δ_H(270 MHz; CDCl₃) 7.30-7.22 (2H, m, ArH and H-2), 7.02-7.00 (2H, m, ArH), 6.98 (1H, d, J 8.1, ArH), 6.27-6.21 (1H, ddd, J 2.7, 5.1 and 9.5, H-3), 6.14-6.19 (1H, ddd, J 1.0, 2.0 and 9.5, H-4), 4.81 (1H, d, J 7.8, H-10b), 4.32-4.27 (1H, td, J 2.0 and 8.0, H-44), 3.91 (3H, s, CO₂CH₃), 3.38 (3H, s, NCH₃); δ_C(CDCl₃) 166.9 (1C, q, C=O), 140.6 (1C, q), 134.3 (1C, t), 129.1 (1C, q), 128.3 (1C, t), 128.1 (1C, t), 127.5 (1C, t), 125.9 (1C, t), 124.9 (1C, q), 123.7 (1C, t), 117.1 (1C, t), 57.3 (1C, p, OCH₃), 52.5 (1C, t), 34.3 (1C, p, NCH₃), 32.2 (1C, t); m/z (EI) 303 (M⁺-2), 241, 182 (100%), 167; (Cl) 323 (MNH₄⁺), 242 (100%); (Found: MNH₄⁺, 323.1066. C₁₅H₁₉N₂O₄S requires MNH₄⁺ 323.1066).

Preparation of N-(2-iodophenyl)-2,4,6-trimethylbenzenesulfonylamide (88)

![Chemical Structure](image)

To 2-iodoaniline (1.1 g, 4.9 mmol) and DMAP (33 mg, 0.3 mmol) was added a solution of 2,4,6-trimethylbenzenesulfonyl chloride (1.6 g, 7.3 mmol) in pyridine (12 ml), and the reaction mixture stirred at room temperature for 24 hr.

Pyridine was removed in vacuo, the residue washed with sat. aq. CuSO₄ (20 ml), extracted with DCM (2x15 ml), dried (MgSO₄) and the solvent removed in vacuo. The residue was chromatographed (DCM/petrol 50-100%) to give the sulfonylamide 88.
Experimental

(1.9 g, 95%) as white needles, m.p. 107-108 °C (DCM/petrol); $v_{\text{max}}$(film)/cm$^{-1}$ 3328, 1602, 1583, 1469, 1334 (S=O), 1157 (S=O); $\delta_{\text{H}}(270 \text{ MHz}; \text{CDCl}_3)$ 7.69 (1H, dd, J 1.5 and 8.0, H-3'), 7.29 (1H, dd, J 1.7 and 8.0, H-6'), 7.23 (1H, ddd, J 1.5, 7.6 and 8.0, H-5'), 6.96 (1H, bs, NH), 6.93 (2H, s, H-3 and H-5), 6.78 (1H, dt, J 1.7 and 8.0, H-4'), 2.64 (6H, s, C2-CH$_3$, C6-CH$_3$), 2.29 (3H, s, C4-CH$_3$).

Preparation of $N$-(2-iodophenyl)-$N$,2,4,6-tetramethylbenzenesulfonamide (89)$^4$

To a stirred suspension of NaH (60% dispersion in mineral oil; 0.25 g, 6.4 mmol) in THF (7.5 ml) at room temperature was added a solution of the sulfonamide 88 (1.3 g, 3.2 mmol) in THF (7.5 ml). Vigorous effervescence occurred. After 30 min methyl iodide (1.9 ml; 31 mmol) was added and the reaction mixture stirred for 43 hr at r.t.. Water was added (25 ml) and the solution extracted with DCM (2x20 ml), dried (MgSO$_4$), the solvent removed in vacuo and the residue purified by column chromatography (DCM/petrol 60-100%) to give the sulfonamide 89 (1.2 g, 87%) as white needles, m.p. 77-80 °C (DCM/petrol); $v_{\text{max}}$(film)/cm$^{-1}$ 2938, 1603, 1469, 1329, 1152; $\delta_{\text{H}}(270 \text{ MHz; CDCl}_3)$ 7.79 (1H, dd, J 1.5 and 8.0, H-3'), 7.53 (1H, dd, J 1.6 and 7.9, H-6'), 7.33 (1H, dt, J 1.5 and 7.3, H-5'), 6.98 (1H, ddd, J 1.6, 7.3 and 7.9, H-4'), 6.88 (2H, bs, H-3 and H-5), 3.28 (3H, s, NCH$_3$), 2.42 (6H, s, C2-CH$_3$ and C6-CH$_3$), 2.27 (3H, s, C4-CH$_3$).
Reaction of N-(2-iodophenyl)-N,2,4,6- tetramethylbenzenesulfonamide (89) with tri-n-butyltin hydride

To a stirred solution of the sulfonamide 89 (233 mg, 0.56 mmol) in benzene (12 ml) at reflux, was added a solution of tri-n-butyltin hydride (190 µl; 0.69 mmol) and AIBN (64 mg, 0.39 mmol) in benzene (3.9 ml) dropwise over 17 hr, via a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed in vacuo, the residue washed with sat. aq. KF (15 ml), extracted with ether (3x10 ml), dried (MgSO4) and the solvent removed under reduced pressure. The residue chromatographed (DCM/ petrol 20-50%) to give N,2',4',6'-tetramethyl-1,1'-biphenyl-2-amine (90)4 (82 mg; 65%) as white needles m.p. 46-48°C (Lit. 4 oil) νmax(film)/cm⁻¹ 3400 (bs), 2921, 1602, 1513, 1479, 1315 (S=O), 1166 (S=O); δH (270 MHz; CDCl3) 7.28 (1H, ddd, J 1.7 and 7.3, 8.0, H-4), 6.98 (2H, s, H-Tand H-5'), 6.89 (1H, dd, J 1.7 and 7.3, H-6), 6.78 (1H, dt, J 1.0 and 7.3, H-5), 6.71 (1H, dd, J 1.0 and 8.0, H-3), 3.32 (1H, bs, NH), 2.78 (3H, s, N-CH3), 2.35 (3H, s, C4'-CH3), 1.99 (6H, s, C2'-CH3 and C6'-CH3).
Preparation of (2-iodophenyl) 2,4,6-trimethylbenzenesulfonate (95)\textsuperscript{4}

To 2-iodophenol (1.1 g, 5.0 mmol) and DMAP (31 mg) was added a solution of 2,4,6-trimethylbenzenesulfonyl chloride (1.3 g, 6.0 mmol) in pyridine (10 ml). The mixture was left stirring overnight at r.t. Pyridine was removed \textit{in vacuo}, the residue dissolved in DCM (25 ml), washed with sat. aq. CuSO\textsubscript{4} (2x20 ml) and water (20 ml) dried (MgSO\textsubscript{4}) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 20%) to give the sulfonate 95 (1.7 g, 85%) as white prisms, m.p. 82-83 °C (DCM/petrol) (Lit.\textsuperscript{4} 81-82.5 °C); \textbf{\delta}\textsubscript{H}(270 MHz; CDCl\textsubscript{3}) 7.82 (1H, dd, \textit{J} 1.5 and 8.1, H-3'), 7.26 (1H, dt, \textit{J} 1.7 and 7.8, H-5'), 7.01 (2H, s, H-3 and H-5), 7.00-6.93 (2H, m, H-4' and H-6'), 2.61 (6H, s, C-2 CH\textsubscript{3} and C-6 CH\textsubscript{3}), 2.35 (3H, s, C-4 CH\textsubscript{3}); \textbf{m/z} 402 (M\textsuperscript{+}), 196, 183, 119 (100%).
Reaction of (2-iodophenyl) 2,4,6-trimethylbenzenesulfonate (95) with tri-n-butyltin hydride

To a stirred solution of the sulfonate 95 (357 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 μl, 1.17 mmol) and AIBN (104 mg; 0.63 mmol) in benzene (4.7 ml) dropwise over 11 hr, via a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed in vacuo, the residue dissolved in ethyl acetate (20 ml), sat. KF (15 ml) added and vigorous stirring continued for 2 hr. The suspension was filtered, the ethyl acetate layer washed with sat. KF (15 ml) and water (15 ml) dried (MgSO₄), and concentrated under reduced pressure. Preparative thin layer chromatography (DCM/petrol 75%) gave in order of elution the sulfonate 95 (118 mg, 33%) and 2',4',6'-trimethyl-1,1'-biphenyl-2-ol (96) (94 mg, 50%) as an oil; ν_max(film)/cm⁻¹ 3493 (OH), 2920; δ_H(270 MHz; CDCl₃) 7.27 (1H, m, H-3), 7.03-6.94 (5H, m, H-3', H-5', H-4, H-5 and H-6), 4.62 (1H, s, OH), 2.34 (3H, s, ArCH₃), 2.01 (6H, s, 2xArCH₃); δ_C(CDCl₃) 152.5 (1C, q), 138.1 (1C, q), 137.8 (1C, q), 131.6 (1C, q), 130.0 (1C, t), 128.9 (1C, t), 128.7 (1C, t), 126.4 (1C, q), 120.7 (1C, t), 115.1 (1C, t), 21.1 (1C, p), 20.2 (2C, p); m/z 215 (M⁺), 197 (100%), 182, 119; (Found: M⁺, 212.1209. C₁₅H₁₆O requires M, 212.1201).
Preparation of 2,5-dimethoxy-N-(2-iodophenyl)benzenesulfonamide (97)

To 2-iodoaniline (0.7 g, 3.11 mmol) and DMAP (20 mg, 0.2 mmol) was added a solution of the 2,5-dimethoxybenzenesulfonyl chloride (1.1 g, 4.4 mmol) in pyridine (7 ml), and the reaction mixture was stirred at r.t. for 3 days. Pyridine was removed in vacuo, the residue washed with sat. aq. CuSO₄, extracted with DCM, dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%) to give the sulfonamide 97 (1.0 g, 77%) as white needles, m.p. 117-117.5 °C (DCM/petrol); ν_max(film)/cm⁻¹ 3300 (NH), 2493, 1582, 1495, 1398, 1337 (S=O), 1159 (S=O), 1042, 912, 812, 745; δ_H(270 MHz; CDCl₃) 7.68 (1H, dd, J 1.5 and 7.8, H-3'), 7.57 (1H, dd, J 1.5 and 8.3, H-6'), 7.46 (1H, d, J 3.2, H-6), 7.36 (1H, bs, NH), 7.21 (1H, ddd, J 1.5, 7.8 and 8.3, H-5'), 7.04 (1H, dd, J 3.2 and 9.0, H-4), 6.88 (1H, d, J 9.0, H-3), 6.74 (1H, ddd, J 1.5, 7.8 and 8.3, H-4'), 3.92 (3H, s, OCH₃), 3.77 (3H, s, OCH₃); δ_C (CDCl₃) 152.9 (1C, q), 150.5 (1C, q), 139.3 (1C, t), 138.1 (1C, q), 129.4 (1C, t), 126.7 (1C, q), 125.7 (1C, t), 121.1 (1C, t), 119.6 (1C, t), 115.5 (1C, t), 113.3 (1C, t), 89.3 (1C, q, C-I), 56.7 (1C, p, OCH₃), 56.1 (1C, p, OCH₃); m/z 419 (M⁺, 100%), 218, 201, 137; (Found: M⁺, 418.9691. C₁₄H₁₄INO₄S requires M⁺, 418.9688).
Preparation of 2,5-dimethoxy-N-(2-iodophenyl)-N-methyl-benzenesulfonamide (98)

To a stirred suspension of NaH (60% dispersion in mineral oil; 177 mg, 4.4 mmol) in THF (4.5 ml) at room temperature was added a solution of the sulfonamide 97 (0.93 g, 2.2 mmol) in THF (4.5 ml). Vigorous effervescence occurred. After 30 min methyl iodide (1.2 ml, 19 mmol) was added and the reaction mixture stirred for 4 days. Water (20 ml) was added and the solution extracted with DCM (3x15 ml), dried (MgSO₄) and the solvent removed in vacuo. The residue was chromatographed (DCM/petrol 70-100%) to give the sulfonamide 98 (818 mg; 86%) as white needles, m.p. 122-123 °C (DCM/petrol); \( \nu_{max}(\text{film})/\text{cm}^{-1} \) 2358, 1495, 1340 (S=O), 1274, 1223, 1149 (S=O), 1036; \( \delta_H(270 \text{ MHz; CDCI}_3) \) 7.88 (1H, dd, J 1.7 and 7.8, H-3'), 7.28 (1H, d, J 2.9, H-6), 7.23 (1H, dt, J 1.2 and 7.8, H-5'), 7.07 (1H, dd, J 3.1 and 9.0, H-4), 7.02-6.96 (3H, m, H-3, H-4' and H-6'), 3.91 (3H, s, OCH₃), 3.71 (3H, s, OCH₃), 3.39 (3H, s, NCH₃); \( m/z \) 433 (M⁺), 306 (M⁺+1), 232, 201, 137, 105 (100%); (Found: M⁺, 432.9854. C₁₅H₁₆INO₄S requires M, 432.9845).
Reaction of 2,5-dimethoxy-N-(2-iodophenyl)-N-methyl-benzenesulfonamide (98) with tri-n-butyltin hydride

To a stirred solution of the sulfonamide 98 (293 mg, 0.68 mmol) in benzene (13.5 ml) at reflux, was added a solution of tri-n-butyltin hydride (242 µl, 0.88 mmol) and AIBN (82 mg; 0.5 mmol) in benzene (3.5 ml) dropwise over 18 hr, via a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed in vacuo, the residue washed with sat. aq. KF (15 ml), extracted with ether (3x20 ml), dried (MgSO4) and the solvent removed under reduced pressure. The residue was chromatographed (DCM) to give in order of elution 2',5'-dimethoxy-N-methyl-1,1'-biphenyl-2-amine (101) (112 mg, 63%), and the sulfonamide 98 (77 mg; 26%).

2',5'-dimethoxy-N-methyl-1,1'-biphenyl-2-amine (101) as an oil; \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 3428 (NH), 2935, 1603, 1579, 1494, 1460, 1313, 1267, 1224, 1047, 807, 749; \( \delta_{\text{H}} \) (270 MHz; CDCl\(_3\)) 7.28 (1H, dt, J 1.7 and 7.6, H-3), 7.08 (1H, dd, J 1.7 and 7.6, H-5), 6.94 (1H, d, J 9.0, H-3'), 6.88 (1H, dd, J 2.7 and 9.0, H-4'), 6.82 (1H, d, J 2.7, H-6'), 6.80-6.71 (2H, m, H-4 and H-6), 3.78 (3H, s, OCH\(_3\)), 3.71 (3H, s, OCH\(_3\)), 2.81 (3H, s, NCH\(_3\)); \( m/z \) 243 (M\(^+\)), 212 (M\(^+\)-OMe, 100%), 197, 168. (Found: M\(^+\), 243.1261. C\(_{15}\)H\(_{17}\)NO\(_2\) requires M, 243.1259).
Preparation of 3,4-dimethoxy-N-(2-iodophenyl)-benzenesulfonamide (99)

![Chemical Structure](image)

To 2-iodoaniline (0.68 g, 3.1 mmol) and DMAP (20 mg, 0.2 mmol) was added a solution of 3,4-dimethoxybenzenesulfonyl chloride (1.1 g, 4.5 mmol) in pyridine (7 ml), and the reaction mixture stirred at r.t. for 24 hr. Pyridine was removed in vacuo, the residue dissolved in DCM (20 ml), washed with sat. aq. CuSO₄ (2 x 15 ml), water (15 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 60-100%) to give the sulfonamide 99 (878 mg; 67%) as white plates, m.p. 125-126°C (DCM/petrol); νmax(film)/cm⁻¹ 3300 (bs, NH), 2965 (CH), 1586, 1511, 1469, 1407, 1333 (S=O), 1262, 1156 (S=O); δH(400 MHz; CDCl₃) 7.66 (1H, dd, J 1.5 and 8.1, H-3'), 7.62 (1H, dd, J 1.4 and 8.0, H-6'), 7.35 (1H, dd, J 2.2 and 8.5, H-6), 7.29 (1H, m, H-5'), 7.07 (1H, d, J 2.2, H-2), 6.84-6.80 (1H, m, H-4'), 6.81 (1H, d, J 8.5, H-5), 6.74 (1H, bs, NH), 3.88 (3H, s, OCH₃), 3.76 (3H, s, OCH₃); δC(CDCl₃) 153.1 (1C, q), 149.0 (1C, q), 139.1 (1C, t), 137.7 (1C, q), 130.3 (1C, q), 129.5 (1C, t), 127.0 (1C, t), 122.9 (1C, t), 121.6 (1C, t), 110.4 (1C, t), 109.8 (1C, t), 92.9 (1C, q, C-I), 56.2 (2C, p, 2xOCH₃); m/z 419 (M⁺), 355 (M⁺-SO₂), 314 (M⁺-NHSO₂), 218, 201, 137; (Found: C, 39.9; H, 3.5; N, 3.2. C₁₄H₁₄INO₄S requires C, 40.1; H, 3.4; N, 3.3%).
Preparation of 3,4-dimethoxy-N-(2-iodophenyl)-N-methylbenzenesulfonamide (100)

To a stirred suspension of NaH (60% dispersion in mineral oil; 130 mg, 3.2 mmol) in THF (3.5 ml) at r.t. was added a solution of the sulfonamide 99 (0.68 g, 1.6 mmol) in THF (3.5 ml). Vigorous effervescence occurred. After 30 min methyl iodide (0.9 ml, 14 mmol) was added and the reaction mixture stirred for 24 hr. Water (25 ml) was added and the solution extracted with DCM (3x20 ml), dried (MgSO4), the solvent removed under reduced pressure. The residue was chromatographed (DCM) to give the sulfonamide 100 (703 mg, 99%) as white prisms; m.p. 170-171 °C (DCM/petrol); νmax(film)/cm⁻¹ 2926, 1587, 1510, 1462, 1349 (S=O), 1262, 1138 (S=O), 1021; δH(270 MHz; CDCl₃) 7.91 (1H, dd, 7.15 and 7.80, H-3'), 7.47 (1H, dd, J 2.2 and 8.3, H-6), 7.32-7.26 (2H, m, H-5' and H-2), 7.09-6.99 (2H, m, H-6' and H-4'), 6.95 (1H, d, J 8.3, H-5), 3.96 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 3.13 (3H, s, NCH₃); δC(CDCl₃) 152.7 (1C, q), 148.8 (1C, q), 143.7 (1C, q), 140.2 (1C, t), 130.0 (1C, q), 129.8 (1C, t), 128.9 (2C, t), 122.1 (1C, t), 110.8 (1C, t), 110.3 (1C, t), 101.6 (1C, q, C-I), 56.2 (1C, p, OCH₃), 56.1 (1C, p, OCH₃), 38.6 (1C, NCH₃); m/z 433 (M⁺), 306 (M⁺-I), 232, 201, 185 (100%), 137; (Found: M⁺, 432.9845. C₁₅H₁₆INO₄S requires M, 432.9845).
Reaction of 3,4-dimethoxy-N-(2-iodophenyl)-N-methylbenzenesulfonamide (100) with tri-n-butyltin hydride

To a stirred solution of the sulfonamide 100 (284 mg, 0.65 mmol) in benzene (13 ml) at reflux, was added a solution of tri-n-butyltin hydride (233 µl, 0.85 mmol) and AIBN (76 mg; 0.46 mmol) in benzene (3.4 ml) dropwise over 18 hr, via a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed in vacuo, the residue washed with sat. aq. KF (10 ml), extracted with ether (3x20 ml) and dried (MgSO4). The solvent was removed under reduced pressure and the residue chromatographed (DCM/petrol 75-100%, methanol/DCM 1%) to give in order of elution N-Methyl-3',4'-dimethoxy-5-iodo-1,1'-biphenyl-2-amine (102) (5 mg; 2.0%), an inseparable mixture (4:1; 68 mg) of 3',4'-dimethoxy-N-methyl-1,1'-biphenyl-2-amine (103, 33%) and dimethoxy-6-methyl-6H-dibenzo[c,e][1,2]thiazine-S,S-dioxide (104, 8%), which was resolved by HPLC, and the sulfonamide (100) (68 mg; 24%).

N-methyl-3',4'-dimethoxy-5-iodo-1,1'-biphenyl-2-amine (102) as yellow prisms, m.p. 110-112 °C; \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3450 (bs, NH), 2932, 1587, 1503, 1469, 1324, 1208, 1169, 1027; \( \delta_{\text{H}} \) (270 MHz; CDCl3) 7.49 (1H, dd, J 2.2 and 8.5, H-4), 7.35 (1H, dd, J 2.2 and 8.5, H-6), 6.95-6.86 (3H, m, H-2', H-5' and H-6'), 6.44 (1H, d, J 8.5, H-3), 3.92 (3H, s, OCH3), 3.88 (3H, s, OCH3), 2.76 (3H, s, NCH3); \( m/z \) 369 (M+, 100%), 241 (M+H), 226, 183.; FAB 368 (M+H); (Found: M+H, 368.0143. C15H15INO2 requires \( M \), 368.0148).
Experimental

3',4'-dimethoxy-N-methyl-1,1'-biphenyl-2-amine (103) as white prisms, m.p. 95-96 °C; v_max(film)/cm⁻¹ 3415 (NH), 2933 (CH), 1504, 1249, 1169; δ_H(400 MHz; CDCl₃) 7.25 (1H, dt, 1.6 and 8.1, H-4), 7.08 (1H, dd, 1.5 and 7.6, H-6), 6.94-6.91 (3H, m, H₂⁻, H₅⁻ and H₆⁻), 6.75 (1H, dt, J 1.1 and 7.5, H-5), 6.67 (1H, d, J 8.2, H-3), 4.00 (1H, bs, NH), 3.91 (3H, s, OCH₃), 3.87 (3H, s, OCH₃); 8_c(CDCl₃) 149.1 (1C, q), 148.1 (1C, q), 146.2 (1C, q), 131.9 (1C, q), 129.9 (1C, t), 128.6 (1C, t), 127.4 (1C, q), 121.4 (1C, t), 116.7 (1C, t), 112.6 (1C, t), 111.4 (1C, t), 109.8 (1C, t), 55.9 (2C, p, OCH₃), 30.8 (1C, p, NCH₃); m/z 243 (M⁺), 84 (100%), 86 (100%); (Found: M⁺, 243.1253. C₁₅H₁₇NO₂ requires M, 243.1259).

1,2-dimethoxy-6-methyl-6H-dibenzo[c,e][1,2]thiazine-S,S-dioxide (104) as a clear oil; v_max(film)/cm⁻¹ 2941 (CH), 1456, 1325 (S=O), 1264, 1147 (S=O); δ_H(400 MHz; CDCl₃) 8.61 (1H, dd, 1.5 and 7.9, H-10), 7.75 (1H, d, J 8.6, H-4), 7.46 (1H, dt, J 1.5 and 7.5, H-8 or H-9), 7.32-7.27 (2H, m, H-7 and H-8 or H-9), 7.08 (1H, d, J 8.7, H-3), 3.97 (3H, s, OCH₃), 3.71 (3H, s, OCH₃), 3.35 (3H, s, NCH₃); δ_C(CDCl₃) 156.6 (1C, q), 146.3 (1C, q), 139.5 (1C, q), 130.6 (1C, t), 129.9 (1C, t), 128.3 (1C, q), 126.0 (1C, q), 124.6 (1C, t), 122.6 (1C, q), 119.5 (1C, t), 119.4 (1C, t), 111.6 (1C, t), 60.4 (1C, p, OCH₃), 56.3 (1C, p, OCH₃), 32.8 (1C, p, NCH₃); m/z 305 (M⁺), 290 (M⁺-Me), 49 (100%); (Found: MH⁺, 306.0803. C₁₅H₁₆NO₄S requires MH, 306.0800).

