The synthesis of novel linked heterocycles

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The Synthesis of Novel Linked Heterocycles

by

Jason Bloxham

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy of Loughborough University

December 1996

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Abstract

Chapter 1 reviews the literature with regard to the synthesis of substituted carbazoles via the cycloaddition reactions of indole-2,3-quinodimethanes and its equivalents with dienophiles. Particular attention is paid to the synthesis and reactions of pyrano[3,4-\(b\)]indol-3-ones.

Chapter 2 describes the synthesis of a variety of linked indole-3-acetic acid derivatives, where the linkage is either through the indole nitrogen, the 2-position or the acetic acid residue in the 3-position. The preparation and subsequent Diels-Alder reactions of the derived linked pyrano[3,4-\(b\)]indol-3-ones are also described.

Chapter 3 investigates the possibility of forming a benzothiophene containing polymer via a novel double Diels-Alder reaction. The preparation of thieno[2,3-\(c\)]pyran-3-ones and their transformation into benzothiophenenes are described.

Chapter 4 briefly discusses the relevance of molecular recognition to a variety of fields and introduces the idea of folded and stretched conformations in non-rigid systems. The work described concentrates on the solid state structures obtained for a variety of simple linked heterocycles.
Acknowledgements

The work contained in this thesis and its preparation would not have been possible without the help of a number of people. I have often cursed my supervisor, Christopher J. Moody, for giving me this project but it has always been challenging and ultimately I have enjoyed it and would therefore like to thank him for his support. Chemical stimulation and discussion with Andrew Lightfoot, Dave Miller and Mike Simcox has helped greatly on days when the highs and lows of chemistry are all too close.

Those hours, rare or otherwise, away from the lab wouldn't have been the same without Andrew Lightfoot whose antics on most fronts has been great to both witness and at times participate in. Neil Cruden deserves a special note for putting up with my excuses over all these years and for still being the best of friends. Kirk Lewis and particularly his sense of tact have caused much amusement to me and I will miss him. Fawaz Aldabbagh, Natalie Bell and Julie Ince all deserve a special mention for being good friends.

I would like to thank the EPSRC for the funding I have received particularly the extra 3 months due to unforeseen circumstances. I appreciate the technical support that I have received and would especially like to thank Alex Slawin for excellent work on X-ray crystal structures and Linda Sands for mass spectra.

Special thanks must go to Rachel who has always believed in me. The amount and depth of her love for me is still a surprise if at times completely undeserved.

My greatest thanks must go to my parents. They have always supported all my decisions, encouraged me and given me all their love. Without them I would never have got this far and I dedicate this thesis to them.
Can't rest on your laurels now.....
Not when you've got none.

Joy Division (Ian Curtis)
To

Mum and Dad

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Indole-2,3-quinodimethanes and their Stable Equivalents in the Synthesis of Carbazoles

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Abbreviations

Ac    acetyl
Ar    aryl
Bn    benzyl
Boc   tert-butoxycarbonyl
Bu    butyl
Bz    benzoyl
DCM   dichloromethane
DMAD  dimethyl acetylenedicarboxylate
DMAP  4-dimethylaminopyridine
DMF   N,N-dimethylformamide
DMSO  dimethylsulfoxide
Et    ethyl
LDA   lithium diisopropylamide
mCPBA meta-chloroperbenzoic acid
Me    methyl
NBS   N-bromosuccinimide
Ph    phenyl
PPA   polyphosphoric acid
Pr    propyl
pTSA  para-toluenesulfonic acid
PVK   poly(vinylcarbazole)
py    pyridine
PyOTs pyridinium tosylate
TBAF  tetrabutylammonium fluoride
TCNQ  tetracyano-p-quinodimethane
TFAA  trifluoroacetic anhydride
THF   tetrahydrofuran
TLC   thin layer chromatography
TMS   trimethylsilyl
TTF   tetrathiofulvalene
Chapter One

Indole-2,3-quinodimethanes and their Stable Equivalents in the Synthesis of Carbazoles
1.1. Introduction

Carbazole was first discovered as a component of coal tar in 1872 by Graebe and Glaser\(^1\) however carbazole containing alkaloids were not identified until the 1960's.\(^{1a}\) The usually highly functionalised carbazole nucleus of these new natural product targets presented organic chemists with a new problem since polyfunctionalisation of carbazole in a regioselective sense was not known. A potential route to carbazoles is via the Diels-Alder reaction.

The Diels-Alder reaction has proved to be one of, if not the most, synthetically useful tool in the organic chemists armoury for the construction of 6-membered rings. Although some claim that the Diels-Alder reaction has stopped organic chemists thinking, it has allowed the fast assembly of comparatively complex ring structures often with high levels of regiocontrol.

The use of reactive intermediates or transient species in Diels-Alder reactions has been exemplified using ortho-quinodimethanes (ortho-xylylenes).\(^2,3\) In most cases these are non-isolable species which are generated in situ. Elimination from 1,2-bis(bromomethyl)benzene gave ortho-quinodimethane 1 which underwent Diels-Alder reaction with N-phenylmaleimide (Scheme 1).\(^4\)

\[\text{Scheme 1}\]

This same methodology can be extended to the use of a heterocyclic analogues of o-quinodimethanes. A Diels-Alder reaction of these analogues then gives a route into substituted heterocycles (Scheme 2).
In particular such reactions of indole-2,3-quinodimethanes have been used as a route to polysubstituted carbazoles. This chapter reviews the literature concerning the synthesis of carbazoles by the Diels-Alder reaction of indole-2,3-quinodimethanes or their stable equivalents.

1.2. Generation and Reaction of Indole-2,3-quinomethanes

There has been considerable interest in the facile generation of indole-2,3-quinodimethanes. Some of the standard methods for the generation of o-quinodimethanes, e.g. heating 1,2-benzenecyclobutene, would be inappropriate for the synthesis of heterocyclic derivatives due to the complexity of their formation. Magnus investigated the possibility of using 2 (Scheme 3), after treatment with TBAF, as a source of indole-2,3-quinodimethane 3 for an intramolecular reaction. His findings, however, suggested that a simple methyl substituent in the 2-position (4) should be sufficient to deliver the required reactive intermediate. This was indeed found to be the case. The methodology was then extended to the synthesis of aspidospermidine 7 (Scheme 4).

The imine precursor 4 was prepared from the corresponding aldehyde and the amine. The cyclisation was bought about by treatment with β,β,β-trichloroethyl chloroformate at 135 °C to give the cis-fused tetracyclic carbamate (41%). Zinc/acetic acid reduction cleaved the carbamate (71%) and subsequent reaction with PhSCH2COCl followed by mCPBA oxidation gave the sulfoxide 5. Pummerer type reaction was then carried out using trifluoroacetic anhydride initially at 0 °C and then at 130 °C to give 6. The thio-phenyl group was removed with Raney nickel.
Lithium aluminium hydride reduced both the carbonyl and the isolated alkene to furnish the natural product 7.

Magnus has further exploited this methodology for the synthesis of both enantiomers of methoxytabersonine using 8 as both an acylating agent and a chiral auxiliary.6

The work of Magnus involved the intramolecular Diels-Alder reaction of an indole-2,3-quinodimethane but Marinelli has pioneered the work concerning the generation and intermolecular cycloadditions of indole-2,3-quinodimethanes.7 The indole-2,3-quinodimethane was generated in this case by the removal of a silyl group and subsequent elimination of trimethylamine from 9. The synthesis of 9 started with the 2-methylindole, Mannich reaction (AcOH, NHMe2, CH2O) yielded the gramine derivative. Boc protection, followed by lithiation (n-BuLi) and TMSCl quench gave the silyl derivative. Quaternisation with methyl iodide in ethanol gave 9.
Treatment with TBAF in acetonitrile in the presence of N-phenylmaleimide gave 57% of the desired tetrahydrocarbazole 10 (Scheme 5). The cycloaddition with methyl acrylate was found to occur only if 40 equivalents of dienophile were employed, otherwise a dimeric species was produced. The reactivity when a methyl was introduced rather than Boc was found to be disappointing by comparison.

Nandin de Carvalho and co-workers used a slightly different method of generation of indole-2,3-quinodimethanes before trapping them after a variety of cycloadditions. The di(bromomethyl)indole 11 (Scheme 6) was treated at -78 °C with sodium iodide to produce the diiodomethylindole 12, the excess iodide present then causes the elimination of iodine and generates the reactive intermediate. Diels-Alder reactions with N-phenylmaleimide or dimethyl fumarate yield the expected tetrahydrocarbazoles in good yield (80 and 77% respectively).

The most interesting of the products, however, was produced by reacting the indole-2,3-quinodimethane with SO₂ (Figure 1).

This 1,3-dihydrothieno[3,4-d]indole-2,2-dioxide is a masked stable indole-2,3-quinodimethane equivalent. Heating these compounds at 80-110 °C resulted in the formation of the indole-2,3-quinodimethane, which was then capable of undergoing
cycloadditions, due to expulsion of sulfur dioxide. The results obtained on generating the indole-2,3-quinodimethane (R = COMe, SO2CF3, CO2CMe3 or COCF3) in the presence of methyl acrylate (Scheme 7) showed a definite trend, the ratio of the 3:2 isomers were between 66:34 and 75:25.

![Scheme 7]

The previous examples all generated indole-2,3-quinodimethanes which then underwent a cycloaddition. There are a number of examples of molecules which are equivalent to indole-2,3-quinodimethanes and undergo similar cycloadditions but they are more stable. These compounds are easy to handle, however, further manipulation of the cycloaddition products may be required to give the desired products.

1.3. Stable Indole-2,3-quinodimethane Equivalents

4-(Phenylsulfonyl)-4H-furo[3,4-b]indoles

These compounds have been developed as stable indole-2,3-quinodimethane equivalents by Gribble. The synthesis of 4-(phenylsulfonyl)-4H-furo[3,4-b]indole 15 was achieved as in Scheme 8. Indole-3-carboxaldehyde was protected using LDA and benzenesulfonyl chloride to yield the N-phenylsulfonyl derivative 13. The aldehyde was then reduced to the alcohol using sodium borohydride. Treatment with 2.1 eq. of t-butyllithium generated the dianion which was quenched with N,N-dimethylformamide to give the aldehyde 14. Ring closure was then brought about using potassium fluoride and hydroquinone in acetic acid.
This 4-(phenylsulfonyl)-4H-furo[3,4-b]indole was then reacted with benzyne to give 16 (Scheme 9). Deoxygenation was then achieved using sodium borohydride/trifluoroacetic acid followed by methanolic sodium hydroxide to afford the carbazole 17. The Diels-Alder reactions with dimethyl acetylenedicarboxylate and N-phenylmaleimide have also been described.

A more complex target is 18 and this too has been achieved using a 4H-furo[3,4-b]indole (Scheme 10). The important feature of this system was of course the initial double Grignard addition to form the alcohol 19 which can then be converted, via a similar sequence to that already described, to the diene 20. Reaction with 2-equivalents of benzyne followed by deprotection and deoxygenation yielded the bis-carbazole 18.
This methodology has been extended to the synthesis of ellipticine and isoellipticine. The synthesis of 21 was carried out in a similar method to that previously described. Pyridyne was then generated *in situ* and the Diels-Alder reaction produced a 38% yield of two regioisomeric products (Scheme 11).
Deoxygenation and deprotection were achieved by sodium borohydride in refluxing methanol. Moody has also approached this product via the Diels-Alder reaction of 1,4-dimethylpyrano[3,4-b]indol-3-one with pyridyne and also found no regioselectivity, but the number of steps in his synthesis is less.\textsuperscript{12}

2,4-Dihydropyrrolo[3,4-b]indole

Sha has shown that analogues of 22 can be used in Diels-Alder reactions.\textsuperscript{13} This type of compound was first reported by Welch after lithium aluminium hydride reduction of the corresponding 1,4-dihydropyrrolo[3,4-b]indol-3(2H)-one, but its ability to react as a diene was not investigated.\textsuperscript{14}

The synthesis of 22 started from 2-methyl-3-formylindole followed by a Knoevenagel condensation with diethyl malonate (Scheme 12). Treatment with N-bromosuccinimide gave the bromide which was then displaced to give the azide 23 using sodium azide. The azide 23 immediately underwent a 1,3-dipolar cycloaddition to give 24 which on treatment with p-toluenesulfonic acid gave 22.

\begin{center}
\textbf{Scheme 12}
\end{center}

The use of 22 in cycloaddition reactions proved unsuccessful, but reaction with methyl chloroformate gave the N-ethyl ester, which was suitable for Diels-Alder reactions with both benzyne and N-phenylmaleimide. Similar work has been carried out using methoxy substituents on the pyrrole ring and a t-butyl group on the pyrrole nitrogen.\textsuperscript{15}
Selenium and Sulfur Containing Analogues

Shafiee has reported the use of 25 and 26 as indole-2,3-quinodimethane equivalents. Their syntheses (Scheme 13) first involved addition of phenyllithium to the acid to produce the ketone, subsequent N-benzylation and bromination (N-bromosuccinimide) gave 27. Reaction with thioacetamide (or N,N-diethylselenopropionamide) produced the corresponding heterocycle.

Diels-Alder reaction of both of these heterocycles with dimethyl acetylenedicarboxylate furnished the expected carbazole product in low yield (20-25%).

Anionic Indole-2,3-quinodimethane Equivalents

It has been found that the anion of 28 can also act as a indole-2,3-quinodimethane equivalent. Cycloaddition reaction of 29 with diethyl acetylenedicarboxylate produced the expected 2,3,4-trisubstituted product in moderate yield. Use of an unsymmetric alkyne resulted in the formation of the isomer with the ester in the 3-position (Scheme 14).
Recent work has shown the use of an enolate as a indole-2,3-quinodimethane equivalent (Scheme 15). Treatment of N-methyl-2-methyl-3-formylindole with LDA generated the enolate 30.

Diels-Alder reaction with a series of activated dienophiles give either the dihydrocarbazole 31 or the carbazole 32 depending on the conditions employed. The reactions showed regioselectivity with the activating group residing in the 3-position of the product.

Dihydropyranoindolones.

Plieninger first reported dihydropyranoindolones (33) in 1964 and they too have been used as stable precursors to indole-2,3-quinodimethanes, but their use in synthesis has been limited. Nandin de Carvalho and co-workers have also used dihydropyranonindolones as precursors; these were synthesised by hydrogenation of the pyrano[3,4-b]indol-3-one derivative using palladium catalysis (Scheme 16). Intermolecular cycloadditions were then carried out with methyl vinyl ketone. The reactions resulted in a 72:28 ratio (2-ketone: 3-ketone) with a hydrogen on the nitrogen, i.e. almost identical to that obtained with indole-2,3-quinodimethane. Replacement of the hydrogen with the acetyl group produced a 99:1 ratio of the same isomeric products. It appears that the effects of having a substituent on the diene and an electron withdrawing group on nitrogen present in the same molecule caused an increase in the selectivity.
Moody has synthesised dihydropyranoindolones with either alkyl groups or a hydrogen in the 1-position and with hydrogen or a methyl ester on the nitrogen. His synthesis (Scheme 17) was made more complicated by the difficulty of introducing the formyl group into the 2-position of indole. The synthesis of 34 was achieved by treatment of 2-acetoxymethylindole with ethyl diazoacetate under copper catalysis. Removal of the acetate and subsequent hydrolysis afforded the hydroxy acid 35. Cyclodehydration with isobutyl chloroformate gave the desired lactone 36.

The synthesis of the other dihydropyranoindolones used were attempted by hydrogenolysis but this was found to be unsuccessful.

The indole-2,3-quinodimethanes were generated by refluxing in bromobenzene and subsequently reacted with N-phenylmaleimide to give the expected products. The lactone 36 was then reacted with a variety of other dienophiles (including dimethyl acetylenedicarboxylate and maleic anhydride) but complex mixtures or poor yields were obtained. Interestingly reaction with either 1,4-benzoquinone or 1,4-naphthoquinone produced the fully aromatic carbazoles in moderate yield. Similar results have been obtained by Pindur using benzoquinone or naphthoquinone and 1-methylpyrano[3,4-b]indol-3-one.
The dihydropyranoindolones proved to be rather poor dienes in Diels-Alder reactions, however, the corresponding unsaturated derivatives, pyrano[3,4-b]indol-3-ones, were much better dienes. A considerable amount of work has been carried out in this area, and the discussion of this forms the bulk of this chapter.

1.4. Preparation of Pyrano[3,4-b]indole-3-ones

Plieninger discovered in 1964 that treatment of indole-3-acetic acid with an anhydride in the presence of boron trifluoride etherate yielded a pyrano[3,4-b]indol-3-one (37) as a stable orange solid (Scheme 18).19

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{Ac}_2\text{O} \quad \text{BF}_3\text{.Et}_2\text{O} \\
\text{H} & \quad \text{Me} \\
\end{align*}
\]

Scheme 18

1-Substituted-pyrano[3,4-b]indol-3-ones can be prepared by a number of methods, the most straightforward is perhaps the initial method employed by Plieninger. Pindur has carried out an amount of work in the field of pyrano[3,4-b]indol-3-ones and as a result has conducted a study into the mechanism of formation of these stable indole-2,3-quinodimethanes (Scheme 19).22

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{38} \quad \text{BF}_3\text{.Et}_2\text{O} \\
\text{H} & \quad \text{Me} \\
\end{align*}
\]

Scheme 19

It has been assumed by both Plieninger and Pindur that the first step of this transformation is the formation of the mixed anhydride 38. The question is then whether the delivery of the acyl group into the 2 position is inter or intramolecular.
Attempts to isolate the intermediate 39 failed. The synthesis of the mixed anhydride 38 was achieved from the parent acid, acetyl chloride and pyridine. Subsequent treatment of the mixed anhydride with boron trifluoride etherate or phosphorus pentachloride failed to yield the desired product. However, when the anhydride was treated with boron trifluoride and acetic anhydride the expected pyranone product was observed indicating that the 2-acyl substituent was introduced by an intermolecular reaction with a second molecule of acetic anhydride.

Plieninger also reported that if 2-acylindole-3-acetic acid derivatives were heated in acetic anhydride then the desired pyranone was produced by cyclodehydration. The 2-acylindole-3-acetic acid derivatives can be produced via a Friedel-Crafts reaction and subsequent hydrolysis or from the pyranone as a method of purification. This method has been used by Moody.

The other method that has regularly been used to produce 1-arylpyrano[3,4-b]indol-3-ones was well illustrated by Dorofeenko (Scheme 20).

Scheme 20

It was found that heating benzoic acid with indole-3-acetic acid in polyphosphoric acid yielded the 1-phenylpyrano[3,4-b]indol-3-one in good yield. Moody found that these conditions were too extreme and that yields of the 1-phenylpyrano[3,4-b]indol-3-one could only be obtained (17%) if less concentrated PPA was employed. The problem with this approach appeared to be due to the ease with which indole-3-acetic acid and its derivatives polymerised under strongly acidic conditions.

An interesting method for the preparation of 9-methylpyrano[3,4-b]indol-3-ones was also reported by Dorofeenko (Scheme 21). If 1-methylindole-3-acetic acid was reacted with a solution of acetyl perchlorate (from acetic anhydride and perchloric acid) in acetic acid then the product was 1,2-dimethyl-3-hydroxyindole[2,3-c]pyrylium perchlorate (40).
Treatment with water then yields the 9-methyl-1-methylpyrano[3,4-b]indol-3-one. The isolation of the pyrylium salt is notable since Plieninger did not observe any such species in his boron trifluoride method.

The synthesis of other 9-substituted pyrano[3,4-b]indol-3-ones has also been reported. 9-Methyl-1-phenylpyrano[3,4-b]indol-3-one has been synthesised by treatment of 1-methylindole-3-acetic acid with benzoic acid and PPA to give 95% of the pyranone. A similar method using acetic acid allowed 1,9-dimethylpyrano[3,4-b]indol-3-one and 9-benzyl-1-methylpyrano[3,4-b]indol-3-one to be synthesised in good yield.

There are several examples of the derivatisation of pyrano[3,4-b]indol-3-ones in the literature. 1-Methylpyrano[3,4-b]indol-3-one was derivatised by treatment with sodium hydride in DMF followed by acetic anhydride to give 9-acetyl-1-methylpyrano[3,4-b]indole-3-one (41) in 35% yield (Scheme 22).

In addition Moody has synthesised 9-acylpyrano[3,4-b]indol-3-one and 9-ethoxycarbonyl-1-methylpyrano[3,4-b]indol-3-one.

Moody has also synthesised a variety of 1-substituted pyrano[3,4-b]indol-3-ones using the corresponding anhydride and boron trifluoride etherate (Scheme 23).
The yields obtained for simple straight chain 1-alkyl substituents were good but increasing the size of the alkyl group in the electrophile, such as isopropyl- or tert-butyl, significantly decreased the yield (Table 1). This apparent steric effect was presumably due to the interaction between the electrophile and the acetic acid residue in the indole-3-position. The Diels-Alder reactions of these \( \alpha \)-pyranones with dimethyl acetylenedicarboxylate gave generally very good yields of trisubstituted carbazole products.

### Table 1

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (42) (%)</th>
<th>Yield (43) (%)</th>
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<tr>
<td>Me</td>
<td>66</td>
<td>81</td>
</tr>
<tr>
<td>Et</td>
<td>87</td>
<td>54</td>
</tr>
<tr>
<td>Pr</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>Bu</td>
<td>46</td>
<td>71</td>
</tr>
<tr>
<td>C(_5)H(_11)</td>
<td>62</td>
<td>88</td>
</tr>
<tr>
<td>iPr</td>
<td>24</td>
<td>89</td>
</tr>
<tr>
<td>tBu</td>
<td>15</td>
<td>--</td>
</tr>
</tbody>
</table>

The synthesis of pyrano[3,4-\(b\)]indol-3-ones is not limited to those with a 1-substituent, there are also examples where a 4-substituent is present, these arise from \( \alpha \)-substituted indole-3-acetic acid derivatives. The examples in the literature are however limited to 4-methyl-1-methylpyrano[3,4-\(b\)]indol-3-one\(^{28,29}\) and 4-methyl-1-phenylpyrano[3,4-\(b\)]indol-3-one.\(^{30}\) Both examples are formed in lower yields (43 and 17\% respectively) than when no \( \alpha \)-substituent is present.
1.5. Diels-Alder Reactions of Pyrano[3,4-b]indol-3-ones

Alkynes as Dienophiles

Intermolecular

The first example of the Diels-Alder reaction of pyrano[3,4-b]indol-3-ones with alkynes was reported by Plieninger in his ground breaking work and involved 1-methylpyrano[3,4-b]indol-3-one being heated in an excess of dimethyl acetylenedicarboxylate (Scheme 24).\(^{19}\)

![Scheme 24](image)

Presumably the initial cycloaddition occurs to yield adduct 44 which then loses carbon dioxide to form the aromatic carbazole. The next usage of pyrano[3,4-b]indol-3-ones in Diels-Alder reactions was some 20 years later by Moody.\(^{29}\) This and subsequent work showed that the reactions take place at reflux in a high boiling solvent rather than a neat mixture. Toluene has been used but it was generally found that the pyrano[3,4-b]indol-3-ones were too insoluble in this solvent and as a result, chloro- or bromobenzene was usually employed.

Pyrano[3,4-b]indol-3-ones readily underwent cycloadditions if the alkyne is activated by the presence of electron withdrawing groups. Pindur has carried out the cycloaddition of 4-methyl-1-phenylpyrano[3,4-b]indol-3-one with DMAD (Scheme 25) and found that heating the mixture for 4 hours in acetonitrile was sufficient to achieve a 56% yield of 45.\(^{30}\)
The number of symmetric alkynes other than DMAD which have been used is limited to dibenzoylacetylene\textsuperscript{28} and benzyne (Scheme 26).\textsuperscript{21,29}

![Scheme 26](image)

The use of unsymmetric alkynes introduces the question of regioselectivity in the carbazole product and the main body of work in this area has been carried out by Moody.\textsuperscript{23} To probe the regioselectivity of a simple system the reaction of a range of pyrano[3,4-\textit{b}]indol-3-ones with ethyl propiolate was carried out (Scheme 27).

![Scheme 27](image)

The results clearly showed that the regioselectivity of this reaction was low in most cases only becoming significant when the bulk of the substituent increases (Table 2). The steric interaction between the ester and the 1-substituent obviously increased with the bulk of the substituent and as a result of this repulsion when R=\textsuperscript{i}Bu only the 3-isomer was observed.

<table>
<thead>
<tr>
<th>R</th>
<th>Combined Yield (%)</th>
<th>Ratio 46:47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>74</td>
<td>1.7:1</td>
</tr>
<tr>
<td>Et</td>
<td>44</td>
<td>1.9:1</td>
</tr>
<tr>
<td>Pr</td>
<td>66</td>
<td>1.9:1</td>
</tr>
<tr>
<td>Bu</td>
<td>78</td>
<td>1.9:1</td>
</tr>
<tr>
<td>C\textsubscript{5}H\textsubscript{11}</td>
<td>77</td>
<td>2.5:1</td>
</tr>
<tr>
<td>\textsuperscript{i}Pr</td>
<td>62</td>
<td>4.0:1</td>
</tr>
<tr>
<td>\textsuperscript{t}Bu</td>
<td>50</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

Table 2
Work by Pindur involving the reaction of 1-phenylpyrano[3,4-b]indol-3-one with ethyl propiolate produced the rather unexpected result where a 2:1 ratio of 2-ester:3-ester was observed. Introduction of a methyl group into the 4-position reversed this selectivity to give 1:2.5. This result is somewhat surprising in view of the apparent steric factor observed by Moody.23

![Scheme 28](image)

Diels-Alder reactions of 1-methylpyrano[3,4-b]indol-3-one with unsymmetric terminal alkynes shows two marked trends (Scheme 28)(Table 3).23

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Combined Yield (%)</th>
<th>Ratio 48:49</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂Me</td>
<td>H</td>
<td>84</td>
<td>1:1</td>
</tr>
<tr>
<td>COPr</td>
<td>H</td>
<td>87</td>
<td>2.8:1</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>32</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>C₅H₁₁</td>
<td>H</td>
<td>16</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>tBu</td>
<td>H</td>
<td>8</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

Table 3

As the size of X increases so did the selectivity of the cycloaddition so that only one isomer was observed (48). These results also reflected the need for activation of the alkyne. In the examples involving the ester and the ketone the yields were very good. The use of a phenyl substituent causes a drop in yield and the introduction of alkyl groups further reduced the yield so they were of little synthetic use. If instead of using terminal alkynes the hydrogen is replaced by a substituent then a marked reversal of selectivity is observed (Table 4). The activating group was now being incorporated into the carbazole in the 2-position with some degree of selectivity and it was noted with a much longer reaction time. It was suggested that the differences between terminal alkynes and methyl substituted alkynes was a steric not electronic effect and this is supported by observations in other Diels-Alder reactions.30a
<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Combined Yield (%)</th>
<th>Ratio 48:49</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂Me</td>
<td>Me</td>
<td>36</td>
<td>1:5</td>
</tr>
<tr>
<td>COPr</td>
<td>Me</td>
<td>42</td>
<td>1:3</td>
</tr>
<tr>
<td>CO₂Me</td>
<td>Ph</td>
<td>74</td>
<td>1:3.4</td>
</tr>
<tr>
<td>CO₂Me</td>
<td>Pr</td>
<td>33</td>
<td>1:10</td>
</tr>
<tr>
<td>CO₂Me</td>
<td>tBu</td>
<td>28</td>
<td>1:&gt;:20</td>
</tr>
<tr>
<td>CO₂Me</td>
<td>PrCH(OH)</td>
<td>64</td>
<td>1:&gt;:20</td>
</tr>
<tr>
<td>CO₂Me</td>
<td>PrCO</td>
<td>93</td>
<td>1:1.2</td>
</tr>
</tbody>
</table>

Table 4

The regioselectivity of the Diels-Alder reaction with an alkyne could be controlled in a predictable manner if the dienophile used was ethyl 3-trimethylsilylpropynoate. Hence the cycloaddition between 1-methylpyran-3,4-b]indol-3-one and ethyl 3-trimethylsilylpropynoate in refluxing bromobenzene gave 77% of trisubstituted carbazole 50 and only one isomer (ester in the 2-position) was observed in the 250 MHz 1H NMR spectrum. The selectivity of this cycloaddition has been exploited in the synthesis of a number of naturally occurring carbazoles. Using this methodology the first syntheses of carbazomycin A and B were achieved (Scheme 29).25,31

![Scheme 29](image-url)
After the cycloaddition, the ester 50 was reduced to the methyl compound using LiAlH₄ in refluxing dioxane. Mercurio-desilylation using mercury(II) acetate in acetic acid gave the arylmercury compound. Hydroboration using excess borane-THF converted the arylmercury compound to the arylborane, addition of alkaline hydrogen peroxide then oxidised the arylborane to the 3-hydroxycarbazole 51. Treatment of the 3-hydroxycarbazole with potassium carbonate and methyl iodide in acetone gave an excellent yield of the ether 52. Boc protection of the nitrogen then deactivated the 6-position so that on treatment with N-bromosuccinimide the 4-bromocarbazole 53 was produced. Lithium-halogen exchange using tert-butyllithium gave the aryllithium, addition of trimethyl borate and subsequent oxidative work-up gave the 4-hydroxycarbazole 54. The Boc group was removed by thermolysis to yield carbazomycin B, methylation then gave carbazomycin A.

Hyellazole²⁵,³¹ and carazostatin have also been synthesised utilising the ethyl 3-trimethylsilylpropynoate dienophile and similar functional group interconversions.³²

Intramolecular

There is only one set of examples of the intramolecular Diels-Alder reaction of a pyrano[3,4-\textit{b}]indol-3-ones and these are shown in Scheme 30.³³
The dienophile in this series is attached via the 1-position of the pyranone. The synthesis of these alkynylpyranoindolones is achieved by the treatment of indole-3-acetic acid with the corresponding alkynyl anhydride and boron trifluoride etherate. The yields for the formation of these pyranones range from 41-12%. The intramolecular reactions proceeded smoothly for n=3 or 4 to give yields of 53-82%, the reaction times are notably less than those for the intermolecular variant. Comparison with the Diels-Alder reaction of hept-1-yne which gave 16% yield after 72 hours at reflux in bromobenzene shows that the unactivated intramolecular cases occur much more readily. In the case of the 7-membered ring, n=5, benzonitrile, a solvent with a higher boiling point (190 °C) than those commonly employed, was required to obtain 35% yield. Interestingly if the pyranone n=3 has an alkene unit instead of an alkyne then only 16% yield of the dihydrocyclopentacarbazole was obtained.

