The synthesis of novel indolequinones

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Abstract

Mitomycin C (MMC), obtained from *Streptomyces caespitosus*, a clinically useful antitumour antibiotic, is the archetypical quinone bioreductive alkylating agent. The reductive activation mechanism of MMC, involves quinone reduction sequentially activating electrophilic sites in the drug molecule (C-1 and C-10 for MMC). This research project was designed to investigate the role of the C-10 in alkylation processes by preparing compounds in which the electrophilicity at C-1 is much reduced by substituting a cyclopropane for the aziridine ring. The resulting pyrrolo[1,2-α]indole, cyclopropamitosenes, could on reductive activation, by either 1- or 2-electron processes, followed by elimination of the carbamate, generate a powerful electrophile capable of alkylating DNA (or other nucleophiles) at C-10.

A range of compounds was prepared utilising the azidocinnamate decomposition route to substituted indoles and an intramolecular [3 + 2] cycloaddition strategy was employed to synthesise the pyrrolo[1,2-α]indole nucleus.

The rapid ring opening of cyclopropylcarbinyl radicals is briefly outlined. The reduction-initiated ring opening of the cyclopropane ring is investigated, thereby establishing its relevance to the potent bioreductive anticancer action of the cyclopropamitosenes, novel analogues of MMC.

The design and synthesis of fused [1,2-α]indoles without the cyclopropane ring, is examined for comparative purposes. The key step in the synthesis is the formation of the [1,2-α]indole nucleus via a radical cyclisation.

Biological data were recorded for the cyclopropamitosenes and correlated with their structures.
Acknowledgements

Initially, my sincere thanks go to my supervisor, Professor Christopher J. Moody, for all his advice and encouragement throughout the course of this work.

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To my parents and family, Viv and Mick without their love and continual encouragement along the way, I would not be in the position I am today. Finally, I am eternally grateful to Paul. For his love, encouragement and support I dedicate this work.
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<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>FAB</td>
<td>Fast Atom Bombardment</td>
</tr>
<tr>
<td>ESR</td>
<td>Electron Spin Resonance</td>
</tr>
<tr>
<td>GC</td>
<td>Gas Chromatography</td>
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<tr>
<td>IR</td>
<td>Infra-red</td>
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<tr>
<td>MMA</td>
<td>Mitomycin A</td>
</tr>
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<td>MMC</td>
<td>Mitomycin C</td>
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<tr>
<td>m.p.</td>
<td>Melting Point</td>
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<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
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<tr>
<td>py</td>
<td>pyridine</td>
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<tr>
<td>r.t.</td>
<td>room temperature</td>
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<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
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<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
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<tr>
<td>Ts</td>
<td>4-Toluenesulfonyl</td>
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Chapter One

Mitomycins: Chemical and Biological Perspectives
Mitomycins: Chemical and Biological Perspectives

1. Introduction

The Mitomycins, exemplified by Mitomycin C (MMC) 1, are among the most potent antitumour agents in clinical chemotherapy. The first mitomycins A and B were isolated from *Streptomyces caespitosus* by Hata in 1956, followed by the isolation of MMC by Wakaki in 1958.1,2

Over the last thirty years, developments in isolation and structural elucidation techniques, coupled with continued research into the mitomycins has led to the discovery of a large family of closely related structures, most of which possess some antitumour or antibacterial activity.3,4 These fall broadly into three main categories based on similarities in chemical structure. They are designated the A, B and G types after the first member of each type to be isolated, as illustrated below.5
All members of the mitomycins in groups A, B and G are characterised by the azirino[2',3':3,4]pyrrolo[1,2-a]indole ring system. Mitomycins in groups A and B possess three carcinostatic functional groups namely (i) the aziridine ring (ii) the carbamate and (iii) the quinone moiety on the same pyrrolo[1,2-a]indole nucleus. There is some confusion about the nomenclature and numbering of the mitomycin structures. In the initial structure elucidation of the mitomycins, the name mitosane was proposed for structures of types A and B, the numbering system as illustrated in Figure 1. However, Chemical Abstracts uses the systematic numbering for azirino[2',3':3,4]pyrrolo[1,2-a]indole, where the aziridine nitrogen is the starting point. The trivial name for mitomycin C is 7-amino-9a-methoxymitosane, but it is known in Chemical Abstracts as 6-amino-1,1a,2,8,8a,8b-hexahydro-8-(hydroxymethyl)-8a-methoxy-5-methyl-azirino[2',3',3,4]pyrrolo[1,2-a]indole-4,7-dione carbamate.

*Figure 1 Mitomycin C numbering. Bottom left, Mitosane: bottom right, Chemical Abstracts*
1.2 Mode of Action of Mitomycin C

Mitomycin C 1 is the archetypical quinone bioreductive alkylating agent, whereby reductive activation is necessary before covalent binding to DNA (alkylation). It is only recently that the details of this activation process and the formation of a powerful electrophile that can alkylate DNA, have begun to emerge. Therefore, the understanding of the reductive activation mechanism of MMC and related mitosenes, such as aziridinomitosenes 2 and the indolequinone EO9 4, in which the quinone reduction sequentially activates electrophilic sites in the drug molecule (C-1 and C-10 for MMC), has increased markedly in recent years due to the efforts of several research groups.6-8

\[
\begin{align*}
\text{Z = NR} & \quad \text{aziridinomitosene 2} \\
\text{Z = CR}_2 & \quad \text{cyclopropamitosene 3}
\end{align*}
\]

In 1964 Iyer and Szybalski achieved the first covalent binding to DNA with MMC in vitro.9 They perceived that mitomycins and porfiromycin behave as bifunctional alkylating agents upon chemical reduction with sodium dithionite, sodium borohydride, catalytic hydrogenation utilising 5% palladium on carbon, or enzymatic reduction using the cell lysate Sarcina lutea. A high content of guanine and cytosine favoured this cross-linking reaction. Iyer and co-workers discovered that in their natural oxidised form MMC and related compounds exhibit hardly any alkylating function when reacted with thiosulfate at acid or neutral pH or with γ-(4-nitrobenzyl)pyridine, although they all contain the aziridine ring. The authors related this lack of reactivity to the partial withdrawal of electrons from the nitrogen into the quinone ring.

From these observations, it was concluded that the C-1 aziridine and the C-10 carbamate groups were two masked alkylating functions which became 'allylic' under reductive activation conditions, affording the hydroquinone 5, as shown in Scheme 1. Consequent spontaneous elimination of the tertiary 9a-methoxy or hydroxyl group probably caused by the regaining of electrons by the nitrogen coupled with the high driving force for the formation of the aromatic indole system led to the subsequent bond breakage of the
aziridine ring, to afford the intermediate 7. This intermediate can then react further to give the mono-DNA adduct 8 or cross-linked DNA 9.

It took many years to provide the experimental evidence to confirm this postulated mechanism. Moore amended this hypothesis by speculating that both displacements were \( \text{SN}_1 \) types taking place sequentially.\(^{10}\)

**Scheme 1 Iyer and Szybalski mechanism for the mode of action of MMC in vitro**

Iyer and Szybalski made the assumption that under reductive activation conditions the reactive species was the hydroquinone, but recently the hypothesis is that a semiquinone radical anion is the reactive species.
In 1974 Tomasz et al. provided experimental evidence, supporting the theory that the initial binding to DNA is via a semiquinone radical anion $^{10}$. In earlier efforts to prepare extensively substituted DNA-mitomycin complexes Tomasz and also Iyer-Szybalski only achieved incorporation of 1 unit of MMC per 150 nucleotides with native DNA and 50 nucleotides with denatured DNA. Tomasz hypothesized the inability to produce the substituted DNA-MMC complexes may be due to an imperfection in the activation mechanism originally developed by Iyer and Szybalski (1964).$^9$ Iyer et al. previously noted that after the addition of the reducing agent MMC lost its ability to cross-link, thus indicating that not the fully reduced drug, but the semiquinone radical anion form, is the active species.

Tomasz and co-workers tested this theory by adding the required (stoichiometric) amount of sodium dithionite in five portions at five minute intervals to a solution of polynucleotide and MMC in a sodium phosphate buffer (pH 7.5) under anaerobic conditions. This allowed temporary build up of the semiquinone radical anion before the reduction was completed. Using this technique, resulted in approximately 5 and 2-3 binding ratios in native and denatured DNA respectively, which was a vast enhancement. During the course of the reaction, nonreduced MMC was kept in excess maximising the concentration of the semiquinone at the expense of the hydroquinone. This is due to the disproportionation equilibrium being reversed by excess quinone and because the excess quinone competes effectively for the available reducing agent with the semiquinone. Although Tomasz and co-workers provided experimental evidence suggesting a semiquinone radical anion, the participation of the hydroquinone and the existence of oxygen radicals cannot be ruled out in the reductive activation of MMC.

In 1987 Tomasz and Nakanishi isolated and characterised a covalent cross-link adduct between MMC and DNA providing experimental evidence that MMC was a bisalkylating agent.$^{12}$ The cross-linked adduct was achieved by exposing MMC to
Micrococcus luteus DNA in neutral buffer at room temperature under reductive conditions (sodium dithionite), the resulting complex was digested by a mixture of deoxyribonuclease I, snake venom diesterase and alkaline phosphatase. The digest was analysed by HPLC which allowed them to fully characterise both a mono C-1 11 and bis C-1 and C-10 adduct 13. Isolated was the decarbamoyl adduct 12 which resulted from nucleophilic attack of water at the iminium intermediate, linked through C-1. All three are linked through the N-2 position of 2'-deoxyguanosine.13-15

During their experimental studies into the isolation and structure of a covalent cross-link adduct between MMC and DNA, Tomasz et al. discovered that the reducing conditions influence how MMC reacts with DNA. When the authors activated MMC by catalytic hydrogenation using hydrogen/platinum oxide conditions, they obtained the C-1 mono adduct 11 as the major component and the minor components being the 10-decarbamoyl adduct 12, and a bifunctional adduct 13. Alternatively, when sodium dithionite was used to activate MMC, no mono adduct was isolated, instead the predominant adducts were 12 and 13. More surprisingly, when poly (dG-dC) was treated with MMC
activated with sodium dithionite the bifunctional adduct 13 was the sole product of alkylation.

In an attempt to rationalise these observations in the binding of MMC to DNA the authors suggest that the activated semiquinone radical anion 21 can react further by two pathways. The first pathway results in quenching of 21 via electron transfer to unreacted MMC resulting in a C-1 cross-link/quinone. This reaction is thermodynamically favourable due to difference in reduction potentials between mitosenes and mitosanes (MMC). Therefore, C-1 cross-link/quinone is the favourable pathway. However in the absence of MMC activated mitosene, 21 undergoes a retro Michael-type elimination of carbamate to produce an iminium species, which when attacked by the appropriate nucleophile forms a C1/C10 reduced cross-link. Therefore, due to the rapid kinetics of MMC reduction by sodium dithionite, the second pathway, is presumably operative in alkylation reactions. Thus, efficient bifunctional DNA alkylation in sodium dithionite occurs because the MMC-reducing reaction in this case is much faster than in hydrogen/platinum oxide.

Tomasz et al. also predicted that O₂ inhibits the formation of the bis-adduct due to its activation of the active intermediate 10,12 This may be attributed to the greater toxicity of MMC under hypoxic conditions for example, to cells in solid tumours. In the presence of oxygen, the active form of MMC may be reoxidised to the quinone under concomitant formation of superoxide anion radicals (O₂⁻).16 This process is generally known as redox cycling. The O₂⁻ radicals can dismutate either spontaneously or enzymatically to form hydrogen peroxide. In the presence of ferrous ions (Fe²⁺), hydrogen peroxide can be converted into hydroxyl radicals. These hydroxyl radicals are capable of damaging DNA, proteins and cell membranes. However, in the absence of oxygen, reoxidation of activated MMC occurs to a lesser extent and so relatively more of the alkylating agent will bind to DNA. In vivo a significant difference between normal tissue and solid tumours is the presence of hypoxic cells, located in poorly vascularised regions of the tumour.17 The existence of hypoxic cells in solid tumours is an obstacle to effective cancer treatment. Residual malignant cells, protected from radiotherapy by hypoxia, may be capable of proliferating and causing the tumour to recur. Hence, the need to develop bioreductive alkylating agents which exploit the metabolic characteristics unique to cells in hypoxia, causing death of solid tumour cells.

Since the isolation of a covalent cross-link adduct between MMC and DNA, research into the characteristics of the cross-link has increased markedly. In 1993 Hopkins and
co-workers demonstrated that DNA interstrand cross-linking reactions are not limited to MMC, but can be extended to pyrrole-derived bifunctional electrophiles, thus providing evidence for a common target site in DNA. They suggested that MMC, pyrrolizidine alkaloids and simple bifunctional pyrroles share a common bifunctional electrophilic substructure, and subsequently preferentially cross-link a common target in DNA, the exocyclic amino groups of deoxyguanosine residues at the duplex sequence $5'$-d(CG).

In 1987 scientists at Fujisawa Pharmaceutical Co. isolated and characterised a family of antitumour agents similar in structure to the mitomycins. The initial reports described FR900482 14. Other members of this family include FR66972 16, a dihydro derivative of FR900482 isolated from the same fermentation broth and FK973 15, a synthetic triacetate of FR900482.

$$\begin{align*} \text{FR900482} & \quad 14 \\ R = H \quad & \quad \text{FR66972} \quad 16 \\ R = \text{COCH}_3 \quad & \quad \text{FK973} \quad 15 \end{align*}$$

In 1994 Hopkins et al. reported the DNA-DNA interstrand cross-linking reactions of FR900482 and FR66979 despite the lack of the pyrrole functional group as seen in reductively activated MMC. Fukuyama and Goto recognised that reductive scission of the N-O bond of FR900482 would in principle permit formation of the required pyrrole, Scheme 2. A related mechanism in which an attack nucleophile at C-5 cleaves the key N-O bond by an $S_N2$ reaction was proposed by Danishefsky and McClure. Finally, Williams and Rajski have noted that FR900482 at approximately millimolar concentrations possess DNA interstrand cross-linking activity in the absence of added reductant or nucleophiles, and they suggested that the analogy to the mitomycins might not pertain i.e. that a mitosene analog might not be involved in this reaction.
On the basis of these studies and the efforts of several other research groups, a proposed mechanism of action of MMC, \textit{in vivo} has been suggested, illustrated in \textit{Scheme 3}.

The initial step is a single electron reduction of MMC to the semiquinone radical anion 10. The radical anion 10 then readily loses methanol. The activated mitosene semiquinone formed 19 is now rendered electrophilic both at C-1 and C-10 by opening of the aziridine ring which is assisted by the radical anion, and by elimination of the carbamate group assisted by the indole nitrogen, respectively. However, the first alkylation of DNA is thought to occur at C-1. Evidence for this comes from the isolation, after oxidation, of a mono DNA adduct 8. However since it is still a radical it can readily lose the carbamoyleoxy substituent to afford an iminium compound 22 which can cross link to give a bis C-1/C-10 DNA adduct 9. In both the opening of the aziridine ring and elimination of the carbamate group, the products formed are attacked by nucleophiles, apparently by an \textit{S_N}1 type mechanism.
Scheme 3

**Mitomycin semiquinone radical anion 10**

**Aziridinomitosene semiquinone 1'**

**Mono-DNA adduct 8**

**Iminium 22**

**Cross-linked DNA 9**
1.3 Chemical Reduction

It is generally accepted that MMC must be activated by reduction before alkylation can occur. Reductive activation can be brought about in a variety of ways, and as previously discussed, chemical reduction has been performed using sodium borohydride, sodium dithionite and catalytically using hydrogen over platinum oxide. MMC has been activated electrochemically by reduction on a mercury or platinum electrode. Finally, MMC can be activated enzymatically. At least six different enzymes have been shown to be capable of reductively activating MMC, e.g. NADH cytochrome \( b_5 \) reductase, NADPH cytochrome P450 reductase, xanthine dehydrogenase, xanthine oxidase, carbonyl reductase and DT-diaphorase.

Several chemical methods have been used in the reductive activation of MMC. Initial studies were undertaken to gain information on the mutual binding sites between MMC and DNA. Szybalski & Iyer introduced sodium dithionite as an efficient reducing agent for in vitro studies and illustrated that reduced MMC can react in the presence of DNA by monofunctional and bifunctional alkylation. This has emerged as the method of choice for generating high yields of MMC-DNA adducts.

More recently, Kohn et al. examined the use of sodium dithionite for the reductive activation of MMC in the absence of DNA and discovered contrasting results with an increase in the number of MMC products. This was attributed to \( \text{HSO}_3^- \), a byproduct in the reductive activation process and a contaminant in commercial sodium dithionite. Previously Hornemann et al. observed that sodium dithionite reduction of aqueous solutions of MMC at 0°C followed by quenching by oxygen furnished 7-aminomitosane-9a-sulfonate.

\[
\text{Where } X = \text{OCH}_3 \quad 1 \\
X = \text{SO}_3^- \quad 24
\]

Kohn et al. utilised two procedures, noting significant differences between product profiles for the incremental addition of sodium dithionite versus a protocol in which the
equivalent amount of sodium dithionite was added in a single administration. These differences include higher amounts of C-1 electrophilic versus C-1 nucleophilic products in the single administration and an increase in the number of C-1 sulfonato adducts from the nucleophilic product pool of the single technique. The authors observed greater amounts of C-1/C-10 mitosene adducts using the incremental protocol. Finally, on the basis of their studies the authors proposed a mechanism for the sodium dithionite mediated MMC reductive process as shown in Scheme 4.

Scheme 4 illustrates the reaction of the iminium species 25 with HSO₃⁻ in a reversible process to give 26. The authors demonstrated that 24 is more efficiently converted to mitosene products than 1 at near neutral pH values. This can be attributed to the necessity of acid for the removal of the C-9a methoxy group in MMC and the enhanced leaving group ability of the sulfonate group over methoxide ion. Kohn supported this theory by demonstrating the relative reactivity of 5 versus 26 increased over 20-fold in reducing the pH from 7.4 to 5.5.
Scheme 4

1 \[ \xrightarrow{\text{Na}_2\text{S}_2\text{O}_4} \] 5

24 \[ \xleftrightarrow{\text{[Red]} \leftrightarrow \text{[Ox]}} \] 26

6 \[ \xrightarrow{} \] 7

25
1.4 Enzymology

Reductive activation of MMC leads to ring opening of the aziridine ring and elimination of the carbamate group leading to DNA adduct formation. The most important of these DNA adducts is considered to be the DNA interstrand cross-link, which would render the cell unable to replicate, subsequently resulting in cell death.

Various ways of reduction can be used for activation of MMC. As described, MMC can be activated chemically, electrochemically or catalytically.26-29 However, in vivo, MMC is reductively activated by several reducing enzymes, e.g. xanthine dehydrogenase, NADPH cytochrome P450 reductase, NADH cytochrome c reductase, NADH cytochrome b5 reductase, and DT-diaphorase. Also xanthine oxidase, a degradation product of xanthine dehydrogenase, has been used frequently for in vitro activation of bioreductive alkylating drugs.30-35

These reducing enzymes activate MMC via one electron reduction generating the semiquinone radical anion. However, DT-diaphorase reductively activates MMC via a two electron process yielding the hydroquinone.35 In 1984 Pan et al. investigated the reductive activation of MMC catalysed by purified microsomal NADPH-cytochrome P-450 reductase and bovine milk xanthine oxidase.32 MMC was dissolved in DMSO and added to the reaction mixture of 0.1 M phosphate buffer at pH 7.8 (xanthine oxidase) and pH 7.4 (NADPH-cytochrome P-450 reductase). The metabolites were isolated by reversed phase HPLC, as shown in Scheme 5.

The authors suggested that one electron reduction activates MMC shown by the fact that NADPH-cytochrome P-450 reductase and xanthine oxidase favour one electron transfer to suitable receptors. MMC thus receives one electron to form a semiquinone radical anion which then undergoes subsequent conversion to metabolites. Pan et al. obtained EPR (Electron Paramagnetic Resonance) evidence which also confirmed the concept.
Scheme 5

\[
\text{MMC 1} \quad \xrightarrow{\text{Enzyme}} \quad 2,7\text{-diaminomitosene 27} +
\]

\[
\text{R} = \text{OH; cis 28 and trans 2,7-Diamino-1-hydroxymitosene 29}
\]
\[
\text{R} = \text{OP(O)(OH)_2; cis 30 and trans 2,7-Diaminomitosene-1-phosphate 31}
\]

In 1986 Tomasz et al. studied the formation of a covalent complex with calf thymus DNA.\(^{39}\) Reductive activation of MMC, under anaerobic conditions, in the presence of either NADPH-cytochrome P-450 reductase/NADPH, xanthine oxidase/NADH, or via hydrogenation resulted in the formation of a C-1 mono adduct. More recently, Maliepaard et al. presented extensive investigations \textit{in vitro} reductive activation of several mitosenes. These are structurally related to MMC and related mitosenes, such as aziridinomitosenes and EO9. The group reductively activated the mitosenes by purified reducing enzyme xanthine oxidase, which is mainly a one electron reducing enzyme when using NADH as a cofactor.

Maliepaard et al. concluded that xanthine oxidase-mediated activation of mitosenes results in formation of DNA cross-linked species.\(^{40}\) However, the cross-links are dependent on several other factors, \textit{e.g.} the presence of oxygen, pH. Therefore, these results implicate that the relative importance of certain reducing enzymes for antitumour activity of mitosenes and related bioreductive alkylating agents (MMC) should be judged for each compound separately.

In 1958 Emster & Navazio published the first report highlighting the discovery of DT-diaphorase (DTD).\(^{41}\) They described the activity of the two electron reducing enzyme
in the soluble fraction of rat liver homogenates, which catalysed the oxidation of NADH and NADPH with equal facility. Subsequently, Ernster and co-workers partially purified and characterised DTD. However, since the discovery in 1958, the role of DTD in the reductive activation of MMC has been the subject of much controversy. Early studies by Satorelli et al. relied on the use of dicoumarol as a specific inhibitor of DTD. The authors, discovered that dicoumarol inhibits the cytotoxicity of MMC in EMT-6 mouse mammary tumour cells, which suggest a role for DTD in the bioreductive activation of this drug. This data indirectly implicated a role for DTD in the reductive activation of MMC.

Ross et al. implicated DT-diaphorase (DTD) involvement in the reductive activation of MMC under aerobic conditions. They observed an association between elevated DTD levels in human colon carcinoma cells, human fibroblasts and aerobic MMC activity. The data supported a role for DTD in the reductive activation of MMC. However, the authors discovered MMC was not acting as a substrate for purified DTD isolated from either human kidney or rat liver at pH 7.8, but found that reductive activation by either rat hepatic or human kidney DTD was pH-dependent. At pH 7.8, two-electron reduction of MMC by DTD leads to inhibition of the enzyme. 2,7-Diaminomitosene was the major metabolite detected during activation of MMC by DTD at pH values between 5.8-7.0, under either aerobic or anaerobic conditions.

In 1992 Ross et al. studied the reductive activation of MMC in a cell free system, in order to confirm the role of individual reducing enzymes in the process. Glutathione conjugates and also binding to DNA with interstrand cross-linking were observed during DTD-mediated activation as shown in Scheme 6. The major metabolite, 2,7-diaminomitosene was prepared from MMC either enzymatically using DTD at pH 5.8 or via sodium borohydride mediated reduction of MMC. Enzymatic preparation was performed by the addition of 110 μL of purified DTD (3.5 mg/mL) to 5 mg (15 μmol) of MMC and 21 mg (30 μmol) of NADH in 10 mL of 0.1 M potassium phosphate buffer (pH 5.8) under aerobic conditions. The reaction mixture was stirred at 22 °C for 4-6 h. The metabolite 2,7-diaminomitosene was then isolated by HPLC. Preparation of the glutathione conjugate was performed by sodium borohydride (10 mM) mediated reduction of MMC (0.1 mM) under aerobic conditions in potassium phosphate buffer, (100 mM), pH 5.8 (100 mL), containing GSH(1 mM) and the metabolite isolated by HPLC.
Since DTD is a two-electron reductase, reductive activation occurs via the hydroquinone.\textsuperscript{46} However, this does not rule out the participation of radicals following enzymatic reduction even though Ross and co-workers failed to observe any oxygen uptake during DTD-mediated activation of MMC under aerobic conditions. In 1986, Peterson and Fisher illustrated the ambivalent behaviour of the quinone methide of MMC, which at pH 7.8 can function as an electrophile leading to enzyme alkylation and inhibition.\textsuperscript{47} At lower pH values the quinone methide is covalently trapped by a proton leading to 2,7-diaminomitosene formation and maintenance of enzyme integrity. Ross \textit{et al.} discovered increasing amounts of DNA cross-linking were observed during DTD-mediated reductive activation of MMC, as the pH was lowered from 7.8 to 5.8. This mechanism was not consistent with formation of the major metabolite 2,7-diaminomitosene, since low pH values would be expected to favour protonation of the quinone methide to form the non cross-linking 2,7-diaminomitosene. In an attempt to rationalise these observations, the authors, suggest that the precursor to DNA cross-linking could be the protonated leucomitomycin C\textsuperscript{32} or the leucoaziridinomitosene\textsuperscript{33}. The pK\textsubscript{a} of the aziridine ring in leucomitomycin C has been reported to be 5.1, which would allow significant protonation at pH 5.8.