Preparation of (2-iodophenyl) 2,5-dimethoxybenzenesulfonate (105)

To 2-iodophenol (1.1 g, 5.0 mmol) and DMAP (30 mg) was added a solution of 2,5-dimethoxybenzenesulfonyl chloride (1.3 g, 5.5 mmol) in pyridine (12 ml). The mixture was left under stirring for 2 days at r.t.. Pyridine was removed under reduced pressure the residue dissolved in DCM (25 ml), washed with sat. aq. CuSO₄ (2x25 ml) and water (20 ml), dried (MgSO₄) and the solvent removed under reduced pressure.
The residue was chromatographed (DCM/petrol 50-75%) to give the sulfonate 105 (1.9 g, 88%) as a white prisms, m.p. 74.5-75.5 °C; \( \nu_{\text{max (film)}} \text{ cm}^{-1} \) 2945 (CH), 1499, 1373 (S=O), 1170 (S=O), 886, 858, 705; \( \delta_H \) (270 MHz; CDCl\(_3\)) 7.76 (1H, dd, J 8.1 and 1.7, H-3'), 7.39 (1H, d, J 3.2, H-6), 7.27 (1H, ddd, J 1.5, 7.3 and 8.3, H-5'), 7.19-7.13 (2H, m, H-6' and H-4), 6.98 (1H, d, J 8.8, H-3), 6.94 (1H, dt, J 1.5 and 7.8, H-4'), 3.78 (3H, s, OCH\(_3\)), 3.74 (3H, s, OCH\(_3\)); \( \delta_C \) (CDCl\(_3\)) 152.6 (1C, q), 151.9 (1C, q), 150.6 (1C, q), 139.8 (1C, t), 129.2 (1C, t), 127.9 (1C, t), 124.5 (1C, q), 122.6 (1C, t), 122.4 (1C, t), 115.5 (1C, t), 114.0 (1C, t), 89.5 (1C, q, C-I), 56.5 (1C, p, OCH\(_3\)), 55.9 (1C, p, OCH\(_3\)); \( m/z \) 420 (M\(^+\)), 201, 137, 122, 107 (100%); (Found: C, 39.7; H, 2.9. C\(_{14}\)H\(_{13}\)IO\(_5\)S requires C, 40.0; H, 3.1%).

Reaction of (2-iodophenyl) 2,5-dimethoxybenzenesulfonate (105) with tri-n-butyltin hydride

\[
\begin{array}{c}
\text{I} & \text{OMe} \\
\text{OMe} & \text{OMe} \\
\text{S}_2 & \text{O}_2 \\
\end{array}
\quad \rightarrow \quad
\begin{array}{c}
\text{OMe} \\
\text{OMe} \\
\text{OH} \\
\end{array}
\quad +
\begin{array}{c}
\text{OMe} \\
\text{OMe} \\
\text{OMe} \\
\end{array}
\quad +
\begin{array}{c}
\text{OMe} \\
\text{OMe} \\
\text{OMe} \\
\end{array}
\quad +
\text{Starting Material}
\end{array}
\]

To a stirred solution of the sulfonate 105 (380 mg, 0.90 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 |xl, 1.17 mmol) and AIBN (107 mg, 0.65 mmol) in benzene (4.7 ml) dropwise over 11 hr, via a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to r.t., carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed in vacuo, the residue dissolved in DCM (20 ml), washed with sat. aq. KF (2x15 ml) and water (15 ml), dried (MgSO\(_4\)), concentrated in vacuo and the residue chromatographed (ether/petrol 30-100%) to give in order of elution 2',5'-dimethoxy-1,1'-biphenyl-2-ol (106) (90 mg, 43%), the sulfonate 105 (121 mg, 32%) and 1,4-dimethoxy-dibenz[c,e]oxathiine-S,S-dioxide (107) (17 mg, 7%).
Experimental

2',5'-dimethoxy-1',1'-biphenyl-2-ol (106) as an oil; νmax(film)/cm⁻¹ 3393 (OH), 2941 (CH), 1271, 1219; δH (400 MHz; CDCl₃) 7.33-7.28 (2H, m, H-4 and H-6), 7.06-7.01 (2H, m, H-3 and H-5), 7.00 (1H, d, J 8.7, H-3), 6.95-6.90 (2H, m, H-4' and H-6'), 6.54 (1H, bs, OH), 3.84 (3H, s, OCH₃), 3.81 (3H, s, OCH₃); δC(CDCl₃) 154.7 (1C, q), 153.7 (1C, q), 149.6 (1C, q), 131.1 (1C, t), 129.3 (1C, t), 128.3 (1C, q), 126.2 (1C, q), 121.0 (1C, t), 117.7 (1C, t), 117.6 (1C, t), 114.3 (1C, t), 113.4 (1C, t), 57.1 (1C, p, OCH₃), 55.7 (1C, p, OCH₃); m/z 230 (M⁺, 100%), 215, 200, 184; (Found: M⁺, 230.0943. C₁₄H₁₄O₃ requires M, 230.0943).

1,4-dimethoxy-dibenz[c,e]oxathiine-S,S-dioxide (107) as white prisms, m.p. 155-156 °C (DCM/petrol); νmax(film)/cm⁻¹ 2944 (CH), 1374 (S=O), 1257, 1175 (S=O); δH (270 MHz; CDCl₃) 8.48 (IH, dd, J 1.7 and 8.1, H-10), 7.44-7.27 (3H, m, H-7, H-8 and H-9), 7.24, (1H, d, J 9.3, H-2 or H-3), 7.05 (1H, d, J 9.3, H-2 or H-3), 3.97 (3H, s, OCH₃), 3.91 (3H, s, OCH₃); δC(CDCl₃) 150.6 (1C, q), 150.3 (1C, q), 148.2 (1C, q), 130.3 (1C, t), 129.9 (1C, t), 125.8 (1C, t), 123.1 (1C, q), 121.8 (1C, q), 120.4 (1C, q), 119.4 (1C, t), 117.9 (1C, t), 113.6 (1C, t), 57.2 (1C, p, OCH₃), 56.7 (1C, p, OCH₃); m/z 292 (M⁺, 100%), 277; (Found: M⁺, 292.0420. C₁₄H₁₂O₅S requires M, 292.0405).

Preparation of (2-iodophenyl) 3,4-dimethoxybenzenesulfonate (108)

To 2-iodophenol (1.1 g, 5.0 mmol) and DMAP (30 mg) was added a solution of 3,4-dimethoxybenzenesulfonyl chloride (1.5 g, 6.5 mmol) in pyridine (10 ml). The mixture was stirred overnight at r.t.. Pyridine was removed in vacuo, the residue dissolved in DCM (25 ml), washed with sat. aq. CuSO₄ (2x25 ml) and water (20 ml), dried (MgSO₄), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-75%) to give the sulfonate 108 (2.0 g, 96%) as white plates, m.p. 91-92 °C (DCM/petrol); νmax(film)/cm⁻¹ 2935 (CH), 1508, 1375 (S=O),
Experimental

1266, 1168 (S=O); δH (270 MHz; CDCl₃) 7.75 (1H, dd, J 1.0 and 7.6, H-3'), 7.51 (1H, dd, J 2.0 and 8.5, H-6), 7.35-7.32 (3H, m, H-2, H-5' and H-6'), 6.95-7.00 (1H, m, H-4'), 6.92 (1H, d, J 8.5, H-5), 3.95 (3H, s, OCH₃), 3.87 (3H, s, OCH₃); δC (CDCl₃) 154.1 (1C, q), 150.1 (1C, q), 149.1 (1C, q), 140.0 (1C, t), 129.4 (1C, t), 128.3 (1C, t), 126.9 (1C, q), 123.3 (1C, t), 123.0 (1C, t), 111.0 (1C, t), 110.4 (1C, t), 90.2 (1C, q, C-O), 56.3 (2C, p, 2xOCH₃); m/z 420 (M⁺), 201, 137 (100%); (Found: C, 39.7; H, 3.0. C₁₄H₁₃O₅S requires C, 40.0; H, 3.1).

Reaction of (2-iodophenyl) 3,4-dimethoxybenzenesulfonate (108) with tri-n-butyltin hydride

To a stirred solution of the sulfonate 108 (381 mg, 0.90 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 μl, 1.17 mmol) and AIBN (110 mg; 0.67 mmol) in benzene (4.7 ml) dropwise over 11 hr, via a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to r.t., carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (20 ml), washed with sat. aq. KF (2x15 ml) and water (15 ml), dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (DCM/petrol 60-100%) to give in order of elution 1,2-dimethoxy-dibenz[c,e]oxathiine-S,S-dioxide (109) (27 mg, 10%), 2,3-dimethoxy-dibenz[c,e]oxathiine-S,S-dioxide (110) (64 mg, 24%) and 3',4'-dimethoxy-1,1'-biphenyl-2-ol (111) (38 mg, 19%).
1,2-dimethoxy-dibenz[c,e]oxathiine-S,S-dioxide (109) as white prisms, m.p. 144.5-145.5 °C (DCM/petrol); $v_{\text{max}}$(film)/cm$^{-1}$ 2945 (CH), 1493, 1414, 1370 (S=O), 1183 (S=O); $\delta$H(270 MHz; CDCl$_3$) 8.62 (1H, dd, J 1.5 and 7.8, H-10), 7.75 (1H, d, J 8.5, H-4), 7.49-7.30 (3H, m, H-7, H-8 and H-9), 7.09 (1H, d, J 8.5, H-3), 3.99 (3H, s, OCH$_3$), 3.79 (3H, s, OCH$_3$); $m/z$ 292 (M+, 100%), 277; (Found: M+, 292.0414. C$_{14}$H$_{12}$O$_5$S requires M, 292.0405).

2,3-dimethoxy-dibenz[c,e]oxathiine-S,S-dioxide (110) as white needles, m.p. 218 °C (DCM/petrol); $v_{\text{max}}$(CHCl$_3$)/cm$^{-1}$ 2939 (CH), 2850, 1603, 1515, 1368 (S=O), 1170 (S=O), 1030, 861; $\delta$H(270 MHz; CDCl$_3$) 7.81 (1H, dd, J 1.7 and 7.6, H-10), 7.41-7.28 (5H, m, ArH), 4.03 (3H, s, OCH$_3$), 3.98 (3H, s, OCH$_3$); $\delta$C(CDCl$_3$) 153.3 (1C, q), 149.7 (1C, q), 149.4 (1C, q), 130.3 (1C, t), 126.4 (1C, t), 125.3 (1C, q), 124.5 (1C, t), 121.5 (1C, q), 119.9 (1C, t), 106.7 (1C, t), 106.0 (1C, t), 56.5 (1C, p, OCH$_3$), 56.4 (1C, p, OCH$_3$); $m/z$ 292 (M+, 100%), 277, 228 (M$^+$-SO$_2$); (Found: M$^+$, 292.0420. C$_{14}$H$_{12}$O$_5$S requires M, 292.0405).

3',4'-dimethoxy-1,1'-biphenyl-2-ol (111) as orange prisms, m.p. 121-122 °C (DCM/petrol); $v_{\text{max}}$(film)/cm$^{-1}$ 3439 (OH), 2935 (CH), 1268, 1220; $\delta$H(270 MHz; CDCl$_3$) 7.25-7.21 (2H, m, H-4 and H-6), 7.03-6.95 (5H, m, H-3, H-5, H-2', H-5' and H-6'), 5.4 (1H, bs, OH), 3.92 (3H, s, OCH$_3$), 3.89 (3H, s, OCH$_3$); $\delta$C(CDCl$_3$) 152.5 (1C, q), 149.5 (1C, q), 148.7 (1C, q), 130.0 (1C, t), 129.5 (1C, q), 128.8 (1C, t), 127.9 (1C, q), 121.1 (1C, t), 120.6 (1C, t), 115.6 (1C, t), 112.3 (1C, t), 111.7 (1C, t), 55.9 (2C, p, 2xOCH$_3$); $m/z$ 230 (M$^+$, 100%), 215; (Found: M$^+$, 230.0943. C$_{14}$H$_{14}$O$_3$ requires M, 230.0943).
Preparation of (2-iodophenyl)methyl 4-methoxyphenyl sulfide (112)

\[
\begin{align*}
\text{SH} & \quad + \quad \text{I} \quad \text{Cl} \\
\text{OMe} & \quad \rightarrow \\
\text{I} & \quad \text{S} \\
\text{OMe} & \quad \text{2} \\
\text{3'} & \quad \text{112}
\end{align*}
\]

To a stirred suspension of NaH (60% dispersion in mineral oil; 395 mg, 10 mmol) in THF (19 ml) at 0°C was added 4-methoxythiophenol (1.0 ml, 8.1 mmol). Vigorous effervescence occurred. After 30 min the mixture was allowed to warm to r.t., a solution of 2-iodobenzyl chloride (3.1 g, 12 mmol) in THF (10 ml) was added and the reaction mixture stirred for 24 hr. Water (20 ml) was added and the solution extracted with DCM (3 x 20 ml), dried (MgSO₄), the solvent removed \textit{in vacuo} and the residue chromatographed (DCM/petrol 5-50%) to give the sulfide \textbf{112} (2.7 g, 91%) as an oil; \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3056, 3001, 2936 (CH), 1590, 1492, 1285, 1172, 1012, 827; \( \delta_H(270 \text{ MHz; } \text{CDCl}_3) \) 7.38 (1H, dd, J 1.2 and 7.8, H-3'), 7.28 (2H, d, J 8.9, H-3 and H-5'), 7.18 (1H, dt, J 1.2 and 7.6, H-5'), 7.05 (1H, dd, J 1.7 and 7.6, H-6'), 6.90 (1H, dt, J 1.7 and 7.8, H-4'), 6.80 (2H, d, J 8.9, H-2 and H-6), 4.08 (2H, s, CH₂), 3.79 (3H, s, OCH₃); \( m/z \) 356 (M⁺), 217 (100%), 139, 90; (Found: C, 47.2; H, 3.5. C₁₄H₁₃IOS requires C, 47.2; H, 3.7%)
Preparation of (2-iodophenylmethyl)-(4-methoxyphenyl)sulfone (113)

To m-chloroperbenzoic acid (4.6 g, 27 mmol) was added a solution of the sulfide 112 (2.1 g, 6.0 mmol) in DCM (60 ml) at 0 °C. The mixture was allowed to warm to r.t. and left overnight. The mixture was washed with NaHCO₃ (50 ml) water (50 ml), dried (MgSO₄), the solvent removed in vacuo and the residue chromatographed (DCM) to give the sulfone 113 (383 mg, 17%) as white prisms, m.p. 134-136 °C (DCM/petrol), νmax(film)/cm⁻¹ 2927, 1595, 1495, 1321 (S=O), 1263, 1135 (S=O), 1015, 777; δH(270 MHz; CDCl₃) 7.73 (1H, dd, J 1.2 and 7.8, H-3'), 7.53 (2H, d, J 9.0, H-2 and H-6), 7.49 (1H, dd, J 1.7 and 7.6, H-6'), 7.35 (1H, dt, J 1.2 and 7.3, H-5'), 7.00 (1H, dt, J 1.7 and 7.8, H-4'), 6.90 (2H, d, J 9.0, H-3 and H-5), 4.56 (2H, s, CH₂), 3.85 (3H, s, OCH₃); δC(CDCl₃) 164.1 (1C, q), 139.8 (1C, t), 132.2 (2C, t and q), 131.2 (2C, t), 130.3 (1C, t), 129.8 (1C, q), 128.5 (1C, t), 114.2 (2C, t), 102.3 (1C, q, C-I), 66.3 (1C, s, CH₂), 55.7 (1C, p, OCH₃); m/z 388 (M⁺), 324 (M⁺-SO₂, 261, 217 (100%), 90; (Found: M⁺, 387.9621. C₁₄H₁₃IO₃S requires M, 387.9630).
Reaction of (2-iodophenylmethyl)-(4-methoxyphenyl)sulfone (113) with tri-n-butyltin hydride

To a stirred solution of the sulfone 113 (348 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 μl, 1.17 mmol) and AIBN (107 mg, 0.65 mmol) in benzene (4.7 ml) dropwise over 11 hr, via a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to r.t., carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed under reduced pressure, the residue dissolved in ethyl acetate (20 ml), washed with sat. aq. KF (2x15 ml) and water (15 ml) dried (MgSO₄), concentrated in vacuo and the residue chromatographed (ethyl acetate/petrol 15-100%), to give in order of elution 4-methoxy-2'-methyl-1,1'-biphenyl (114) (18 mg, 10%), 4-methoxyphenyl phenylmethylsulfone (115) (31 mg, 13%) and 2-methoxy-6H-dibenzo[b,d]thieine-S,S-dioxide (116) (105 mg, 45%).

4-methoxy-2'-methyl-1,1'-biphenyl (114) as an oil; νmax(film)/cm⁻¹ 2930 (CH), 1613, 1515, 1484, 1268, 1244, 1176, 1039, 834, 761; δH(270 MHz; CDCl₃) 7.19-7.28 (6H, m, H-2', H-3', H-4', H-5', H-2 and H-6), 6.97 (2H, d, J 8.8, H-3 and H-5), 3.86 (3H, s, OCH₃), 2.29 (3H, s, ArCH₃); δC(CDCI₃) 158.5 (1C, q), 141.5 (1C, q), 135.5 (1C, q), 134.4 (1C, q), 130.3 (1C, t), 130.2 (2C, t), 129.9 (1C, t), 126.9 (1C, t), 125.7 (1C, t), 113.5 (2C, t), 55.3 (1C, p, OCH₃), 20.5 (1C, p, CH₃); m/z 198 (M⁺, 100%), 183, 167.

4-methoxyphenyl phenylmethylsulfone (115) as white prisms m.p. 103-104 °C (DCM/petrol); νmax(film)/cm⁻¹ 2943 (CH), 1317 (S=O), 1296, 1149 (S=O), 1090, 837,
696; δ\(_H\) (270 MHz; CDCl\(_3\)) 7.52 (2H, d, J 9.0, H-2 and H-6), 7.31-7.22 (3H, m, H-3', H-4' and H-5'), 7.08 (2H, dd, J 1.7 and 7.8, H-2' and H-6'), 6.88 (2H, d, J 9.0, H-3 and H-5), 4.27 (2H, s, CH\(_2\)), 3.85 (3H, s, OCH\(_3\)); δ\(_C\)(CDCl\(_3\)) 163.7 (1C, q), 130.8 (t), 129.4 (1C, q), 128.6 (t), 128.5 (2C, t), 114.1 (1C, q), 114.0 (t), 63.1 (1C, s, CH\(_2\)), 55.6 (1C, p, OCH\(_3\)); m/z 262 (M\(^+\)), 198, 91 (100%); (Found: M\(^+\), 262.0664. C\(_{14}\)H\(_{14}\)O\(_3\)S requires M, 262.0664).

2-methoxy-6H-dibenzo[b,d]thiine-S,S-dioxide (116) as white plates, m.p. 168-169 °C (DCM/petrol); \(ν_{\text{max}}\) (film)/cm\(^{-1}\) 2969 (CH), 1595, 1562, 1306 (S=O), 1236, 1192, 1164 (S=O); δ\(_H\) (270 MHz; CDCl\(_3\)) 7.98 (1H, d, J 8.8, H-4), 7.80 (1H, d, J 7.6, H-10), 7.47 (1H, dt, J 1.5 and 7.6 H-8 ou H-9), 7.38 (1H, dt, J 1.5 and 7.6, H-8 ou H-9), 7.30 (2H, m, H-1 and H-7), 7.00 (1H, dd, J 2.4 and 8.8, H-3), 4.37 (2H, s, CH\(_2\)), 3.90 (3H, s, OCH\(_3\)); δ\(_C\)(CDCl\(_3\)) 163.5 (1C, q), 137.1 (1C, q), 131.0 (1C, q), 130.4 (1C, t), 129.5 (1C, t), 129.4 (1C, t), 128.4 (1C, q), 127.5 (1C, q), 126.2 (1C, t), 126.0 (1C, t), 113.4 (1C, t), 111.9 (1C, t), 22.9 (1C, s, CH\(_2\)), 21.6 (1C, p, CH\(_3\)); m/z 260 (M\(^+\), 100%), 196, 195, 181; (Found: M\(^+\), 260.0493. C\(_{14}\)H\(_{14}\)O requires M, 260.0507).

Preparation of \(N\)-(t-butoxycarbonyl)indoline (117)\(^6\)

\[
\begin{align*}
\text{H} & \quad \text{N} \\
\text{O} & \quad \text{Boc} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \quad \text{117}
\end{align*}
\]

To a solution of di-tert-butyl dicarbonate (18 g, 83 mmol) in THF (60 ml) was added a solution of indoline (8.1 g, 68 mmol) in THF (25 ml) and the mixture was left stirring at room temperature overnight. The solvent was removed under reduced pressure and the residue distilled twice by Kugelroh to give the indoline 117 (14 g, 92%) as white prisms, m.p. 47-48 °C (Lit.\(^6\) liquid); \(ν_{\text{max}}\) (film)/cm\(^{-1}\) 2981(CH), 1704 (C=O); δ\(_H\) (400 MHz; CDCl\(_3\)) 7.80 (1H, bs, H-7), 7.13-7.09 (2H, m, H-4 and H-6), 6.88 (1H, dt, J 0.9 and 8.3, H-5), 3.95-3.91 (2H, bs, H-2), 3.05 (2H, t, J 8.5, H-3), 1.50 (9H, s, C(CH\(_3\))\(_3\)); m/z 219 (M\(^+\)), 163, 146, 119.
Preparation of \( N-(t\text{-butoxycarbonyl})-7\text{-iodoindoline} \) (118)\(^6\)

\[
\text{[Diagram showing molecular structures of 117 and 118]}
\]

To a solution of indoline 117 (14 g, 63 mmol) and TMEDA (12.5 ml, 83 mmol) in ether (300 ml), under nitrogen, at \(-78^\circ\text{C}\) was added sec-BuLi in cyclohexane (1.3 M, 75.6 ml), dropwise. After stirring the mixture for 1 hr, a solution of iodine (16 g, 63 mmol) in ether (120 ml) was added and stirring continued for a further 45 min. The cooling bath was removed and after 1.5 hr at room temperature the mixture was quenched with aq. \(\text{NH}_4\text{Cl} \) (10%, 150 ml), extracted with ether (3x100 ml), washed with water (200 ml), brine (200 ml), dried (MgSO\(_4\)) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 40%) to give the iodooindoline 118 (16 g, 76%) as an oil; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2976, 1704 (C=O), 1366, 1333, 1245, 1157; \(\delta\)H (400 MHz; \(\text{CDCl}_3\)) 7.59 (1H, d, \(J = 7.9\), H-6), 7.13 (1H, d, \(J = 7.3\), H-4), 6.71 (1H, t, \(J = 7.5\), H-5), 4.07 (2H, t, \(J = 7.6\), H-2), 2.99 (2H, t, \(J = 7.6\), H-3), 1.54 (9H, s, C(CH\(_3\))\(_3\)); \(\delta\)C (CDCl\(_3\)) 153.0 (1C, q, C=O), 146.3 (1C, q, CN), 138.1 (1C, t), 136.6 (1C, q), 125.7 (1C, t), 124.1 (1C, t), 85.4 (1C, q, C-I), 81.5 (1C, q, C(CH\(_3\))\(_3\)), 51.4 (1C, s, NCH\(_2\)), 30.4 (1C, s, ArCH\(_2\)), 28.3 (3C, p, CH\(_3\)); \(m/z\) 345 (M\(^+\)), 290, 272 (M\(^+\) - tBuO), 245 (100%).
Preparation of 7-iodoindoline (119)

To a stirred solution of the iodoindoline 118 (13 g, 38 mmol) in DCM (30 ml) was added trifluoracetic acid (20 ml) and effervescence occurred. After 5.5 hr the mixture was neutralized with aq NaHCO₃ (10%), the organic layer washed with water (2x20 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (ether/petrol 10%) to give 7-iodoindoline (119) (7.7 g, 83%) as a clear oil; ν_{max} (film) cm⁻¹ 3374 (NH), 2947, 1602, 1458, 1251, 753; δH (400 MHz; CDCl₃) 7.35 (1H, dd, 7.09 and 8.0, H-6), 7.04 (1H, dd, J 1.1 and 7.2, H-4), 6.44 (1H, dd, J 7.3 and 7.9, H-5), 3.89 (1H, bs, NH), 3.62 (2H, t, J 8.5, NCH₂), 3.21 (2H, t, J 8.5, ArCH₂); δC (CDCl₃) 153.4 (1C, q), 135.5 (1C, t), 129.2 (1C, q), 124.2 (1C, t), 120.1 (1C, t), 75.1 (1C, q, C-I), 46.0 (1C, s, NCH₂), 31.3 (1C, s, ArCH₂); m/z 245 (M⁺, 100%), 117 (M⁺-HI), 91; (Found: M⁺, 244.9709. C₈H₇IN requires M⁺, 244.9702).