The use of alkynes as dienophiles with pyrano[3,4-b]indol-3-ones give a route to fully unsaturated carbazole products via either an inter or an intramolecular Diels-Alder reaction. The dienophile can also be an alkene and in this case a dihydrocarbazole product would be predicted.

Alkenes as Dienophiles.

Intermolecular.

A study of the reactions of pyrano[3,4-b]indol-3-ones with mono and disubstituted alkenes has been carried out. The substrates featured a variety of alkyl substituents (Me, Et, Bn, H, iPr) on both the 1-position and nitrogen of the diene. The reaction of 1-methyl-9-methylpyrano[3,4-b]indol-3-one with methyl vinyl ketone, acrylonitrile or acrolein resulted in the formation of 1,2-dihydrocarbazoles (Scheme 31).
The formation of the 1,2-dihydrocarbazoles rather than the expected 2,3-isomer 56 can be rationalised by a 1,5-hydrogen shift to give the more highly conjugated system. Repeating the Diels-Alder reaction of 1,9-dimethylpyrano[3,4-b]indol-3-one with methyl acrylate, 2-vinylpyridine or styrene initially resulted in formation of the 1,2-dihydrocarbazoles but during subsequent purification these aromatised to give the carbazoles 57 (Scheme 32).

Other workers have managed to isolate, in low yield, the 1,2-dihydrocarbazole resulting from the cycloaddition of the diene R=H and R¹=Me with methyl acrylate. The yields of the aromatised carbazoles could be increased if palladium-on-carbon was used in toluene and hence this gave an alternative method to the use of an alkyne as a dienophile in the Diels-Alder reaction. The treatment of 1,2-dihydrocarbazoles with acetic acid has also been shown to produce the corresponding 3-substituted carbazoles. The sensitivity of these reactions to the conditions employed is shown by 2-vinylpyridine. If the reaction of 2-vinylpyridine was conducted under acidic conditions the 1,2-dihydrocarbazole could be isolated whereas under the previously employed neutral conditions aromatisation occurred. These results all suggest that the presence of a highly electron withdrawing group in the 3-position stabilises the 1,2-dihydrocarbazoles and hence disfavour formation of the fully aromatic carbazole. The regioselectivity which can be achieved by the Diels-Alder reaction of alkenes with pyrano[3,4-b]indol-3-ones has been exploited by Narasimhan in the synthesis of 1,3-disubstituted carbazoles (Scheme 33).
The reaction of an electron deficient chloroethylene with 1-methylpyrano[3,4-b]indol-3-one in THF in the presence of collidine gave, after thermal decarboxylation and elimination of HCl, the 3-isomer 58 as the only product. If the reaction was conducted in neat collidine at the same temperature no regioselectivity was observed. The regioselectivity of this reaction could then be exploited with subsequent conversion of the cyano group into the amine and from there into carbazole alkaloids.34

The electronic considerations are not the only ones which determine the products of the Diels-Alder reactions and their regiochemistry. The bulk of the substituents on the diene were also found to have a great influence on the products obtained. In previous examples methyl vinyl ketone furnished the dihydrocarbazole product, however, its reaction with the non-bulky diene 1-methylpyrano[3,4-b]indol-3-one gave only the carbazole product 59 (Scheme 34). By contrast the reaction of the more bulky 9-benzyl-1-methylpyrano[3,4-b]indol-3-one with methyl acrylate, which when employed as the dienophile in previous examples favoured the fully aromatic carbazole, gave only the 1,2-dihydrocarbazole 60.26 In these cases it appears that the steric interaction between the 1-substituent and the substituent on nitrogen and not the electronic properties arising from the dienophile determine the products. Presumably the interaction between the benzyl group and the methyl in the second example are minimised if they are not brought into the same plane by aromatisation.
Reaction with 1,2-disubstituted olefins show a preference for 1,2-dihydrocarbazole formation if R on the diene is reasonably large, e.g. iPr. They also showed the need for an electron withdrawing group in the 3-position for 1,2-dihydrocarbazole formation. The presence of this group in the 2-position rather than the 3-position results in aromatisation (Scheme 35).\textsuperscript{26}

The work has been extended to trisubstituted alkenes, and shows dramatic changes (Scheme 36).\textsuperscript{35} If R\textsuperscript{2} and R\textsuperscript{2'} are both alkyl then no reaction was observed but the reaction of R\textsuperscript{2} and R\textsuperscript{2'} being carbonyls produced one regioisomer, 61, in good yields 92-97\%. It appears that the mechanism for the cycloaddition of trisubstituted alkenes may be rather more stepwise and that of disubstituted alkenes more concerted.
An interesting comparison is provided by the reactions of the dienes with \( R = \text{Et}, \) \( R^1 = \text{H} \) and \( R = R^1 = \text{Me} \) with 62 (Scheme 37). With the unsubstituted diene the only product is 63 where the 2-acetyl is initially introduced into the 3-position (67%), with the disubstituted diene only 33% of the corresponding product is observed the rest of the mixture comprises the regioisomeric dihydrocarbazoles which readily lose acetaldehyde to furnish the carbazole 64.35

The cycloaddition of 65 showed a complete contrast to that of methyl vinyl ketone (Scheme 38). The reaction with the disubstituted alkene gave only the isomer with the ketone in the 3-position but with this cyclic trisubstituted alkene the regiochemistry was totally reversed with the ketone now observed in the 2-position.35

![Scheme 36](image)

![Scheme 37](image)

![Scheme 38](image)
The cycloaddition of alkynes to pyrano[3,4-b]indol-3-ones required activation by the presence of an electron withdrawing group unless the reaction was intramolecular. The reaction of pyrano[3,4-b]indol-3-ones with electron rich alkenes has however been reported. It has been found that heating 1-methyl-9-methylpyrano[3,4-b]indol-3-one in cyclohexene resulted in the formation of the expected tetracycle 66 (Scheme 39).

![Scheme 39](image)

The cycloaddition reactions could also be carried out utilising enol ethers as dienes to give the fully aromatic carbazoles as products. The ether functionality was however only retained in the case of cyclic ethers (Scheme 40).

![Scheme 40](image)

The use of enamides gave much more useful results than the enol ethers. Hence the reaction of N-vinylpyrrolidone and 1-methyl-9-methylpyrano[3,4-b]indol-3-one in the presence of palladium-on-charcoal gave the expected carbazole 67 (Scheme 41).

![Scheme 41](image)

Although there are a number of reports of Diels-Alder reactions involving carbon based dienophiles with pyrano[3,4-b]indol-3-ones there are very few reports of
attempted hetero-Diels-Alder reactions with these compounds. Moody reacted ethyl cyanofomrate with 1-methylpyrano[3,4-b]indol-3-one and this may be expected to undergo a hetero-Diels-Alder reaction but the N-ethoxycarbonyl compound was the only product obtained.  

![Scheme 42](image)

Pindur took the same pyranone (Scheme 42) and reacted it with diethyl mesoxalate to give 2,3-difunctionalised indole 68. The formation of this compound could be rationalised by a cycloaddition/cycloreversal sequence.

### 1.6. Pyrano[4,3-b]indol-3-ones

This class of compounds which are isomeric to the pyrano[3,4-b]indol-3-ones are also indole-2,3-quinodimethane equivalents. Their use in synthesis is limited in comparison to their isomers at least in part because indole-2-acetic acid from which they are derived is not commercially available.

The synthesis of ethyl indole-2-acetate can be carried out in four steps from commercially available 2-nitrophenylacetic acid (Scheme 43). The 2-nitrophenylacetyl chloride is reacted with Meldrums acid in the presence of Hunigs base and then decarboxylated to give the ketoester 69. Reductive cyclisation using titanium(III) chloride in aqueous acetone gave the desired indole.
Moody has synthesised the pyrano[4,3-b]indol-3-ones (Scheme 44) with either a proton or a methyl group at the 1-position. The standard method of producing pyranones namely acetic anhydride and boron trifluoride etherate, failed in the case of indole-2-acetic acid and so a Friedel-Crafts approach was required. The reaction of ethyl indole-2-acetate with acetyl chloride and tin(IV) chloride gave the required keto-ester 70, subsequent hydrolysis and cyclodehydration gave the 4-methyl substituted compound 71. A similar sequence utilising Vilsmeier formylation allowed the unsubstituted pyranone to be synthesised.

The pyrano[4,3-b]indol-3-ones do act as indole-2,3-quinodimethane equivalents as expected but Diels-Alder reactions carried out on these compounds showed marked differences to those of the isomeric series (Scheme 45).

Firstly the 1-methylpyrano[4,3-b]indol-3-one was much less reactive than the unsubstituted example, even with DMAD, furnishing 30% yield after 144 hours as compared to 92% after 44 hours. The introduction of a Boc group onto the nitrogen increased the reaction rate but the reaction was complicated by the thermal removal of the Boc group. In all cases the Diels-Alder reactions were found to proceed much more slowly than those of the related pyrano[3,4-b]indol-3-ones. The use of ethyl propiolate showed, in common with the other series, very little regioselectivity, but once again the use of bulky activated alkynes (Y=ester, X=Ph or SiMe₃) resulted in the formation of one regioisomer. In this case however the predominant isomer was that with the ester in the 3-position.
The advantage of using the pyrano[4,3-b]indol-3-ones rather than its isomer was that the 3-position in the starting material (ethyl indole-2-acetate) is unsubstituted. The 3-position on indole is so much more reactive than the 2-position and so more complex manipulation of these compounds can be achieved.

Moody has carried out intramolecular Diels-Alder reactions using these systems to afford [c]-annelated carbazoles. The starting point for these carbazoles was t-butyl indole-2-acetate which is made via the same method as the ethyl ester. Treatment with oxalyl chloride followed by the corresponding alkynol gives the glyoxylate (Scheme 46). Removal of the t-butyl group using p-toluenesulfonic acid produced the acid which can then be cyclodehydrated to the pyrano[4,3-b]indol-3-one using acetic anhydride at room temperature.

The Diels-Alder reaction was found to proceed in good yield (76%) for n=0 and R=H, the introduction of R=Me caused the yield to drop to 37% while using n=1 and R=H produced only a 13% yield.

![Scheme 46](image)

Similar methodology but utilising lactams has allowed the synthesis of staurosporine aglycon. The starting point was once again ethyl indole-2-acetate, treatment with oxalyl chloride followed by amine gave the glyoxylate amide in 76% yield. Hydrolysis with potassium hydroxide in methanol furnished the acid in 97% (Scheme 47). Cyclodehydration with acetic anhydride at room temperature
gave the desired pyranone 78. The Diels-Alder reaction in refluxing bromobenzene under nitrogen gave a dihydrocarbazole which on subsequent refluxing open to the air furnished 79. It should be noted that carrying out the initial Diels-Alder reaction open to the atmosphere resulted in a more complex mixture and a cyclic imide resulting from the oxidation of the lactam was isolated. Staurosporine aglycon 80 was synthesised by cyclisation using triethyl phosphite. Attempts at using an intramolecular Diels-Alder reaction involving an alkyne were discarded due to problems with both the amide formation and subsequent hydrolysis.
1.7. Summary.

The cycloaddition reactions of indole-2,3-quinodimethanes furnish carbazole and dihydrocarbazole products. The regioselectivity of these reactions is usually low unless the process is intramolecular.

There are a number of indole-2,3-quinodimethane equivalents which have been synthesised and undergo the Diels-Alder reaction with either alkenes or alkynes to give the products with regioselectivity ranging from absolute to zero.

The two indole-2,3-quinodimethane equivalents most used are the 4H-furo[3,4-b]indoles and the pyrano[3,4-b]indol-3-ones. The use of pyrano[3,4-b]indol-3-ones is preferable on a number of counts;

- the synthesis of the substrates is generally one step from commercially available materials,

- no protection of the nitrogen is required unlike all the other variants,

- the decarboxylation occurs in the same 'pot' as the Diels-Alder reaction so no extra steps are needed.
Chapter Two

The Synthesis of 'Linked'
Pyrano[3,4-\textit{b}]indol-3-ones
2.1. Introduction

Carbazole compounds have received considerable attention as building blocks for new materials as they are known to possess multifunctional properties including photoconductivity and unique second-order non-linear properties.\(^{41}\) In 1963 Hoegl discovered that sensitized poly(N-vinylcarbazole) (PVK) exhibited high levels of photoconductivity.\(^{42}\) A photoconductive material is defined as one which exhibits an increase in electrical conductivity upon illumination.\(^{43}\) This discovery led to the use of PVK in electrophotographic processes and initiated further interest in the use of electron rich carbazoles in the field of materials.\(^{44}\)

\[
\text{PVK}
\]

PVK and many other carbazoles readily forms 1:1 charge-transfer complexes with electron deficient aromatic species such as 2,4,7-trinitrofluorenone and these complexes are found, in general, to be fairly stable.\(^{45}\) These complexes are now under investigation for use in the field of non-linear optics.

During the course of our work on carbazoles other groups have shown considerable interest in carbazole containing macrocycles\(^ {41}\) and polymers\(^ {46}\) possessing the same sub-unit (Figure 2), for use in non-linear optics.

\[
\text{Figure 2}
\]

The use of organic molecules in materials chemistry is not a new venture, but the use of tetracyano-p-quinodimethane (TCNQ) with tetrathiofulvalene (TTF) has introduced the concept of the organic metal.\(^ {47,48}\) When these two compounds are mixed in solution a stable 1:1 complex is formed which exhibits
the largest maximum electrical conductivity of any organic compound. The high levels of conductivity arise from the nature of the crystal structure where it was found that the molecules are packed face-to-face. Charge-transfer and π-interactions allowed delocalisation of electrons over the stack and conductivity was observed.

![TTF and TCNQ structures]

The synthesis of organic polymers by a Diels-Alder reaction is well illustrated by the work of Stille. Initially the work employed bis(tetraarylated cyclopentadienones) (81) as the dienes which were prepared over 5 steps in low yields (2-10%). These dienes were then reacted with diethynylbenzenes to form polymers (Scheme 48).

![Scheme 48]

The yields of cycloaddition product obtained, after elimination of carbon monoxide from the intermediate adduct, were between 75 and 99%. Later the work turned to the Diels-Alder reaction between 5,5'-p-phenylenebis-2-pyrone and p-diethynylbenzene to produce polymers (Scheme 49).
Once again the polymer was formed in excellent yield and it was found that the structure of the polymer varied with the method of preparation.

There has been much work carried out within the Moody group concerning the synthesis of carbazoles. It was postulated that Diels-Alder reaction of a bis-pyrano[3,4-b]indol-3-one, where two pyrano[3,4-b]indol-3-ones are linked in someway, would produce linked carbazoles. The incorporation of an electron deficient aromatic guest may then, with analogy to the TCNQ system, possess interesting electronic properties. To achieve the synthesis of such a bis-pyrano[3,4-b]indol-3-one moiety the synthesis of the corresponding bis-indole-3-acetic acid derivatives is necessary.

2.2. Synthesis of 'Linked' Indole-3-acetic acid Derivatives.

2.2.1. Linkage Through the 2-Position of Indole

As elaborated in Chapter 1, Pindurs work has indicated that the mechanism for pyrano[3,4-b]indol-3-one formation requires 2 equivalents of anhydride. As a consequence the reaction of indole-3-acetic acid with a bis-anhydride should only give a pyranone with an alkyl chain terminating with an acid functionality and not the desired linked product.

It seemed appropriate to study the reaction of indole-3-acetic acid with a number of anhydrides containing functionality. The reaction of indole-3-acetic acid with
glutaric anhydride and boron trifluoride etherate did produce pyranone 82 (Scheme 50), but unfortunately purification of this compound proved impossible due to its extreme polarity and its instability to chromatography.

Scheme 50

Acrylic anhydride under the same conditions gave a bright red solution presumably as a result of polymerisation, while phthalic anhydride and bromoacetic anhydride both failed to react.

Methods for the introduction of acyl substituents into the 2-position of indole are rather limited. The 3-position is the most reactive towards electrophiles and it has been hypothesised that in cases where the 3-position is substituted that electrophilic attack takes place in the 3-position before migrating to the 2-position.

Our attention turned quite logically to the use of esters of indole-3-acetic acid and to the possible use of a double Friedel-Crafts reaction. Methyl indole-3-acetate was readily prepared from indole-3-acetic acid using methanol and acid catalysis. It was desirable to be able to produce a pyranone which was linked by an aromatic ring, to achieve this aim introduction of a terephthaloyl group would be necessary and so as a model benzoylation was attempted. Treatment of methyl indole-3-acetate with benzoyl chloride and aluminium chloride in nitrobenzene gave a very low yield of the corresponding 2-benzoyl indole, this result is in agreement with those of Moody concerning the synthesis of 1-phenylpyrano[3,4-b]indol-3-one where it was found the introduction of a 2-benzoyl group was very difficult (Scheme 51).²⁵

Figure 51
Methyl oxalyl chloride is a much more reactive electrophile than benzoyl chloride and it was found that using this electrophile, methyl indole-3-acetate and aluminium(III) chloride in 1,2-dichloroethane, that the glyoxylate ester 83 was produced in 27% yield (Scheme 52).

Encouraged by this result we turned our attention to the use of oxalyl chloride as the electrophile. The reaction of ethyl indole-3-acetate, 0.5 equivalents of oxalyl chloride and aluminium chloride in 1,2-dichloroethane furnished the desired linked indole 84 as a bright red solid in 28% yield (Scheme 53).

Simple hydrolysis and subsequent cyclodehydration would then give the desired pyranone (Scheme 53). Disappointingly it was found that despite the use of a variety of hydroxides, trimethylsilyl iodide and boron trichloride none of the desired product could be obtained. Presumably the α,β-diketone functionality is rather sensitive and under hydrolytic conditions the molecule simply breaks down.
The use of other bis-acid chlorides such as adipoyl chloride failed to give any of the required products.

1-Methylindole-3-acetic acid derivatives.

1-Methylindole-3-acetic acid has been used, as previously mentioned, to prepare pyrano[3,4-b]indol-3-ones. We questioned whether the reactivity of the 2-position of this compound towards electrophiles was, due to the presence of the methyl group, greater than that of the parent NH compound.

Two methods were employed for the synthesis of methyl 1-methylindole-3-acetate. The first method is a modification of the procedure developed by Heaney and Ley. Treatment of indole-3-acetic acid with potassium hydroxide in DMSO produced the dianion as a green solution after 4 hours. The dianion was then treated with methyl iodide to give the desired compound 85 as well as a small amount of α-methylated compound 86 (Scheme 54). The purification of the desired compound (85) was not facile so a two-step route was devised.

\[
\text{KOH/ DMSO} \quad \text{MeI}\]

Scheme 54

1-Methylindole reacts readily with oxalyl chloride, addition of methanol then gives the glyoxylate ester 87 (Scheme 55). Reduction of the ketone using palladium-on-carbon and sodium hypophosphite in water and dioxane gave the required ester 85.
The formylation of methyl indole-3-acetate has not been achieved but treatment of methyl 1-methylindole-3-acetate with the preformed Vilsmeier reagent gave 52% of the 2-formylated product 88 (Scheme 56). This result exemplifies the increased nucleophilicity of the indole 2-position upon 1-methylation.

\[
\text{[Diagram showing reaction between DMF/POCl}_3 \text{ and 1,2-dichloroethane to form 88]}
\]

Scheme 56

Hydrolysis of this product using lithium hydroxide gave the acid 89, which could then be heated in acetic anhydride to afford, after cyclodehydration, 9-methylpyrano[3,4-b]indol-3-one (90) (Scheme 57).

\[
\text{[Diagram showing reaction between LiOH and 89 to form 90]}
\]

Scheme 57

The Diels-Alder reaction of this pyranone with DMAD progressed smoothly to give 40% yield of the carbazole 91 (Scheme 58).\(^{56}\) The yield from the Diels-Alder reaction is relatively low and is in agreement with Moody’s work on pyrano[3,4-b]indol-3-one when the reaction with DMAD gave only 40% yield.\(^{23}\)

\[
\text{[Diagram showing reaction between DMAD and 91 to form 91]}
\]

Scheme 58

The success with formylation of methyl 1-methylindole-3-acetate prompted the investigation into its reactivity with other electrophiles. The reaction of methyl 1-methylindole-3-acetate with benzoyl chloride and aluminium chloride in 1,2-dichloroethane provided, after 8 hours at reflux, 2 compounds (Scheme 59). Chromatographic separation gave 26% yield of the desired 2-benzoyl compound.
92 and ~30% of a compound which was assigned as the 5-benzoyl compound. The increase in the size of the incoming electrophile appears to have vastly increased the steric interaction with either the methyl or the acetic acid residue in the 3-position and hence attack has taken place at the less reactive 5-position.

![Scheme 59]

Again the introduction of the 1-methyl substituent completely changes the reactivity of the 2-position since the earlier attempted benzoylation of methyl indole-3-acetate gave a very low yield. The methyl 1-methyl-2-benzoylindole-3-acetate was then hydrolysed (Scheme 60) using lithium hydroxide to give 93. It was found that the hydrolysis of this compound was much slower than that of the 2-formyl compound under similar conditions. The increased resistance to hydrolysis may be due to the increase in steric demand caused by the benzoyl group. Cyclodehydration proceeded smoothly to give 94 and the subsequent Diels-Alder reaction with DMAD gave the expected trisubstituted carbazole 95 in 86% yield.

![Scheme 60]

With the chemistry in place for the formation of previously challenging pyrano[3,4-b]indol-3-one analogues, the double Friedel-Crafts reaction between
methyl 1-methylindole-3-acetate and terephthaloyl chloride was investigated (Scheme 61).

Scheme 61

The reaction produced one main product under standard conditions, unfortunately this product appears to be the compound where the linkage has taken place via the 5-position to give 97 instead of the desired 96 (Scheme 62). Perhaps this is not surprising when considering the ratio of products obtained with the somewhat smaller benzoyl electrophile, after the first acylation reaction the size of the electrophile increases greatly and hence attack at the 5-position is observed.

Scheme 62

The employment of adipoyl chloride as an electrophile surprisingly resulted in very little reaction but even more surprising was the reaction with oxalyl chloride (Scheme 63). Under standard conditions the reaction of methyl 1-methylindole-3-acetate gave just the mono compound 98. This is a complete contrast to the reaction of the same electrophile with methyl indole-3-acetate where the bis compound is formed.
Attempts at double Friedel-Crafts reactions gave none of the desired products but the employment of the Friedel-Crafts reaction was still appealing. The reaction of methyl 1-methylindole-3-acetate with p-bromobenzoyl chloride gave a new route to the desired products (Scheme 64).

Once again two products were formed and were assigned as the 2- and 5- isomers. Only 16% of the required 2-isomer 99 was obtained along with ~40% of the 5-isomer. As expected the steric interactions of the incoming electrophile with the substituents at the 1- and 3-positions of the indole are large and hence the amount of attack at the 5-position is large. The increase in the amount of attack at the 5-position, relative to the benzoyl example, is not adequately explained by steric or electronic effects but could be caused a reversible reaction.

Hydrolysis of methyl 1-methyl-2-(p-bromobenzoyl)indole-3-acetate with lithium hydroxide again progressed smoothly and rather slowly to give 100. Cyclodehydration furnished the corresponding pyranone 101 which could then be converted to the carbazole 102 on reaction with DMAD (Scheme 65).
The presence of a bromine in the 4-position of the benzoyl ring leads to the possibility of producing a biphenyl linked pyranone via a homo aryl-bromide coupling. Iyoda has taken 4-bromoacetophenone with nickel(II) dibromo-bis(triphenylphosphine), zinc and tetraethylammonium iodide in THF to accomplished the desired homo-aryl coupling in 71% yield (Scheme 66).

The synthesis of the nickel(II) catalyst was carried out from nickel(II) bromide using a literature procedure. After drying the zinc dust, nickel catalyst and tetra-ethylammonium iodide under vacuum for 2 days, THF was added and the formation of the active catalyst was observed. The indole was introduced and the mixture heated gently for 24 hours (Scheme 67).
Unfortunately only starting material and the reduced compound were obtained. Despite subsequent repeating and varying the conditions employed in this reaction no homo-coupled product has been obtained.

The 2-position is of course not the only site available for possible linkage hence the indole nitrogen seemed an ideal place for derivatisation.

2.2.2. Linkage Through the Indole Nitrogen

The indole nitrogen of indole-3-acetic acid and its derivatives has been alkylated by a number of groups using a variety of conditions. The ideal form of linkage was through the bisalkylation of 1-methylpyrano[3,4-b]indol-3-one to form a linked pyranone.

Deprotonation of a pyranone has only been reported once and this involved treatment with sodium hydride in DMF followed by acylation with acetic anhydride (Scheme 68).27

The yield for this process was a reasonable 35%, but our attempts to alkylate with methyl iodide under these or other conditions met with failure.
Treatment of 1-methylpyrano[3,4-b]indol-3-one with methanol causes ring opening to give methyl 2-acetylindole-3-acetate (103). The presence of the acetyl group in the 2-position increases the acidity of the proton on nitrogen and so we reasoned that alkylation would then be readily facilitated. This compound is obviously also just a ring opened pyranone so simple hydrolysis and cyclodehydration of the derivative would then give the desired linked pyranone (Scheme 69).

On addition of either sodium or potassium hydride to a solution of methyl 2-acetylindole-3-acetate in THF or DMF the liberation of hydrogen was observed (Scheme 70). The addition of methyl iodide did not produce the desired product instead only starting material was recovered. Repeating these reactions with benzyl bromide or α,α'-dibromo-p-xylene also gave only recovered starting material. Utilisation of other bases such as Hunigs base, potassium tert-butoxide, triethylamine and sodium hydroxide all failed to yield any product. It seems likely that the proton is removed but that the subsequent anion is too well stabilised and hence is not alkylated.

Increasing the amount of base employed did allow very small amounts of alkylated products to be obtained as well as recovered starting material, but the major product resulted from alkylation of the methylene group of the acetic acid residue (Scheme 71).
The next logical step is to alkylate indole-3-acetic acid or one of its derivatives. There are a number of reports in the literature concerning N-alkylation of both the parent compounds and its esters.\textsuperscript{59-61} The conditions which have been employed are summarised below (Scheme 72).

\begin{align*}
\text{R} &= \text{Me}, \text{E} = \text{Me} \text{ using KOtBu, 18-crown-6 and methyl iodide in diethyl ether;}^{59} \\
\text{R} &= \text{Me} \text{ E} = \text{CH}_2\text{-CH} = \text{CHBr} \text{ using KOtBu, 18-crown-6 and 1,3-dibromopropene;}^{60} \\
\text{R} &= \text{Et}, \text{E} = \text{Me} \text{ using KOH and methyl iodide in acetone.}^{61}
\end{align*}

Attempts at repeating these methods by us and others have however proved rather unsatisfactory.\textsuperscript{62} With either low yields being furnished even with simple reactive alkylating agents such as methyl iodide or benzyl bromide.

Instead a stepwise synthesis of the desired linked indole-3-acetic acid was attempted (Scheme 73). The first N,N-linked indole 104 was synthesised by treating indole with potassium hydroxide in DMSO and adding 1,5-diiodopentane. It was gratifying to find that the good yields obtained for simple alkylation of indole were also observed with this bis-electrophile. Formation of the glyoxylate 105 was then achieved using oxalyl chloride followed by ethanol and triethylamine.
There are several reported methods for the reduction of the glyoxylate to the acetate, the need for a high yielding process is amplified by the presence of 2-glyoxylates in the one molecule. One method involves the reaction of the glyoxylic acid with p-toluenesulfonylhydrazide to form the hydrazone 106, subsequent reduction with sodium borohydride in refluxing THF gives the desired indole-3-acetic acid in moderate yield (Scheme 74).\textsuperscript{63}

More impressive results were reported by Demopoulos carrying out the reduction using palladium-on-carbon and sodium hypophosphite. It was these conditions that were employed in the reduction of the linked glyoxylate (Scheme 75).\textsuperscript{64}

After reduction the ester 107 could readily be hydrolysed to the acid 108 with lithium hydroxide in THF/water. It should be noted that the quality of the sodium hypophosphite is critical to the yield, use of material which has been allowed to stand for some months results in considerably lower yields than those obtained with newer material.
The synthesis of two other 1-alkylated indole-3-acetic acid derivatives were also achieved by the same method. The use of α,α'-dibromo-p-xylene as the electrophile allowed the synthesis of the linked indole 109, treatment with oxalyl chloride and ethanol gave 110 (Scheme 76).

The glyoxylate was then reduced to the ester 111 which was converted to 112 on treatment with aqueous lithium hydroxide (Scheme 77). The use of benzyl bromide gave the corresponding 1-benzyl indole-3-acetic acid.
It was subsequently found that indole-3-acetic acid could be readily alkylated using \( \alpha,\alpha'-\text{dibromo-}p\)-xylene, 1,5-diiodopentane or benzyl bromide if a 1:1 mixture of dichloromethane and sodium hydroxide (50%) in the presence of benzyltrimethylammonium chloride was heated to reflux (Scheme 78). The yields of the products were low to moderate but the purification by this method was problematic. The use of the stepwise approach means that the ester precursor is purified and hence the acid is furnished essentially pure upon hydrolysis and is the preferred method.

The previously mentioned 1-methylindole-3-acetic acid was the first 1-alkylated compound that was subjected to the standard pyranone formation conditions of acetic anhydride and boron trifluoride etherate (Scheme 79).
The reaction yielded a highly encouraging 78% of the desired pyranone 113 which readily underwent Diels-Alder reaction with DMAD to the 1-methyl trisubstituted carbazole 114.

The novel 1,5-di(3-carboxymethyl-indol-1-yl)pentane was placed in acetic anhydride and boron trifluoride etherate was added (Scheme 80).