The authors did not observe any differences under aerobic or anaerobic conditions suggesting that the mechanism for reductive activation of MMC should be the same in each case. They supported this theory with the observation that little difference occurs in glutathione conjugate formation. Again, the authors illustrated the pH-dependence in the reductive activation of MMC confirming earlier evidence that metabolism and bioactivation increases as the pH is decreased from pH 7.8 to 5.8. Finally, in 1993 Ross \textit{et al.} demonstrated that the reductive activation process of MMC by DTD results predominantly in monoalkylation of DNA at the guanine N-7 position, within 5'-GG-3' and 5'-GTC-3' sequences.\textsuperscript{48} The preferential sequence for DNA interstrand cross-linking was also determined using singly end-labelled oligonucleotide duplexes, isolating cross-linking of DNA at 5'-CG-3' sequences. Overall, the authors postulate that attempts to modulate pH in combination with MMC treatment could be a viable approach for the therapy of tumours high in DTD activity such as certain human colon and non-small-cell lung cancers.\textsuperscript{49,50}
As described, the use of reductants (enzymatic, chemical and electrochemical) demonstrate that MMC reductive activation leads first to the formation of C-1 adducts. However, the C-1 product profile is dependant on pH. In the absence of DNA, under slightly acidic conditions, the electrophilic product 2,7-diaminomitosene 27 dominated whereas in moderate base, trans-29 and cis-1-hydroxy-2,7-diaminomitosene 28 were generated in high yields.

In 1993 Kohn et al. reported that the proton transfer process of MMC to quinone methide to 2,7-diaminomitosene is the major pathway for reductively activated MMC at all operational pH values (pH 5.5-8.5) in the absence of external nucleophiles. The authors proposed the formation of 28 and 29 were attributed to the hydrolysis of the 7-aminoaziridinomitosene 35.51

1.5 Cyclopropylcarbinyl Radicals

Much research has gone into establishing the molecular basis for the antitumour action of MMC, and although the exact details are still the subject of some uncertainty, the generally accepted overall mechanism is shown in Scheme 3.

Our own work was designed to investigate the role of C-10 in alkylation processes by preparing compounds in which the electrophilicity at C-1 is much reduced by substituting a cyclopropane for the aziridine ring.52,53 This led to the design of the cyclopropamitosene 3 system, which on reductive activation, by 1- or 2-electron processes, followed by elimination of the carbamate, generates a powerful electrophile capable of alkylating suitable nucleophiles, illustrated in Scheme 7.54

Ionic ring opening of the cyclopropane, analogous to that proposed for the natural aziridine is extremely unlikely, although results suggest that the cyclopropane ring is
necessary for the potent biological activity of cyclopropamitosenes. In vitro toxicity experiments under aerobic and anaerobic conditions were performed. Chinese hamster V79 cells were exposed to the cyclopropamitosenes and related mitosenes for 3 hours at 37°C under these conditions. Toxicity was measured using the MTT assay and values of IC₅₀, the concentration required to kill 50% of the cells, were determined. The results illustrate that the cyclopropamitosene 36 is clearly more potent than the dimethyl compound 38, with the cyclopentane 37 having intermediate potency. Under anaerobic conditions 36 is even more potent, by a factor of 25, indicating that oxygen inhibits activity, suggesting that initial 1-electron processes (which are reversed by O₂) are important in the reductive activation of the cyclopropamitosene 36.

The above results, indicating the importance of the cyclopropane ring for antitumour activity and the involvement of 1-electron reductive activation processes, strongly suggest that radical induced ring opening of the cyclopropane maybe responsible for the enhanced biological activity of CPMs. The resulting highly reactive radical would be capable of abstracting hydrogen from DNA, as indicated in Scheme 7, and hence causing damage, e.g. strand cleavage.
The rapid ring opening of cyclopropylcarbinyl radicals is one of the most studied radical processes, and the demonstration that single electron transfer to nitro- or to acyl-cyclopropanes can initiate ring opening is highly relevant.

\[
k = 10^8 \text{s}^{-1}
\]

\[
k = 10^3 \text{s}^{-1}
\]

The rates involved have been accurately determined and used as a radical clock by Ingold and co-workers. ‘Radical clocks’ can be used to ‘time’ competing processes and a variety of unimolecular radical rearrangements have been calibrated for clock purposes. The above cyclopropylcarbinyl radical ring opening is the archetypical fast
radical reaction with a rate constant at 25°C of $1 \times 10^8$ s$^{-1}$. The addition of radical stabilising groups (X) or the incorporation of cyclopropylcarbinyl radical into a more highly strained system results in rate accelerations over that of the parent that can amount to several orders of magnitude.

In 1991 Ingold et al. reported that at 25°C polymethyl-sustituted cyclopropylcarbinyl radicals rearrange with rate constants of up to $4 \times 10^9$ s$^{-1}$, and Newcombe et al. determined the bicyclo[2.1.0]pent-2-yl radical ring opens with a rate constant of $1.5 \times 10^9$ s$^{-1}$ and phenyl-substituted cyclopropylcarbinyl radicals ring open with rates of $3.5 \times 10^{11}$ s$^{-1}$. More recently, Newcombe and Choi established rate constants for ring openings of the \(\text{(trans-2-ethoxycarbonylcyclopropyl)methyl radical}\) and the \(\text{(trans-2-tert-butoxycarbonylcyclopropyl)methyl radical}\) determined by the PTOC-thiol method with PhSeH trapping. At 25°C, these radicals rearrange with rate constants of 7 and $12 \times 10^{10}$ s$^{-1}$, respectively.60

Pereyre et al. in 1979 showed that the methylcyclopropyl carbinyl radical \(\text{trans-49}\) was generated by treating the corresponding chloride or bromide with tributyltin hydride at 25 and 45°C, and the regioselectivity of ring-opening being determined by GC analysis of the alkenes which were formed.61 The intermediate radical \(\text{51}\) was also prepared from the corresponding acyclic bromide \(\text{50, Scheme 8}\). Hence, they established through studies of the equilibria involved that the manifold may be approached from either the homoallylic halide or the cyclopropyl derivative.
The authors demonstrated that the ring-opening was regioselective in favour of the primary alkyl radical \(51\) but that, when the concentration of tin hydride was low, the acyclic radicals \(51\) and \(52\) can equilibrate through the cyclic radical \(49\), prior to hydrogen atom capture and pent-1-ene is formed as the major thermodynamic product. Also the radicals, *cis-* and *trans-* \(49\), \(51\) and \(52\) were generated photolytically at low temperature. Ring opening of \(49\) was irreversible and whereas *cis-* \(49\) gave principally the secondary alkyl radical \(52\), the *trans-* \(49\) compounds gave the primary alkyl radicals \(51\). Pereyre *et al.* extended the reaction to the ring-opening of *cis-* and *trans-*2-methylcyclobutylcarbiny radicals \(55\), *Scheme 9.*
Ring opening was relatively slow and irreversible and both cis- and trans- 55 gave principally the secondary alkyl radical 57.

The rapid ring opening of cyclopropylcarbinyl radicals has been extended to regio- and stereospecific construction of bicyclic systems. In 1992, Motherwell et al. generated a bicyclic system via a tandem free radical cyclopropylcarbinyl rearrangement-cyclisation strategy.62 This reaction was specifically targeted towards regiospecific generation of spirocyclic quaternary carbon centres. Thus, construction of the spiro[4.5]decane 67 was achieved via a suitable bicyc[4.1.0] precursor 63, Scheme 10. 1,2 Addition of 4-lithio-1-trimethylsilylbut-1-yn to the enol ether of dimedone 60 gave, after acidic work up, enone 61 in 80% yield. Subsequent reaction with diisobutylaluminium hydride followed by hydroxyl directed Simmons-Smith cyclopropanation furnished the alcohol 63. Finally, Motherwell achieved quantitative conversion to the thiocarbonylimidazole derivative thus establishing a suitable precursor for carbon centred radical generation. Slow addition of tri-n-butyltin hydride to a refluxing solution of 64 using azobisisobutyronitrile (AIBN) as initiator led to their desired spirocyclic system 67.
Clive et al. utilised a hydroxyl directed Simmons-Smith cyclopropanation to achieve a general method for the attachment of alkyl and also substituted alkyl groups to existing cyclic structures. The route also enables the use of stereo and regiocontrol in the preparation of the alkyl-substituted cycloalkenes, Scheme 11.
Scheme 11

(i), Cyclopropanation, (ii), Mitsunobu inversion, (iii), stannane

The authors also examined the use of the phenylseleno group as a low temperature radical trigger for cyclopropyl ring opening of variously substituted bicyclic derivatives.
Table 1

<table>
<thead>
<tr>
<th>Substrate (0.1-0.2 M)</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="substance1.png" alt="Substrate 75" /></td>
<td>Ph₃SnH, AIBN, benzene, reflux 1h</td>
<td><img src="product1.png" alt="Product 76" /></td>
</tr>
<tr>
<td><img src="substance2.png" alt="Substrate 77" /></td>
<td>Ph₃SnH, sunlamp, Pyrex, toluene, -20 to -10°C, 2.5 h</td>
<td><img src="product2.png" alt="Product 78" /></td>
</tr>
<tr>
<td><img src="substance3.png" alt="Substrate 79" /></td>
<td>nBu₃SnH, sunlamp, Pyrex, hexane, 0°C, 2.5 h</td>
<td><img src="product3.png" alt="Product 80" /></td>
</tr>
<tr>
<td><img src="substance4.png" alt="Substrate 81" /></td>
<td>nBu₃SnH, sunlamp, Pyrex, hexane, 10-30°C, 2.5 h</td>
<td><img src="product4.png" alt="Product 82" /></td>
</tr>
</tbody>
</table>

The addition of arenesulfonyl radicals to vinylcyclopropanes has also been studied by Motherwell and coworkers as a novel route to 1,5-difunctionalised derivatives. The authors used p-toluenesulfonyl iodide in a thermal reaction for the preparation of substituted 1-iodo-5-paratoluene sulfonyl pent-3-enes under mild conditions.
More recently the necessity for processes which lead to concomitant incorporation or retention of useful functionality for further manipulation has increased. The case of radical ring opening reactions of cyclopropyl ketones has been studied by Motherwell and co-workers. The ring opening is mediated by samarium (II) iodide acting as a single electron reducing agent, generating useful metal enones.

The authors recognised the synthetic potential of intermediate 85 which results from stereochemical controlled ring opening of the exocyclic cyclopropyl carbon-carbon bond in a bicyclic system, Scheme 12. The generation of the new carbon-centred radical offers possibilities for either simple hydrogen atom abstraction from solvent, or intramolecular carbon-carbon bond formation by introduction of a pendant chain possessing an unsaturated radicophilic acceptor. The authors report the use of samarium (II) iodide/THF/DMPU as an effective reagent for the formation of intermediate 85.

Scheme 12

As the process involved results in the formation of a samarium enolate, the authors decided to examine whether such a species could be effectively quenched or used further in situ carbon-carbon bond formation. They discovered that direct formation of both enolic derivatives and carbon alkylated products is possible under the reaction conditions, with the overall outcome suggesting that both tri- and tetrasubstituted samarium enolates can be usefully employed.

In 1990 Murphy et al. went on to demonstrate radical-induced carbon-nitrogen bond cleavage of a series of fused aziridines to afford allylic amines or pyrrolidines. They synthesised the aziridine 87 from isophorol 86 using the aziridination procedure used by Atkinson, Scheme 13. Reaction of 87 with thiocarbonyldiimidazole in dichloromethane generated the imidazolide 88 in situ. They then reacted this with tri-n-butyltin hydride in THF and a catalytic amount of AIBN which afforded the allylic amine 89. The authors saw no evidence for carbon-carbon bond cleavage of the aziridine.
More recently, Schwan et al. reported the rapid ring opening of 2-aziridinylmethyl radicals to produce aminyl radicals by carbon-nitrogen cleavage and also, $\alpha$-aminyl carbon radicals via carbon-carbon bond homolysis, Scheme 14. The authors prepared a series of radical precursors, 2-aziridinylmethyl selenides, 2-aziridinylmethyl xanthates and in one case 2-aziridinyl sulfide from 2-carboalkoxy aziridines. They discovered when the nitrogen has a phenyl or benzyl group attached the products are obtained via carbon-nitrogen bond homolysis as in the case of Murphy’s compounds. However, when the functionality at the carbon three position is a phenyl group then that group increases the rate of carbon-carbon homolysis to a level competitive with carbon-nitrogen homolysis.
In Summary: Bioreductive activation provides a novel, exploitable pathway for the design and development of new anticancer agents, targeting the hypoxic fractions of solid tumours. Single electron reduction leads to the formation of C-1 mono and Cl/C10 bis DNA adducts. This process proceeds via a semiquinone radical anion as opposed to the hydroquinone first postulated by Iyer in 1964. However, DT-diaphorase reductively activates bioreductive agents via a two electron process yielding the hydroquinone. Also, in the presence of oxygen, the toxicity of the semiquinone radical anion is limited, by redox cycling and oxygen radical generation which is relatively non toxic. Therefore, cytotoxic events are induced with greater efficiency in the order of semiquinone > hydroquinone > oxygen radicals. Furthermore, various reductases have been implicated in the bioreductive activation creating an enzyme-directed approach to drug development.

Finally, the rapid ring opening of cyclopropylcarbinyl radicals is highly relevant in understanding the single electron transfer which can initiate ring opening of the cyclopropane of cyclopropamitosenes and related mitosenes.
Chapter Two

Cyclopropamitosenes: Novel Bioreductive Anticancer Agents
2.1 Introduction

As described in Chapter 1, MMC is a clinically useful antitumour antibiotic, showing remarkable antitumour activities against several tumour lines, especially solid tumours e.g. stomach and lung cancers. Unfortunately, this drug has strong side effects such as myelosuppression and gastrointestinal toxicities. To control its toxicities, studies for the schedule of dosage were developed and these studies showed MMC to be a practical antitumour agent. Simultaneously, in order to find a more effective yet less toxic derivative, several research groups have been modifying the mitomycins. However, despite the efforts of different research groups only one analogue, EO9, has proved superior to MMC.

Our first objective was to design and synthesise novel MMC analogues, which may enhance the antitumour activity, but decrease cumulative myelosuppression. As described in Chapter 1, our own work in the field was designed to investigate the role of the C-10 in alkylation processes by preparing compounds in which the electrophilicity at C-1 is much reduced by substituting a cyclopropane for the aziridine ring. The resulting cyclopropamitosene could on reductive activation, by either 1- or 2- electron processes, followed by elimination of the carbamate, generate a powerful electrophile capable of alkylation DNA at C-10.

Several approaches have been attempted in the synthesis of the pyrrolo[1,2-α]indole nucleus. In 1965 Weiss et al. published the first synthesis of 7-methoxymitosene. Starting with 2,5-xylenol, this was converted to phenylpyruvic acid via a sequence, nitration para to the phenol, then methylation of the hydroxyl group, followed by condensation with ethyl oxalate and ester hydrolysis to give 95, as shown in Scheme 15.

Reductive cyclisation of 95 then gave indole acid 96 via a Reissert type synthesis. Next, the methyl ester of 96 was subjected to a process involving base catalysed 1,4-addition to methyl acrylate followed by Dieckmann ring closure. Decarboxymethylation followed by Wolff-Kishner reduction afforded the required pyrrolo[1,2-α]indole nucleus 99. Weiss et al. completed the synthesis by formylation, oxidation to the quinone and elaboration of the side chain. The methodology established by Weiss and co-workers is extremely logical and future workers frequently utilised various parts of the synthetic route.
In 1983 Rapoport et al. proposed an alternative route to the pyrrolo[1,2-α]indole nucleus using palladium catalysis, Scheme 16.\textsuperscript{70}

Scheme 16

More recently, Michael et al. optimised reaction conditions whilst synthesising the pyrrolo[1,2-α]indoles by means of an intramolecular Heck reaction on N-(2-bromoaryl) vinylogous urethanes and related enaminones, Scheme 17.\textsuperscript{71} The authors then oxidised the tricyclic product of the Heck reaction to the quinone.

Scheme 17

Edstrom et al. developed a route illustrating the viability of 4-oxotetrahydroindoles 111 as precursors to pyrrolo[1,2-α]indoles.\textsuperscript{72} Oxidation of the simple hexahydro-8-oxo-1\textit{H}-pyrrolo[1,2-α]indoles 111, Scheme 18, by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gives either the phenolic product 113 or C-1 substituted ethers 115. Thus, two mechanistic pathways are possible in the oxidation leading to the carbocationic
intermediates 112 and 114 via hydride abstraction at the C-5 or C-1 positions, respectively.

Scheme 18

The authors treated the C-9 substituted 8-oxopyrrolo[1,2-a]indole system 116 with DDQ affording a good yield of the 8-hydroxy-2,3-dihydro-1H-pyrrolo[1,2-a]indole 117 (82%).

In 1985 Verboom and Reinhoudt reacted aniline 118 with an acid chloride to give a Madelung type indole precursor 119, Scheme 19. Reaction of 119 with potassium t-butoxide in THF then forms the five membered lactam derived from attack at the amide, which spontaneously gives pyrrolo[1,2-a]indole 120 in 85% yield by attack of the alpha cyano anion at the lactam carbonyl. Thus the pyrrolo[1,2-a]indole nucleus is set up in one efficient process.
More recently, Zorgdrager and Gen provided a new route for the construction of the pyrrolo[1,2-a]indole nucleus using 2-(diphenylphosphinyl)pyrrolidine and 2-methoxy-3-methyl-1,4-benzoquinone as starting materials. Oxidative addition of 121 to 122 gave the substituted pyrrolidinylbenzoquinone 123. Subsequent protection of the quinone and addition of an aldehyde to the anion of this compound, followed by treatment with a catalytic amount of para-toluenesulfonic acid in toluene afforded pyrrolidine ketone 125. In situ addition of an equivalent amount of para-toluenesulfonic acid induced conversion of the amino-ketone into the benzylated pyrrolo[1,2-a]indole 126. Debenzylation, by hydrogenolysis using Pd/C followed by air oxidation gave the pyrrolo[1,2-a]indole quinone 127, Scheme 20.
In 1965 Weiss tried novel approaches to introduction of the aziridine function but, all attempts proved to be fruitless. 76 In 1968 Hirata et al. incorporated the aziridine ring by introducing functionality on the C-ring of the pyrrolo[1,2-a]indole nucleus, as shown in Scheme 21. 77 Cyclisation of the iodo-amine 130 or its hydrochloride with sodium methoxide in boiling methanol afforded a crystalline mixture which was treated with methyl chloroformate and triethylamine to give 131.
Frank's group reported another interesting approach for the incorporation of an aziridine by effecting an intermolecular 1,3-dipolar cycloaddition, followed by photolysis,Scheme 22. 78

Alternatively, a route was described by Cory in 1983 which was effectively a one step bicycloannulation forming the pyrrolo[1,2-a]indole 135 incorporating an aziridine ring, in a single operation. 79 The authors formed the sodium salt of the imine in THF at 0°C, and in the presence of methyl 2-bromopropenoate, they obtained the aziridine directly, in 60% yield. It was presumed that 133 formed initially, which then closed by attack of
the carbanion on the imine double bond to give 134. Subsequent ring closure to the aziridine could then be effected via displacement of the bromine, Scheme 23. However the route as published is limited to N-phenyl aziridine.

Scheme 23

Finally, the extensive research described above, has contributed in part, to the total synthesis of a mitomycin, first reported in 1977 by Kishi’s group at Harvard University.80,81 They describe the synthesis of MMF and porfiromycin and also a route to MMC 1 and MMA. In 1987 Fukuyama published a total synthesis of MMA and MMC and so two entirely different synthetic routes to the mitomycins were available, giving access to all of the A-type mitomycin family.82 Also, extensive research has been carried out into the synthesis of MMH and MMK.83 Recently, Danishefsky published the total synthesis of FR900482 14, a novel compound related to the mitomycins by structure and mechanism of action.84

Hence, our own work in the design and synthesis of cyclopropapyrrolo[1,2-a]indoles was based on Padwa’s research into the intramolecular 1,3-dipolar cycloaddition of a diazo compound to an alkene double bond.85 In 1989, Moody and Jones reported the initial studies on the synthesis of a ring system in which the electrophilicity at the C-1 is much reduced, the previously unknown cyclopropapyrrolo[1,2-a]indole.52,53,86 In this Chapter we report the details of the synthesis of cyclopropamitosenes 3, novel bioreductive anticancer agents.
2.2 Synthesis of 9-Hydroxymethyl-7-methoxy-1,2-dihydro-3H-1,2-cyclopropapyrrolo[1,2-a]indole-5,8-dione carbamate.

Where $X = \text{OMe}$, $Y = \text{OCONH}_2$, $n = 1136$

$X = \text{OMe}$, $Y = \text{OCOOPh}$, $n = 2, 137$

The key intermediate is 4-benzyloxy-5-methoxyindole-2-carboxaldehyde 143, prepared from $o$-vanillin 138. The indole ring system was established by azidocinnamate decomposition, developed in the Hofmann Laboratory at Imperial College. $o$-Vanillin 138 was chosen as the ideal starting material due to its commercial availability and relative cheapness. Thus, protection of the phenolic group of $o$-vanillin 138 to prevent the functional hydroxyl group from participating in any side reactions, during the course of the synthetic route, gave 2-benzyloxy-3-methoxybenzaldehyde 139 as a colourless solid (95%). The phenol was protected as the benzyl ether by treatment of $o$-vanillin 138 with benzyl chloride in refluxing ethanol using potassium hydroxide as the base.

![Chemical structure of 2-benzyloxy-3-methoxybenzaldehyde 139](image)

2-Benzyloxy-3-methoxybenzaldehyde 139 was then condensed with methyl azidoacetate using sodium methoxide as the base, to afford the azidocinnamate 140 in 72% yield, thermolysis of which in boiling xylene gave the indole-2-ester 141 (84%), Scheme 24. It was very important that this thermolysis reaction was carried out in dilute solution, as the reaction was considerably less clean when carried out in more concentrated solution. Finally, the indole-2-carboxylate 141 was converted into the desired indole-2-carboxaldehyde 143 by reduction (94%) and reoxidation (66%). The indole-2-carboxylate 141 was reduced to the corresponding alcohol 142 with lithium aluminium hydride in refluxing THF. The indole-2-methanol 142 was oxidised to the indole-2-carboxaldehyde 143 using standard conditions, manganese (IV) oxide, which is specific for allylic and benzylic hydroxyl groups under mild conditions. The alcohol 142 was
stirred with a ten fold excess of manganese (IV) oxide in refluxing dichloromethane for 15 hours furnishing indole-2-carboxaldehyde 143.

Scheme 24

The construction of the tetracyclic cyclopropapyrrolo[1,2-a]indole ring system relies on the previously developed intramolecular cycloaddition reaction. Alkylation of the indole nitrogen 143, followed by reaction of the aldehyde with tosyl hydrazide gave the tosylhydrazone 145, decomposition of which gave the desired tetracycle 146 in 94% yield. The C-10 carbon was introduced by Vilsmeier-Haack formylation and the O-benzyl group was hydrogenolysed over Pd/C in ethyl acetate in the presence of a small amount of dilute sulfuric acid. In the absence of acid, hydrogenolysis was considerably slower, and a certain amount of reductive cleavage of the cyclopropane was observed. Oxidation of the phenol 148 with Fremy's salt gave the corresponding indolequinone 149 (82%). Finally, elaboration of the C-10 side chain by reduction of the formyl group in the quinone aldehyde 149 with sodium borohydride gave the quinone alcohol 150 as an orange solid (74%), treatment of which with phenyl chloroformate afforded the
phenyl carbonate 151 (92%). Finally the phenyl carbonate 151 was treated with ammonia yielding the required carbamate 136 (81%). The desired novel cyclopropamitosene urethane 136 was synthesised in 14 steps from the commercially available o-vanillin 138 in an overall yield of 18.2 %. Despite the extensive synthetic route it was possible to furnish hundreds of milligrams of the final urethane enabling its biological evaluation.
2.3 Synthesis of 10-Hydroxymethyl-8-methoxy-1,2-dihydro-3,H4-H-1,2-cyclopropapyrido[1,2-a]indole-6,8-dione carbamate

Where X = OMe, Y = OCOOPh 137

From the outset of this project one of the main objectives was to design and synthesise novel MMC analogues, in order to find less toxic derivatives but simultaneously enhance the potency. As described, our own work in the area was designed to investigate the role of the C-10. Hence, the synthesis of the parent cyclopropapyrido[1,2-a]indole-5,8-dione carbamate 136. In order to investigate the mechanistic possibilities, and to evaluate the biological activities of cyclopropamitosenes, a range of compounds was required. Therefore, structurally modified analogues of the parent cyclopropapyrido[1,2-a]indole-5,8-dione carbamate 136 were synthesised. Initially, the homologue of 136 was prepared by introducing a carbon into the C-ring of the tetracyclic cyclopropapyrido[1,2-a]indole.

This synthetic route was again started from o-vanillin 138 and followed the route to the key intermediate, 4-benzylxy-5-methoxyindole-2-carboxaldehyde 143, Scheme 24. The key difference between the two synthetic routes was in the alkylation of the indole nitrogen. Treatment of the indole aldehyde 143 with sodium hydride in DMF, and then quenching with 4-bromo-1-butene gave the alkylated indole nitrogen 152 in 35% yield. This yield was considerably worse than the corresponding analogous allyl compound 144, which was obtained in 99%. Thus, addition of a catalytic amount of sodium iodide to the reaction mixture instigated an in situ Finkelstein reaction and in so doing improved the yield to 70%. The N-alkylated indole 152 was converted into the precursor 153 for the key intramolecular cycloaddition reaction by condensation with toluene-p-sulfonyl hydrazide in methanol at 40°C, in 89% yield.
To effect the intramolecular cycloaddition, the tosylhydrazone 153 was converted into its sodium salt which was heated in boiling chlorobenzene to give the cyclopropapyrido[1,2-α]indole homologue 154, in 76% yield.