Preparation of methyl 2-(7-iodoindoline-N-sulfonyl)benzoate (120)

To 7-iodoindoline (119) (1.2 g, 5.1 mmol) and DMAP (59 mg) was added a solution of methyl 2-(chlorosulfonyl)benzoate (1.5 g, 6.2 mmol) in pyridine (10 ml)
and the mixture stirred at r.t. for 20 hr. The pyridine was removed under reduced pressure, the residue dissolved in DCM (50 ml), washed with a sat. solution of CuSO₄ (2x25 ml), water (30 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 80%) to give the sulfonamide 120 (1.2 g, 52%) as white prisms, m.p. 194-195 °C; νmax(filml/cm⁻1 2960 (CH), 1734 (C=O), 1361 (S=O), 1297, 1259, 1169 (S=O); δH(400 MHz; CDCl₃) 7.70 (1H, dd, J 0.9 and 7.9, H-6), 7.57 (1H, dt, J 1.2 and 7.5, H-4), 7.52 (1H, dd, J 0.9 and 8.1, H-3), 7.48 (1H, dd, J 1.2 and 7.5, H-6'), 7.40 (1H, dt, J 1.4 and 8.1, H-5), 7.09 (1H, dd, J 1.0 and 7.4, H-4'), 6.85 (1H, t, J 7.8, H-5'), 4.12 (2H, t, J 7.1, NCH₂), 3.93 (3H, s, CO₂CH₃), 2.52 (2H, t, J 7.1, ArCH₂); δC(CDCl₃) 168.4 (1C, q, C=O), 145.6 (1C, q), 139.4 (1C, q), 139.1 (1C, t), 135.9 (1C, q), 133.3 (1C, q), 133.0 (1C, t), 129.9 (1C, t), 129.5 (1C, t), 128.3 (2C, t), 124.6 (1C, t), 87.9 (1C, q, C-D), 53.3 (1C, p, OCH₃), 52.4 (1C, s), 30.6 (1C, s); m/z 443 (M⁺), 412 (M⁺-OMe), 199 (100%), 117 (100%); (Found: C, 43.2; H, 3.1; N, 3.0. C₁₆H₁₄INO₄S requires C, 43.35; H, 3.2; N, 3.2%).

Reaction of methyl 2-(7-iodoindoline-N-sulfonyl)benzoate (120) with tri-n-butyltin hydride

To a stirred solution of 120 (399 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (106 mg; 0.64 mmol) in benzene (4.7 ml) dropwise over 11 hr, via a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed in vacuo, the residue dissolved in ethyl acetate (20 ml), sat. aq. KF (15 ml) added and vigorous stirring continued for 2 hr. The suspension was filtered, the ethyl acetate layer washed with sat. aq. KF (15 ml) and water (15 ml), dried (MgSO₄), and concentrated under reduced pressure. The residue was chromatographed (ethyl acetate/petrol 6-20%,) to give in order of elution
methyl 2-[indolin-7-yl]benzoate (129) (29 mg, 13%), the sulfonamide 120 (39 mg, 10%) and methyl 4,5-dihydro-dibenzo[c,e]pyrro[1,2-b]thiazine-S,S-dioxide-7-carboxylate (130) (110 mg, 39%).

methyl 2-[indolin-7-yl]benzoate (129) as brown prisms, m.p. 78-79 °C (DCM/petrol); v_{max}(film)/cm^{-1} 3368 (NH), 2949, 1722 (C=O), 1454, 1305, 1121, 753; δ_{H} (400 MHz; CDCl3) 8.21 (1H, s, H-6), 7.95 (1H, d, J 7.9, H-4), 7.73 (1H, d, J 7.7, H-3), 7.47 (1H, t, J 7.7, H-5), 7.11 (1H, d, J 7.2, ArH), 7.08 (1H, d, J 7.6, ArH), 6.78 (1H, t, J 7.4, ArH), 3.91 (3H, s, CO_{2}CH_{3}), 3.53 (2H, t, J 8.3, H-2'), 3.08 (2H, t, J 8.3, H-2'); δ_{C} (CDCl3) 167.0 (1C, q, C=O), 148.9 (1C, q), 139.8 (1C, q), 132.4 (1C, t), 130.6 (1C, q), 129.9 (1C, q), 128.9 (1C, t), 128.8 (1C, t), 127.9 (1C, t), 127.3 (1C, t), 124.1 (1C, t), 121.8 (1C, q), 119.1 (1C, t), 52.2 (1C, p, OCH_{3}), 47.2 (1C, s, NCH_{2}), 29.9 (1C, s, ArCH_{2}); m/z 253 (M^{+}, 100%), 220, 193; (Found: M^{+}, 253.1103. C_{16}H_{15}NO_{2} requires M, 253.1103).

methyl 4,5-dihydro-dibenzo[c,e]pyrro[1,2-b]thiazine-S,S-dioxide-7-carboxylate (130) as white prisms, m.p. 194-196 °C (DCM/petrol); v_{max}(film)/cm^{-1} 2953, 1736 (C=O), 1324 (S=O), 1165 (S=O); δ_{H} (400 MHz; CDCl3) 8.02 (1H, dd, J 1.2 and 8.0, H-8), 7.70 (1H, t, J 7.9, H-9), 7.69 (1H, d, J 7.7, H-1), 7.60 (1H, dd, J 1.2 and 7.6, H-10), 7.28 (1H, d, J 7.4, H-3), 7.15 (1H, t, J 7.7, H-2), 4.25 (2H, t, J 8.5, NCH_{2}), 3.99 (3H, s, CO_{2}CH_{3}), 3.32 (2H, t, J 8.5, ArCH_{2}); δ_{C} (CDCl3) 167.5 (1C, q, C=O), 141.7 (1C, q), 133.6 (2C, q), 132.2 (1C, t), 131.1 (2C, q), 128.1 (1C, t), 126.7 (1C, t), 126.3 (1C, t), 124.2 (1C, t), 122.1 (1C, t), 117.9 (1C, q), 53.4 (1C, p, OCH_{3}), 44.9 (1C, s, NCH_{2}), 28.3 (1C, s, ArCH_{2}); m/z 315 (M^{+}), 199, 118, 117, 43 (100%); (Found: M^{+}, 315.0565. C_{16}H_{13}NO_{4}S requires M, 315.0565).
Preparation of N-(3-bromopropyl)saccharine (131)

To a stirred suspension of NaH (60% dispersion in mineral oil; 602 mg, 15 mmol) in DMF (15 ml) at room temperature was added a solution of saccharine (1.8 g, 10 mmol) in DMF (15 ml). Vigorous effervescence occurred. After 30 min, 1,3-dibromopropane (3.0 ml, 30 mmol) was added and the reaction mixture heated at 100 °C for 1 hr. The mixture was cooled and the solvent removed under reduced pressure. Water was added (40 ml), the solution extracted with DCM (3x20 ml), dried (MgSO4), and the solvent removed under reduced pressure. The residue was chromatographed (ethyl acetate/petrol 5-25%) to give N-(3-bromopropyl)saccharine (131) (1.8 g; 61%); as white plates, m.p. 87-90 °C (DCM/petrol); v_{max}(film)/cm^{-1} 2937, 1731 (C=O), 1594, 1463, 1334, 1181; δ_H(270 MHz; CDCl3) 7.80-8.09 (4H, m, ArH), 3.94 (2H, t, J 6.8, H-3'), 3.50 (2H, t, J 6.6, H-1'), 2.40 (2H, qt, J 6.6, H-2'); m/z 305 ([M+2]^+), 303 (M^+), 224 (M^+-Br), 196 (100%), 159, 104; (Found M^+, 304.9544. C_{10}H_{10}Br_{8}^{1}NO_{3}S requires M, 304.9524).

Reaction of N-(3-bromopropyl)saccharine (131) with tri-n-butyltin hydride

To a stirred solution of N-(3-bromopropyl)saccharine (131) (297 mg, 0.97 mmol) in benzene (20 ml) under reflux, was added a solution of tri-n-butyltin hydride (350 µl, 1.28 mmol) and AIBN (120 mg, 0.7 mmol) in benzene (5 ml), dropwise, over
11 hr, via a needle placed above the refluxing solution. After a further hour, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 1 hr. The solvent was removed in vacuo the residue dissolved in DCM (30 ml), washed with sat. aq. KF (3x20 ml) and water (20 ml), dried (MgSO4) and the solvent removed under reduced pressure. The residue was chromatographed (ethyl acetate/petrol 20%) to give N-propyl saccharine (132) (83 mg, 38%) as white plates, m.p. 69-72 °C; νmax(film)/cm⁻¹ 1731 (C=O), 1333 (S=O), 1184 (S=O); δH(270 MHz; CDCl3) 8.06 (1H, dd, J 1.7 and 6.4, H-7), 7.79-7.94 (3H, m, ArH), 3.75 (2H, t, J 7.6, H-1'), 1.89 (2H, q, J 7.6, H-2'), 1.02 (3H, t, J 7.6, CH3); m/z 225 (M+), 210, 196 (100%); (Found M+, 225.0460. C10H11NO3S requires M, 225.0460).

Preparation of N-(4-chlorobutyl)saccharine (133)

To a stirred suspension of NaH (60% dispersion in mineral oil; 600 mg, 15 mmol) in DMF (15 ml) at room temperature was added a solution of saccharine (1.8 g, 10 mmol) in DMF (15 ml). Vigorous effervescence occurred. After 30 min. 1-bromo-4-chlorobutane (2.8 ml, 24 mmol) was added and the reaction mixture heated at 110°C for 1 hr. The mixture was cooled and the solvent removed in vacuo. The residue was dissolved in DCM (50 ml), washed with water (3x20 ml), dried (MgSO4), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75-100%) to give N-(4-chlorobutyl)saccharine (133) (1.8 g, 66%) as white prisms, m.p. 63-64 °C; νmax(film)/cm⁻¹ 2944, 1730 (C=O), 1595, 1461, 1336 (S=O), 1183 (S=O); δH(270 MHz; CDCl3) 8.05 (1H, dd, J 1.7 and 5.9, H-7), 7.80-7.94 (3H, m, ArH), 3.82 (2H, t, J 6.8, H-1'), 3.59 (1H, t, J 6.1, H-4'), 3.46 (1H, t, J 6.1, H-4'), 1.56-2.08 (4H, m, H-2' and H-3'); m/z 273 (M+), 238, 196(100%);
Preparation of \(N\)-(4-iodobutyl)saccharine (134)

To sodium iodide (1.7 g, 11 mmol) was added a solution of \(N\)-(4-chlorobutyl)saccharine (133) (1.5 g, 5.5 mmol) in acetone (7 ml) and the mixture refluxed overnight. The mixture was then cooled and ether (6 ml) was added, filtered and the solvent removed under reduced pressure. The residue was dissolved in ether (6 ml), washed with NaOH (2%; 2x25 ml), water (25 ml), dried (MgSO\(_4\)) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75-100%) to give \(N\)-(4-iodobutyl)saccharine (134) (1.8 g, 90%) as white prisms, m.p. 65-67 °C (DCM/petrol); \(v_{\text{max}}\) (film)/cm\(^{-1}\) 2935, 1728 (C=O), 1460, 1333 (S=O), 1183 (S=O); \(\delta\)H(270 MHz; CDCl\(_3\)) 8.06 (1H, dd, \(J\) 1.7 and 6.3, H-7), 7.80-7.94 (3H, m, H-4, H-5 and H-6), 3.81 (2H, t, \(J\) 6.6, H-1'), 3.23 (2H, t, \(J\) 6.6, H-4'), 1.90-2.01 (4H, m, H-2' and H-3'); \(m/z\) 238 (M\(^+-1\)), 196 (100%), 184; (Found: C, 36.3; H, 3.3; N, 3.8. \(\text{C}_{11}\text{H}_{12}\text{INO}_{3}\text{S}\) requires C, 36.2; H, 3.3; N, 3.8%).

Reaction of \(N\)-(4-iodobutyl)saccharine (II-19) with tri-n-butyltin hydride

To a stirred solution of \(N\)-(4-iodobutyl)saccharine (134) (331 mg, 0.9 mmol) in benzene (18 ml) under reflux, was added a solution of tri-n-butyltin hydride (320 \(\mu\)l, 1.17 mmol) and AIBN (114 mg, 0.7 mmol) in benzene (4.7 ml), dropwise, over 11 hr,
via a needle placed above the refluxing solution. After a further hour, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 1 hr. The solvent was removed in vacuo and analysis of the \( \text{H} \) nmr spectrum of the crude mixture showed reduced product \( \text{N-butyl-saccharine} \) (135); \( \delta \text{H}(270 \text{ MHz}; \text{CDCl}_3) \) 8.05 (dd, \( J \) 1.7 and 7.3), 7.93-7.81 (m), 3.78 (t, \( J \) 7.5, N-CH\(_2\)).

**Preparation of \( \text{N-(5-chloropentyl)saccharine} \) (136)**

![Reaction Diagram]

To a stirred suspension of NaH (60% dispersion in mineral oil; 600 mg, 15 mmol) in DMF (12 ml) at room temperature was added a solution of saccharine (1.8 g, 10 mmol) in DMF (15 ml). Vigorous effervescence occurred. After 1 hr 1-bromo-5-chloropentane (3.3 ml, 25 mmol) was added and the reaction mixture heated at 100 °C for 2 hr. The mixture was cooled and the solvent removed in vacuo. The residue was dissolved in DCM (50 ml), washed with water (3x20 ml), dried (MgSO\(_4\)), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75-100%) to give \( \text{N-(5-chloropentyl)saccharine} \) (136) (1.7 g, 60%) as a clear oil; \( \nu \text{max(film)/cm}^{-1} \) 2940, 1731 (C=O), 1596, 1461, 1335 (S=O), 1183 (S=O); \( \delta \text{H}(270 \text{ MHz}; \text{CDCl}_3) \) 8.06 (1H, dd, \( J \) 1.7 and 6.3, H-7), 7.82-7.94 (3H, m, ArH), 3.79 (2H, t, \( J \) 7.5, H-1'), 3.54 (1H, t, \( J \) 6.6, H-5'), 3.41 (1H, t, J 6.6, H-5'), 1.96-1.82 (4H, m, H-2' and H-4'), 1.63-1.54 (2H, m, H-3'); \( m/z \) 287 (M\(^+\)), 252, 196 (100%), 184; (Found: MNH\(_4\)\(^+\), 305.0727. C\(_{12}\)H\(_{18}\)Cl\(_3\)N\(_2\)O\(_3\)S requires MNH\(_4\), 305.0727).
Preparation \(N-(5\text{-iodopentyl})\text{ saccharine} \) (137)

\[
\begin{align*}
\text{136} & \quad \text{137} \\
\end{align*}
\]

To sodium iodide (1.5 g, 10 mmol) was added a solution of \(N-(5\text{-chlorobutyl})\text{saccharine} \) (136) (1.4 g, 5 mmol) in acetone (5 ml) and the mixture refluxed overnight. The mixture was then cooled, ether (6 ml) was added, filtered and the solvent removed under reduced pressure. The residue was dissolved in ether (40 ml), washed with an aq. solution of NaOH (2%, 2x25 ml), water (25 ml), dried (MgSO\(_4\)) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75-100%) to give \(N-(5\text{-iodopentyl})\text{saccharine} \) (137) (1.7 g, 87%) as white prisms, m.p. 62-63 °C (DCM/petrol), \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2937, 1636 (C=O), 1334 (S=O), 1259, 1185 (S=O); \(\delta_H\) (270 MHz; CDCl\(_3\)) 8.05 (1H, m, H-7), 7.82-7.94 (3H, m, ArH), 3.78 (2H, m, H-1'), 3.20 (2H, m, H-5'), 1.94-1.82 (4H, m, H-2' and H-4'), 1.59-1.54 (2H, m, H-3'); \(m/z\) 252 (M+-I), 196, 184, 68 (100%); (FAB) 380 (MH\(^+\)); (Found: M\(^+\), 379.9813. C\(_{12}\)H\(_{15}\)INO\(_3\)S requires M, 379.9817).

Reaction of \(N-(5\text{-iodopentyl})\text{saccharine} \) (137) with tri-n-butyltin hydride

\[
\begin{align*}
\text{137} & \quad \text{138} \\
\end{align*}
\]

To a stirred solution of \(N-(5\text{-iodopentyl})\text{saccharine} \) (137) (343 mg, 0.9 mmol) in benzene (18 ml) under reflux, was added a solution of tri-n-butyltin hydride (310 \(\mu\)l, 1.13 mmol) and AIBN (107 mg, 0.65 mmol) in benzene (4.7 ml), dropwise, over 11 hr, via a needle placed above the refluxing solution. After a further hour, the reaction was
cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 1 hr. The solvent was removed in vacuo the residue dissolved in DCM (25 ml), washed with KF (3x20 ml), water (20 ml), dried (MgSO4) and the solvent removed under reduced pressure. Analysis of the 1H nmr spectrum of the crude mixture showed reduced product N-pentyl-saccharine (138); δH(270 MHz; CDCl3) 8.1 (dd, J 1.7 and 7.3), 8.0-7.8 (m), 3.8 (t, J 7.5, N-CH2).

Preparation of N-(6-chlorohexyl)saccharine (139)

To a stirred suspension of NaH (60% dispersion in mineral oil; 600 mg, 15 mmol) in DMF (13 ml) at room temperature was added a solution of saccharine (1.8 g, 10 mmol) in DMF (17 ml). Vigorous effervescence occurred. After 1 hr 1-bromo-6-chlorohexane (3.1 ml, 20 mmol) was added and the reaction mixture heated at 100 °C for 1.5 hr. The mixture was cooled and the solvent removed under reduced pressure. Water was added (50 ml) and the solution extracted with DCM (3x50 ml), dried (MgSO4), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 70-100%) to give N-(6-chlorohexyl)saccharine (139) (1.7 g, 55%) as white prisms, m.p. 61-63 °C (DCM/petrol); vmax(film)/cm⁻¹ 2938, 2862, 1730 (C=O), 1595, 1462, 1336 (S=O), 1184 (S=O); δH(270 MHz; CDCl3) 8.06 (1H, dd, J 6.4 and 1.7, H-7), 7.80-7.94 (3H, m, ArH), 3.78 (2H, t, J 7.3, H-1'), 3.53 (1H, t, J 6.6, H-6'), 3.40 (1H, t, J 6.6, H-6'), 1.92-1.74 (4H, m, H-2' and H-5'), 1.57-1.41 (4H, m, H-3' and H-4'); m/z 301 (M⁺), 266, 252, 238, 224, 210, 196 (100%), 184; (FAB) 304, 302 (MH⁺); (Found: MH⁺, 302.0614. C_{13}H_{17}Cl_{35}NO_{3}S requires MH, 302.0618).
Preparation of N-(6-iodohexyl)saccharine (140)

To sodium iodide (1.5 g, 10 mmol) was added a solution of N-(6-chlorohexyl)saccharine (139) (1.5 g, 5 mmol) in acetone (5.5 ml) and the mixture refluxed overnight. The mixture was then cooled, ether (6 ml) was added, filtered and the solvent removed under reduced pressure. The residue was dissolved in ether (40 ml), washed with an aq. solution of sodium thiosulphate (10%, 25 ml), water (25 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%) to give N-(6-iodohexyl)saccharine (140) (1.3 g, 69%) as white prisms, m.p. 70-73 °C; \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2935, 2859, 1731 (C=O), 1336 (S=O), 1184 (S=O); \( \delta_H \) (270 MHz; CDCl₃) 8.06 (1H, dd, \( J \) 6.4 and 1.7, H-7), 7.79-7.94 (3H, m, ArH), 3.53 (2H, t, \( J \) 6.6, H-1'), 3.18 (2H, t, \( J \) 6.8, H-6'), 1.92-1.77 (4H, m, H-2' and H-5'), 1.57-1.40 (4H, m, H-3' and H-4'); \( m/z \) (EI) 266 (M⁺-I), 196, 184, 82 (100%); FAB 394 (MH⁺); (Found: MH⁺, 393.9970. C₁₃H₁₇INO₃S requires MH⁺, 393.9974).

Reaction of N-(6-iodohexyl)saccharine (140) with tri-n-butyltin hydride

To a stirred solution of N-(6-iodohexyl)saccharine (140) (353 mg, 0.9 mmol) in benzene (18 ml) under reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (107 mg, 0.65 mmol) in benzene (4.7 ml), dropwise, over 11 hr,
via a needle placed above the refluxing solution. After a further hour, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 1 hr. The solvent was removed in vacuo the residue dissolved in DCM (25 ml), washed with sat. aq. KF (3x20 ml), water (20 ml), dried (MgSO4) and the solvent removed under reduced pressure. Analysis of the 1H nmr spectrum of the crude mixture showed reduced product (141) δH(270 MHz, CDCl3) 8.02 (dd, J 1.7 and 6.4), 7.90-7.76 (m), 3.74 (t, J 7.6, N-CH2); and traces of benzylic protons δ 2.48 (t).