The formation of the characteristic yellow hue of a pyranone was barely visible during this reaction and subsequent addition of ether did not produce the expected yellow solid but instead a black gum. Attempted purification by column chromatography resulted in visible decomposition of the small amount of pyranone product 115.

A possible problem with the first experiment was the lack of solubility of the acid in acetic anhydride. The reaction was repeated using dichloromethane as the co-solvent, this allowed the indole-3-acetic acid derivative to be in solution. The reaction however proceeded in the same way giving a black gum. The gum was heated with DMAD in bromobenzene to achieve the Diels-Alder reaction yielding 116 (Scheme 81).
The carbazole product 116 was obtained in 12% yield, this proved that the desired pyranone was being formed since it is the only way that the carbazole could be formed. The yield however was very low considering how well the Diels-Alder reactions with DMAD proceed. Further attempts to optimise this reaction did not increase the yield nor did they allow the pyranone to be isolated.

Our previous success with the 2-acylation of methyl 1-methylindole-3-acetate prompted the investigation into the Friedel-Crafts reaction of 1,5-di(3-ethyloxymethylindol-1-yl)pentane with acetyl chloride and aluminium chloride in 1,2-dichloroethane (Scheme 82).

One major product was obtained but analysis of the $^1$H NMR spectrum showed 2 apparent singlets in the aromatic region suggesting that attack had taken place in the 5-position on indole to yield 117. This finding was further confirmed when after hydrolysis attempted cyclodehydration by heating in acetic anhydride failed to give any pyranone product. It appears that the steric bulk of the group on the indole nitrogen is preventing the acylating species approaching the 2-position.
and, as before, attack occurs in the 5-position. This steric factor must also be present in the reaction with acetic anhydride and boron trifluoride etherate but the incoming electrophile may be smaller or directed in by the acid functionality as some attack at the 2-position is observed.

The reaction of 1-benzylindole-3-acetic acid with acetic anhydride and boron trifluoride etherate produced even more disappointing results (Scheme 83).

The crude $^1$H NMR spectrum of the reaction mixture showed only a trace of the desired pyranone, subsequent Diels-Alder reaction with DMAD produced only 1% yield of the carbazole 118. The Friedel-Crafts reaction of methyl 1-benzylindole-3-acetate with acetyl chloride once again produced only the isomer where substitution had occurred in the 5-position reflecting the effect of a large group on the indole nitrogen.

It appears that the presence of a substituent much larger than methyl on the nitrogen of indole-3-acetic acid derivatives repels the attack of incoming electrophiles with the result that attack occurs in the 5-position. The other position on indole-3-acetic acid that can be readily derivatised is the methylene of the acetic acid residue in the 3-position.
2.2.3. Linkage Through the α-Position of Indole-3-acetic acid Derivatives.

The protons of the methylene group at the 3-position of indole-3-acetic acid derivatives are acidic due to the presence of the adjacent carboxyl functionality and the connected indole ring. Bergman, Demerson and Adam have all exploited the acidity of this position. Bergman found that if indole-3-acetic acid were treated with 2 equivalents of n-butyllithium and 1 equivalent of t-butyllithium then the resulting trianion could be treated with iodine to form 119 in 38% yield (Scheme 84).

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme84.png}
\end{center}

Use of the corresponding ester with 2 equivalents of LDA and iodine gave an even better 85% yield of the desired product.  

Our interests lay with the reaction of the above anion with either 1,5-diiodopentane or α,α'-dibromo-p-xylene. Initial attempts to carry out the reaction with the trianion were met with failure resulting in the recovery of the starting material. Use of methyl indole-3-acetate with LDA and 1,5-diiodopentane gave ~20% of the mono-alkylated product. It seemed prudent to further protect the methyl indole-3-acetate by introducing the Boc group so that the only possible site for deprotonation was at the α-position. The Boc group was introduced using di-tert-butyl-dicarbonate, DMAP and acetonitrile to give 91% of the desired compound 120. Addition of methyl N-tBoc-indole-3-acetate to a solution of 1.5 equivalents of LDA in THF generated the anion to which was added 1,5-diiodopentane (Scheme 85).
The product which was isolated from this reaction was the mono-alkylated compound 121, the desired linked compound 122 was never observed. The yield of this iodo compound could be increased to 78% if 3 equivalents of 1,5-diiodopentane were used. The iodo compound 121 should in theory act as an electrophile and hence treatment of the anion of methyl N-tBoc-indole-3-acetate would give the desired product (Scheme 86).

Surprisingly 121 did not act as an electrophile and only the two starting materials were recovered.
The use of the more electrophilic α,α'-dibromo-p-xylene proved much more successful. In early experiments α,α'-dibromo-p-xylene was added in solution in THF to the preformed anion but the yields of product were disappointingly low (15%). However if the electrophile were added as a solid from an internal solid addition funnel the yield of linked product 123 was very good (~80%) (Scheme 87).

Scheme 87

The linked compound could then be hydrolysed and upon acid work up the Boc group was also removed to give 124. This linked acid was then treated with acetic anhydride and boron trifluoride etherate at 0 °C (Scheme 88).

Scheme 88
Much to our disappointment virtually no pyranone was observed, this observation was confirmed by the Diels-Alder reaction with DMAD which produced a compound which was tentatively assigned as 125.

125 arises from the formation of the pyranone on one of the indole rings but not on the other. Synthesis of the α-benzylindole-3-acetic acid by the same approach allowed the pyranone formation reaction and Diels-Alder reaction to be carried out, once again the yield of carbazole 126 is very low (<1%) (Scheme 89).

Moody has previously synthesised the α-methyl compound and observed a 20% drop in the yield compared to that without this substituent. An explanation for these results may be that the presence of the sterically demanding linking group firstly prevents the approach of the electrophile and secondly obstructs removal of the α-proton which is necessary for pyranone formation.
The formylation reaction of methyl 1-methylindole-3-acetate had been successful; it therefore seemed logical to try the same approach to this series. In the formation of methyl 1-methylindole-3-acetate by a modified Heaney/Ley method, methyl 1-methyl-α-methylindole-3-acetate\(^6\) had been the major side product due to unwanted deprotonation and subsequent methylation of the methylene position. This appeared the ideal model compound for our system. Methyl 1-methyl-α-methylindole-3-acetate was added to the preformed Vilsmeier complex and the reaction heated to reflux for 3 hours (Scheme 90).

![Scheme 90](image)

We were somewhat surprised to find that two products had been formed in this reaction when in the corresponding reaction with methyl 1-methylindole-3-acetate only one product was observed. The desired 2-formyl compound 127 was obtained in 30% along with ~30% of the other compound which was assigned as the 5-formyl derivative 128. Hydrolysis yielded 129 and cyclodehydration with acetic anhydride gave the desired pyranone 130 (Scheme 91).

![Scheme 91](image)

4,9-Dimethylpyrano[3,4-b]indol-3-one then underwent a Diels-Alder reaction with DMAD to give the expected dimethyl 4,9-dimethylcarbazole-2,3-dicarboxylate (131).

Having successfully synthesised our model compound, albeit in rather low yield, our attention turned to the alkylation of the anion generated by the treatment of methyl 1-methyl-indole-3-acetate with LDA. From work in the previous series...
α,α'-dibromo-μ-xylene had given the best results, treatment of the anion of methyl 1-methylindole-3-acetate with this electrophile at -78°C gave the desired compound 132 in 50% yield (Scheme 92).

The structure of this compound was confirmed by X-ray crystallography (Figure 3).

Formylation of this compound under the previously employed conditions gave a multicomponent mixture from which the desired product was not recovered. It is clear from these results that substitution of the α-position has a vast effect on the reactivity of the 2-position. Comparison of the formylation of methyl 1-methylindole-3-acetate with that of the α-methylated case shows the effect of the introduction of the comparatively small methyl group (the yield of the 2-isomer drops and the 5-isomer is produced). The use of the bulkier benzyl or p-xylyl group have an even greater effect and also introduce the possibility of electrophilic substitution onto their aromatic rings.
Utilisation of methyl 1-methyl-2-formylindole-3-acetate as a preorganised pyranone is an obvious route to linked pyranones. The methylene position should be particularly acidic due to the formyl group in the 2-position. Methyl 1-methyl-2-formyl-indole-3-acetate was treated with 1.5 equivalents of LDA and methyl iodide was added to the resulting red solution (Scheme 93).

![Scheme 93](image)

After work up it was surprising to find only the starting material was present although not all of it was recovered. The presence of the formyl group in the 2-position allows the formation of the enolate 133 which is presumably fairly stable (Scheme 93). This case is perhaps analogous to the generation of indole-2,3-quinodimethane equivalents by treatment with strong base. Repeating the deprotonation of methyl 1-methyl-2-formylindole-3-acetate in the presence of DMAD instead of the electrophile failed to produce any cycloaddition product.

### 2.3. Summary

The synthesis of a number 1-methylpyrano[3,4-b]indol-3-ones has been achieved. It was found that the 2-acylation of methyl 1-methylindole-3-acetate is much easier with most electrophiles examined than that of methyl indole-3-acetate. The exception is when oxalyl chloride is used and this gave in the case of methyl indole-3-acetate a 2,2'-linked indole. Unfortunately this compound could not be converted into the desired pyranone.

The synthesis of novel $N,N'$ linked indole-3-acetic acids has been achieved for both pentyl and p-xylyl linkers. The formation of a double pyranone was observed but its isolation proved impossible. Its subsequent Diels-Alder reaction with DMAD shows that these linked pyranones have the potential to form carbazole containing polymers if better yields of the intermediate could be formed.
Two α,α'-linked indole-3-acetic acid derivatives have been synthesised employing the p-xylyl linker but their steric bulk prevents electrophilic attack and hence pyranone formation.
Chapter Three

The Synthesis of Thieno[2,3-c]pyran-3-one Derivatives
3.1. Introduction

The use of heterocyclic o-xylylene equivalents is not limited to indole-2,3-quinodimethanes and the synthesis of carbazoles. The use of 2,3-dimethylenethiophene (134) with dienophiles affords, \textit{via} a Diels-Alder reaction, benzothiophenes.\textsuperscript{70} As was the case with indole-2,3-quinodimethanes there are a number of sources of the dimethylenethiophene. The routes to these unstable intermediates are very similar to those discussed in Chapter 1 for the indole analogues, hence elimination from 135 or 136, using sodium iodide\textsuperscript{71} or TBAF\textsuperscript{72} respectively, generates dimethylenethiophene as does heating the cyclic sulfone\textsuperscript{73} (137) which is itself generated from dimethylenethiophene.

![Chemical structures](image)

Stable dimethylenethiophene analogues have also been reported and it was found that thieno[3,4-c]pyrroles\textsuperscript{74} (138), thieno[2,3-c]furans\textsuperscript{75} (139) and the anionic dienes\textsuperscript{76} 140 underwent cycloadditions with suitable dienophiles.

![Chemical structures](image)

Moody has synthesised a range of thieno[2,3-c]pyran-3-ones and the isomeric [3,2-c]pyranones which are the thiophene analogues of the pyrano[3,4-b]indol-3-ones.\textsuperscript{77} These compounds are stable equivalents of dimethylenethiophenes and as such undergo similar cycloadditions followed by extrusion of carbon dioxide to yield the desired benzothiophenes.

The synthesis of these stable analogues can be achieved using a similar approach to that employed for the pyrano[3,4-b]indol-3-ones namely treatment of the parent acid with an anhydride and boron trifluoride etherate (Scheme 94).
This method however tends to give relatively low yields of the desired product, this is presumably due to the possibility of attack at two positions on the thiophene ring (2 or 5 position).

A more attractive approach is via the initial acylation of ethyl thiophen-3-acetate (Scheme 95). Acetylation using tin(IV) chloride resulted in a 6:1 ratio in favour of the desired isomer, formylation using dichloromethyl methyl ether however resulted in a 1:1 ratio. Hydrolysis and cyclodehydration produce the thieno[2,3-c]pyran-3-one 141 in good yield.

The Diels-Alder reactions of thieno[2,3-c]pyran-3-ones with DMAD proceed rapidly in refluxing bromobenzene to produce good to excellent yields of the corresponding trisubstituted benzothiophene 142 (Scheme 96).

The reaction of thieno[2,3-c]pyran-3-ones with unsymmetrical dienophiles introduces the question of regioselectivity in the benzothiophene product (Scheme 97).
The results obtained with ethyl propiolate (X=H, Y=CO₂Et) mirror exactly those seen with the same dienophile and pyrano[3,4-b]indol-3-ones. Hence the selectivity observed for 143 over 144 never rises above 2:1 although the yields of product are good (62-96%). Use of ethyl trimethylsilylpropynoate in the Diels-Alder reactions with pyrano[3,4-b]indol-3-ones furnished exclusively one isomeric product which was found to be that with the bulky trimethylsilyl group in the 3-position. Use of the same alkyne (X=SiMe₃, Y=CO₂Et) with the thiophene analogues again favours the formation of 143 with the trimethylsilyl group in the 3-position but the ratios although still useful, are noticeably lower (4:1 for R¹=R²=H to 12:1 for R¹=H, R²=C₅H₁₁).

The preparation of thieno[2,3-c]pyran-3-ones bearing an alkyne group has also been achieved by Moody when heated these compounds undergo an intramolecular Diels-Alder reaction leading to indenothiophenes (Scheme 98). This chemistry also follows closely the results obtained with pyrano[3,4-b]indol-3-ones where the corresponding carbazole products were obtained.
There has been little or no work carried out involving polymers containing benzothiophenes in the literature but the high electron density of the benzothiophene ring system may introduce useful electronic properties to such a polymer. The synthesis of linked thieno[2,3-c]pyran-3-ones would allow a route, via a double Diels-Alder reaction with a bis-alkyne, into these new and interesting compounds.

3.2. The Synthesis of Thieno[2,3-c]pyran-3-ones

The compound that we envisaged as being potentially most interesting was that where the thieno[2,3-c]pyran-3-ones were linked through a phenyl group in the 1-position as shown below.

![Chemical structure](image)

We envisaged the synthesis of this compound starting from the Friedel-Crafts reaction of ethyl thiophene-3-acetate with terephthaloyl chloride. As a model for this reaction, and more particularly the regioselectivity, the reaction of ethyl thiophene-3-acetate with benzoyl chloride was examined (Scheme 99).

![Scheme 99](image)

The reaction was carried out in 1,2-dichloroethane with both tin(IV) chloride and aluminium chloride at room temperature. At room temperature virtually no reaction occurred and so heating to reflux was necessary. In the case of both Lewis acids the ratio of 2-benzoylation (145) vs. 5-benzoylation (146) was approximately 1:1. This value was determined by the relative integration of the singlets due to
methylene group in the 3-position of the thiophene in the $^1$H NMR spectrum. This result was somewhat disappointing by comparison with those obtained by Moody$^78$ on acetylation of the same compound and may be explained by the elevated temperature employed. At lower temperatures the ester may direct the electrophile into the 2-position through chelation with the Lewis acid but at a higher temperature this chelation is reduced and hence the reaction is less discriminative. It was also found that the two isomers, 145 and 146, were not separable by column chromatography, however, after hydrolysis with potassium hydroxide recrystallisation with toluene gave just the desired regio isomer 147. Subsequent cyclodehydration gave 1-phenylpyrano[2,3-c]thiophen-3-one 148. This compound then smoothly underwent the Diels-Alder reaction with DMAD to give the expected benzothiophene 149 (Scheme 100).

Despite further investigation of the temperature of the initial Friedel-Crafts reaction no ratio better than 1:1 was achieved.

The Friedel-Crafts reaction of ethyl thiophene-3-acetate with terephthaloyl chloride presented one major problem. The reaction with benzoyle chloride had given a 1:1 mixture of the two isomers so by analogy the double Friedel-Crafts reaction with terephthaloyl chloride should at best give the three products 150, 151 and 152 (Scheme 101) in a statistical ratio of 1:2:1 and hence a maximum yield of 25% of the desired product.
The reaction was carried out in the presence of aluminium(III) chloride in refluxing 1,2-dichloroethane for 8 hours. Analysis of the reaction mixture by $^1$H NMR spectroscopy showed the two signals due to the methylene groups with approximately equal integration, this of course only confirms that attack has taken place at the 2- and 5-positions and does not prove that 150 is formed. Column chromatography generally failed to separate the isomers which could not be separated by TLC either. On one occasion elution of a column after chromatography unexpectedly yielded a yellow solid which was found to possess all the data expected for the desired compound 150. Attempts to repeat this method of purification in subsequent reactions by recrystallisation or column chromatography have all failed. The pure isomer 150 was subsequently hydrolysed and cyclodehydrated to give the pyranone 153 (Scheme 102).

This procedure furnished a small quantity of 153 albeit in a rather impure form so we approached the double Diels-Alder reaction with DMAD (Scheme 103).
We were delighted to find that the reaction proceeded smoothly to give the desired linked benzothiophene as a high melting solid. Attempts to carry out the Friedel-Crafts reaction, hydrolysis and cyclodehydration without separating the isomers, with a view to separating them by chromatography at the pyranone stage surprisingly failed with no pyranone apparently being formed. It is interesting to note that the use of 2.2 equivalents of aluminium(III) chloride changed the ratio of the peaks in $^1$H NMR spectrum to 2:1 in favour of the undesired isomer.

The problems associated with the separation of the desired isomer mean that this method is not realistic for the synthesis of polymers although the one Diels-Alder reaction of the pyranone worked well.

Coupling reactions now form an integral part of synthetic chemistry and so the introduction of a suitable handle into this thiophene system would allow us to couple two units to form a linked thieno[2,3-c]pyran-3-one. The introduction of a bromo substituent was achieved by reaction of ethyl thiophene-3-acetate with $p$-bromobenzoyl chloride and aluminium chloride in 1,2-dichloroethane (Scheme 104).
Once again the ratio of the two isomers, 155 and 156, was found to be approximately 1:1. Coupling the aryl-bromides at this stage was not an option as the reaction would be expected to produce a mixture of 3 isomeric biphenyls. Separation of the two isomers was not possible at this stage so the mixture was hydrolysed to the acids 157 and 158. Due to the polarity of the acid groups the acids could not be separated and so they were treated with acetic anhydride to give the pyranone 159 which could readily be separated from the unwanted acid by column chromatography (Scheme 105).

As expected 159 could then be reacted with DMAD to afford the desired benzothiophene 160 in good yield (Scheme 106).
Treatment of the pyranone 159 with ethanol and base then gave ethyl 2-(p-bromobenzoyl)thiophene-3-acetate (155). Homo aryl-bromide coupling was then attempted using the nickel(II) dibromo bis(triphenylphosphine) catalyst previously mentioned in Chapter 2 (Scheme 107).\textsuperscript{57}

Disappointingly the thiophene proved resistant to the coupling procedure with starting material being returned, once again the chemistries of the thiophene and indole series are unfortunately very similar.

3.3. Summary

The synthesis of novel 1-aryllthieno[2,3-c]pyran-3-ones has been achieved using simple chemistry and the subsequent Diels-Alder reactions produce the desired trisubstituted benzothiophenes.

The first synthesis of a linked thieno[2,3-c]pyran-3-one has been achieved. The double Diels-Alder reaction of this substrate has been successfully carried out
indicating that the linked pyranone would be a good route to polymers. The difficulty in preparation of the linked pyranone means that further investigation of polymer formation has not been carried out.
Chapter Four

Molecular Tweezers, Preorganised Clefts and Folded Molecules.
4.1. Introduction

Molecular recognition is one of the key features of life. Nature uses particular cavities or clefts within enzymes and receptor sites to bind specific molecules. The molecules which are incorporated into the enzyme are dependent on the properties of the cavities. The recognition is a result of certain key features within the cavity, these features are commonly hydrogen bonding, hydrophobic interactions and electrostatic forces. The interest in molecular recognition is widespread encompassing such diverse fields as organic synthesis, bioorganic chemistry and electronic devices.

In bioorganic chemistry the interest is in forming synthetic receptors for biologically active molecules such as nucleotide bases. Rebek has carried out much research in the field of molecular recognition particularly in the use of clefts for the binding of heterocyclic diamines. The general structure of these synthetic receptors is shown in Figure 4.

![Figure 4](image)

The size and shape of the cavity are essential features. Optimal binding occurs when the receptor and the substrate chelate and have the possibility of additional aryl-aryl stacking interactions. The aryl groups which have been employed in these receptors are carbazole, acridine, fluorene and naphthalene. Hamilton has investigated a similar idea using a macrocycle for nucleotide base recognition (Figure 5).
Whitlock has produced a series of cyclophane hosts (Figure 6) where there can either be just the two diyne linkers or the case where an extra tether containing an aryl system is also introduced. These systems were found to be good hosts for a variety of aromatic compounds.\textsuperscript{80}

![Figure 6](image)

**Figure 6**

**Molecular Tweezers**

The phrase 'molecular tweezer' was first introduced by Whitlock,\textsuperscript{81} but recently it has been used by Zimmerman to describe a host system which binds an aromatic host \textit{via} a $\pi$-$\pi$ interaction.\textsuperscript{82} The criteria for an idea binding site for a electron deficient aromatic guest is that the chromophores should be $\sim 7\text{"A}$ apart and oriented parallel directly over each other. The spacing is then twice the Van der Waals radii so maximum interaction between the chromophores and guest is achieved. Obviously to bind an electron deficient molecule in an electron donor-acceptor (EDA) fashion the chromophore must itself be electron rich. Zimmerman's choice of the dibenz[c,h]acridine spacer was driven by the 7.24 Å gap this provides and also by the fact that this spacer allowed the attached chromophores to be alligned in a parallel fashion. The system that Zimmerman has employed is shown in Figure 7.
The choice of acridine as the chromophore is again attractive for two reasons; firstly it is well known that it binds to electron deficient aromatics although rather weakly and secondly the synthesis of acridines can be carried out by a fairly short route (Scheme 108). Recently Lehn has synthesised a macrocycle incorporating acridine with a view to aromatic or DNA intercalation.83

The cleft present in this molecular tweezer is said to be preorganised since the rigid spacer unit fixes the acridine moieties in position. To study the ability of molecular tweezers 1H NMR titrations have been carried out using 2,4,7-
trinitrofluorenone as the guest. Results of this titration showed that the use of a flexible linker between the acridines gave very poor binding, however, use of the rigid dibenz[c,h]acridine system gave high $K_{assoc}$ values indicating effective binding.\textsuperscript{82} Zimmerman has also used a modified molecular tweezer for the binding of nucleotide bases.\textsuperscript{84} The introduction of a carboxylic acid into the cleft of the tweezer allows both hydrogen-bonding and $\pi-\pi$ interaction with the guest.

**Folded Molecules.**

Nagao and co-workers have noted the profound effect that the nature of a linking group may have on the conformation of a non-rigid molecule.\textsuperscript{85} The conformations which would be expected to form from a simple linked compound involving 2 aromatic systems are shown below (Figure 8).

![Diagram of folded molecules](image)

Figure 8

Nagao's initial work involved the linkage of $N$-substituted-3-nitro-1,2,4-triazoles to a benzene ring either through a sulfonic or a carboxylic ester (Figure 9).
It was found that molecules possessing the triazole ring system (with or without the nitro group) and the sulfonate linkage adopted a folded conformation while the use of a carboxylate ester with the same triazole gave a stretched conformation as determined by X-ray analysis. There was no evidence of charge transfer in any of the examples examined so the effect was attributed to weak forces such as Van der Waals and electrostatic interactions.

The same group have also incorporated two sulfonates to link three aromatics (Figure 10).86

The use of the nitro-triazole moiety again produced a crystal structure showing a folded conformation, in this case with 3 aromatic rings the pattern is sigmoidal. The use of Ar=Ph also gave a sigmoidal pattern indicating that the triazole is not necessary for this conformation. Extension of the alkyl chain between the aromatic residue and the hydroxy functionality by one CH₂ unit resulted, for the case of Ar=Ph, in the formation of the stretched conformation. These results suggest that the essential features for the formation of a folded conformation are the sulfonate ester and the two CH₂ units from the heterocycle to the alcohol.
The shape of any polymer that we could potentially form (Chapter 2) would effect its properties so we were interested in making simple model systems containing initially two heterocycles which were linked in some way. This idea then introduced the possibility of forming molecular tweezers and probing molecular shape.

4.2. Synthesis of Linked Indoles and Carbazoles.

Previously we developed a simple methodology for the N-alkylation of indole using a bis-electrophile as part of the synthesis of linked indole-3-acetic acid derivatives (Chapter 2). We wondered whether we could further exploit this methodology for the synthesis of simple molecular tweezers.

In previous work we synthesised 104 and 109 (Scheme 109). In both cases we were able to obtain single crystal X-ray structures (Figure 11).

The 1,5-bis(indolyl)pentane adopted the expected conformation where the floppy side chain allows the indole rings to move away from each other. More impressive was the structure exhibited by 109. The indole rings were found to adopt an almost parallel arrangement although the rings were pointing in opposite directions and hence not overlapping. Although in the solid state the indole rings are not overlapping in solution the structure should be freely rotating and therefore the rings should pass over each other, this would then allow 109 to act as a molecular tweezer.
The use of the para-xylyl linker had given a compound showing an interesting conformation so the ortho- and meta-isomers were synthesised. Treatment of indole with potassium hydroxide in DMSO generates the indole anion, this was then reacted with both α,α'-dibromo-o-xylene and α,α'-dibromo-m-xylene (Scheme 109).

![Scheme 109](image)

The meta-linked compound was produced in good yield but it proved resistant to all attempts to form crystals suitable for X-ray analysis. The ortho-isomer 162 was likewise produced in good yield but in this case a crystal suitable for X-ray crystallography was obtained and the structure was determined (Figure 12).

![Figure 12](image)

The steric repulsion between the two indoles was expected to be very large in the case of this ortho-isomer and indeed the X-ray structure reflects this. The two
indole rings repel each other to such an extent that they point in opposite directions and are twisted away from each other.

In the literature there are plenty of examples of complexes formed between electron deficient aromatics and the electron rich carbazole. We wondered whether the corresponding carbazole compounds would adopt similar conformations.

The use of potassium hydroxide in DMSO with the appropriate electrophile allowed the linked carbazoles to be synthesised in ≈70% yield (Scheme 110).

The results obtained with this carbazole series closely mirrored those of indole. The meta-isomer 165 would not afford suitable crystals for X-ray analysis but both the ortho- (166) and para- (164) isomers gave acceptable crystals from acetone (Figure 13, Figure 14).

The ortho- isomer 166 displays a large steric repulsion with the result that the carbazole rings adopt a conformation reminiscent of helicopter blades.
The para-isomer 164 also adopts a conformation which mirrors that of the indole series, hence the two carbazole rings are pointing away from each other but their orientation is almost parallel. This result was encouraging in our search for a simple model system for molecular tweezers.

With the knowledge that we could link unfunctionalised heterocycles our attention turned to systems where we could alter the electron density present on the heterocyclic ring.

Dimethyl 1-methylcarbazole-2,3-dicarboxylate is readily available through the well established Diels-Alder reaction of 1-methylpyran[3,4-b]indol-3-one with DMAD.\textsuperscript{19,23} The use of potassium hydroxide and DMSO to deprotonate this substituted carbazole was an unattractive proposition due to the possibility of hydrolysing the esters so an alternative method had to be used.

The most obvious method of alkylation of the substituted carbazole was from generation of the anion by a metal hydride. Initially the N-alkylation of carbazole was attempted using sodium hydride and α,α'-dibromo-p-xylene in THF, as a model system. The resulting yields of linked product were however low (~25%). Replacing the THF with DMF did not increase the yield nor did the use of potassium hydride. The N-alkylation of 2-hydroxycarbazole using sodium hydride as the base has been reported, but the most impressive results were obtained when 2 equivalents of DMF in THF were employed in conjunction with this base (Scheme 111).\textsuperscript{87}
When these conditions were employed in the reaction of carbazole and \(\alpha,\alpha'-\)dibromo-\(p\)-xylene the yields were greatly improved. With a reliable and high yielding method for alkylation of carbazoles the linkage of the diester was attempted.

Treatment of dimethyl 1-methylcarbazole-2,3-dicarboxylate with sodium hydride and two equivalents of DMF in THF generated the carbazole anion, addition of \(\alpha,\alpha'\)-dibromo-\(p\)-xylene gave the linked carbazole 167 (Scheme 112).

The use of \(\alpha,\alpha'\)-dibromo-\(m\)-xylene under the same conditions afforded the expected meta- compound 168. Unfortunately neither of these substituted carbazoles were suitable for X-ray analysis so no information on the conformation of these compounds was obtained.

We had previously synthesised 116 by the Diels-Alder reaction of 115 with DMAD (Scheme 113).
It was thought necessary to synthesise this compound by an independent route hence addition of a solution of dimethyl 1-methylcarbazole-2,3-dicarboxylate in THF/DMF to sodium hydride followed by 1,5-diiodopentane gave an identical compound (Scheme 114).

Although 116 was obtained as a crystalline solid good crystals could not be obtained so no more structural information on this compound could be obtained.

These alkylation conditions proved very useful on the few occasions when the standard method using potassium hydroxide failed. The synthesis of 169 had proved very difficult giving low yields and purification problems. The use of sodium hydride, THF and DMF however furnished the product in 76% yield.
In all cases we had examined the use of a meta-xylene linked compound had not resulted in a crystal structure. The ortho-isomer had provided structural data but the steric crowding in these molecules meant they would be of little interest to us as potential molecular tweezers. The para-isomer had given us several excellent crystals so the decision was made to concentrate on the para-linked compounds.

In an effort to change the electronics of the heterocycle, 5-nitroindole was treated with potassium hydroxide in DMSO and then, after formation of the bright red anion, with α,α’-dibromo-p-xylene (Scheme 116).

The reaction proceeded smoothly to give 170 but the subsequent purification was complicated by the extreme insolubility of this compound. This system did furnish a suitable crystal for X-ray analysis and this showed a similar pattern to that on indole and carbazole (Figure 15). Since the introduction of an electron withdrawing group onto the indole ring had barely changed the conformation of the linked compound we wondered whether the introduction of an electron donating substituent would alter the shape.
As expected 5-methoxyindole could readily be alkylated with α,α'-dibromo-\(p\)-xylene under our standard conditions (Scheme 117).