Thus the tetracyclic ring system of the cyclopropamitosene was established directly from an indole in excellent yield, and it remained only to introduce the side chain at C-9 and oxidise the benzene ring to the quinone level.

In 1980 Padwa et al. predicted that tricyclic cyclopropanes were formed via pyrazolines, derived from a 1,3-dipolar concerted pericyclic addition of a diazoalkane to a C=C bond. The authors examined the thermolysis of the sodium salt of 155, which gave the cycloadduct 158 via the diazoalkene 156, Scheme 26.
The diazo moiety was generated by a variation of the Bamford-Stevens reaction, namely the thermolysis of the sodium salt of tosylhydrazones. In 1989, Moody and Jones applied the intramolecular cycloaddition to the synthesis of cyclopropapyrrolo[1,2-\(a\)]indoles. They isolated the pyrazoline 161 by using tosylhydrazone 160 as the diazo precursor to generate the parent tetracyclic system 162, as shown in Scheme 27.
The tosylhydrazone 160 was converted into its sodium salt by reaction with sodium hydride in THF. The salt was collected by filtration, thermolysis of which in boiling benzene gave a 29% yield of pyrazoline 161. When the temperature was raised, the thermolysis of the pyrazoline was achieved in refluxing xylene and the desired cyclopropapyrrolo[1,2-a]indole was isolated in 89% yield. Moody and Jones investigated different diazo precursors, notably the imine 163 derived from N-amino-2,3-diphenyl aziridine, for the formation of pyrazoline 164. Thus, condensation of allylic indole with amine in dry THF gave 164 in 52% yield, thermolysis of which in boiling benzene gave an increased yield (40%) of pyrazoline 161.

The C-10 carbon was introduced by a variation of the Vilsmeier Haack reaction, which involves formylation of active aromatic rings (phenol and amine) and heterocycles using disubstituted formamides and phosphorus oxychloride. The cyclopropapyrido[1,2-a]indole 154 behaves as a simple indole and so it was possible to formylate successfully at the C-9 position. The tetracycle 154 was stirred with a mixture of DMF and phosphorus oxychloride and hydrolysed with an aqueous solution of sodium acetate to afford the C-9 formylated cyclopropapyrido[1,2-a]indole 165 in 57% yield.
Confirmation of the structure was achieved using X-ray crystallography, as shown in Figure 2.

The O-benzyl group should have been easily removed by hydrogenolysis over palladium-carbon (10%) to give the corresponding phenol 167 but proved to be extremely difficult. Previously, O'Sullivan and Moody found hydrogenolysis of 147 resulted in removal of the O-benzyl group and reductive cleavage of the cyclopropane 166.

Therefore, they modified the procedure by the introduction of a small amount of dilute sulfuric acid to the reaction mixture. Unfortunately this proved unsuccessful in debenzylation of the cyclopropapyrido[1,2-a]indole 165 and at this stage it was proposed that new reaction conditions were required. The O-benzyl group was hydrogenolysed over Pd/C in ethanol under an atmosphere of hydrogen (60 psi) for 12 h to afford the phenol 167 in 69% yield.

The next step involved formation of the quinone moiety via oxidation of the phenol 167. Ortho and para diols are easily oxidised to ortho- and para-quinones, respectively. Literature precedent has shown that either or both groups can be replaced by NH₂ groups to give the same products, though for the preparation of ortho-quinones only OH groups are normally satisfactory.
Figure 2 X-Ray Determination of 165
The reaction has been successfully carried out with other groups *para* to OH or NH$_2$ e.g. halogen, OR, Me, $t$-Bu. Also several oxidising agents have been used such as acid dichromate, silver oxide, lead tetraacetate and atmospheric oxygen, to name a few. However, when there is only one OH or NH$_2$ present, as is the case for cyclopropapyrido[1,2-a]indole 167, a particularly effective reagent is dipotassium nitrosodisulfonate ((KSO$_3$)$_2$N-O') more commonly known as Fremy's salt.

The phenol 167 was oxidised with Fremy's salt in a mixture of water and acetone which was buffered with sodium dihydrogen phosphate to give the indolequinone 168 directly, isolated as an orange solid (89%). The precise mechanism for the oxidation of phenols and aromatic amines to quinones is equivocal. Fremy's salt is a stable free radical, thus the sequence, as shown in Scheme 28, is a likely mechanism, for the formation of the quinone. Initially, (KSO$_3$)$_2$N-O' abstracts a hydrogen atom from the phenol 167 generating a phenoxide radical which leads to radical 169. Radical 169 combines with the Fremy's salt to generate intermediate 170. The nitrogen-oxygen bond of (KSO$_3$)$_2$N-OR is very labile and HN(SO$_3$K)$_2$ is eliminated, generating the desired tetracyclic quinone 168.
During the oxidation of the phenol 167, not only was the desired cyclopropapyrido[1,2-a]indole-6,9-dione 168 formed but also the cyclopropane ring opened unexpectedly giving 172. Previously, compound 171 had not been isolated in the comparative oxidation of the cyclopropapyrrolo[1,2-a]indole 148 to the relevant quinone 149.

Unfortunately, the indolequinone 168 and suspected ring opened product 172 were unable to be separated at this stage of the synthetic route. Therefore, the mixture was reacted further with sodium borohydride in methanol. The quinone aldehyde was initially reduced to the hydroquinone, accompanied by disappearance of the orange colour, which upon reoxidation by blowing air rapidly through the solution gave a red crystalline quinone alcohol. Purification of the resulting residue by column
chromatography (ethyl acetate) isolated the quinone alcohols 173 and 174 in 36 and 30% yields, respectively.

\[ 168/172 \xrightarrow{\text{NaBH}_4, \text{MeOH}} 173 + 174 \]

The structure of 174 was proved by considering the \(^1\text{H}\) NMR, where noticeable differences occur between the spectra of 173 and 174. The spectrum for 174 product shows an intense signal at 1.14 ppm appearing as a doublet. This can be assigned to the methyl protons attached to the C-2 position, generated as a result of cyclopropane ring-opening.

\(^{13}\text{C}\) NMR data illustrate a marked difference in chemical shifts between the two quinone alcohols. The characteristic cyclopropane chemical shifts, 12.47 (C-2), 9.80 (C-1a) and 8.43 (C-1) as seen in the quinone 173 are absent in compound 174. In the quinone alcohol 174 the methyl carbon appears at 21.20 ppm. C-1 and C-2 are now further downfield at 29.97 and 26.30, respectively. All signals were assigned using the DEPT spectra.

Other signals in the \(^1\text{H}\) NMR were assigned via the three dimensional contour plot of a COSY spectrum (CORrelated Spectroscopy). Therefore, the possibility of an alternative reaction product 175 could be eliminated. Initially, the two C-1 protons, as seen in the \(^1\text{H}\) NMR spectrum appear further downfield (2.95 and 2.27 ppm) than the C-2 proton (2.03 ppm). This can be attributed to the deshielding effect of the C-1 protons due to the indole ring. Further evidence appears in the coupling of the C-1 protons e.g. the proton at 2.27 ppm appears as a double doublet. A specific coupling pattern which would not be seen in the alternative product 175.
$^1$H-$^{13}$C correlated spectra confirmed the assigned $^{13}$C signals, thus the NMR data of the unexpected product 174 is fully assigned. Finally, the mass spectra data support the structure of quinone alcohol 174. Compound 174 had a molecular weight of 275 to correspond with the observed mass ion of 275 ($M^+$).
Figure 3 1H NMR Data for Compound 174
Figure 4 Cosy Spectrum for Compound 174
The rationale for the formation of 172 can be explained in the mechanism for the formation of the quinone 168. In this, the key step is the abstraction of the hydrogen atom from the phenol 167 generating an alkoxide radical 176 which can lead to cyclopropane ring opening, as shown in Scheme 29. The radical 178 then abstracts a hydrogen atom from another phenol 167 forming intermediate 179. The intermediate undergoes nucleophilic conjugate addition to form the enolate 180, protonation of which gives 181. Generation of the stable cyclopropapyrido[1,2-α]indole system eventually leads to the formation of the hydroquinone 182, which upon reoxidation regenerates the quinone 172.

As stated, the comparative ring opened pyrrolo[1,2-α]indole-5,8-dione 171 was not isolated. It appears that the isolation of a ring-opened product is dependent on the quality of the Fremy’s salt used in the oxidation. In the oxidation of the cyclopropapyrido[1,2-α]indole 167 to the corresponding quinone aldehyde 168 poor quality Fremy’s salt was used. Therefore, the phenoxide radical 176, as shown in Scheme 29, had the opportunity to form radical 177 before reacting with a second Fremy’s salt, as shown in the previous Scheme 28. As described in Chapter I, rapid ring opening of cyclopropylcarbinyl radicals is one of the most studied radical processes. Thus, the formation of radical 177, illustrated in Scheme 29, would then lead to the rapid ring-opening of the cyclopropane.

Hence the isolation of compound 174 provides some evidence for the feasibility of cyclopropane ring-opening under radical conditions.
Scheme 29

(KSO₃)₂N-Ő

167 → 176

MeO      MeO

178

Ar-O-H

179

MeO      CH₂

177

OH

MeO

180

OH

181

[O]

MeO

172
Transformation of the quinone alcohol 173 into the desired final quinone urethane 183 proved to be fruitless. It was possible however to obtain the phenyl carbonate 137 by treatment of the quinone alcohol 173 with phenyl chloroformate in THF containing a few drops of pyridine and under nitrogen for 2 hours.

\[
\begin{align*}
\text{MeO} & \quad \text{PhOCOCl, py} & \quad \text{MeO} \\
\text{173} & \quad 75\% & \quad \text{137}
\end{align*}
\]

Direct ammoniolysis with ammonia in dichloromethane at -78°C did not afford the desired urethane 183 but recovery of the starting phenyl carbonate 137. Alternative reaction conditions were attempted for the conversion of the phenyl carbonate 137 to the final quinone urethane 183.

\[
\begin{align*}
\text{MeO} & \quad \text{OCO}_{2}\text{Ph} \\
\text{137} & \quad \text{MeO} & \quad \text{OCO}_{2}\text{Ph} \\
\text{183}
\end{align*}
\]

Ammoniolysis of the phenyl carbonate 137 in dichloromethane with either (i) ammonia gas at room temperature, or (ii) 0.88 ammonia solution, again only starting material was recovered. Alternatively the ammoniolysis was carried out in methanol with either (i) ammonia gas at -78°C, or (ii) ammonia gas at room temperature and finally (iii) 0.88 ammonia solution. In a last attempt to get this extremely difficult reaction to give the final urethane 183 the phenyl carbonate 137 in methanol was refluxed with ammonia gas bubbling through the reaction mixture. Unfortunately, this did not afford the desired urethane 183 but resulted in baseline material.

It was likely that the desired final urethane 183 was not isolated due to cyclopropane ring sterically hindering the carbonyl group of the phenyl carbonate 137, thus preventing attack by the ammonia and subsequent substitution.
Chapter Three

Mechanistic Issues: The Role of the Cyclopropane Ring
3.1 Introduction

Continuing the research into the design and synthesis of the cyclopropamitosenes, this chapter addresses the mechanistic issues involved, and in particular the role of the cyclopropane ring. One of the main objectives of the investigation was to study the reduction-initiated ring opening of the cyclopropane ring, thereby establishing its relevance to the potent bioreductive anticancer action of these novel analogues of MMC.

As described in Chapter 1, much research has gone into establishing the molecular basis for the antitumour action of MMC. Our own work led to the design of the cyclopropamitosene system which on reductive activation, by 1- or 2-electron processes, followed by elimination of the carbamate, generates a powerful electrophile capable of alkylation suitable nucleophiles, *Scheme 7*. 
Ionic ring opening of the cyclopropane, analogous to that proposed for the natural aziridine is extremely unlikely, although results suggest that the cyclopropane ring is necessary for the potent biological activity of cyclopropamitosenes. In 1994, Moody et al. published the chemistry, electrochemistry and biological studies of a range of cyclopropamitosenes, pyrrolo[1,2-a]indolequinones and 1,2-dimethylindolequinones.
The authors, displaced the methoxy group in the indolequinones by various nitrogen nucleophiles (ammonia, 2-methoxyethylamine, aziridine, 2-methylaziridine, pyrrolidine) in 22-88% yield, extending the range of compounds.
Table 2 Substitution Reactions of the Methoxyindolequinones

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R</th>
<th>R'</th>
<th>X</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>CH₂OCONH₂</td>
<td>H</td>
<td>NH₂</td>
<td>190</td>
</tr>
<tr>
<td>36</td>
<td>CH₂OCONH₂</td>
<td>H</td>
<td>MeOCH₂CH₂NH</td>
<td>191</td>
</tr>
<tr>
<td>36</td>
<td>CH₂OCONH₂</td>
<td>H</td>
<td>pyrrolidinyl</td>
<td>192</td>
</tr>
<tr>
<td>36</td>
<td>CH₂OCONH₂</td>
<td>H</td>
<td>aziridinyl</td>
<td>193</td>
</tr>
<tr>
<td>184</td>
<td>CH₂OCONH₂</td>
<td>H</td>
<td>2-methylaziridinyl</td>
<td>194</td>
</tr>
<tr>
<td>184</td>
<td>CH₂OCONH₂</td>
<td>Me</td>
<td>pyrrolidinyl</td>
<td>195</td>
</tr>
<tr>
<td>184</td>
<td>CH₂OCONH₂</td>
<td>Me</td>
<td>aziridinyl</td>
<td>196</td>
</tr>
<tr>
<td>186</td>
<td>H</td>
<td>H</td>
<td>aziridinyl</td>
<td>197</td>
</tr>
<tr>
<td>186</td>
<td>H</td>
<td>H</td>
<td>2-methylaziridinyl</td>
<td>198</td>
</tr>
<tr>
<td>37</td>
<td>CH₂OCONH₂</td>
<td></td>
<td>aziridinyl</td>
<td>199</td>
</tr>
<tr>
<td>37</td>
<td>CH₂OCONH₂</td>
<td></td>
<td>2-methylaziridinyl</td>
<td>200</td>
</tr>
<tr>
<td>188</td>
<td>H</td>
<td></td>
<td>aziridinyl</td>
<td>201</td>
</tr>
<tr>
<td>188</td>
<td>H</td>
<td></td>
<td>2-methylaziridinyl</td>
<td>202</td>
</tr>
<tr>
<td>38</td>
<td>CH₂OCONH₂</td>
<td></td>
<td>pyrrolidinyl</td>
<td>203</td>
</tr>
<tr>
<td>38</td>
<td>CH₂OCONH₂</td>
<td></td>
<td>aziridinyl</td>
<td>204</td>
</tr>
<tr>
<td>38</td>
<td>CH₂OCONH₂</td>
<td></td>
<td>2-methylaziridinyl</td>
<td>205</td>
</tr>
<tr>
<td>189</td>
<td>H</td>
<td></td>
<td>pyrrolidinyl</td>
<td>206</td>
</tr>
<tr>
<td>189</td>
<td>H</td>
<td></td>
<td>aziridinyl</td>
<td>207</td>
</tr>
<tr>
<td>189</td>
<td>H</td>
<td></td>
<td>2-methylaziridinyl</td>
<td>208</td>
</tr>
</tbody>
</table>

The resulting amino substituted quinones, together with their methoxy precursors, were studied by cyclic voltammetry to determine their reduction potentials, which, in DMF solution, lie in the range -1.355 to -1.597V (vs. ferrocene). Also, in vitro toxicity experiments under aerobic and anaerobic conditions were performed. Reductive activation of the novel cyclopropamitosenes and related indolequinones can occur via a 1-electron reduction, by enzymes such as cytochrome P450 reductase. This involves a semiquinone radical anion, in a process that is potentially reversible by oxygen. Also, the cyclopropamitosène can undergo a 2-electron reduction to give a hydroquinone, generally carried out by the obligate 2-electron reductase DT-diaphorase, in a process that is oxygen independent. The subsequent level of the alkylating species is then governed by any disproportionation reaction between the semi- and hydroquinones.

Moody and co-workers investigated the effect of oxygen on the cytotoxicity of the cyclopropamitosenes and related indolequinones by performing experiments under air and under nitrogen. Chinese hamster V79 cells were exposed to the
cyclopropamitosenes for 3 h at 37°C under these conditions. Toxicity was measured using the MTT assay and the values for IC50, the concentration required to kill 50% of the cells, were determined, as illustrated in Tables 2, 3 and 4.

Table 3 Biological Activity of Cyclopropamitosenes

<table>
<thead>
<tr>
<th>product</th>
<th>IC50 (air) (μmol dm⁻³)</th>
<th>IC50 (N2) (μmol dm⁻³)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>193</td>
<td>0.003</td>
<td>0.003</td>
<td>1</td>
</tr>
<tr>
<td>194</td>
<td>1.2</td>
<td>0.06</td>
<td>20</td>
</tr>
<tr>
<td>36</td>
<td>4.8</td>
<td>0.14</td>
<td>34</td>
</tr>
<tr>
<td>184</td>
<td>3.0</td>
<td>0.12</td>
<td>25</td>
</tr>
<tr>
<td>MMC 1</td>
<td>0.8</td>
<td>0.4</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 4 Biological Activity of Pyrrolo[1,2-a]indolequinones

<table>
<thead>
<tr>
<th>product</th>
<th>IC50 (air) (μmol dm⁻³)</th>
<th>IC50 (N2) (μmol dm⁻³)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>199</td>
<td>0.07</td>
<td>0.005</td>
<td>14</td>
</tr>
<tr>
<td>200</td>
<td>0.2</td>
<td>0.07</td>
<td>3.5</td>
</tr>
<tr>
<td>37</td>
<td>6</td>
<td>0.1</td>
<td>60</td>
</tr>
<tr>
<td>187</td>
<td>11</td>
<td>0.45</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 5 Biological Activity of 1,2-Dimethylindolequinones

<table>
<thead>
<tr>
<th>product</th>
<th>IC50 (air) (μmol dm⁻³)</th>
<th>IC50 (N2) (μmol dm⁻³)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>204</td>
<td>0.5</td>
<td>0.025</td>
<td>20</td>
</tr>
<tr>
<td>205</td>
<td>4</td>
<td>0.7</td>
<td>6</td>
</tr>
<tr>
<td>38</td>
<td>25</td>
<td>0.3</td>
<td>83</td>
</tr>
<tr>
<td>203</td>
<td>1000</td>
<td>1000</td>
<td>1</td>
</tr>
</tbody>
</table>

The activities of the indolequinones span a large range, with the 7-aziridinylcyclopropamitosene 193 being the most active. However, in terms of structure/activity relationships, the main interest was the effect of the cyclopropane ring. To date there is no evidence to suggest that the compound is trifunctional, with involvement of the cyclopropane, but the cyclopropane ring does appear to have some effect, since, in general, the cyclopropamitosenes are clearly more potent than the simple 1,2-dimethylindolequinones, with the pyrrolo[1,2-a]indolequinones having intermediate potency. Under anaerobic conditions the 7-(2-methylaziridinyl) compound 194 and 7-methoxycyclopropamitosenes 36 and 184 all become more toxic than MMC.
1, indicating that oxygen inhibits activity, suggesting that initial 1-electron processes (which are reversed by oxygen) are important in reductive activation of the cyclopropamitosenes.

The above results, indicating the importance of the cyclopropane ring for anticancer activity and the involvement of 1-electron reductive activation process, strongly suggests that radical induced ring opening of the cyclopropane is responsible for the enhanced biological activity of the cyclopropamitosenes. The resulting highly reactive radical would be capable of abstracting hydrogen from DNA.

As discussed in Chapter I, the rapid ring opening of cyclopropylcarbinyl radicals is one of the most studied radical processes, and the demonstration that single electron transfer to nitro- or acyl- cyclopropanes can initiate ring opening is highly relevant. Thus, just as Motherwell et al. demonstrated the reduction of the ketone 83 results in cyclopropane ring opening and the formation of the radical 85, reduction of the cyclopropamitosene 209 can lead, via the semiquinone 210, to radical 211. Therefore, the relatively stabilised semiquinone radical is irreversibly transformed into a highly reactive CH₂ centred radical, which readily abstracts hydrogen.

As described in Chapter 2, the cyclopropane ring of the cyclopropapyrido[1,2-α]indole homologue 137 ring opened via a radical mechanism during oxidation, using Fremy's salt, of the phenol 167 to the corresponding indolequinone 168. Thus providing circumstantial evidence for the radical induced ring opening of the cyclopropane.

Hence, in order to address the mechanistic issues the effect of substituents on the cyclopropane ring was studied by the preparation of cyclopropamitosenes, in which
such substituents can stabilise the developing radical centre. In this chapter we report the details of the synthesis of a cyclopropapyrrolo[1,2-α]indole, where the cyclopropane substituent is a phenyl.
3.2 Synthesis of 9-Hydroxymethyl-7-methoxy-1,2-dihydro-1a-phenyl-3H-1,2-cyclopropapyrrolo[1,2-a]indole-5,8-dione carbamate

Cyclopropamitosene

Where X = MeO, Y = OCONH₂

The synthesis of cyclopropamitosene was based on the previously described route. The key intermediate is 4-benzyloxy-5-methoxyindole-2-carboxaldehyde 143, prepared from the commercially available o-vanillin 138. Thus, treatment of 4-benzyloxy-5-methoxyindole-2-carboxaldehyde 143 with sodium hydride in DMF, and then quenching with cinnamyl bromide gave the alkylated indole nitrogen 213 as a yellow solid, in 66% yield. The N-alkylated indole 213 was converted into the tosylhydrazone 214 by condensation with toluene-p-sulfonyl hydrazide in methanol at 40°C, in 61% yield. Again, the previously developed intramolecular cycloaddition reaction was applied. Formation of the sodium salt by thermolysis in chlorobenzene furnished the tetracyclic cyclopropapyrrolo[1,2-a]indole ring system 215, in 84% yield. The initial intramolecular cycloaddition led to the formation of the exo adduct with no evidence of the alternative endo mode of addition, Scheme 30.
The cyclopropapyrrolo[1,2-a]indole 215 was then formylated via the Vilsmeier-Haack reaction to give the tetracycle 216 as a pale yellow solid, in 59% yield. Confirmation of the structure of 216 was achieved using X-ray crystallography, as shown in Figure 5. The $^1$H NMR spectrum of compound 216 provides evidence for the formation of the exo adduct as the major diastereomer, as shown in Figure 6. However, repeating the intramolecular cycloaddition, in order to provide sufficient material for subsequent synthetic steps, the formation of the cyclopropapyrido[1,2-a]indole tetracyclic system 217 gave a ca. 1.4:1 mixture of exo:endo adducts calculated from the $^1$H NMR data. Formylation of the mixture of diastereomers using POCl$_3$ and DMF gave the cyclopropapyrrolo[1,2-a]indole-9-carboxaldehyde 218 in 59% yield, Scheme 31. The O-benzyl group was hydrogenolysed over Pd/C in ethanol under an atmosphere of hydrogen (60 psi) for 12 hours, to afford the phenol 219 as a colourless solid 76% yield.
Figure 5 X-Ray Determination of Compound 216
Scheme 31

Oxidation of the phenol 219 with Fremy's salt gave the corresponding indolequinone 220 (43%), the side chain of which was elaborated in the usual way to give the desired cyclopropapyrrolo[1,2-a]indole 223, as shown in Scheme 32.

Scheme 32

Figure 7 clearly illustrates the exo:endo adducts of the final urethane in the $^1$H NMR spectrum of the desired cyclopropapyrrolo[1,2-a]indole carbamate 223. In particular the signals representing the 6-H and MeO are doubled up, thus indicating two
diastereomers. Also, the two protons of the C-3 for the endo adduct have different chemical shift values of 4.32 and 3.89 ppm respectively. This can be attributed to the close proximity of the phenyl group to the C-3 protons in the endo adduct.
The $O$-benzyl group of diastereomer 216 was hydrogenolyzed over Pd/C in ethanol under an atmosphere of hydrogen (60 psi) for 12 hours, to afford the phenol 224, in 87% yield.

Oxidation of the phenol 224 with Fremy's salt gave the corresponding indolequinone 225, as orange crystals, in 94% yield. As previously described, oxidation of the phenol 167 to the quinone 168 lead to the formation of the cyclopropane ring opened product 172. However, the pyrrolo[1,2-$a$]indole 227 was not isolated in the oxidation of the cyclopropapyrrolo[1,2-$a$]indole to the indolequinone 225, *Scheme 33*.
The C-10 side chain was elaborated in the usual way. The quinone aldehyde 225 was reduced to the alcohol 228 with sodium borohydride in methanol, in 78% yield. The alcohol 228 was then transformed to the final urethane 230 by ammonolysis of the phenyl carbonate 229 in DCM at -78°C, to afford 230 a single diastereomer of cyclopropamitosene 212, as an orange crystalline solid, in 89% yield.
Chapter Four

1,2-Fused Indoles *via* Radical Cyclisation
4.1 Introduction

In order to compare the properties of the cyclopropane containing indolequinones, the next logical extension to the work was the preparation of fused \([1,2-a]\)indoles. Initially, it was necessary to synthesise the pyrido\([1,2-a]\)indole, thus providing a comparison to the cyclopropapyrido\([1,2-a]\)indole homologue 137, as described in Chapter 2. Previously, pyrrolo\([1,2-a]\)indoles were prepared from the key intermediate, 4-benzyloxy-5-methoxyindole-2-carboxaldehyde 143 by reaction with vinyltriphenylphosphonium bromide in the presence of sodium hydride. This reagent is known to be useful for the annulation of both pyrrole- and indole-2-carbaldehyde to give pyrrolo-pyrroles and -indoles respectively. Reaction of the sodium salt of the indole-2-carboxaldehyde 143 with the phosphonium salt gave the \(9H\)-pyrrolo\([1,2-a]\)indole 231, as shown in Scheme 34. Prolonged hydrogenation of over Pd/C at 3 atmospheres pressure resulted in \(O\)-debenzylation and reduction of one double bond (followed by isomerisation) to give the pyrrolo\([1,2-a]\)indole 232.