Preparation of N-(10-bromodecyl)saccharine (142)

\[ \text{To a stirred suspension of NaH (60\% dispersion in mineral oil; 399 mg; 10 mmol in DMF (14 ml) at room temperature was added a solution of saccharine (1.8 g; 10 mmol) in DMF (15 ml). Vigorous effervescence occurred. After 1.5 hr 1,10-dibromodecane (4.6 ml; 20 mmol) was added and the reaction mixture heated at 100 °C for 2 hr. The mixture was cooled and the solvent removed in vacuo. Water was added (50 ml) and the solution extracted with DCM (3x50 ml), dried (MgSO4), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 25-100\%) to give N-(10-bromodecyl)saccharine (142) (2.7 g, 67\%) as white prisms, m.p. 41-42 °C (DCM/petrol); νmax(film)/\text{cm}^{-1} 3447, 2929, 2855, 1730 (C=O), 1336 (S=O), 1183 (S=O); δH (270 MHz; CDCl3) 8.07-7.81 (4H, m, ArH), 3.76 (2H, t, J 7.6, H-1'), 3.40 (2H, t, J 7.8, H-10'), 1.89-1.79 (4H, m, H-2' and H-9'), 1.43-1.23 (12H, m, H-3',H-4',H-5',H-6',H-7', and H-8'); m/z 322 (M+Br), 258, 184 (100\%); (Found: C, 50.7; H, 5.6; N, 3.3. C17H24BrNO3S requires C, 50.75; H, 6.0; N, 3.5).} \]
Reaction of N-(10'-bromodecyl)saccharine (142) with tri-n-butyltin hydride

To a stirred solution of N-(10'-bromodecyl)saccharine (142) (367 mg, 0.9 mmol) in benzene (18 ml) at reflux was added a solution of tri-n-butyltin hydride and AIBN (106 mg, 0.65 mmol) in benzene (4.7 ml), dropwise, over 11 hr, via a needle placed above the refluxing solution. After a further hour, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 1 hr. The solvent was removed in vacuo the residue dissolved in ether (30 ml), washed with sat. aq. KF (3x20 ml) and water (20 ml), dried (MgSO4) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%) to give N-decyl-saccharine (143) (196 mg, 66%) as a clear oil; νmax(film)/cm⁻¹ 2925, 2855, 1737 (C=O), 1338 (S=O), 1184 (S=O); δH (400 MHz; CDCl₃) 8.03 (1H, dd, 7 1.3 and 7.0, H-7), 7.90 (1H, dd, J 1.7 and 7.0, H-4), 7.86-7.78 (2H, m, H-5 and H-6), 3.74 (2H, t, J 7.7, H-1'), 1.85 (2H, qt, J 7.6, H-2'), 1.42-1.24 (14H, 7xCH₂), 0.85 (3H, t, J 7.0, CH₃); ²C (CDCl₃) 158.9 (1C, q, C=O), 137.7 (1C, q), 134.6 (1C, t), 134.2 (1C, t), 127.4 (1C, q), 125.1 (1C, t), 120.9 (1C, t), 39.5 (1C, s), 31.8 (1C, s), 29.5 (1C, s), 29.4 (1C, s), 29.2 (1C, s), 29.0 (1C, s), 28.4 (1C, s), 26.8 (1C, s), 22.7 (1C, s), 14.1 (1C, p, CH₃); m/z 323 (M⁺), 196 (100%), 184 (100%), 133 (100%); (Found MNH₄⁺, 341.1899. C₁₇H₂₉N₂O₃S requires MNH₄, 341.1899).
Preparation of 2,3-dihydro-1,2-benzisothiazole-1,1-dioxide (144)\(^8,9\)

![Chemical Structure](image)

A mixture of saccharine (35 g, 0.2 mol) and phosphorous pentachloride (70 g; 0.3 mol), was heated at 175-180° C for 90 min; at the end of this period the evolution of HCl had ceased. POCI\(_3\) was removed by distillation, the residue poured onto ice (100 ml), extracted with DCM (3x100 ml), dried (MgSO\(_4\)) and the solvent removed under reduced pressure to give \textit{pseudosaccharine chloride}, which was used without further purification.

![Chemical Structure](image)

Sodium borohydride (4.1 g, 108 mmol) was added in small portions to a solution of pseudosaccharine chloride (II-11) (5.0 g, 27 mmol) in THF (100 ml) at 0 °C. After stirring the mixture for 24 hr at r.t., water (15 ml) was added while cooling, the solvent was removed \textit{in vacuo} and the mixture was further hydrolysed with HCl (4 N) until pH 4. The aqueous layer was extracted with DCM (3x75 ml), combined organic layers were dried (MgSO\(_4\)) and the solvent removed under reduced pressure to give \textit{2,3-dihydro-1,2-benzisothiazole-1,1-dioxide} (II-12) as white plates, m.p. 110-112 °C (DCM/petrol) (Lit.\(^9\); 110-112 °C); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3267 (NH), 1288 (S=O), 1164 (S=O); \(\delta_H\) (270 MHz; CDCl\(_3\)) 7.82 (1H, d, 7.76, H-7), 7.63 (1H, t, 7.76, H-5), 7.54 (1H, t, 7.76, H-6), 7.41 (1H, t, 7.6, H-4), 4.70 (1H, bs, NH), 4.55 (2H, d, 4.2, CH\(_2\)); \(m/z\) 169 (M\(^+\), 100%), 168, 104.
Preparation of 2-(10-bromodecyl)-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide (145)

To a stirred suspension of NaH (60% dispersion in mineral oil; 46 mg, 2.4 mmol) in DMF (2.5 ml) at room temperature was added a solution of 2,3-dihydro-1,2-benzisothiazole-1,1-dioxide (144) (336 mg, 2.0 mmol) in DMF (3 ml). Vigorous effervescence occurred. After 30 min 1,10-dibromodecane (0.7 ml, 3.1 mmol) was added and the reaction mixture heated at 100 °C for 2 hr. The mixture was then cooled and the solvent removed under reduced pressure. Water was added (15 ml) and the solution extracted with DCM (3 x 10 ml), dried (MgSO4), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%) to give 2-(10-bromodecyl)-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide (145) (426 mg, 55%) as a clear oil; νmax(film)/cm⁻¹ 2930, 2854, 1296 (S=O), 1171 (S=O); δH(270 MHz; CDCl3) 7.81 (1H, d, J 7.3, H-7), 7.49-7.62 (2H, m, H-5 and H-6), 7.38 (1H, d, J 7.6, H-4), 4.35 (2H, s, NCH2), 3.40 (2H, t, J 6.8, H-1' or H-10'), 3.28 (2H, t, J 7.6, H-1' or H-10'), 1.90-1.68 (4H, m, H-2' and H-9'), 1.55-1.25 (12H, m, H-3' to H-8'); m/z (FAB) 390, 388 (MH⁺); (Found: MH⁺, 388.0942. C17H27Br79NO2S requires MH, 388.0946).
Reaction of 2-(10-bromodecyl)-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide (145) with tri-n-butyltin hydride

To a stirred solution of 2-(10-bromodecyl)-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide (145) (273 mg, 0.7 mmol) in benzene (14 ml) at reflux was added a solution of tri-n-butyltin hydride (250 µL, 0.9 mmol) and AIBN (84 mg, 0.5 mmol) in benzene (3.6 ml), dropwise, over 11 hr, via a needle placed above the refluxing solution. After a further hour, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 1 hr. The solvent was removed in vacuo and analysis of the 1H nmr spectrum showed peaks corresponding to the reduced product 146 at δH (270 MHz, CDCl3) 7.80 (d), 7.62-7.45 (m), 7.38 (d), 4.35 (s), 3.28 (t).

Preparation of N-methyl-p-toluenesulfonamide (150)

To a suspension of p-toluenesulfonyl chloride (1.9 g, 10 mmol) in aq. NaOH (10%, 14 ml) was added methylvamine (25-30% in water, 2.8 ml) and the mixture stirred vigorously for 23 hr. The reaction mixture was diluted with water (20 ml), extracted with DCM (3x25 ml), dried (MgSO4) and the solvent removed under reduced pressure, to give the sulfonamide 150 (1.5 g, 83%) as white prisms, m.p. 79-80 °C (DCM/petrol);
Experimental 168

\[ \nu_{\text{max}} \text{ (film)/cm}^{-1} = 3294 \text{ (NH), } 1319 \text{ (S=O), } 1157 \text{ (S=O); } \delta_H \text{ (270 MHz; CDCl}_3\text{) 7.75 (2H, d, } J = 8.3, \text{ H-2 and H-6), 7.32 (2H, d, } J = 8.3, \text{ H-3 and H-5), 4.37 (1H, bs, NH), 2.64 (3H, d, } J = 5.4, \text{ NCH}_3\text{), 2.43 (3H, s, ArCH}_3\text{); } m/z \text{ 185 (M}^+\text{), 155, 139, 91 (100%).} \]

Preparation of \( N\)-(2-bromoethyl)-\( N\)-methyl-p-toluenesulfonamide (151)

\[
\begin{align*}
\text{O}_2\text{S}^- & \text{NHMe} \\
\text{O}_2\text{S}^- & \text{N} \\
\text{Me} & \\
\text{Br} & \\
\text{Br} & \\
\end{align*}
\]

To a suspension of NaH (60\% dispersion in mineral oil; 725 mg, 18 mmol) in DMF (20 ml) was added a solution of the sulfonamide 150 (2.8 g, 15 mmol) in DMF (30 ml). The mixture was left for 1 hr and then 1,2-dibromoethane (3.9 ml, 45 mmol) was added. After 2 hr at 95 °C another portion of 1,2-dibromoethane (2 ml, 23 mmol) was added and the reaction kept at 95 °C for 20 hr. The solvent was removed under reduced pressure, the mixture dissolved in DCM (30 ml), washed with water (3x20 ml), dried (MgSO\textsubscript{4}), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 60-100\%) to give sulfonamide 151 (1.2 g, 28\%) as white prisms, m.p. 75-76 °C (DCM/petrol); \( \nu_{\text{max}} \text{ (film)/cm}^{-1} = 3029, 2978, 2926, 1597, 1462, 1315 \text{ (S=O), 1157 \text{ (S=O); } \delta_H \text{ (270 MHz; CDCl}_3\text{) 7.68 (2H, d, } J = 8.3, \text{ H-2 and H-6), 7.33 (2H, d, } J = 8.6, \text{ H-3 and H-5), 3.50-3.35 (2H, m, H-1'} & \text{ and H-2'), 2.83 (3H, s, NCH}_3\text{), 2.43 (3H, s, ArCH}_3\text{); } \delta_C \text{ (CDCl}_3\text{) 143.7 (1C, q), 134.6 (1C, q), 129.8 (2C, t), 127.3 (2C, t), 51.8 (1C, s, H-1'), 36.0 (1C, p, NCH}_3\text{), 28.9 (1C, s, H-2'), 21.5 (1C, p, ArCH}_3\text{); } m/z \text{ 293, 291 (M}^+\text{), 212, 198, 155, 91 (100%); (Found: C, 41.2; H, 4.6; N, 4.65. C}_{10}H_{14}BrNO_2S \text{ requires C, 41.1; H, 4.8; N, 4.8%)} \]
Reaction of \(N\)-(2-bromoethyl)-\(N\)-methyl-\(p\)-toluenesulfonamide (151) with tri-\(n\)-butyltin hydride

To a stirred solution of sulfonamide 151 (260 mg, 0.89 mmol) in benzene (18 ml) at reflux, was added a solution of tri-\(n\)-butyltin hydride (320 µl, 1.17 mmol) and AIBN (123 mg; 0.75 mmol) in benzene (4.7 ml) dropwise over 11 hr, via a needle placed directly above the refluxing solution. After further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed in vacuo, the residue dissolved in ethyl acetate (20 ml), sat. aq. KF (15 ml) was added, and left with strong stirring for 2 hr. The suspension was filtered, the organic layer washed with sat. aq. KF (15 ml) and water (15 ml) dried (MgSO₄), and concentrated under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%,) to give in order of elution sulfonamide 151 (13 mg, 5%), \(N\)-ethyl-\(N\)-methyl-\(p\)-toluenesulfonamide (152) (28 mg, 15%) and 3,4-dihydro-2,6-dimethyl-2\(H\)-benzo[e]thiazine-\(S,S\)-dioxide (153) (51 mg, 27%).

\(N\)-ethyl-\(N\)-methyl-\(p\)-toluenesulfonamide (152) as an oil; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2977, 1598, 1454, 1338 (S=O), 1159 (S=O); \(\delta\)\(\text{H}\) (270 MHz; CDCl₃) 7.66 (2H, dd, \(J\) 1.7 and 8.3, H-2 and H-6), 7.30 (2H, dd, \(J\) 0.7 and 8.5, H-3 and H-5), 3.07 (2H, \(J\) 7.3, CH₂), 2.71 (3H, s, NCH₃), 2.41 (3H, s, ArCH₃), 1.12 (3H, \(J\) 7.3, CH₂CH₃); \(\delta\)\(\text{C}\) (CDCl₃) 143.1 (1C, q), 129.8 (1C, q), 129.6 (2C, t), 127.3 (2C, t), 44.8 (1C, s), 33.9 (1C, p, NCH₃), 21.4 (1C, p, ArCH₃), 13.0 (1C, p, CH₂CH₃); \(m/z\) 213 (M⁺), 198, 155, 91 (100%); (Found: MNH₄⁺, 231.1167. C₁₀H₁₉N₂O₂S requires MNH₄⁺, 231.1167).

3,4-dihydro-2,6-dimethyl-2\(H\)-benzo[e]thiazine-\(S,S\)-dioxide (153) as white prisms, 68-71 °C (DCM/petrol); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2928, 1326 (S=O), 1171 (S=O), 1144, 719;
\( \delta_H \) (270 MHz; CDCl3) 7.71 (1H, d, \( J = 8.1 \), H-8), 7.18 (1H, dd, \( J = 0.7 \) and 8.1, H-7), 7.03 (1H, s, H-5), 3.84 (2H, t, \( J = 6.4 \), H-3), 2.97 (2H, t, \( J = 6.4 \), H-4), 2.86 (3H, s, NCH\(_3\)), 2.36 (3H, s, ArCH\(_3\)); \( \delta_C \) (CDCl3) 142.5 (1C, q), 134.7 (1C, q), 133.0 (1C, q), 129.7 (1C, t), 128.4 (1C, t), 125.0 (1C, t), 48.2 (1C, s, NCH\(_2\)), 35.1 (1C, p, NCH\(_3\)), 22.9 (1C, s, ArCH\(_2\)), 21.4 (1C, p, ArCH\(_3\)); m/z 211 (M\(^+\)), 146, 104 (100%); (Found: MNH\(_4^+\), 229.1010. C\(_{10}\)H\(_{17}\)N\(_2\)O\(_2\)S requires MNH\(_4^+\), 229.1010).

Preparation of 2-iodo-N-methyl benzamide (158)

\[
\begin{array}{c}
\text{CO}_2\text{H} \\
\text{NHMe} \\
\text{I} \\
\text{I}
\end{array}
\rightarrow
\begin{array}{c}
\text{O} \\
\text{NHMe} \\
\text{I} \\
\text{158}
\end{array}
\]

To a stirred solution of 2-iodobenzoic acid (5.0 g, 20 mmol) in diethyl ether (20 ml) was added oxalyl chloride (4.4 ml, 50 mmol). Upon cooling to 0 °C, one drop of DMF was added which was accompanied by a vigorous effervescence. After 90 min, the solvent was removed under reduced pressure. Aqueous NaOH (10%, 25 ml) was then added, followed by a 25-30% solution of methylamine in water (5.2 ml). After stirring vigorously for 4 hr, the resulting solid was filtered off, washed with water, dissolved in DCM and dried (MgSO\(_4\)). The solvent was removed under reduced pressure to give the benzamide 158 (4.3 g, 82 %) as white prisms, m.p. 150-150.5 °C (DCM/petrol); \( \delta_H \) (270 MHz; CDCl3) 7.81 (1H, dd, 1.5 and 7.8, H-3), 7.34-7.30 (2H, m, H-5 and H-6), 7.06 (1H, m, H-4), 5.99 (1H, bs, NH), 2.96 (3H, d, \( J = 4.9 \), NCH\(_3\)).
Preparation of \(N-[(2,5\text{-dimethoxyphenyl})\text{sulfonyl}]-2\text{-iodo-}N\text{-methylbenzamide}\) (159)

\[
\begin{align*}
\text{I} & \quad \text{NHMe} \\
\text{O} & \\
\text{158} & \quad \rightarrow \\
\text{O} & \\
\text{S} & \\
\text{Me} & \\
\text{159} & \\
\end{align*}
\]

To a suspension of NaH (60% dispersion in oil; 614 mg, 15 mmol) in THF (5 ml) was added a solution of the benzamide 158 (2.0 g, 7.7 mmol) in THF (20 ml). Slow effervescence occurred. The solution was stirred at room temperature for 3 hr. A solution of 2,5-dimethoxybenzenesulfonyl chloride (2.2 g, 9.2 mmol) in THF (10 ml) was then added and the resulting mixture was stirred for 25 hr. Water (20 ml) was added and the mixture extracted with DCM (3x20 ml), dried (MgSO\(_4\)) and the solvent removed in vacuo. The residue was chromatographed (DCM/petrol 75-100%) to give the benzamide 159 (3.4 g, 96%) as white needles m.p. 136-138 °C (DCM/ether); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2954, 1691 (C=O), 1583, 1496, 1353 (S=O), 1276, 1225, 1166 (S=O); \(\delta_{\text{H}}\) (270 MHz; CDCl\(_3\)) 7.71 (1H, dd, \(J = 0.7\) and 7.8, H-3), 7.32 (1H, dt, \(J = 1.0\) and 7.5, H-4 or H-5), 7.14-7.01 (4H, m, H-4 or H-5 and H-6, H-4' and H-6'), 6.96 (1H, d, \(J = 9.5\), H-3'), 3.95 (3H, s, OCH\(_3\)), 3.69 (3H, s, OCH\(_3\)), 3.42 (3H, s, N-CH\(_3\)); \(\delta_{\text{C}}\) (CDCl\(_3\)) 169.7 (1C, q, C=O), 152.7 (1C, q), 151.3 (1C, q), 140.9 (1C, q), 139.0 (1C, q), 130.7 (1C, t), 128.0 (1C, t), 127.4 (1C, t), 126.8 (1C, q), 122.5 (1C, t), 114.9 (1C, t), 113.6 (1C, t), 92.3 (1C, q, C-2), 56.7 (1C, p, OCH\(_3\)), 55.8 (1C, p, OCH\(_3\)), 34.3 (1C, p, NCH\(_3\)); \(m/z\) 461(M\(^+\)), 397 (M\(^+\)-SO\(_2\)), 366, 334, 244 (100%), 231, 203; (Found: M\(^+\), 460.9805. C\(_{16}\)H\(_{16}\)INO\(_5\)S requires \(M\), 460.9794).
Reaction of \(N-[\text{(2,5-dimethoxyphenyl)sulfonyl}]-2\text{-ido-}N\text{-methylbenzamide} \ (159)\) with tri-n-butyltin hydride

To a stirred solution of the benzamide 159 (410 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (310 µl, 1.13 mmol) and AIBN (104 mg, 0.6 mmol) in benzene (4.5 ml), dropwise, over 11 hr, \(\text{via a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed \textit{in vacuo}, the residue dissolved in DCM (40 ml), washed with sat. aq. KF (3x25 ml) and water (30 ml), dried (MgSO}_4\), concentrated \textit{in vacuo} and the residue chromatographed (ethyl acetate/petrol 10-40%) to give, in order of elution, the benzamide 159 (57 mg, 14%) and \(N\text{-methyl benzamide} \ (160)^{11} \ (20 \text{ mg, 17%})\), as white needles, m.p. 75-76 °C (Lit.\(^{11a} \ 82 \degree \text{C}); \nu_{\text{max}} \text{(film)/cm}^{-1} \ 3320 \ (\text{NH}), 2938, 1643 \ (\text{C}=\text{O}), 1549, 1310, 694; \delta \text{H} \text{(270 MHz; CDCl}_3\)} \ 7.76 \ (2\text{H, dd, } J \ 1.7 \text{ and } 8.1, \text{ H-2 and H-6}), 7.48-7.38 \ (3\text{H, m, H-3, H-4 and H-5}), 6.23 \ (1\text{H, bs, NH}), 3.00 \ (3\text{H, d, } J \ 4.9, \text{ NCH}_3); \delta \text{C} \text{(CDCl}_3\)} \ 168.2 \ (1\text{C, q, C}=\text{O}), 134.6 \ (1\text{C, q, C-1}), 131.3 \ (1\text{C, t, C-4}), 128.5 \ (2\text{C, t, C-2 and C-6}), 126.8 \ (2\text{C, t, C-3 and C-5}), 26.8 \ (1\text{C, p, CH}_3); \text{m/z} \ 135 \ (\text{M}^+), 105 \ (100\%), 77.
Preparation of \(N-[(3,4\text{-dimethoxyphenyl})\text{sulfonyl}]\)-2-iodo-\(N\)-methylbenzamide (161)

\[
\begin{align*}
\text{O} & \text{C} & \text{NHMe} \\
I & \text{SO}_2\text{Cl} & \\
\text{Me} & & \\
158 & \rightarrow & 161 \\
\text{Me} & & \\
\end{align*}
\]

To a suspension of NaH (60% dispersion in oil; 614 mg) in THF (5 ml), was added a solution of the benzamide 158 (2.0 g; 7.7 mmol) in THF (20 ml). Slow effervescence occurred. The solution was stirred at room temperature for 3 hr. A solution of 3,4-dimethoxybenzenesulfonyl chloride (2.2 g) in THF (6 ml) was then added and the resulting mixture was stirred for 25 hr. Water was added and the mixture extracted with DCM (3x20 ml) dried (MgSO4) and the solvent removed in vacuo. The product was chromatographed (DCM/petrol 75-100%) to give the benzamide 161 (3.4 g, 95%) as white prisms, m.p. 119-120 °C (DCM/ether); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2933, 1689 (C=O), 1508, 1363 (S=O), 1265, 1167 (S=O); \(\delta_{\text{H}}\) (270 MHz; CDCl3) 7.79 (1H, d, J 7.8, H-3), 7.60 (1H, dd, J 2.2 and 8.5, H-6\(^{-}\)), 7.45 (1H, d, J 2.2, H-2\(^{-}\)), 7.40 (1H, t, J 7.8, H-5), 7.24 (1H, dd, J 1.7 and 7.8, H-6), 7.11 (1H, dt, J 1.7 and 7.8, H-4), 6.95 (1H, d, J 8.5, H-5\(^{\prime}\)), 3.96 (3H, s, OCH\(_3\)), 3.93 (3H, s, OCH\(_3\)), 3.26 (3H, s, NCH\(_3\)); \(\delta_{\text{C}}\) (CDCl3) 168.5 (1C, q, C=O), 153.7 (1C, q), 148.8 (1C, q), 141.3 (1C, q), 139.2 (1C, t), 131.0 (1C, t), 129.5 (1C, q), 128.0 (1C, t), 127.5 (1C, t), 122.9 (1C, t), 111.3 (1C, t), 110.3 (1C, t), 91.6 (1C, q, C-2), 56.3 (1C, p, OCH\(_3\)), 56.2 (1C, p, OCH\(_3\)), 34.3 (1C, p, NCH\(_3\)); \(m/z\) 461 (M\(^{+}\)), 431, 397 (M\(^{+}\)-SO\(_2\)), 244 (100%), 231 (100%); (Found: M\(^{+}\), 460.9769. C\(_{16}\)H\(_{16}\)INO\(_5\)S requires \(M\), 460.9794).
Experimental

Reaction of \(N\)-[(3,4-dimethoxyphenyl)sulfonyl]-2-iodo-\(N\)-methylbenzamide (161) with tri-n-butyltin hydride

To a stirred solution of the benzamide 161 (409 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (310 \(\mu\)l, 1.13 mmol) and AIBN (103 mg, 0.6 mmol) in benzene (4.5 ml), dropwise, over 11 hr, via a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed \textit{in vacuo} the residue dissolved in DCM (40 ml), washed with sat. aq. KF (3x25 ml) and water (30 ml), dried (MgSO\(_4\)), concentrated \textit{in vacuo} and the residue chromatographed (ethyl acetate/petrol 10-60%) to give, in order of elution the benzamide 161 (21 mg, 5%), \(N\)-(3,4-dimethoxyphenylmethyl) benzamide (162 (67 mg, 22%) and 2,3-dimethoxy-5-methylbenzo[c]quinoline-5H-6-one (163) (60 mg, 25%)

\(N\)-[(3,4-dimethoxyphenylsulfonyl)methyl]benzamide (162) as a foam; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3343, 3061, 2936, 1669 (C=O), 1508, 1320, 1263, 1130; \(\delta_\text{H}\) (400 MHz; CDCl\(_3\)) 7.66 (2H, d, J 7.2, H-2 and H-6), 7.49-7.54 (2H, m, H-4 and H-6'), 7.42 (2H, t, J 7.5, H-3 and H-5), 7.26 (1H, d, J 2.2, H-2'), 6.91 (2H, bd, J 8.4, H-5' and NH), 4.86 (2H, d, J 6.7, CH\(_2\)), 3.90 (3H, s, OCH\(_3\)), 3.74 (3H, s, OCH\(_3\)); \(\delta_\text{C}\) (CDCl\(_3\)) 166.4 (1C, q, C=O), 153.9 (1C, q), 149.2 (1C, q), 132.7 (1C, q), 132.4 (1C, t), 128.7 (2C, t), 128.2 (1C, q), 127.1 (2C, t), 123.0 (1C, t), 110.8 (2C, t), 61.0 (1C, s, CH\(_2\)), 56.2 (1C, p, OCH\(_3\)), 56.1 (1C, p, OCH\(_3\)); \(m/z\) (El) 270 (M-H\(^+\)), 239, 105 (100%); (Found: MH\(^+\), 272.1287. C\(_{16}\)H\(_{18}\)NO\(_3\) requires MH, 272.1287).