Scheme 117

Compound 171 gave a crystal which was suitable for X-ray analysis (Figure 16). The structure was somewhat surprising in light of the other results we had obtained with the same \(para\)-xylyl linker. The indole rings are considerably twisted and are now in a linear array with the methoxy groups at 180° to each other.
The result obtained with 5-methoxyindole showed that the electronics of the ring systems may be able to change the conformation of the system. All the examples which we had investigated were totally symmetrical, could the use of an unsymmetrical system where one ring was electron deficient and the other electron rich further change the conformation? We hypothesised that the two rings should then be attracted to each other and that the conformation would then be folded rather than stretched.

To construct the desired unsymmetrical para-xylyl linked compounds three routes were obvious. Firstly one heterocycle could be added to a suspension of potassium hydroxide in DMSO and then the electrophile added, a solution of the other heterocycle which had previously been treated with potassium hydroxide to form the anion could then be added. Secondly both heterocycles could be treated with the standard conditions to form the anions and then α,α'-dibromo-p-xylene could be added. Both of these reactions should give a statistical mixture of the symmetrical products and the desired unsymmetrical product. It was anticipated that the purification of this mixture would prove difficult so the third, more stepwise, approach was employed. The compound that was initially required was the benzyl bromide derivative 172.

![Chemical Structure](image)

Treatment of 5-nitroindole with potassium hydroxide generated the anion as before but in this case 2 equivalents of α,α'-dibromo-p-xylene were added rather than the 0.5 which we had previously employed. The excess electrophile should minimise the formation of the linked species and maximise the formation of the desired benzyl bromide derivative (Scheme 118).
The reaction furnished the expected benzyl bromide 172 in 34% yield but ~40% of the linked compound was also isolated. Repeating this reaction with further excesses of electrophile still gave rise to a considerable amount of the undesired linked compound while the presence of this excess electrophile caused complications to the purification due to its insolubility. It would seem that the introduction of one 5-nitroindole onto the electrophile activates the other end and hence the linked compound is observed.

To complete the synthesis of the unsymmetrical compounds the benzyl bromide derivative 172 then had to be employed as the electrophile. Therefore treatment of 5-methoxyindole under our standard conditions followed by addition of 172 gave the desired unsymmetrical compound 173 in 47% (Scheme 119).

Although this compound was crystalline no single crystals could be produced so another example of this type was required. The use of carbazole instead of 5-
methoxyindole did however afford a compound 174 from which crystals could be obtained (Scheme 120).

![Scheme 120](image)

The X-ray structure obtained (Figure 17) showed that the rings were now overlapping. This change from the symmetrical carbazole system where the rings point in opposite directions to this unsymmetrical case is very marked. We attribute this change to an intramolecular electrostatic interaction between the heterocycles.

![Figure 17](image)

The work of Nagao on folded conformations led us to question whether using a similar system utilising indole or carbazole instead of triazole would give similar results. Of particular interest was whether the presence of an electron withdrawing group on the aryl group would allow an electrostatic interaction with the electron rich heterocycle.

2-Indolyl-ethanol (175) was chosen as a starting point for these simple esters. Although there are a number of methods for the synthesis of this compound in the literature the use of indole under our standard conditions with 2-chloroethanol as the electrophile seemed most attractive (Scheme 121).
We were gratified to find that this alcohol could be produced in 71% yield by this highly versatile alkylation procedure. Another compound, which has been assigned as 176, was also isolated. 176 is presumably formed from the initial alcohol which is further deprotonated by the excess potassium hydroxide and then reacts with 2-chloroethanol. The formation of 176 could also be explained by the attack of the alkoxide on ethylene-oxide which can be formed by the action of base on 2-chloroethanol (Scheme 122).

The esters 177, 178 and 179 could then be formed in good yield by the simple addition of triethylamine and the desired acid chloride to the alcohol (Scheme 123).
Both the benzenesulfonate and benzoate esters failed to give a suitable crystals although both were highly crystalline. The \( p \)-nitrobenzoate ester could however be analysed by X-ray crystallography (Figure 18).

**Figure 18**

The main interaction that was noted in this case would appear to be due to an intermolecular nature between the \( p \)-nitrobenzoate ring and that of the indole. This structure is reminiscent of one that is described by Nagao as a "non-stacked conformation" since it is not truly stretched.

A potentially more interesting compound was that obtained from the reaction of 2-indolylethanol with terephthaloyl chloride and triethylamine (Scheme 124).

**Scheme 124**

The desired product 180 was obtained in good yield and fortunately gave a single crystal suitable for X-ray analysis (Figure 19).

**Figure 19**
The crystal structures show that the molecule adopts a stretched conformation in agreement with Nagao.

An equivalent series of compounds involving carbazole was also synthesised. Treatment of carbazole with potassium hydroxide and subsequent reaction with 2-chloroethanol gave the alcohol 181 as expected (Scheme 124).^89

\[
\text{KOH/DMSO} \quad \text{Cl-} \text{(CH}_2\text{)}_2\text{-OH} \quad \text{N} \quad \text{H} \quad \text{KOH/DMSO} \quad \text{Cl-} \text{(CH}_2\text{)}_2\text{-OH} \quad \text{N} \quad \text{H}
\]

Scheme 124

The benzoate, p-nitrobenzoate and sulfonate esters could then be prepared as before (Scheme 125) although the use of terephthaloyl chloride gave an insoluble compound which appeared to be neither starting material nor product.

\[
\text{NEt}_3/ \text{ArXOCI} \quad \text{(CH}_2\text{)}_2\text{-OH} \quad \text{p-nitrobenzoate ester}
\]

Scheme 125

Once again the p-nitrobenzoate ester produced suitable crystals for X-ray analysis (Figure 20).
The compound adopts a similar conformation to the indole analogue and once again its conformation could be governed by an intermolecular interaction rather than the desired intramolecular one.

In this series we found that the benzoate ester 183 also gave rise to a crystal structure (Figure 21).

![Figure 21](image)

This crystal structure shows a rather similar pattern to the two previous examples. In this case however there is no nitro group and so this result is not due to an intermolecular interaction.

The success with which the unsymmetrical compounds 173 and 174 were synthesised raised the possibility of synthesising larger molecules by a similar approach. We questioned whether an extended version of 171, where the two 5-methoxyindole rings pointed away from each other, would adopt a similar conformation and hence 185 was suggested as the target (Figure 22).

![Figure 22](image)
The synthesis of 185 started with the reaction of 5-methoxyindole with potassium hydroxide and an excess of α,α'-dibromo-p-xylene (Scheme 126).

![Scheme 126](image)

The benzyl bromide 186 was afforded as a light sensitive solid in low yield. Repeating this reaction proved extremely difficult furnishing a rapidly decomposing purple oil.

The compound that was then necessary was a linked indole still possessing a proton on the nitrogen. It was then necessary to O-alkylate 5-hydroxyindole. The alkylation was achieved using potassium carbonate and α,α'-dibromo-p-xylene in refluxing acetone (Scheme 127).

![Scheme 127](image)

The linked compound 187 was produced in moderate yield after column chromatography. The linked indole was then treated with the usual conditions to form the dianion, addition of the 5-methoxyindole benzyl bromide then afforded the 'tetramer' 185 (Scheme 128).
Attempted purification of 185 by column chromatography resulted in rapid decomposition. A small amount of this compound was obtained and the $^1$H NMR spectrum was recorded which suggested the desired product. In the course of recording the $^{13}$C NMR spectrum it was noted that unexpected peaks appeared and that the spectrum became noisier with time. When the NMR tube was removed the solution had set solid, this occurred on a subsequent occasion and is presumably due to the formation of a polymer. The 3-position of the very electron rich indole ring reacts with the trace of acid in CDCl$_3$ this electrophilic species then reacts with another indole in the 3-position to yield larger molecules and hence polymers (Scheme 129).
Two $^1$H NMR spectra were recorded of the tetramer 185 at 30 minute intervals, in the first there are 3 distinct signals due to benzylic CH$_2$'s, in the second there are 4 benzylic CH$_2$'s this shows that a reaction is actually occurring and the molecule is becoming unsymmetrical as the CH$_2$'s are no longer equivalent.

In an attempt to make a more stable tetramer the initial benzyl bromide was synthesised using carbazole instead of 5-methoxyindole (Scheme 130).

![Scheme 130](image)

The carbazole benzyl bromide 188 was obtained as a stable white solid in 29% yield. This contrasts with the 5-methoxyindole example and presumably this is due to reduced nucleophilicity of carbazole relative to 5-methoxyindole. Deprotonation of the linked indole 187 as before produced the dianion which was subsequently quenched with the carbazole derived benzyl bromide to produce the desired tetramer 189 (Scheme 131).

![Scheme 131](image)
The tetramer was furnished as a white solid in 81% yield. $^1$H and $^{13}$C NMR spectra of the product were recorded but on removal of the NMR tube it was noticed that once again there was a white precipitate, on further standing more precipitation was observed. The structure was confirmed by mass spectroscopy but no crystals could be obtained.

4.3. $^1$H NMR Studies of Molecular Tweezers.

To investigate the potential of our non-rigid systems as potential molecular tweezers $^1$H NMR studies were carried out using 9-cyanomethylene-2,4,7-trinitrofluorene as the guest and 9-benzylcarbazole and 163 as the hosts. 9-Benzy1carbazole was included so that a comparison between the binding achieved by a non-linked carbazole and a linked one could be made. The study was carried out in CDCl$_3$ using a concentration of guest of 1.37x10$^{-3}$ mol dm$^{-3}$. The shift in the signals due to the guest with the addition of host were then recorded (Table 5).

<table>
<thead>
<tr>
<th>Proton</th>
<th>$^1$H NMR Studies of Molecular Tweezers.</th>
<th>[Host] mol dm$^{-3}$</th>
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<tr>
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<td></td>
<td></td>
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<td>0.089</td>
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<tr>
<td>$\Delta\delta x$</td>
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<td>0.064</td>
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<tr>
<td>$\Delta\delta y$</td>
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</tr>
<tr>
<td>$\Delta\delta z$</td>
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<td>0.040</td>
</tr>
</tbody>
</table>

Table 5 the titration using linked carbazole ($\Delta\delta w$, $\Delta\delta x$, $\Delta\delta y$ and $\Delta\delta z$ refer to the change in shift values for the aromatic protons of the guest).

<table>
<thead>
<tr>
<th>Proton</th>
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<table>
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</tr>
<tr>
<td>$\Delta\delta z$</td>
<td>0.038</td>
</tr>
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</table>

Table 6 the titration using 9-benzylcarbazole
The results show that shift values for the linked and non-linked systems closely mirror each other. Of course the concentration of the two guest solutions is somewhat misleading since the linked system has twice the number of carbazole moieties so in light of this fact it seems that there is no increase in binding created by this being introduced into a carbazole system. This result shows that the carbazole rings are not both interacting with the same guest molecule. This is probably due to two factors:

1. the inter ring distance is below 7 Å,
2. the backbone is not rigid and hence the carbazoles need not lay over each other.

4.4. Summary

The syntheses of simple symmetrical molecules involving two carbazoles or two indoles have been achieved and in a number of cases the conformation in the solid phase has been determined.

Extension to unsymmetrical molecules has allowed the conformation of the molecule to be totally changed from a stretched one to folded.

The synthesis of larger more complicated arrays has been achieved but no crystals have been obtained. It appears that these large molecules are generally unstable in solution and rapidly polymerise.

Molecules involving a heterocycle linked to a carbocyclic aromatic system through either an ester have been achieved, the crystal structures obtained for those involving a carboxylate linkage show the expected stretched conformation.

Investigation of the properties of our proposed molecular tweezer 163 showed that although the 9-cyanomethylene-2,4,7-trinitrofluorene was bound the binding was of a very similar level to that shown by N-benzylcarbazole.
Chapter Five

Experimental Details
5.1. General Experimental Points

'Light petroleum' refers to the fraction of petroleum ether boiling between 40 °C and 60 °C, and ether refers to diethyl ether. Dichloromethane was distilled over phosphorus pentoxide, light petroleum, ether and ethyl acetate were distilled over anhydrous calcium chloride. Anhydrous tetrahydrofuran was purchased from Aldrich. Commercially available compounds were generally used without further purification. Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with phosphomolybdic acid reagent, followed by heating. Flash column chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60; Samples were applied as saturated solutions in an appropriate solvent.

Infra red spectra were recorded in the range 4000-600 cm\(^{-1}\) using either a Nicolet FT-205 or a Perkin Elmer Paragon 100 spectrometer, with internal calibration. \(^1\)H and \(^13\)C NMR spectra were recorded on using either a Bruker AC-250 or Ac-400 instrument in deuteriochloroform or deuteriodimethyl sulfoxide as solvent. NMR chemical shifts are quoted in ppm relative to tetramethylsilane as the internal standard. In reporting NMR spectra for inseparable mixtures of isomers, assignments of the isomers are made where possible. Spectroscopic data is annotated with the following abbreviations; s - singlet; d - doublet; t - triplet; q - quartet; m - multiplet. High and low resolution mass spectra were recorded on a Kratos MS80 instrument or on a VG Analytical ZAB-E instrument (EPSRC Mass Spectroscopy Service Swansea). Melting points were determined on Leica Galen III.
5.2 Experimental Details for Chapter 2

**Dimethyl 2-glyoxyindole-3-acetate 83**

![Chemical structure of Dimethyl 2-glyoxyindole-3-acetate 83]

Aluminium(III) chloride (292 mg, 2.2 mmol) was added, in portions over 1 hour, to a solution of methyl indole-3-acetate (378 mg, 2.0 mmol) and methyl oxalyl chloride (245 mg, 2.0 mmol) in 1,2-dichloroethane (2 mL) under nitrogen, at 0 °C. The reaction was stirred overnight. Water (40 mL) was added and extracted with dichloromethane (2x50 mL). The combined organics were washed with water (3x40 mL), brine (2x30 mL) and dried (MgSO4). The solvent was removed under reduced pressure. Column chromatography (ether) yielded the title compound (149 mg, 27%) as a yellow solid, m.p. 210-212 °C, (Found: C, 60.9; H, 4.6; N, 4.8%; C14H13NOS requires C, 61.1; H, 4.7; N, 5.1%); (Found: M+, 275.0786. C14H13NO5 requires M, 275.0794); δ_H (250 MHz; CDCl3) 10.2 (IH, br-s, NH), 7.67 (1H, d, J 8.2 Hz, Ar-4H), 7.39 (2H, d, J 8.3 Hz, ArH), 7.18 (1H, m, ArH), 4.22 (2H, s, Ar-CH2), 3.96 (3H, s, COO2CH3), 3.72 (3H, s, CO2CH3); δ_C (62.9 MHz; CDCl3) 172.7, 171.1, 162.9, 137.1, 129.3, 128.0 (ArCH), 127.4, 121.9, 121.3 (ArCH), 121.0 (ArCH), 112.7 (ArCH), 53.3 (OCH3), 52.1 (OCH3), 30.9 (Ar-CH2); m/z (El) 275 (M+, 80%), 244 (9), 216 (21), 188 (100), 156 (76), 128 (35).

**1,1'-Bis(3-carboethoxymethylindol-2-yl)oxalate 84**

![Chemical structure of 1,1'-Bis(3-carboethoxymethylindol-2-yl)oxalate 84]

Aluminium(III) chloride (217 mg, 1.63 mmol) was added, in portions, to a solution of ethyl indole-3-acetate (300 mg, 1.48 mmol) and oxalyl chloride (94 mg, 0.74 mmol) in dichloromethane (4 mL) at 0 °C. The reaction was stirred at room temperature overnight. Water (50 mL) was added and the mixture extracted with
dichloromethane (3 x 50 mL). The combined organics were washed with HCl (50 mL (2 N)), water (50 mL), brine (50 mL) and dried (MgSO₄). The solvent was removed under reduced pressure. Column chromatography (1:20 ether:dichloromethane) yielded the *title compound* (190 mg, 28%) as an orange solid, m.p. 210-212 °C, (Found: M⁺, 460.1638. C₂₆H₂₄N₂O₆ requires M, 460.1634); νmax. (nujol mull) 3357, 1725, 1621, 1158, 740 cm⁻¹; δH (250 MHz; d₆DMSO) 11.99 (2H, br-s, NH), 7.73 (2H, d, J 8.1 Hz, Ar-4H), 7.49 (2H, d, J 8.1 Hz, Ar-7H), 7.36 (2H, ddd, J 7.9, 6.6, 1.0 Hz, ArH), 7.11 (2H, ddd, J 8.0, 6.8, 1.0 Hz, ArH), 4.01 (4H, s, Ar-OCH₂), 3.84 (4H, q, J 7.1 Hz, OCH₂), 1.00 (6H, t, J 7.1 Hz, OCH₂); δC (62.9 MHz; d₆DMSO) 184.9, 170.0, 137.9, 129.0, 127.6, 127.1 (ArCH), 121.4 (ArCH), 120.5 (ArCH), 119.1, 113.0 (ArCH), 60.2 (OCH₂), 30.2 (Ar-CH₂), 13.8 (OCH₂); m/z (Cl) 460 (M⁺, 7%), 285 (5), 202 (100), 156 (52), 128 (31).

*Methyl 1-methylindole-3-acetate 85*¹⁻³

![Methyl 1-methylindole-3-acetate 85](image)

Indole-3-acetic acid (4.79 g, 27.4 mmol) was added to a stirred suspension of KOH (9.20 g, 164.3 mmol) in DMSO (50 mL) under nitrogen. After 4 h the reaction mixture was added, with filtration to a solution of methyl iodide (5.1 mL, 83.2 mmol) in DMSO (20 mL) under nitrogen. The reaction was stirred for 2 h. Water (50 mL) was added and the mixture extracted with dichloromethane (3x100 mL), the combined organics were washed with brine (5x100 mL) and dried (MgSO₄). The solvent was removed under reduced pressure. Purification by column chromatography (1:4 ethyl acetate:light petroleum) yielded the *title compound* as a yellow oil (3.56 g, 64%); νmax. (film) 2951, 1737, 1475, 1332, 742 cm⁻¹; δH (250 MHz; CDCl₃) 7.60 (1H, d, J 7.8 Hz, Ar-4H), 7.32-7.20 (2H, m, ArH), 7.13 (1H, dt, J 1.3, 7.6 Hz, ArH), 7.05 (1H, s, Ar-2H), 3.78 (3H, s, OCH₃), 3.77 (2H, s, ArCH₂), 3.70 (3H, s, NCH₃).
**Methyl α-Methyl-1-methylindole-3-acetate 86**

Isolated from above reaction. (1.13 g, 19%)
as a yellow oil, (Found: M⁺, 217.1109. C₁₃H₁₅NO₂ requires M, 217.1103); νmax.
(film) 2950, 1736, 1332, 1164, 742 cm⁻¹; δH (250 MHz; CDCl₃) 7.67 (1H, d, J 8.0
Hz, Ar-4H), 7.31-7.20 (2H, m, ArH), 7.12 (1H, dt, J 1.2, 7.9 Hz, ArH), 7.01 (1H, s, Ar-2H), 4.03 (1H, q, J 7.1 Hz, CH₂CH₃), 3.76 (3H, s, OCH₃), 3.68 (3H, s, NCH₃), 1.61 (3H, d, J 7.1 Hz, CH₂CH₃); δC (62.9 MHz; CDCl₃) 175.7, 137.0, 126.9, 126.3 (ArCH), 121.8
(ArCH), 119.3 (ArCH), 119.2 (ArCH), 114.0, 109.4 (ArCH), 51.9 (OCH₃), 36.9
(CH₂Me), 32.6 (NCH₃), 18.1 (CH₂Me); m/z (EI) 217 (M⁺, 54%), 202 (3), 158 (100), 143
(19), 115 (12).

**Methyl 3-(1-methylindolyl)glyoxylate 87**

Oxalyl chloride (10.3 mL, 118 mmol) in ether (10 mL) was added to a solution of
1-methylindole (10.3 g, 78.4 mmol) in ether (200 mL) at 0 °C under an atmosphere
of nitrogen over 1 h. The reaction was stirred at room temperature for 1 h. The
solvent and excess oxalyl chloride were removed under reduced pressure. The
resultant solid was redissolved in dichloromethane (200 mL) and cooled to 0 °C,
when a solution of triethylamine (20 mL) in methanol (30 mL) was added. The
reaction mixture was stirred overnight. The solvent was removed under reduced
pressure and the crude product purified by column chromatography (ether) to
yield the title compound (12.1 g, 71%) as a yellow solid m.p. 93-94 °C (lit.⁵⁵ 96-97
°C); νmax. 1729, 1647, 1525, 1466, 1201, 1084 cm⁻¹;
Methyl 1-methylindole-3-acetate 85

A solution of sodium hypophosphite (24.2 g, 275.0 mmol) in water (20 mL) was added to a solution of methyl 1-methyl-indole-3-glyoxylate (12.0 g, 55.0 mmol) and palladium-on-carbon (10%)(2.4 g) in 1,4-dioxan (100 mL). The mixture was refluxed, with vigorous stirring, for 5 h. The solution was allowed to cool, filtered through a pad of Celite and washed with ethyl acetate. The solvent was removed under reduced pressure. Column chromatography (1:99 ethyl acetate : dichloromethane), yielded the title compound (8.42 g, 75%) as a yellow oil, δH (250 MHz; CDCl3) 7.61 (1H, d, J 7.9 Hz, Ar-4H), 7.33-7.21 (2H, m, ArH), 7.14 (1H, dt, J 1.3, 7.3 Hz, ArH), 7.05 (1H, s, Ar-2H), 3.78 (3H, s, OCH3), 3.77 (2H, s, Ar-CH2), 3.71 (3H, NCH3).

Methyl 1-methyl-2-formylindole-3-acetate 88

Phosphorus oxychloride (0.71 mL, 7.6 mmol) was added to N,N-dimethylformamide (5 mL), at 0 °C under nitrogen. The reaction was stirred at room temperature for 0.75 h. The reaction was cooled to 0 °C and diluted with 1,2-dichloroethane (5 mL). Methyl 1-methylindole-3-acetate (773 mg, 3.8 mmol) in 1,2-dichloroethane (5 mL) was added and then the mixture refluxed for 3 h. After a further 2 h stirring at room temperature aqueous saturated sodium acetate (20 mL) was added. The mixture was extracted with ethyl acetate (4x50 mL). The combined organics were washed with brine (3x30 mL) and dried (MgSO4). The solvent was removed under reduced pressure and the crude material purified by column chromatography (dichloromethane) to yield the title compound (454 mg, 52%) as a yellow solid, m.p. 93-94 °C (toluene/light
petroleum), (Found: M+, 231.0896. C₁₃H₁₃NO₃ requires M, 231.0895); νₘₐₓ.
(CH₂Cl₂) 1738, 1664, 1474 cm⁻¹; δH (250 MHz; CDCl₃) 10.2 (1H, s, CHO), 7.73 (1H, d,
J 8.2 Hz, Ar-4H), 7.47-7.35 (2H, m, ArH), 7.23-7.16 (1H, m, ArH), 4.11 (2H, s, Ar-
CH₂), 4.08 (3H, s, OCH₃), 3.70 (3H, s, NCH₃); δC (62.9 MHz; CDCl₃) 181.8 (CHO),
171.0, 139.5, 131.6, 127.3 (ArCH), 126.3, 121.2 (ArCH), 121.0, 120.9 (ArCH), 110.4
(ArCH), 52.4 (OCH₃), 31.6 (NCH₃), 29.7 (Ar-CH₂); m/z (El) 231 (M+, 42%), 217 (8),
199 (27), 172 (100), 144 (32).

1-Methyl-2-formylindole-3-acetic acid 89

\[ \text{CO}_2\text{H} \]
\[ \text{Me} \]
\[ \text{CHO} \]

Lithium hydroxide (345 mg, 8.2 mmol) in water (5 mL) was added to a solution of
methyl 1-methyl-2-formylindole-3-acetate (190 mg, 0.8 mmol) in THF (15 mL).
The reaction was stirred for 12 h. The reaction mixture was acidified (HCl),
extracted with dichloromethane (3x80 mL), the combined organics were washed
with brine (2x50 mL) and dried (MgSO₄). The solvent was removed under
reduced pressure. Purification by column chromatography (1:1 ethyl acetate:
dichloromethane) yielded the title compound (159 mg, 89%) as a white solid,
m.p. 119-122 °C, (Found: M⁺, 217.0739. C₁₂H₁₁NO₃ requires M, 217.0739); νₘₐₓ.
(CH₂Cl₂) 1715, 1665, 1615, 1473, 1383 cm⁻¹; δH (250 MHz; CDCl₃) 10.1 (1H, s, CHO),
7.70 (1H, d, J 8.1 Hz, Ar-4H), 7.45-7.33 (2H, m, ArH), 7.20-7.14 (1H, m, ArH), 4.10
(2H, s, Ar-CH₂), 4.05 (3H, s, NCH₃); δC (62.9 MHz; CDCl₃) 181.6 (CHO), 176.1
(CO₂H), 139.2, 131.6, 127.4 (ArCH), 126.0, 121.0 (ArCH), 121.0 (ArCH), 120.2, 110.4
(ArCH), 31.4 (NCH₃), 29.6 (Ar-CH₂); m/z (El) 217 (M⁺, 4%), 199 (2), 172 (10), 144 (5),
69 (100).
A suspension of 1-methyl-2-formylindole-3-acetic acid (120 mg, 0.55 mmol) in acetic anhydride (25 mL) was heated at reflux, under nitrogen, for 2.25 h. The solvent was removed under reduced pressure. Column chromatography (1:4 ethyl acetate: dichloromethane) yielded the title compound (61 mg, 55%) as an orange solid, m.p. 210 °C (Dec.), (Found: M⁺, 199.0640. C₁₂H₉NO₂ requires M, 199.0633); νmax. (CH₂Cl₂) 1702, 1614 cm⁻¹; δH (250 MHz; CDCl₃) 7.76 (1H, d, J 7.5 Hz, ArH), 7.59 (1H, d, J 1.5 Hz, Ar-1H), 7.56-7.49 (1H, m, ArH), 7.05-7.00 (2H, m, ArH), 6.55 (1H, d, J 1.4 Hz, Ar-4H), 3.41 (3H, s, NCH₃); δC (62.9 MHz; CDCl₃) 163.0, 148.8, 145.6, 133.2 (ArCH), 130.9 (ArCH), 124.1 (ArCH), 120.4, 119.6 (ArCH), 119.4, 108.5 (ArCH), 100.6 (ArCH), 29.4 (NCH₃); m/z (EI) 199 (M⁺, 100%), 186 (25), 158 (26), 143 (40).

Dimethyl 9-methylcarbazole-2,3-dicarboxylate 91

Dimethyl acetylenedicarboxylate (47 mg, 0.33 mmol) was added to a solution of pyranone (55 mg, 0.28 mmol) in chlorobenzene (10 mL). The mixture was refluxed for 4 h under nitrogen. The solvent was removed under reduced pressure. Purification by column chromatography (dichloromethane) yielded the title compound (33 mg, 40%) as a yellow solid, m.p. 145-146 °C, νmax. (CH₂Cl₂) 2953, 1724, 1601, 1436, 1114 cm⁻¹; δH (250 MHz; CDCl₃) 8.51 (1H, d, J 3.2 Hz, Ar-4H), 8.08 (1H, d, J 7.8 Hz, ArH), 7.61 (1H, d, J 3.2 Hz, Ar-1H), 7.54 (1H, dd, J 8.2, 7.0 Hz, ArH), 7.40 (1H, d, J 8.1 Hz, ArH), 7.30 (1H, dd, J 7.9, 7.0 Hz, ArH), 3.98 (3H, s, OCH₃), 3.96 (3H, s, OCH₃), 3.82 (3H, s, NCH₃); δC (62.9 MHz; CDCl₃) 169.6, 168.1, 142.1, 141.4, 130.6, 127.1 (ArCH), 123.6, 122.4 (ArCH), 122.1, 121.0, 120.9 (ArCH), 120.2 (ArCH), 109.0 (ArCH), 108.9 (ArCH), 52.7 (OCH₃), 52.4 (OCH₃), 29.2 (NCH₃).
Aluminium(III) chloride (410 mg, 3.08 mmol) was added to a solution of methyl indole-3-acetate (289 mg, 1.42 mmol) and benzoyl chloride (0.33 mL, 2.80 mmol) in 1,2-dichloroethane (5 mL) at 0 °C under nitrogen. The mixture was refluxed for 8 h. Water (10 mL) was added and the mixture then extracted with dichloromethane (3×80 mL). The combined organics were washed with water (50 mL), brine (100 mL) and dried (MgSO₄). The solvent was removed under reduced pressure. Column chromatography (dichloromethane, then 1:50 ethyl acetate: dichloromethane) yielded the title compound (115 mg, 26%) as a yellow oil, (Found: M⁺, 307.1210. C₁⁹H₁⁷NO₃ requires M, 307.1208); νmax. (CH₂Cl₂) 1738, 1640, 1247, 1166 cm⁻¹; δH (250 MHz; CDCl₃) 7.85 (2H, d, J 7.6 Hz, ArH), 7.62 (2H, t, J 8.0 Hz, ArH), 7.49 (2H, t, J 7.5 Hz, ArH), 7.41-7.39 (2H, m, ArH), 7.23-7.17 (1H, m, ArH), 3.81 (3H, s, OCH₃), 3.64 (2H, s, Ar-CH₂), 3.58 (3H, s, NCH₃); δC (100 MHz; CDCl₃) 190.9 (C=O), 172.3 (CO₂), 140.4, 139.6, 135.7, 134.1 (ArCH), 130.5 (ArCH), 129.6 (ArCH), 127.8, 126.3 (ArCH), 121.7 (ArCH), 121.6 (ArCH), 114.9, 111.2 (ArCH), 52.8 (OCH₃), 32.9 (NCH₃), 32.0 (Ar-CH₂); m/z (EI) 307 (M⁺, 58%), 248 (100), 231 (40), 77 (52).