Scheme 34

![Scheme 34](image)

However, in this reaction two other products were isolated, firstly the corresponding \(O\)-benzyl compound 233 and secondly the debenzyalted starting material 234. Therefore, a more direct approach to the formation of pyrrolo\([1,2-a]\)indoles was sought. Also it was necessary to be able to extend the viability of such an approach to the synthesis of 5,6 and 7-membered fused \([1,2-a]\)indoles.
Free radical cyclisations now constitute a major tactic in the synthesis of mono-, bi-, and polycyclic ring systems. Among such reactions, the intramolecular addition of radicals to an aromatic ring, often under oxidative conditions, has considerable synthetic potential, although it has not been widely used with heteroaromatic rings. Muchowski and co-workers devised an efficient method of effecting oxidative radical cyclisation to aromatic systems. The authors successfully cyclised N-(ω-iodoalkyl)indoles via addition of excess hydrogen peroxide to a sonicated solution of iron(II)sulfate heptahydrate in DMSO to afford the pyrrolo[1,2-α]indoles in 14-85% yields.

\[
\text{R} \quad \text{CH}_2(\text{CH}_2)_n\text{CH}_2\text{I} \quad \xrightarrow{\text{H}_2\text{O}_2/\text{FeSO}_4.7\text{H}_2\text{O}} \quad \text{R} \quad \text{(CH}_2)_n
\]

Where \( R = \text{CHO, CO}_2\text{Me, COMe, CN, Me and H} \)

In view of our own work, oxidative radical cyclisation of precursors 235 and 237 where \( R = \text{CHO} \) gave the fused [1,2-α]indoles 236 and 238 in 60 and 45% yields, respectively. In 1990, Murphy et al. reported an intramolecular radical addition to pyridinium salts using tributyltin hydride. The use of tributyltin hydride as an approach to mild, non-oxidative radicals has led to reactions which avoid the aggressive hydrogen-atom abstraction processes involved in the chemistry of oxidative radicals.

The authors, treated the pyridium salt with tributyltin hydride under nitrogen and in the presence of AIBN to afford the bicycle. However, in relation to our own work...
concerning the preparation of fused \([1,2-a] \text{indoles}\), Ziegler \textit{et al.} developed a method for the synthesis of the \(3H\)-pyrrolo\([1,2-a]\)indole nucleus.\(^{99-102}\) The authors, effected an intramolecular radical cyclisation onto the indole 2-position demonstrating that alkyl, vinyl, oxiranyl and aziridinyl radicals cyclise under photochemical or reductive conditions to give mainly 1,2-fused 2,3-dihydroindoles (or their dimers).

Recently, Caddick and co-workers discovered intramolecular free radical addition of alkyl radicals to tosyl substituted indoles provided access to fused \([1,2-a] \text{indoles}\).\(^{103,104}\) Radical \textit{ipso-}substitution of a \(\text{SPh, SOPh or } \text{SO}_2\text{Ar group from the indole 2-position led to the formation of } 5, 6 \text{ and } 7 \text{ membered ring systems. Therefore, in this Chapter we report some new results in the synthesis of } 1,2\text{-fused indoles.}
4.2 Synthesis of 10-Formyl-8-methoxy-1,2,3,4-tetrahydropyrido[1,2-a]indole-6,9-dione.

\[
\text{Mitose} \quad \text{Where } X = \text{MeO}, \ Y = \text{CHO} \quad 241
\]

Our first objective was to establish suitable methodology for the formation of the comparative pyrido[1,2-a]indole 241, as shown above. In view of our own work on the synthesis of 1,2-fused indoles, we were interested in the recent report by Muchowski. Thus, it was planned to form the tricyclic system of the desired mitose via an intramolecular oxidative radical cyclisation.

The synthetic route started from o-vanillin 138 and followed the route to the key intermediate, 4-benzyloxy-5-methoxyindole-2-carboxaldehyde 143, as described in chapter 2. Decarbonylation of the C-2 aldehyde, of 143 by heating with bis(triphenylphosphine)carbonyl rhodium chloride afforded 4-benzyloxy-5-methoxyindole 242 as a brown solid, in 90% yield. Formylation of 242 proceeded without incident to give, 4-benzyloxy-5-methoxyindole-3-carboxaldehyde 243, in 57% yield.
Thus, alkylation of the indole-3-carboxaldehyde 243 with 1-bromo-4-chlorobutane using potassium hydroxide in DMSO gave the chloroalkyindole 244 as a colourless solid, in 84% yield. Mass spectral data supported the 1-(α-chloroalkyl)indole structure. The isotopic chlorine consists of $^{35}\text{Cl}$ and $^{37}\text{Cl}$ in the ratio of approximately 3:1, thus the molecular ion 371 ($M^+$) in the compound 244 gave rise to the characteristic isotope pattern of chlorine, as observed in the mass spectra. Reaction of the chloride 244 with sodium iodide in acetonitrile, afforded the corresponding iodide 245 as a colourless solid, in good yield (72%).
To effect the intramolecular oxidative radical cyclisation, the iodide 245 was cyclised by addition of excess hydrogen peroxide (10 eq) to a sonicated solution of iron(II)sulfate heptahydrate in DMSO to afford the pyrido[1,2-α]indole 246, albeit in poor yield (33%).

\[
\begin{align*}
\text{MeO} & \text{O} \text{Bn} \\
\text{CHO} & \text{MeO} \\
\text{245} & \text{246} \\
\end{align*}
\]

The reaction mechanism proceeds under Fenton conditions in which methyl radicals are generated from DMSO, as shown in Equation 1.

**Equation 1**

\[
\text{MeSOMe} + \text{H}_2\text{O}_2 + \text{Fe(II)} \rightarrow \text{Me}^\cdot + \text{MeSO}_2\text{H} + \text{Fe(III)} + \text{OH}^-
\]

The methyl radical abstracts the iodide from the 1-(ω-iodoalkyl)indole-3-carboxaldehyde 245 on the basis of the favourable equilibrium in Equation 2.

**Equation 2**

\[
\text{Me}^\cdot + \text{RI} \rightleftharpoons \text{R}^\cdot + \text{MeI}
\]

Intramolecular cyclisation proceeds generating radical species 248. Oxidation of 248 leads to the formation of re-aromatised 246, Scheme 35.
Unfortunately, the poor yield of the oxidative radical cyclisation hindered the continued progress of the synthetic route. Therefore, an alternative approach to the cyclisation was necessary. Caddick et al. used tributyltin hydride and azobisisobutyronitrile (AIBN) in their radical ipso-substitutions of a tosyl group from the indole-2-position, to effect the formation of 1,2-fused indoles.\textsuperscript{104} Therefore, regarding our own work the conditions utilised by Caddick were applied to the radical cyclisation of 1-(ω-iodoalkyl)indole-3-carboxaldehyde 245. Treatment of the iodide 245 via slow addition of tributyltin hydride and AIBN in boiling toluene gave the pyrido[1,2-a]indole 246 as a colourless oil, increasing the yield to 73%.

Oxidations during reductive cyclisations using tributyltin hydride are becoming increasingly common, and although disproportionation, or oxidation of an intermediate radical by AIBN as proposed by Curran, cannot be ruled out, the preferred mechanism for the radical cyclisation is one proposed by Bowman involving a ‘pseudo’ SRN 1 mechanism, as shown in Scheme 36.\textsuperscript{105,106,107}
Loss of H⁺ from the intermediate radical 248 yields a highly delocalised radical anion 250. Radical anion 250 then undergoes a single electron transfer with the (iodoalkyl)indole 251 to generate, after loss of iodide, the initial radical 247, thereby continuing the chain reaction i.e. single electron transfer between the starting material 245 and radical anion 250 to yield the product 246 and the new intermediate radical 251.
Following the cyclisation the O-benzyl group was hydrogenolysed over Pd/C in ethanol under an atmosphere of hydrogen (60psi) for 12 hours, to afford the phenol 166, in 69% yield. Oxidation of the phenol 166 with Fremy's salt gave the corresponding indolequinone 241, as an orange solid, in 53% yield. Unfortunately, the synthetic route could not be taken to the final urethane due to the small quantities of indolequinone produced. It was not considered useful at this stage to repeat the entire sequence again, due to lack of time.
4.3 Synthesis of Fused [1,2-a]indoles

As the cyclisation of the iodide using tributyltin hydride and AIBN with oxidation was a new result in terms of the formation of 1,2 fused indoles, the applications of this radical cyclisation were explored further. Initially, for comparative purposes, the simpler indole derivative was prepared. Also, the viability of the radical cyclisation provided access to 5,6 and 7 membered fused[1,2-a]indoles.

Thus, alkylation of the indole-3-carboxaldehyde 252 with 1-bromo-ω-chloroalkane using potassium hydroxide in DMSO gave the corresponding 1-(ω-chloroalkyl)indoles, in good yield (86-97%).

Reactions of the chlorides with sodium iodide in acetonitrile gave the corresponding iodides again in good yield (73-92%).
The cyclisation reactions were carried out by slow addition of tributyltin hydride and AIBN to the iodoalkylindoles in boiling toluene. This resulted in the formation of the desired 1,2-fused indoles (43-75%).

4.4 Synthesis of Substituted Fused [1,2-a]indoles related to the mitomycins

The synthesis of 10-formyl-8-methoxy-1,2,3,4-tetrahydropyrido[1,2-a]indole-6,9-dione 241 produced a 6,5,6-ring system. The rationale for the formation of 241 was to compare the properties of the cyclopropane containing indolequinone 137 with the simpler derivative lacking a cyclopropane ring. As described in Section 4.3, the radical cyclisation provided access to 5,6 and 7-membered fused [1,2-a]indoles. Therefore, in order to complete the series, the 6,5,5- and 6,5,7-substituted ring systems were prepared.

The substrates for the radical cyclisation were 4-benzyloxy-1-(3-iodopropyl)-5-methoxyindole-3-carboxaldehyde 259 and 4-benzyloxy-1-(5-iodopentyl)-5-methoxyindole-3-carboxaldehyde 260, respectively. Thus, alkylation of the indole with 1-bromo-3-chloropropane using potassium hydroxide in DMSO gave the corresponding 4-benzyloxy-1-(3-chloropropyl)-5-methoxyindole-3-carboxaldehyde 258 as a yellow oil, in 74% yield. The iodide 260 was prepared directly from aldehyde by alkylation with 1,5-diiodopentane, in 70% yield. Again the cyclisation were effected by slow addition.
of tributyltin hydride and AIBN to the iodoalkyindoles in boiling toluene. This resulted in the formation of indoles 261 and 262 in 47 and 29% yield, respectively.

\[
\begin{align*}
243 & \quad \xrightarrow{\text{KOH, DMSO}} \quad 261, \quad 262 \\
& \quad n = 1 \ (47\%) \\
& \quad n = 3 \ (29\%)
\end{align*}
\]

\[
\begin{align*}
258 & \quad n = 1 \ (74\%) \\
\end{align*}
\]

\[
\begin{align*}
259 & \quad n = 1 \ (85\%) \\
260 & \quad n = 3 \ (70\%)
\end{align*}
\]
Chapter Five

Biological Evaluation: Cyclopropamitosenes as Potential Anticancer Agents
Biological Evaluation: Cyclopropamitosenes as Potential Anticancer Agents

5.1 Introduction to Bioreductive Drugs

Bioreductive drugs are defined as compounds that are selectively toxic to hypoxic tumour cells. As described in Chapter 1, in vivo a significant difference between normal tissue and solid tumours is the presence of hypoxic cells, located in poorly vascularised regions of the tumour. Therefore, bioreductive drugs are capable of selectively targeting cells in hypoxia, causing death of solid tumour cells. This selective hypoxic cytotoxicity is partly due to the ability of an enzyme to metabolise these drugs to a toxic species under hypoxic conditions. Many enzymes have been implicated in this reaction, including NADPH cytochrome P450 reductase, xanthine dehydrogenase, xanthine oxidase and DT-diaphorase.

Reductive activation of bioreductive drugs is dependent on the ability of the drug to act as a substrate for the intracellular reductase(s) and the expression of these enzyme(s) within the particular cell type. Furthermore, reducing enzyme(s) activate bioreductive drugs via a one or two electron reduction. One electron reduction (by enzymes such as cytochrome P450 reductase) leads to the formation of a semiquinone radical anion in a process that is potentially reversible by oxygen, as discussed in Chapter 1. However, 2-electron reduction gives a hydroquinone in a process generally carried out by DT-diaphorase in a process that is oxygen independent. These factors all contribute to the variability of cytotoxic efficiency observed in different cell types and also the variable magnitude of the hypoxic/oxic differential.

5.2 Biological Activity

The main objective of this study was to investigate the effect of oxygen on the cytotoxicity of cyclopropamitosenes (the synthesis of which had been previously discussed) by determining the antitumour activity in vitro. The biological experiments were carried out under the direction of Dr Ian Stratford at the MRC Radiobiology Unit.

Initially, the in vitro activity of the cyclopropamitosenes was determined on V79 cell types both under oxic and hypoxic conditions, as shown in Table 5. The MTT assay was used to estimate toxicity in these experiments. The in vitro activities are represented as IC50 value, indicating the concentration (μM) of drug that inhibits survival by 50%
following exposure to cells for 3 hours at 37°C. The structure of the various novel cyclopropamitosenes are illustrated in Figure 8.

**Figure 8**

![Structures of cyclopropamitosenes](image)

*Table 6 Biological Activity of Cyclopropamitosenes*

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Structure R</th>
<th>IC50 (µmol dm⁻³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMC 1</td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>136 A</td>
<td>OCONH₂</td>
<td>4.8</td>
</tr>
<tr>
<td>150 A</td>
<td>OH</td>
<td>100</td>
</tr>
<tr>
<td>173 B</td>
<td>OH</td>
<td>75</td>
</tr>
<tr>
<td>230 C</td>
<td>OCONH₂</td>
<td>0.63</td>
</tr>
<tr>
<td>223 D</td>
<td>OCONH₂</td>
<td>0.68</td>
</tr>
<tr>
<td>228 C</td>
<td>OH</td>
<td>31</td>
</tr>
</tbody>
</table>

The results from Table 6 illustrate that even the small structural modifications resulted in very significant differences in *in vitro* activity of the cyclopropamitosenes. Some of these compounds showed better *in vitro* activity than the lead compound MMC. Under anaerobic conditions compound 136 became significantly more toxic than MMC. This possibly means that it is a better substrate for 1-electron reductases than MMC or reflects the difference in the stability of the semiquinone radical anion (and hence the position of equilibrium between semiquinone and hydroquinone).
The results indicate that the cyclopropapyrido[1,2-α]indole homologue 173 is more potent than the parent cyclopropapyrrolo[1,2-α]indole 150 suggesting that alterations in the ring system from 6,5,5 to 6,5,6 increases the cytotoxicity. However, more information regarding other ring systems such as the 6,5,7 and their analogues is necessary before any correlation between ring systems and potency of these compounds can be confirmed.

Clearly, from Table 6, cyclopropamitosenes which posses a carbamate group at the C-10 position are more potent than the comparative quinone alcohols. These results suggest that a good leaving group at the C-10 position is necessary for the potent antitumour activity.

The higher potency of cyclopropamitosenes 230 and 223 over MMC and the 7-methoxycyclopropamitosene 136 in air may be due to the fact that it is activated by DT-diaphorase in V79 cells, and MMC/136 less so. The cyclopropamitosenes 230 and 223 do not show greater specificity for hypoxic cells in comparison to the 7-methoxycyclopropamitosene 136. This is illustrated by the fact that compound 136 is considerably more active than 230 and 223 under hypoxic conditions and the hypoxic/hypoxic differential of 34 for 135 is much greater than that of 230 and 223 which are 2.6 and 1.9 respectively. Reductive activation of 230 and 223 by DT-diaphorase to give a hydroquinone contradicts the mechanistic issue of the semiquinone radical anion inducing ring opening of the cyclopropane. Formation of the hydroquinone eliminates the possibility of radical ring opening of the cyclopropane, in which the phenyl stabilises the developing radical centre. However, the fact that little difference is seen in the IC50 values under aerobic and hypoxic conditions for compounds 230 and 223 may be attributed to the steric effects incurred by the presence of a phenyl group on the cyclopropane ring.

In summary, 7-methoxycyclopropamitosene 136 appears to be more specific for hypoxic cells than MMC indicating that it is a better substrate for 1-electron reductases. Compounds 230 and 223 are equally effective at killing aerobic and hypoxic cells suggesting they may be reductively activated by DT-diaphorase. This excludes the possibility of radical induced ring opening of the cyclopropane ring. Therefore, more information on the enzymatic activation of these compounds may be needed to allow prediction of these differentials. Also, the potential steric effects from the phenyl substituent attached to the cyclopropane ring cannot be eliminated. Initial studies of the cytotoxic effects when modifying the cyclopropamitosene ring system indicate the 6,5,6 to be more potent than the 6,5,5-ring system. However, more evidence to confirm this
correlation is needed. Finally, cyclopropamitosene analogues with the carbamate group at the C-10 position were more potent in vitro than the corresponding derivatives with the hydroxyl group.
Chapter Six

Experimental Section
6.1 General Information

Solvents and Reagents—Commercially available solvents were used throughout without further purification, except those detailed below which were purified as described. ‘Light petroleum’ refers to the fraction of petroleum ether boiling between 40°C and 60°C and was distilled through a 36 cm Vigreux column before use. ‘Ether’ refers to diethyl ether, ether and xylene were dried by standing over sodium wire for several days. THF was distilled from sodium benzophenone ketyl under nitrogen, prior to use. Dichloromethane was distilled from phosphorus pentoxide. Acetonitrile was dried over anhydrous potassium carbonate and distilled from phosphorus pentoxide before storing over activated 4Å molecular sieves under nitrogen. DMF and DMSO was dried by stirring over calcium hydride for 15 h, decanted and distilled under reduced pressure before storing over activated 4Å molecular sieves under nitrogen. Pyridine and triethylamine were distilled from and stored over, potassium hydroxide pellets. Methanol and ethanol were distilled from magnesium turnings and iodine and stored over activated 4Å molecular sieves under nitrogen. Aziridine was prepared according to literature procedure and distilled from potassium hydroxide pellets and stored over, sodium hydroxide pellets, under nitrogen, in the refrigerator.

Chromatographic Procedures—Analytical thin layer chromatography (TLC) 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 chromatography was carried out using Merck Kieselgel 60 H silica or Sorbsil C 60 silica gel. Pressure was applied at the column head with hand bellows. Gravity chromatography was carried out using Merck Kieselgel 60 (70-230 mesh) silica. Samples were pre-adsorbed on silica or as a saturated solution in an appropriate solvent.

Spectroscopic Techniques—Infra red spectra were recorded in the range 4000-600 cm⁻¹ using a Nicolet FT-250 spectrometer, with internal calibration. Spectra were recorded as solutions in chloroform, thin films or as a nujol mull. Elemental analyses were carried out on a Perkin Elmer 2400 Elemental Analyser. ¹H and ¹³C NMR spectra were recorded using Bruker AC-250 and Bruker WH-400 instruments. ¹H NMR spectra are referenced against residual undeuterated solvent, in the case of deuterochloroform this is 7.260 ppm. Signals are described as singlets (s), doublets (d), quartets (q), double doublets (dd) etc. High and low resolution mass spectra were recorded on a Kratos MS80 instrument or on a VG Analytical ZAB-F instrument (EPSRC mass spectrometry service Swansea).
Other Data and Instrumentation- Melting points were measured on a Reichert-Kofler hot stage apparatus or an Electrothermal digital melting point apparatus and are uncorrected.

All of the following experimental reactions were carried out under an atmosphere of nitrogen except in cases where it was obviously unnecessary.

Synthesis or Preparation of General Reagents

Methyl Azidoacetate
Methyl chloroacetate (50.0 g, 0.461 mmol) was added followed by sodium azide (37.65 g, 0.579 mmol) to a stirred mixture of water (50 cm³) and acetone (75 cm³). The stirred mixture was refluxed for 16 h. After this time, the mixture was cooled to room temperature and the acetone removed \textit{in vacuo} to afford a yellow liquid/white solid (sodium chloride). The mixture of liquid and solid was then extracted with ether (3 x 150 cm³). The ethereal extracts were washed with water (3 x 100 cm³), brine (150 cm³), dried (MgSO₄) and then condensed \textit{in vacuo} to give the azide (44.6 g, 82%) as a pale yellow liquid, δ\textsubscript{H} (250 MHz; CDCl₃) 4.95 (2H, s, CH₂) and 3.96 (3H, s, Me).

Note: Care was taken at all times when handling this compound. Methyl azidoacetate is potentially explosive. Hence, this compound was not purified by distillation.

Fremy's Salt \([K₂ON(SO₃)_2]\)
A solution of sodium nitrite (5.8 g, 0.08 mmol) in water (15 cm³) was well cooled in an ice bath and crushed ice (35 g) stirred in, with continuous stirring. A solution of sodium metabisulphite (7.3 g, 0.04 mmol) in water (15 cm³) was added next, followed by glacial acetic acid (3.5 cm³). The mixture was rendered alkaline by adding ammonia (0.88, 2.5 cm³) and was then continously stirred in the ice bath during addition of an ice cold solution of potassium permanganate (2.1 g, 0.013 mmol) in water (65 cm³). The precipitate of manganese dioxide was filtered off through a bed of Celite. To the cooled violet filtrate was added a saturated solution (85 cm³) of potassium chloride (33 g/100 cm³ water). An orange solid precipitated out, which was filtered under suction. The orange solid was washed several times with 5% potassium hydroxide, then twice with ethanol containing approximately 5% v/v 0.88 ammonia and finally with acetone. Air was not drawn through the solid but it was spread on a watch glass and the acetone allowed to evaporate over 10-15 min. The product was dried in a desiccator over ammonium carbonate and calcium oxide.
2-Benzylxy-3-methoxybenzaldehyde 139
Potassium hydroxide pellets (16.0 g, 286 mmol) were added to a stirred solution of o-
vanillin 138 (40.0 g, 264 mmol) in ethanol (98%, 240 cm³), followed by benzyl chloride
(32.8 ml, 286 mmol). The stirred mixture was refluxed for 12 h, then water (200 cm³)
was added and the mixture extracted with diethyl ether (3 x 300 cm³). The ethereal
extracts were washed with water (2 x 100 cm³), potassium hydroxide solution (2M, 5 x
200 cm³), water (2 x 200 cm³) and brine (200 cm³). The organic layer was dried
(MgSO₄), then condensed in vacuo, to give the title compound 139 (60.7 g, 95%) as a
colourless solid on trituration with hexane, m.p. 45-47°C (lit. 88 44-45°C); ν max (Nujol)
1695, 1584, 1367, 1266, 1247 and 1222 cm⁻¹; δ H (250 MHz; CDCl₃) 10.23 (1 H, s,
CHO), 7.40-7.09 (8 H, m, Ar-H), 5.17 (2 H, s, OCH2Ph) and 3.94 (3 H, s, OMe); δ C
(62.9 MHz; CDCl₃) 190.00 (CHO), 153.04, 136.38, 130.28, 128.65, 128.57, 128.50,
124.25, 118.97, 118.00, 76.29 (OCH2Ph) and 56.05 (OMe).

Methyl 2-azido-3-(2'-benzylxy-3'-methoxyphenyl)propenoate 140
Sodium metal (7.60 g, 330 mmol) was added to dry methanol (150 cm³). The solution
was cooled to -15°C and a solution of methyl azidoacetate (38.02 g, 330 mmol) and 2-
benzylxy-3-methoxybenzaldehyde 139 (20.00 g, 82.0 mmol) in dry methanol (15 cm³)
was introduced, dropwise, by means of a pressure equalising dropping funnel. The
mixture was stirred at -10°C for 3 h then at 4°C for 12 h. Water (50 cm³) was cautiously
added to the mixture, which was then extracted with ethyl acetate (2 x 250 cm³). The
combined extracts were washed with water (500 cm$^3$), brine (250 cm$^3$) and dried (MgSO$_4$). Removal of the solvent in vacuo gave a pale yellow residue, which was triturated with a small quantity of diethyl ether and the resulting precipitate filtered off. The remaining oily residue was purified by column chromatography (50% light petroleum/50% diethyl ether) to give the title compound 140 (20.35 g, 72%) as pale yellow rhomboids, m.p. 66-67°C; $\nu_{\text{max}}$ (film) 2120, 1712, 1457, 1260 and 1218 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 7.79 (1 H, d, J 8.0, 6'-H), 7.44-7.27 (5 H, m, Ar-H), 7.13 (1 H, s, 3-H), 6.96 (1 H, t, J 8.0, 5'-H), 6.93 (1 H, d, J 8.0, 4'-H), 4.99 (2 H, s, OCH$_2$Ph), 3.89 (3 H, s, CO$_2$CH$_3$) and 3.85 (3 H, s, OMe); $\delta_C$ (62.9 MHz; CDCl$_3$) 164.04 (CO$_2$CH$_3$), 152.66, 146.77, 137.08, 128.76, 128.68, 128.33, 128.14, 127.85, 125.59, 123.93, 122.05, 120.05, 119.65, 113.52, 75.86 (OCH$_2$Ph), 55.88 (OMe) and 52.77 (CO$_2$CH$_3$).