2,3-dimethoxy-5-methyl-5H-benzo[c]quinoline-6-one (163) as a clear oil; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2970, 1639 (C=O), 1528, 1493, 1256; \(\delta_\text{H}\) (270 MHz; CDCl\(_3\)) 8.45 (1H, dd, J 1.0 and 8.1, H-10), 7.98 (1H, d, J 8.3, H-7), 7.65 (1H, dt, J 1.2 and 8.3, H-8), 7.50
Experimental

(1H, s, H-4), 7.46 (1H, dt, J 1.0 and 8.1, H-5), 6.72 (1H, s, H-1), 3.96 (6H, s, 2xOCH₃),
3.70 (3H, s, NCH₃); δC (CDCl₃) 161.4 (1C, q, C=O), 150.6 (1C, q), 144.9 (1C, q),
133.3 (1C, q), 132.8 (1C, q), 132.1 (1C, t), 128.8 (1C, t), 126.7 (1C, t), 124.5 (1C, q),
120.8 (1C, t), 111.7 (1C, q), 105.1 (1C, t), 98.4 (1C, t), 56.2 (1C, p, OCH₃), 55.9 (1C, p, OCH₃),
29.9 (1C, p, NCH₃); m/z 269 (M⁺, 100%), 254, 226; (Found: M⁺, 269.1052. C₁₆H₁₅NO₃ requires M, 269.1052).

Preparation of 2-iodo-N-methyl-N-p-toluenesulfonyl benzamide (168)⁴

To a suspension of NaH (60% dispersion in oil; 228 mg) in THF (5 ml), was
added a solution of the benzamide 158 (771 mg; 2.95 mmol) in THF (10 ml). Slow
effervescence occurred. The solution was stirred at room temperature for 3 hr. A
solution of tosyl chloride (728 mg; 3.82 mmol) in THF (3 ml) was then added and the
resulting mixture was stirred for 25 hr. Water (20 ml) was added and the mixture
extracted with DCM (3x20 ml), dried (MgSO₄) and the solvent removed in vacuo. The
residue was chromatographed (DCM/petrol 75-100%) to give the benzamide 168 (1.1 g,
92%) as white prisms, m.p. 107-109 °C (DCM/petrol); δH (270 MHz; CDCl₃) 7.84
(2H, d, J 8.3, H-2' and H-6'), 7.77 (1H, dd, J 0.8 and 8.1, H-3), 7.40 (1H, dt, J 1.0 and
7.6, H-5), 7.33 (2H, d, J 8.5, H-3' and H-5'), 7.22 (1H, dd, J 1.6 and 7.7, H-6), 7.11 (1H, ddd, J 1.7, 7.5 and 7.9, H-4), 3.27 (3H, s, NCH₃), 2.45 (3H, s, ArCH₃); δC (CDCl₃)
169.4 (1C, q, C=O), 145.1 (1C, q), 141.2 (1C, q), 139.1 (1C, t), 135.1 (1C, q), 131.0
(1C, t), 129.4 (2C, t), 128.6 (2C, t), 128.0 (1C, t), 127.4 (1C, t), 91.5 (1C, q, C-2), 34.2
(1C, p, NCH₃), 21.6 (1C, p, ArCH₃).
Reaction of 2-iodo-N-methyl-N-p-toluenesulfonyl benzamide (168) with tri-n-butyltin hydride

To a stirred solution of the benzamide 168 (371 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (105 mg, 0.6 mmol) in benzene (4.7 ml), dropwise, over 11 hr, via a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed *in vacuo* the residue dissolved in ethyl acetate (15 ml), and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The product was chromatographed (ether/petrol 30 %) to give in order of elution the benzamide 168 (65 mg, 18%) and 3,5-dimethyl-5H-benzo[c]quinoline-6-one (169) (50 mg, 25%) as white needles, m.p. 112-114 °C (DCM/petrol); δ_H (270 MHz; CDCl₃) 8.54 (1H, dd, J 1.4 and 8.0, H-10), 8.24 (1H, d, J 8.2, H-1 or H-7), 8.17 (1H, d, J 8.2, H-1 or H-7), 7.74 (1H, ddd, J 1.4, 7.1 and 8.3, H-9), 7.55 (1H, ddd, J 1.0, 7.0 and 8.0, H-8), 7.23 (1H, s, Ar-H-4), 7.15 (1H, dd, J 1.1 and 8.2, H-2), 3.81 (3H, s, NCH₃), 2.52 (3H, s, ArCH₃); m/z (CI) 224 (MH⁺); (Found: C, 80.6; H, 5.95; N, 6.1. C₁₅H₁₃NO requires C, 80.2; H, 5.8; N, 6.2).
Preparation of N-(2-bromophenylmethyl)-N,4-dimethyl-benzenesulfonamide (170)

To a suspension of NaH (60% dispersion in oil; 242 mg) in THF (6 ml), was added a solution of the sulfonamide 150 (917 mg; 5.0 mmol) in THF (8 ml). Effervescence occurred and the mixture was stirred at room temperature for 2 hr. Then, 2-bromo benzyl bromide (2.4 g, 9.8 mmol) was added and the mixture stirred for 20 hr. Then, water (50 ml) was added and the mixture extracted with ether (3x30 ml) dried (MgSO₄) and the solvent removed under reduced pressure. The product was chromatographed (ether/petrol 50-100%) to give the sulfonamide 170 (1.6 g; 93%) as white prisms m.p. 81-82 °C (DCM/petrol); νmax (film)/cm⁻¹ 2923, 1339 (S=O), 1163 (S=O), 748; δH (270 MHz; CDCl₃) 7.75 (2H, d, J 8.3, H-2' and H-6'), 7.54 (1H, t, J 8.3, H-5), 7.38-7.30 (4H, m, H-3', H-5', H-3 and H-6), 7.15 (1H, t, J 8.1, H-4), 4.29 (2H, s, CH₂), 2.67 (3H, s, NCH₃), 2.46 (3H, s, ArCH₃); δC (CDCl₃) 146 (1C, q), 134.9 (1C, q), 134.3 (1C, q), 132.7 (1C, t), 129.8 (3C, t), 129.2 (1C, t), 127.8 (1C, t), 127.4 (2C, t), 123.4 (1C, q), 53.5 (1C, s), 35.0 (1C, p, NCH₃), 21.5 (1C, p, ArCH₃); m/z 355 (M⁺), 353, 274, 198, 91 (100%); (Found: M⁺, 355.0024. C₁₅H₁₆BrNO₂S requires M, 355.0065); (Found: C, 50.7; H, 4.9; N, 4.0. C₁₅H₁₆BrNO₂S requires C, 50.9; H, 4.55; N, 3.95).
Experimental 178

Preparation of 2,5-dimethoxy-N-methylbenzenesulfonamide (171)

To a suspension of 2,5-dimethoxybenzenesulfonyl chloride (2.0 g, 8.4 mmol) in aq. NaOH (10%, 16 ml) was added methylamine (25-30% in water, 2 ml) and the mixture stirred vigorously for 23 hr. The reaction mixture was diluted with water (20 ml) extracted with DCM (3x50 ml), dried (MgSO4) and evaporated under reduced pressure, to give the sulfonamide 171 (1.6 g, 82%) as white prisms, m.p. 112-113 °C (DCM/petrol); νmax (film)/cm⁻¹ 3322 (NH), 2949, 1497, 1323 (S=O), 1276, 1223, 1161 (S=O); δH (270 MHz; CDCl3) 7.45 (1H, d, J 2.2, H-6), 7.08 (1H, dd, J 2.2 and 9.0, H-4), 6.98 (1H, d, J 9.0, H-3), 4.82 (1H, bs, NH), 3.93 (3H, s, OCH3), 3.81 (3H, s, OCH3), 2.59 (3H, d, J 5.6, NCH3); δC (CDCl3) 153.4 (1C, q, C-5), 150.2 (1C, q, C-2), 126.7 (1C, q, C-1), 120.5 (1C, t, C-4), 115.1 (1C, t, C-3), 113.8 (1C, t, C-6), 57.1 (1C, p, OCH3), 56.0 (1C, p, OCH3), 29.6 (1C, p, NCH3); m/z 231 (M⁺, 100%), 202, 170; (Found: M⁺, 231.0554. C9H13NO4S requires M, 231.0565).
Preparation of \(N-(2\text{-bromophenylmethyl})\)-2,5-dimethoxy-\(N\text{-methylbenzenesulfonamide}\) (172)

To a suspension of NaH (60% dispersion in oil; 107 mg) in THF (2.5 ml) was added a solution of the sulfonamide 171 (465 mg; 2.0 mmol) in THF (3.5 ml). Effervescence occurred and the mixture was stirred at room temperature for 30 min. Then, \(o\text{-bromobenzyl bromide}\) (750 mg, 3.0 mmol) was added and the mixture left under stirring for 20 hr. Water was added (20 ml) and the mixture extracted with ether (3x15 ml) dried (MgSO\(_4\)) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%) to give the sulfonamide 172 (704 mg, 91%) as white needles, m.p. 95-96 °C (DCM/petrol); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2943, 1494, 1334 (S=O), 1275, 1224, 1158 (S=O); \(\delta\)H (270 MHz; CDCl\(_3\)) 7.55 (1H, d, \(J = 7.7\), H-3'), 7.52 (1H, dd, \(J = 1.1\) and 7.6, H-6'), 7.50 (1H, dd, \(J = 3.0, H-6\)), 7.33 (1H, dt, \(J = 1.2\) and 7.6, H-5'), 7.12 (1H, dt, \(J = 1.5\) and 7.7, H-4'), 7.06 (1H, dd, \(J = 3.2\) and 9.0, H-4), 6.96 (1H, d, \(J = 9.0\), H-3), 4.52 (2H, s, CH\(_2\)), 3.92 (3H, s, OCH\(_3\)), 3.80 (3H, s, OCH\(_3\)), 2.76 (3H, s, NCH\(_3\)); \(m/z\) 401, 399 (\(M^+ + 2\) and \(M^+\)), 320, 202 (100%), 542 (1C, s, CH\(_2\)), 153.0 (1C, q), 150.8 (1C, q), 153.9 (1C, q), 132.6 (1C, t), 129.2 (1C, t), 128.9 (1C, t), 127.9 (1C, t), 127.3 (1C, q), 123.1 (1C, q), 120.4 (1C, t), 116.1 (1C, t), 113.6 (1C, t), 56.5 (1C, p, OCH\(_3\)), 56.0 (1C, p, OCH\(_3\)), 54.2 (1C, s, CH\(_2\)), 35.0 (1C, p, NCH\(_3\)); \(\text{Found:} \ M^+,\ 401.0114\). \(\text{C}_{16}H_{18}Br_{81}NO_{4}S\) requires \(M, 401.0119\).
Preparation of (2-iodophenyl)methyl 4-methylbenzenesulfonate (175)

To a suspension of NaH (60% dispersion in oil; 297 mg) in THF (7 ml) was added a solution of o-iodobenzyl alcohol (1.4 g; 6.0 mmol) in THF (12 ml). Effervescence occurred and the mixture was stirred at room temperature for 20 min. A solution of p-toluenesulfonyl chloride (1.7 g, 9.0 mmol) in THF (10 ml) was added and the mixture left under stirring for 24 hr. Water (30 ml) was added and the mixture extracted with DCM (3x25 ml) dried (MgSO₄) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 25-75 %) to give the sulfonate 175 (2.0 g, 87%) as white prisms, m.p. 56-57 °C (DCM/petrol); νmax (film)/cm⁻¹ 3064, 1360 (S=O), 1190, 1177 (S=O), 937, 666; δH (270 MHz; CDCl₃) 7.84 (2H, d, J 8.3, H-2 and H-6), 7.79 (1H, dd, J 1.2 and 8.1, H-3'), 7.38-7.28 (4H, m, H-5', H-6', H-3 and H-5), 7.00 (1H, dd, J 2.2 and 7.8, H-4'), 5.09 (2H, s, CH₂), 2.44 (3H, s, CH₃); δC (CDCl₃) 144.9 (1C, q), 139.5 (1C, t), 136.1 (1C, q), 133.0 (1C, q), 130.5 (1C, t), 130.0 (1C, t), 129.9 (2C, t), 128.5 (1C, t), 128.1 (2C, t), 98.2 (1C, q, C-2'), 75.2 (1C, s, CH₂), 21.7 (1C, p, ArCH₃); m/z 388 (M⁺), 261 (M⁺-I), 233, 217 (100%); (Found: M⁺, 387.9620. C₁₄H₁₃IO₃S requires M, 387.9630).
Reaction of (2-iodophenyl)methyl 4-methylbenzenesulfonate (175) with tri-n-butyltin hydride

To a stirred solution of the sulfonate 175 (349 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (104 mg, 0.6 mmol) in benzene (4.7 ml), dropwise, over 11 hr, via a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed in vacuo, the residue dissolved in ethyl acetate (15 ml) and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The product was chromatographed (ethyl acetate/petrol 5-100%) to give, in order of elution the sulfonate 175 (11 mg, 3%), and 2-methyl-7H-dibenz[c,e]oxathiepin-S,S-dioxide (176) (23 mg, 10%) as white prisms, m.p. 148-150 °C (DCM/petrol); νmax (film)/cm⁻¹ 2925, 1351 (S=O), 1179 (S=O), 936, 770; δH (270 MHz; CDCl₃) 8.04 (1H, d, J 8.1, H-4), 7.60-7.56 (2H, m, ArH), 7.49-7.37 (4H, m, ArH), 5.03 (2H, s, CH₂), 2.53 (3H, s, ArCH₃); δC (CDCl₃) 145.2 (1C, q), 140.6 (1C, q), 138.8 (1C, q), 132.0 (1C, q), 131.8 (1C, q), 131.0 (1C, t), 130.7 (1C, t), 130.5 (1C, t), 129.3 (1C, t), 129.2 (1C, t), 128.6 (1C, t), 128.5 (1C, t), 72.8 (1C, s, CH₂), 21.6 (1C, p, ArCH₃); m/z 260 (M⁺), 195 (100%), 181, 165; (Found: M⁺, 260.0531. C₁₄H₁₂O₃S requires M, 260.0507).
Preparation of (2-iodophenyl)methyl 4-methoxybenzenesulfonate (177)

To a suspension of NaH (60% dispersion in oil; 290 mg) in THF (10 ml) was added a solution of o-iodobenzyl alcohol (1.4 g; 6.0 mmol) in THF (10 ml). Effervescence occurred and the mixture was stirred at room temperature for 30 min. A solution of 4-methoxy-benzenesulfonyl chloride (1.9 g, 9.0 mmol) in THF (10 ml) was added and the mixture left under stirring for 24 hr. Water was added (30 ml) and the mixture extracted with DCM (3x25 ml) dried (MgSO4) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 25-75 %) to give the sulfonate 177 (1.9 g, 76%) as white prisms, m.p. 82-83 °C; \( v_{max} \) (film)/cm\(^{-1} \) 2948, 1598, 1360 (S=O), 1263, 1171 (S=O), 1099, 1020; \( \delta_H \) (270 MHz; CDCl\(_3\)) 7.88 (2H, d, J 9.0, H-2 and H-6), 7.78 (1H, dd, J 1.0 and 7.8, H-3'), 7.37-7.28 (2H, m, ArH), 7.03-6.96 (1H, m, ArH), 6.99 (2H, d, J 9.0, H-3 and H-5), 5.07 (2H, s, CH\(_2\)), 3.88 (3H, s, OCH\(_3\)); \( \delta_C \) (CDCl\(_3\)) 163.8 (1C, q), 139.5 (1C, t), 136.0 (1C, q), 130.5 (1C, t), 130.3 (2C, t), 130.0 (1C, t), 128.4 (1C, t), 127.3 (1C, q), 114.4 (2C, t), 98.6 (1C, q, C-2'), 75.0 (1C, s, CH\(_2\)), 55.7 (1C, p, OCH\(_3\)); m/z 404 (M\(^+\)), 277 (M\(^+\)-I), 233, 217 (100%), 171; (Found: M\(^+\), 403.9602. C\(_{14}\)H\(_{13}\)I\(_2\)O\(_4\)S requires M, 403.9579).
Reaction of (2-iodophenyl)methyl 4-methoxybenzenesulfonate (177) with tri-n-butyltin hydride

To a stirred solution of the sulfonate 177 (362 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (106 mg, 0.6 mmol) in benzene (4.7 ml), dropwise, over 11 hr, via a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed in vacuo the residue dissolved in ethyl acetate (15 ml) and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried (MgSO4) and the solvent removed under reduced pressure. The product was chromatographed (ethyl acetate/petrol 8-20%) to give, in order of elution, the dihydro compound 179 (35 mg, 14%) and 2-methoxy-7H-dibenz[c,e]oxathiepin-S,S-dioxide (178) (48 mg, 19%).

**dihydro compound 179** as beige prisms, m.p. 160-162 °C (DCM/petrol); νmax (film)cm⁻¹ 1567, 1349 (S=O), 1171 (S=O), 1157, 1022; The interpretation of the 1H nmr is based on the discussion on page 91. δH (400 MHz; CDCl3) 7.43-7.37 (2H, m, H-9 and H-10), 7.32 (1H, d, J 7.0, H-8), 7.16 (1H, d, J 7.6, H-11), 6.87 (1H, d, J 6.7, H-4), 5.63 (1H, d, J 13.5, CH₂O), 5.05 (1H, dd, J 2.2 and 6.7, H-3), 5.03 (1H, d, J 13.5, CH₂O), 4.15 (1H, d, J 8.4, H-11b), 3.80 (3H, s, OCH₃), 3.23 (1H, d, dd, J 2.2 and 17.3, H-1a), 2.87 (1H, d, J 17.1, H-1b); δC (CDCl3) 163.2 (1C, q), 139.1 (1C, q), 133.4 (1C, q), 132.6 (1C, t), 132.5 (1C, t), 131.2 (1C, t), 129.9 (1C, t), 127.4 (1C, t), 125.5 (1C, t), 90.4 (1C, t), 72.3 (1C, s), 55.9 (1C, t), 34.4 (1C, p, OCH₃), 30.7 (1C, s); m/z 278 (M⁺), 214 (M⁺-SO₂), 165, 152, 91 (100%); (Found: M⁺, 278.0613. C₁₄H₁₄O₄S requires M⁺, 278.0613).
**Experimental**

2-methoxy-7H-dibenz[c,e]oxathiepin-S,S-dioxide (178) as white prisms, m.p. 164-165 °C (DCM/petrol); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2945, 1593, 1563, 1350 (S=O), 1177 (S=O), 769; \( \delta_H \) (270 MHz; CDCl\(_3\)) 8.08 (1H, d, \( J = 8.8, \) H-4), 7.60-7.57 (2H, m, ArH), 7.50-7.48 (2H, m, ArH), 7.11 (1H, d, \( J = 2.4, \) H-1), 7.04 (1H, dd, \( J = 2.7 \) and 8.8, H-3), 5.03 (2H, s, CH\(_2\)O), 3.95 (3H, s, OCH\(_3\)); \( \delta_C \) (CDCl\(_3\)) 163.8 (1C, q), 140.9 (1C, q), 140.4 (1C, q), 131.8 (1C, q), 131.0 (1C, t), 130.8 (1C, t), 130.6 (1C, t), 129.5 (1C, t), 128.4 (1C, t), 126.6 (1C, q), 115.9 (1C, t), 113.0 (1C, t), 72.6 (1C, s, CH\(_2\)), 55.8 (1C, p, OCH\(_3\)); \( m/z \) 276 (M\(^{+}\)), 212 (M\(^{+}\)-SO\(_2\)), 211 (100%); (Found: M\(^{+}\), 276.0467. C\(_{14}\)H\(_{12}\)O\(_4\)S requires \( M = 276.0456 \)).