A solution of lithium hydroxide (157 mg, 3.7 mmol) in water (3 mL) was added to a solution of methyl 1-methyl-2-benzoylindole-3-acetate (115 mg, 0.37 mmol) in THF (10 mL). After 24 h lithium hydroxide (314 mg, 7.4 mmol) in water (5 mL)
was added. After a further 72 h the mixture was acidified (conc. HCl) and extracted with dichloromethane (3x80 mL), the combined organics were washed with water (50 mL), brine (100 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to yield the title compound (106 mg, 97%) as a yellow solid, m.p. 101-105 °C, (Found: M⁺, 293.1057. C₁₈H₁₅NO₃ requires M, 293.1052); νmax. (CH₂Cl₂) 2927, 1750, 1715, 1636, 1422 cm⁻¹; δH (250 MHz; CDCl₃) 7.83 (2H, d, J 7.8 Hz, ArH), 7.71 (1H, d, J 8.1 Hz, ArH), 7.61 (1H, d, J 7.4 Hz, ArH), 7.49 (2H, t, J 7.8 Hz, ArH), 7.44-7.37 (2H, m, ArH), 7.26-7.19 (1H, m, ArH), 3.74 (2H, s, Ar-CH₂), 3.71 (3H, s, NCH₃); δC (62.9 MHz; CDCl₃) 188.8, 175.6, 138.7, 137.7, 133.8 (ArCH), 129.9 (ArCH), 129.5, 128.9 (ArCH), 128.5, 126.3 (ArCH), 121.2 (ArCH), 120.9 (ArCH), 114.3, 110.4 (ArCH), 32.9 (NCH₃), 32.3 (Ar-CH₂); m/z (El) 293 (M⁺, 6%), 248 (19), 77 (16), 69 (100).

**9-Methyl-1-phenylpyrano[3,4-b]indol-3-one**

![Chemical Structure](image)

A solution of 1-methyl-2-benzoylindole-3-acetic acid (106 mg, 0.36 mmol) in acetic anhydride (6 mL) was refluxed for 4 h. The solvent was removed under reduced pressure. Column chromatography (2:25 ethyl acetate:dichloromethane) yielded the title compound (85 mg, 85%) as an orange solid, m.p. 177-179 °C (lit.²⁴ 165°C), (Found: M⁺, 275.0951. C₁₅H₁₃NO₂ requires M, 275.0946); νmax. (CH₂Cl₂) 1699, 1613, 1563 cm⁻¹; δH (250 MHz; CDCl₃) 7.84 (1H, d, J 7.5 Hz, Ar-5H), 7.68-7.64 (2H, m, ArH), 7.59-7.48 (4H, m, ArH), 7.13-7.07 (2H, m, ArH), 6.61 (1H, s, Ar-4H), 3.20 (3H, s, NCH₃); δC (62.9 MHz; CDCl₃) 162.8, 150.3, 147.6, 143.4, 133.0 (ArCH), 131.4, 129.9 (ArCH), 129.4 (ArCH), 128.2 (ArCH), 127.2, 123.5 (ArCH), 120.0 (ArCH), 119.9, 109.6 (ArCH), 98.8 (ArCH), 33.4 (NCH₃); m/z (El) 275 (M⁺, 100%), 247 (22), 218 (45).
**Dimethyl 9-methyl-1-phenylcarbazole-2,3-dicarboxylate 95.**

![Diagram of Dimethyl 9-methyl-1-phenylcarbazole-2,3-dicarboxylate]

DMAD (23 mg, 0.16 mmol) was added to a solution of 9-methyl-1-phenylpyrano[3,4-b]indol-3-one (37 mg, 0.13 mmol) in chlorobenzene (5 mL) under nitrogen. The mixture was refluxed for 6 h. The solvent was removed under reduced pressure. Column chromatography (1:99 ethyl acetate: dichloromethane) yielded the **title compound** (43 mg, 86%) as a yellow solid, m.p. 181-183 °C, (Found: M+, 373.1319. C_{23}H_{19}N_{2}O_{4} requires M, 373.1314); \( \nu_{\text{max}} \) (CHCl\(_3\)) 1733, 1716, 1592, 1360, 1146, 794 cm\(^{-1}\); \( \delta_{H} \) (250 MHz; CDCl\(_3\)) 8.84 (1H, s, Ar-4H), 8.18 (1H, d, J 7.5 Hz, ArH), 7.55-7.32 (8H, m, ArH), 3.97 (3H, s, OCH\(_3\)), 3.59 (3H, s, OCH\(_3\)), 3.22 (3H, s, NCH\(_3\)); \( \delta_{C} \) (100 MHz; CDCl\(_3\)) 169.3, 166.5, 142.8, 140.1, 135.6, 134.2, 130.9 (ArCH), 128.2 (ArCH), 127.6 (ArCH), 126.9 (ArCH), 123.4, 123.2, 122.2 (ArCH), 122.2, 120.4 (ArCH), 120.3 (ArCH), 117.5, 109.1 (ArCH), 52.2 (OCH\(_3\)), 51.9 (OCH\(_3\)), 31.9 (NCH\(_3\)); m/z (EI) 373 (M\(^{+}\), 100%), 342 (60), 254 (23).

**1,4-Bis(3-carbomethoxymethyl-1-methyl-indol-5-ylcarbonyl)benzene 97**

![Diagram of 1,4-Bis(3-carbomethoxymethyl-1-methyl-indol-5-ylcarbonyl)benzene]

Aluminium(III) chloride (1.05 g, 7.87 mmol) was added to a solution of methyl 1-methylindole-3-acetate (0.73 g, 3.58 mmol) and terephthaloyl chloride (0.36 g, 1.79 mmol) in 1,2-dichloroethane (20 mL) at 0 °C under nitrogen. The mixture was
then refluxed for 16 h. Water (10 mL) was added and the mixture extracted with dichloromethane (3x80 mL). The combined organics were washed with water (80 mL), brine (2x80 mL) and dried (MgSO4). The solvent was removed under reduced pressure. Column chromatography (1:50 ethyl acetate:dichloromethane) yielded the title compound as a yellow solid, m.p. 230-232 °C, (Found: M+, 536.1948. C32H28N2O6 requires M, 536.1947); v max. (CH2Cl2) 1738, 1641, 1165, 934 cm⁻¹; δH (250 MHz; CDCl3) 7.94 (4H, s, ArH), 7.65 (2H, d, J 8.0 Hz, Ar-4H), 7.43-7.41 (4H, m, ArH), 7.25-7.18 (2H, m, ArH), 3.86 (3H, CH3), 3.68 (2H, s, Ar-CH2), 3.60 (3H, s, NCH3); δC (62.9 MHz; CDCl3) 189.1, 171.2, 142.9, 138.8, 134.3, 129.7 (ArCH), 126.8, 125.9 (ArCH), 120.9 (ArCH), 120.8 (ArCH), 115.0, 110.4 (ArCH), 52.1 (OCH3), 32.1 (NCH3), 31.1 (Ar-CH2); m/z (El) 536 (M+, 3%), 274 (8), 217 (13), 186 (12), 155 (31), 31 (100).

Methyl 1-methyl-2-(p-bromobenzoyl)indole-3-acetate

Aluminium(III) chloride (0.98 g, 7.31 mmol) was added, in portions, to a solution of methyl 1-methylindole-3-acetate (0.99 g, 4.88 mmol) and p-bromobenzoyl chloride (1.61 g, 7.31 mmol) in 1,2-dichloroethane (10 mL) at 0 °C under nitrogen. The mixture was refluxed for 6 h. Water (10 mL) was added and the mixture was extracted with dichloromethane (3x80 mL). The combined organics were washed with water (50 mL), brine (100 mL) and dried (MgSO4). The solvent was removed under reduced pressure. Column chromatography (dichloromethane) yielded the title compound (302 mg, 16%) as a yellow solid, m.p. 148-150 °C, (Found: M+, 385.0314. C19H16N03Br requires M, 385.0314); v max. (CH2Cl2) 1738, 1643, 1586, 1408, 1166, 937 cm⁻¹; δH (250 MHz; CDCl3) 7.73 (2H, d, J 8.5 Hz, benzoylH), 7.64-7.62 (1H, m, ArH), 7.63 (2H, d, J 8.6 Hz, benzoylH), 7.42-7.40 (2H, m, ArH), 7.24-7.18 (1H, m, ArH), 3.80 (3H, s, OCH3), 3.66 (2H, s, Ar-CH2), 3.60 (3H, s, NCH3); δC (62.9 MHz; CDCl3) 188.7 (C=O), 171.3 (CO2), 138.8, 138.2, 134.4, 132.1 (ArCH), 131.2 (ArCH), 128.3, 126.8, 125.6 (ArCH), 120.8 (ArCH), 120.7 (ArCH), 114.2, 110.4 (ArCH), 52.0 (OCH3), 32.0 (NCH3), 31.0 (Ar-CH2); m/z (El) 387 (M(81Br)+, 28%), 385 (M(79Br)+, 29%), 326 (18), 247 (100), 218 (37).
I-Methyl-2-(p-bromobenzoyl)indole-3-acetic acid

A solution of lithium hydroxide (408 mg, 9.7 mmol) in water (6 mL) was added to a solution of methyl 1-methyl-2-(p-bromobenzoyl)indole-3-acetate (150 mg, 0.39 mmol) in THF (10 mL). The reaction was stirred for 16 h. The mixture was acidified (conc.HCl), extracted with dichloromethane (3x80 mL) and the organics were washed with brine (80 mL). The solvent was removed under reduced pressure to yield the title compound (140mg, 97%) as a yellow solid, m.p. 125-126 °C (light petroleum/dichloromethane), (Found: M+, 371.0159. C_{18}H_{14}NO_{3}Br requires M, 371.0158); ν max. (CH₂Cl₂) 1751, 1713, 1638, 1586, 1407, 1249 cm⁻¹; δ _{H} (250 MHz; CDCl₃) 7.75-7.63 (5H, m, ArH), 7.48-7.36 (2H, m, ArH), 7.26-7.21 (1H, m, ArH), 3.77 (2H, s, Ar-CH₂), 3.67 (3H, s, NCH₃); δ _{C} (62.9 MHz; CDCl₃) 188.9 (C=O), 175.9 (CO₂), 138.9, 137.8, 134.7, 132.2 (ArCH), 131.2 (ArCH), 128.7, 126.7, 126.0 (ArCH), 121.1 (ArCH), 120.8 (ArCH), 114.5, 110.5 (ArCH), 32.4 (NCH₃), 31.4 (Ar-CH₂); m/z (El) 373 (M⁺{^{81}Br}⁺, 15%), 371 (M⁺{^{79}Br}⁺, 16%), 247 (100), 218 (52).

9-Methyl-1-(p-bromophenyl)pyrano[3,4-b]indol-3-one

1-Methyl 2-(p-bromobenzoyl)indole-3-acetic acid (133 mg, 0.36 mmol) was heated to reflux in acetic anhydride (8 mL) for 4 h. The solvent was removed under reduced pressure. Column chromatography (2:25 ethyl acetate:dichloromethane) yielded the title compound (84 mg, 66%) as an orange solid, m.p. 178-180 °C, (Found: M⁺, 353.0017. C_{18}H_{12}BrNO₂ requires M, 353.0055); ν max (CH₂Cl₂) 1700,
A solution of 9-methyl-1-\((p\)-bromophenyl\)pyrano\[3,4-\(b\)\]indol-3-one (45 mg, 1.28x10\(^{-4}\) mol) and DMAD (27 mg, 1.92x10\(^{-4}\) mol) in chlorobenzene (4 mL) was refluxed under nitrogen for 6 h. The solvent was removed under reduced pressure. Purification by column chromatography (dichloromethane) yielded the title compound (44 mg, 76\%) as a yellow solid, m.p. 190-192 °C, (Found: M\(^+\), 451.0421. \(C_{23}H_{18}NO_4Br\) requires M, 451.0420); \(\delta_{\max}\) (CH\(_2\)Cl\(_2\)) 1732, 1715, 1491, 1360, 1146, 829 cm\(^{-1}\); \(\delta_H\) (250 MHz; CDCl\(_3\)) 8.93 (1H, s, Ar-4H), 8.17 (1H, d, J 7.7 Hz, ArH), 7.60 (2H, d, J 8.2 Hz, ArH), 7.58-7.51 (1H, m, ArH), 7.37-7.34 (2H, m, ArH), 7.33 (2H, d, J 8.2 Hz, ArH), 3.96 (3H, s, OCH\(_3\)), 3.62 (3H, s, OCH\(_3\)), 3.26 (3H, s, NCH\(_3\)); \(\delta_C\) (62.9 MHz; CDCl\(_3\)) 169.3, 166.5, 142.9, 140.0, 134.7, 134.3, 132.7 (ArCH), 131.1 (ArCH), 127.2 (ArCH), 123.7, 122.8, 122.7 (ArCH), 122.3, 121.7, 120.6 (ArCH), 120.6 (ArCH), 117.7, 109.3 (ArCH), 52.3 (OCH\(_3\)), 52.2 (OCH\(_3\)), 32.3 (NCH\(_3\)); \(m/z\) (EI) 453 (M\(^{81Br}\)+, 97\%), 451 (M\(^{79Br}\)+, 100), 422 (44), 180 (53).
1,5-Bis(indol-1-yl)pentane 104\(^{90}\)

![Chemical structure of 1,5-Bis(indol-1-yl)pentane](image)

Indole (4.00 g, 34.2 mmol) was added to a suspension of potassium-hydroxide (7.66 g, 136.8 mmol) in DMSO (60 mL) under nitrogen. After 0.75 h the mixture was cooled and 1,5-diiodopentane (5.40 g, 17.1 mmol) was added. After 16 h water (20 mL) was added and the mixture extracted with dichloromethane (3x80 mL). The combined organics were washed with water (3x80 mL), brine (3x80 mL) and dried (MgSO\(_4\)). The solvent was removed under reduced pressure. Purification by column chromatography (1:1 dichloromethane:light petroleum) yielded the title compound (8.2 g, 80%) as a white crystalline solid, m.p. 84-86 °C (lit. 90 81 °C), (Found: M\(^+\), 302.1785. C\(_{21}\)H\(_{22}\)N\(_2\) requires M, 302.1783); \(\nu\)\(_{\text{max}}\) (Nujol) 1510, 1446, 1438, 1317, 746 cm\(^{-1}\); \(\delta\)\(_{\text{H}}\) (250 MHz; CDCl\(_3\)) 7.77 (2H, d, J 7.4 Hz, ArH), 7.43-7.21 (6H, m, ArH), 7.09 (2H, d, J 3.1 Hz, Ar-2H), 6.60 (2H, d, J 3.3 Hz, Ar-3H), 4.09 (4H, t, J 7.0 Hz, NCH\(_2\)), 1.89 (4H, tt, J 7.2 Hz, NCH\(_2\)CH\(_2\)) 1.41-1.34 (2H, m, NCH\(_2\)CH\(_2\)CH\(_2\)); \(\delta\)\(_{\text{C}}\) (62.9 MHz; CDCl\(_3\)) 136.0, 128.4, 127.8 (ArCH), 121.5 (ArCH), 121.1 (ArCH), 119.3 (ArCH), 109.4 (ArCH), 101.1 (ArCH), 46.1 (NCH\(_2\)), 29.9 (NCH\(_2\)CH\(_2\)), 24.5 (NCH\(_2\)CH\(_2\)CH\(_2\)); m/z (El) 302 (56), 172 (13), 130 (100), 103 (10), 77 (10).

1,5-Bis(3-ethoxyglyoxyindol-1-yl)pentane 105

![Chemical structure of 1,5-Bis(3-ethoxyglyoxyindol-1-yl)pentane](image)

Oxalyl chloride (6.3 mL, 72.3 mmol) in ether (3.7 mL) was added to a suspension of 1,5 di(indol-1-yl)pentane (8.4 g, 27.8 mmol) in ether (200 mL) at 0 °C under
nitrogen. The mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure. The residue was redissolved in dichloromethane (150 mL), cooled to 0 °C and a solution of triethylamine (19.4 mL, 139 mmol) in ethanol (20 mL) was added. The mixture was stirred overnight. The solvent was removed under reduced pressure and the purple residue was purified by column chromatography (1:99 ethyl acetate: dichloromethane) to yield the title compound (11.3 g, 81%) as a yellow solid, m.p. 122-123 °C, (Found: M⁺, 502.2094. C₂₉H₃₀N₂O₆ requires M, 502.2104); v_max. (CH₂Cl₂) 2939, 1727, 1646, 1521, 737 cm⁻¹; δ_H (250 MHz; CDCl₃) 8.45-8.42 (2H, m, ArH), 7.35-7.29 (6H, m, ArH), 4.39 (4H, q, J 7.1 Hz, OCH₂), 4.12 (4H, t, J 7.1 Hz, NCH₂), 1.91 (4H, tt, J 7.2, 7.6 Hz, NCH₂CH₂), 1.43 (6H, t, J 7.1 Hz, OCH₂CH₃), 1.38-1.30 (2H, m, NCH₂CH₂CH₂); δ_C (62.9 MHz; CDCl₃) 177.6 (C=O), 162.9 (CO₂), 139.1 (ArCH), 136.4, 127.1, 124.1 (ArCH), 123.5 (ArCH), 122.9 (ArCH), 112.9, 109.9 (ArCH), 62.0 (OCH₂), 47.0 (NCH₂), 29.3 (NCH₂CH₂), 24.1 (NCH₂CH₂CH₂), 14.1 (OCH₂CH₃); m/z (El) 502 (M⁺, 1%), 429 (11), 401 (11), 267 (17), 217 (21), 155 (45), 51 (59), 28 (100).

1,5-Bis(3-carboethoxyxymethylindol-1-yl)pentane

A solution of sodium hypophosphite (14.6 g, 16.5 mmol) in water (14 mL) was added to a solution of 1,5-di(3-ethoxyglyoxyindol-1-yl)pentane (8.3 g, 16.5 mmol) and palladium-on-carbon (10%) (1.6 g) in 1,4-dioxane (120 mL). The mixture was refluxed for 4 h then allowed to cool. Sodium hypophosphite (14.6 g, 16.5 mmol) in water (15 mL) was added and the solution was refluxed overnight. The mixture was cooled, filtered through Celite and washed with ethyl acetate. The solvent was removed under reduced pressure and the residue purified by column chromatography (dichloromethane) to yield the title compound (6.19 g, 79%) as a pale yellow oil, (Found: M⁺, 474.2519. C₂₉H₃₄N₂O₄ requires M, 474.2518); v_max. (film) 2980, 2937, 1734, 1470, 1152, 741 cm⁻¹; δ_H (250 MHz; CDCl₃) 7.63 (2H, d, J 8.0 Hz, ArH), 7.30-7.22 (4H, m, ArH), 7.15 (2H, m, ArH),
7.04 (2H, s, Ar-2H), 4.18 (4H, q, J 7.2 Hz, OCH2), 4.05 (4H, t, J 7.0 Hz, NCH2), 3.76 (4H, s, Ar-CH2), 1.84 (4H, tt, J 7.2, 7.6 Hz, NCH2CH2), 1.34-1.30 (2H, m, NCH2CH2CH2), 1.28 (6H, t, J 7.1 Hz, OCH2CH3); δC (62.9 MHz; CDCl3) 172.1 (CO2), 136.1, 127.8, 126.6 (ArCH), 121.6 (ArCH), 119.1 (ArCH), 119.1 (ArCH), 109.3 (ArCH), 107.0, 60.7 (OCH2), 46.0 (NCH2), 31.3 (Ar-CH2), 29.9 (NCH2CH2), 24.4 (NCH2CH2CH2), 14.2 (OCH2CH3); m/z (EI) 474 (M+, 5%), 444 (8), 428 (16), 343 (12), 198 (22), 184 (29), 130 (100).

1,5-Bis(3-carboxymethyl-indol-1-yl)pentane 108

A solution of lithium hydroxide (310 mg, 7.4 mmol) in water (6 mL) was added to a solution of 1,5-bis(3-carboethoxymethylindol-1-yl)pentane (689 mg, 1.45 mmol) in THF (10 mL). The reaction was stirred for 16 h. The mixture was acidified with HCl (2 M) and filtered off to yield the title compound as a purple solid, m.p. 111-114 °C, (Found: MH+ 419.1970. C25H26N2O4 requires MH, 419.1971); δmax (CH2Cl2) 3070 (br), 1711, 1470, 1422 cm⁻¹; δH (250 MHz; CDCl3) 7.58 (2H, d, J 7.8 Hz, ArH), 7.24 (2H, d, J 7.6 Hz, ArH), 7.22-7.07 (4H, m, ArH), 6.94 (2H, s, Ar-2H), 3.97 (4H, t, J 6.8 Hz, NCH2), 3.74 (4H, s, Ar-CH2), 1.75 (4H, tt, J 6.8, 7.6 Hz, NCH2CH2), 1.27-1.20 (2H, m, NCH2CH2CH2); δC (62.9 MHz; CDCl3) 178.0, 135.9, 127.6, 126.9 (ArCH), 121.7 (ArCH), 119.2 (ArCH), 118.9 (ArCH), 109.4 (ArCH), 106.1, 46.0 (NCH2), 30.9 (Ar-CH2), 29.6 (NCH2CH2), 24.4 (NCH2CH2CH2); m/z (Cl) 436 (MNH4+, 5%), 419 (MH+, 14), 375 (14), 132 (100).
Indole (4.0 g, 34.2 mmol) was added to a stirred solution of powdered potassium hydroxide (7.66 g, 136.8 mmol) in DMSO (50 mL) under nitrogen. The mixture was stirred for 1 hour after which α,α' dibromo-p-xylene (4.51 g, 17.1 mmol) was added with external cooling. The mixture was stirred overnight. Water (50 mL) was added and the mixture extracted with dichloromethane (3x80 mL). The combined organics were washed with brine (5x100 mL) and dried (MgSO4). The solvent was removed under reduced pressure. Column chromatography (dichloromethane) yielded the title compound (5.2 g, 91%) as a white solid, m.p. 127-128 °C (lit. 91 115 °C (ethanol)), (Found: M+, 336.1631, C24H20N2 requires M, 336.1626); υmax. (CH2Cl2) 1514, 1484, 1463, 1318, 1184 cm⁻¹; δH (250 MHz; CDCl3) 7.65 (2H, dd, J 6.6, 1.5 Hz, ArH), 7.25 (2H, d, J 6.8 Hz, ArH), 7.20-7.08 (6H, m, ArH), 7.03 (4H, s, xylylH), 6.54 (2H, dd, J 3.6, 0.8 Hz, Ar-3H), 5.28 (4H, s, NCH2); δC (62.9 MHz; CDCl3) 137.0, 136.5, 128.7, 128.2 (ArCH), 127.1 (ArCH), 121.7 (ArCH), 121.0 (ArCH), 119.6 (ArCH), 109.6 (ArCH), 101.8 (ArCH), 49.7 (NCH2); m/z (EI) 336 (M⁺, 12%), 217 (15), 155 (28), 113 (29), 51 (58), 28 (100).
Oxaly chloride (3.1 mL, 35.5 mmol) in ether (7 mL) was added to a suspension of 1,4-bis(indol-1-yl)benzene (4.27 g, 12.7 mmol) in ether (100 mL) at 0 °C under nitrogen. After stirring for 1 hour at 0 °C the mixture was allowed to warm to room temperature and stirred for a further hour. The solvent was removed under reduced pressure and the solid redissolved in dichloromethane (100 mL). A solution of triethylamine (10 mL) in ethanol (15 mL) was added slowly and the mixture was stirred overnight. The solvent was removed under reduced pressure. Purification by column chromatography (dichloromethane) yielded the title compound (5.2 g, 76%) as an orange solid, m.p. 188-189 °C, ν_max. (CH_2Cl_2) 1727, 1649, 1522, 1393, 1171 cm⁻¹; δ_H (250 MHz; CDCl₃) 8.39 (2H, d, J 6.8 Hz, ArH), 8.35 (2H, s, Ar-2H), 7.31-7.20 (6H, m, ArH), 7.09 (4H, s, xylylH), 5.33 (4H, s, NCH₂), 4.37 (4H, q, J 7.1 Hz, OCH₂), 1.40 (6H, t, J 7.1 Hz, OCH₂CH₃); δ_C (62.9 MHz; CDCl₃) 177.6 (C=O), 162.8 (CO₂Et), 139.5 (ArCH), 136.6, 135.5, 127.6 (ArCH), 127.1, 124.2 (ArCH), 123.6 (ArCH), 122.8 (ArCH), 113.3, 110.4 (ArCH), 62.0 (OCH₂), 50.5 (NCH₂), 14.0 (OCH₂CH₃).
To a solution of 1,4-bis(3-ethoxyglyoxyindol-1-yl)benzene (4.19 g, 7.80 mmol) in 1,4 dioxan (70 mL) was added palladium-on-carbon (10%) (0.84 g) followed by a solution of sodium hypophosphite (6.88 g, 78.0 mmol) in water (10 mL). The mixture was refluxed for 4 h. The reaction was cooled and sodium hypophosphite (6.88 g, 78.0 mmol) in water (10 mL) was added. The mixture was refluxed for a further 4 h. The mixture was filtered through a pad of Celite and washed with ether (200 mL). The solvent was removed under reduced pressure. Column chromatography (dichloromethane) yielded the title compound (2.46 g, 61%) as a white solid, m.p. 134-136 °C, (Found: MH+, 509.2440. C32H32N2O4 requires MH, 509.2440); \( \nu_{\text{max}} \) (CH2Cl2) 1731, 1468, 1180 cm\(^{-1}\); \( \delta_{\text{H}} \) (400 MHz; CDC13) 7.60 (2H, d, J 7.2 Hz, Ar-4H), 7.21-7.10 (6H, m, ArH), 7.08 (2H, s, Ar-2H), 7.01 (4H, s, xylylH), 5.20 (4H, s, NCH2), 4.14 (4H, q, J 7.1 Hz, OCH2), 3.74 (4H, s, Ar-CF3), 1.23 (6H, t, J 7.1 Hz, OCH2CH3); \( \delta_{\text{C}} \) (100 MHz; CDCl3) 172.0 (CO2), 137.0, 136.5, 128.0, 127.1 (ArCH), 127.0 (ArCH), 122.0 (ArCH), 119.4 (ArCH), 119.2 (ArCH), 109.7 (ArCH), 107.8, 60.7 (OCH2), 49.6 (NCH2), 31.4 (Ar-CF3), 14.2 (OCH2CH3); m/z (Cl) 526 (MNH4+, 11%), 509 (MH+, 3.6%), 308 (19), 221 (37), 204 (100), 132 (36).
A solution of lithium hydroxide (840 mg, 20.0 mmol) in water (5 mL) was added to a solution of 1,4-bis(3-carboxymethylindol-1-yl)benzene (508 mg, 1.0 mmol) in THF (20 mL). The mixture was stirred overnight. The solution was acidified (conc. HCl) and the precipitated acid was filtered off to yield the title compound (384 mg, 85%) as a brown solid, m.p. 218-222 °C, \( \nu_{\text{max}} \) (CHCl\(_3\)) 1709, 1613, 1167 cm\(^{-1}\); \( \delta_H \) (250 MHz; \( \text{d}_6\) DMSO) 7.49 (2H, d, J 7.4 Hz, Ar-4H), 7.37 (2H, d, J 7.5 Hz, ArH), 7.32 (2H, s, Ar-2H), 7.10 (4H, s, xylylH), 7.07-6.95 (4H, m, ArH), 3.62 (4H, s, ArQH\(_2\)), 3.62 (4H, s, Ar-CH\(_2\)); \( \delta_C \) (62.9 MHz; \( \text{d}_6\) DMSO) 178.2 (CO\(_2\)), 142.6, 141.0, 132.9, 132.7 (ArCH), 132.4 (ArCH), 126.5 (ArCH), 124.1 (ArCH), 123.9 (ArCH), 115.1 (ArCH), 112.8, 53.7 (NCH\(_2\)), 36.0 (Ar-CH\(_2\)).

1-Methylindole-3-acetic acid

A solution of lithium hydroxide (1.24 g, 29.6 mmol) in water (10 mL) was added to a solution of methyl 1-methylindole-3-acetate (1.20 g, 5.9 mmol) in THF (60 mL). The reaction was stirred for 24 h. The mixture was acidified (conc. HCl) and extracted with dichloromethane (3x80 mL). The combined organics were washed with water (50 mL), brine (100 mL) and dried (MgSO\(_4\)). The solvent was removed under reduced pressure to yield the title compound (1.04 g, 93%) as a white solid, \( \nu_{\text{max}} \) (CHCl\(_3\)) 1715, 1665, 1615, 1473 cm\(^{-1}\); \( \delta_H \) (250 MHz; CDCl\(_3\)) 10.64 (1H, br-s, CO\(_2\)H), 7.74 (1H, d, J 7.8 Hz, Ar-4H), 7.42-7.34 (2H, m, ArH), 7.31-7.24 (1H, m, ArH),
7.10 (1H, s, Ar-2H), 3.91 (2H, s, Ar-CH₂), 3.78 (3H, s, NCH₃); δC (62.9 MHz; CDCl₃) 178.7 (CO₂H), 136.8, 127.8 (ArCH), 127.4, 121.7 (ArCH), 119.2 (ArCH), 118.8 (ArCH), 109.2 (ArCH), 105.9, 32.5 (NCH₃), 30.9 (Ar-CH₂).

1,9-Dimethylpyrano[3,4-b]indol-3-one 113

Boron trifluoride etherate (1 mL) was added to a suspension of 1-methylindole-3-acetic acid (1.0 g, 5.29 mmol) in acetic anhydride (5 mL), at 0 °C under nitrogen. After 2 hours ether (10 mL) was added and the resultant precipitate filtered off. The residue was washed with sodium hydrogen carbonate (half saturated, 5x80 mL) and water (100 mL). Drying under reduced pressure gave the title compound (1.44 g, 78%) as an orange solid, m.p. 208-210 °C (Dec.) (lit. 26 214 °C (dec.)); δH (250 MHz; CDCl₃) 7.82 (1H, d, J 7.9 Hz, ArH), 7.49 (1H, t, J 8.0 Hz, ArH), 7.13 (1H, d, J 7.8 Hz, ArH), 7.01 (1H, t, J 7.9 Hz, ArH), 6.39 (1H, s, Ar-4H), 3.64 (3H, s, NCH₃), 2.65 (3H, s, Ar-CH₃).