![Image of compound 141]

**Methyl 4-benzyloxy-5-methoxyindole-2-carboxylate 141**

A solution of methyl 2-azido-3-(2'-benzyloxy-3'-methoxyphenyl)propenoate 140 (5.00 g, 14.8 mmol) in dry xylene (200 cm$^3$) was introduced, dropwise, by means of a pressure equalising dropping funnel, to refluxing dry xylene (800 cm$^3$). After the addition was complete (ca. 1 h), the solution was refluxed for a further 45 min. Removal of solvent in vacuo gave a yellow solid residue. The residue was triturated with a small quantity of diethyl ether and the resulting precipitate was filtered off. The remaining oily residue was purified by column chromatography (dichloromethane) to give the title compound 141 (3.14 g, 84%) as pale yellow needles, m.p. 97-100°C; $\nu_{\text{max}}$ (Nujol) 3342, 3031, 1697, 1528, 1453 and 1257 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 8.82 (1 H, s, NH), 7.53 (2 H, m, Ar-H), 7.52-7.34 (3 H, m, Ar-H), 7.33 (1 H, s, 3-H), 7.08 (2 H, s, 6'H), 5.26 (2 H, s, CH$_2$), 3.92 (3 H, s, CO$_2$Me) and 3.91 (3 H, s, OMe); $\delta_C$ (62.9 MHz; CDCl$_3$) 162.55 (CO$_2$CH$_3$), 145.12, 141.78, 137.89, 134.20, 128.35, 128.0, 127.88, 127.31, 123.13, 116.26, 107.21, 106.15, 75.04 (OCH$_2$Ph), 58.45 (OMe) and 52.03 (CO$_2$CH$_3$).
4-Benzylxoy-5-methoxyindole-2-methanol 142
A solution of methyl-4-benzyloxy-5-methoxyindole-2-carboxylate 141 (10.0 g, 32.15 mmol) in dry THF (200 cm³) was added dropwise to a stirred suspension of lithium aluminium hydride (1.22 g, 32.15 mmol) in dry THF (100 cm³), such that the mixture achieved gentle reflux. After 30 min, water (1.2 cm³), sodium hydroxide (15%, 1.2 cm³) and water (3.6 cm³), were added to the mixture and the resultant precipitate removed by filtration (through a bed of Celite). The filtrate was dried (MgSO₄), then condensed in vacuo to give the title compound 142 (8.55 g, 94%) as a colourless crystalline solid; m.p. 91°C; νmax (Nujol) 3479, 3282, 1506, 1324, 1283, 1244, 1091 and 701 cm⁻¹; δH (250 MHz; CDCl₃) 8.24 (1 H, s, NH), 7.49 (2 H, m, Ar-H), 7.33-7.29 (3 H, m, Ar-H), 6.97 (2 H, AB, J 9.0, 7/6-H), 6.39 (1 H, s, 3-H), 5.21 (2 H, s, OCH₂Ph), 4.74 (2 H, s, CH₂OH), 3.88 (3 H, s, OMe) and 1.67 (1 H, s, OH); δC (62.9 MHz; CDCl₃) 144.94, 140.00, 138.36, 138.07, 133.57, 128.33, 128.10, 127.84, 123.10, 111.63, 106.45, 97.56, 75.05 (OCH₂Ph), 58.29 (OMe) and 58.22 (CH₂OH); m/z 283 (M⁺, 27%), 192 (100), 174 (28) and 91 (38).

4-Benzylxoy-5-methoxyindole-2-carboxaldehyde 143
Manganese dioxide (14.0 g, 160 mmol) was added to a stirred solution of 4-benzyloxy-5-methoxyindole-2-methanol 142 (9.0 g, 32.0 mmol) in dichloromethane (1000 cm³). The suspension was refluxed for 12 h, then the mixture was filtered and the residue washed with dichloromethane (3 x 500 cm³). The combined filtrate and washings were evaporated to give an oil, which was purified by column chromatography (diethyl ether) to give the title compound 143 (5.96 g, 66%) as a yellow crystalline solid, m.p. 143-
145°C; $\nu_{\text{max}}$ (Nujol) 3188, 1667, 1446, 1148 and 1094 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 9.75 (1 H, s, CHO), 9.05 (1 H, s, NH), 7.52-7.21 (5 H, m, Ar-H), 7.15 (1 H, d, J 8.8, 7/6-H), 7.12 (1 H, d, J 8.8, 67-H), 5.28 (2 H, s, CH$_2$) and 3.91 (3 H, s, OMe); $\delta_C$ (62.9 MHz; CDCl$_3$) 182.08 (CHO), 145.23, 142.20, 137.78, 136.20, 135.11, 128.42, 128.13, 128.02, 123.43, 118.33, 112.47, 107.61, 75.22 (OCH$_2$Ph) and 58.42 (OMe).

1-Allyl-4-benzyloxy-5-methoxyindole-2-carboxaldehyde 144

To a flask charged with sodium hydride (80%; 0.475 g, 15.8 mmol) was added dry light petroleum (10 cm$^3$). The mixture was stirred for 10 min, the petroleum removed by syringe and the flask contents dried under reduced pressure. 4-Benzyloxy-5-methoxyindole-2-carboxaldehyde 143 (3.56 g, 12.7 mmol) in DMF (51 cm$^3$) was added dropwise and the mixture was stirred at room temperature for 30 min. Allyl bromide (1.36 cm$^3$, 15.8 mmol) was added and the mixture was stirred at room temperature. After 1 h, water (150 cm$^3$) was cautiously added and the mixture was extracted with diethyl ether (4 x 250 cm$^3$). The combined ethereal extracts were washed with water (8 x 200 cm$^3$), brine (200 cm$^3$), dried (MgSO$_4$) and evaporated to give the title compound 144 (4.03 g, 99%) as a yellow solid, m.p. 69-70°C; $\nu_{\text{max}}$ (Nujol) 1670, 1490, 1407, 1248 and 1141 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 9.77 (1 H, s, CHO), 7.51 (2 H, m, Ar-H), 7.25 (3 H, m, Ar-H), 7.20 (1 H, s, 3-H), 7.17 (1 H, d, J 9.0, 7/6-H), 7.14 (1 H, d, J 9.0, 67-H), 5.97 (1 H, m, CH$_2$CH=CH$_2$), 5.28 (2 H, s, OCH$_2$Ph), 5.16 (3 H, m, CH$_2$CH=CH$_2$ and CH$_2$CH=CHH), 4.94 (1 H, d, J 18.0, CH$_2$CH=CHH) and 3.91 (3 H, s, OMe); $\delta_C$ (62.9 MHz; CDCl$_3$) 182.00 (CHO), 145.17, 137.83, 137.44, 135.33, 133.45, 128.43, 128.11, 122.00, 118.15, 116.33, 115.23, 105.90, 75.23 (OCH$_2$Ph), 58.49 (OMe) and 46.98 (NCH$_2$).
1-allyl-4-benzylodo-5-methoxyindole-2-carboxaldehyde tosylhydrazone 145

1-Allyl-4-benzylodo-5-methoxyindole-2-carboxaldehyde 144 (2.43 g, 7.57 mmol) was added to a stirred solution of 4-toluenesulfonyl hydrazide (1.69 g, 9.08 mmol) in methanol (20 ml). The mixture was stirred at 40°C for 45 min. Removal of the solvent in vacuo, gave a dark green residue which was recrystallised from diethyl ether and the resulting precipitate filtered off. The remaining mother liquors were purified by column chromatography (50% light petroleum/50% diethyl ether) to give the title compound 145 (3.29 g, 89%) as a colourless solid, m.p. 49-50°C (dec.); \( \nu_{\text{max}} \) (Nujol) 2956, 1718, 1492, 1456, 1358 and 1166 cm\(^{-1}\); \( \delta \) \(_{H}\) (250 MHz; CDCl\(_3\)) 7.83 (2 H, m, Ar-H), 7.81 (2 H, m, NH and CH=N), 7.47 (2 H, m, Ar-H), 7.38-7.30 (5 H, m, Ar-H), 7.04 (1 H, d, J 7.5, 7/6-H), 6.95 (1 H, d, J 7.5, 6/7-H), 6.67 (1 H, s, 3-H), 5.85 (1 H, m, CH=CH\(_2\)), 5.20 (2 H, s, OCH\(_2\)Ph), 5.04 (3 H, m, CH\(_2\)CH=CH\(_2\) and CH\(_2\)CH=CHH), 4.85 (1 H, d, J 17.5, CH\(_2\)CH=CHH), 3.87 (3 H, s, OMe) and 2.42 (3 H, s, Ts-Me); \( \delta \) \(_{C}\) (62.9 MHz; CDCl\(_3\)) 144.33, 141.15, 138.08, 136.78, 135.25, 133.68, 131.74, 129.86, 129.68, 128.36, 128.09, 128.05, 127.89, 116.14, 114.79, 107.34, 105.23, 75.10 (OCH\(_2\)Ph), 58.38 (OMe), 47.41 (NCH\(_2\)) and 21.58 (Ts-CH\(_3\)).

8-benzyloxy-7-methoxy-1,2-dihydro-3H-1,2-cyclopropapyrrolo[1,2-a]indole 146

Sodium hydride (50%, 0.291 g, 6.07 mmol) was added to a stirred solution of the tosylhydrazone 145 (1.98 g, 4.05 mmol) in dry THF (60 cm\(^3\)). After 10 min the solution was filtered and the filtrate evaporated. The residue was dissolved in dry chlorobenzene (600 cm\(^3\)) and the solution refluxed for 3 h. The solvent was evaporated and the residue purified by column chromatography (50% light petroleum/50% diethyl ether) to give the
**title compound 146** (1.16 g, 94%) as a pale yellow oil; \( \nu_{\max} \) (film) 1500, 1495, 1288, 1234 and 750 cm\(^{-1}\); \( \delta_H \) (250 MHz; CDCl\(_3\)) 7.53 (2 H, m, Ar-H), 7.41-7.23 (3 H, m, Ar-H), 6.82 (1 H, d, J 7.5, 6/5-H) 6.78 (1 H, d, J 7.5, 5/6-H), 5.27 (2 H, s, OCH\(_2\)Ph), 4.06 (2 H, m, 3-H), 3.86 (3 H, s, OMe), 2.37 (2 H, m, 1,2-H), 1.25 and 0.65 (each 1 H, m, 1a-H).

![Chemical Structure](147.png)

8-Benzylcxy-7-methoxy-1,2-dihydro-3H-1,2-cyclopopyrrolo[1,2-ajindole-9-carboxaldehyde 147

DMF (10 cm\(^3\)) and phosphorus oxychloride (0.15 ml, 1.61 mmol) were stirred under nitrogen for 30 min. The resulting yellow solution was cooled to 0°C and 8-benzylxy-7-methoxy-1,2-dihydro-3H-1,2-cyclopopyrrolo[1,2-ajindole 146 (0.250 g, 0.819 mmol) in DMF (2 cm\(^3\)) was added and the mixture stirred for 45 min. Sodium acetate (1M, 6 cm\(^3\)) was added and the mixture was extracted with diethyl ether (6 x 20 cm\(^3\)). The combined ethereal extracts were washed with brine (6 x 50 cm\(^3\)) and dried (MgSO\(_4\)). Removal of the solvent in vacuo gave a green oily residue which was recrystallised with a small quantity of diethyl ether and the resulting precipitate filtered off. The mother liquors were purified by column chromatography (diethyl ether) to give the title compound 147 (0.145 g, 53%) as a colourless solid, m.p. 128-130°C; \( \nu_{\max} \) (Nujol) 1648, 1536, 757 and 702 cm\(^{-1}\); \( \delta_H \) (250 MHz; CDCl\(_3\)) 10.32 (1 H, s, CHO), 7.49 (2 H, m, Ar-H), 7.40-7.26 (3 H, m, Ar-H), 6.90 and 6.85 (each 1 H, d, J 8.7, 6/5-H), 5.18 (2 H, s, OCH\(_2\)Ph), 4.10 (2 H, m, 3-H), 4.03 (3 H, s, OMe), 2.99 (1 H, m, 1-H), 2.46 (1 H, m, 2-H), 1.48 and 0.72 (each 1 H, m, 1a-H); \( \delta_C \) (62.9 MHz; CDCl\(_3\)) 186.57 (CHO), 154.56, 147.97 (4a-C), 141.49, 137.50 (8-C), 129.49 (9a/8a-C), 125.28 (8/9a-C), 110.49 (6/5-C), 110.06 (9-C), 105.31 (5/6-C), 74.86 (OCH\(_2\)Ph), 57.72 (OMe), 47.57 (3-C), 21.59 (1-C), 18.06 (2-C) and 17.50 (1a-C).
8-Hydroxy-7-methoxy-1,2-dihydro-3H-1,2-cyclopropapyrrolo[1,2-a]indole-9-carboxaldehyde 148

To a solution of 8-benzyloxy-7-methoxy-1,2-dihydro-3H-1,2-cyclopropapyrrolo[1,2-a]indole-9-carboxaldehyde 147 (0.200 g, 0.601 mmol) in ethyl acetate (100 cm³) was added 10% palladium on carbon (0.04 g) and dilute sulfuric acid (4 drops). The mixture was stirred under an atmosphere of hydrogen for 12 h. After this time, the suspension was filtered and washed with dichloromethane. The combined filtrate and washings were washed with water (3 x 50 cm³), brine (40 cm³) and dried (MgSO₄). The organic layer was evaporated to dryness to give a brown solid. Purification of the residue by column chromatography (ethyl acetate) gave the title compound 148 (0.133 g, 91%) as a colourless solid, m.p. 146-147°C; vₘₐₓ 1606, 1304, 1252 and 825 cm⁻¹; δₜ (250 MHz; CDCl₃) 10.87 (1 H, s, OH), 9.58 (1 H, s, CHO), 6.82 (1 H, d, J 8.5, 6/5-H), 6.46 (1 H, d, J 8.5, 5/6-H), 4.04 (2 H, m, 3-H), 3.88 (3 H, s, OMe), 2.56 (2 H, m, 1,2-H), 1.45 and 0.72 (each 1 H, m, 1a-H); δₜ (62.9 MHz; CDCl₃) 183.20 (CHO), 159.64, 142.62, 141.15 129.70, 118.84, 111.95 (6/5-C), 110.69, 99.94 (5/6-C), 57.55 (OMe), 47.91 (3-C), 21.88 (1-C), 17.28 (1a-C) and 15.93 (2-C).

9-Formyl-7-methoxy-1,2-dihydro-3H-1,2-cyclopropapyrrolo[1,2-a]indole-5,8-dione 149

Potassium nitrosodisulfonate (0.607 g, 2.26 mmol) was added to a solution of 8-hydroxy-7-methoxy-1,2-dihydro-3H-1,2-cyclopropapyrrolo[1,2-a]indole-9-carboxaldehyde 148 (0.250 g, 1.03 mmol) in acetone (100 cm³), sodium dihydrogen phosphate solution (0.167M, 30 cm³) and water (30 cm³) and the resulting suspension
stirred at room temperature for 12 h. The mixture was extracted with dichloromethane (3 x 50 cm³) and the combined organic extracts were dried (Na₂SO₄) and evaporated. Purification of the residue by column chromatography (ethyl acetate) gave the title compound 149 (0.232 g, 82%) as orange needles, m.p. 217-218°C; λₘₐₓ (MeOH) 447 (log ε 3.75), 329 (4.42), 280 (4.99) and 219 nm (5.03); νₘₐₓ (Nujol) 1684, 1666, 1637, 1588, 1502, 1242 and 1212 cm⁻¹; δₓ (250 MHz; CDCl₃) 10.37 (1 H, s, CHO), 5.68 (1 H, s, 6-H), 4.32 (2 H, m, 3-H), 3.85 (3 H, s, OMe), 2.86 (1 H, m, 1-H), 2.47 (1 H, m, 2-H), 1.47 and 0.65 (each 1 H, m, 1a-H); δₓ (62.9 MHz; CDCl₃) 187.84, 186.58 (CHO), 177.98, 160.64, 150.77, 115.78, 106.47, 105.29 (6-C), 56.65 (OMe), 50.46 (3-C), 22.07 (1-C), 16.74 (2-C) and 16.53 (1a-C).

9-Hydroxymethyl-7-methoxy-1,2-dihydro-3H-1,2-cyclopropapyrrolo[1,2-a]indole-5,8-dione 150
Sodium borohydride (0.200 g, 5.26 mmol) was added to a stirred solution of 9-formyl-7-methoxy-1,2-dihydro-3H-1,2-cyclopropapyrrolo[1,2-a]indole-5,8-dione 149 (0.200 g, 0.778 mmol) in methanol (150 cm³). After stirring for 1 h at room temperature, air was blown rapidly through the solution and the mixture was extracted with dichloromethane (3 x 200 cm³). The combined extracts were washed with water (2 x 200 cm³), brine (2 x 200 cm³) and dried (Na₂SO₄). The solvent was evaporated and the residue purified by column chromatography (ethyl acetate) to give the title compound 150 (0.149 g, 74%) as an orange solid, m.p. 150-151°C; λₘₐₓ (MeOH) 471 (log ε 3.95), 348 (4.30), 290 (4.96) and 238 nm (4.99); νₘₐₓ (Nujol) 3312, 1668, 1630, 1586 and 722 cm⁻¹; δₓ (250 MHz; CDCl₃) 5.61 (1 H, s, 6-H), 4.68 (2 H, m, 10-H), 4.26 (2 H, m, 3-H), 3.89 (1 H, t, J 7.1, OH), 3.82 (3 H, s, OMe), 2.36 (2 H, m, 1,2-H), 1.30 and 0.60 (each 1 H, m, 1a-H); δₓ (62.9 MHz; CDCl₃) 177.65, 160.85 143.81, 121.08, 117.36 (6-C), 56.63 (OMe), 56.52 (10-C), 50.04 (3-C), 26.90 (1-C), 16.42 (1a-C) and 14.23 (2-C).
9-Hydroxymethyl-7-methoxy-1,2-dihydro-3H-1,2-cyclopropapyrrolo[1,2-a]indole-5,8-dione phenyl carbonate 151

Phenyl chloroformate (0.03 cm³, 0.232 mmol) was added dropwise to a stirred, ice cold solution of the alcohol 150 (0.040 g, 0.153 mmol) in dry pyridine (10 cm³). The mixture was stirred at room temperature for 2 h, then water (4 cm³) was added. The mixture was extracted with diethyl ether (3 x 25 cm³) and the combined organic extracts were washed with brine (6 x 25 cm³), water (2 x 25 cm³), saturated aqueous copper sulfate solution (2 x 25 cm³), water (2 x 25 cm³) and dried (Na₂SO₄). The solvent was evaporated and the residue purified by column chromatography (ethyl acetate) to give the title compound 151 (0.054 g, 92%) as an orange solid, m.p. 40-43°C (dec.); λ_max (MeOH) 475 (log ε 3.00), 348 (3.29), 271 (4.61) and 213 nm (4.68); ν_max (Nujol) 1785, 1758 and 1592 cm⁻¹; δ_H (250 MHz; CDCl₃) 7.27 (5 H, m, Ar-H), 5.60 (1 H, S, 6-H), 5.28 (2 H, m, 10-H), 4.28 (2 H, m, 3-H), 3.80 (3 H, s, OMe), 2.35 (1 H, m, 1-H), 2.17 (1 H, m, 2-H), 1.26 and 0.57 (each 1 H, m, 1a-H).

9-Hydroxymethyl-7-methoxy-1,2-dihydro-3H-1,2-cyclopropapyrrolo[1,2-a]indole-5,8-dione carbamate 136

A solution of phenyl carbonate 151 (0.110 g, 0.290 mmol) in dry dichloromethane (80 cm³) was cooled to -78°C. Ammonia gas was bubbled into the solution for approximately 45 min, after which time the contents were allowed to warm to room temperature and the solvent removed in vacuo. Trituration of the residue with hot dichloromethane gave the title compound 136 (0.071 g, 81%) as red needles, m.p. 175-177°C; λ_max (MeOH, qualitative) 234, 293, 346 and 459 nm; ν_max (Nujol) 3408, 3212,
1764, 1668, 1620, 1584, 1350, 1306 and 1242 cm⁻¹; δ_{H} (250 MHz; CDCl₃/DMSO) 5.56 (1 H, s, 6-H), 4.92 (2 H, m, 10-H), 4.42 (2 H, br s, NH₂), 3.55 (2 H, m, 3-H), 3.06 (3 H, s, OMe), 1.83 (1 H, m, 1-H), 1.65 (1 H, m, 2-H), 0.58 and 0.03 (each 1 H, m, 1a-H); δ_{C} (62.9 MHz; CDCl₃) 177.68 (8-C), 177.20 (5-C), 160.44 (7-C/CONH₂), 156.77 (CONH₂/7-C), 146.31 (4a-C), 129.24 (9a/8a-C), 123.90 (8a/9a-C), 111.33 (9-C), 105.35 (6-C), 57.87 (10-H), 56.38 (OMe), 50.00 (3-C), 20.63 (1-C), 16.17 (1a-C) and 14.69 (2-C).
4-Benzylorg-(but-3-enyl)-5-methoxyindole-2-carboxaldehyde 152

To a flask charged with sodium hydride (60%; 0.282 g, 11.73 mmol) was added dry light petroleum (10 cm³). The mixture was stirred for 10 min, the petroleum removed by syringe and the flask contents dried under vacuum. 4-Benzylorg-5-methoxyindole-2-carboxaldehyde 143 (2.20 g, 7.82 mmol) in DMF (150 cm³) was added dropwise and the mixture was stirred at room temperature for 30 min. 4-Bromo-1-butene (4.22 g, 31.38 mmol) was added and the mixture was stirred at room temperature. After 15 h, water (100 cm³) was cautiously added and the mixture was extracted with ethyl acetate (3 x 200 cm³). The combined extracts were washed with water (3 x 200 cm³), dried (MgSO₄) and evaporated to give the title compound 152 (1.83 g, 70%) as a yellow oil; (Found: C, 75.19; H, 6.12; N, 4.14. C₂₁H₂₁N₂O₃ requires C, 75.20; H, 6.31; N, 4.18%); ν_max (Nujol) 1714, 1673, 1614, 1520, 1467, 1417, 1355 and 1121 cm⁻¹; δ_H (250 MHz; CDCl₃) 9.80 (1H, s, CHO), 7.49 (2H, m, Ar-H), 7.36 (3H, m, Ar-H), 7.25 (1H, s, 3-H), 7.19 (1H, d, J 8.66, 7/6-H), 7.06 (1H, d, J 8.66, 6/7-H), 5.77 (1H, m, CH₂CH₂CH=CH₂), 5.28 (2H, s, OCH₂Ph), 4.99 (2H, m, NCH₂), 4.55 (2H, m, CH₂CH₂CH=CH₂), 3.91 (3H, s, OMe) and 2.50 (2H, m, CH₂CH₂CH=CH₂); δ_C (69.2 MHz; CDCl₃) 182.00 (CHO), 144.92, 137.31, 135.37, 134.51 (CH₂CH₂CH=CH₂), 128.35, 128.01, 127.93, 122.26, 117.99 (7/6-C), 117.22 (CH₂CH₂CH=CH₂), 115.14 (3-C), 105.70 (6/7-C), 75.11 (OCH₂Ph), 58.45 (OMe), 44.30 (NCH₂), 34.70 (CH₂CH₂CH=CH₂); m/z 335 (M⁺, 18%), 244 (53), 204 (15), 91 (100), and 55 (31).
4-Benzylxoy-1-(but-3-enyl)-5-methoxyindole-2-carboxaldehyde tosylhydrazone 153

4-Benzylxoy-1-(but-3-enyl)-5-methoxyindole-2-carboxaldehyde 152 (1.824 g, 5.44 mmol) was added to a stirred solution of 4-toluene sulfonyl hydrazide (1.640 g, 8.81 mmol) in methanol (50 cm³). After stirring at 40°C for 15 h, the solvent was removed in vacuo and the residue was purified by column chromatography (50% light petroleum/50% diethyl ether) to give the title compound 153 (2.446 g, 89%) as a pale yellow oil; (Found: M+H+, 504.1960. C₂₉H₂₉N₃O₄S requires M+H, 504.1957); νmax (film) 2935, 1598, 1492, 1463, 1434, 1345, 1249 and 1166 cm⁻¹; δH (8.52 (1H, br s, NH), 7.82 (2H, d, J 8.5, Ts-H), 7.76 (1H, s, HC=N), 7.46 (2H, m, Ar-H), 7.36-7.16 (5H, m, Ar-H), 6.97 (2H, AB, J 8.75, 6/7-H), 6.60 (1H, s, 3-H), 5.73 (1H, m, CH₂CH₂CH=CH₂), 5.18 (2H, s, OCH₂Ph), 5.00 (2H, m, NCH₂), 4.34 (2H, m, CH₂CH₂CH=CH₂), 3.85 (3H, s, OMe) and 2.34 (5H, m, CH₂CH₂CH=CH₂ and Ar-Me); δC 144.96, 144.24, 141.30 (HC=N), 141.10, 138.04, 136.66, 135.39, 134.85 (CH₂CH₂CH=CH₂), 114.52 (7/6-C), 107.13 (3-C), 105.07 (6/7-C), 75.06 (OCH₂Ph), 58.37 (OMe), 44.55 (NCH₂), 34.26 (CH₂CH₂CH=CH₂) and 21.51 (Me); m/z (FAB, 3-NBA Matrix) 504 (M + H⁺, 65%), 412 (100), 348 (8), 258 (13), 228 (25), 216 (25), 201 (9), 185 (8), 115 (5) and 105 (7).