**Preparation of methyl 2-(2-iodophenylmethylxysulfonyl)benzoate (180)**

![Chemical Structure](image)

To a suspension of NaH (60% dispersion in oil; 115 mg) in THF (2 ml) was added a solution of o-iodobenzyl alcohol (937 mg; 4.0 mmol) in THF (6 ml). Effervescence occurred and the mixture was stirred at room temperature for 30 min. Then, a solution of 2-carbomethoxybenzenesulfonyl chloride (1.2 g, 5.3 mmol) in THF (6 ml) was added and the mixture left under stirring for 24 hr. Water was added (30 ml) and the mixture extracted with DCM (3x25 ml) dried (MgSO\(_4\)) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 50%) to give the sulfonate 180 (354 mg, 21%) as white prisms, m.p. 95-97 °C (DCM/petrol); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2951, 1737 (C=O), 1366 (S=O), 1298, 1184 (S=O); \( \delta_H \) (270 MHz; CDCl\(_3\)) 8.03 (1H, td, \( J = 1.0 \) and 7.6, H-6), 7.78 (1H, dd, \( J = 1.0 \) and 7.8, H-3'), 7.67-7.57 (3H, m, H-3, H-4 and H-5), 7.41 (1H, dd, \( J = 1.7 \) and 7.6, H-6'), 7.30 (1H, dt, \( J = 1.2 \) and 7.6, H-5'), 6.99 (1H, dt, \( J = 1.7 \) and 7.8, H-4'), 5.22 (2H, s, CH\(_2\)), 3.93 (3H, s, CO\(_2\)CH\(_3\)); \( \delta_C \) (CDCl\(_3\)) 166.8 (1C, q), 139.3 (1C, t), 135.7 (1C, q), 133.9 (1C, q), 133.5 (1C, t), 133.0 (1C, q), 130.7 (1C, t), 130.4 (1C, t), 129.8 (1C, t), 129.6 (1C, t), 129.2 (1C, t), 128.3 (1C, t), 97.9 (1C, q, C-2'), 75.8 (1C, s, CH\(_2\)), 53.0 (1C, p, OCH\(_3\));
Experimental

\[ m/z \ (\text{EI}) \ 433 \ (\text{MH}^+), \ 217, \ 199 \ (100\%); \ (\text{Cl, NH}_3) \ 450 \ (\text{MNH}_4^+, \ 100\%); \ (\text{Found: C, 41.45; H, 3.1. C}_{15}\text{H}_{13}\text{IO}_5\text{S}\text{ requires C, 41.7; H, 3.0}). \]

Reaction of methyl 2-(2-iodophenylmethyloxysulfonyl)benzoate (180) with tri-n-butyltin hydride

To a stirred solution of the sulfonate 180 (386 mg, 0.89 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (110 mg, 0.67 mmol) in benzene (4.7 ml), dropwise, over 11 hr, via a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed in vacuo the residue dissolved in ethyl acetate (15 ml) and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 50-75 %) to give in order of elution 5H-dibenz[c,e]oxepin-7-one (181) (143 mg, 76%) and methyl 2-(2'-hydroxymethyl-1,1'-biphenyl)-carboxylate (182) (29 mg, 14%).

5H-dibenz[c,e]oxepin-7-one (181) as white needles, m.p. 133-135 °C (DCM/petrol); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 1715 (C=O), 1277, 1111, 739; \( \delta_H \) (400 MHz; CDCl\(_3\)) 7.97 (1H, dd, \( J \) 1.3 and 7.9, H-8), 7.67-7.58 (3H, m, ArH), 7.54-7.48 (2H, m, ArH), 7.50 (1H, d, \( J \) 11.3, H-5a), 5.03 (1H, d, \( J \) 11.3, H-5b); \( \delta_C \) (CDCl\(_3\)) 170.2 (1C, q, C=O), 138.9 (1C, q), 137.2 (1C, q), 134.8 (1C, q), 132.5 1C, t), 131.9 (1C, t), 130.6 (1C, q), 130.1 (1C, t), 128.7 (1C, t), 128.6 (1C, t), 128.5 (1C, t), 128.2 (1C, t), 128.4 (1C, t), 69.2 (1C, s, CH\(_2\)); \( m/z \) 210 (M\(^+\), 100%), 181, 165, 152; (Found: M\(^+\), 210.0684. C\(_{14}\)H\(_{10}\)O\(_2\) requires M, 210.0681).
methyl 2-(2'-hydroxymethyl-1,1'-biphenyl)carboxylate (182) as an oil; $\nu_{\max}$ (film)/cm$^{-1}$ 3411 (OH), 2951, 1722 (C=O), 1309, 1244, 749; $\delta_H$ (400 MHz; CDCl$_3$) 8.03 (2H, m, H-3), 7.56 (2H, m, ArH), 7.48 (1H, t, J 7.8, ArH), 7.40 (1H, dt, J 1.4 and 7.4, ArH), 7.35 (1H, dt, J 1.7 and 7.5, ArH), 7.26 (1H, dd, J 1.5 and 7.5, ArH), 4.58 (2H, d, J 3.6, CH$_2$O), 3.90 (3H, s, CO$_2$CH$_3$), 166.9 (1C, q, C=O), 140.9 (1C, q), 140.2 (1C, q), 137.9 (1C, q), 133.6 (1C, t), 130.2 (1C, t), 130.0 (1C, t), 128.5 (1C, t), 128.4 (1C, t), 128.3 (1C, t), 128.1 (1C, t), 127.8 (1C, t), 63.0 (1C, s, CH$_2$O), 52.2 (1C, p, OCH$_3$); $m/z$ 242 (M$^+$), 224 (M$^+$-H$_2$O), 165 (100%); (Found: M$^+$, 2242.0941. C$_{15}$H$_{14}$O$_3$ requires $M$, 242.0943).

Preparation of (2-iodophenyl)methyl 2,4,6-trimethylbenzenesulfonate (183)

To a suspension of NaH (60% dispersion in oil; 289 mg) in THF (14 ml) was added a solution of o-iodobenzyl alcohol (1.4 g; 6.0 mmol) in THF (10 ml). Effervescence occurred and the mixture was stirred at room temperature for 30 min. A solution of mesitylenesulfonyl chloride (2.0 g, 9.0 mmol) in THF (10 ml) was added and the mixture left under stirring for 24 hr. Water was added (30 ml) and the mixture extracted with DCM (3x25 ml) dried (MgSO$_4$) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 20-50%) to give the sulfonate 183 (1.9 g, 76%) as white prisms, m.p. 72-75 °C (DCM/petrol); $\nu_{\max}$ (film)/cm$^{-1}$ 2978, 1605, 1439, 1356 (S=O), 1175 (S=O); $\delta_H$ (270 MHz; CDCl$_3$) 7.80 (1H, dd, J 1.2 and 8.0, H-3'), 7.38-7.28 (2H, m, H-5' and H-6'), 7.01 (1H, m, H-4'), 6.97 (2H, s, H-3 and H-5), 5.05 (2H, s, CH$_2$), 2.66 (6H, s, 2xCH$_3$), 2.32 (3H, s, CH$_3$); $\delta_C$ (CDCl$_3$) 143.4 (1C, q), 140.0 (2C, q), 139.5 (1C, t), 136.2 (1C, t), 131.7 (2C, t), 130.6 (1C, q), 130.4 (1C, t), 129.9 (1C, t), 128.5 (1C, t), 98.3 (1C, q, C-2'), 74.4 (1C, s, CH$_2$),
Experimental 187

22.7 (2C, p, ArCH3), 21.0 (1C, p, Ar CH3); m/z 416 (M+), 289, 217 (100%); (Found: M+, 415.9921. C16H17O3S requires M, 415.9943).

Reaction of (2-iodophenyl)methyl 2,4,6-trimethylbenzenesulfonate (183) with tri-n-butyltin hydride

```
O

I

183

HO

3

3'

184
```

To a stirred solution of the sulfonate 183 (375 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 μl, 1.17 mmol) and AIBN (104 mg, 0.6 mmol) in benzene (4.7 ml), dropwise, over 11 hr, via a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed in vacuo the residue dissolved in ethyl acetate (15 ml), and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried (MgSO4) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 50-75 %) to give 2',4',6'-trimethyl-1,1'-biphenyl-4-ylmethanol (184) (72 mg, 36%) as an oil; v max (film)/cm⁻¹ 3340 (OH), 2918, 1613, 1451, 1377; δH (270 MHz; CDC13) 7.59-7.55 (1H, m, H-3), 7.36-7.42 (2H, m, H-4 and H-5), 7.08-7.05 (1H, m, H-6), 6.97 (2H, s, H-3' and H-5'), 4.33 (2H, s, CH2), 2.36 (3H, s, ArCH3), 1.95 (6H, s, 2xArCH3); δC (CDC13) 139.1 (1C, q), 138.3 (1C, q), 136.7 (1C, q), 136.6 (1C, q), 135.7 (2C, q), 129.3 (1C, t), 128.0 (2C, t), 127.6 (1C, t), 127.3 (1C, t), 127.2 (1C, t), 62.9 (1C, s, CH2), 20.9 (1C, p, ArCH3), 20.3 (2C, p, 2xArCH3); m/z 226 (M+), 208 (M+·H2O), 193 (100%), 178, 165; (Found: M+, 226.1361. C16H18O requires M, 226.1358).
Preparation of methyl p-tolyl sulfone (185)$_{12}$

To a mixture of sodium p-toluenesulfinate (11 g, 50 mmol) and sodium bicarbonate (8.4 g, 0.1 mol) was added dimethyl sulfate (7.1 ml, 75 mmol) and some water (3 ml) was added to make the mixture fluid enough for stirring. The rest of the water (15 ml) was added dropwise and the mixture heated at reflux for 22 hr. After cooling to room temperature, the mixture was diluted with water (30 ml), extracted with DCM (3x25 ml), dried (MgSO$_4$) and the solvent removed under reduced pressure to give the sulfone 185 (6.9 g, 81%) as white prisms, m.p. 87.5-88 °C (Lit.$^{12}$ 83-87.5 °C), $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2926, 1300 (S=O), 1289, 1148 (S=O), 1091; $\delta$H (400 MHz; CDCl$_3$) 7.82 (2H, d, $J$ 8.2, H-2 and H-6), 7.36 (2H, d, $J$ 8.2, H-3 and H-5), 3.04 (3H, s, SO$_2$CH$_3$), 2.45 (3H, s, ArCH$_3$); $\delta$C (CDCl$_3$) 144.6 (1C, q, C-1), 137.6 (1C, q, C-4), 129.9 (2C, t, C-2 and C-6), 127.3 (2C, t, C-3 and C-5), 44.6 (1C, p, SO$_2$CH$_3$), 21.6 (1C, p, ArCH$_3$).
Preparation of [2-(2-iodophenyl)ethyl] (4-methylphenyl) sulfone (186)

To a solution of the sulfone 185 (1.0 g, 6 mmol) in THF (30 ml) at -70 °C, under nitrogen, was added a solution of nBuLi (2.5 M in cyclohexane; 2.6 ml) and left for 1 hr. Then, a solution of 2-iodobenzyl chloride (1.8 g, 7.2 mmol) in THF (10 ml) was added and the mixture allowed to warm to 0 °C over 1.5 hr. The cooling bath was removed and the mixture allowed to warm to room temperature over 1 hr. The reaction mixture was quenched with NH₄Cl (30 ml) and extracted with DCM (3x30 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 40%) to give the bis-alkylated compound 186a (867 mg, 24%), the sulfone 186 (1.1 g, 46%) and the sulfone 185 (218 mg, 21%).

bis[2-(2-iodophenyl)methyl]methyl(4-methylphenyl) sulfone (186a) as white prisms, m.p. 100-102 °C (DCM/petrol); v max (film)/cm⁻¹ 2925, 1305 (S=O), 1138 (S=O), 1079, 745; δH (400 MHz; CDCl₃) 7.68 (2H, td, J 1.9 and 8.5, 2xH-3'), 7.60 (2H, dd, J 1.2 and 7.9, H-2 and H-6), 7.21-7.12 (6H, m, ArH), 6.78 (2H, dt, J 1.9 and 7.8, 2xH-4'), 4.22 (1H, m, CHSO₂), 3.39 (2H, dd, J 6.5 and 14.3, 2x1H-CH₂), 2.95 (2H, dd, J 8.0 and 14.4, 2x1H-CH₂), 2.36 (3H, s, ArCH₃); δC (CDCl₃) 144.3 (1C, q), 139.5 (2C, t), 139.2 (2C, q), 135.4 (1C, q), 131.9 (2C, t), 129.5 (2C, t), 128.7 (2C, t), 128.5 (2C, t), 128.0 (2C, t), 100.5 (2C, q, 2xC-2), 61.3 (1C, t, CHSO₂), 39.0 (2C, s, 2xCH₂), 21.6 (1C, p, ArCH₃); m/z (EI) 602 (M⁺), 475 (M⁺-I), 446, 259, 230 (100%); (FAB) 303 (MH⁺, 100%); (Found: MH⁺, 602.9350. C₂₂H₂₁I₂O₂S requires MH⁺, 602.9352).

[2-(2-iodophenyl)ethyl] (4-methylphenyl) sulfone (186) as white prisms, m.p. 68-69 °C (DCM/petrol); v max (film)/cm⁻¹ 2917, 1312 (S=O), 1152 (S=O), 1079, 745; δH (400 MHz; CDCl₃) 7.82 (2H, d, J 8.1, H-2' and H-6'), 7.73 (1H, d, J 7.9, H-3), 7.36 (2H, d, J 8.1, H-3' and H-5'), 7.24 (1H, t, J 7.5, H-5), 7.17 (1H, dd, J 1.4 and 7.7, H-6), 6.88 (1H, dt, J 1.7 and 7.7, H-4), 3.30 (2H, m, CH₂), 3.07 (2H, m, CH₂), 2.44 (3H, s, ArCH₃); δC (CDCl₃) 144.8 (1C, q), 140.2 (1C, q), 139.7 (1C, t), 135.6 (1C, q), 129.9
(2C, t), 129.8 (1C, t), 128.8 (1C, t), 128.3 (2C, t), 99.8 (1C, q, C-2), 55.7 (1C, s, CH$_2$SO$_2$), 34.3 (1C, s, ArCH$_2$), 21.7 (1C, p, ArCH$_3$); m/z 387 (MH$^+$), 259 (100%), 230; (Found: C, 46.3; H, 3.7. C$_{15}$H$_{13}$IO$_2$S requires C, 46.6; H, 3.9).

Reaction of [2-(2-iodophenyl)ethyl] (4-methylphenyl) sulfone (186) with tri-n-butyltin hydride

To a stirred solution of the sulfone 186 (349 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (110 mg, 0.67 mmol) in benzene (4.7 ml), dropwise, over 11 hr, via a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed in vacuo the residue dissolved in ethyl acetate (15 ml), and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried (MgSO$_4$) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 50-100 %) to give in order of elution 2-methyl-9,10-dihydro-phenanthrene (187) (25 mg, 14%), (phenylethyl) (4-methylphenyl) sulfone (188) (62 mg, 26%), a dihydro compound 190 (7 mg, 3%) and 2-methyl-6,7-dihydro-dibenzo-[b,d]-thiepin-S,S-dioxide (189) (51 mg, 22%)

2-methyl-9,10-dihydro-phenanthrene (187) as an oil; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2933, 1484, 764; $\delta_H$ (400 MHz; CDCl$_3$) 7.74 (1H, d, $J$ 7.7, H-4 or H-5), 7.66 (1H, d, $J$ 8.0, H-5 or H-4),
Experimental

7.32-7.21 (3H, m, H-6, H-7 and H-8), 7.13 (1H, d, J 7.9, H-3), 7.08 (1H, bs, H-1), 2.87 (4H, m, 2xCH2), 2.39 (3H, s, ArCH3); δC (CDCl3) 137.3 (1C, q), 137.1 (1C, q), 137.0 (1C, q), 134.5 (1C, q), 131.7 (1C, q), 128.8 (1C, t), 128.0 (1C, t), 127.6 (1C, t), 126.9 (1C, t), 126.8 (1C, t), 123.6 (1C, t), 123.4 (1C, t), 29.1 (1C, s), 29.0 (1C, s), 21.2 (1C, p, ArCH3); m/z 194 (M+, 100%), 179 (M+-CH3); (Found: M+, 194.1104. C15H14 requires M, 194.1096).

(2-phenylethyl) (4-methylphenyl) sulfone (188) as an oil, νmax (film)/cm⁻¹ 1302 (S=O), 1149 (S=O), 1084; δH (400 MHz; CDCl3) 7.79 (2H, d, J 8.2, H-2' and H-6'), 7.34 (2H, d, J 8.3, H-3' and H-5'), 7.26-7.20 (3H, m, H-3, H-4 and H-5), 7.09 (2H, d, J 6.7, H-2 and H-6), 3.34-3.29 (2H, m, SO₂CH₂), 3.03-2.99 (2H, m, ArCH₂), 2.44 (3H, s, ArCH3); δC (CDCl3) 144.8 (1C, q), 137.5 (1C, q), 135.9 (1C, q), 129.9 (2C, t), 128.7 (2C, t), 128.2 (2C, t), 128.1 (2C, t), 126.8 (1C, t), 57.6 (1C, s, CH₂SO₂), 28.8 (1C, s, ArCH₂), 21.6 (1C, p, ArCH3); m/z 259 (M-H+), 180 (100%), 91 (100%); (Found: M-H+, 259.0790. C15H15O₂S requires M, 259.0793).

dihydro compound 190 as white prisms, m.p. 180-181 °C (DCM/petrol); νmax (film)/cm⁻¹ 1586, 1291 (S=O), 1124 (S=O), 726; δH (400 MHz; CDCl3) 7.28-7.21 (3H, m, ArH), 6.99-6.97 (1H, m), 6.80 (1H, d, J 5.6), 5.84-5.81 (1H, m), 4.04 (1H, d, J 7.3), 3.50-3.41 (2H, m), 3.12-3.06 (1H, m), 3.02-2.91 (2H, m), 2.72 (1H, dd, J 1.7 and 18.3), 2.13 (3H, s, ArCH₃); δC (CDCl3) 143.8 (1C, q), 139.9 (1C, q), 137.5 (1C, q), 133.2 (1C, q), 131.6 (1C, t), 130.5 (1C, t), 127.6 (2C, t), 125.8 (1C, t), 117.4 (1C, t), 56.2 (1C, s), 33.6 (1C, t), 33.1 (1C, s), 29.6 (1C, s), 23.5 (1C, p, CH₃); m/z 260 (M⁺), 195, 181 (100%), 165; (Found: M⁺, 260.0870. C15H16O₂S requires M, 260.0871).

2-methyl-6,7-dihydro-dibenzo[b,d]thiepin-S,S-dioxide (189) as white prisms, m.p. 134-135 °C (DCM/petrol); νmax (film)/cm⁻¹ 1303 (S=O), 1152, 1125 (S=O), 756, 745; δH (400 MHz; CDCl3) 8.02 (1H, d, J 7.8, H-4), 7.44-7.32 (6H, m, ArH), 3.77 (2H, m, SO₂CH₂), 2.98 (2H, bs, ArCH₂), 2.51 (3H, s, ArCH₃); δC (CDCl3) 145.1 (1C, q), 140.3 (1C, q), 139.5 (1C, q), 135.3 (1C, q), 134.2 (1C, q), 131.5 (1C, t), 128.9 (2C, t), 128.8 (1C, t), 128.5 (1C, t), 128.4 (1C, t), 128.0 (1C, t), 63.6 (1C, s, CH₂SO₂), 29.6 (1C, s, ArCH₂), 21.6 (1C, p, ArCH₃); m/z 258 (M⁺), 193 (100%), 178; (Found: M⁺, 258.0709. C15H14O₂S requires M, 258.0714).
Preparation of (2-iodophenyl) tosylmethyl ketone (191)

To a solution of the sulfone 185 (1.5 g, 8.6 mmol) in THF (35 ml) at -78 °C, under N2, was added a solution of n-BuLi (2.5 M in cyclohexane; 7 ml). After 1 hr a solution of 2-iodobenzoyl chloride (1.9 g, 7.2 mmol) in THF (10 ml) was added and left for another hour. The mixture allowed to warm to room temperature over 1 hr and quenched with NH4Cl (30 ml), extracted with DCM (3x30 ml), dried (MgSO4) and the solvent removed under reduced pressure. The mixture was purified by recrystallisation (DCM/ether/petrol) to give the sulfone 191 (2.1 g, 73%) as white plates, m.p. 98-100 °C; v_max (film)/cm⁻¹ 1691 (C=O), 1322 (S=O), 1153 (S=O); δH (400 MHz; CDCl₃) 7.90 (1H, dd, 7 1.1 and 7.8, H-3), 7.75 (2H, d, J 8.4 H-2' and H-6'), 7.55 (1H, dd, J 1.6 and 7.6, H-6), 7.42 (1H, dt, J 1.0 and 7.6, H-5), 7.33 (2H, d, J 8.6, H-3' and H-5'), 7.15 (1H, dt, J 1.7 and 7.8, H-4), 4.73 (2H, s, CH₂), 2.43 (3H, s, ArCH₃); δC (CDCl₃) 191.1 (1C, q, C=O), 145.4 (1C, q), 141.9 (1C, q), 141.0 (1C, t), 135.6 (1C, t), 132.9 (1C, t), 130.1 (1C, t), 129.9 (2C, t), 128.6 (2C, t), 128.2 (1C, t), 91.8 (1C, q, C-2'), 65.4 (1C, s, CH₂), 21.7 (1C, p, ArCH₃); m/z (FAB) 401 (MH⁺); (Found: M⁺, 399.9627. C₁₅H₁₃O₃IS requires M, 399.9630).
Reaction of \( \text{2-iodophenyl tosylmethyl ketone (191)} \) with \( \text{tri-n-butyltin hydride} \)

To a stirred solution of the ketone \( \text{191} \) (360 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of \( \text{tri-n-butyltin hydride} \) (320 \( \mu l \), 1.17 mmol) and \( \text{AIBN} \) (107 mg, 0.67 mmol) in benzene (4.7 ml), dropwise, over 11 hr, \text{via} a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, \( \text{carbon tetrachloride (10 ml)} \) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed \text{in vacuo} \text{the residue dissolved in ethyl acetate (15 ml), and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried (MgSO}_4 \) and the solvent removed under reduced pressure. The product was chromatographed (ethyl acetate/petrol 3-10%) to give in order of elution the \( \text{2-acetyl-4'-methyl-1,1'-biaryl (192)} \) (20 mg, 11%), \( \text{2-methyl-9-phenanthrenol (193)} \) (42 mg, 22%) and the \( \text{ketone 191} \) (117 mg, 32%).

\( \text{2-acetyl-4'-methyl-1,1'-biaryl (192)} \) as an oil; \( \nu_{\text{max}} \text{ (film)}/\text{cm}^{-1} \) 2923, 1682 (C=O), 1261; \( \delta_H \) (400 MHz; CDCl\(_3\)) 7.53 (1H, d, \( J \text{ 7.6, H-3} \)), 7.49 (1H, t, \( J \text{ 7.5, H-5} \)), 7.42-7.37 (2H, m, H-4 and H-6), 7.24 (4H, s, ArH), 2.41 (3H, s, ArCH\(_3\)), 2.02 (3H, s, COCH\(_3\)); \( \delta_C \) (CDCl\(_3\)) 140.8 (1C, q), 140.5 (1C, q), 137.8 (1C, q), 137.7 (1C, q), 130.6 (1C, t), 130.2 (1C, t), 129.4 (2C, t), 128.7 (2C, t), 127.8 (1C, t), 127.2 (1C, t), 30.5 (1C, p, COCH\(_3\)), 21.2 (1C, p, ArCH\(_3\)); \( m/z \) (EI) 210 (M\(^+\)), 195 (M-Me\(^+\), 100%), 165, 152; (FAB) 211 (MH\(^+\)); (Found: M\(^+\), 210.1054. C\(_{15}\)H\(_{14}\)O requires M, 210.1045).