Dimethyl 1,9-dimethylcarbazole-2,3-dicarboxylate 114

DMAD (0.367 mg, 2.59 mmol) was added to a solution of 1,9-dimethylpyrano[3,4-b]indol-3-one (0.501 g, 2.35 mmol) in chlorobenzene (15 mL). The reaction mixture was refluxed under nitrogen for 4 h. The solvent was removed under reduced pressure. Purification by column chromatography (1:50 ether:dichloromethane) yielded the title compound (0.60 g, 82%) as a pale yellow solid, m.p. 136-138°C; δH (250 MHz; CDCl₃) 8.51 (1H, s, Ar-4H), 8.03 (1H, d, J 7.7 Hz, ArH), 7.51 (1H, t, J 7.7 Hz, ArH), 7.36 (1H, d, J 8.3 Hz, ArH), 7.28 (1H, t, J 7.9 Hz, ArH), 4.04 (3H, s, OCH₃), 4.02 (3H, s, OCH₃), 3.94 (3H, s, NCH₃), 2.72 (3H, s, Ar-CH₃).
\( \text{CH}_3 \); \( \delta_C \) (100 MHz; CDCl\(_3\)) 169.5, 165.4, 141.2, 140.1, 132.7, 125.3 (Ar-CH), 121.6, 121.0, 119.7 (Ar-CH), 119.0 (Ar-CH), 118.8 (Ar-CH), 116.7, 116.3, 107.7 (Ar-CH), 51.3 (OCH\(_3\)), 50.8 (OCH\(_3\)), 31.2 (NCH\(_3\)), 14.9 (Ar-CH\(_3\)).

1,5-Bis(1-methyl-2,3-dicarbomethoxycarbazol-9-yl)pentane 116

Boron trifluoride etherate (0.9 mL) was added to a stirred solution of 1,5-bis(3-carboxymethylindol-3-yl)pentane (500 mg, 1.2 mmol) in acetic anhydride (3 mL) at 0 °C under nitrogen. The mixture was stirred for 2 h. Ether (10 mL) was added followed by water (25 mL). The mixture was then extracted with dichloromethane (3x80 mL). The combined organics were then washed with sodium hydrogen carbonate (2x50 mL, half saturated), water (2x50 mL), brine (80 mL) and dried (MgSO\(_4\)). The solvent was removed under reduced pressure. The resulting gum was dissolved in bromobenzene (30 mL) and then heated with dimethyl acetylenedicarboxylate (150 mg, 1.1 mmol) for 3 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (1:25 ether:dichloromethane) to yield the title compound (95 mg, 12%) as a yellow solid, m.p. 168-169 °C, (Found: M\(\text{NH}_4^+\), 680.2970. C\(_{39}\)H\(_{38}\)N\(_2\)O\(_8\) requires M, 680.2972); \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)) 2360, 1734, 1717, 1261, 795 cm\(^{-1}\); \( \delta_H \) (250 MHz; CDCl\(_3\)) 8.64 (2H, s, Ar-4H), 8.09 (2H, d, J 7.7 Hz, ArH), 7.50 (2H, t, J 7.6 Hz, ArH), 7.35 (2H, d, J 7.8 Hz, ArH), 7.30 (2H, t, J 7.3 Hz, ArH), 4.48 (4H, t, J 7.4 Hz, NCH\(_2\)), 4.02 (6H, s, OCH\(_3\)), 3.95 (6H, s, OCH\(_3\)), 2.68 (6H, s, Ar-CH\(_3\)), 1.86 (4H, tt, J 7.3, 7.9 Hz, NCH\(_2\)CH\(_2\)), 1.45-1.36 (2H, m, NCH\(_2\)CH\(_2\)CH\(_2\)); \( \delta_C \) (100 MHz; CDCl\(_3\)) 171.2, 167.0, 142.6, 141.3, 134.9, 127.3 (ArCH), 124.1, 123.1, 121.8 (ArCH), 121.0 (ArCH), 120.9 (ArCH), 119.0, 117.7, 109.8 (ArCH), 53.0 (OCH\(_3\)), 52.6 (OCH\(_3\)), 45.3 (NCH\(_2\)), 31.1 (NCH\(_2\)CH\(_2\)), 24.7 (NCH\(_2\)CH\(_2\)CH\(_2\)), 16.6 (Ar-CH\(_3\)); m/z (Cl) 266 (10), 98 (27), 84 (33), 58 (52), 52 (44), 44 (100).
Dimethyl 9-benzyl-1-methyl-carbazole-2,3-dicarboxylate

Boron trifluoride etherate (0.9 mL) was added to a solution of 9-benzylindole-3-acetic acid (1.0 g, 3.8 mmol) in acetic anhydride (5 mL) at 0 °C under nitrogen. The mixture was stirred for 2 h. Ether (20 mL) was added and the mixture extracted with dichloromethane (150 mL), washed with sodium hydrogencarbonate (3x100 mL, half saturated), water (100 mL), brine (100 mL) and dried (MgSO4). The resultant gum was dissolved in bromobenzene (20 mL) and treated with excess dimethylacetylene dicarboxylate. The mixture was refluxed under nitrogen for 5 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (dichloromethane) to yield the title compound (15 mg, 1%) as a yellow oil, \( \nu_{\text{max}} \) 1729, 1717, 1348, 1234 cm\(^{-1}\); \( \delta_H \) (400 MHz; CDCl3) 8.74 (1H, s, Ar-4H), 8.18 (1H, dd, J 1.4, 7.2 Hz, ArH), 7.49 (1H, dt, J 1.3, 7.6 Hz, ArH), 7.37-7.27 (5H, m, ArH), 7.04-7.02 (2H, m, ArH), 5.82 (2H, s, NCH2), 3.99 (3H, s, OCH3), 3.98 (3H, s, OCH3), 2.59 (3H, s, Ar-QH); \( \delta_C \) (100 MHz; CDCl3) 171.1 (CO2), 167.1 (CO2), 143.1, 142.0, 138.1, 134.9, 129.5 (ArCH), 128.0 (ArCH), 127.5 (ArCH), 125.8 (ArCH), 124.1, 123.2, 121.8 (ArCH), 121.2 (ArCH), 120.9 (ArCH), 119.3, 118.3, 110.0 (ArCH), 53.0 (OCH3), 52.6 (OCH3), 49.1 (NCH2), 16.2 (Ar-CH3).

Methyl 1-Boc-indole-3-acetate

4-Dimethylaminopyridine (0.25 g, 2.1 mmol) was added to a solution of di-tert-butyl-carbonate (5.54 g, 25.0 mmol) and methyl indole-3-acetate (4.0 g, 21.0 mmol) in acetonitrile (40 mL). The mixture stirred overnight. Sodium
hydrogencarbonate (40 mL, saturated solution) was added and the mixture was extracted with ether (3x70 mL). The combined organics were washed with water (2x70 mL) and dried (MgSO₄). Column chromatography (dichloromethane) yielded the title compound (5.7 g, 90%) as a white solid, m.p. 58-60 °C. (Found: M⁺, 289.1319. C₁₆H₁₉NO₄ requires M, 289.1314); δH (250MHz; CDCl₃) 8.15-8.21 (1H, m, Ar-H), 7.53-7.60 (2H, m, Ar-H), 7.20-7.30 (2H, m, Ar-H), 3.73 (5H, s, Ar-CH₂ and OCH₃), 1.67 (9H, s, (C(CH₃)); δC (62.9MHz; CDCl₃) 172.0, 149.5, 136.0, 130.0, 124.5 (ArCH), 124.4 (ArCH), 122.6 (ArCH), 118.9 (ArCH), 115.2 (ArCH), 112.5, 84.0, 52.0 (OCH₃), 30.8 (Ar-CH₂), 28.1 (C(CH₃)); m/z (El) 289 (M⁺, 11%), 233 (42), 189 (20), 174 (16), 130 (100), 57 (100).

**Methyl 1-boc-α(5-iodopentyl)indole-3-acetate 121**

![Chemical structure](image)

n-BuLi (5.3 mL, 8.48 mmol) was added to a stirred solution of diisopropylamine (1.20 mL, 8.50 mmol) in THF (20 mL) at -78 °C under nitrogen. Stirring was continued at -78 °C for 20 minutes then warmed to 0 °C and stirred for a further 20 minutes. The reaction was cooled to -78 °C where a solution of methyl 1-boc-indole-3-acetate (1.63 g, 5.65 mmol) in THF (5 mL) was added. After a further 20 mins 1,5-diiodopentane (2.52 mL, 17.0 mmol) was added. The reaction was stirred overnight. Water (20 mL) was added and the mixture extracted with dichloromethane (3x80 mL). The combined organics were washed with water (2x50 mL), brine (2x100 mL) and dried (MgSO₄). Purification by column chromatography (1:2 dichloromethane:light petroleum) yielded the title compound (2.14 g, 78%) as a colourless oil, (Found: M⁺, 485.1057. C₂₁H₂₈NO₄ requires M, 485.1065); νmax. (film) 2934, 1735, 1453, 1157 cm⁻¹; δH (250 MHz; CDCl₃) 8.13 (1H, d, J 8.2 Hz, Ar-4H), 7.61 (1H, d, J 8.2 Hz, Ar-7H), 7.53 (1H, s, Ar-2H), 7.35-7.29 (1H, m, ArH), 7.27-7.21 (1H, m, ArH), 3.81 (1H, dd, J 8.0, 6.7 Hz, ArCH), 3.68 (3H, s, OCH₃), 3.16 (2H, t, J 6.9 Hz, CH₂I), 2.17 (1H, dd, J 13.9, 6.7 Hz, ArCH₂CH), 1.92 (1H, dd, J 13.9, 8.0 Hz, ArCH₂CH), 1.79 (2H, quintet, J 7.0 Hz, CH₂CH₂), 1.67 (9H, s, C(CH₃)₃), 1.48-1.32 (4H, m, CH₂CH₂CH₂CH₂CH₂CH₂) δC (62.9 MHz; CDCl₃) 174.0 (CO₂), 135.6, 129.2, 124.5 (ArCH), 123.4 (ArCH), 122.5 (ArCH), 123.0 (ArCH)
119.2 (ArCH), 118.4, 115.3 (ArCH), 83.8 (C(CH3)3), 52.0 (OCH3), 42.5 (ArCH), 33.1 (CH2), 31.8 (CH2), 30.1 (CH2), 28.1 (C(CH3)3), 26.5 (CH2), 6.8 (CH2); m/z (EI) 485 (M+, 5.4%), 429 (40), 385 (19), 326 (39), 57 (100).

1,4-Di(3-carbethoxymethyl-1-boc-indolyl-α-methyl)benzene123

\[
\begin{align*}
\text{Boc} & \quad \text{CO2Me} \\
\text{CH2} & \\
\text{CH2} & \\
\text{CO2Me} & \\
\text{Boc} &
\end{align*}
\]

\text{n-BuLi (10.7 mL, 18.2 mmol) was added to a stirred solution of diisopropylamine (2.56 mL, 18.2 mmol) in THF (40 mL) at -78 °C under nitrogen. Stirring was continued at -78 °C for 20 minutes then warmed to 0 °C and stirred for a further 20 minutes. The reaction was cooled to -78 °C where a solution of methyl 1-boc-indole-3-acetate (3.50 g, 12.1 mmol) in THF (10 mL) was added. After a further 20 mins α,α’dibromo-p-xylene (1.58 g, 6.0 mmol) was added. The reaction was stirred overnight. Water (20 mL) was added and the mixture extracted with dichloromethane (3x80 mL). The combined organics were washed with water (2x50 mL), brine (2x100 mL) and dried (MgSO4). Purification by column chromatography (1:2 then 2:1 dichloromethane:light petroleum) yielded the title compound (3.3 g, 81%) as a white solid, m.p. 182-185 °C (dichloromethane), (Found: MNH4+, 698.3440. C40H44N2O8 requires MNH4, 698.3442; νmax. 1731, 1720, 1540, 1434 cm\(^{-1}\); δH (250 MHz; CDCl3) 8.13 (2H, d, J 8.1 Hz, ArH), 7.60 (2H, d, J 7.2, 1.2 Hz, ArH), 7.55 (2H, s, Ar-2H), 7.25-7.20 (4H, m, ArH), 7.10 (4H, s, xylylH), 4.08 (2H, dd, J 9.3, 6.0 Hz, ArCH), 3.58 (6H, s, OCH3), 3.43 (2H, dd, J 9.4, 13.7 Hz, ArCH(CH)3), 3.14 (2H, dd, J 6.0, 13.7 Hz, ArCH(CH)3), 1.67 (18H, s, C(CH3)3); δC (62.9 MHz; CDCl3) 173.4 (CO2Me), 149.6 (NCO2), 137.2, 135.2, 129.2, 128.9 (xylylCH), 124.5 (ArCH), 123.5 (ArCH), 122.6 (ArCH), 119.2 (ArCH), 118.0, 115.3 (ArCH), 83.7
A solution of lithium hydroxide (2.0 g, 49.0 mmol) in water (80 mL) was added to a solution of 1,4-di(3-methyloxymethyl-1-boc-indolyl-α-methyl)benzene (3.3 g, 4.9 mmol) in THF (80 mL). The reaction was stirred overnight. The reaction was acidified (conc. HCl) and stirred for 1 hour. The mixture was extracted with ethyl acetate (3x80 mL). The combined organics were washed with water (100 mL), brine (100 mL) and dried (MgSO₄). The solvent was removed under reduced pressure. Column chromatography (ether) yielded the title compound (0.91 g, 41%) as a white solid, m.p. 108-113 °C; ν_max. (CH₂Cl₂) 3467, 1710, 1422 cm⁻¹; δ_H (250 MHz; CDCl₃) 9.30 (2H, br-s, NH), 7.62 (2H, d, J 7.8 Hz, Ar-4H), 7.23 (2H, s, Ar-2H), 7.07-6.92 (10H, m, ArH), 3.99 (2H, dd, J 8.9, 6.7 Hz, ArCH), 3.28 (2H, dd, J 8.8, 13.7 Hz, ArCH(CH)), 3.03 (2H, dd, J 6.6, 13.7 Hz, ArCHCH); δ_C (100 MHz; d₆DMSO) 175.9 (CO₂H), 137.6, 136.3, 128.8 (xylylCH), 126.5, 122.8 (ArCH), 121.6 (ArCH), 119.2 (ArCH), 119.1 (ArCH), 113.0, 111.4 (ArCH), 45.0 (Ar-C), 38.3 (CH-CH₂); m/z (CI) 453 (MH⁺, 1%), 409 (5), 365 (4), 132 (51), 118 (100).
Phosphorus oxychloride (0.24 mL, 2.5 mmol) was added to N,N-dimethylformamide (2 mL), at 0 °C under nitrogen. The reaction was stirred at room temperature for 0.75 h. The reaction was cooled to 0 °C and diluted with 1,2-dichloroethane (5 mL). Methyl 1-methyl-α-methylindole-3-acetate (195 mg, 0.9 mmol) in 1,2-dichloroethane (2 mL) was added and then the mixture refluxed for 3 h. After a further 2 h stirring at room temperature aqueous saturated sodium acetate (20 mL) was added. The reaction mixture was extracted with ethyl acetate (4x50 mL). The organics were washed with brine (3x30 mL) and dried (MgSO₄). The solvent was removed under reduced pressure and the crude material purified by column chromatography (dichloromethane) to yield the title compound (66 mg, 30%) as a yellow oil, (Found: M⁺, 245.1056. C₁₄H₁₅NO₃ requires M, 245.1052); νmax. (film) 2950, 1732, 1668, 1472, 1209, 890, 747 cm⁻¹; δH (250 MHz; CDCl₃) 10.24 (1H, s, CHO), 7.79 (1H, d, J 8.2 Hz, Ar-4H), 7.43-7.38 (2H, m, ArH), 7.19-7.14 (1H, m, ArH), 4.53 (1H, q, J 7.2 Hz, QICH₃), 4.07 (3H, s, OCH₃), 3.67 (3H, s, NCH₃), 1.70 (3H, d, J 7.2 Hz, CH₃); δc (62.9 MHz; CDCl₃) 181.6 (CHO), 174.1, 139.6, 130.8, 127.6, 127.0 (ArCH), 124.7, 122.0 (ArCH), 120.7 (ArCH), 110.4 (ArCH), 52.2 (OCH₃), 35.8 (CH₂CH₃), 31.5 (NCH₃), 18.8 (CH₃); m/z (El) 245 (M⁺, 30%), 216 (11), 186 (100), 158 (10), 143 (15), 115 (12).

1-Methyl-2-formyl-α-methylindole-3-acetic acid 129

A solution of lithium hydroxide (99 mg, 2.4 mmol) in water (5 mL) was added to a solution of methyl 1-methyl-2-formyl-α-methylindole-3-acetate (58 mg, 0.24
mmol) in THF (10 mL). The mixture was stirred for 12 h. The reaction was acidified (conc. HCl) and extracted with dichloromethane (3x50 mL), the combined organics were washed with brine (80 mL) and dried (MgSO4). The solvent was removed under reduced pressure to yield the title compound (50 mg, 91%) as a yellow solid, m.p. 123-126 °C; \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)) 1717, 1664, 1473, 1382 cm\(^{-1}\); \( \delta_H \) (250 MHz, CDCl\(_3\)) 10.23 (1H, s, CHO), 7.80 (1H, d, J 8.3 Hz, Ar-4H), 7.46-7.35 (2H, m, ArH), 7.15 (1H, dddd, J 8.0, 6.4, 1.4 Hz, ArH), 4.56 (1H, q, J 7.2 Hz, CH\(_3\)), 4.06 (3H, s, NCH\(_3\)), 1.71 (3H, d, J 7.2 Hz, CH\(_3\)));

\( \delta_C \) (62.9 MHz; CDCl\(_3\)) 181.8 (CHO), 178.7, 139.9, 130.7, 127.2 (ArCH), 126.9, 124.8, 122.2 (ArCH), 120.9 (ArCH), 110.5 (ArCH), 35.9 (CH\(_3\)), 31.6 (NCH\(_3\)), 18.4 (CH\(_3\)).

1,4-Dimethyl-pyranolo[3,4-b]indol-3-one 130

A solution of 1-methyl-2-formyl-\( \alpha \)-methylindole-3-acetic acid (50 mg, 0.22 mmol) in acetic anhydride (10 mL) was refluxed for 2.5 h. The solvent was removed under reduced pressure. Purification by column chromatography (1:10 ethyl acetate:dichloromethane) yielded the title compound (28 mg, 61%) as an orange solid, m.p. 198-200 °C (dec.), (Found: M\(^+\), 213.0791. C\(_{13}\)H\(_{11}\)NO\(_2\) requires M, 213.0790); \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)) 2254, 1685, 1639, 1614, 1584 cm\(^{-1}\); \( \delta_H \) (250 MHz; CDCl\(_3\)) 7.95 (1H, d, J 7.8 Hz, Ar-5H), 7.56-7.50 (2H, m, ArH), 7.11-7.03 (2H, m, ArH), 3.43 (3H, s, NCH\(_3\)), 2.51 (3H, s, Ar-CH\(_3\)); m/z (EI) 213 (M\(^+\), 3%), 217 (5), 189 (24), 174 (12), 130 (100).

Dimethyl 4,9-dimethyl-carbazole-2,3-dicarboxylate 131
DMAD (19 mg, 13.0x10^{-5} mol) was added to a solution of 4-methyl-9-methylpyrano[3,4-b]indol-3-one (19 mg, 8.7x10^{-5} mol) in chlorobenzene (4 mL). The mixture was refluxed for 4 h. The solvent was removed under reduced pressure. Purification by column chromatography (1:5 ethylacetate:dichloromethane) yielded the title compound (20 mg, 74%) as a white solid, m.p. 158-160 °C, (Found: M+, 311.1160. C_{18}H_{17}NO_{4} requires M, 311.1158); \nu_{\text{max}} \text{ (CH}_{2}Cl_{2} \text{)} 2953, 1724, 1332, 1156, 1074 \text{ cm}^{-1}; \delta_{H} (250 \text{ MHz; CDCl}_{3}) 8.25 (1H, d, J 8.0 Hz, ArH), 7.95 (1H, s, Ar-1H), 7.58 (1H, dd, J 8.1, 7.3 Hz, ArH), 7.47 (1H, d, J 8.1 Hz, ArH), 7.31 (1H, dd, J 7.9, 7.4 Hz, ArH), 4.00 (3H, s, OCH_{3}), 3.96 (3H, s, OCH_{3}), 3.90 (3H, s, NCH_{3}), 2.87 (3H, s, Ar-CH_{3}); \delta_{C} (100 \text{ MHz; CDCl}_{3}) 171.1, 167.5, 142.9, 140.3, 131.6, 127.2 (ArCH), 126.8, 125.5, 124.8, 123.8 (ArCH), 123.1, 120.2 (ArCH), 109.3 (ArCH), 108.9 (ArCH), 52.9 (OCH_{3}), 52.8 (OCH_{3}), 29.6 (NCH_{3}), 17.9 (Ar-CH_{3}); m/z (EI) 311 (M^+, 100%), 280 (89), 221 (58), 193 (61).

1,4-Bis(3-carbomethoxymethyl-1-methylindolyl-α-methyl)benzene 132

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{Me} & \quad \text{CH}_2 \\
\text{N} & \quad \text{CO}_2\text{Me} \\
\text{CH}_2 & \\
\text{Me} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

n-BuLi (10.7 mL, 18.2 mmol) was added to a stirred solution of diisopropylamine (2.56 mL, 18.2 mmol) in THF (40 mL) at -78 °C under nitrogen. Stirring was continued at -78 °C for 20 minutes then warmed to 0 °C and stirred for a further 20 minutes. The reaction was cooled to -78 °C where a solution of methyl 1-methylindole-3-acetate (3.50 g, 12.1 mmol) in THF (10 mL) was added. After a further 20 mins α,α’-dibromo-p-xylene (1.58 g, 6.0 mmol) was added. The reaction was stirred overnight. Water (20 mL) was added, extracted with dichloromethane (3x80 mL), the organics were washed with water (2x50 mL), brine (2x100 mL) and dried (MgSO_{4}). The solvent was removed under reduced pressure. Column
chromatography (dichloromethane) yielded the title compound (1.52 g, 50%) as a yellow crystalline solid, m.p. 158-160 °C, (Found: M+, 508.2362. C32H32N2O4 requires M, 508.2362); νmax. (CH2Cl2) 2952, 1733, 1332, 1155 cm⁻¹; δH (250 MHz; CDCl3) 7.82 (2H, d, J 7.7 Hz, Ar-4H), 7.36-7.23 (6H, m, ArH), 7.20 (4H, s, xylylH), 7.09 (2H, s, Ar-2H), 4.27 (2H, dd, J 6.0, 9.4 Hz, ArCHCH2), 3.77 (6H, s, OCH3), 3.66 (6H, s, NCH3), 3.55 (2H, dd, J 9.4, 13.6 Hz, ArCHCH), 3.30 (2H, dd, J 6.0, 13.6 Hz, ArCHCH); δC (62.9 MHz; CDCl3) 174.5, 137.6 (x2), 137.0, 128.9 (xylylCH), 126.9 (ArCH), 121.8 (ArCH), 119.3 (ArCHx2), 112.1, 109.4 (ArCH), 51.8 (OCH3), 45.1 (ArCH), 38.9 (Ar-CHCH), 38.8 (Ar-CHCH), 32.7 (NCH3); m/z (EI) 508 (M+, 7%), 202 (100), 186 (13), 155 (30).
5.3. Experimental Details for Chapter 3

Ethyl 2-benzoyl-thiophene-3-acetate 145 and ethyl 2-benzoyl-thiophene-4-acetate 146

Aluminium(III) chloride (0.86 g, 6.46 mmol) was added to a solution of ethyl thiophene-3-acetate (1.00 g, 5.87 mmol) and benzoyl chloride (0.75 mL, 6.46 mmol) in 1,2-dichloroethane (20 mL) at 0 °C under nitrogen. The reaction mixture was refluxed for 8 h. Water (10 mL) was added and the mixture was extracted with dichloroethane (3 x 100 mL). The combined organics were washed with water (80 mL), brine (100 mL) and dried (MgSO₄). The solvent was removed under reduced pressure. Column chromatography (1:1 dichloromethane:light petroleum) gave the title compound (1.19 g, 74%) as a pale yellow oil, (Found: M⁺, 274.0663. C₁₅H₁₅O₃S requires M, 274.0664); νmax. (film) 1735, 1638, 1413, 1277 cm⁻¹; δH (250 MHz; CDCl₃) 7.88-7.83 (4H, m, ArH), 7.59-7.44 (8H, m, ArH), 7.56 (1H, d, J 5.0 Hz, ArH(2,3-isomer)), 7.16 (1H, d, J 5.0 Hz, ArH(2,3-isomer)), 4.21-4.13 (4H, m, OCH₂), 4.03 (2H, s, Ar-CH₂(2,3-isomer)), 3.65 (2H, s, Ar-CH₂(2,4-isomer)), 1.30-1.22 (6H, s, OCH₂CH₃); δc (62.9 MHz; CDCl₃) 188.6, 187.5, 170.1 (2x), 143.1, 140.9, 139.2, 137.6, 135.8 (ArCH), 135.6, 134.6, 132.0 (ArCH), 131.6 (ArCH), 131.3 (ArCH), 130.7 (ArCH), 128.8 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 60.7 (OCH₂), 60.5 (OCH₂), 35.3 (Ar-CH₂), 35.1 (Ar-CH₂), 13.8 (OCH₂CH₃); m/z (El) 274 (M⁺, 28%), 229 (12), 201 (100), 171 (14), 105 (55), 77 (56).
2-Benzoylthiophene-3-acetic acid 147

![Structure of 2-Benzoylthiophene-3-acetic acid](image)

An aqueous solution of potassium hydroxide (10 mL, 2N) was added to a solution of ethyl 2-benzoylthiophene-3-acetate and ethyl 2-benzoylthiophene-4-acetate (0.56 g, 2.04 mmol) in THF (20 mL). After 2 h the mixture was acidified (conc. HCl) and extracted with dichloromethane (3x80 mL). The combined organics were washed with water (50 mL), brine (100 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to yield the isomeric products. The title compound (0.16 g, 31%) was obtained upon recrystallisation from toluene as an off white solid, m.p. 132-133 °C (toluene), (Found: M⁺, 246.0351. C₁₃H₁₀O₃S requires M, 246.0351; v max. (CH₂Cl₂) 1767, 1638, 1597, 1412 cm⁻¹; δH (250 MHz; CDCl₃) 7.90 (2H, d, J 8.7 Hz, benzoylH), 7.63 (1H, d, J 5.0 Hz, ArH), 7.62-7.59 (1H, m, benzoylH), 7.52-7.47 (2H, m, benzoylH), 7.21 (1H, d, J 5.0 Hz, ArH), 4.05 (2H, s, ArCH₂); δC (62.9 MHz; CDCl₃) 190.2, 173.6, 141.4, 138.7, 135.9, 133.2 (ArCH), 132.5 (ArCH), 131.9 (ArCH), 129.8 (ArCH), 128.5 (ArCH), 36.7 (Ar-CH₂); m/z (EI) 246 (M⁺, 7%), 215 (64), 201 (100), 171 (29), 105 (38), 77 (90).