9-Benzylxoy-8-methoxy-1,2-dihydro-3H,4H-1,2-cyclopropapyrido[1,2-a]indole 154

Sodium hydride (60%; 0.152 g, 6.34 mmol) was added to a stirred solution of the tosylhydrazone 153 in dry THF (20 cm³). After 20 min, the solution was filtered and the filtrate evaporated. The residue was dissolved in dry chlorobenzene (250 cm³) and
the solution refluxed for 3 h. The solvent was evaporated and the residue purified by column chromatography (50% light petroleum: 50% diethyl ether) to give the title compound 154 (1.179 g, 76%) as a pale yellow oil; (Found: C, 78.33; H, 6.74; N, 4.28. C_{21}H_{21}NO_{2} requires C, 78.97; H, 6.63; N, 4.39); v_{max} (film) 1556, 1495, 1326 and 1271 cm^{-1}; δH (400 MHz; CDCl3) 7.59 (2H, m, Ar-H), 7.43-7.28 (3H, m, Ar-H), 6.88 (2H, s, 7/6-H), 6.42 (1H, br s, 10-H), 5.25 (2H, s, OCH_{2}Ph), 4.17 (1H, m, 4-CHH), 3.90 (3H, s, OMe), 3.55 (1H, ddd, J 3 and 8, 4-CHH), 2.31-2.19 (3H, m, 3-CH_{2} and 1-H), 1.69 (1H, m, 2-H), 1.07 and 0.92 (each 1H, m, 1a-H); δC (100.6 MHz; CDCl3) 145.57, 140.80, 139.15, 139.01, 133.72, 128.66, 128.32, 127.99, 123.26, 110.37 (7/6-C), 103.58 (6/7-C), 95.05 (10-C), 75.21 (OCH_{2}Ph), 59.03 (OMe), 37.52 (4-C), 21.64 (3-C), 12.42 (2-C), 10.91 (1-C) and 9.96 (1a-C); m/z 319 (M^+, 13%), 228 (100), 185(18) and 91 (43).

[Diagram of 165]

9-Benzoyloxy-8-methoxy-1,2-di hydro-3H,4H-1,2-cyclopropapyridol,2-ajindole-10-carboxaldehyde 165

DMF (0.51 cm³; 0.481 g, 6.52 mmol) and phosphorus oxychloride (0.14 cm³; 0.226 g, 1.48 mmol) were stirred at -5°C for 30 min. A solution of 9-benzyloxy-8-methoxy-1,2-dihydro-3H,4H-1,2-cyclopropapyrrolol[1,2-a]indole 154 (0.421 g, 1.32 mmol) in DMF (3 cm³) was added slowly dropwise maintaining the temperature below 10°C. After the addition was complete the mixture was stirred at 35°C for 1 h. Ice water (10 cm³) followed by sodium hydroxide solution (37%; 10 cm³) was added and the mixture extracted with diethyl ether (3 x 100 cm³). The ether layer was dried (MgSO_{4}) and concentrated in vacuo. The crude mixture was columned (diethyl ether) giving the title compound 165 (0.263 g, 57%) as a pale yellow solid; m.p. 135.9°C (Found C, 75.89; H, 5.80; N, 4.08. C_{22}H_{21}NO_{3} requires C, 76.06; H, 6.09; N, 4.03.); v_{max} (Nujol) 1634, 1523, 1255 and 742 cm^{-1}; δH (250 MHz; CDCl3) 10.52 (1H, s, CHO), 7.41-7.26 (5H, m, Ar-H), 6.91 (2H, s, 7/6-H), 5.17 (2H, s, OCH_{2}Ph), 4.17 (1H, m, 4-CHH), 3.84 (3H, s, OMe), 3.52 (1H, ddd, J 13 and 5.25 4-CHH), 3.39 (1H, ddd, J 8.75 and 4.25, 1-H), 2.33 (1H, m, 3-CHH), 2.13 (1H, m, 3-CHH), 1.77 (1H, m, 2-H), 1.30 and 1.08 (each 1H, m, 1a-H); δC (69.2 MHz; CDCl3) 187.68 (CHO), 148.19, 147.94, 137.44, 132.43, 128.38, 127.96, 113.19, 109.97 (7/6-C), 104.29 (6/7-C), 74.71 (OCH_{2}Ph), 57.63 (OMe), 37.43
9-Hydroxy-8-methoxy-1,2-dihydro-3H,4H-1,2-cyclopropapyrido[1,2-a]indole-10-carboxaldehyde 167

To a solution of 9-benzyloxy-8-methoxy-1,2-dihydro-3H,4H-1,2-cyclopropapyrrido[1,2-a]indole-10-carboxaldehyde 165 (0.263 g, 0.76 mmol) in ethanol (200 cm³) was added 10% palladium on carbon (0.097 g). The mixture was stirred under an atmosphere of hydrogen (60 psi) for 12 h. After this time the suspension was filtered and washed with dichloromethane (250 cm³). The combined filtrate and washings were washed with water (3 x 100 cm³), brine (75 cm³) and dried (MgSO₄). The organic layer was condensed in vacuo to give a yellow solid. Purification of the residue by column chromatography (50% ethyl acetate: 50% light petroleum) gave the title compound 167 (0.134 g, 69%) a pale yellow solid, m.p. 183°C (Found: M+H⁺, 258.1130. C₁₅H₁₅NO₃ requires M+H, 258.1130); νmax (film) 1733, 1645, 1602, 865 and 779 cm⁻¹; δH (250 MHz; CDCl₃) 11.24 (1H, s, OH), 9.69 (1H, s, CHO), 6.91 (1H, d, J 8.75, 7/6-H), 6.58 (1H, d, J 8.75, 6/7-H), 4.15 (1H, m, 4-CHH), 3.91 (3H, s, OMe), 3.49 (1H, ddd, J 13 and 5.25, 4-CHH), 2.59 (1H, ddd, J 8.4 and 4.25, 1-H), 2.36 (1H, m, 3-CHH), 2.18 (1H, m, 3-CHH), 1.93 (1H, m, 2-H), 1.35 and 1.17 (each 1H, m, la-H); δC (100.6 MHz; CDCl₃) 182.74 (CHO), 152.65, 143.11, 141.37, 133.21, 115.55, 114.98, 112.14 (7/6-C), 98.84 (6/7-C), 57.76 (OMe), 37.55 (4-C), 19.95 (3-C), 13.69 (2-C), 11.37 (1a-C) and 8.58 (1-C); m/z 257 (M⁺, 24%), 217 (15), 186 (14), 155 (26), 124 (15), 113 (26), 70 (13), 51 (55) and 28 (100).
Potassium nitrosodisulfonate (0.223 g, 0.83 mmol) was added to a solution of 9-hydroxy-8-methoxy-1,2-dihydro-3H,4H-1,2-cyclopropapyrido[1,2-α]-6,9-dione 167 (0.097 g, 0.38 mmol) in acetone (65 cm³), sodium dihydrogen phosphate solution (0.167 M; 25 cm³) and water (25 cm³) and the resulting suspension stirred at room temperature for 12 h. The mixture was extracted with ethyl acetate (3 x 75 cm³) and the combined organics were dried and evaporated. Purification of the residue by column chromatography (ethyl acetate) gave the title compound 168 (0.091 g, 89%) as orange crystals, m.p. 168°C, (Found: M⁺, 271.0853. C₁₅H₁₃NΟ₄ requires 271.08445); \( \lambda_{\text{max}} \) (MeOH) 458 (log ɛ 2.99), 331 (3.58), 282 (4.27) and 227 nm (4.30); \( \nu_{\text{max}} \) (Film) 1678, 1663, 1637, 1603, 1512, 1486, 1237, 1219, 1152 and 834 cm⁻¹; \( \delta_{\text{H}} \) (250 MHz; CDCl₃) 10.54 (1H, s, CHO), 5.66 (1H, s, 6-H), 5.11 (1H, m, 4-CHH), 3.84 (3H, s, OMe), 3.57 (1H, ddd, J 14.8 and 5.25, 4-CHH), 3.14 (1H, ddd, J 8.75 and 4.5, 1-H), 2.27 (1H, m, 3-CHH), 2.08 (1H, m, 3-CHH), 1.79 (1H, m, 2-H), 1.27 and 1.13 (each 1H, m, 1a-H); \( \delta_{\text{C}} \) (100.6 MHz; CDCl₃) 188.06 (CHO), 179.04 (9-C), 177.77 (6-C), 159.65, 145.34, 128.01, 122.55, 119.33, 106.44 (7-C), 56.65 (OMe), 40.42 (4-C), 19.94 (3-C), 13.58 (2-C), 10.24 (1a-C) and 9.97 (1-C); \( m/z \) 271 (M⁺, 100%), 228 (15), 200 (17), 186 (23), 155 (29), 132 (19), 113 (27), 77 (18), 51 (59) and 28(97).
10-Hydroxymethyl-8-methoxy-1,2-dihydro-3H,4H-1,2-cyclopropapyrido[1,2-ajindole-6,9-dione 173

Sodium borohydride (0.039 g, 1.02 mmol) was added to a stirred solution of 10-formyl-8-methoxy-1,2-dihydro-3H,4H-1,2-cyclopropapyrido[1,2-a]indole-6,9-dione 168 (0.034 g, 0.13 mmol) in methanol (30 cm³). After stirring for 1 h at room temperature, air was blown rapidly through the solution and the mixture was extracted with dichloromethane (3 x 50 cm³). The combined extracts were washed with water (2 x 50 cm³), brine (2 x 50 cm³) and dried (MgSO₄). The solvent was removed and the residue purified by column chromatography to give the title compound 173 (0.012 g, 36%) as an orange solid, m.p. 175°C (Found: M⁺, 273.0991. C₁₅H₁₃NO₄ requires M, 273.1001); λmax (MeOH) 483 (log ε 3.35), 354 (3.54), 292 (4.30) and 245 nm (4.38); vmax (film) 3409, 1667, 1594 and 1153 cm⁻¹; δH (400 MHz; CDCl₃) 5.52 (1H, s, 7-H), 4.92 (1H, m, 4-CHH), 4.62 (2H, m, 11-H), 3.88 (1H, br s, OH), 3.74 (3H, s, OMe), 3.49 (1H, m, 4-CHH), 2.06 (3H, m, 3-H and 1-H), 1.61 (1H, m, 2-H), 0.88 and 0.80 (each 1H, m, 1a-H); δC (62.9 MHz; CDCl₃) 179.82 (9-C), 178.82 (6-C), 159.89, 136.65, 128.21, 122.53, 122.21, 107.49, 56.94 (OMe), 55.80 (11-C), 40.43 (4-C), 20.92 (3-C), 12.47 (2-C), 9.80 (1a-C) and 8.43 (1-C); m/z 273 (M⁺, 13%), 212 (11), 163 (8), 155 (15), 132 (9), 113 (17), 69 (14), 51 (18), 28 (100).

10-Hydroxymethyl-8-methoxy-1H,3H,4H-2-methylpyrido[1,2-a]indole-6,9-dione 174

The title compound 174 was isolated in (0.010 g, 30%) as an orange solid, m.p. 173°C (Found: M⁺, 275.1157. C₁₅H₁₇NO₄ requires M, 275.11575); vmax (film) 3419, 1670,
1634, 1596, 1219, 1149 and 1054 cm⁻¹; δ_H (250 MHz; CDCl₃) 5.63 (1H, s, 7-H), 4.68 (1H, m, 4-CH_H), 4.58 (2H, m, 11-H), 4.02 (2H, m, 4-CH_H and OH), 3.82 (3H, s, OMe), 2.95 (1H, m, 1-CH_H), 2.27 (1H, m, 1-CH_Hf), 2.03 (2H, m, 3-CH_H and 2-H), 1.62 (1H, m, 1-CH_H) and 1.14 (3H, d, J 6.5, Me); δ_C (100.6 MHz; CDCl₃) 179.45 (9-C), 178.29 (6-C), 159.77, 134.41, 128.74, 122.39, 121.61, 107.09, 56.53 (OMe), 55.39 (11-C), 45.44 (4-C), 30.62 (3-C), 29.97 (1-C), 26.30 (2-C) and 21.20 (Me); m/z 275 (M⁺, 18%), 217 (16), 163 (16), 151 (31), 124 (19), 113 (33), 57 (29), 51 (100), 40 (29), 31 (51).

![](image)

**10-Hydroxymethyl-8-methoxy-1,2-dihydro-3H,4H-1,2-cyclopropapyrido[1,2-a]indole-6,9-dione phenyl carbonate 137**

Phenyl chloroformate (0.009 cm³; 0.011 g, 0.07 mmol) was added dropwise to a stirred, ice cold solution of alcohol 173 (0.012 g, 0.04 mmol) in dry THF (10 cm³) and pyridine (5 drops). The mixture was stirred at room temperature for 2 h then water (5 cm³) was added. The mixture was extracted with dichloromethane (3 x 25 cm³). The combined extracts were washed with water (3 x 25 cm³), brine (50 cm³) and dried (Na₂SO₄). The solvent was evaporated and the residue purified by column chromatography (diethyl ether) to give the phenyl carbonate 137 (0.013 g, 75%) as an orange gummy solid; m.p. 54°C (dec.); λ_max (MeOH) 480 (log ε 3.11), 346 (3.29), 292 (4.09), 244 (4.14) and 223 nm (4.20); u_max (film) 1669, 1630 and 1597 cm⁻¹; δ_H (400 MHz; CDCl₃) 7.29-6.94 (5H, m, Ar-H), 5.57 (1H, s, 7-H), 5.36 (2H, AB, J 12, 11-H), 5.01 (1H, m, 4-CH_H), 3.79 (3H, s, OMe), 3.56 (1H, m, 4-CH_Hf), 2.32-2.16 (3H, m, 3-CH_H and 1-H), 1.61 (1H, m, 2-H) and 0.97 (2H, m, 1a-CH_H); δ_C (100.6 MHz; CDCl₃) 178.64 (9-C), 178.22 (6-C), 159.61 (8-C/OCOOPh), 158.75 (OCOOPh/8-C), 139.47 (4a-C), 129.43, 127.29, 121.46, 120.91, 116.48, 115.18, 106.73 (7-C), 60.60 (11-C), 56.41 (OMe), 40.08 (4-C), 20.55 (3-C), 12.11 (2-C), 9.42 (1a-C) and 8.37 (1-C).
Experimental for Chapter Three

4-Benzylxoy-5-methoxy-1-(1-phenyl-1-propenyl)indole-2-carboxaldehyde 213

To a flask charged with sodium hydride (80%; 0.202 g, 8.41 mmol) was added dry light petroleum (10 cm³). The mixture was stirred for 10 min, the petroleum removed by syringe and the flask contents dried under reduced pressure. 4-Benzylxoy-5-methoxyindole-2-carboxaldehyde 143 (1.873 g, 6.66 mmol) in DMF (150 cm³) was added dropwise and the mixture was stirred at room temperature for 1 h. Cinnamyl bromide (2.625 g, 13.32 mmol) was added and the mixture was stirred at room temperature. After 12 h, water (85 cm³) was cautiously added and the mixture was extracted with diethyl ether (4 x 150 cm³). The combined ethereal extracts were washed with water (8 x 100 cm³), brine (100 cm³), dried (MgSO₄) and evaporated to give the title compound 213 (1.746 g, 66%) as a yellow solid, m.p. 105° C; (Found: C, 78.7; H, 5.9; N, 3.3 C₂₆H₂₃N0₃ requires C, 78.6; H, 5.8; N, 3.5%); \(\nu_{max}\) (Nujol) 1666, 1519, 1488, 1377 and 1142 cm⁻¹; \(\delta_H\) (250 MHz; CDCl₃) 9.81 (1H, s, CHO), 7.49 (2H, m, Ar-H), 7.38-7.25 (4H, m, Ar-H), 7.22 (4H, m, Ar-H), 7.17 (2H, m, 7/6-H), 7.12 (1H, s, 3-H), 6.34 (2H, m, N-CH₂), 5.32 (2H, m, CH₂CH=CHPh), 5.29 (2H, s, OCH₂Ph) and 3.91 (3H, s, OMe); \(\delta_C\) (69.2 MHz; CDCl₃) 182.45 (CHO) 145.19, 137.82, 137.40, 136.31, 135.28, 131.85, 128.83, 128.46, 128.41, 128.07, 127.99, 127.69, 126.43, 126.20, 124.87, 118.17, 115.33, 105.93, 75.19 (OCH₂Ph), 58.43 (OMe) and 46.55 (NCH₂); m/z 397 (MH⁺, 8%), 155 (14), 117 (88), 91 (100) and 51 (56).
4-Benzylxy-5-methoxy-1-(1-phenyl-1-propenyl)indole-2-carboxaldehyde
tosylhydrazone 214

4-Benzylxy-5-methoxy-1-(1-phenyl-1-propenyl)indole-2-carboxaldehyde 213 (0.842 g, 2.12 mmol) was added to a stirred solution of toluenesulfonyl hydrazide (0.510 g, 2.74 mmol) in dry methanol (25 cm³). After stirring the mixture at 40°C for 3 h, the solvent was removed in vacuo and the dark green residue was purified by column chromatography (50% diethyl ether : 50% light petroleum) to give a cream foam. Recrystallisation of this foam from ethyl acetate and light petroleum gave the title compound 214 (0.731 g, 61%) as a colourless solid; m.p. 142°C, (Found: C, 70.2; H, 5.2; N, 7.7. C₃₃H₃₁N₃O₄S requires C, 70.1; H, 5.5; N, 7.4%); νₘₐₓ (Nujol) 3209, 3185, 1711, 1517 and 1162 cm⁻¹; δₜ (250 MHz; CDCl₃) 7.75 (3H, m, Ar-H), 7.46 (2H, s, N-CH₃), 7.25-7.22 (8H, m, Ar-H), 7.00 (4H, m, 7/6-H and Ar-H), 6.66 (1H, s, 3-H), 6.23 (2H, m, CH₂CH=CHPh), 5.20 (2H, s, OCH₂Ph), 5.19 (2H, s, N-CH₂), 3.86 (3H, s, OMe) and 2.18 (3H, s, Ar-Me); m/z (FAB, 3-NBA Matrix) 566 (MH⁺, 63%), 474 (54), 290 (18) and 117 (100).

8-Benzylxy-7-methoxy-1,2-dihydro-1a-phenyl-3H-1,2-cyclopropypyrrolo[1,2-ajindole 215

Sodium hydride (80%; 0.069 g, 2.85 mmol) was added to a stirred solution of the tosylhydrazone 214 (0.253 g, 0.45 mmol) in dry THF (10 cm³). After 2 h the solution
was filtered and the filtrate evaporated. The residue was dissolved in dry chlorobenzene (100 cm$^3$) and the solution refluxed for 12 h. The solvent was evaporated and the residue purified by column chromatography (50% diethyl ether/50% light petroleum) to give the *title compound* 215 (0.144 g, 84%) as a pale yellow oil (Found: $M^+$, 381.1735. C$_{26}$H$_{23}$NO$_2$ requires $M$, 381.1729); $\nu_{\text{max}}$ (film) 1602, 1577, 1570, 1561, 1491, 1454, 1434 and 1254 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 7.53 (2H, m, Ar-H), 7.36-7.19 (6H, m, Ar-H), 7.07-7.04 (2H, m, Ar-H), 6.83 (2H, m, 6/5-H), 6.25 (1H, s, 9-H), 5.21 (2H, s, OCH$_2$Ph), 4.17 (2H, m, NCH$_2$), 3.86 (3H, s, OMe), 2.66 (2H, m, 1-H and 2-H) and 2.06 (1H, m, 1a-H); $\delta_C$ (62.9 MHz; CDCl$_3$) 145.94, 145.25, 139.99, 131.01, 130.55, 129.53, 128.53, 128.29, 127.96, 127.67, 126.26, 126.12, 125.52, 110.44 (6/5-C), 104.24 (5/6-C), 89.81, 74.93 (OCH$_2$Ph), 58.50 (OMe), 47.17, 34.62 (1a-C), 31.51 (2-C) and 27.05 (1-C); $m/z$ 381 ($M^+$, 10%), 290 (41), 247 (7), 200 (9), 170 (8), 117(14) and (100).

8-Benzylxoy-7-methoxy-1,2-dihydro-1a-phenyl-3H-1,2-cyclopropapyrollo[1,2-
a]indole-9-carboxaldehyde 216

DMF (0.58 cm$^3$) and phosphorus oxychloride (0.70 cm$^3$) were stirred under a calcium oxide drying tube for 10 min. The resulting yellow precipitate was cooled to 0°C and an amount of this yellow precipitate (0.212 g, 0.069 g, 0.94 mmol DMF and 0.144 g, 0.94 mmol phosphorus oxychloride) was added to 8-benzylxoy-7-methoxy-1,2-dihydro-1a-phenyl-3H-1,2-cyclopropapyrollo[1,2-a]indole 215 (0.298 g, 0.78 mmol) in DMF (20 cm$^3$). The mixture was stirred at room temperature for 2 h. Sodium acetate (1M, 5 cm$^3$) was added to the mixture which was then extracted with ethyl acetate (3 x 20 cm$^3$). The combined extracts were washed with water (6 x 20 cm$^3$), brine (50 cm$^3$) and dried (MgSO$_4$). Removal of the solvent in vacuo gave a brown solid which was triturated with a small quantity of ethyl acetate and the resulting precipitate filtered off. The mother liquors were purified by column chromatography (diethyl ether) to give the *title compound* 216 (0.188 g, 59%) as pale yellow solid, m.p.144°C (Found: $M^+$, 409.1723. C$_{27}$H$_{23}$NO$_3$ requires $M$, 409.1678); $\nu_{\text{max}}$ (Nujol) 1648, 1529 and 1491 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 10.34 (1H, s, CHO), 7.51-7.47 (2H, m, Ar-H), 7.40-7.22 (6H, m, Ar-H), 7.14-7.10 (2H, m, Ar-H), 6.91 (2H, m, 5-H and 6-H), 5.19 (2H, s, OCH$_2$Ph), 4.26 (2H,
m, NCH$_2$), 3.92 (3H, s, OMe), 3.30 (1H, m, 1-H), 2.73 (1H, m, 2-H) and 2.13 (1H, t, J 3.44, 1a-H); $\delta$C (62.9 MHz; CDCl$_3$) 186.30 (CHO), 153.07, 148.01, 141.57, 138.78, 137.47, 129.61, 128.59, 128.47, 128.45, 128.07, 126.75, 125.05, 123.02, 110.63 (6/5-C), 110.09, 105.37 (5/6-C), 74.90 (OCH$_2$Ph), 57.69 (OMe), 48.13 (3-C), 34.78 (1a-C), 31.07 (2-C) and 28.18 (1-C); m/z 409 (M$^+$, 15%), 318 (64), 91 (77), 51 (100).