\( \text{2-methyl-9-phenanthrenol (193)} \) as orange needles, m.p. 162-165 °C (DCM/petrol); \( \nu_{\text{max}} \text{ (film)}/\text{cm}^{-1} \) 3206, 1626, 1602, 1220, 1067, 757; \( \delta_H \) (400 MHz; CDCl\(_3\)) 8.64 (1H, d, \( J \text{ 8.2, H-4} \)), 8.49 (1H, d, \( J \text{ 8.4, H-3} \)), 8.30 (1H, dd, \( J \text{ 0.9 and 8.0, H-8} \)), 7.67 (1H, dt, \( J \text{ 1.3 and 8.1, H-6} \)), 7.62 (1H, dt, \( J \text{ 1.3 and 8.2, H-7} \)), 7.49 (1H, bs, OH), 7.34 (1H, dd, \( J \text{ 1.7 and 8.4, H-5} \)), 6.95 (1H, s, H-1), 5.31 (1H, s, H-10), 2.54 (3H, s, ArCH\(_3\)); \( \delta_C \) (CDCl\(_3\)) 150.8 (1C, q), 136.2 (1C, q), 133.3 (1C, q), 131.4 (1C, q), 126.6 (1C, t), 126.1
Preparation of 2-chloro-N-methyl-N-(p-toluenesulfonyl)acetamide (195)

To a suspension of NaH (60% dispersion in oil; 728 mg) in THF (20 ml) was added a solution of N-methyl-p-toluenesulfonamide 150 (2.8 g, 15 mmol) in THF (30 ml). Effervescence occurred and the mixture was stirred for 30 min. Chloroacetyl chloride (1.8 ml, 23 mmol) was added and the mixture stirred for 2 days. Water (50 ml) was added and the mixture extracted with ether (3x40 ml), dried (MgSO4) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 60%) to give the acetamide 195 (3.1 g, 79%) as white prisms, m.p. 70-72 °C (ether/petrol); v_max(film)/cm⁻¹ 2924 (CH), 1712 (C=O), 1360 (S=O), 1164 (S=O), 665; δ_H(270 MHz; CDCl₃) 7.77 (2H, d, J 8.6, H-2' and H-6'), 7.38 (2H, d, J 8.6, H-3' and H-5'), 4.61 (2H, s, CH₂), 3.24 (3H, s, NCH₃), 2.46 (3H, s, ArCH₃); δ_C(CDCl₃) 166.4 (1C, q, C=O), 145.6 (1C, q, C-1), 135.0 (1C, q, C-4), 130.2 (2C, t, C-2), 127.4 (2C, t, C-3), 44.4 (1C, s, CH₂Cl), 33.4 (1C, p, NCH₃), 21.6 (1C, p, ArCH₃); m/z (EI) 225 (M⁺-HCl), 199 and 197 (M⁺-SO₂), 185, 155, 90 (100%); (Cl) 281, 279 (MNH₄⁺, 100%), 264, 262 (MH⁺), 203; (Found: C, 45.6; H, 4.5; N, 5.5. C₁₀H₁₂ClNO₃S requires C, 45.9; H, 4.6; N, 5.35 %)
Preparation of 2-iodo-N-methyl-N-(p-toluenesulfonyl)acetamide (196)

To sodium iodide (3.4 g, 24 mmol) in acetone (25 ml) at reflux was added the acetamide 195 (3.1 g, 12 mmol) and the mixture left overnight under reflux. Ether (25 ml) was added, the mixture filtered and the solvent removed under reduced pressure. The residue was dissolved in DCM (20 ml), washed with aq. sodium thiosulfate (10%, 2x15 ml), water (20 ml), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75%) to give the acetamide 196 (2.4 g, 58%) as white prisms, m.p. 67-68 °C (DCM/petrol); νmax(fil/Å/cm⁻¹) 2952, 1685, 1355 (S=O), 1166 (S=O), 705; δ_H(270 MHz; CDCl₃) 7.82 (2H, d, J 8.5, H-2' and H-6'), 7.37 (2H, d, J 8.5, H-3' and H-5'), 4.24 (2H, s, CH₂), 3.26 (3H, s, NCH₃), 2.45 (3H, s, ArCH₃); δ_C(CDCl₃) 167.6 (1C, q, C=O), 145.4 (1C, q, C-1), 135.0 (1C, q, C-4), 129.9 (2C, t, C-2 and C-6), 127.7 (2C, t, C-3 and C-5), 33.8 (1C, p, NCH₃), 21.6 (1C, p, ArCH₃), -1.5 (1C, s, CH₂I); m/z 289 (M⁺-SO₂), 226 (M⁺-I), 155, 91 (100%); (Found: C, 34.1; H, 3.5; N, 3.7. C₁₀H₁₂INO₃S requires C, 34.0; H, 3.4; N, 4.0 %).
Reaction of 2-iodo-N-methyl-N-(p-toluenesulfonyl)acetamide (196) with tri-n-butyltin hydride

To a stirred solution of the acetamide 196 (312 mg, 0.88 mmol) in benzene (17.6 ml) at reflux, was added a solution of tri-n-butyltin hydride (313 µl, 1.15 mmol) and AIBN (115 mg; 0.7 mmol) in benzene (4.6 ml) dropwise over 11 hr, via a needle placed directly above the refluxing solution. After further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed in vacuo, the residue dissolved in ethyl acetate (20 ml), added sat. aq. KF (15 ml) and left with strong stirring for 2 hr. The suspension was filtered, the organic layer washed with sat. aq. KF (15 ml) and water (15 ml) dried (MgSO4), and concentrated under reduced pressure. The residue was chromatographed (ether/petrol 25-50% and EtOAc) to give in order of elution N-methyl-N-(p-toluenesulfonyl)acetamide (197) (58 mg, 29%), 2,3-dihydro-1,6-dimethyl-indol-2-one (198) (20 mg, 14%) and N-methyl-p-tolylacetamide (199) (24 mg, 17%).

N-methyl-N-(p-toluenesulfonyl)acetamide (197) as orange prisms, m.p. 45-50 °C (DCM/petrol); νmax(film)/cm⁻¹ 2955, 1702 (C=O), 1597, 1494, 1362 (S=O), 1164 (S=O); δH (270 MHz; CDCl3) 7.50 (2H, d, J 8.3, H-2 and H-6), 7.34 (2H, d, J 8.1, H-3 and H-5), 3.24 (3H, s, NCH3), 2.43 (3H, s, ArCH3), 2.37 (3H, s, CH3CO); δC (CDCl3) 170.3 (1C, q, C=O), 144.9 (1C, q, C-1), 136.1 (1C, q, C-4), 129.9 (2C, t, C-2 and C-6), 127.2 (2C, t, C-3 and C-5), 32.9 (1C, p, NCH3), 24.9 (1C, p, COCH3), 21.5 (1C, p, ArCH3); m/z (EI) 185 (M⁺-CH3CO), 163, 155, 91, 56 (100%); (CI) 472 ([2M+NH4]⁺), 228 (MH⁺, 100%); (Found: MH⁺, 228.0694. C₁₀H₁₄NO₃S requires MH, 228.0694).
2,3-dihydro-1,6-dimethyl-indol-2-one (198) as beige needles, m.p. 92-93 °C (DCM/petrol); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2939, 1701 (C=O), 1622, 1376, 949, 801; \( \delta_{\text{H}} \) (270 MHz; CDCl\(_3\)) 7.11 (1H, d, \( J \) 7.6, H-4), 6.84 (1H, d, \( J \) 7.6, H-5), 6.64 (1H, s, H-7), 3.46 (2H, s, CH\(_2\)), 3.18 (3H, s, NCH\(_3\)), 2.38 (3H, s, ArCH\(_3\)); \( \delta_{\text{C}} \) (CDCl\(_3\)) 175.5 (1C, q, C=O), 145.3 (1C, q), 137.9 (1C, q), 124.0 (1C, q), 124.0 (1C, t), 122.8 (1C, t), 109.0 (1C, t), 35.5 (1C, s, CH\(_2\)), 26.1 (1C, p, NCH\(_3\)), 21.7 (1C, p, ArCH\(_3\)); \( m/z \) 161 (M\(^+\), 100%), 146, 132; (Found: M\(^+\), 161.0841. C\(_{10}\)H\(_{11}\)NO requires M, 161.0841).

N-methyl-\( p \)-tolylacetamide (199) as white needles, m.p. 116-117 °C (DCM/petrol); \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 3292 (NH), 1653 (C=O), 1558, 1403; \( \delta_{\text{H}} \) (270 MHz; CDCl\(_3\)) 7.15 (4H, s, ArH), 5.30 (1H, bs, NH), 3.53 (2H, s, CH\(_2\)), 2.74 (3H, d, NCH\(_3\)), 2.34 (3H, s, ArCH\(_3\)); \( \delta_{\text{C}} \) (CDCl\(_3\)) 171.8 (1C, q, C=O), 136.9 (1C, q, C-1), 131.8 (1C, q, C-4), 129.6 (2C, t, C-2 and C-6), 129.3 (2C, t, C-3 and C-5), 43.2 (1C, s, CH\(_2\)), 26.4 (1C, p, NCH\(_2\)), 21.0 (1C, p, ArCH\(_3\)); \( m/z \) 163 (M\(^+\), 100%), 91; (Found: M\(^+\), 163.0997. C\(_{10}\)H\(_{13}\)NO requires M, 163.0997).

Photochemical reaction of 2-iodo-N-methyl-\( p \)-(toluenesulfonyl)acetamide (196)

A solution of acetamide 196 (101 mg, 0.28 mmol) in benzene (5.6 ml), bis(tri-n-butyltin) (143 \( \mu \)l, 0.28 mmol) and ethyl iodide (91 \( \mu \)l, 1.12 mmol), was irradiated using a medium pressure mercury vapour lamp (125 W) for 7 hr. Analysis of the \( ^1\)H nmr spectrum of the crude mixture showed only the acetamide 199.
Preparation of 2-chloro-N-(2,5-dimethoxyphenylsulfonyl)N-methyl acetamide (203)

To a suspension of NaH (60% dispersion in oil; 167 mg) in THF (4 ml) was added a solution of benzenesulfonamide 171 (805 mg, 3.5 mmol) in THF (9 ml). Effervescence occurred and the mixture was stirred for 1/2hr. Chloroacetyl chloride (420 µl, 5.3 mmol) was added and the mixture stirred for 2 days. Water (20 ml) was added and the mixture extracted with ether (3x10 ml), dried (MgSO4) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75%) to give the acetamide 203 (673 mg, 63%) as white prisms, m.p. 117-119 °C (DCM/petrol); ν_max(film/cm⁻¹ 2952 (CH), 1712 (C=O), 1500, 1359 (S=O), 1159 (S=O); δH (270 MHz; CDCl₃) 7.49 (1H, d, J 3.2, H-6), 7.16 (1H, dd, J 3.2 and 9.0, H-4), 6.97 (1H, d, J 9.0, H-3), 4.80 (2H, s, CH₂), 3.86 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 3.06 (3H, s, NCH₃); δC (CDCl₃) 167.7 (1C, q, C=O), 153.2 (1C, q, C-5), 150.7 (1C, q, C-2), 124.9 (1C, q, C-1), 122.3 (1C, t, C-6), 115.5 (1C, t, C-4), 113.7 (1C, t, C-3), 56.6 (1C, p, OCH₃), 56.1 (1C, p, OCH₃), 45.5 (1C, s, CH₂), 33.2 (1C, p, NCH₃); m/z 309, 307 (M⁺), 243, 245 (M⁺-SO₂), 231, 201, 180, 137, 90 (100%); (Found: M⁺, 307.0281. C₁₁H₁₄Cl³⁵NO₅S requires M, 307.0281).
Preparation of 2-iodo-N-(2,5-dimethoxyphenylsulfonyl)N-methyl acetamide (204)

To sodium iodide (602 mg, 4.3 mmol) in acetone (2 ml) at reflux was added a solution of acetamide 203 (647 mg, 2.1 mmol) in acetone (7 ml) and the mixture left overnight under reflux. DCM (10 ml) was added, the mixture filtered and the solvent removed under reduced pressure. The residue was dissolved in DCM (15 ml), washed with sodium thiosulfate (2x15 ml), water (10 ml), dried (MgSO4) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75%) to give acetamide 204 (536 mg, 64%) as white prisms, m.p. 109-110 °C (DCM/petrol); \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2948, 1668 (C=O), 1573, 1499, 1355 (S=O), 1164 (S=O); \( \delta_{\text{H}} \) (270 MHz; CDCl\(_3\)) 7.47 (1H, d, J 3.2, H-6), 7.13 (1H, dd, J 3.2 and 9.3, H-4), 6.96 (1H, d, J 9.3, H-3), 4.37 (2H, s, CH\(_2\)), 3.85 (3H, s, OCH\(_3\)), 3.80 (3H, s, OCH3), 3.13 (3H, s, NCH\(_3\)); \( m/z \) 399 (M\(^+\)), 335 (M\(^+\)-SO\(_2\)), 304, 272 (M\(^+\)-I), 231, 182 (100%); (Found: C, 33.0; H, 3.4; N, 3.6. C\(_{11}\)H\(_{14}\)INO\(_5\)S requires C, 33.1; H, 3.5; N, 3.5%).
Experimental

Reaction of 2-iodo-N-(2,5-dimethoxyphenylsulfonyl)-N-methyl acetamide (204) with tri-n-butyltin hydride

To a stirred solution of acetamide 204 (184 mg, 0.46 mmol) in benzene (9 ml) at reflux, was added a solution of tri-n-butyl tin hydride (163 µl, 0.60 mmol) and AIBN (54 mg; 0.33 mmol) in benzene (2.4 ml) dropwise over 11 hr, via a needle placed directly above the refluxing solution. After further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (5 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed in vacuo, the residue dissolved in ethyl acetate (15 ml), sat. aq. KF (10 ml) added and stirred vigorously for 2 hr. The suspension was filtered, the organic layer washed with sat. aq. KF (10 ml) and water (10 ml) dried (MgSO₄), and concentrated under reduced pressure. The residue was chromatographed (ethyl acetate/petrol 40-100%,) to give in order of elution N-(2,5-dimethoxyphenylsulfonyl)-N-methyl acetamide (205) (26 mg, 21%), and N-(2,5-dimethoxyphenyl)-N-methyl acetamide (206) (49 mg, 51%).

N-(2,5-dimethoxyphenylsulfonyl)-N-methyl acetamide (205) as an orange oil; ν_max(film)/cm⁻¹ 2952, 1700 (C=O), 1500, 1466, 1354 (S=O), 1161 (S=O); δH (270 MHz; CDCl₃) 7.52 (1H, d, J 3.2, H-6), 7.13 (1H, dd, J 3.2 and 9.0, H-4), 6.96 (1H, d, J 9.4, H-3), 3.86 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 3.16 (3H, s, NCH₃), 2.40 (3H, s, COCH₃); δC (CDCl₃) 171.0 (1C, q, C=O), 153.0 (1C, q, C-5), 150.8 (1C, q, C-2), 126.5 (1C, q, C-1), 121.8 (1C, t, C-6), 115.3 (1C, t, C-4), 113.7 (1C, t, C-3), 56.5 (1C, p, OCH₃), 56.1 (1C, p, OCH₃), 32.8 (1C, p, NCH₃), 25.0 (1C, p, COCH₃); m/z 273 (M⁺), 231, 209, 178, 56 (100%); (Found: MNH₄⁺, 291.1015. C₁₁H₁₉N₂O₅S requires MNH₄⁺, 291.1015).

N-(2,5-dimethoxyphenyl)-N-methyl acetamide (206) as white needles, m.p. 84-86 °C (DCM/petrol); ν_max(film)/cm⁻¹ 3302 (NH), 2940, 1652 (C=O), 1503, 1227, 1046; δH
(270 MHz; CDCl₃) 6.83-6.74 (3H, m, ArH), 5.77 (1H, bs, NH), 3.79 (3H, s, OCH₃), 3.74 (3H, s, OCH₃), 3.51 (2H, s, CH₂), 2.71 (3H, d, J 4.6, NCH₃); δC (CDCl₃) 171.6 (1C, q, C=O), 153.7 (1C, q, C-5), 151.2 (1C, q, C-2), 124.7 (1C, q, C-1), 116.9 (1C, t), 113.1 (1C, t), 111.8 (1C, t), 56.0 (1C, p, OCH₃), 55.6 (1C, p, OCH₃), 38.5 (1C, s, CH₂), 26.3 (1C, p, NCH₃); m/z 209 (M⁺), 151, 137 (100%), 121; (Found: C, 63.0; H, 7.3; N, 6.9. C₁₁H₁₅NO₃ requires C, 63.1; H, 7.2; N, 6.7%)

Preparation of N-methyl-3,4-dimethoxybenzenesulfonamide (207)

To a suspension of 3,4-dimethoxybenzenesulfonyl chloride (3.6 g, 15 mmol) in aq. NaOH (10%, 21 ml) was added methylamine (25-30% in water, 4.6 ml) and the mixture stirred vigorously for 24 hr. The reaction mixture was diluted with water (20 ml), extracted with DCM (3x30 ml), dried (MgSO₄) and the solvent removed under reduced pressure, to give the sulfonamide 207 (2.1 g, 61%) as white needles, m.p. 123-124 °C; v_max(film)/cm⁻¹ 3291 (NH), 2939, 1325 (S=O), 1158 (S=O); δH (270 MHz; CDCl₃) 7.47 (1H, dd, J 2.2 and 8.6, H-6), 7.34 (1H, d, J 2.0, H-2), 6.94 (1H, d, J 8.3, H-5), 4.59 (1H, bs, NH), 3.93 (3H, s, OCH₃), 3.91 (3H, s, OCH₃), 2.63 (3H, d, J 5.6, NCH₃); δC (CDCl₃) 152.5 (1C, q, C-4), 149.1 (1C, q, C-3), 130.3 (1C, q, C-1), 121.2 (1C, t, C-6), 110.5 (1C, t, C-2), 109.6 (1C, t, C-5), 56.2 (1C, p, OCH₃), 55.6 (1C, p, OCH₃), 29.2 (1C, p, NCH₃); m/z 231 (M⁺), 201, 137 (100%); (Found: C, 46.7; H, 5.5; N, 5.9. C₉H₁₃NO₄S requires C, 46.7; H, 5.7; N, 6.1%)
Preparation of 2-chloro-N-(3,4-dimethoxyphenylsulfonyl)-N-methyl acetamide (208)

To a suspension of sodium hydride (60% dispersion in oil; 212 mg) in THF (5 ml) was added a solution of benzenesulfonamide 207 (1.0 g, 4.3 mmol) in THF (12 ml). Effervescence occurred and the mixture was stirred for 30 min. Chloroacetyl chloride (0.7 ml, 8.9 mmol) was added and the mixture stirred for 2 days. Water (50 ml) was added and the mixture extracted with DCM (3x50 ml), dried (MgSO4) and the solvent removed under reduced pressure. The residue was chromatographed (EtOAc/petrol 30-100%) to give acetamide 208 (630 mg, 47%) as white prisms, m.p. 118-120 °C (DCM/petrol); νmax (film)/cm⁻¹ 2939, 1709, 1509, 1371 (S=O), 1266, 1162 (S=O); δH (270 MHz; CDCl3) 7.51 (1H, dd, J 2.4 and 8.5, H-6), 7.32 (1H, d, J 2.4, H-2), 6.98 (1H, d, J 8.5, H-5), 4.61 (2H, s, CH₂Cl), 3.96 (3H, s, OCH₃), 3.93 (3H, s, OCH₃), 3.24 (3H, s, NCH₃); δC (CDCl3) 166.4 (1C, q, C=O), 154.0 (1C, q, C-4), 149.5 (1C, q, C-3), 129.2 (1C, q, C-1), 121.9 (1C, t, C-6), 110.8 (1C, t, C-2), 109.7 (1C, t, C-5), 56.3 (2C, p, OCH₃), 44.1 (1C, s, CH₂Cl), 33.4 (1C, p, NCH₃); m/z 309, 307 (M⁺), 154 (100%), 137 (100%), 90 (100%); (Found: C, 42.8; H, 4.25; N, 4.4. C₁₁H₁₄ClNO₅S requires C, 42.9; H, 4.6; N, 4.55%)
Preparation of \(N-(3,4\text{-dimethoxyphenylsulfonyl})-2\text{-iodo-}N\text{-methyl acetamide (209)}\)

To sodium iodide (779 mg, 5.5 mmol) in acetone (5 ml) at reflux was added a solution of acetamide 208 (562 mg, 1.8 mmol) in acetone (6 ml) and the mixture left overnight under reflux. The mixture was cooled to room temperature, DCM (10 ml) was added, filtered and the solvent removed under reduced pressure. The residue was dissolved in DCM (15 ml), washed with sodium thiosulfate (2x15 ml), water (10 ml), dried (MgSO4) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75-100%) to give acetamide 209 (527 mg, 72%) as white prisms, m.p. 87-89 °C; \(\nu_{\text{max}}(\text{film})/\text{cm}^{-1}\) 2952, 1684 (C=O), 1353 (S=O), 1164 (S=O); \(\delta_H (270 \text{ MHz; CDCl}_3)\) 7.57 (1H, dd, J 2.4 and 8.5, H-6), 7.42 (1H, d, J 2.2, H-2), 6.97 (1H, d, J 8.5, H-5), 4.27 (2H, s, CH\(_2\)I), 3.96 (3H, s, OCH\(_3\)), 3.95 (1H, s, OCH\(_3\)), 3.24 (3H, s, NCH\(_3\)); \(\delta_C (\text{CDCl}_3)\) 167.7 (1C, q, C=O), 153.9 (1C, q, C-4), 149.3 (1C, q, C-3), 129.2 (1C, q, C-1), 122.3 (1C, t, C-6), 110.6 (1C, t, C-2), 109.1 (1C, t, C-5), 56.4 (1C, p, OCH\(_3\)), 56.3 (1C, p, OCH\(_3\)), 33.8 (1C, p, NCH\(_3\)), -1.6 (1C, s, CH\(_2\)I); \(m/z\) 399 (M\(^+\)) 335, 231, 201, 182, 154 (100%); (Found: M\(^+\), 398.9637. C\(_{11}\)H\(_{14}\)INO\(_5\)S requires \(M^+\), 398.9637).
Experimental

Reaction of \(N-(3,4\text{-dimethoxyphenyl}sulfonyl)-2\text{-iodo-N-methyl acetamide} \(209\)) with tri-n-butyltin hydride

\[
\text{MeO} \quad \text{NHMe} \\
\text{MeO} \\
\text{MeO} \quad \text{OMe}
\]

To a stirred solution of acetamide \(209\) (344 mg, 0.86 mmol) in benzene (167 ml) at reflux, was added a solution of tri-n-butyltin hydride (310 \(\mu\)l, 1.13 mmol) and AIBN (100 mg; 0.61 mmol) in benzene (4.5 ml) dropwise over 11 hr, \(\text{via}\) a needle placed directly above the refluxing solution. After further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed \(\text{in vacuo}\), the residue dissolved in ethyl acetate (20 ml), sat. aq. KF (15 ml) added and stirred vigorously for 2 hr. The suspension was filtered to a separation funnel, the organic layer washed with sat. aq. KF (15 ml) and water (15 ml) dried (MgSO\(_4\)), and concentrated under reduced pressure. Analysis of the \(^1\text{H}\) nmr spectrum of the crude mixture shows a doublet at 2.75 ppm and a singulet at 3.53 ppm, which probably corresponds to the \textit{ipso} product \(211\text{a}\) in a relative ratio of the three products of 1:1:1. Due to its high polarity it could not be removed from the silica, when the mixture was chromatographed. The residue was chromatographed (ethyl acetate/petrol 50-100%) to give in order of elution \(N-(3,4\text{-dimethoxyphenyl}sulfonyl)\)-\(N\)-methyl acetamide \(210\) (62 mg, 26%) and 5,6-dimethoxy-2,3-dihydro-1-methyl-indol-2-one \(211\) (37 mg, 21%).