1-Phenylthieno[2,3-c]pyran-3-one 148

![Structure of 1-Phenylthieno[2,3-c]pyran-3-one](image)

A solution of 2-benzoylthiophene-3-acetic acid (110 mg, 0.45 mmol) in acetic anhydride (5 mL) was heated at reflux, under nitrogen, for 2 h. The solvent was removed under reduced pressure. Purification by column chromatography (1:4 ether:dichloromethane) gave the title compound (53 mg, 51%) as a yellow oil,
Dimethyl 1-phenylbenzothiophene-2,3-dicarboxylate 149

DMAD (37 mg, 0.26 mmol) was added to a solution of 1-phenylthieno[2,3-c]pyran-3-one (30 mg, 0.13 mmol) in chlorobenzene (5 mL). The mixture was refluxed for 6 h. The solvent was removed under reduced pressure. Column chromatography (1:25 ethyl acetate:dichloromethane) gave the title compound (30 mg, 69%) as a white solid, m.p. 141-143 °C, (Found: M+, 326.0617. C_{18}H_{14}O_4S requires M, 326.0613); \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)) 1726, 1354, 1285, 1225 cm\(^{-1}\); \( \delta_H \) (250 MHz; CDCl\(_3\)) 8.49 (1H, s, Ar-4H), 7.55 (1H, d, J 5.4 Hz, ArH), 7.50-7.45 (6H, m, ArH), 3.93 (3H, s, OCH\(_3\)), 3.65 (3H, s, OCH\(_3\)); \( \delta_C \) (62.9 MHz; CDCl\(_3\)) 168.8, 166.4, 145.1, 139.3, 137.3, 135.0, 130.1 (ArCH), 129.7, 128.8 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 124.9 (ArCH), 124.8, 124.6 (ArCH), 52.5 (OCH\(_3\)), 52.2 (OCH\(_3\)); m/z (EI) 326 (M+, 57%), 295 (100), 201 (69), 77 (52).
1,4-Bis(3-carboethoxymethylthien-2-ylcarbonyl)benzene 150, 1,4-(3-carboethoxymethyl-thien-2-ylcarbonyl)(4-carboethoxymethylthien-2-ylcarbonyl)benzene 151 and 1,4-bis(4-carboethoxymethylthien-2-ylcarbonyl)benzene 152

[Chemical structures of 150, 151, and 152]

Aluminium(III) chloride (0.91 g, 6.8 mmol) was added to a solution of ethyl thiophene-3-acetate (1.05 g, 6.2 mmol) and terephthaloyl chloride (0.63 g, 3.1 mmol) in 1,2-dichloroethane (35 mL) at 0 °C under nitrogen. The mixture was refluxed for 5 h. Water (20 mL) was added and then extracted with dichloromethane (3x70 mL). The combined organics were washed with water (50 mL), brine (50 mL) and dried (MgSO4). The solvent was removed under reduced pressure. Column chromatography (dichloromethane) yielded the title compounds (1.03 g, 71%) as a yellow solid, elution with methanol gave title compound (150) (150 mg, 10%) as a yellow solid, m.p. 123-125 °C, (Found: MH+, 471.0936. C24H23O6S2 requires MH, 471.0939); \( \nu_{max} \) (Nujol) 1728, 1629, 1412, 1330, 1274, 1175 cm\(^{-1}\); \( \delta_H \) (250 MHz; CDCl\(_3\)) 7.92 (4H, s, terephthaloylH), 7.60 (2H, d, J 5.0 Hz, ArH), 7.18 (2H, d, J 5.0 Hz, ArH), 4.18 (4H, q, J 7.1 Hz, OCH\(_2\)), 4.07 (4H, s, Ar-CH\(_2\)), 1.27 (6H, t, J 7.1 Hz, OCH\(_2\)CH\(_3\)) \( \delta_C \) (100 MHz; CDCl\(_3\)) 188.4, 170.4, 142.4, 142.0, 131.9 (ArCH), 131.6 (ArCH), 128.8 (terephthaloylCH), 60.9 (OCH\(_2\)), 35.5 (Ar-CH\(_2\)), 14.1 (OCH\(_2\)CH\(_3\)); \( m/z \) (Cl) 471 (MH+, 100%), 425 (16), 159 (13), 46 (13), 44 (14).
A solution of potassium hydroxide (10 mL, 2N) was added to a solution of 1,4-bis(3-carboethoxymethylthien-2-ylcarbonyl)benzene (50 mg, 0.11 mmol) in THF (10 mL). After 3 h the mixture was acidified (conc. HCl) and extracted with dichloromethane (3x50 mL). The combined organics were washed with water (20 mL), brine (40 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure. The residue was then dissolved in acetic anhydride (4 mL) and refluxed, under nitrogen, for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in chlorobenzene (5 mL) and added to DMAD (60 mg, 0.44 mmol). The mixture was refluxed under nitrogen for 6 h. The solvent was removed under reduced pressure. Column chromatography (1:12 ethyl acetate:dichloromethane) yielded the title compound (25 mg, 41%) as a white solid, m.p. 291-293 °C. (Found: M⁺, 574.0755. C₃₀H₂₂O₈S₂ requires M, 574.0756); νmax. (CH₂Cl₂) 1727, 1441, 1281, 1227 cm⁻¹; δH (250 MHz; CDCl₃) 8.52 (2H, s, Ar-H), 7.61 (2H, d, J 5.5 Hz, Ar-H), 7.58 (4H, s, phenyl-H), 7.51 (2H, d, J 5.5 Hz, Ar-H), 3.97 (6H, s, OCH₃), 3.71 (6H, s, OCH₃); δC (100 MHz; CDCl₃) 167.3, 164.9, 143.3, 137.8, 136.1, 132.9, 128.5 (ArCH), 128.3, 127.5 (phenylCH), 123.6 (ArCH), 123.3, 123.1 (ArCH), 51.0 (OCH₃), 50.7 (OCH₃); m/z (EI) 574 (M⁺, 12%), 217 (31), 155 (58), 31 (100).
Aluminium(III) chloride (592 mg, 4.44 mmol) was added to a stirred solution of ethyl thiophene-3-acetate (686 mg, 4.03 mmol) and p-bromobenzoyl chloride (971 mg, 4.42 mmol) in 1,2-dichloroethane (10 mL) at 0 °C under nitrogen. The mixture was refluxed for 8 h. Water (15 mL) was added and the mixture extracted with dichloromethane (3x80 mL). The combined organics were washed with water (50 mL), brine (100 mL) and dried (MgSO4). The solvent was removed under reduced pressure. Column chromatography (1:1 dichloromethane:light petroleum) yielded the title compounds (960 mg, 67%) as a yellow oil, (Found: M+, 351.9767. C15H13BrO3S requires M, 351.9769); \( \nu_{\text{max}} \) (film) 2982, 1735, 1638, 1586, 1271, 1177, 904 cm\(^{-1} \); \( \delta_H \) (250 MHz; CDCl3) 7.62-7.58 (4H, m, ArH), 7.50-7.43 (7H, m, ArH). 7.03 (1H, d, \( J \) 4.9 Hz, ArH(major)), 4.04 (4H, q, \( J \) 7.1 Hz, OCH\(_2\)(both isomers)), 3.91 (2H, s, Ar-CH\(_2\)(major)), 3.54 (2H, s, Ar-CH\(_2\)(minor)), 1.16-1.09 (6H, m, OCH\(_2\)CH\(_3\)(both isomers)); \( \delta_C \) (62.9 MHz, CDCl3) 187.6 (C=O, major), 186.5 (C=O, minor), 170.3 (CO\(_2\), minor), 170.3 (CO\(_2\), major), 142.9, 141.7, 138.2, 136.6, 136.1 (ArCH), 135.4, 135.1, 132.3 (ArCH), 131.9 (ArCH), 131.7 (ArCH), 131.5, 131.2 (ArCH), 130.9 (ArCH), 130.7 (ArCH), 130.2 (ArCH), 127.2, 61.0 (OCH\(_2\), minor), 60.8 (OCH\(_2\), major), 35.5 (Ar-CH\(_2\), minor), 35.4 (Ar-CH\(_2\), major), 14.2 (OCH\(_2\)CH\(_3\)); \( m/z \) (EI) 354 (M\(^{81}\)Br\(^+\), 40%), 352 (M\(^{79}\)Br\(^+\), 40), 279 (82), 200 (100), 171 (44).
2-(p-bromobenzoyl)-thiophene-3-acetic acid 157 and 2-(p-bromobenzoyl)-thiophene-4-acetic acid 158

An aqueous solution of potassium hydroxide (15 mL, 2 N) was added to a solution of 2-(p-bromobenzoyl)-thiophene-3-acetic acid and 2-(p-bromobenzoyl)-thiophene-4-acetic acid (0.85 g, 2.40 mmol) in THF. After 4 h the mixture was acidified (conc. HCl) and extracted with dichloromethane (3x80 mL). The combined organics were washed with water (50 mL), brine (100 mL) and dried (MgSO4). The solvent was removed under reduced pressure to give the title compound (0.59 g, 75%) as a yellow oil, (Found: M+, 323.9454. C13H9O3SBr requires M, 323.9456); *υ*max (CH2Cl2) 1753, 1715, 1605, 1587, 1423 cm⁻¹; δH (250 MHz; CDCl3) 10.55 (1H, br-s, CO2H (both isomers)), 7.74-7.69 (4H, m, ArH), 7.62-7.55 (7H, m, ArH), 7.16 (1H, d, J 5.0 Hz, ArH (major)), 4.04 (2H, s, ArCH2 (major)), 3.67 (2H, s, ArCH2 (minor)); δC (62.9 MHz; CDCl3) 188.8 (both isomers), 171.1 (both isomers), 144.0, 142.8, 140.0, 137.6, 137.0 (ArCH), 136.5, 136.1, 133.6 (ArCH), 132.7 (ArCH), 132.6 (ArCH), 132.2, 132.0 (ArCH), 131.4 (ArCH), 131.0 (ArCH), 128.0, 36.6 (Ar-CH2, minor), 36.5 (Ar-CH2, major); m/z (EI) 326 (M(81Br)+, 5.6 %), 324 (M(79Br)+, 5.7), 280 (56), 201 (100), 171 (57).

1-(p-Bromophenyl)thieno[3,4-b]pyran-3-one 159
A solution of 2-(p-bromobenzoyl)-thiophene-3-acetic acid and 4-(p-
bromobenzoyl)-thiophene-3-acetic acid (0.51 g, 1.57 mmol) in acetic anhydride (8
mL) was heated to reflux, under nitrogen, for 2 h. The solvent was removed
under reduced pressure. Column chromatography (1:10 ethyl
acetate:dichloromethane) gave the title compound (221 mg, 46%) as a yellow
solid, m.p. 198-199 °C; (Found: M+, 305.9357. C13H7D2SBr requires M, 305.9351);
$\nu_{\text{max.}}$ (CH2Cl2) 1708, 1534, 1486, 834 cm$^{-1}$; $\delta$H (250 MHz; CDCl3) 7.86 (2H, d, J 8.7 Hz,
phenylH), 7.68 (2H, d, J 8.7 Hz, phenylH), 7.59 (1H, d, J 5.7 Hz, ArH), 6.89 (1H, d, J
5.7 Hz, ArH), 6.45 (1H, s, Ar-4H); $\delta$C (62.9 MHz; CDCl3) 162.1, 157.8, 153.9, 140.6
(ArCH), 132.4 (phenylCH), 130.4, 128.7 (phenylCH), 125.8, 122.1 (ArCH), 117.1,
103.2 (ArCH); m/z (EI) 308 (M(81Br)+, 63%), 306 (M(79Br)+, 61), 280 (84), 278 (78),
199 (68), 171 (100).

Dimethyl 1-(p-bromophenyl)-benzothiophene-2,3-dicarboxylate 160

A solution of 1-(p-bromophenyl)thieno[3,4-b]pyran-3-one (49 mg, 0.16 mmol) and
DMAD (45 mg, 0.32 mmol) were heated to reflux in chlorobenzene (5 mL) for 8 h.
The solvent was removed under reduced pressure. Column chromatography
(DCM) yielded the title compound (44 mg, 68%) as a white solid, m.p. 121-123 °C;
(Found: M+, 403.9715 C18H13O4SBr requires M, 403.9718); $\nu_{\text{max.}}$ (CH2Cl2) 1728,
1355, 1282, 1225 cm$^{-1}$; $\delta$H (250 MHz; CDCl3) 8.50 (IH, s, Ar-4H), 7.61 (2H, d, J 8.4 Hz,
phenylH), 7.58 (1H, d, J 5.5 Hz, ArH), 7.48 (1H, d, J 5.5 Hz, ArH), 7.36 (2H, d, J 8.4
Hz, phenylH), 3.94 (3H, s, OCH3), 3.68 (3H, s, OCH3); $\delta$C (62.9 MHz; CDCl3) 168.9,
166.3, 139.4, 136.1, 133.7, 131.8 (phenylCH), 130.6 (phenylCH), 130.4, 130.1 (ArCH),
129.6, 125.2 (ArCH), 124.9, 124.7 (ArCH), 123.0, 52.6 (OCH3), 52.4 (OCH3); m/z (EI)
406 (M(81Br)+, 38%), 404 (M(79Br)+, 36), 375 (33), 373 (31), 294 (17), 167 (29), 155 (59),
31 (100).
Indole (1.50 g, 12.8 mmol) was added to a suspension of potassium hydroxide (2.87 g, 51.3 mmol) in DMSO (25 mL) under an atmosphere of nitrogen. The mixture was stirred for 1 h, then α,α' dibromo-o-xylene (1.70 g, 6.4 mmol) was added with external cooling. The mixture was stirred overnight. Water (10 mL) was added and extracted with dichloromethane (3x90 mL), the organics were then washed with brine (3x100 mL) and dried (MgSO₄). Column chromatography (1:49 ether:light petroleum) yielded the title compound (1.66 g, 77%) as a white solid, m.p. 114-115 °C (ethanol), (Found: M⁺, 336.1628. C₂₄H₂₀N₂ requires M⁺, 336.1626); νₓₓ (CH₂Cl₂) 1514, 1484, 1463, 1319, 1269 cm⁻¹; δₜ (250 MHz; CDC₁₃) 7.70-7.66 (2H, m, ArH), 7.26-7.12 (8H, m, ArH), 6.98 (2H, d, J 3.2 Hz, Ar-2H), 6.91-6.87 (2H, m, ArH), 6.58 (2H, d, J 3.2 Hz, Ar-3H), 5.24 (4H, s, NCH₂); δₓ (62.9 MHz; d₆DMSO) 136.3, 134.8, 128.8, 128.4 (ArCH), 128.3 (ArCH), 127.8 (ArCH), 121.9 (ArCH), 121.2 (ArCH), 119.8 (ArCH), 109.5 (ArCH), 102.2 (ArCH), 47.6 (NCH₂); m/z (EI) 336 (M⁺, 27%), 218 (100), 104 (8).

1,3-Bis(indol-1-ylmethyl)benzene 163
Indole (1.50 g, 12.8 mmol) was added to a suspension of potassium hydroxide (2.87 g, 51.3 mmol) in DMSO (25 mL) under an atmosphere of nitrogen. The mixture was stirred for 1 h, then \( \alpha,\alpha' \) dibromo-\( m \)-xylene (1.70 g, 6.4 mmol) was added with external cooling. The mixture was stirred overnight. Water (20 mL) was added and extracted with dichloromethane (3x80 mL); the organics were then washed with brine (4x100 mL) and dried (MgSO\(_4\)). Column chromatography (dichloromethane) yielded the title compound (1.63 g, 75%) as a white solid, m.p. 112-113 °C (ethanol), (Found: C, 85.7; H, 5.8; N, 8.0%; \( \text{C}_{24}\text{H}_{20}\text{N}_{2} \) requires C, 85.7; H, 6.0; N, 8.3%); (Found: M\(^+\), 336.1628. \( \text{C}_{24}\text{H}_{20}\text{N}_{2} \) requires M, 336.1626); \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)) 1514, 1484, 1463, 1334, 1317, 1270 cm\(^{-1}\); \( \delta_{\text{H}} \) (250 MHz; CDCl\(_3\)) 7.69-7.66 (2H, m, ArH), 7.26-7.11 (6H, m, ArH), 7.09 (2H, d, J 3.2 Hz, Ar-2H), 6.98-6.95 (4H, m, ArH), 6.56 (2H, d, J 3.3 Hz, Ar-3H), 5.26 (4H, s, NCH\(_2\)); \( \delta_{\text{C}} \) (62.9 MHz; CDCl\(_3\)) 138.1, 136.0, 129.2 (ArCH), 128.7, 128.1 (ArCH), 126.0 (ArCH), 125.1 (ArCH), 121.7 (ArCH), 120.9 (ArCH), 119.5 (ArCH), 109.6 (ArCH), 101.7 (ArCH), 49.9 (NCH\(_2\)); \( m/z \) (EI) 336 (M\(^+\), 100%), 220 (65), 168 (16), 104 (16).

1,4-Bis(carbazol-9-ylmethyl)benzene164

Carbazole (500 mg, 2.99 mmol) was added to a suspension of potassium hydroxide (671 mg, 12.0 mmol) in DMSO (10 mL) under nitrogen. The mixture was stirred for 0.75 h after which time \( \alpha,\alpha' \) dibromo-\( p \)-xylene (395 mg, 1.50 mmol) was added. The reaction was stirred overnight. Addition of water (50 mL) caused precipitation of the crude product, the solid was filtered and washed with water and brine. Column chromatography (1:1 dichloromethane:light petroleum) yielded the title compound (483 mg, 74%) as a white solid, m.p. 246-248 °C (toluene), (Found: C, 87.8; H, 5.5; N, 6.3%; \( \text{C}_{32}\text{H}_{24}\text{N}_{2} \) requires C, 88.0; H, 5.6; N, 6.4%); (Found: M\(^+\), 436.1941. \( \text{C}_{32}\text{H}_{24}\text{N}_{2} \) requires M, 436.1939); \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)) 1486, 139
1460, 1333, 1326 cm⁻¹; δ_H (250 MHz; CDCl3) 8.09 (4H, dd, J 7.8, 0.9 Hz, ArH), 7.39 (4H, ddd, J 7.4, 7.5, 1.0 Hz, ArH), 7.30 (4H, d, J 7.4 Hz, ArH), 7.22 (4H, ddd, J 7.8, 7.3, 1.0 Hz, ArH), 7.02 (4H, s, xylylH), 5.45 (4H, s, NCH2); δ_C (100 MHz; CDCl3) 140.5, 136.5, 126.8 (ArCH), 125.8 (ArCH), 122.9, 120.3 (ArCH), 119.2 (ArCH), 108.8 (ArCH), 46.1 (NCH2); m/z (El) 436 (M⁺, 2%), 91 (100), 65 (13).

1,3-Bis(carbazol-9-ylmethyl)benzene 165

![1,3-Bis(carbazol-9-ylmethyl)benzene](image)

Carbazole (501 mg, 3.00 mmol) was added to a suspension of potassium hydroxide (672 mg, 12.0 mmol) in DMSO (10 mL) under nitrogen. The mixture was stirred for 0.75 h after which time α,α’-dibromo-m-xylene (396 mg, 1.50 mmol) was added. The reaction was stirred overnight. Addition of water (50 mL) caused precipitation of the crude product, the solid was filtered and washed with water and brine. Column chromatography (1:1 dichloromethane:light petroleum) yielded the title compound (445 mg, 68%) as a white solid, m.p. 208-210 °C, (Found: C, 87.8; H, 5.5; N, 6.3%; C32H24N2 requires C, 88.0; H, 5.6; N, 6.4%); (Found: M⁺, 436.1939. C32H24N2 requires M, 436.1939); v_max. (CH2Cl2) 1610, 1513, 1484, 1463, 1439, 1317, 1187 cm⁻¹; δ_H (250 MHz; CDCl3) 8.14 (4H, dd, J 7.0, 1.8 Hz, ArH), 7.41 (4H, ddd, J 7.0, 1.8, 1.1 Hz, ArH), 7.29-7.23 (8H, m, ArH), 7.13-6.94 (4H, m, ArH), 5.40 (4H, s, NCH2); δ_C (62.9 MHz; CDCl3) 140.7, 137.8, 129.3 (xylylCH), 125.8 (ArCH), 125.5 (xylylCH), 124.6 (xylylCH), 123.0, 120.3 (ArCH), 119.2 (ArCH), 108.8 (ArCH), 46.3 (NCH2); m/z (El) 436 (M⁺, 100%), 270 (29), 180 (7), 104 (13).
Carbazole (1.67 g, 10.0 mmol) was added to a suspension of potassium hydroxide (2.24 g, 40.0 mmol) in DMSO (15 mL) under nitrogen. The mixture was stirred for 0.75 h after which time α,α’-dibromo-o-xylene (1.32 g, 5.0 mmol) was added. The reaction was stirred overnight. Addition of water (20 mL) caused precipitation of the crude product. The solid was filtered off, dissolved in dichloromethane (250 mL) and washed with brine (6x100 mL). Column chromatography (1:1 dichloromethane:light petroleum) yielded the title compound (1.55 g, 71%) as a white solid, m.p. 227-228 °C (toluene). (Found: M⁺, 436.1936. C₃₂H₂₄N₂ requires M, 436.1939); uₘₐₓ. (CH₂Cl₂) 1486, 1454, 1326, 1216 cm⁻¹; δH (250 MHz; CDCl₃) 8.17 (4H, d, J 7.7 Hz, Ar-4H), 7.44 (4H, dd, J 8.2, 7.6 Hz, ArH), 7.29 (4H, t, J 7.4 Hz, ArH), 7.20 (4H, d, J 8.1 Hz, Ar-2H), 7.05 (2H, dd, J 5.7, 3.3 Hz, xylylH), 6.74 (2H, dd, J 5.4, 3.6 Hz, xylylH), 5.45 (4H, s, NCH₂); δC (62.9 MHz; CDCl₃) 140.6, 133.6, 128.0 (xylylCH), 126.7 (xylylCH), 126.0 (ArCH), 123.2, 120.6 (ArCH), 119.5 (ArCH), 108.9 (ArCH), 44.4 (NCH₂); m/z (El) 436 (M⁺, 6%), 268 (22), 91 (100), 65 (12).

1,4-Bis(1-methyl-2,3-dicarbomethoxycarbazo-9-ylmethyl)benzene 167
A solution of dimethyl 1-methyl-9H-carbazole,2,3-dicarboxylate (496 mg, 1.67 mmol) and DMF (0.25 mL, 3.24 mmol) in THF (3.5 mL) was added to sodium hydride (60 mg, 2.50 mmol) under nitrogen. After stirring for 0.25 h α,α’- dibromo-p-xylene (220 mg, 0.83 mmol) was added. The mixture was refluxed for 4 h. Filtration followed by column chromatography (1:24 ether:dichloromethane) yielded the title compound (350 mg, 60%) as a white solid, m.p. 318-320 °C, (Found: C, 72.7; H, 5.0; N, 3.8%; C42H36N2O8 requires C, 72.4; H, 5.2; N, 4.0%); (Found: M+, 696.2470. C42H36N2O8 requires M, 696.2471); v max. (CH2Cl2) 1728, 1715, 1349, 1234, 1073 cm-1; δH (250 MHz; CDCl3) 8.68 (2H, s, Ar-4H), 8.13 (2H, d, J 7.8 Hz, ArH), 7.46 (2H, dt, J 1.2, 7.7 Hz, ArH), 7.34-7.26 (4H, m, ArH), 6.90 (4H, s, xylylH), 5.73 (4H, s, NCH2), 3.97 (6H, s, OCH3), 3.94 (6H, s, OCH3), 2.53 (6H, s, Ar-CH3); δC (100 MHz; CDCl3) 169.6 (C=O), 165.5 (C=O), 141.5, 140.3, 136.2, 133.4, 126.1 (ArCH), 125.1 (XylylCH), 122.6, 121.6, 120.3 (ArCH), 119.7 (ArCH), 119.4 (ArCH), 117.8, 116.7, 108.4 (ArCH), 51.5 (OCH3), 51.1 (OCH3), 47.2 (NCH2), 14.8 (Ar-CH3); m/z (EI) 696 (M+, 5%), 400 (31), 266 (22), 264 (87), 179 (53), 104 (100).

1,3-Bis(1-methyl-2,3-dicarboxymethoxycarbazol-9-ylmethyl)benzene 168

A solution of dimethyl 1-methyl-9H-carbazole,2,3-dicarboxylate (1.00 g, 5.99 mmol) and DMF (0.50 mL, 6.48 mmol) in THF (10 mL) was added to sodium hydride (0.22 g, 9.17 mmol) under nitrogen. After stirring for 0.25 h α,α’- dibromo-m-xylene (440 mg, 1.67 mmol) was added. The mixture was refluxed for 3 h. Filtration followed by column chromatography (1:24 ether:dichloromethane) yielded the title compound (1.03 g, 88%) as a white solid, m.p. 165-166 °C (toluene), (Found: M+, 696.2470. C42H36N2O8 requires M, 696.2471); v max. (CH2Cl2) 1728, 1714, 1438, 1356, 1234 cm-1; δH (250 MHz; CDCl3) 8.62 (2H, s, Ar-4H), 8.08 (2H,
d, J 7.9 Hz, ArH), 7.39 (2H, dt, J 1.2, 7.6 Hz, ArH), 7.31-7.15 (5H, m, ArH), 6.88 (2H, d, J 7.7 Hz, ArH), 6.44 (1H, s, ArH), 5.64 (4H, s, NCH2), 3.99 (6H, s, OCH3), 3.97 (6H, s, OCH3), 2.43 (6H, s, Ar-CH3); δC (62.9 MHz; CDCl3) 170.6 (C=O), 166.6 (C=O), 142.3, 141.2, 138.8, 129.8 (ArCH), 127.0 (ArCH), 124.6 (ArCH), 123.5, 122.5, 122.2 (ArCH), 121.2 (ArCH), 120.7 (ArCH), 120.4 (ArCH), 118.7, 117.6, 109.3 (ArCH), 52.5 (OCH3), 51.2 (OCH3), 48.3 (NCH2), 15.6 (Ar-CH3); m/z (El) 696 (M+, 31%), 664 (35), 400 (24), 367 (78), 336 (100), 265 (67), 179 (72), 104 (100).

1,5-Bis(1-methyl-2,3-dicarbomethoxycarbazol-9-yl)pentane 116

![Chemical structure](image)