8-Hydroxy-7-methoxy-1,2-dihydro-1a-phenyl-3H-1,2-cyclopropapyrrolo[1,2-a]indole-9-carboxaldehyde 224

To a solution of 8-benzylxy-7-methoxy-1,2-dihydro-1a-phenyl-3H-1,2-cyclopropapyrrolo[1,2-a]indole-9-carboxaldehyde 216 (0.131 g, 0.32 mmol) in ethanol (150 cm$^3$) was added 10% palladium on carbon (0.093 g). The mixture was stirred under an atmosphere of hydrogen for 12 h. After this time, the suspension was filtered and washed with dichloromethane (150 cm$^3$). The combined filtrate and washings were washed with water (3 x 50 cm$^3$), brine (50 cm$^3$) and dried (MgSO$_4$). The organic layer was evaporated to dryness to give a brown residue. Purification of the residue by column chromatography (diethyl ether) gave the title compound 224 (0.093 g, 87%) as a colourless solid, m.p. 176°C, (Found: M$^+$, 318.1135. C$_{20}$H$_{16}$N$_2$O$_3$ requires M, 318.1130); $\nu_{\max}$ (film) 1603, 1298, 1252 and 732 cm$^{-1}$; $\delta$H (400 MHz; CDCl$_3$) 10.84 (1H, s, OH), 9.24 (1H, s, CHO), 7.34-7.23 (5H, m, Ar-H), 6.84 (1H, d, J 8.5, 6/5-H), 6.50 (1H, d, J 8.5, 5/6-H), 4.08-4.01 (2H, m, NCH$_2$), (3H, s, OMe), 2.97 (1H, m, 1-H), 2.89 (1H, m, 2-H) and 2.23 (1H, t, J 3.6, 1a-H); $\delta$C (100.6 MHz; CDCl$_3$) 183.32 (CHO), 157.72, 143.23, 141.85, 138.08, 130.26, 128.88, 128.69, 127.18, 125.76, 119.22, 112.86 (6/5-C), 111.14, 99.93 (5/6-C), 57.87 (OMe), 48.59 (3-C), 34.71 (1a-C), 31.09 (2-C) and 26.57 (1-C); m/z 318 (M$^+$, 3%), 267 (15), 186 (23), 155 (39), 91 (30), 51 (67) and 31 (100).
Potassium nitrosodisulfonate (0.089 g, 0.33 mmol) was added to a solution of 8-hydroxy-7-methoxy-1a-phenyl-3H-1,2-cyclopropapyrrolo[1,2-a]indole-9-carboxaldehyde 224 (0.048 g, 0.15 mmol) in acetone (17 cm³), sodium dihydrogen phosphate (0.167M, 17 cm³) solution and water (6 cm³) and the resulting suspension stirred at room temperature for 12 h. The mixture was extracted with ethyl acetate (3 x 50 cm³) and the combined organics were dried (Na₂SO₄) and evaporated. Purification of the residue by column chromatography (ethyl acetate) gave the title compound 225 (0.085 g, 94%) as orange crystals, m.p. 185°C, (Found: M⁺, 333.0991. C₂₀H₁₅NO₄ requires M, 333.1001); λₚₑᵧ (MeOH) 455 (log ε 2.36), 283 (3.74) and 223 nm (3.81); νₚₑᵧ (Nujol) 1678, 1671, 1666, 1639, 1594 and 1508 cm⁻¹; δₜ (250 MHz; CDCl₃) 10.36 (1H, s, CHO), 7.37-7.18 (5H, m, Ar-H), 5.70 (1H, s, 6-H), 4.39 (1H, m, 3-CH₃), 3.96 (1H, m, 3-CH₂), 3.85 (2H, s, OMe), 3.33 (2H, m, 1H and 2-H) and 2.91 (1H, m, 1a-H); δₑ (100.6 MHz; CDCl₃) 186.41 (CHO), 178.10 (8-C), 177.21 (5-C), 160.83 (7-C), 149.56 (4a-C), 138.37 (9a/8a-C), 138.00 (8a/9a-C), 128.70, 127.05, 126.10, 115.90 (9-C), 105.56, 105.43 (6-C), 56.77 (OMe), 51.07 (3-C), 33.93 (1a-C), 30.77 (2-C) and 26.66 (1-C); m/z 333 (M⁺, 16%), 267 (24), 217 (30), 186 (28), 155 (56), 113 (51) and 51 (100).
9-Hydroxymethyl-7-methoxy-1,2-dihydro-1a-phenyl-3H-1,2-cyclopapyrrolo[1,2-ajindole-5,8-dione 228
Sodium borohydride (0.051 g, 1.34 mmol) was added to a stirred solution of the quinone aldehyde 225 (0.063 g, 0.19 mmol) in methanol (43 cm³). After stirring for 1 h at room temperature, air was blown rapidly through the solution and the mixture was extracted with dichloromethane (3 x 75 cm³). The combined extracts were washed with water, (3 x 75 cm³), brine (75 cm³) and dried (Na₂SO₄). The solvent was evaporated and the residue purified by column chromatography (ethyl acetate) to give the title compound 228 (0.049 g, 78%) as a red solid, m.p. 157°C, (Found: M⁺ 335.1160. C₂₀H₁₇N₀₄ requires M, 335.1158); λmax (MeOH) 474 (log ε 1.99), 346 (2.31), 285 (3.06), 244 (3.23) and 205 nm (3.27); νmax (Film) 3400, 1669, 1635, 1586 and 1492 cm⁻¹; δH (250 MHz; CDCl₃) 7.36-7.06 (5H, m, Ar-H), 5.64 (1H, s, 6-H), 4.68 (2H, m, 10-H), 4.43 (2H, m, 3-CH₂), 3.90 (1H, m, OH), 3.84 (3H, s, OMe), 2.66 (2H, m, 1H and 2-H) and 2.04 (1H, m, la-H); δC (100.6 MHz) 178.85 (8-C), 177.68 (5-C), 160.70 (7-C), 142.81, 138.76, 128.72, 127.35, 126.78, 125.59, 125.01, 117.51, 105.90 (6-C), 56.69 (10-C), 56.49 (OMe), 50.51 (3-C), 33.65 (1a-C), 30.69 (2-C) and 24.83 (1-C); m/z 335 (M⁺, 19%), 317 (15), 267 (17), 236 (14), 217 (21), 186 (21), 155 (45), 124 (27), 113 (40), 91 (37), 70 (23), 51 (100) and 31 (73).
9-Hydroxymethyl-7-methoxy-1,2-dihydro-1a-phenyl-3H-1,2-cyclopropapyrrolo[1,2-a]indole-5,8-dione carbamate 230

Phenyl chloroformate (0.018 cm³; 0.022 g, 0.14 mmol) was added dropwise to a stirred, ice cold solution of the alcohol 228 (0.0296 g, 0.09 mmol) in dry THF (10 cm³) and pyridine (10 drops). The mixture was stirred at room temperature for 2 h, then water (5 cm³) was added. The mixture was extracted with dichloromethane (3 x 25 cm³) and the combined extracts were washed with water (3 x 25 cm³), CuSO₄ (25 cm³), brine (50 cm³) and dried (Na₂SO₄). The solvent was evaporated and the residue purified by column chromatography (diethyl ether) to give the phenyl carbonate as an orange gummy solid.

A solution of phenyl carbonate in dry dichloromethane (25 cm³) was cooled to -78°C. Ammonia gas was bubbled into the solution for approximately 45 min (150 cm³), after which time the contents were allowed to warm to room temperature and the solvent removed in vacuo. Purification of the residue by column chromatography (diethyl ether) gave the title compound 230 (0.0298 g, 89%) as an orange crystalline solid, m.p. 144°C, (Found: PegH, 415.2545. C₂₁H₁₈N₂O₅ requires PegH, 415.2543), λ_max (MeOH) 462 (log ε 2.04), 345 (2.22), 289 (3.17) and (233 (3.19), υ_max (Film) 3379, 3211, 1767, 1671, 1636, 1590, 1498, 1401, 1347 and 1237 cm⁻¹, δ_H (400 MHz; CDCl₃) 7.30-7.09 (5H, m, Ar-H), 5.62 (1H, s, 6-H), 5.26 (2H, m, 10-H), 4.58 (2H, br s, NH₂), 4.43 (2H, m, 3-H), 3.80 (3H, s, OMe), 2.82 (1H, m, 1-H or 1a-H), 2.63 (1H, m, 1-H or 1a-H) and 2.02 (2H, m, 2-H); δ_C (100.6 MHz; CDCl₃) 177.87 (8-C), 177.63 (5-C), 160.56 (7-C/CONH₂), 156.79 (CONH₂/7-C), 146.38 (4a-C), 129.35 (9a/8a-C), 123.90 (8a/9a-C), 117.53 (9-C), 105.94 (6-C), 56.72 (10-C), 56.53 (OMe), 50.62 (2-C), 33.89 (1a-C), 30.74 (2-C) and 25.03 (1-C); m/z 379 (M + H⁺, 11%), 330 (15), 308 (15), 290 (12), 179 (15), 156 (23) and 140 (20).
6.5 Experimental for Chapter Four

4-Benzyloxy-5-methoxyindole 242
Bis (triphenylphosphine) carbonylrhodium chloride (0.197 g, 0.29 mmol) was suspended in dry degassed mesitylene (20 cm$^3$) and warmed to 80°C. After 10 min, 1,3-bis (diphenylphosphino)propane (0.344 g, 0.84 mmol) was added and a yellow precipitate formed. After a further 10 min 4-benzyloxy-5-methoxyindole-2-carboxaldehyde 143 (0.750 g, 2.67 mmol) was added and the flask plunged into a woods metal bath at 190°C. The mixture was refluxed for 2 h. The crude mixture was concentrated and purified by column chromatography (50% diethyl ether/50% light petroleum) to give the title compound 242 (0.608 g, 90%) as a brown solid; m.p. 83-84°C (lit. 83-84°C); $\nu_{\text{max}}$ (Nujol) 3327, 3024 and 1490 cm$^{-1}$; $\delta_H$ (250 MHz; CDCl$_3$) 8.09 (1H, br s, NH), 7.54-7.51 (2H, m, Ar-H), 7.40-7.26 (3H, m, Ar-H), 7.03 (3H, m, 7/6-H and 2-H), 6.55 (IH, m, 3-H), 5.24 (2H, s, OCH$_2$Ph) and 3.88 (3H, s, OMe); $\delta_C$ (69.2 MHz; CDCl$_3$) 145.11, 138.35, 132.80, 128.31, 128.06, 127.75, 124.55, 118.40, 112.13, 107.40, 106.22, 100.02, 74.99 (OCH$_2$Ph), 58.54 (OMe).

4-Benzyloxy-5-methoxyindole-3-carboxaldehyde 243
DMF (0.68 cm$^3$; 0.652 g, 8.92 mmol) and phosphorus oxychloride (0.19 cm$^3$; 0.316 g, 2.06 mmol) were stirred at -5°C for 30 min. A solution of 4-benzyloxy-5-methoxyindole 242 (0.466 g, 1.84 mmol) in DMF (3 cm$^3$) was added slowly dropwise maintaining the temperature below 10°C. After the addition was completed the mixture was stirred at 35°C for 1 h. Ice water (10 cm$^3$) followed by sodium hydroxide solution
(37%; 10 cm³) was added and the mixture extracted with diethyl ether (3 x 100 cm³). The ether layer was dried (MgSO₄) and concentrated in vacuo. The crude mixture was columned (50% diethyl ether/50% light petroleum) giving the title compound 243 (0.269 g, 57%) as a colourless solid, mp. 113-114°C (lit. 113-114°C); \( \nu_{\text{max}} \) (Nujol) 3033, 2964, 1712 and 1634 cm⁻¹; \( \delta_H \) (250 MHz; CDCl₃) 10.26 (IH, s, CHO), 10.25 (1H, br s, NH), 7.75 (1H, d, J 3.23, 2-H), 7.49-7.28 (5H, m, Ar-H), 7.04 (1H, d, J 8.75, 7/6-H), 6.93 (1H, d, J 8.75, 6/7-H), 5.20 (2H, s, OCH₂Ph), 3.90 (3H, s, OMe); \( \delta_C \) (69.2 MHz; CDCl₃) 187.28, 147.82, 140.80, 137.36, 133.40, 132.43, 128.65, 128.47, 128.19, 120.95, 118.28, 111.94 (7/6-C), 108.28 (6/7-C), 75.42 (OCH₂Ph), 57.63 (OMe).

4-Benzylxoy-1-(3-chloropropyl)-5-methoxyindole-3-carboxaldehyde 258

A mixture of 4-benzyloxy-5-methoxyindole-5-carboxaldehyde 243 (0.122 g, 0.43 mmol), powdered 87% potassium hydroxide (0.033 g, 0.59 mmol) and DMSO (3 cm³) was sonicated for 10 min, and then cooled to 0°C. 1-Bromo-3-chloropropane (0.16 cm³, 0.252 g, 1.60 mmol) was added at 0°C, and the mixture was stirred at room temperature. After 4 h, water (15 cm³) was added and the mixture was extracted with ethyl acetate (3 x 75 cm³). The combined extracts were washed with water (6 x 50 cm³), brine (2 x 25 cm³) and dried (Na₂SO₄). The solvent was removed in vacuo and the residue was purified by column chromatography (50% light petroleum/50% ethyl acetate) to give the title compound 258 (0.115 g, 74%) as a yellow oil, (Found: \( M^+ \), 357.1132. C₂₀H₂₀ClNO₃ requires \( M \), 357.1132); \( \nu_{\text{max}} \) (film) 1651, 1517, 1497, 1260, 1175 and 1122 cm⁻¹; \( \delta_H \) (400 MHz; CDCl₃) 10.35 (1H, s, CHO), 7.86 (1H, s, CHO), 7.49 (2H, m, Ar-H), 7.40-7.33 (3H, m, Ar-H), 7.15 (1H, d, J 8.4, 7/6-H), 7.06 (1H, d, J 8.4, 6/7-H), 5.26 (2H, s, OCH₂Ph), 4.35 (2H, t, J 6.8, NCH₂), 3.98 (3H, s, OMe), 3.50 (2H, t, J 6.0, CH₂Cl) and 2.32 (2H, q, J 6.4, CH₂); \( \delta_C \) (100.6 MHz; CDCl₃) 188.81 (CHO), 149.77, 143.71, 139.32, 135.34, 134.96 (2-C), 130.38, 130.05, 129.98, 123.92, 119.61, 113.99 (7/6-C), 107.75 (6/7-C), 76.98 (OCH₂Ph), 59.74 (OMe), 45.86 (NCH₂), 43.16 (CH₂) and 34.04 (CH₂Cl); \( m/z \) 357 (\( M^+ \), 6%), 329 (6), 266 (38), 251 (12), 91 (100), 77 (12) and 65 (29).
4-Benzyl oxy-1-(3-iodopropyl)-5-methoxyindole-3-carboxaldehyde 259
A solution of 4-benzyl oxy-1-(3-chloropropyl)-5-methoxyindole-3-carboxaldehyde 258 (0.092 g, 0.26 mmol) in acetonitrile (8 cm³) containing sodium iodide (0.218 g, 1.45 mmol) was heated at reflux temperature for 12 h. Water (5 cm³) was added and the mixture extracted with dichloromethane (3 x 50 cm³). The extract was washed with water (3 x 25 cm³), saturated aqueous sodium sulfite solution (50 cm³) and dried (Na₂SO₄). The solvent was removed in vacuo and the residue purified by column chromatography (diethyl ether) to give the title compound 259 (0.098 g, 85%) as a yellow oil, (Found: M⁺, 449.0488. C₂₀H₂₀INO₃ requires M⁺, 449.0488); νmax (film) 1652, 1515, 1497, 1260, 1123 and 1060 cm⁻¹; δH (400 MHz; CDCl₃) 10.25 (1H, s, CHO), 7.77 (1H, s, 2-H), 7.39 (2H, m, Ar-H), 7.28-7.23 (3H, m, Ar-H), 7.05 (1H, d, J 8.8, 7/6-H), 6.96 (1H, d, J 8.8, 6/7-H), 5.15 (2H, s, OCH₂Ph), 4.17 (2H, t, J 6.4, NCH₂), 3.87 (3H, s, OMe), 3.00 (2H, t, J 6.4, CH₂), and 2.25 (2H, q, J 6.8, CH₂); δC (100.6 MHz; CDCl₃) 186.86 (CHO), 147.85, 141.80, 137.37, 133.39, 132.90 (2-C), 128.44, 128.11, 128.35, 122.00, 117.68, 112.07 (7/6-C), 105.87 (6/7-C), 75.05 (OCH₂Ph), 57.81 (OMe), 47.22 (NCH₂), 32.82 (CH₂) and 1.64 (CH₂); m/z 449 (M⁺, 11%), 421 (8), 358 (34), 91 (100), 51 (15) and 28 (21).

8-Benzyl oxy-7-methoxy-1,2-dihydro-3H-pyrrolo[1,2-a]indole-9-carboxaldehyde 261
A solution of tri-n-butyltin hydride (0.10 cm³; 0.109 g, 0.38 mmol) and AIBN (0.038 g, 0.23 mmol) in toluene (2 cm³) was added to 4-benzyl oxy-1-(3-iodopropyl)-5-methoxyindole-3-carboxaldehyde 259 (0.0841 g, 0.19 mmol) in toluene (1.65 cm³) at reflux over 15 min. The reaction was stirred at reflux for 3 h and a further portion of tri-
n-butyltin hydride (0.03 cm$^3$)/AIBN (0.013 g) was added over 5 min. After a further 20 min at reflux the mixture was allowed to cool to room temperature and the solvent removed in vacuo. Water (0.25 cm$^3$), ethyl acetate (3 cm$^3$) and potassium fluoride (0.150 g) were added and the mixture stirred at room temperature. After 12 h, a further portion of water, ethyl acetate and potassium fluoride were added and the mixture stirred for 2 h. Potassium carbonate was added, the mixture filtered and the solvent removed in vacuo. The residue was purified by column chromatography (diethyl ether) to give the title compound 261 (0.028 g, 47%) as a pale yellow oil; (Found: $M^+$, 321.1365. C$_{20}$H$_{19}$N$_{03}$ requires $M$, 321.1365); $\nu$$_{max}$ (film) 1645, 1490, 1388, 1256, 1099 and 700 cm$^{-1}$; $\delta$$_H$ (400 MHz; CDCl$_3$) 10.32 (1H, s, CHO), 7.47 (2H, m, Ar-H), 7.38-7.30 (3H, m, Ar-H), 6.95 (2H, AB, J 8.4, 6.5-H), 5.20 (2H, s, OCH$_2$Ph), 4.07 (2H, t, J 7.2, NCH$_2$), 3.93 (3H, s, OMe), 3.31 (2H, t, J 7.2, 1-H) and 2.66 (2H, m, 2-H); $\delta$$_C$ (100.6 MHz; CDCl$_3$) 186.81, 153.22, 148.02, 142.50, 137.58, 129.58, 128.46, 128.07, 125.90, 110.96 (6.5-C), 109.96, 105.86 (5.6-C), 74.87 (OCH$_2$Ph), 57.77 (OMe), 44.57 (NCH$_2$), 26.69 (2-C) and 26.66 (1-H); $m/z$ 321 ($M^+$, 21%), 230 (100), 215 (40), 91 (40), 77 (10), 65 (26) and 51 (8).

4-Benzylxy-1-(4-chlorobutyl)-5-methoxyindole-3-carboxaldehyde 244

A mixture of 4-benzylxy-5-methoxyindole-3-carboxaldehyde 243 (0.357 g, 1.27 mmol), powdered 87% potassium hydroxide (0.089 g, 1.59 mmol) and DMSO (7 cm$^3$) was sonicated for 10 min, and then cooled to 0°C. 1-Bromo-4-chlorobutane (0.44 cm$^3$; 0.653 g, 4.81 mmol) was added at 0°C, and the mixture was then stirred at room temperature for 4 h. The reaction mixture was poured into water (15 cm$^3$), and the product was extracted into ethyl acetate (3 x 150 cm$^3$). The extract was washed with water (6 x 100 cm$^3$), brine (2 x 75 cm$^3$) and dried (Na$_2$SO$_4$). The solvent was removed in vacuo and the residue was purified by column chromatography (diethyl ether) to give the title compound 244 (0.395 g, 84%) as a colourless solid, m.p. 82°C; (Found: C, 67.5; H, 6.0; N, 4.0. C$_{21}$H$_{22}$ClN$_{03}$ requires C, 67.8; H, 6.0; N, 3.8%); $\nu$$_{max}$ (Nujol) 1709, 1645, 1517, 1496, 1255 and 1120 cm$^{-1}$; $\delta$$_H$ (400 MHz; CDCl$_3$) 10.33 (1H, s, CHO),
7.82 (1H, s, 2-H), 7.49-7.46 (2H, m, Ar-H), 7.37-7.32 (3H, m, Ar-H), 7.06 (2H, AB, J 8.81, 7/6-H), 5.24 (2H, s, OCH2Ph), 4.15 (2H, t, J 6.8, NCH2), 3.96 (3H, s, OMe), 3.54 (2H, t, J 6.0, CH2Cl), 2.06 (2H, m, 2-CH2) and 1.80 (2H, m, 3-CH2); δC (100.6 MHz; CDCl3) 186.93 (CHO), 147.82, 141.83, 137.46, 133.49, 132.77 (2-C), 128.35, 128.48, 128.14, 122.06, 117.51, 112.04 (7/6-C), 105.88 (6n-C), 75.07 (OCH2Ph), 57.86 (OMe), 46.72 (NCH2), 44.07 (2-C), 29.57 (3-C), 27.03 (CH2Cl); m/z 371 (M+, 45%), 373 (17), 280 (100), 245 (17), 190 (11) and 91 (70).

4-Benzylxoy-1-(4-iodobutyl)-5-methoxyindole-3-carboxaldehyde 245

A solution of the chloride 244 (0.359 g, 0.97 mmol) in acetonitrile (12 cm³) containing sodium iodide (0.599 g, 4.00 mmol) was heated at reflux temperature for 12 h. The solution was poured into water (15 cm³) and extracted with dichloromethane (3 x 100 cm³). The extract was washed with water (3 x 75 cm³), saturated aqueous sodium sulfite solution (50 cm³) and dried (Na2SO4). The solvent was removed in vacuo and the residue purified by column chromatography (diethyl ether) to give the title compound 245 (0.322 g, 72%) as a colourless solid, m.p. 96°C; (Found: M+, 463.0650. C21H22IN03 requires M, 463.0646); νmax (Nujol) 1651, 1511, 1494, 1254, 1120 and 1052 cm⁻¹; δH (400 MHz; CDCl3) 10.32 (1H, s, CHO), 7.79 (1H, s, 2-H), 7.46 (2H, m, Ar-H), 7.37-7.30 (3H, m, Ar-H), 7.05 (2H, AB, J 9.6, 7/6-H), 5.23 (2H, s, OCH2Ph), 4.12 (2H, t, J 7.2, NCH2), 3.95 (3H, s, OMe), 3.16 (2H, t, J 6.8, CH2I), 2.00 (2H, m, 2-CH2) and 1.82 (2H, m, 3-CH2); δC (100.6 MHz; CDCl3) 186.91 (CHO), 147.82, 141.82, 137.45, 133.47, 132.74 (2-C), 128.47, 128.13, 122.04, 117.51, 112.03 (7/6-C), 105.89 (6n-C), 75.06 (OCH2Ph), 57.86 (OMe), 46.36 (NCH2), 30.50 (2-C), 30.30 (3-C), 4.99 (CH2I); m/z 463 (M+, 15%), 435 (13), 372 (57), 244 (22), 202 (15), 174 (17), 155 (13), 113 (10), 91 (100), 65 (21), 55 (31) and 28 (85).
9-Benzylx-8-methoxy-1,2,3,4-tetrahydropyridino[1,2-ajindole-10-carboxaldehyde 246

(a) To an ultrasonically irradiated solution of iron(II)sulfate heptahydrate (0.041 g, 0.15 mmol) and the iodide 245 (0.054 g, 0.12 mmol) in DMSO (4 cm$^3$) was added 30% hydrogen peroxide (0.13 cm$^3$; 0.040 g, 1.16 mmol) dropwise as rapidly as was feasible so that the reaction temperature did not exceed 40°C. This addition never required more than 30 min. When the peroxide addition was completed, the reaction was poured into water (15 cm$^3$) and extracted with dichloromethane (3 x 75 cm$^3$). The extract was washed with water (3 x 50 cm$^3$), 10% aqueous sodium sulfite solution (5 x 25 cm$^3$) and dried (Na$_2$SO$_4$). Removal of the solvent in vacuo gave a brown solid which was purified by column chromatography (diethyl ether) to give the title compound 246 (0.013 g, 33%) as a colourless oil, (Found: $M^+$, 335.1524. C$_{21}$H$_{21}$NO$_3$ requires $M$, 335.1521); $v_{\text{max}}$ (film) 1642, 1491, 1392, 1287, 1093 and 735 cm$^{-1}$; $\delta_H$ (400 MHz; CD$_3$C$_6$H$_2$CD$_3$) 10.49 (1H, s, CHO), 7.51-7.48 (2H, m, Ar-H), 7.39-7.32 (3H, m, Ar-H), 6.98 (2H, AB, $J$ 8.8, 7/6-H), 5.19 (2H, s, OCH$_2$Ph), 4.04 (2H, t, $J$ 6.0, NCH$_2$), 3.94 (3H, s, OMe), 3.35 (2H, t, $J$ 6.4, 1-H), 2.09 (2H, m, 3/2-H) and 1.94 (2H, m, 2/3-H); $\delta_C$ (100.6 MHz; CDCl$_3$) 187.56 (CHO), 148.23, 146.43, 141.26, 137.59, 133.03, 128.47, 128.04, 121.86, 112.76, 110.34 (7/6-C), 105.21 (6/7-C), 74.82 (OCH$_2$Ph), 57.96 (OMe), 42.59 (NCH$_2$), 25.29 (1-C), 22.31 (3-C) and 19.54 (2-C); $m/z$ 335 ($M^+$, 14%), 267 (13), 244 (100), 186 (15), 155 (29), 91 (43), 51 (50) and 28 (41).

(b) A solution of tri-n-butyltin hydride (0.50 cm$^3$; 0.550 g, 1.19 mmol) and AIBN (0.157 g, 0.96 mmol) in toluene (16 cm$^3$) was added to 4-benzyloxy-1-(4-iodobutyl)-5-methoxyindole-3-carboxaldehyde (0.438 g, 0.95 mmol) in toluene (12 cm$^3$) at reflux over 15 min. The reaction was stirred at reflux for 3 h and a further portion of tri-n-butyltin hydride (0.20 cm$^3$/AIBN (0.053 g) was added over 5 min. After a further 20 min at reflux the mixture was allowed to cool to room temperature and the solvent removed in vacuo. Water (0.25 cm$^3$) ethyl acetate (3 cm$^3$) and potassium fluoride (0.150 g) were added and the mixture stirred at room temperature. After 12 h, a further portion of water, ethyl acetate and potassium fluoride were added and the mixture stirred for 2 h. Potassium carbonate was added, the mixture filtered and the solvent removed in vacuo. The residue was purified by column chromatography (diethyl ether) to give the
**Title Compound 246** (0.231 g, 73%) as a colourless solid; spectroscopic data identical to the sample prepared by the above route.