\(N-(3,4\text{-dimethoxyphenyl}sulfonyl)\)-\(N\)-methyl acetamide \(210\) as an orange oil; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2943, 1694 (C=O), 1510, 1356 (S=O), 1261, 1154 (S=O); \(\delta\)(CDCl\(_3\)) 7.47 (1H, dd, \(J\) 2.2 and 8.5, H-6), 7.30 (1H, d, \(J\) 2.2, H-2), 6.94 (1H, d, \(J\) 8.5, H-5), 3.93 (3H, s, OCH\(_3\)), 3.91 (3H, s, OCH\(_3\)), 3.25 (3H, s, NCH\(_3\)), 2.37 (3H, s, COCH\(_3\)); \(\delta\)(CDCl\(_3\)) 170.2 (1C, q, C=O), 153.4 (1C, q), 149.2 (1C, q), 130.5 (1C, q), 121.4 (1C, t), 110.6 (1C, t), 109.7 (1C, t), 56.2 (2C, p, OCH\(_3\)), 32.9 (1C, p, NCH\(_3\)),...
5,6-dimethoxy-2,3-dihydro-1-methyl-indol-2-one (211) as red needles, m.p. 118-119.5 °C (DCM/petrol); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2937, 1703 (C=O), 1378, 1070; $\delta_{\text{H}}$ (270 MHz; CDCl$_3$) 6.86 (1H, s, H-7), 6.44 (1H, s, H-4), 3.90 (3H, s, OCH$_3$), 3.83 (3H, s, OCH$_3$), 3.44 (2H, s, ArCH$_2$), 3.18 (3H, s, NCH$_3$); $\delta_{\text{C}}$(CDCl$_3$) 175.4 (10, q, C=O), 149.4 (1C, q), 144.9 (1C, q), 138.9 (1C, q), 115.1 (1C, q), 109.9 (1C, t), 94.4 (1C, t), 56.9 (1C, p, OCH$_3$), 56.4 (1C, p, OCH$_3$), 35.8 (1C, s, ArCH$_2$), 26.2 (1C, p, NCH$_3$); m/z EI: 207 (M$^+$), 192 (100%), 164, 136;

Preparation of trichloro-$N$-(p-toluenesulfonyl) acetamide (214)

To a suspension of sodium hydride (60% dispersion in oil; 569 mg) in THF (14 ml) was added a solution of benzenesulfonamide 150 (2.2 g, 12 mmol) in THF (20 ml). Effervescence occurred and the mixture was stirred for 1 hr. Trichloroacetyl chloride (2.0 ml, 18 mmol) was added and the mixture stirred for 4 days. Water (40 ml) was added and the mixture extracted with DCM (3x30 ml), dried (MgSO$_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75%) to give acetamide 214 (1.9 g, 47%) as white needles, m.p. 130-132.5 °C (DCM/petrol); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1695 (C=O), 1361 (S=O), 1169 (S=O); $\delta_{\text{H}}$ (270 MHz; CDCl$_3$) 7.92 (2H, d, $J$ 8.3, H-2 and H-6), 7.35 (2H, d, $J$ 8.3, H-3 and H-5), 3.78 (3H, s, NCH$_3$), 2.45 (3H, s, ArCH$_3$); $\delta_{\text{C}}$ (CDCl$_3$) 158.9 (1C, q, C=O), 145.7 (1C, q, C=O), 134.4 (1C, q, C-4), 129.6 (2C, t, C-2 and C-6), 128.6 (2C, t, C-3 and C-5), 92.2 (1C, q, CCl$_3$), 36.1 (1C, p, NCH$_3$), 21.7 (1C, p, ArCH$_3$); m/z 265, 267, 269 (M$^+$-SO$_2$), 173, 155; (Found: C, 36.4; H, 2.85; N, 4.4. C$_{10}$H$_{10}$Cl$_3$NO$_3$S requires C, 36.3; H, 3.05; N, 4.2%).
Reaction of trichloro-N-(p-toluenesulfonyl) acetamide (214) with Copper (I) Chloride

To the sulfonamide 214 (98.6 mg; 0.30 mmol) and CuCl (9 mg; 0.09 mmol) in DCM (2 ml), under argon, was added TMEDA (45 μl, 0.30 mmol) and the mixture turned immediately dark green. After 1 hr, the solvent was removed under reduced pressure, and the residue chromatographed (DCM/petrol 50-100% and EtOAc) to give in order of elution sulfonamide 214 (14 mg, 14%), dichloro-N-(p-toluenesulfonyl) acetamide (215) (traces), dichloro-N-methyl-p-tolylacetamide (216) (25 mg, 36%), and sulfonamide 150 (21 mg, 39%);

dichloro-N-(p-toluenesulfonyl) acetamide (215) as a clear oil; ν_max(film)/cm⁻¹ (C=O), (S=O), (S=O); δ_H (270 MHz; CDCl₃) 7.82 (2H, d, J 8.5, H-2 and H-6), 7.39 (2H, d, J 8.5, H-3 and H-5), 7.11 (1H, s, CHCl₂), 3.26 (3H, s, NCH₃), 2.46 (3H, s, ArCH₃); δ_C (CDCl₃) 164.3 (1C, q, C=O), 146.1 (1C, q, C-S), 134.2 (1C, q, C-C), 130.2 (2C, t), 127.9 (2C, t), 64.8 (1C, t, CHCl₂), 33.9 (1C, p, NCH₃), 21.7 (1C, p, ArCH₃); m/z (FAB) 300, 298, 296 (MH⁺), 155, 91; (Found: MH⁺, 295.9912. C₁₀H₁₂Cl₂NO₃S requires MH, 295.9915).

dichloro-N-methyl-p-tolylacetamide (216) as a clear oil; ν_max(film)/cm⁻¹ 3351 (NH), 2925, 1680 (C=O), 1518; δ_H(270 MHz; CDCl₃) 7.59 (2H, d, J 8.5, H-2 and H-6), 7.20 (2H, d, J 8.5, H-3 and H-5), 6.80 (1H, bs, NH), 2.94 (3H, d, J 4.9, NCH₃), 2.36 (3H, s, ArCH₃); δ_C(CDCl₃) 166.2 (1C, q, C=O), 140.0 (1C, q, C-S), 136.7 (1C, q), 129.1 (2C, t), 126.5 (2C, t), 86.7 (1C, q, CCl₂), 27.7 (1C, p, NCH₃), 21.1 (1C, p, ArCH₃); m/z 235, 233, 231 (M⁺), 196, 176, 174 (100%), 58; (Found: MH⁺, 232.0292. C₁₀H₁₂Cl₂NO requires MH, 232.0296).
Preparation of \(N-(p\text{-toluenesulfonyl})\ (O\text{-methylthiocarbonate})\ acetamide (221)

![Chemical structure](image)

To a suspension of NaH (60\% dispersion in oil; 120 mg) in THF (10 ml) was added methanol (120 \(\mu l\), 3.0 mmol). After 20 min. carbon disulfide (540 \(\mu l\), 9.0 mmol) was added and the mixture left at r.t. for 30 min. Then, a solution of the sulfonamide 196 (1.1 g, 3 mmol) in THF (10 ml) was added and the mixture left for another hour. Acetic acid (2 ml) was added and the mixture poured onto water, extracted with ether (3x25 ml), dried (MgSO4) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50\%) to give the xanthate 221 (731 mg, 73\%) as yellow prisms, m.p. 66-68 °C; \(\nu_{max}\) (film)/cm\(^{-1}\) 2946, 1702 (C=O), 1358 (S=O), 1234, 1162 (S=O), 1066; \(\delta\)H (400 MHz; CDCl\(_3\)) 7.83 (2H, d, \(J\ 8.4, \text{H-2 and H-6}\)), 7.36 (2H, d, \(J\ 8.6, \text{H-3 and H-5}\)), 4.46 (2H, s, CH\(_2\)), 4.11 (3H, s, OCH\(_3\)), 3.27 (3H, s, NCH\(_3\)), 2.44 (3H, s, ArCH\(_3\)); \(\delta\)C (CDCl\(_3\)) 166.9 (1C, q, C=O), 145.4 (1C, q, C-1), 135.3 (1C, q, C-1), 130.1 (2C, t, C-2 and C-6), 127.6 (2C, t, C-3 and C-5), 60.8 (1C, p, OCH\(_3\)), 42.3 (1C, s, SCH\(_2\)), 33.5 (1C, s, NCH\(_3\)), 21.7 (1C, p, ArCH\(_3\)); \(m/z\) (EI) 333 (M\(^+\)), 149, 91 (100\%); (CI) 351 (M\(^+\)+NH\(_4\)), 334 (MH\(^+\)), 149 (100\%); (Found: MH\(^+\), 334.0241. C\(_{12}\)H\(_{16}\)NO\(_4\)S\(_3\) requires \(MH^+, 334.0241\)).
Reaction of \( N\)-(p-toluenesulfonyl) (O-methyldithiocarbonate) acetamide (221) under UV light

A solution of the xanthate 221 (101 mg, 0.3 mmol) in toluene (6 ml) at reflux was irradiated for 16 hr using a medium pressure mercury vapour lamp (125 W). The solvent was removed under reduced pressure and the residue chromatographed on silica gel (ether/petrol 25-100% and EtOAc) to give, in order of elution, indolone 198 (5 mg, 10%) and acetamide 199 (13 mg, 27%).

Preparation of O-ethyl triphenyltin xanthate (222)

To a mixture of chlorotriphenyltin (3.9 g, 1.0 mmol) and potassium O-ethyl xanthate (1.6 g, 1.0 mmol) under argon was added dry ether (25 ml), and stirred at r.t. for 24 hr. The mixture was filtered by cannula and the solvent removed under reduced pressure to give O-ethyl triphenyltin xanthate (222) (3.3 g, 69%), which was used without further purification.
Reaction of 196 under visible light, in the presence of tri-phenyltin xanthate

![Chemical structure](image)

A solution of the acetamide 196 (108 mg, 0.31 mmol), O-ethyl triphenyltin xanthate (222) (289 mg, 0.61 mmol) and hexaphenylditin (32 mg) in benzene (6 ml) was irradiated with a tungsten lamp (500W) for 5 hr. The solvent was removed under reduced pressure and the residue chromatographed (ether/petrol 10-100% and EtOAC) to give, in order of elution, \(N\)-(p-toluenesulfonyl) (O-ethyldithiocarbonate) acetamide (223) (82 mg, 77%) and sulfonamide 150 (10 mg, 17%).

\(N\)-(p-toluenesulfonyl) (O-ethyldithiocarbonate) acetamide (223) as an oil;

\[\nu_{\text{max}}(\text{film})/\text{cm}^{-1} \quad 1702 (\text{C}=\text{O}), 1359 (\text{S}=\text{O}), 1231, 1163 (\text{S}=\text{O}), 1049; \delta_H(400 \text{ MHz}; \text{CDCl}_3) \quad 7.82 (2\text{H, d, } J 8.4, \text{H-2 and H-6}), 7.35 (2\text{H, d, } J 7.9, \text{H-3 and H-5}), 4.55 (2\text{H, q, } J 7.1, \text{OCH}_2), 4.44 (2\text{H, s, S-CH}_2), 3.27 (3\text{H, s, NCH}_3), 2.43 (3\text{H, s, ArCH}_3), 1.35 (3\text{H, t, } J 7.1, \text{CH}_2\text{CH}_3); \delta_C(\text{CDCl}_3) \quad 166.9 (1\text{C, q, C}=\text{O}), 145.3 (1\text{C, q}), 135.3 (1\text{C, q}), 130.2 (2\text{C, t}), 127.6 (2\text{C, t}), 70.7 (1\text{C, s, OCH}_2), 41.9 (1\text{C, s, S-CH}_2), 33.4 (1\text{C, p, NCH}_3), 21.6 (1\text{C, p, ArCH}_3), 13.7 (1\text{C, p, CH}_2\text{CH}_3); m/z \quad 347 (\text{M}^+), 155, 91 (100%)\]
References

Appendix 1
Appendix 2
Details of the crystal structure determination of C$_{11}$H$_{17}$O$_{5}$S$_{1}$.

A colourless single crystal of approximate size 0.65×0.50×0.38 mm was mounted on a glass fibre. All geometric and intensity data were taken from this sample using an automated four-circle diffractometer (Nicolet R3mV) equipped with Mo-Kα radiation (λ=0.71073 Å). Important crystallographic parameters are summarised in the table.

The lattice vectors were identified by application of the automatic indexing routine of the diffractometer to the positions of 22 reflections taken from a rotation photograph and centred by the diffractometer. The ω-2θ technique was used to measure 1370 reflections (1231 unique) in the range 5°≤2θ≤50°. Three standard reflections (remeasured every 97 scans) showed no significant loss in intensity during data collection. The data were corrected for Lorentz and polarisation effects. The 1061 unique data with I≥2.0σ(I) were used to solve and refine the structure in the orthorhombic space group Pn2₁a.

The structure was solved by direct methods and developed by using alternating cycles of least-squares refinement and difference-fourier synthesis. The non-hydrogen atoms were refined anisotropically while hydrogens were placed in idealised positions (C-H 0.96 Å) and assigned a common isotropic thermal parameter (U=0.08 Å$^2$). The final cycle of least-squares refinement included 180 parameters for 1061 variables and did not shift any parameter by more than 0.005 times its standard deviation. The final R values were 0.0388 and 0.0447, and the final difference-fourier was featureless with no peaks greater than 0.24 eÅ$^{-3}$.

Structure solution used the SHELXTL PLUS program package on a microVax II computer.
Table 1. Crystallographic data for \( \text{C}_{14}\text{H}_{12}\text{O}_{5}\text{S}_{1}. \)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>( \text{C}<em>{14}\text{H}</em>{12}\text{O}<em>{5}\text{S}</em>{1} )</td>
</tr>
<tr>
<td>Space group</td>
<td>Pn2(\overline{1})a</td>
</tr>
<tr>
<td>(a, \AA)</td>
<td>8.526(2)</td>
</tr>
<tr>
<td>(b, \AA)</td>
<td>10.190(2)</td>
</tr>
<tr>
<td>(c, \AA)</td>
<td>15.297(4)</td>
</tr>
<tr>
<td>(\alpha, \text{deg})</td>
<td>90.0</td>
</tr>
<tr>
<td>(\beta, \text{deg})</td>
<td>90.0</td>
</tr>
<tr>
<td>(\gamma, \text{deg})</td>
<td>90.0</td>
</tr>
<tr>
<td>(V, \AA^3)</td>
<td>1329</td>
</tr>
<tr>
<td>(Z)</td>
<td>4</td>
</tr>
<tr>
<td>(F(000))</td>
<td>608</td>
</tr>
<tr>
<td>(d_{calc}, \text{g/cm}^3)</td>
<td>1.46</td>
</tr>
<tr>
<td>Cryst. size, mm</td>
<td>0.65x0.50x0.38</td>
</tr>
<tr>
<td>(\mu(\text{Mo-K}_\alpha), \text{cm}^{-1})</td>
<td>2.47</td>
</tr>
<tr>
<td>Data collection instrument</td>
<td>Nicolet R3mV</td>
</tr>
<tr>
<td>Radiation</td>
<td>(\text{Mo-K}_\alpha (\lambda = 0.71073 \AA) )</td>
</tr>
<tr>
<td>Orientation reflections: no.;</td>
<td>22</td>
</tr>
<tr>
<td>range (2(\Theta))</td>
<td>16(\leq)2(\Theta)(\leq)24(\text{o})</td>
</tr>
<tr>
<td>Temp., K</td>
<td>293</td>
</tr>
<tr>
<td>Data measured</td>
<td>1370</td>
</tr>
<tr>
<td>Unique data</td>
<td>1231</td>
</tr>
<tr>
<td>No. of unique with (I \geq 2.0\sigma(I))</td>
<td>1061</td>
</tr>
<tr>
<td>No. of parameters</td>
<td>180</td>
</tr>
<tr>
<td>(R^a)</td>
<td>0.0388</td>
</tr>
<tr>
<td>(R_w^b)</td>
<td>0.0447</td>
</tr>
<tr>
<td>Weighting scheme</td>
<td>(w^{-1} = \sigma^2(F) + 0.00158F^2)</td>
</tr>
<tr>
<td>Largest shift/esd, final cycle</td>
<td>0.005</td>
</tr>
<tr>
<td>Largest peak, (e/\AA^3)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

\(^a\) \(R = \Sigma|F_o| - |F_c|/\Sigma|F_o|\)

\(^b\) \(R_w = \Sigma w^b [|F_o| - |F_c|]/\Sigma w^b |F_o|\)
Table 1. Atomic coordinates ($x10^4$ Å) and equivalent isotropic displacement parameters ($Å^2x10^3$) for C$_{14}$H$_2$O$_2$S$_1$.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)</td>
<td>2384(1)</td>
<td>2284</td>
<td>9160(1)</td>
<td>52(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>1861(4)</td>
<td>2177(6)</td>
<td>8281(2)</td>
<td>78(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>1836(4)</td>
<td>3334(4)</td>
<td>9690(3)</td>
<td>70(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>1914(4)</td>
<td>933(3)</td>
<td>9594(2)</td>
<td>48(1)</td>
</tr>
<tr>
<td>O(4)</td>
<td>6797(4)</td>
<td>3332(5)</td>
<td>11553(2)</td>
<td>65(1)</td>
</tr>
<tr>
<td>O(5)</td>
<td>8992(3)</td>
<td>2508(5)</td>
<td>11001(2)</td>
<td>69(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>2551(4)</td>
<td>620(4)</td>
<td>10424(3)</td>
<td>37(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>1675(5)</td>
<td>-293(5)</td>
<td>10886(3)</td>
<td>44(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>2203(5)</td>
<td>-685(5)</td>
<td>11691(3)</td>
<td>48(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>3569(5)</td>
<td>-185(5)</td>
<td>12031(3)</td>
<td>50(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>4425(5)</td>
<td>729(5)</td>
<td>11549(3)</td>
<td>43(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>3945(4)</td>
<td>1149(4)</td>
<td>10729(2)</td>
<td>36(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>4862(4)</td>
<td>2194(5)</td>
<td>10226(2)</td>
<td>38(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>4450(5)</td>
<td>2233(6)</td>
<td>9256(2)</td>
<td>46(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>5148(6)</td>
<td>1126(5)</td>
<td>8745(3)</td>
<td>56(2)</td>
</tr>
<tr>
<td>C(10)</td>
<td>6551(6)</td>
<td>668(6)</td>
<td>8975(3)</td>
<td>60(2)</td>
</tr>
<tr>
<td>C(11)</td>
<td>7371(5)</td>
<td>1253(6)</td>
<td>9704(3)</td>
<td>53(2)</td>
</tr>
<tr>
<td>C(12)</td>
<td>6632(4)</td>
<td>1998(5)</td>
<td>10286(3)</td>
<td>42(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>7450(5)</td>
<td>2683(5)</td>
<td>11014(3)</td>
<td>47(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>9877(6)</td>
<td>3186(7)</td>
<td>11654(3)</td>
<td>77(2)</td>
</tr>
</tbody>
</table>

Equivalent isotropic $U$ defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

Table 2. Bond lengths (Å) for C$_{14}$H$_2$O$_2$S$_1$.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)-O(1)</td>
<td>1.421 (4)</td>
</tr>
<tr>
<td>S(1)-O(3)</td>
<td>1.580 (4)</td>
</tr>
<tr>
<td>O(3)-C(1)</td>
<td>1.416 (5)</td>
</tr>
<tr>
<td>O(5)-C(13)</td>
<td>1.327 (5)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.387 (6)</td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.395 (7)</td>
</tr>
<tr>
<td>C(6)-C(7)</td>
<td>1.528 (6)</td>
</tr>
<tr>
<td>C(7)-C(12)</td>
<td>1.525 (5)</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.331 (7)</td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.329 (7)</td>
</tr>
</tbody>
</table>
### Table 4: Anisotropic displacement parameters (×10^3) for C'H^+9.5^+.

<table>
<thead>
<tr>
<th>(T) 18-</th>
<th>(T) 20-</th>
<th>(T) 9-</th>
<th>(T) 7-</th>
<th>(T) 10-</th>
<th>(T) 1-</th>
<th>(T) 5-</th>
<th>(T) 0-</th>
<th>(T) 6-</th>
<th>(T) 1-</th>
<th>(T) 6-</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
<td>0.013</td>
</tr>
</tbody>
</table>

**Table 5:** Bond angles (°) for C'H^+9.5^+. Appendix 220
Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement parameters ($\AA^2 x10^4$) for C$_4$H$_{12}$O$_5$S$_1$.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(2A)</td>
<td>720</td>
<td>-640</td>
<td>10648</td>
<td>80</td>
</tr>
<tr>
<td>H(3A)</td>
<td>1610</td>
<td>-1307</td>
<td>12027</td>
<td>80</td>
</tr>
<tr>
<td>H(4A)</td>
<td>3933</td>
<td>-464</td>
<td>12595</td>
<td>80</td>
</tr>
<tr>
<td>H(5A)</td>
<td>5380</td>
<td>1073</td>
<td>11790</td>
<td>80</td>
</tr>
<tr>
<td>H(7A)</td>
<td>4615</td>
<td>3034</td>
<td>10475</td>
<td>80</td>
</tr>
<tr>
<td>H(8A)</td>
<td>4861</td>
<td>3034</td>
<td>9018</td>
<td>80</td>
</tr>
<tr>
<td>H(9A)</td>
<td>4579</td>
<td>758</td>
<td>8263</td>
<td>80</td>
</tr>
<tr>
<td>H(10A)</td>
<td>7000</td>
<td>-63</td>
<td>8669</td>
<td>80</td>
</tr>
<tr>
<td>H(11A)</td>
<td>8480</td>
<td>1118</td>
<td>9761</td>
<td>80</td>
</tr>
<tr>
<td>H(14B)</td>
<td>10973</td>
<td>2994</td>
<td>11589</td>
<td>80</td>
</tr>
<tr>
<td>H(14C)</td>
<td>9711</td>
<td>4113</td>
<td>11593</td>
<td>80</td>
</tr>
<tr>
<td>H(14D)</td>
<td>9531</td>
<td>2907</td>
<td>12221</td>
<td>80</td>
</tr>
</tbody>
</table>