A solution of dimethyl 1-methyl-9H-carbazole,2,3-dicarboxylate (481 mg, 1.62 mmol) and DMF (0.25 mL, 3.24 mmol) in THF (3.5 mL) was added to sodium hydride (58 mg, 2.42 mmol) under nitrogen. After stirring for 0.25 h 1,5-diiodopentane (0.12 mL, 0.80 mmol) was added. The reaction was refluxed for 4 h. The solvent was removed under reduced pressure. Column chromatography (1:24 ether:dichloromethane) yielded the title compound as a yellow solid, m.p. 171-173 °C (toluene), (Found: C, 70.4; H, 5.6; N, 4.0%; C39H38N2O8 requires C, 70.7; H, 5.8; N, 4.2%); (Found: M+, 662.2630. C39H38N2O8 requires M, 662.2627); νmax. (CH2Cl2) 1729, 1715, 1594, 1348, 1236 cm⁻¹; δH (250 MHz; CDCl3) 8.65 (2H, s, Ar-4H), 8.10 (2H, d, J 7.6 Hz, ArH), 7.51 (2H, t, J 7.7 Hz, ArH), 7.33 (2H, d, J 7.8 Hz, ArH), 7.30 (2H, t, J 7.3 Hz, ArH), 4.38 (4H, t, J 7.5 Hz, NCH2), 4.02 (6H, s, OCH3), 3.94 (6H, s, OCH3), 2.63 (6H, s, Ar-CH3), 1.91-1.79 (4H, m, NCH2CH2), 1.52-1.41 (2H, m, NCH2CH2CH2); δC (62.9 MHz; CDCl3) 170.8 (C=O), 166.6 (C=O), 142.0, 140.7, 134.3, 126.8 (ArCH), 123.5, 122.6, 121.2 (ArCH), 120.4 (ArCH), 120.4 (ArCH), 118.3, 117.2, 109.3 (ArCH), 52.6 (OCH3), 52.2 (OCH3), 44.8 (NCH2), 30.6 (NCH2CH2), 24.2 (NCH2CH2CH2), 16.1 (Ar-CH3); m/z (El) 662 (M+, 23%), 334 (100), 310 (86), 265 (88).
A solution of carbazole (322 mg, 1.93 mmol) and DMF (0.15 mL, 1.93 mmol) in THF (5 mL) was added to sodium hydride (116 mg, 4.8 mmol) under nitrogen. After 0.25 h 1,8-bis(bromomethyl)naphthalene (303 mg, 0.96 mmol) was added. The reaction was heated at 50 °C for 4 h. The solvent was removed under reduced pressure. Purification by column chromatography (3:10 dichloromethane:light petroleum) yielded the title compound (355 mg, 76%) as a white solid, m.p. 268-270 °C, (Found: C, 88.4; H, 5.3; N, 5.6%; C_{36}H_{26}N_{2} requires C, 88.8; H, 5.4; N, 5.8%); (Found: M⁺, 486.2099. C_{36}H_{26}N_{2} requires M, 486.2096); ν_{max}. (CH₂Cl₂) 1599, 1487, 1457, 1222 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 8.20 (4H, d, J 7.5 Hz, ArH), 7.78 (2H, d, J 8.0 Hz, naphthaleneH), 7.49-7.42 (4H, m, ArH), 7.34-7.30 (4H, m, ArH), 7.30 (4H, d, J 7.8 Hz, ArH), 7.18 (2H, t, J 7.7 Hz, naphthaleneH), 6.74 (2H, d, J 7.2 Hz, naphthaleneH), 6.35 (4H, s, NCH₂); δ_{C} (62.9 MHz; CDCl₃) 145.1, 140.8, 137.3, 135.2, 134.2 (naphthaleneCH), 130.7 (ArCH), 130.1 (naphthaleneCH), 129.7 (naphthaleneCH), 127.7, 125.1 (ArCH), 124.2 (ArCH), 113.8 (ArCH), 53.0 (NCH₂); m/z (El) 486 (M⁺, 6%), 317 (22), 267 (42), 167 (74), 155 (80), 51 (100).
5-Nitroindole (486 mg, 3.0 mmol) was added to a stirred suspension of potassium hydroxide (672 mg, 12.0 mmol) in DMSO (10 mL) under nitrogen. The mixture was stirred for 0.75 h, then α,α’-dibromo-β-xylene (396 mg, 1.5 mmol) was added. The mixture was stirred overnight. Water (30 mL) was added and the resultant suspension was filtered off. Column chromatography (dichloromethane) yielded the title compound (428 mg, 67%) as a yellow solid, m.p. 205-206 °C (toluene), (Found: C, 67.2; H, 4.1; N, 12.6%; C_{24}H_{18}N_{4}O_{4} requires C, 67.6; H, 4.3; N, 13.1%); (Found: M⁺, 426.356. C_{24}H_{18}N_{4}O_{4} Requires M, 426.1328); νmax (CH₂Cl₂) 1518, 1336, 731 cm⁻¹; δ_H (360 MHz; d₆DMSO) 8.56 (2H, d, J 2.2 Hz, Ar-4H), 7.96 (2H, dd, J 9.1, 2.2 Hz, Ar-6H), 7.73 (2H, d, J 3.2 Hz, Ar-2H), 7.64 (2H, d, J 9.1 Hz, Ar-7H), 7.17 (4H, s, xylylH), 6.77 (2H, d, J 3.1 Hz, Ar-3H), 5.47 (4H, s, NCH₂); δ_C (100 MHz; d₆DMSO) 146.5, 144.2, 142.5, 138.5 (ArCH), 133.1, 133.0 (xylylCH), 123.2 (ArCH), 122.1 (ArCH), 116.2 (ArCH), 109.6 (ArCH), 54.7 (NCH₂); m/z (EI) 277 (22%), 116 (22), 91 (49), 84 (68), 49 (100).
5-Methoxyindole (294 mg, 2.0 mmol) was added to a suspension of potassium hydroxide (450 mg, 8.0 mmol) in DMSO (5 mL) under nitrogen. The mixture was stirred for 0.75 h, then α,α′dibromo-p-xylene (264 mg, 1.0 mmol) was added. The reaction mixture was stirred overnight. Water (30 mL) was added and the mixture extracted with dichloromethane (2x100 mL). The combined organics were then washed with brine (5x100 mL) and dried (MgSO₄). The solvent was removed under reduced pressure. Column chromatography (1:1 dichloromethane:light petroleum) yielded the title compound (294 mg, 74%) as a white solid, m.p. 164-165 °C (toluene), (Found: C, 78.8; H, 6.0; N, 7.0%; C₂₆H₂₄N₂O₂ requires C, 78.8; H, 6.1; N, 7.1%); (Found M⁺, 396.1838. C₂₆H₂₄N₂O₂ requires M, 396.1838); v_max. (CH₂Cl₂) 1487, 1422, 1240, 1152 cm⁻¹; δH (360 MHz; CDCl₃) 7.11-7.09 (4H, m, ArH), 7.06 (2H, d, J 3.1 Hz, Ar-2H), 6.99 (4H, s, xylylH), 6.80 (2H, dd, J 8.8, 2.5 Hz, ArH), 6.44 (2H, d, J 3.0 Hz, Ar-3H), 5.23 (4H, s, NCH₂), 3.83 (6H, s, OCH₃); δC (100 MHz; CDCl₃) 154.1, 137.1, 131.6, 129.1, 128.7 (ArCH), 127.3 (xylylCH), 112.0 (ArCH), 110.4 (ArCH), 102.4 (ArCH), 101.3 (ArCH), 55.8 (OCH₃), 49.9 (NCH₂); m/z (El) 396 (M⁺, 100%), 250 (42), 146 (65), 104 (35).
5-Nitroindole (486 mg, 3.0 mmol) was added to a suspension of potassium hydroxide (670 mg, 12.0 mmol) in DMSO (20 mL) under nitrogen. The reaction was stirred for 0.75 h, then \( \alpha,\alpha' \)-dibromo-\( p \)-xylene (1.56 g, 6.0 mmol) was added and the reaction stirred for 3 h. Water (40 mL) was added and extracted with dichloromethane (3x80 mL). The combined organics were then washed with brine (4x100 mL) and dried (MgSO\(_4\)). Column chromatography (3:2 dichloromethane:light petroleum) yielded the title compound (350 mg, 34%) as a yellow solid, m.p. 128-129 °C, (Found: M\(^+\), 344.0155. C\(_{16}\)H\(_{13}\)BrN\(_2\)O\(_2\) requires M, 344.0161); \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)) 1518, 1336, 1256, 1070, 774 cm\(^{-1}\); \( \delta_H \) (250 MHz; CDCl\(_3\)) 8.58 (1H, d, J 2.2 Hz, Ar-4H), 8.05 (1H, dd, J 9.1, 2.2 Hz, Ar-6H), 7.34 (2H, d, J 8.1 Hz, xylylH), 7.28 (1H, d, J 3.2 Hz, Ar-2H), 7.27-7.25 (1H, d, J 9.2 Hz, Ar-7H), 7.07 (2H, d, J 8.0 Hz, xylylH), 6.73 (1H, d, J 3.2 Hz, Ar-3H), 5.36 (2H, s, NCH\(_2\)), 4.45 (2H, s, BrCH\(_2\)); \( \delta_C \) (62.9 MHz; CDCl\(_3\)) 142.0, 139.0, 137.9, 136.5, 131.4 (ArCH), 129.6 (xylylCH), 127.9, 127.1 (xylylCH), 118.2 (ArCH), 117.4 (ArCH), 109.5 (ArCH), 104.5 (ArCH), 50.2 (NCH\(_2\)), 32.7 (BrCH\(_2\)); \( m/z \) (El) 346 (M\(^+\), 29%), 344 (30), 265 (12), 185 (39), 183 (41), 104 (100), 91 (29), 78 (18).
5-Methoxyindole (122 mg, 0.83 mmol) was added to a suspension of potassium hydroxide (186 mg, 3.3 mmol) in DMSO (5 mL) under nitrogen. After 0.75 h 4-[5-nitroindol-1-yl)methyl]benzyl bromide (300 mg, 0.87 mmol) was added. The reaction was stirred overnight. Addition of water (15 mL) and filtration gave the crude product. Column chromatography (3:7 dichloromethane:light petroleum) yielded the title compound (160 mg, 47%) as a yellow solid, m.p. 117-118 °C (toluene), (Found: M+, 411.1584. C_{25}H_{21}N_{3}O_{3} requires M, 411.1583); ν\text{max.} (CH_{2}Cl_{2}) 3055, 1518, 1450, 1335, 1240, 1152, 1070 cm\textsuperscript{-1}; δ\text{H} (250 MHz; CDCl\textsubscript{3}) 8.59 (1H, d, J 2.2 Hz, Ar-4H(NO\textsubscript{2})); 8.05 (1H, dd, J 9.1, 2.2 Hz, Ar-6H(NO\textsubscript{2})); 7.26-7.23 (2H, m, ArH), 7.12-7.06 (3H, m, ArH), 7.02 (4H, d, J 2.0 Hz, xylylH), 6.82 (1H, dd, J 9.0, 2.4 Hz, Ar-6H(OMe)), 6.71 (1H, d, J 3.2 Hz, Ar-3H(NO\textsubscript{2})), 6.47 (1H, d, J 3.0 Hz, Ar-3H(OMe)), 5.30 (2H, s, NCH\textsubscript{2}), 5.24 (2H, s, NCH\textsubscript{2}), 3.84 (3H, s, OCH\textsubscript{3}); δ\text{C} (62.9 MHz; CDCl\textsubscript{3}) 154.1, 141.6, 138.9, 137.7, 135.6, 131.4 (ArCH), 129.1, 128.7 (ArCH), 127.9, 127.2 (xylylCH), 127.1 (xylylCH), 118.2 (ArCH), 117.4 (ArCH), 112.0 (ArCH), 110.3 (ArCH), 109.5 (ArCH), 104.4 (ArCH), 102.7 (ArCH), 101.4 (ArCH), 56.8 (OCH\textsubscript{3}), 50.1 (NCH\textsubscript{2}), 49.8 (NCH\textsubscript{2}); m/z (EI) 411 (13%), 186 (14), 155 (34), 78 (43), 44 (47), 31 (100).
Carbazole (121 mg, 0.72 mmol) was added to a suspension of potassium hydroxide (162 mg, 2.90 mmol) in DMSO (5 mL) under nitrogen. After 0.75 h 4-[(5-nitroindolyl)methyl]benzyl bromide (250 mg, 0.72 mmol) was added. The reaction was stirred overnight. Water (15 mL) was added to give the crude product as a precipitate. Filtration followed by column chromatography (3:7 dichloromethane:light petroleum) yielded the title compound (230 mg, 74%) as a yellow solid, m.p. 184-185 °C (toluene), (Found M+, 431.1638. C28H21N3O2 requires M, 431.1634); νmax(CH2Cl2) 1517, 1485, 1453, 1335, 1070 cm⁻¹; δH (250 MHz; CDCl3) 8.59 (1H, d, J 2.1 Hz, indole-4H), 8.13 (2H, d, J 7.7 Hz, Ar-4H), 8.05 (1H, dd, J 9.1, 2.2 Hz, indole-6H), 7.43 (2H, dt, J 1.0, 7.6 Hz, ArH), 7.31-7.21 (6H, m, ArH), 7.09 (2H, d, J 8.1 Hz, ArH), 6.97 (2H, d, J 8.1Hz, ArH), 6.70 (1H, d, J 3.2 Hz, indole-3H), 5.49 (2H, s, NCH2), 5.29 (2H, s, NCH2); δC (100 MHz; CDCl3) 142.2, 140.9, 139.4, 135.9, 131.8 (ArCH), 128.3, 127.6 (ArCH), 127.5 (ArCH), 126.3 (ArCH), 123.5, 120.9 (ArCH), 119.8 (ArCH), 118.7 (ArCH), 117.9 (ArCH), 109.9 (ArCH), 109.1 (ArCH), 104.9 (ArCH), 50.6 (CH2), 46.5 (CH2); m/z (EI) 431 (M+, 42%), 267 (46), 236 (32), 155 (67), 31 (100).
1-(2-Hydroxyethyl)indole 175

Indole (2.34 g, 20.0 mmol) was added to a suspension of potassium hydroxide (4.48 g, 80.0 mmol) in DMSO (20 mL) under an atmosphere of nitrogen. The mixture was stirred for 1 h, then 2-chloroethanol (2.0 g, 25.0 mmol) was added with external cooling. The mixture was stirred overnight. Water (20 mL) was added and the mixture was extracted with dichloromethane (3x 80 mL). The combined organics were then washed with brine (6x100 mL) and dried (MgSO4). Column chromatography (dichloromethane) yielded the title compound as a pale yellow oil (2.57 g, 71%), v_max. (film) 3367 (br), 2935, 1510, 1464, 1315, 1064, 742 cm⁻¹; δ_H (250 MHz; CDCl₃) 7.64 (1H, d, J 7.9 Hz, Ar-4H), 7.38 (1H, d, J 8.3 Hz, Ar-7H), 7.24 (1H, dd, J 8.2, 7.7 Hz, ArH), 7.20-7.09 (2H, m, ArH), 6.52 (1H, d, J 3.0 Hz, Ar-3H), 4.12 (2H, t, J 5.3 Hz, OCH₂), 3.76 (2H, t, J 5.2 Hz, NCH₂), 1.80 (1H, s-br, OH); δ_C (62.9 MHz; CDCl₃) 136.0, 128.5, 128.4 (ArCH), 121.6 (ArCH), 121.0 (ArCH), 119.5 (ArCH), 109.3 (ArCH), 101.4 (ArCH), 61.8 (OCH₂), 48.6 (NCH₂).

4-Nitrobenzoic acid (2-indol-1-ylethyl ester) 177

p-Nitrobenzoyl chloride (835 mg, 4.5 mmol) was added to a solution of 1-(2-hydroxyethyl)indole (483 mg, 3.0 mmol) and triethylamine (0.48 mL, 4.5 mmol) in dichloromethane (5 mL) under an atmosphere of nitrogen. The mixture was stirred overnight. The solvent was removed under reduced pressure and the residue purified by column chromatography (3:1 dichloromethane:light petroleum) to yield the title compound (828 mg, 89%) as a yellow solid, m.p. 103-
104 °C (light petroleum), (Found: M+, 310.0953. C\textsubscript{17}H\textsubscript{14}N\textsubscript{2}O\textsubscript{4} requires M, 310.0954); \(\nu_{\text{max}}\) (CHCl\textsubscript{3}) 2254, 1728, 1531, 1351, 1270, 740 cm\textsuperscript{-1}; \(\delta_{\text{H}}\) (250 MHz; CDCl\textsubscript{3}) 8.23 (2H, d, J 8.7 Hz, benzoateH), 8.05 (2H, d, J 8.8 Hz, benzoateH), 7.66 (1H, d, J 7.8 Hz, Ar-4H), 7.41 (1H, d, J 8.2 Hz, ArH), 7.24 (1H, d, J 5.6 Hz, ArH), 7.21-7.11 (2H, m, ArH), 6.56 (1H, d, J 0.6 Hz, Ar-3H), 4.69 (2H, d, J 5.3 Hz, CH\textsubscript{2}), 4.57 (2H, d, J 5.4 Hz, CH\textsubscript{2}); \(\delta_{\text{C}}\) (62.9 MHz; CDCl\textsubscript{3}) 164.8 (C=O), 150.8, 136.0, 134.8, 130.7 (benzoateCH), 128.4, 127.6 (ArCH), 123.5 (benzoateCH), 121.8 (ArCH), 121.2 (ArCH), 119.7 (ArCH), 109.0 (ArCH), 102.2 (ArCH), 64.4 (OCH\textsubscript{2}), 44.8 (NCH\textsubscript{2}); \(\textit{m/z}\) (El) 310 (M+, 31%), 267 (10), 180 (49), 143 (45), 130 (100).

\textit{Benzoic acid (2-indol-1-ylethyl) ester}178

Benzoyl chloride (0.78 mL, 6.8 mmol) was added to a solution of 1-(2-hydroxyethyl)indole (725 mg, 4.5 mmol) and triethylamine (1.0 mL, 7.2 mmol) in dichloromethane (5 mL) under an atmosphere of nitrogen. The mixture was stirred overnight. The solvent was removed under reduced pressure and the residue purified by column chromatography (dichloromethane) to yield the \textit{title compound} (668 mg, 56%) as a white solid, m.p. 103-104 °C (toluene), (Found: C, 76.8; H, 5.7; N, 5.1%; C\textsubscript{17}H\textsubscript{15}NO\textsubscript{2} requires C, 77.0; H, 5.7; N, 5.3%); (Found: M+, 265.1104. C\textsubscript{17}H\textsubscript{15}NO\textsubscript{2} requires M, 265.1103); \(\nu_{\text{max}}\) (CHCl\textsubscript{3}) 1718, 1270, 741, 710, 668 cm\textsuperscript{-1}; \(\delta_{\text{H}}\) (250 MHz; CDCl\textsubscript{3}) 7.96 (2H, d, J 7.2 Hz, ArH), 7.65 (1H, d, J 7.8 Hz, ArH), 7.55 (1H, d, J 7.3 Hz, ArH), 7.45-7.39 (3H, m, ArH), 7.28-7.11 (3H, m, ArH), 6.55 (1H, d, J 3.2 Hz, Ar-3H), 4.65 (2H, t, J 5.5 Hz, CH\textsubscript{2}-CH\textsubscript{2}), 4.52 (2H, t, J 5.5 Hz, CH\textsubscript{2}-CH\textsubscript{2}); \(\delta_{\text{C}}\) (62.9 MHz; CDCl\textsubscript{3}) 166.0 (C=O), 135.9, 133.0 (ArCH), 129.4 (ArCH), 128.5, 128.2 (ArCH), 127.9, 127.8 (ArCH), 121.5 (ArCH), 120.9 (ArCH), 119.4 (ArCH), 109.1 (ArCH), 101.7 (ArCH), 63.4 (OCH\textsubscript{2}), 44.7 (NCH\textsubscript{2}); \(\textit{m/z}\) (El) 265 (M+, 31%), 143 (100), 130 (95), 105 (27), 77 (51).
Benzenesulfonyl chloride (0.86 mL, 6.75 mmol) was added to a solution of 1-(2-hydroxyethyl)indole (543 mg, 3.37 mmol) and triethylamine (0.72 mL, 6.75 mmol) in dichloromethane (5 mL) under an atmosphere of nitrogen. The mixture was stirred overnight. The solvent was removed under reduced pressure and the residue purified by column chromatography (3:2 dichloromethane:light petroleum) to yield the title compound (860 mg, 95%) as a white solid, m.p. 72-73 °C. (Found: C, 63.9; H, 4.7; N, 4.5%; C_{16}H_{15}NO_3S requires C, 63.8; H, 5.0; N, 4.6%); (Found: M+, 301.0776. C_{16}H_{15}NO_3S requires M, 301.0773); \nu_{\text{max}} (\text{CHCl}_2) 1365, 1188, 1178, 1178, 907 \text{ cm}^{-1}; \delta_H (360 \text{ MHz; CDCl}_3) 7.62-7.58 (3H, m, ArH), 7.50 (1H, t, J 7.5 Hz, ArH), 7.33 (2H, t, J 7.9 Hz, ArH), 7.18-7.07 (3H, m, ArH), 7.03 (1H, d, J 3.2 Hz, Ar-2H), 6.46 (1H, d, J 3.2 Hz, Ar-3H), 4.40 (2H, t, J 5.1 Hz, CH_2-CH_2), 4.32 (2H, t, J 5.1 Hz, CH_2-CH_2); \delta_C (100 \text{ MHz; CDCl}_3) 136.1, 135.5, 134.1 (ArCH), 129.7 (ArCH), 129.5, 128.4 (ArCH), 127.9 (ArCH), 122.3 (ArCH), 121.5 (ArCH), 120.1 (ArCH), 109.2 (ArCH), 102.6 (ArCH), 68.5 (OCH_2), 45.5 (NCH_2); m/z (EI) 301 (M+, 30%), 143 (16), 130 (100), 91 (32), 77 (18).

Terephthalic acid di-(2-indol-1-ylethyl ester) 180

Terephthaloyl chloride (391 mg, 1.93 mmol) was added to a solution of 1-(2-hydroxyethyl)indole (620 mg, 3.85 mmol) and triethylamine (0.5 mL) in
dichloromethane (4 mL). The mixture was stirred overnight. The solvent was removed under reduced pressure. Column chromatography (1:1 ether:dichloromethane) yielded the title compound (497 mg, 57%) as a white solid, m.p. 143-144 °C (toluene), (Found: C, 74.4; H, 5.2; N, 6.0%; C₂₈H₂₄N₂O₄ requires C, 74.3; H, 5.3; N, 6.2%); (Found: M⁺, 452.1741. C₂₈H₂₄N₂O₄ requires M, 452.1736); vmax. (CH₂Cl₂) 1724, 1282, 1246, 1121 cm⁻¹; δH (250 MHz; CDCl₃) 7.96 (4H, s, terephthaloylH), 7.67 (2H, dd, J 6.9, 1.1 Hz, ArH), 7.43 (2H, dd, J 6.8, 0.8 Hz, ArH), 7.28-7.22 (2H, m, ArH), 7.19-7.13 (4H, m, ArH), 6.56 (2H, d, J 3.3 Hz, Ar-3H), 4.65 (4H, t, J 5.1 Hz, CH₂-CH₂), 4.53 (4H, t, J 5.2 Hz, CH₂-CH₂); δC (100 MHz; CDCl₃) 165.8 (C=O), 136.6, 134.0, 130.1 (terephthaloylCH), 129.2, 128.3 (ArCH), 122.3 (ArCH), 121.6 (ArCH), 120.2 (ArCH), 109.6 (ArCH), 102.6 (ArCH), 64.5 (OCH₂), 45.4 (NCH₂); m/z (EI) 452 (M⁺, 29%), 143 (100), 51 (18).

1-(2-Hydroxyethyl)carbazole 181

![181](image)

Carbazole (1.67 g, 10.0 mmol) was added to a suspension of potassium hydroxide (2.24 g, 40.0 mmol) in DMSO (20 mL) under an atmosphere of nitrogen. The mixture was stirred for 1 h, then 2-chloroethanol (0.74 mL, 11.0 mmol) was added with external cooling and the mixture stirred overnight. Water (20 mL) was added and the mixture extracted with dichloromethane (4x100 mL). The combined organics were then washed with water (2x100 mL), brine (4x100 mL) and then dried (MgSO₄). The solvent was removed under reduced pressure. Column chromatography (99:1 dichloromethane:ether) yielded the title compound (1.21 g, 57%) as a white solid, m.p. 93-94 °C, (Found: M⁺, 211.0996. C₁₄H₁₃NO requires M, 211.0997); vmax. (CH₂Cl₂) 3612, 1598, 1485, 1326, 912 cm⁻¹; δH (250 MHz; CDCl₃) 8.14 (2H, dd, J 7.8, 0.8 Hz, ArH), 7.53 (2H, dt, 7.6, 0.8 Hz, ArH), 7.36-7.30 (4H, m, ArH), 4.13 (2H, t, J 5.3 Hz, NCH₂), 3.60 (2H, t, J 5.3 Hz, OCH₂), 2.45 (1H, br-s, OH); δC (62.9 MHz; CDCl₃) 140.7, 125.8 (ArCH), 122.9, 120.4 (ArCH), 119.2 (ArCH), 109.0 (ArCH), 60.9 (OCH₂), 45.2 (NCH₂); m/z (EI) 211 (M⁺, 44%), 180 (100), 152 (16).
p-Nitrobenzoyl chloride (300 mg, 1.62 mmol) was added to a solution of 1-(2-hydroxyethyl)carbazole (284 mg, 1.34 mmol) and triethylamine (0.75 mL) in dichloromethane (5 mL). The reaction was stirred overnight. The solvent was removed under reduced pressure. Column chromatography (dichloromethane) yielded the title compound (383 mg, 79%) as a yellow solid, m.p. 173-174 °C (toluene), (Found: C, 70.1; H, 4.4; N, 7.8%; C_{21}H_{16}N_{2}O_{4} requires C, 70.0; H, 4.5; N, 7.8%); (Found: M^+, 344.1157. C_{21}H_{16}N_{2}O_{3} requires M, 344.1161); \nu_{\text{max.}} (\text{CH}_2\text{Cl}_2) 1728, 1530, 1351, 1273 \text{ cm}^{-1}; \delta_{\text{H}} (250 \text{ MHz; CDCl}_3) 9.14 (2\text{H}, d, J 8.8 \text{ Hz, benzoateH}), 9.11 (2\text{H}, d, J 7.7 \text{ Hz, ArH}), 8.88 (2\text{H}, d, J 8.8 \text{ Hz, benzoateH}), 8.46 (4\text{H}, d, J 7.7 \text{ Hz, ArH}), 8.29-8.23 (2\text{H}, m, ArH), 4.75 (4\text{H}, s, \text{CH}_2\text{-CH}_2); \delta_{\text{C}} (100 \text{ MHz; CDCl}_3) 164.9 (\text{C=O}), 150.9, 140.8, 135.2, 131.1 (\text{ArCH}), 126.3 (\text{ArCH}), 123.8 (\text{ArCH}), 123.6, 121.0 (\text{ArCH}), 119.9 (\text{ArCH}), 108.9 (\text{ArCH}), 63.9 (\text{OCH}_2), 41.9 (\text{NCH}_2); m/z (\text{EI}) 193 (24%), 180 (100), 152 (14).

Benzoic acid (2-carbazol-9-ylethyl ester)

Triethylamine (0.2 mL, 1.4 mmol) was added to a solution of 1-(2-hydroxyethyl)carbazole (232 mg, 1.1 mmol) and benzoyl chloride (0.19 mL, 1.65 mmol) in dichloromethane (4 mL). The mixture was stirred overnight. The solvent was removed under reduced pressure. Column chromatography
(dichloromethane) yielded the title compound (222 mg, 64%) as a white solid, m.p. 147-148 °C (toluene), (Found: C, 79.9; H, 5.3; N, 4.2%; C_{21}H_{17}NO_2 requires C, 80.0; H, 5.4; N, 4.4%); v\text{max.} (CH_2Cl_2) 3070, 1719, 1465, 1273 cm^{-1}; \delta_H (250 MHz; CDCl_3) 8.12 (2H, d, J 7.7 Hz, ArH), 7.84 (2H, dd, J 7.7, 1.3 Hz, ArH), 7.53-7.44 (5H, m, benzoateH), 7.36 (2H, t, J 7.6 Hz, ArH), 7.26 (2H, t, J 7.7 Hz, ArH), 4.72 (4H, s, CH_2-CH_2); \delta_C (100 MHz; CDCl_3) 166.5 (C=O), 140.5, 133.1 (ArCH), 129.7 (ArCH), 129.6, 128.3 (ArCH), 125.8 (ArCH), 123.1, 120.5 (ArCH), 119.3 (ArCH), 108.7 (ArCH), 62.7 (OCH_2), 41.8 (NCH_2).

Benzenesulfonic acid (2-carbazol-9-yethyl ester)

![Structure of 184](image)

Triethylamine (1.0 mL, 7.2 mmol) was added to a solution of 1-(2-hydroxyethyl)indole (378 mg, 1.79 mmol) and benzenesulfonyl chloride (0.46 mL, 3.6 mmol) in dichloromethane (5 mL) under nitrogen. The reaction was stirred overnight. The solvent was removed under reduced pressure. Column chromatography (1:1 dichloromethane:light petroleum, then dichloromethane) yielded the title compound (590 mg, 94%) as a white solid, m.p. 71-72 °C, (Found: C, 68.2; H, 4.6; N, 3.8%; C_{20}H_{17}NO_3S requires C, 68.4; H, 4.9; N, 4.0%); (Found: M+, 351.0928. C_{20}H_{17}NO_3S requires M, 351.0929); v\text{max.} (CH_2Cl_2) 1598, 1486, 1460, 1365, 1188, 917 cm^{-1}; \delta_H (250 MHz; CDCl_3) 8.02 (2H, d, J 7.8 Hz, ArH), 7.45-7.39 (4H, m, ArH), 7.36-7.31 (2H, m, ArH), 7.27-7.20 (3H, m, ArH), 7.17-7.11 (2H, m, ArH), 4.56 (2H, t, J 5.6 Hz, CH_2-CH_2), 4.43 (2H, t, J 5.6 Hz, CH_2-CH_2); \delta_C (100 MHz; CDCl_3) 140.4, 135.4, 133.8 (ArCH), 129.2 (ArCH), 127.6 (ArCH), 126.3 (ArCH), 123.5, 120.7 (ArCH), 119.9 (ArCH), 108.8 (ArCH), 67.8 (OCH_2), 42.2 (NCH_2); m/z (El) 351 (M+, 17%), 180 (72), 130 (13), 91 (100).
α,α′Dibromo-p-xylene (245 mg, 0.93 mmol) was added to a solution of potassium carbonate (2.31 g, 16.7 mmol) and 5-hydroxyindole (247 mg, 1.86 mmol) in acetone (10 mL). The mixture was refluxed for 16 h. The mixture was filtered and the solid washed with acetone. The solvent was removed under reduced pressure. Column chromatography (dichloromethane) gave the title compound (196 mg, 29%) as a white solid, m.p. 220-222 °C, (Found: M+, 368.1527. C_{24}H_{20}N_{2}O_{2} requires M, 368.1525); ν_{max.} (CHCl_3) 3686, 2927, 1455, 1151 cm^{-1}; δ_H (250 MHz; d_6DMSO) 10.91 (2H, br-s, NH), 7.48 (4H, s, xylylH), 7.31-7.28 (4H, m, ArH), 7.13 (2H, d, J 2.1 Hz, Ar-2H), 6.82 (2H, dd, J 8.8, 2.3 Hz, Ar-6H), 6.33 (2H, d, J 1.9 Hz, Ar-3H), 5.10 (4H, s, OCH_2); δ_C (62.9 MHz; d_6DMSO) 157.4, 142.3, 136.3, 133.1, 132.7 (xylylCH), 131.0 (ArCH), 117.1 (ArCH), 116.9 (ArCH), 108.5 (ArCH), 106.0 (ArCH), 74.7 (OCH_2); m/z (El) 368 (M+, 20%), 236 (34), 155 (37), 132 (100), 104 (55).

4-(Carbazol-9-ylmethyl)benzyl bromide 188

A solution of carbazole (0.50 g, 3.0 mmol) and DMF (0.46 mL, 6.0 mmol) in THF (10 mL) was added to sodium hydride (0.18 g, 7.5 mmol) under nitrogen. The reaction was stirred for 0.25 h after which time α,α′dibromo-p-xylene (1.06 g, 4.0 mmol) was added. The reaction was heated to 50 °C for 3 h. The solvent was removed under reduced pressure. Column chromatography (3:10 dichloromethane:light petroleum) yielded the title compound (397 mg, 38%) as a
white solid, m.p. 135-136 °C, (Found: M+, 349.0467. C20H16NBr requires M, 349.0466); δH (250 MHz; CDCl3) 8.15 (2H, d, J 7.7 Hz, ArH), 7.48-7.42 (2H, m, ArH), 7.37-7.25 (6H, m, ArH), 7.12 (2H, d, J 8.0 Hz, ArH), 5.52 (2H, s, NCH2), 4.44 (2H, s, CH2Br); δC (62.9 MHz; CDCl3) 140.6, 137.6, 137.1, 129.5 (ArCH), 126.9 (ArCH), 126.0 (ArCH), 123.1, 120.5 (ArCH), 119.4 (ArCH), 108.9 (ArCH), 46.3 (NCH2), 33.1 (CH2Br); m/z (EI) 351 (M(81Br)+, 100%), 349 (M(79Br)+, 99), 270 (41), 183 (39), 166 (63), 104 (84).

1,4-Bis[1,4-(carbazol-9-ylmethyl)(5-hydroxymethylindolyl)benzene]benzene 189

![Chemical structure](attachment:189.png)

1,4-Di(O-5-hydroxymethyl-1H-indolyl)benzene (120 mg, 0.33 mmol) was added to a suspension of potassium hydroxide (146 mg, 2.61 mmol) in DMSO (5 mL) under nitrogen. After 1 h 4-(carbazol-9-ylmethyl)benzyl bromide (240 mg, 0.69 mmol) was added. The reaction was stirred overnight. Water (10 mL) was added and the resulting precipitate was filtered off. Purification by column chromatography (3:1 dichloromethane:light petroleum) yielded the title compound (254 mg, 86%) as a white solid, m.p. 107-108 °C, (Found: MH+, 907.4024 C64H50N4O2 requires MH, 907.4012); δH (250 MHz; CDCl3) 8.12 (4H, d, J 7.6 Hz, carbazoleH), 7.47 (4H, s, OCH2C6H4), 7.40 (4H, d, J 7.9 Hz, ArH), 7.33 (4H, d, J 8.0 Hz, ArH), 7.27-7.22 (6H, m, ArH), 7.16 (2H, d, J 2.3 Hz, indoleH), 7.08 (2H, d, J 3.4 Hz, indoleH), 7.06-7.05 (4H, m, ArH), 6.97 (4H, m, ArH), 6.88 (2H, dd, 8.8, 2.3 Hz, indoleH), 6.43 (2H, d, J 3.0 Hz, indole-3H), 5.47 (4H, OCH2), 5.21 (4H, s, NCH2), 5.09 (4H, s, NCH2); δC (62.9 MHz; CDCl3) 153.4, 140.6, 137.3, 137.0, 136.7, 131.8, 129.1, 128.8 (ArCH), 127.7 (ArCH), 127.2 (ArCH), 126.9 (ArCH), 125.9 (ArCH), 123.1, 120.5 (ArCH), 119.3 (ArCH), 112.8 (ArCH), 110.4
(ArCH), 108.9 (ArCH), 104.3 (ArCH), 101.4 (ArCH), 70.7 (OCH₂), 49.9 (NCH₂), 46.2 (NCH₂); m/z (FAB) 907 (MH⁺, 94%), 505 (48), 401 (51), 270 (100), 166 (61).
References
References

42. Hoegl, H.; Sus, O.; Neugebauer, W. German Patent 1 068 115 to Kalle A/G 1957.


Appendix

Selected X-Ray Crystallography Data
### Crystal Data for 132

<table>
<thead>
<tr>
<th>Property</th>
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<td>(\beta)</td>
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<td>(\gamma)</td>
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### Crystal Data for 104

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<td>b</td>
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<td>c</td>
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<td>Crystal Data for 109</td>
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### Crystal Data for 164

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### Crystal Data for 171

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### Crystal Data for 177

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