![Diagram](image)

**9-Hydroxy-8-methoxy-1,2,3,4-tetrahydropyrido[1,2-a]indole-10-carboxaldehyde 166**

To a solution of 9-benzyloxy-8-methoxy-1,2,3,4-tetrahydropyrido[1,2-a]indole-10-carboxaldehyde 246 (0.018 g, 0.054 mmol) in ethanol (50 cm³) was added 10% palladium on carbon (0.04 g). The mixture was stirred under an atmosphere of hydrogen (60 psi) for 12 h. After this time, the suspension was filtered and washed with dichloromethane. The combined filtrate and washings were washed with water (3 x 25 cm³), brine (20 cm³) and dried (Na₂SO₄). The organic layer was evaporated to dryness to give a brown solid. Purification of the residue by column chromatography (diethyl ether) gave the **title compound 166** (0.009 g, 69%) as a colourless solid, m.p. 110°C; (Found: M⁺, 245.1044. C₁₄H₁₅NO₃ requires M, 245.1052); νmax (film) 1597, 1579, 1506, 1434, 1314, 1254 and 1079 cm⁻¹; δH (250 MHz; CDCl₃) 11.11 (1H, s, OH), 9.61 (1H, s, CHO), 6.94 (1H, d, J 8.5, 7/6-H), 6.65 (1H, d, J 8.5, 6/7-H), 4.00 (2H, t, J 6.0, NCH₂), 3.92 (3H, s, MeO), 3.23 (2H, t, J 6.25, 1-H), 2.13 (2H, m, 3/2-H) and 1.99 (2H, m, 2/3-H); δH (100.6 MHz; CDCl₃) 182.92, 150.32, 143.34, 141.38, 133.77, 115.69, 114.21, 112.51 (7/6-C), 107.55 (6/7-C). 57.83 (MeO), 42.59 (NCH₂), 29.71 (1-C), 22.26 (3-C) and 19.27 (2-C); m/z 245 (M⁺, 10%), 149 (29), 71 (62), 57 (100), 43 (51) and 28 (13).
10-Formyl-8-methoxy-1,2,3,4-tetrahydropyrido[1,2-a]indole-6,9-dione 241
Potassium nitrosodisulfonate (0.022 g) was added to a solution of the phenol 166 (0.009 g, 0.037 mmol) in acetone (5 cm³), sodium dihydrogen phosphate solution (0.167M, 2 cm³) and water (2 cm³) and the resulting suspension stirred at room temperature for 12 h. The mixture was extracted with dichloromethane (3 x 10 cm³) and the combined organic extracts were dried (Na₂SO₄) and evaporated. Purification of the residue by column chromatography (ethyl acetate) gave the title compound 241 (0.005 g, 53%) as orange needles, m.p. (Found: M⁺, 259.0845. C₁₄H₁₃N⁰₄ requires M, 259.0845); νmax (400 MHz; CDCl₃) 10.17 (1H, s, CHO), 5.62 (1H, s, 7-H), 4.32 (2H, t, J 6.4, NCH₂), 3.77 (3H, s, MeO), 3.11 (2H, t, J 6.4, 1-H), 1.95 (2H, m, 3/2-H) and 1.82 (2H, m, 2/3-H); δC (100.6 MHz; CDCl₃) 189.34 (CHO), 180.32 (9/6-C), 179.35 (6/9-C), 161.33, 144.66, 120.48, 108.06 (7-C), 58.10 (MeO), 47.78 (NCH₂), 26.02 (1-C), 23.70 (3-C) and 20.23 (2-C); m/z 259 (M⁺, 100), 203 (47), 91 (18), 77 (19), 69 (27) and 41 (15).

4-Benzyl-oxy-1-(5-iodopentyl)-5-methoxyindole-3-carboxaldehyde 260
A mixture of 4-benzyloxy-5-methoxyindole-5-carboxaldehyde 243 (0.104 g, 0.37 mmol), powdered 87% potassium hydroxide (0.046 g, 0.83 mmol) and DMSO (4 cm³) was sonicated for 10 min, and then cooled to 0°C. 1,5-Diodopentane (0.16 cm³; 0.346 g, 1.07 mmol) was added at 0°C, and the mixture was stirred at room temperature. After 4 h, water (15 cm³) was added and the mixture was extracted with ethyl acetate (3 x 75 cm³). The combined extracts were washed with water (6 x 50 cm³), brine (2 x 25 cm³)
and dried (Na₂SO₄). The solvent was removed in vacuo and the residue was purified by column chromatography (50% light petroleum/50% diethyl ether) to give the title compound 260 (0.124 g, 70%) as a yellow oil, (Found: M⁺, 477.0801. C₂₂H₂₄INO₃ requires M, 477.0803); νmax (film) 1651, 1516, 1461, 1389, 1259, 1172, 1060 and 760 cm⁻¹; δH (400 MHz; CDCl₃) 10.33 (1H, s, CHO), 7.83 (1H, s, 2-H), 7.49 (2H, m, Ar-H), 7.40-7.33 (3H, m, Ar-H), 7.07 (2H, AB, J 8.8, 7/6-H), 5.25 (2H, s, OCH₂Ph), 4.13 (2H, t, J 7.2, NCH₂), 3.97 (3H, s, OMe), 3.16 (2H, t, J 7.2, CH₂I), 1.89 (4H, m, 2 and 4-CH₂) and 1.47 (2H, m, 3-CH₂); δC 187.15 (CHO), 148.04, 142.05, 137.71, 133.76 (2-C), 133.13, 128.71, 128.36, 122.77, 117.62, 112.20 (7/6-C), 106.16 (6/7-C), 75.29 (OCH₂Ph), 58.11 (OMe), 47.43 (NCH₂), 33.02 (4-C), 28.83 (2-C), 28.59 (3-C) and 6.05 (CH₂I); m/z 477(M⁺, 12%), 449 (13), 386 (71), 258 (17), 216 (28), 155 (29), 91 (100), 51 (53) and 28 (63).

10-Benzyl-8-methoxy-1,2,3,4-tetrahydro-5H-azepino[1,2-a]indole-11-carboxaldehyde 262
A solution of tri-n-butyltin hydride (0.07 cm³; 0.081 g, 0.28 mmol) and AIBN (0.029 g, 0.18 mmol) in toluene (2 cm³) was added to 4-benzyloxy-1-(5-iodopentyl)-5-methoxyindole-3-carboxaldehyde 260 (0.067 g, 0.14 mmol) in toluene (1.65 cm³) at reflux over 15 min. The reaction was stirred at reflux for 3 h and a further portion of tri-n-butyltin hydride (0.02 cm³)/AIBN (0.010 g) was added over 5 min. After a further 20 min at reflux the mixture was allowed to cool to room temperature and the solvent removed in vacuo. Water (0.25 cm³) ethyl acetate (3 cm³) and potassium fluoride (0.150 g) were added and the mixture stirred at room temperature. After 12 h, a further portion of water, ethyl acetate and potassium fluoride were added and the mixture stirred for 2 h. Potassium carbonate was added; the mixture filtered and the solvent removed in vacuo. The residue was purified by column chromatography (diethyl ether) to give the title compound 262 (0.014 g, 29%) as a colourless solid, m.p. 116°C; (Found: M⁺, 349.1678. C₂₂H₂₃NO₃ requires M, 349.1678); νmax (Nujol) 1650, 1493, 1393, 1258, 1104 and 774 cm⁻¹; δH (400 MHz; CDCl₃) 9.69 (1H, s, CHO), 7.41 (2H, m, Ar-H), 7.31-7.23 (3H, m, Ar-H), 6.92 (2H, AB, J 8.8, 8/7-H), 5.10 (2H, s, OCH₂Ph), 4.08 (2H,
1-(3-Chloropropyl)indole-3-carboxaldehyde 253

A mixture of indole-3-carboxaldehyde 252 (0.503 g, 3.47 mmol), powdered 87% potassium hydroxide (0.254 g, 4.52 mmol) and DMSO (8 cm³) was sonicated for 10 min, and then cooled to 0°C. 1-Bromo-3-chloropropane (1.02 cm³; 1.626 g, 10.33 mmol) was added at 0°C, and the mixture was stirred at room temperature. After 4 h, water (50 cm³) was added and the mixture was extracted with ethyl acetate (3 x 150 cm³). The combined extracts were washed with water (6 x 100 cm³), brine (2 x 75 cm³) and dried (Na₂SO₄). The solvent was removed in vacuo and the residue was purified by column chromatography (50% light petroleum/50% diethyl ether) to give the title compound 253 (0.696 g, 91%) as a colourless solid, m.p. 46°C (lit. 96 47-48.5°C) (Found: M⁺, 221.0607. C₁₂H₁₂ClN₂O requires M, 221.0607); νmax (Nujol) 1656, 1533 and 1401 cm⁻¹; δH (400 MHz; CDCl₃) 10.00 (1H, s, CHO), 8.31 (1H, m, 4-H), 7.75 (1H, s, 2-H), 7.42-7.30 (3H, m, Ar-H), 4.41 (2H, t, J 6.4, NCH₂), 3.48 (2H, t, J 5.6, CH₂Cl) and 2.33 (2H, q, J 6.4, CH₂); δC (100.6 MHz; CDCl₃) 184.51 (CHO), 138.37 (2-C), 137.02, 125.55, 124.21, 123.09, 122.33, 118.47, 109.90, 43.80 (NCH₂), 41.30 (CH₂) and 32.00 (CH₂Cl); m/z 221(M⁺, 51%), 158 (100), 144 (12), 130 (29), 51 (9) and 28 (17).
**1-(3-Iodopropyl)indole-3-carboxaldehyde 235**

A solution of 1-(3-chloropropyl)-5-methoxyindole-3-carboxaldehyde 253 (0.621 g, 2.80 mmol) in acetonitrile (12 cm³) containing sodium iodide (0.1673 g, 11.16 mmol) was heated at reflux temperature for 12 h. The solution was poured into water (50 cm³) and extracted with dichloromethane (3 x 150 cm³). The extract was washed with water (3 x 100 cm³), saturated aqueous sodium sulfite solution (50 cm³) and dried (Na₂SO₄). The solvent was removed *in vacuo* and the residue purified by column chromatography (diethyl ether) to give the *title compound* 235 (0.694 g, 79%) as a colourless oil, (Found: M⁺, 312.9964. C₁₂H₁₂INO requires M⁺, 312.9965); νₘₐₓ (film) 1647, 1530, 1261, 1217, 1166 and 1038 cm⁻¹; δₜ (400 MHz; CDCl₃) 10.05 (1H, s, CHO), 8.35 (1H, m, 4-H), 7.81 (1H, s, 2-H), 7.46-7.34 (3H, m, Ar-H), 4.38 (2H, t, J 6.4, NCH₂), 3.13 (2H, t, J 6.4, CH₂), 2.39 (2H, q, J 6.4, CH₂); δ_c (100.6 MHz; CDCl₃) 184.47 (CHO), 138.13 (2-C), 136.99, 125.57, 124.19, 123.11, 122.36, 118.48, 109.90, 47.04 (NCH₂), 32.63 (CH₂) and 1.94 (CH₂); m/z 313 (M⁺, 56%), 217 (9), 186 (10), 158 (100), 130 (26), 77 (15), 51 (43) and 28 (56).

**1,2-Dihydro-3H-pyrrole[1,2-ajindole-9-carboxaldehyde 236**

A solution of tri-n-butylin hydride (0.29 cm³; 0.314 g, 1.08 mmol) and AIBN (0.089 g, 0.54 mmol) in toluene (7 cm³) was added to 1-(3-iodopropyl)indole-3-carboxaldehyde 235 (0.169 g, 0.54 mmol) in toluene (5 cm³) at reflux over 15 min. The reaction was stirred at reflux for 3 h and a further portion of tri-n-butylin hydride (0.10 cm³) /AIBN (0.030 g) was added over 5 min. After a further 20 min at reflux the mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Water (0.25 cm³) ethyl acetate (3 cm³) and potassium fluoride (0.150 g) were added and the mixture
stirred at room temperature. After 12 h, a further portion of water, ethyl acetate and potassium fluoride were added and the mixture stirred for 2 h. Potassium carbonate was added, the mixture filtered and the solvent removed in vacuo. The residue was purified by column chromatography (diethyl ether) to give the title compound 236 (0.064 g, 64%) as a colourless solid; m.p. 136°C (lit. 146-147°C); (Found: M⁺, 185.0841. C₁₂H₁₁NO requires M, 185.0841); νmax (Nujol) 1642, 1538, 1303, 1245, 1121, 1041, and 747 cm⁻¹; δH (400 MHz; CDCl₃) 10.00 (1H, s, CHO), 8.19 (1H, m, 4-H), 7.29-7.22 (3H, m, Ar-H), 4.12 (2H, t, J 6.8, NCH₂), 3.28 (2H, t, J 7.2, 1-H) and 2.71 (2H, m, 2-H); δC (100.6 MHz; CDCl₃) 183.44 (CHO), 155.45, 133.22, 130.00, 122.83, 122.75, 121.42, 110.28, 110.00, 44.53 (NCH₂), 26.85 (2-C) and 24.55 (1-H); m/z 185 (M⁺, 85%), 156 (29), 128 (18), 77 (12), 51 (11) and 28 (22).

I-(4-Chlorobutyl)indole-3-carboxaldehyde 254
A mixture of indole-3-carboxaldehyde 252 (0.501 g, 3.45 mmol), powdered 87% potassium hydroxide (0.256 g, 4.56 mmol) and DMSO (8 cm³) was sonicated for 10 min, and then cooled to 0°C. 1-Bromo-4-chlorobutane (1.19 cm³; 1.77 g, 10.33 mmol) was added at 0°C, and the mixture was stirred at room temperature. After 4 h, water (50 cm³) was added and the mixture was extracted with ethyl acetate (3 x 150 cm³). The combined extracts were washed with water (6 x 100 cm³), brine (2 x 75 cm³) and dried (Na₂SO₄). The solvent was removed in vacuo and the residue was purified by column chromatography (50% light petroleum/50% diethyl acetate) to give the title compound 254 (0.785 g, 97%) as a colourless solid, m.p. 63°C (lit. 62-64°C); (Found: M⁺, 235.0764. C₁₃H₁₄ClNO requires M, 235.0764); νmax (Nujol) 1659, 1523, 1378, 1319 and 1171 cm⁻¹; δH (400 MHz; CDCl₃) 10.01 (1H, s, CHO), 8.31 (1H, m, 4-H), 7.71 (1H, s, 2-H), 7.39-7.30 (3H, m, Ar-H), 4.23 (2H, t, J 7.2, NCH₂), 3.55 (2H, t, J 6.4, CH₂Cl), 2.09 (2H, m, 2-CH₂) and 1.82 (2H, m, 3-CH₂); δC (100.6 MHz; CDCl₃) 184.44 (CHO), 137.80 (2-C), 137.16, 125.55, 124.12, 123.01, 122.26, 118.38, 109.93, 46.57 (NCH₂), 44.08 (2-C), 29.63 (3-C) and 27.22 (CH₂Cl); m/z 235 (M⁺, 44%), 158 (100), 144 (16), 130 (24), 51 (27) and 28 (22).
1-(4-Iodobutyl)indole-3-carboxaldehyde 237
A solution of 1-(4-chlorobutyl)-5-methoxyindole-3-carboxaldehyde 254 (0.499 g, 2.12 mmol) in acetonitrile (12 cm³) containing sodium iodide (1.306 g, 8.71 mmol) was heated at reflux temperature for 12 h. The solution was poured into water (50 cm³) and extracted with dichloromethane (3 x 150 cm³). The extract was washed with water (3 x 100 cm³), saturated aqueous sodium sulfite solution (50 cm³) and dried (Na₂SO₄). The solvent was removed in vacuo and the residue purified by column chromatography (diethyl ether) to give the title compound 237 (0.504 g, 73%) as a colourless solid; m.p 57°C (lit. 96-59°C); (Found: M⁺, 327.0120. C₁₃H₁₄INO requires M, 327.0120.; vₘₐₓ (Nujol) 1645, 1533, 1468, 1401, 1135 and 752 cm⁻¹; δₜₜ (400 MHz; CDCl₃) 10.04 (1H, s, CHO), 8.34 (1H, m, 4-H), 7.73 (1H, s, 2-H), 7.42-7.34 (3H, m, Ar-H), 4.42 (2H, t, J 7.2, NCH₂), 3.20 (2H, t, J 7.2, CH₂I), 2.07 (2H, m, 2-CH₂) and 1.88 (2H, m, 3-CH₂); δₜₜ (100.6 MHz; CDCl₃) 186.67 (CHO), 139.99 (2-C), 139.38, 127.80, 126.36, 125.26, 124.51, 120.63, 112.17, 48.45 (NCH₂), 32.93 (2-C), 32.61 (3-C) and 7.18 (CH₂I); m/z 327 (M⁺, 68%), 170 (26), 158 (91), 130 (100), 116 (45), 77 (46) and 55 (62).

1,2,3,4-Tetrahydropyrido[1,2-ajindole-10-carboxaldehyde 238
A solution of tri-n-butyltin hydride (0.10 cm³; 0.107 g, 0.37 mmol) and AIBN (0.030 g, 0.18 mmol) in toluene (7 cm³) was added to 1-(4-iodobutyl)indole-3-carboxaldehyde 237 (0.060 g, 0.18 mmol) in toluene (5 cm³) at reflux over 15 min. The reaction was stirred at reflux for 3 h and a further portion of tri-n-butyltin hydride (0.03 cm³) /AIBN (0.01 g) was added over 5 min. After a further 20 min at reflux the mixture was allowed to cool to room temperature and the solvent removed in vacuo. Water (0.25 cm³) ethyl acetate (3 cm³) and potassium fluoride (0.150 g) were added and the mixture stirred at
room temperature. After 12 h, a further portion of water, ethyl acetate and potassium fluoride were added and the mixture stirred for 2 h. Potassium carbonate was added, the mixture filtered and the solvent removed in vacuo. The residue was purified by column chromatography (diethyl ether) to give the title compound 238 (0.027 g, 75%) as a colourless solid, m.p. 124°C (lit. 96 121-125°C); (Found: M⁺, 199.0997. C₁₃H₁₃NO requires M, 199.0997.); νmax (Nujol) 1640, 1519, 1313, 1249, 1169, 1061, and 748 cm⁻¹; δH (400 MHz; CDCl₃) 10.16 (1H, s, CHO), 8.20 (1H, m, Ar-H), 7.31-7.23 (3H, m, Ar-H), 4.10 (2H, t, J 6.0, NCH₂), 3.31 (2H, t, J 6.4, 1-H), 2.15 (2H, m, 3-H) and 1.98 (2H, m, 2-H); δC (100.6 MHz; CDCl₃) 183.50 (CHO), 148.00, 136.50, 126.01, 123.13, 122.74, 120.56 (9-C), 112.95, 109.12, 42.44 (NCH₂), 22.84 (1-C), 22.49 (3-C) and 19.69 (2-C); m/z 199 (M⁺, 100%), 170 (46), 155 (27), 113 (21), 51 (51) and 28 (57).

1-(5-Chloropentyl)indole-3-carboxaldehyde 255
A mixture of indole-3-carboxaldehyde 252 (0.500 g, 3.44 mmol), powdered 87% potassium hydroxide (0.300 g, 5.34 mmol) and DMSO (8 cm³) was sonicated for 10 min, and then cooled to 0°C. 1-Bromo-5-chloropentane (1.36 cm³; 1.916 g, 10.33 mmol) was added at 0°C, and the mixture was stirred at room temperature. After 4 h, water (50 cm³) was added and the mixture was extracted with ethyl acetate (3 x 150 cm³). The combined extracts were washed with water (6 x 100 cm³), brine (2 x 75 cm³) and dried (Na₂SO₄). The solvent was removed in vacuo and the residue was purified by column chromatography (50% light petroleum/50% diethyl acetate) to give the title compound 255 (0.764 g, 86%) as a colourless solid, m.p. 64°C; (Found: M⁺, 249.0920. C₁₄H₁₆ClNO requires M, 249.0920.); νmax (Nujol) 1655, 1525, 1243, 1311 and 1174 cm⁻¹; δH 10.00 (1H, s, CHO), 8.31 (1H, m, 4-H), 7.70 (1H, s, 2-H), 7.38-7.29 (3H, m, Ar-H), 4.18 (2H, t, J 7.2, NCH₂), 3.51 (2H, t, J 6.8, CH₂Cl), 1.93 (2H, m, 2-CH₂), 1.79 (2H, m, 4-CH₂) and 1.51 (2H, m, 3-CH₂); δC (100.6 MHz; CDCl₃) 184.44 (CHO), 138.04 (2-C), 137.16, 125.53, 124.00, 122.93, 122.20, 118.22, 109.98, 47.909 (NCH₂), 44.48 (4-C), 31.96 (2-C), 29.11 (3-C) and 24.20 (CH₂Cl); m/z 249 (M⁺, 39%), 186 (7), 158 (100), 144 (14), 130 (34), 77 (16) and 51 (9).
1-(5-Iodopentyl)-5-methoxyindole-3-carboxaldehyde 256
A solution of 1-(5-chloropentyl)-5-methoxyindole-3-carboxaldehyde 255 (0.545 g, 2.18 mmol) in acetonitrile (12 cm³) containing sodium iodide (1.336 g, 8.91 mmol) was heated at reflux temperature for 12 h. The solution was poured into water (50 cm³) and extracted with dichloromethane (3 x 150 cm³). The extract was washed with water (3 x 100 cm³), saturated aqueous sodium sulfite solution (50 cm³) and dried (Na₂SO₄). The solvent was removed *in vacuo* and the residue purified by column chromatography (diethyl ether) to give the *title compound* 256 (0.683 g, 92%) as a colourless solid; m.p. 72-74°C; (Found: *M*⁺ 341.0277; C₁₄H₁₆INO requires *M*, 341.0277); νₘₐₓ (Nujol) 1646, 1531, 1260, 1234, 1169, 1137 and 1015 cm⁻¹; δ H (400 MHz; CDCl₃) 10.04 (1H, s, CHO), 8.34 (1H, m, 4-H), 7.74 (1H, s, 2-H), 7.40-7.32 (3H, m, Ar-H), 4.22 (2H, t, J 6.8, NCH₂), 3.18 (2H, t, J 6.8, CH₂I), 1.97-1.84 (4H, m, 2 and 4-CH₂) and 1.51 (2H, m, 3-CH₂); δ C (100.6 MHz; CDCl₃) 184.79 (CHO), 138.33 (2-C), 137.51, 125.92, 124.38, 123.31, 122.59, 118.61, 110.33, 47.42 (NCH₂), 33.10 (4-C), 29.11 (2-C), 28.12 (3-C) and 6.26 (CH₂I); *m/z* 341 (M⁺, 54%), 186 (19), 158 (100), 130 (47), 77 (16) and 51 (6).

1,2,3,4-Tetrahydro-5H-azepino[1,2-a]indole-11-carboxaldehyde 257
A solution of tri-n-butyltin hydride (0.36 cm³; 0.388 g, 1.33 mmol) and AIBN (0.110 g, 0.67 mmol) in toluene (7 cm³) was added to 1-(5-iodopentyl)indole-3-carboxaldehyde 256 (0.228 g, 0.67 mmol) in toluene (5 cm³) at reflux over 15 min. The reaction was stirred at reflux for 3 h and a further portion of tri-n-butyltin hydride (0.10 cm³) /AIBN (0.03 g) was added over 5 min. After a further 20 min at reflux the mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. Water (0.25 cm³) ethyl
acetate (3 cm$^3$) and potassium fluoride (0.150 g) were added and the mixture stirred at room temperature. After 12 h, a further portion of water, ethyl acetate and potassium fluoride were added and the mixture stirred for 2 h. Potassium carbonate was added, the mixture filtered and the solvent removed \textit{in vacuo}. The residue was purified by column chromatography (diethyl ether) to give the title compound 257 (0.061 g, 43\%) as a colourless solid, m.p. 114°C; (Found: $M^+$, 213.1154. \textit{C$_{14}$H$_{15}$NO} requires $M$, 213.1154.); $\nu_{\max}$ (Nujol) 1645, 1576, 1533, 1376, 1203, 1047 and 743 cm$^{-1}$; $\delta_H$ (400 MHz; CDCl$_3$) 10.08 (1H, s, CHO), 8.24 (1H, m, Ar-H), 7.28-7.16 (3H, m, Ar-H), 4.12 (2H, t, J 4.8, NCH$_2$), 3.16 (2H, t, J 5.2, 1-H), 1.84 (2H, m, 3-H) and 1.73 (4H, m, 2 and 4-H); $\delta_C$ (100.6 MHz; CDCl$_3$) 184.44 (CHO), 153.98, 136.74, 126.05, 123.43, 122.93, 121.63 (10-C), 113.73, 109.38, 45.20 (NCH$_2$), 31.06 (3-C), 28.55 (4/2-C), 26.87 (2/4-C), 25.41 (1-C); $m/z$ 213 ($M^+$, 100\%), 184 (59), 156 (21), 77 (11), 51 (10) and 28 (11).
References


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**Appendix 1 X-ray crystallographic data**

All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation.

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<th>Direct Methods (SIR88)</th>
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*Figure 2 compound 165*

**Crystal Data**

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**Intensity Measurements**

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<td>Corrections</td>
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Structure Solution and Refinement

p-factor 0.0090
No. Observations (I > 3.00σ(I)) 1330
No. Variables 236
Reflection/Parameter Ratio 5.64
Residuals: R, Rw 0.051: 0.047
Goodness of Fit Indicator 2.90
Max Shift/Error in Final Cycle 0.09
Maximum peak in Final Diff. Map 0.18 e⁻/Å³
Minimum peak in Final Diff. Map -0.15 e⁻/Å³

Figure 6 compound 216

Crystal Data

Empirical Formula C₂₇H₂₃NO₃
Formula Weight 409.48
Crystal System triclinic

Lattice Parameters
a = 10.485 (2) Å
b = 11.811 (1) Å
c = 9.161 (1) Å
α = 92.667 (9)°
β = 105.26 (1)°
γ = 98.78 (1)°

Space Group P2₁/a
Z value 2
Dcalc 1.262 g/cm³
μ (CuKα) 6.19 cm⁻¹

Intensity Measurements

Cu radiation λ = 1.54178 Å
Scan Type ω-2θ
No. of Reflections Measured Total: 3410
Unique: 3208 (Rint = 0.038)
Corrections  Lorentz-polarisation

**Structure Solution and Refinement**

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